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

Matthias Schmitt, Prasad Gunaruwan, Nicola Payne, Justin Taylor, Leong Lee, Andrew J.M. Broadley, Angus K. Nightingale, John R. Cockcroft, Allan D. Struthers, John V. Tyberg, Michael P. Frenneaux

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

A nimal 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 NPRA-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, Nω-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 ATII-antagonist and, unless contraindicated or previously not tolerated, using maximally tolerated doses of beta-blockers. Their symptomatic status had remained unchanged on previously not tolerated, using maximally tolerated doses of beta-blockers. Their symptomatic status had remained unchanged on

{| Table 1. Baseline Characteristics |
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<td>Age, y (range)</td>
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<td>63 (42–79)</td>
<td>67 (53–77)</td>
<td>63 (38–79)</td>
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<tr>
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<td>NYHA class</td>
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<td>31.7±1.7</td>
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<td>Forearm volume, mL</td>
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<td>1694±53</td>
<td>1690±94</td>
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<td>FBF, mL/100 mL FV</td>
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<td>LV ejection fraction, %</td>
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<td>BP systolic, mm Hg</td>
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<td>β-Blocker</td>
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</table>

Continuous data are presented as mean±SEM. *P<0.01, †P<0.001, comparison between both ANP groups (unpaired t test). 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; *Climafila, Läufelfingen/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.

Statistics

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

Assessment of Venous Function

Changes in forearm vascular volume (FVV), compliance, and venous tone were assessed by radionuclide plethysmography, as described previously.14 Changes in flow ratios after NP infusions are then expressed as percentage changes from the baseline (ie, normal saline infusion) that preceded the administration of each drug.

Assessment of Arterial Resistance-Vessel Effects

The forearm resistance vasculature was assessed using conventional venous occlusion plethysmography (VOP) as described elsewhere.14 We interpreted the forearm flow changes to have been caused by changes in VV and changes in venous capacitance (venous tone) or compliance.

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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
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>
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<tr>
<td></td>
<td>ANP</td>
<td>URODILATIN</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
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<tr>
<td>Serum Na⁺, mmol/L</td>
<td>139.4±0.5</td>
<td>139.3±0.6</td>
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<tr>
<td>Urinary Na⁺, mmol/L</td>
<td>77±14</td>
<td>59±13</td>
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<tr>
<td>Serum creatinine, μmol/L</td>
<td>88±4</td>
<td>118±7</td>
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<tr>
<td>Serum urea, mmol/L</td>
<td>6.3±0.5</td>
<td>8.8±1.2</td>
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<td>Serum albumin, g/L</td>
<td>44.3±0.5</td>
<td>43.9±0.7</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>14.2±0.3</td>
<td>14.4±0.3</td>
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<tr>
<td>Hct</td>
<td>0.41±0.01</td>
<td>0.42±0.01</td>
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<tr>
<td>Heart rate, min⁻¹</td>
<td>65±7</td>
<td>66±8</td>
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<tr>
<td>Mean BP, mm Hg</td>
<td>83±3</td>
<td>80±3</td>
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<tr>
<td><strong>End of study</strong></td>
<td></td>
<td></td>
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<tr>
<td>Serum Na⁺, mmol/L</td>
<td>138.2±0.5</td>
<td>138.6±0.6</td>
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<tr>
<td>Urinary Na⁺, mmol/L</td>
<td>96±21</td>
<td>92±16</td>
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<tr>
<td>Serum creatinine, μmol/L</td>
<td>82±4*</td>
<td>97±8‡</td>
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<tr>
<td>Serum urea, mmol/L</td>
<td>6.1±0.5*</td>
<td>7.8±1.2†</td>
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<tr>
<td>Serum albumin, g/L</td>
<td>42.1±0.8*</td>
<td>39.1±1.2‡</td>
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<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±0.01</td>
<td>0.40±0.01‡</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>
</tr>
</tbody>
</table>

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

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.

ANP Levels
Baseline plasma ANP levels in the control and CHF group were 21.7±4.8 pg/mL and 100.5±8.1 pg/mL, respectively (P<0.0001). Intra-arterial ANP infusions of 0.05 μg/min, 0.5 μg/min, and 1.0 μg/min raised ANP concentrations in the venous effluent to 196±62 pg/mL, 785±256 pg/mL, and 1113±244 pg/mL (P<0.01 for all) in the control group and to 208±33 pg/mL, 234±38 pg/mL, and 280±32 pg/mL (P<0.05 for all) in the CHF group. The increase in venous ANP concentration at 0.5 μg/min and 1 μg/min was significantly higher in controls than patients (P<0.01, for both).
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).

