Author's response to reviews

Title: The Prevalence of Gastro-Esophageal Reflux Disease and Esophageal Dysmotility in Chinese Patients with Idiopathic Pulmonary Fibrosis

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Author's response to reviews: see over
1 Reviewer's report
Title: The Prevalence of Gastro-Esophageal Reflux Disease and Esophageal Dysmotility in Chinese Patients with Idiopathic Pulmonary Fibrosis
Version: 2 Date: 14 April 2014
Reviewer: Jeffrey Swigris
Reviewer's report:
Congratulations on completing your work. The topic of the association between GERD and IPF is an interesting one that merits additional investigation.
Thank you for your suggestion.
Major Compulsory Revisions:
1. The investigators excluded patients with coronary artery disease, HTN or DM--comorbid conditions extremely common among patients with IPF. Doing so, further decreases (in addition to the single-center cohort) the ability to generalize results to the larger IPF universe. As a reader, I would like to see two things in regard to this: 1) mention of this in the "limitations" section of the Discussion; and 2) a flow diagram detailing exactly how many potential subjects were approached for consideration for inclusion, and how many were excluded and for what reason(s).
Between July 2011 and July 2013, 346 patients undertook both HRiM and MII/pH, 88 of them with IPF, 19 of them also with coronary artery disease, diabetes and connective tissue disease so only 69 patients were enrolled. The life signs of all 346 patients were stable but in some severe patients who need inspired oxygen, we decided that they should not undertake the procedure. Whilst this means there is somewhat of a selection bias for patients at the mild end of the IPF spectrum, we felt justified to use these inclusion criteria on grounds of patient safety and to exclude the contributions of other underlying diseases (such as connective tissue disease) to oesophageal motility.
2. The timing between FVC/DLCO ascertainment and the esophageal studies needs to be stated.
We acknowledge this point and have adjusted in the paper.
Mise K et al. reported lower DLCO in patients with recently diagnosed GERD in comparison with healthy controls. Bonacin et al. showed statistically significantly increasing FVC in the GERD group in comparison with the non-GERD group. Among the GERD group, values of DLCO and DLCO/VA were significantly lower and intrapulmonary shunt was significantly higher in comparison with the non-GERD group, confirming the correlation between GERD and damaged lung function. Their results suggest an additional pathological mechanism-development of intrapulmonary shunts due to the microatelectasis resulting from surfactant damage caused by micro-aspiration of stomach contents. They both stated the need for early lung function testing in all GERD patients.


3. Please describe what the normal saline swallows and synthetic gel swallows are used for. Does this confirm position of the catheters? Remember, there will be plenty of pulmonologists interested in this study, and enough information should be given so that the study could be repeated.

Measurements of oesophageal physiology have been standardized in recent years so that acquired data is comparable across sites and between research studies. The standardized protocol (Chicago Classification) requires each patient to swallow 10 x 5ml liquid boli (1 swallow per minute approximately) in order to assess parameters of normal peristalsis. Saline is used (as opposed to water) as it increases the signal detected by the electric impedance electrodes which track bolus transit. As liquid is relatively easy to clear for most people, an additional ‘peristaltic challenge’ is often used by swallowing a viscous gel which better resembles normal food. This can often reveal abnormalities in peristalsis that are not seen with liquid.

4. From where do the normal values come? Are these normal for the catheter
manufacturer in Aurora, Colorado, or are these normal for the Chinese population? If they are not normal for the Chinese, then this should be mentioned as a limitation.

Normal HRiM values are from our study between 2010 and 2011 (in press).
Normal MII/pH is from USA reference [10].

5. How much does the PPI rebound effect have after three days? The possibility that this could have influenced results should be made explicit and commented on in the Discussion.

We have confirmed that 3-days of PPI was a typographic error in the text, patients were at least 7 days off PPI and H2 receptor antagonist and 3 days off β receptor agonist, aminophylline, and nitrates. 186 Patients that saw pulmonologists in our hospital first with the main symptom cough had not had PPI’s before attending EFT.

From the patient cohort, there were 20 patients with cough and typical reflux symptom using PPI prescribed by gastroenterologists, but they did not have IPF.

6. Please spell out specific criteria used to define “GERD+”…the reference alone is not satisfactory.

Patients were divided into GERD+ and GERD- groups according to the results of 24-hour pH monitoring (presenting an abnormal acid exposure time and/or a positive symptom association probability index) [10], and without evidence of motility disorders according to Chicago classification criteria (achalasia, distal esophageal spasm, jackhammer esophagus) [8]. Abnormal upright (≥6.3%) or recumbent (≥1.2%) or total (≥4.2%) acid exposure time and/or Demeester score higher than 14.7.

