Acute Hemodynamic Effects of Alpha Human Atrial Natriuretic Polypeptide in Patients with Congestive Heart Failure

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SUMMARY

Acute hemodynamic and humoral effects of synthesized alpha human atrial natriuretic polypeptide (α-hANP, 0.025 µg/kg/min for 40 min) on 6 patients with severe congestive heart failure were assessed. Plasma α-hANP concentration was high in patients and increased further (from 463±360 to 1,282±670 pg/ml, mean±SD, p<0.01) following α-hANP infusion, but plasma norepinephrine (1,030±865 to 971±785 pg/ml) was not changed. Increases in urine output (1.0±0.8 to 2.6±2.3 ml/min) and Na+ excretion rate (87±89 to 257±211 mEq/min/m²) were statistically insignificant. A significant reduction was induced in mean aortic pressure (99±25 to 96±26 mmHg, p<0.05), mean right atrial pressure (11±9 to 7±8 mmHg, p<0.01), mean pulmonary arterial pressure (39±13 to 33±12 mmHg, p<0.05) and mean pulmonary capillary wedge pressure (27±8 to 20±7 mmHg, p<0.01). Heart rate, cardiac index, systemic vascular resistance and pulmonary vascular resistance were not altered. In conclusion, α-hANP induced decreases in left ventricular filling pressure and rightside heart pressure which were attributed to venodilation rather than natriuresis in patients with congestive heart failure. Preserved cardiac output with decreased preload suggested that α-hANP improved cardiac function.

Additional Indexing Words:
Alpha human atrial natriuretic polypeptide Congestive heart failure Plasma norepinephrine Systemic vascular resistance Venodilator

The important role of alpha human natriuretic polypeptides (28 amino acid polypeptide, α-hANP) in cardiovascular regulation has been pos-
tulated, and several studies concerning the hemodynamic effects of synthesized α-hANP in experimental animals have been reported in recent years. However, these reports are now highly controversial and there have been no reports of the hemodynamic effects of synthesized α-hANP on patients with heart failure in which the peptide is expected to be activated. Therefore, we assessed the hemodynamic effects of synthesized α-hANP concurrent with the changes in plasma norepinephrine and natriuresis in patients with severe congestive heart failure.

**Patients and Methods**

Six patients with severe chronic congestive heart failure were studied. They were 5 men and 1 woman ranging in age from 38 to 71 (mean: 52 ± 13 years). The cause of the heart failure was mitral regurgitation in 4 patients, mitral stenosis in 1 patient and tricuspid regurgitation secondary to pulmonary hypertension in 1 patient. All patients had been symptomatic for at least 2 weeks before the study and mean pulmonary capillary wedge pressure was above 15 mmHg. Four patients were in functional class IV and 2 patients were in functional class III according to the New York Heart Association classification. At the time of the study, treatment with digitalis was maintained. Diuretics, catecholamines and vasodilators were discontinued at least 24 hours before the study.

The protocol was approved by the Research Trial Committee of Tokyo University Hospital, and informed consent was obtained from each patient before he or she entered the study.

Catheterization of the right heart was performed percutaneously via either of the subclavian veins. A 7 French balloon-tip thermodilution catheter (Gould Inc., California) was introduced into the pulmonary artery and connected to a Statham P50 pressure transducer (Gould Inc.).

A 23 gauge polyethylene tube was inserted into the radial artery percutaneously and connected to another Statham P50 pressure transducer to obtain systemic arterial pressure.

Signals were amplified by a Fukuda Denshi DS-1100 patient monitor system (Fukuda Denshi Ltd., Tokyo) and recorded on a thermal recorder AU-5001 (Fukuda Denshi Ltd.) at a paper speed of 50 mm/sec.

Measurements of cardiac output by thermodilution were performed in triplicate using a Fukuda Denshi EH-11 thermodilution computer (Fukuda Denshi Ltd.).

Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) in dynes·sec·cm⁻⁵ were calculated using the following formulas:
SVR = \langle(mAP - mRAP)/CO\rangle \times 80
PVR = \langle(mPAP - mPCWP)/CO\rangle \times 80

where mAP = mean arterial pressure; mRAP = mean right atrial pressure; CO = cardiac output; mPAP = mean pulmonary arterial pressure; mPCWP = mean pulmonary capillary wedge pressure.

Plasma norepinephrine was measured by the HPLC-IHI method. Plasma α-hANP concentration was determined by the radioimmunoassay method.

Fifteen to 30 min after the measurements of hemodynamic parameters, when the heart rate and pressures were stabilized, control measurements were recorded. Then 0.025 μg/kg/min of α-hANP was infused intravenously for 40 min and on completion of infusion hemodynamic measurements and blood sampling were repeated. Urinary volume and Na⁺ excretion before and during α-hANP infusion were also measured.

We compared measurements before and after α-hANP infusion using Student’s t-test for paired data. Values are expressed as mean±SD.

