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 because of reduced O₂ delivery to, and utilization by, skeletal muscle, resulting in a reduction in VO₂ peak. Skeletal muscle strength, velocity, and power, however, are also markedly reduced in HF. This muscle dysfunction also plays an important role in the compromised exercise capacity and reduced quality of life in HF. Moreover, diminished muscle function is a powerful prognostic indicator of survival in HF, even more powerful than a reduction in VO₂ peak.

Background—Skeletal muscle strength, velocity, and power are markedly reduced in patients with heart failure, which contributes to their impaired exercise capacity and lower quality of life. This muscle dysfunction may be partially because of decreased nitric oxide (NO) bioavailability. We therefore sought to determine whether ingestion of inorganic nitrate (NO₃⁻) would increase NO production and improve muscle function in patients with heart failure because of systolic dysfunction.

Methods and Results—Using a double-blind, placebo-controlled, randomized crossover design, we determined the effects of dietary NO₃⁻ in 9 patients with heart failure. After fasting overnight, subjects drank beetroot juice containing or devoid of 11.2 mmol of NO₃⁻. Two hours later, muscle function was assessed using isokinetic dynamometry. Dietary NO₃⁻ increased (P<0.05–0.001) breath NO by 35% to 50%. This was accompanied by 9% (P=0.07) and 11% (P<0.05) increases in peak knee extensor power at the 2 highest movement velocities tested (ie, 4.71 and 6.28 rad/s). Maximal power (calculated by fitting peak power data with a parabola) was therefore greater (ie, 4.74±0.41 versus 4.20±0.33 W/kg; P<0.05) after dietary NO₃⁻ intake. Calculated maximal velocity of knee extension was also higher after NO₃⁻ ingestion (ie, 12.48±0.95 versus 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 NO₃⁻ intake was well tolerated and enhanced NO bioavailability and muscle power in patients with systolic heart failure. 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 ■ muscle strength ■ nitrates ■ nitric oxide ■ nutrition theory ■ quality of life

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 because of reduced O₂ delivery to, and utilization by, skeletal muscle, resulting in a reduction in VO₂ peak. Skeletal muscle strength, velocity, and power, however, are also markedly reduced in HF. This muscle dysfunction also plays an important role in the compromised exercise capacity and reduced quality of life in HF. Moreover, diminished muscle function is a powerful prognostic indicator of survival in HF, even more powerful than a reduction in VO₂ peak.

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The mechanisms responsible for altered muscle contractile properties in HF have not been fully elucidated. Notably, patients with HF are weaker, slower, and less powerful even when compared with equally sedentary healthy subjects with comparable limb muscle mass, indicating that these changes are not solely because of physical inactivity or muscle atrophy. Rather, muscle dysfunction in HF seems 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, a slowing of cross-bridge kinetics, and an increase in the percentage of muscle fibers expressing multiple myosin isoforms. Other studies of HF have demonstrated abnormalities in skeletal muscle sarcoplasmic...
reticulum Ca\(^{2+}\) ATPase and ryanodine receptor content 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-cyclic GMP (cGMP) signaling.\(^{11}\) This is true despite enhanced expression of the inducible form of NO synthase.\(^{12}\) 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 NO synthase pathway, it is also derived from dietary nitrate (NO\(_{3}^{-}\)).\(^{15,16}\) In this alternative pathway, NO\(_{3}^{-}\) is first reduced to nitrite (NO\(_{2}^{-}\)) by oral facultative anaerobic bacteria. After NO\(_{2}^{-}\) is swallowed, acidic conditions in the stomach or other tissues (eg, contracting muscle) can further reduce it to NO. Notably, unlike the NO synthase pathway, this dietary pathway does not use O\(_{2}\) and is stimulated rather than inhibited by low pH.\(^{15,16}\) To summarize, there is a heretofore underappreciated 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 NO\(_{3}^{-}\), 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 NO\(_{3}^{-}\) ingestion would improve muscle function in patients with HF, in whom NO bioavailability and muscle function are reduced. Because dietary NO\(_{3}^{-}\) can result in a small-to-moderate drop in blood pressure,\(^{18}\) we were also interested in evaluating the safety of this intervention in patients with HF, who might become hypotensive because of the combination of compromised cardiac function, medication use, and dietary NO\(_{3}^{-}\).

