Effects of Exogenous and Endogenous Natriuretic Peptides on Forearm Vascular Function in Chronic Heart Failure

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Objective—Natriuretic peptides (NPs) reduce central venous pressure in patients with chronic heart failure (cHF) despite attenuation of arterial, renal, and humoral effects. This suggests a preserved venodilator response. This study had 4 aims: to compare the venodilator effects of human NPs in patients with cHF; to assess the contribution of basal ANP and BNP levels to regulation of forearm vascular volume (FVV); to test the hypothesis that venous ANP responsiveness is preserved in cHF; and to assess the involvement of endothelial nitric oxide-synthase (eNOS) in NP-induced vascular effects.

Methods and Results—Venous and arterial forearm vascular responses to incremental intra-arterial doses of ANP, Urodilatin, BNP, CNP, or the ANP receptor antagonist A71915 were studied in 53 patients and 11 controls. ANP receptor antagonism reduced FVV by 4.4% ± 1.2% (P < 0.05). The forearm blood flow (FBF) response to ANP was significantly blunted in patients versus controls (P < 0.01), whereas FVV increased similarly in both groups (maximum 14.7% and 13.4%, both P < 0.001). The eNOS blockade reduced ANP-induced FBF changes in controls but not in patients (P < 0.05), whereas similar reductions in FVV changes were seen in groups (both P < 0.001).

Conclusions—In cHF venous, but not arterial, ANP responsiveness is preserved. Arterial endothelial dysfunction may contribute to NP resistance. (Arterioscler Thromb Vasc Biol. 2004;24:911-917.)

Key Words: veins □ capacitance □ receptor antagonism □ A71915

Animal and human studies have suggested a variable reduction in hormonal, renal, and resistance vessel responsiveness to natriuretic peptides (NPs) in heart failure (HF).1–7 Despite minimal effects on plasma volume and resistance vessel tone, infusion of NPs in patients with HF has consistently been shown to reduce central venous pressure (CVP).8,9 This raises the possibility that the venodilator effects of NPs may be preserved in HF.

Although earlier data suggested that NPs exert their effects solely via a nonendothelium-dependent, particulate guanylate cyclase (GC) pathway,10 recent evidence suggests that the vaso-relaxant effects may, at least in part, be mediated via an endothelium-dependent pathway involving nitric oxide (NO) and soluble GC.11,12 Endothelial dysfunction may therefore theoretically contribute to the phenomenon of NP hyporesponsiveness (NP resistance). We previously demonstrated preserved venous endothelial function in patients with chronic HF (cHF) despite the presence of marked arterial endothelial dysfunction.13 We hypothesized that cHF patients may have preserved venous ANP responsiveness despite diminished resistance-vessel responsiveness and that this may be explained by preservation of venous endothelium-dependent NO release.

The current study had 4 aims: to compare the effects of the currently known human NPs (ANP99–126, ANP95–126 [Urodilatin], BNP, CNP) on the forearm capacitance vasculature in 53 cHF patients using optimal therapy; to examine the contribution of basal NP (ANP, BNP) plasma levels to regulation of regional vascular volume (VV) and venous tone by intra-arterial infusion of the NPr1-selective ANP-receptor blocker A71915; to test the hypothesis that venous responsiveness to exogenous ANP was preserved but resistance-vessel responsiveness attenuated in cHF patients versus controls; and to assess the contribution of NO to NP-induced changes in capacitance and resistance vessels by co-infusion with the endothelial NO-synthase inhibitor, N⁶-monomethyl-L-arginine (LNMMA).

Methods

Subjects
Fifty-three consecutive patients with cHF were recruited from the Heart Failure Clinic at the University Hospital of Wales and enrolled...
to receive intra-arterial ANP, BNP, CNP, Urodilatin, or A71915. All patients satisfied the European Society of Cardiology criteria for the diagnosis of cHF and had impaired left ventricular systolic function (ejection fraction [EF]<45%) as assessed by radionuclide ventriculography. Patients with hypertensive heart disease were excluded. All were using diuretics, a maximally tolerated dose of an ACE inhibitor, or an AT1-antagonist and, unless contraindicated or previously not tolerated, using maximally tolerated doses of beta-blockers. Their symptomatic status had remained unchanged on stable medical therapy for at least 2 months. Long-acting nitrates (n=5) were stopped 24 hours before the study and all medications were withheld on the morning of the study. Eleven healthy volunteers with no history of or evidence for cardiovascular disease or other cardiovascular risk factors were also studied as a control group. None was using any medication. All had normal clinical examination, ECGs, and ventricular function (EF) as assessed by radionuclide ventriculography. Volunteer and patient characteristics of each drug.

