ORIGINAL RESEARCH—CLINICAL

Delayed Gastric Emptying Neither Contributes to Gastroesophageal Reflux nor Disease Severity in Patients With Respiratory Disease

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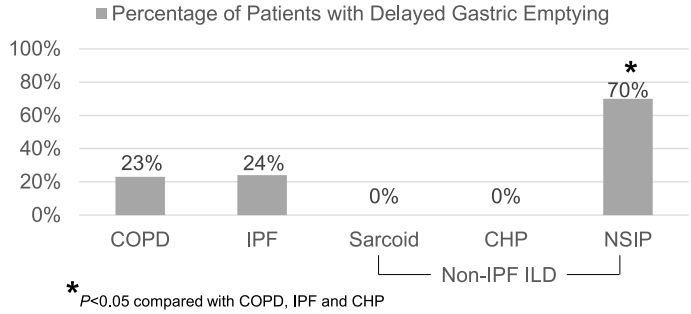

Key: COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; ILD, interstitial lung disease; Sarcoid, sarcoidosis; CHP, chronic hypersensitivity pneumonitis; NSIP, fibrotic non-specific interstitial pneumonia

Delayed gastric emptying (DGE) was not associated with:

- Increased gastroesophageal reflux
- Higher intra-abdominal pressures
- Specific esophageal dysmotility
- Worse pulmonary function

➡ **DGE is not associated with reflux and unlikely to be a factor in respiratory disease, including patients being evaluated for lung transplantation**

Gastro Hep Advances

BACKGROUND AND AIMS: Gastroesophageal reflux (GER) is common and thought to contribute to disease progression in patients with respiratory disease. Delayed gastric emptying (DGE) can increase GER in patients with GER disease, but its effect in patients with respiratory disease, and how differing lung structure (eg, scarring, inflammation) and mechanics (eg, decreased thoracic pressure in restrictive disease, increased abdominal pressure in obstructive disease) influences this is unknown. Our aim was to understand these interrelationships and association with pulmonary function in patients with chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF) and non-IPF interstitial lung disease (non-IPF ILD). **METHODS:** We prospectively recruited 22 COPD (aged 34–75 years), 33 IPF (45–74 years), and 19 non-IPF ILD (37–74 years) patients who underwent gastric emptying studies, high resolution impedance manometry, 24-hr pH-impedance, and pulmonary function testing, as part of routine lung transplantation assessment. **RESULTS:** Gastric emptying was delayed in a total of 20(27%) patients; 5(23%) with COPD, 8(24%) with IPF and 7(37%) with non-IPF ILD. Notably, all 7 non-IPF ILD patients with DGE had nonspecific interstitial pneumonia (NSIP; ie, 70% of NSIP patients; $P < .02$ compared with other groups). DGE irrespective of disease type was not associated with increased acid exposure time, total bolus exposure time or number of reflux events. Furthermore, DGE was not associated with higher intra-abdominal pressure, specific esophageal dysmotility, or worse pulmonary function in any of the respiratory diseases.

Abbreviations used in this paper: **AP, abdominal pressure; aTAPG, adjusted thoracoabdominal pressure gradient; BALF, bronchoalveolar lavage fluid; CCv4.0, Chicago Classification version 4.0; CF, cystic fibrosis; CHP, Chronic hypersensitivity pneumonitis; COPD, chronic obstructive pulmonary disease; DGE, delayed gastric emptying; EGJOO, esophagogastric junction outflow obstruction; EL, esophageal length; ELI, esophageal length index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GER, gastroesophageal reflux; HRIM, high resolution impedance manometry; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; LTx, lung transplantation; MII-pH, 24-hr pH-impedance; NSIP, nonspecific interstitial pneumonia; OLD, obstructive lung disease; PDE-5, phosphodiesterase-5; PPI, proton pump inhibitor; RLD, restrictive lung disease; TAPG, thoracoabdominal pressure gradient; TBET, total bolus exposure time.**

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CONCLUSION: Significantly more NSIP patients have DGE compared with other respiratory diseases. Irrespective of this, DGE had little effect on GER or pulmonary function in any of the respiratory diseases.

Keywords: esophageal motility; gastric emptying; lung mechanics; obstructive lung disease; reflux; restrictive lung disease

Introduction

Gastroesophageal reflux (GER) is common and thought to contribute to worse pulmonary function and progression of disease in patients with respiratory disorders.[1] The detection of gastric pepsin and/or bile in bronchoalveolar lavage fluid (BALF) or sputum supports the occurrence of microaspiration of refluxate in these patients.[2–4] Moreover, studies in patients with idiopathic pulmonary fibrosis (IPF) have reported that the degree of fibrosis correlates with BALF concentrations of both pepsin and bile acid[2], although similar observations have not been reported in patients with chronic obstructive pulmonary disease (COPD).[3]

Various factors can predispose subjects to increased exposure of the esophagus to reflux, including ineffective esophageal motility (IEM),[5–7] abnormal lung mechanics and breathing patterns,[8] and delayed gastric emptying.[9–12] Studies report that between approximately 27% and 58% of patients with restrictive lung disease (RLD) and obstructive lung disease (OLD) lung disease exhibit IEM.[13–15] IPF patients with IEM have more severe pulmonary function and more proximal reflux compared with patients with normal motility.[13] In patients with COPD these associations with esophageal dysmotility are less clear, and although reflux has been associated with frequent exacerbation, IEM and objective measurements of reflux have not been shown to associate with worse pulmonary function.[14,16] Greater negative intrathoracic pressures in IPF patients with IEM also inversely correlates with the number of reflux events reaching the proximal esophagus, and positively with pulmonary function (ie, the greater the negative intrathoracic pressure, the lower the percent predicted forced vital capacity [FVC] and percent predicted forced expiratory volume in 1 second [FEV_1]).[13] A similar negative correlation between intrathoracic pressure and proximal acid exposure has been reported in patients with COPD.[17] The discoordination between the phases of breathing and swallowing may also impact esophageal function and reflux clearance. In healthy volunteers, increasing the frequency of breathing and voluntarily changing the contributions of the ribcage and abdomen can influence intraesophageal pressure and thus potentially reflux,[18] whereas hyperventilation and partial expiration can impair esophagogastric junction relaxation and esophageal peristalsis, delaying esophageal transit and clearance.[19]

Lastly, gastric emptying has been shown to be delayed in up to 50% of patients with respiratory disease,[15,20–25] with the prevalence being no different between those with RLD and OLD.[15,20,21] One study however, did report that in respiratory patients with delayed gastric emptying, there was a tendency for more patients to have cystic fibrosis (CF) or non-scleroderma non-IPF interstitial lung disease (ILD), and less likely to have IPF.[22] This study also looked at the relationship between delayed gastric emptying and lung function, reporting that those with delayed emptying were more likely to have moderate to severe disease (i.e. FEV_1<60% predicted).[22] However, the percentage of patients with moderate/severe disease was high in both those with and without delayed gastric emptying (100% vs 81%), and the cohort was a mixture of patients with CF, ILD, COPD, scleroderma, sarcoidosis, and IPF. Thus, whether delayed gastric emptying is associated with increased reflux and/or worse pulmonary function, in those with restrictive compared with obstructive disease, and between different restrictive diseases, such as IPF and non-IPF ILD, and how the contrasting respiratory mechanics seen in these different disease types, along with esophageal dysmotility, influences the impact of delayed gastric emptying on lung function is unknown. This is important, as it is unclear whether delayed gastric emptying, especially if patients are asymptomatic, should be treated due to concern of potential increased GER and its aspiration into the lungs. Moreover, whether certain patients with end-stage lung disease should be prioritized more than others who undergo lung transplantation (LTx) based on gastric emptying is unclear.