**Methods**

**Subjects**

We studied HF patients with systolic dysfunction, that is, an ejection fraction of <45%. Subjects had to be ≥18 years of age, on a stable HF treatment regimen, and without significant orthopedic limitations or other contraindications to exercise. All underwent a medical history, physical examination, 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 the use of antacids or proton pump or xanthine oxidase inhibitors, which can affect the reduction of NO\(_{3}^{-}\) and NO\(_{2}^{-}\) to NO.\(^{19}\) Individuals taking phosphodiesterase inhibitors (eg, Viagra) were also excluded, as these can potentiate NO effects.\(^{20}\) After screening of 37 subjects, 9 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. 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- to 2-week washout period between treatments. Because the half-life of the increase in plasma NO\(_{3}^{-}\) after acute dietary intake is <8 hours,\(^{21}\) 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 it 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. On questioning after 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 days before 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 NO\(_{3}^{-}\), NO\(_{2}^{-}\), and NO levels. Because chewing gum or antibacterial mouthwash can block conversion of NO\(_{3}^{-}\) to NO\(_{2}^{-}\) 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 hours before study.

**Experimental Protocol**

On the subject’s arrival at the Clinical Research Unit at 8 AM, an antecubital venous catheter was inserted and a blood sample was obtained for subsequent determination of plasma NO\(_{3}^{-}\} and NO\(_{2}^{-}\} 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; Aerocine 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 hour and 2 hours after BRJ ingestion, after which exercise testing began. This timing was based on previous studies demonstrating that plasma NO\(_{3}^{-}\} \geq 22\text{ to} 24\) and breath NO\(_{3}^{-}\) \geq 2 hours after dietary NO\(_{3}^{-}\} intake. A 6-minute walk test was first conducted to determine the effects of dietary NO\(_{3}^{-}\} 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 isotonic dynamometer (Biodex Medical Systems, Shirley, NY). After adjustment of the dynamometer, subjects performed 3 to 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).
Data analyses

The isokinetic dynamometer data were analyzed as previously described. 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 normality test. Data were subsequently analyzed using 2-way (treatment x order) ANOVA, with the subject as a repeated measures factor within each treatment. A P value of <0.05 was considered significant. Sample size was chosen based on our recent study of the effects of dietary NO3– on muscle power in healthy individuals44 and enabled us to detect any effect size of ±0.69 with a power (ie, 1−β) of 0.80 at an α 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 NO3–; all other variables measured were considered secondary.

Results

Subject characteristics are listed in Table 1. All subjects had a nonischemic cardiomyopathy; all were treated with β-blockers, and most were treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker. 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 large, that is, ~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 this study not statistically significant, elevation in plasma NO2– compared with the placebo trial. Whole-body NO bioavailability, on the other hand, did increase significantly after dietary NO3–, as evidenced by a 35% to 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 2 highest angular velocities tested (ie, 4.71 and 6.28 rad/s) by 9% (P<0.05) and 11% (Figure 2), respectively. Consequently, calculated maximal knee extensor power was 13% higher (P<0.05) in the NO3– trial (Figure 3, top). Calculated maximal knee extensor velocity was also 12% higher (P<0.05) after dietary NO3– (Figure 3, bottom). 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–] versus 517±31 m [placebo]; P=0.29) and maximal isometric torque (1.99±0.10 Nm/kg [NO3–] versus 1.98±0.16 Nm/kg [placebo]; P=0.86) also did not change significantly with NO3–. 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 NO3– intake.27,28
No significant treatment×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$_3^-$ increases plasma NO$_3^-$ 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, that is, in the maximal velocity and hence power of the knee extensor muscles. Just as importantly, in this pilot study, acute dietary NO$_3^-$ intake was well tolerated by patients with HF, and in particular, it did not lead to deleterious changes in blood pressure or other major untoward clinical effects.

