Acute Dietary Nitrate Intake Improves Muscle Contractile Function in Patients with Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Trial

Coggan et al: Dietary NO3 Improves Muscle Function in HF

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Abstract

**Background**—Skeletal muscle strength, velocity, and power are markedly reduced in heart failure (HF) patients, which contributes to their impaired exercise capacity and lower quality of life. This muscle dysfunction may be partially due to decreased nitric oxide (NO) bioavailability. We therefore sought to determine whether ingestion of inorganic nitrate (NO$_3^-$) would increase NO production and improve muscle function in patients with HF due to systolic dysfunction.

**Methods and Results**—Using a double-blind, placebo-controlled, randomized crossover design, we determined the effects of dietary NO$_3^-$ in nine HF patients. After fasting overnight, subjects drank beetroot juice containing or devoid of 11.2 mmol NO$_3^-$. Two hours later, muscle function was assessed using isokinetic dynamometry. Dietary NO$_3^-$ increased (P<0.05-0.001) breath NO by 35-50%. This was accompanied by 9% (P=0.07) and 11% (P<0.05) increases in peak knee extensor power at the two highest movement velocities tested (i.e., 4.71 and 6.28 rad/s). Maximal power (calculated by fitting peak power data with a parabola) was therefore greater (i.e., 4.74±0.41 vs. 4.20±0.33 W/kg; P<0.05) after dietary NO$_3^-$ intake. Calculated maximal velocity of knee extension was also higher following NO$_3^-$ ingestion (i.e., 12.48±0.95 vs. 11.11±0.53 rad/s; P<0.05). Blood pressure was unchanged, and no adverse clinical events occurred.

**Conclusions**—In this pilot study, acute dietary NO$_3^-$ intake was well-tolerated and enhanced NO bioavailability and muscle power in patients with systolic HF. Larger-scale studies should be conducted to determine whether the latter translates into an improved quality of life in this population.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01682356.

**Key Words:** heart failure, muscle contraction, nitric oxide, exercise capacity, nutrition
Heart failure (HF) decreases both quantity and quality of life. A primary factor in the reduced quality of life is exercise intolerance. This impaired exercise capacity is partially due to reduced O₂ delivery to, and utilization by, skeletal muscle, resulting in a reduction in VO₂peak (1). Skeletal muscle strength, velocity, and power, however, are also markedly reduced in HF (2,3). This muscle dysfunction also plays a very important role in the compromised exercise capacity and reduced quality of life in HF (4). Moreover, diminished muscle function is a powerful prognostic indicator of survival in HF - even more powerful than a reduction in VO₂peak (5).

The mechanisms responsible for altered muscle contractile properties in HF have not been fully elucidated. Notably, HF patients are weaker, slower, and less powerful even when compared to equally-sedentary healthy subjects with comparable limb muscle mass (3), indicating that these changes are not solely due to physical inactivity or muscle atrophy. Rather, muscle dysfunction in HF appears to be due, at least in part, to derangements at the molecular level. Specifically, HF has been associated with a selective reduction in myosin protein content (6), a slowing of cross-bridge kinetics (7), and an increase in the percentage of muscle fibers expressing multiple myosin isoforms (8). Other studies (9,10) of HF have demonstrated abnormalities in skeletal muscle sarcoplasmic reticulum Ca²⁺ ATPase and ryanodine receptor content and/or function.

Although changes in protein quantity/quality undoubtedly contribute to diminished muscle function in HF, other factors likely also play a role. In particular, in failing cardiac muscle increased production of reactive oxygen species leads to a decline in nitric oxide (NO) bioavailability, and hence reduced NO-soluble guanyl cyclase (sGC)-cyclic GMP (cGMP) signaling (11). This is true despite enhanced expression of the inducible form of NO synthase (NOS) (12). The reduction in cGMP production in turn contributes to reduced cardiac
contractility in HF (13,14). Increased oxidative stress may also reduce NO bioavailability and hence cGMP production in skeletal muscle in HF, thus contributing to the muscle dysfunction described above.

