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MINI-FOCUS ISSUE: REDUCED, PRESERVED, AND BORDERLINE EJECTION FRACTION

One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction

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CME Objective for This Article: After reading this article, the reader should be able to: 1) describe the pharmacokinetics and effects of inorganic nitrates and explain how inorganic nitrates differ from organic nitrates; 2) explain why patients with HFpEF have exercise intolerance; and 3) describe the effects of beet root juice on exercise performance in older adults with HFpEF.

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One Week of Daily Dosing With Beetroot Juice Improves Submaximal Endurance and Blood Pressure in Older Patients With Heart Failure and Preserved Ejection Fraction

ABSTRACT

OBJECTIVES This study sought to determine whether a relatively low single dose or a week-long dosage of dietary inorganic nitrate could improve exercise tolerance in patients with heart failure with preserved ejection fraction (HFpEF).

BACKGROUND Exercise intolerance is the primary manifestation of HFpEF and is largely due to noncardiac factors that reduce oxygen delivery to active skeletal muscles. A recent study showed improved exercise capacity in patients with HFpEF after a single, acute dose of beetroot juice (BRJ) (12.9 mmol inorganic nitrate) while another recent study showed neutral and negative effects of an organic nitrate.

METHODS Twenty HFpEF patients (69 ± 7 years of age) were enrolled in an initial cross-over design comparing a single, acute dose of BRJ (6.1 mmol nitrate) to a nitrate-depleted placebo BRJ. A second phase, 1 week of daily doses, used an all-treated design in which patients consumed BRJ for an average of 7 days. The primary outcome of the study was submaximal aerobic endurance, measured as cycling time to exhaustion at 75% of measured maximal power output.

RESULTS No adverse events were associated with the intervention. Submaximal aerobic endurance improved 24% after 1 week of daily BRJ dosing ($p = 0.02$) but was not affected by the single, acute dose of the BRJ compared to placebo. Consumption of BRJ significantly reduced resting systolic blood pressure and increased plasma nitrate and nitrite in both of the dosing schemes.

CONCLUSIONS One week of daily dosing with BRJ (6.1 mmol inorganic nitrate) significantly improves submaximal aerobic endurance and blood pressure in elderly HFpEF patients. (J Am Coll Cardiol HF 2016;4:428–37)

Heart failure with preserved ejection fraction (HFpEF) is the most common form of HF, is nearly unique to the older population, particularly older women, and is increasing in prevalence (1,2). HFpEF has a distinct pathophysiology compared to heart failure with reduced ejection fraction and thus warrants distinct targeted treatment (3). Exercise intolerance is the primary clinical feature in chronic HFpEF and is a major determinant of these patients' severely reduced quality of life (4). Endurance exercise training is currently the only therapy proven to improve aerobic capacity in older HFpEF patients (5–7). Medications tested to date, most of which have primarily targeted cardiac mechanisms, have been unsuccessful (8–10).

We reported that, in older HFpEF patients, noncardiac factors contribute significantly to their exercise intolerance and are the major contributors to exercise improvement following endurance exercise training (7,11,12). Specifically, skeletal muscle abnormalities,

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ABBREVIATIONS AND ACRONYMS

BRJ = beetroot juice

HFpEF = heart failure with preserved ejection fraction

NO = nitrite oxide

NO_2^- = inorganic nitrite

NO_3^- = inorganic nitrate

VO_2 = oxygen consumption

including reduced capillary density, percentage of type I oxidative fibers, and mitochondrial mass and function coupled with impaired skeletal muscle perfusion may contribute significantly to reduced exercise tolerance in older HFpEF patients (5,13–15). Moreover, it has been suggested that impaired perfusion results are due, at least partially, to low availability of the vasodilator nitric oxide (NO) (16).

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Emerging evidence suggests that dietary inorganic nitrate (NO_3^-) supplementation has beneficial effects on blood pressure control, vascular health, exercise capacity, and oxygen metabolism though targeted NO production (17–19). It is important to discern inorganic nitrate from organic nitrates such as nitroglycerine and isosorbide mononitrate. The latter was recently shown to decrease daily activity and not affect exercise capacity in patients with HFpEF (20). Both of these compounds are thought to produce NO or one of its active congeners, but the pharmacokinetics differ considerably between them. Organic nitrates rapidly release relatively large amounts of NO, whereas inorganic nitrate slowly produces NO and thereby produces milder but sustained vasodilation (21,22). Perhaps most importantly, inorganic nitrate, through its conversion to inorganic nitrite, targets NO delivery to areas of low oxygen and low pH, such as occur in skeletal muscle during exercise (21–23).

