Clinical application of atrial natriuretic polypeptide in patients with congestive heart failure: beneficial effects on left ventricular function

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ABSTRACT Synthetic α-human atrial natriuretic polypeptide was infused in patients with congestive heart failure (CHF) (New York Heart Association class III or IV) and in those without CHF. The infusion of atrial natriuretic polypeptide (ANP) at a rate of 0.1 μg/kg/min significantly decreased pulmonary capillary wedge pressure and increased stroke volume index in all of the patients with CHF, whereas it decreased pulmonary capillary wedge pressure but caused no significant change in stroke volume index in the patients without CHF. Concomitant significant reductions in total systemic resistance were observed in both groups of patients. The ANP infusion significantly increased the urine volume, the excretion of sodium, and endogenous creatinine clearance in the patients without CHF. In the patients with CHF, it also showed a tendency to increase all these variables, but the urine volume did not correlate with the reduction in pulmonary capillary wedge pressure. The ANP infusion also decreased plasma aldosterone concentrations in these patients, although no significant difference was observed in the decrement of the plasma aldosterone concentration in the patients with and those without CHF. These findings indicate that the ANP infusion improves left ventricular function in patients with CHF, and suggest that this improvement results mainly from the vasodilating activity of ANP.


AFTER THE EPOCHAL discovery of the potent diuretic, natriuretic, and vasorelaxant activities in an extract from rat atria by de Bold et al.,1 multiple forms of natriuretic polypeptides with high and low molecular weights have been isolated from rat and human atria and implicated in the control of blood pressure, water, and electrolyte balance.2–8 Accumulating evidence indicates that α-atrial natriuretic polypeptide (α-ANP) with 28 amino acids is secreted through the coronary sinus from the heart and circulates in the body as a hormone9–14 and that intravenous administration of synthetic α-human ANP causes rapid diuresis, natriuresis, vasodilation, and inhibition of the aldosterone secretion in humans10,15–17 and experimental animals.18–21 In addition, it has also been suggested that ANP suppresses the secretion of renin18,19 and vasopressin.22,23 Thus, ANP is a cardiac hormone with fluid volume–reducing and vasodilating activities.

The conventional treatment of congestive heart failure (CHF) consists of diuretics, positive inotropic agents, and vasodilating agents. ANP has diuretic and vasodilating activities and is considered to be useful to improve cardiac performance in patients with CHF. However, plasma ANP concentrations in patients with CHF have been demonstrated to be elevated compared with those in normal subjects,24–28 and ANP binding sites have been reported to be down-regulated in CHF.29 The administration of ANP for the treatment of...
CHF therefore differs from conventional replacement therapy for a hormone deficiency state such as diabetes mellitus, hypothyroidism, or other hypofunctional endocrine disorders and raises a question as to its clinical usefulness for the treatment of CHF. At present, there exist only a few preliminary reports concerning the usefulness of the administration of ANP for the treatment of CHF, and comparisons of the effects of ANP in patients with and without CHF have not yet been reported.

To clarify whether or not ANP is clinically useful for the treatment of CHF, we have examined the effects of the continuous infusion of α-human ANP on the left ventricular, renal, and endocrine functions in patients with CHF and compared them with those functions in patients without CHF.

Methods

Patients. Six patients with clinically overt CHF (New York Heart Association [NYHA] class III or IV) and six patients without CHF participated in this study. There were 10 men and two women ranging in age from 32 to 70 years (mean ± SE 51 ± 3). The cause of CHF was dilated cardiomyopathy in four, aortic regurgitation in one, and hypertensive heart failure in one. In all patients with CHF a Swan-Ganz catheter was inserted for therapeutic use at bedside. Five of the six patients without CHF underwent diagnostic cardiac catheterization (because of old myocardial infarction in two, suspicion of angina pectoris in three) and a Swan-Ganz catheter was inserted in the remaining patient as part of the treatment of acute myocardial infarction. One patient with CHF and two patients without CHF had not been treated. Five patients with CHF were receiving drugs, including diuretics and cardiac glycosides. Four patients without CHF had been receiving coronary vasodilators. All vasodilators, diuretics, and inotropic agents were discontinued at least 24 hr before the study. Informed consent was obtained from each patient. This study was approved by the ethical committee on human research of Kyoto University (No. 61-9).

