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The effect of dietary nitrate supplementation on the oxygen cost of cycling, walking performance and resting blood pressure in individuals with chronic obstructive pulmonary disease: A double blind placebo controlled, randomised control trial

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) results in exercise intolerance. Dietary nitrate supplementation has been shown to lower blood pressure (BP), reduce the oxygen cost of exercise, and enhance exercise tolerance in healthy volunteers. This study assessed the effects of dietary nitrate on the oxygen cost of cycling, walking performance and BP in individuals with mild–moderate COPD.
Methods: Thirteen patients with mild–moderate COPD were recruited. Participants consumed 70 ml of either nitrate-rich (6.77 mmol nitrate; beetroot juice) or nitrate-depleted beetroot juice (0.002 mmol nitrate; placebo) twice a day for 2.5 days, with the final supplement ~3 hours before testing. BP was measured before completing two bouts of moderate-intensity cycling, where pulmonary gas exchange was measured throughout. The six-minute walk test (6MWT) was completed 30 minutes subsequent to the second cycling bout.
Results: Plasma nitrate concentration was significantly elevated following beetroot juice *vs.* placebo (placebo; 48 ± 86 *vs.* beetroot juice; 215 ± 84 μM, $P = 0.002$). No significant differences were observed between placebo *vs.* beetroot juice for oxygen cost of exercise (933 ± 323 *vs.* 939 ± 302 ml: min^{-1}; $P = 0.88$), distance covered in the 6MWT (456 ± 86 *vs.* 449 ± 79 m; $P = 0.37$), systolic BP (123 ± 14 *vs.* 123 ± 14 mmHg; $P = 0.91$), or diastolic BP (77 ± 9 *vs.* 79 ± 9 mmHg; $P = 0.27$).
Conclusion: Despite a large rise in plasma nitrate concentration, two days of nitrate supplementation did not reduce the oxygen cost of moderate intensity cycling, increase distance covered in the 6MWT, or lower BP.

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1. Introduction

Exercise in individuals with COPD is limited by multiple factors which can result in hypoxemia. These include loss of normal lung architecture, impaired cardiac function [1], abnormal pulmonary blood flow distribution [2] and peripheral muscle de-conditioning [3]. Oxygen uptake in the lungs and delivery of oxygen to the working muscle is impaired by increases in pulmonary blood flow which increase shunting through blood vessels resulting in incomplete gas exchange [4] and cor pulmonale later in the disease course. These abnormalities result in feelings of breathlessness and fatigue [5], with individuals often finding that activities of daily living are physically challenging.

The beneficial effects of a diet rich in vegetables upon cardiovascular health [6], risk of morbidity and mortality [7], and COPD development [8,9] have been well described. These positive effects have, in part, been attributed to inorganic nitrate which is found in particularly high quantities in leafy green vegetables and some root vegetables such as beetroot [10]. Nitrate supplementation in the form of sodium nitrate or nitrate-rich beetroot juice has been shown to have remarkable effects in healthy young individuals and athletes, including reductions in the oxygen cost of exercise [11], enhanced exercise tolerance/performance and reduced blood pressure (BP) [11,12]. Some of these effects have subsequently been

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observed in individuals with peripheral artery disease following dietary nitrate supplementation [13]. These findings have been attributed to an increase in the bioavailability of nitric oxide (NO).

NO is a signalling molecule with multiple functions including regulation of vascular tone, mitochondrial respiration and skeletal muscle function [14–16]. These factors are important in the physiological response to exercise. NO is produced in two distinct ways in man. The best known is the classical L-arginine nitric oxide synthase (NOS) pathway which is oxygen dependent [17]. The second is the entero-salivary pathway and is oxygen independent. Briefly, nitrate from the diet is rapidly and extensively absorbed in the stomach and proximal small intestine with bioavailability approaching 100% [18]. Nitrate is then concentrated in the salivary glands, with concentrations 10 fold greater in saliva than in plasma. Nitrate secreted in saliva is reduced to nitrite by facultative anaerobic bacteria on the dorsum of the tongue [19]. On swallowing, the acidic environment of the stomach results in NO formation with important local effects on gastric function and host defence [6,20]. Some nitrite is absorbed into the circulation where it acts as a storage pool for subsequent NO production [14]. The conversion of nitrite to NO is expedited in conditions of acidosis [21] or hypoxemia [14] which often occur in the exercising muscle of individuals with COPD [22].

In many individuals with COPD, functional capacity is reduced to a level where activities of daily living may impose a challenge due to an energy requirement representing a high fraction of their maximal oxygen uptake. Whilst a number of cardiovascular and physiological benefits have been shown as a result of dietary nitrate supplementation in healthy populations, little is known about possible effects in clinical populations. We aimed to determine whether dietary nitrate supplementation has a beneficial impact upon the oxygen cost of sub-maximal cycling exercise, walking performance and BP in individuals with COPD.

