Sodium Nitrite Improves Exercise Hemodynamics and Ventricular Performance in Heart Failure With Preserved Ejection Fraction

Barry A. Borlaug, MD, Katlyn E. Koepp, BS, Vojtech Melenovsky, MD, PhD

ABSTRACT

BACKGROUND There is no effective medical treatment for heart failure with preserved ejection fraction (HFpEF). Increases in pulmonary capillary wedge pressure (PCWP) develop in patients with HFpEF during exercise coupled with impaired nitric oxide (NO) signaling. Nitrite can be reduced to bioactive NO in vivo, particularly under conditions of tissue hypoxia, as with exercise.

OBJECTIVES This study sought to determine whether acute nitrite administration improves exercise hemodynamics and cardiac reserve in HFpEF.

METHODS In a double-blind, randomized, placebo-controlled, parallel-group trial, subjects with HFpEF (N = 28) underwent invasive cardiac catheterization with simultaneous expired gas analysis at rest and during exercise, before and 15 min after treatment with either sodium nitrite or matching placebo.

RESULTS Before the study drug infusion, HFpEF subjects displayed an increase in PCWP with exercise from 16 ± 5 mm Hg to 30 ± 7 mm Hg (p < 0.0001). After study drug infusion, the primary endpoint of exercise PCWP was substantially improved by nitrite compared with placebo (adjusted mean: 19 ± 5 mm Hg vs. 28 ± 6 mm Hg; p = 0.0003). Nitrite-enhanced cardiac output reserve improved with exercise (+0.5 ± 0.7 l/min vs. –0.4 ± 0.7 l/min; p = 0.002) and normalized the increase in cardiac output relative to oxygen consumption. Nitrite improved pulmonary artery pressure-flow relationships in HFpEF and increased left ventricular stroke work with exercise versus placebo, indicating an improvement in ventricular performance with stress.

CONCLUSIONS Acute sodium nitrite infusion favorably attenuates hemodynamic derangements of cardiac failure that develop during exercise in individuals with HFpEF. Prospective trials testing long-term nitrite therapy in this population are warranted. (Acute Effects of Inorganic Nitrite on Cardiovascular Hemodynamics in Heart Failure With Preserved Ejection Fraction; NCT01932606) (J Am Coll Cardiol 2015;66:1672–82) © 2015 by the American College of Cardiology Foundation.
designed to improve symptoms and outcome in HFpEF.

Numerous lines of evidence indicate that abnormalities in nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling play a central role in causing these reserve limitations (11-13). Organic nitrates can improve NO-cGMP signaling but may be limited by the development of tolerance or symptomatic hypotension (14,15). Indeed, 1 factor complicating HFpEF treatment is that the hemodynamic perturbations causing symptoms are often absent at rest but observed only during physiological stresses, such as exercise (2).

METHODS

This double-blind, randomized, placebo-controlled, parallel-group trial was designed to study the effects of intravenous sodium nitrite on cardiovascular hemodynamics at rest and during exercise in subjects with HFpEF. Patients referred to the Mayo Clinic cardiology catheterization laboratory for invasive hemodynamic exercise stress testing were enrolled. Written informed consent was provided by all subjects before participation in study-related procedures. The Mayo Clinic Institutional Review Board approved the study.

STUDY POPULATION AND PROTOCOL. HFpEF was defined by clinical symptoms of chronic heart failure (dyspnea, fatigue), normal ejection fraction (>50%), and increased left heart filling pressures (pulmonary capillary wedge pressure [PCWP]) at rest (>15 mm Hg) and/or with exercise (>25 mm Hg) (1,2). Exclusion criteria included significant valvular heart disease (>mild stenosis, >moderate regurgitation), cor pulmonale, significant pulmonary disease, congenital heart disease, glucose 6-phosphate dehydrogenase deficiency, left-to-right shunt, unstable coronary artery disease, myocardial infarction within 60 days, hypertrophic or infiltrative cardiomyopathy, primary renal or hepatic disease, high-output heart failure, or constrictive pericarditis. Subjects receiving long-term treatment with organic nitrates or phosphodiesterase 5 inhibitors also were excluded.

