Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1443

Reviewer A

This is an interesting topic for study but I have a number of problems with the current investigation and manuscript. Specific points are listed below, but the main concerns I have are the small study size (n=23, only 10 with cough), and the retrospective/ post hoc design.

Answer:
Thank you for your useful comments. We have modified our manuscript as advised. As you mentioned, this study was a single-center retrospective study of a limited number of patients, and further studies are essential. We hope to first present this report as a "brief report" and would like to re-examine when more cases are accumulated.

1. Introduction. Prior literature needs to be more fully explored, including the review by Van Manen et al in European Respiratory Review, 2016

Answer:
Thank you for your useful comment. We have explored prior literature including the review by Van Manen et al in European Respiratory Review 2016 again, and modified our text and cited the following references as advised (see Page 5, line 14).

Although mechanisms involved in the cough of IPF patients have been proposed, the exact pathophysiology and appropriate treatments for these patients remain unclear (13-16).

13. van Manen MJG, Birring SS, Vancheri C, et al. Cough in idiopathic pulmonary fibrosis. Eur Respir Rev 2016; 25: 278-86.
14. Myall KJ, Kavanagh JE, Birring SS. Idiopathic pulmonary fibrosis-associated cough: Mechanisms and management. Pulm Pharmacol Ther 2019; 56: 100-3.
15. Mann J, Goh NSL, Holland AE, et al. Cough in idiopathic pulmonary fibrosis. Front Rehabil Sci 2021; 2: 751798.
16. Liu S, Ye X. Assessment and Management of Cough in Idiopathic Pulmonary Fibrosis: A Narrative Review. Lung 2023; 201: 531-544.

Methods

2. How was the presence of cough assessed? Were patients actively asked about this routinely at every clinic visit? Was any attempt made to assess cough severity (e.g. visual analogue scale or 'score out of 10'?)

Answer:
Thank you for your useful comment. We routinely asked about the presence of cough at every clinic visit, even if the patients did not have a cough during the examination. Unfortunately, we objectively evaluated the frequency and severity of cough with the use of established cough assessment tools only in a limited number of patients in this study. This point is serious limitation, and we have described at the end of discussion (see Page 16, line 2). We have modified our text as advised (see Page 7, line 4).

Page 7, line 4
At every clinic visit we asked each patient about the presence of cough, even if cough was not observed during the visit.

Page 16, line 2
We could not objectively evaluate the frequency and severity of cough with the use of established cough assessment tools.

3. Did all patients routinely have a capsaicin cough challenge test?

Answer:
Thank you for your useful comment. We carefully reviewed our database again, and only 15 of 23 patients (5 patients with cough and 10 patients without cough) underwent a capsaicin cough challenge test. One of the patients with cough had hyperventilation syndrome during the capsaicin cough challenge test, and the test was stopped. We have changed part of Table 2 as follows.

Table 2. Patients with idiopathic pulmonary fibrosis (N = 23): Pulmonary function at diagnosis

	With cough n = 6	Without cough n = 17	P value
FVC, %predicted	77.5 ± 30.4	99.9 ± 0.5	0.046
FEV_1, %predicted	85.8 ± 28.2	96.7 ± 24.7	0.52
FRC, %predicted	77.4 ± 16.4	85.6 ± 18.2	0.40
RV, %predicted	71.4 ± 18.6	79.6 ± 21.0	0.36
TLC, %predicted	72.3 ± 22.5	87.9 ± 19.1	0.25
RV/TLC, %predicted	102.3 ± 25.1	90.9 ± 15.9	0.40
DLco, %predicted	48.4 ± 21.9	53.7 ± 14.2	0.26
FeNO, ppb	19.0 ± 6.0	29.2 ± 16.7	0.29

C5, μM (With cough n = 5, without cough n = 10)	20.6 ± 26.6	12.7 ± 8.1	0.62
Increased cough receptor sensitivity to capsaicin, n (%)	2/5 (40)	1/10 (10)	0.16

Abbreviations: N, total number of patients evaluated; n, number in subgroups; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion; C5, capsaicin concentration eliciting 5 or more coughs

4. Line 67-8: radiologically how was 'bronchiectasis' defined? Did both radiologists independently report the same images? How were discrepancies of opinion between them addressed?

Answer:
Thank you for your useful comment. We defined bronchiectasis as a bronchoarterial ratio greater than 1.0 and lack of tapering. High-resolution computed tomography (HRCT) findings were analyzed by 2 radiologists. In this study, 1 of the two radiologists analyzed the HRCT images, and the other radiologist verified the analysis of the first radiologist. There were no discrepancies between the opinions of the 2 radiologists. We modified our text as advised (see Page 6, line 7).

