Associations Between Esophageal Motility, Reflux, and Lung Mechanics and Function Are Disease-Specific, Both Between and Within Restrictive and Obstructive Lung Disease

Ali Alghubari, MSc[1,2], Caroline Olson, MD[3], Jessica Bradley, MBChB (UK) MRCP (UK)[1], Ramsah Cheah, PhD[1], Sadia Z. Shah, MD[4], Abdel-Rahman N. Naser, MD[5], Augustine S. Lee, MD[6], Kenneth R. DeVault, MD, FACG[3] and Lesley A. Houghton, PhD, AGAF[1,3]

INTRODUCTION **Gastroesophageal reflux is common in respiratory disease, but the interplay between gastrointestinal mechanisms that expose individuals to reflux and potentially aspiration, and lung mechanics and function remain incompletely understood. Our aim was to investigate this in patients with chronic obstructive pulmonary disease (COPD) and non-idiopathic pulmonary fibrosis (IPF) interstitial lung disease (non-IPF ILD), and compare with our published findings in IPF.**

METHODS **Fifty-seven patients with COPD (aged: 34–75 years) and 64 with non-IPF ILD (22–75 years) who underwent high-resolution impedance manometry and 24-hour pH impedance together with pulmonary function assessment were compared with 35 IPF patients (51–84 years).**

RESULTS **COPD patients were less likely to exhibit ineffective esophageal motility (IEM) and/or absent contractility ($P = 0.009$; $P = 0.028$), and tended to exhibit esophagogastric junction outflow obstruction (EGJOO) and/or hypercontractility ($P = 0.09$, $P = 0.14$) than IPF and non-IPF ILD patients. Notably, integrated relaxation pressure correlated with esophageal length index (ELI) ($P = 0.048$) and inspiratory LESP ($P = 0.003$), with latter 2 correlating with each other ($P < 0.001$). EGJOO patients tended to have fewer proximal reflux events and reduced pulmonary function, with the latter inversely correlating with ELI ($P < 0.05$). Non-IPF ILD patients were less likely to exhibit EGJOO than COPD patients ($P = 0.27$), and less likely to exhibit IEM ($P = 0.07$) than IPF patients. However, those with IEM or EGJOO exhibited greater proportions of reflux events reaching the proximal esophagus than those with normal motility ($P < 0.03$), which in contrast to IPF, seemed not to associate with worse pulmonary function.**

DISCUSSION **Associations between esophageal motility, and lung mechanics and function, and consequently reflux, are very disease-specific.**

KEYWORDS: restrictive lung disease; obstructive lung disease; esophageal motility; reflux

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INTRODUCTION

Gastroesophageal reflux disease is common in most respiratory disorders, including idiopathic pulmonary fibrosis (IPF), non-IPF interstitial lung disease (non-IPF ILD), and chronic obstructive pulmonary disease (COPD), among others. Its pathological role across these respiratory diseases is less clear. For example, studies in IPF show that the severity of acid and non-acid reflux combined, but not acid alone, associates with worse pulmonary function (1) and may be an independent predictor of poor pulmonary outcome and mortality (2,3), whereas studies in

[1]Division of Gastroenterology & Surgical Sciences, Leeds Institute of Medical Research, University of Leeds, Leeds, UK; [2]Respiratory Therapy Program, Department of Nursing, College of Nursing and Health Sciences, Jazan University, Kingdom of Saudi Arabia; [3]Department of Gastroenterology & Hepatology, Mayo Clinic, Jacksonville, Florida, USA; [4]Transplantation, Mayo Clinic, Jacksonville, Florida, USA; [5]Department of Surgery, University of Florida College of Medicine, Jacksonville, Florida, USA; and [6]Pulmonary Medicine, Mayo Clinic, Jacksonville, Florida, USA. **Correspondence:** Lesley A. Houghton. E-mail: L.A.Houghton@Leeds.ac.uk.

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COPD have shown no association with disease severity or pulmonary function (4,5). The latter studies, however, only assessed acid reflux. Nevertheless, studies have shown that proximal esophageal reflux associates with increased exacerbations of disease in COPD (6). Similarly, evidence for microaspiration is inconsistent. Studies in IPF report a correlation between the degree of fibrosis and concentrations of gastric pepsin and bile acid found in bronchoalveolar lavage fluid (7), but studies in COPD report no association between the presence of pepsin in sputum and pulmonary function (5).

Reasons for these differences may lie with the techniques used to measure reflux and/or microaspiration. However, others likely relate to the complexity of factors that contribute to the occurrence of reflux, its proximal esophageal extent, and possible aspiration into the lungs. These may include lower esophageal sphincter pressure (LESP), esophageal motility, reflexes that heighten upper esophageal sphincter pressure (UESP), and differing lung structures (e.g., scaring and stiffening of lungs in restrictive lung disease [RLD], inflammation and airway narrowing in obstructive lung disease [OLD]), mechanics and breathing patterns associated with different respiratory diseases. Most studies tend to look at factors in isolation, even if measuring 2 or more, and have not investigated how their interaction influences the occurrence of reflux and its proximal extent. One example is the influence esophageal motility can have on the effect that LESP has on reflux. In IPF patients with normal motility defined using Chicago Classification v3.0 (CCv3.0), inspiratory LESP (iLESP) inversely correlated with the number of proximal reflux events, but in those with ineffective esophageal motility (IEM), there was a direct correlation between these parameters (8). Furthermore, in those with IEM, there is an inverse correlation between pulmonary function, and both basal LESP (bLESP) and iLESP, which was not seen in patients with normal motility (8). Similar relationship analyses have not been undertaken in patients with non-IPF ILD or COPD, nor these analyses compared with those in IPF, which may help better understand mechanisms of reflux in respiratory disease. Moreover, previous studies have either investigated patients with RLDs in combination (e.g., IPF and non-IPF ILD together) and/or included scleroderma and cystic fibrosis (CF), conditions not necessarily isolated to the lungs but involving the gut too.

We hypothesize that similar to IPF, there is a complex inter-relationship between proximal reflux, LES and esophageal function, and pulmonary function in patients with other respiratory diseases, which varies depending on the lung structure and mechanics of the respiratory disease.

Our aim was to use high-resolution impedance manometry (HRIM) along with 24-hour pH/impedance (MII-pH) to determine the prevalence of dysmotility, measure intrathoracic and abdominal pressure (AP), along with the thoraco-abdominal pressure gradient (TAPG), and determine their inter-relationship with reflux, particularly that reaching the proximal esophagus and pulmonary function in both non-IPF ILD and COPD patients, and compare with IPF. Our secondary aim was to compare non-IPF ILD with COPD patients.

METHODS

Patients

This was a retrospective analysis of 156 consecutive patients (99 with RLD and 57 with OLD) referred for HRIM and MII-pH at Mayo Clinic, Jacksonville, USA, and Leeds Teaching Hospital NHS Trust, UK, between November 2017 and January 2022. Patient data included age, sex, body mass index (BMI), height, pulmonary function, and medication. The Mayo Clinic Institutional Review Board (IRB# 18-005280) and Yorkshire and Humber-Bradford Leeds Research Ethics Committee (REC number 18/YH/0387) approved the study.

HRIM. HRIM was performed using a solid-state catheter with 36 circumferential pressure sensors spaced at 1-cm intervals and 18 impedance channels (Medtronic, Shoreview, MN). The catheter was positioned transnasally with distal sensors for both pressure and impedance in the proximal stomach. After a baseline of at least 30 seconds to identify the upper esophageal sphincter (UES) and LES, 10 5 mL saline swallows were given at least 30 seconds apart with the patient supine (9).

MII-pH. MII-pH was measured using a single antimony pH probe (5 cm above the LES) with 8 impedance electrodes (Sandhill Scientific, Highlands Ranch, CO) (9).

Data analysis

HRIM. ManoVIEW analysis software v3.01 (Medtronic, Shoreview, NM) was used to manually analyze the recordings. Classification of esophageal motility was based on 10 wet swallows according to CC v4.0 (10). As the majority of testing was performed in very sick patients requiring lung transplantation, with most testing conducted before the publication of CC v4.0, additional postural assessment of swallows or following provocation testing was not performed. Each 5 mL swallow was evaluated to determine (i) integrated relaxation pressure (IRP), (ii) distal contractile integral (DCI), (iii) distal latency, and (iv) isobaric contour (pressurization). Contractile pattern was classified as normal, weak, failed peristalsis, fragmented, or hypercontractile swallow (10).

CC v4.0 diagnoses included (i) achalasia or esophagogastric junction outflow obstruction (EGJOO) and (ii) disorders of peristalsis, such as absent contractility, distal esophageal spasm (DES), hypercontractile esophagus (single peak hypercontractile swallow, Jackhammer, and hypercontractile LES), and IEM (10). Given the above noted limitations related to the timing of the studies relative to the publication of CCv4.0, for the purpose of these studies, we elected to use the nomenclature "inconclusive EGJOO" (iEGJOO).

TAPG TAPG was calculated by subtracting the intra-AP (proximal stomach 1 cm below the lower border of the LES, referenced to atmospheric pressure) from the mean intrathoracic pressure (TP; distal esophagus between 1 and 5 cm above the upper border of the LES, referenced to atmospheric pressure) during inspiration. iLESP, referenced to the pressure at the level of the intra-AP (i.e., 1 cm below lower border of the LES), was also measured, and an adjusted TAPG (aTAPG) was calculated by subtracting LESP from the TAPG during inspiration. A cutoff value of aTAPG to predict risk of reflux was set at >0 mm Hg, based on the hypothesis that reflux may occur when TAPG overcomes the LESP (11).