Dietary NO_3^- is particularly abundant in beetroot juice (BRJ). Indeed, BRJ supplementation has been shown in multiple studies to improve exercise performance and oxygen metabolism in younger healthy individuals (24–31) and in older patients with peripheral arterial disease (32). Specifically, BRJ supplementation has been shown to increase time to exhaustion during high-intensity exercise and to reduce oxygen consumption (VO_2) during submaximal exercise (i.e. reduce oxygen cost at a given submaximal work rate) (25,28,29,32).

In healthy older adults, BRJ supplementation improved VO_2 kinetics but did not alter overall exercise performance or the oxygen cost of exercise (33), and not all studies in younger adults have shown a positive effect (34–36). In addition, some positive effects were seen after 1 week of daily doses that were not seen after a single, acute dose (29,31). In a recent study in patients with HFpEF, a single, acute BRJ dose (12.9 mmol) increased total work performed and cardiac output while decreasing systemic vascular resistance during a maximal exercise test but did not affect exercise efficiency (as defined by total work/total oxygen consumed) compared to placebo (37). As the optimal BRJ supplementation strategy (single, acute versus loading over several days) remains uncertain (29), we conducted a pilot study to assess the feasibility (recruitment, retention, safety) and preliminary efficacy of either a smaller single, acute dose (6.1 mmol) or short-term (1 dose per day of 6.1 mmol for 6 to 8 days) BRJ supplementation in older HFpEF patients. We hypothesized that 1 week of daily doses would be more efficacious than a single dose in improving submaximal aerobic endurance.

METHODS

PARTICIPANTS. As previously described in studies from our laboratory (4,6,11,12,38) and in accord with the American College of Cardiology Foundation/American Heart Association 2013 HF management guidelines (39), HFpEF was defined as symptoms and signs of HF according to the National Health and Nutrition Examination Survey: HF clinical score of ≥3 and criteria of Rich et al. (40,41); preserved resting left ventricular systolic function (EF ≥50% and no segmental wall motion abnormalities) and no significant ischemic or valvular heart disease, pulmonary disease, anemia, or other disorder that could explain the patients' symptoms (4,6,11). All patients were required to have significant exercise intolerance (peak VO_2 ≤16.0 ml/kg/min for women and ≤20.0 ml/kg/min for men, a reduction of >25% compared to age-matched healthy controls in our laboratory). Furthermore, patients could not be taking prescription nitroglycerine, other nitrate preparations used for angina, phosphodiesterase type 5 inhibitors, or medication regimens to alter stomach pH (e.g., antacids, proton pump inhibitors, H_2 antagonists). The protocol was approved by the institutional review board, and all participants provided written, informed consent.

BRJ AND PLACEBO. The BRJ and placebo (70 ml; Beet It Sport Shot, James White Drinks, Ipswich, United Kingdom) were identical in appearance, taste, smell, and nutrient composition, except that the NO_3^- was removed by the manufacturer to make the placebo juice. As measured in our laboratory, the BRJ contained 0.38 g (6.1 mmol) of NO_3^-, and the placebo contained 0.0003 g (4.8 μmole) of NO_3^-. The person responsible for dispensing the juice was not involved in study testing or analysis.

STUDY DESIGN. In total, participants completed 5 clinic visits over a period of approximately 4 weeks (Online Figure 1). We initially screened 252 patients from previous study participant lists, electronic medical records, and community advertisements. Fifty-seven participants appeared to initially qualify

and were scheduled for a screening visit. Of those 57 participants, 32 signed informed consent and completed the screening visit. Ultimately, 20 participants met all inclusion and exclusion criteria and were enrolled in the study. Following the initial screening visit and a second visit to refine the exercise testing parameters (as described below), participants were assigned to a double-blinded, randomized crossover design to receive BRJ or placebo. A single bottle of the assigned juice was consumed for the crossover visits (single, acute dosing), which were separated by a 3- to 7-day washout period. Following the last crossover visit, all participants consumed 1 bottle of the BRJ once per day for 6 to 8 days (1 week of daily dosing) and returned for the final clinic visit. Importantly, participants were unaware whether they were consuming BRJ or placebo during the 1 week of daily doses. For all visits, the participant consumed the juice ~45 min before arriving at the clinic.