Subjects were studied on their long-term medications in the post-absorptive state and supine position. Cardiac catheterization was performed with simultaneous expired gas analysis at rest and during supine exercise at a 20-W workload for 5 min, as previously described (2,8). After the first exercise phase (before any drug administration) and after return to steady-state baseline hemodynamic values, subjects were randomized 1:1 to infusion of placebo (normal saline solution) or sodium nitrite (50 mg/kg/min) (Hope Pharmaceuticals, Scottsdale, Arizona) for 5 min. The nitrite/placebo infusions were identical in appearance and prepared by the research pharmacy, ensuring double-blinding of infusion content. After 10 min, hemodynamic measurements were repeated at rest, followed by repeat supine exercise at a 20-W workload for 5 min, identical to the study’s first phase. Arterial and venous blood samples and hemodynamic and expired gas data were acquired during each stage of the protocol.

Right heart catheterization was performed through a 9-F sheath via the internal jugular vein. Transducers were zeroed at mid-axilla. Right atrial pressure (RAP), pulmonary artery (PA) pressure, and PCWP were measured at end-expiration (mean of ≥3 beats) using 2-F, high-fidelity micromanometer-tipped catheters (Millar Instruments, Houston, Texas) advanced through the lumen of a 7-F, fluid-filled catheter (Arrow, Teleflex, Morrisville, North Carolina) (2,8). Mean RAP and PCWP were taken at mid A wave. PCWP position was verified by typical waveforms, appearance on fluoroscopy, and direct oximetry (saturation ≥94%). Continuously recorded pressure tracings were digitized (240 Hz) and analyzed offline.

Arterial blood pressure (BP) was measured continuously through a 4- to 6-F radial arterial cannula. Oxygen consumption (VO2) was measured from expired gas analysis (MedGraphics, St. Paul, Minnesota) taken as the average from the 60 s preceding arterial and mixed venous blood sampling (8). Ventilatory efficiency was assessed by the increase in minute ventilation relative to carbon dioxide production (VCO2). Arteriovenous O2 content difference (CAO2 – CVO2) was measured directly as the difference between systemic arterial and PA O2 content. CO was determined by the direct Fick method (VO2/[CAO2 – CVO2]). Stroke volume (SV) was determined from the quotient of CO...
and heart rate. Pulmonary vascular resistance (PVR) (mean PA – PCWP/CO), PA compliance (SV/PA pulse pressure), and systemic vascular resistance (SVR) (mean BP – RAP × 80)/CO were calculated using standard formulas. LV systolic performance was assessed by LV stroke work ([mean BP – PCWP] × SV × 0.0136) (2,8).

Central venous and arterial blood samples were obtained during each stage to measure the methemoglobin level and blood gases. Plasma nitrite concentrations were assessed in the final 6 subjects enrolled in the trial using a liquid chromatography-fluorometric assay (BASI, West Lafayette, Indiana) as previously described (20).

**STUDY ENDPOINTS.** The primary endpoint of the trial was the PCWP during exercise. Secondary endpoints included changes in resting PCWP as well as rest and exercise changes in RAP, PA pressure, PVR, PA compliance, systemic BP, heart rate, SV, stroke work, CO, VO2, and CaO2 – CVO2. Adequacy of CO reserve was assessed by comparing the CO/VO2 slope before and after study drug infusion, whereas PA pressure-flow relationships were assessed to integrate changes in right heart loading with exercise. Methemoglobin level (%) was assessed as a safety endpoint.

