Title: THE PERILS AND PITFALLS OF ESOPHAGEAL DYSMOTILITY IN IDIOPATHIC PULMONARY FIBROSIS

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ABSTRACT

Introduction: Gastroesophageal reflux plays a significant role in idiopathic pulmonary fibrosis (IPF). Given the morbidity and mortality associated with IPF, understanding the mechanisms responsible for reflux is essential if patients are to receive optimal treatment and management, especially given the lack of clear benefit of anti-reflux therapies. Our aim was to understand the inter-relationships between esophageal motility, lung mechanics and reflux (particularly proximal reflux -a prerequisite of aspiration), and pulmonary function in IPF patients.

Methods: We prospectively recruited 35 IPF patients (aged 53-75yrs; 27 male) who underwent high-resolution impedance manometry and 24-hr pH-impedance, together with pulmonary function assessment.

Results: Twenty-two (63%) patients exhibited dysmotility, 16(73%) ineffective esophageal motility (IEM) and 6(27%) esophagogastric junction outflow obstruction. Patients with IEM had more severe pulmonary disease (%FVC:p=0.032) and more proximal reflux (p=0.074) than patients with normal motility. In patients with IEM, intra-thoracic pressure inversely correlated with the number of proximal events (r=-0.429;p=0.098). Surprisingly, inspiratory lower esophageal sphincter pressure (LESP) positively correlated with the percentage of reflux events reaching the proximal esophagus (r=0.583;p=0.018), whilst in patients with normal motility it inversely correlated with the bolus exposure time (r=-0.478;p=0.098) and number of proximal events (r=-0.542;p=0.056). %FVC in IEM patients inversely correlated with the percentage of reflux events reaching the proximal esophagus (r=-0.520;p=0.039) and inspiratory LESP (r=-0.477;p=0.062), and positively correlated with intra-thoracic pressure (r=0.633;p=0.008).

Conclusions: We have shown that pulmonary function is worse in patients with IEM which is associated with more proximal reflux events, the latter correlating with lower intra-thoracic pressures and higher LESPs.

Study Highlights

What is known:

- Aspiration of gastroesophageal reflux is believed to be a trigger of lung epithelial cell injury in patients with idiopathic pulmonary fibrosis.
- The severity of reflux (i.e. acid and non-acid reflux combined) appears to associate with the worse pulmonary function, and may be an independent predictor of poor pulmonary outcome.
- However, anti-reflux therapies, including acid suppression and fundoplication, appear to provide unclear benefit.
- Understanding the mechanics of gastroesophageal reflux, particularly what drives reflux to the proximal regions of the esophagus, a prerequisite for aspiration, may better guide therapy.

What is new here:

- Pulmonary function in IPF patients with ineffective esophageal motility is worse than those with normal motility.
- This is associated with more reflux events reaching the proximal esophagus.
- Higher lower esophageal sphincter pressure (LESP) and greater negative intra-thoracic pressure correlated with proximal esophageal reflux in patients with IEM.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is common in idiopathic pulmonary fibrosis (IPF),[1] leading to concerns that aspiration of gastric contents may be causing repetitive alveolar epithelial cell injury and worsening disease. This is supported by studies suggesting that the severity of acid and non-acid reflux combined, but not acid reflux alone, associates with the severity of pulmonary function[2] and may be an independent predictor of poor pulmonary outcome over 1 year.[3] Other support includes the observation that the number of proximal reflux events, along with concentrations of the stomach proteolytic enzyme, pepsin, and bile acid found in bronchoalveolar lavage fluid correlates with the degree of fibrosis in patients with IPF.[4] Despite this, evidence that acid suppression[5,6,7] or fundoplication[8,9] has any genuine benefit is poor and/or conflicting.

Understanding the mechanisms responsible for reflux, particularly its proximal extent (a prerequisite of aspiration) is essential if patients are to receive optimal treatment for their gastroesophageal reflux. Weak esophageal peristalsis, and both decreased[10] and normal[11] lower esophageal sphincter pressure (LESP) have been reported, but their association with the severity of reflux, its proximal extent and lung function was not addressed. Patients have also been shown to exhibit a more negative intra-thoracic pressure and a greater thoraco-abdominal pressure gradient (TAPG) than healthy controls, with the adjusted TAPG (i.e. TAPG minus LESP) weakly correlating with acid reflux.[11] The association with lung function was not addressed.

We hypothesize that esophageal dysmotility, even minor peristaltic abnormalities in association with increases in TAPG, have a significant impact on both swallowed and reflux bolus exposure, and thus exposure of the proximal esophagus to luminal fluids, and thence pulmonary function in patients with IPF. Our aim therefore was to use High Resolution Impedance Manometry (HRIM) along with 24-hr pH-impedance (MII-pH) to determine the prevalence of dysmotility using the Chicago

Classification v3.0 (CCv3.0), measure TAPGs, and determine their inter-relationship with reflux, particularly that reaching the proximal esophagus, and pulmonary function in patients with IPF.

MATERIALS AND METHODS

Patients

This was a prospective study of 35 consecutive patients with IPF undergoing HRIM and MII-pH at Leeds Teaching Hospital NHS Trust, Leeds, U.K. and Mayo Clinic, Jacksonville, U.S.A., between October 2018 and December 2019. A diagnosis of IPF was made according to the 2018 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines.[12,13] At both centers, a multi-disciplinary panel, comprising pulmonologists, chest radiologists and lung pathologists reviewed each case to achieve a consensus of diagnosis. Patients who had undergone any upper gastrointestinal surgery or endoscopically improved LESP were excluded. The Yorkshire and the Humber-Bradford Leeds Research Ethics Committee (REC reference 18/YH/0387) and the Mayo Clinic Institutional Review Board (IRB)(IRB# 18-005280) approved the study. No patient received compensation for taking part in this study.

