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High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis

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ABSTRACT: **The aim of this prospective study was to determine the prevalence and characteristics of acid gastro-oesophageal reflux (GER) in patients with idiopathic pulmonary fibrosis (IPF).**

Sixty-five consecutive patients with well-defined IPF were subjected to 24-h pH monitoring and oesophageal manometry. A total of 133 consecutive patients with intractable asthma and symptoms of GER were used as comparisons.

The prevalence of abnormal acid GER in IPF patients was 87%, with 76% and 63% demonstrating abnormal distal and proximal oesophageal acid exposures, respectively. Abnormal acid GER was significantly more common in IPF patients than asthma patients. Only 47% of IPF patients experienced classic GER symptoms. Despite treatment with standard doses of proton pump inhibitors (PPIs), 12 out of 19 patients receiving PPIs during the 24-h pH monitoring had abnormal oesophageal acid exposures by pH probe. There was no correlation between IPF severity and acid GER severity.

In conclusion, abnormal acid gastro-oesophageal reflux is highly prevalent, but often clinically occult in patients with idiopathic pulmonary fibrosis. Standard doses of proton pump inhibitors may not suppress the acid gastro-oesophageal reflux in this population. Therefore, further studies are needed to determine if acid abnormal gastro-oesophageal reflux represents an important risk factor for idiopathic pulmonary fibrosis development or progression, and if optimal suppression of acid gastro-oesophageal reflux slows the progression of idiopathic pulmonary fibrosis and/or decreases episodic exacerbations of idiopathic pulmonary fibrosis.

KEYWORDS: **Aspiration, cryptogenic fibrosing alveolitis, gastro-oesophageal reflux disease, idiopathic pulmonary fibrosis, usual interstitial pneumonia**

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Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia [1]. The prevalence of IPF is estimated to range 13.2–20.2 cases per 100,000 people [2]. The aetiology of IPF is unknown and current therapies show little effect on this relentlessly progressive and fatal disease.

The identification of risk factors for IPF might lead to new treatment strategies. Reported risk factors include cigarette smoking [3] and exposure to metal and wood dust [4]. Abnormal acid gastro-oesophageal reflux (GER) may also be a risk factor for IPF [5]. While GER seems to occur in normal individuals, it is estimated that 20–30% of the USA population have excessive GER [6]. GER disease (GERD) has been associated with several respiratory disorders, including chronic bronchitis [7], bronchiectasis [8], diffuse panbronchiolitis [9], recurrent pneumonia [8, 10], chronic cough [11], hoarseness [12], and asthma [13].

Several studies have suggested that IPF may be related to repeated aspiration of gastric contents over long periods of time [14, 15]. Pulmonary fibrosis (PF) has been induced by direct instillation of acid into the airways of animals in experimental models of PF [16–18]. In a pilot study, abnormal acid GER was documented in 16 out of 17 patients with IPF [19]. To better understand the association between acid GER and IPF, a prospective study was undertaken to assess the prevalence and clinical symptoms of GER in a large, carefully defined population of patients with IPF, and the findings were compared to a population of patients with intractable asthma manifesting symptoms of GER.

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METHODS

Consecutive patients who were newly referred to one of the current authors (G. Raghu) for further management of IPF at the interstitial lung disease (ILD) clinic (University of Washington Medical Center, Seattle, WA, USA) during an 18-month period were enrolled. Comparison patients included consecutive patients with intractable asthma and symptoms of GER who were referred specifically for further evaluation of acid GER during the same study period. Acid GER was identified using an ambulatory 24-h oesophageal pH probe. Both an ambulatory oesophageal pH probe study and oesophageal manometry were performed in all patients.

Subjects

A review of clinical information included a recent (*i.e.* within 2 months of entry into the current study) high-resolution computed tomography (HRCT) scan of the chest, all available serial chest radiographs, and all transbronchial lung biopsy or surgical lung biopsy materials. Only patients who met the international consensus statement definition of IPF were enrolled [5]. Any patient with other known causes of ILD, including environmental/occupational exposures, hypersensitivity pneumonitis, inherited disorders (metabolic storage diseases) and collagen vascular diseases, were excluded. Patients who had participated in a previous small pilot study [19] were excluded in this investigation. Comparison patients were patients known to have pre-existing and intractable asthma (uncontrolled by maximal inhaled bronchodilators and inhaled corticosteriods conventionally used, or oral corticosteroids with or without a leukotriene receptor antagonist) who were referred to the gastrointestinal motility clinic (University of Washington, Seattle, WA, USA) for assessment of their co-existing symptoms of GER. The patients were identified through a research database using a search strategy that required the date of the pH probe procedure to fall within the same period of time as the dates of the pH probe procedures in subjects with IPF. The current study received institutional review board approval.