Synthetic α-human ANP. α-Human ANP (human ANF 99–126) was synthesized as previously described. The homogeneity of the α-human ANP used in this study was confirmed by reverse-phase, high-performance liquid chromatography and amino acid analysis. The α-human ANP was dissolved in saline with 10% lactose and was sterilized by passage through a 0.22 μm Millipore filter (Bedford, MA). The chemical nature and content of the α-human ANP in vials were verified by high-performance liquid chromatography and radioimmunoassay (RIA), as reported elsewhere.

Study protocol. After 30 min of bed rest, two serial baseline measurements were obtained in each subject at an interval of 15 min and then the ANP infusion was begun at a rate of 0.1 μg/kg/min for 30 min through a peripheral vein with the use of an infusion pump (Nipro SP-50, Nipro Co., Ltd., Osaka, Japan) with a flow rate of 0.4 ml/min. Hemodynamic measurements and collections of blood and urine samples were performed as summarized in figure 1. These investigations were carried out before the arteriograms and ventriculograms.

Hemodynamic measurements. Pulmonary capillary wedge pressure, pulmonary arterial pressure, and right atrial pressure were determined with a Swan-Ganz catheter (Heparin Coated Thermolisation Catheter Model SP 5107, Gould Inc., Oxnard, CA) connected to a Gould P23ID pressure transducer (Gould Inc., Oxnard, CA). The zero pressure reference level was taken at mid chest. Systolic and diastolic arterial pressures were determined with a No. 8F end-hole catheter connected to a Gould P23ID pressure transducer, and mean arterial pressure was obtained by electrical dumping in five patients who underwent the study in the catheterization laboratory. In seven patients who underwent the examinations at bedside, systolic and diastolic arterial blood pressures were measured with a standard sphygmomanometer and mean arterial pressure was calculated by a standard formula. Systemic and intracardiac pressures were recorded 15 min before the ANP infusion and every 5 min from 0 to 60 min after the initiation of the ANP infusion. Cardiac output was determined in triplicate by the thermodilution technique at −15, 0, 15, 30, 45, and 60 min. Heart rate was continuously monitored by the electrocardiogram in lead II. Cardiac index, stroke volume, stroke volume index, total systemic resistance, and total pulmonary resistance were calculated by standard formulas.

Blood sampling. Blood samples were taken through an indwelling cannula inserted into the antecubital or the femoral vein at −15, 0, 15, 30, 45, and 60 min. Blood samples for the measurement of the plasma ANP concentration were transferred to chilled disposable tubes containing aprotinin (1000 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 −20°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 and urine was collected for 30 min before, during, and after the ANP infusion.

Measurements of the plasma hormones. The plasma ANP concentration was measured by a specific RIA for α-ANP reported previously. Briefly, this RIA recognizes a carboxyterminal fragment of ANP, α-ANP (17–28), and the minimal detectable quantity of α-human ANP is 1 pg/tube. Plasma renin activity and the plasma aldosterone concentration were measured with commercially available kits, Renin RIA beads (Dainabot Co., Ltd., Tokyo, Japan) and Aldosterone Test Shionogi (Shionogi Co., Ltd., Osaka, Japan), which are based on previously reported methods. Plasma norepinephrine and epinephrine levels were measured by high-performance liquid chromatography combined with the trihydroxyindole fluorometric procedure.

Other biochemical measurements. The sodium, potassium, and chloride concentrations in serum and urine were measured by the ion electrode method (Hitachi 736, Hitachi Medical Corporation, Tokyo, Japan). Serum and urine osmolalities were determined by the freezing point depression (Auto stat OM-6010 Kyotodaiichikagaku Co., Ltd., Kyoto, Japan). Serum and urine creatine concentrations were determined by Jaffe’s procedure.
dure (Hitachi 736, Hitachi Medical Corporation, Tokyo, Japan). 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 the mean ± SE. Comparisons between values recorded during the control period and those obtained during the ANP infusion or recovery period were made by the paired Student's t test. When a p value was <.05, the difference was considered statistically significant.

Results

The plasma ANP concentration. The time course of the plasma ANP concentration in each individual patient in this study is summarized in table 1. Plasma ANP concentrations before the ANP infusion were significantly higher in the patients with CHF than in those without CHF (1490 ± 459 vs 161 ± 44 pg/ml, p < .05). Plasma ANP levels promptly increased, reaching a peak at 15 min after the start of the ANP infusion, and returned to the preinfusion level at 15 min after the end of the infusion in the patients with CHF. In those without CHF, plasma ANP levels were the highest at 30 min of the infusion period and gradually decreased during the 30 min postinfusion period.

