The vasodilator potency of atrial natriuretic peptide in man

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ABSTRACT The vasodilating potency of α-human atrial natriuretic peptide (α-hANP) was investigated in the forearms of 16 normotensive subjects, 22 to 48 (mean 28) years old, with the use of venous occlusion plethysmography. α-hANP, 0.005 to 1.5 μg/min/100 ml forearm volume (FAV), infused in nine dose steps into the brachial artery increased forearm blood flow (FAF; ml/min/100 ml FAV) from 2.8 ± 0.4 (SEM) to a maximum of 9.6 ± 1.1. Forearm vascular resistance (mean arterial pressure/FAF) decreased by 72%. The α-hANP dose that produced a 50% vasodilator response was 0.09 ± 0.016 μg/min/100 ml FAV (n = 11) and it resulted in a venous plasma concentration of ANP (pANP) of 115 ± 7 pmol/liter (normal 2 to 80; radioreceptor assay). Intraindividually, the maximum dose of α-hANP induced an increase in FAF that was 60% of the maximum response to sodium nitroprusside (14.1 ± 1.8). Combined infusions (n = 9) of maximum forearm vasodilator doses of α-hANP and nitroprusside increased FAF to 22.7 ± 3.4; this additive vasodilator effect of α-hANP and nitroprusside is consistent with their different actions on the guanylate cyclase system. In man, the direct vasorelaxant effect of α-hANP occurs at concentrations within the upper normal range of pANP, suggesting a physiologic vasodilator role for α-hANP.


ATRIAL PEPTIDES1–4 contained in specific granules of the mammalian atria5–9 and released into the circulation on atrial distention10–12 may play a physiologic role in circulatory homeostasis because they exhibit potent vasorelaxant,13 natriuretic,4, 7, 8, 14 and aldosterone-inhibiting effects.15, 16 Atrial peptides oppose the vascular smooth muscle contraction induced by norepinephrine, angiotensin II,17, 18 and serotonin, histamine, and methoxamine.19 They have been shown to bind to specific high-affinity receptors in adrenal,20 renal, and vascular tissue,21, 22 and act via stimulation of particulate cyclic 3’,5’-guanosine monophosphate (cGMP) and eventually cellular calcium extrusion.23

In man, circulating concentrations of the 28-amino acid peptide α-human atrial natriuretic peptide (α-hANP)24 have been measured in plasma.11, 12, 25–28 ANP may induce natriuresis,12, 29, 30 but evidence for a direct vasorelaxant action has not yet been demonstrated. The effects of intravenous α-hANP on blood pressure in man are variable29, 31 because reflex sympathetic stimulation may counter a fall in blood pressure caused by ANP-induced vasodilation. The vascular bed of the forearm allows investigation of direct vascular responses without interference from systemic hemodynamic reflex mechanisms. It therefore was used to examine the vasodilative potency of α-hANP by venous occlusion plethysmography. The α-hANP–induced vasodilator response was also compared with that induced by sodium nitroprusside since the two may induce vasodilation by similar mechanisms.17, 19, 32, 33

Subjects and methods

Sixteen healthy volunteers (11 men; five women) who were 22 to 48 (mean 28) years old and had diastolic pressure at rest of less than 90 mm Hg (sitting, Korotkoff V) were studied. They did not take any medication and had refrained from smoking and from caffeine-containing beverages for the last 8 hr before the start of the investigations. The study protocol was approved by the hospital ethical committee on use of human subjects in
clinical investigations and informed consent was obtained from each participant.