**STATISTICAL ANALYSIS.** Results are reported as mean ± SD, median (interquartile range) or n (%). Between-group differences at individual time points were tested using the Student t test, Wilcoxon rank sum test, or Fisher exact test. Within-group differences are assessed by the paired Student t test. The effect of nitrite on the primary endpoint of exercise PCWP was assessed by analysis of covariance, using the initial exercise PCWP measured before study drug infusion as the covariate. Between-group differences in rest or exercise hemodynamic responses were compared by an unpaired Student t test after accounting for respective pre-study drug values. Linear regression was performed to compare hemodynamic responses to exercise before and after study drug infusion, with variables log-transformed as necessary for analysis. All tests were 2-sided, with p < 0.05 considered significant. Analyses were performed using JMP version 10.0.0 (SAS Institute, Cary, North Carolina).

**RESULTS**

A total of 28 subjects were enrolled in the trial between January and September 2014. Baseline characteristics were not significantly different between treatment groups (Table 1). Subjects were older, obese, and predominantly female, with a high prevalence of hypertension. On average, subjects displayed normal LV chamber size and mass, left atrial enlargement, mild LV diastolic dysfunction, and increased N-terminal pro-B-type natriuretic peptide levels (Table 1).

At rest, subjects were hypertensive, with slightly increased right and left heart filling pressures, mild pulmonary hypertension, slightly increased PVR, and normal CO (Table 2). With exercise, participants displayed significant increases in heart rate, BP, CO, VO2, and CaO2 – CVO2. Mean RAP and PCWP increased dramatically during exercise, with secondary increase in PA pressures. Pulmonary vasodilation was impaired during exercise, manifest by lack of a decrease in PVR and acute decreases in PA compliance compared with rest (Table 2). VE/VCO2 slope was increased (37 ± 5), consistent with marked ventilatory inefficiency during exercise.

The increase in CO relative to metabolic demand (ΔCO/ΔVCO2 slope) in the HFpEF subjects was 4.7 ± 2.7 ml/ml. Most participants (75%) displayed an abnormal ΔCO/ΔVCO2 slope (defined as ≪6 ml/ml) (21), indicating significant limitation in CO reserve during
exercise. The median slope of increase in PA pressure relative to CO (ΔPA/ΔCO) slope was 9.4 (interquartile range: 5.3 to 14.3) mm Hg/l/min. The vast majority of subjects (93%) displayed abnormal PA pressure-flow relationships with exercise (defined as >3.0 mm Hg/l/min) (22). There were no between-group differences in any of the indexes of resting or exercise hemodynamics, expired gas data, or ventricular function.

**NITRITE EFFECTS.** Hypotension or other adverse events after study drug infusion did not develop in any subjects. Nitrite modestly increased methemoglobin levels compared with placebo (+0.5 ± 0.3% vs. +0.1 ± 0.4%; p = 0.002), but no clinically meaningful methemoglobinemia developed in any subject (>5%). The highest methemoglobin level observed (2.4%) was in a subject randomized to nitrite with an increased resting level (1.6%).

Compared with placebo, nitrite infusion modestly reduced RAP, PCWP, and PA pressures at rest (Table 3). There was no statistically significant effect of nitrite on resting heart rate, BP, PVR, SVR, PA compliance, LV stroke work, VO2, Co, CaO2 – Cvo2, or SV compared with placebo.

The primary endpoint of exercise PCWP was significantly improved with nitrite compared with placebo (adjusted mean: 19 ± 5 mm Hg vs. 28 ± 6 mm Hg; p = 0.0003) (Table 4, Figure 1A). The magnitude of decrease in exercise PCWP was similar across all PCWP values achieved during the initial exercise phase (Figure 1B), and the decrease in exercise PCWP remained significant after adjusting for renin-angiotensin inhibitor and beta-blocker use (both p ≤ 0.001). Nitrites reduced exercise PCWP more than 2-fold greater than the reduction in resting PCWP (mean difference: 8.1 ± 1.4 mm Hg; p < 0.0001), indicating a greater effect of nitrite on stress PCWP compared with resting PCWP.

