Hemodynamic, Renal, and Hormonal Responses to Brain Natriuretic Peptide Infusion in Patients With Congestive Heart Failure

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Background. This study was designed to examine the hemodynamic, renal, and hormonal effects of brain natriuretic peptide (BNP) infusion in patients with congestive heart failure (CHF) and in control subjects.

Methods and Results. We infused synthetic human BNP at a rate of 0.1 \( \mu \)g/kg/min. BNP infusion decreased pulmonary capillary wedge pressure (control, from 5±1 to 2±1 mm Hg, \( p<0.01 \); CHF, from 21±3 to 14±4 mm Hg, \( p<0.05 \)) and systemic vascular resistance (control, from 1,264±75 to 934±52 dyne⋅sec⋅cm\(^{-5} \); CHF, from 2,485±379 to 1,771±195 dyne⋅sec⋅cm\(^{-5} \); \( p<0.01, \) respectively) and increased stroke volume index (control, from 49.9±2.7 to 51.5±2.3 ml/m\(^{2} \), \( p=NS \); CHF, from 25.6±3.8 to 32.0±3.9 ml/m\(^{2} \), \( p<0.01 \)). BNP infusion significantly increased urine volume (control, from 2.3±0.7 to 7.5±1.9 ml/min; CHF, from 0.8±0.2 to 5.3±1.0 ml/min; \( p<0.01 \), respectively), excretion of sodium (control, from 79.2±21.6 to 332.8±70.9 µEq/min; CHF, from 77.4±20.8 to 753.5±108.0 µEq/min; \( p<0.01 \), respectively), and excretion of chloride (control, from 72.5±18.4 to 256.0±43.3 µEq/min; CHF, from 74.0±19.6 to 708.8±103.3 µEq/min; \( p<0.01 \), respectively). Urinary excretion of sodium and of chloride in response to BNP infusion was higher in patients with CHF than in control subjects (\( p<0.01 \), respectively). BNP infusion increased the levels of plasma atrial natriuretic peptide (control, from 65±11 to 84±14 pg/ml; CHF, from 262±65 to 301±62 pg/ml; \( p<0.05 \), respectively) and decreased plasma aldosterone concentrations in both groups (control, from 43.3±12.1 to 27.3±7.1 pg/ml; CHF, from 91.1±34.3 to 66.3±27.2 pg/ml; \( p<0.05 \), respectively).

Conclusions. We conclude that BNP infusion improves left ventricular function in patients with CHF by vasodilation and prominent natriuretic action. (Circulation 1991;84:1581–1588)

Atrial natriuretic peptide (ANP) is a circulating hormone with a wide range of potent biological effects, including natriuresis, diuresis, vasodilatation, and inhibition of the renin-angiotensin-aldosterone system.\(^{-5} \) and there is now increasing evidence that ANP plays an important role in the regulation of fluid volume and blood pressure.\(^{2-5} \) ANP is secreted mainly from atria,\(^{1-6} \) and its plasma levels are increased in patients with congestive heart failure (CHF).\(^{6-13} \) We and others\(^{13-15} \) have shown that ANP is synthesized and secreted also from the left ventricle in patients with CHF. We and others\(^{16-18} \) have shown further that infusion of ANP improves left ventricular function by reducing both preload and afterload in patients with CHF.\(^{16-18} \)

Brain natriuretic peptide (BNP), first isolated from the brains of pigs\(^{19} \) and subsequently from the hearts of pigs\(^{20} \) and rats,\(^{21,22} \) forms a peptide family with ANP involved in the regulation of blood pressure and fluid volume.\(^{23-25} \) However, the molecular form of BNP varies among species. Recently, we isolated human BNP from human atrium, determined its amino acid sequence,\(^{26} \) and established a specific
radioimmunoassay for human BNP by developing a monoclonal antibody against it.27–29 We have demonstrated that BNP is a novel cardiac hormone secreted predominantly from the ventricle20–22,27–29 and that plasma levels of BNP are markedly increased in patients with CHF (in proportion to its severity) and surpass plasma levels of ANP in severe cases.27–29 We have also shown that the synthesis, secretion, and clearance of BNP differ from those of ANP, and we have suggested that BNP has discrete physiological and pathological roles in the dual natriuretic peptide system.29 However, the precise roles of BNP in the regulation of fluid volume and blood pressure have not been elucidated in humans.

