Short-Term Intravenous Sodium Nitrite Infusion Improves Cardiac and Pulmonary Hemodynamics in Heart Failure Patients

Julian O.M. Ormerod, PhD*; Sayya Arif, MBChB*; Majid Mukadam, MBBS; Jonathan D.W. Evans, MBChB; Roger Beadle, PhD; Bernadette O. Fernandez, PhD; Robert S. Bonser, MD†; Martin Feilisch, PhD; Melanie Madhani, PhD*; Michael P. Frenneaux, MD*

**Background**—Nitrite exhibits hypoxia-dependent vasodilator properties, selectively dilating capacitance vessels in healthy subjects. Unlike organic nitrates, it seems not to be subject to the development of tolerance. Currently, therapeutic options for decompensated heart failure (HF) are limited. We hypothesized that by preferentially dilating systemic capacitance and pulmonary resistance vessels although only marginally dilating resistance vessels, sodium nitrite (NaNO₂) infusion would increase cardiac output but reduce systemic arterial blood pressure only modestly. We therefore undertook a first-in-human HF proof of concept/safety study, evaluating the hemodynamic effects of short-term NaNO₂ infusion.

**Methods and Results**—Twenty-five patients with severe chronic HF were recruited. Eight received short-term (5 minutes) intravenous NaNO₂ at 10 μg/kg/min and 17 received 50 μg/kg/min with measurement of cardiac hemodynamics. During infusion of 50 μg/kg/min, left ventricular stroke volume increased (from 43.2±21.5 to 51.8±23.6 ml; P=0.003), with marked falls in pulmonary vascular resistance (by 29%; P=0.03) and right atrial pressure (by 40%; P=0.007), but with only modest falls in mean arterial blood pressure (by 4 mmHg; P=0.004). The increase in stroke volume correlated with the increase in estimated trans-septal gradient (=pulmonary capillary wedge pressure–right atrial pressure; r=0.67; P=0.003), suggesting relief of diastolic ventricular interaction as a contributory mechanism. Directionally similar effects were observed for the above hemodynamic parameters with 10 μg/kg/min; this was significant only for stroke volume, not for other parameters.

**Conclusions**—This first-in-human HF efficacy/safety study demonstrates an attractive profile during short-term systemic NaNO₂ infusion that may be beneficial in decompensated HF and warrants further evaluation with longer infusion regimens. (Circ Heart Fail. 2015;8:565-571. DOI: 10.1161/CIRCHEARTFAILURE.114.001716.)

**Key Words:** heart failure ■ hemodynamics ■ methemoglobinemia ■ nitric oxide ■ nitrite

Although there have been considerable advances in pharmacological and device therapies for chronic heart failure (HF) that have improved both morbidity and mortality, there has been relatively little progress in the management of decompensated HF, and the mortality of patients hospitalized with HF remains high.¹

**Clinical Perspective on p 571**

In some patients with decompensated HF, intravenous diuretics are safe and well tolerated, but in others may be associated with a marked worsening of renal function. In these circumstances, intravenous organic nitrates are commonly used. At low doses, these agents preferentially dilate capacitance vessels but, although of lesser magnitude, also dilate resistance vessels at higher doses and reduce arterial wave reflection.² They usually increase cardiac output (CO). Some patients with HF are relatively resistant to organic nitrates, and almost all patients rapidly develop tolerance during sustained infusion.³ An effective agent devoid of tolerance would therefore be attractive. Unfortunately, several novel pharmacological agents that have shown promise in early phase trials have not been successful in larger hard end-point–driven trials.⁴⁻⁵

Sodium nitrite (NaNO₂) has a vasodilator profile that is potentially attractive for the treatment of decompensated HF. In healthy subjects, NaNO₂ exhibits hypoxic augmentation of its vasodilator properties when administered intravenously or intra-arterially.

Received August 15, 2014; accepted March 22, 2015.

From the Centre for Cardiovascular Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom (J.O.M.O., S.A., J.D.W.E., R.B., M.M.); Department of Cardiothoracic Surgery, Queen Elizabeth Hospital Birmingham NHS Trust, Birmingham, United Kingdom (M.M.); R.S.B.); Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, United Kingdom (B.O.F., M.F.); and Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, United Kingdom (M.F.F.).

*Dr Omerod, S. Arif, Dr Madhani, and Dr Frenneaux contributed equally to this work.

†Exceased.