Although NO is mostly produced via the NOS pathway, it is also derived from dietary nitrate (NO₃⁻) (15,16). In this alternative pathway, NO₃⁻ is first reduced to nitrite (NO₂⁻) by oral facultative anaerobic bacteria. After NO₂⁻ is swallowed, acidic conditions in the stomach and/or other tissues (e.g., contracting muscle) can further reduce it to NO. Notably, unlike the NOS pathway this dietary pathway does not utilize O₂ and is stimulated rather than inhibited by low pH (15,16). In sum, there is a heretofore under-appreciated NO production system that potentially may be exploited to improve NO availability and, hence, muscle contractile function in patients with HF.

In this context, we recently demonstrated that acute ingestion of NO₃⁻, in the form of a concentrated beetroot juice (BRJ) supplement, increases NO bioavailability (as indicated by an increase in breath NO) and maximal muscular velocity and power in healthy men and women (17). We therefore hypothesized that dietary NO₃⁻ ingestion would improve muscle function in HF patients, in whom NO bioavailability and muscle function are reduced. Since dietary NO₃⁻ can result in a small-to-moderate drop in blood pressure (18), we were also interested in evaluating the safety of this intervention in HF patients, who might become hypotensive due to the combination of compromised cardiac function, medication use, and dietary NO₃⁻.

**Methods**

**Subjects:** We studied HF patients with systolic dysfunction, i.e., an ejection fraction (EF) of ≤45%. Subjects had to be ≥18 y of age, on a stable HF treatment regimen, and without
significant orthopedic limitations or other contraindications to exercise. All underwent a medical history, physical exam, and blood tests for fasting chemistries. Subjects were excluded if they had major organ system dysfunction other than HF or were pregnant or were unable to give informed consent. Other exclusion criteria included use of antacids or proton pump or xanthine oxidase inhibitors, which can affect reduction of NO$_3^-$ and NO$_2^-$ to NO (19). Individuals taking phosphodiesterase inhibitors (e.g., Viagra) were also excluded, as these can potentiate NO effects (20). After screening of 37 subjects, nine subjects were enrolled and completed the study (Figure 1). Subjects provided written, informed consent, and the study was approved by the Human Research Protection Office at Washington University School of Medicine.

**Experimental design:** Each subject was studied twice using the same experimental protocol (see below). On one occasion they were tested after ingesting 140 mL of a concentrated BRJ supplement (Beet It Sport®; James White Drinks, Ipswich, UK) containing 11.2 mmol of NO$_3^-$, and on the other after ingesting the same volume of NO$_3^-$-depleted BRJ. There was a 1-2 wk washout period between treatments. Since the half-life of the increase in plasma NO$_3^-$ following acute dietary intake is <8 h (21), this length of washout period was considered more than sufficient to minimize any possible carryover effects. The placebo, which is prepared by the manufacturer by extracting NO$_3^-$ from BRJ using an ion exchange resin, is indistinguishable from the standard product in packaging, color, texture, taste, and smell, and does not alter plasma NO$_3^-$ or NO$_2^-$ concentrations (22,23) or breath NO levels (17). Both the subjects and the investigators were blinded to the order of treatment, which was randomized using http://www.randomization.com. Upon questioning following completion of their second visit, subjects were unable to reliably identify the active trial. Subjects were instructed to avoid high NO$_3^-$ foods for 10 d prior to intervention and throughout the study. Food records were obtained.
during the washout period and reviewed for adherence to the diet. These measures were instituted to minimize variation in baseline NO₃⁻, NO₂⁻, and NO levels. Since chewing gum or antibacterial mouthwash can block conversion of NO₃⁻ to NO₂⁻ by bacteria in the oral cavity (24), subjects were also instructed to avoid these products on study days. Finally, subjects were instructed to avoid food, caffeine, alcohol, and exercise for 12 h prior to study.