As indicated above, dietary NO$_3^-$ ingestion resulted in a significant increase in breath NO. However, both the baseline value and the magnitude of the increase after NO$_3^-$ intake were slightly, but significantly ($P<$0.05), lower than those we found recently in a parallel study of healthy, younger men and women. The former is consistent with previous studies of patients with systolic HF.27,28 This reduction in breath NO has been shown to be predictive of reduced exercise capacity28 and increased mortality risk in this population. The somewhat lesser rise in breath NO, these data indirectly support the hypothesis that the impaired skeletal muscle contractile performance of patients with HF is due in part to reduced NO-soluble guanyl cyclase-cGMP signaling, as is thought to be true in cardiac muscle. More importantly, however, these data illustrate the efficacy of dietary NO$_3^-$ in enhancing muscle function in patients with HF. Indeed, on the basis of the study by Toth et al., in which patients with HF 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 this study seems 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, that is, β-blockers, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, 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 with that resulting from 2 to 3 months of resistance exercise training in patients with HF,32,33 which has been shown to result in significant improvement in Minnesota Living with Heart Failure Questionnaire score. Longer-term, larger-scale studies would be needed to determine whether dietary NO$_3^-$ is similarly effective.

Despite this apparently slightly blunted increase in NO bioavailability in patients with HF, acute dietary NO$_3^-$ intake resulted in considerable improvements in muscle velocity and power. In fact, compared with the healthy, younger subjects we studied previously, the patients with HF in this study seemed to benefit even more from dietary NO$_3^-$ supplementation. Specifically, in patients with HF, 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 patients with HF, $P_{\text{max}}$ increased by 13% ($P<0.05$) after 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 function in patients with HF is due in part to reduced NO-soluble guanyl cyclase-cGMP signaling, as is thought to be true in cardiac muscle. More importantly, however, these data illustrate the efficacy of dietary NO$_3^-$ in enhancing muscle function in patients with HF. Indeed, on the basis of the study by Toth et al., in which patients with HF 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 this study seems 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 and, that is, β-blockers, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and aldosterone antagonists, which have proven ineffective in improving skeletal muscle contractile function in HF. The magnitude of the improvement in isokinetic muscle function that we observed is comparable with that resulting from 2 to 3 months of resistance exercise training in patients with HF, which has been shown to result in significant improvement in Minnesota Living with Heart Failure Questionnaire score. Longer-term, larger-scale studies would be needed to determine whether dietary NO$_3^-$ is similarly effective.

![Figure 2. Effect of ingestion of beetroot juice containing either or devoid of 11.2 mmol of NO$_3^-$ on peak knee extensor power at varying angular velocities in patients with heart failure. Peak power significantly higher in NO$_3^-$ trial vs placebo trial at those velocities: *$P=0.07$ and †$P<0.05$.](image-url)
studies should therefore be conducted to determine whether this dietary NO$_{3}^{-}$-induced increase in muscle power enhances habitual physical activity and quality of life (or possibly even survival) 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 50 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. 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 minutes. The latter may simply reflect a type II error, as the effect size was moderate (ie, Cohen $d$=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-minute walk distance in HF patients. Nonetheless, in a relative sense, the nonsignificant increase 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, previous studies of the effects of dietary NO$_{3}^{-}$ on blood pressure in other subject groups. Our data, however, are in keeping with the results of Kapil et al, who found that the 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 (in post hoc analyses, we found no sex-related differences in this study). It is also consistent with the results of a recent study by Zamani et al of patients with HF with preserved ejection fraction, in whom dietary NO$_{3}^{-}$ supplementation also did not reduce blood pressure.

