Low-Dose C-Type Natriuretic Peptide Does Not Affect Cardiac and Renal Function in Humans

Giuseppe Barletta, Chiara Lazzeri, Sabrina Vecchiarino, Riccarda Del Bene, Gianni Messeri, Antonio Dello Sbarba, Massimo Mannelli, Giorgio La Villa

Abstract—In experimental animals, C-type natriuretic peptide (CNP) has vasodilating, hypotensive, and natriuretic activities. The role of circulating CNP in the overall regulation of cardiac and renal function in humans is less defined, in both health and disease. We measured cardiac volumes, diastolic and systolic functions, systemic (Doppler echocardiography) and renal hemodynamics, intrarenal sodium handling (lithium clearance method), plasma and urinary cGMP, plasma renin concentration, and plasma aldosterone level in six healthy volunteers (mean age, 33±3 years) receiving CNP (2 and 4 pmol/kg per minute for 1 hour each) in a single-blind, placebo-controlled, random-order, crossover study. During CNP infusion, plasma CNP increased from 1.17±0.23 to 41.52±4.61 pmol/L (ie, 4- to 10-fold higher levels than those observed in disease states) without affecting plasma and urinary cGMP, cardiac volumes, dynamics of left and right heart filling, cardiac output, arterial pressure, renal hemodynamics, intrarenal sodium handling, sodium excretion, or plasma levels of renin and aldosterone. The finding that increments in plasma CNP within the pathophysiological range have no effects on systemic hemodynamics, renal function, or the renin-angiotensin system do not support the hypothesis that CNP may act as a circulating hormone in humans. (Hypertension. 1998;31:802-808.)

Key Words: echocardiography ■ hemodynamics ■ systole ■ diastole ■ natriuretic peptides

The natriuretic peptide system consists of at least three structurally homologous peptides: ANP, BNP, and CNP. ANP and BNP are cardiac hormones that contribute to the overall regulation of cardiovascular homeostasis and fluid volume due to their natriuretic, vasodilating, and renin-aldosterone-inhibiting actions.1–3 CNP, first isolated in porcine brain,4 is a 22-amino acid peptide that shares a high homology with ANP and BNP within the ring structure but lacks the carboxyl-terminal extension.5 Outside the central nervous system, CNP is mainly produced by the vascular endothelium,1–4 in which it is thought to act as a local paracrine factor for the control of vascular tone. Endothelial production of CNP is remarkably augmented by various cytokines and growth factors such as transforming growth factor-β and tumor necrosis factor-α, suggesting that CNP may be of pathophysiological relevance in various vascular disorders.6 Like the other natriuretic peptides, CNP is detectable in plasma of healthy subjects, although at much lower concentrations than ANP and BNP.6,8–12 Plasma CNP levels are increased in patients with chronic renal failure,9,10 septic shock,11 and cor pulmonale,12 raising the possibility that CNP may be a circulating hormone involved in the regulation of cardiovascular function.

CNP exerts its biological effects by selectively activating the NPR-B,14,15 leading to an increase in cGMP in target cells. In experimental animals, the administration of CNP induces vasodilation of both arteries and veins16; reduces cardiac filling pressures,17 CO,18,19 and arterial pressure; and increases sodium excretion.3,19,20 In addition, CNP exerts an antiproliferative activity on vascular smooth muscle cells in culture.21,22 Studies in humans are more limited and somewhat conflicting. Systemic administration of CNP induced either a reduction in arterial pressure and an increase in creatinine clearance and sodium excretion10 or no appreciable effects on CO, arterial pressure, and renal function.23,24

Measurements of CO and arterial pressure do not provide a comprehensive evaluation of cardiac function because preload and contractility are the other critical factors in determination of the pumping ability of the heart.25 We recently showed that intravenous infusion of low-dose BNP markedly affects cardiac function in the absence of any appreciable changes in CO and peripheral vascular resistance.26,27

These considerations prompted us to evaluate cardiac volumes, filling and emptying dynamics, and systemic hemodynamic parameters during CNP infusion. In addition, we assessed the renal effects of CNP by evaluating RPF, GFR, and intrarenal sodium handling.