Protocol

All patients with IPF were evaluated using pulmonary function tests (PFTs; *i.e.* spirometry, lung volumes, and the carbon monoxide diffusing capacity of the lung ($D_{L,CO}$)) within 4 weeks of their ambulatory 24-h oesophageal pH probe and oesophageal manometry studies. Patients who were already taking proton pump inhibitors (PPIs) were allowed to continue with this medication as prescribed during the oesophageal pH probe testing. Prior to insertion of the oesophageal pH probe, patients were questioned as to the presence and frequency rate of symptoms potentially related to GER using a standard symptom assessment form.

All patients underwent oesophageal manometry to determine the position of the upper oesophageal sphincter (UOS) and the position, length, pressure, percentage relaxation, and relaxation duration of the lower oesophageal sphincter (LOS). The oesophageal manometer was also used to record characteristic features of oesophageal peristalsis. Oesophageal pH monitoring was performed using a Zinetics 24ME multi-use pH catheter (Medtronic, Shoreview, MN, USA). Each catheter contained either two or four monocrystalline antimony electrodes, calibrated prior to each procedure in pH 7.0 and 1.0 buffer solutions at 37°C. In each subject, the catheter was inserted through the nose into the oesophagus and positioned by oesophageal manometry. In 44 IPF patients, a two-electrode catheter was positioned such that the distal pH sensor was located 5 cm rostral to the LOS and the proximal pH sensor 15 cm rostral to the LOS. In 21 IPF patients, the proximal pH sensor of a four-electrode catheter was positioned 2 cm above the UOS with the distal pH sensor 13 cm caudal to the UOS. All patients with asthma were tested with the same two-electrode style catheter.

Subsequently, the pH electrodes were connected to a portable digital data recorder (Mark III Gold; Medtronic), which stored pH data every 4 s for up to 24 h. Patients were allowed to be ambulatory *ad libitum* at home and instructed to record meal and sleep times, the time of any gastro-intestinal or pulmonary symptoms (such as heartburn or regurgitation), their daily routines and other symptoms while the catheter was in place for a duration of 20–24 h. Patients returned the next day and the catheters were removed.

Abnormal distal oesophageal acid exposure was defined by a pH of <4 for $\geqslant 4.5\%$ of the total time by the most distal pH sensor [20]. Abnormal proximal oesophageal acid exposure was defined by a pH of <4 for $\geqslant 1\%$ of the total time by the most proximal pH sensor [20]. Symptoms with reflux episodes involving either distal or proximal pH sensors if the pH dropped to <4 within the preceding 2 min were considered to correlate with acid GER [21].

Statistical analysis

The Chi-squared test was used to compare differences in proportions and a paired t-test or Wilcoxon rank-sum test was used to compare differences in means or medians as appropriate for the distribution. The association between percentage reflux time and PFT results was assessed using linear regression and the Spearman rank correlation test.

RESULTS

A total of 65 patients, who were newly referred for further management of IPF, met the criteria for IPF diagnosis and were enrolled in the current study. In the appropriate clinical setting, 49% of patients had surgical lung biopsy and HRCT features of usual interstitial pneumonia (UIP) pattern [22]. The remaining patients had HRCT features of UIP pattern and fulfilled all the major and minor criteria for the diagnosis of IPF [5]. The median age of the present subjects with IPF was 62 yrs. The majority of patients were male (63%), Caucasian (89%) and suffered from moderate-to-severe restrictive lung disease (table 1). None of the patients with IPF had obstructive airway disease, emphysema (*i.e.* forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio <0.65, residual volume $\geqslant 120\%$ predicted) or a positive bronchodilator response (*i.e.* a 12% increase, calculated from the pre-bronchodilator value, and a 200-mL increase in either FVC or FEV_1).

