

## Original Article

## Post-bronchodilator Reversibility of FEV<sub>1</sub> and Eosinophilic Airway Inflammation in COPD



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## ABSTRACT

**Introduction:** The relationship between bronchodilator responsiveness and eosinophilic airway inflammation has not been well documented in COPD. It has been investigated in this retrospective study. This issue has grown in importance due to increasing interest in the asthma-COPD overlap syndrome.

**Methods:** 264 stable COPD patients with no past history of asthma were retrospectively analyzed. Correlation analyses between FEV<sub>1</sub> reversibility and sputum eosinophil levels were conducted. Sputum eosinophil levels were dichotomized using FEV<sub>1</sub> reversibility cut-off points (>0.4 L and >15% vs. >0.2 L and >12%) and compared. The effectiveness of FEV<sub>1</sub> reversibility to predict sputum eosinophilia (>3%) was analyzed with a logistic regression and a ROC analysis.

**Results:** 82 (31.1%) patients with higher FEV<sub>1</sub> reversibility values (0.14 vs. 0.11 L,  $P=.01$ ) presented sputum eosinophilia. FEV<sub>1</sub> reversibility was weakly correlated with the sputum eosinophil level ( $r = 0.162$ ,  $P=.008$ ). Patients with FEV<sub>1</sub> > 0.4 L and >15% increment had higher sputum eosinophil levels (6.11 vs. 1.02%,  $P=.049$ ) whereas the level did not differ when dichotomized by FEV<sub>1</sub> increment >0.2 L and >12%. Very positive FEV<sub>1</sub> reversibility (>0.4 L and >15%) predicted sputum eosinophilia after adjustment for age, baseline FEV<sub>1</sub> and FVC (OR: 4.262,  $P=.029$ ). In the ROC analysis, the AUC was 0.58 ( $P=.034$ ), and FEV<sub>1</sub> increment >0.4 L and >15% had a positive predictive value of 63.6% and an overall accuracy of 70.1%.

**Conclusions:** FEV<sub>1</sub> reversibility was weakly correlated with sputum eosinophil levels in COPD. Positive FEV<sub>1</sub> reversibility (>0.4 L and >15%) is moderately successful in predicting sputum eosinophilia (>3%).

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### Reversibilidad del FEV<sub>1</sub> postbroncodilatador e inflamación eosinofílica de la vía aérea en la EPOC

## RESUMEN

**Introducción:** La relación entre la reactividad al broncodilatador y la inflamación eosinofílica de la vía aérea no está bien documentada en la EPOC y se ha investigado en este estudio retrospectivo. Esta cuestión ha adquirido mayor importancia debido al creciente interés que despierta el fenotipo mixto asma-EPOC.

**Métodos:** Se analizó retrospectivamente a 264 pacientes con EPOC estable y sin antecedentes de asma. Se efectuaron análisis de correlación entre la reversibilidad del FEV<sub>1</sub> y las concentraciones de eosinófilos en esputo, que se compararon una vez dicotomizadas en función de diferentes puntos de corte de la reversibilidad del FEV<sub>1</sub> (> 0,4 l y > 15% vs. > 0,2 l y > 12%). La utilidad de la reversibilidad del FEV<sub>1</sub> para

## Palabras clave:

EPOC

Eosinófilo

Prueba broncodilatadora

Reversibilidad del FEV<sub>1</sub>

Fenotipo mixto asma-EPOC

**Abbreviations:** ACOS, asthma-COPD overlap syndrome; PBT, a positive bronchodilator test; VPBT, a very positive bronchodilator test; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; ΔFEV<sub>1</sub>, post-bronchodilator FEV<sub>1</sub> increment; ROC curve, receiver operating characteristic curve; CI, confidence interval; OR, odds ratio.

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predecir la eosinofilia del esputo (> 3%) se evaluó mediante una regresión logística y un análisis de la curva ROC.

**Resultados:** En los 82 pacientes (31,1%) que presentaban eosinofilia del esputo, la reversibilidad del FEV<sub>1</sub> fue mayor (0,14 vs. 0, 1 l,  $p=0,01$ ). La reversibilidad del FEV<sub>1</sub> se correlacionó débilmente con la concentración de eosinófilos en esputo ( $r=0,162$ ,  $p=0,008$ ). Los pacientes con incrementos del FEV<sub>1</sub> > 0,4 l y > 15% mostraron mayores concentraciones de eosinófilos en el esputo (6,11 vs. 1,02%,  $p=0,049$ ), aunque las concentraciones no difirieron tras dicotomizarlas de acuerdo a un incremento del FEV<sub>1</sub> > 0,2 l y > 12%. Tras ajustarla en función de la edad, el FEV<sub>1</sub> inicial y la FVC, la reversibilidad del FEV<sub>1</sub> muy alta (> 0,4 l y > 15%) continuó siendo significativa para predecir la eosinofilia del esputo (OR: 4,262,  $p=0,029$ ). El análisis de la curva ROC mostró que el valor predictivo positivo de un AUC de 0,58 ( $p=0,034$ ) y un incremento del FEV<sub>1</sub> > 0,4 l y > 15% es del 63,6%, con una precisión total del 70,1%.

