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Improved lung function following dietary antioxidant supplementation in exercise-induced asthmatics

Stephanie P. Kurti*, Jill D. Murphy, Christine S. Ferguson, Kelly R. Brown, Joshua R. Smith, Craig A. Harms

Department of Kinesiology, Kansas State University, Manhattan, KS, USA

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ABSTRACT

Introduction: Oxidative stress is a characteristic of exercise-induced asthma (EIA), however antioxidant supplementation may attenuate EIA. The purpose of this study was to determine if ascorbic (AsA) and α-tocopherol supplementation would improve airway function in subjects with EIA.
Methods: A single-blind randomized crossover design with eight clinically diagnosed EIA subjects (22.0 ± 0.7 year) and five healthy control subjects (28.2 ± 1.4 year) was used. Subjects consumed vitamins (V) (AsA 500 mg; α-tocopherol 300 IU) or placebo (PLA) daily for three weeks, followed by a three week washout period and then three weeks of the alternative treatment. Ten-minute treadmill tests (90% $VO2_{peak}$) were performed with pulmonary function testing (forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and between 25 and 75% ($_{FEF25–75\%}$), and peak expiratory flow rates (PEFR)) measured pre-exercise and 1, 5, 15, and 30 min post-exercise.
Results: Supplementation led to significant improvements at minute 5 and minute 15 in FVC; FEV_1; PERF; $FEF_{25–75\%}$ and minute 30 in FEV_1 and $FEF_{25–75\%}$ post-exercise.
Conclusion: AsA and α-tocopherol may aid the recovery of pulmonary function in subjects with EIA.

1. Introduction

Exercise-induced asthma (EIA) is a subcategory of asthma and is exhibited by a hyper-reactive, intermittent narrowing of the airways triggered by physical activity (McFadden and Gilbert, 1994). Although EIA occurs in approximately 90% of asthmatics, about 10% of individuals solely experience bronchospams post-exercise (Gotshall, 2002). Symptoms of an acute asthma attack are wheezing, chest tightness, coughing, decreased forced vital capacity (FVC) and difficulty breathing (Weiler, 1996). These symptoms occur due to the narrowing of the airways, which is known as bronchoconstriction. Typically the amount of bronchoconstriction is quantified by a decrease >10% in the amount of air forcefully exhaled in one second following a maximal inhalation (FEV_1; forced expiratory volume in 1-s) or a decrease of >15% in peak expiratory flow recorded by a flow meter (Godfrey and Bar-Yishay, 1993; Anderson and Scheoffel, 1985). This reduced lung function may impact both the ability to perform physical activity in asthmatics trying to maintain an exercise program as well asthmatics that are already active.

Bronchoconstriction during or after exercise may be caused by several different mechanisms including heat loss, water loss and excessive drying of the airways, airway inflammation and inflammatory mediator release (Anderson and Kippelen, 2005; Anderson and Daviskas, 2000). Rapid rewarming of the airways following exercise may lead to vascular hyperemia and airway edema (McFaddden et al., 1986). Although multiple causes contribute to the bronchoconstriction during, and/or after exercise, there is still speculation to the predominant cause of EIA. It is well established that excess reactive oxygen species (ROS) are produced in asthmatics (Malmgren et al., 1986). This may be in part due to reduced antioxidant defenses (Grievink et al., 1999; Wood et al., 2012) that leave asthmatics susceptive to the excess ROS production, and also a reduced antioxidant status to combat the excessive ROS. Wood et al. (2005) reported that asthmatics with a normal dietary intake still presented reduced antioxidant compounds (i.e., lycopene). These deficiencies have been reported in plasma (Misso et al., 2005), decreased ascorbic acid (vitamin C) from bronchoalevolar lavages (Kelly et al., 1999), and decreased α-tocopherol (i.e., vitamin E) in the airways (Wood et al., 2008).

Although these deficiencies reduce the protection against oxidative stress in the airways, there is a growing body of literature suggesting increasing the antioxidant status via dietary supplementation decreases the inflammatory burden, possibly

* Corresponding author at: 1A Natatorium, Kansas State University, Manhattan, KS, USA. Fax: +1 785 577 4098.
E-mail address: stephkurti@ksu.edu (S.P. Kurti).

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attenuating the decline in exercise-induced bronchoconstriction. Supplementation of vitamin C has been shown to have attenuated bronchoconstriciton post-exercise (Tecklenburg et al., 2007). Increasing dietary carotenoids (Hu and Cassano, 2000) and lutein (Schunemann et al., 2002) has been reported to improve respiratory status and lung function (Grievink et al., 2000). Although several studies have reported improved post-exercise lung function after taking vitamin C supplementation (Tecklenburg et al., 2007); other studies do not support these findings (Schachter and Schlesinger, 1982; Malo et al., 1986; Nadi et al., 2012). Similarly, there are reported improvements in pulmonary function with vitamin E supplementation in combination with vitamin C (Chatham et al., 1987; Dow et al., 1996) but not with vitamin E alone (Hackney et al., 1981; Pearson et al., 2004). These studies were performed to investigate EIB either in the elderly or in the presence of ozone. No studies, to our knowledge, have investigated supplementation with simultaneous vitamin C and vitamin E as a therapeutic option to reduce bronchoconstriction in exercise-induced asthmatics. Therefore the purpose of this study was to determine if ascorbic (AsA) and α-tocopherol supplementation would improve airway function in subjects with EIA. We were also interested in determining the time course of improvements over the supplementation period. It was hypothesized that daily supplementation of AsA and α-tocopherol for three weeks in subjects with EIA would reduce the airway bronchoconstrictor response to exercise.