Nitrite had no effect on exercise heart rate or systolic BP, but it tended to reduce mean BP during exercise more than placebo (p = 0.05) (Table 4). Nitrite decreased exercise RAP and PA pressure compared with placebo (Figure 2, Table 4). The nitrite-mediated decrease in exercise PA pressure was exclusively due to lowering of the PCWP, as there was no effect on exercise PVR or PA compliance. Nitrite tended to reduce Vf/Vco2 slope compared with placebo (−0.2 ± 0.5 vs. +0.7 ± 0.3; p = 0.2). Exercise SVR was reduced with nitrite, consistent with systemic arterial vasodilation (Figure 2B). Nitrite lowered the slope of the PA pressure-flow relationship compared with placebo (change in log ΔPA/ΔCO: −1.2 ± 1.1 vs. 0.0 ± 0.6; p = 0.002; ANCOVA p = 0.004) (Figures 2C and 2D).

By design, the external workload performed during exercise was equivalent before and after study drug infusion (20 W), but despite this, nitrite slightly increased the VO2 achieved at 20 W compared with placebo (Table 4); this VO2 increase was coupled to greater enhancement in exercise CO (Figure 3A), with no change in Cao2 – Cvo2 compared with to placebo (Table 4). Nitrite infusion increased the ΔCO/ΔVO2 slope compared with placebo (+2.1 ± 2.2 ml/min vs. +0.3 ± 1.7 ml/min; p = 0.025) to a mean value that falls within the normal range for humans without heart failure (dotted line, Figure 3B), indicating an improvement in CO reserve relative to metabolic demand.

The increase in exercise CO with nitrite was caused exclusively by greater enhancement in SV (Figure 3C), as there was no effect on exercise heart rate (Table 4). Although the enhanced SV reserve with nitrite might have been related in part to systemic vasodilation (lower SVR), importantly, there was also a greater increase in LV stroke work with nitrite (Figure 3D), indicating an acute increase in LV systolic performance, independent of changes in cardiac loading (23).

**PLASMA NITRITE LEVELS.** Venous plasma nitrite levels were obtained in 4 subjects randomized to

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**TABLE 2 Baseline and Exercise Hemodynamics Before Study Drug Infusion**

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>20-W Exercise</th>
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<tbody>
<tr>
<td><strong>Vital signs</strong></td>
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<tr>
<td>Heart rate, beats/min</td>
<td>68 ± 8</td>
<td>92 ± 13†</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>155 ± 15</td>
<td>179 ± 22†</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>98 ± 7</td>
<td>113 ± 13†</td>
</tr>
<tr>
<td><strong>Central pressures</strong></td>
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<td></td>
</tr>
<tr>
<td>RA, mm Hg</td>
<td>10 ± 4</td>
<td>21 ± 10†</td>
</tr>
<tr>
<td>PA systolic, mm Hg</td>
<td>44 ± 13</td>
<td>67 ± 15†</td>
</tr>
<tr>
<td>PA mean, mm Hg</td>
<td>28 ± 7</td>
<td>47 ± 12†</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>17 ± 4</td>
<td>30 ± 8†</td>
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<tr>
<td><strong>Vascular and ventricular function</strong></td>
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<tr>
<td>PVR, mm Hg/min</td>
<td>2.3 ± 1.7</td>
<td>2.5 ± 1.8</td>
</tr>
<tr>
<td>PA compliance, ml/mm Hg</td>
<td>3.5 ± 1.5</td>
<td>2.9 ± 1.3†</td>
</tr>
<tr>
<td>SVR, DSC</td>
<td>1,370 ± 360</td>
<td>1,050 ± 250†</td>
</tr>
<tr>
<td>LVSW, g/beat</td>
<td>89 ± 24</td>
<td>92 ± 27†</td>
</tr>
<tr>
<td><strong>Integrated function and metabolism</strong></td>
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<tr>
<td>VO2, ml/min</td>
<td>233 ± 50</td>
<td>731 ± 168†</td>
</tr>
<tr>
<td>Cao2 – Cvo2, ml/dl</td>
<td>4.4 ± 1.0</td>
<td>9.4 ± 1.2†</td>
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<tr>
<td>CO, l/min</td>
<td>5.4 ± 1.3</td>
<td>8.0 ± 2.1†</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>81 ± 20</td>
<td>88 ± 23</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Columns show rest-exercise hemodynamics before study drug infusion in subjects randomized to placebo or nitrite. All between-group comparisons at rest and with exercise are p < 0.05 versus baseline, within-subject change. †p < 0.0001 versus baseline, within-subject change.