This study was designed to examine the hemodynamic, renal, and hormonal effects of BNP in humans by infusing synthetic human BNP in patients with CHF and in control subjects.

Methods

Patients

Seven patients with clinically overt CHF (New York Heart Association class II, III, or IV) and eight control subjects were included in this study. The group of patients with CHF consisted of five men and two women with a mean age of 60, ranging from 50 to 71 years; the control group consisted of five men and three women with a mean age of 51, ranging from 31 to 62 years. The cause of CHF was dilated cardiomyopathy in five, prior myocardial infarction in one, and mitral valve regurgitation in one. Eight control subjects complained of chest pain but were diagnosed to have no cardiac disease on the basis of physical, electrocardiographic, echocardiographic, and diagnostic catheterization including coronary arteriogram and left ventriculogram.

Written informed consent was obtained from each patient and his or her family. This study protocol was in agreement with the guidelines of the ethical committee of our institutions.

Synthetic Human BNP

Human BNP was purchased from Peptide Institute Inc., Minoh, Japan. The homogeneity of human BNP was confirmed by reverse-phase, high-performance liquid chromatography and amino acid analysis. Human BNP was dissolved in saline with 10% lactose and sterilized by passage through a 0.22-μm Millipore filter (Bedford, Mass.). The chemical nature and content of BNP in vials were verified by high-performance liquid chromatography and radioimmunoassay (RIA).

Study Protocol

A Swan-Ganz catheter was inserted 1 day before the study, and patients were kept at rest in bed overnight. All drugs were stopped at least 24 hours before the study except in one patient with CHF, who had been treated with digitalis until 10 hours before the study.

Two serial baseline measurements were obtained in each patient at 15-minute intervals. BNP infusion was begun at a rate of 0.1 μg/kg/min for 30 minutes through a peripheral vein with the use of an infusion pump at a flow rate of 0.4 ml/min. Hemodynamic measurements, collection of blood samples from the pulmonary artery, and urine samples were performed according to the protocol indicated in Figure 1.

Hemodynamic measurements. Pulmonary capillary wedge pressure, pulmonary arterial pressure, right atrial pressure, and systolic and diastolic blood pressures were measured 15 minutes before, immediately before BNP infusion, and every 5 minutes after initiation of the infusion for 60 minutes. Cardiac output was determined in triplicate by the thermodilution technique 15 minutes before, immediately before the infusion, and every 15 minutes after the initiation of infusion for 60 minutes. Heart rate was continuously monitored by the electrocardiogram in lead II. Cardiac index, stroke volume, stroke volume index, systemic vascular resistance, and pulmonary vascular resistance were calculated by standard formulas.

Blood sampling. Blood samples were taken from the pulmonary artery through the inserted Swan-Ganz catheter 15 minutes before, immediately before the infusion, and every 15 minutes after the initiation of the infusion for 60 minutes. Blood samples for the measurements of plasma levels of ANP, BNP, and guanosine 3',5'-cyclic monophosphate (cGMP) were transferred to chilled disposable tubes containing aprotonin (1,000 kallikrein inactivator units/ml) and EDTA (1 mg/ml). The blood samples were immediately placed on ice and promptly centrifuged at 4°C, and aliquots of plasma were immediately stored at −80°C until the assay. For the measurements of other hormone levels and biochemical analyses, plasma and sera were also suitably obtained.

Urine sampling. A bladder catheter was inserted before the study. Total urine sample for 30 minutes was collected before, during, and after the BNP infusion.
Measurement of Plasma Hormones