Hemodynamic effects of ANP. Five of the six patients with CHF showed a marked reduction in pulmonary capillary wedge pressure of 10 mm Hg or greater and an increase in stroke volume index of 25% or greater during the ANP infusion. The remaining patient (No. 6), whose stroke volume index was the highest, showed a reduction in pulmonary capillary wedge pressure of 4 mm Hg and an increase in stroke volume index of 5%. On the other hand, the ANP infusion decreased pulmonary capillary wedge pressure by 2 to 9 mm Hg in the patients without CHF, but it resulted in no significant change in stroke volume index in these patients. The mean hemodynamic responses to the ANP infusion in the patients with and without CHF are presented in figures 2, 3, and 4. As presented in figure 2, A, pulmonary capillary wedge pressure began to decline within 5 min and a significant response occurred within 15 to 25 min and was sustained for 25 to 30 min after the end of the ANP infusion in both groups of patients, although the change was greater in the patients with CHF than in those without it. The infusion of ANP produced a change in right atrial pressure (figure 2, B) similar to that in pulmonary capillary wedge pressure in both groups of patients. Mean pulmonary arterial pressure also significantly decreased during the infusion of ANP (from 38.9 ± 3.2 to 29.8 ± 4.3 mm Hg) in the patients with CHF and decreased from 12.0 ± 1.5 to 8.5 ± 1.1 mm Hg in the patients without CHF. In the patients with CHF, mean arterial pressure fell slightly but significantly without a concomitant increase in heart rate, whereas it decreased by about 10 mm Hg in the patients without

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<td>Time course of plasma ANP concentration and maximal hemodynamic responses to the ANP infusion in each patient</td>
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<th>Maximal responses to the ANP infusion</th>
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<td>F</td>
<td>IHF</td>
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<td>M</td>
<td>OM</td>
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<td>161</td>
<td>±51</td>
<td>±713</td>
<td>±899</td>
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</table>

NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; SVI = stroke volume index; MAP = mean arterial pressure; DCM = dilated cardiomyopathy; HH = hypertensive heart failure; AR = aortic regurgitation; IHD = ischemic heart disease; AMI = acute myocardial infarction; OM = old myocardial infarction.
Total systemic resistance was significantly higher in the patients with CHF than in the patients without CHF (p < .05) before the infusion of ANP. During the infusion, in the patients with CHF a significant reduction in total systemic resistance was observed at 15 min (1737 ± 293 dynes·sec·cm⁻², p < .01), at 30 min (1598 ± 207 dynes·sec·cm⁻², p < .01), and at 45 min (1568 ± 170 dynes·sec·cm⁻², p < .05) compared with the control value (2129 ± 293 dynes·sec·cm⁻²; figure 4, B). Total pulmonary resistance decreased in a similar fashion (908 ± 137 dynes·sec·cm⁻² at control, 623 ± 95 dynes·sec·cm⁻² at 30 min [p < .05], 651 ± 130 dynes·sec·cm⁻² at 45 min [p < .01]). In the patients without CHF, total systemic resistance also fell significantly during the infusion of ANP and returned to the control value within 15 min after the end of the infusion (figure 4, B); total pulmonary resistance tended to decrease.

Figure 5 shows effects of the infusion of ANP on the relationship between pulmonary capillary wedge pressure and stroke volume index. In the patients with CHF, all plots significantly moved upward and to the left, indicating an improvement in left ventricular function. In the patients without CHF, however, the

CHF, with a concomitant significant increase in heart rate (figure 3).

Stroke volume index increased significantly to 31.6 ± 4.1 ml/m² at the end of the infusion (p < .05) from a control value of 26.2 ± 4.2 ml/m² in the patients with CHF and this enhancement lasted over 15 min after the end of the infusion. In the patients without CHF, however, stroke volume index did not change significantly during the infusion of ANP, but fell from 48.7 ± 3.4 to 42.1 ± 4.8 ml/m² at 15 min after the end of the infusion (p < .05; figure 4, A). In contrast, significant augmentations in cardiac index were observed in both groups of patients during the infusion of ANP (from a control value of 2.18 ± 0.29 to 2.60 ± 0.30 liters/min/m² at 30 min in the patients with CHF, p < .001; and from a control value of 2.93 ± 0.12 to 3.37 ± 0.27 liters/min/m² at 15 min, p < .05, in the patients without CHF).
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![Graph A: SVI (ml/m²) vs. Time (min)](https://example.com/graph-a)

![Graph B: TSR (dyn·sec·cm⁻⁵) vs. Time (min)](https://example.com/graph-b)

**FIGURE 4.** Changes in stroke volume index (SVI, A) and total systemic resistance (TSR, B) in patients with (closed circles) and without (open circles) CHF. *p < .05; **p < .01; ***p < .001 compared with values at time 0.

plot representing the average value moved to the left but not upward significantly.