HRIM

HRIM was performed using a solid-state catheter with 36 circumferential pressure sensors spaced at 1cm intervals and 18 impedance channels (Medtronic Inc. Shoreview, MN,USA) or 36 pressure channels and 12 impedance channels (Medical Measurement Systems [MMS], Enschede, The Netherlands). The catheter was positioned transnasally with distal sensors for both pressure and impedance in the proximal stomach. Following at least a 30s baseline to identify the upper esophageal sphincter (UES) and LES, ten 5 ml saline swallows were given at least 30s apart with the

patient supine.[14,15] HRIM recordings were analyzed manually, blinded to pulmonary function data, using appropriate dedicated software (ManoView Analysis Software v3.01, Medtronic Inc., Shoreview, MN or Solar GI HRM, MMS, Enschede, The Netherlands). CCv3.0 algorithms were applied to make a diagnosis of normal or an esophageal motility disorder.[16] Basal LESP was considered hypertensive if >43mmHg on ManoView and >45mmHg using MMS, and hypotensive if <13mmHg using ManoView and <10mmHg using MMS.[16]

Impedance tracings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings.[17] Subjects were classified as complete bolus transit when clearance was seen in ≥80% of swallows.[18]

TAPG was calculated by subtracting the intra-abdominal pressure (proximal stomach 1cm below the lower border of the LES, and referenced to atmospheric pressure) from the mean intra-thoracic pressure (distal esophagus between 1-5cm 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-abdominal pressure (i.e. 1cm below the lower border of the LES) was also measured, and an adjusted TAPG calculated by subtracting LESP from the TAPG during inspiration. A cut-off value of adjusted TAPG to predict the risk of reflux was set at >0mmHg, based on the hypothesis that reflux may occur when TAPG overcomes the LESP.[19]

MII-pH

MII-pH (Sandhill Scientific Inc., CO, USA/MMS, Enschede, The Netherlands) was performed off acid suppressants using a single antimony pH probe (5cm above the LES) with 8 impedance electrodes.[14] Data were manually analyzed (BioVIEW Analysis software, Sandhill Scientific Inc. or MMS Investigation and diagnostic software, MMS, Enschede, The Netherlands) 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.[20,21,22]

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 (non-parametric data) tests. Significance was evaluated at the 2-tailed, p-value of <0.05 taken as significant.

RESULTS

Demographics and the clinical characteristics of the IPF patient cohort are shown in Table 1. As is typical of the disease, the mean age of the cohort was 66 years, 77% were male and the majority of patients (83%) suffered from moderate (%FVC: 67.5%[61.0%-69.0%], median[IQR]) to severe (%FVC: 40.0%[37.0%-45.0%]) restrictive lung disease.

HRIM (CCv3.0)

Sixty three percent of IPF patients (22/35) exhibited abnormal esophageal motility, 16(73%) ineffective esophageal motility (IEM) and 6(27%) esophagogastric junction outflow obstruction (EGJOO)(Table 2). Of the 6 patients with EGJOO, 2 patients exhibited IEM and 4 normal esophageal body motility. LESP was normal in the majority (69%) of patients (Table 2).

Bolus Transit

Sixty six percent of IPF patients exhibited incomplete transit of boluses swallowed, and across the whole patient cohort a median of 70% of swallows were incomplete (Table 2). There was a direct

correlation between the proportion of swallows that were associated with incomplete bolus transit (IBT) and the proportion of esophageal peristatic events that were ineffective (r=0.457;p=0.006).

TAPG

Six (17%) patients exhibited a TAPG that was greater than basal LESP, 4 with TAPG greater than inspiratory LESP, and 3 had both.

MII-pH

Fifteen (43%) IPF patients had abnormal total bolus exposure time (i.e. acid and non-acid combined) and 15(43%) acid exposure time (AET) (Table 2). Twelve (34%) had both abnormal total bolus exposure time and AET. Only 20% of patients had an abnormal number of proximal and distal reflux events, with the majority of events occurring in the upright compared with the supine posture (p≤0.01)(Table 2). However, of the reflux events occurring, up to 78% reached the proximal esophagus (30%[0-78%]; median[range]).

Associations between esophageal motility, and reflux, bolus clearance and pulmonary function

Pulmonary Function: Patients with IEM had a lower (i.e. worse) forced vital capacity (FVC,L: p=0.062), percent predicted FVC (%FVC: p=0.012), percent predicted forced expiratory volume in the first second (%$FEV_{1:}$ p=0.013) and percent predicted diffusing capacity of lung carbon monoxide (%DLCO: p=0.05) compared with patients with CCv3.0 normal motility (Table 3). Patients with EGJOO did not differ from those with normal motility (Table 3). Age, body mass index, height, along with use of acid suppressants, opiates and anti-fibrotics, did not significantly differ between motility sub-groups (Table 3).

Motility parameters and swallowed bolus clearance: As expected, patients with IEM had a significantly lower distal contractile integral (DCI) compared with patients with normal motility

(p<0.0001) and those with EGJOO (p=0.021), and a tendency for more swallows to be associated with IBT (p=0.075)(Table 4). More IEM patients were defined as having IBT than patients with normal motility (p=0.064). Patients with EGJOO had a higher resting UESP, LESP and integrated relaxation pressure (IRP) than patients with normal motility (p=0.012, p=0.002, p<0.005, respectively) and IEM (p=0.027, p=0.010, p<0.005). Indeed, 5 out of 6 (83%) patients with EGJOO had both a hypertensive UESP (p=0.016 compared with normal motility) and hypertensive LESP (p=0.016 compared with normal motility, and p=0.001 compared with IEM) (Table 3).