**Measurement of forearm blood flow (FAF).** FAF was measured bilaterally by venous occlusion plethysmography. A mercury-in-silicone rubber strain gauge was placed at the upper third of the forearm, which rested comfortably on a support slightly above the level of the heart. The strain gauge was coupled to an electronically calibrated plethysmograph (Hokanson EC). Venous occlusion was achieved by a blood pressure cuff applied proximal to the elbow and inflated to 40 mm Hg by a rapid cuff inflator (Hokanson EC10). The hand was excluded from the circulation by inflation of a pediatric blood pressure cuff placed around the wrist to 50 mm Hg above the systolic pressure 1 min before and during the measurement of FAF. This was done to eliminate the unpredictable drug responses of arteriovenous shunts in the hand. Experiments were done on the left (experimental) forearm while blood flow measurements in the right (control) arm served as control values. Forearm vascular resistance (FVR) was calculated by dividing mean arterial pressure by FAF. To correct results obtained in the experimental arm for spontaneous alterations in blood flow, the ratio of FVR in the "experimental"/control arm (rFVR) was calculated. The electrocardiogram was monitored throughout the study.

**Study protocol.** The studies started at 8 A.M. and lasted for approximately 4 hr. The subjects were supine in a quiet, air-conditioned room with a constant temperature of 20° to 22° C. Forearm volumes were measured by water displacement. Under local anesthesia (lidocaine 1%), a catheter (Autochath, Plastimed, St.-Leu-La Forêt, France) was inserted into the left brachial artery for regional infusions of α-hANP and sodium nitroprusside and for recording arterial pressure with use of a Statham P23Db pressure transducer. In seven subjects an indwelling cannula was placed into an antecubital vein of the left arm for the measurement of plasma concentrations of ANP (pANP) in the venous effluent from the arterially infused arm. In four subjects a cannula was inserted into an antecubital vein of the right arm to measure systemic pANP during the course of the study. After completion of the instrumentation the subjects were allowed to rest for 30 min. Thereafter, arterial blood samples were taken for the measurement of basal pANP by radioreceptor assay, plasma renin activity (PRA) by radioimmunoassay, and plasma epinephrine and norepinephrine concentrations by radioenzymatic assay.

After recording of basal FAF and intra-arterial blood pressure, α-hANP was infused into the left brachial artery of 11 subjects in nine increasing dose steps from 0.001 to 1.5 μg/min/100 ml forearm volume (FAV) with use of a constant-rate infusion pump (Sage Instruments Inc., New York) for 3 to 4 min. The mean values for FAF from the last minute were recorded for statistical analysis. Immediately afterward, but still during the intra-arterial infusion, blood for determination of venous pANP was drawn from the left (n = 7) or right arm (n = 4). In five subjects, after cessation of the infusion blood was drawn from the left brachial artery at each α-hANP dose step for determination of epinephrine, norepinephrine, and PRA. In the first nine subjects the infusion of α-hANP was preceded by infusions of 0.2 to 6.0 μg/min Physiogel alone (see below), each lasting for 3 to 4 min. Approximately 60 min after the infusion of α-hANP, when FAF had returned to basal levels, nitroprusside was infused at a concentration of 0.6 μg/min/100 ml FAV for 2 min and the mean of five subsequent flow curves of plateau response were recorded for statistical evaluation. In previous studies this dose of intra-arterial nitroprusside was found to produce a maximal vasodilator response in the forearm without systemic hemodynamic effects. In four of these 11 subjects and in five additional ones combined infusions of the maximum vasodilator doses of α-hANP (0.75 μg/min/100 ml FAV) and nitroprusside (0.6 μg/min/100 ml FAV) were administered.

**Preparation of solutions for infusions.** α-hANP (Bisendorf GmbH, Wedemark, F.R.G.) in ampules containing 50 μg of lyophilized synthetic α-hANP (batch No. 49114) was diluted in Physiogel (1 ml solution 4%, molecular weight 22,000; Swiss Red Cross central laboratory, Berne, Switzerland) to contain either 0.0125 μg/ml or 0.25 μg/ml of 100 ml FAV for intra-arterial infusions. Dilution was done in Physiogel to avoid binding of ANP to the plastic tubing or the syringes. Preparatory studies using radiolabeled ANP (Novabiochem, Switzerland) showed a loss of up to 50% in the tubing when ANP was diluted in physiologic saline as compared with 13% when Physiogel was used. Consequently, nitroprusside (Ni-pride, Hoffmann-La Roche, Basel, Switzerland) was also diluted in Physiogel, to a solution containing 1.0 μg/ml/100 ml FAV. Solutions were freshly prepared immediately before infusion; those containing nitroprusside were protected from light. The volumes infused in this study varied between 0.15 and 6 ml/min.