There was no significant correlation between the preinfusion plasma ANP level and the maximal response of pulmonary capillary wedge pressure \((r = -0.45)\) or of stroke volume index \((r = 0.26; \text{table 1})\). The plasma ANP level during the ANP infusion did not correlate with either the maximal change in pulmonary capillary wedge pressure \((r = -0.12)\) or the maximal change in stroke volume index \((r = 0.24; \text{table 1})\).

One patient without CHF whose basal heart rate, mean arterial pressure, stroke volume index, and pulmonary capillary wedge pressure were 63 beats/min, 76.7 mm Hg, 52 ml/m², and 4 mm Hg, respectively, complained of chest discomfort and became pale, followed by sudden decreases in heart rate and systolic arterial pressure at 10 min after the infusion of ANP. The injection of 0.25 mg atropine sulfate alleviated this condition immediately. The other 11 patients did not experience side effects of any kind.

**Renal effects of ANP.** The renal responses to the ANP infusion are summarized in table 2. During the control period, there was no significant difference in renal function in the patients with and those without CHF. However, creatinine clearance and the excretion of sodium, potassium, and chloride were somewhat lower in the patients with CHF than in those without CHF. In two of the six patients with CHF, creatinine clearance was 27 and 35 ml/min before the examination. Tl > infusion of ANP resulted in three- to sixfold increases in the urine volume, and in the excretion of sodium, potassium, and chloride in the patients without CHF. In the patients with CHF similar responses were noted that were, however, not statistically significant. The renal effects of the infusion of ANP were blunted in the two patients with CHF who had preexisting disturbances in renal function. In one patient with CHF, however, the urine volume increased significantly from a control value of 8 ml/30 min to 530 ml/30 min during the infusion. This patient also had marked increases in the excretion of sodium and chloride and in creatinine clearance.

Urine volume during the infusion of ANP did not

![Graph C: SVI (ml/m²) vs. PCWP (mmHg)](https://example.com/graph-c)

**FIGURE 5.** Relationship between pulmonary capillary wedge pressure (PCWP) and stroke volume index (SVI) immediately before and at the end of the infusion of ANP in patients with (closed circles) and without (open circles) CHF. The average values are shown by the large symbols and heavy lines. Asterisk indicates the patient (No. 5) who showed a substantial increase in the urine volume during the infusion of ANP (530 ml/30 min).
TABLE 2
Effects of the infusion of ANP on renal function

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<th>Group</th>
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<td></td>
<td>-30 to 0 min</td>
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<tr>
<td>All patients</td>
<td>26.2 ± 7.3</td>
<td>158.2 ± 56.4</td>
<td>82.9 ± 23.3</td>
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<td>CHF</td>
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<td>136.6 ± 98.8</td>
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<td>UNaV (µeq/min)</td>
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<td>All patients</td>
<td>23.0 ± 3.3</td>
<td>71.6 ± 17.2</td>
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<td>CHF</td>
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<td>No CHF</td>
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<td>CCr (ml/min)</td>
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<td>All patients</td>
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<td>No CHF</td>
<td>74.0 ± 7.0</td>
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<td>58.4 ± 17.7</td>
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UV = urine volume; UNaV = excretion of sodium; Uv = excretion of potassium; Uv = excretion of chloride; CCr = creatinine clearance.

*p < .05 vs -30 to 0.

