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Dietary nitrate supplementation improves exercise performance and decreases blood pressure in COPD patients

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ABSTRACT

Dietary nitrate (NO_3^-) supplementation via beetroot juice has been shown to increase the exercise capacity of younger and older adults. The purpose of this study was to investigate the effects of acute NO_3^- ingestion on the submaximal constant work rate exercise capacity of COPD patients. Fifteen patients were assigned in a randomized, single-blind, crossover design to receive one of two treatments (beetroot juice then placebo or placebo then beetroot juice). Submaximal constant work rate exercise time at 75% of the patient's maximal work capacity was the primary outcome. Secondary outcomes included plasma NO_3^- and nitrite (NO_2^-) levels, blood pressure, heart rate, oxygen consumption (VO_2), dynamic hyperinflation, dyspnea and leg discomfort. Relative to placebo, beetroot ingestion increased plasma NO_3^- by 938% and NO_2^- by 379%. Median (+interquartile range) exercise time was significantly longer ($p = 0.031$) following the ingestion of beetroot versus placebo (375.0 + 257.0 vs. 346.2 + 148.0 s, respectively). Compared with placebo, beetroot ingestion significantly reduced iso-time ($p = 0.001$) and end exercise ($p = 0.008$) diastolic blood pressures by 6.4 and 5.6 mmHg, respectively. Resting systolic blood pressure was significantly reduced ($p = 0.019$) by 8.2 mmHg for the beetroot versus the placebo trial. No other variables were significantly different between the beetroot and placebo trials. These results indicate that acute dietary NO_3^- supplementation can elevate plasma NO_3^- and NO_2^- concentrations, improve exercise performance, and reduce blood pressure in COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease affecting the airways and/or lung parenchyma of primarily older adults that results in a mostly irreversible airway obstruction [1,2]. Pathophysiological consequences of COPD include skeletal muscle deconditioning, ventilatory and gas exchange impairments resulting in tissue hypoxia, and psychological disturbances all of which result in a shortness of breath (dyspnea) and a poor exercise tolerance. Because of these problems, COPD patients engage in lower levels of physical activity as compared with age-matched controls [3–5]. This reduction in activity leads to further cardiovascular and musculoskeletal system deconditioning and increases in activity-related dyspnea thus provoking further decreases in physical activity. Unless interrupted, this spiral of dyspnea, inactivity, and deconditioning ultimately leads to the inability of COPD patients to perform basic activities of daily living. This loss of physical function has the potential to further increase the risk of morbidity and mortality as well as healthcare costs. Exercise [6–8] and optimal pharmacological management [9,10] have both been shown to improve the exercise capacity and physical function of COPD patients.

Recently, dietary nitrate (NO_3^-) has been shown to be a nutraceutical that can improve exercise capacity in young healthy individuals [11–13]. Dietary NO_3^- supplementation has been shown to exert its effects as a result of its conversion to NO_2^- and then to NO. NO is recognized as an endogenous effector molecule that has a role in a variety of physiological functions including vasoregulation, vascular homeostasis, neurotransmission, cellular metabolism and immune function [14,15]. Following NO_3^- consumption, it is

Abbreviations: COPD, chronic obstructive pulmonary disease; VO_2, oxygen consumption; $VO_{2\ max}$, maximal oxygen consumption; W, watts.

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absorbed in the stomach and small intestines. While approximately 75% of the NO_3^- is excreted by the kidneys, the remainder is taken up by the salivary glands and concentrated in the saliva [16]. Salivary NO_3^- is then reduced to NO_2^- via facultative bacteria found in the oral cavity [17]. Once swallowed and within the acidic environment of the stomach, NO_2^- is then converted to NO [18,19]. This $NO_3^-\rightarrow NO_2^-\rightarrow NO$ pathway has been proposed as a complementary pathway to the L-arginine nitric oxide synthase (NOS) system as a source of NO [14]. Given the L-arginine NOS system is oxygen dependent, whereas activity of the $NO_3^-\rightarrow NO_2^-\rightarrow NO$ pathway increases as oxygen tensions decrease, the latter pathway can be viewed as a back-up system for NO production during hypoxic conditions, which can occur in COPD patients and during exercise.

Vegetables are a primary source of NO_3^- in the human diet. In particular, green leafy vegetables and beetroots have a high NO_3^- concentration. Nitrate supplementation via beetroot juice has been shown to reduce oxygen consumption (VO_2) during submaximal exercise and increase the time to exhaustion during high intensity exercise in young healthy subjects [11,20]. Vanhatalo et al. recently found that in young healthy subjects NO_3^- supplementation via beetroot juice reduced muscle metabolic perturbations during hypoxic exercise and restored exercise tolerance and oxidative function to values observed in normoxia [21]. These results suggest that stimulating the $NO_3^-\rightarrow NO_2^-\rightarrow NO$ pathway via ingestion of dietary NO_3^- may have important therapeutic applications for improving muscle energetics and functional capacity during hypoxic conditions such as exercise in patients with cardiovascular, pulmonary and/or sleep disorders.