Plasma ANP concentration was measured with a specific RIA for α-human ANP as previously reported. This RIA recognizes a carboxyterminal sequence of ANP, and the minimal detectable quantity of α-human ANP is 1 pg per tube. The intra-assay and interassay coefficients of variation were 7.2% and 7.8%, respectively. The cross-reactivity with human BNP was less than 0.01% on a molar basis. Plasma BNP concentration was measured with a specific RIA by using monoclonal antibody that recognized the ring structure of human BNP, and the minimal detectable quantity of human BNP was 1 pg per tube as previously reported. The cross-reactivity with α-human ANP was less than 0.005% on a molar basis. The intra-assay and interassay coefficients of variation were 8.4% and 6.4%, respectively. Plasma concentration of cGMP was measured by RIA after succinylation. The minimal detectable quantity of cGMP was 5 fmol per tube, and the coefficients of variation were 8.0% for intra-assay and 13.5% for interassay. Plasma renin activity and plasma aldosterone concentration were measured with commercially available kits, renin RIA beads (Dainabot Co., Tokyo) and aldosterone RIA kit II (Dainabot Co.), respectively. Plasma levels of norepinephrine and epinephrine were measured with high-performance liquid chromatography combined with the trihydroxyindole fluorometric procedure (HLC8030, Tosoh Co., Tokyo).

Other Biochemical Measurements

Sodium, potassium, and chloride concentrations in serum and urine were measured with the ion electrode method (Hitachi 736, Hitachi Medical Co., Tokyo). Serum and urine creatinine concentrations were determined with Jaffe’s procedure (Hitachi 736). An endogenous creatinine clearance was calculated based on a standard formula as an index of glomerular filtration rate.

Statistical Analysis

All values were expressed as mean±1 SEM. Comparisons among values obtained in the control period and during and after BNP infusion were made by one-way analysis of variance for repeated measures with subsequent Dunnett’s t test. A value of p<0.05 was considered statistically significant. Hemodynamic parameters, urine volume, and hormone levels were compared between two groups with the unpaired t test.

Results

Hemodynamic Responses to BNP

Hemodynamic responses to BNP infusion in patients with CHF and control subjects are described in Figure 2.

Heart rate did not change significantly during the infusion in the CHF group. On the other hand, it significantly increased at the end of the infusion (p<0.05) in the control group.
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<td>193±61†</td>
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<td>84±14*§</td>
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<td>316±50*§</td>
<td>301±62*§</td>
<td>264±68§</td>
<td>231±70‡</td>
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<td>16.4±4.1</td>
<td>46.5±6.4†</td>
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<td>65.6±26.6</td>
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<td>45.8±18.4†</td>
<td>47.8±20.6†</td>
<td>60.0±32.5</td>
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<td>43.3±12.1</td>
<td>32.5±6.8*</td>
<td>27.3±7.1*</td>
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<td>CHF</td>
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<td>67.0±23.4</td>
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<td>Norepinephrine (pg/ml)</td>
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<td>All patients</td>
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<td>468±156</td>
<td>516±131†</td>
<td>576±114†</td>
<td>583±131†</td>
<td>545±123†</td>
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<tr>
<td>Control</td>
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<td>303±29§</td>
<td>400±28§</td>
<td>371±54§</td>
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<td>725±170§</td>
<td>739±139§</td>
<td>776±111§</td>
<td>814±128§</td>
<td>768±118§</td>
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<td>Epinephrine (pg/ml)</td>
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<td>74±22</td>
<td>73±29</td>
<td>57±22*</td>
<td>67±23</td>
<td>57±21*</td>
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<tr>
<td>Control</td>
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<td>41±12</td>
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<tr>
<td>CHF</td>
<td>83±30</td>
<td>81±28</td>
<td>96±38</td>
<td>72±27</td>
<td>86±28</td>
<td>72±26</td>
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</table>

Values are mean±SEM. BNP, brain natriuretic peptide; CHF, congestive heart failure; ANP, atrial natriuretic peptide; cGMP, guanosine 3',5'-cyclic monophosphate; PRA, plasma renin activity.

* p<0.05, † p<0.01 vs. time 0. § p<0.05, ‡ p<0.01 control vs. CHF.

| *Calculated as 10 pg/ml for five concentrations less than the minimal detectable level of 10 pg/ml.

1/min/m² versus 3.4±0.2 l/min/m², p<0.01) and increased significantly at the end of the infusion to 3.2±0.3 ml/min/m² (p<0.05) in the CHF group and to 4.3±0.3 l/min/m² (p<0.01) in the control group. Stroke volume index was significantly lower in the CHF group than in the control group (25.6±3.8 ml/m² versus 49.9±2.7 ml/m², p<0.01) and increased significantly to 32.0±3.9 ml/m² (p<0.01) at the end of the infusion in the CHF group but did not change in the control group during the infusion.