Experimental protocol: Upon the subject’s arrival at the Clinical Research Unit at 8 a.m., an antecubital venous catheter was inserted and a blood sample was obtained for subsequent determination of plasma NO₃⁻ and NO₂⁻ levels using a commercial kit (Cayman Chemicals, Ann Arbor, MI). Heart rate and blood pressure were then measured, after which a portable analyzer (NIOX MINO, Aerocrine Inc., Morrisville, NC) was used to measure breath NO as a biomarker of whole-body NO production (17,25). The subject then ingested the BRJ and rested quietly while it was digested/absorbed. The aforementioned measurements were repeated 1 h and 2 h after BRJ ingestion, after which exercise testing began. This timing was based on previous studies demonstrating that plasma NO₃⁻ (22-24) and breath NO (17,25) peak ~2 h after dietary NO₃ intake. A 6 min walk test was first conducted to determine the effects of dietary NO₃ on aerobic exercise performance and also to serve as a warm-up for the subsequent muscle function testing. The latter was performed using a Biodex 4 isokinetic dynamometer (Biodex Medical Systems, Shirley, NY). After adjustment of the dynamometer, subjects performed 3-4 maximal knee extensions at angular velocities of 0, 1.57, 3.14, 4.71, and 6.28 rad/s (0, 90, 180, 270, and 360 °/s), with 2 min of rest between each set of contractions. Isometric testing was conducted at a knee angle of 1.22 rad (70°). Following the final rest period, subjects performed an “all out” (i.e., non-paced) 50 contraction fatigue test (at 3.14 rad/s) to determine whether dietary NO₃⁻ influenced fatigue during repetitive, maximal muscle activation. Strong verbal encouragement
was provided during this and all other portions of the isokinetic testing. To limit changes in heart rate and blood pressure, subjects were not allowed to use the handholds of the dynamometer, and were reminded periodically to not perform a Valsalva maneuver. Heart rate was monitored continuously and blood pressure was measured after the isometric testing and before, immediately after, and 10 min after completion of the fatigue test. Plasma NO$_3^-$ and NO$_2^-$ as well as breath NO were also measured at this final time point.

*Data analyses:* The isokinetic dynamometer data were analyzed as previously described (17). Briefly, torque data were “windowed” and smoothed using the manufacturer’s software, after which the highest torque generated at each velocity was used to calculate peak power at that velocity. The peak power-velocity data were then fit with a parabolic function to determine maximal knee extensor power and velocity.

All statistical analyses were performed using GraphPad Prism version 6.05 (GraphPad Software, La Jolla, CA). Normality of data distribution was first tested using the D’Agostino-Pearson omnibus test. Data were subsequently analyzed using two-way (treatment x order) ANOVA, with subject as a repeated measures factor within treatment. A P value of <0.05 was considered significant. Sample size was chosen based on our recent study of the effects of dietary NO$_3^-$ on muscle power in healthy individuals (18) and enabled us to detect any effect size $\geq 0.69$ with a power (i.e., 1-$\beta$) of 0.80 at an $\alpha$ of 0.05 assuming a within-subject correlation of 0.95. Primary outcome variables were changes in breath NO and peak and maximal muscle power and velocity in response to dietary NO$_3^-$; all other variables measured were considered secondary.
Results

Subject characteristics are listed in Table 1. All subjects had a nonischemic cardiomyopathy, and all were treated with β-blockers and most were treated with an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB). No patient had a change in HF medication during the study.

As intended, ingestion of BRJ containing 11.2 mmol of NO₃⁻ resulted in a very large, i.e., ~20-fold increase (P<0.0001), in plasma NO₃⁻ concentration (Table 2). Consistent with the literature (21,22), this was accompanied by a much smaller, and in the present study not statistically significant, elevation in plasma NO₂⁻ compared to the placebo trial. Whole-body NO bioavailability, on the other hand, did increase significantly following dietary NO₃⁻, as evidenced by a 35-50% increase (P<0.001-0.05) in breath NO over baseline (Table 2).

Hemodynamic data are shown in Table 3. Heart rate and blood pressure were not affected by NO₃⁻ ingestion, and no significant adverse clinical events occurred. One subject, however, did report some abdominal cramping and loose stools.