In total, 46 (71%) IPF patients were not receiving PPI therapy at the time of study (table 1; fig. 1). The prevalence of abnormal acid GER in this sample was 87%. Twelve (63%) of the patients on standard doses of PPI (20–40 $mg \cdot day^{-1}$ of omeprazole) at

TABLE 1 Characteristics of patients with idiopathic pulmonary fibrosis

Characteristics	
Subjects n	65
Age yrs	
Mean	60.7
Median	62 (20–85)
Males %	63
Ethnicity %	
Caucasian	89
American Indian	5
African American	2
Hispanic	2
Other	2
Tobacco use %	
Current smokers	5
Ex-smokers	65
Never-smokers	30
Smoking pack-yrs#	36.3±29.5
Method of diagnosis¶ %	
Major and minor criteria	51
Surgical lung biopsy and major criteria	49
IPF therapy %	
Prednisone and azathioprine+	48
Prednisone and pirfenidone	7
Prednisone and cyclophosphamide	3
Prednisone alone	19
Other	6
None	17
Anti-GER therapy %	
Proton pump inhibitor	29
H_2 blocker therapy	14
Pulmonary function tests	
FEV_1	
$L \cdot s^{-1}$	1.97±0.65
% pred	65
FVC	
$L \cdot s^{-1}$	2.41±0.89
% pred	62
TLC	
L	3.75±1.20
% pred	63
$D_{L,CO}$§	
$mL \cdot min^{-1}$	9.95±4.32
% pred	36

Data are presented as n, mean±SD, median (range) and %. IPF: idiopathic pulmonary fibrosis; GER: gastro-oesophageal reflux; FEV_1: forced expiratory volume in one second; % pred: % predicted; FVC: forced vital capacity; TLC: total lung capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung. #: tobacco users only; ¶: in accordance with the international consensus statement definition of IPF [5]; +: five patients were additionally treated with cyclosporine; §: corrected for haemoglobin.

the time of their oesophageal pH probe study continued to have elevated oesophageal acid exposures. Among the subjects not on PPIs at the time of study, 63% exhibited abnormal

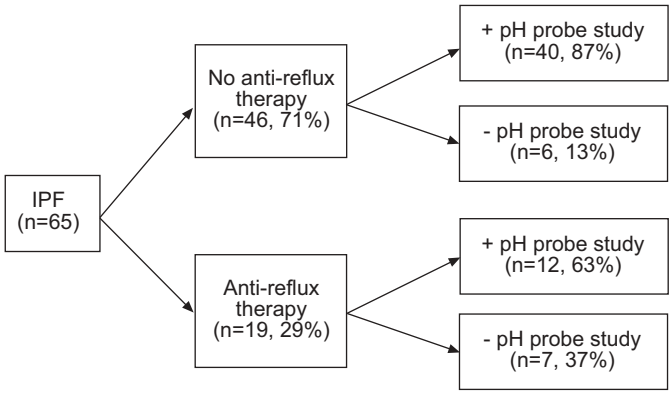

FIGURE 1. Prevalence of acid gastro-oesophageal reflux (87%) in patients with idiopathic pulmonary fibrosis (IPF) with and without proton pump inhibitor therapy at the time of the pH probe study. This is a conservative estimate based on 46 subjects not receiving anti-reflux therapy at the time of pH probe study. +: positive; -: negative.

proximal GER, and 76% exhibited abnormal distal GER (table 2). The percentage of patients that demonstrated either abnormal distal or proximal oesophageal acid exposure did not vary significantly according to the type of oesophageal pH probe used. The mean percentage of time that subjects exhibited abnormal acid GER in the proximal and distal oesophagus was 3.4% and 9.6%, respectively. Abnormal acid GER occurred in both the upright and supine positions (table 2). There was no correlation between the severity of acid GER measured by percentage proximal and distal reflux time, and severity of IPF measured by PFTs (fig. 2).