Correspondence to M.P. Frenneaux, MD, Head of Medical School, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, NR4 7TJ, United Kingdom. E-mail m.frenneaux@uea.ac.uk

© 2015 The Authors. Circulation: Heart Failure is published on behalf of the American Heart Association, Inc., by Wolters Kluwer. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Circ Heart Fail is available at http://cireheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.114.001716

Downloaded from http://cireheartfailure.ahajournals.org at UNIVERSITY EAST ANGLIA on May 21, 2015.
Table 2. The Effect of Short-Term Sodium Nitrite Infusion on Cardiac and Pulmonary Hemodynamics in Heart Failure Patients

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Group 1 (n=9)</th>
<th>Baseline</th>
<th>10 µg/kg</th>
<th>Mean Δ From</th>
<th>PValue</th>
<th>Baseline</th>
<th>50 µg/kg</th>
<th>Mean Δ From</th>
<th>PValue</th>
<th>Baseline</th>
<th>50 µg/kg</th>
<th>Mean Δ From</th>
<th>PValue</th>
<th>Δ 10 vs 50 µg</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats per minute</td>
<td></td>
<td>67±9</td>
<td>65±9</td>
<td>0.07</td>
<td>-2.5±4.3</td>
<td>79±18</td>
<td>78±18</td>
<td>0.12</td>
<td>-0.8±2.8</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAPB, mmHg</td>
<td></td>
<td>80±12</td>
<td>80±11</td>
<td>0.49</td>
<td>-0.04±7</td>
<td>78±7</td>
<td>74±6</td>
<td>0.004*</td>
<td>-3±4</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SV, ml</td>
<td></td>
<td>51.1±18.7</td>
<td>59.0±21.2</td>
<td>0.01*</td>
<td>7.9±7.9</td>
<td>51.1±20.8</td>
<td>56.1±19.6</td>
<td>0.002‡</td>
<td>9.6±8.5</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td></td>
<td>21.5±10.2</td>
<td>18.6±9.4</td>
<td>0.13</td>
<td>-2.4±5.1</td>
<td>18.7±10.2</td>
<td>17.7±10.3</td>
<td>0.28</td>
<td>-0.9±6.4</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSB, mmHg</td>
<td></td>
<td>7.5±9.0</td>
<td>13.8±12.6</td>
<td>0.14</td>
<td>4.0±8.6</td>
<td>8.8±7.2</td>
<td>11.0±7.0</td>
<td>0.002‡</td>
<td>3.0±5.7</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ea, mm Hg/mL</td>
<td></td>
<td>2.09±0.65</td>
<td>1.86±0.71</td>
<td>0.08</td>
<td>-0.23±0.4</td>
<td>1.55±0.71</td>
<td>1.60±0.53</td>
<td>0.002‡</td>
<td>-0.35±0.4</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial oxygen saturation, %</td>
<td></td>
<td>96.1±3.2</td>
<td>95.3±1.9</td>
<td>0.14</td>
<td>-0.75±1.8</td>
<td>97.29±2.50</td>
<td>96.76±2.51</td>
<td>0.19</td>
<td>-0.53±2.45</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Δ 10 vs 50 µg, changes between treatment groups from baseline. Group 1, 10 µg/kg/min (n=9); and Group 2, 50 µg/kg/min (n=17). Data expressed as mean±SD. CO indicates cardiac output measured by Fick; Ea, arterial elastance; MAPB, mean arterial blood pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SV, systemic vascular resistance; and TSB, transcapillary gradient.

*P=0.05. †Based on 7 patients because of 1 missing value. ‡P=0.001.

shown in Table 1. Hemodynamic parameters are shown in Table 2. At baseline (ie, before infusion of sodium nitrite), hemodynamic parameters were similar in group 1 and group 2, except heart rate was significantly higher in group 2 (P=0.046) and systemic vascular resistance (SVR) was significantly higher in group 2 (P=0.03).

Blood Pressure and Heart Rate Effects
As shown in Table 2, there was no statistically significant change in heart rate at either infusion rate. 10 µg/kg/min NaNO2 infusion did not significantly affect MAPB, whereas in contrast 50 µg/kg/min of NaNO2 infusion modestly but significantly decreased MAPB by a mean of 4 mmHg (P=0.004).