**Determination of pANP.** Venous and arterial blood samples were collected in EDTA-coated ice-cold glass tubes (Vacutainer) and were approximately 7 ml each. Blood was spun in a refrigerated centrifuge and the plasma was stored at −40° C. pANP was measured with a radioreceptor assay that has been described in detail elsewhere. In brief, the assay involves competition for ANP receptors in bovine adrenal cortex membranes between endogenous ANP in plasma and a synthetic 24-amino acid radio ligand (125I-CGP 34 089) in which tyrosine has been synthesized to the N-terminal of atrial peptide II and iodinated. Synthetic α-hANP (Novabiochem, Switzerland) was also iodinated for use as a tracer and both 125I-CGP 34 089 and 125I-α-hANP were purified and characterized by high-pressure liquid chromatography. Unlabeled α-hANP was used to construct a standard curve with known concentrations in the range of 10−12 M to 10−7 M. ANP concentrations in plasma extracts were determined by comparison with the standard curve with use of a four-parametric logistic function. Results are expressed in terms of equivalent concentrations of α-hANP after correction for recovery. The detection limit of this assay is 2.5 pmol/liter plasma, the intra-assay variability 8.2%, and the interassay variability 10.1%. It is specific for ANP as there are no cross-reactions with a large number of other peptide hormones. The normal range of pANP as determined in 45 healthy subjects is 2 to 80 (mean 27) pmol/liter.

**Statistical analysis.** Results are expressed as mean ± SEM unless indicated otherwise. Statistical analysis was by analysis of variance (ANOVA) for repeated measures. The methods of Sheffe and Dunnett were used for a posteriori testing. The paired t test was used for comparison of vasodilator effects of α-hANP and nitroprusside. A significant difference was assumed to be present when p < .05. The infused dose of α-hANP that induced a 50% vasodilator response (ED50) as reflected in the changes in FAF and rFVR was determined with an extended least square nonlinear regression model. The response to the intra-arterial infusion of the highest dose of α-hANP (1.5 μg/ min/100 ml FAV) was taken as maximum response for the construction of these dose-response curves.

**Results**

Baseline data for all 16 subjects are listed in table 1. Basal pANP was higher in arterial than in venous blood. There was no relationship between basal PRA, norepinephrine, and epinephrine and basal pANP or pANP or basal values for FAF or FVR. Table 2 shows the re-
TABLE 1
Baseline characteristics of 16 subjects (mean ± SEM)

<table>
<thead>
<tr>
<th>Intra-arterial pressure (mm Hg)</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>119.3 ± 3.9</td>
<td>62.0 ± 2.4</td>
<td>81.2 ± 2.8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60.6 ± 2.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FAV (ml/min/100 ml FAV)

<table>
<thead>
<tr>
<th>FAV (ml/min/100 ml FAV)</th>
<th>Experimental, left arm</th>
<th>Control, right arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1008 ± 26.8</td>
<td>1031 ± 28.0</td>
</tr>
</tbody>
</table>

FAF (ml/min/100 ml FAV)

<table>
<thead>
<tr>
<th>FAF (ml/min/100 ml FAV)</th>
<th>Experimental, left arm</th>
<th>Control, right arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.7 ± 0.3</td>
<td>2.1 ± 0.1</td>
</tr>
</tbody>
</table>

FVR (mm Hg/FAF)

<table>
<thead>
<tr>
<th>FVR (mm Hg/FAF)</th>
<th>Experimental, left arm (FVR exp)</th>
<th>Control, right arm (FVR con)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33.8 ± 3.1</td>
<td>41.7 ± 3.6</td>
</tr>
</tbody>
</table>