Manometric esophageal length and index Esophageal length (EL) was measured from the lower border of the UES to the upper border of the LES at end inspiration, from which esophageal length index (ELI) was calculated by dividing EL in centimeters by patient height in meters (12).

MII-pH. Data were manually analyzed (BioVIEW Analysis software, Sandhill Scientific, CO) excluding meals for reflux episodes based on the retrograde impedance decrease to 50% of baseline in at least 2 distal adjacent channels. Abnormalities in reflux exposure were as defined by Lyon consensus 2.0 (13), with the exception of proximal reflux events, which were as described by Shay et al, reaching at least 15 cm above the upper margin of the LES, and abnormality was defined as a value of >31 (8,14,15).

Statistics

Group differences were evaluated using Student's *t*-tests or Mann-Whitney *U*-tests. Tests for proportionality between groups were assessed using χ^2 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 2-tailed level, and *P* value of <0.05 taken as statistically significant.

RESULTS

Of the 156 patients recruited (mean age 61 [95% confidence interval (CI): 60–63] years; mean BMI 27.0 [26.2–27.7] kg/m^2; mean height 1.69 [1.68–1.71] meters; 70 female), 99 had RLD, of which 35 had IPF (aged 66 [64–69] years) and 64 were non-IPF ILD patients (aged 58 [55–61] years), and 57 had OLD, diagnosed as COPD (aged 62 [60–64] years). Note that although patient data were collected consecutively between 2017 and 2022, the IPF cohort findings presented here have been previously published using CCv3.0 (8). Most patients suffered from moderate (% predicted forced vital capacity [%FVC] 51–79%) or severe (% FVC ≤50%) disease, with no significant difference in the proportions of patients between diseases. As would be clinically expected, more COPD patients exhibited very severe forced expiratory volume in 1 second (%FEV1 ≤ 50%) compared with IPF or non-IPF ILD patients (56% vs 3%, $P < 0.001$ and 8%, $P < 0.001$, respectively) (Table 1). COPD patients had higher total lung capacity and residual volume (RV) (%pred/L) than patients with IPF and non-IPF ILD patients ($P < 0.001$ for both). In addition, non-IPF ILD patients had higher RV (%pred/L) compared with IPF patients ($P = 0.002$ and $P = 0.101$, respectively). Table 1 shows the demographics, along with medication use.

HRIM (CCv4.0)

Forty-nine percent of IPF patients, 45% of non-IPF ILD patients, and 42% of COPD patients exhibited abnormal esophageal motility (Table 2).

Compared with our published findings in IPF patients using CCv3.0 (8), 5 of 16 (31%) patients with IEM became normal using CCv4, and thus, only 11 IPF patients had IEM using CCv4. Despite these modifications using CCv4, COPD patients were less likely to exhibit IEM than IPF patients (7% vs 31%; $P = 0.003$) and tended to more likely exhibit iEGJOO than non-IPF ILD patients (26% vs 17%; $P = 0.270$) (Table 2). Non-IPF ILD patients tended to less likely exhibit IEM (16%, $P = 0.077$), similar to COPD patients, but to similarly exhibit iEGJOO (17% vs 17%) compared with IPF patients. Summarizing, COPD patients were less likely to exhibit IEM and/or absent contractility (5.9%) than IPF (11.31%; $P = 0.009$) or non-IPF ILD (16.25%; $P = 0.028$) patients and tended to be more likely to exhibit iEGJOO and/or hypercontractility (19.33%) than IPF (6.17%; $P = 0.099$) or non-IPF ILD (13.20%; $P = 0.14$) patients. Non-IPF ILD did not differ from IPF.

Similar percentages of patients in each cohort exhibited normal UESP and LESP (Table 2), although there were trends for more IPF patients to have hypertensive UESP compared with non-IPF ILD patients ($P = 0.107$), and for COPD patients to have increased bLESP compared with IPF and non-IPF ILD patients ($P = 0.101$ and $P = 0.150$, respectively). Furthermore, patients with COPD exhibited higher iLESP than IPF ($P = 0.006$) and non-IPF ILD ($P = 0.066$) patients, with non-IPF ILD patients also tending to have higher iLESPs than IPF patients ($P = 0.116$). Notably, the pressure difference between iLESP and expiratory LESP (eLESP) (iLESP-eLESP) directly correlated with bLESP in COPD (r = 0.339; $P = 0.010$) and non-IPF ILD (r = 0.270; $P = 0.031$) patients, but not IPF patients. DCI was higher in non-IPF ILD ($P = 0.008$) and COPD ($P < 0.001$) than IPF patients, and was higher in COPD than non-IPF ILD patients ($P = 0.069$). More IPF patients had LES-crural diaphragm (CD) separation >2 cm than non-IPF ILD ($P = 0.004$) and COPD ($P = 0.177$) patients.

Association with pulmonary function. Notably, the shift of 5 IPF patients with IEM (CCv3) (8) to normal in this follow-up comparative analysis using CCv4 resulted in loss of statistically significant difference in pulmonary function seen between IPF patients with IEM and normal motility using CCv3 (Table 3) (8). This was explained by the 5 IPF patients with CCv3.0 IEM having poor pulmonary function (%FVC 40 [40–43], FVCL 1.7 [1.6–2.0], %FEV1 45 [42–55] and FEV1L 1.3 [1.3–1.7]). Pulmonary function tended to remain lower in those with IEM compared with normal motility using CCv4 (Table 3).

In contrast to COPD patients, it was those with iEGJOO and/or hypercontractility who were more likely to have very severe pulmonary function (i.e., %FEV1 <30%; 74%) than those with normal motility (52%; $P = 0.149$) or IEM and/or absent motility (20%; $P = 0.047$). FEV1L and FVCL tended to be lower in COPD patients with iEGJOO than those with IEM ($P = 0.147$; $P = 0.162$, respectively) or normal motility ($P = 0.213$; $P = 0.189$) (Table 3). In non-IPF ILD patients, there was no difference in pulmonary function between the different motility diagnoses (Table 3).

BLESP, iLESP, and iLESP-eLESP inversely correlated with key parameters of pulmonary function (e.g., FEV1, FVC) in patients with COPD. However, in COPD patients with iEGJOO, bLESP directly correlated with measures of static lung volume (e.g., RV, total lung capacity). In IPF patients, bLESP and/or iLESP inversely correlated with both parameters of pulmonary function and static lung volume, whereas in non-IPF ILD patients with normal motility, bLESP only weakly inversely correlated with % RV (Table 4).

ELI

ELI was greater in COPD patients than non-IPF ILD ($P < 0.001$) and IPF patients ($P < 0.001$). In addition, ELI was greater in non-IPF ILD patients than those with IPF ($P < 0.001$) (Table 2).

In COPD patients, there was a direct correlation between iLESP (but not bLESP) and ELI (r = 0.480; $P < 0.001$) (Figure 1A), particularly those with iEGJOO (ELI: r = 0.700; $P = 0.004$). Patients with non-IPF ILD with iEGJOO had a similar correlation (ELI: r = 0.618; $P = 0.043$). However, notably and conversely, non-IPF ILD patients with IEM showed an inverse correlation between iLESP/bLESP and ELI (r = −0.903; $P < 0.001$ (Figure 1B), r = −0.782; $P = 0.008$). Given that iLESP directly correlated with IRP in COPD patients (r = 0.387;