NITRITE AND NITRATE. After 10 min of supine rest (~1 h after the participant consumed the juice), venous blood samples were drawn into 4-ml lithium heparin tubes and centrifuged at 4,000 rpm at 20°C for 3 min within 1 minute of collection. Plasma was transferred in 400-μl volumes to sterile 500-μl polypropylene microtubes (Sarstedt, Nümbrecht, Germany) containing no additives and frozen at −70°C for later analysis. Nitrite (NO_2^-) and nitrate were measured as described previously (42), using an ENO-20 nitric oxide analyzer (EICOM, San Diego, California).

EXERCISE TESTING. As previously described (8,38), all exercise tests were performed with the participant in an upright position on an electronically braked cycle ergometer, with the pedal rate at ~60 rpm. At the initial screening visit, a maximal, graded (10-W per minute) exercise test was performed to assess peak capacity (43). The maximal work rate was defined as the greatest work rate that could be maintained for ≥30 s. At all subsequent visits, a submaximal constant work rate exercise test at ~75% of maximal work rate was performed. During all tests, heart rate and rhythm were monitored continuously, using an electrocardiogram, and blood pressure measurements were made at rest (following 2 min of quiet breathing) and every 2 min during the test. Breath-by-breath gas exchange data (Medgraphics Ultima, Minneapolis, Minnesota) were measured continuously at rest and during exercise. All submaximal constant work rate tests were performed ~1.5 to 2 h after the participant consumed the juice.

SUBMAXIMAL AEROBIC ENDURANCE. The submaximal constant work rate exercise test began with a 2-min period of unloaded pedaling followed by an immediate increase to the specified submaximal work rate, which was maintained until volitional exhaustion. In addition, the test was terminated if the pedal rate fell below 50 rpm for ~10 s. Submaximal work rate was initially prescribed at 75% of maximal power output. At the second visit (pre-randomization), the adequacy of this work rate was confirmed. If the participant was not able to maintain the work rate for ≥4 min, the work rate was decreased by ~10 W for subsequent tests. Likewise, if the participant was able to maintain the work rate for ≥10 min, the work rate was increased by ~10 W for subsequent tests. Importantly, the submaximal work rate was the same for all post-randomization efficacy visits.

STUDY OUTCOMES. Feasibility was assessed by examining recruitment yield, retention and adherence rates, and safety events. The predetermined primary efficacy outcome was aerobic endurance defined as the exercise time to volitional exhaustion during submaximal cycling at 75% of maximal power output.

Secondary efficacy outcomes included plasma NO_3^- and NO_2^- levels, VO_2, and blood pressure at rest, after unloaded cycling, at 2 and 4 min, and at volitional exhaustion, and heart rate and other gas exchange measures at volitional exhaustion. Values for VO_2 were averaged from the entire resting period and from the final 2 15-s averaged values prior to the specified time point during exercise.

STATISTICAL METHODS. Using preliminary data from another study at our institution, the study was designed to have 80% power to detect a 25% difference in the primary efficacy outcome, submaximal exercise time. To determine the single, acute dosing effect of BRJ using the randomized cross-over design, comparison of outcome measures were made by repeated measures analysis of variance, controlling for visit. To determine the effect of 1 week of daily doses of BRJ, outcome measures were compared using a paired Student *t* test, with the placebo visit during the cross-over design as the baseline value and the visit following 1 week of daily doses as the final value. A 2-tailed p value of <0.05 was required for significance.

RESULTS

PARTICIPANTS. Twenty older HFpEF patients (69 ± 7 years of age) with typical characteristics of HFpEF were enrolled in the study (Table 1). All participants were New York Heart Association functional class II (70%) or class III (30%), and 100% had a history of hypertension.

