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Influence of repeated maximal exercise testing on biomarkers and fatigue in sarcoidosis

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ABSTRACT

Fatigue in the immune mediated inflammatory disease sarcoidosis is thought to be associated with impaired exercise tolerance. This prospective study assessed fatigue and recuperative capacity after repeated exercise, and examined whether changing concentrations in biomarkers upon exercise are associated with fatigue.

Twenty sarcoidosis patients and 10 healthy volunteers performed maximal cardiopulmonary exercise tests on two successive days. Concentrations of cytokines, stress hormones, ACE and CK were assessed before and after the two exercise tests, and 3 days thereafter. All participants completed a sleep diary.

Severely fatigued patients showed significant lower VO_2 max ($p = 0.038$, $p = 0.022$) and maximal workload ($p = 0.034$, $p = 0.028$) on both exercise tests compared to healthy controls. No impairment of maximal exercise testing was demonstrated during the second cycling test in any group. Fatigue was not correlated with changes in concentrations of biomarkers upon exercise. Severely fatigued patients rated both tests as significantly more fatiguing, and reported significant lower mean subjective night sleeping time during the testing period.

Fatigue in sarcoidosis patients cannot be objectified by reduction of exercise capacity after repeated maximal exercise testing, and is not correlated with significant changes in biomarkers. Severe fatigue is only and consistently featured by patient reported outcomes.

1. Introduction

Sarcoidosis is an immune mediated multisystem inflammatory disease of unknown cause. It commonly affects young and middle-aged adults and frequently presents with bilateral hilar lymphadenopathy, pulmonary infiltration, and ocular and skin lesions. Liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas (Statement on Sarcoidosis, 1999; Baughman et al., 2003; Iannuzzi et al., 2007).

Fatigue is often reported by sarcoidosis patients, especially during the onset and the active phase of this multi-systemic granulomatous disorder (De Kleijn et al., 2009; Drent et al., 2012; De Vries et al., 2004). However, when sarcoidosis patients are tested for cardiovascular, pulmonary, and aerobic capacity by means of exercise tests, the results of these tests are usually within reference limits (Matthews and Hooper, 1983; Medinger et al., 2001; Costable, 2005). Nonetheless, many patients state that they are completely exhausted after completing the exercise test. Also in daily life they experience severe malaise during 24 h or more following a single moderate exertion. These complaints may be so severe that they cannot fulfil their daily work the same and the next day(s). This leads to difficulties in private life and may regularly result in labour disputes (Korenromp et al., 2011).

The etiology of fatigue in sarcoidosis patients is unclear (De Kleijn et al., 2009). It is thought that elevated levels of inflammatory markers as cytokines and chemokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) play an important role and may be responsible for symptoms like fatigue (Drent et al., 2012; Prior et al., 1996; Rothkrantz-Kos et al., 2003; Spruit et al., 2005). However, just deregulation of the immune system

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may not be the sole factor related to fatigue. Physical exercise is known to provoke an increase in a number of pro- and anti-inflammatory cytokines like IL-6 and TNF-α also in healthy subjects (Pedersen et al., 2003; Steinberg et al., 2007). In the present study, we hypothesize that compared to healthy controls, the immune response to exercise is aggravated in severely fatigued sarcoidosis patients and that these increased levels of inflammatory markers and cytokines may explain the excessive fatigue complaints.

Another influencing factor might be the endocrine system. It is now well established that the immune system communicates with the endocrine system via various routes (Besedovsky and Del Rey, 1996; Eskandari et al., 2003; Elenkov et al., 2000). The hypothalamic pituitary adrenal (HPA) axis is one of the major pathways in this bi-directional communication between both systems. Deregulation of the HPA axis has often been implicated in relation to excessive fatigue. Hypocortisolism and blunted adrenocorticotropic hormone (ACTH) responses in challenge tests have been reported in patients diagnosed with chronic fatigue syndrome (Van Den Eede et al., 2007; Nater et al., 2008; Silverman et al., 2010). In sarcoidosis decreased baseline levels of ACTH and cortisol in plasma are highly correlated with complaints of persistent and severe fatigue (Korenromp et al., 2012). In the present study we raise the question whether the HPA axis might be involved in the presence of fatigue complaints in newly diagnosed sarcoidosis patients. As exercise not only influences the immune system but also activates the HPA axis, (Hill et al., 2008) we tested the responsiveness of the HPA axis by subjecting the participants to repetitive maximal exercise tests on two subsequent days.

This prospective study examines whether the complaints of excessive fatigue in sarcoidosis patients after exercise can be objectified. It hypothesizes that compared to healthy controls the recuperative capacity of sarcoidosis patients is decreased.