Methods

Study Protocol
Six healthy male volunteers (mean age, 33±3 years; age range, 31 to 39 years) gave their informed written consent to participate in a

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Selected Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CI = cardiac index
ClLi = lithium clearance
CNP = C-type natriuretic peptide
CO = cardiac output
E/A ratio = peak early to late flow velocity ratio
EDVI = end-diastolic volume index
ESVI = end-systolic volume index
FDDNa = fractional distal sodium delivery
FDRNa = fractional distal sodium reabsorption
FENa = fractional sodium excretion
FPRNa = fractional proximal sodium reabsorption
GFR = glomerular filtration rate
HR = heart rate
LAVI = left atrial volume index
LV = left ventricle
MAP = mean arterial pressure
NPR = natriuretic peptide receptor
PAC = plasma aldosterone concentration
PAH = p-aminohippurate
PRC = plasma renin concentration
RAV1 = right atrial volume index
RPF = renal plasma flow
SVR = systemic vascular resistance
UFR = urine flow rate

single-blind, placebo-controlled, random-order, crossover study. The investigation conforms to the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee. No subject had a history of hypertension, cardiovascular, renal, respiratory, hepatic, or metabolic diseases or was on any drugs. Physical examination, blood pressure, urinalysis, blood cell count, fasting serum glucose, blood urea nitrogen, creatinine, electrolytes, electrophoresis of serum proteins, enzymes, and ECG and echocardiographic findings also were normal, with absence of abnormalities of LV geometry and/or segmental kinetics. All subjects were maintained on a standard, 100-nmol sodium diet for 1 week before and throughout the study period.

On the first day of the study, a 24-hour urine collection was obtained to measure UNaV. On the same day, at 5:00 PM, lithium carbonate (600 mg) was administered orally to calculate ClLi. The next day, subjects had breakfast at 7:30 AM. Thereafter, they remained supine until 1:30 PM, when they were transferred to the study room and administered an oral water load (10 mL/kg of body wt). An antecubital vein in each arm was cannulated for infusion of substances and blood sampling. All subjects then were administered an intravenous priming dose of PAH, followed by continuous infusion throughout the study. To obtain adequate UFRs, subjects also received 250 mL/h 5% dextrose. The cuff of an automated apparatus (Dinamap; Critikon), validated against standard sphygmomanometry before each experiment, was positioned in the nondominant arm for blood pressure and HR recordings. After 60-minute equilibration, urine was obtained through spontaneous voiding and discarded. Thereafter, 3 consecutive 1-hour clearance periods were performed, respectively, under baseline conditions (first clearance period) and during the administration of synthetic human CNP-22 (Clinalfa), at 2 (second clearance period) or 4 (third clearance period) pmol/kg per minute or placebo. CNP solution was prepared by dissolving the calculated amount of natriuretic peptide in 5% dextrose (90 mL) plus Hemaccel (10 mL; Behring), which is used to minimize the adsorption of CNP onto the walls of the infusion set.26 Placebo consisted of the vehicle (90 mL 5% dextrose plus 10 mL Hemaccel). Both CNP and placebo were infused at increasing rates (25 and 50 mL/h, respectively) with the use of a peristaltic pump. Blood samples were obtained (1) every 30 minutes for measurements of CNP; (2) every 60 minutes for measurements of packed cell volume and plasma concentrations of ANP, BNP, renin (PRLC), aldosterone, and cGMP; and (3) in the middle of each 1-hour clearance period for determinations of PAH, creatinine, lithium, and sodium. Urine was collected through spontaneous voiding at the end of each 1-hour clearance period to measure UFR and the urinary excretion of PAH, creatinine, lithium, sodium, and cGMP. All subjects remained supine throughout the entire study period, except when voiding. Echocardiographic measurements were obtained in the same sequence every 30 minutes and were always followed by blood sampling and then by urine sampling. The above protocol was repeated after 4 days, with crossing over of the treatments.