BP = blood pressure; Cao2 – Cvo2 = arteriovenous O2 content difference; CO = cardiac output; DSC = dynes/cm²; LVSW = left ventricular stroke work; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial; SVR = systemic vascular resistance; VO2 = oxygen consumption; W = watt.
nitrite and 2 randomized to placebo. Levels were undetectable at baseline and with exercise before study drug infusion in all subjects. Nitrite levels remained undetectable after study drug infusion in subjects receiving placebo, but increased to 8.39 ± 1.88 µM at rest in subjects receiving active drug (p = 0.004 vs. baseline). After the 5-min exercise period, levels decreased to 3.36 ± 0.42 µM in the active therapy group (p < 0.01 compared with pre-exercise values). The calculated half-life from these data was 3.9 ± 0.6 min, which is 10-fold faster than the previously reported kinetics for sodium nitrite in humans at rest (30 to 40 min) (20), indicating active consumption during exercise.

**DISCUSSION**

This double-blind, randomized, placebo-controlled trial tested the effects of acute infusion of inorganic sodium nitrite on cardiovascular hemodynamics and ventricular function at rest and during low-level exercise in subjects with HFpEF. The rationale for this design was based on the fact that hemodynamic derangements in patients with HFpEF often develop only during exercise, when a reduction of nitrite to NO is believed to be enhanced because of tissue hypoxia. The primary endpoint of exercise PCWP was significantly improved by nitrite, resulting in a 37% reduction in left heart filling pressures with exercise (Central Illustration). Beneficial reductions in PCWP were coupled to improvements in exercise CO reserve, reductions in PA pressures and PA pressure-flow relationships, and enhanced systemic vasodilator reserve.

Importantly, nitrite therapy was associated with beneficial myocardial effects in addition to vascular effects, evidenced by a greater increase in LV stroke work with exercise, an integrated index of LV diastolic and systolic performance. Beneficial effects on hemodynamics and ventricular function were of greater magnitude during exercise compared with rest, and, among participants with nitrite levels assessed, there was greater than expected decay in nitrite levels during exercise, consistent with active nitrite consumption. The beneficial effects of acute nitrite infusion on multiple hemodynamic derangements developing during exercise in HFpEF provides compelling rationale to pursue longer term clinical trials of inorganic nitrates in patients with HFpEF, a population for whom there is currently no effective treatment.

**PATHOPHYSIOLOGY OF HFpEF AND RATIONALE FOR NO-ENHANCING THERAPIES.** The pathophysiology of HFpEF is complex, related to abnormalities in LV diastolic function and diastolic reserve as well as to limitations in systolic reserve, abnormal peripheral and pulmonary vasodilation, endothelial dysfunction, chronotropic incompetence, right ventricular dysfunction, and, as recently shown,
limitations in the periphery (1–8,10,11,24–26). The subjects enrolled in the current study displayed many of these hemodynamic abnormalities, with a slight increase in resting RAP, PA pressure, and PCWP and dramatic increases during exercise that were coupled to limitations in CO reserve and abnormal pulmonary vascular function. These hemodynamic abnormalities importantly contribute to central congestion and inadequate tissue perfusion during stress and, thus, represent viable targets for therapeutic intervention.

