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Original Article

Blood flow regulation and oxidative stress during submaximal cycling exercise in patients with cystic fibrosis

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Abstract

Background: The impact of blood flow regulation and oxidative stress during exercise in cystic fibrosis (CF) has yet to be investigated.
Methods: A maximal graded exercise test was conducted to determine exercise capacity (VO_2 peak) and peak workload in 14 pediatric patients with mild CF (age 14 ± 3 y, FEV_1 93 ± 16 % predicted) and 14 demographically-matched controls. On a separate visit, participants performed submaximal cycling up to 60% of peak workload where brachial artery blood velocity was determined using Doppler ultrasound. Retrograde and antegrade components were further analyzed as indices of blood flow regulation.
Results: The cumulative AUC for retrograde velocity was lower in patients versus controls (1770 ± 554 vs. 3440 ± 522 cm, $P = 0.038$). In addition, an exaggerated oxidative stress response during exercise occurred in patients only ($P = 0.004$).
Conclusion: These data suggest that patients with mild CF exhibit impaired blood flow regulation and an exaggerated oxidative stress response to submaximal exercise.

Keywords: Exercise intolerance; Reactive oxygen species; Retrograde velocity; Electron paramagnetic resonance spectroscopy

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive genetic disorder that is the result of a mutation in the cAMP-dependent cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel protein. There are many systemic complications in CF which include dysfunction of pulmonary, gastrointestinal, immune, endocrine, and musculoskeletal systems [1,2]. While the primary cause of morbidity and mortality in CF is pulmonary dysfunction and lung infection [3], exercise intolerance is a hallmark of CF [4,5] and a reduction in maximal aerobic capacity (VO_2 peak) is a significant predictor of mortality in this patient population, independent of lung function [6,7]. However, the mechanisms which contribute to exercise intolerance in CF remain unclear.

The ability to maintain adequate oxygen delivery to the working musculature is of critical importance, particularly under conditions of increased demand, such as during exercise. Both macro- and micro-vascular endothelial dysfunction is present in patients with

Abbreviations: 8-ISO, 8-isoprostane; AOC, antioxidant capacity; CRP, C-reactive protein; DXA, dual-energy X-ray absorptiometry; EPR, electron paramagnetic resonance; FRAP, ferric reducing antioxidant potential; LPO, lipid hydroperoxides; PBN, α-phenyl-tert-butylnitrone; PC, protein carbonyls; PFT, pulmonary function test; TEAC, trolox-equivalent antioxidant capacity; VO_2, volume of oxygen uptake

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CF [8,9]. Accordingly, it is plausible that impaired nutritive flow to the working musculature during exercise may contribute to exercise intolerance [10,11]. In fact, the pattern of brachial artery flow during lower limb cycling can provide valuable information regarding appropriate exercise induced vasodilatory/vasoconstrictor responses [12]. While a previous study demonstrated similar forearm blood flow responses during handgrip exercise in patients with CF versus healthy counterparts [13], whether or not 1) patients with CF exhibit abnormal blood flow regulation during exercise of large muscle-mass or 2) dysfunctional blood flow regulation affects exercise capacity in this patient population remains unknown.

There is convincing evidence to indicate the presence of chronic oxidative stress in patients with CF [14,15]. Oxidative stress in its basic form represents an imbalance between free radical production and neutralization of radicals by antioxidants and has been suggested to contribute to the multi-organ pathophysiology [14] and decline in pulmonary function over time in CF [16]. Oxidative stress is related to exercise capacity in several patient populations [17,18] and may partly be linked to pancreatic insufficiency and the intestinal malabsorption of endogenous fat-soluble vitamins and antioxidants in CF [19]. However, whether or not oxidative stress impacts exercise capacity in patients with CF is unknown.

While exercise intolerance in CF is related to a number of factors, the degree to which blood flow regulation and oxidative stress influences maximal exercise capacity in CF is unknown. Therefore, this study sought to test the hypotheses that 1) blood flow regulation during submaximal cycling exercise is compromised in patients with CF compared to controls, and 2) patients with CF exhibit an exaggerated increase in oxidative stress during exercise compared to controls.

2. Materials and methods

2.1. Participants

A total of 28 volunteers (14 patients with CF and 14 healthy controls) ages 8–20 years old participated in this study. Patients were enrolled if they had a clinical diagnosis of CF based on positive sweat test metrics and genotype analysis. Based on the patients' characteristics, demographically-matched apparently healthy controls were recruited. Detailed exclusion criteria can be found in the online supplement. All study protocols were approved by the Institutional Review Board at Augusta University and written and verbal assent/consent was obtained by all participants and parents prior to participation.

2.2. Experimental design

All participants reported for two days of testing; a preliminary and an experimental visit. The preliminary visit consisted of the informed consent process, body composition assessments, a baseline pulmonary function test (PFT), and a maximal exercise capacity test. On the experimental visit, a second PFT was performed prior to beginning the submaximal exercise protocol. Brachial artery diameter and blood velocity were measured while sitting on a cycle ergometer at baseline and during submaximal cycling exercise at 20, 40 and 60% of peak workload. Blood samples were taken at baseline and at 60% intensity for assessment of oxidative stress biomarkers. Patients were instructed to adhere to the timing of their daily treatments and report to the laboratory following their morning airway clearance technique and inhaled medicine regimen.

2.3. Participant characteristics and clinical laboratory values

Participant testing included assessments of height, weight, calculated body mass index (BMI), and body composition via dual-energy X-ray absorptiometry (DXA; QDR-4500 W; Hologic, Waltham, MA). An estimate of daily physical activity levels was determined from a self-reported health-history questionnaire. Blood pressure was measured in triplicate according to American Heart Association recommendations. Concentrations of total cholesterol (TC), high-density lipoproteins (HDL), low-density lipoproteins (LDL), triglycerides (TG), glucose, and high sensitivity C-reactive protein (hsCRP) were obtained using a Cholestech LDX point of care analyzer (Alere Inc., Scarborough, ME). Hemoglobin and hematocrit were obtained using a HemoPoint H2 analyzer (Stanbio Laboratory, Boerne, TX).

2.4. Pulmonary function testing

Pulmonary function testing (PFT) was performed in all participants using closed circuit spirometry (ParvoMedics, Sandy, UT) according to the American Thoracic Society standards [20] to determine forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and forced expiratory flow at 25–75% ($FEF_{25–75}$). The national health and nutrition examination survey (NHANES) III spirometric reference standards were used to determine the percent predicted data outcomes.

2.5. Maximal exercise capacity

On the preliminary visit, maximal exercise capacity (VO_2 peak) was determined on a cycle ergometer using the Godfrey Protocol [21]. Briefly, participants pedaled on an appropriate sized electronically braked cycle ergometer (Lode Corival or Lode Corival Pediatric, Groningen, Netherlands) with work intensities increasing every minute until volitional fatigue, breathlessness, chest discomfort, and/or any other signs observed by the investigators that the test should be terminated. Throughout maximal exercise testing, breath by breath expired gases were analyzed by a TruOne® 2400 metabolic cart (ParvoMedics, Sandy, UT) and reported as 30 s averages to obtain VO_2 peak. Heart rate, blood pressure, and SpO_2 were monitored throughout the test.

2.6. Submaximal exercise

On the experimental visit (at least one week following preliminary testing), all participants performed submaximal exercise on a cycle ergometer at 20, 40, and 60% of the maximum workload (Watts) that was obtained from the maximal exercise test. Following a 2 min unloaded warm-up, each workload intensity

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