**Table 1. Plasma Levels of CNP and cGMP Under Baseline Conditions (0 to 60 min) and During Administration of CNP at 2 (60 to 120 min) or 4 (120 to 180 min) pmol/kg per Minute or Placebo**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Plasma CNP, pmol/L</th>
<th>Plasma cGMP, pmol/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>CNP</td>
</tr>
<tr>
<td>0</td>
<td>1.22±0.13</td>
<td>1.17±0.23</td>
</tr>
<tr>
<td>30</td>
<td>1.15±0.15</td>
<td>1.06±0.19</td>
</tr>
<tr>
<td>60</td>
<td>1.16±0.20</td>
<td>1.14±0.14</td>
</tr>
<tr>
<td>120</td>
<td>1.23±0.24</td>
<td>19.99±5.00*</td>
</tr>
<tr>
<td>150</td>
<td>1.19±0.13</td>
<td>32.24±3.29*</td>
</tr>
<tr>
<td>180</td>
<td>1.21±0.14</td>
<td>41.52±4.61*</td>
</tr>
</tbody>
</table>

*P<.001 vs placebo.
†Repeated measures two-way ANOVA: F=182.53, P<.0001.
flow so no angle correction was used. Pulsed Doppler recordings were taken at the end of normal expiration to eliminate respiratory effects on LV filling. Maximum velocities were measured as modal velocities. Peak early and late flow velocities were measured, and the E/A ratio was calculated. Good-quality pulmonary venous flow velocity tracings were recorded in all subjects, allowing calculation of the time-velocity integral of forward flow during systole (systolic flow integral) and diastole (diastolic flow integral). Systolic fraction of pulmonary venous flow was calculated as the ratio between the systolic flow integral and the sum of systolic and diastolic flow integrals. Flow in the hepatic veins was measured in mild expiration as the maximal forward presystolic modal velocity. All the recordings were taken at a sweep speed of 100 mm/s, and at least three nonconsecutive cycles were analyzed; each parameter was calculated as the average of these three measurements. All M-mode and Doppler tracings were recorded on videotapes (Panasonic AG-7300). LV volumes and CO were determined from LV diameters and HR with the use of the Teichholz formula. Atrial volumes were obtained with the use of the ellipsoidal formula. All volumes and COs were normalized according to body surface area. SVR was calculated as SVR = MAP/CO × 80, where MAP is diastolic pressure plus one third pulse pressure.

### Evaluation of Renal Function

Plasma and urine PAH concentrations were measured according to a fluorimetric technique. Lithium was measured in diluted (1:10) serum, and urine samples were measured with atomic absorption spectrophotometry. The clearances of PAH, creatinine, and lithium were calculated as estimations of RPF, GFR, and distal sodium delivery, respectively. Segmental sodium handling was assessed by calculating FENa, FPRNa, FDDNa, and FDRNa, according to Koomans et al. ANP and CNP were measured with radioimmunoassay (Phoenix Laboratories). The recovery of the extraction procedure, as determined by the addition of synthetic human ANP-28 or CNP-22 to plasma, was 75±2% for ANP and 70±3% for CNP. Between- and within-assay coefficient of variations were 9% and 6% for ANP and 13% and 9% for CNP, respectively. BNP was measured with radioimmunoassay, as reported elsewhere.

Plasma renin concentration was measured with a two-site immunoassay with the use of reagents purchased from Nichols Institute Diagnostics BV. Two different monoclonal antibodies to human active renin were used in the assay: one coupled to solid phase and one labeled with 125I. A concentration as low as 1.4 mU/L of active renin can be detected through this method. Intra-assay and interassay imprecision was always <3.0 and <10.0 mU/L, respectively, for measurement of concentrations of 70 to 300 mU/L.

