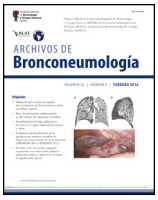
Arch Bronconeumol. 2017;53(3):120–127

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Original Article

Prognostic Role of Exhaled Breath Condensate pH and Fraction Exhaled Nitric Oxide in Systemic Sclerosis Related Interstitial Lung Disease☆

Alfredo Guillen-del Castillo,[a,*] Sara Sánchez-Vidaurre,[b,c] Carmen P. Simeón-Aznar,[a] María J. Cruz,[b,c] Vicente Fonollosa-Pla,[a] Xavier Muñoz[b,c,d]

[a] Unitat de Malalties Autoimmunes Sistèmiques, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
[b] Servei de Pneumologia, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain
[c] Ciber de Enfermedades Respiratorias (CIBERES), Spain
[d] Departament de Biologia Cel·lular, Fisiologia i Immunologia, Universitat Autònoma de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 9 May 2016
Accepted 6 September 2016
Available online 8 December 2016

Keywords:
Exhaled breath
Interstitial lung disease
Nitric oxide
pH
Systemic sclerosis

ABSTRACT

Introduction: Interstitial lung disease (ILD) is one of the major causes of death in systemic sclerosis (SSc). This study investigated exhaled breath (EB) and exhaled breath condensate (EBC) biomarkers in patients with SSc and analyzed their role as a prognostic tool in SSc-related ILD.
Methods: Fraction exhaled nitric oxide (FeNO) and exhaled carbon monoxide (eCO) measured in EB, together with pH, nitrite, nitrate and interleukin-6 levels measured in EBC were prospectively analyzed in 35 patients with SSc. Twelve patients had established ILD by chest high-resolution computed tomography (HRCT), and 23 patients showed no evidence of ILD. EB and EBC biomarkers were determined at inclusion, and pulmonary function tests were annually performed during 4 years of follow-up.
Results: No differences at baseline biomarkers levels were found between groups. In all patients studied, low EBC pH levels were associated with a decreased diffusing capacity for carbon monoxide (DLCO) during follow-up. Low FeNO levels were correlated with lower forced vital capacity (FVC) at baseline, 4 years of follow-up and with a decrease in FVC and DLCO during monitoring. Among ILD patients, high eCO levels were correlated with lower baseline FVC. In the global cohort, a worse progression-free survival was identified in patients with EBC pH values lower than 7.88 and FeNO levels lower than 10.75 ppb (log Rank P=0.03 and P<0.01, respectively).
Conclusions: EB and EBC could help to detect patients likely to present a deterioration on lung function during follow up.

Valor pronóstico del pH en el condensado de aire exhalado y de la fracción exhalada de óxido nítrico en la enfermedad pulmonar intersticial asociada a esclerosis sistémica

Palabras clave:
Aire exhalado
Enfermedad pulmonar intersticial
Óxido nítrico
pH
Esclerosis sistémica

RESUMEN

Introducción: La enfermedad pulmonar intersticial (EPI) es una de las principales causas de muerte en los pacientes con esclerosis sistémica (ES). En este estudio se investigaron biomarcadores en el aire exhalado (AE) y en el condensado de aire exhalado (CAE) y se analizó su posible papel como factores pronóstico de la EPI en pacientes con ES.
Métodos: Se analizó prospectivamente la fracción exhalada de óxido nítrico (FeNO) y el monóxido de carbono exhalado (COe) en AE, y se determinaron los valores de pH, nitritos, nitratos e interleucina-6 en

☆ Please cite this article as: Guillen-del Castillo A, Sánchez-Vidaurre S, Simeón-Aznar CP, Cruz MJ, Fonollosa-Pla V, Muñoz X. Valor pronóstico del pH en el condensado de aire exhalado y de la fracción exhalada de óxido nítrico en la enfermedad pulmonar intersticial asociada a esclerosis sistémica. Arch Bronconeumol. 2017;53:120–127.

* Corresponding author.
E-mail address: alguille@vhebron.net (A. Guillen-del Castillo).