7. Statistical Methods: a) which correlation coefficient was used in correlation analyses? b) In Table 2, the p value for “Peristalsis” is 0.020; and although the poor format of the table makes it difficult to discern, I believe there is a 3x2 table analyzed for “Peristalsis.” If this is true, the correct analysis would thus be a Cochrane Mantel Haenszel test and not a chi-square. This should be added to the Methods section.

We have deleted the correlation analyses and re-formatted the table in this version.
8. The first mention of sensitivity and specificity are in the Discussion. These values should be stated in the Results section. Furthermore, positive and negative predicted values would be helpful.

We have computed the sensitivity, specificity, PPV and NPV in this version and added to the results section.

9 What do breaks (either large or small) in peristalsis signify?

The oesophagus comprises striated muscle in the proximal third of oesophageal body and smooth muscle in the distal two-thirds. Where these two types of muscle meet there is a ‘transition zone’ which can lead to a ‘break’ in the peristaltic wave as it travels distally. This occurs in health, but it has been shown that if this break is greater than 2cm, this can lead to the bolus not being completely transported and cleared into the stomach. In patients with weak peristalsis these breaks can often be characterized as small (2-5cm) or large (>5cm). It has been demonstrated that among healthy volunteers weak peristalsis of the esophageal body predicted incomplete bolus clearance [24] and may account for delayed bolus transit and impaired esophageal reflux clearance in patients with GERD [25, 26]. In addition, weak peristalsis with large breaks is associated with high acid exposure and delayed reflux clearance in the supine position in GERD patients [26].


10. Line 144: “The significant differences were…” To what are the authors
referring? Do they mean values from the GERD+ group versus the GERD-group?

We have modified this to make more clear.

11. Pulmonologist readers will want to see the correlation between pulmonary function (both FVC and DLCO) and esophageal parameters (motility and reflux).

In our study, oesophageal function parameters in IPF patients with GERD did not correlate with worsened pulmonary function (FVC or DLCO). We also did not find the significant correlation in our research between FVC or DLCO and motility or reflux. This may be due to the relatively small numbers used in the study (when comparing quite variable parameters as the study was not powered to detect these changes) and the inclusion of IPF patients at the milder end of the spectrum.

12. Do these modalities give one the ability to detect hiatal hernia? If so, then the # of subjects with HH should be stated.

HRiM can show detect the presence of a hiatus hernia by observing a double high pressure zone at the oesophageal-gastric junction. The lower high pressure zone represent the crural diaphragm contraction during inspiration whereas the more proximal high pressure zone represent the true LOS. The size of the gap between the two high pressure zones allows you to determine the size of the hiatus hernia. This finding is some time intermittent in patients with a sliding hiatus hernia, however, we saw convincing evidence of a hiatus hernia in 7 IPF patients.

13. Can the authors add to the discussion (lines 192-196) by stating how those results should influence our thinking in terms of the upper esophagus and risk for aspiration in particular.

Our research showed patients with IPF did have more esophageal proximal reflux and poor esophageal peristaltic and clearance function which increases the possibility of reflux aspiration into the airways, especially in the GERD+ group. Therefore we believe that chronic micro-aspiration may play role in the pathobiology of IPF.
14. A very important variable missing from Table 1 is the # of subjects on PPI for the GERD+ and GERD-groups. Then, a discussion of those results (whatever they are) is needed in the Discussion section.

This has been added to the manuscript.

15. Table 4 is almost impossible to interpret in its current form and should be reformatted.

Thank you for your suggestion we have re-formatted this.

16. The discussion of the Table 4 results is inadequate: tell the reader the take-away message and how this information helps us in further sorting out the association between the esophagus and IPF.

The take away message from this study is that patients with IPF have a higher prevalence of oesophageal dysfunction than non-IPF patients and this dysmotility worsened in the presence of reflux thus supporting the role of both factors in IPF.

17. The figures are generally unhelpful.

We have deleted the figure in this version.

Minor Essential Revisions:

1. Several grammatical errors throughout the manuscript (e.g., line 61: first use of "EFT" is not spelled out; Table 1 "Heartburn" is misspelled).

We acknowledge this point and have adjusted in the paper.

Discretionary Revisions:

1. I am surprised there is no pulmonologist on the author line (or one acknowledged for having read the paper prior to submission). Since this paper is likely to be read by pulmonologists (perhaps more pulm than gastro), it may be worthwhile to consider this, since there is a perspective that merits consideration.

We acknowledge this point and have adjusted in the paper in the section of acknowledgements. For many pulmonologists advised patients with cough symptoms to take HRiM and MII/pH now, even more than gastroenterologist in our hospital for patients with typical reflux symptom for gastroenterologists advised endoscopy first.
Reviewer's report

Gao et al. present a prospective case series of esophageal function tests in 69 patients with IPF. There are other studies showing the high prevalence of GERD in these patients. The authors could fill some blanks in the literature by discussing their findings from the point of view of an esophageal physiologist.