Our aim was therefore to examine the interrelationships between gastric emptying, esophageal motility and lung mechanics, and their impact on GER and lung function in patients with COPD, IPF, and non-IPF ILD.

Materials and Methods

Patients

154 consecutive patients were referred for gastric emptying studies, esophageal high resolution impedance manometry (HRIM), and 24-hr pH-impedance (MII-pH) as part of their routine clinical work-up for LTx at Mayo Clinic, Florida between November 2016 and October 2022. 80 patients who did not complete all tests were excluded. We therefore analyzed complete data from the 74 remaining patients (median age 64 (range 34–75) years, 25 (33.8%) females, mean body mass index 28.1 (95% confidence interval; 27.1–29.1). All medications were stopped 48 hrs prior to the tests. Patients had a diagnosis of COPD, IPF, or non-IPF ILD confirmed by a multidisciplinary panel prior to inclusion in the study. Patients with scleroderma, previous lung or gastrointestinal surgery, or current lung or gastrointestinal malignancy, were excluded.

Gastric Emptying Scintigraphy

Gastric emptying was measured using the established, validated, scintigraphic technique employed by Mayo Clinic.[26] After an overnight fast of at least 8 hours, patients ate a ^{99m}Tc-labeled

meal of two scrambled eggs (standard size), 1 slice of whole wheat bread and 1 glass (240ml) of skimmed (<1% fat) milk (320 kcal, 30% fat). Abdominal images were obtained with a dual anterior/posterior gamma camera. Following consumption of the standardized meal, 2-minute static images were obtained. The patient then returned for scanning at 1, 2, and 4 hours.[26]

HRIM

HRIM was performed using a solid-state catheter with 36 pressure sensors 1cm apart and 18 impedance sensors (Medtronic, 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 and lower esophageal sphincter (LES), ten 5 ml saline swallows were given at least 30s apart with the patient supine.[27]

Impedance tracings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings.[28] Subjects were classified as complete bolus transit when clearance was seen in ≥80% of swallows.[29]

MII-pH

MII-pH was performed using a single antimony pH probe (5cm above the LES) with 8 impedance electrodes (Sandhill Scientific, CO).[30]

Pulmonary Function Testing

Pulmonary function data was obtained from patient records at the time of gastric emptying assessment, including FEV_1, FVC, and FEV_1/FVC ratio. Respiratory disease severity was categorized as severe if FEV_1 ≤50% predicted, moderate if FEV_1 51%–79%, and mild if FEV_1 ≥80% predicted. Percentage predicted values were obtained using patient age, height and ethnicity as per American Thoracic Society/European Respiratory Society recommendations.[31]

Data Analysis

Gastric emptying. Abdominal images at 1, 2, and 4hr post-meal were evaluated, and the data at 4hrs used to categorize patients as having either normal gastric emptying (retention ≤10%) or delayed gastric emptying (retention >10%).[32,33]

HRIM. ManoVIEW analysis software (v3.01; Medtronic, Shoreview, NM) was used to manually analyze the recordings. Esophageal motility was classified based upon Chicago Classification (CCv4.0).[27] Each 5ml swallow was evaluated to determine the following: 1) integrated relaxation pressure, 2) distal contractile integral, 3) distal latency, and 4) isobaric contour (pressurization).[28] Contractile pattern was classified as normal, weak, failed peristalsis, fragmented, or hypercontractile swallow.[27]

CCv4.0 diagnoses included the following: 1) achalasia or esophagogastric junction outflow obstruction (EGJOO), and 2) disorders of peristalsis, such as absent contractility, distal esophageal spasm, hypercontractile esophagus (single peak hypercontractile swallow, Jackhammer esophagus and hypercontractile LES), and IEM.[27] As HRIM was performed in very sick patients requiring lung transplant, with most tests carried out before the publication of CCv4.0, additional provocation or alternate position testing to confirm EGJOO was not performed. We thus use the term 'inconclusive EGJOO' to describe patients with suspected EGJOO.

Thoracoabdominal pressure gradient (TAPG). TAPG was calculated by subtracting the intra-abdominal pressure (intra-AP; proximal stomach 1cm below the lower border of the LES and referenced to atmospheric pressure) from the mean intrathoracic pressure (distal esophagus between 1 and 5cm 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-AP (ie, 1 cm below the lower border of the LES), was also measured, and an adjusted thoracoabdominal pressure gradient (aTAPG) was calculated by subtracting lower esophageal sphincter pressure (LESP) from the TAPG during inspiration. A cutoff value of aTAPG to predict the risk of reflux was set at >0mmHg, based on the hypothesis that reflux may occur when TAPG overcomes the LESP.[8,13]

Esophageal length (EL) and esophageal length index (ELI). EL was measured from the lower border of the upper esophageal sphincter to the upper border of LES at end-inspiration. ELI was calculated by dividing EL (centimeters) by height (meters).[15]

MII-pH

Data were manually analysed (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.[13,34] In addition, the main meal during the study was identified and total bolus exposure time (TBET) 4hrs post-meal was recorded.

Statistics

Differences between disease cohorts with respect to continuous measures were assessed using the 1-way analysis of variance test or Kruskal-Wallis test, followed by Student's 2-sample t tests or Mann-Whitney U test, as appropriate based on the distribution of data. We adjusted for multiple comparisons using a Bonferroni correction. Binary logistic regression was used to determine the impact of diagnosis, and proton pump inhibitor (PPI) and immunomodulator use on gastric emptying, defined as either normal (4hr post-meal retention ≤10%) or delayed (4hr post-meal >10% retention). Categorical measures between groups were evaluated using either the chi square or Fishers Exact tests, depending on group size. Relationships between continuous variables were assessed using scatterplots and quantified using Pearson's correlation or Spearman rank correlation. Significance was evaluated at the 2-tailed, P value of <0.05 taken as significant.

Results

Of the 74 patients recruited, 22(30%) COPD (median age 62 [range, 34–75] years), 33(44%) had IPF (aged 65 [45–74] years), and 19 (26%) non-IPF ILD (aged 60 [37–74] years). Of the non-IPF ILD patients, 10 (53%) had fibrotic nonspecific interstitial pneumonia (NSIP), 5 (26%) chronic

hypersensitivity pneumonitis (CHP), and 4 (21%) sarcoidosis. The majority of patients suffered from moderate or severe disease (FEV_1% 36 [48.6%] severe, 32 [43.2%] moderate, and 6 [8.1%] mild). Table 1 shows the demographic data, along with medication use in the three cohorts. All tests were completed within a median of 5 days (interquartile range: 2–8 days).