Table 1. Demographic and clinical characteristics

	IPF (n = 35)	Non-IPF ILD (n = 64)	*P* value-A	COPD (n = 57)	*P* value-B	*P* value-C
[a]Age, yr	66 (64–69)	58 (55–61)	$P < 0.001$	62 (60–64)	$P = 0.002$	$P = 0.132$
Male:female ratio	27:8	33:31	$P = 0.017$	28:29	$P = 0.009$	—
[a]Body mass index, kg/m^2	27.8 (26.0–29.5)	27.2 (26.1–28.3)	—	26.4 (25.0–27.8)	—	$P = 0.181$
[a]Height, m	1.71 (1.68–1.74)	1.70 (1.67–1.72)	—	1.67 (1.65–1.70)	$P = 0.060$	—
Ethnicity, n (%)						
White	31 (89%)	47 (73%)	$P = 0.122$	52 (91%)	—	$P = 0.017$
Black	3 (9%)	12 (19%)	—	3 (5%)	—	$P = 0.029$
Hispanic	0 (0%)	1 (2%)	—	1 (2%)	—	—
Asian	1 (3%)	2 (3%)	—	1 (2%)	—	—
Mixed	0 (0%)	1 (2%)	—	0 (0%)	—	—
Other	0 (0%)	1 (2%)	—	0 (0%)	—	—
Tobacco use, n (%)						
Current smokers	2 (6%)	1 (2%)	—	1 (2%)	—	—
Ex-smokers	23 (66%)	23 (36%)	$P = 0.011$	54 (95%)	$P < 0.001$	$P < 0.001$
Never smokers	10 (29%)	38 (59%)	$P = 0.003$	2 (4%)	$P < 0.001$	$P < 0.001$
Missing	0 (0%)	2 (3%)	—	0 (0%)	—	—
Medications, n (%)						
Patients taking PPIs	15 (43%)	28 (44%)	—	16 (28%)	$P = 0.176$	$P = 0.090$
Patients taking H2R antagonists	3 (9%)	6 (9%)	—	4 (7%)	—	—
Patients taking antifibrotics, n (%)						
Pirfenidone	8 (23%)	4 (6%)	$P = 0.023$	0 (0%)	$P < 0.001$	$P = 0.121$
Nintedanib	3 (9%)	4 (6%)	—	0 (0%)	$P = 0.052$	$P = 0.121$
Patients taking corticosteroids						
Oral corticosteroids (ICS)	3 (9%)	33 (52%)	$P < 0.001$	14 (25%)	$P = 0.094$	$P = 0.002$
Inhaled corticosteroids (OCS)	9 (26%)	17 (27%)	—	43 (75%)	$P < 0.001$	$P < 0.001$
Patients taking inhaled anticholinergics	3 (9%)	6 (9%)	—	30 (53%)	$P < 0.001$	$P < 0.001$
Patients taking inhaled beta-agonists	7 (20%)	14 (22%)	—	41 (72%)	$P < 0.001$	$P < 0.001$
Patients requiring O2 supply	17 (49%)	48 (75%)	$P = 0.014$	49 (86%)	$P < 0.001$	$P = 0.172$
Patients taking opiates	3 (9%)	5 (8%)	—	5 (9%)	—	—
Pulmonary function						
[b]FEV1, L	1.9 (1.4–2.5)	1.5 (1.2–2.0)	$P = 0.009$	0.7 (0.5–1.1)	$P < 0.001$	$P < 0.001$
[b]FEV1, % pred	69 (49–83)	57 (42–67)	$P = 0.003$	27 (20–43)	$P < 0.001$	$P < 0.001$
Patients with FEV1≥80%	10 (29%)	5 (8%)**	$P = 0.009$	5 (9%)	$P = 0.019$	—
Patients with FEV1 51–79%	16 (46%)	32 (50%)	—	6 (11%)	$P < 0.001$	$P < 0.001$
Patients with FEV1 30–50%	8 (23%)	22 (34%)	—	14 (25%)	—	—
Patients with FEV1 < 30	1 (3%)	5 (8%)	—	32 (56%)	$P < 0.001$	$P < 0.001$
[b]FVC, L	2.2 (1.7–3.0)	2.0 (1.6–2.5)	$P = 0.169$	2.1 (1.6–2.9)	—	—
[b]FVC, % pred	61 (45–72)	57 (41–66)	$P = 0.050$	65 (46–77)	—	$P = 0.025$
Patients with FVC≥80%	6 (17%)	5 (8%)	$P = 0.189$	11 (19%)	—	$P = 0.105$
Patients with FVC 51-79	18 (51%)	34 (53%)	—	29 (51%)	—	—
Patients with FVC ≤50	11 (31%)	25 (39%)	—	17 (30%)	—	—
[b]FEV1/FVC ratio	0.86 (0.82–0.89)	0.84 (0.81–0.88)	—	0.37 (0.3–0.43)	$P < 0.001$	$P < 0.001$
[b]TLC, L	3.5 (2.8–4.2)	3.3 (2.9–3.9)	—	6.8 (5.6–8.3)	$P < 0.001$	$P < 0.001$
[b]TLC, % pred	54 (49–60)	56 (49–66)	—	120 (111–138)	$P < 0.001$	$P < 0.001$

Table 1. (*continued*)

	IPF (n = 35)	Non-IPF ILD (n = 64)	*P* value-A	COPD (n = 57)	*P* value-B	*P* value-C
[b]RV, L	1.1 (0.9–1.3)	1.3 (1.1–1.6)	$P = 0.101$	4.2 (3.0–5.1)	$P < 0.001$	$P < 0.001$
[b]RV, % pred	46 (35–59)	63 (49–77)	$P = 0.002$	204 (146–248)	$P < 0.001$	$P < 0.001$

COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; H2R, histamine 2-receptor antagonists; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; *P* value-A, comparison between IPF and non-IPF ILD; *P* value-B, comparison between IPF and COPD; *P* value-C, comparison between non-IPF ILD and COPD; PPIs, proton pump inhibitors; RV, residual volume; TLC, total lung capacity.
[a]Results expressed as mean (95% CI) and number (percentage) for categorical variables.
[b]Results expressed as median (IQR).

$P = 0.003$), it was not unexpected that ELI directly correlated with IRP in COPD patients (r = 0.263; $P = 0.048$). No similar correlations were seen in IPF or non-IPF ILD.

Furthermore, in COPD patients, there was a direct correlation between ELI and DCI (r = 0.354; $P = 0.007$) but not in non-IPF ILD or IPF.

Association with pulmonary function. In COPD patients, ELI inversely correlated with parameters of pulmonary function, but directly correlated with parameters of static lung volume (Figure 1C). However, in non-IPF ILD patients, ELI directly correlated with parameters of both pulmonary function and static lung volume (Figure 1D). No significant correlations were seen in IPF patients (Table 4).

TAPG

There were no differences in the numbers of patients who exhibited TAPG greater than (i) bLESP (COPD: 5 [9%], non-IPF ILD: 11 [17%], IPF: 6 [17%]), (ii) iLESP (4 [7%], 4 [6%], 4 [11%]), or (iii) both (2 [4%], 0 [0%], 3 [9%]) between groups.

However, IPF patients had a more negative intra-TP than both non-IPF ILD ($P = 0.012$) and COPD patients ($P < 0.001$) (Table 2). Moreover, despite no difference in BMI between the 3 groups, non-IPF ILD ($P < 0.001$) and COPD ($P < 0.001$) patients had greater intra-AP than IPF patients (Table 2). Thus, TAPG was not different between the 3 cohorts although the aTAPG was lower in COPD compared with non-IPF ILD ($P = 0.052$) and IPF ($P = 0.008$), likely because iLESP was greater in COPD patients than non-IPF ILD ($P = 0.066$) and IPF patients ($P = 0.006$) (Table 2). As expected, in COPD patients, there were inverse correlations between aTAPG and ELI (r = −0.462; $P < 0.001$) (Figure 1E), which were even stronger in those with iEGJOO (ELI: r = −0.732; $P = 0.002$ [Figure 1F]). There were no correlations between ELI and TAPG, intra-TP or intra-AP.

Association with pulmonary function. As expected, intra-TP directly correlated with both pulmonary function and static lung volume parameters in IPF patients with IEM and intra-AP directly correlated with %RV in the whole IPF cohort (Table 4). Thus, aTAPG directly correlated with pulmonary function in both the whole and normal motility cohorts of IPF. In the non-IPF ILD patients with IEM, only intra-TP directly correlated with %TLC. In COPD patients, intra-AP directly correlated with %RV in those with normal motility and inversely correlated with % FEV1 in those with iEGJOO. aTAPG directly correlated with various parameters of pulmonary function in the whole COPD cohort and those with either normal motility or iEGJOO.

MII-pH

More IPF patients exhibited acid exposure time (AET) > 6.0 ($P = 0.164$, $P = 0.014$, respectively), an abnormal number of proximal events (>31; $P = 0.08$, $P \leq 0.02$) than non-IPF ILD and COPD patients, and an abnormal number of reflux events (>80) than patients with COPD (Table 5). Consequently, AET ($P \leq 0.001$), the total number of reflux events ($P \leq 0.001$), and the number of proximal reflux events ($P \leq 0.05$) were greater in IPF patients than non-IPF ILD and COPD patients. There were no differences between non-IPF ILD and COPD (Table 5).

Effect of CCv4 esophageal motility diagnosis, DCI, LESP, and UESP. IPF patients with IEM exhibited greater total bolus exposure time (TBET) ($P = 0.037$, $P = 0.027$, respectively) and a greater number of reflux events ($P = 0.034$, $P = 0.070$) than IPF patients with normal motility and iEGJOO (Table 3). There were trends toward greater AET ($P = 0.059$. $P = 0.087$). The number of proximal reflux events was also increased in IPF patients with IEM compared with those with iEGJOO ($P = 0.039$). Similarly, in non-IPF ILD patients, those with IEM exhibited greater AET ($P = 0.096$), proximal reflux events ($P = 0.021$), and proportion of reflux events reaching the proximal esophagus ($P = 0.013$) than non-IPF ILD patients with normal motility. Interestingly, in non-IPF ILD patients, those with iEGJOO exhibited a greater proportion of reflux events reaching the proximal esophagus ($P = 0.027$) and tended to exhibit more proximal events ($P = 0.107$) than those with normal motility (Table 4). By contrast, COPD patients, with iEGJOO tended to have fewer proximal reflux events than those with normal motility ($P = 0.097$) (Table 3).

As previously seen using CCv3, there were trends for DCI to inversely correlate with the total number of reflux events (r = −0.618; $P = 0.043$), TBET (r = −0.464; $P = 0.151$), and bolus clearance time (r = −0.539; $P = 0.168$) in IPF patients with IEM, but not normal motility. However, correlations between the number of ineffective peristaltic events and various reflux parameters using CCv3 were lost when using CCv4 in IPF patients with IEM, likely because of reduction in patients with IEM. No significant correlations were seen in non-IPF ILD patients with IEM between the various reflux parameters and both the number of ineffective peristaltic events and DCI, although the number of ineffective peristaltic events correlated with the number of total reflux events (r = 0.377; $P = 0.040$) in those with normal motility. No correlations were seen in COPD patients.