Nitrite Infusion Decreases Pulmonary and Systemic Vascular Resistance
As shown in Table 2, 50 µg/kg/min of NaNO2 infusion significantly decreased PVR by 29% (P=0.03), and systemic vascular resistance fell by 12% (P=0.01; Table 2). Arterial elastance fell by 18% from 1.95±0.71 to 1.60±0.53 mmHg/mL (P=0.002; Table 2). Infusion of 10 µg/kg/min NaNO2 infusion resulted in directionally similar effects, but these were not significant.

Nitrite Reduces Pulmonary Capillary Wedge Pressure and Right Atrial Pressure and Improves Cardiac Output
As shown in Table 2, in the 50 µg/kg/min group, there was a significant reduction in mean RAP by 40% and PCWP fell by 7% (nonsignificant). Consequently, estimated TSG significantly increased by a mean of 3 mmHg. CO significantly increased by 13% and SV significantly increased by 14%. 10 µg/kg/min NaNO2 infusion resulted in a significant increase in SV by 15.5%, but the increase in CO was not significant. As shown in the Figure, the change in SV during 50 µg/kg/min nitrite infusion was significantly correlated with the change in estimated TSG (r=0.67; P=0.003). Mean arterial oxygen saturation remained unchanged at either infusion rate.

Impact of Baseline SVR on SV Response to IV Nitrite
Patients receiving the higher dose infusion regimen were divided into those with SVR above versus below the mean for the group at baseline (33.17 wood units). There was no significant difference in the change in LV SV between these 2 groups (9.9±8.5 versus 5.1±4.8 mL; P=0.3).

Changes in SV in Patients With PCWP > and <15 mmHg
In 11 patients with PCWP >15 mmHg (mean 22.4±8.0 mmHg), infusion of sodium nitrite at the higher concentration increased SV by 20% from 43.22±21.5 to 51.84±23.6 mL (P=0.003), whereas in those with PCWP <15 mmHg (n=6), there was no significant change in SV (62.5±22.02 to 65.1±21.09 mL; P=0.24). Estimated TSG

Figure. Changes in estimated trans-septal gradient positively correlated with change in stroke volume (SV) in all patients infused with 50 µg/kg/min sodium nitrite.
important mechanism, the increase in SV was only observed in the group of patients with PCWP > 15 mm Hg—a cutoff that we have previously shown to identify HF patients with significant DVI.14 In this subgroup, the SV increased by 20%.16 In accordance with this concept, the reduction in RA pressure (an indirect measure of both RVEDP and pericardial pressure)17 was greater than the reduction in PCWP; hence, the estimated TSG (ie, the pressure gradient across the interventricular septum at end diastole)—a measure of the true filling pressure of the LV at end diastole18—was increased by sodium nitrite. Furthermore, the increase in SV was significantly correlated with the change in estimated TSG. We cannot exclude a significant direct myocardial effect of nitrite as a contributory mechanism. In the vertebrate, heart nitrite positively modulated the Frank-Starling response via a NO-dependent mechanism.19 In contrast, another study reported negative inotropic effects via a NO/cGMP-dependent mechanism in the Langendorff rat heart.20 In a recent study, chronic oral inorganic nitrite supplementation ameliorated the development of HF in a marine thoracic aortic constriction model in association with an upregulation of cytoprotective pathways.21

Intravenous sodium nitroprusside is sometimes used in the treatment of acute decompensated HF. Fifer et al reported the effects of intravenous sodium nitroprusside in patients with severe CHF.22 Cardiac index increased substantially (by 25%), but systemic vascular resistance also fell substantially (by 25%) and MABP fell by 13 mm Hg. The reduction in mean PCWP (by 14 mm Hg) was substantially greater than that of RA pressure (by 4 mm Hg), that is, mean TSG fell substantially, which suggests that relief of DVI was not an important mechanism of the increase in CO.22