High-resolution computed tomography (HRCT) findings were analyzed by 2 radiologists. Specifically, 1 of the two radiologists analyzed the HRCT images, and the other radiologist verified the analysis of the first radiologist. Lung specimens were evaluated in a similar manner by 2 pathologists. We defined HRCT findings as follows: honeycombing, clusters of cystic airspaces just below the pleura; emphysema, abnormal enlargement of the airspaces distal to the terminal bronchioles plus destruction of alveolar walls; and traction bronchiectasis, bronchoarterial ratio greater than 1.0 and lack of tapering.

5. Rather than 'bronchiectasis', the term 'traction bronchiectasis' is better in the context of pulmonary fibrosis, even better still 'traction bronchial dilatation', so as not to confuse with suppurative bronchiectasis/ chronic lung infection.

Answer:
Thank you for your useful comment. We modified 'bronchiectasis' to 'traction bronchiectasis' in our text as advised.

6. Line 78-80: "cough due to IPF was defined as a cough that required central antitussive drugs for cough control or that was not easy to control despite the use of

central antitussive drugs". This definition is unusual and complicates matters. Why not just stick with 'refractory chronic cough', as per international guidelines, e.g. ERS 2020? Then cough in association with IPF would be the symptom of interest, taking care to control contributory factors such as GORD, ACE inhibitor use, asthma, etc.

Answer:
Thank you for your useful comment. In this study, we performed complete evaluations and treatments for comorbidities that cause cough. If the cough did not resolve after specific treatments for each comorbidity, we concluded that the cough was due to IPF and used central antitussive agents. Therefore, cough due to IPF in this study was similar to refractory chronic cough in international guidelines (ERS 2020), and the definition was changed as advised. We modified our text, and cited literature as advised (see Page 7, line 13, Page 9, line 2, Page 9, line 9 and Page 15, line 17).

Page 7, line 13
In this study, cough due to IPF was defined as a cough that persisted despite complete evaluations and treatments for comorbidities that cause cough, which were based on published practice guidelines (19).

19. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J 2020; 55: 1901136.

Page 9, line 2
Finally, among the 23 patients there were 6 (26.1%) with refractory cough associated with IPF.

Page9, line 9
None of the patients received angiotensin-converting enzyme (ACE) inhibitors.

Page 15, line 17
Finally, we defined "refractory cough due to IPF" as a cough that persists despite complete evaluations and treatments for comorbidities that cause cough, which are based on published practice guidelines (19).

Discussion

7. Line 153-5: "With reference to the results of the previous report and our study, we speculate that the increased sensitivity of the cough reflex to chemical irritants is probably not a major cause of refractory cough in IPF patients."
- What is the basis for this statement?

Answer:
Thank you for your useful comment. In this study, the sensitivity of the cough reflex to capsaicin was only increased in 3 patients (2 patients with refractory cough and 1 without cough), and the difference between the sensitivity of the cough reflex to capsaicin in the 2 groups of patients was not significant. With reference to this result, we speculated that the increased sensitivity of the cough reflex to chemical irritants is probably not a major cause of refractory cough in IPF patients. However, this study was very small, and a capsaicin cough challenge test was performed only in 15 of 23 patients (5 patients with cough and 10 patients without cough). Therefore, to clarify the association of this mechanism with cough in IPF patients, further studies are essential. We modified our text as advised (see Page 11, line 11).

There have been a few reports that the sensitivity of the cough reflex to chemical irritants is increased in patients with IPF (11, 23). One of the published reports on patients with IPF examined their sensitivity of the cough reflex to capsaicin; patients with comorbidities associated with cough such as BA, gastroesophageal reflex disease (GERD), respiratory tract infections, and ACE inhibitors were excluded (11). However, patients with other conditions, in particular AC, may not have been completely excluded because of an incomplete history on specific preventative treatments such as inhaled corticosteroids and histamine H1 receptor antagonists. Indeed, cough has been dramatically reduced by steroid therapy, which is not recommended for IPF patients because it is not effective, and AC might have been a concomitant condition in some studies (11). In our study, the sensitivity of the cough reflex to capsaicin was only increased in 3 patients (2 patients with refractory cough and 1 without cough), and the difference between the sensitivity of the cough reflex to capsaicin in the 2 groups of patients was not significant. However, a capsaicin cough challenge test was assessed for only 15 of 23 patients (5 patients with cough and 10 patients without cough). Additional studies are needed to clarify the association of the sensitivity of the cough reflex to capsaicin to cough in IPF patients.