Systemic vascular resistance was significantly higher in the CHF group than in the control group (2,485±379 dyne·sec·cm⁻⁵ versus 1,264±75 dyne·sec·cm⁻⁵, p<0.05) and decreased significantly at the end of the infusion to 1,771±195 dyne·sec·cm⁻⁵ (p<0.05) in the CHF group and to 934±52 dyne·sec·cm⁻⁵ (p<0.01) in the control group. Pulmonary vascular resistance, which was not different between the two groups (132±29 dyne·sec·cm⁻⁵ versus 93±16 dyne·sec·cm⁻⁵), did not change significantly during infusion in the CHF group but decreased significantly from 93±16 dyne·sec·cm⁻⁵ before the infusion to 78±12 dyne·sec·cm⁻⁵ 15 minutes after the end of the infusion (p<0.05) in the control group.

**Hormonal Responses to BNP**

The results of all hormonal effects are summarized in Table 1. Plasma BNP levels were much higher in the CHF group than in the control group before BNP infusion (453±190 pg/ml versus 34±13 pg/ml, p<0.01). After the beginning of BNP infusion, plasma BNP levels promptly increased, reaching a peak at the end of the infusion in both the CHF group and the control group (9,129±1,194 pg/ml and 7,687±1,100 pg/ml, respectively). After the end of the infusion, plasma levels decreased gradually but were significantly higher at 30 minutes after the end of the infusion than baseline levels both in the CHF group (1,519±368 pg/ml, p<0.01) and in the control group (471±107 pg/ml, p<0.01). Plasma levels of ANP in...
the CHF group were also higher than those in the control group (262±65 versus 65±11 pg/ml, p<0.01) before BNP infusion. Plasma ANP levels significantly increased in the CHF group (from 262±65 pg/ml to 316±50 pg/ml, p<0.05) and in the control group (from 65±11 pg/ml to 87±15 pg/ml, p<0.05). The plasma cGMP levels before BNP infusion were significantly higher in the CHF group than in the control group (25.1±3.3 pmol/ml versus 7.7±1.1 pmol/ml, p<0.01). cGMP levels increased in both groups (p<0.01, respectively) during infusion and remained elevated over 30 minutes after the end of the infusion in both groups (p<0.01, respectively). The difference of plasma cGMP levels between the two groups disappeared during and after the infusion. Plasma renin activity was higher in the CHF group than in the control group (2.9±0.9 ng/ml/hr versus 0.8±0.2 ng/ml/hr, p<0.05) before infusion and did not change significantly during infusion in both groups.

Plasma aldosterone levels tended to be higher in the CHF group than in the control group (91.1±34.3 pg/ml versus 43.3±12.1 pg/ml) and were significantly suppressed by BNP infusion.

Plasma norepinephrine levels were significantly higher in the CHF group than in the control group at baseline (725±170 pg/ml versus 216±25 pg/ml, p<0.01) and increased significantly to 400±28 pg/ml (p<0.01) at the end of the infusion in the control group. There were no significant changes in plasma epinephrine levels in response to BNP infusion in both groups.

Renal Responses to BNP

Renal responses to BNP infusion are summarized in Figure 3.

Urine volume increased significantly during BNP infusion in both groups (from 2.3±0.7 ml/min to 7.5±1.9 ml/min, p<0.01 for the control group and from 0.8±0.2 ml/min to 5.3±1.0 ml/min, p<0.01 for the CHF group) and after the end of the infusion in the CHF group (from 0.8±0.2 ml/min to 4.3±0.8 ml/min, p<0.01).