Assessment of Arterial Resistance-Vessel Effects
The forearm resistance vasculature was assessed using conventional venous occlusion plethysmography (VOP) as described elsewhere. We interpreted the forearm flow changes to have been caused by changes in VV and changes in venous capacitance (venous tone) or compliance.

Assessment of Venous Function
Changes in forearm vascular volume (FVV), compliance, and venous tone were assessed by radionuclide plethysmography, as described previously. We interpreted changes in FVV to have been caused by changes in VV and changes in venous capacitance (venous tone) or compliance.

Statistics
Continuous data are expressed as mean±SEM. The baseline characteristics of the cHF groups (ANP, BNP, CNP, Urodilatin) were

Protocol
All studies commenced between 8:30 and 9:30 AM and lasted between 2.5 and 3.5 hours. Forearm volume (FV) was assessed by water displacement. Antecubital veins of both arms were cannulated with 18-gauge cannulae and baseline blood sampling was performed. After red cell labeling, a 27-gauge unmounted steel needle connected to an epidural catheter and sealed with dental wax was inserted into the brachial artery of the nondominant arm under sterile conditions. Each arm was then positioned on the face of a gamma camera. Thirty minutes after infusion of saline was commenced, FBF was assessed. This was followed-up by recording of 2 baseline venous pressure–volume relations (PVR). Thereafter, incremental NP (ANP*, BNP*, CNP*: 0.05 µg/min, 0.5 µg/min, 1.0 µg/min, respectively; *Climaf, Lüfflingen/Switzerland, Urodilatin Cardiopep, Hannover/Germany; or A71915* 0.5 µg/min and 1 µg/min in 7 subjects and 20 µg/min in 4 further subjects) infusions were commenced at a volume infusion rate of 1 mL/min. After a 5-minute run-in period (10 minutes for A71915), FBF was assessed, followed by a 2-minute gap and measurement of 1 PVR. This was repeated during co-infusion of NP (1 µg/mL) plus LNMMA (12 mg/mL) after a 15-minute run-in period.

Plasma ANP Levels and cGMP Spillover
Venous-effluent blood samples were taken from the infused arm at the end of each infusion period for assessment of plasma NP and cGMP. NP and cGMP measurements were performed by blinded operators using standard competitive radioimmunoassay (Peninsula Laboratories, Bachem Ltd, UK) and enzyme immunoassay kits (Cayman Chemical), respectively. In both ANP groups, the difference between plasma cGMP concentration at the baseline and after the maximum dose of ANP was multiplied by the increase in FBF from the baseline level induced by the corresponding maximum dose, and the resulting values were taken as representative of the change in the amount of forearm cGMP spillover.

TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>CHF Patients</th>
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<tbody>
<tr>
<td></td>
<td>ANP</td>
<td>ANP</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>57 (34–69)</td>
<td>63 (42–79)</td>
</tr>
<tr>
<td>Sex, M/F, n</td>
<td>10/1</td>
<td>18/0</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.3±0.1</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>Cause, (H/D/DCM), n</td>
<td>12/6</td>
<td>7/1</td>
</tr>
<tr>
<td>Smoking history, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.1±1.2*</td>
<td>29.2±0.7</td>
</tr>
<tr>
<td>Forearm volume, mL</td>
<td>1709±77</td>
<td>1694±53</td>
</tr>
<tr>
<td>FBF, mL/100 mL FV</td>
<td>2.14±0.37</td>
<td>2.18±0.18</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>50±1†</td>
<td>29±3</td>
</tr>
<tr>
<td>BP systolic, mm Hg</td>
<td>119±4</td>
<td>110±4</td>
</tr>
<tr>
<td>BP diastolic, mm Hg</td>
<td>64±3</td>
<td>65±3</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>65±4</td>
<td>66±5</td>
</tr>
<tr>
<td>Diuretic/Spironolactone</td>
<td>18/5</td>
<td>8/2</td>
</tr>
<tr>
<td>ACE/AT2</td>
<td>17/1</td>
<td>8/0</td>
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<tr>
<td>β-Blocker</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean±SEM. *P<0.01, †P<0.001, comparison between both ANP groups (unpaired t test).
compared using χ² tests and 1-way analysis of variance (ANOVA) for categorical variables and continuous data, respectively. Baseline characteristics between both ANP groups were compared using the unpaired t test. Changes in FBF and FVV results are expressed as mean values with 95% CI. The effects of NP on FBF and FVV (within-group comparisons) were assessed by two-way ANOVA with post-hoc comparison to baseline. Between-group comparisons for cHF were performed using repeated-measures ANOVA. The comparison of the ANP dose–response curves (Figure A and B) between cHF patients and controls was performed using the trapezoid rule, as is conventional when presenting FBF data. Correlation between baseline plasma ANP levels and venous responsiveness was assessed by Spearman rank correlation; P<0.05 was considered statistically significant. To allow presentation of grouped data, results are presented as percentages.

**Results**

**Subject Characteristics**

The patient groups were well matched, without any significant differences in their baseline characteristics, including humoral, urinary, and hemodynamic parameters. The ANP control group had a significantly higher EF and lower body mass index than the ANP cHF group. These data are summarized in Tables 1 and 2.

**TABLE 2. Humoral, Urinary, and Hemodynamic Parameters at Baseline and End of Study**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>CHF Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ANP</td>
<td>ANP</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na⁺, mmol/L</td>
<td>139±0.5</td>
<td>139.3±0.6</td>
</tr>
<tr>
<td>Urinary Na⁺, mmol/L</td>
<td>77±14</td>
<td>59±13</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>88±4</td>
<td>118±7</td>
</tr>
<tr>
<td>Serum urea, mmol/L</td>
<td>6.3±0.5</td>
<td>8.8±1.2</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>44.3±0.5</td>
<td>43.9±0.7</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.2±0.3</td>
<td>14.4±0.3</td>
</tr>
<tr>
<td>Hct</td>
<td>0.41±0.01</td>
<td>0.42±0.01</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>65±7</td>
<td>66±8</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>83±3</td>
<td>80±3</td>
</tr>
<tr>
<td><strong>End of study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Na⁺, mmol/L</td>
<td>138±2.5</td>
<td>138.6±0.6</td>
</tr>
<tr>
<td>Urinary Na⁺, mmol/L</td>
<td>96±21</td>
<td>92±16 ankles</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>82±4*</td>
<td>97±8f</td>
</tr>
<tr>
<td>Serum urea, mmol/L</td>
<td>6.1±0.5*</td>
<td>7.8±1.2†</td>
</tr>
<tr>
<td>Serum albumin, g/L</td>
<td>42.1±0.8*</td>
<td>39.1±1.2†</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.8±0.4*</td>
<td>13.8±0.3†</td>
</tr>
<tr>
<td>Hct</td>
<td>0.40±0.01f</td>
<td>0.40±0.01f</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>66±7</td>
<td>67±6</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td>82±4</td>
<td>81±4</td>
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</table>

Continuous data are presented as mean±SEM. *P<0.05, †P<0.01, ‡P<0.001, comparison to baseline (paired t test).

Changes in FVV (A) and FBF (B) after incremental cumulative dose rates of ANP are shown. *P<0.05, †P<0.01, ‡P<0.001; these refer to within-group comparison using 2-way ANOVA. P within the figure (P=NS in A; and P<0.01 in B) refer to AUC comparison between both groups (patients=■, controls=□).
Linear regressions were performed for all PVR, and R values were 0.88 to 1 (mean 0.96±0.03). Although PVR varied in slope (compliance) between individuals, within individuals there was very little change in slope at different stages of the study. In other words, shifts in the plots induced by infusion of the active agents were parallel and were caused by changes in venous tone rather than compliance.

Baseline cGMP levels in the control and cHF group were 0.73±0.15 pg/mL and 8.98±1.0 pg/mL, respectively (P<0.0001). The cGMP spillover was 20.0±9.2 pmol/min per 100 mL FV in the control group and 11.6±4.5 pmol/min per 100 mL FV in patients (P=NS).