Previous trials testing inhibitors of the renin-angiotensin-aldosterone system failed to show benefit in HFrEF, and there is currently no proven treatment (1). Numerous lines of evidence point to limitations in NO-cGMP as playing a key role in determining the functional and hemodynamic abnormalities developing in HFrEF (11–13). Sildenafil, an inhibitor of phosphodiesterase-5 (which catabolizes cGMP), did not enhance exercise capacity or clinical status in a recent multicenter trial (27). However, elegant work from van Heerebeek et al. (12) showed that cGMP limitation in HFrEF is not related to excessive breakdown but rather inadequate production, suggesting that NO-cGMP-providing therapies may be the more effective approach. A major barrier in managing many patients with HFrEF is related to the fact that the increase in cardiac filling pressures and PA pressure is confined to exercise, whereas hemodynamics at rest may be more normal (1–8). Thus, an agent that enhances NO-cGMP signaling preferentially during exercise would be expected to provide more targeted hemodynamic improvements precisely at the time of greatest need.

THE NITRATE-NITRITE-NO PATHWAY IN HEART FAILURE. Inorganic nitrite and nitrate were previously considered to be inert byproducts of NO metabolism, but recent work has shown these serve as an important in vivo reservoir of NO (16–19). Dietary nitrate is absorbed, secreted in saliva, and then converted by oral bacteria to nitrite, which is absorbed and then reduced by a number of enzymes, including deoxygenated hemoglobin or myoglobin, to NO (19,28,29). This reaction is believed to be enhanced in the setting of hypoxia and acidosis, which develop in the tissues and venous circulation during exercise, potentially allowing for hypoxic vasodilation that complements the alternative oxygen-dependent NO synthase pathway (16,18,19).

In contrast to the organic nitrates that require aldehyde dehydrogenase and other enzymes for activation (14), there is no tolerance with nitrate-nitrite (17). The greater reduction in SVR with exercise in the current study is consistent with previously described vasodilatory effects in humans, and the fact that SVR reduction was only observed during exercise is consistent with the hypoxia potentiation of nitrite effect (16–18).

Recent studies have begun to explore the potential role for the nitrate-nitrite-NO pathway in the treatment of heart failure. Zamani et al. (30) performed a noninvasive double-blind, crossover study in 17 subjects with HFrEF comparing nitrate-rich beetroot juice with nitrate-depleted beetroot juice. The authors observed significant improvements in peak VO₂, peak exercise workload, exercise CO (assessed by echocardiography), and exercise vasodilation (reduction

**FIGURE 1 Effects of Nitrite on Exercise Pulmonary Wedge Pressure**

(A) Compared with placebo (blue), nitrite infusion (red) significantly lowered the exercise pulmonary capillary wedge pressure (PCWPEX) relative to the pre-study drug exercise phase. Error bars = SEM. (B) The magnitude of reduction in PCWPEX was similar across pre-study drug PCWPEX levels. ANCOVA = analysis of covariance; PCWP = pulmonary capillary wedge pressure.
The improvement in CO reserve observed with nitrate therapy was due to a greater increase in heart rate, with no significant effect on SV.

The current invasive hemodynamic data extend the noninvasive findings of Zamani et al. (30), showing greater increases in CO and improved systemic vasodilation with nitrite in HfPfEF subjects, assessed using gold-standard techniques. The increase in CO noted in the current study greatly exceeded the small increase in VO2, indicating an acute increase in the ability of the heart to provide blood flow relative to metabolic needs (CO/VO2 slope), which has been shown to be impaired on average in HfPfEF (10). In contrast to Zamani et al. (30), the enhanced CO reserve observed in the current study was related to a greater increase in SV with exercise, with no effect on rest or exercise heart rate.