Urinary excretion of sodium increased significantly during and after the end of the infusion in both groups (from 79.2±21.6 μEq/min to 332.8±70.9 μEq/min during infusion, p<0.01, to 242.7±64.8 μEq/min after the end of the infusion in the control group, p<0.01; and from 77.4±20.8 μEq/min to 753.5±108.0 μEq/min during infusion, p<0.01, to 612.9±61.6 μEq/min after the end of the infusion, p<0.01, in the CHF group). Urinary excretion of chloride increased significantly during and after the end of the infusion in both groups (from 72.5±18.4 μEq/min to 256.0±43.3 μEq/min during infusion, p<0.01, to 214.2±53.0 μEq/min after the end of the infusion in the control group, p<0.05; and from 74.0±19.6 μEq/min to 708.8±103.3 μEq/min during infusion, p<0.01, to 584.6±55.5 μEq/min after the end of the infusion, p<0.01, in the CHF group). The degree of urinary sodium and degree of chloride excretion were significantly greater in the CHF group than in the control group during and after the end of the infusion (p<0.01, respectively). Urinary potassium excretion increased significantly both during and after the end of the infusion in the CHF group (p<0.01, respectively) and during infusion in the control group (p<0.05).

Creatinine clearance increased during infusion in both groups, but the increase was significant only in the control group (p<0.05).

Effects of BNP on Blood Cell Counts and Blood Biochemistry

BNP infusion showed no significant effects on the values of blood cell counts or of blood biochemistry including serum sodium, potassium, and chloride concentrations, osmotic pressure, and serum transaminases.

Discussion

BNP, first isolated from the brains of pigs,20 rats,21,22 and

FIGURE 3. Bar graph shows renal responses to the infusion of brain natriuretic peptide. Urinary volume (UV), excretion of sodium (\(U_{Na}V\)), potassium (\(U_{K}V\)), and chloride (\(U_{Cl}V\)), and creatinine clearance (Ccr) increased markedly during infusion in control subjects and patients with congestive heart failure (CHF). Excretion of \(U_{Na}V\) and \(U_{Cl}V\) were significantly increased in patients with CHF. *p<0.05, **p<0.01 compared with values at time 0. †p<0.05, ‡p<0.01 control vs. CHF. NS, not significant.
humans,26 forms a peptide family with ANP involved in the regulation of blood pressure and blood volume.23–25 We have isolated human BNP and determined its 32-amino-acid sequence,26 which has structural diversity among species. It has been subsequently cleared that the biological actions of BNP are species specific, unlike those of ANP.33 We have also shown that BNP is secreted predominantly from the ventricle29 and that its plasma levels are markedly increased in patients with CHF (in relation to its severity) and surpass plasma levels of ANP.27–29

Previous studies have shown that the infusion of ANP decreases pulmonary capillary wedge pressure and systemic vascular resistance and increases cardiac output, thereby improving left ventricular function by reducing both preload and afterload in patients with CHF.16–18 Diuretic and natriuretic responses to ANP infusion, however, were blunted in these patients.16–18 The present study has shown that plasma levels of BNP are increased in patients with CHF compared with control subjects at baseline; this is in agreement with the results of our previous studies.27–29 The baseline levels in control subjects were slightly higher than in our previous reports.27–29 This is probably because one patient with mild hypertension and two patients with history of mild hypertension were included in the control group in this study. During the infusion of BNP, plasma BNP levels increased markedly to approximately 150-fold of baseline levels in control subjects and 20-fold in patients with CHF; levels remained elevated even at 30 minutes after the end of the infusion. This is in agreement with the results of our previous report, which demonstrated that the clearance of BNP in the circulation is slower than that of ANP.29

The infusion of BNP decreased pulmonary capillary wedge pressure, right atrial pressure, and systemic vascular resistance, and increased stroke volume index in patients with CHF, indicating that infusion of BNP improves left ventricular function in patients with CHF. In control subjects, however, BNP infusion did not increase stroke volume index, although it decreased pulmonary capillary wedge pressure and systemic vascular resistance. Thus, BNP has a beneficial effect on left ventricular function in patients with CHF (hemodynamic effects of BNP are similar to those of ANP).