**Effects of NP on FBF in Health and cHF**
The effects of ANP on the FBF ratio in patients with cHF and healthy controls are shown in Figure B and Table 3.

ANP infusions of 0.05 μg/min, 0.5 μg/min, and 1 μg/min increased FBF in the infused arm of controls from 2.14±0.37 mL/100 mL FV to 3.22±0.48 mL/100 mL FV (95% CI: −0.1 to 2.27), to 3.65±0.44 mL/100 mL FV (95% CI: 0.32 to 2.70; P<0.05), to 4.50±0.75 mL/100 mL FV (95% CI: 1.17 to 3.55; P<0.001), respectively. In patients, FBF increased in the infused arm from 2.18±1.18 mL/100 mL FV to 2.86±0.78 mL/100 mL FV (95% CI: −0.13 to 1.09), to 3.02±0.54 (95% CI: 0.12 to 1.3, P<0.05), to 3.27±0.47 (95% CI: 0.48 to 1.7, P<0.001), respectively. Changes in FBF were significantly blunted in patients when compared with controls (AUC; P<0.01).

The effects of Urodilatin, BNP, and CNP on the FBF ratio in patients are summarized in Table 3.

**Changes in Forearm Venous Tone**
Linear regressions were performed for all PVR, and R values were 0.88 to 1 (mean 0.96±0.03). Although PVR varied in slope (compliance) between individuals, within individuals there was very little change in slope at different stages of the study. In other words, shifts in the plots induced by infusion of the active agents were parallel and were caused by changes in venous tone rather than compliance.

The baseline slope of the PVR was 7.3±1.2 counts/second per mm Hg in the ANP-cHF group and 7.5±0.8 counts/second per mm Hg in the controls (P=NS). Furthermore, the baseline slope was similar in the different NP groups.

**Effects of NP on FVV in Health and in cHF**
ANP caused a significant and similar dose-dependent increase in FVV in controls and in patients. The results are summarized in Figure A and Table 3.

The effects of Urodilatin, BNP, and CNP on FVV in patients and controls are shown in Table 3.

The overall effects of ANP on FVV in cHF patients were significantly greater than those of Urodilatin, BNP, and CNP (P<0.05 for all, repeated measures ANOVA).

There was no significant correlation between baseline ANP plasma level and maximal venous responsiveness to intra-arterial ANP infusion (r=−0.19; P=NS).

**Effects of A71915 on FBF and FVV in Patients With cHF**
Intra-arterial infusion of A71915 at 0.5 μg/min and 1 μg/min (n=7) had no significant effect on FBF or FVV. Infusion of 20 μg/min (n=4) reduced FBF by 4.4±1.2% (P<0.05 without significant changes in FVV).

**Effects of eNOS Blockade on NP-Induced Changes in FBF and FVV in Health and cHF**
The eNOS-blockade reduced ANP-induced FBF changes in controls but not in patients (P<0.05), whereas similar reductions in FVV changes were seen in both ANP groups (both P<0.001). The effects of LNMMA/NP co-infusion on all NP-induced changes in FBF and FVV are summarized in Table 4.
Second, basal NPs contribute the rank order of potency in the forearm capacitance bed was a venodilator of forearm capacitance vessels than other NPs, demonstrated that in cHF, ANP is a significantly more potent NP-induced vasodilation.