ADHERENCE, RETENTION, SAFETY. Adherence to the supplementation, as measured by returned bottle

count, was 100%. One participant did not complete the study due to personal time conflicts; therefore, 19 participants completed the study. In addition, 1 participant was excluded from the analysis due to knee pain that resulted in failure to complete the final exercise test. There were no adverse events related to the supplementation.

PLASMA NO_3^- AND NO_2^-. With a single, acute dose, plasma NO_3^- (362 ± 158 μM vs. 85 ± 104 μM; $p < 0.001$) and NO_2^- (0.81 ± 0.91 μM vs. 0.34 ± 0.26 μM; $p = 0.01$) were significantly increased compared to placebo. Similarly, with 1 week of daily doses, plasma NO_3^- (461 ± 229 μM vs. 85 ± 104 μM; $p < 0.001$) and NO_2^- (0.78 ± 0.52 μM vs. 0.34 ± 0.26 μM; $p < 0.001$) were significantly increased compared to placebo (Figure 1).

SUBMAXIMAL AEROBIC ENDURANCE. With a single, acute dose, there were no differences in the primary outcome of submaximal aerobic endurance (BRJ: 352 ± 116 s vs. placebo: 377 ± 134 s; $p = 0.47$), but with 1 week of daily doses, there was a significant increase (BRJ: 449 ± 180 s vs. placebo: 363 ± 125 s; 24% increase; $p = 0.02$) (Figure 2, Tables 2 and 3).

With both the single, acute and the 1 week of daily doses, there were no differences between VO_2 in the BRJ group and that in the placebo group at rest or at any time point measured during exercise, including at volitional exhaustion (Figure 3). Notably, mean respiratory exchange ratio at exhaustion was >1.15 with all treatments, indicating that, although a work rate of ~75% of maximal was used, a similar exhaustive, severe intensity level was reached at the end of the test. Finally, with both the single, acute and 1 week of daily doses, there were no differences in heart rate or gas exchange measurements at volitional exhaustion (Tables 2 and 3).

BLOOD PRESSURE. With a single, acute dose of BRJ, resting systolic blood pressure was significantly reduced compared to placebo (127 ± 14 mm Hg vs. 134 ± 14 mm Hg; $p = 0.008$) and there was a strong trend