Aldosterone and cGMP in plasma and urine were measured with commercial kits (ALDO Kit [Cea Sorin] and cGMP RIA Kit [Amersham], respectively). Results of urine cGMP measurements were corrected for the corresponding UFRs and expressed as the urinary excretion rate of cGMP.

### Statistical Analysis

Data are reported as mean±SD. Statistical analysis was performed using the SPSS for Windows statistical package 7.0. Data for before and during CNP administration were analyzed using the two-way analysis of variance for repeated measures, followed as appropriate by the t test with Bonferroni's correction. Relationships were assessed by using the Pearson's correlation coefficient. A value of P<0.05 was considered significant.

### Results

All subjects completed the study. Sodium excretion ranged from 90 to 105 mmol in the days before the infusions of either placebo or CNP, confirming adherence to the diet.

#### Plasma CNP Levels and cGMP Measurements

Administration of CNP induced a progressive increase in plasma CNP levels, up to a maximum of 41.52±4.61 pmol/L (Table 1), without affecting either the plasma levels (Table 1)
or the urinary excretion rate of cGMP (placebo: 0.49±0.17, 0.36±0.21, and 0.39±0.16; CNP: 0.44±0.19, 0.47±0.15, and 0.42±0.20 nmol/min in the first, second, and third clearance period, respectively).

**Hemodynamic Effects**

Hemodynamic data related to the first hour of the baseline study and the two 1-hour infusion steps of either CNP or placebo are shown in Table 2. HR, arterial blood pressure, CI, and SVR did not differ at any stage. LV, right, and left atrial volumes are reported in Table 3. No significant differences were found between baseline and CNP infusion values. Doppler data are reported in Table 4. Mitral E/A ratio, pulmonary vein systolic fraction, and presystolic, systolic, and diastolic flow velocities of hepatic veins did not significantly differ at any stage.

Packed cell volume did not show any appreciable changes during the administration of either placebo (0.41±0.03, 0.41±0.03, and 0.40±0.03 at the end of the first, second, and third infusion period, respectively) or CNP (0.41±0.03, 0.41±0.03, and 0.41±0.04, respectively).

**Renal and Endocrine Effects**

Data of renal hemodynamics, intrarenal sodium handling, and the plasma concentrations of ANP, BNP, renin, and aldosterone are given in Tables 5 and 6. Neither placebo nor CNP administration exerted any appreciable effects on RPF, GFR, sodium excretion, intrarenal sodium handling, ANP, BNP, PRC, or plasma aldosterone levels.

**Discussion**

Experimental studies suggested that CNP might have a role in physiology and pathophysiology of circulation by acting as a mixed (venous and arterial) vasodilator. In animals, in fact, CNP infusion dilated arterial and venous beds, inducing a decrease in arterial pressure, CO, and arterial pressure. In one of these studies, CNP modified systemic hemodynamics in the sheep when infused at the dosage of 1 pmol/kg per minute, raising its plasma levels from a baseline level of 2 to 3 to 10±1.2 pmol/L (mean±SEM).

The role of circulating CNP in the overall regulation of cardiovascular and renal function in healthy humans and disease states is less defined. Intra-arterial administration of CNP to humans induced vasodilatation of coronary and forearm resistance vessels. Barr et al observed a reduction in arterial pressure and CO but no changes in HR, plasma renin activity, and plasma aldosterone in response to the intravenous infusion of 50 ng/kg per minute CNP (~22.75 pmol/kg per minute) for 30 minutes. Igaki et al administered a CNP bolus (430 pmol/kg) to 13 healthy volunteers. Plasma CNP levels promptly increased up to 770±92.6 pmol/L (mean±SEM), and this was associated with significant increases in plasma (+75%) and urinary (+144%) cGMP, creatinine clearance (from 178.9±7.5 to 412.5±53.1 mL/min), diuresis (+117%), and natriuresis (+160%). In addition, there were significant