8. Lines 163-6: “Our study found that bronchiectasis and distorted architecture of the airways were specific features of patients with IPF and refractory cough. However, the differences between the rates of honeycombing and emphysema in our study patients with and without refractory cough were not significant.”
- Honeycombing is also architectural distortion. How do you theorise that this does not also cause cough?

Answer:
Thank you for your useful comment. Previous animal studies have shown that bronchopulmonary C-fibers and Aδ-fibers play important roles in the cough reflex. C-fibers, which densely innervate the epithelium and the region around the epithelium of whole airways, are sensitive to a diverse range of chemical and environmental

irritants. On the other hand, Aδ-fibers, which sparsely innervate the space between the epithelium and smooth muscle in the proximal airways, are insensitive to most chemical irritants but are sensitive to mechanical stimuli. Rapidly adapting receptors and slowly adapting receptors, which mainly innervate the peripheral airways, are other important vagal afferent nerves and have been found to regulate the respiratory cycle and bronchomotor tone, but do not directly impact the cough reflex. Considering the distribution of these sensory nerves, we speculate that not architectural distortion of the alveoli, i.e., honeycombing, but traction dilatation of the bronchi, where Aδ-fibers are principally distributed, is a more important factor associated with cough in IPF patients at least cough caused by mechanical stimulation. We modified our text and references as advised (see Page 13, line 2).

Previous studies have shown that bronchopulmonary C-fibers and Aδ-fibers play an important role in the cough reflex (26, 27). C-fibers, which densely innervate the epithelium and the region around the epithelium of whole airways, are sensitive to a diverse range of chemical and environmental irritants.
On the other hand, Aδ-fibers, which sparsely innervate the space between the epithelium and smooth muscle in the proximal airways, are insensitive to most chemical irritants, but are sensitive to mechanical stimuli. The distribution of sensory nerves combined with our study findings, suggest that architectural distortion of the bronchi exerts mechanical stress on the airways and leads to increased stimulation of the Aδ-fibers, which results in cough.

26. Narula M, McGovern AE, Yang SK, et al. Afferent neural pathways mediating cough in animals and humans. J Thorac Dis 2014; 6: S712-9.
27. Canning BJ, Chang AB, Bosler DC, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. Chest 2014; 146: 1633-48.

9. Lines 173-183. The MUC5B story in IPF is complex. Cough is usually dry in IPF. The suggestion here is that the finding of a dry cough in the current study goes against a role for MUC5B. In reality, genetic variants in the protein may lead changes in mucus properties rather than quantity, which may be relevant for IPF pathogenesis.

Answer:
Thank you for your useful comment. As you mentioned, in this study, all patients with refractory cough had a dry cough, and the MUC5B story in IPF could not be evaluated. To evaluate a role for MUC5B in cough due to IPF, further studies are essential. We modified our text as advised (see Page 14, line 2).

In our study, all patients with refractory cough had a dry cough, and the association between accumulation of mucus in the airways and cough in IPF patients could not be

evaluated. Additional studies are needed to clarify the association of the accumulation of mucus in the airways with cough in IPF patients.

Reviewer B

1) It is obscure which evaluation and treatment was given to identify and treat comorbidities.

Answer:
Thank you for your useful comment. In our institution, with or without IPF, we routinely perform the following investigations, such as blood tests, chest and sinus X-ray, chest CT, spirometry, bronchodilator reversibility testing, fractional exhaled nitric oxide testing, and capsaicin cough sensitivity testing on patients with chronic cough. We use the results of these investigations to try to diagnose the cause of cough before treatment. If the diagnosis cannot be arrived at by the results of the listed investigations, the patient receives a diagnosis based on his or her response to a treatment specific for each causative disease (e.g., inhaled corticosteroids for bronchial asthma, bronchodilators for cough-variant asthma, histamine H1 receptor antagonists for atopic cough, proton pump inhibitors for gastroesophageal reflex disease, and macrolides and expectorants for sinobronchial syndrome). In this study, we also performed these investigations and treatments, and tried to identify a comorbidity that was more likely to cause cough than IPF. We modified our text as advised (see Page 7, line 5).

We performed the following investigations: blood tests; radiography of the chest and sinuses; chest CT; spirometry; bronchodilator reversibility test; FeNO test; and on patients with cough, the capsaicin cough sensitivity test. The results of the investigations allowed us to identify patients with comorbidities that were more likely to cause cough, such as bronchial asthma (BA), cough-variant asthma (CVA), atopic cough (AC), and sinobronchial syndrome (SBS), and treated each of those patients specifically for his or her concomitant disease (e.g., inhaled corticosteroids for BA, bronchodilators for CVA, histamine H1 receptor antagonists for AC, and macrolides and expectorants for SBS).

