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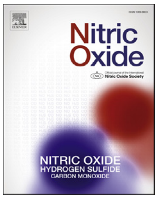

Effects of supervised exercise and dietary nitrate in older adults with controlled hypertension and/or heart failure with preserved ejection fraction

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ABSTRACT

Aerobic exercise training is an effective therapy to improve peak aerobic power (peak VO_2) in individuals with hypertension (HTN, AHA/ACC class A) and heart failure patients with preserved ejection fraction (HFpEF). High nitrate containing beetroot juice (BRJ) also improves sub-maximal endurance and decreases blood pressure in both HTN and HFpEF. We hypothesized that combining an aerobic exercise and dietary nitrate intervention would result in additive or even synergistic positive effects on exercise tolerance and blood pressure in HTN or HFpEF. We report results from two pilot studies examining the effects of supervised aerobic exercise combined with dietary nitrate in patients with controlled HTN ($n = 26$, average age 65 ± 5 years) and in patients with HFpEF ($n = 20$, average age 69 ± 7 years). All patients underwent an aerobic exercise training regimen; half were randomly assigned to consume a high nitrate-containing beet juice beverage (BRJ containing 6.1 mmol nitrate for the HFpEF study consumed three times a week and 8 mmol nitrate for the HTN study consumed daily) while the other half consumed a beet juice beverage with the nitrate removed (placebo). The main result was that there was no added benefit observed for any outcomes when comparing BRJ to placebo in either HTN or HFpEF patients undergoing exercise training ($p \geq 0.14$). There were within-group benefits. In the pilot study in patients with HFpEF, aerobic endurance (primary outcome), defined as the exercise time to volitional exhaustion during submaximal cycling at 75% of maximal power output, improved during exercise training within each group from baseline to end of study, 369 ± 149 s vs 520 ± 257 s ($p = 0.04$) for the placebo group and 384 ± 129 s vs 483 ± 258 s for the BRJ group ($p = 0.15$). Resting systolic blood pressure in patients with HFpEF also improved during exercise training in both groups, 136 ± 16 mm Hg vs 122 ± 3 mm Hg for the placebo group ($p < 0.05$) and 132 ± 12 mm Hg vs 119 ± 9 mm Hg for the BRJ group

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($p < 0.05$). In the HTN pilot study, during a treadmill graded exercise test, peak oxygen consumption (primary outcome) did not change significantly, but time to exhaustion (also a primary outcome) improved in both groups, 504 ± 32 s vs 601 ± 38 s ($p < 0.05$) for the placebo group and 690 ± 38 s vs 772 ± 95 s for the BRJ group ($p < 0.05$) which was associated with a reduction in supine resting systolic blood pressure in BRJ group. Arterial compliance also improved during aerobic exercise training in both the HFpEF and the HTN patients for both BRJ and placebo groups. Future work is needed to determine if larger nitrate doses would provide an added benefit to supervised aerobic exercise in HTN and HFpEF patients.

1. Introduction

The most common form of heart failure is preserved ejection fraction (HFpEF)[3]; it almost exclusively affects older adults and is characterized by exercise intolerance that manifests in a poor quality of life [1–3]. Population studies show that about 90% of HFpEF patients have a history of chronic hypertension (HTN). HTN and HFpEF often share common cardiovascular abnormalities including increased arterial stiffness, left ventricular hypertrophy, left atrial dilation, and frequent abnormal diastolic function [4]. Symptoms of both HTN and HFpEF can be improved by aerobic exercise training [5–8]. Blood pressure in treated hypertensives is typically controlled using various drug interventions while aerobic exercise regimens can also reduce blood pressure and improve vascular function [9,10]. Habitual exercise also improves exercise capacity [10]. To date, the only treatment confirmed in clinical trials to improve exercise capacity in patients with HFpEF is aerobic exercise training [5,11,12].