During the same study period, 133 patients with intractable asthma who were specifically studied to observe acid GER served as comparison patients. None of the asthma patients

TABLE 2 Results of ambulatory oesophageal pH probe studies in IPF patients and a comparison population of asthma patients referred for pH probe study due to symptoms of GER

Parameter	IPF#	Asthma#	p-value
	Mean±SD	Mean±SD	
Acid GER %	87±34	68±47	0.014*
Proximal GER %	63±49	61±49	0.80
Distal GER %	76±43	57±50	0.020*
Proximal time %	3.4±4.6	3.4±5.7	0.96
Distal time %	9.6±7.8	7.4±8.3	0.12
Distal upright time %	11.7±9.5	9.2±10.7	0.16
Distal supine time %	6.1±10.1	5.9±12.8	0.94
DeMeester score	35.6±28.4	30.4±34	0.36

GER: gastro-oesophageal reflux; IPF: idiopathic pulmonary fibrosis. #: subjects not on proton pump inhibitor therapy at the time of their oesophageal pH probe study (IPF patients: n=46, except for distal upright time, distal supine time and DeMeester score where n=44; asthma patients: n=133, except for DeMeester score where n=131). *: $p<0.05$.

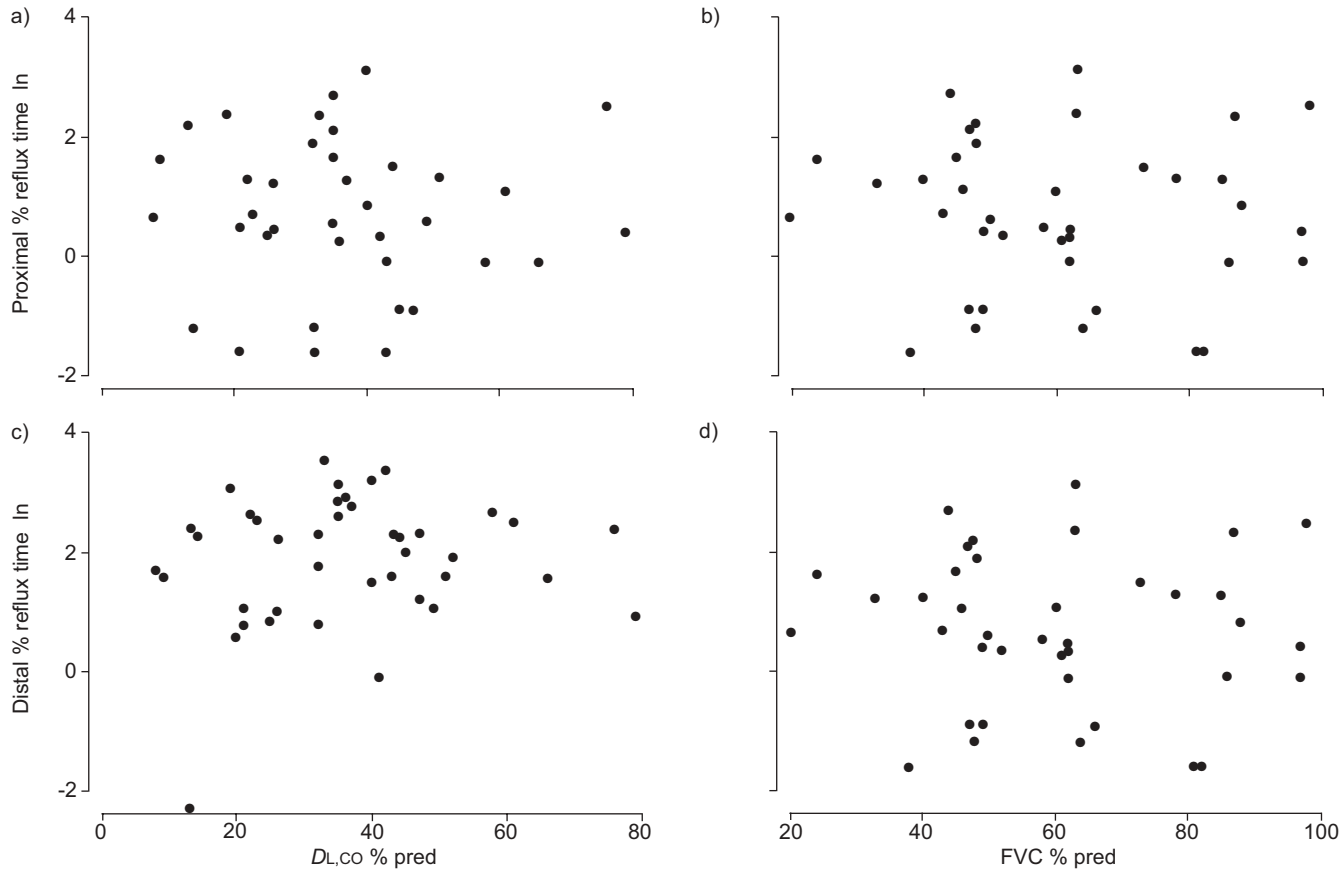

FIGURE 2. There was no correlation between severity of gastro-oesophageal reflux, quantified as the percentage proximal (a, b) or distal reflux time (c, d), and the severity of idiopathic pulmonary fibrosis. $D_{L,CO}$: carbon monoxide diffusion capacity of the lung; % pred: % predicted; FVC: forced vital capacity.

were taking PPIs during the 24-h pH probe testing. These patients were, however, not matched to the IPF population with respect to age and sex. In keeping with the known clinical profile, the patients with asthma were relatively younger than patients with IPF (data not shown). The prevalence of acid GER in this population was 68%, which is significantly lower than in the IPF patients ($p=0.014$; table 2) and consistent with other reported values [23]. Patients with IPF were more likely to have distal GER than the subjects with asthma (76% *versus* 57%; $p=0.020$). However, there was no difference in the prevalence of proximal reflux between the two groups (63% *versus* 61%; $p=0.80$).

Although the vast majority of patients with IPF had abnormal acid GER, only 47% exhibited symptoms of GER (table 3). Seventy-eight per cent of subjects had at least one symptom suggestive of GER. The most common complaints were belching (51%) and heartburn (47%). This is, however, higher than that observed in a previous pilot study, since 25% of the 16 out of 17 patients with IPF had symptoms of GER [19].