2) Given the uncertainty in defining comorbidities, I suggest the authors also make a comparison between IPF with cough (n=10) vs. IPF without cough (n=13).

Answer:
Thank you for your useful comment. In this study, we performed complete evaluations and treatments for comorbidities that were more likely to cause cough, and the cough of 4 patients was resolved after treatment of their concomitant condition. Hence, we think that the cough of these 4 patients was not likely to be

caused by IPF only. However, as you mentioned, comorbidities may not be adequately ruled out, in particular GERD. Following your advice, we added some data as supplemental data (See page 15, line 16, Supplementary Table 1 and Supplementary Table 2).

The differences between the characteristics of the patients with cough (n = 10) and without cough (n = 13) were not significant (supplementary tables 1 and 2).

Supplementary Table 1. Patients with idiopathic pulmonary fibrosis (N = 23): Characteristics, laboratory data, and HRCT findings at diagnosis

	With cough n = 10	Without cough n = 13	P value
Age, years, median (range)	65 (38-79)	67 (55-79)	0.19
Sex, n (%)			1
Male	8 (80)	11 (84.6)	
Female	2 (20)	2 (15.4)	
BMI, kg/m^2	20.6 ± 3.1	22.5 ± 2.8	0.17
Smoking status, n (%)			1
Never smoked	1 (10)	2 (15.4)	
Current or former smoked	9 (90)	11 (84.6)	
Medications, n (%)			
Anti-fibrotic drugs	7 (70)	8 (61.5)	1
Pirfenidone	7 (70)	6 (46.2)	0.40
Nintedanib	4 (40)	4 (30.8)	0.69
Prednisolone	0 (0)	3 (23.1)	0.23
Proton pump inhibitor	5 (50)	5 (38.5)	0.69
Expectorant	3 (30)	0 (0)	0.07
Peripheral blood eosinophil counts, mm^3	166.2 ± 124.4	345.1 ± 377.6	0.10
Total serum IgE, IU/ml	204.2 ± 325.9	207.4 ± 224.2	0.75
KL-6, U/ml	945.0 ± 291.5	865.8 ± 559.0	0.26
GAP index, n (%)			0.84
Stage I	7 (70)	7 (53.8)	
Stage II	2 (20)	4 (30.8)	
Stage III	1 (10)	2 (15.4)	
HRCT findings, n (%)			
Traction bronchiectasis	5 (50)	2 (15.4)	0.17
Honeycombing	10 (100)	11 (84.6)	0.49
Emphysema	3 (30)	6 (46.2)	0.67

Abbreviations: N, total number of patients evaluated; n, number in subgroups; BMI, body mass index; IgE, Immunoglobulin E; GAP, gender (G), age (A), and 2 lung

physiology variables (P) (FVC and DLco); FVC, forced vital capacity; DLco, diffusing capacity of carbon monoxide; HRCT, high-resolution computed tomography

Supplementary Table 2. Patients with idiopathic pulmonary fibrosis (N = 23): Pulmonary function at diagnosis

	With cough n = 10	Without cough n = 13	P value
FVC, %predicted	91.7 ± 31.9	95.9 ± 21.2	0.54
FEV_1, %predicted	94.6 ± 30.3	93.3 ± 22.3	0.88
FRC, %predicted	84.7 ± 20.3	83.1 ± 16.6	0.95
RV, %predicted	77.4 ± 19.0	78.0 ± 22.0	0.79
TLC, %predicted	83.9 ± 24.6	84.7 ± 18.2	0.85
RV/TLC, %predicted	95.2 ± 20.6	92.3 ± 17.4	0.95
DLco, %predicted	53.9 ± 18.2	51.5 ± 14.7	1
FeNO, ppb	21.9 ± 7.8	30.5 ± 18.6	0.42
C5, μM (With cough n = 9, without cough n = 6)	15.8 ± 19.8	14.6 ± 9.8	0.9
Increased cough receptor sensitivity to capsaicin, n (%)	2/9 (22.2)	1/6 (16.7)	0.56

Abbreviations; N, total number of patients evaluated; n, number in subgroups; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; DLco, diffusing capacity of carbon monoxide; FeNO, fraction of exhaled nitric oxide; C5, capsaicin concentration eliciting 5 or more coughs

3) Please provide the methodology in defining honeycombing, emphysema, BE, and architectural distortion. Also, their extent and severity should be quantified.

