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

Ormerod et al: Sodium Nitrite in Heart Failure

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Abstract

**Background**—Nitrite exhibits hypoxia-dependent vasodilator properties, selectively dilating capacitance vessels in healthy subjects. Unlike organic nitrates it appears 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 while 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**—25 patients with severe chronic HF were recruited. Eight received short term (5 minutes) intravenous NaNO₂ at 10 mcg/kg/min, and seventeen received 50 mcg/kg/min with measurement of cardiac hemodynamics. During infusion of 50mcg/kg/min left ventricular stroke volume increased (from 43.22±21.5 to 51.84±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 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 (TSG = pulmonary capillary wedge pressure (PCWP) – right atrial pressure (RAP)) (r=0.67; p=0.003) suggesting relief of diastolic ventricular interaction (DVI) as a contributory mechanism. Directionally similar effects were observed for the above hemodynamic parameters with 10mcg/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.

**Key Words:** nitrite, nitric oxide, heart failure, hemodynamics, methemoglobinemia
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 hospitalised with HF remains high.¹

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. 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 endpoint 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, presumably because it is reduced under hypoxic conditions to nitric oxide (NO).⁶-⁸ We previously demonstrated that in healthy subjects breathing room air, intra-arterial NaNO₂ only modestly dilated forearm resistance vessels while markedly dilating forearm capacitance vessels.⁶ When these subjects breathed a hypoxic gas mixture the forearm resistance vessel dilation was augmented.⁶ Furthermore NaNO₂ reduced pulmonary vascular resistance in experimental models of pulmonary hypertension⁹ and systemic nitrite infusion substantially ameliorated
the pulmonary vasoconstriction associated with systemic hypoxaemia in healthy volunteers.\textsuperscript{10} Previous studies have suggested that nitrite therapy may not be subject to the development of tolerance.\textsuperscript{7, 11}

Based on these observations we hypothesized that intravenous NaNO\textsubscript{2} infusion may substantially increase venous capacitance and reduce pulmonary vascular resistance in patients with severe HF, leading to an increase in cardiac output by relieving external constraint to left ventricular filling from the pericardium (pericardial constraint) and right ventricle (diastolic ventricular interaction), whilst only modestly reducing systemic vascular resistance and therefore resulting in only a minor fall in blood pressure. We therefore undertook a proof-of-concept study to evaluate the hemodynamic effects of systemic short-term NaNO\textsubscript{2} infusion in patients with severe chronic HF. We chose a brief (5 minute) infusion for safety reasons because this was a first-in-man use of intravenous nitrite in HF.

**Methods**

Twenty-five patients with severe chronic HF who were undergoing right heart catheterization as part of their heart transplant assessment protocol were recruited to the study. The study conformed to the Declaration of Helsinki and was approved by the University of Birmingham (ERN10-0247) and Local Research Ethics Committee (08/H1207/67). Each patient gave written informed consent after satisfying the inclusion criteria (aged 18 years or over, admission to hospital for pulmonary artery catheterisation, under the transplant protocol) and exclusion criteria (pre-existing inotrope therapy, recent (3 months) myocardial infarction, G6PD deficiency and women of child-bearing potential or nursing mothers). The patients had a diagnosis of HF with reduced LV ejection fraction (<40\%) of various aetiologies and
all patients were on optimal tolerated standard HF therapy (Table 1). Baseline characteristics of the patients enrolled in the study are listed in Table 1.

**Right heart catheterisation**

Patients were randomized (on a 1:2 basis; Table 2) to receive either 10 mcg/kg/min (group 1; n=8) or 50 mcg/kg/min (group 2; n=17) of NaNO$_2$ (Martindale Pharmaceuticals, UK). The patients were then placed in a supine position to allow the insertion of a Swanz-Ganz catheter via a sheath into the right internal jugular vein under local anaesthesia with positioning confirmed by fluoroscopy and pressure waveform. After 15 minutes of stabilisation at baseline, the following pressures were measured at end-expiration: pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), and right atrial pressure (RAP). The trans-septal pressure gradient (TSG) was estimated as PCWP-RAP. Cardiac output was measured using the Fick technique from the mixed venous and arterial oxygen saturations and from predicted oxygen consumption. Systemic vascular resistance (Wood units) was calculated as (mean arterial pressure – right atrial pressure/ cardiac output).