Controls and evaluated the effects of eNOS blockade on patients with optimally treated cHF with those in normal controls across a venous plasma concentration range spanning from physiological values to those seen in severe HF.16 That study differed from ours in 3 aspects. First and most importantly, the ANP was given as a single systemic bolus dose that produced hypotension. The authors commented that baroreflex-mediated adjustments to the hypotension might have overcome any local venodilator effects of ANP. Second, our patients were using optimal contemporary medical therapy. In contrast, that study was undertaken in the pre-ACE inhibitor era. Third, they used strain-gauge VOP that, in contrast to radionuclide plethysmography, measures total limb volume rather than venous volume.15 These observations suggest that in contrast to the lack of effect seen in conduit veins, ANP dilates small veins and venules, which contain most of the venous (and total vascular) volume. In the present study, brachial artery ANP infusion resulted in a similar increase in FVV in cHF patients versus healthy controls, in marked contrast with the attenuated effects in the forearm resistance beds. To the best of our knowledge, there is only 1 other published study of the venous effects of ANP in HF;20 that study differed from ours in 3 aspects. First and most importantly, the ANP was given as a single systemic bolus dose that produced hypotension. The authors commented that baroreflex-mediated adjustments to the hypotension might have overcome any local venodilator effects of ANP. Second, our patients were using optimal contemporary medical therapy. In contrast, that study was undertaken in the pre-ACE inhibitor era. Third, they used strain-gauge VOP that, in contrast to radionuclide plethysmography, measures total limb volume rather than VV.15 Our observations raise the fascinating question of why the venous effects of ANP are preserved in patients with cHF when the resistance-vessel responses are markedly attenuated.

Discussion

Many studies have detailed the central hemodynamic, arterial, renal, and adrenal effects of exogenous1–5 and endogenous6 NPs in animal models of HF6,7 and in human HF,1–9 but little is known about the effects of NPs on the capacitance vasculature in this condition. In the present study, we assessed the effects of all 4 currently known human NPs on the forearm vasculature in matched groups of optimally treated cHF patients. We also studied, for the first time to our knowledge, the effects of basal NP levels on forearm vascular function in patients with cHF. Furthermore, we compared the effects of ANP on the forearm capacitance vasculature in patients with optimally treated cHF with those in normal controls and evaluated the effects of eNOS blockade on NP-induced vasodilation.

The principal findings were as follows. First, we demonstrated that in cHF, ANP is a significantly more potent venodilator of forearm capacitance vessels than other NPs, the rank order of potency in the forearm capacitance bed was ANP > BNP > CNP/Urodilatin. Second, basal NPs contribute to regulation of FVV and venous tone in cHF, but the contribution appears to be less than that previously shown by us in younger normal volunteers.16 Third, we demonstrated that venous responsiveness to exogenous ANP is preserved in patients with cHF, despite marked attenuation of its effects in the forearm resistance vasculature. Fourth, eNOS blockade reduced ANP-induced FBF changes in controls but not in patients, whereas similar reductions in FVV were seen in both groups.

Mechanism of the Attenuated Forearm Resistance-Vessel Response to ANP in cHF

Our observation of an attenuated forearm resistance-vessel response to intra-arterial ANP infusion is consistent with most of the literature, which documents attenuated arterial, renal, and endocrine responses to ANP in patients with HF.2–7 Hirooka et al4 and Nakamura et al6,17 reported reduced forearm resistance-vessel responses to intra-arterial infusion of ANP and BNP (but not CNP) in HF patients versus healthy controls. Interestingly, in these studies, changes in FBF to BNP and CNP were less than those in ANP (on an equimolar basis) in healthy controls, but approximately equipotent in patients with HF. The mechanisms responsible for reduced NP responsiveness in patients with HF are likely to be complex and may differ between the hormonal, renal, and vascular responses to these peptides. All of the following have been implied to contribute:18 NPRA receptor down-regulation, NPRC (clearance receptor) and NEP upregulation, receptor desensitization, fetal NP gene activation, downstream signaling abnormalities beyond cGMP generation, and increased activity of functional antagonists of the NP system, such as increased sympathetic nerve activity (especially renal sympathetic activity) and activation of the RAAS. The present study suggests that endothelial dysfunction might contribute to arterial NP resistance (see later). Furthermore, our finding that identical ANP infusions caused a significantly greater increase in venous effluent plasma ANP levels in controls compared with cHF patients would be in keeping with the notion of upregulation of NPRC-receptor density in this condition.