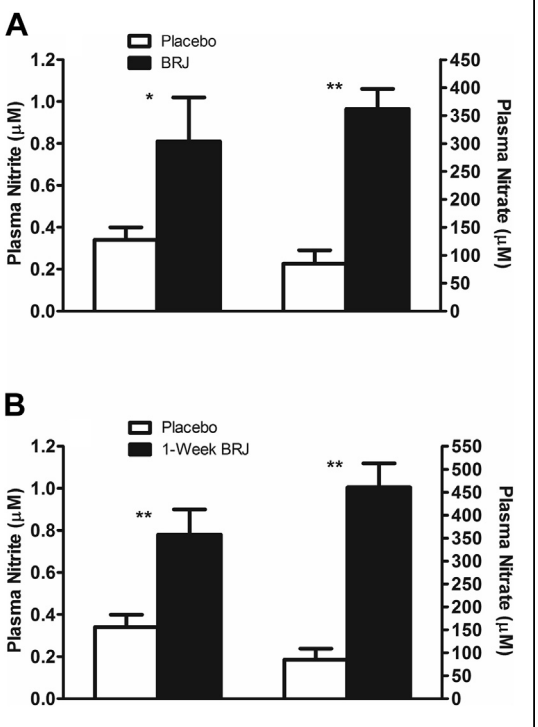
TABLE 1 Participant Characteristics

	HFpEF (N=20)
Age (yrs)	69.0 ± 6.8
Female subjects (%)	17 (85)
White subjects (%)	12 (60)
Body weight (kg)	89 ± 16
BMI (kg/m^2)	32.9 ± 5.6
Patients with NYHA functional class (%)	
II	14 (70)
III	6 (30)
Patients with diastolic function (%)	
Normal	3 (15)
Impaired relaxation	17 (85)
Pseudonormal	0 (0)
Restrictive	0 (0)
e′ (cm/s)	6.5 ± 2.0
E/e′ ratio	13.2 ± 6.6
BNP*	21 ± 19
Patients with diabetes mellitus (%)	7 (35)
Patients with Hx hypertension (%)	20 (100)
Systolic BP (mm Hg)	145 ± 15
Diastolic BP (mm Hg)	70 ± 10
Patients currently taking medications (%)	
ACE inhibitors	7 (35)
Diuretics (all)	13 (65)
Loop diuretics	3 (15)
Beta-blockers	5 (25)
Calcium channel blockers	7 (35)
ARBs	6 (30)
Peak VO_2 (ml/kg/min)	12.0 ± 2.1
Peak workload (W)	58 ± 21

Values are mean ± SD, or n (%). *BNP median (25th to 75th percentiles) was 15 (9–24).

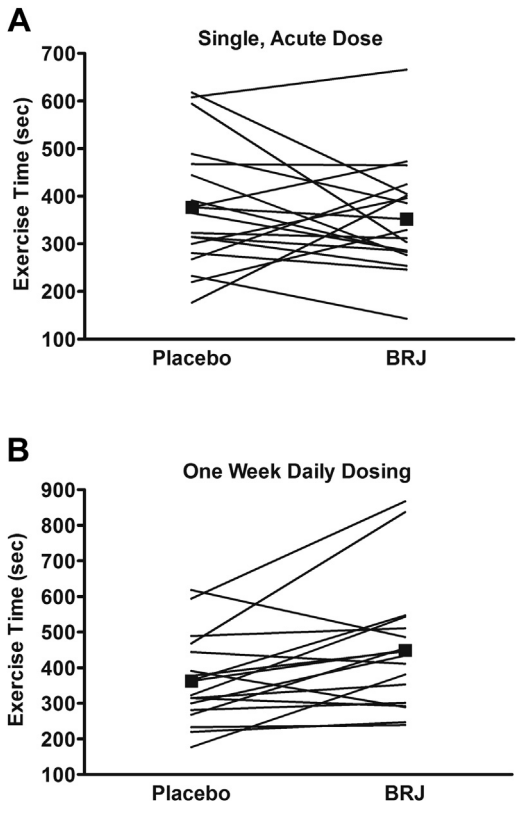
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; E = early mitral velocity; e′ = mitral annulus velocity; HFpEF = heart failure with preserved ejection fraction; Hx = history; NYHA = New York Heart Association.

FIGURE 1 Plasma Nitrite and Nitrate



Mean ± SE of plasma nitrite and plasma nitrate after a single acute dose **(A)** and after 1 week of daily dosing **(B)**. **Open columns** are placebo, and **solid columns** are beet root juice. *$p < 0.05$; **$p < 0.001$.

FIGURE 2 Exercise Time



Submaximal exercise time (s) with placebo and single, acute dose of BRJ **(A)** and with placebo and 1 week of daily dosing of BRJ **(B)**. **Solid squares** are mean values. **Circles** and **lines** are individual values. BJR = beet root juice.

to reduced systolic blood pressure after unloaded cycling ($p = 0.06$). Further, there were trends to reduced systolic blood pressure at 2 min and volitional exhaustion ($p = 0.15$ for both) (Figure 3). There were no differences in diastolic blood pressure or rate pressure product at any time-point.

With 1 week of daily doses, systolic blood pressure was significantly reduced at rest (120 ± 13 mm Hg vs. 134 ± 14 mm Hg, respectively; $p < 0.001$) and after unloaded cycling ($p = 0.03$). There was a strong trend to reduced systolic blood pressure at volitional exhaustion (159 ± 17 mm Hg vs. 166 ± 16 mm Hg, respectively; $p = 0.054$), and there were trends to reduced systolic blood pressure at 2 and 4 min ($p = 0.08$ and 0.11, respectively) (Figure 3). Furthermore, there was a strong trend toward reduced rate pressure product at rest ($p = 0.051$), with no differences at any other time point. There were no differences in diastolic blood pressure at any time point.