Four patients with IEM, 4 with normal motility and 1 with EGJOO exhibited a LES-crural diaphragm (LES-CD) separation greater than 2cm.

MII-pH: There was no differences in any of the reflux parameters between the three motility sub-classifications, as defined by CCv3.0. However, 4 of the patients with CCv3.0 normal motility had between 1-4 swallows associated with IEM, and comparison with those with completely normal motility (i.e. those with no ineffective peristaltic events) showed them to have significantly higher AET (median[IQR]: 11.30%[8.60%-15.80%] vs 4.80%[3.10%-7.10%];p=0.003), increased numbers of proximal reflux events (32[18.5-47.5] vs 8.0[6.0-11.0];p=0.076) and proportion of distal reflux events reaching the proximal esophagus (40.1%[36.8%-59.7%] vs 19.35%[13.9%-29.0%];p=0.034), and to be more likely to exhibit abnormal AET (>6%: 100%vs33%;p=0.07), distal (>80 events: 50%vs0%;p=0.077), and proximal (>31 events: 75%vs0%;p=0.014) events than those with completely normal motility.

Consequently, patients with CCv3.0 defined IEM exhibited over twice as many proximal reflux events (19.00[7.50-29.00]) than patients with completely normal motility (8.0[6.0-11.0];p=0.074); though not quite reaching statistical significance. Pulmonary function remained worse in CCv3.0 IEM patients

compared with those with completely normal motility (%FVC: 69.0%[61.0%-71.0%] vs 48.5%[40.0%-67.5%];p=0.032, %FEV_1: 77.0%[68.0%-83.0%] vs 54.0%[42.0%-72.5%];p=0.037).

Reflux parameters were generally higher in the upright compared with the supine posture, but there was no significant difference between the motility sub-groups (Table 4). However, the proportion of patients with IEM who exhibited an abnormal number of proximal reflux events tended to be higher in the supine compared with upright posture (38% vs 6%;p=0.085); findings not seen in the other two motility sub-groups.

Given the limited numbers of patients with EGJOO (n=6), formal comparisons with the other motility sub-groups is not discussed, other than the differences in UESP and LESP. But of note, only one EGJOO patient had abnormal AET and total bolus exposure time, and none had abnormal numbers of proximal or distal reflux events.

Correlations: In patients with IEM (CCv3.0) there was a direct correlation between the number of ineffective peristaltic events and total bolus exposure time (total: r=0.524;p=0.037, upright: r=0.518;p=0.040, supine: r=0.520;p=0.047), the number of distal reflux events (total: r=0.560;p=0.024, upright: r=0.548;p=0.028) and bolus clearance time (total: r=0.679;p=0.011, upright: r=0.756;p=0.003); correlations not observed in patients with normal motility. This translated into inverse correlations between DCI and total bolus exposure time (total: r=-0.515;p=0.041, upright: r=-0.474;p=0.064, supine: r=-0.514;p=0.050), the number of distal reflux events (total: r=-0.593;p=0.015, upright: r=-0.600;p=0.014) and bolus clearance time (total: r=-0.618;p=0.024, upright: r=-0.668;p=0.013) in patients with IEM but not normal motility. DCI strongly inversely correlated with the proportion of reflux events reaching the proximal esophagus in CCv3.0 defined normal motility (total: r=-0.648;p=0.017, upright: r=-0.621;p=0.024) and even more strongly in those with completely normal motility (total: r=-0.917;p=0.001, upright: r=-0.817;p=0.007). Furthermore, the

greater the number of peristaltic events that were ineffective (i.e. 0-4 events) the greater the percentage of reflux events reached the proximal esophagus in patients with normal motility (total: r=0.629;p=0.021, upright: r=0.501;p=0.081, supine: r=0.498;p=0.084).

As might be expected there was a trend for inspiratory LESP to inversely correlate with total bolus exposure time in patients with CCv3.0 defined normal motility (n=13, total: r=-0.478;p=0.098 (Figure 1A), upright: r=-0.489;p=0.09, supine: r=-0.595;p=0.032) and those with completely normal motility (total: r=-0.617;p=0.077, upright: r=-0.567;p=0.112, supine: r=-0.628,p=0.070) but not those with IEM. A similar relationship was seen in the whole IPF patient cohort (n=35, total: r=-0.386;p=0.022, upright: r=-0.362;p=0.033). Inspiratory LESP also inversely correlated with the number of proximal reflux events (total: r=-0.542;p=0.056 (Figure 1B), supine: r=-0.594;p=0.032)and proportion of reflux events reaching the proximal esophagus in the supine position (r=-0.495;p=0.086) but not distal reflux events in patients with CCv3.0 defined normal motility. Conversely and surprisingly, there was a direct correlation between inspiratory LESP and the number of proximal reflux events in the supine posture (r=0.472;p=0.065) and the proportion of reflux events reaching the proximal esophagus (total: r=0.583;p=0.018 (Figure 1C), upright: r=0.568;p=0.022, supine: r=0.518;p=0.040) in patients with IEM i.e. the higher the inspiratory LESP the more likely that reflux events occurring reached the proximal esophagus in patients with IEM.

UESP directly correlated with TBET (r=0.688;p=0.005), and the number of distal (r=0.519;p=0.039) and proximal (r=0.415;p=0.110) reflux events in patients with IEM but not normal motility.