The results from the oesophageal manometry are reported in table 4. Mean LOS length, pressure and percentage relaxation of IPF patients were within the normal range [24]. Although abnormal peristaltic waves (simultaneous waves) were rarely documented (representing, on average, 9.7% of recorded peristaltic activity), the majority of subjects with IPF had normal peristaltic activity.

When comparing the PFTs in IPF patients with abnormal acid GER to those values obtained in IPF patients with normal oesophageal acid exposures, no significant difference was found (table 5).

DISCUSSION

Although GER has been associated with a variety of respiratory disorders, this is the first prospective study demonstrating a very high prevalence of abnormal acid GER in a large number of patients with well-defined IPF. In a study of 48 patients with radiographic evidence of PF of unknown aetiology, MAYS *et al*. [14] reported a higher prevalence of GER by contrast radiographic upper gastrointestinal series. RAIHA *et al*. [25] performed oesophageal pH probe studies in 137 elderly patients (aged >60 yrs) with abdominal complaints and noted that bilateral scarring of the lung parenchyma on chest radiograph was significantly more common in patients with acid GER. Recently, EL-SERAG and SONNENBERG [26] compared USA military veterans with and without erosive oesophagitis or oesophageal stricture and, in a multivariate logistic regression model, found a significant association between the presence of one of these disorders and the presence of PF. While previous studies have suggested an association between GER and PF, the current study is the first prospective study to identify acid GER by 24-h pH probe technology in patients with well-defined IPF and compare the prevalence with asthma patients who are at risk of acid GER.

TABLE 3 Symptoms of gastro-oesophageal reflux in subjects with idiopathic pulmonary fibrosis[#]

Symptom	Mean score[¶]	Score ⩾1 %
Classic GERD symptoms		47
Heartburn	1.5±1.4	45
Regurgitation	0.6±1.1	16
Any GERD symptoms		78
Abdominal pain	0.3±0.9	7
Aspiration	0.5±0.9	15
Belching	1.9±1.9	51
Bloating	0.9±1.4	27
Chest pain	0.9±1.3	24
Choking	0.4±0.9	13
Globus	0.5±1.3	13
Hoarseness	1.2±1.3	31
Liquid dysphagia	0.2±0.7	7
Solid dysphagia	0.5±1.1	16
Odynophagia	0.2±0.7	4
Nausea	0.4±0.9	13

Data are presented as mean±SD, unless otherwise stated. GERD: gastro-oesophageal reflux disease. [#]: n=55; [¶]: 0=never, 1=once per month, 2=once per week, 3=once daily, 4=several times per day.

