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ORIGINAL ARTICLE

Acute exercise amplifies inflammation in obese patients with COPD☆

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Abstract Systemic inflammation has been implicated in the pathogenesis of chronic obstructive pulmonary disease (COPD) systemic effects. However, most COPD patients do not suffer from persistent systemic inflammation even after exacerbations and exercise and scientific evidence has provided conflicting results. Our aim is to evaluate inflammatory gene expression at rest and at 1 and 24 h after strenuous exercise in COPD patients and study the patient variables associated with inflammatory expression.

A cross-sectional study was conducted in COPD patients who were recruited on entry to a pulmonary rehabilitation (PR) program. Demographic, clinical and functional data were collected. Blood samples were collected and gene expression was analyzed by reverse transcriptase polymerase chain reaction for IFNg, IL1b, IL6, IL8, TNFa, TGFb1 and iNOS.

The study included 21 patients (15 men, 71.4%), mean age 66.1 years old (SD = 8.27), mean FEV_1 46.76% (SD 20.90%), 67% belonging to GOLD grade D, mean BODE index of 3.9, 90.5% with smoking history, mean BMI 25.81 (SD = 4.87), median of 1.29 exacerbations in the previous year.

There was no statistical significant difference between inflammatory expression at rest and at 1 h and 24 h after the maximal exercise test for all tested genes.

We found an association between BMI and inflammatory expression at all the points of time checked, a slight inverse association occurs with low BMI for mRNA IL1b, IL6, TNFa, TGFb1 and iNOS, and there was a more pronounced positive association for obese patients for all tested genes.

This preliminary study did not show an enhanced inflammatory gene expression from rest to 1 h and 24 h after short-term exercise, but did show an increased inflammatory gene expression

☆ Study was carried out at the Pulmonary Rehabilitation Unit, Pneumology Service, CHLN-Hospital Pulido Valente and in South Luso-Transplant Centre.

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in both BMI extremes, both at rest and after exercise, suggesting not only malnourishment, but also obesity as potential links between COPD and systemic inflammation. Studies with larger samples and designed to definitely exclude OSA or OHS as confounding factors in obese patients are required.

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with important extrapulmonary manifestations, including weight loss, skeletal muscle dysfunction, cardiovascular disease, depression, osteoporosis, reduced exercise tolerance, and poor health status.[1–3] Although the pathobiology of COPD has not been fully determined, persistent systemic inflammation has been implicated in the pathogenesis of the majority of these systemic effects.[3,4] Elevated circulating levels of white blood cells, C-reactive protein (CRP), interleukins 6 (IL-6) and 8 (IL-8), fibrinogen and tumor necrosis factor alpha (TNFa) have been reported in patients with COPD.[5] However, the ECLIPSE study[5] has demonstrated that a large group of patients with COPD do not suffer from systemic inflammation.

The role of exercise in COPD inflammatory process has also been a matter of debate.[6–15] Patients with COPD are exposed to a systemic inflammation that is amplified by exhaustive exercise. Inflammatory response to exercise is more pronounced in patients with COPD when compared to healthy controls, even at lower levels of exercise intensity.[9,15] However, scientific literature on this subject is also not consensual, as several studies have shown a reduction in the level of TNFa protein expression in COPD subjects.[10] As pointed out by Canavan and colleagues,[11] some of the heterogeneity of these results might be caused by the different methods that were used in the studies (patient characterization, exercise protocols, and assay techniques). Crul and colleagues[12] did not find any evidence of muscle inflammation in patients with COPD, independently of whether they were in a stable or an acute exacerbation state. Conversely, others have suggested an anti-inflammatory effect of regular exercise in some low systemic inflammation chronic diseases, with beneficial outcomes in disease prevention and symptomatic improvement.[6,13,14]

In this study we aim to evaluate the inflammatory and immune regulatory gene expression profiling in peripheral blood determined at rest in patients with COPD, and the possible modification after strenuous exercise, and search for variables and patients' characteristics associated with inflammatory expression.

Material and methods

Patients

A cross-sectional study was conducted on a sample of 21 patients diagnosed with COPD, according to the Global Initiative for Obstructive Lung Disease Project (GOLD)[16] as post bronchodilator $FEV_1/FVC < 0.70$. Patients were consecutively recruited on entry to a pulmonary rehabilitation (PR) program at our PR Unit, from January to December 2010. Participants were selected if clinically stable in the previous four weeks and able to exercise and to answer health status questionnaires. Patients diagnosed with other significant lung diseases, e.g. asthma, bronchiectasis or other conditions that might cause dyspnea or affect exercise performance, were excluded.

Data collection

Data collection included age, body mass index (BMI), smoking history, number of exacerbations in the previous year and comorbidities. Clinical data were obtained by interview and from medical records, including the review of concomitant medications. Charlson,[17] Charlson-age[18] and COTE (COPD specific comorbidity test)[19] indexes were calculated based on comorbidities data. Participants completed questionnaires on dyspnea (modified Research Council breathlessness scale and Mahler' baseline dyspnea index),[20] activities of daily living (London Chest Activity of Daily Living scale – LCADL),[21] anxiety and depression (Hospital Anxiety and Depression scale – HADS),[22] and health status (St. George's Respiratory Questionnaire – SGRQ).[23]

Pulmonary function data were obtained using standardized equipment (SensorMedics Corporation, Yorba Linda, CA, USA). Post-bronchodilator spirometric values were obtained. Data were measured as absolute values (*L*) and as percent predicted of reference values.

Exercise test and laboratory procedures

Patients were subjected to an incremental exercise test to maximum tolerated on a treadmill or on a cycle ergometer (Fig. 1). Treadmill protocol started with a three minutes warming up at 2.0 km/h and 0° inclination, followed by 0.5 km/h increments per minute and 0° inclination until the patient attained a brisk walking speed without running, and then increments of 2° inclination every minute until exhaustion. Cycle ergometer protocol starts with a three minutes warm up with no added resistance, followed by 10 W of increments each minute until exhaustion. Safety criteria for terminating the exercise test were applied according to ATS/ACCP guidelines.[24]

Whole blood samples were collected from each patient at three different time points: at rest (T0), and at one hour (T1) and 24 h (T2) after the exercise test. Additionally,

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