Arterial elastance (a lumped measure of pulsatile and static LV afterload) was calculated as (0.9 x systolic arterial pressure/ stroke volume).$^{12}$ Left ventricular stroke work was calculated as stroke volume x mean arterial blood pressure. Arterial oxygen saturation was measured by pulse oximetry. The measurements were repeated 5 minutes later to ensure stability. NaNO$_2$ was then infused intravenously over 5 minutes and the above hemodynamic measurements were repeated at the end of the infusion. Blood pressure, electrocardiogram and oxygen saturation were monitored continuously.
Blood samples

Venous blood samples were taken at baseline and following infusion of NaNO₂ for methemoglobin (metHb), plasma nitrite/nitrate and total nitroso species (RXNO) measurements. Blood for determination of venous plasma nitrite, nitrate and RXNO concentrations were collected into EDTA tubes and immediately centrifuged (800xg for 10 minutes at 4°C). Samples were stored at -80°C prior to assay. Plasma nitrite, nitrate and RXNO concentrations were determined, following addition of N-ethylmaleimide (10mM final concentrations) during the thawing process, via HPLC and chemiluminescence as previously described.¹³

Statistical analysis

Data are presented as mean ± SD. Hemodynamic comparisons were performed by paired one-tailed Student t-test. Changes from baseline between treatment groups were performed by unpaired one-tailed Student t-test; a p-value of <0.05 was taken to indicate statistical significance. Changes in trans-septal gradient (i.e. LVEDP-RVEDP) during NaNO₂ infusion were estimated as change in PCWP – RAP.¹⁴ Statistical analysis was undertaken using Prism software (version 5.0, GraphPad Software, CA).

Results

Demographics

The demographics for the entire cohort and the groups receiving 10 mcg/kg/min (group 1) and 50 mcg/kg/min (group 2) are shown in Table 1. Hemodynamic parameters are shown in Table 2. At baseline (i.e. prior to infusion of sodium nitrite) hemodynamic parameters were similar in group 1 and group 2, except HR was significantly higher in group 2 (p=0.046) and 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 (HR) at either infusion rate. 10 mcg/kg/min NaNO₂ infusion did not significantly affect MABP, while in contrast 50 mcg/kg/min of NaNO₂ infusion modestly but significantly decreased MABP by a mean of 4mmHg (p<0.004).

**Nitrite infusion decreases pulmonary and systemic vascular resistance**

As shown in Table 2, 50 mcg/kg/min of NaNO₂ infusion significantly decreased pulmonary vascular resistance (PVR) by 29% (p=0.03), and systemic vascular resistance (SVR) 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 mcg/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 mcg/kg/min group, there was a significant reduction in mean RAP by 40%; and PCWP fell by 7% (non-significant). Consequently, estimated trans-septal gradient (TSG) significantly increased by a mean of 3mmHg. Cardiac output (CO) significantly increased by 13% and stroke volume significantly increased by 14%. 10 mcg/kg/min NaNO₂ infusion resulted in a significant increase in stroke volume by 15.5%, but the increase in cardiac output was not significant. As shown in the Figure the change in SV during 50 mcg/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 i.v nitrite

Patients receiving the higher dose infusion regime were divided into those with SVR above vs below the mean for the group at baseline (33.17 wood units). There was no significant difference in the change in LV stroke volume between these two groups (9.9 ± 8.5 vs 5.1 ± 8.8 mls; p = 0.3).

Changes in SV in patients with PCWP > and < 15mmHg

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 increased by 3.6 mmHg in the high PCWP subgroup (from 11.9±6.8 to 15.5±4.7 mmHg; p=0.005) and by 2 mmHg in the lower PCWP subgroup (from 3.2±3.4 to 5.2±5.3; p=0.13).

Short-term intravenous nitrite infusion increases circulating NO metabolites

As shown in Table 3, 10mcg/kg/min NaNO₂ infusion did not significantly alter plasma RXNO or plasma nitrate concentrations but significantly increased plasma nitrite. 50mcg/kg/min NaNO₂ infusion significantly increased all measured NO metabolites from baseline.

Methemoglobinemia increased within safe levels

As shown in Table 3 a modest dose-dependent increase in metHb was observed following 10mcg/kg/min and 50mcg/kg/min of sodium nitrite.
Discussion

Herein, we demonstrate for the first time the short-term hemodynamic effects of intravenous NaNO₂ in patients with severe but stable chronic HF. As hypothesised, effects were favourable, with an increase in LV stroke volume and cardiac output with only a minor reduction in blood pressure. As anticipated there was a substantial reduction in PVR but only a modest reduction in SVR. The hemodynamic effects were statistically significant at 50mcg/kg/min. At 10 mcg/kg/min, directionally similar effects were observed but apart from a significant increase in SV these were non-significant. There was no significant difference in the magnitude of the hemodynamic effects seen with 10 vs 50 mcg/kg/min, but given the smaller sample size of the former group caution should be exercised in drawing conclusions about the dose-response relationship.