TABLE 4 Oesophageal manometry in subjects with idiopathic pulmonary fibrosis

Parameter	Subjects n	Mean±SD	Normal values/ ranges
LOS length cm	40	3.0±0.7	3
LOS abdominal length cm	40	3.4±5.7	2
LOS pressure mmHg	41	13.7±7.6	10–45
LOS relaxation %	40	99.9±0.3	>90
LOS relaxation duration s	37	5.0±2.0	>5
Peristalsis %	41	88.2±24.1	>80
Simultaneous waves %	39	9.7±23.8	0
Dropped waves %	39	3.3±6.7	<30
Maximum distal amplitude mmHg	42	86.9±46.8	60–140
Maximum proximal amplitude mmHg	42	57.8±27.7	35–95

LOS: lower oesophageal sphincter.

TABLE 5 Pulmonary function tests of idiopathic pulmonary fibrosis (IPF) patients with and without gastro-oesophageal reflux (GER)[#]

Parameter	GER present		GER absent		p-value
	Mean±SD	Subjects n	Mean±SD	Subjects n	
FEV_1					
$L \cdot s^{-1}$	2.0±0.7	39	1.5±0.4	6	0.11
% pred	64±20	39	60±20	6	0.69
FVC					
$L \cdot s^{-1}$	2.5±0.9	39	1.7±0.4	6	0.07
% pred	61±20	39	53±20	6	0.40
FEV_1/FVC	0.82±0.07	39	0.88±0.09	6	0.057
TLC					
L	3.8±1.4	36	3.2±0.45	4	0.37
% pred	62±21	36	66±21	4	0.72
$D_{L,CO}$[¶]					
$mL \cdot min^{-1}$	10.4±4.7	37	6.2±2.5	5	0.057
% pred	38±17	37	25±11	5	0.12

FEV_1: forced expiratory volume in one second; % pred: per cent of normal predicted value; FVC: forced vital capacity; TLC: total lung capacity; $D_{L,CO}$: carbon monoxide diffusing capacity of the lung. [#]: IPF subjects not receiving proton pump inhibitor therapy at the time of their oesophageal pH probe study only; [¶]: corrected for haemoglobin.

The prevalence of abnormal acid GER in the current IPF patients was 87%. This value is consistent with that observed in a previous pilot study (n=17) [19]. In the study by TOBIN *et al*. [19], abnormal acid GER was reported in 16 out of 17 IPF patients who were not taking PPIs at the time of the pH probe studies. In the present study, patients receiving PPIs were included; the current findings should, therefore, be considered as a conservative estimate. The comparison population used was expected to have a high prevalence of acid GER, *i.e.* patients with intractable asthma and presence of GER symptoms. As a matter of routine, the asthma patients who were taking PPIs were asked to withhold this medication during the 24-h period of testing. Considering the significant association between asthma and abnormal acid GER is well known [13] and that all patients with asthma in the present study had symptoms of GER, IPF patients had a significantly higher prevalence of acid GER than the asthma patients using pH probe testing. Furthermore, 63% of IPF patients treated with standard doses of PPIs (20–40 $mg \cdot day^{-1}$ of omeprazole) at the time of the oesophageal pH probe studies demonstrated persistently elevated oesophageal acid exposures. This ''response'' rate to PPIs is substantially lower than that reported for other populations of patients with acid GER [6]. While it is unclear why patients with IPF might be physiologically resistant to standard doses of PPIs, the current findings suggest that patients might require higher doses of medical therapy and follow-up studies to document adequacy of treatment with PPIs, and a need for fundoplication in a subgroup of patients with IPF.

In the vast majority of patients with IPF, the abnormal acid GER was clinically occult as less than half of the patients exhibited symptoms of GER. This is consistent with data from other studies of patients suspected of chronic aspiration, including that by PELLEGRINI *et al*. [27], where ~50% of 48 patients suspected of pulmonary aspiration reported a history of ''heartburn''. These findings suggests that all IPF patients with or without apparent symptoms of GER should be evaluated with an oesophageal pH probe to detect clinically silent acid GER and address adequate treatment for acid GER independent of IPF treatment.