Kelly et al. hypothesized that NO_3^- supplementation may also provide beneficial effects for older adults because of the age associated decline in NO signaling [22]. This NO defect is a result of reduced availability of L-arginine or the cofactor tetrahydrobiopterin, reduced endothelial NOS activity and/or increased superoxide production [23,24]. Kelly et al. reported that dietary supplementation of NO_3^- over a 2.5 day period significantly increased plasma NO_2^- levels and decreased resting blood pressure and the mean response time of VO_2 in healthy older adults [22]. These results suggest that dietary NO_3^- intake has the potential to improve the exercise capacity of older adults.

Given COPD patients experience greater degrees of tissue hypoxia, have a decreased exercise capacity, are often older and the fact that dietary NO_3^- has been shown to improve exercise performance, it was the purpose of this investigation to examine the effects of acute NO_3^- supplementation, via beetroot juice consumption, on submaximal constant work rate exercise in patients with COPD. If NO_3^- supplementation can increase exercise tolerance in COPD patients by reducing the oxygen cost of exercise at a given work rate, this molecule could potentially serve as a therapeutic agent allowing these patients to retain physical function and remain active thus delaying or even preventing the loss of physical function and independence.

2. Methods

2.1. Design and overview

This investigation was a single-blind, placebo-controlled, cross-over study with submaximal constant work rate exercise time as the primary outcome. Patients completed four visits as part of the study protocol. During visit 1, patients completed baseline pulmonary function testing, health status questionnaires, had a brief medical examination and completed an incremental exercise test on an electronically braked cycle ergometer to determine their maximal exercise work rate. Visit 2 was performed approximately 1 week later and consisted of additional pulmonary function and lung volume testing, as well as a familiarization submaximal constant work rate exercise test on an electronically braked cycle ergometer at 75% of patients' maximal work rate. This type of exercise test has been used in previous trials with COPD patients examining the effects of pharmaceutical agents on exercise performance and is designed to exhaust the patient between 4 and 10 min [10,25,26]. Upon successful completion of visits 1 and 2, patients were randomized into the single-blind, cross-over treatment segment of the study. In this part of the study, patients were randomly assigned to one of two treatments, beetroot juice (visit 3) and placebo (visit 4) or placebo (visit 3) and beetroot juice (visit 4). Visits 3 and 4 were separated by at least a 7 day wash-out period. All visits were performed at a similar time in the morning. While patients were informed that the purpose of the study was to examine the effects of dietary NO_3^- on exercise performance, they were not informed by the study staff as to which beverage was high in NO_3^-. Investigators collecting study related data and supplying the beverages to the patients were not aware of the beverage supplied to the patient. Additionally, all patients were asked not to inform the study staff as to which beverage they had consumed when they returned for follow-up testing on visits 3 and 4. A schematic of the study visits is shown in Fig. 1.

2.2. Patients

The study sample consisted of 15 COPD patients; 11 white males, 1 African-American male and 3 white females. Subjects were recruited from previous exercise interventions with COPD patients as well as newspaper adverts. All subjects who agreed to participate signed an informed consent form approved by the Institutional Review Board at Wake Forest University. Exclusion criteria and screening methods are listed in Table 1.

2.3. Study procedures

2.3.1. Visit 1

After signing the informed consent, patients completed pulmonary function tests to determine if they qualified to participate. These

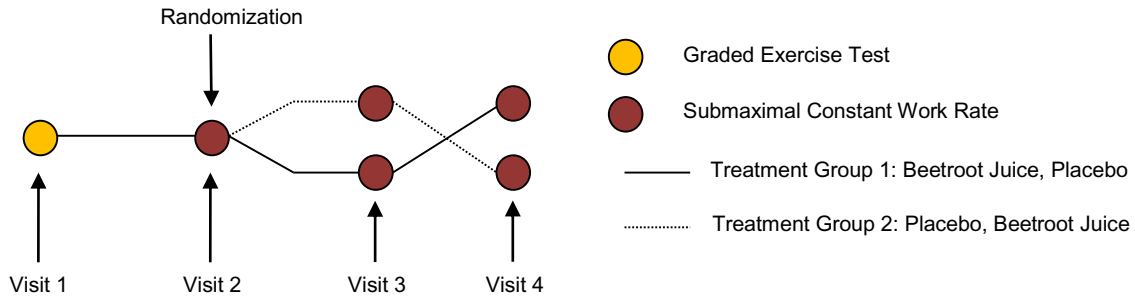

Fig. 1. Illustrates the schematic of trial visits.