Gastric Emptying

Gastric emptying was delayed in a total of 20 (27%) patients; 5 (23%) with COPD, 8 (24%) with IPF, and 7 (37%) with non-IPF ILD (Table 2). Subanalysis of the non-IPF ILD patients revealed that all seven patients with delayed gastric emptying had fibrotic NSIP, which was significantly higher than the percentages seen in patients with CHP ($P = .026$) and sarcoidosis ($P = .070$). Furthermore, a greater proportion of non-IPF ILD patients with fibrotic NSIP had delayed gastric emptying compared with COPD ($P = .018$) and IPF ($P = .019$) patients.

Indeed logistic regression analysis using diagnosis (IPF, COPD, fibrotic NSIP, CHP, and sarcoid), PPI, and immunomodulator use, identified fibrotic NSIP but not PPI or immunomodulator use, to be an independent predictor of delayed gastric emptying (OR 10.6, 95% confidence interval 1.8–63.8; $P = .010$).

Of the 5 patients with diabetes, 2 patients (both IPF) had delayed gastric emptying.

Association With Reflux

Examining the whole cohort showed that there were no statistically significant differences in any of the reflux parameters between patients who had normal and delayed gastric emptying (Table 3). Similarly, examining the disease groups separately showed no statistically significant differences in reflux parameters between patients with normal and delayed gastric emptying in COPD, non-IPF ILD, or IPF (Tables 4, 5, 6) (NB that all non-IPF ILD patients with delayed gastric emptying had fibrotic NSIP). This also applied to TBET during the 4hrs post-main meal of the day. However, patients with non-IPF ILD who had delayed gastric emptying did tend to have a higher proportion of distal reflux events reaching the proximal esophagus ($P = .068$) than patients with normal gastric emptying (Table 6).

Association With Thoracic Pressure, Abdominal Pressure, TAPG, and aTAPG

As expected, patients with COPD (20.6 mmHg [16.7–24.5] mmHg) tended to have higher APs than IPF (16.0 mmHg [12.8–19.3] mmHg; $P = .072$) but not non-IPF ILD (19.4 mmHg [14.8–23.9] mmHg; $P = .673$) patients. Also patients with IPF (−5.3 mmHg [−8.6–2.0] mmHg) had lower thoracic pressures than COPD (3.4 mmHg [−0.3–7.1] mmHg; $P < .001$) and non-IPF ILD (0 mmHg [−4.8–4.8] mmHg; $P = .059$) patients, and thus greater TAPG than COPD (21.4 mmHg [17.9–24.9] mmHg vs 17.2 mmHg [14.3–20.0] mmHg; $P = .081$) but not non-IPF ILD (19.4 mmHg [13.9–24.9] mmHg) patients. There were no differences between patients with non-IPF ILD and COPD.

However, whether patients with COPD, IPF, or non-IPF ILD had delayed gastric emptying did not significantly affect intra-AP compared with those with normal gastric emptying (Table 3). Likewise, thoracic pressure, TAPG, and aTAPG were not significantly different between those with normal and delayed gastric emptying (Table 3).

Association With Esophageal Motility and Bolus Transit

There were no differences in esophageal motility diagnoses or basal LESP between patients with normal and delayed gastric emptying in patients with COPD, non-IPF ILD, and IPF (Tables 4, 5 and 6). Moreover, the tendency for increased proportion of reflux events to reach the proximal esophagus in non-IPF ILD with delayed gastric emptying was not related to differences in IEM, as only 1 patient with delayed gastric emptying had IEM (Table 3). Similarly, there were no differences in bolus transit between those with delayed and normal gastric emptying (Tables 4, 5,6).

Association With EL and ELI

ELI was significantly greater in patients with COPD (15.9(15.2–16.0) compared with IPF (12.8(12.3–13.4); $P < .001$) and non-IPF ILD (14.3(13.5–15.0); $P < .001$). Non-IPF ILD patients had a higher ELI than IPF patients ($P = .002$). There were no significant differences in ELI between patients with normal or delayed gastric emptying in the whole cohort, or the separate respiratory groups (Tables 3, 4, 5, and 6).

Association With Pulmonary Function

There was no difference in pulmonary function between patients with normal and delayed gastric emptying in any of the respiratory disease groups (Tables 4, 5 and 6). There were no correlations between 1, 2, or 4 hour % clearance and FEV_1%, FVC%, percent predicted total lung capacity%, or percent predicted residual volume% for any of the disease groups.

Discussion

We have shown for the first time that more than two thirds of non-IPF ILD patients with fibrotic NSIP (excluding scleroderma) have delayed gastric emptying, but along with patients with COPD, IPF, and other non-IPF ILD diseases, all of whom have differing lung structure and mechanics, delayed gastric emptying was not associated with increased numbers of reflux events, or worse pulmonary function. Furthermore, delayed gastric emptying did not affect intra-

Table 1. Demographic and Clinical Characteristics

	Total n = 74	COPD n = 22	IPF n = 33	Non-IPF ILD n = 19	*P* value
Age[a], y	63.5 (58.0–67.0)	62.0 (58.0–66.0)	65.0 (62.0–68.0)	60.0 (50.0–65.0)[c]	.048
Body mass index[b], kg/m^2	28.1 (27.1–29.1)	27.2 (25.2–29.3)	28.8 (27.3–30.2)	28.0 (25.6–30.4)	.470
Weight[a], kg	79.7 (73.3–91.0)	74.8 (66.5–83.7)	84.7 (77.3–94.2)	78.1 (73.3–89.2)	.059
Male, n (%)	49 (66.2%)	10 (45.5%)	27 (81.8%)[f]	12 (63.2%)	.019
Female	25 (33.8%)	12 (54.5%)	6 (18.2%)	7 (36.8%)	
Ethnicity n (%)					
White	63 (85.1%)	19 (86.4%)	32 (97.0%)	13 (68.4%)	0.211
Black	7 (9.5%)	2 (9.1%)	1 (3.0%)	4 (21.0%)	
Asian	2 (2.7%)	1 (4.5%)	0	1 (5.3%)	
Other	2 (2.7%)	0	0	1 (5.3%)	
Tobacco use n (%)					
Never smoked	29 (39.2%)	1 (4.5%)	13 (39.4%)[f]	15 (78.9%)[d,g]	<0.001
Ex-smoker	45 (60.8%)	21 (95.5%)	20 (60.6%)	4 (21.1%)	
Current smoker	0	0	0	0	
Medication use n (%)					
PPIs	29 (39.2%)	5 (22.7%)	16 (48.5%)	8 (42.1%)	0.152
Opiates	2 (2.7%)	0	2 (6.1%)	0	0.279
ICS, LAMA, LABA, or combination inhalers	35 (47.3%)	20 (90.9%)	7 (21.2%)[g]	8 (42.1%)[f]	<0.001
Immunomodulators[h]	11 (14.9%)	2 (9.1%)	3 (9.1%)	6 (31.6%)	0.060
PDE-5 inhibitors	4 (5.4%)	0	1 (3.0%)	3 (15.8%)	0.060
Antifibrotics	24 (32.4%)	0	20 (60.6%)[g]	4 (21.1%)[d,e]	<0.001
Comorbidities n (%)					
Diabetes mellitus	5 (6.8%)	0	3 (9.1%)	2 (10.5%)	0.315
Hiatus hernia	3 (4.1%)	2 (9.5%)	1 (3%)	0	0.312
Pulmonary function tests					
FEV_1[a], %	51.0 (33.0–66.1)	28.0 (22.0–43.0)	57.0 (47.1–67.0)[g]	58.0 (37.0–72.0)[f]	<0.001
FVC[a], %	57.7 (46.0–66.0)	64.0 (54.0–77.0)	52.0 (43.0–61.0)[f]	57.3 (39.0–67.0)	<0.001
FEV_1/FVC ratio[a]	0.82 (0.52–0.87)	0.37 (0.28–0.43)	0.84 (0.81–0.89)[g]	0.85 (0.77–0.89)[g]	<0.001
TLC[a], %	61.9 (50–108)	127.0 (108–139)	52.0 (47–58)[g]	57.8 (42–64)[g]	<0.001
RV[a], %	65.6 (50–170)	208.5 (154–270)	53.5 (46–59)[g]	57.0 (49–72)[g]	<0.001
Proportion with moderate to severe disease n (%)					
FEV_1, % (<80%)	68 (91.9%)	20 (90.9%)	31 (93.9%)	17 (89.5%)	0.834
FVC, % (<80%)	68 (91.9%)	17 (77.3%)	33 (100%)[f]	18 (94.7%)	0.009
Domiciliary oxygen n (%)					
Domiciliary oxygen	59 (79.7%)	19 (86.4%)	28 (84.8%)	12 (63.2%)	0.113
Esophageal length & index					
Esophageal length[b], cm	24.1 (23.3–24.9)	26.8 (25.6–28.1)	22.0 (21.1–23.0)[g]	24.4 (23.2–25.7)[d,f]	<0.001
Esophageal length index[b]	14.1 (13.7–14.6)	15.9 (15.2–16.6)	12.8 (12.3–13.4)[g]	14.3 (13.5–15.0)[d,f]	<0.001

