Limitations of Compensation by Endogenous Atrial Natriuretic Peptide in Heart Failure

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To evaluate the role of endogenous atrial natriuretic peptide (ANP) in patients with congestive heart failure (CHF), the relationship between plasma ANP and cyclic guanosine monophosphate (cGMP) levels and the prognosis of patients with CHF was examined. In patients with chronic mild to moderate CHF, there was a positive correlation between plasma ANP and cGMP levels ($r=0.81$, $p<0.001$). However, there was no significant correlation between these plasma levels in patients with chronic severe CHF, in whom the cGMP concentration reached a plateau in spite of high levels of ANP. The ANP extraction level and the cGMP production level in the pulmonary and systemic circulation correlated significantly in patients with mild CHF. In contrast, there was no significant correlation between the 2 parameters in patients with severe CHF, and the molar ratios of cGMP production to ANP extraction in the pulmonary and systemic circulation were significantly lower than those in patients with mild CHF. In 44 patients with chronic severe CHF who were followed up over 2 years, plasma ANP levels provided more sensitive and specific prognostic information than any other parameters. These results indicate that ANP receptors coupled to guanylate cyclase may be down-regulated in patients with chronic severe CHF, suggesting that high plasma ANP levels as a prognostic predictor may be associated with limitations of compensation by endogenous ANP.

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Various neurohumoral factors which increase in patients with heart failure are thought to play important roles in the pathogenesis of heart failure1–3. Since atrial natriuretic peptide (ANP) has a diuretic, natriuretic and vasodilator effect and suppresses the secretion of renin and aldosterone4–7, endogenous ANP is thought to improve the condition of patients with heart failure through reduction of the preload and afterload. The purpose of the present study was to evaluate the mechanism of neurohumoral factors to compensate for heart failure, while their limitations were examined with the focus on ANP and cyclic guanosine monophosphate (cGMP), the second messenger of ANP.

METHODS

Measurements of neurohumoral factors

After informed consent was obtained, blood samples for measurement of neurohumoral factors were drawn after 30 min of bed rest with the patients in the supine position. Plasma levels of ANP were determined

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Fig.1. Relationship between plasma ANP and cGMP levels in patients with heart failure.
**: p < 0.01

The relationship between plasma ANP concentration and prognosis

Plasma levels of ANP, NE and PRA were measured in 44 inpatients with chronic severe heart failure (24 patients in class III, 20 in class IV). The left ventricular ejection fraction (LVEF) was also determined by left ventriculography using a contrast medium or radioisotope method. The patients were followed up for 2 years.

The relationship between ANP extraction and cGMP production in pulmonary and systemic circulation

Sixty-four patients with chronic heart failure were studied. The patients were divided into a mild heart failure group (NYHA I or II, 47 patients) and a severe heart failure group (NYHA class III or IV, 17 patients). During cardiac catheterization, blood was sampled from the main pulmonary artery (PA), the pulmonary capillary wedge region.

by radioimmunoassay (RIA) as previously reported. Plasma concentrations of cGMP were measured by RIA with a commercial kit (Yamasa Shoyu Co., Ltd., Choshi, Japan). Plasma renin activity (PRA) was also determined by RIA and plasma norepinephrine (NE) levels by high performance liquid chromatography.

Fig. 3. Relationship between the ANP extraction and the cGMP production in pulmonary circulation. (A: NYHA Class I or II patients, B: NYHA Class III or IV patients).
PA: main pulmonary artery, PC: pulmonary capillary wedge region, CO: cardiac output, Ht: hematocrit.

Statistical Analyses
All values were expressed as mean ± SEM. The least square method was used for linear regression analysis. Statistical comparisons were made with the paired or unpaired Student’s t test. A p value of <0.05 was considered statistically significant.

RESULTS
Plasma ANP concentrations increased with the severity of heart failure (NYHA class I (n=29): 34 ± 12 pg/ml, class II (n=82): 85 ± 33 pg/ml, class III (n=47): 241 ± 91 pg/ml, class IV (n=16): 404 ± 137 pg/ml; Fig. 1). Plasma cGMP levels also increased with the NYHA class up to class III; for class IV patients, however, plasma cGMP levels were not significantly different from those of class III patients (NYHA class I (n=29): 3.1 ± 1.3 pmol/ml, class II (n=82): 5.4 ± 2.5 pmol/ml, class III (n=16): 11.8 ± 3.4 pmol/ml, class IV (n=16): 13.3 ± 4.1 pmol/ml; Fig. 1). In patients with
chronic mild to moderate heart failure (NYHA class I to III), there was a positive correlation between plasma levels of ANP and cGMP ($r = 0.81$, $p < 0.001$). Moreover, in patients with acute severe heart failure (NYHA class IV), the plasma cGMP concentration increased in proportion to the plasma ANP level. However, there was no significant correlation between plasma levels of ANP and cGMP in patients with chronic severe heart failure (NYHA class IV) and the cGMP concentration reached a plateau in spite of high levels of ANP (Fig. 1).