The patients studied had severe but stable chronic HF and were undergoing assessment as candidates for cardiac transplantation. We chose a brief (5 minute) infusion regime as a proof of concept for safety reasons because this was a first-in-man study of systemic nitrite infusion in chronic HF. The effects were observed at the 50mcg/kg/min infusion rate and although directionally similar were not significant at the 10mcg/kg/min infusion rate, although the latter may, partly be due to a smaller sample size in the lower dose group. Whilst only modest increases in methemoglobin levels were observed with either dose, based on studies in healthy volunteers sustained infusion of 50mcg/kg/min would be expected to cause marked (and potentially dangerous) methemoglobinemia. However, we have subsequently undertaken pilot studies (data not shown) in patients with chronic HF (without hemodynamic assessment) and have demonstrated that sustained infusion of 10mcg/kg/min caused a progressive increase in plasma nitrite and RXNO such that by 3 hours these levels were almost as high as we observed in the present study with 50mcg/kg/min infused over 5
minutes, without inducing dangerous methemoglobinemia and without inducing significant hypotension. In a study in healthy volunteers Pluta and colleagues reported that sustained infusion (several hours) of doses of approximately 5mcg/kg/min sodium nitrite resulted in significant hypotension and methemoglobin >5%. Further studies are therefore warranted to evaluate whether sustained infusion of lower doses of NaNO2 would have similar favourable hemodynamic effects to those observed with short-term infusion of 50mcg/kg/min without inducing methemoglobinemia or resulting in hypotension. Whereas patients with decompensated HF but without frank pulmonary oedema and associated arterial hypoxaemia may be expected to exhibit preferential dilation of capacitance vessels and pulmonary vasculature, in the latter setting substantial resistance vessel dilation might be anticipated with an attendant fall in blood pressure. Preferential vasodilation of pulmonary vessels to underventilated alveoli has the potential to worsen ventilation-perfusion matching, however we observed no reduction in arterial oxygen saturations in this study despite a substantial fall in pulmonary vascular resistance.

The increase in stroke volume in the face of a reduced pulmonary capillary wedge pressure represents an ‘apparent’ descending limb of the Starling curve. This is because in severe chronic HF, despite high left ventricular end diastolic pressures, LV filling is impeded by external constraint from the stretched pericardium (pericardial constraint) and via the interventricular septum, from the right ventricle (diastolic ventricular interaction – DVI), usually in the context of pulmonary hypertension. By preferentially dilating the systemic capacitance and pulmonary resistance vessels, nitrite may be expected to reduce RV volume and hence pericardial stretch, thereby augmenting LV filling and SV. Consistent with relief of DVI as an important mechanism, the increase in stroke volume was only observed in the group of patients with PCWP > 15mmHg – a cutoff that we have previously shown to
identify HF patients with significant DVI. In this subgroup the stroke volume increased by 20%. In accordance with this concept, the reduction in RA pressure (an indirect measure of both RVEDP and pericardial pressure) was greater than the reduction in PCWP, hence the estimated trans-septal gradient – (i.e. the pressure gradient across the interventricular septum at end diastole) a measure of the true filling pressure of the LV at end diastole - was increased by sodium nitrite. Furthermore, the increase in stroke volume was significantly correlated with the change in estimated trans-septal gradient. 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. In contrast, another study reported negative inotropic effects via a NO/cGMP dependent mechanism in the Langendorff rat heart. In a recent study, chronic oral inorganic nitrite supplementation ameliorated the development of HF in a murine thoracic aortic constriction model in association with an up-regulation of cytoprotective pathways.

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. Cardiac index increased substantially (by 25%) but systemic vascular resistance also fell substantially (by 25%) and mean arterial blood pressure fell by 13mmHg. The reduction in mean PCWP (by 14mmHg) was substantially greater than that of RA pressure (by 4mmHg), i.e. mean trans-septal gradient fell substantially, which suggests that relief of DVI was not an important mechanism of the increase in cardiac output.