TABLE 3
Plasma hormone responses to the infusion of ANP

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<th>Time (min)</th>
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<td>All patients</td>
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<td>All patients</td>
<td>99.3 ± 15.8</td>
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<td>Cortisol (µg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>13.3 ± 1.5</td>
<td>12.3 ± 1.2</td>
<td>12.7 ± 1.1</td>
<td>11.4 ± 1.0</td>
<td>11.6 ± 0.9</td>
<td>11.6 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>11.5 ± 2.2</td>
<td>11.1 ± 1.5</td>
<td>10.8 ± 1.3</td>
<td>10.3 ± 1.0</td>
<td>9.7 ± 0.8</td>
<td>9.2 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>No CHF</td>
<td>15.2 ± 2.2</td>
<td>13.6 ± 1.9</td>
<td>15.0 ± 1.4</td>
<td>12.5 ± 1.9</td>
<td>13.5 ± 1.3</td>
<td>14.6 ± 2.2</td>
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<tr>
<td>NE (pg/ml)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>All patients</td>
<td>249.2 ± 49.5</td>
<td>238.3 ± 41.0</td>
<td>253.3 ± 39.1</td>
<td>264.2 ± 32.6</td>
<td>233.3 ± 40.9</td>
<td>203.3 ± 27.6</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>321.7 ± 83.9</td>
<td>310.0 ± 62.1</td>
<td>291.7 ± 67.4</td>
<td>268.3 ± 57.9</td>
<td>295.0 ± 69.3</td>
<td>235.0 ± 45.1</td>
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</tr>
<tr>
<td>No CHF</td>
<td>176.7 ± 40.5</td>
<td>166.7 ± 38.5</td>
<td>215.0 ± 39.9</td>
<td>260.0 ± 36.4</td>
<td>171.7 ± 32.0</td>
<td>171.7 ± 30.2</td>
<td></td>
</tr>
<tr>
<td>E (pg/ml)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>58.3 ± 11.6</td>
<td>46.7 ± 5.6</td>
<td>45.0 ± 10.1</td>
<td>50.9 ± 11.7</td>
<td>40.0 ± 6.6</td>
<td>44.2 ± 9.0</td>
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<tr>
<td>CHF</td>
<td>61.7 ± 19.6</td>
<td>50.0 ± 8.2</td>
<td>41.7 ± 18.2</td>
<td>56.0 ± 25.6</td>
<td>43.3 ± 8.4</td>
<td>48.3 ± 14.7</td>
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</tr>
<tr>
<td>No CHF</td>
<td>55.0 ± 14.3</td>
<td>43.3 ± 8.0</td>
<td>48.3 ± 10.8</td>
<td>46.7 ± 4.2</td>
<td>36.7 ± 10.9</td>
<td>40.0 ± 11.5</td>
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</table>

PRA = plasma renin activity; NE = norepinephrine; E = epinephrine; CHF = congestive heart failure.

*p < .05; **p < .01 vs value at time 0.

correlate with the reduction in pulmonary capillary wedge pressure during the infusion in the patients with CHF.

Endocrine effects of ANP. The effects of the ANP infusion on plasma hormone levels are presented in Table 3. Before the infusion of ANP plasma renin activity, aldosterone, norepinephrine, and epinephrine concentrations tended to be elevated in the patients with CHF compared with those in subjects without heart failure. The plasma aldosterone concentration was suppressed by ANP in both groups of patients, but the suppression was not statistically significant in either group (0.05 < p < .1). When data from the two groups were combined, the suppressive effect of ANP on the plasma aldosterone level became significant (p < .01). No significant difference in the reduction in the plasma aldosterone concentration in patients with and those without CHF was observed. The absolute reduction in the plasma aldosterone level did not correlate with the urine volume during the infusion of ANP. The infusion of ANP resulted in no significant changes in plasma renin activity in either group of patients, although it showed a tendency to increase after the end of the infusion in the patients without CHF. Plasma cortisol levels did not change during or after ANP. Plasma norepinephrine concentrations tended to decrease from
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a control value of 321.7 ± 84 to 268.3 ± 57.9 pg/ml at 30 min and to 235.0 ± 45.1 pg/ml at 60 min in the patients with CHF, whereas a significant increase in the plasma norepinephrine concentration was observed at 15 and 30 min in the patients without CHF. The infusion of ANP produced no significant change in the plasma epinephrine concentration in these patients.

Other biochemical findings. The serum sodium, potassium, and chloride concentrations did not change during or after ANP. The ANP infusion did not affect the concentrations of SGOT, SGPT, alkaline phosphatase, lactate dehydrogenase, γ-glutamyl transpeptidase, creatinine, nor blood urea nitrogen. There were no significant changes in red blood cell, white blood cell, or platelet counts between before and after the ANP infusion.