1.1. Purpose

The aim of this study was to assess the effects of 2.5 days of dietary nitrate supplementation on the oxygen cost of sub-maximal cycling, walking performance, and resting BP in individuals with mild–moderate COPD.

2. Methods

2.1. Patients

Fourteen individuals with mild–moderate COPD (see Table 1 for patient characteristics) gave written informed consent to participate in this double-blind, placebo-controlled, cross-over design study between April 2013 and January 2014. The study was registered as a clinical trial at ClinicalTrials.gov (NCT01712386). The Exeter NRES Committee gave ethical approval (12//SW//0327). Patients were recruited if lung function was between 30 and 80% of predicted FEV_1 values, aged 40–75 years old and able to give informed consent. Participants were excluded if they had chronic kidney disease (estimated glomerular filtration rate <30 ml/min/1.73 m^2), uncontrolled hypertension (systolic BP > 160 mmHg or diastolic >100 mmHg), were smokers (smoked within past 3 months), consumed regular organic nitrate or nicorandil. Patients taking phosphodiesterase inhibitors were asked to refrain from doing so for the duration of the study.

Table 1
Characteristics of the patients included in the final analyses. Data are mean ± SD or as a % of the cohort on a medication.

Age (years)	64.7 ± 7.7
FEV_1 (%)	57 ± 9
FVC (l)	3.6 ± 0.9
FEV_1/FVC	41 ± 16
Body mass index (kg/m^2)	29 ± 8
Baseline SBP (mmHg)	132 ± 15
Baseline DBP (mmHg)	85 ± 10
No. of 30+ minutes of exercise per week	4.7 ± 3.6
ARB/ACEi (%)	23
Calcium channel blocker (%)	15
Short-acting β2-agonists (%)	77
Long-acting β2-agonists (%)	77

2.2. Pre-experimental tests

Participants arrived at the Heart and Lung unit at Torbay Hospital where informed consent, medical history, anthropometric measures, BP, lung function and an ECG were performed. Participants completed a ramp incremental cycle ergometer test (10 W min^{-1}) to determine their gas exchange threshold (GET). Breath-by-breath pulmonary gas exchange was measured throughout and the GET was determined using the V-slope method as described previously [23].

2.3. Experimental overview

Participants consumed 70 ml of nitrate-rich beetroot juice (beetroot juice; 6.77 mmol nitrate; Beet it, James White Drinks Ltd., Ashbocking, UK) or nitrate-depleted beetroot juice as a placebo (placebo; 0.002 mmol nitrate; Beet it, James White Drinks Ltd., Ashbocking, UK), with one beverage in the morning and one in the evening for two days preceding testing. On study days, participants consumed a final 70 ml beetroot juice drink ~3 hours prior to exercising. Participants self-reported concordance with the supplementation regime which was confirmed by measurement of plasma nitrate concentration. After exercise testing the participants began a washout period (7 days) before entering the opposing arm of the study. The placebo was indistinguishable from the nitrate-rich juice in taste, colour, texture, appearance and odour as described previously [24].

Participants arrived at the laboratory in a fully hydrated state, having avoided consumption of caffeine, alcohol, cruciferous vegetables, leafy greens, beetroot, and completion of strenuous exercise 24 hours prior to testing. Participants were asked to record their food intake for 24 hours prior to testing and to replicate this after the crossover and this was verbally confirmed on the second exercise visit. Participants avoided antibacterial mouthwash for 7 days prior to testing. Participants arrived 45 minutes before the initiation of exercise following ingestion of the randomised juice with their morning meal. Brachial artery BP was taken, after a 10 minute resting period whilst supine, with an automated sphygmomanometer (Omron M6, Kyoto, Japan). Five measurements were performed and the mean of the last three was recorded. Venous blood was drawn and processed for plasma nitrate concentration as per our previously described chemiluminescence technique [25]. Participants completed two bouts of cycling at 80% of their GET on a cycle ergometer (Ergoselect 100, Bitz, Germany) with 30 minutes recovery between bouts. Following 30 minutes rest, participants performed a six-minute walk test to assess functional capacity. Participants walked around a clear rectangular corridor (14 × 12 m) for a total of 52 m per lap, covering as much distance as possible. Standardised verbal encouragement was given throughout.

2.4. Measurements

Pulmonary gas exchange and ventilation were measured during the cycling exercise (Vmax™ Encore, Yorba, Linda, CA). Before each session the analysers were calibrated using gases of known concentration. The volume transducer was calibrated using a 3-litre syringe (Hans Rudolph, Kansas City, MO, USA).

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