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 furosemide or positive airways pressure in the management of patients with acute
pulmonary oedema. These agents dilate capacitance and resistance vessels.25 At lower doses the vasodilator effects of GTN are predominantly on capacitance vessels, but at higher doses effects on vascular resistance are increasingly observed.26 Rabinowitz et al reported the hemodynamic effects of intravenous isosorbide dinitrate in patients with decompensated HF. Cardiac output increased similarly to our study (by 17%) but the reduction in systemic vascular resistance (35%) and the fall in mean arterial pressure (10mmHg) were substantially more than we observed with sodium nitrite. The increase in cardiac output was substantially greater in those patients with high resting SVR suggesting that afterload reduction may have been an important contributor to the increase in cardiac output.27 Armstrong et al reported the effects of GTN infusion in patients with severe CHF. Cardiac output increased by approximately 20%. Systemic vascular resistance fell by approximately 21% and mean arterial blood pressure by 7mmHg. In contrast to our findings with nitrite, the fall in PCWP (by 8mmHg) was greater than that of right atrial pressure (by 5mmHg) indicating that overall the estimated trans-septal gradient 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, stroke volume 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 appears 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%)22 or Isosorbide dinitrate (35%)27 suggesting that this may play a less important role in the increase in cardiac output with sodium nitroprusside. Furthermore in our study there was no significant difference in the
change in stroke volume induced by sodium nitrite between those with higher vs lower systemic vascular resistance prior to 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. 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 stroke volume largely mediated via relief of DVI due to relatively selective and potent dilation of capacitance vessels and pulmonary vasculature. Based on changes in estimated trans-septal gradient 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 due to increased oxidative stress. In contrast, during intra-arterial infusion of NaNO₂ we observed an enhanced response in patients with HF vs controls. Furthermore, organic nitrate therapy is subject to the rapid development of tolerance. In primates tolerance was not observed with sodium nitrite.

**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 nitroso
species (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 proteins\textsuperscript{33} or some form of “NO delivery” from a circulating plasma storage form of NO (perhaps nitrosated albumin)\textsuperscript{13} to heart and vasculature. While 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 favourable hemodynamic response to short term NaNO\textsubscript{2} 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 randomised controlled trial of sodium nitrite vs current therapy in decompensated HF focussing on “hard” end points. Sodium nitrite could be administered either intravenously in such studies or perhaps in nebulised form,\textsuperscript{34} the latter may be particularly attractive in decompensated HF. Unfortunately several therapies shown to have attractive acute hemodynamic profiles have failed in phase 3 trials in decompensated HF.\textsuperscript{35} However a notable exception was a recent study of Serelaxin in patients with acute HF with dyspnoea, in which a significant reduction in dyspnoea score and 6 month mortality was reported.\textsuperscript{36}

**Acknowledgements**

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Disclosures

None.

References


Table 1. Demographics and cardiovascular disease profile of the heart failure patients

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Entire Cohort (25)</th>
<th>Group 1 (n=8) 10µg/kg/min nitrite</th>
<th>Group 2 (n=17) 50µg/kg/min nitrite</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>48±13</td>
<td>50±12</td>
<td>47±14</td>
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<tr>
<td>Gender, m</td>
<td>18</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>26.6±3.84</td>
<td>26.1±4.02</td>
<td>26.7±3.87</td>
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<td><strong>Aetiology of heart failure</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Dilated cardiomyopathy</td>
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<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>6</td>
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<td>4</td>
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<tr>
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<tr>
<td>Other</td>
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<td>3</td>
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<td><strong>Medication</strong></td>
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<tr>
<td>ACEI/AT1 receptor blocker</td>
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<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>17</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>23</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>14</td>
<td>2</td>
<td>12</td>
</tr>
</tbody>
</table>

