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Original Article

Effect of Continuous Positive Airway Pressure and Upper Airway Surgery on Exhaled Breath Condensate and Serum Biomarkers in Patients With Sleep Apnea☆

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ABSTRACT

Introduction: Studies on inflammation biomarkers in serum and in exhaled breath condensate (EBC) in obstructive sleep apnea (OSA) have shown conflicting results. The objective of this study is to assess EBC and serum biomarkers in OSA patients at baseline and after continuous positive airway pressure (CPAP) or upper airway surgery (UAS).
Patients and methods: Nine OSA patients referred for UAS were matched for anthropometric characteristics and apnea–hypopnea index with 20 patients receiving CPAP. pH, nitrite (NO_2^-), nitrate, and interleukin 6 in EBC and NO_2^-, nitrate, leukotriene B_4, and interleukin 6 in serum were determined. EBC and serum samples were collected at baseline and 3 months after CPAP or UAS.
Results: Patients' mean body mass index was 30 (range 24.9–40) kg/m^2. EBC biomarker levels at baseline were within normal range and did not differ significantly after CPAP or UAS. No significant changes were observed in the serum concentration of the biomarkers determined after CPAP but the serum concentration of NO_2^- increased significantly at 3 months after UAS (P=.0078).
Conclusion: In mildly obese OSA patients, EBC biomarkers of inflammation or oxidative stress were normal at baseline and remained unchanged 3 months after UAS or CPAP. Although UAS was not effective in terms of reducing OSA severity, it was associated with an increase in serum NO_2^-.

Efecto de la presión positiva continua en las vías aéreas y de la cirugía de las vías aéreas superiores sobre los biomarcadores en condensado de aire exhalado y en suero en pacientes con apnea del sueño

Palabras clave:
Presión positiva continua de vías aéreas
Biomarcadores exhalados
Condensado de respiración exhalada
Inflamación
Apnea del sueño

RESUMEN

Introducción: Los estudios de los biomarcadores inflamatorios en suero y en el condensado de aire exhalado (CAE) en la apnea obstructiva del sueño (AOS) han producido resultados contradictorios. El objetivo de este estudio es evaluar los biomarcadores en CAE y en suero en pacientes con AOS en la situación basal y después de la aplicación de presión positiva continua de vías aéreas (CPAP) o de cirugía de las vías aéreas superiores (CVAS).
Pacientes y métodos: Nueve pacientes con AOS que fueron remitidos para CVAS fueron emparejados según sus características antropométricas y el índice de apnea-hipopnea con 20 pacientes que fueron tratados

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con CPAP. Se efectuaron determinaciones de pH, nitrito (NO_2^-), nitrato e interleucina 6 en CAE, y de NO_2^-, nitrato, leucotrieno B_4 e interleucina 6 en suero. Se obtuvieron muestras de CAE y de suero en la situación basal y 3 meses después de la CPAP o la CVAS.

Resultados: El valor medio del índice de masa corporal de los pacientes fue de 30 (rango 24,9–40) kg/m^2. Los niveles de marcadores en CAE en la situación basal estuvieron dentro del rango normal y no presentaron diferencias significativas tras la CPAP o la CVAS. No se observaron cambios significativos en las concentraciones séricas de los biomarcadores evaluados tras la CPAP, pero la concentración sérica de NO_2^- aumentó significativamente a los 3 meses de la CVAS (p = 0,0078).

Conclusión: En los pacientes con AOS y obesidad leve, los biomarcadores de la inflamación o el estrés oxidativo en el CAE presentaron unos niveles basales normales y se mantuvieron inalterados 3 meses después de la CVAS o la CPAP. La CVAS, aunque no resultó efectiva por lo que respecta a la reducción de la gravedad de la AOS, se asoció a un aumento de los niveles séricos de NO_2^-.