In IPF patients, iLESP directly correlated with the percentage of reflux events reaching the proximal esophagus (r = 0.673; $P = 0.023$) in patients with IEM and tends to inversely correlate with AET (r = −0.457; $P = 0.056$), TBET (r = −0.425; $P = 0.079$), and total number of reflux events (r = −0.457; $P = 0.057$) in patients

Table 2. HRIM findings in IPF, non-IPF ILD, and COPD patients

HRIM	IPF (n = 35)	Non-IPF ILD (n = 64)	*P* value-A	COPD (n = 57)	*P* value-B	*P* value-C
[a]UES resting basal pressure, mm Hg	79.6 (50.1–121.5)	78.4 (47.8–101.2)	—	80.9 (45.2–110.2)	—	—
Patients with normal UES pressure, n (%)	18 (51%)	43 (67%)	*P* = 0.136	35 (61%)	—	—
Patients with hypotensive UES pressure, n (%)	3 (9%)	6 (9%)	—	7 (12%)	—	—
Patients with hypertensive UES pressure, n (%)	14 (40%)	15 (23%)	*P* = 0.107	15 (26%)	—	—
[a]Nadir UES residual pressure, mm Hg	3.6 (−2.3 to 8.9)	1.1 (−3.7 to 4.6)	*P* = 0.177	3.8 (−0.4 to 7.5)	—	*P* = 0.011
[a]LES resting basal pressure, mm Hg	29.8 (20.7–44.8)	31.5 (22.1–42.2)	—	36.3 (27.6–47.1)	*P* = 0.101	*P* = 0.150
Patients with normal LES pressure, n (%)	24 (69%)	46 (72%)	—	37 (65%)	—	—
Patients with hypotensive LES pressure, n (%)	2 (6%)	4 (6%)	—	1 (2%)	—	—
Patients with hypertensive LES pressure, n (%)	9 (26%)	14 (22%)	—	19 (33%)	—	—
[a]Inspiratory LES pressure (iLESP), mm Hg	44.3 (34.3–70.7)	61.1 (42.5–72.6)	*P* = 0.116	68.7 (43.4–94.7)	*P* = 0.006	*P* = 0.066
[a]Expiratory LES pressure (eLESP), mm Hg	31.3 (15.6–40.4)	22.2 (16.6–31.4)	*P* = 0.144	30.7 (24.3–47.3)	*P* = 0.148	*P* < 0.001
[a]Difference between iLESP and eLESP	15.0 (1.3–45.3)	37.1 (16.9–50.8)	*P* = 0.020	28.3 (10.3–51.33)	*P* = 0.038	—
Patients with LES-CD separation >2 cm, n (%)	9 (26%)	3 (5%)	*P* = 0.004	8 (14%)	*P* = 0.177	*P* = 0.112
[a]Mean IRP, mm Hg	10 (7–16)	10 (6–13)	—	11 (7–15)	—	—
[a]Median IRP, mm Hg	10 (7–16)	10 (6–13)	—	10 (7–15)	—	—
[a]DL, s	6.8 (6.3–7.6)	8.5 (7.1–9.6)	*P* < 0.001	7.9 (6.6–9.0)	*P* < 0.001	*P* = 0.179
[a]DCI, mmHg/s/cm	726 (412–1,296)	1,083 (653–3,125)	*P* = 0.008	2,106 (966–4,083)	*P* < 0.001	*P* = 0.069
CC v4.0 classification						
Normal, n (%)	18 (51%)	35 (55%)	—	33 (58%)	—	—
Achalasia, n (%)	0	0	—	0	—	—
EGJOO, n (%)	6 (17%)	11 (17%)	—	15 (26%)	—	—
Absent contractility, n (%)	0	6 (9%)	*P* = 0.087	1 (2%)	—	*P* = 0.118
IEM, n (%)	11 (31%)	10 (16%)	*P* = 0.077	4 (7%)	*P* = 0.003	*P* = 0.164
Hypercontractile esophagus	0	2 (3%)	—	4 (7%)	—	—
Single-peak hypercontractile	0	0	—	0	—	—
Jackhammer	0	1 (2%)	—	0	—	—
Hypercontractile LES	0	1 (2%)	—	4 (7%)	—	—
Thoracoabdominal pressure gradient (TAPG), mm Hg						
[a]Intra-abdominal pressure	11.3 (6.0–15.8)	17.3 (12.5–23.4)	*P* < 0.001	17.8 (12.0–23.9)	*P* < 0.001	—
[a]Intrathoracic pressure	−4.6 (−9.6 to −1.7)	−1.8 (−6.0 to 5.0)	*P* = 0.012	0.35 (−4.2 to 3.5)	*P* < 0.001	—
[a]TAPG	15.9 (11.9–18.6)	17.6 (11.6–23.5)	—	17.2 (11.4−22.3)	—	—

Table 2. (*continued*)

HRIM	IPF (n = 35)	Non-IPF ILD (n = 64)	*P* value-A	COPD (n = 57)	*P* value-B	*P* value-C
[a]Adjusted TAPG	−30.5 (−50.8 to −17.7)	−43.9 (−55.6 to −25.7)	*P* = 0.151	−54.3 (−79.3 to 29.4)	*P* = 0.008	*P* = 0.052
Esophageal length index (ELI)						
[b]ELI	12.9 (12.4–13.4)	14.4 (14.1–14.7)	*P* < 0.001	15.5 (15.1–15.9)	*P* < 0.001	*P* < 0.001

CD, crural diaphragm; COPD, chronic obstructive pulmonary disease; DCI, distal contractile integral; DL, distal latency; EGJOO, esophagogastric junction outflow obstruction; ELI, esophageal length index; HRIM, high resolution impedance manometry; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LESP, lower esophageal sphincter pressure; *P* value-A, comparison between IPF and non-IPF ILD; *P* value-B, comparison between IPF and COPD; *P* value-C, comparison between non-IPF ILD and COPD; TAPG, thoraco-abdominal pressure gradient; UES, upper esophageal sphincter.
[a]Results expressed as median (IQR),
[b]Results expressed as mean (95% CI) and number (percentage) for categorical variables.

with normal motility (CCv4.0). In COPD patients, iLESP only weakly inversely correlated with TBET (r = −0.339; *P* = 0.077) in patients with normal motility and not in non-IPF ILD patients.

UESP directly correlated with TBET (r = 0.764; *P* = 0.006) and bolus clearance time (r = 0.850; *P* = 0.007) in patients with IPF with IEM but not normal motility. Similar correlations were not seen in non-IPF ILD and COPD.

Effects of TP, AP, and TAPG. Inspiratory negative intra-TP inversely correlated with both the number and the proportion of reflux events reaching the proximal esophagus in IPF patients with IEM (r = −0.624, *P* = 0.040 and r = −0.609, *P* = 0.047, respectively) but not those with normal motility. aTAPG directly correlated with AET (r = 0.418; *P* = 0.084), TBET (r = 0.458; *P* = 0.056), and the number of distal reflux events (r = 0.442; *P* = 0.066) in IPF patients with normal motility, and similarly with TBET (r = 0.745; *P* = 0.008) in IPF patients with IEM. However, aTAPG inversely correlated with the proportion of reflux events reaching the proximal esophagus in IPF patients with IEM (r = −0.591; *P* = 0.056). While inspiratory negative intra-TP inversely correlated with the number of distal reflux events (r = −0.810; *P* = 0.015) and TAPG directly correlated with the number of distal events (r = 0.810; *P* = 0.015) in non-IPF patients with IEM, the correlations not seen above in IPF patients were also not seen in non-IPF ILD patients with normal motility. In COPD patients with normal motility, no significant correlations were found and correlation analyses were not performed in the 4 patients with IEM.

Association with pulmonary function. Pulmonary function inversely correlated with the proportion of reflux events reaching the proximal esophagus in IPF patients with IEM (Figure 2A–B) but not those with normal motility (Table 4). Conversely, pulmonary function directly correlated with the proportion of reflux events reaching the proximal esophagus in COPD patients with normal motility (Figure 2C–D). Analysis was not undertaken in the 4 COPD patients with IEM. Similarly, pulmonary function directly correlated with the proportion of reflux events reaching the proximal esophagus in non-IPF ILD patients with both normal motility and IEM (Figure 2E–F).

DISCUSSION

We have shown for the first time that esophageal motility and its association with the lung structure, mechanics, and function, and consequently its impact on reflux, differ not only between patients with RLD and OLD but also between different RLDs, namely, IPF and non-IPF ILD. Specifically, COPD patients seem to less likely exhibit IEM and/or absent contractility and to more likely exhibit iEGJOO and/or hypercontractility than both IPF and non-IPF ILD patients, whereas non-IPF ILD patients, similar to those with IPF, are less likely to exhibit iEGJOO compared with COPD patients, but less likely to exhibit IEM than IPF patients. Moreover, disease severity and associated changes in lung volume and consequently EL in these respiratory diseases associate with varying effects on iLESP, DCI, and thoraco-abdominal pressures and subsequently on reflux and its proximal esophageal extent within the esophagus.