Finally and notably, both %FVC (total: r=-0.520;p=0.039 (Figure 2A), upright: r=-0.490;p=0.054) and $\%FEV_1$ (total: r=-0.667;p=0.005 (Figure 2A), upright: r=-0.640;p=0.008, supine: r=-0.523;p=0.038) but not %DLCO moderately to strongly inversely correlated with the proportion of reflux events reaching the proximal esophagus in patients with IEM but not normal motility. Similarly, %FVC weakly and

inversely correlated with both the basal LESP (r=-0.446;p=0.084) and inspiratory LESP (r=-0.477;p=0.062), as did %FEV_1 (basal: r=-0.492;p=0.053, inspiratory: r=-0.541;p=0.031) in patients with IEM (Figure 2B and C) but not those with normal motility.

Influence of TAPG on reflux, bolus clearance and pulmonary function

The 6 patients in whom TAPG was greater than basal LESP (TAPG>LESP) had a greater AET (p=0.019), total bolus exposure time (p=0.009), and more distal (p=0.055) and proximal (p=0.093) reflux events than patients with a lower TAPG than their basal LESP (TAPG<LESP) (Figure 3). This equated to a larger percentage of patients with TAPG>LESP exhibiting abnormal AET (>6%: 100%vs31%;p=0.003), total bolus exposure time (≥1.4%: 100%vs31%;p=0.003), numbers of distal (>73: 50%vs14%;p=0.079, >80: 50%vs3%;p=0.011) and proximal (50%vs14%;p=0.079) reflux events than patient with TAPG<LESP. Likewise, the percentage of patients with abnormal total bolus exposure time was significantly higher in patients with TAPG>inspiratory LESP than those with TAPG<inspiratory LESP (100%vs36%;p=0.026).

Correlations: There was a tendency for inspiratory negative intra-thoracic pressure to inversely correlate with the number of reflux events reaching the proximal esophagus (r=-0.429;p=0.098) but not the number of distal reflux events or total bolus exposure time in patients with IEM. This association was not observed in patients with normal motility.

Both %FVC (r=0.506;p=0.045) and %FEV_1 (r=0.548;p=0.028) positively correlated with the adjusted TAPG (Figure 2D) but not with TAPG in patients with IEM, likely because the higher the inspiratory LESP (thus, lower adjusted TAPG) the lower %FVC and %FEV_1 (Figure 2C). As might be expected, %FVC tended to positively correlate with inspiratory intra-thoracic pressure in the whole cohort studied (r=0.253;p=0.143) and significantly in patients with IEM (r=0.633;p=0.008) (i.e. the greater the negative intra-thoracic pressure the lower the %FVC) but significance was not reached in patients

with normal motility. Likewise, $\%FEV_1$ positively correlated with inspiratory intra-thoracic pressure in IEM patients (r=0.617;p=0.011).

DISCUSSION

We have shown for the first time that pulmonary function in IPF patients with IEM is worse than patients with normal motility, and associated with more reflux events reaching the proximal esophagus. This appeared to be exacerbated by greater negative intra-thoracic pressures and possibly by higher LESPs, especially during inspiration. Indeed, %FVC and $\%FEV_1$ inversely correlated with the percentage of reflux events reaching the proximal esophagus (irrespective of posture) and both basal and inspiratory LESP, and positively correlated with intra-thoracic pressures in patients with IEM. This supports a complex and somewhat unique relationship between proximal reflux exposure, LES function and pulmonary mechanics in patients with IPF.

Interestingly, a much smaller percentage of IPF patients exhibited an abnormal number of reflux events compared with total bolus exposure time or AET, suggesting that the increased esophageal reflux exposure seen in some patients may be due to poor clearance rather than increased transient lower esophageal sphincter relaxation (tLESR), the main mode by which reflux occurs in typical reflux patients. Patients with EGJOO did not exhibit abnormal numbers of proximal or distal reflux events, and only one patient had an abnormal AET and total bolus exposure time.

A possible mechanical explanation for the proximal migration and poor clearance of reflux events seen in some IPF patients may be gained from our observations that in patients with IEM there was a direct correlation between the number of ineffective peristaltic events and total bolus exposure time, the number of reflux events and bolus clearance time; a relationship not seen in patients with CCv3.0 normal motility. Moreover, the association between occasional ineffective peristaltic events and reflux in IPF patients, was highlighted by more patients with CCv3.0 defined normal motility, who

had between 1 and 4 ineffective peristaltic events, exhibiting clinically increased AET, and both proximal and distal reflux events than patients with completely normal motility. Moreover, in patients with CCv3.0 defined normal motility, we showed a direct correlation between the proportion of peristaltic events, which were ineffective (0-40%) and the percentage of reflux events that reached the proximal esophagus. These observations support our previous findings that minor peristaltic abnormalities not classified as abnormal by CCv3.0 can associate with increased reflux exposure in respiratory patients.[14,15] In contrast, in IPF patients with normal motility, DCI strongly and inversely correlated with the proportion of reflux events reaching the proximal esophagus, a relationship not seen with total reflux exposure, likely because the inter-patient variation in DCI will be small in patients with normal motility and tLESRs appeared to be not increased. Thus, in patients with respiratory disease, such as IPF, ineffective esophageal peristaltic events, along with potentially other motor features not measured in this study, such as abnormal esophageal tone and post-reflux swallow-induced peristaltic wave (PSPW) index, may be associated with poor clearance and proximal migration of reflux events, possibly aided by factors not present in patients with GERD only, such as greater negative intra-thoracic pressure. Further studies, perhaps using prolonged combined motility and reflux monitoring, will be needed to confirm these associations. Generally, all measured reflux parameters were greater in the upright compared with supine posture in patients with IPF, and not significantly different between motility groups, but there was a tendency for a greater proportion of patients with IEM to have an abnormal number of reflux events reaching the proximal esophagus in the supine (38%) compared with the upright (6%) posture.

