Internal and Emergency Medicine
https://doi.org/10.1007/s11739-018-1960-5

IM - REVIEW

The pathogenetic mechanisms of cough in idiopathic pulmonary fibrosis

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Received: 14 August 2018 / Accepted: 24 September 2018

Abstract

Idiopathic pulmonary fibrosis is a peripheral subpleural interstitial lung disorder limited to the lung not involving the airways. It has a poor prognosis (survival less than 5 years) and commonly an interstitial pneumonia radiological pattern. Patients complain of a chronic dry cough in 80% of cases. A cough is often the first symptom of this rare disease, preceding dyspnea by years, and is associated with a poor prognosis, high dyspnea scores and low FVC percentages. The pathogenetic mechanisms leading to coughing in IPF are unclear. This review focuses on recent evidence of cough pathophysiology in this disease. Gastroesophageal reflux may promote coughing in IPF patients; bile salts and pepsin may be abundant in BAL of these patients, inducing overproduction of TGF-β by airway epithelial cells and mesenchymal transition with fibroblast recruitment/activation and extracellular matrix deposition. Patients have an enhanced cough reflex to capsaicin and substance P with respect to control subjects. Moreover, patients with the MUC5B polymorphism show more severe coughing as MUC5B encodes for the dominant mucin in the honeycomb cysts of IPF patients. Comorbidities, including asthma, gastroesophageal reflux, hypersensitivity pneumonitis, bronchiectasis, chronic obstructive pulmonary disease and emphysema, can induce coughing in IPF patients. There is no clear explanation of the causes of coughing in IPF. Further research into the pathophysiology of IPF and the pathogenetic mechanisms of coughing is necessary to improve survival and quality of life.

Keywords Idiopathic pulmonary fibrosis · Cough · Pathogenesis

Abbreviations

IPF	Idiopathic pulmonary fibrosis
ILD	Interstitial lung diseases
HRCT	High resolution computed tomography
BAL	Bronchoalveolar lavage
GER	Gatroesophageal reflux
NSIP	Non specific interstitial pneumonia
FVC	Forced vital capacity
TGF-β	Tumour growth factor
UIP	Usual interstitial pneumonia
GPCR	G-Protein coupled receptor

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Introduction

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disorder limited to the lung and associated with poor prognosis (mean survival less than 5 years) and commonly an interstitial pneumonia (UIP) radiological pattern. Late diagnosis of IPF is common because the signs and symptoms of this disease are nonspecific. Eighty percent of patients complain of a chronic dry cough, but the prevalence of coughing in IPF has not been clearly established due to different definitions and assessment methods [1]. Coughing is often the first symptom of this interstitial lung disease, preceding dyspnea by years [2–5]. It is an independent marker of disease severity, being associated with a poor prognosis, high dyspnea scores, low FVC percentages, and high rates of exertion desaturation [1]. Coughing is more common in IPF patients who have never smoked than in smokers [50]. All ages and both genders are equally affected. The cough is dry, severe, diurnal, induced, for example, by speaking (favoured by vibration or mechanical stimulation of nerve receptors) and refractory to pharmacological therapies [1, 5]. It can affect quality of life by limiting exercise tolerance and determining

Published online: 29 September 2018

social health problems [4–7]. Coughing related to IPF may be associated with coughing induced by comorbidities such as asthma, gastroesophageal reflux (GER) disease, upper airway cough syndrome and medications [5].

New approved therapies for IPF have only been partially assessed for coughing, although there is growing interest in the topic. There is no specific approved therapy for coughing in IPF. Only one trial with thalidomide in a limited population of IPF patients with refractory coughing has been published [8]. Our research group recently conducted a randomised, double blind, placebo-controlled trial on the effectiveness of aerosolised carcainium chloride (VRP700) in controlling coughing in patients with interstitial lung diseases (ILD) [9]. Nebulised VRP700 therapy improves cough and quality of life in hospitalised ILD patients, and is without any significant side effects. In a multicentre trial, Birring et al. recently evaluate the efficacy of a new formulation of inhaled sodium cromoglycate in the treatment of chronic coughing in IPF patients [10].

There is no clear explanation of the causes of coughing in IPF patients, especially those never exposed to cigarette smoking. The pathogenetic mechanisms of coughing in IPF are unclear. Here we review recent evidence concerning the pathophysiology of coughing in this disease.

Gastroesophageal reflux

Bile salts and pepsin may be abundant in bronchoalveolar lavage (BAL) fluid from IPF patients, inducing overproduction of TGF-β by airway epithelial cells and mesenchymal transition with fibroblast recruitment/activation and extracellular matrix deposition [11–14]. The development of IPF seems to be facilitated by recurrent lung insult due to microaspiration of *Helicobacter pylori* from gastric juice as a consequence of GER [14–18]. Gastroesophageal reflux (GER) is common in IPF patients, while in the general population, the prevalence of GER disease exceeds that of IPF and only a small proportion of subjects with GER develops IPF [11]. Non-acid reflux seems to influence coughing in IPF more than acid reflux. Pharmacological therapy with pump inhibitors does not improve cough symptoms. Therapy with proton pump inhibitors is able to increase non-acid reflux [11], and some interesting research articles suggest that the most apt strategy to treat gastroesophageal reflux in patients with IPF should target acid and non-acid reflux [4]. Prokinetic therapies, rather than acid suppression therapy alone, may be proposed as relevant potential targets of treatment [4].