Results expressed as: Median (IQR), Mean (95% CI), and number (%) for categorical variables. 95% CI, 95% confidence interval; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonists; PDE-5 inhibitors, phosphodiesterase-5 inhibitors; PPI, proton pump inhibitor; RV, residual volume; TLC, total lung capacity.
[a]Median (IQR).
[b]Mean (95% CI).
[c]$P < .05$ compared with IPF.
[d]$P < .01$ compared with IPF.
[e]$P < .05$ compared with COPD.
[f]$P < .01$ compared with COPD.
[g]$P < .001$ compared with COPD.
[h]Immunomodulators include mycophenolate mofetil, azathioprine.

AP, or associate with any particular esophageal motility abnormality in any of the respiratory disease types.

Our observations support those of Derousseau et al[22] that patients with non-IPF ILD (along with CF, as expected) appear more prevalent among respiratory patients with delayed compared with normal gastric emptying. That study also reported that patients with delayed gastric emptying (mixed cohort of respiratory disease) pre-LTx were also 3.56 times more likely to develop acute cellular rejection within 1-year post-LTx, which was independent of both pre-LTx lung function and reflux. However, they did not specifically report on the association between delayed gastric emptying and reflux pre-LTx, the latter suggested in other studies to also predict outcome following LTx.[20,22] Indeed, out of the 83 patients

Table 2. Gastric Emptying in Patients With COPD, IPF, and Non-IPF ILD, Including Fibrotic Nonspecific Interstitial Pneumonia (NSIP), Chronic Hypersensitivity Pneumonitis (CHP), and Sarcoidosis

	Total n = 74	COPD n = 22	IPF n = 33	Non-IPF ILD				
				Total n = 19	Fibrotic NSIP n = 10	CHP n = 5	Sarcoidosis n = 4	*P* value
Gastric emptying findings								
Normal GE, n (%)	54 (73.0%)	17 (77.3%)	25 (75.8%)	12 (63.2%)	3 (30%)	5 (100%)	4 (100%)	.011
Delayed GE	20 (27.0%)	5 (22.7%)	8 (24.2%)	7 (36.8%)	7 (70%)[b]	0	0	
1 h % retention[a]	69 (61–76)	66 (55–72)	69 (63–74)	72 (63–76)	71 (63–76)	76 (70–76)	65 (54–78)	.441
2 h % retention[a]	44 (31–53)	41 (24–52)	43 (32–50)	51 (38–58)	53 (38–68)	47 (46–51)	35 (22–52)	.199
4 h % retention[a]	5 (1–11)	5 (1–9)	4 (1–10)	9 (2–17)	17 (2–38)	8 (6–9)	4 (2–7)	.177

Results expressed as: Median (IQR), and number (percentage) for categorical variables.
CHP, chronic hypersensitivity pneumonitis; GE, gastric emptying; IQR, interquartile range; NSIP, nonspecific interstitial pneumonia.
[a]Median (IQR).
[b]$P < .05$ compared with COPD, IPF, and CHP.

recruited, only 25 (30%) underwent pH testing, of which only 7 (28%) tested positive for GER, all of whom had normal gastric emptying.[22] Moreover, how lung mechanics might influence their findings was not investigated.

Despite excluding patients with scleroderma in our study, we have shown that 70% of patients with fibrotic NSIP have delayed gastric emptying, which was significantly higher than that seen in patients with IPF (24%) and COPD (23%). Why patients with fibrotic NSIP have a high prevalence of delayed gastric emptying is unclear, but NSIP can associate with other connective tissue diseases, and recent studies have reported that patients with gastroparesis symptoms (ie, gastrointestinal, not respiratory patients) can exhibit elevated levels of antinuclear antibodies associated with connective tissue disease, though they showed no association with objective measures of gastric emptying.[35,36] Unfortunately, closer examination of the medical records of our fibrotic NSIP patients provided no additional clues, with 4 patients with idiopathic NSIP and 3 with idiopathic inflammatory myositis having delayed emptying, and 1 with rheumatoid related ILD and two with interstitial pneumonia and autoimmune features having normal gastric emptying.

Studies in patients with GER disease have suggested that delayed gastric emptying can increase transient LES relaxations, the main mechanism of GER, mediated by abdominal distension.[11,12] In our study, delayed gastric emptying did not increase the number of reflux events entering into the distal esophagus or TBET in any of the three respiratory diseases. However, non-IPF ILD patients with delayed emptying (ie, fibrotic NSIP patients) did tend to exhibit a great proportion of distal reflux events reaching the proximal esophagus. The reason for this is unclear as both abdominal and thoracic pressure along with the TAPG or aTAPG and EL/ELI were no different between those with normal and delayed gastric emptying. Moreover, those with delayed gastric emptying exhibited no more IEM than those with normal gastric emptying, a motility abnormality that has been shown to associate with increased proximal esophageal reflux in patients with IPF.[13] Thus, as maybe expected we observed no differences in pulmonary function between those with normal and delayed gastric emptying in any of the three respiratory diseases.