Forty-four patients with CHF of NYHA class III or IV were divided into 2 groups, those who died from heart failure ($n = 17$) and those who survived ($n = 27$). There was no significant difference between the 2 groups in terms of age, disease, treatment, NYHA class, LVEF, or NE concentration. The respective values for non-survivors and survivors were: NYHA classes: $3.6 \pm 0.5$ and $3.4 \pm 0.5$; LVEF: $30 \pm 3.5\%$ and $35 \pm 5\%$; and NE concentrations: $453 \pm 25$ pg/ml and $320 \pm 75$ pg/ml. Plasma renin activity (PRA) and plasma ANP concentration were significantly higher for non-survivors than survivors (PRA: $10.4 \pm 2.4$ ng/ml/h vs $3.1 \pm 0.9$ ng/ml/h, ANP: $422 \pm 56$ pg/ml vs $177 \pm 22$ pg/ml; Fig. 2). It is noteworthy that 16 out of 17 patients with a plasma ANP concentration of more than 300 pg/ml died from heart failure and 24 of 27 patients with a plasma ANP concentration of less than 300 pg/ml survived for 2 years (Fig. 2).

The plasma ANP concentrations measured during cardiac catheterization according to the sampling sites were as follows: PA: $236 \pm 34$ pg/ml, PC: $184 \pm 22$ pg/ml, Ao: $208 \pm 26$ pg/ml, and V: $173 \pm 21$ pg/ml. The plasma ANP concentration decreased significantly in both pulmonary (between PA and PC) and systemic circulation (between Ao and V). The cGMP concentrations were: PA: $6.2 \pm 0.4$ pmol/ml, PC: $7.8 \pm 0.5$ pmol/ml, Ao: $6.8 \pm 0.4$ pmol/ml, and V: $7.6 \pm 0.5$ pmol/ml. The plasma cGMP concentration thus increased significantly in pulmonary (between PA and PC) and systemic circulation (between Ao and V). For the pulmonary circulation, there was a positive correlation between ANP extraction and cGMP production in patients with mild heart failure ($r = 0.79$, $p < 0.001$; Fig. 3). However, no correlation was observed between these 2 parameters in patients with severe heart failure and the molar ratio of cGMP production to ANP extraction was significant lower for these patients than for patients with mild heart failure. As for the systemic circulation, a similar positive correlation between ANP extraction and cGMP production was found in patients with mild heart failure ($r = 0.78$, $p < 0.001$; Fig. 4), while no correlation was observed between these 2 parameters in patients with severe heart failure and the molar ratio of cGMP production to ANP extraction was also significantly lower than in patients with mild heart failure.

**DISCUSSION**

Although plasma ANP concentrations in patients with heart failure have been reported to be higher than those in normal subjects and to increase further as the severity of heart failure progresses, the role of endogenous ANP in heart failure remains unknown. Exogenously administered ANP elevates the plasma levels of cGMP, the intracellular second messenger of ANP, in accordance with its physiological effects, such as natriuresis and vasodilation. Therefore, in the present study, we decided to use plasma cGMP concentration as an index of the physiological effects of endogenous ANP.

We found that plasma cGMP level correlated with plasma ANP concentrations in patients with mild heart failure (NYHA class I to III). In patients with chronic severe heart failure (NYHA class IV), however, no such correlation was observed and cGMP concentrations reached a plateau in spite of high concentrations of ANP (Fig. 1). In contrast, patients with acute severe heart failure showed plasma cGMP concentrations correlating with plasma ANP levels in spite of high concentrations of ANP. These results indicate that cGMP production in target cells of ANP, such as vascular smooth muscle cells, may be reduced in patients with chronic severe heart failure whose levels of ANP continue to be high. The attenuation of cGMP production in the pulmonary and
systemic circulation of patients with chronic severe heart failure also suggests the down-regulation of ANP receptors coupled to guanylate cyclase.

Gottlieb et al.\textsuperscript{13} have reported that high plasma ANP concentrations may indicate a poor prognosis in patients with heart failure. In the present study, it is noteworthy that plasma ANP levels constitute a more sensitive and specific predictor for patients with NYHA III or IV than do PRA or NE. Since the plasma ANP concentration reflects the left ventricular end-diastolic pressure,\textsuperscript{8} one of the predictors of prognosis, and since, in biventricular heart failure, the plasma ANP concentration is further elevated by increasing pressure in the right-side of the heart in addition to a high left ventricular end-diastolic pressure, it is reasonable to assume that plasma ANP concentration is highly correlated with prognosis. As shown in Fig. 2, patients with a plasma ANP value of more than 300 pg/ml had a poor prognosis, and we concluded that the plasma ANP level is an excellent prognostic predictor in patients with heart failure.

Endogenous ANP is thought to fulfill compensatory functions in heart failure. In the present study, we examined the relationship between ANP extraction and cGMP production in the pulmonary and peripheral vascular beds. Our results indicate that in patients with mild heart failure, an increase in the endogenous ANP level affects the pulmonary and peripheral vessels and may compensate for heart failure by reducing the preload and afterload. However, in patients with severe heart failure where a high level of plasma ANP is sustained for a long time, a down-regulation of ANP receptors in the vascular beds may occur, resulting in a reduction in the vasodilatory action of elevated endogenous ANP. The other effects of ANP that may compensate for heart failure, such as diuresis and the suppression of renin and aldosterone secretion, were not examined here. However, since ANP is a receptor-mediated hormone, it is reasonable to assume that down-regulation of the ANP receptors develops in chronic heart failure as indicated by Schiffrin.\textsuperscript{14} A high plasma ANP level as a prognostic predictor may thus be associated with the limitations of compensation by endogenous ANP.

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