Precisely why dietary NO$_{3}^{-}$ lowers blood pressure in some subject groups but not, apparently, in HF patients with reduced (or preserved) ejection fraction is difficult to determine. It is possible that the endothelial dysfunction characteristic of HF blunts the vasodilatory response to dietary NO$_{3}^{-}$-derived NOjust as it limits the vasodilation that occurs in response to, for example, nitroprusside. Alternatively, as recently discussed by Shepherd et al, it is possible that common vasoactive medications, that is, β-blockers, angiotensin-converting enzyme

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>Maximum</th>
<th>Average</th>
<th>First Third</th>
<th>Last Third</th>
<th>Ratio</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.68±0.13</td>
<td>0.82±0.08</td>
<td>15.4±1.8</td>
<td>4.5±0.5</td>
<td>0.30±0.02</td>
<td>28.1±3.2</td>
</tr>
<tr>
<td>Nitrate</td>
<td>1.78±0.15</td>
<td>0.86±0.11</td>
<td>16.1±1.9</td>
<td>4.4±0.4</td>
<td>0.28±0.02</td>
<td>28.8±3.3</td>
</tr>
</tbody>
</table>

Values are mean±SE for n=9.
inhibitor/angiotensin receptor blocker, and aldosterone antagonists, somehow interfere with the blood pressure–lowering effect of dietary NO$_3$. Finally, it is also possible that there is a differential sensitivity of smooth muscle and skeletal muscle to the effects of dietary NO$_3$, at least in patients with HF, such that the present dose of dietary NO$_3$ was simply insufficient to reduce blood pressure although it did increase muscle contractile function. Regardless, the fact that the dose of dietary NO$_3$ we used (ie, 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 (eg, hyperkalemia) were observed in the present pilot study, although 1 subject did experience mild gastrointestinal symptoms after drinking the BRJ. Longer-term studies will be required to determine the ultimate safety and tolerability of dietary NO$_3$ supplementation in this patient population, as well as to determine whether tolerance develops as often occurs with pharmaceutical nitrates, for example, trinitroglycerin.$^{42}$ Although there is no evidence of tolerance in terms of the blood-pressure–lowering effects of dietary NO$_3$,$^{16}$ 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 (ie, breath NO and muscle power), our study may have been underpowered to detect relatively small changes in secondary outcomes (eg, plasma NO$_3$ and 6-minute 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 NO$_3$ 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 NO$_3$ foods during the study. Thus, although previous research has demonstrated that even severe restriction of dietary NO$_3$ intake for several days only lowers plasma NO$_3$ concentration by $\sim 10\%$, 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 NO$_3$/NO$_2$ and breath NO to be able to address the specific mechanisms by which acute dietary NO$_3$ intake improves the muscle dysfunction of patients with HF.

In summary, in this pilot study, we found that acute dietary NO$_3$ 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.

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Disclosures

None.

References


CLINICAL PERSPECTIVE

Although cardiologists are accustomed to evaluating and treating reduced aerobic capacity and its resultant symptom, that is, dyspnea, in heart failure (HF), decreased muscle power is also a major problem in HF. Decreased muscle power impairs an ability of patient with HF to perform most activities of daily living (eg, walking short distances, climbing stairs, getting out of a chair, and lifting groceries). Decreased power also predicts increased mortality in HF. We found that within ~2.5 hours, ingestion of a single dose of a concentrated beetroot juice supplement containing 11.2 mmol of inorganic nitrate (NO−3) improved peak and maximal muscle power in patients with HF by ~10%. This improvement apparently erased 1/3 of the deficit in muscle power resulting from HF. Stated another way, this degree of improvement in isokinetic power is comparable with that resulting from 2–3 months of resistance training in patients with HF, which has been shown to significantly improve health-related quality of life in such individuals. Thus, the magnitude of improvement we observed is significant. Moreover, other current pharmacologic drug therapies for HF that improve survival (eg angiotensin-converting enzyme inhibitors and ß-blockers) have not been shown to improve muscle power. Thus, acute dietary NO−3 intake is an effective treatment for improving muscle power in patients with HF. Future largescale, longer-term studies are needed to determine whether chronic treatment is equally or more effective and whether this improves habitual physical activity or health-related quality of life in this population.
Acute Dietary Nitrate Intake Improves Muscle Contractile Function in Patients With Heart Failure: A Double-Blind, Placebo-Controlled, Randomized Trial
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