Previous studies examining the incidence of motility abnormalities have either compared RLD and OLD (12,16,17), included patients with scleroderma and/or CF (18–22), only reported the incidence of abnormalities in mixed cohorts and/or not statistically compared individual diseases (19–24), or not used the Chicago Classification (18,19). Indeed, only one study used CCv4.0 (22). Posner et al (2018) did state that no single etiology of lung disease had a higher prevalence of motility pattern, but no data were provided (20).

Of note, COPD patients had higher bLESP than non-IPF ILD and IPF patients, which directly correlated with the difference between iLESP and eLESP, with the latter inversely correlating with pulmonary function, suggesting that abnormal breathing, especially in the presence of greater ELI, increases bLESP (see below). Non-IPF ILD patients also had elevated iLESP compared with IPF patients, with iLESP-eLESP directly correlating with bLESP.

Examining associations with other parameters showed that in COPD patients, worse pulmonary function (i.e., decreased pulmonary function and increased static lung volume) was associated with greater ELI, which directly correlated with increased DCI, IRP, and iLESP, the latter particularly in those with iEGJOO, suggesting that extension of the esophagus may be at least partly related to the greater incidence of iEGJOO and hypercontractility in COPD. Our findings support the findings of Masuda et al that

Table 3. Pulmonary function and MII-pH findings for the various key esophageal motility diagnoses in IPF, non-IPF ILD, and COPD patients

IPF	Normal (n = 18)	EGJOO (n = 6)	*P* value-A	IEM (n = 11)	*P* value-B	*P* value-C
Pulmonary function						
[a]FEV1, L	2.1 (1.4–2.5)	2.1 (1.7–2.6)	—	1.9 (1.1–2.4)	—	—
[a]FEV1, % predicted	71 (55–83)	77 (62–80)	—	55 (42–83)	—	—
[a]FVC, L	2.4 (1.7–2.9)	2.4 (1.8–3.1)	—	1.8 (1.3–3.0)	—	—
[a]FVC, % predicted	63 (43–71)	71 (53–77)	—	51 (40–68)	—	—
[a]FEV1/FVC ratio	0.85 (0.82–0.88)	0.85 (0.83–0.91)	—	0.86 (0.84–0.89)	—	—
MII-pH						
[a]AET, %	4.7 (2.3–8.2)	3.3 (1.6–4.5)		12.6 (1.1–17.6)	$P = 0.059$	$P = 0.087$
Patients with abnormal AET (>6%), n (%)	7 (39%)	1 (17%)	—	7 (64%)	—	$P = 0.131$
Patients with inconclusive AET (4–6%), n (%)	4 (22%)	1 (17%)	—	1 (9%)	—	—
[a]TBET, %	0.78 (0.34–1.45)	0.60 (0.30–1.30)	—	1.50 (0.90–3.90)	$P = 0.037$	$P = 0.027$
Patients with abnormal TBET (≥1.4), n (%)	7 (39%)	1 (17%)	—	7 (64%)	—	$P = 0.131$
[a]Total no. of events, n	32 (26–62)	35 (24–53)	—	51 (38–76)	$P = 0.034$	$P = 0.070$
[a]Total no. of acid events (pH ≤ 4), n	25 (11–40)	20 (18–35)	—	38 (20–60)	$P = 0.150$	$P = 0.122$
[a]Total no. of nonacid events (pH ≤ 4), n	12 (7–16)	12.5 (6–15)	—	14 (6–29)	—	—
Patients with abnormal no. of events (>80)	2 (11%)	0 (0%)	—	2 (18%)	—	—
Patients with inconclusive no. of events (40–80)	5 (28%)	2 (33%)	—	6 (55%)	—	—
[a]Total no. of proximal events, n	9 (6–23)	6 (3–16)	—	23 (10–31)	$P = 0.144$	$P = 0.039$
Patients with abnormal no. of events (>31)	4 (22%)	0 (0%)	—	3 (27%)	—	—
[a]Proximal events/total events, %	32.1 (13.8–47.0)	29.7 (10.8–40.0)	—	31.2 (20.2–47.0)	—	—
[a]Bolus clearance time, s	11 (9–13)	13 (9–13)	—	12.5(11–16.2)	—	—
Non-IPF ILD	**Normal (n = 30)**	**EGJOO (n = 9)**	***P* value-A**	**IEM (n = 8)**	***P* value-B**	**I value-C**
Pulmonary function						
[a]FEV1, L	1.6 (1.1–2.1)	1.4 (1.2–2.3)	—	1.5 (1.1–2.4)	—	—
[a]FEV1, % predicted	56 (44–67)	47 (40–69)	—	54 (34–64)	—	—
[a]FVC, L	2.0 (1.7–2.5)	2.0 (1.5–2.7)	—	2.0 (1.6–3.1)	—	—
[a]FVC, % predicted	59 (40–66)	53 (43–69)	—	58 (41–67)	—	—
[a]FEV1/FVC ratio	0.84 (0.81–0.89)	0.83 (0.76–0.88)	—	0.82 (0.75–0.84)	—	—
MII-pH						
[a]AET, %	1.1 (0.4–4.2)	3.4 (0.8–13.5)	—	4.5 (1.2–8.6)	$P = 0.096$	—
Patients with abnormal AET (>6%), n (%)	6 (20%)	4 (44%)	—	3 (38%)	—	—
Patients with inconclusive AET (4–6%), n (%)	3 (10%)	0 (0%)	—	1 (13%)	—	—
[a]TBET, %	1.3 (0.4–2.0)	1.0 (0.4–1.4)	—	1.4 (1.3–3.3)	—	—
Patients with abnormal TBET (≥1.4), n (%)	14 (47%)	3 (33%)	—	4 (50%)	—	—
[a]Total no. of events, n	31 (15–42)	23 (13–46)	—	37 (24–46)	—	—
[a]Total no. of acid events (pH ≤ 4), n	10 (5–21)	19 (3–20)	—	19 (7–29)	—	—
[a]Total no. of nonacid events (pH ≤ 4), n	12 (5–26)	11 (5–21)	—	17 (9–27)	—	—
Patients with abnormal no. of events (>80)	0 (0%)	2 (22%)	$P = 0.049$	0 (0%)	—	—
Patients with inconclusive no. of events (40–80)	11 (37%)	1 (11%)	—	3 (38%)	—	—

Table 3. (*continued*)

Non-IPF ILD	Normal (n = 30)	EGJOO (n = 9)	*P* value-A	IEM (n = 8)	*P* value-B	I value-C
[a]Total no. of proximal events, n	7 (2–13)	12 (7–18)	*P* = 0.107	18 (12–22)	*P* = 0.021	—
Patients with abnormal no. of events (>31)	0 (0%)	2 (22%)	*P* = 0.049	1 (13%)	—	—
[a]Proximal events/total events, %	22.5 (8.0–44.2)	39.1 (30.8–59.5)	*P* = 0.027	44.5 (32.5–61.6)	*P* = 0.013	—
[a]Bolus clearance time, s	13 (9–22)	12 (9–15)	—	14 (12–40)	—	—
COPD	**Normal (n = 28)**	**EGJOO (n = 10)**	***P* value-A**	**IEM (n = 4)**	***P* value-B**	***P* value-C**
Pulmonary function						
[a]FEV1, L	0.8 (0.6–1.1)	0.6 (0.5–1.0)	—	1.3 (0.8–2.1)	—	*P* = 0.147
[a]FEV1, % predicted	27 (22–39)	24 (14–48)	—	43 (24–70)	—	—
[a]FVC, L	2.3 (1.7–3.0)	1.7 (1.6–2.3)	*P* = 0.189	2.5 (2.0–3.9)	—	*P* = 0.162
[a]FVC, % predicted	65 (45–76)	57 (34–78)	—	76 (59–86)	—	—
[a]FEV1/FVC ratio	0.37 (0.29–0.43)	0.35 (0.31–0.48)	—	0.44 (0.29–0.67)	—	—
MII-pH						
[a]AET, %	1.2 (0.35–3.1)	2.1 (0.7–3.5)	—	2.3 (1.0–6.9)	—	—
Patients with abnormal AET (>6%), n (%)	4 (14%)	1 (10%)	—	1 (25%)	—	—
Patients with inconclusive AET (4–6%), n (%)	1 (4%)	1 (10%)	—	0 (0%)	—	—
[a]TBET, %	1.0 (0.34–2.0)	0.4 (0.4–0.9)	—	0.8 (0.32–0.95)	—	—
Patients with abnormal TBET (≥1.4), n (%)	12 (43%)	1 (10%)	*P* = 0.118	0 (0%)	—	—
[a]Total no. of events, n	25 (18–39)	19 (11–40)	—	24 (12–35)	—	—
[a]Total no. of acid events (pH ≤ 4), n	15 (5–23)	11 (7–26)	—	17 (8–23)	—	—
[a]Total no. of nonacid events (pH ≤ 4), n	9 (5–19)	10 (5–12)	—	9 (3–13)	—	—
Patients with abnormal no. of events (>80)	1 (4%)	0 (0%)	—	0 (0%)	—	—
Patients with inconclusive no. of events (40–80)	5 (18%)	3 (30%)	—	1 (25%)	—	—
[a]Total no. of proximal events, n	9 (4–17)	4 (2–5)	*P* = 0.097	10 (6–15)	—	—
Patients with abnormal no. of events (>31)	1 (4%)	0 (0%)	—	0 (0%)	—	—
[a]Proximal events/total events, %	40.4 (14.4–49.2)	20.4 (18.1–28.6)	—	46.3 (32.5–59.0)	—	*P* = 0.142
[a]Bolus clearance time, s	13 (10–16)	11 (6–14)	—	13 (7–23)	—	—

AET, acid exposure time; COPD, chronic obstructive pulmonary disease; EGJOO, esophagogastric junction outflow obstruction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LES, lower esophageal sphincter; MII-pH, 24-hour pH impedance; *P* value-A, comparison between normal motility and EGJOO; *P* value-B, comparison between normal motility and IEM; *P* value-C, comparison between EGJOO and IEM; TBET, total bolus exposure time (i.e., % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Results expressed as median (IQR) and number (percentage) for categorical variables.