Medications, such as immunomodulators (eg, mycophenolate mofetil and azathioprine) and antifibrotics (eg, nintedanib and pirfenidone) used to treat respiratory disease can cause gastrointestinal side effects, such as nausea, abdominal pain and diarrhea, but the effect of these medications on gastric emptying, as far as we are aware, have never been studied. However, although five (50%) of the fibrotic NSIP patients were taking immunomodulators, their use was not an independent predictor of delayed gastric emptying. Moreover, despite the use of antifibrotics been higher in the IPF and non-IPF ILD patients (as expected), there usage was not associated with delayed gastric emptying compared with nonantifibrotic usage. There was low usage of phosphodiesterase-5 inhibitors, which can delay gastric emptying, with 3 patients with Non-IPF ILD using Tadalafil (2 with NGE, 1 with delayed gastric emptying [DGE]) and 1 patient with IPF using Sildenafil (NGE). DGE was also not related to opiate use, as only two patients with IPF were on these medications. Likewise, although a few patients were on other medications that may affect gastric emptying,[32] such as calcium channel blockers (n = 3), azithromycin (n = 4), tricyclic antidepressants (n = 1), insulin (n = 1), loperamide (n = 1) and ondansetron (n = 1), all these medications were stopped 48 hours prior to gastric emptying testing, and all these patients had normal gastric emptying. Lastly, twenty nine patients were taking PPIs, which were stopped prior to investigations, and were shown not to independently predict DGE.

Our observations could have potential important clinical implications as it is generally believed that DGE may increase GER, which in patients with respiratory disease, with

Table 3. Comparison of Reflux Parameters, Thoracic and Abdominal Pressures, Esophageal Motility, and Esophageal Length/Esophageal Length Index in Patients With Normal and Delayed Gastric Emptying, in the Total Cohort of Respiratory Patients

	Normal gastric emptying	Delayed gastric emptying	
Total cohort	n = 54	n = 20	P value
MII-pH findings			
AET[a], %	1.6 (0.3–5.7)	3.2 (1.0–9.4)	.092
Pts with abnormal AET (>6%), n (%)	13 (24.1%)	7 (35.0%)	.347
TBET[a], %	1.4 (0.4–2.0)	1.2 (0.7–2.5)	.860
Pts with abnormal TBET (≥1.4%), n (%)	28 (51.9%)	8 (40%)	.365
Total no. of distal events[a], n	36 (19–49)	29 (19–45)	.507
Pts with abnormal no. of distal events (>80), n (%)	2 (3.7%)	0	1.000
Total no. of proximal events[a], n	10 (3–20)	14 (3–19)	.976
Pts with abnormal no. of proximal events (>31), n (%)	7 (13.0%)	1 (5%)	.435
% of distal events reaching proximal esophagus[a], %	32.9 (17.5–51.3)	40.0 (23.0–52.1)	.473
4 h post-meal TBET[a], %	1.9 (1.1–3.9)	1.6 (0.6–3.2)	.648
Pulmonary function tests			
FEV_1[a], %	49.5 (31.0–63.0)	54.5 (36.5–71.5)	.309
FVC[a], %	55.0 (43.0–65.0)	60.0 (48.5–70.0)	.450
FEV_1/FVC ratio[a]	0.83 (0.44–0.87)	0.79 (0.60–0.87)	.918
TLC, %[a]	62.0 (50.0–106.5)	60.0 (47.0–111.0)	.718
RV, %[a]	71.5 (50.0–182.0)	57.5 (50.0–94.0)	.565
Thoracoabdominal pressure gradients			
Abdominal pressure, mmHg[b]	18.1 (15.9–20.4)	18.5 (11.0–23.1)	.910
Inspiratory LES pressure, mmHg[b]	60.8 (52.5–69.2)	61.6 (45.6–77.6)	.930
Thoracic pressure, mmHg[b]	−1.5 (−3.9 – 0.8)	−0.9 (−6.9 – 5.0)	.819
TAPG, mmHg[b]	19.7 (17.3–22.1)	19.4 (14.3–24.6)	.913
Adjusted TAPG, mmHg[b]	−41.2 (−49.7 – −32.6)	−42.2 (−56.7 – −27.6)	.903
CCv4 motility findings n (%)			
Normal	35 (64.8%)	13 (65.0%)	.839
IEM	6 (11.1%)	2 (10%)	
iEGJOO	10 (18.5%)	5 (25%)	
DES	1 (1.9%)	0	
Hypercontractile	2 (3.7%)	0	
LES findings			
LES basal pressure, mmHg[a]	37.1 (24.9–49.9)	34.7 (29.5–43.9)	.688
Median IRP, mmHg[b]	10.8 (9.3–12.3)	11.3 (8.7–13.9)	.730
LES length, cm[a]	5.0 (4.0–5.7)	4.0 (4.0–5.0)	.291
Incomplete bolus transit			
Incomplete bolus transit, n (%)	43 (79.6%)	15 (75.0%)	.753
IBT[a], %	65 (30–90)	64 (23–100)	.854
Esophageal length & index			
Esophageal length, cm[b]	24.2 (23.2–25.2)	23.8 (22.5–25.1)	.698
Esophageal length index[b]	14.2 (13.6–14.8)	14.0 (13.3–14.8)	.817

Results expressed as: Median (IQR), Mean (95% CI), and number (percentage) for categorical variables.
95% CI, 95% confidence interval; AET, acid exposure time; DES, distal esophageal spasm; IBT, incomplete bolus transit; iEGJOO, inconclusive esophagogastric junction outflow obstruction; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; MII-pH, 24-h pH-impedance; TAPG, thoracoabdominal pressure gradient; TBET, total bolus exposure time (ie, % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Median (IQR).
[b]Mean (95% CI).

additional lung mechanic alterations in both intrathoracic (reduced in RLD) and AP (increased in OLD) could lead to significant enhancement in GER, does not appear to be the case. The rather low prevalence of DGE in patients with COPD, IPF and non-IPF ILD, excluding those with NSIP, suggests the routine practice of pre-LTx gastric emptying testing, especially given the absence of increased reflux in these patients with severe lung disease, may not add value for patients or clinicians. However, what impact DGE might have on mortality or morbidity in those with fibrotic NSIP, despite lack of increased reflux, needs further investigation.

Our study has strengths and limitations. A strength is that we have generated data on particular respiratory

Table 4. Comparison of Reflux Parameters, Thoracic and Abdominal Pressures, Esophageal Motility, and Esophageal Length/Esophageal Length Index in Patients With Normal and Delayed Gastric Emptying in Patients With COPD