1579-2129/

CAE, en 35 pacientes con ES. La tomografía computarizada de alta resolución (TACAR) torácica mostró signos de EPI en 12 pacientes, no estando presentes en los 23 restantes. En el momento de la inclusión se determinaron los biomarcadores en el AE y en el CAE, y durante los 4 años de seguimiento se efectuaron anualmente pruebas de función respiratoria.
Resultados: No se observaron diferencias entre grupos en los valores iniciales de los diferentes biomarcadores. En todos los pacientes examinados los valores disminuidos de pH en CAE se asociaron con una reducción en la capacidad de difusión de monóxido de carbono (DLCO) durante el seguimiento. Valores disminuidos de FeNO se correlacionaron con una menor capacidad vital forzada (FVC) inicial y a los 4 años, así como con una reducción de FVC y DLCO durante el seguimiento. En los pacientes con EPI los valores más altos de COe se correlacionaron con FVC más disminuidas al inicio. En el conjunto de la cohorte se identificó una menor supervivencia libre de progresión en los pacientes con un pH en CAE inferior a 7,88 y en los que presentaban un FeNO inferior a 10,75 ppb (Log Rank: p = 0,03 y p < 0,01, respectivamente).
Conclusiones: Los biomarcadores en el AE y en el CAE son útiles para detectar pacientes con una mayor probabilidad de presentar un deterioro de la función pulmonar durante el seguimiento de la enfermedad.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by small-vessel vasculopathy, fibroblast dysfunction with excessive collagen production, fibrosis, and immunological abnormalities.[1] Currently, interstitial lung disease (ILD) is one of the leading causes of SSc-related deaths.[2,3] The prevalence of SSc-associated ILD varies depending on the population studied, case definition, and sensitivity of diagnostic methods. Goh et al.[4] proposed a simple stratification scheme based on the extent of disease on high resolution computed tomography (HRCT) and the impact on pulmonary function testing (PFT), which yielded the best prediction of disease progression and long-term mortality. Recently, serum interleukin-6 (IL-6) has been reported as a predictor of SSc-ILD progression, specifically in patients with early-mild stages.[5]

An increase in inflammatory cells on bronchoalveolar lavage (BAL) is a common feature in SSc-related ILD.[6,7] However, there is no correlation with long-term survival or progression,[8] therefore it is only used to exclude an infection and for research purposes.[3] Although the study of several biomarkers in induced sputum, exhaled breath (EB) and exhaled breath condensate (EBC) has been reported to be useful in scleroderma pulmonary involvement,[9–13] their potential value is still controversial, and additional non-invasive biomarkers are needed to predict disease progression.

We sought to demonstrate that SSc-related ILD might be mediated by an autoimmune inflammatory process in the lung, causing a release of cytokines and metabolites that could be measured non-invasively in EB and/or EBC. This study had 2 main objectives: first, to analyze EB and EBC biomarkers in scleroderma patients based on the presence of ILD, and study their association with baseline PFTs; and secondly, to determine whether these biomarkers correlate with disease progression at 4 years, having a potential prognostic significance.

Methods

Patients

A prospective study was performed including 35 Caucasian patients (32 women) diagnosed with SSc. All patients fulfilled the ACR/EULAR 2013 classification criteria,[14] had undergone a baseline HRCT, and were followed-up for 4 years. Patients were consecutively assessed in the Scleroderma Unit at our hospital and followed up by the same specialist every 4 months in moderate-severe ILD patients, or every 6 months in patients with no pulmonary involvement or mild ILD, following international guidelines.[15] The study was approved by the hospital's Ethics Committee for Clinical Research, and all the patients provided informed consent for their participation, according to the Declaration of Helsinki. The exclusion criteria were the presence of other inflammatory respiratory diseases (such as asthma, COPD or others), atopic features at inclusion, or an infection of the respiratory tract during the previous month.

Study Groups

The study population was divided into 2 groups: the ILD group included 12 patients with ILD defined as radiological evidence of interstitial disease on HRCT, containing 1 patient with pulmonary hypertension associated to ILD (PH-ILD); and 23 SSc patients with no evidence of ILD were selected as the control group, including 2 patients with isolated pulmonary arterial hypertension (PAH). PH was defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg in right heart catheterization (RHC). PH-ILD was considered if PH was diagnosed in a patient with ILD and lower than 60% predicted forced vital capacity (FVC) or moderate-severe interstitial disease in the HRCT.[16] Isolated PAH was diagnosed by RHC according to international guidelines.[16,17] Other SSc comorbidities were also recorded as previously described.[18] All patients underwent complete PFTs, fraction of exhaled NO (FeNO), exhaled CO (eCO) and EBC collection at baseline. Subjects were instructed to refrain from food intake and smoking during the 2 and 24 h prior to sample collection, respectively. All samples were analyzed in the same laboratory.

Pulmonary Function Tests

Spirometry, static lung volumes and transfer lung studies were performed annually using MasterLab equipment (MasterLab, Jaegger, Germany) following the ERS-ATS recommendations.[19] The PFTs outcomes were analyzed as the change in % predicted FVC or diffusing capacity for carbon monoxide (DLCO) compared to baseline.

Fraction of Exhaled NO Measurement

FeNO measurements were performed using NIOX MINO® device (Aerocrine AB, Solna, Sweden) according to current guidelines.[20] Patients sat in an upright position and wore a nose clip during the process. Patients inhaled NO-free air through the device and subsequently exhaled at a fixed flow rate of 50 mL/s for approximately 10 s. The first technically acceptable FeNO measurement was used for analysis.[21]