While the current study confirms that abnormal acid GER is highly prevalent in patients with IPF, the precise nature of this relationship is uncertain. The current study was not designed to investigate the possibility of a causal association between acid GER and IPF; however, the data supports a long-standing hypothesis that acid GER causes or contributes to the development or progression of PF through recurrent exposure of the pulmonary parenchyma to the acidity of the refluxed contents. An alternative explanation is that acid GER may be a sequelae of physiological perturbations associated with advanced fibrotic lung disease. In normal humans, pleural pressure swings associated with respiration are greater nearer the lung bases than at the lung apices [28, 29]. Decreased lung compliance in IPF patients may result in more negative pleural pressures during inspiration and, possibly, exaggerated swings in pleural pressure [30]. Since the pleural pressure is transmitted directly to the oesophagus, these physiological derangements may contribute to oesophageal or LOS dysfunction. It can be speculated that the permanently open LOS (due to the fibrotic lung) may explain why PPI therapy was of little effect in IPF patients compared with asthma patients. Further studies are indicated to establish and clarify the cause–effect relationship of the comorbid association of acid GER in IPF.

No correlation between the severity of IPF and the severity of acid GER was found. If reductions in lung compliance associated with IPF induced GER, a positive correlation would be anticipated. In fact, when comparing patients with and without abnormal acid GER, subjects without acid GER had lower mean values for FVC and $D_{L,CO}$ (table 5). However, the small number of patients with normal pH monitor results (n=6) in the present study precludes definitive conclusions.

Current concepts in the pathogenesis of IPF implicate epithelial–fibroblast interactions as a result of repeated insults to the lung parenchyma by a noxious stimulus over a long period of time, thus causing PF [10]. The nature of the triggering and/or recurrent injury to the lung is unknown. Based on the very high prevalence of acid GER in IPF, we hypothesise that chronic micro-aspiration of acid droplets associated with GER causes or contributes in part to the recurrent insults to the lung and development or progression of IPF. Considering that the prevalence of acid GER is much higher in the general population than the prevalence of IPF, an as yet undetermined genetic predisposition seems to be necessary for the lungs from such susceptible patients to become fibrotic and for patients to manifest IPF.

Additionally, the study was not designed to detect the presence of gastric contents in the lung parenchyma or airways of the current IPF subjects. It must be noted that while acid GER was significantly more common in the current IPF subjects than the high-risk population of patients with intractable asthma, the prevalence of proximal acid GER was not significantly different between the two populations. It is unclear whether this finding argues against the hypothesis that acid GER induces PF or whether it is simply a reflection of the limitations of the sample size or the sensitivity of the ambulatory 24-h oesophageal pH probe for detecting proximal reflux and pulmonary aspiration. The current study is limited by the lack of an ideal control population with which to compare the present IPF subjects. The ideal control population would consist of age- and sex-matched normal subjects and/or subjects with nonfibrotic lung disease. However, the relatively younger asthma population used as a comparison group for this study represents a clinically relevant population for validating the oesophageal pH probe. Another potential limitation of the present study is that it was conducted in one tertiary centre with recognised expertise in the management of IPF and GERD.

In summary, it was demonstrated that abnormal acid gastro-oesophageal reflux is highly prevalent in a large and well-defined population of patients with established idiopathic pulmonary fibrosis. The majority of patients with idiopathic pulmonary fibrosis are asymptomatic for acid gastro-oesophageal reflux. In addition, the majority of idiopathic pulmonary fibrosis patients on standard doses of proton pump inhibitors have persistently abnormal acid gastro-oesophageal reflux. Acid gastro-oesophageal reflux may represent an important risk factor and contribute, in part, to the relentless progressive nature of idiopathic pulmonary fibrosis. Further studies are indicated to clarify if there is a cause–effect relationship between idiopathic pulmonary fibrosis and acid gastro-oesophageal reflux, and to determine if optimal control of acid gastro-oesophageal reflux has a role in the treatment of idiopathic pulmonary fibrosis.