	Normal gastric emptying	Delayed gastric emptying	
COPD	n = 17	n = 5	*P* value
MII-pH findings			
AET[a], %	1.2 (0.2–3.4)	2.9 (1.3–9.9)	.218
Pts with abnormal AET (>6%), n (%)	2 (11.8%)	2 (40%)	.210
TBET, %[a]	1.3 (0.9–1.8)	1.0 (0.7–1.1)	.283
Pts with abnormal TBET (≥1.4%), n (%)	8 (47.1%)	0	.115
Total no. of distal events[a], n	33 (18–53)	22 (17–29)	.543
Pts with abnormal no. of distal events (>80), n (%)	1 (5.9%)	0	1.000
Total no. of proximal events[a], n	10 (4–16)	8 (4–18)	.940
Pts with abnormal no. of proximal events (>31), n (%)	1 (5.9%)	0	1.000
% of distal events reaching proximal esophagus[a], %	41.6 (21.4–51.3)	31.9 (28.6–47.1)	.940
4 h post-meal TBET[a], %	1.9 (0.5–3.0)	1.0 (0.8–2.1)	.543
Pulmonary function tests			
FEV_1[a], %	29.0 (22.0–43.0)	24.0 (22.0–38.0)	1.000
FVC[a], %	65.0 (51.0–77.0)	60.0 (58.0–73.0)	.704
FEV_1/FVC ratio[a]	0.37 (0.27–0.44)	0.34 (0.29–0.40)	1.000
TLC[a], %	125.0 (105.0–139.0)	129.3 (114.0–132.0)	.649
RV[a], %	191.0 (154.0–270.0)	228.0 (180.0–235.0)	.940
Thoracoabdominal pressure gradients			
Abdominal pressure, mmHg[b]	21.3 (17.3–25.3)	18.1 (2.6–33.7)	.495
Inspiratory LES pressure, mmHg[b]	67.3 (52.8–81.9)	62.3 (10.5–114.1)	.756
Thoracic pressure, mmHg[b]	4.6 (0.4–8.8)	−0.6 (−11.2 – 10.1)	.238
TAPG, mmHg[b]	16.7 (13.2–20.3)	18.7 (13.1–24.3)	.560
Adjusted TAPG, mmHg[b]	−50.6 (−65.8 – −35.4)	−43.6 (−92.2 – 4.9)	.670
CCv4 motility findings n (%)			
Normal	11 (64.7%)	3 (60%)	.627
IEM	2 (11.8%)	0	
iEGJOO	3 (17.6%)	2 (40%)	
DES	0	0	
Hypercontractile	1 (5.9%)	0	
LES findings			
LES basal pressure, mmHg[a]	39.1 (28.7–47.9)	33.9 (32.9–38.6)	.649
Median IRP, mmHg[b]	10.4 (8.0–12.7)	11.8 (4.3–19.4)	.569
LES length, cm[a]	4.0 (4.0–5.0)	4.3 (4.0–4.7)	.649
Incomplete bolus transit			
Incomplete bolus Transit, n	14 (82.4%)	3 (60.0%)	.548
IBT, %[a]	70 (40–90)	60 (20–60)	.543
Esophageal length & index			
Esophageal length, cm[b]	27.4 (26.1–28.8)	24.8 (21.2–26.8)	.069
Esophageal length index[b]	16.2 (15.4–17.0)	15.0 (13.1–17.0)	.158

Results expressed as: Median (IQR, Mean (95% CI) and number (percentage) for categorical variables.
95% CI, 95% confidence interval; AET, acid exposure time; DES, distal esophageal spasm; IBT, incomplete bolus transit; iEGJOO, inconclusive esophagogastric junction outflow obstruction; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; MII-pH, 24-h pH-impedance; TAPG, thoracoabdominal pressure gradient; TBET, total bolus exposure time (ie, % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Median (IQR).
[b]Mean (95% CI).

disease types and have for the first time investigated associations with reflux, TAPGs, and esophageal motility and length. Another strength is that at the time of this study, gastric emptying testing was routine regardless of symptoms in our center. An obvious limitation is that the numbers of patients with DGE was small in some disease types. As a result, the logistic regression analysis used may have overfitted the data. However, a reasonable number of patients (n = 20; 27%) in the total cohort did have DGE, and to have increased patient numbers in the disease subtypes would have required over 250/300 patients in total to be recruited, numbers difficult to obtain at 1 center. Nevertheless,

Table 5. Comparison of Reflux Parameters, Thoracic and Abdominal Pressures, Esophageal Motility, and Esophageal Length/Esophageal Length Index in Patients With Normal and Delayed Gastric Emptying in Patients With IPF

IPF	Normal gastric emptying n = 25	Delayed gastric emptying n = 8	*P* value
MII-pH findings			
AET[a], %	2.1 (0.5–5.7)	1.9 (0.8–7.0)	.578
Pts with abnormal AET (>6%), n (%)	6 (24%)	2 (25%)	1.000
TBET[a], %	1.6 (0.4–2.5)	1.15 (0.5–3.6)	.918
Pts with abnormal TBET (≥1.4%), n (%)	13 (52%)	3 (37.5%)	.688
Total no. of distal events[a], n	36 (20–61)	35 (19–54)	.789
Pts with abnormal no. of distal events (>80), n (%)	1 (4%)	0	1.000
Total no. of proximal events[a], n	15 (3–28)	5 (3–21)	.496
Pts with abnormal no. of proximal events (31), n (%)	6 (24%)	1 (12.5%)	.651
% of distal events reaching proximal esophagus[a], %	40.6 (17.5–53.8)	33.0 (12.9–43.2)	.636
4 h post-meal TBET[a], %	1.9 (1.1–4.1)	1.6 (0.35–5.95)	.853
Pulmonary function tests			
FEV_1[a], %	57.0 (48.0–65.0)	54.0 (41.2–67.5)	.757
FVC[a], %	53.0 (46.0–61.0)	50.5 (35.8–63.5)	.821
FEV_1/FVC ratio[a]	0.84 (0.82–0.89)	0.82 (0.74–0.88)	.420
TLC[a], %	51.0 (48.0–57.0)	53.0 (39.0–62.0)	.866
RV[a], %	51.5 (46.0–70.0)	55.5 (49.8–57.0)	.871
Thoracoabdominal pressure gradients			
Abdominal pressure, mmHg[b]	15.5 (17.6–19.3)	17.6 (9.9–25.3)	.576
Inspiratory LES pressure, mmHg[b]	61.0 (47.0–75.0)	62.9 (35.0–90.8)	.892
Thoracic pressure, mmHg[b]	−5.8 (−8.4 – −3.1)	−4.0 (−17.3 – 9.3)	.760
TAPG, mmHg[b]	21.3 (17.1–25.5)	21.6 (13.9–29.2)	.945
Adjusted TAPG, mmHg[b]	−39.7 (−53.6 – −25.8)	−41.3 (−71.9 – −10.7)	.910
CCv4 motility findings n (%)			
Normal	16 (64%)	6 (75%)	.815
IEM	2 (8%)	1 (12.5%)	
iEGJOO	6 (24%)	1 (12.5%)	
DES	1 (4%)	0	
Hypercontractile	0	0	
LES findings			
LES basal pressure, mmHg[b]	39.9 (32.6–47.3)	36.9 (22.5–51.2)	.670
Median IRP, mmHg[b]	11.5 (9.2–13.9)	9.1 (4.4–13.9)	.297
LES length, cm[a]	5.0 (4.0–5.7)	4.0 (4.0–4.6)	.162
Incomplete bolus transit			
Incomplete bolus transit, n	20 (80.0%)	7 (87.5%)	1.000
IBT[a], (%)	60 (33–90)	55 (33–100)	.821
Esophageal length & index			
Esophageal length, cm[b]	21.7 (20.6–22.8)	23.1 (20.8–25.3)	.222
Esophageal length index[b]	12.6 (12.0–12.3)	13.4 (12.0–14.8)	.209