Ratio FVR exp/FVR con (rFVR)

| Ratio FVR exp/FVR con (rFVR) | 0.85 ± 0.06 |

Arterial plasma concentrations

<table>
<thead>
<tr>
<th>Arterial plasma concentration</th>
<th>Norepinephrine (pg/ml)</th>
<th>Epinephrine (pg/ml)</th>
<th>PRA (ng/ml/h)</th>
<th>pANP (pmol/l)</th>
<th>Venous pANP (n = 11)</th>
<th>Arterial pANP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>129.4 ± 14.3</td>
<td>36.4 ± 5.9</td>
<td>2.7 ± 0.5</td>
<td>31.8 ± 5.2</td>
<td>40.5 ± 8.5</td>
<td></td>
</tr>
</tbody>
</table>

Responses of FAF and FVR to increasing volumes of intra-arterially infused Physiogel. FAF remained unchanged. Although FVR decreased slightly, the rFVR remained unchanged. Thus, dilution of α-hANP and nitroprusside in Physiogel did not influence the vasodilator response to these two substances.

Full vasodilator response to a given dose of α-hANP occurred within 2 min of the onset of the infusion, with 65% of the increase in FAF being evident after 30 sec and 85% after 1 min. After cessation of the intra-arterial infusion of α-hANP, FAF returned to basal values within 40 to 60 min (figure 1). Figure 2 demonstrates the dose-dependent increase in FAF and the corresponding pANP in the venous effluent from the forearm in which drug was infused. There was a close correlation between the dose of α-hANP and pANP in the venous effluent from infused forearm (r = .991).

Responses of arterial pressure, FAF, and FVR to increasing doses of intra-arterially infused α-hANP in 11 subjects are shown in table 3. FAF increased a maximum of 3.4-fold; FVR decreased 3.6-fold, and rFVR decreased 3.8-fold in response to the infusion of 0.75 and 1.5 μg/min/100 ml FAV α-hANP (all p < .001; ANOVA for repeated measures). The FAF plateau was reached after the 0.75 μg/min/100 ml FAV dose; the increase in the dose of α-hANP to 1.5 μg did not result in an additional increase in FAF. The further decrease in FVR and rFVR on increasing the dose of α-hANP from 0.75 to 1.5 μg was due to the fall in mean blood pressure in the presence of a practically unchanged FAF and an increase in FVR in the control arm. Venous pANP measured in the control arm showed little change except for a threefold increase after intra-arterial infusion of 1.5 μg α-hANP.

The ED$_{50}$ was calculated by taking the vasodilator response to 1.5 μg/min/100 ml FAV as maximum response. Figure 3 shows the respective dose response curves for ΔFAF and ΔFVR. Accordingly, the ED$_{50}$ for ΔFAF was 0.093 ± 0.016 and that for ΔFVR was 0.041 ± 0.005 μg/min/100 ml FAV. As depicted in figure 1, the intra-arterial infusion of these doses resulted in a venous plasma level of 115 pmol/liter.

Sodium nitroprusside (0.6 μg/min/100 ml FAV) increased FAF to 14.1 ± 1.8 ml/min/100 ml FAV and decreased FVR to 7.0 ± 1.0 units and rFVR to 0.16 ± 0.02 (all p < .01 vs α-hANP 1.5 μg/min/100 ml FAV; table 4). Hence, in this intravascular comparison the maximum increase in FAF in response to α-hANP was 60% of that to nitroprusside and the maximum α-hANP-induced decrease in FVR and rFVR amounted to 90% and 92%, respectively, of that induced by

TABLE 2
Mean arterial pressure (MAP), FAF, and FVR in the "experimental" and control arm and the rFVR after intra-arterial infusion of Physiogel in nine normotensive subjects (mean ± SEM)