The infusion of BNP markedly increased urine volume and urinary excretion of sodium, potassium, and chloride in patients with CHF and in control subjects. The degree of urinary excretion of sodium and of chloride during BNP infusion was, however, significantly higher in patients with CHF than in control subjects. This is in sharp contrast with the case of ANP infusion, to which the patients with CHF showed blunted natriuretic response.16–18 It is not clear why the enhanced natriuretic response occurs to BNP infusion in patients with CHF. There was no significant difference in plasma BNP levels during the infusion between patients with CHF and control subjects. Creatinine clearance or glomerular filtration rate increased significantly during infusion in control subjects but not in patients with CHF. Thus, the increase in urinary sodium excretion in patients with CHF is due to the reduced tubular sodium reabsorption. It has been shown recently that BNP as well as ANP is cleared by two mechanisms. One mechanism is binding to receptors34,35 or clearance (C)-receptors not linked to guanylate cyclase (GC) and the other is degradation by neutral endopeptidases (NEP).36,37 which are concentrated mostly within the brush border of the proximal tubule of the kidney.37–39 ANP and BNP exert many of their biological effects by stimulating GC-linked receptors,40–42 leading to increases in cGMP concentration in target cells. Recent studies have shown that there are two forms of the GC-linked receptor, GC-A-receptors and GC-B-receptors,41,42 the former having a higher affinity for ANP and the latter for BNP; tissue distribution of these two receptors are different, and only the GC-A-receptor has been demonstrated in the human kidney.41,43 Recent studies also suggest that the renal degradation of ANP by NEP is enhanced in the presence of elevated plasma levels of ANP.43–46 Cavero and coworkers44 suggested that enhanced renal degradation of ANP by NEP in CHF may contribute to the attenuated renal natriuretic response in CHF. It is not clear why BNP does not show attenuated renal natriuretic response in CHF. Large amounts of infused BNP also seem to compete with endogenous ANP for C-receptors, thereby increasing plasma levels of endogenous ANP as shown in this study. The possibility that large amounts of BNP may modulate other intrarenal peptides of hormonal systems such as the renin-angiotensin system or prostaglandins in CHF cannot be excluded.

During infusion of BNP, plasma ANP levels increased significantly compared with those of baseline both in control subjects and in patients with CHF. This is surprising because BNP infusion reduced pulmonary capillary wedge pressure and right atrial pressure, which is expected to lead to decreased ANP secretion.2–5 It is probable that large amounts of infused BNP compete with endogenous ANP for binding to C-receptors, resulting in increased amounts of ANP not being cleared.

During infusion of BNP, plasma levels of cGMP increased markedly both in patients with CHF and in control subjects and became similar between the two groups.

Infusion of BNP did not change plasma renin activity in patients with CHF or in control subjects. Because diuretics and vasodilators stimulate the renin-angiotensin system, no change in plasma renin activity (despite the decrease in blood pressure and increased sodium excretion shown in this study) suggests that BNP exerts an inhibitory effect on the juxtaglomerular apparatus. Despite the absence of changes in plasma renin activity, BNP infusion decreased plasma aldosterone levels significantly. Therefore, the inhibition of plasma aldosterone by
BNP was probably due to a direct effect on the adrenal gland, as is the case for ANP. It is likely that inhibition of aldosterone secretion may contribute to natriuresis with the longer period of BNP infusion.

Plasma norepinephrine levels increased significantly in control subjects and tended to increase in patients with CHF in response to BNP infusion. This is probably due to baroreceptor-mediated sympathetic discharge in response to peripheral vasodilation and a decrease in arterial blood pressure. It is interesting to note that ANP infusion decreased or tended to decrease plasma levels of norepinephrine in patients with CHF, probably because ANP has a sympatholytic effect and baroreceptor activity is blunted in these patients. BNP thus seems to have less effect than ANP on the sympathetic nervous system.

We have previously reported that plasma levels of BNP as well as ANP are increased as the severity of CHF increases and suggested discrete physiological and pathophysiological roles of BNP in the dual natriuretic peptide system. The present study shows that BNP infusion decreases both preload and afterload and increases cardiac output in patients with CHF. Moreover, in contrast with ANP, the natriuretic response to BNP was not blunted in patients with CHF. These results indicate that increased secretion of BNP plays an important role in the compensation of CHF in association with ANP. Because BNP has an enhanced natriuretic effect and a longer duration of action in patients with CHF, this study raises the possibility that BNP is more advantageous than ANP as a therapeutic agent for CHF. The dose of BNP infused in this study was large, however, and plasma levels were increased up to one order of magnitude higher than the pathologically increased endogenous levels. Thus, the effects of BNP infusion in this study may be pharmacological rather than physiological. Further studies using lower doses will be required to assess the physiological and pathophysiological significance of BNP.

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References


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