Dietary NO₃⁻ improved several measures of muscle contractile function. Specifically, NO₃⁻ ingestion increased peak torque and hence peak power at the two highest angular velocities tested (i.e., 4.71 and 6.28 rad/s) by 9% (P=0.07) and 11% (Figure 2), respectively. Consequently, calculated maximal knee extensor power was 13% higher (P<0.05) in the NO₃⁻ trial (Figure 3, top panel). Calculated maximal knee extensor velocity was also 12% higher (P<0.05) after dietary NO₃⁻ (Figure 3, bottom panel). On the other hand, no differences in muscle function were observed during the 50 contraction fatigue test conducted at 3.14 rad/s (Table 4). Six minute walk distance (528±30 m NO₃⁻ vs. 517±31 m placebo; P=0.29) and maximal isometric torque (1.99±0.10 Nm/kg NO₃⁻ vs. 1.98±0.16 Nm/kg placebo; P=0.86) also did not change significantly.
with NO\textsuperscript{3−}. The latter is in keeping with previous studies that have also failed to observe any change in maximal voluntary isometric torque as a result of dietary NO\textsuperscript{3−} intake (17,26).

No significant treatment x order interaction effects were observed for any variable, verifying the absence of any carryover effects.

**Discussion**

In this study we have shown for the first time that dietary NO\textsuperscript{3−} increases plasma NO\textsuperscript{3−} concentration and hence NO bioavailability (as indicated by an increase in breath NO levels) in patients with systolic HF. This was accompanied by a significant improvement in muscle contractile function, i.e., in the maximal velocity and hence power of the knee extensor muscles. Just as importantly, in this pilot study acute dietary NO\textsuperscript{3−} intake was well-tolerated by HF patients and in particular did not lead to deleterious changes in blood pressure or other major untoward clinical effects.

As indicated above, dietary NO\textsuperscript{3−} ingestion resulted in a significant increase in breath NO. However, both the baseline value and the magnitude of the increase following NO\textsubscript{3} intake were slightly, but significantly (P<0.05), lower than those we found recently in a parallel study of healthy, younger men and women (17). The former is consistent with previous studies of patients with systolic HF (27,28). This reduction in breath NO has been shown to be predictive of reduced exercise capacity (28) and increased mortality risk in this population (29). Presumably, lower baseline breath NO in HF is at least partially the result of decreased NOS-mediated NO synthesis, as evidenced by diminished urinary excretion of \textsuperscript{15}NO\textsuperscript{3−} following intravenous infusion of L-[\textsuperscript{15}N]arginine (30). To our knowledge, however, the effect of dietary NO\textsuperscript{3−} on breath NO has not been previously assessed in this population. The somewhat lesser rise in breath NO following...
dietary NO$_3^-$ intake in HF patients could be due to differences in the rate of NO$_3^-$ absorption and/or reduction, as suggested by the insignificant increase in plasma NO$_2^-$ that we observed. Alternatively (or in addition), however, it may also reflect more rapid destruction of NO as a result of increased oxidative stress in HF (11).