Venous Effects of NPs in cHF

Studies in conduit veins (eg, saphenous vein and dorsal hand vein) have suggested that NPs have minimal or absent vasorelaxant effect on veins.19 In contrast, we have previously demonstrated that intra-brachial ANP infusion causes a significant increase in forearm venous capacitance in healthy controls across a venous plasma concentration range spanning from physiological values to those seen in severe HF.16 These observations suggest that in contrast to the lack of effect seen in conduit veins, ANP dilates small veins and venules, which contain most of the venous (and total vascular) volume. In the present study, brachial artery ANP infusion resulted in a similar increase in FVV in cHF patients versus healthy controls, in marked contrast with the attenuated effects in the forearm resistance beds. To the best of our knowledge, there is only 1 other published study of the venous effects of ANP in HF;20 that study differed from ours in 3 aspects. First and most importantly, the ANP was given as a single systemic bolus dose that produced hypotension. The authors commented that baroreflex-mediated adjustments to the hypotension might have overcome any local venodilator effects of ANP. Second, our patients were using optimal contemporary medical therapy. In contrast, that study was undertaken in the pre-ACE inhibitor era. Third, they used strain-gauge VOP that, in contrast to radionuclide plethysmography, measures total limb volume rather than VV.15 Our observations raise the fascinating question of why the venous effects of ANP are preserved in patients with cHF when the resistance-vessel responses are markedly attenuated.

### Table 4. Effects of LNMMA on NP-Induced Changes in FBF and FVV

<table>
<thead>
<tr>
<th>Group</th>
<th>ANP-Controls (n=10)</th>
<th>ANP-CHF (n=10)</th>
<th>Urodilatin-CHF (n=8)</th>
<th>BNP-CHF (n=8)</th>
<th>CNP-CHF (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Change in FBF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP (1.0 μg/min) vs</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NP/LNMMA coinfusion</td>
<td>−1.37 (−2.5 to −0.3)*</td>
<td>−0.64 (−1.3 to 0.03)</td>
<td>−0.81 (−1.2 to −0.4)†</td>
<td>−0.73 (−1.2 to −0.3)†</td>
<td>−0.56 (−1.1 to −0.1)*</td>
</tr>
<tr>
<td><strong>Mean change in FVV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP (1.0 μg/min) vs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NP/LNMMA coinfusion</td>
<td>−6.32 (−8.5 to −4.1)‡</td>
<td>−8.00 (−11.9 to −4.1)‡</td>
<td>−7.46 (−10.7 to −4.2)‡</td>
<td>−6.86 (−11.0 to −2.7)‡</td>
<td>−8.97 (−13.1 to −4.8)†</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001, within-group comparison (2 way-ANOVA).

Change in FBF (mL/100 mL FV) reflects mean absolute change (95% CI). FVV (forearm vascular volume) is expressed in %.
ated. There is growing evidence for an interdependence between both GC systems (ie, soluble and particulate), particularly in situations with altered NO bioavailability.\(^1\)\(^1\) We recently demonstrated that carbachol-induced, NO-mediated venodilation was preserved in the forearm of patients with cHF, whereas endothelial function in arterial vessels was markedly impaired.\(^1\)\(^1\) Emmick and Cohen previously demonstrated that in older animals, vascular ANP responsiveness declined in arteries while it remained preserved in veins.\(^2\)\(^3\) Taken together, there seems to be a decline in arterial, but a preservation in venous, ANP responsiveness with aging and with cHF. The same appears to be true for vascular NO responsiveness, and it is therefore conceivable that an NO-dependent component of ANP-induced vasodilation accounts for these observations.

Effects of Basal ANP Levels
A71915 is an ANP analogue capable of interfering with ANP-induced cyclic GMP accumulation. The binding affinity of A71915 to NPR\(_a\) is only 22-times lower than that of ANP.\(^2\)\(^2\) A71915 has previously been shown to antagonise the cGMP-dependent renal\(^2\)\(^3\) and vascular responses\(^1\)\(^6\) of ANP (the renal and vascular tissue is rich in NPR\(_a\) receptors) without inhibiting ANP-induced (and CNP) cGMP production in nonpigmented ciliary epithelial cells (tissue rich in NPR\(_b\) and NPR\(_c\) receptors but devoid of NPR\(_a\) receptors).\(^2\)\(^4\)

Infusion of A71915 at a rate identical to that which had previously shown to induce venoconstriction in healthy controls\(^1\)\(^6\) had no effect. Given that basal ANP plasma levels in our patients were 10-fold higher than in the normal controls of the previous (and the present) study, the lack of effect can be explained by a rightward shift of the dose–response curve, in keeping with a competitive antagonism between endogenous ANP and exogenous A71915. Infusion of a 20-fold higher concentration was able to elicit a significant, albeit in relative terms still reduced (4.4% in present study versus 9.6% in previous study\(^1\)\(^6\)), reduction in FVV. The latter might be explained by the observation that β-ANP, an antiparallel dimer of α-ANP with reduced biological action, is the principal form of circulating ANP in patients with cHF.\(^2\)\(^5\)

These observations may also help to explain why acute administration of exogenous NPs have marked beneficial hemodynamic effects\(^2\)\(^6\) while potentiating endogenous NPs by preventing their breakdown has been somewhat disappointing.