Results expressed as: Median (IQR), Mean (95% CI), and number (percentage) for categorical variables.
95% CI, 95% confidence interval; AET, acid exposure time; DES, distal esophageal spasm; IBT, incomplete bolus transit; iEGJOO, inconclusive esophagogastric junction outflow obstruction; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; MII-pH, 24-h pH-impedance; TAPG, thoracoabdominal pressure gradient; TBET, total bolus exposure time (ie, % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Median (IQR).
[b]Mean (95% CI).

our observations do prompt recognition by gastroenterologists, pulmonologists, and transplant physicians when considering patients for LTx, and support future larger multicenter studies, taking into account lung structure and mechanics. Symptoms associated with DGE, such as nausea, vomiting, and early satiety, were also not recorded, but previous studies in respiratory patients have shown little association with DGE.[21,22,37] We also did not measure sputum and/or BALF gastric pepsin levels, the latter because currently there are substantial methodological concerns about the techniques used to measure these markers,[38] and new and better validated tests are needed. Lastly, this is a cross-sectional study, and thus only associations rather than cause and effect between various parameters can be concluded. Note, these were patients with severe respiratory disease, awaiting LTx, and it would not have been possible to follow-up.

Table 6. Comparison of Reflux Parameters, Thoracic and Abdominal Pressures, Esophageal Motility and Esophageal Length/Esophageal Length Index in Patients With Normal and Delayed Gastric Emptying in Patients With Non-IPF ILD

	Normal gastric emptying	Delayed gastric emptying[c]	
Non-IPF ILD	n = 12	n = 7	*P* value
MII-pH findings			
AET[a], %	2.7 (0.7–7.6)	4.4 (1.0–22.8)	.536
Pts with abnormal AET (>6%), n (%)	5 (41.7%)	3 (42.9%)	1.000
TBET[a], %	1.4 (0.5–2.3)	2.0 (1.2–2.7)	.432
Pts with abnormal TBET (≥1.4%), n (%)	7 (58.3%)	5 (71.4%)	.656
Total no. of distal events[a], n	35 (20–43)	34 (21–43)	.773
Pts with abnormal no. of distal events (>80), n (%)	0	0	
Total no. of proximal events[a], n	7 (4–15)	18 (12–19)	.100
Pts with abnormal no. of proximal events (31), n (%)	0	0	
% of distal events reaching proximal esophagus[a], %	21.1 (13.4–37.7)	45.7 (39.1–70.6)	.068
4 h post-meal TBET[a], %	2.5 (1.2–4.3)	2.5 (1.0–6.5)	.967
Pulmonary function tests			
FEV_1[a], %	45.5 (37.0–68.5)	71.0 (51.0–78.0)	.167
FVC[a], %	46.0 (39.0–65.4)	61.0 (47.0–73.0)	.227
FEV_1/FVC ratio[a]	0.86 (0.72–0.87)	0.85 (0.77–0.91)	.967
TLC, %[a]	55.9 (45.0–64.0)	60.0 (42.0–64.0)	.967
RV, %[a]	63.0 (48.0–91.0)	56.0 (49.0–59.0)	.536
Thoracoabdominal pressure gradients			
Abdominal pressure, mmHg[b]	19.2 (16.4–21.9)	19.7 (5.5–33.8)	.933
Inspiratory LES pressure, mmHg[b]	51.3 (34.4–68.2)	59.6 (27.0–92.1)	.570
Thoracic pressure, mmHg[b]	−1.3 (−7.0 – 4.4)	2.2 (−8.8 – 12.3)	.469
TAPG, mmHg[b]	20.5 (15.3–25.7)	17.5 (2.4–32.5)	.591
Adjusted TAPG, mmHg[b]	−30.8 (−47.9 – −13.8)	−42.1 (−62.2 – −22.0)	.359
CCv4 motility findings n (%)			
Normal	8 (66.7%)	4 (57.1%)	.613
IEM	2 (16.7%)	1 (14.3%)	
iEGJOO	1 (8.3%)	2 (28.6%)	
DES	0	0	
Hypercontractile	1 (8.3%)	0	
LES findings			
LES basal pressure, mmHg[a]	29.4 (25.1–46.2)	31.5 (27.9–42.0)	.711
Median IRP, mmHg[b]	9.7 (5.5–14.0)	13.4 (9.0–17.8)	.224
LES length, cm[b]	4.6 (3.8–5.4)	4.3 (3.2–5.4)	.637
Incomplete bolus transit			
Incomplete bolus Transit, n	9 (75.0%)	5 (71.4%)	1.000
IBT, (%)[a]	45 (23–84)	80 (12–100)	.482
Esophageal length & index			
Esophageal length, cm[b]	24.7 (23.1–26.3)	24.0 (21.2–26.8)	.598
Esophageal length index[b]	14.4 (13.4–15.5)	14.0 (12.7–15.3)	.596

Results expressed as: Median (IQR), Mean (95% CI) and number (percentage) for categorical variables.
95% CI, 95% confidence interval; AET, acid exposure time; DES, distal esophageal spasm; IBT, incomplete bolus transit; iEGJOO, inconclusive esophagogastric junction outflow obstruction; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; MII-pH, 24-h pH-impedance; TAPG, thoracoabdominal pressure gradient; TBET, total bolus exposure time (ie, % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Median (IQR).
[b]Mean (95% CI).
[c]All patients with delayed gastric emptying had fibrotic NSIP.

Conclusion

Our observations suggest that DGE in patients with respiratory disease does not lead to excessive GER, despite lower intrathoracic pressures in patients with RLD, increased APs in patients with OLD, and differences in esophageal motility and length, or associate with worse pulmonary function. Our finding that a high proportion of patients with fibrotic NSIP have DGE requires further study, and the potential impact this may have on morbidity and mortality.