Despite this apparently slightly-blunted increase in NO bioavailability, in HF patients acute dietary NO$_3^-$ intake resulted in considerable improvements in muscle velocity and power. In fact, compared to the healthy, younger subjects we studied previously (17) the HF patients in the present study seemed to benefit even more from dietary NO$_3^-$ supplementation. Specifically, in HF patients dietary NO$_3^-$ increased peak knee extensor power at 4.71 and 6.28 rad/s by 9% (P=0.07) and 11% (P<0.05), respectively, whereas in healthy subjects we found no difference at the lower velocity and only a 4% (P<0.01) increase at the higher velocity. Correspondingly, in the HF patients Pmax increased by 13% (P<0.05) following dietary NO$_3^-$ ingestion, versus the 6% (P<0.05) we observed in healthy subjects. In light of the slightly-but-significantly smaller increase in breath NO, these data indirectly support the hypothesis that the impaired skeletal muscle contractile performance of HF patients is due in part to reduced NO-sGC-cGMP signaling, as is thought to be true in cardiac muscle (14). More importantly, however, these data illustrate the efficacy of dietary NO$_3^-$ in enhancing muscle function in patients with HF. Indeed, based on the study of Toth et al. (3), in which HF patients were carefully matched with control subjects on the basis of age, sex, leg lean mass, habitual physical activity, and use of statins, ingestion of dietary NO$_3^-$ in the present study appears to have acutely erased approximately one-third of the deficit in muscle power typically resulting from HF. This is in stark contrast to the effects of commonly-prescribed HF drugs, i.e., β-blockers, ACEi, ARB, and aldosterone antagonists, which have proven ineffective in improving skeletal muscle contractile function in
HF (31). The magnitude of the improvement in isokinetic muscle function that we observed is comparable to that resulting from 2-3 mo of resistance exercise training in HF patients (32,33), which has been shown to result in significant improvement in Minnesota Living with Heart Failure Questionnaire score (34). Longer-term, larger-scale studies should therefore be conducted to determine whether this dietary-NO$_3^-$-induced increase in muscle power enhances habitual physical activity and/or quality-of-life (or possibly even survival (5)) in patients with HF.

In contrast to the improvements in peak muscle power at 4.71 and 6.28 rad/s, and hence in calculated maximal power and velocity, described above, no differences were observed during the fifty contraction fatigue test conducted at 3.14 rad/s. This is in keeping with our previous study of healthy subjects, in whom acute dietary NO$_3^-$ intake did not influence performance during repeated maximal knee extensions at this velocity (17). Somewhat along the same lines, dietary NO$_3^-$ intake also did not significantly improve the distance the HF patients were able to walk in 6 min. The latter may simply reflect a type II error, as the effect size was moderate (i.e., Cohen’s $d = 0.55$) and post-hoc analyses indicated that 28 subjects would have been needed to provide adequate statistical power to detect differences in this secondary outcome. Further research will therefore be required to definitively determine whether acute dietary NO$_3^-$ ingestion can improve 6 min walk distance in patients with HF. Nonetheless, in a relative sense the non-significant increase in 6 min walk distance we observed was small compared to the significant changes found in muscle power (i.e., ~2 vs. ~10%). This, along with the lack of changes during fatigue test, implies that acute dietary NO$_3^-$ intake improves physical function in patients with HF primarily by acting upon the contractile machinery of muscle itself rather than via other mechanisms, as discussed below.
Before its precise chemical nature was known, NO was referred to simply as “endothelium derived relaxing factor” - indeed, the physiological importance of NO was first recognized based on its ability to stimulate sGC and hence cause relaxation of smooth muscle (35). It may therefore be tempting to speculate that our results are due to vasodilation and hence an increase in muscle blood flow. It is unclear, however, how such an effect could influence force and hence power during isolated muscle contractions lasting only a few hundred milliseconds. On the other hand, NO stimulates sGC and thus increases cGMP levels in numerous tissues, including skeletal muscle, in which activation of this pathway has been shown to increase maximal shortening velocity and hence maximal power, especially in fast-twitch fibers (36). Thus, our results seem to be most likely the result of this latter mechanism, and not an increase in blood flow. Nonetheless, it remains possible that dietary NO$_3^-$ supplementation may enhance other aspects of physical function in HF patients by increasing blood flow and/or via additional mechanisms, e.g., by reducing O$_2$ demand (22,23) or improving muscle energetics (26) during exercise.

Importantly, although dietary NO$_3^-$ resulted in significant increases in muscle velocity and power, it did not reduce either systolic or diastolic blood pressure in our small cohort of subjects. This is in contrast to the results of some, but not all, prior studies of the effects of dietary NO$_3^-$ on blood pressure in other subject groups (18). Our data, however, are in keeping with the results of Kapil et al. (37), who found that magnitude of the reduction in systolic or diastolic blood pressure in response to dietary NO$_3^-$ was inversely related to baseline blood pressure, especially in men. (Note: in post-hoc analyses we found no sex-related differences in the present study.) It is also consistent with the results of a recent study by Zamani et al. (38) of
patients with HF with preserved EF, in whom dietary NO₃⁻ supplementation also did not reduce blood pressure.

