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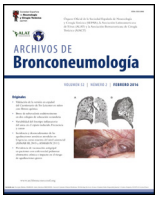

Original Article

Alveolar and Bronchial Nitric Oxide in Chronic Obstructive Pulmonary Disease and Asthma–COPD Overlap☆

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ABSTRACT

Introduction: Exhaled nitric oxide (F_{ENO}) measurements differentiate COPD phenotypes from asthma–COPD overlap (ACO). To date, no study has been conducted to determine whether alveolar and bronchial components differ in this group of patients.
Methods: This was an observational cross-sectional study recruiting ambulatory COPD patients. F_{ENO} was measured, differentiating alveolar (C_{ANO}) from bronchial (J_{awNO}) components using a multiple-flow technique. C_{ANO} and J_{awNO} values were compared between eosinophilic COPD patients (defined as ≥300 eosinophils/μL in peripheral blood test, or ≥2% eosinophils or ≥3% eosinophils), and a linear regression analysis was performed to determine clinical and biological variables related to these measurements.
Results: 73 COPD patients were included in the study. Eosinophil counts were associated with increased values of C_{ANO} and J_{awNO} (for the latter only the association with ≥300 or ≥3% eosinophils was significant). C_{ANO} was also associated with CRP, and J_{awNO} with smoking.
Conclusions: Patients with COPD and ACO characteristics show increased inflammation in the large and small airways. C_{ANO} and J_{awNO} are associated with clinical and biological variables.

Óxido nítrico alveolar y bronquial en la enfermedad pulmonar obstructiva crónica y el solapamiento de asma y EPOC (ACO)

Palabras clave:
EPOC
Óxido nítrico
Óxido nítrico alveolar
Óxido nítrico bronquial

RESUMEN

Introducción: La medición del óxido nítrico en el aire exhalado diferencia fenotipos de pacientes con EPOC del solapamiento de asma y EPOC (ACO). Hasta el momento no se ha estudiado si existen diferencias entre los componentes alveolar y bronquial del F_{ENO} en este grupo de pacientes.
Métodos: Estudio observacional transversal realizado en consultas externas de Neumología, incluyendo a pacientes con diagnóstico de EPOC a los que se les realizó una determinación del óxido nítrico en aire exhalado – F_{ENO}– diferenciando en esta medida el componente alveolar –C_{ANO}– y el de vía aérea central –J_{awNO}–, y realizando las mediciones a distintos flujos. Se compararon los valores de C_{ANO} y J_{awNO} entre los pacientes con eosinofilia (definidos como aquellos pacientes con ≥300 eosinófilos/μL en sangre periférica, o bien ≥2% eosinófilos o ≥3% eosinófilos) y se realizó un análisis de regresión lineal para estudiar las variables clínicas y biológicas que se asociaban a estas mediciones.

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Resultados: Participaron en el estudio 73 pacientes con EPOC. Los criterios de eosinofilia utilizados se asociaban a incrementos de los valores de C_{ANO} y de J_{awNO} (en este último caso solo los criterios ≥300 eosinófilos y ≥3% eosinófilos). C_{ANO} se asoció al recuento de eosinófilos y PCR, y J_{awNO} se asoció a tabaquismo y recuento de eosinófilos.
Conclusiones: Los pacientes diagnosticados de EPOC y que tienen características de ACO muestran mayor inflamación a nivel bronquial y de vía aérea pequeña. C_{ANO} y J_{awNO} se relacionan con variables clínicas y biológicas.

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as chronic, irreversible airflow limitation, which is usually progressive and associated with an abnormal inflammatory reaction mainly caused by smoking.[1,2] This characteristic inflammatory response in COPD is mediated by macrophages, neutrophils, and cytotoxic T-cells (CD9+), and is accompanied by structural changes that can cause narrowing of the airways, changes in the arteries, pulmonary parenchymal emphysema, or combinations of all three.[3] These structural changes begin in the early stages of the disease,[4] especially in the small airways. In some patients, the inflammatory response is mediated primarily by Th2 lymphocytes and eosinophils, generating clinical symptoms that share features with bronchial asthma. Although the characteristics have not been clearly defined, this syndrome is currently known as asthma–COPD overlap (ACO).[5–7] One of the biological factors distinguishing COPD patients with this phenotype is their eosinophil count in peripheral blood,[8] but so far, no optimal cut-off points have been clearly established.