Entire cohort (group 1 and 2; n=25). Group 1 - 10µg/kg/min nitrite heart failure patient group (n=8) and Group 2 - 50µg/kg/min nitrite heart failure patient group (n=17). All continuous variables are expressed as mean ± SD.
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=8)</th>
<th>Group 2 (n=17)</th>
<th>Δ 10 vs 50 mcg</th>
<th>P value</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>10 mcg/kg</td>
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<td></td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67±9</td>
<td>65±9</td>
<td>0.07</td>
<td>-2.5±4.3</td>
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<tr>
<td>MABP (mmHg)</td>
<td>80±12</td>
<td>80±11</td>
<td>0.49</td>
<td>-0.04±7</td>
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<tr>
<td>SVR (Wood units)</td>
<td>25.6±7.3</td>
<td>23.7±8.9</td>
<td>0.097</td>
<td>-1.92±3.8</td>
</tr>
<tr>
<td>PVR (Wood units)</td>
<td>2.3±1.3</td>
<td>1.8±0.7†</td>
<td>0.28</td>
<td>-0.3±1.3†</td>
</tr>
<tr>
<td>RAP (mmHg)</td>
<td>14.0±8.6</td>
<td>9.5±5.8†</td>
<td>0.31</td>
<td>-2.8±10.1†</td>
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<tr>
<td>CO (L/min)</td>
<td>3.4±1.2</td>
<td>3.7±1.1</td>
<td>0.08</td>
<td>0.4±0.7</td>
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<tr>
<td>SV (ml)</td>
<td>51.1±18.7</td>
<td>59.0±21.2</td>
<td>0.01*</td>
<td>7.9±7.9</td>
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<td>PCWP (mmHg)</td>
<td>21.5±10.2</td>
<td>18.6±9.4†</td>
<td>0.13</td>
<td>-2.4±5.1†</td>
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<tr>
<td>TSG (mmHg)</td>
<td>7.5±9.0</td>
<td>13.8±12.8†</td>
<td>0.14</td>
<td>4.8±8.6†</td>
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<tr>
<td>Ea (mmHg/ml)</td>
<td>2.09±0.66</td>
<td>1.86±0.71</td>
<td>0.08</td>
<td>-0.23±0.4</td>
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<tr>
<td>Arterial oxygen Saturation (%)</td>
<td>96.13±2.42</td>
<td>95.38±1.69</td>
<td>0.14</td>
<td>-0.75±1.83</td>
</tr>
</tbody>
</table>

MABP = mean arterial blood pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; RAP = right atrial pressure; CO = cardiac output measured by FICK; PCWP = pulmonary capillary wedge pressure, TSG = transeptal gradient; Ea = arterial elastance. Δ 10 vs 50 mcg = changes between treatment groups from baseline. Group 1 – 10 mcg/kg/min (n=8) and Group 2 – 50 mcg/kg/min (n=17). † based on 7 patients because of 1 missing value. *P < 0.05; ** P<0.001. Data expressed as mean ± SD.
Table 3. Plasma concentrations of nitrite, nitrate and total nitroso species RXNO and methemoglobin (MetHb) content of venous blood of heart failure patients at baseline and post sodium nitrite infusion

<table>
<thead>
<tr>
<th>Blood analysis</th>
<th>Group 1 (n=8)</th>
<th>Group 2 (n=17)</th>
<th>Group 2 (n=17)</th>
<th>P value</th>
<th>Mean Δ from baseline</th>
<th>Mean Δ from baseline</th>
<th>Δ 10 vs 50 mcg</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>10 mcg/kg</td>
<td>P value</td>
<td></td>
<td>Mean Δ from baseline</td>
<td>Mean Δ from baseline</td>
<td></td>
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<tr>
<td>Nitrite (µM)</td>
<td>1.29±0.52</td>
<td>4.38±2.16</td>
<td>0.005**</td>
<td>3.09±2.25</td>
<td>1.64±3.0</td>
<td>16.13±10.9†</td>
<td>0.0001***</td>
<td>14.29±8.97†</td>
</tr>
<tr>
<td>Nitrate (µM)</td>
<td>26.87±10.5</td>
<td>27.61±9.76</td>
<td>0.17</td>
<td>0.75±1.92</td>
<td>21.55±11.79†</td>
<td>35.51±14.0§</td>
<td>0.0001***</td>
<td>15.58±6.19§</td>
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<tr>
<td>Nitroso species (RXNO; nM)</td>
<td>13.76±8.0</td>
<td>10.93±2.96</td>
<td>0.14</td>
<td>-2.83±5.76</td>
<td>12.92±4.83</td>
<td>40.27±21.65†</td>
<td>0.0001***</td>
<td>27.86±19.27†</td>
</tr>
<tr>
<td>MetHb (%)</td>
<td>0.44±0.13</td>
<td>0.61±0.17</td>
<td>0.008**</td>
<td>0.18±0.16</td>
<td>0.33±0.12‡</td>
<td>1.02±0.54‡</td>
<td>0.0001***</td>
<td>0.68±0.57‡</td>
</tr>
</tbody>
</table>

Δ 10 vs 50 mcg = changes between treatment groups from baseline. Group 1 – 10 mcg/kg/min (n= 8) and Group 2 – 50 mcg/kg/min (n=17). † based on 16 patients because of 1 missing value. ‡ based on 15 patients. *P<0.05, ** P< 0.001 and *** P<0.0001. Data expressed as mean ± SD.
**Figure Legend**

**Figure.** Changes in estimated trans-septal gradient positively correlated with change in stroke volume (SV) in all patients infused with 50mcg/kg/min sodium nitrite.
Short-Term Intravenous Sodium Nitrite Infusion Improves Cardiac and Pulmonary Hemodynamics in Heart Failure Patients

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