OLD patients have longer esophagus and greater prevalence of Jackhammer esophagus than RLD patients, although they did not statistically investigate the relationships between parameters (12). In non-IPF ILD patients, we observed similar direct correlations between ELI and static lung volumes, but in contrast to COPD, a direct correlation with pulmonary function was observed, suggesting that worse disease is associated with a shorter esophagus. Moreover, in non-IPF ILD patients, ELI did not correlate with DCI nor IRP although it did directly correlate with iLESP in those with iEGJOO, like in COPD. Interestingly, in non-IPF ILD patients with IEM, ELI inversely correlated with iLESP. The reason for this is unclear, but maybe non-IPF ILD patients with iEGJOO have more airway involvement, as in COPD patients (e.g. autoimmune disorders and hypersensitivity pneumonitis might have components of bronchiolitis), whereas those with IEM might have less airway involvement and air trapping, but more pure parenchymal fibrotic involvement, as in IPF. In IPF patients, we found no correlations between ELI and pulmonary function, DCI, IRP, or iLESP. This may be because honeycombing and fibrosis in IPF start in the subpleural peripheral basilar areas of the lungs, which may not affect ELI as much, until later in the disease when fibrosis is more diffuse, whereas more central and peribronchovascular or upper lung involvement seen with non-IPF ILD is more likely to affect ELI. Indeed, the EL in our IPF cohort was similar to that reported in healthy volunteers (25).

Both COPD and non-IPF ILD patients had higher intra-TP and higher APs than IPF patients, the latter despite no difference in BMI between groups, supporting the notion that downward

Table 4. Correlations with pulmonary function and static lung volume in IPF, non-IPF ILD, and COPD patients

	Pulmonary function				Static lung volume	
	FEV1L	FEV1%	FVCL	FVC%	RV%	TLC%
IPF						
Basal LESP						
Whole cohort	r = −0.352; $P = 0.038$	r = −0.370; $P = 0.029$	r = −0.384; $P = 0.023$	r = −0.355; $P = 0.037$	—	—
Normal motility	r = −0.542; $P = 0.020$	r = −0.488; $P = 0.040$	r = −0.529; $P = 0.024$	r = −0.543; $P = 0.020$	—	r = −0.496; $P = 0.051$
IEM	—	r= −0.536; P=0.089	—	r = −0.436; $P = 0.180$	—	r = −0.564; $P = 0.071$
Inspiratory LESP						
Whole cohort	r = −0.367; $P = 0.030$	r = −0.358; $P = 0.035$	r = −0.396; $P = 0.018$	r = −0.342; $P = 0.044$	—	—
Normal motility	r = −0.534; $P = 0.023$	r = −0.489; $P = 0.039$	r = −0.513; $P = 0.030$	r = −0.533; $P = 0.023$	—	—
Thoraco-abdominal pressure gradient (TAPG)						
Intrathoracic pressure						
IEM	—	r = 0.691; $P = 0.019$	—	r = 0.691; $P = 0.019$	r = 0.750; $P = 0.052$	r = 0.645; $P = 0.032$
Intra-abdominal pressure						
Whole cohort	—	—	—	—	r = 0.460; $P = 0.028$	—
Adjusted TAPG						
Whole cohort	r = 0.369; $P = 0.029$	r = 0.364; $P = 0.032$	r = 0.397; $P = 0.018$	r = 0.350; $P = 0.039$	—	—
Normal motility	r = 0.476; $P = 0.046$	r = 0.446; $P = 0.064$	r = 0.461; $P = 0.054$	r = 0.494; $P = 0.037$	—	—
MII-pH						
Proportion of reflux events reaching the proximal esophagus						
IEM	—	r = −0.573; $P = 0.066$	—	r = −0.518; $P = 0.102$	—	
Non-IPF ILD						
Basal LESP						
Normal motility	—	—	—	—	r = −0.343; $P = 0.093$	—
ELI						
Whole cohort	—	—	—	r = 0.279; $P = 0.026$	r = 0.261; $P = 0.083$	r = 0.401; $P = 0.002$
Thoraco-abdominal pressure gradient (TAPG)						
Intrathoracic pressure						
IEM	—	—	—	—	—	r = 0.731; $P = 0.040$
MII-pH						
Proportion of reflux events reaching the proximal esophagus						
Normal motility	—	—	—	r = 0.342; $P = 0.065$	—	—
IEM	r = 0.690; $P = 0.058$	—	r = 0.881; $P = 0.004$	r = 0.786; $P = 0.021$	—	—

Table 4. (*continued*)

	Pulmonary function				Static lung volume	
	FEV1L	FEV1%	FVCL	FVC%	RV%	TLC%
COPD						
Basal LESP						
Whole cohort	r = −0.415; $P = 0.001$	r = −0.410; $P = 0.002$	r = −0.438; $P < 0.001$	r = −0.418; $P = 0.001$	—	—
Normal motility	—	—	r = −0.413; $P = 0.017$	—	—	—
EGJOO	—	—	—	—	r = 0.845; $P = 0.004$	r = 0.847; $P < 0.001$
Inspiratory LESP						
Whole cohort	r = −0.404; $P = 0.002$	r = −0.396; $P = 0.002$	r = −0.415; $P = 0.001$	r = −0.391; $P = 0.003$	—	—
Normal motility	r = −0.413; $P = 0.017$	r = −0.333; $P = 0.089$	r = −0.351; $P = 0.045$	—	—	—
EGJOO	—	r = −0.509; $P = 0.053$	r = −0.596; $P = 0.019$	r = −0.588; $P = 0.031$	—	—
Inspiratory LESP minus expiratory LESP (iLESP-eLESP)						
Whole cohort	r = −0.300; $P = 0.023$	r = −0.267; $P = 0.044$	r = −0.337; $P = 0.010$	r = −0.362; $P = 0.006$	—	—
ELI						
Whole cohort	r = −0.441; $P < 0.001$	r = −0.369; $P = 0.005$	r = −0.323; $P = 0.014$	r = −0.284; $P = 0.032$	r = 0.364; $P = 0.018$	r = 0.399; $P = 0.017$
TAPG						
Intra-abdominal pressure						
Normal motility	—	—	—	—	r = 0.350; $P = 0.086$	—
EGJOO	—	r = −0.452; $P = 0.091$	—	—	—	—
Adjusted TAPG						
Whole cohort	r = 0.357; $P = 0.006$	r = 0.338; $P = 0.010$	r = 0.395; $P = 0.002$	r = 0.347; $P = 0.008$	—	—
Normal motility	r = 0.375; $P = 0.032$	—	r = 0.331; $P = 0.060$	—	—	—
EGJOO	—	—	r = 0.493; $P = 0.062$	r = 0.456; $P = 0.087$	—	—
MII-pH						
Proportion of reflux events reaching the proximal esophagus						
Normal motility	r = 0.409; $P = 0.031$	r = 0.584; $P = 0.001$	—	—	—	—

Data denoted by "—" or missing mean no correlation.
COPD, chronic obstructive pulmonary disease; EGJOO, esophagogastric junction outflow obstruction; ELI, esophageal length index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LESP, lower esophageal sphincter pressure; MII-pH, 24-hour pH impedance; RV, residual volume; TAPG, thoraco-abdominal pressure gradient; TLC, total lung capacity; UESP, upper esophageal sphincter pressure.

displacement of the crural diaphragm increases intra-AP. There were no differences between non-IPF ILD and COPD patients, highlighting the significance of differentiating between patients with different RLDs. Thus, TAPG was not different between groups although aTAPG was lower and inversely correlated with ELI in COPD, likely because of increased iLESP. As expected, aTAPG in COPD patients directly correlated with various pulmonary function factors in the whole cohort and those with normal motility and iEGJOO. AP directly correlated with %RV in those with normal motility and inversely correlated with measures of pulmonary function in those with iEGJOO. Similar associations were seen in IPF patients, with aTAPG directly