Patients with normal motility who exhibited higher LESPs suffered from less reflux exposure and fewer events reaching the proximal esophagus than patients with reduced LESPs. However, there was no association between LESP and the number of reflux events, probably because the majority of reflux events occur during tLESR. In patients with IEM the higher the inspiratory LESP, the more

likely reflux events occurring reached the proximal esophagus whether in an upright or supine posture. Fundoplication, particularly the full fundoplication preferred in the United States, increases LES pressure and produces outflow obstruction, as measured by manometry and demonstrated radiographically even in those with normal esophageal function[23,24]. It is thus important to at least consider the possibility that fundoplication could potentially increase bolus retention and worsen rather than improve the situation for a sub-set of IPF patients with IEM. This might at least partially explain why a trial of laparoscopic anti-reflux surgery in IPF patients with undefined esophageal motility was unable to show a significant slowing of rate of change in FVC or significant improvement in acute exacerbations, respiratory related hospitalizations and non-elective hospitalizations over a 48-week follow-up period.[9] Interestingly, although patients with IEM were more likely to have proximal reflux and reduced pulmonary function, these patients also appeared to have a higher resting UESP than patients with normal motility, suggesting mechanisms for protection of the airways from aspiration may have been initiated. Previous studies in healthy volunteers have shown that the presence of liquid in the esophagus volume dependently causes contraction of the UES[25]. Whether the proximal extent of reflux contributed towards increased UESP in IPF patients with IEM remains unclear, as does whether it affords any protection.

Although not reaching statistical significance, inspiratory thoracic pressure was nearly twice as negative in patients with IEM as normal motility, and positively correlated with %FVC in the whole patient cohort, and particularly those with IEM. The low number of patients with an abnormal number of distal reflux events would suggest that TAPG was not driving many reflux events during tLESR. Instead when reflux events occurred, the greater the negative intra-thoracic pressure, the more likely distal reflux events migrated to more proximal regions of esophagus in IEM patients. A similar relationship was not seen in patients with normal motility, likely because the strength and

coordination of peristaltic contractions helped over-ride the effect of greater negative intra-thoracic pressures.

Whether IEM is independent of IPF, or whether it is a consequence of dis-coordination between the phases of breathing and swallowing is unclear. In healthy volunteers, increasing the frequency of breathing and voluntarily changing the contributions of the ribcage and abdomen can influence intra-esophageal pressure and thus potentially reflux,[26] whilst hyperventilation (increased breathing frequency and tidal volume) and partial expiration, can impair esophagogastric junction (EGJ) relaxation and esophageal peristalsis, delaying esophageal transit and clearance.[27] In patients with advancing fibrotic lung disease, the increased ventilation required for exercise becomes more dependent upon an increased respiratory rate (tachypnoea) as lung compliance and tidal volume are increasingly limited. It is unknown whether such a breathing pattern influences esophageal motility. Psychological stress, which might be expected to be high in such patients, can induce abnormal breathing patterns similar to partial expiration, with increases in the tone of the crural diaphragm and impairment of EGJ relaxation.[28] Stress can also influence esophageal motility.[29,30] Lastly, whether breathing pattern is responsible for EGJOO in IPF patients is unclear, but two thirds had normal esophageal body motility. Alternatively, EGJOO might simply be the consequence of distortion of the esophagogastric junction because of shrinkage of lung volumes in some patients.

Our study has strengths and limitations. A significant strength is that we included patients across the spectrum of disease severity. A limitation is that no explicit statistical adjustment were made for the multiple comparisons performed in this study, but the relatively high proportion of significance/borderline results obtained in our cohort of 35 patients with IPF, and their physiological inter-relationship/correlation (irrespective of posture), probably excludes the possibility of finding these results by chance. Second, some patients were taking anti-fibrotic drugs, acid suppressants and

opiates, but the numbers of patients were not significantly different between motility sub-groups, and interestingly no patient with EGJOO was taking opiates. All acid suppressants were stopped before HRIM and MII-pH testing. Thirdly, we did not measure pharyngeal function or reflux, 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[1], and new and better validated tests need to be developed. Lastly, this was a cross-sectional study and thus only associations rather than cause-and-effect between various parameters can be concluded.

In conclusion, our observations call for increased attention to esophageal motility in patients with IPF, if not most patients with fibrotic lung disease, and highlight the benefit of performing HRIM, as well as MII-pH, particularly the assessment of the proximal extent of reflux. They also call for (i) a full understanding of esophageal physiology when considering improving LES function endoscopically or with fundoplication, and (ii) re-consideration of the IPF management guidelines from the ATS/ERS/JRS/ALAT which provisionally recommend the empiric use of acid suppression therapy in the treatment of IPF, irrespective of the presence of reflux symptoms.[31] This is particularly important given the growing evidence that acid suppression may in fact be deleterious,[1] with higher rates of lower respiratory tract infection and lower FEV_1 and FVC been reported.[7] A physiologic profile for these patients can be created with the combination of HRIM and MII-pH, which may subsequently be used to help guide therapy directed at the esophagus and aspiration. Lastly, our results call for continued research into the classification of ineffective esophageal motility in respiratory disease, the potential interaction of altered tonic and phasic motility, secondary peristalsis and PSPW in the clearance of reflux events and into other modes of treatment of gastroesophageal reflux in patients with IPF, such as prokinetics.

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FIGURE LEGENDS

Figure 1: Correlation between inspiratory LESP and (A) total bolus exposure time in patients with normal motility (CCv3.0), (B) number proximal reflux events in patients with normal motility (CCv3.0) and (C) percentage of reflux events reaching the proximal esophagus in patients with IEM (CCv3.0).