**TABLE 4. Doppler Data Under Baseline Conditions (0 to 60 min) and During Administration of CNP at 2 (60 to 120 min) or 4 (120 to 180 min) pmol/kg per Minute or Placebo**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>Placebo</th>
<th>CNP</th>
<th>Placebo</th>
<th>CNP</th>
<th>Placebo</th>
<th>CNP</th>
<th>Placebo</th>
<th>CNP</th>
<th>Placebo</th>
<th>CNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral E/A Ratio</td>
<td>min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1.56±0.34</td>
<td>1.58±0.31</td>
<td>0.52±0.02</td>
<td>0.50±0.04</td>
<td>0.17±0.09</td>
<td>0.17±0.09</td>
<td>0.36±0.08</td>
<td>0.38±0.08</td>
<td>0.29±0.08</td>
<td>0.31±0.07</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1.55±0.34</td>
<td>1.62±0.34</td>
<td>0.51±0.04</td>
<td>0.50±0.03</td>
<td>0.17±0.09</td>
<td>0.17±0.09</td>
<td>0.35±0.04</td>
<td>0.42±0.10</td>
<td>0.28±0.05</td>
<td>0.29±0.06</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>1.56±0.34</td>
<td>1.62±0.31</td>
<td>0.51±0.04</td>
<td>0.50±0.05</td>
<td>0.17±0.09</td>
<td>0.17±0.09</td>
<td>0.35±0.08</td>
<td>0.38±0.08</td>
<td>0.28±0.07</td>
<td>0.25±0.05</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>1.62±0.37</td>
<td>1.62±0.38</td>
<td>0.52±0.05</td>
<td>0.51±0.05</td>
<td>0.17±0.09</td>
<td>0.16±0.08</td>
<td>0.35±0.08</td>
<td>0.36±0.05</td>
<td>0.27±0.08</td>
<td>0.24±0.04</td>
</tr>
</tbody>
</table>

Mitral E/A indicates early to late mitral flow maximal velocity, hepatic A wave, presystolic maximal forward velocity, hepatic C wave, systolic maximal reverse velocity; and hepatic V wave, diastolic maximal reverse velocity.

**TABLE 5. Renal Function Under Baseline Conditions (First 1-Hour Clearance Period) and During Administration of CNP at 2 (Second Clearance Period) and 4 (Third Clearance Period) pmol/kg per Minute or Placebo**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Clearance Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
</tr>
<tr>
<td>RPF, mL/min</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>700±28</td>
</tr>
<tr>
<td>Placebo</td>
<td>691±35</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>116±4</td>
</tr>
<tr>
<td>Placebo</td>
<td>124±6</td>
</tr>
<tr>
<td>UNaV, μmol/min</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>149±16</td>
</tr>
<tr>
<td>Placebo</td>
<td>135±15</td>
</tr>
<tr>
<td>FENa, %</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>0.94±0.08</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.79±0.07</td>
</tr>
<tr>
<td>Clu, mL/min</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>28±1</td>
</tr>
<tr>
<td>Placebo</td>
<td>33±2</td>
</tr>
<tr>
<td>FPRNa, %</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>76±1</td>
</tr>
<tr>
<td>Placebo</td>
<td>74±1</td>
</tr>
<tr>
<td>FDMNa, %</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>24±1</td>
</tr>
<tr>
<td>Placebo</td>
<td>26±1</td>
</tr>
<tr>
<td>FORNa, %</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>96.1±0.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>96.9±0.4</td>
</tr>
<tr>
<td>UFR, mL/min</td>
<td></td>
</tr>
<tr>
<td>CNP</td>
<td>7.9±1.9</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.2±1.6</td>
</tr>
</tbody>
</table>
reductions in systolic and diastolic blood pressure (~4 mm Hg) and a concomitant increase in HR (+7 bpm). Finally, plasma aldosterone showed a 22% decrease 30 minutes after CNP injection, whereas plasma ANP and BNP showed a ~3-fold increase, probably as a consequence of the occupation of type C receptors, flooded by excessive amounts of exogenous CNP. Hunt et al.23 gave a 2-hour intravenous infusion of synthetic human CNP-22 (5 pmol/kg per minute) to nine healthy men. Plasma CNP increased from undetectable baseline levels up to ~60 pmol/L. There also were significant increases in plasma cGMP and ANP and a significant reduction in plasma aldosterone but no changes in arterial pressure, HR, creatinine clearance, diuresis, natriuresis, and the urinary excretion rate of cGMP. Furthermore, CNP did not affect the increases in arterial pressure and plasma aldosterone induced by a coinfusion of angiotensin II. Similar results were obtained by Cargill et al.,24 who used a higher dose of CNP (10 pmol/kg per minute for 30 minutes). Plasma CNP concentration raised from 0.46±0.06 to 126.9±15.9 pmol/L (mean±SEM) in the absence of any appreciable changes in CO, HR, systemic and pulmonary arterial pressures, and plasma aldosterone. The pressor and aldosterone responses to angiotensin II also were unaffected by CNP infusion. Neither plasma cGMP nor sodium excretion was measured in that study.