TABLE 2 Acute Effect of Beetroot Juice Versus Placebo

	Effect of Placebo	Effect of Beetroot Juice	p Value
Exercise time at constant work rate, s*	377 ± 134	352 ± 116	0.47
At exhaustion			
VO_2, ml/kg/min	11.9 ± 2.2	11.8 ± 2.4	0.63
VO_2, ml/min	1,054 ± 315	1,040 ± 312	0.43
VCO_2, ml/min	1,239 ± 418	1,211 ± 383	0.28
Respiratory exchange ratio	1.17 ± 0.09	1.16 ± 0.08	0.69
Heart rate, beats/min	120 ± 20	121 ± 21	0.69
Systolic blood pressure, mm Hg	167 ± 16	163 ± 21	0.15
Diastolic blood pressure, mm Hg	78 ± 10	78 ± 10	0.73
Rate pressure product, beats/min · mm Hg	20,245 ± 4,491	19,997 ± 5,009	0.66

Values are mean ± SD. *Mean constant work rate = 45 W. Exercise time excluded the 2-min unloaded pedaling period.
VO_2 = volume of oxygen consumption; Vco_2 = volume of carbon dioxide produced.

DISCUSSION

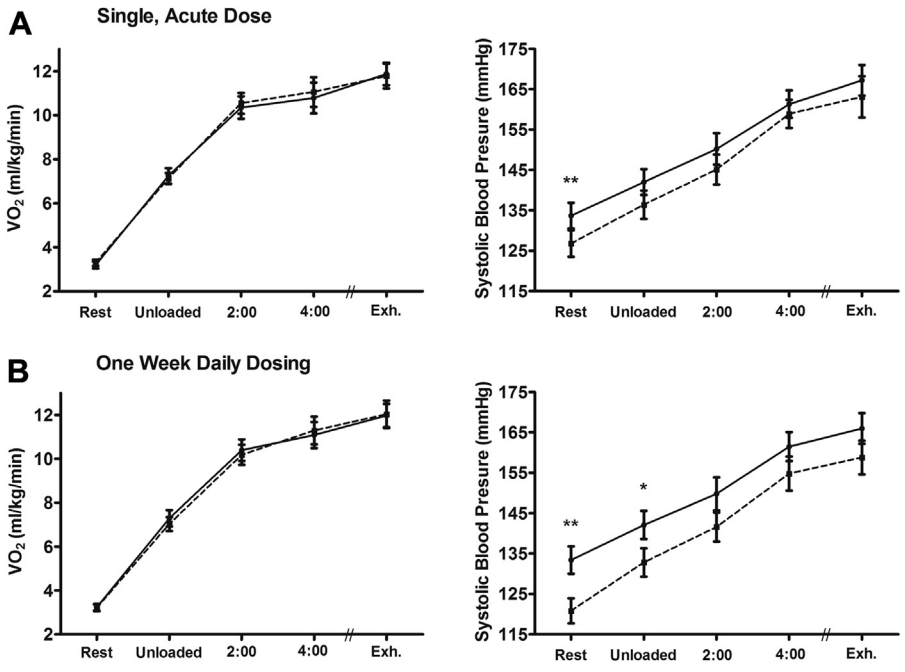
The primary symptom in patients with chronic HFpEF, even when well compensated, is severe exercise intolerance; this symptom is associated with reduced quality of life (4). Only endurance exercise training has been shown to improve exercise capacity in these patients, as standard medications tested to date have proven ineffective (5-8,10). Increased NO bioavailability has been suggested to partially account for the efficacy of exercise training (16). Our study is the first to examine the safety and efficacy of 1 week of daily doses with dietary nitrate in older patients with HFpEF. The major new findings of this study are that: 1) BRJ supplementation was feasible and safe; 2) 1 week of daily doses improved submaximal aerobic endurance; and 3) both the single, acute and 1 week of daily doses reduced resting systolic

TABLE 3 Short Term Daily Dosing Effect of 1 Dose of Placebo Versus 1 Week of Beetroot Juice