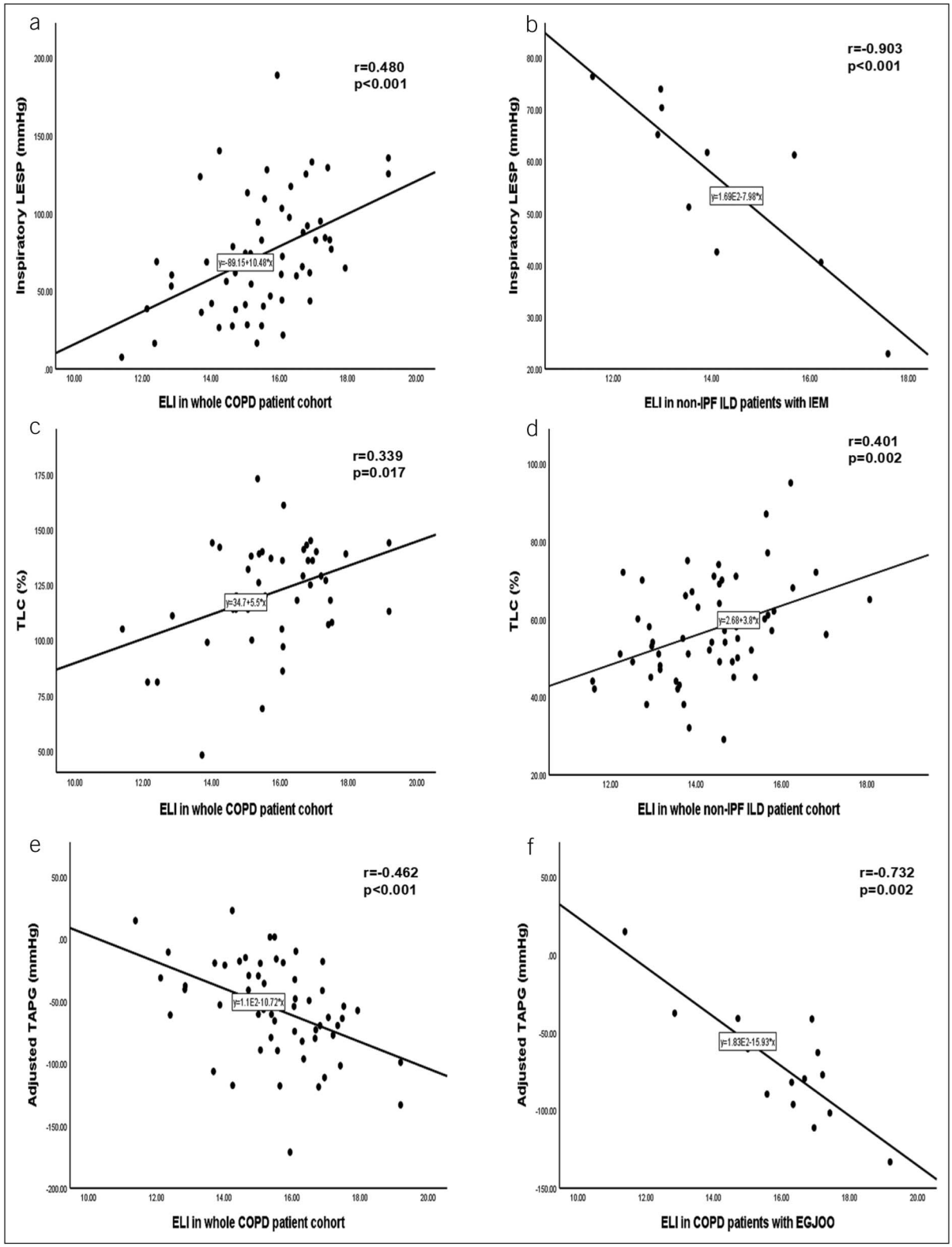

Figure 1. Correlations between esophageal length index (ELI) and inspiratory LESP in the (A) whole COPD patient cohort and (B) non-IPF ILD patients with IEM; percentage of total lung capacity (%TLC) in (C) whole COPD and (D) whole non-IPF ILD patient cohorts; and adjusted thoraco-abdominal pressure gradient (TAPG) in (E) the whole COPD patient cohort and (F) COPD patients with iEGJOO. COPD, chronic obstructive pulmonary disease; iEGJOO, inconclusive EGJOO; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LESP, lower esophageal sphincter pressure.

Table 5. MII-pH findings in IPF, non-IPF ILD, and COPD patients

MII-pH	IPF (n = 35)	Non-IPF ILD (n = 53)	*P* value-A	COPD (n = 46)	*P* value-B	*P* value-C
[a]AET, %	4.8 (1.6–9.6)	1.5 (0.4–6.2)	$P < 0.001$	1.4 (0.5–3.5)	$P < 0.001$	—
Patients with abnormal AET (>6%), n (%)	15 (43%)	14 (26%)	$P = 0.164$	8 (17%)	$P = 0.014$	—
Patients with inconclusive AET (4–6%), n (%)	6 (17%)	5 (9%)	—	2 (4%)	$P = 0.071$	—
[a]TBET, %	0.9 (0.4–1.6)	1.2 (0.4–1.9)	—	0.7 (0.4–1.8)	—	—
Patients with abnormal TBET (≥1.4), n (%)	15 (43%)	22 (42%)	—	14 (30%)	—	—
[a]Total no. of events, n	38 (26–65)	29 (14–42)	$P < 0.001$	24 (15–39)	$P < 0.001$	—
[a]Total no. of acid events (pH ≤ 4), n	28 (18–43)	9 (2–20)	$P < 0.001$	15 (6–23)	$P < 0.001$	—
[a]Total no. of nonacid events (pH ≤ 4), n	13 (6–20)	11 (5–25)	—	8 (3–16)	$P = 0.038$	$P = 0.085$
Patients with abnormal no. of events (>80)	4 (11%)	2 (4%)	—	1 (2%)	$P = 0.160$	—
Patients with inconclusive no. of events (40–80)	13 (37%)	15 (28%)	—	9 (20%)	$P = 0.129$	—
[a]Total no. of proximal events, n	10 (6–25)	8 (2–16)	$P = 0.041$	6 (2–14)	$P = 0.017$	—
Patients with abnormal no. of events (>31)	7 (20%)	3 (6%)	$P = 0.082$	1 (2%)	$P = 0.018$	—
[a]Proximal events/total events, %	30.3 (14.7–47.1)	28.6 (14.3–46.1)	—	29.3 (18.2–50.0)	—	—
[a]Bolus clearance time, s	11.5 (9–13)	12 (9–21)	—	12.0 (9–16)	—	—

AET, acid exposure time; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; MII-pH, 24-hour pH impedance; *P* value-A, comparison between IPF and non-IPF ILD; *P* value-B, comparison between IPF and COPD; *P* value-C, comparison between non-IPF ILD and COPD; TBET, total bolus exposure time (i.e., % of monitored time that the esophagus was exposed to reflux of any nature).
[a]Results expressed as median (IQR) and number (percentage) for categorical variables.

correlating with pulmonary function and inversely correlating with static lung volumes (e.g., %RV). AP also directly correlated with static lung volumes in the whole IPF cohort, maybe this time suggesting that the smaller the lungs, the lower the AP. In addition, unlike COPD patients, in IPF patients, intra-TP directly correlated with pulmonary function in those with IEM. A similar positive correlation was seen between intra-TP and static lung volume (e.g. %TLC) in non-IPF ILD patients, though not for any of the other associations presented above, again probably because of the mixed effects that inflammatory, air trapping, and fibrotic factors have on lung mechanics and gastrointestinal anatomy.

Examination of the relationships to MII-pH data showed that IPF patients have more reflux, with more events reaching the proximal esophagus than non-IPF ILD and COPD patients and that there was no difference between non-IPF ILD and COPD. However, notably, both IPF and non-IPF ILD patients with IEM had more reflux and events reaching the proximal esophagus than those with normal motility, although this was only statistically significantly different from those with iEGJOO in IPF. This is probably related to the fact that non-IPF ILD patients with iEGJOO have more reflux and events reaching the proximal esophagus than those with normal motility. By contrast, reflux exposure and the proportion of events reaching the proximal esophagus in COPD patients were not different between those with IEM and normal motility (although numbers with IEM were small), whereas those with iEGJOO had reduced rather than increased proximal reflux events seen in non-IPF ILD patients. There was a trend for DCI to inversely correlate with TBET and bolus clearance time in IPF, but not non-IPF ILD or COPD patients, again indicating the importance of strong propagated motility in limiting esophageal reflux exposure.

As previously shown using CCv3 in IPF (8), there were an inverse correlation between iLESP and reflux exposure in those with CCv4-defined normal motility, and a direct correlation between iLESP and the proportion of reflux events reaching the proximal esophagus in those with IEM, suggesting that if a IPF patient has IEM, strengthening the LESP might be a disadvantage. In COPD patients but not non-IPF ILD patients, iLESP also weakly inversely correlated with reflux exposure in those with normal motility. Again, our observations in non-IPF ILD patients maybe related to the more complex mix of inflammatory, air trapping, and fibrotic factors and its impact on upper GI anatomy in these patients. As previously seen using CCv3 (8), UESP directly correlated with TBET and bolus clearance time in IPF patients with IEM but not normal motility, and also not in any of the motility subtypes of non-IPF ILD and COPD patients, suggesting that the proximal extent of reflux seen in IPF patients might be triggering a protective reflex to increase UESP (26).

Similarly, as shown using CCv3 (8), negative intra-TP and aTAPG inversely correlated with the number and/or proximal extent of reflux in IPF patients with IEM. aTAPG positively correlated with TBET and the number of distal reflux events in IPF patients with normal motility but not IEM. These observations suggest that more negative intra-TP together with IEM and/or higher iLESP (which reduces aTAPG) can associate with more reflux and likelihood of more proximal reflux exposure. A similar situation was seen in non-IPF ILD patients with IEM, with intra-TP inversely correlating and TAPG directly correlating with the number of distal reflux events, but notably not proximal reflux extent. Conversely, in COPD patients, the number and proximal extent of reflux did not associate with TP, AP, or TAPGs.

