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

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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 ($+0.5 \pm 0.7$ 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.

Approximately one-half of patients with heart failure have heart failure with preserved ejection fraction (HFpEF), and there is no effective treatment (1). During exercise, the normal left ventricle can fill to a larger diastolic volume with no increase in pressure, but in individuals with HFpEF, a marked increase in left ventricular (LV) filling pressures with exercise develops, contributing to increases in morbidity and mortality (2-9). Many patients with HFpEF also display impaired cardiac output (CO) reserve with exercise, which further contributes to exercise intolerance (6-8,10,11). Thus, increased filling pressures and inadequate CO reserve represent viable targets for new interventions

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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).

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Inorganic nitrite is now recognized as an alternative in vivo source of NO-cGMP that is independent of the traditional NO synthase pathway (16–19). Intriguingly, the reduction of nitrite to bioactive NO may be enhanced by tissue hypoxia and acidosis (19), which develop during exercise. This suggests that nitrite might more selectively target hemodynamic derangements developing during stress in people with HFpEF (2,10), with less risk of hypotension at rest (15). The current study tests the hypothesis that, compared with placebo, acute infusion of sodium nitrite would improve exercise hemodynamics and enhance cardiac reserve in patients with HFpEF.

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 cardiac 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 μg/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 (V_{O_2}) 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 (V_E/V_{CO_2}). Arteriovenous O_2 content difference ($Ca_{O_2} - Cv_{O_2}$) was measured directly as the difference between systemic arterial and PA O_2 content. CO was determined by the direct Fick method ($V_{O_2}/[Ca_{O_2} - Cv_{O_2}]$). Stroke volume (SV) was determined from the quotient of CO

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

$Ca_{O_2} - Cv_{O_2}$ = arteriovenous oxygen content difference

cGMP = cyclic guanosine monophosphate

CO = cardiac output

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

NO = nitric oxide

PA = pulmonary artery

PCWP = pulmonary capillary wedge pressure

PVR = pulmonary vascular resistance

RAP = right atrial pressure

SV = stroke volume

SVR = systemic vascular resistance

V_{O_2} = oxygen consumption

V_E/V_{CO_2} = ventilatory efficiency