	Effect of 1 Placebo Dose	Effect of 1 Week of Beetroot Juice	p Value
Exercise time at constant work rate, s*	363 ± 125	449 ± 180	0.02
At exhaustion			
VO_2, ml/kg/min	12.0 ± 2.2	12.0 ± 2.6	0.79
VO_2, ml/min	1,065 ± 321	1,069 ± 341	0.82
Vco_2, ml/min	1,259 ± 421	1,239 ± 422	0.46
Respiratory exchange ratio	1.18 ± 0.08	1.16 ± 0.09	0.32
Heart rate, beats/min	121 ± 21	122 ± 23	0.59
Systolic blood pressure, mm Hg	166 ± 16	159 ± 17	0.054
Diastolic blood pressure, mm Hg	77 ± 9	75 ± 6	0.38
Rate pressure product, beats/min·mm Hg	20,187 ± 4622	19,616 ± 5,182	0.43

Values are mean ± SD. *Mean constant work rate = 45 W. Exercise time excluded the 2-minute unloaded pedaling period.
Abbreviations as in Table 2.

FIGURE 3 Oxygen Consumption and Blood Pressure



VO_2 (ml/kg/min) and systolic blood pressure (mm Hg) at rest, after unloaded cycling, after 2 and 4 min of cycling, and at volitional exhaustion with single, acute dosing **(A)** and with 1 week of daily dosing **(B)**. **Solid line** represents placebo, and **dotted line** represents BRJ. *$p < 0.05$; **$p < 0.001$. Abbreviations as in Figure 2.

blood pressure, tended to decrease exercise systolic blood pressure, and increased circulating plasma levels of NO_3^- and NO_2^-. These results suggest that 1 week of daily BRJ supplementation could be a potential therapeutic option to improve submaximal aerobic endurance (as occurs during instrumental and recreational activities of daily living) with a reduction in blood pressure (and thus afterload) in the growing population of older HFpEF patients.

Compared to placebo, both a single, acute dose and 1 week of daily doses of BRJ significantly increased plasma NO_2^-, by 138% and 129% respectively. Blood samples were collected ~1 h after juice consumption, and recent evidence suggests that in healthy older adults, plasma NO_2^- levels peaked 2 to 3 h after BRJ consumption (44). Thus, NO_2^- levels were likely even higher when the exercise test was performed 1.5 to 2 h after BRJ consumption. The increase in plasma NO_2^- is similar to other studies in younger and older adults without HF that have reported a significant increase in plasma NO_2^- following dietary NO_3^- supplementation (24,27,32,33).

One week of daily doses with BRJ improved submaximal aerobic endurance; no significant effect was found for this outcome with a single, acute BRJ dose. However, a recent study by Zamani et al. (37) observed an increase in total work performed after a single, acute dose of BRJ in HFpEF patients compared to that in placebo patients in a cross-over study (37). These investigators also observed increased cardiac output, decreased systemic vascular resistance, and reduced aortic augmentation index due to BRJ compared to placebo, but no improvement in exercise efficiency (total work/total oxygen consumed) was observed (37), a finding confirmed in our study (**Figure 3**).

It is important to note that our study used a 6.1-mmol dose, whereas Zamani et al. (37) administered a 12.9-mmol dose of NO_3^-. A larger nitrate dose results in increased plasma nitrite (45) which is the essential factor in producing physiological changes. The dose we administered resulted in significantly higher plasma nitrite than with placebo (**Figure 1**), but the response was also variable. Comparison of the 2 studies suggests that a higher nitrate dose may be more effective, at least for acute, single-dose effects. The fact that we observed positive effects at the smaller dose we used with the chronic but not with the acute dose schedule is consistent with some previous observations (29,31). That we did not see an improvement in VO_2 suggests that intrinsic

mitochondrial function was probably not primarily improved. An increase in perfusion could be dependent on increasing functional capillary density that is achievable after a large single, acute nitrate dose, but needs chronic administration to be achieved with a smaller dose. This is consistent with the notion that microvascular function may be important in oxygen delivery in HFpEF patients (46).

