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Dietary nitrate supplementation in COPD: An acute, double-blind, randomized, placebo-controlled, crossover trial ☆

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ABSTRACT

Background: The acute consumption of dietary nitrate has been shown to improve exercise capacity in athletes, healthy adults and subjects with peripheral vascular disease. Many COPD patients have reduced exercise capacity. We hypothesized that acute nitrate consumption might increase incremental shuttle walk test (ISWT) distance in COPD subjects.
Methods: Eleven COPD subjects were randomly assigned to consume either a high nitrate or a matched, low nitrate beverage in a double-blind, randomized, placebo-controlled, crossover design. ISWT distance was measured both before and 3 h after the beverage and change was recorded. After a 7-day washout, ISWT distances were re-measured before and 3 h after the alternate beverage and changes were recorded.
Results: We observed an increase in ISWT distance after consuming the high nitrate juice (25 m) compared with a reduction after the low nitrate juice (14 m) ($p < 0.01$). This improvement in exercise capacity was associated with significant increases in serum nitrate ($p < 0.000005$) and nitrite ($p < 0.01$) levels and a significant lowering of resting blood pressure (<0.05).
Conclusions: In patients with stable COPD, the acute consumption of dietary nitrate increased serum nitrate/nitrite levels and exercise capacity and was associated with a decrease in resting blood pressure. Nitrate consumption might alter exercise capacity in COPD patients.

1. Introduction

COPD is associated with exercise limitation, leading to a poor quality of life [1]. Important factors that limit exercise capacity in COPD include circulatory impairment, skeletal muscle dysfunction and airflow obstruction. Airflow limitation is a central characteristic of COPD and may result in failure to adequately supply blood and oxygen (O_2) to working tissues. This inability to deliver O_2 at a rate to match demand in working tissues limits exercise tolerance.

Nitric oxide (NO), a potent systemic and pulmonary arterial vasodilator [2,3] is vital for skeletal muscle contraction [4]. During exercise, NO contributes to matching of blood flow and oxygen (O_2) delivery to requirement in skeletal-muscle [5]. NO synthesis *in vivo* occurs mainly via NO synthase (NOS). However NO is also produced from nitrite, derived from reduction of dietary nitrate in a NOS-independent pathway [6]. Blood nitrite concentrations have been shown to reflect vascular NO bioavailability [7] as well as exercise capacity in healthy adults [8] and elite athletes [9]. Acute nitrate consumption increases blood nitrate/nitrite levels and exercise performance in healthy [10], athletic [11], and peripheral vascular disease (PVD) [12] subjects. However, inhaled NO is contraindicated in COPD due to fears about ventilation perfusion mismatching [13]. No consensus exists about the benefits and risks of dietary nitrate consumption in COPD patients.

Hypoxemia and lactic acidosis contribute to exercise limitation in COPD [14]. The L-arginine–NOS–NO pathway is O_2 dependent and

Abbreviations: COPD, chronic obstructive pulmonary disease; ISWT, incremental shuttle walk test; NO, nitric oxide; O_2, oxygen; NOS, nitric oxide synthase; PVD, peripheral vascular disease; h, hour; BRJ, beetroot juice; PL, placebo; ml, millilitre; min, minute; $\%SpO_2$, arterial oxygen concentration; HR, heart rate; BP, blood pressure; MAP, mean arterial pressure; ATS, American Thoracic Society; ERS, European Respiratory Society; RPM, rate per minute; SD, standard deviation; m, meters; BMI, body mass index; FEV_1, forced expiratory volume in one second; kcal, kilocalorie.

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Mr. Kerley also presented preliminary results at the Irish Section meeting of the Nutrition Society (Dublin 2013): http://journals.cambridge.org/download.php?file=%2FPNS%2FPNS72_OCE3%2FS0029665113001705a.pdf&code=3c68f1cf33b49e234579326df0a7aa58.

This trial was registered at ClinicalTrials.gov (Identifier: NCT02148289).

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malfunctions under hypoxic/acidic conditions, conversely the nitrate–nitrite–NO pathway is upregulated under these conditions [6]. Thus nitrite, derived from dietary nitrate, has potential to increase NO, particularly in areas of low pH and/or O_2. Dietary nitrate may increase the efficiency of energy production per unit of O_2 consumed [10]. This may be relevant when tissue oxygenation is limited. Our objective was to assess the acute effect of dietary nitrate ingestion on exercise capacity in COPD subjects.

2. Materials and methods

2.1. Subjects

We recruited clinically stable, COPD out-patients from respiratory clinics of Connolly Hospital (Dublin, Ireland) by physician referral between December 2012 and February 2013. We excluded subjects taking vasodilators, including organic nitrates and subjects with pulmonary hypertension, obstructive sleep apnoea, angina or active musculo-skeletal conditions which could impair exercise capacity. Subjects on long-term oxygen therapy (LTOT) were eligible only if they were able to perform the protocol without supplemental oxygen use. This study was approved by the Human Research Ethics Committee of Connolly Hospital, Dublin and written informed consent was obtained from all subjects.