In the above studies, cardiac function was evaluated in terms of CO and afterload, without consideration that cardiac performance also is determined on the basis of myocardial contractility and preload. This study was designed to overcome this limitation and thoroughly evaluate most of the parameters that may contribute to ventricular function. In fact, changes in preload as well as in inotropism might compensate for the reduction in afterload induced by vasodilation,40 resulting in the maintenance of CO and arterial pressure. Indeed, such a phenomenon has been observed by our group in healthy subjects26 and patients with essential hypertension27 receiving low-dose BNP. In fact, BNP significantly reduced LV EDVI and stroke volume, whereas CO did not decline, due to compensatory increases in HR and in LV emptying, as indicated by increments in ejection fraction and reductions in ESVI.

In the current investigation, CNP was infused at lower doses than those used in previous studies in humans.10,23,24,39 Nevertheless, plasma CNP concentrations achieved in this study were ~30-fold higher than those observed in our healthy volunteers at baseline and 4~ to 10-fold higher than those observed in pathophysiological states characterized by higher-than-normal plasma CNP levels.32,36 The results of this study confirm that CNP infusion does not change CO, arterial pressures, and HR and demonstrate for the first time that this natriuretic peptide does not modify cardiac volumes and the dynamics of left and right heart filling. Therefore, changes in plasma CNP within the “physiological-pathophysiological” range seem to have no hemodynamic effects in healthy humans. Similarly, CNP did not modify renal hemodynamics and function, nor did it affect the renin-aldosterone axis. With respect to the latter point, the discrepancy between our data and the results by Hunt et al.21 who observed a decrement in plasma aldosterone during CNP infusion, is probably due to the fact that in the study of Hunt et al.,23 CNP interfered with the degradation of ANP, leading to a small but significant increase in plasma ANP levels. Indeed, plasma aldosterone concentration significantly decreased in response to the administration of low-dose ANP41 or BNP,42 resulting in changes in their plasma levels entirely within the physiological range.

CNP exerts its biological activities by activating NPR-B.14,15 Studies in isolated human arteries and veins by Ikeda et al.43 showed that NPR-B is expressed in low quantity in both arteries and veins, whereas NPR-A is expressed as much as NPR-B in veins but more abundantly (by 1 or 2 orders of magnitude) in arteries. These findings are in agreement with data by Wei et al.40 in dogs and Zhang et al.48 in humans, showing that ANP is markedly more effective than CNP in determining vasodilation in isolated arteries. In addition, in contrast with NPR-A, which is expressed in great abundance in endothelial cells, NPR-B is preferentially expressed in vascular smooth muscle cells.15,45–47 It is therefore conceivable