Precisely why dietary NO₃⁻ lowers blood pressure in some subject groups but not, apparently, in HF patients with reduced (or preserved) EF is difficult to determine. It is possible that the endothelial dysfunction characteristic of HF (39,40) blunts the vasodilatory response to dietary-NO₃⁻-derived NO just as it limits the vasodilation that occurs in response to, e.g., nitroprusside (39). Alternatively, as recently discussed by Shepherd et al. (41) it is possible that common vasoactive medications, i.e., β-blockers, ACEi/ARB, and/or aldosterone antagonists somehow interfere with the blood-pressure-lowering effect of dietary NO₃⁻. Finally, it also possible that there is a differential sensitivity of smooth muscle and skeletal muscle to the effects of dietary NO₃⁻, at least in HF patients, such that the present dose of dietary NO₃⁻ was simply insufficient to reduce blood pressure even though it did increase muscle contractile function.

Regardless, the fact that the dose of dietary NO₃⁻ we employed (i.e., 11.2 mmol) did not significantly reduce blood pressure in patients with HF makes this a potentially viable treatment for increasing muscle function in such individuals. It is also worth noting that no other serious adverse effects (e.g., hyperkalemia) were observed in the present pilot study, although one subject did experience mild gastrointestinal symptoms after drinking the BRJ. Additional, longer-term studies will be required to determine the ultimate safety and tolerability of dietary NO₃⁻ supplementation in this patient population, as well as to determine if tolerance develops as often occurs with pharmaceutical nitrates, e.g., trinitroglycerin (42). While there is no evidence of tolerance in terms of the blood-pressure-lowering effects of dietary NO₃⁻ (16), the same may not necessarily be true in terms with respect to its effects on muscle function.
There are limitations to the present investigation. As indicated previously, although we had adequate statistical power to detect significant changes in our primary outcome variables (i.e., breath NO, muscle power), our study may have been underpowered to detect relatively small changes in secondary outcomes (e.g., plasma NO2⁻, 6 min walk distance). Similarly, the acute nature of the intervention prevents us from drawing any conclusions about the possible benefits or detrimental effects of chronically-increased dietary NO3⁻ intake in patients with HF. The improvements in breath NO and muscle function that we observed occurred in subjects who had been instructed to avoid high NO3⁻ foods during the study. Thus, although previous research has demonstrated that even severe restriction of dietary NO3⁻ intake for several days only lowers plasma NO3⁻ concentration by ~10% (21), it is possible that the effects of the BRJ supplement were magnified by the dietary controls that we imposed to assure stable baseline values. Finally, in this initial proof-of-concept study we did not make any measurements beyond plasma NO3⁻ /NO2⁻ and breath NO to be able to address the specific mechanisms by which acute dietary NO3⁻ intake improves the muscle dysfunction of patients with HF.

In summary, in this pilot study we found that acute dietary NO3⁻ intake, in the form of a concentrated BRJ supplement, was well-tolerated and markedly enhanced NO bioavailability in patients with systolic HF. This increase in NO was associated with significant improvement in muscle contractile function. Additional research will be required to determine whether this improvement in muscle function results in an improved quality of life in this population.
Acknowledgements

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Disclosures

None.

