Arch Bronconeumol. 2016;52(7):361–367

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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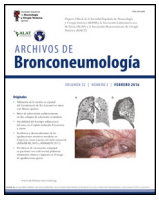

Original Article

Lack of Correlation Between Pulmonary and Systemic Inflammation Markers in Patients with Chronic Obstructive Pulmonary Disease: A Simultaneous, Two-Compartmental Analysis☆

Belen Núñez,[a,b,c] Jaume Sauleda,[a,b,c,*] Judith Garcia-Aymerich,[d,e,f] Aina Noguera,[a,b,g] Eduard Monsó,[c,h] Federico Gómez,[c,i] Esther Barreiro,[c,e,j,k] Alicia Marín,[c,h] Josep Maria Antó,[d,e,f] Alvar Agusti[c,l], Members of the Phenotype Characterization and Evolution of Chronic Obstructive Pulmonary Disease (PAC-COPD) Study Group[◊]

[a] *Servei de Pneumologia, Hospital Universitari Son Espases, Palma de Mallorca, Spain*
[b] *Instituto de Investigación Sanitaria de Palma (IdisPa), Palma de Mallorca, Spain*
[c] *CIBER Enfermedades Respiratorias (CIBERES), Spain*
[d] *Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain*
[e] *Departament de Ciències Experimentals i de la Salut (CEXS), Universitat Pompeu Fabra, Barcelona, Spain*
[f] *CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain*
[g] *Servei d'Anàlisis Clíniques, Hospital Universitari Son Espases, Palma de Mallorca, Spain*
[h] *Hospital Parc Taulí, Sabadell, Barcelona, Spain*
[i] *Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
[j] *Grupo de Investigación en Mecanismos de Predisposición al Cáncer de Pulmón, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain*
[k] *Servei de Pneumologia, Hospital del Mar, Barcelona, Spain*
[l] *Institut del Tòrax, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 26 October 2015
Accepted 12 January 2016
Available online 26 May 2016

Keywords:
Chronic bronchitis
Emphysema
Cytokines
C-reactive protein

ABSTRACT

Introduction: The origin of systemic inflammation in chronic obstructive pulmonary disease (COPD) patients remains to be defined, but one of the most widely accepted hypothesis is the 'spill over' of inflammatory mediators from the lung to the circulation.
Objective: To evaluate the relationship between pulmonary and systemic inflammation in COPD quantifying several inflammatory markers in sputum and serum determined simultaneously.
Methodology: Correlations between various inflammatory variables (TNFα, IL6, IL8) in sputum and serum were evaluated in 133 patients from the PAC-COPD cohort study. A secondary objective was the evaluation of relationships between inflammatory variables and lung function.
Results: Inflammatory markers were clearly higher in sputum than in serum. No significant correlation was found (absolute value, r=0.03–0.24) between inflammatory markers in blood and in sputum. There were no significant associations identified between those markers and lung function variables, such as FEV1, DLCO and PaO_2 neither.
Conclusions: We found no correlation between pulmonary and systemic inflammation in patients with stable COPD, suggesting different pathogenic mechanisms.

☆ Please cite this article as: Núñez B, Sauleda J, Garcia-Aymerich J, Noguera A, Monsó E, Gómez F, et al. Ausencia de correlación entre marcadores de inflamación pulmonar y sistémica en pacientes con enfermedad pulmonar obstructiva crónica: un análisis bi-compartimental simultáneo. Arch Bronconeumol. 2016;52:361–367.

* Corresponding author.
E-mail address: jaume.sauleda@ssib.es (J. Sauleda).

◊ Members of the Phenotype Characterization and Evolution of Chronic Obstructive Pulmonary Disease (PAC-COPD) Study Group are listed in Appendix A.

1579-2129/

Ausencia de correlación entre marcadores de inflamación pulmonar y sistémica en pacientes con enfermedad pulmonar obstructiva crónica: un análisis bi-compartimental simultáneo