### TABLE 6. Endocrine Measurements Under Baseline Conditions (0 to 60 min) and During Administration of CNP at 2 (60 to 120 min) and 4 (120 to 180 min) pmol/kg per Minute or Placebo

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP, pmol/L</td>
<td>9.87±0.92</td>
<td>10.50±0.75</td>
<td>11.78±1.41</td>
<td>11.10±1.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>10.34±1.11</td>
<td>11.14±1.02</td>
<td>10.96±0.97</td>
<td>10.15±1.26</td>
</tr>
<tr>
<td>BNP, pmol/L</td>
<td>2.76±0.31</td>
<td>2.54±0.29</td>
<td>2.73±0.35</td>
<td>2.69±0.34</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.51±0.36</td>
<td>2.63±0.34</td>
<td>2.57±0.38</td>
<td>2.58±0.32</td>
</tr>
<tr>
<td>PRC, mL/L</td>
<td>18.78±3.72</td>
<td>16.58±3.48</td>
<td>19.97±3.83</td>
<td>15.61±2.35</td>
</tr>
<tr>
<td>Placebo</td>
<td>16.53±3.34</td>
<td>19.36±2.98</td>
<td>13.19±2.21</td>
<td>15.60±4.08</td>
</tr>
<tr>
<td>PAC, pmol/L</td>
<td>264±49</td>
<td>221±53</td>
<td>274±63</td>
<td>246±57</td>
</tr>
<tr>
<td>Placebo</td>
<td>241±57</td>
<td>265±62</td>
<td>234±58</td>
<td>252±40</td>
</tr>
</tbody>
</table>

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that the vasodilating effect of CNP would be reduced or even abolished by an intact endothelium. Indeed, CNP-induced relaxation of isolated canine veins is greater in vessels without than in those with endothelium. Several mechanisms may explain why the biological effects of CNP are attenuated in the presence of an intact endothelium. In fact, endothelium may act as a diffusion barrier to smooth muscle cells, and/or it may enhance CNP clearance by NPR-C or degradation by neutral endopeptidases 24,41.

In this study, administration of low-dose CNP did not influence renal hemodynamics and intrarenal sodium handling. This is in keeping with the evidence that within the kidney, CNP stimulates less cGMP generation than does ANP, even if NPR-Bs are expressed in the kidney. This blunted response may be due to either an intrinsically low guanylate cyclase activity of NPR-B or a low number of these receptors. The latter hypothesis may explain why renal NPR-Bs are not detectable with autoradiography or radioreceptor-binding assay. In addition, Ritter et al found that the cellular distribution of NPR-Bs is quite different from that of NPR-As. NPR-As were detected in glomeruli, thin limbs of Henle loop, cortical collecting ducts, and inner medullary collecting duct. NPR-Bs were found in the same nephron segments as NPR-As, with the exception of the thin limb. In the cortical collecting tubules, NPR-As were found in both principal and intercalated cells, whereas NPR-Bs were restricted to intercalated cells. In the inner medullary collecting duct cells, in which ANP is believed to exert its natriuretic activity by inhibiting an amiloride-sensitive sodium channel, NPR-As were found on the basal membrane, whereas NPR-Bs were located primarily in the apical pole, where they may not be available to circulating CNP.

In conclusion, the administration of low-dose CNP, raising its circulating levels to the pathophysiologic range, did not exert any appreciable effects on cardiac function, systemic and renal hemodynamics, and tubular sodium handling, nor did it influence the renin-angiotensin system. These results are not consistent with the hypothesis that CNP may act as a circulating hormone in humans.

Acknowledgments
This work was supported by grants from the University of Florence and the Italian Ministero per l’Università e la Ricerca Scientifica e Tecnologica (Minister of the University and Scientific Research).

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Hypertension. 1998;31:802-808
doi: 10.1161/01.HYP.31.3.802

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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