Discussion

α-Human ANP is a cardiac hormone secreted through the coronary sinus from the heart9-14 and has potent vasodilating and diuretic activities.10,14-21 Since vasodilators and diuretics have been widely used to treat severe CHF, the infusion of ANP would be expected to produce beneficial effects on left ventricular function of the failing heart. The present study demonstrates that the ANP infusion increases stroke volume index and decreases pulmonary capillary wedge pressure in patients with CHF, indicating that the infusion of ANP improves left ventricular function of the failing heart, as defined by a shift upward and to the left on the left ventricular function-curve plot (figure 5). These results are consistent with the recent studies described by Riegger et al.28 and by Xu et al.30 that showed that a bolus injection of ANP (200 μg or 400 μg) had beneficial effects on left ventricular function in patients with CHF. Recent pharmacokinetic studies37,38 have revealed, however, that α-human ANP is very short acting (fast and slow half-lives are 1.7 min and 13.3 min, respectively). Therefore, a continuous infusion is recommended to obtain sustained effective plasma ANP concentrations.

In the present study, we adopted an ANP infusion rate of 0.1 μg/kg/min, which has been reported to have both vasorelaxant and diuretic actions.18 Since Breuhaus et al.39 and Kleinert et al.40 reported that the infusion of ANP resulted in a deterioration rather than an improvement in the left ventricular function of normal sheep, probably because of the decreased venous return, we sought to compare the effects of the infusion of ANP in patients with and without CHF. In the patients without CHF there was no significant increase in the stroke volume index and moreover, one of the six patients without CHF experienced excessive hypotension. It therefore should be noted that ANP has a more beneficial effect on left ventricular function in patients with CHF than in those without CHF. In the present study, no significant difference in the plasma ANP concentration during the infusion of the drug was observed between the patients with and without CHF, and the plasma ANP concentration during the ANP infusion did not correlate with the maximal change either in pulmonary capillary wedge pressure or in stroke volume index. It is therefore unlikely that the difference observed in hemodynamic responses between the patients with and without CHF resulted from differences in the plasma ANP concentration during its infusion. The hemodynamic results observed in this study are compatible with the established concept that conventional balanced vasodilators produce a greater improvement in left ventricular function of the failing heart than in the normal heart.41-44 Riegger et al.28 also studied the effects of the infusion of ANP in four patients with CHF but did not compare them with effects in patients without heart failure.

In the present study, patients with CHF had much higher plasma ANP levels than those without CHF before the ANP infusion, confirming the previous observations that the plasma ANP concentration shows a graded rise in patients with CHF.24-27 Nevertheless, an improvement in left ventricular function was brought about by the infusion of ANP in such patients with high plasma ANP levels in the present study. This indicates that the additional administration of ANP is effective in patients with CHF. Although the exact mechanism responsible for the beneficial effects of ANP is not clear at present, this may be explained in part by the large distribution volume of α-human ANP.37 The large distribution volume would raise the possibility that the ANP receptors are not saturated in patients with CHF, even if they are down-regulated.29,45,46 The plasma ANP level in patients without CHF in this study was about two to four times higher than the normal value.9,24,27,47-50 Blood samples were obtained during cardiac catheterization in this study. Therefore, stress and other conditions associated with cardiac catheterization might contribute to the increased plasma level of ANP, because stress is reported to increase the plasma level of ANP in rats.40 In addition, it has been reported that certain patients with myocardial infarction or with other heart diseases who are in New York Heart Association class I or show normal pulmonary capillary wedge pressure have elevated plasma levels of ANP.25,26

The performance of the left ventricle as a pump is
affected by its end-diastolic fiber length (preload), the wall tension required to eject blood (afterload), and the functional characteristics of the muscle (contractility). Since studies using autoradiography with labeled ANP have indicated few binding sites for ANP in the ventricular myocardium, it is unlikely that ANP acts on the myocardium directly and changes myocardial contractility. The decreased total systemic resistance observed in this study indicates that ANP dilates resistance vessels. Several studies have shown that 10^-8 M to 10^-7 M of ANP causes relaxation of various arterial and venous ring preparations. The plasma ANP concentrations during the infusion of ANP in the present study were approximately 2 to 3 x 10^-9 M and were comparable to those used in these studies in vitro. It is therefore conceivable that ANP causes arteriolar and venous dilatation. These results suggest that the infusion of ANP alters the loading conditions on the heart by dilating both arterioles and veins, and thereby improves left ventricular function in the same manner as conventional balanced vasodilators.