**Conclusiones:** En pacientes con EPOC, la reversibilidad del FEV<sub>1</sub> se correlacionó débilmente con las concentraciones de eosinófilos en esputo. Una reversibilidad del FEV<sub>1</sub> muy alta (> 0,4 l y > 15%) puede predecir la eosinofilia del esputo (> 3%), pero su rendimiento es modesto.

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## Introduction

COPD and asthma are common obstructive lung diseases, both characterized by chronic airway inflammation and airflow limitation. Despite similar symptoms, they are thought of as two distinct conditions in terms of disease onset, frequency of symptoms and reversibility of airway obstruction and pathophysiology.<sup>1</sup> However, the line between asthma and COPD is not well-demarcated, since a substantial number of patients may share features of both diseases. Patients occupying this gray area are now categorized as mixed COPD-asthma or asthma-COPD overlap syndrome (ACOS).<sup>2,3</sup>

Enhanced bronchodilator response and eosinophilic airway inflammation are considered characteristic of asthma, and their presence may support diagnosis.<sup>4</sup> These features are also observed in a substantial number of COPD patients.<sup>5</sup> Unlike asthma, the implication of bronchodilator responsiveness and eosinophilic airway inflammation in COPD has not been well documented. The role of these features has also been highlighted in the context of ACOS.<sup>2</sup> Based on expert consensus, the recent Spanish COPD guidelines have adopted sputum eosinophilia and a very positive bronchodilator test ([VPBT]: FEV<sub>1</sub> increase >15% and >400 ml over baseline) as the major diagnostic criteria of ACOS, while a positive bronchodilator test ([PBT]: FEV<sub>1</sub> increase >12% and >200 ml over baseline) as one of the minor criteria.<sup>2</sup> Nonetheless, the criteria established to define bronchodilator reversibility seem arbitrary, and evidence supporting these criteria or cut-offs is limited.

We hypothesized that bronchodilator reversibility would be linked to sputum eosinophilia in COPD. In this study, we evaluated the correlation between sputum eosinophil levels and the extent of bronchodilator reversibility in COPD patients. We also determine whether or not COPD patients with PBT or VPBT have eosinophilic airway inflammation evidenced by sputum eosinophil levels.

## Materials and Methods

The study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 2015-09-004AC) and reported in accordance with the STROBE statement.<sup>6</sup>

### Study Subjects

Data from sputum analyses and bronchodilator tests from COPD patients included in our prospective clinical trials from 2002 to 2012<sup>7–10</sup> were retrospectively collected and analyzed. The process of patient selection is detailed in Fig. A1 in the appendix. The data were collected in the outpatient pulmonary clinic of Taipei Veterans General Hospital after obtaining written informed consent in

each case. Due to no further follow-up or contact with the patients, the IRB approved the protocol of the current study and waived the requirement of a second informed consent.

These patients were diagnosed with COPD based on GOLD guidelines.<sup>11</sup> Inclusion criteria were: age >40 years, smoking history  $\geq 20$  pack-years, either newly diagnosed or no use of oral/inhaled corticosteroids for a minimum of 3 months, and post-bronchodilator FEV<sub>1</sub>/FVC (forced expiratory volume in 1 s/forced vital capacity) <70%. Subjects with acute exacerbation of COPD, respiratory tract infection within the 4 weeks prior to pulmonary function testing, or a past history of asthma, rhinitis or eczema, and other chronic lung disease were excluded.

### Bronchodilator Reversibility, Sputum Analysis and Allergen Test

Bronchodilator tests were carried out in the morning, followed by sputum induction on the same day. Bronchodilator reversibility was defined as change in FEV<sub>1</sub> ( $\Delta$ FEV<sub>1</sub>) over pre-bronchodilator baseline levels 30 min after inhalation of 400  $\mu$ g of salbutamol.<sup>12</sup> Sputum was induced and processed as described previously.<sup>7</sup> The allergen test was assessed by specific IgE levels against common aeroallergens, which were measured with fluoroenzyme immunoassay (ImmunoCAP, Pharmacia Diagnostics).<sup>9,10</sup> The results were interpreted using 0.35 kU/l as a cutoff.

### Statistical Analyses

Statistical analyses were performed utilizing SPSS software (version 17.0; SPSS, Inc., Chicago, IL). Data were expressed as median (interquartile range) or percentage. Correlation was analyzed using Pearson's correlation test. Patients were dichotomized by the different definitions of bronchodilator response – PBT ( $\Delta$ FEV<sub>1</sub> >0.2 L and >12%) or VPBT ( $\Delta$ FEV<sub>1</sub> >0.4 L and >15%).<sup>2</sup> Comparisons of continuous variables were assessed using the Mann–Whitney *U* test, due to their non-parametric distribution. Categorical variables were compared using the *Chi* square/Fisher's Exact Test. A binary logistic regression model was used for multivariate adjustment. A receiver operating characteristic (ROC) curve analysis was performed to determine the efficacy of FEV<sub>1</sub> reversibility as a predictor of sputum eosinophilia (>3%)<sup>10,13</sup> and its sensitivity/specificity/positive predictive value/negative predictive value/overall accuracy at the cut-off of 0.4 L and 15% increment.<sup>14</sup> Values of two-sided  $P < .05$  were considered significant.

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