Figure 2: Correlations between %FVC and $\%FEV_1$ and (A) percentage of reflux events reaching the proximal esophagus, (B) basal LESP, (C) inspiratory LESP and (D) the adjusted TAPG in patients with IEM (CCv3.0).

Figure 3: AET, total bolus exposure time, number of distal and proximal reflux events between patients with TAPG less than and larger than basal LESP.

Table 1. Demographics and Clinical Characteristics of IPF Cohort

General characteristics	
Number of patients	35
[b]Age, years	66 (64 - 69)
Male:Female ratio	27:8
[b]Body mass index, kg/m^2	27.8 (26.0 - 29.5)
[b]Height, m	1.71 (1.68-1.74)
Ethnicity, n (%)	
White	31 (88.6%)
Black	3 (8.6%)
Asian	1 (2.9%)
Tobacco use, n (%)	
Current smokers	2 (5.7%)
Ex-smokers	23 (65.7%)
Never-smokers	10 (28.6%)
Medication	
Patients taking PPIs, n (%)	15 (42.9%)
Patients taking H2R antagonists, n (%)	3 (8.6%)
Patients taking anti-fibrotics	13 (37.1%)
Pirfenidone, n (%)	8 (22.9%)
Nintedanib, n (%)	3 (8.6%)
Patients taking opiates, n (%)	3 (8.6%)
PFTs	
[a]FVC, L	2.2 (1.7 - 3.0)
[a]FVC, % pred	61 (45 - 72)
Patients with FVC ≥80%, n (%)	6 (17.1%)
Patients with FVC 50-80%, n (%)	18 (51.4%)
Patients with FVC ≤50%, n (%)	11 (31.4%)
[a]FEV_1, L	1.9 (1.4 - 2.5)
[a]FEV_1, % pred	69 (49 - 83)
[a]FEV_1/FVC ratio	0.86 (0.82 – 0.89)
[a]TLC, %	54 (48.5 - 60)
[a]DLCO, %	31 (25.5 - 38)
Patients requiring O2 supply, n (%)	17 (48.6%)

Results expressed as either [a]median (IQR) or [b]mean (95% CI), and number (percentage) for categorical variables. Note that HRIM and MII-pH were performed off acid suppressant medications. PPI, proton pump inhibitor; PFTs, pulmonary function tests; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide.

Table 2. HRIM and MII-pH findings in IPF patient cohort

HRIM			
[a]UES resting pressure, mmHg	79.6 (50.1 - 121.5)		
Patients with normal UES pressure, n (%)	18 (51.4%)		
Patients with hypotensive UES pressure, n (%)	3 (8.6%)		
Patients with hypertensive UES pressure, n (%)	14 (40.0%)		
[a]Nadir UES residual pressure, mmHg	3.6 (-2.3 - 8.9)		
Patients with abnormal nadir UES residual pressure, n (%)	3 (8.6%)		
[a]LES resting pressure, mmHg	29.8 (20.7 - 44.8)		
Patients with normal LES pressure, n (%)	24 (68.6%)		
Patients with hypotensive LES pressure, n (%)	2 (5.7%)		
Patients with hypertensive LES pressure, n (%)	9 (25.7%)		
[a]LES inspiratory pressure, mmHg	44.3 (34.3 – 70.7)		
Patients with LES-CD separation >2cm, n (%)	9 (25.7%)		
[a]Mean IRP, mmHg	10.0 (7.4 - 16.4)		
[a]Median IRP, mmHg	10.1 (6.8 - 15.9)		
[a]DL, s	6.8 (6.3 - 7.6)		
[a]DCI, mmHg/s/cm	726.0 (411.9 - 1296.1)		
CCv3.0, n (%)			
Normal, n (%)	13 (37.1%)		
EGJOO, n (%)	6 (17.1%)		
IEM, n (%)	16 (45.7%)		
TAPG			
[a]Intra-abdominal pressure, mmHg	11.3 (6.0 - 15.8)		
[a]Intra-thoracic pressure, mmHg	-4.6 (-9.6 - -1.7)		
[a]TAPG, mmHg	15.9 (11.9 - 18.6)		
[a]Adjusted TAPG, mmHg	-30.5 (-50.8 - -17.7)		
Bolus transit findings			
Patients with IBT, n (%)	23 (65.7%)		
[a]Swallows with IBT, %	70 (10 - 100)		
MII-pH	**Total**	**Upright**	**Supine**
[a]AET, %	4.8 (1.6 - 9.6)	6.3 (1.8 - 10.8)‡	0.7 (0 - 7.5)
Patients with abnormal AET (>6%)[20], n (%)	15 (42.9%)		
[a]TBET, %	0.9 (0.4 - 1.6)	1.3 (0.5 - 2.3)‡	0.1 (0.1 - 0.3)
Patients with abnormal TBET (≥1.4)[21], n (%)	15 (42.9%)		
[a]Total no. of events, n	38 (26 - 65)	31 (23 - 55)‡	3 (1 - 9)
Total no. of acid events (pH≤4), n	28 (18 – 43)†		
Total no. of non-acid events (pH>4), n	13 (6 – 20)		
Patients with abnormal no. of events (>73)[21], n (%)	7 (20.0%)		
Patients with abnormal no. of events (>80)[20], n (%)	4 (11.4%)		
[a]Total no. of proximal events, n	10 (6 - 25)	8 (4 - 19)‡	0 (0 - 3)
Patients with abnormal no. of events (>31)[21], n (%)	7 (20.0%)		
[a]Percentage of proximal events/total events, %	30.3 (14.7 - 47.1)	31.0 (16.1 - 43.6)‡	0 (0 - 33.3)
[a]Bolus clearance time, s	11.5 (9.0 - 13.0)	11.8 (9.0 - 13.0)	10.5 (5.0 - 15.0)