Organic nitrates are more commonly used in the treatment of decompensated HF. Indeed intravenous isosorbide dinitrate has been shown to be superior to either intravenous furosemide23 or positive airways pressure24 in the management of patients with acute pulmonary edema. These agents dilate capacitance and resistance vessels.25 At lower doses, the vasodilator effects of glyceryl trinitrate (GTN) are predominantly on capacitance vessels, but at higher doses, effects on vascular resistance are increasingly observed.26 Robinovitz et al reported the hemodynamic effects of intravenous isosorbide dinitrate in patients with decompensated HF. CO increased similarly to our study (by 17%), but the reduction in systemic vascular resistance (35%) and the fall in mean arterial pressure (10 mm Hg) were substantially more than we observed with sodium nitrite. The increase in CO was substantially greater in those patients with high resting SVR, suggesting that afterload reduction may have been an important contributor to the increase in CO.27 Armstrong et al reported the effects of GTN infusion in patients with severe CHF; CO increased by 20%. Systemic vascular resistance fell by 21% and MABP by 7 mm Hg. In contrast to our findings with nitrite, the fall in PCWP (by 8 mm Hg) was greater than that of RAP (by 5 mm Hg), indicating that overall the estimated TSG fell with this therapy rather than the increase we observed with sodium nitrite infusion.28 However, Dupuis and colleagues showed that during sustained (72 hour) infusion of GTN, SV increased in a subgroup of patients in whom LV end diastolic volume increased and fell in those in whom LV end diastolic volume fell during GTN infusion.29 These data suggest that GTN may relieve DVI in some patients with decompensated HF, but this effect seems less marked than we have observed in this study with intravenous sodium nitrite.

The reduction in SVR (by 12%) observed in the present study was substantially less than that observed in the above studies with either sodium nitroprusside (25%)30 or isosorbide dinitrate (35%), suggesting that this may play a less important role in the increase in CO with sodium nitroprusside. Furthermore, in our study, there was no significant difference in the change in SV induced by sodium nitrite between those with higher versus lower systemic vascular resistance before infusion. However, left ventricular afterload has a pulsatile component, as well as a static component, and changes in SVR do not therefore completely describe effects on LV afterload. GTN has previously been shown to reduce wave reflection.31 In the present study, the reduction in arterial elastance (a measure of LV afterload encompassing both static and pulsatile components) was 18%.

In summary, our data are consistent with an effect of sodium nitrite on SV largely mediated via relief of DVI because of relatively selective and potent dilation of capacitance vessels and pulmonary vasculature.32 Based on changes in estimated TSG, this mechanism may be less marked with organic nitrates and sodium nitroprusside, and changes in LV afterload may be relatively more important for these drugs than with sodium nitrite.

Nitrite has further characteristics that may make it a potentially attractive agent for the treatment of decompensated HF and therefore worthy of further investigation based on the findings of this short-term proof of concept/safety study. Some patients with HF exhibit nitrate (and NO) resistance, potentially because of increased oxidative stress.32-34 In contrast, during intra-arterial infusion of NaNO2, we observed an enhanced response in patients with HF versus controls.35 Furthermore, organic nitrate therapy is subject to the rapid development of tolerance. In primates, tolerance was not observed with sodium nitrite.36

Study Limitations
Although nitrite infusion resulted in clear increases in plasma nitrite concentrations at both infusion rates, only the one associated with a concomitant elevation in circulating RXNO levels increased CO. This suggests that, in this setting, the beneficial hemodynamic effects of nitrite are associated either with the involvement of a post-translational modification of cardiac tissue proteins37 or some form of NO delivery from a circulating plasma storage form of NO (perhaps nitrosated albumin)38 to heart and vasculature. Although intriguing, establishing the mechanistic basis for this observation was well beyond the scope of the present study.

Clinical Implications: Future Studies
This is the first-in-man proof of concept/safety study demonstrating a potentially favorable hemodynamic response to short-term NaNO2 infusion in patients with severe chronic HF. Further studies are warranted to assess longer term safety and hemodynamic efficacy, and if these are confirmed, this may warrant a randomized controlled trial of sodium nitrite
CLINICAL PERSPECTIVE

Nitrite exhibits hypoxia dependent vasodilator properties. We therefore hypothesized that by preferential dilation of venous capacitance vessels and pulmonary arterioles (low ambient oxygen) with lesser effects on systemic arterioles (higher ambient oxygen tension), sodium nitrite would increase stroke volume in patients with heart failure by relief of pericardial constraint and diastolic ventricular interaction. We therefore performed a short-term (5 minute) proof of concept/safety study in 25 patients with severe but stable chronic heart failure who were undergoing precardiac transplant assessment. As hypothesized, there was a marked reduction in pulmonary vascular resistance and right atrial pressure with a lesser fall in pulmonary capillary wedge pressure and a modest reduction in systemic vascular resistance. Estimated trans-septal gradient (i.e., pulmonary capillary wedge pressure – right atrial pressure) therefore increased, and this was correlated with the observed increase in stroke volume consistent with relief of diastolic ventricular interaction as an important mechanism. This is a potentially attractive hemodynamic profile in decompensated heart failure, but further studies are required to assess the safety and efficacy of longer-term infusion.