In IPF, the cough itself may promote GER through an increase in trans-diaphragm pressure; concomitant pulmonary fibrosis causes traction of neighbouring structures, weakening the lower esophageal sphincter and aggravating gastric reflux [4, 18]. The surgical approach to GER in IPF patients does not yield a significant improvement in cough symptoms [19, 20]. Controversial findings have been reported on the potential role of GER in IPF pathogenesis. Some authors fail to confirm the increased pepsin concentrations reported in BAL and exhaled breath condensate from IPF patients, suggesting that these findings may not be reproducible [19]. Some research groups find higher DLCO percentages in patients with IPF and GER than in those with no reflux [15].

Architectural distortion of the lungs

In obstructive lung disorders, coughing is generally due to airway involvement, but since IPF is not an airway disease, the reason for coughing in this peripheral ILD is unclear [21]. Idiopathic pulmonary fibrosis causes architectural distortion and traction bronchiectasis; mechanical forces activate rapidly adapting receptors in small airways, stimulating coughing [22, 23].

The airway traction occurring in IPF may promote the development of a cough, particularly in the advanced phase of the disease. There is progressive loss of alveolar integrity, recruitment/activation of myofibroblasts and excessive collagen deposition damage parenchymal architecture, causing airway distortion [22, 23].

Lung fibrosis can destroy the nerves involved in cough inhibition, facilitating the symptom. In 2011, Jones et al. demonstrated that percussive stimuli to the respiratory tract induce coughing in IPF patients, but not in controls, and that the cough increases when the base of the lungs (where IPF arises) is stimulated. Transmission of vibration caused by talking, or even coughing itself, may increase mechanical stimulation of sensory receptors, perpetuating the vicious circle of IPF and coughing [22].

Increased cough reflex sensitivity

Idiopathic pulmonary fibrosis patients have an enhanced cough reflex response to capsaicin and substance P with respect to controls, irrespective of the entity of fibrosis and GER [24]. The urge to cough, induced by inhalation of capsaicin, activates many areas of the cerebral cortex, especially in IPF patients (Fig. 1). Stimulation of chemical cough receptors may be related to subclinical inflammation. Eosinophils and other inflammatory markers have been found elevated in BAL fluid of IPF patients [25–28]. These mediators may modulate the cough reflex by increasing the presence of G protein coupled receptor (GPCR) and substance P in human airway nerves. C-fibre sensory nerves seem to be involved in cough development, and it is possible to reduce the dry cough associated with IPF by reducing

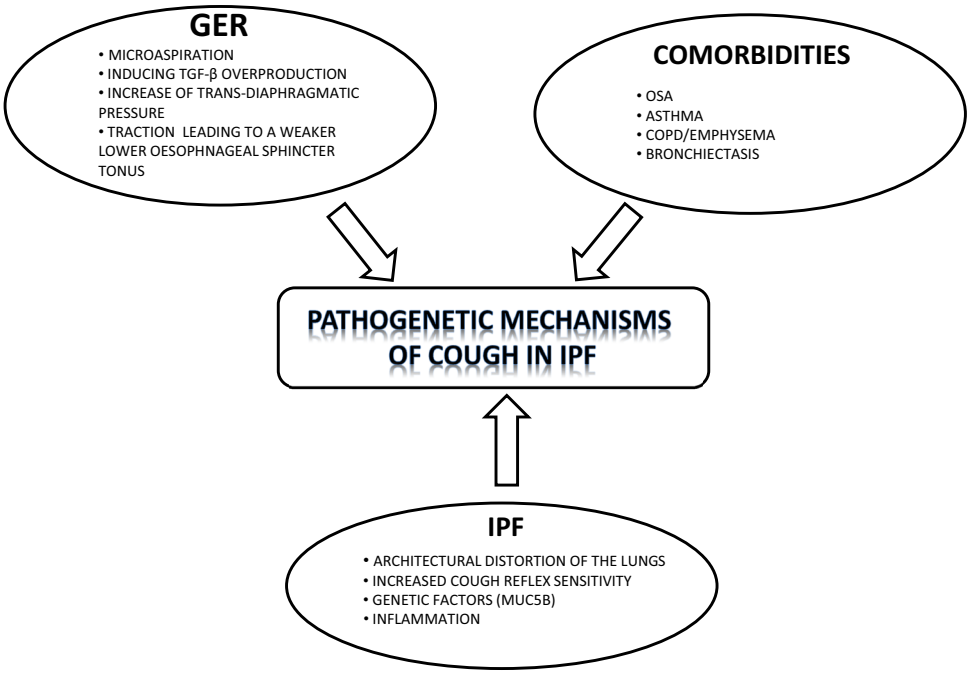

Fig. 1 Pathogenetic mechanisms of cough in idiopathic pulmonary fibrosis (IPF)

C-fibre nerve activity through a specific receptor [30–34, 50].