2.2. Procedure

During this randomized, placebo-controlled, double-blinded, crossover study, subjects were tested on two separate days at least 7 days apart (Fig. 1). On days 1 and 8, subjects consumed an identical light, self-selected breakfast, took relevant medications as prescribed and refrained from alcohol and tobacco. On both days, in an identical manner and at the same time of day, we performed resting blood pressure measures, blood draws, and incremental shuttle walk tests (ISWT) before and 3 h after consumption of a beverage. We assessed dyspnoea, heart rate (HR) and arterial oxygen concentration (%SpO2) immediately pre- and post-ISWT. This protocol was repeated 3 h after beverage consumption (nitrate-rich concentrated beetroot juice; BRJ) or placebo beverage (PL). The 3 h delay was to allow recovery from baseline testing, and to allow blood nitrite concentrations to peak following dietary nitrate consumption [12].

2.2.1. Beverages

Following completion of day 1 pre-supplementation assessments, subjects were randomized in a double-blind, crossover design to receive BRJ or PL. Thus subjects underwent assessments on four occasions – before and 3 h after both BRJ and PL supplementation separated by a 7-day washout period (Fig. 1), during which they were advised not to change behaviours which may influence NO pharmacokinetics or exercise capacity during the washout period, including habitual diet and exercise patterns.

On the morning of each visit, an investigator assembled plastic beakers to contain 140 ml nitrate-rich BRJ (James White Drinks Ltd) + 200 ml blackcurrant cordial or 140 ml water + 200 ml blackcurrant cordial (table 1). This investigator, not involved in data recording, blinded the beverages and solely held the trial codes until trial completion. We selected this dose of BRJ as the nitrate content (12.9 mmol) is attainable with a diet rich in vegetables [15]. The same cordial, with negligible nitrate/nitrite content, was used for all formulations and served to blind the beverages in terms of colour and taste. All data-recording investigators and subjects were blinded to treatment sequence. At each visit, the subjects underwent baseline assessments followed by consumption of the 340 ml beverage (BRJ or PL) over a 5-min period and rested quietly for 180 ± 10 min. During this time, tobacco use and physical activity were prohibited, but subjects were allowed to eat and drink low nitrate foodstuffs.

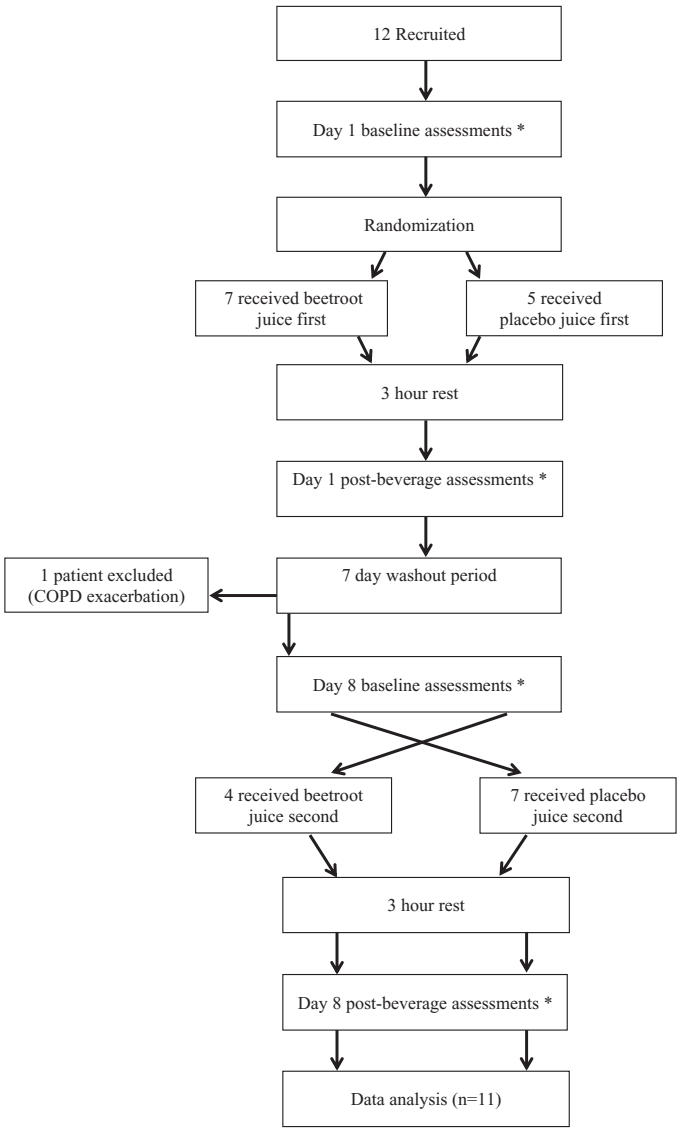

Fig. 1. Trial design. Study protocol. * Assessments included: Resting blood pressure, blood draw, resting, pre-ISWT dyspnoea and arterial oxygen concentration, ISWT, post-ISWT dyspnoea and arterial oxygen concentration, BRJ = beetroot juice, PL = placebo.

Any ingestion had to be replicated on the crossover visit and this was confirmed via self-report to the research dietician (CK). Subjects consumed a similar, low nitrate breakfast before both study visits.

Table 1
Composition of the experimental beverages.

Ingredients	Nitrate-rich	Placebo
	140 ml concentrated BRJ	140 ml water
	200 ml concentrated, sugar-free blackcurrant cordial	200 ml concentrated, sugar free blackcurrant cordial
Energy (kcal)	146	26
Carbohydrate (g) of which sugars (g)	34.9 34.9	2.9 2.9
Protein (g)	5.4	0.4
Fat (g)	<0.1	<0.1
Nitrate (mmol)	12.9	<0.5
Total volume (ml)	340	340

BRJ = beetroot juice, kcal = kilocalories, g = grams, mmol = millimoles, ml = millilitres.