In addition to its vasodilator activity, ANP has diuretic and natriuretic activities. A volume contraction due to these activities would contribute to a reduction in the preload. In the present study, the patients with CHF showed only a tendency to increased urine volume and excretion of sodium during the peptide infusion, although significant diuretic and natriuretic responses were observed in the patients without CHF. In addition, no significant correlation was observed between the urine volume and the reduction in pulmonary capillary wedge pressure during the infusion in the patients with CHF. Thus, these findings indicate that the renal effects of ANP on a decrease in the preload are not major components in improving left ventricular function in the patients with CHF. However, one patient with CHF experienced substantial diuresis (530 ml/30 min) during the infusion of ANP (indicated by an asterisk in figure 5), and the reduction in pulmonary capillary wedge pressure in this patient was the greatest in our study group (from 26 to 5 mm Hg). This observation suggests that a more prominent decline in the preload can be anticipated as a result of the combined vasodilating and diuretic effects of ANP. The blunted diuresis observed in the patients with CHF might be attributable to the effect of furosemide in five patients, since they took it until 24 hr before the study, and to decreased renal function in two patients. However, since Scriven and Burnett reported that the diuretic and natriuretic responses to ANP were attenuated in anesthetized dogs with acute low-output failure in spite of normal renal function, further studies are necessary to elucidate the efficacy of ANP as a diuretic in patients with CHF.

The renin-angiotensin-aldosterone system generally plays a compensatory role in the pathophysiology of CHF by elevating peripheral vascular resistance and by inducing the retention of salt and water to maintain blood flow to vital organs. In an advanced stage of CHF, however, these compensatory changes themselves overburden the already failing heart. In the present study, the infusion of ANP decreased the plasma aldosterone concentration, as has also been shown in patients with essential hypertension and in animal studies. It is possible, therefore, that ANP alleviates the sodium and water retention associated with CHF by decreasing the circulating level of aldosterone. This effect, however, may not have contributed significantly to the improvement in left ventricular function of the failing heart in this study, because ANP produced no significant increase in diuresis or natriuresis in the patients with CHF over the period of this study. The infusion of ANP resulted in no significant change in plasma renin activity, and the effect of ANP on renin release is still inconclusive at present. Richards et al. reported that plasma renin activity was not altered by a bolus injection of ANP in patients with essential hypertension, but other investigators have shown an inhibitory effect of the peptide on renin release in normal dogs and in cultured renal juxtaglomerular cells. Since angiotensin converting–enzyme inhibitors are known to be effective in the long-term treatment of patients with CHF, and since there are several lines of evidence showing a possible functional antagonistic relationship between ANP and the renin-angiotensin-aldosterone system, further studies with a longer infusion period of ANP may be necessary to elucidate the participation of the ANP-induced inhibition of the renin-angiotensin–aldosterone system in the improvement in left ventricular function.

This study shows that the plasma norepinephrine level tends to decrease during the infusion of ANP in patients with CHF. This decrement in the plasma norepinephrine level may reflect sympathetic withdrawal due to the improvement in left ventricular function in these patients. In the patients without CHF the plasma norepinephrine level rose in parallel with a fall in blood pressure. This rise in the plasma norepinephrine level may be accounted for by an arterial baroreceptor-mediated increase in sympathetic nerve activity. The augmented cardiac output without a significant increase in stroke volume in the patients without CHF in
the present study can be explained by an increased heart rate due to sympathetic activation.

In conclusion, the infusion of ANP improves left ventricular function in patients with CHF and this beneficial effect seems to result from the vasodilating activity of ANP rather than its diuretic activity or its inhibitory activity on the aldosterone secretion. Since ANP has the great advantage of being an endogenous substance, further large-scale blinded studies are necessary to confirm its usefulness for the treatment of patients with CHF.

We thank Dr. N. Morii, Dr. T. Yamada, Dr. H. Itoh, Dr. S. Shiono, Dr. M. Mukoyama and Dr. H. Arai for their encouragement and advice. We acknowledge clinical staffs of the cardiac catheterization laboratory in Kumamoto University Hospital for their assistance in performance of this study and Shionogi Co. Ltd., Osaka, Japan, for clinical examinations. The excellent secretarial work of Mrs. H. Tabata and Miss A. Furu is also gratefully acknowledged.

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Circulation. 1987;76:115-124
doi: 10.1161/01.CIR.76.1.115
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

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