References

1. Houghton LA, Lee AS, Badri H, et al. Respiratory disease and the oesophagus: reflux, reflexes and microaspiration. Nat Rev Gastroenterol Hepatol 2016;13:445–460.
2. Savarino E, Roberto C, Elisa M, et al. Gastro-oesophageal reflux and gastric aspiration in idiopathic pulmonary fibrosis patients. Eur Respir J 2013;42:1322.
3. Lee AL, Button BM, Denehy L, et al. Proximal and distal gastro-oesophageal reflux in chronic obstructive pulmonary disease and bronchiectasis. Respirology (Carlton, Vic.) 2014;19:211–217.
4. Lee AL, Button BM, Denehy L, et al. Exhaled breath condensate pepsin: potential noninvasive test for gastroesophageal reflux in COPD and bronchiectasis. Respir Care 2015;60:244–250.
5. Triadafilopoulos G, Tandon A, Shetler KP, et al. Clinical and pH study characteristics in reflux patients with and without ineffective oesophageal motility (IEM). BMJ Open Gastroenterol 2016;3:e000126.
6. Rogers BD, Rengarajan A, Mauro A, et al. Fragmented and failed swallows on esophageal high-resolution manometry associate with abnormal reflux burden better than weak swallows. Neurogastroenterology Motil 2020;32:e13736.
7. Rogers BD, Rengarajan A, Ribolsi M, et al. Postreflux swallow-induced peristaltic wave index from pH-impedance monitoring associates with esophageal body motility and esophageal acid burden. Neurogastroenterology Motil 2021;33:e13973–n/a.
8. Ayazi S, DeMeester SR, Hsieh C-C, et al. Thoraco-abdominal pressure gradients during the phases of respiration contribute to gastroesophageal reflux disease. Dig Dis Sci 2011;56:1718–1722.
9. Gourcerol G, Benanni Y, Boueyre E, et al. Influence of gastric emptying on gastro-esophageal reflux: a combined pH-impedance study. Neurogastroenterology Motil 2013;25:800-e634.
10. Bensinger A, Clayton S. 420 assessing the prevalence of gastroesophageal reflux in gastroparesis: putting the G back in GERD. Am J Gastroenterol 2019;114:S247.
11. Emerenziani S, Sifrim D. Gastroesophageal reflux and gastric emptying, revisited. Curr Gastroenterol Rep 2005;7:190–195.
12. Holloway RH, Hongo M, Berger K, et al. Gastric distention: a mechanism for postprandial gastroesophageal reflux. Gastroenterology 1985;89:779–784.
13. Cheah R, Chirnaksorn S, Abdelrahim AH, et al. The perils and pitfalls of esophageal dysmotility in idiopathic pulmonary fibrosis. Am J Gastroenterol 2021;116:1189–1200.
14. Iliaz S, Iliaz R, Onur ST, et al. Does gastroesophageal reflux increase chronic obstructive pulmonary disease exacerbations? Respir Med 2016;115:20–25.
15. Masuda T, Mittal SK, Kovács B, et al. Foregut function before and after lung transplant. J Thorac Cardiovasc Surg 2019;158:619–629.
16. Bigatao AM, Herbella FAM, Del Grande LM, et al. Chronic obstructive pulmonary disease exacerbations are influenced by gastroesophageal reflux disease. Am Surg 2018;84:51–55.
17. Del Grande LM, Herbella FA, Bigatao AM, et al. Pathophysiology of gastroesophageal reflux in patients with chronic pulmonary obstructive disease is linked to an increased transdiaphragmatic pressure gradient and not to a defective esophagogastric barrier. J Gastrointest Surg 2016;20:104–110.
18. Irvin CG, Sampson M, Engel L, et al. Effect of breathing pattern on esophageal pressure gradients in humans. J Applied Physiology 1984;57:168–175.
19. Mittal RK, Shaffer HA, Parollisi S, et al. Influence of breathing pattern on the esophagogastric junction pressure and esophageal transit. Am J Physiol - Gastrointest Liver Physiol 1995;269:577–583.
20. Raviv Y, D'Ovidio F, Pierre A, et al. Prevalence of gastroparesis before and after lung transplantation and its association with lung allograft outcomes. Clin Transplantation 2012;26:133–142.
21. D'Ovidio F, Singer LG, Hadjiliadis D, et al. Prevalence of gastroesophageal reflux in end-stage lung disease candidates for lung transplant. The Ann Thoracic Surgery 2005;80:1254–1260.
22. Derousseau T, Chan WW, Cangemi D, et al. Delayed gastric emptying in prelung transplant patients is associated with posttransplant acute cellular rejection independent of reflux. J Clin Gastroenterol 2022;56:e121–e125.
23. Cangemi D, Derousseau T, Gavini S. Prevalence of gastroparesis among patients undergoing pre-lung transplantation evaluation: 1225. Am J Gastroenterol 2017;112:S670.
24. Pauwels A, Blondeau K, Mertens V, et al. Gastric emptying and different types of reflux in adult patients with cystic fibrosis: gastric emptying and reflux in cystic fibrosis. Aliment Pharmacol Therapeutics 2011;34:799–807.
25. Bodet-Milin C, Querellou S, Oudoux A, et al. Delayed gastric emptying scintigraphy in cystic fibrosis patients before and after lung transplantation. J Heart Lung Transplant 2006;25:1077–1083.
26. Camilleri M, Zheng T, Vosoughi K, et al. Optimal measurement of gastric emptying of solids in gastroparesis or functional dyspepsia: evidence to establish standard test. Gut 2023;72:2241–2249.
27. Yadlapati R, Kahrilas PJ, Fox MR, et al. Esophageal motility disorders on high-resolution manometry: Chicago classification version 4.0. Neurogastroenterol Motil 2021;33:e14058.
28. Roman S, Lin Z, Fau - Kwiatek MA, et al. Weak peristalsis in esophageal pressure topography: classification and association with Dysphagia. Am J Gastroenterol 2010;106:349–356.
29. 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.
30. Almansa C, Smith JA, Morris J, et al. Weak peristalsis with large breaks in chronic cough: association with poor esophageal clearance. Neurogastroenterology Motil 2015;27:431–442.
31. Graham BL, Steenbruggen I, Miller MR, et al. Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. Am J Respiratory Critical Care Med 2019;200:e70–e88.

32. Camilleri M, Kuo B, Nguyen L, et al. ACG clinical guideline: gastroparesis. Am J Gastroenterol 2022; 117:1197–1220.
33. Pasricha PJ, Grover M, Yates KP, et al. Functional dyspepsia and gastroparesis in tertiary care are interchangeable syndromes with common clinical and pathologic features. Gastroenterol 2021;160:2006–2017.
34. Gyawali CP, Yadlapati R, Fass R, et al. Updates to the modern diagnosis of GERD: lyon consensus 2.0. Gut 2024;73:361–371.
35. Chaudhary D, Jiang Y, Khan F, et al. Evaluating autoimmune markers in relation to gastrointestinal measures in patients with symptoms of gastroparesis. J Clin Gastroenterol 2024. http://doi.org/10.1097/MCG.0000000000002062.
36. Parkman HP, Van Natta ML, Makol A, et al. Prevalence and clinical correlates of antinuclear antibody in patients with gastroparesis. Neurogastroenterol Motil 2022;34:e14270.
37. Hauser B, De Schepper J, Malfroot A, et al. Gastric emptying and gastro-oesophageal reflux in children with cystic fibrosis. J Cystic Fibrosis 2016;15:540–547.
38. Li Y, Xu G, Zhou B, et al. Effects of acids, pepsin, bile acids, and trypsin on laryngopharyngeal reflux diseases: physiopathology and therapeutic targets. Eur Arch Otorhinolaryngol 2022;279:2743–2752.

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Jessica Bradley: Conceived and drafted the study; collected the data; analysed and interpreted the data; drafted the manuscript. Caroline Olson: Recruited the patients; collected the data. Ali Alghubari: Collected the data. Ramsah Cheah: Collected the data. Sadia Z Shah: Recruited the patients; collected the data. Augustine S Lee: Recruited the patients; collected the data. Kenneth R DeVault: Conceived and drafted the study; recruited the patients; collected the data. Lesley A Houghton: Conceived and drafted the study; analysed and interpreted the data; drafted the manuscript.
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Study data will be made available to other investigators on reasonable request.

Reporting Guidelines:
Chicago Classification v4.0.; Lyon Consensus v2.0.; American College of Gastroenterology Clinical Guideline: Gastroparesis.