The above observations complement those on pulmonary function, with pulmonary function inversely correlating with the proportion of reflux events reaching the proximal esophagus in IPF patients with IEM but not normal motility, but interestingly in non-IPF ILD patients, where changes in the TAPG seemed to have little effect on the proximal extent of reflux, worse pulmonary function was actually associated with less reflux events reaching the proximal esophagus in both patients with normal

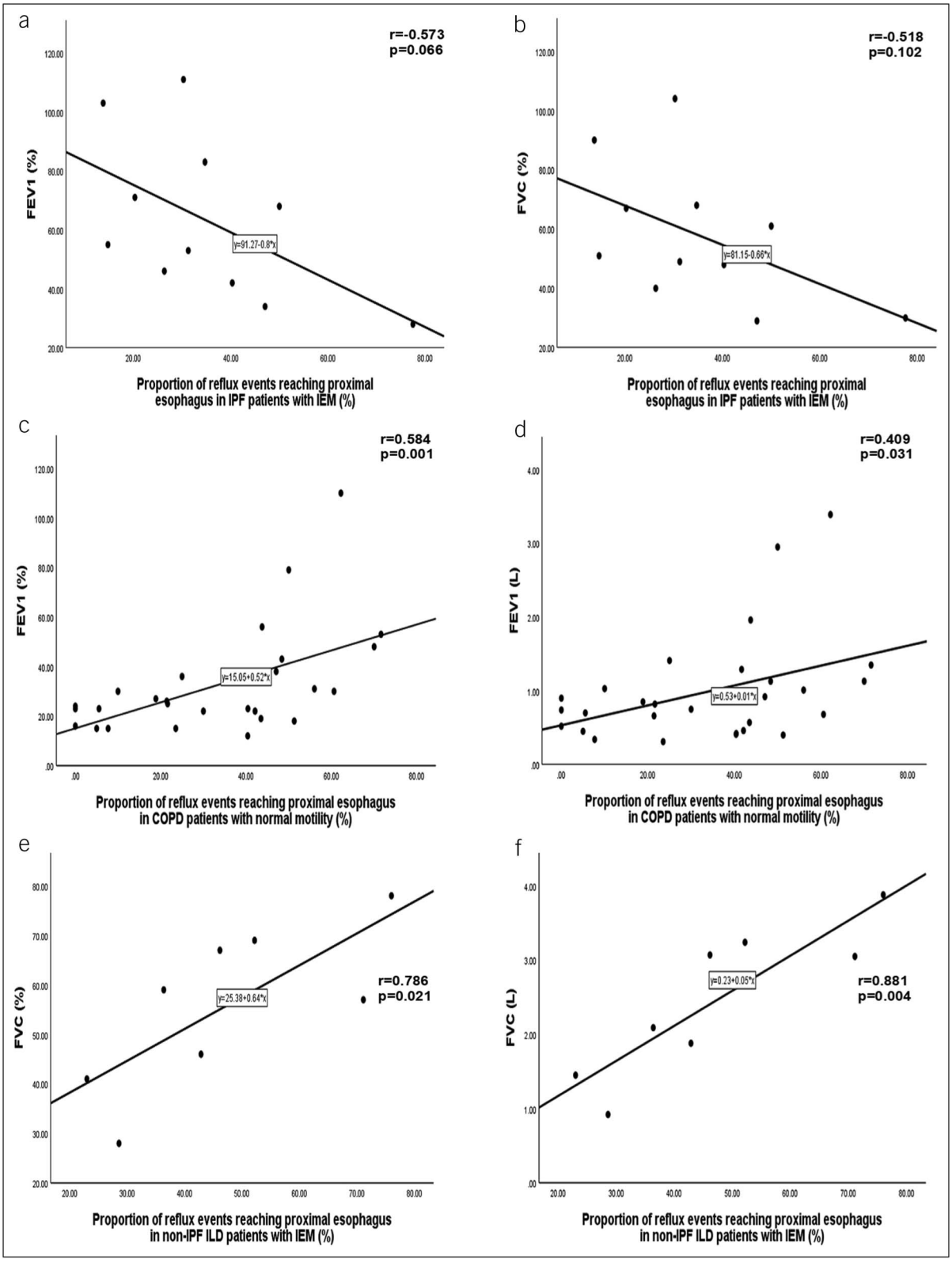

Figure 2. Correlations between proportion of reflux events reaching the proximal esophagus and (A) percentage of forced expiratory volume in the first second (%FEV1) and (B) percentage of forced vital capacity (%FVC) in IPF patients with IEM; (C) %FEV1 and (D) FEV1L in COPD patients with normal motility; and (E) %FVC and (F) FVCL in non-IPF ILD patients with IEM. COPD, chronic obstructive pulmonary disease; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

motility and IEM. Similar observations were seen in COPD patients with normal motility. These observations in non-IPF ILD and COPD patients suggest that the extension of the esophagus with worsening lung disease, despite the presence of IEM and changes in TP and/or AP, prevents reflux reaching the proximal esophagus, supporting previous observations that there seems to be no association between the presence of pepsin in sputum and pulmonary function in COPD (5).

Our study has strengths and limitations. A significant strength is that we compared significant numbers of patients across the spectrum of respiratory diseases and did not include diseases with associated concomitant gut dysfunction (e.g., CF). A limitation is that no explicit statistical adjustments were made for the multiple comparisons performed, but the relatively high proportion of significance/borderline results obtained in our cohorts, and their physiological inter-relationship/correlation, probably excludes the possibility of finding results by chance. Second, patients would be taking different medications for their conditions, with fewer COPD patients tending to take PPIs compared with the other 2 cohorts, but similarly low percentages (≤9%) of patients taking opiates, with interestingly none with iEGJOO. All acid suppressants were stopped before HRIM and MII-pH testing. Third, we cannot categorically say our patients had CCv4 EGJOO as measurements were not acquired in different postural positions and no follow-up provocation tests were performed; hence, we refer to inconclusive EGJOO (iEGJOO). However, in COPD patients, IRP directly correlated with both iLESP and ELI, supporting genuine incomplete relaxation of the LES and thus iEGJOO. Fourth, we did not measure pharyngeal function or sputum and/or bronchoalveolar lavage fluid gastric pepsin concentrations, the latter because currently there are substantial methodological concerns about the techniques used to measure these markers (26). Finally, this was a cross-sectional study, and thus, only associations rather than cause-and-effect between various parameters can be concluded. Given that these are pretransplant patients, follow-up studies were not possible.

In conclusion, our observations call for increased attention to the altered relationships seen between lung anatomy, mechanics, and esophageal function in patients with different respiratory diseases, even within those with RLD or OLD. Our findings also call for a full understanding of esophageal physiology when considering improving LES function endoscopically or with fundoplication and further research into the classification of IEM and iEGJOO in respiratory disease.

CONFLICTS OF INTEREST

Guarantor of the article: Lesley A. Houghton.

Specific author contributions: AA, KRD, and LAH conceived and drafted the study. SZS, ASL, and KRD recruited the patients. AA, CO, RC, SZS, ASL, and KRD collected the esophageal recordings and demographic and respiratory data. ASL, JB, and SZS provided clinical advice on the respiratory diseases. AA analyzed the data, and AA and LAH 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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Study Highlights

WHAT IS KNOWN

- ✓ Gastroesophageal reflux is common in most respiratory diseases.
- ✓ The interplay between gastrointestinal mechanisms that expose individuals to reflux, and lung mechanics and function is poorly understood, particularly in non-idiopathic pulmonary fibrosis (IPF) interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) patients, compared with IPF.

WHAT IS NEW HERE

- ✓ COPD patients were less likely to exhibit ineffective esophageal motility (IEM) and more likely exhibited inconclusive esophagogastric junction outflow obstruction (iEGJOO) and/or hypercontractility, whereas non-IPF ILD patients were less likely to exhibit IEM, similar to COPD patients, but to similarly exhibit iEGJOO compared with IPF patients.
- ✓ In COPD, worse pulmonary function was associated with greater esophageal length index (ELI), which directly correlated with increased distal contractile integral (DCI), integrated relaxation pressure (IRP), and inspiratory lower esophageal sphincter pressure (iLESP), particularly those with iEGJOO, suggesting that extension of the esophagus seems to be related to greater incidence of iEGJOO and hypercontractility.
- ✓ In non-IPF ILD, although similar correlations were seen between ELI and static lung volume, there was a direct correlation with pulmonary function, suggesting worse disease associated with shorter esophagus. ELI did not correlate with DCI or IRP although it did correlate with iLESP in those with iEGJOO.
- ✓ In IPF, there were no correlations between ELI and pulmonary function, DCI, IRP, or iLESP.
- ✓ Non-IPF ILD and IPF patients with IEM have more reflux reaching the proximal esophagus than those with normal motility, an observation not seen in COPD.
- ✓ Non-IPF patients with iEGJOO have more reflux events reaching the proximal esophagus than those with normal motility, whereas COPD patients with iEGJOO had reduced proximal reflux compared with non-IPF ILD. iLESP weakly inversely correlated with reflux exposure in COPD.

TRANSLATIONAL IMPACT

- ✓ New understanding of interplay between gastrointestinal mechanisms that expose individuals to reflux and potentially aspiration, and lung mechanics and function, not only between obstructive and restrictive respiratory diseases, but also between different restrictive respiratory diseases.
- ✓ Potential importance for patient management and consideration for lung transplantation

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