Thank you for your suggestion.

Major Compulsory Revisions

1) According to the findings, the esophagogastric barrier is normal in patients with GERD +. In consequence, is GERD secondary to an increased transdiaphragmatic pressure gradient and not the primary cause for IPF? Please discuss.

LES pressure has been shown to be lower in GERD patients when compared to controls but this is by no means the only mechanism by which reflux occurs. Factors such as inappropriate transient lower oesophageal sphincter relaxations mediated by vagal hypersensitivity play a major role in reflux events also but we cannot measure these with conventional ambulatory testing. So whilst IPF had normal LESP and UESP, the LESP and UESP level are indeed lower in comparison with those of 62 healthy volunteers (done between 2010 and 2011). In addition, 7 patients showed hiatal hernia, and 13 patients with IPF had hypotensive LES (LESP<10 mmHg). In the present study, abnormal proximal exposure was commonly observed in patients with IPF and may be associated with microaspiration.

2) What was the contribution of MII-pH in the study? How many patients had
abnormal non-acid reflux and normal acid reflux?

Thank you suggestion. We have added a new table (3) now. MII-pH was used to diagnose GERD, with abnormal acid exposure time, and measure distal reflux (5cm above LEs) and proximal reflux events (15cm above LES) and is now considered the gold standard for reflux testing. Impedance can detect the number of non-acid and acid reflux. 23 patients had abnormal distal non-acid reflux and normal acid reflux, 22 patients had abnormal proximal non-acid reflux and normal acid reflux.

Minor Essential Revisions

1) Figures are not contributory.

We acknowledge this point and have adjusted in the paper.

2) Table 4 is not clear

We acknowledge this point and have adjusted in the paper.

3) et al., not et al

We acknowledge this point and have adjusted in the paper.
This is a good paper describing detailed characterisation of state-of-the-art esophageal physiology measurements in a cohort of Chinese patients with IPF. The paper illustrates the different parameters measured by different techniques and the associations (or lack of) between them, and highlights that "typical" GERD symptoms are poor markers of abnormal esophageal physiology in IPF.

Thank you for your suggestions.

Major corrections (compulsory)

The authors should define early in the paper what they define as “gastro-esophageal reflux disease”, “GERD+” and “GERD-“. I presume the definition is based on 24h esophageal pH.

Patients were divided into GERD+ and GERD- groups according to the results of 24-hour pH monitoring (presenting an abnormal acid exposure time and/or a positive symptom association probability index) [10], and without evidence of motility disorders according to Chicago classification criteria (achalasia, distal esophageal spasm, jackhammer esophagus) [8]. Abnormal upright (≥6.3%) or recumbent (≥1.2%) or total (≥4.2%) acid exposure time and/or Demeester score higher than 14.7.

Comment on the validity of the various “normal values” described in the text and tables. What is the normal population and how does it compare to the demographics (especially older age) of the IPF population?

We had normal values from 62 healthy volunteers done between 2010 and 2011, and the problem is the healthy volunteers were younger than patients with IPF.

The normal values of MII/pH are from USA.
A validated questionnaire with typical symptoms defined as heartburn, regurgitation, chest pain and atypical symptoms such as cough, dyspnea on exertion, belch, difficulty swallowing, globus sensation, hoarseness and epigastric pain.

Include some discussion of acid vs non-acid reflux, including discussion of the high prevalence of abnormal physiology in the GERD-group.

GERD has long been known to be an important cause of chronic cough. Indeed a diagnosis of acid gastroesophageal reflux associated cough (GERC) is often made following a successful, empirical trial of high-dose acid suppression therapy. Thus, a particular attraction of the reflux hypothesis is that it could explain both the pathogenesis of IPF and the associated symptom of cough. However, the lack of improvement in cough symptoms despite effective acid suppression therapy indicates that acid gastroesophageal reflux alone is not responsible for cough in the majority of patients with IPF. A recent advance in the assessment of non-acid reflux is the technique of combined esophageal pH and impedance monitoring which provides a means of detecting acid and non-acid reflux. Savarino et al. [27] reported high number of acid reflux events, non-acid reflux events, and reflux reaching the proximal esophagus in patients systemic sclerosis and interstitial lung disease. And our study also found patients with IPF had more distal and proximal reflux events, especial non-acid reflux, which showed combined impedance and pH recordings provide a more accurate assessment of the pattern of reflux.

Discuss why the GERD+ group had more weak peristalsis

Weak peristalsis can be caused by reflux presumably by altering oesophageal sensorimotor responsiveness or via inflammatory changes. It has been demonstrated that among healthy volunteers weak peristalsis of the esophageal body predicted incomplete bolus clearance [24], may account for delayed bolus transit and impaired esophageal reflux clearance in patients with GERD [25, 26].