2. Methods

Eight subjects with clinically diagnosed exercise-induced asthma (EIA) and five healthy controls (CON) volunteered for this study. Subjects were recruited from the Kansas State University campus. All subjects completed a medical health questionnaire and signed informed consent prior to participation, which was approved by the Kansas State Institutional Research Board (*Protocol #2125*). All subjects were non-smokers, and were at various fitness levels. Standard pulmonary function tests were performed on all subjects as part of the initial screening process (SensorMedics 229 Metabolic Cart, SensorMedics Corp., Yorba Linda, CA). Bronchoconstriction was verified in our EIA subjects as determined by at least 10% decrease in FEV_1 following the first exercise-challenge (Anderson et al., 1985). All subjects (EIA and CON) had not been taking AsA or α-tocopherol supplementation in the prior six months to testing.

2.1. Experimental design

A randomized single blind cross over design was used over a consecutive six-week period. Subjects were instructed to refrain from any therapeutic medications and vigorous exercise 12 h prior to testing. First, subjects performed an incremental treadmill test to exhaustion to determine peak aerobic capacity ($\dot{V}O_{2peak}$). Then, EIA and CON subjects were randomly assigned to either a placebo (PLA) or vitamin (VIT) supplementation group for three weeks. An exercise challenge was performed each week of the supplementation period. The exercise challenge consisted of subject running at a workload eliciting 90% $\dot{V}O_{2peak}$ until exhaustion. Prior to and following the exercise challenge pulmonary function was assessed. After a 3 week washout period, subjects were then given the alternate regimen for the remaining three weeks, such that subjects served as their own control. For all exercise testing sessions, an emergency bronchodilator was in the laboratory if necessary. No subjects needed to use the inhaler at any time point during or after the exercise tests.

2.2. Vitamin supplementation

The vitamin treatment included 250 mg of AsA and 100 IU of α-tocopherol with breakfast, and 250 mg of AsA, 200IU of α-tocopherol, and a multivitamin to be consumed with dinner. The dosage of AsA is the same as previous studies (Kordansky et al., 1979; Schachtner et al., 1982), and the dosage of α-tocopherol is similar to what has previously been investigated in the presence of ozone (Trenga et al., 2001). Additionally, a three week wash-out period and three weeks of supplementation is more conservative than previous studies investigating AsA (Tecklenburg et al., 2007) and α-tocopherol (Trenga et al., 2001) supplementation where a one week washout period was used. These supplements are known to completely washout in less than three weeks (Podmore et al., 1998; Dimitrov et al., 1991). Including the multivitamin (Standard One-A-Day multivitamin: 60 mg AsA; 22.5 IU α-tocopherol), total dietary intake was 933% of the DRI for AsA and 2444% for vitamin E. Both quantities are within healthy limits and are considered non-toxic (Levine et al., 2005; Weber et al., 1997). Daily vitamins were given at the beginning of each week to be self-administered by the subject at breakfast and dinner meals. Vitamin supplementation also included 500 mg AsA and 200 IU of α-tocopherol one-hour prior to exercise. Acute supplementation was taken with a candy bar containing 10 g of fat for maximal absorption of α-tocopherol. Subjects not undergoing vitamin treatment were supplemented with placebo (lactose) capsules throughout the three weeks and acutely one hour prior to exercise.

2.3. Peak aerobic capacity ($\dot{V}O_{2peak}$)

All subjects initially underwent a graded incremental treadmill test (Quinton Instrument Company, Model Q65, Seattle, WA) until exhaustion to determine maximal aerobic capacity ($\dot{V}O_{2peak}$). The exercise protocol was individualized for each subject to choose a speed that they felt was comfortable on a 0% grade. Subjects were allowed to complete a self-determined warm-up (5–10 min). Subsequently, testing began at 0% grade and increased 2% every 90 s until volitional fatigue. Breath-by-breath metabolic data were collected at baseline and throughout exercise (SensorMedic 229 Metabolic Cart, SensorMedics Corp., Yorba Linda, CA). Heart rate (HR) was assessed using ECG leads. Arterial oxygen saturation (SpO_2) was continuously monitored via a pulse oximeter (Datex-Ohmeda 3900P) attached to the earlobe. Criteria for a successful $\dot{V}O_{2peak}$ test included RER $\geq$ 1.15, heart rate within 10% predicted max, and/or a plateau in oxygen consumption (150 mL/min) with an increase in workload.

2.4. Exercise challenge

Within one week of initial testing, subjects performed an exercise challenge. Exercise challenges were repeated on day 7 (week 1), 14 (week 2), and 21 (week 3) of each treatment group. Ambient temperature did not differ significantly from trial to trial ($23.5 \pm 0.1\,^{\circ}C$). Subjects warmed-up for 5 min at a 4 mph walk before the exercise challenge. The exercise challenge consisted of exercising at a workload that corresponded to 90% of $\dot{V}O_{2peak}$ (EIA = $92.0 \pm 0.1\%\,\dot{V}O_{2peak}$; CON = $94.0 \pm 0.1\%\,\dot{V}O_{2peak}$) for 10 min. If subjects were unable to complete the 10 min of exercise, they were encouraged to exercise as long as possible. All subjects went at least six minutes for each of the exercise challenge tests. Prior to testing, a 3 mL venous blood draw was taken from the antecubital vein of the arm to determine hemoglobin ([Hb]). Maximum flow-volume loops measurements were taken prior to and immediately upon cessation of exercise and at 5, 15, and 30 mins post-exercise. Rate of perceived exertion (RPE) and dyspnea ratings were recorded at minutes 5, 8, and 10 of exercise. Plasma levels for AsA and α-tocopherol determi-