Although the greater increase in SV in the current study was likely mediated in part by improved afterload reduction, we also observed beneficial effects of nitrite on ventricular performance, assessed by the greater increase in LV stroke work with exercise. Stroke work is independent of afterload, but varies directly with preload (end-diastolic volume) (23). Therefore, we cannot determine whether the beneficial effect of nitrite on LV performance in the current study was mediated by improvements in diastolic reserve (greater increase in end-diastolic volume despite lower filling pressures), systolic reserve (increased contractility), or both. However, given the fact that both diastolic and systolic reserves are known to contribute to the pathophysiology of HfPfEF, the observation of a direct myocardial benefit from nitrite is an important observation.

The main novel finding and primary endpoint of the trial was the greater reduction in PCWP during exercise, a key force mediating symptoms of exertional dyspnea in people with HfPfEF. The magnitude of decrease in exercise PCWP with nitrite was much greater than the resting PCWP, consistent with greater

**Figure 2** Effects of Nitrite on Pulmonary and Systemic Vascular Load

Compared with placebo (blue), nitrite (red) significantly reduced exercise pulmonary artery pressure (PA meanEX) (A) and exercise systemic vascular resistance (SVREX). Error bars = SEM (B). Placebo infusion did not alter the pulmonary artery pressure (PAP)-flow (CO) relationship with exercise (C), whereas nitrite infusion shifted the PAP-flow relationship down, with a reduction in slope (D). Data points in C and D are mean pressure and CO coordinates for the groups; p values reflect a paired Student t test comparing log PAP-flow slopes before versus after study drug infusion in the placebo and nitrite groups. CO = cardiac output.
effectiveness of nitrite during exercise, as noted earlier. This represents an important advantage of inorganic nitrite for HFpEF patients, especially those with early-stage disease in which PCWP is normal at rest and increased only during exercise. The decrease in exercise PCWP was coupled with significant reductions in RAP and PA pressure with stress, and an acute decrease in the slope of the PA pressure-flow relationship, indicating an improvement in right ventricular afterload (22). Given the enhanced afterload sensitivity of the right ventricle in HFpEF, this decrease in PA pressure would be expected to greatly improve right ventricular performance as well (24).

Although decreases in rest and exercise PA pressure were observed, there was no significant effect of nitrite on PVR or PA compliance at rest or during exercise. Several animal studies have observed improvements in PA pressure and vascular remodeling with nitrate or nitrite, but most of these model systems are characterized by more severe pulmonary vascular disease (31). Subjects in the current study displayed pulmonary vasoconstriction compared with normal reference values (32), but increases in PVR and decreases in PA compliance were relatively modest and not in the range associated with adverse outcomes in heart failure patients (33). Mean PA pressure-flow slopes were extremely increased in the study subjects, but this was predominantly due to post-capillary (pulmonary venous) disease. Mean PA pressure is equal to the product of CO and PVR summed downstream PCWP. In patients with advanced pulmonary vascular disease, PA pressure is high because of increased PVR, but in the current study, increased PA pressure-flow slopes were caused almost exclusively by high PCWP. The current data may not be applicable to patients with pulmonary hypertension.

Other groups have noted improvements in the O2 cost of exercise with inorganic nitrite (34,35) in contrast to the current study in which VO2 during submaximal exercise was slightly enhanced. The reason for the discrepancy is not clear, but may relate to the level of work performed and the subjects studied. For example, Larsen et al. (35) studied young
Nitrite (NO$_2$) is reduced to nitric oxide (NO) modestly under normoxic conditions, as at rest, but markedly under conditions of venous hypoxia, as with exercise. This preferentially targets hemodynamic derangements that develop during exercise in heart failure with preserved ejection fraction (HFpEF), favorably reducing left ventricular (LV) filling pressures, enhancing cardiac output reserve, and reducing pulmonary artery (PA) pressure during exercise, to ultimately improve exercise capacity and reduce symptoms of exercise intolerance.