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REFERENCES

1 Carrington CB, Gaensler EA, Coutu RE, Fitzgerald MX, Gupta RG. Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med* 1978; 298: 801–809.
2 Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med* 1994; 150: 967–972.
3 Baumgartner KB, Samet J, Stidley CA, Colby TV, Waldron JA. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1997; 155: 242–248.
4 Baumgartner KB, Samet JM, Coultas DB, *et al.* Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case control study. *Am J Epidemiol* 2000; 152: 307–315.
5 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000; 161: 646–664.
6 Pope CE. Acid-reflux disorders. *N Engl J Med* 1994; 331: 656–660.
7 Ducolone A, Vandevenne A, Jouin H, *et al.* Gastro-esophageal reflux in patients with asthma and chronic bronchitis. *Am Rev Respir Dis* 1987; 135: 327–332.
8 Davis MV. Relationship between pulmonary disease, hiatal hernia, and gastro-esophageal reflux. *NY State J Med* 1972; 72: 935–938.
9 Matsuse T, Oka T, Kida K, Fukuchi Y. Importance of diffuse aspiration bronchiolitis caused by chronic occult aspiration in the elderly. *Chest* 1996; 110: 1289–1293.

10 Perrin-Fayolle M. Gastroesophageal reflux and chronic respiratory disease in adults: influence of surgical therapy. *Clin Rev Allergy* 1990; 8: 457–469.
11 Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990; 141: 640–647.
12 Wiener GJ, Koufman JA, Wu WC, Cooper JB, Richter JE, Castell DO. Chronic hoarseness secondary to gastroesophageal reflux disease: documentation with 24-h ambulatory pH monitoring. *Am J Gastroenterol* 1989; 84: 1503–1508.
13 Sontag SJ, O'Connell S, Khandelwal S, *et al.* Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. *Gastroenterology* 1990; 99: 613–620.
14 Mays EE, Dubois JJ, Hamilton GB. Pulmonary fibrosis associated with tracheobronchial aspiration. *Chest* 1976; 69: 512–515.
15 Pearson JE, Wilson RS. Diffuse pulmonary fibrosis and hiatus hernia. *Thorax* 1971; 26: 300–305.
16 Popper H, Juettner F, Pinter J. The gastric juice aspiration syndrome (Mendelson syndrome). Aspects of pathogenesis and treatment in the pig. *Virchows Arch A Pathol Anat Histopathol* 1986; 409: 105–117.
17 Teabeut JR. Aspiration of gastric contents. An experimental study. *Am J Pathol* 1952; 28: 51–62.
18 Mitsuhashi T, Masayoshi S, Chanoki Y, Kuwahara H, Sakai T, Masuda H. Experimental pulmonary fibrosis induced by trisodium citrate and acid-citrate-dextrose. *Exp Mol Pathol* 1985; 42: 261–270.
19 Tobin RW, Pope CE 2nd, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998; 158: 1804–1808.
20 Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol* 1993; 88: 25–29.
21 Lam HG, Breumelhof R, Roelofs JM, Van-Berge-Henewen, Smout AJ. What is the optimal window in symptom analysis of 24-hour esophageal pressure and pH data? *Dig Dis Sci* 1994; 39: 402–409.
22 American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277–304.
23 Harding SM, Guzzo MR, Richter JE. The prevalence of gastroesophageal reflux in asthma patients without reflux symptoms. *Am J Respir Crit Care Med* 2000; 162: 34–39.
24 Bremner RM, Costantini M, DeMeester TR, *et al.* Normal esophageal body function: a study using ambulatory esophageal manometry. *Am J Gastroenterol* 1998; 93: 183–187.
25 Raiha I, Manner R, Hietanen E, Hartiala J, Sourander L. Radiographic pulmonary changes of gastro-oesophageal reflux disease in elderly patients. *Age Ageing* 1992; 21: 250–255.
26 El-Serag HB, Sonnenberg A. Comorbid occurrence of laryngeal or pulmonary disease with esophagitis in United States military veterans. *Gastroenterology* 1997; 113: 755–760.
27 Pellegrini CA, DeMeester TR, Johnson LF, Skinner DB. Gastroesophageal reflux and pulmonary aspiration: incidence, functional abnormality, and results of surgical therapy. *Surgery* 1979; 86: 110–119.
28 D'angelo E, Sant'Ambrogio G, Agostoni E. Effect of diaphragm activity of paralysis on distribution of pleural pressure. *J Appl Physiol* 1974; 37: 311–315.
29 Roussos CS, Fixley M, Genest J, *et al.* Voluntary factors influencing the distribution of inspired gas. *Am Rev Respir Dis* 1977; 116: 457–467.
30 Brennan NJ, Morris AJR, Green M. Thoracoabdominal mechanics during tidal breathing in normal subjects and in emphysema and fibrosing alveolitis. *Thorax* 1983; 38: 62–66.