<table>
<thead>
<tr>
<th>Physiogel (ml/min)</th>
<th>MAP (mm Hg)</th>
<th>FAF (ml/min/100 ml FAV)</th>
<th>FVR (MAP/FAF)</th>
<th>rFVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>87.9 ± 2.3</td>
<td>3.0 ± 0.5</td>
<td>2.1 ± 0.3</td>
<td>34.6 ± 5.2</td>
</tr>
<tr>
<td>0.2</td>
<td>85.1 ± 2.1</td>
<td>3.1 ± 0.6</td>
<td>2.2 ± 0.6</td>
<td>34.4 ± 7.3</td>
</tr>
<tr>
<td>0.4</td>
<td>85.8 ± 2.5</td>
<td>2.9 ± 0.5</td>
<td>2.2 ± 0.2</td>
<td>34.2 ± 5.0</td>
</tr>
<tr>
<td>0.8</td>
<td>87.3 ± 2.6</td>
<td>3.3 ± 0.6</td>
<td>2.3 ± 0.2</td>
<td>33.3 ± 5.9</td>
</tr>
<tr>
<td>1.5</td>
<td>87.0 ± 2.2</td>
<td>3.0 ± 0.5</td>
<td>2.3 ± 0.2</td>
<td>34.4 ± 5.3</td>
</tr>
<tr>
<td>3.0</td>
<td>86.8 ± 2.2</td>
<td>3.3 ± 0.6</td>
<td>2.4 ± 0.2</td>
<td>32.8 ± 5.0</td>
</tr>
<tr>
<td>6.0</td>
<td>87.2 ± 2.4</td>
<td>3.3 ± 0.6</td>
<td>2.3 ± 0.2</td>
<td>31.6 ± 4.7</td>
</tr>
</tbody>
</table>

Differences from baseline values are not significant.
nitroprusside. The effect of the combined infusion of a maximum forearm vasodilator dose of α-hANP (0.75 μg/min/100 ml FAV) together with a maximum dose of nitroprusside in nine subjects doubled the nitroprusside-induced increase in FAF and tripled maximum α-hANP–induced vasodilation (table 4 and figure 4). After cessation of the nitroprusside infusion basal values for FAF and FVR were reached within 10 to 15 min.

Heart rate varied between 60 and 65 beats/min independent of the dose of intra-arterial α-hANP or nitroprusside. After the combined infusion of α-hANP and nitroprusside heart rate increased to 69.5 beats/min (p < .05). Plasma norepinephrine and epinephrine concentrations and PRA remained unchanged during the study. There was no relationship between basal PRA, norepinephrine, epinephrine and pANP with the changes in FAF or FVR during α-hANP–induced vasodilation.

**Discussion**

α-hANP infused intra-arterially into the forearm of normotensive subjects increased FAF about fourfold and lowered FVR in a dose-dependent manner, which
TABLE 3  
Mean arterial pressure (MAP), FAF, and FVR in the “experimental” and control arm and the rFVR after intra-arterial infusions of increasing doses of \( \alpha \)-hANP and a maximum vasodilator dose of sodium nitroprusside in 11 normotensive subjects (mean \( \pm \) SEM)  