P9 line 208-210. The authors claim that screening should be performed in IPF, but the their results do not directly support this claim. This would require a study
of screening vs conventional care in IPF and comparison of outcomes.

We acknowledge this point and have deleted it in the paper.

Line 210-212. Suggest replace this sentence with “whether treatment of reflux and abnormal esophageal function alters outcomes in IPF”, or something similar.

Some researchers have showed anti-reflux surgery can improve lung function of GERD patients so further studies are required to determine whether anti-reflux surgery or using PPI might improve the prognosis of IPF patients.

Minor corrections (compulsory)

A number of spelling or grammatical errors

P2 line 29 delete “predictive”
P3 line 61 define EFT
P6 line 139 “were” not “was”
Line 141 “are shown” not “was showed”
Line 144 last sentence is clumsy.

Table 1 spelling “Heartburn”

We acknowledge these points and have adjusted in the paper.

Thank you.
The article entitled "The Prevalence of Gastro-Esophageal Reflux Disease and Esophageal Dysmotility in Chinese Patients with Idiopathic Pulmonary Fibrosis" by Gao et al. is a prospective study designed to evaluate the prevalence of GERD and esophageal motility disorders in 69 Chinese IPF patients by using HiRM and impedance-pH monitoring. The main results of the investigation were:
1) GERD prevalence was higher among IPF patients; 2) IPF patients with GERD had an increased prevalence of weak peristalsis, greater acid exposure percentage, higher bolus exposure time and more episodes of distal and proximal reflux than those without reflux; 3) symptoms presence alone were not a good predictor of the presence of reflux due to poor sensitivity and specificity.

The main idea of the study is not original since previous studies have already assessed this issue (Am J Respir Crit Care Med Vol 179. pp 408–413, 2009; Eur Respir J 2013; 42: 1322–1331). In the latter investigations it has been shown as patients with IPF or scleroderma with lung involvement presented less commonly with typical reflux symptoms (heartburn and regurgitation) than patients without IPF, higher esophageal acid exposure time, greater number of reflux episodes (impedance-pH testing was used!) and a positive correlation between severity of reflux with pulmonary fibrosis. Thus, it appears almost incredible that the authors did not analyse them in order to compare their results with those observed previously in Western population by using the same technique. This is a pity because this study has also few points of strength (use of the state-of-the-art techniques to assess both reflux disease and esophageal motility, the prospective design and the number of patients enrolled with IPF) that make this
investigation, although only confirmatory of previous findings, relevant for the topic (reflux in IPF).

Thank you for your comments.

Major Compulsory Revisions:

1. Methods. The period of wash-out PPI therapy before impedance-pH testing is too short (at least 7 days are necessary for the stomach to restore its capability to produce acid at pre-therapy level). Please, justify this decision and include them among the limitations of the study.

   We have confirmed that 3-days of PPI was a typographic error in the text, patients were at least 7 days off PPI and H2 receptor antagonist and 3 days off β receptor agonist, aminophylline, and nitrates.

2. Methods. There was no control group in this study. Please, comment on that among the limitations of the study

   We acknowledge this point and have adjusted in the paper.

   Chinese healthy volunteers as control group of HRiM, and GERD patients without IPF as control group of GERD patients with IPF.

3. Methods. Reference 11 is inappropriate since no normal values are provided

   We acknowledge this point and have adjusted in the paper.

4. Methods. It is not clear which parameters have been considered for GERD + and GERD -. Please, clarify on the methods when an IPF was positive for GERD (i.e. abnormal acid exposure and/or abnormal number of reflux episodes and/or……?)

   Patients were divided into GERD+ and GERD- groups according to the results of 24-hour pH monitoring (presenting an abnormal acid exposure time and/or a positive symptom association probability index) [10], and without evidence of motility disorders according to Chicago classification criteria (achalasia, distal esophageal spasm, jackhammer esophagus) [8]. Abnormal upright (≥6.3%) or recumbent (≥1.2%) or total (≥4.2%) acid exposure time and/or Demeester score higher than 14.7.
5. Results. Data on PPI use among subjects have not been provided and discussed. Please, add this crucial information

186 patients that saw pulmonologists in our hospital first with the main symptom cough had not had PPI’s before attending EFT.

From the patient cohort, there were 20 patients with cough and typical reflux symptom using PPI prescribed by gastroenterologists, but they did not have IPF.

6. Discussion. Data on Sens, Spec, PPV and PNV of GERD symptoms should be provided in the results and then explained and discussed in the Discussion section.

We acknowledge this point and have adjusted in the paper.

7. Data on bolus transit should be highlighted as they are unique of this study.

We acknowledge this point and have adjusted in the paper. We use TBTT and CBTR in the paper.

Level of interest: An article whose findings are important to those with closely related research interests.