Low nitric oxide (NO) bioavailability results in hypertension and restoration of NO is the basis for the mechanism of action of some current medications [13–15]. Low NO bioavailability has also been suggested to contribute to poor skeletal muscle perfusion in patients with HFpEF [16], which (along with other non-cardiac factors) contributes to exercise intolerance [11,17–19]. One attractive means to deliver NO is through the anion nitrite (NO_2^-) as nitrite is reduced to NO preferentially in areas of low oxygen and pH so that delivery is well-targeted to metabolically active tissue such as at the muscles involved in exercise [20]. This is often accomplished through the nitrate (NO_3^-)-nitrite-NO pathway [21,22]. Plasma nitrate is derived from endogenous mechanisms (including the oxidation of NO) and from dietary consumption (especially vegetables including beets and beet root juice [23]). Bacteria in the oral cavity partially reduce salivary nitrate to nitrite [24]. Nitrate and nitrite in the gastrointestinal tract are transferred to the plasma. Nitrite is then reduced to NO, preferentially under hypoxic and acidic conditions, through mechanisms proposed to involve a variety of heme and non-heme proteins, as recently reviewed [25]. Plasma nitrate is concentrated in salivary glands and secreted back into the oral cavity so that the nitrate-nitrite-NO pathway cycles for an extended period with the half-life of plasma nitrate being about 6 h [21,26,27].

Several studies have demonstrated the therapeutic potential of the nitrate-nitrite-NO pathway including that dietary nitrate lowers blood pressure and improves exercise performance in patients with chronic obstructive pulmonary disease [28], improves exercise performance in patients with peripheral artery disease [29], and improves exercise capacity and endurance in patients with HFpEF [30,31]. Numerous studies have shown that dietary nitrate improves exercise efficiency or performance, or lowers blood pressure in healthy volunteers [32]. A recent double-blind, placebo controlled study demonstrated sustained blood pressure lowering due to dietary nitrate in hypertensive individuals that were both taking medication and drug-naïve [33]. In addition, it has recently been shown that infused [34] or inhaled [35] nitrite (the active metabolite of nitrate) improves hemodynamics in patients with HFpEF.

We hypothesized that the combination of oral nitrate and aerobic exercise training will improve nitric oxide bioavailability as well as blood pressure and result in improved exercise performance beyond what is observed with aerobic exercise training alone. This hypothesis is based on the notion that the effect of aerobic exercise training may be limited by poor NO bioavailability due to endothelial dysfunction. Simultaneous administration of oral nitrate could improve aerobic exercise training and subsequent outcomes. This hypothesis is supported by recent work showing that dietary nitrate results in similar physiological responses as exercise therapy in a diabetic rat model [36]. We tested our hypothesis in two separate studies: patients with HFpEF and individuals with controlled hypertension.

2. Methods

2.1. Study design

Both studies (HFpEF and HTN) were approved by the institutional review board, and all participants provided written, informed consent.

2.1.1. HFpEF study

This pilot study was an extension of a recent study of 20 HFpEF patients (average age 69 ± 7 years) investigating dietary nitrate (but no exercise) [31]. Briefly, the recent published study examined effects of a single acute dose and one week of daily dosing of BRJ (with no exercise). This portion of the study that did not involve exercise training lasted between 12 and 22 days from the end of baseline exercise testing and the last visit of that previous study. Immediately following the final study visit of the previous report

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[3] Abbreviations: heart failure is preserved ejection fraction (HFpEF); hypertension (HTN); exercise (EX); beet root juice (BRJ); peak volume oxygen consumption ($VO_{2\ peak}$); stroke volume (SV); cardiac output (CO); systemic vascular resistance (SVR); total arterial compliance (TAC); velocity index (VI); acceleration index (AI); left cardiac work index (LCWI); impedance cardiography (ICG); systolic blood pressure (SBP); diastolic blood pressure (DBP); heart rate variability (HRV); blood pressure variability (BPV); and baroreflex sensitivity (BRS); low frequency (LF); and high frequency (HF); standard deviation of normal beat-to-beat interval (SDRR); root of mean of successive differences (rMSSD); Blood pressure variability (BPV); standard deviation of the mean arterial pressure (SDMAP); best-responder (BR), good-responder (GR); non-responder (NR); analysis of variance (ANOVA); body mass index (BMI); angiotensin converting enzyme (ACE); angiotensin receptor blocker (ARB); New York Heart Association (NYHA); mitral annulus velocity (e'); early mitral velocity (E); history (Hx); respiratory exchange ratio (RER); heart rate (HR); minute ventilation (VE); ventilatory anaerobic threshold (VAT); ambulatory blood pressure measurements (APBM); mean blood pressure (MBP); Power of spectrum in high frequency range (Hfa); slope of the baroreflex gain curve measured by the sequence method in the UP or Down direction (Seq UP & DOWN).