<table>
<thead>
<tr>
<th>Dose (( \mu )g/min/100 ml FAV)</th>
<th>MAP (mm Hg)</th>
<th>FAF (ml/min/100 ml FAV)</th>
<th>FVR (MAP/FAF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
<td>Experimental</td>
</tr>
<tr>
<td>Basal</td>
<td>83.4±3.6</td>
<td>2.8±0.4</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>( \alpha )-hANP 0.005</td>
<td>82.7±3.7</td>
<td>3.5±0.5</td>
<td>2.4±0.3</td>
</tr>
<tr>
<td>0.01</td>
<td>82.1±3.5</td>
<td>4.0±0.5</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>0.02</td>
<td>82.4±3.8</td>
<td>4.3±0.7</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>0.05</td>
<td>82.4±3.3</td>
<td>5.7±0.8(^a)</td>
<td>2.4±0.2</td>
</tr>
<tr>
<td>0.1</td>
<td>83.7±3.6</td>
<td>5.8±0.6(^a)</td>
<td>2.3±0.2</td>
</tr>
<tr>
<td>0.2</td>
<td>82.7±3.6</td>
<td>7.1±0.9(^b)</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>0.38</td>
<td>82.9±3.9</td>
<td>7.5±0.9(^b)</td>
<td>2.3±0.3</td>
</tr>
<tr>
<td>0.75</td>
<td>82.1±3.9</td>
<td>9.6±1.1(^b)</td>
<td>2.3±0.2</td>
</tr>
<tr>
<td>1.5</td>
<td>80.3±3.7</td>
<td>9.3±1.0(^b)</td>
<td>1.9±0.2</td>
</tr>
<tr>
<td>Nitroprusside 0.6</td>
<td>82.0±3.6</td>
<td>14.1±1.8(^c)</td>
<td>2.0±0.2</td>
</tr>
</tbody>
</table>

\(^a\)p < .05; \(^b\)p < .01 by a posteriori testing according to the method of Sheffe and Dunnett.  
\(^c\)p < .01 vs 1.5 \( \mu \)g \( \alpha \)-hANP, paired t test.  

is consistent with the potent vasorelaxant effect of this drug observed in animal experiments\(^3, 13, 17, 18, 41\) and with observed increases in skin blood flow in man after systemic ANP administration.\(^42\) The rapid onset of the vasorelaxant effect suggests that decreases in blood pressure after infusions of ANP\(^29, 31\) may primarily be due to vasodilation rather than natriuresis. Infusion of 0.75 \( \mu \)g/min/100 ml FAV induced a maximum vasodilator effect; raising the dose to 1.5 \( \mu \)g did not result in greater vasodilation but caused an increase in systemic pANP. No dose of \( \alpha \)-hANP was associated with diuresis. The maximum forearm vasodilator response to \( \alpha \)-hANP amounted to 60% of that produced by sodium nitroprusside. This is twice the vasorelaxing effect of postjunctional \( \alpha_\_ \)\(^-\)\(^43\) or \( \alpha_\_\)2-adrenoceptor blockade\(^44\) and is comparable to that of vascular \( \beta_\_ \)2-adrenoceptor stim-

FIGURE 3. Dose-response curves for intra-arterial (brachial artery) \( \alpha \)-hANP. The response to 1.5 \( \mu \)g/min/100 ml FAV was taken as the maximum response (E_{max}). The ED_{50} was 0.093 ± 0.016 \( \mu \)g/min/100 ml FAV for the increase in FAF Δ FAF; dotted line) and 0.041 ± 0.005 \( \mu \)g/min/100 ml FAV for the decrease in FVR expressed as the ratio experimental/control arm (ΔFVR; full line). E = response to a given dose of ANP; Eb = basal value.
TABLE 4
Mean arterial pressure (MAP), FAF, and FVR in the “experimental” and control arm and the rFVR after intra-arterial infusions of α-hANP and sodium nitroprusside (NIP) alone and in combination in nine normotensive subjects (mean ± SEM)

<table>
<thead>
<tr>
<th>Infusion</th>
<th>MAP (mm Hg)</th>
<th>FAF (ml/min/100 ml FAV)</th>
<th>FVR (MAP/FAV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>75.0 ± 3.1</td>
<td>2.5 ± 0.2</td>
<td>31.9 ± 2.3</td>
</tr>
<tr>
<td>α-hANP, 0.75</td>
<td>71.8 ± 2.8</td>
<td>7.6 ± 1.3</td>
<td>11.5 ± 1.6</td>
</tr>
<tr>
<td>NIP, 0.6</td>
<td>74.8 ± 3.3</td>
<td>11.7 ± 2.2</td>
<td>7.7 ± 1.0</td>
</tr>
<tr>
<td>α-hANP, 0.75 + NIP, 0.6</td>
<td>73.8 ± 3.7</td>
<td>22.7 ± 3.46</td>
<td>3.8 ± 0.50</td>
</tr>
</tbody>
</table>

*p < .05; †p < .01, paired t test for α-hANP vs nitroprusside alone.

