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Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease

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Fatigue severity

Summary
Objective: To determine if, in patients with interstitial lung disease (ILD), fatigue might be lessened after vigorous aerobic exercise.
Methods: 13 physically inactive patients (5 men and 8 women; age 57.2 ± 9.1 years, BMI 28.2 ± 4.6 kgm^{-2}) with ILD of heterogeneous etiology and able to walk on a motor driven treadmill without physical limitation were enrolled. Subjects underwent cardiopulmonary exercise (CPET) and 6-min walk (6MWT) tests and completed Fatigue Severity Scale and Human Activity Profile questionnaires before and after an aerobic exercise-training regimen. The training regimen required participation in at least 24 of 30 prescribed aerobic exercise training sessions at a target heart rate of 70–80% of the heart rate reserve, 30 min per session, 3 times per week for 10 weeks.
Results: After training, a 55% ($p < 0.001$) increase in time to anaerobic threshold on the CPET, and an 11% ($p = 0.045$) reduction in performance fatigability index (PFI), calculated from the performance on the 6MWT were observed. Distance walked on the 6MWT (6MWD) increased by 49.7 ± 46.9 m ($p = 0.002$). Significant improvements in scores on the Fatigue Severity Scale ($p = 0.046$) and Human Activity Profile (AAS $p = 0.024$; MAS $p = 0.029$) were also observed. No adverse events related to the training regimen were noted.

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Conclusion: After training, the decrease in fatigability appeared to result in increased 6MWD and was associated with physical activity. Since significant declines in 6MWD may be a marker for impending mortality in ILD, a better understanding of the etiological state of fatigue in patients with ILD and its reversal might provide fundamental insight into disease progression and even survival. [ClinicalTrials.gov identifier NCT00678821].

Introduction

Fatigue is a state of physiological decline in response to over exertion. The state manifests symptomatically as feelings of tiredness or weariness and can be observed as a decrease in physical or mental performance. Fatigability is a quantifiable phenotype in which the physiological decline is measured as a function of the duration, intensity or frequency of exertion, representing an important aspect of functionality. For example, hypothetical Groups A and B report similar levels of fatigue on a given instrument even though Group A reports participating in less physical activity. Group A would therefore appear to fatigue more easily and thus be more fatigable than Group B. Fatigability can be measured more definitively in the laboratory where the processes of physiological decline can be quantified as a response to controlled perturbations such as physical exercise. All humans are fatigable but fatigability is increased by poor physical fitness and becomes even more severe with medical conditions, such as interstitial lung disease (ILD) [1], in which cardiorespiratory function is impaired.

ILD is a condition resulting from over 200 etiologies [2—4]. Homogeneity within the condition results from diffuse and irreversible fibrotic repair of the alveolar parenchyma, regardless of the underlying etiology. A progressive decline in alveolar diffusion capacity and restriction of pulmonary ventilation ensues, which creates a gas exchange impediment that is often abetted by diminished alveolar blood flow resulting from capillary destruction and hypoxic vasoconstriction [2,5]. Exercise capacity is severely limited [1] and patients often find it difficult to sustain even moderate levels of physical functioning including instrumental activities of daily living and the ability to maintain employment [6].

The total distance that patients can walk (6MWD) on a 6-min walk test (6MWT) is a surrogate measure of exercise capacity [7—14]. Progressive decline in 6MWD may predict one-year mortality in patients with ILD, specifically those with idiopathic pulmonary fibrosis [14]. Clinically significant increases in 6MWD have been observed following aerobic exercise training in patients with ILD [7—13] and one study found the increase in 6MWD to be concurrent with a reduction in the severity of patient-reported fatigue [9].

In addition to significant increases in 6MWD, we have observed a novel pattern of adaptation to aerobic exercise training in patients with ILD [15]. The adaptation is characterized by an improvement in work economy despite the absence of increases in the peak capacity of the cardiorespiratory system. It therefore seems plausible that, fatigability might still be modulated by cardiorespiratory function, even though limitations on the maximum capacity of the system seem to be irreversible.

A more complete understanding of how fatigability is modulated could provide important insight into the progression of ILD, how fatigue severity might be diminished, and how treatment might be further advanced in general. Moreover, because fatigability is believed to be a factor contributing to 6MWD limitation, a greater understanding of its modulation may provide insight into improving clinical status and life expectancy in patients with ILD and perhaps those with advanced lung disease in the broader sense. In the current study we examined the hypothesis that variability in cardiorespiratory function could exert a modulating influence on fatigability that is independent of variability in the maximum capacity of the system.

Methods

Subjects

The authors' respective institutional review boards approved this study and signed informed consent was attained from all participants prior to implementation of any of the study procedures or data collection. Subjects were recruited from local outpatient lung disease clinics within the Washington DC metropolitan area and enrolled in the National Institutes of Health Exercise Therapy for Advanced Lung Disease Trial [ClinicalTrials.gov identifier NCT00678821]. Subjects were required to be at least 21 years of age and physically inactive, defined as not having participated in any pulmonary rehabilitation program or structured exercise-training regimen of 30 min per session or longer, three or more days per week, during the 6 months prior to enrollment. None of the subjects had a history of ischemic heart disease, dilated, hypertrophic, or non-idiopathic cardiomyopathy, hepatic or renal dysfunction, severe psychiatric condition, use of antiretroviral therapy, uncontrolled diabetes mellitus, mitochondrial disease, acute cor pulmonale, disabling stroke, cancer, or evidence of these conditions at baseline physical examination. Pregnant women and potential subjects admitting to ongoing use of tobacco or abuse of alcohol or controlled or illegal substances were also excluded. Patients were eligible to enroll only if they had right ventricular systolic pressure (RVSP) $\leq$40 mmHg measured by echocardiogram within one year of enrollment, FEV_1/FVC ratio $\geq$65%, and ejection fraction $\geq$40%. Subjects were instructed to abstain from performing any exercise outside of the protocol procedures during their participation in the study.