The measurement of nitric oxide in exhaled air as a marker of airway inflammation has advanced greatly in recent years, to the extent that several equations are now available that separate the alveolar or distal airway component (C_{ANO}) from the central bronchial component (J_{awNO}).[9–11] Both components have been widely studied in patients with bronchial asthma: the alveolar component (C_{ANO}) has been shown to be higher among patients with more severe asthma, suggesting greater inflammation in this region.[12,13] Measuring C_{ANO} can also help identify patients who are likely to improve with the use of inhaled corticosteroids (ICS)[14] and patients who present an increased risk of comorbidity.[15]

Different types of COPD patients can be identified by measuring nitric oxide in exhaled air (F_{ENO}).[16,17] This variable is also associated with the presence of eosinophils in sputum,[18,19] a typical finding in ACO. F_{ENO} levels are also a good predictor of response to the use of ICS.[20,21] Studies differentiating the alveolar fraction from the bronchial fraction of F_{ENO} in COPD patients have shown that inflammation is distal in some cases,[22] a phenomenon also observed in patients with severe asthma.

In a cross-sectional study conducted in Spain, elevated F_{ENO} levels were found in patients defined as having ACO, with an optimal cut-off of 20 parts per billion (ppb) for the diagnosis of ACO.[16]

However, the differences between the alveolar and bronchial components and the clinical and biological variables associated with inflammation in either of the territories have not been studied in depth.

The aim of this study is to determine differences in F_{ENO} levels between the alveolar and bronchial compartments in patients fulfilling biological criteria for ACO, and whether these differences are associated with other clinical or biological variables which might determine whether inflammation occurs more in a particular territory (C_{ANO} and J_{awNO}).

Materials and Methods

Study design

This was an observational, cross-sectional study to evaluate the differences in the production of C_{ANO} and J_{awNO} and the relationship of these variables with clinical variables in a consecutive series of COPD patients who performed complete lung function testing (measurement of lung volumes and diffusion) in our respiratory outpatient clinic. The study was performed between November 2014 and May 2015.

Study population

The study population comprised adult patients over 40 years of age, smokers, or non-smokers with an accumulated pack-year index of at least 10, and a diagnosis of COPD according to national and international guidelines and recommendations.[1] Exclusion criteria were the presence of any respiratory disease other than COPD that might significantly affect the examination (including a history of bronchial asthma), a history of COPD exacerbation in the 4 weeks before the test, inability to perform the study procedures or complete the questionnaires, and participation in any other clinical trial or research study.

Study variables

Clinical variables: for each patient, data were collected on their respiratory disease, including time since onset, toxic habits, comorbidities, baseline dyspnea measured according to the modified Medical Research Council (mMRC) scale, COPD Assessment Test (CAT®) questionnaire, and history of exacerbations in the previous year (classified as moderate if treated with systemic corticosteroids and/or antibiotics in an outpatient setting, and severe in the case of admission > 24 h to a hospital or emergency department).

Blood tests: before lung function tests were performed, peripheral blood was obtained for the determination of absolute eosinophil counts and percentages, and for the measurement of C-reactive protein (CRP).

Measurement of the alveolar (C_{ANO}) *and bronchial* (J_{awNO}) *component of nitric oxide in exhaled air:* before lung function tests were performed, patients performed 3 F_{ENO} maneuvers at 50 mL/s (F_{ENO50}) followed by additional determinations at 100 mL/s, 200 mL/s, and 350 mL/s (at least 2 each) in order to obtain C_{ANO} and J_{awNO} levels, according to international guidelines.[23,24] An NO chemiluminescence analyzer (HypAir F_{ENO}®, Medisoft, Belgium) was used.

Lung function variables: patients performed spirometry at baseline and after inhaling salbutamol 400 μg in accordance with national and international guidelines.[25,26] Lung volumes and diffusing capacity of the lung for carbon monoxide were also determined according to applicable recommendations.[27,28] All measurements were performed on the same lung function testing equipment (MasterLab, Jaeger GmbH, Germany).