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Review article

# Etiology and treatment of cough in idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a progressive disease of dysregulated wound healing leading to unremitting scarring and loss of lung function. The predominant symptoms are dyspnea on exertion and a persistent dry cough. For patients with IPF, cough is more than just bothersome; it has a significant negative impact on quality of life and is a marker of disease severity and progression. The etiology of cough in IPF is unclear but may be due to architectural distortion of the lungs, increased sensitivity of the cough reflex, airway inflammation, or changes in mucus production and clearance. There also may be an overlap between IPF cough and cough due to other common etiologies such as asthma, gastroesophageal reflux disease, upper airway cough syndrome, and medications. There are no approved therapies to specifically treat IPF cough, and recently approved medications for IPF have not been evaluated in cough. Few clinical trials have focused on treatments for IPF cough. To date, there is only one randomized, placebo control therapeutic study for IPF cough with thalidomide, which significantly reduced IPF cough and improved quality of life. Two additional cohort studies report that interferon-α and prednisolone also decrease IPF cough. However, no medication is approved to treat IPF cough. Currently, the mainstay of therapy for IPF cough is standard cough suppressants, which have limited efficacy and often intolerable side effects. Future studies are needed to determine an effective therapy to alleviate this particularly debilitating symptom and improve overall quality of life for patients suffering with IPF.



**Contents**



## 1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease of unknown etiology characterized by unremitting scarring of the lungs due to excessive and dysregulated extracellular matrix deposition within the lungs. The prevalence is 6–20 per 100,000 individuals, with increasing prevalence as the population ages [1,2]. Currently, no treatments have been effective at reversing or halting

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the progressive fibrosis, and the median life expectancy from the time of diagnosis is only 3–5 years [3–6]. The main symptoms of patients with IPF are dyspnea on exertion and a persistent dry cough or mildly productive cough. The IPF cough is often refractory to antitussive therapy and may be a marker of more severe disease as well as an indicator of worse prognosis [7,8]. More importantly, it adversely affects patients' quality of life. Few studies have investigated the cause of or treatments for IPF cough despite its significant negative impact of quality of life and indeed the disease prognosis. In this review, the mechanisms behind, clinical significance of, and treatment options for IPF cough will be reviewed.

### 1.1. IPF cough

The hallmark symptoms of IPF are dyspnea on exertion and dry cough. The first description of IPF in 1976 noted cough as a predominant finding [9]. Although almost universal symptoms in IPF, dyspnea on exertion and cough are quite common in many pulmonary disorders and often patients suffer for years prior to definitive diagnosis. Indeed, the dyspnea may not even be recognized by patients if they are sedentary until they have lost significant lung function. One study found an average of 18 months between the onset of symptoms and the first presentation to a physician [4]. Additionally, because the symptoms tend to be nonspecific and the fact that this typically occurs in older individuals, these symptoms are often initially attributed to other co-morbid diseases such as coronary artery disease, obesity, medications or deconditioning, thus further delaying diagnosis.

In many IPF patients, cough is often the first symptom, preceding dyspnea on exertion sometimes by years. It affects upwards of 70–85% of patients with IPF [9]. Patients typically describe a dry cough that is worse with exercise and talking, especially on the phone. Indeed, the first study to document the actual number of coughs in IPF patients measured a median of 9.4 coughs per hour with a range of 1.9–39.4 coughs an hour in patients with IPF [8]. The IPF cough is more common during the day (median cough count 14.6 cough per hour) compared to at night (1.9 cough per hour) and rarely awakens the patients from sleep [8]. When compared to other disease with cough, IPF cough rates were statistically significantly higher then cough due to asthma but similar to those of chronic idiopathic cough [8]. The cough may co-exist or be exacerbated by co-morbid illnesses such as post-nasal drip, gastroesophageal reflux (GERD), or cough-variant asthma, although rarely completely resolves despite treatment for these illnesses [10,11]. IPF cough is often significant and debilitating, and it is usually refractory to medical therapy [8,12]. Several investigators have demonstrated that IPF cough adversely impacts quality of life [8,13,14]. Indeed, patients often greatly modify their lives to avoid social situations where their excessive, barking cough is embarrassing or due to fear of post-tussive emesis, incontinence or syncope. In addition to hampering quality of life, cough has been shown to be an independent predictor of severity of disease and disease progression [7]. Patients with IPF and cough have more severe disease than those with IPF and no cough as measured by higher dyspnea scores, lower FVC, and higher rates of exertional desaturation [7]. Multivariate analysis has also found that the presence of cough is an independent predictor of disease progression, defined as decline in FVC and/or DLCO, death, or need for lung transplantation [7]. Thus, in patients with IPF, cough is more than just an annoyance, it has a significant impact on quality of life and is a marker of more severe disease.

