Respiratory Medicine (2013) **107**, 1789–1796

Available online at www.sciencedirect.com

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Can exhaled nitric oxide differentiate causes of pulmonary fibrosis?

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Received 2 March 2013; accepted 7 July 2013
Available online 5 September 2013

KEYWORDS
Exhaled nitric oxide;
Hypersensitivity pneumonitis;
Idiopathic pulmonary fibrosis;
Bronchiolar disease

Summary
Background: Interstitial lung diseases (ILD) comprise a heterogeneous group of disorders, and when diagnosed at the stage of pulmonary fibrosis, the underlying lung disease can sometimes be difficult to identify. The aim of the present study was to determine whether there are differences in FE_{NO} (fraction of exhaled nitric oxide) between different subtypes of fibrotic ILD.
Methods: Sixty-one patients, with honeycombing on computed tomography (CT) scan, and whose FE_{NO} levels had been measured during chronic dyspnoea evaluation, were divided into four groups based on pulmonary fibrosis aetiology: idiopathic pulmonary fibrosis (IPF), chronic hypersensitivity pneumonitis (HP), connective tissue disease-associated ILD disorders (CTD-ILD), drug-induced pneumonia. The FE_{NO} values of each group were compared and CT scan features were analysed to identify the mechanisms involved in FE_{NO} change.
Results: The median FE_{NO} value of patients with chronic HP was 51 ppb (IQR 36–74), higher than that of the other groups (22 ppb (IQR 17–30) in IPF, 19 ppb (IQR 17–21) in drug-induced pneumonia, and 25 ppb (IQR 17–37) for CTD-ILD; $p = 0.008$). At the cut-off value of 41 ppb, the optimal sensitivity and specificity to diagnose HP with FE_{NO} were respectively

Abbreviations: CANO, alveolar concentration of exhaled NO; DIP, drug induced pneumonia; FE_{NO}, fractional exhaled nitric oxide; FEF 25–75, 25–75% Forced Expiratory Flow; FEV_1, Forced Expiratory Volume in 1 s; GGO, ground-glass opacities; HP, hypersensitivity pneumonitis; IQR, interquartile range; ILD, interstitial lung disease; CTD-ILD, connective tissue disease-associated ILD disorders; IPF, idiopathic pulmonary fibrosis; $J'aw_{NO}$, conducting airway flux; SSC, systemic sclerosis; TLC, Total Lung Capacity; VC, vital capacity.

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0954-6111/$ - see front matter
http://dx.doi.org/10.1016/j.rmed.2013.07.007

76.9% and 85.4%. On CT scans, only extensive lobular areas with decreased attenuation, a recognized marker of bronchiolar disease, were associated with high FE_{NO} values ($p = 0.0002$). *Conclusion:* FE_{NO} could be a tool for differentiating chronic HP from other types of pulmonary fibrosis. The mechanism involved seems to be bronchiolar disease.

Introduction

Interstitial lung diseases (ILD) comprise a group of heterogeneous disorders which can lead to pulmonary fibrosis with a poor prognosis [1,2]. ILD can be idiopathic, or the consequence of an underlying disease which is sometimes difficult to identify when the diagnosis is made at the stage of fibrosis, characterized by honeycombing on computed tomography (CT) scan. However, it is important to identify the underlying lung disease, as it may influence survival or treatment. For example, the survival rate for systemic sclerosis with ILD is better than for other connective tissue diseases with ILD, and the prognosis for non-specific interstitial pneumonia (NSIP) is much better than for idiopathic fibrosis (IPF) [3,4]. In terms of treatment, oral corticosteroid may be used in hypersensitivity pneumonitis (HP), a cause of ILD, but it has little or no effect on IPF [1,5,6]. Furthermore, the diagnosis of HP in the context of ILD is crucial, so that any contact with the antigen responsible for the disease can be avoided [6].