Nitrite Improves Exercise Hemodynamics in HFpEF: Mechanism of Hemodynamic Benefit During Exercise From Nitrite in Heart Failure

Nitrite (NO$_2$) is reduced to nitric oxide (NO) modestly under normoxic conditions, as at rest, but markedly under conditions of venous hypoxia, as with exercise. This preferentially targets hemodynamic derangements that develop during exercise in heart failure with preserved ejection fraction (HFpEF), favorably reducing left ventricular (LV) filling pressures, enhancing cardiac output reserve, and reducing pulmonary artery (PA) pressure during exercise, to ultimately improve exercise capacity and reduce symptoms of exercise intolerance.

Although the low number of subjects with nitrite levels measured limits our ability to examine pharmacokinetics, it is notable that the observed elimination half-life during 5 min of exercise was 10-fold faster than what has been reported in resting humans (20). This is consistent with greater-than-normal consumption of nitrite during exercise in the study participants, presumably via greater reduction to NO with stress.

**CLINICAL IMPLICATIONS.** Inorganic nitrate-nitrite could be applied therapeutically through naturally occurring sources such as beetroot juice or using oral supplements, although these routes would not achieve plasma nitrite levels in the range of those observed in the current study. Nitrite can also be administered orally and via an inhaled, nebulized device. Either of these routes may be suitable for chronic administration in people with HFpEF. Because of the rapid onset of action, the nebulized preparation may prove useful as a rescue inhaler or taken prophylactically before planned physical activity to reduce symptoms of exercise intolerance. The acute effects of inhaled nitrite on hemodynamics are currently being tested in HFpEF (NCT02262078), and larger phase II studies in this cohort are in the planning stages.

Organic nitrates such as isosorbide mononitrate also can enhance NO-cGMP and are commonly used in managing people with HFpEF (38). However, organic nitrates are limited by the development of tolerance, increases in oxidative stress, and the development of endothelial dysfunction (14). Organic nitrate tolerance can be reduced by ensuring an adequate nitrate-free window, but renal sodium retention may offset the beneficial effects of long-term venodilation. In contrast, there is no tolerance with inorganic nitrite, and, because conversion of nitrite to NO occurs preferentially during exercise, there may be less sodium retention and less risk of excessive BP reduction at rest, which can be problematic in those with HFpEF (15). The effect of organic nitrates on activity tolerance and exercise capacity is currently being investigated in the NEAT-HFpEF (Nitrate’s Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction) trial (38).

**STUDY LIMITATIONS.** This study examined hemodynamics and LV performance at rest and with low-level exercise but not at peak exercise. This was done primarily for feasibility, as it would be difficult for subjects to complete 2 maximal-effort exercise tests in a timely fashion. Thus, we cannot determine whether benefits observed during low-level exercise would extend to peak exercise, although the greater venous...
hypoxia and acidosis at peak would only be expected to further potentiate the benefit. Furthermore, this level of activity is clinically meaningful in that it reflects the level of physical work performed in activities of daily life in typical older people with HFpEF. Right ventricular function and right ventricle–PA coupling may be improved by nitrite, but they were not assessed in this study.

CONCLUSIONS

Inorganic nitrite favorably attenuates hemodynamic derangements that develop during exercise in individuals with HFpEF, including increased cardiac filling pressures, exercise-induced pulmonary hypertension, and inadequate CO reserve. Beneficial effects of nitrite are mediated by both vascular unloading and direct myocardial effects, which are more pronounced during exercise compared with steady state. Prospective trials testing chronic nitrite therapy in patients with HFpEF are warranted.

REFERENCES


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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sodium nitrite, a source of NO, improves hemodynamics during exercise in patients who have HFpEF, supporting a pathophysiological role for abnormal NO signaling in this condition.

TRANSLATIONAL OUTLOOK: Randomized trials of nitrite therapy are needed to evaluate longer term effects on functional capacity and clinical outcomes in patients with HFpEF.


**KEY WORDS** cardiac output, nitrate, pressure, stroke volume