Taken together with the previous study of BRJ and patients with HFpEF (37), the overall data suggest that a single, acute higher dose of BRJ or a smaller dose administered over 1 week can improve aerobic endurance in patients with HFpEF. The mechanism for this effect is likely due to targeted delivery of NO, which decreases systemic vascular resistance. Ingested dietary NO_3^- is reduced to bioactive NO_2^- by bacteria found in the oral cavity; the NO_2^- is then taken up by the plasma from the digestive system and can be converted to nitric oxide (NO), particularly under hypoxic or acidic conditions (23), which can occur in HFpEF and during exercise. In the case of HFpEF, as previously discussed (37,47), improved oxygen cost during exercise was not observed, and increases in exercise capacity were likely due to lower systemic vascular resistance with increased cardiac output (observed in the study by Zamani et al. [37]) and/or more effective shunting of blood flow resulting in increased perfusion of exercising muscles due to the actions of plasma nitrite. Variability in response may be largely due to individual oral nitrate to plasma nitrite conversion which could be improved at larger doses.

A recent study examined the effect of an organic nitrate, isosorbide mononitrate, on improving daily activity level, quality of life score, and 6-minute walk test in 110 patients with HFpEF (20). There were no significant effects of isosorbide mononitrate on quality of life or the 6-min walk test and activity was actually less compared to placebo (20). Another study examined whether a phosphodiesterase inhibitor, which increases the efficacy of a given amount of NO by increasing levels of its downstream signaling agent cyclic guanosine monophosphate, can improve peak oxygen consumption, exercise capacity and clinical status in patients with HFpEF (48). This study also found no improvement in any of the test-outcomes compared to placebo (48). Differences in the pharmacokinetics and especially the ability of inorganic nitrite derived from inorganic nitrate to target delivery of NO to hypoxic areas (21–23), a feature organic nitrates and oral phosphodiesterase inhibitors lack, is most likely the main reason that positive effects have been seen with use of inorganic nitrate but not these other agents. This notion is also reinforced by a recent study where infused inorganic nitrite improved exercise hemodynamics (particularly pulmonary capillary wedge pressure, cardiac output reserve, and left ventricular stroke work) compared to placebo (49).

STUDY LIMITATIONS. Limitations of this study include the small number of participants and lack of mechanistic measures including cardiac output and skeletal muscle perfusion. Another possible limitation would be a learning effect in exercise testing, but previous work in our laboratory showed no learning effect with maximal exercise testing (38). Further work, with larger sample size, is required to fully evaluate the benefits of oral inorganic nitrate on improving exercise tolerance in patients with HFpEF.

Our study found positive effects of week-long dietary inorganic nitrate intake using a lower dose of nitrate whereas the previous study by Zamani et al. (37) demonstrated positive effects of a single, acute larger dose. There are potential benefits to both chronic and acute dosing. For example, if a single, acute dose has an effect, a patient may consume BRJ (probably at a higher dose) a couple of hours before an anticipated activity that may be physically challenging. On the other hand, a patient may chronically consume BRJ (probably at a lower dose) to improve everyday activity and quality of life. However, both studies examining efficacy of inorganic nitrate in treating HFpEF had small sample sizes. Thus, a much larger study should be undertaken to examine both acute (single dose) and chronic (over several weeks) doses of BRJ at several levels of NO_3^-.

CONCLUSIONS

Our finding that submaximal aerobic endurance was increased at a lower blood pressure suggests that HFpEF patients could potentially perform submaximal exercise at a lower intensity and for longer periods which has implications for everyday activities. Given that a hallmark feature of HFpEF is exercise intolerance even while performing submaximal exercise, our findings may have important functional and therapeutic implications.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Reduced quality of life in patients with HFpEF is exacerbated by exercise intolerance. Our study suggests that targeted chronic delivery of NO through dietary consumption of oral inorganic nitrate could improve submaximal exercise tolerance. More, larger clinical trials are needed to determine whether dietary inorganic nitrate can truly help improve quality of life in patients with HFpEF.

TRANSLATIONAL OUTLOOK: A large variety of clinical trials have recently been completed or are underway exploring the use of inorganic nitrite as a therapeutic for a variety of conditions including hypertension, pulmonary hypertension, myocardial infarction, COPD, PAD and (relevant to the current study) HFpEF. These clinical studies illustrate translation of basic science studies demonstrating how nitrite can be reduced to NO. Whereas some clinical studies employ inhaled or infused nitrite, others (such as this one) deliver nitrite through administration of oral nitrate. The efficacy of this method of administration, which is attractive due to its potential use of natural products and applicability to long-term dosing, needs further exploration.

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APPENDIX For supplemental figures, please see the online version of this article.

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