Patient care could therefore be improved by identifying a marker to differentiate causes of honeycombing. In HP, IgG precipitin to the antigen may be missed in the early stages of the disease. Thoracic CT may help to differentiate between causes of honeycombing [7]. Lobular areas of decreased attenuation or centrilobular nodules are mostly observed in HP. Conversely, basal predominance of honeycombing is mostly seen in IPF [7]. However, CT scan features are not specific and surgical lung biopsy is sometimes required to establish the diagnosis [7,8].

Nitric oxide (NO) is produced by airway epithelial cells in the respiratory tract, and by airway and circulatory endothelial cells in both large and peripheral airways. Fractional exhaled nitric oxide (FE_{NO}) is commonly used as a marker of airway inflammation in asthma to determine the optimal dose of inhaled corticosteroid [9,10]. There have been few studies of FE_{NO} in ILD, and they have mostly concerned systemic sclerosis and had conflicting results [11,12]. Furthermore, to the best of our knowledge, no study has focused on FE_{NO} as a marker of pulmonary fibrosis aetiology.

The aim of the present study was to determine whether there are differences in FE_{NO} between different subtypes of fibrotic ILD. We carried out a retrospective analysis of FE_{NO} data of patients presenting with dyspnoea and honeycombing on CT. Patients were divided into four groups: chronic HP, IPF, connective tissue disease-associated ILD disorders (CTD-ILD), and drug-induced pneumonia. FE_{NO} values were compared between groups, and CT scan features were analysed to investigate the relationship between anatomic lesion and increase in FE_{NO}.

Sample and methods

Study sample

The files of patients with pulmonary fibrosis attending the respiratory medicine department of Tours University Hospital between June 2009 and June 2012 were reviewed. Inclusion criteria were honeycombing on CT scan and measurement of fractional exhaled nitric oxide (FE_{NO}) as part of chronic dyspnoea management ($n = 74$). Time to onset of dyspnoea must be superior to 3 months. Patients with a recent increase of dyspnoea were excluded. Honeycombing was defined as subpleural clustered cystic airspaces with thick fibrous walls, as described in the glossary of the Fleischner Society [13]. Patients were excluded if they had symptoms of asthma as defined by GINA, or post-bronchodilatator improvement of FEV_1 on pulmonary function tests [14]. Patients were also excluded if they had no clear aetiology of pulmonary fibrosis and if surgical biopsy was not available ($n = 13$).

Causes of pulmonary fibrosis were divided into four groups: chronic hypersensitivity pneumonitis (HP), idiopathic pulmonary fibrosis (IPF), connective tissue disease with lung involvement (CTD-ILD), and drug-induced pneumonia (DIP). Diagnosis of IPF was based on ATS/ERS criteria [1]. Diagnosis of chronic HP was based on the criteria established by Lacasse et al. or histological features [15—17]. CTD-ILD was identified on the basis of criteria described in the literature [18—20]. The pharmacological criteria proposed by Edwards et al. were used to diagnose drug-induced pneumonia [21]. Precipitins were negative for all patients in the IPF, CTD-ILD and DIP groups and none of them had allergen exposure. Diagnosis was made by two lung specialists who established a consensus. They were blinded to FE_{NO} values and CT quantification of lesions performed by radiologists. Connective tissue diseases were confirmed by a rheumatologist or an internal medicine physician.

Data concerning age, sex, smoking habits, pulmonary function tests, lactate dehydrogenase serum level (LDH), blood eosinophilia, oxygen treatment and immunosuppressive treatment (including corticosteroid treatment) were collected to rule out potential confounding factors of FE_{NO} values. The study was approved by the Institutional Review Board of the French society for respiratory medicine — *Société de Pneumologie de Langue Française* — (CEPRO# 2011-028). All patients gave their informed consent for inclusion in this study.

Pulmonary function tests

Lung function tests were performed using Sensormedics Vmax Encore plethysmography (Carefusion®; San Diego,