Combined infusions of α-hANP and sodium nitroprusside produced an additive vasodilator effect.

α-hANP–induced vasorelaxation is mediated by an increase in cGMP and a rise in the concentrations of cGMP has been found in various target tissues in animals and man, including vascular smooth muscle. In man, the increase in plasma concentrations of cGMP paralleled concentrations of ANP during volume loading–induced stimulation of pANP. It has been suggested that cGMP represents the second messenger for ANP action. While ANP increases cGMP levels through activation of particulate (membrane-bound) cGMP, sodium nitroprusside and other nitrous compounds activate soluble (cytosolic) cGMP. This may explain the additive vasodilator response to combined infusions of α-hANP and nitroprusside into the forearm vascular bed. The rapid onset of the vasodilator action of α-hANP observed in the present study is consistent with that of nitroprusside and other nitrous compounds; their stimulation of guanylate cyclase leads to cGMP accumulation within 1 to 2 min, followed by vasorelaxation. Similar to that induced by nitroprusside, ANP-induced vasodilation does not appear to be dependent on the presence of an intact endothelium. The longer time period necessary for FAF and FVR to reach basal values after the infusion of α-hANP as compared with after nitroprusside also may be due to their activation of different guanylate cyclase systems. The effective arterial concentration of α-hANP can be approximated from the pANP in the venous effluent of the infused arm. Hemodynamically relevant vasodilation may already occur with increases in pANP within the normal range. Therefore, the concentrations of α-hANP that induced vasodilation in the forearm are close to the range of those of ANP known to mediate vasorelaxation. The ED50 for ΔFVR was lower than that for ΔFAF, demonstrating that FVR, when corrected for spontaneous alterations in blood flow, is a more sensitive measurement of vasodilation since blood flow is determined in part by blood pressure. The ED50 for vasodilation appears to be similar to that for natriuresis. This is in agreement with specific binding sites with a high affinity for ANP, as has been found in rabbit aorta and kidney.

It can be estimated that, for example, a 10% increase in forearm blood flow would relate to an increase of about 15 pmol/liter pANP. This would require a rise in right and/or left atrial pressure of about

![Figure 4](image-url)

**FIGURE 4.** Increase in FAF (ΔFAF) in response to a maximum intra-arterial dose of α-hANP (0.75 μg/min/100 ml FAV; hatched bar) and sodium nitroprusside (NIP, 0.6 μg/min/100 ml FAV; dotted bar) when infused alone and in combination (dotted and hatched bar).
2 mm Hg, an increase that would occur, for instance, during exercise. In this situation changes in left atrial pressure may be the decisive component; a notable contribution of left atrial pANP is also indicated by the higher pANP in arterial compared with venous blood under basal conditions observed in this and in another study. Owing to the rapid onset of the vasorelaxant effect, adjustments in the peripheral vasculature to changes in central blood volume can be accomplished practically simultaneously. This suggests that peripheral vasorelaxation represents a mechanism for rapid fine tuning of central blood volume, whereas the natriuretic effect of ANP may be a more coarse regulator and may operate with some delay but with a greater potential for reduction of blood volume. This emphasizes the physiologic role of ANP in blood volume homeostasis and highlights the strategic place of the atria as the main source of ANP linking hemodynamic information with an endocrine signal for vasodilation and natriuresis.

We thank Ms. M. Bürgin, Ms. B. Libisig, and Ms. S. Stucki for technical assistance and Ms. A. de S. Pinto for the secretarial work.

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Circulation. 1987;75:221-228
doi: 10.1161/01.CIR.75.1.221

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/75/1/221

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