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Table 1. Patient characteristics

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<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>N (M/F)</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Height (m)</td>
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<td>Body mass (kg)</td>
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<td>BMI (m/kg²)</td>
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<td>Duration of HF (y)</td>
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<td>NYHA class (I/II/III/IV)</td>
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<td>MLWHFQ (score)</td>
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<td>Ejection fraction (%)</td>
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Values are mean±S.D. for n=9.
Table 2. Effects of dietary NO₃⁻ on plasma NO₃⁻, NO₂⁻, and breath NO in HF patients

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<th>Trial</th>
<th>Time of measurement</th>
<th>Pre ingestion</th>
<th>1 h post ingestion</th>
<th>2 h post ingestion</th>
<th>10 min post exercise</th>
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<tr>
<td>Placebo</td>
<td>Plasma [NO₃⁻] (μmol/L)</td>
<td>32.7 ±5.6</td>
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<td>25.4 ±3.2</td>
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<td>Nitrate</td>
<td>33.9 ±5.5</td>
<td>404.2* ±31.3</td>
<td>492.3* ±48.5</td>
<td>524.6* ±49.3</td>
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<td>Plasma [NO₂⁻] (μmol/L)</td>
<td>0.48 ±0.09</td>
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<td>Placebo</td>
<td>Breath NO (ppb)</td>
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<td>15 ±2</td>
<td>17 ±2</td>
<td>16 ±1</td>
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<td>28 ±2</td>
<td>30‡ ±4</td>
<td>27‡ ±4</td>
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Values are mean±S.E. for n=9. Nitrate trial significantly higher than placebo trial: *P<0.0001, †P<0.001, ‡P<0.05.
Table 3. Effects of dietary NO$_3^-$ on heart rate, blood pressure, and rate-pressure product in HF patients

<table>
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<th>Trial</th>
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<td>Nitrate</td>
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<td>±4</td>
<td>±4</td>
<td>±3</td>
<td>±5</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>102 ±5</td>
<td>102 ±5</td>
<td>101 ±5</td>
<td>106 ±6</td>
</tr>
<tr>
<td>Nitrate</td>
<td></td>
<td>105 ±4</td>
<td>106 ±3</td>
<td>102 ±2</td>
<td>106 ±5</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>66 ±3</td>
<td>66 ±4</td>
<td>65 ±3</td>
<td>68 ±3</td>
</tr>
<tr>
<td>Nitrate</td>
<td></td>
<td>68 ±3</td>
<td>65 ±3</td>
<td>65 ±3</td>
<td>68 ±3</td>
</tr>
</tbody>
</table>

Values are mean±S.E. for n=9.
Table 4. Effects of dietary NO$_3^-$ on results of 50 contraction fatigue test at 3.14 rad/s in patients with heart failure

<table>
<thead>
<tr>
<th></th>
<th>Peak power (W/kg)</th>
<th>Total work (J/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maximum</td>
<td>Average</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.68 ± 0.13</td>
<td>0.82 ± 0.08</td>
</tr>
<tr>
<td>Nitrate</td>
<td>1.78 ± 0.15</td>
<td>0.86 ± 0.11</td>
</tr>
</tbody>
</table>

Values are mean ± S.E. for n=9.
Figure Legends

Figure 1. Flow diagram illustrating progress of subjects through the study.

Figure 2. Effect of ingestion of BRJ either containing or devoid of 11.2 mmol of NO$_3^-$ on peak knee extensor power at varying angular velocities in patients with HF. Peak power significantly higher in NO$_3^-$ trial vs. placebo trial at that velocity: *P=0.07, †P<0.05.

Figure 3. Effect of ingestion of BRJ either containing or devoid of 11.2 mmol of NO$_3^-$ on maximal knee extensor velocity (top panel) and power (bottom panel) in patients with HF. Nitrate trial significantly greater than placebo trial: *P<0.05.
N=37 assessed for eligibility

N=6 met exclusion criteria

N=31 met inclusion criteria

N=15 declined to participate
   N=6 unable to contact
   N=1 sustained injury

N=9 enrolled in study

N=9 completed study protocol
Acute Dietary Nitrate Intake Improves Muscle Contractile Function in Patients with Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Trial
Andrew R. Coggan, Joshua L. Leibowitz, Catherine Anderson Spearie, Ana Kadkhodayan, Deepak P. Thomas, Sujata Ramamurthy, Kiran Mahmood, Soo Park, Suzanne Waller, Marsha Farmer and Linda R. Peterson

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