Results expressed as [a]median (IQR) and number (percentage) for categorical variables.
HRIM, high resolution impedance manometry; MII-pH, 24-hr pH-impedance; UES, upper esophageal sphincter; LES, lower esophageal sphincter; CD, crural diaphragm; IRP, integrated relaxation pressure; DL, distal latency; DCI, distal contractile integral; CCv3.0, Chicago Classification version 3.0; EGJOO, esophagogastric outflow obstruction; IEM, ineffective esophageal motility; TAPG, thoraco-abdominal pressure gradient; IBT, incomplete bolus transit; AET, acid exposure time; TBET, total bolus exposure time (i.e. % of monitored time that the esophagus was exposed to reflux of any nature). ‡p≤0.01 compared with supine, †p<0.001 compared with no. of non-acid reflux events. [X]≡ Reference.

Table 3. Demographics and Clinical Characteristics of IPF patients with various esophageal diagnoses based on CCv3.0

	Normal (n=13)	EGJOO (n=6)	IEM (n=16)
General characteristics			
[b]Age, years	67 (63-71)	66 (58-74)	66 (61-71)
Male:Female ratio	10:3	4:2	13:3
[b]Body mass index. Kg/m^2	29.6 (26.3 - 32.9)	27.8 (22.1 - 33.5)	26.2 (23.8 - 28.7)
[b]Height, m	1.70 (1.65 - 1.74)	1.71 (1.59 - 1.82)	1.72 (1.67 - 1.78)
Medication			
Patients taking PPIs, n (%)	7 (53.8%)	2 (33%)	6 (37.5%)
Patients taking H2R antagonists, n (%)	1 (7.7%)	0	2 (12.5%)
Patients taking anti-fibrotics	6 (46.2%)	2 (33.3%)	5 (31.3%)
Pirfenidone, n (%)	2 (14.4%)	0	3 (18.8%)
Nintedanib, n (%)	4 (30.8%)	2 (33.3%)	2 (12.5%)
Patients taking opiates, n (%)	2 (15.4%)	0	1 (6.3%)
PFTs			
[a]FVC, L	2.5 (2.2 - 3)	2.4 (1.8 - 3.1)	1.8 (1.4 - 2.9)*
[a]FVC, % pred	69 (61 - 72)	70.5 (53 - 77)	48.5 (40 - 67.5) ***#
Patients with FVC ≥80%, n (%)	3 (23.1%)	1 (16.7%)	2 (12.5%)
Patients with FVC 50-80%, n (%)	9 (69.2%)	4 (66.7%)	5 (31.25%)
Patients with FVC ≤50%, n (%)	1 (7.7%)	1 (16.7%)	9 (56.25%)*
[a]FEV_1, L	2.3 (1.9 - 2.5)	2.1 (1.7 - 2.6)	1.6 (1.2 - 2.4)
[a]FEV_1, % pred	75 (68 - 83)	76.5 (62 - 80)	54 (42 - 72.5)***
[a]FEV_1/FVC ratio	0.86 (0.82 - 0.87)	0.85 (0.83 - 0.91)	0.85 (0.82 - 0.89)
[a]TLC, %	55.0 (51.5 - 64)	59.5 (52 - 67)	53.5 (43 - 56)
[a]DLCO, %	36.5 (27 - 51)	31.5 (26 - 37)	28.5 (22 - 33.5)**
Patients require O2 supply, n (%)	5 (38.5%)	2 (33.3%)	10 (62.5%)

Results expressed as either [a]median (IQR) or [b]mean (95% CI), and number (percentage) for categorical variables.
CCv3.0, Chicago Classification version 3.0; EGJOO, esophagogastric outflow obstruction; IEM, ineffective esophageal motility; PPI, proton pump inhibitor; PFTs, pulmonary function tests; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; DLCO, diffusing capacity for carbon monoxide. *** P<0.02, **P≤0.05, *P<0.1 compared with normal motility. ##P≤0.05, #P<0.1 compared with EGJOO.

Table 4. HRIM and MII-pH findings in IPF patient cohort without various esophageal diagnoses based on CCv3.0