### 1.2. Mechanisms of IPF cough

Although cough is a frequent and significant symptom in patients with IPF, the exact mechanism by which it occurs is not entirely known. Some studies suggest that it is mediated by increased cough sensitivity in response to both mechanical and chemical stimuli. Cough is an important reflex by which the body protects the lungs from toxins, particles, and microorganisms in the upper airway that might travel deeper into the respiratory tract and cause damage (Fig. 1). Cough is mediated by two classes of sensory neurons: Aδ-fibers and unmyelinated C-fibers [15–17]. Aδ-fibers can further be divided into three groups: rapidly adapting receptors (RAR), nociceptive, and polymodal [18]. RAR-like Aδ-fibers and polymodal Aδ-fibers respond to mechanical stimulation but not to chemical signals [15,19,20]. Nociceptive Aδ-fibers respond to chemical stimuli such as capsaicin and bradykinin and are less sensitive to mechanical stimulation [17,18]. The other class of cough receptors are C-fibers, which respond to both mechanical stimuli and to chemical mediators, such as histamine, bradykinin, tachykinin, and capsaicin [15,20–23]. These sensory neurons travel along a branch of the vagus nerve from the airways to the brainstem [19]. When stimulated, these neurons exert their effects by release of neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, and neurokinin A [23–28]. These mediators then act on networks of neurons within the brainstem that coordinate breathing to generate a cough [20,29].

The cough reflex is further regulated by other chemical mediators and environmental factors that modulate the activity of the sensory neurons. For example, reduction in pH, as can be seen in inflamed tissues, has been shown to lower the threshold at which mechanical stimulation triggers cough [30]. Histamine has also been found to increase cough sensitivity in guinea pigs, through the activity of P2X receptors found on vagal afferents [31,32]. Allergic inflammation modulates the cough reflex by increasing the presence of CGRP and substance P within airway sensory neurons [33]. Additionally, chronic tobacco smoke exposure has been shown to increase *C*-fiber responsiveness in guinea pigs [34,35]. In human studies, cough sensitivity in response to mechanical stimulation was found to be increased in volunteers with an upper respiratory tract infection [36]. Thus cough is a complex reflex by which chemical and mechanical stimuli are integrated by sensory neurons and transmitted to the brainstem to activate a central cough reflex. Perturbations in this system, as can be seen with infection, inflammation, or exposure to certain chemicals, can result in increased sensitivity of these pathways and thus pathologic cough.

IPF is known to cause architectural distortion within the lungs and traction bronchiectasis, which is theorized to put mechanical stress on airways, leading to increased cough sensitivity [37]. One study found that mechanical stimulation of the chest wall with a device that percussed the chest wall at 20–60 Hz was able to induce cough in patients with IPF but not in healthy controls [38]. This cough response was greatest when percussion was performed at the base of the lung, where patients tend to have more significant fibrosis [38]. Other studies have looked at the cough response to inhaled capsaicin, which is used to measure cough sensitivity because it induces cough in a dose-dependent manner [22]. Patients with IPF were found to cough after receiving a significantly lower concentration of capsaicin than what was required to elicit a cough in healthy controls [39,40]. IPF patients also had a cough response to inhalation of substance P, which healthy controls did not have [39].

Another potential mechanism for cough in IPF may involve the production and clearance of airway mucus. The MUC5B gene codes for an airway mucin, and a polymphorism in MUC5B has been linked to the development of IPF [41]. Within patients who have IPF, presence of this MUC5B polymorphism has been found to be associated with increased cough severity [42]. This polymorphism confers increased expression of MUC5B, and the authors