Within patients, cGMP increased from 2.18±2.86 mL/100 mL FV to 3.22±3.22 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±2.86 mL/100 mL FV to 2.32±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. 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.

### 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-Controls**
- Change in FBF ratio: +0.76* (0.03 to 1.5)
- Change in FVV (%): +0.93 (−7.3 to 9.1)

**ANP-cHF**
- Change in FBF ratio: +0.12 (−0.1 to 0.3)
- Change in FVV (%): +2.15 (−2.3 to 6.6)

**Urodilatin-cHF**
- Change in FBF ratio: +0.12 (−0.2 to 0.4)
- Change in FVV (%): −1.94 (−4.8 to 0.9)

**BNP-cHF**
- Change in FBF ratio: +0.11 (−0.2 to 0.5)
- Change in FVV (%): +1.12 (−4.4 to 6.7)

**CNP-cHF**
- Change in FBF ratio: +0.02 (−0.4 to 0.5)
- Change in FVV (%): −1.52 (−7.0 to 4.0)

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

FBF data are mean absolute changes in the ratio of infused vs noninfused arm (95% CI). Changes in FVV are corrected for systemic changes and expressed in %.

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).

### 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 FVV by 4.4±1.2% (P<0.05 without significant changes in FBB).

### 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.
BNP
ANP
CNP/Urodilatin. Second, basal NPs contribute to vasodilation.

controls and evaluated the effects of eNOS blockade on patients with optimally treated cHF with those in normal controls. Furthermore, we compared 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. An earlier study, although limited in its scope, also found that forearm resistance-vessel responses to ANP were reduced in CHF patients compared with controls.14,15

Our observation of an attenuated forearm resistance-vessel response to ANP in cHF is consistent with most of the literature, which documents attenuated arterial, renal, and adrenal effects of exogenous and endogenous NPs in animal models of HF.2,3 An increase in blood pressure in response to ANP is absent or reduced in most of the animal studies and could be due to the absence of an intact renin-angiotensin-aldosterone system (RAAS) or enhanced sympathetic activity.3,8 The augmentation of the baroreflex-mediated response to ANP by captopril was attributed to the enhancement of ANP availability due to the inhibition of the RAAS.8 In the present study, the reduction in ANP-induced changes in FBF and FVV in cHF compared with healthy controls could be due to the advanced stage of the CHF that could have overcome any local venodilator effects of ANP. The authors commented that baroreflex-mediated adjustments to the hypotension might have overcome any local venodilator effects of ANP.8 ANP-induced vasodilation is mediated by nitric oxide (NO) production mediated by the release of cyclic guanosine monophosphate (cGMP) in conduit and resistance vessels.17 ANP stimulates eNOS in endothelial cells,17 and increased eNOS activity could account for the augmentation in forearm vasodilation in cHF versus controls.20 An alternative to the use of nitric oxide synthase (eNOS) inhibitors is the use of specific NPs with predominant venodilator effects. ANP has been shown to cause a marked increase in forearm venous capacitance in healthy controls but not in patients with CHF, whereas similar reductions in FVV were seen in both groups.

Discussion

Many studies have detailed the central hemodynamic, arterial, renal, and adrenal effects of exogenous and endogenous NPs in animal models of HF and in human HF, 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 NPR A receptor down-regulation, NPR C (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 NPR C-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 from physiological values to those seen in severe HF.16 This study20 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..
ated. There is growing evidence for an interdependence between both GC systems (ie, soluble and particulate), particularly in situations with altered NO bioavailability.11,12 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.13 Emmick and Cohen previously demonstrated that in older animals, vascular ANP responsiveness declined in arteries while it remained preserved in veins.21 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 NPRs is only 22-times lower than that of ANP.22 A71915 has previously been shown to antagonise the cGMP-dependent renal23 and vascular responses16 of ANP (the renal and vascular tissue is rich in NPRs receptors) without inhibiting ANP-induced (and CNP) cGMP production in nonpigmented ciliary epithelial cells (tissue rich in NPRs and NPRr receptors but devoid of NPRs receptors).24 Infusion of A71915 at a rate identical to that which had previously shown to induce venoconstriction in healthy controls16 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 small, and similar 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.17 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/LNMMA 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.

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.30 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/LNMMA 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.

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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References


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