Introduction

There is a growing body of evidence linking inflammatory processes, oxidative stress and endothelial dysfunction with obstructive sleep apnea (OSA) and morbidity and mortality rates.[1] Exhaled breath condensate (EBC) is a noninvasive means of studying inflammatory biomarkers, mainly in asthma patients.[2,3] Some studies have focused on the usefulness of EBC in evaluating the presence of inflammation and oxidative stress in OSA patients.[4–10] These factors are important since the mechanical trauma caused by snoring and repeated upper airway collapse leads to local inflammation that can spread to the respiratory system and the systemic circulation, thereby contributing to the pathogenesis and continuance of OSA. Patients with severe OAS present increased proinflammatory cytokine expression in the mucosal or muscle compartments of the upper airways, accompanied by increased connective tissue deposition.[11] However, the extent to which these anomalies contribute to upper airways dysfunction in OSA and systemic inflammation is still unclear. Previous studies have shown that continuous positive airway pressure (CPAP) reduces high levels of inflammatory and oxidative stress biomarkers in serum, although results are inconclusive.[12–15]

CPAP is the treatment of choice for patients with moderate to severe OSA, although some reject this therapy in favor of surgical treatment to enlarge the upper airways. Although upper airway surgery (UAS) for the treatment of OSA is controversial, we have reported increased survival rates in patients undergoing UAS to treat severe OSA compared to untreated patients,[16] while another study reported lower tumor necrosis factor-alpha (TNF-α) levels after UAS, thereby possibly ameliorating the systemic inflammation and preventing the development of cardiovascular consequences.[17]

The aim of this study was to evaluate the effects of two treatments for OSA based on the hypothesis that both CPAP and UAS can improve local inflammation (pH, interleukin-6 [IL-6], nitrite [NO_2^-], nitrate [NO_3^-]), systemic inflammation (IL-6, leukotriene B_4 [LTB_4]), and endothelial function (NO_2^-, NO_3^-) in patients with OSA.

Materials and Methods

Study Population

Nine patients with OSA (apnea hypopnea index [AHI]>5/h) selected by an otolaryngologist for UAS were matched by age, sex, body mass index (BMI), and AHI with 20 patients with OSA referred to sleep units and offered CPAP if the AHI was >5/h. Patients were included in the study from April 2008 to April 2009.

Inclusion criteria were: never-smoker or ex-smoker for more than 3 months prior to the start of the study; not taking anti-inflammatory treatment (inhaled, nasal, oral or injectable) for 4 weeks prior to the start of the study; and no endocrine disorder or any other known cause of sleep disturbance (disease, drug therapy or other interventions). Other possible causes of upper or lower airway inflammation (allergic rhinitis, asthma or chronic obstructive pulmonary disorder) were ruled out on the basis of the medical history and pulmonary function test results. Patients with obstructive lung diseases (forced expiratory volume in one second [FEV_1]/forced vital capacity [FVC]$\leq$0.7) were excluded. Patients' height (cm) and weight (kg) were measured and BMI was calculated (kg of body weight/height [m^2]).

Criteria for UAS were AHI>5 and fewer than 40 episodes/h in patients with upper airway morphological alterations (velopharyngeal insufficiency) who had refused CPAP therapy. Patients with BMI>35 kg/m^2 or craniofacial abnormalities such as micrognathism and prognathism were ruled out for UAS. The UAS procedure consisted in uvulopalatopharyngoplasty.

The study was approved by the hospital independent ethics committee, and written informed consent was obtained from all subjects.

Respiratory Polygraphy

Nasal airflow, pulse oximetry, respiratory effort, body position, and snoring were monitored overnight using the Somnea device (Compumedics, Abbotsford, Australia). Apneas were defined as the total absence of nasal airflow for at least 10 s, and hypopneas as a significant reduction in nasal airflow for at least 10 s associated with 3% oxygen desaturation. Obstructive apneas were distinguished from central apneas by respiratory effort channels (presence or absence of thoracic and abdominal movement). AHI was obtained by dividing the total number of apneas and hypopneas by the total recorded sleep time. OSA was defined as an AHI$\geq$5. Patients with an AHI of between 5 and 30 were classified as mild to moderate OSA, and those with AHI>30 were considered to have severe OSA.

Continuous Positive Airway Pressure Titration

In patients in the CPAP group, pressure was set using an automatic positive pressure titration device (AutoSet Spirit™; ResMed, Sydney, Australia). The optimal pressure setting was determined visually based on the printed data reports.[18] Following this, patients were prescribed CPAP, which was provided free of charge by the Spanish National Healthcare System.

Pulmonary Function Tests

FEV_1, FVC, and the FEV_1/FVC ratio were determined using a spirometer (MasterScreen™ PFT; Jaeger, Höchberg, Germany).