Answer:
Thank you for your useful comment. As you mentioned, we think that it is very important to provide the definitions of HRCT findings. In this study, we described the structural modification of the airways resulting from traction bronchiectasis as architectural distortion of the airways. Although quantitative evaluation of structural changes on HRCT was also very important, we did not have software that could analyze images, and could not perform quantitative evaluations. This point was a serious limitation, and we have reported it in the discussion (see Page 15, line 7). However, the disease severity of IPF as assessed by GAP scoring did not show an association with cough. We speculate that mechanical stress due to distorted architecture of the airways may be the cause of cough in IPF patients, regardless of

the extent or severity of structural changes. We modified our text as advised (see Page 6, line 11 and Page 15, line 10).

Page 6, line 11
We defined HRCT findings as follows: honeycombing, clusters of cystic airspaces just below the pleura; emphysema, abnormal enlargement of the airspaces distal to the terminal bronchioles plus destruction of alveolar walls; and traction bronchiectasis, bronchoarterial ratio greater than 1.0 and lack of tapering.

Page 15, line 7
Second, the radiological findings were only subjectively evaluated by radiologists. An objective evaluation that includes software that can analyze images is preferable for confirming the relationship between structural changes on HRCT and cough in patients with IPF.

Page 15, line 10
However, the disease severity of IPF as assessed by GAP scoring did not show an association with cough. We speculate that mechanical stress due to distorted architecture of the airways may be the cause of cough in IPF patients, regardless of the extent or severity of structural changes.

4) Please add the IPF disease severity data and analyze it in relation to cough.

Answer:
Thank you for your useful comment. As you mentioned, we think that it is very important to analyze the relation between IPF disease severity and cough. Therefore, we analyzed these relationships using the GAP (gender [G], age [A], and 2 lung physiology variables [P] [forced vital capacity and diffusing capacity of carbon monoxide]) index. There was no relationship between the disease severity of IPF and cough. We modified our text (see Page 9, line 10) and part of Table 1 as advised.

IPF disease severity was evaluated according to the GAP (gender [G], age [A], and 2 lung physiology variables [P] [forced vital capacity (FVC) and diffusing capacity of carbon monoxide]) index (21), and the difference between patients with and without cough was not significant.

21. Ley B, Ryerson CJ, Vittinghoff E, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. Ann Intern Med 2012; 156: 684-91.

Table 1. Patients with idiopathic pulmonary fibrosis (N = 23): characteristics, laboratory data, and
HRCT findings at diagnosis

	With cough n = 6	Without cough n = 17	P value
Age, years, median (range)	60 (38-79)	67 (55-79)	0.19
Sex, n (%)			1
Male	5 (83.3)	14 (82.4)	
Female	1 (16.7)	3 (17.6)	
BMI, kg/m^2	18.8 ± 2.5	22.8 ± 2.5	< 0.01
Smoking status, n (%)			1
Never smoker	1 (16.7)	2 (11.8)	
Current or former smoker	5 (83.3)	15 (88.2)	
Medications, n (%)			
Antifibrotic drugs	6 (100)	9 (52.9)	0.06
Pirfenidone	6 (100)	7 (41.2)	0.02
Nintedanib	4 (66.6)	4 (23.5)	0.13
Prednisolone	0 (0)	3 (21.4)	0.54
Proton pump inhibitor	4 (66.6)	6 (35.3)	0.34
Expectorant	1 (16.7)	2 (11.8)	1
Peripheral blood eosinophil count, mm^3	130.8 ± 91.3	315.5 ± 338.9	0.09
Total serum IgE, IU/mL	139.2 ± 204.0	227.0 ± 183.7	0.68
KL-6, U/mL	1085.0 ± 254.0	835.1 ± 496.9	0.06
GAP index, n (%)			0.82
Stage I	3 (50)	11 (64.7)	
Stage II	2 (33.3)	4 (23.5)	
Stage III	1 (16.7)	2 (11.8)	
HRCT findings, n (%)			
Traction bronchiectasis	5 (83.3)	2 (11.8)	< 0.01
Honeycombing	6 (100)	15 (88.2)	1
Emphysema	1 (16.7)	8 (47.1)	0.34

Abbreviations; N, total number of patients evaluated; n, number in subgroups; BMI, body mass index; IgE, Immunoglobulin E; GAP, gender (G), age (A), and 2 lung physiology variables (P) (FVC and DLco); FVC, forced vital capacity; DLco, diffusing capacity of carbon monoxide; HRCT, high-resolution computed tomography