Palabras clave:
Bronquitis crónica
Enfisema
Citoquinas
Proteína C reactiva

RESUMEN

Introducción: El origen de la inflamación sistémica en pacientes con enfermedad pulmonar obstructiva crónica (EPOC) es poco conocido, y una de las hipótesis más aceptadas es el paso de la inflamación del pulmón a la sangre (*spill-over*).
Objetivo: Evaluar la relación entre la inflamación pulmonar y sistémica en la EPOC mediante la cuantificación de diversos marcadores inflamatorios en esputo y suero obtenidos en el mismo individuo de forma simultánea.
Metodología: De 133 pacientes de la cohorte PAC-EPOC se evaluaron las relaciones entre diferentes variables inflamatorias (TNFα, IL-6, IL-8) en suero y esputo. Como objetivo secundario se evaluaron las relaciones de las variables inflamatorias de suero con la función pulmonar.
Resultados: Los valores de los marcadores inflamatorios fueron claramente superiores en esputo que en suero. No se hallaron correlaciones relevantes (en valor absoluto, *r*=0,03–0,24) entre los marcadores inflamatorios en sangre y en esputo. Tampoco se identificaron asociaciones significativas entre dichos marcadores, con variables de función pulmonar como el FEV_1, DL_{CO} y la PaO_2.
Conclusiones: En pacientes con EPOC estable no existe correlación entre la inflamación pulmonar y sistémica, lo que sugiere mecanismos patogénicos diferentes.

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with pulmonary and systemic inflammation.[1–3] Pulmonary inflammation appears to be more common in patients with greater airflow limitation, although it should be pointed out that current data are based on cross-sectional analyses,[4] so no cause–effect relationship can be established. While systemic inflammation does not occur in all COPD patients, it is associated with higher mortality and exacerbation rates in patients in whom it persists over time.[1]

The origin of systemic inflammation in COPD remains to be defined, but one of the most widely accepted hypothesis is the 'spill-over' of inflammatory mediators from the lung to the blood, suggesting an association between these inflammatory processes. However, the relationship between pulmonary and systemic inflammation in COPD continues to be a topic for debate.[5–7] Studies published to date have several limitations, such as relatively small sample sizes,[6,8,9] or lack of simultaneous quantification (in the same patient) of the same inflammatory markers in both pulmonary and systemic compartments.[10]

The aim of this study was to address these limitations and to evaluate possible relationships between pulmonary and systemic inflammation in COPD, by quantifying inflammatory markers in sputum and serum samples obtained simultaneously from the same individual, in a large sample of COPD patients (*n*=133) from the PAC-COPD study cohort.[11,12] Secondary objectives included the exploration of potential associations between systemic inflammation and lung function variables possibly related with pulmonary inflammation, such as forced expiratory volume in 1 s (FEV_1), diffusing capacity of the lung for carbon monoxide (DL_{CO}) and partial pressure of oxygen in arterial blood (PaO_2).

Method

Population and Ethical Aspects

The PAC-COPD study included 342 patients hospitalized for a first COPD exacerbation in 9 hospitals in Spain between January 2004 and March 2005.[11,12] Patients were followed up for 3 months after hospital discharge (maximum deviation of 1 week). They were in a clinically stable phase (8 weeks without new exacerbations or changes in medication) and followed up in outpatient clinics for 3 years.[12] The COPD diagnosis was established when the patient was clinically stable, in accordance with ATS/ERS recommendations.[13] Patients younger than 45 years of age, with cancer, post-tuberculous sequelae, pneumonectomy and/or pnemoconiosis were excluded. In total, 113 patients (39% of the total cohort) with simultaneously obtained samples evaluable for pulmonary and systemic inflammation took part. The study was approved by the Ethics Committee of all participating hospitals, and all patients signed informed consent forms.

Clinical and Functional Determinations

As described above,[11,12] clinical data and smoking history were obtained from validated questionnaires. Body mass index (BMI) was calculated as the individual's weight divided by the square of their height in meters.[11,12] Forced spirometry with bronchodilator challenge, lung volumes, DL_{CO} and blood gases were quantified using standard methodologies.[14–16] Reference values for spirometry, lung volumes and DL_{CO} correspond to a Mediterranean population.[17,18]

Pulmonary Inflammation

Whenever possible, a spontaneous sputum sample was obtained at least 60 min after the lung function tests (225 patients). If the patient could not expectorate spontaneously, a sputum sample was obtained by induction with saline serum, according to the conventional method.[19] Of the patients who provided a sputum sample (*n*=255), 133 had <20% squamous cells and were included in the analysis.[20]

Concentrations of interleukin 6 (IL-6), IL-8 and tumor necrosis factor alpha (TNFα) (cytokine bead array system, BD Biosciences, San Diego, CA, US) were quantified in sputum supernatant. The lower limits of quantification (LLQ) of IL-6, IL-8 and TNFα were 2.5, 3.6 and 3.7 pg/ml, respectively. According to previous recommendations, patients with values below these levels were assigned a nominal level of half of the LLQ in order to avoid a downward bias.[1] All determinations were performed in duplicate in the central laboratory of the Hospital Universitari Son Espases (Palma de Mallorca, Spain). Since the coefficient of variation was <10% in all cases, the mean of 2 determinations was used for the analysis.