2. Materials and methods

2.1. Study design

This study was a prospective pilot study of a cohort sarcoidosis patients and a control group of healthy volunteers. Study period comprised fourteen days in which all participants underwent two maximal exercise tests on day 6 and 7 of the study. Blood samples were taken before and after the two exercise tests, and in addition on day 10. The study population also completed a sleep diary and filled out health-questionnaires.

2.2. Study population

Patients were recruited from the outpatient clinic of the Rijnstate Hospital Arnhem and the Center Interstitial Lung Diseases Nieuwegein, the Netherlands. Patients were all diagnosed according to the ATS/ERS/WASOG statement on sarcoidosis (Statement on Sarcoidosis, 1999). Study participation was based on the in- and exclusion criteria as shown in Table 1. Healthy volunteers were recruited among employees in both hospitals. All participants signed informed consent. In order to exclude hormonal influences all female participants completed the study in their non-menstrual phase.

2.3. Pulmonary function testing

Spirometry (Jaeger system) was obtained in all participants. In all sarcoidosis patients single breath diffusing capacity for carbon monoxide (DLco) was performed. Testing adhered to American Thoracic Society and European Respiratory Society standards (Miller et al., 2005; ATS, 1995).

2.4. Exercise testing

Each participant underwent a symptom-limited incremental exercise test (ATS/ACCP, 2003) on two consecutive days between 9.00 and 12.00 A.M. Workload was increased each minute using cycle ergometry (Jaeger ergoline, ergometrics 900). Blood pressure, heart rate, electrocardiography (ECG Jaeger ergoline, ergo vac 2000), and pulse oximetry (Nonin pureSAT 9600) were recorded throughout the rest and exercise period. Variables measured or calculated included: workload (Wattage), oxygen consumption (VO_2), and respiratory exchange ratio (RER).

2.5. Questionnaires

Fatigue was measured with the Checklist Individual Strength (CIS) and was completed on the first (5 days before first exercise test) and last day (7 days after second exercise test) of the study (Vercoulen et al., 1994). A cut-off of 35 on the subscale of fatigue-severity was used to identify a severely fatigued and a moderately fatigued group (Vercoulen et al., 1999). State of fatigue was captured by a Visual Analogue Scale (VAS), ranging from 0 to 10. All participants were asked to appraise their state of fatigue before and after both exercise tests (day 6 and 7), and in addition on day 10.

In order to measure patients' overall health status, the Medical Outcomes Study 36-Item Short-Form health Survey (SF-36) which includes 9 subscales was completed on the first study day (Ware and Sherbourne, 1992; Van der Zee and Sanderman, 1993).

2.6. Blood sampling and laboratory analysis

Five blood samples were taken: before and after both exercise tests, and in addition on day 10 (the 3rd day after the second exercise test). Angiotensin converting enzyme (ACE) and creatine kinase (CK) were determined from the same badge of lithium-heparine tubes and analyzed using ACE-Buhlman ACE kinetic and Roche/Hitachi Kit. ACE was corrected for genotype and sex (Kruit et al., 2007). Blood samples for determination of cytokines, soluble cytokine receptors, ACTH and cortisol were directly processed (centrifuged at 4 °C, 1500*g*, 15 min) after withdrawal in ethylene diamine tetra acetic acid (EDTA) tubes and plasma was stored at a temperature of −80 °C. The following panel of cytokines and cytokine receptors was determined: interleukin (IL)-1β IL-1β, IL-4, IL-5, IL-6, IL-8 (CXCL8), IL-10, TNF-α, macrophage inflammatory protein (MIP)-1β (CCL4), monocyte chemotactic protein (MCP)-1 (CCL2), IL-1 receptor antagonist (IL-1RA), soluble IL-1 receptor type 1 (sIL-1R1), sIL-1R2, sIL-2R, sIL-4R, sIL-6R, sTNFRI, sTNFRII. Cytokine analysis was performed by multiplex immunoassay assay (Milliplex MAP kit, Merck Millipore, Billerica, MA, USA), according to the manufacturer's instructions. ACTH was determined using a solid-phase, two-site sequential chemiluminescent immunometric assay (Immulite 2500, Siemens Healthcare Diagnostics). Cortisol was determined using a solid-phase, competitive chemiluminescent enzyme immunoassay for cortisol (Immulite 2500, Siemens Healthcare Diagnostics).

2.7. Sleep diary

Participants completed a paper-and-pencil logbook at home during fourteen consecutive days. Registration started five days in advance of the first exercise test and finished 8 days afterwards. Parameters were: total objective night sleeping time (time reported as "I fell asleep last night" minus time "I woke up this morning"), total subjective night sleeping time (time reported as "I feel to have slept ... hours last night"), napping time, and feeling