	Normal (n=13)	EGJOO (n=6)	IEM (n=16)
HRIM			
[a]UES resting pressure, mmHg	55.5 (45.2 - 83.7)	142.2 (126.0 -162.5)***	82.5 (49.6 - 116.7)##
Patients with normal UES pressure, n (%)	9 (69.2%)	1 (16.7%)	8 (50%)
Patients with hypotensive UES pressure, n (%)	2 (15.4%)	0	1 (6.3%)
Patients with hypertensive UES pressure, n (%)	2 (15.4%)	5 (83.3%)***	7 (43.8%)
Nadir UES residual pressure, mmHg	8.8 (1 - 9.1)	4.2 (1.4 - 13.1)	-0.95 (-4.6 - 4.7)**#
Patients with abnormal nadir UES residual pressure, n (%)	1 (2.9%)	1 (2.9%)	1 (2.9%)
[a]LES resting pressure, mmHg	23.5 (15.6 - 29.8)	48.4 (46.6 - 59.5)****	30.1 (22.1 - 37.2)##
Patients with normal LES pressure, n (%)	9 (69.2%)	1 (16.7%)	14 (87.5%)
Patients with hypotensive LES pressure, n (%)	2 (15.4%)	0	0
Patients with hypertensive LES pressure, n (%)	2 (15.4%)	5 (83.3%)**	2 (12.5%)####
[a]LES inspiratory pressure, mmHg	38.2 (22.7 - 46.0)	59.5 (39.0 - 74.3)	52.2 (35.3 - 68.3)
Patients with LES-CD separation >2cm, n (%)	4 (30.8%)	1 (16.7%)	4 (25%)
[a]Mean IRP, mmHg	10.0 (7.3 - 13.1)	24.6 (22.1 - 28.3)****	8.6 (6.2 - 11.0)####
[a]Median IRP, mmHg	10.1 (6.8 - 14.0)	24.6 (20.3 - 28.2)****	8.6 (5.3 - 11.0)####
[a]DL, s	6.8 (6.3 - 7.8)	7.05 (6.8 - 7.6)	6.7 (6.3 - 7.1)
[a]DCI, mmHg/s/cm	1296.0 (859 - 2130.4)	1212 (620.3 - 1625)	443.3 (215 - 571)****##
TAPG			
[a]Intra-abdominal pressure, mmHg	12.0 (7.7 - 17.3)	10.0 (5.7 - 15.0)	9.5 (4.5 - 14.2)
[a]Intra-thoracic pressure, mmHg	-2.9 (-5.4 - -0.1)	-4.7 (-9.7 - 4.3)	-5.6 (-9.8 - -2.4)
[a]TAPG, mmHg	15.9 (12.6 - 18.6)	11.4 (8.0 - 17.9)	16.0 (12.5 - 18.6)
[a]Adjusted TAPG, mmHg	-24.1 (-33.5 - -8.2)	-40.1 (-65.0 - -28.1)	-35.2 (-50.3 - -21.9)
Bolus transit findings			
Patients with IBT, n (%)	6 (46.2%)	4 (66.7%)	13 (81.3%)*
[a]Swallows with IBT, %	20.0 (0 - 80)	80.0 (8.3 - 100)	80.0 (37 - 100)*
MII-pH			
[a]AET, %	7.1 (3.2 - 8.4)	3.3 (1.6 - 4.5)	4.8 (1.1 - 15.7)
Upright	9.4 (4.8 - 11.5)‡	5.7 (3.1 - 7.9)‡	5.2 (1.6 - 10.0)
Supine	0.7 (0.1 - 5.8)	0.1 (0 - 0.4)	1.0 (0 - 14.8)
Patients with abnormal AET (>6%)[20], n (%)	7 (53.8%)	1 (16.7%)	7 (43.8%)
[a]TBET, %	0.8 (0.5 - 1.5)	0.6 (0.3 - 1.3)	1.2 (0.6 - 2.6)
Upright	1.2 (0.7 - 2.2)‡	0.9 (0.5 - 2.4)‡	1.4 (0.7 - 2.7)‡
Supine	0.1 (0.1 - 0.2)	0.1 (0.1 - 0.1)	0.2 (0.1 - 1.9)
Patients with abnormal TBET (≥1.4)[21], n (%)	6 (46.2%)	1 (16.7%)	8 (50%)
[a]Total no. of events, n	33 (26 - 65)	35 (24 - 53)	45 (33 - 70.5)
Upright	30 (24 - 59)‡	29 (21 - 42)‡	37 (27 - 53)‡
Supine	4 (1 - 6)	4 (2 - 11)	3 (1 - 14)
Acid events (pH≤4)	29 (18 - 46)†	20 (18 - 35)	31 (16.5 - 45.5)†
Non-acid events (pH>4)	15 (8 - 20)	12.5 (6 - 15)	12.5 (6.5 - 22.5)
Patients with abnormal no. of events (>73)[21], n (%)	3 (23.1%)	0	4 (25%)
Patients with abnormal no. of events (>80)[20], n (%)	2 (15.4%)	0	2 (12.5%)
[a]Total no. of proximal events, n	9 (6 - 20)	5.5 (3 - 16)	19 (7.5 - 29)
Upright	8 (6 - 19)‡	6 (3 - 13)‡	13 (6 - 21)‡
Supine	1 (0 - 2)	0 (0)	1 (0 - 5)
Patients with abnormal no. of events (>31)[21], n (%)	3 (23.1%)	0	4 (25%)
[a]Percentage of proximal events/total events, %	29 (18.6 - 38.4)	29.7 (10.8 - 40)	33.0 (17.5 - 48.5)
Upright	30.9 (20.0 - 40.6)	31.4 (11.4 - 43.6)‡	31.8 (18.6 - 52.2)‡
Supine	14.3 (0 - 33.3)	0	16.7 (0 - 42.2)
[a]Bolus clearance time, s	11.5 (9.5 - 16.3)	13 (9 - 13)	11 (9 - 13)
Upright	11.8 (9.5 - 15.0)	13 (10 - 13)	11 (9 - 12)
Supine	11.3 (5.0 - 16.0)	8.5 (3 - 11)	8 (5-14)

Results expressed as [a]median (IQR) and number (percentage) for categorical variables.
HRIM, high resolution impedance manometry; MII-pH, 24-hr pH-impedance; UES, upper esophageal sphincter; LES, lower esophageal sphincter; CD, crural diaphragm; IRP, integrated relaxation pressure; DL, distal latency; DCI, distal contractile integral; CCv3.0, Chicago Classification v3.0; EGJOO, esophagogastric outflow obstruction; IEM, ineffective esophageal motility; TAPG, thoraco-abdominal pressure gradient; IBT, incomplete bolus transit; AET, acid exposure time; TBET, total bolus exposure time (i.e. % of monitored time that the esophagus was exposed to reflux of any nature). ********P<0.005. ***P<0.02, **P≤0.05, *P<0.1 compared with normal motility. ####P<0.005, ###P<0.02, ##P≤0.05, #P<0.1 compared with EGJOO. ‡P<0.05 compared with supine, †P<0.05 compared with non-acid reflux events. [X]≡ Reference