RESULTS

Compared with the mean value of 23 healthy volunteers in our laboratory (mean value: 119±58 pg/ml) plasma α-hANP concentration in patients

Fig. 1. Effects of α-hANP on plasma norepinephrine and α-hANP. (a) on completion of 40 min of α-hANP infusion. (b) before α-hANP infusion. N = normal range of plasma norepinephrine (60–350 pg/ml) and α-hANP (61–177 pg/ml).
with severe congestive heart failure was high and increased further (from 463±360 to 1,282±670 pg/ml, p<0.01) on completion of 40 min of α-hANP infusion, but plasma norepinephrine (1,030±865 to 971±785 pg/ml) was not changed (Fig. 1).

Significant reduction was observed in peak arterial systolic pressure (from 132±39 to 127±39 mmHg, p<0.05), mean arterial pressure (from 99±25 to

Fig. 2. Effects of α-hANP on mean arterial pressure, mean right atrial pressure and mean pulmonary capillary wedge pressure. mAP=mean arterial pressure; mPCW=mean pulmonary capillary wedge pressure; mRA=mean right atrial pressure.

Fig. 3. Effects of α-hANP on heart rate and cardiac output. CI=cardiac index; HR=heart rate.
96±26 mmHg, p<0.05), mean right atrial pressure (from 11±9 to 7±8 mmHg, p<0.01), peak pulmonary arterial pressure (from 58±20 to 48±20 mmHg, p<0.05), mean pulmonary arterial pressure (from 39±13 to 33±12 mmHg, p<0.05) and mean pulmonary capillary wedge pressure (from 27±8 to 20±7 mmHg, p<0.01) (Fig. 2).

Heart rate (from 101±32 to 102±33 /min), cardiac index (from 2.5±0.8 to 2.5±0.5 L/min/m²), systemic vascular resistance (from 1,789±788 to 1,747

Fig. 4. Effects of α-hANP on pulmonary vascular resistance and systemic vascular resistance. PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

Fig. 5. Effects of α-hANP on urine output and Na⁺ excretion rate. Na⁺ ex. = Na⁺ excretion rate; UO = urine output.
±552 dynes·sec·cm⁻⁵) and pulmonary vascular resistance (from 250±136 to 279±185 dynes·sec·cm⁻⁵) were not significantly altered (Figs. 3 and 4).

Although statistically insignificant, urinary volume (from 1.0±0.8 to 2.6±2.3 ml/min) and Na⁺ excretion rate (from 87±89 to 257±211 mEq/min/m²) increased during α-hANP infusion (Fig. 5).

**DISCUSSION**

In our previous study in which α-hANP was infused into healthy volunteers for 20 min, blood pressure declined in a dose dependent manner between an infusion rate of 0.025 and 0.1 µg/kg/min.⁷ Accordingly, in the present study where hemodynamic effects of synthesized α-hANP on patients with severe congestive heart failure were assessed for the first time, we infused the minimum effective dose of 0.025 µg/kg/min. Responses of patients with congestive heart failure in the present study were different from those in animal experiments and studies on normal humans in many respects.

Heart rate was unchanged by α-hANP in anesthetized dogs, but was increased in a study using healthy human volunteers,⁷ and accompanied by elevation of plasma norepinephrine and epinephrine. In the present study heart rate was not altered, probably as a consequence of elevated baseline plasma catecholamine levels.

In animal experiments, α-hANP induced a decline in total peripheral resistance,³ and a decrease in cardiac output.⁴,³ As the cause of this decreased cardiac output, negative inotropism and preload reduction secondary to venodilatation and/or decreased circulatory blood volume induced by natriuresis were proposed. In contrast, however, in the present study the decreases in peak arterial pressure (−4%) and mean arterial pressure (−3%) were very slight and both systemic vascular resistance and pulmonary vascular resistance were unchanged.

Cardiac output was not changed despite a decreased preload under an almost constant afterload. Neurohumoral factors played no role because plasma norepinephrine was not altered. The response can be explained by the enhanced cardiac contractility evoked by direct myocardial stimulation with the peptide, but the possibility that the patients were at the plateau phase of a flattened cardiac function curve where a decreased preload was not necessarily accompanied by a decline in cardiac output cannot be excluded. Since we did not assess the left ventricular contractility directly in the present study, the problem remains to be solved.

Urinary volume increased by 171% during 0.1 µg/kg/min α-hANP infusion in human volunteers.⁷ However, the change in urinary volume was not
statistically significant and the mean urine output during 40 min of α-hANP infusion was only 104 ml/m² in the present study. The urinary volume response was insufficient to be the cause of the decrease in left ventricular filling pressure. Thus, we attributed the underlying mechanism of the reduced preload to venodilatation. The mechanism of the vasodilator action of α-hANP has been considered to be similar to that of nitrates because this substance relaxed both veins and arteries in a manner similar to sodium nitroprusside, and increased intracellular cyclic GMP in smooth muscle, as in the case of nitroglycerine. For this reason α-hANP might have acted mainly on veins rather than arteries under high plasma norepinephrine concentrations.

In summary, the hemodynamic effects of small doses of α-hANP infused into patients with advanced congestive heart failure were unchanged heart rate, negligible arterial dilatation, inconsistent natriuresis and probably enhanced cardiac pump function and venodilatation. These responses which differ from those characteristic responses seen in normal volunteers may be due to elevated baseline catecholamine and α-hANP levels seen in congestive heart failure.

REFERENCES