Neurotrophins may be generated in the lungs of IPF patients from bronchial and alveolar epithelial cells, mesenchymal cells, lymphocytes and macrophages [29, 35]. Neurotrophins regulate different subgroups of sensory neurons, increasing capsaicin sensitivity. Interestingly, immunoblots have revealed neurotrophin overexpression in patients with an UIP, but not a NSIP radiological pattern, although possible differences between cough impact in IPF and NSIP have never been evaluated [36]. Substance P-like immunoreactive material has been found overexpressed in BAL and sputum from IPF patients with respect to healthy individuals, modulating nerve proliferation and neuroplasticity. Neuropeptides, substance P and neurokinin A can stimulate human lung fibroblast proliferation and chemotaxis that regulate the cough reflex [36].

Genetic factors

Cough is an independent predictor of disease progression. It is more severe in IPF patients with MUC5B polymorphism [37]. MUC5B encodes an airway mucin that is the dominant mucin in the honeycomb cysts of IPF patients [38]. Changes in mucin production and clearance aggravate the cough [39–41]. Although IPF is commonly associated with a dry cough, some patients have a chesty productive cough from onset of the disease. In a recent study, the histology of autopsy lungs of IPF patients was compared in relation to wet and dry cough [42]. IPF patients with hypersecretion show mucus gland hypertrophy, accumulation of mucus in the airways and mucus hypersecretion [42].

Inflammation

An elevated percentage of polymorphonuclear cells and mast cells producing an abundance of cytokines and chemokines have been demonstrated in BAL fluid of IPF patients [27, 28]. Among the inflammatory cells overexpressed in BAL and sputum of IPF patients, eosinophils and mast cells are involved in fibrosis and cough development. These cells have been isolated near fibroblastic foci, and produce histamine, tryptase, serotonin and substance P that activate sensory nerve C fibres, promoting coughing [30, 31].

Comorbidities

Many years ago, Madison et al. reported that coughing can be an expression of different concomitant diseases in more than 50% of IPF patients [5]. In particular, the authors suggest that comorbidities that induce coughing in these patients include: obstructive sleep apnea (OSA) syndrome, asthma, GER, hypersensitivity pneumonitis, bronchiectasis, chronic obstructive pulmonary disease and emphysema [5].

Sleep apnea is a possible comorbidity in patients with IPF, and its treatment can improve gastroesophageal reflux, chronic cough and fibrotic lung damage [43, 44] (Table 1). In fact, it has been demonstrated that the intermittent hypoxemia of patients with OSA may promote profibrotic

Table 1 Comorbidities associated with Cough in IPF

IPF comorbidities	Mechanisms of cough
OSAS	Profibrotic hypoxaemia
GER	Non-acid reflux, increase TGF-β
BRONCHIECTASIS	C-fibre nerve activity
COPD	Hypersecretion mucous glandular
ASTHMA	Bronchial hyperactivity

mechanisms, and that obstruction of the upper airways typical of OSA syndrome may increase trans-diaphragm pressure differences, promoting GER and coughing (Fig. 1) [43–46].

The potential role of airway basal cells

Another intriguing aspect is the potential role of airway basal cells in IPF pathogenesis and cough development. Chilosi and coauthors report an aberrant bronchiolization in IPF lung with ΔNP63 expressing cells [47, 48]. IPF animal models reveal that airway basal cells may have a potential role in the early response to fibrosis, and bronchoalveolar subpopulations of ABCs are abundantly present in fibrotic lesions [49]. Migration and proliferation of a CK 5/6 + ΔNP63 + progenitor cell population is an early and key event in the evolution of pulmonary fibrosis [47]. IPF is characterized by fibroblast foci, honeycomb cyst formation and bronchiolization of the alveolar space [47]. In the current model of disease pathogenesis, the bronchiolization and honeycomb cysts formation occur after the formation of myofibroblast foci. ABCs are recruited potentially in response to alveolar epithelial cell injury, and their proliferation and invasion determine the distortion of the alveolar structure that we typically associate with IPF and cough [47–50]. A very recent genetic manuscript reports an unexpected finding: genes from ABCs are highly enriched in the BAL of IPF patients likely to progress, and may suggest an unexpected role of ABCs in the pathogenesis of IPF and cough [49]. It was demonstrated for the first time that IPF might be regarded as a fibrotic lung disease involving and originating by the airways basal cells [49].

Conclusion

There is no clear explanation of the possible causes of coughing in IPF, a peripheral subpleural disorder not involving the airways. Further research into the pathophysiology of IPF and the pathogenetic mechanisms of coughing is necessary to improve survival and quality of life of patients.

Funding The study was unfunded.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest related to this topic.

Statement of human and animal rights All procedures were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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