Relative Potency of the Different NPs
With respect to the effects of ANP and BNP on forearm resistance vasculature, our study largely confirms previous findings discussed.\(^4\)\(^–\)\(^6\)\(^,\)\(^1\)\(^7\)

We found no significant vasodilatory effect of CNP in the resistance vasculature but some venodilation at pharmacological levels (1252±50 pg/mL). It is noted that a previous study by Nakamura et al found no significant increase in FBF at similar doses to those used in our study but a significant, albeit small, and similar increase in FBF in patients and controls at a dose equalling approximately twice our peak infusion rate.\(^1\)\(^7\) Our study suggests that CNP has little or no vasodilatory potency in the forearm resistance vasculature of patients with cHF, at least at physiological and pathophysiological concentrations.

Clinical and Pathophysiological Implications
Systemic infusion of NP\(^b\)\(^2\)\(^7\) (or elevation of endogenous NP by inhibiting their breakdown)\(^9\) has been shown to increase stroke volume (SV)\(^2\)\(^7\) and cardiac index\(^8\) in patients with HF, despite a decrease in CVP,\(^8\)\(^9\) a finding apparently in conflict with the Frank-Starling mechanism. This is almost certainly caused by a decrease in the volume of the right ventricle and a decrease in pericardial pressure, which increases effective LV distending pressure despite a decrease in LVEDP (ie, diastolic ventricular interaction).\(^2\)\(^8\) ANP infusion reduces cardiac filling pressures too rapidly to be solely accounted for by a fluid shift into the interstitial space and, in HF, in absence of significant diuresis or changes in hematocrit.\(^2\)\(^,\)\(^3\)\(^,\)\(^2\)\(^7\) These observations re-emphasize the potentially important venous effects of ANP. Extending our previous findings in healthy controls,\(^1\)\(^6\) the present study suggests that ANP also has important venodilator activity in cHF, but only modest effects on the resistance vasculature. This is in keeping with an earlier study by Serizawa et al\(^2\)\(^9\) who found that ANP reduced cardiac filling pressures in the absence of changes in systemic vascular resistance (SVR). The relatively selective venodilator action of NP in HF results in marked reductions in CVP and increases SV without a major decrease in SVR, avoiding serious hypotension. This is a favorable hemodynamic profile in the treatment of patients with decompensated HF.

Study Limitations
One caveat is that using the radionuclide technique, changes in VV during brachial artery infusion are expressed as a percentage of baseline. If FVV were reduced in CHF patients versus controls, a similar percentage increase in FVV might nevertheless represent a smaller absolute increase in volume. However, forearm radioactive counts at baseline and total forearm volume were similar in patients and controls, making it likely that baseline FVV was similar in the 2 groups. This is perhaps not surprising; although SVR is increased in untreated HF, it is normal or even reduced in patients with well-treated HF such as those we studied.\(^3\)\(^0\) Although small, statistically nonsignificant clinical differences (ie, cardiovascular risk profile) may have had some bearing on the vascular responsiveness to the various NPs, the degree of atherosclerotic burden in the forearm circulation is generally believed to be relatively minor. Furthermore, our study design does not allow us to differentiate if the reduced vasodilation during NP/LNMMMA co-infusion compared with NP infusion is caused by blockade of basal NO or by blockade of an NO-dependent component of (A)NP-induced vasodilation. Finally, this study was intentionally performed in patients who were using contemporary medical therapy for cHF. Our findings may not apply to untreated HF.

Conclusion
Venous ANP responsiveness is preserved in patients with cHF despite markedly diminished responsiveness of the arterial resistance vasculature. This difference may partially be caused by arterial endothelial dysfunction.
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