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Effects of human atrial natriuretic peptide on cardiac function and hemodynamics in patients with high plasma BNP levels

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Abstract

Both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) bind preferentially to the natriuretic peptide A receptor. Therefore, we hypothesized that the positive inotropic and lusitropic effects of ANP might be blunted in patients with moderate congestive heart failure and high BNP levels. Micromanometers and conductance catheters were used to obtain relatively load-insensitive left ventricular pressure–volume analysis in order to compare the myocardial and load-altering actions of ANP in 20 patients with low and high plasma BNP levels. In the low-BNP group (plasma BNP levels <230 pg/ml), ANP infusion significantly decreased end-systolic pressure and end-diastolic pressure and volume, increased end-systolic elastance, and shortened left ventricular relaxation. By contrast, in the high-BNP group (plasma BNP levels >230 pg/ml), the effect of ANP infusion on LV contractility was blunted but its beneficial effects on LV diastolic function and LV-arterial coupling remained. Thus, ANP infusion may improve LV diastolic function even in patients with moderate heart failure and high plasma BNP levels.

Keywords: Atrial natriuretic peptide; Brain natriuretic peptide; Congestive heart failure; Left ventricular function; Patients

Atrial natriuretic peptide (ANP) maintains circulatory homeostasis and changes myocardial performance by modulating cardiac preload and afterload via diuresis or natriuresis, and vasodilatation [1]. In addition to these indirect effects, ANP may directly affect myocardial contraction and relaxation through the natriuretic peptide A receptors which are present on ventricular myocytes [2–5].

Plasma brain natriuretic peptide (BNP) levels are elevated in patients with congestive heart failure (CHF) and reflect the severity of CHF [6–9]. Recent clinical trial, REDHOT, clearly shows that perception of severity of congestive heart failure among emergency department physicians does not in fact correlate well with BNP levels [10]. This gives credence to the connection that a "disconnect" exists between the perceived severity of illness and BNP values. The cardiac effect of ANP infusion may be modulated by preexisting BNP and second messenger cyclic guanosine monophosphate (cGMP) concentrations, because BNP also binds preferentially to the natriuretic peptide A receptor [2,8,11]. In fact, the effects of exogenous administration of ANP on renal production of cGMP are blunted in severe CHF in which circulating levels of BNP are elevated in the plasma, and the hemodynamic response to ANP infusion is attenuated in patients and experimental animals with severe CHF [2,12–14]. However, very little evidence has been presented for the influence of basal BNP levels on the response of cardiac function and hemodynamics to ANP infusion in patients with CHF. On the basis of the previous study, we hypothesize that the positive inotropic and lusitropic effects of ANP might be blunted in patients with moderate CHF and high-BNP levels. To avoid the potentially confounding effects of ANP-produced

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changes in loading conditions, we evaluated LV function using pressure–volume (*P–V*) analysis which provides a relatively load-insensitive evaluation of intact contractile performance [15,16].

1. Methods

1.1. Study group

We studied 20 patients (15 men and 5 women; mean age 60±7 SD) with nonischemic dilated cardiomyopathy who admitted in the Mie University Hospital for symptomatic congestive heart failure. Entry criteria included LV ejection fractions (EF) less than 0.45 using 2-D echocardiography. Patients were excluded from the study if they had atrial fibrillation, symptomatic ventricular tachycardia, LV apical thrombus, aneurismal wall motion, primary valvular heart disease, or had received any inotropic agents within 4 weeks of the study. Patients were in New York Heart Association functional class I (n=4), II (n=9), or III (n=7) heart failure and were receiving digitalis (n=4), diuretics (n=15), ACE inhibitors (n=19), and beta-blockers (n=10) before enrollment in the study (Table 1). All medications were withheld for at least 48 h before cardiac catheterization. Written informed consent was obtained from all patients, and the protocol was approved for use by the Human Studies Subcommittee of Mie University School of Medicine.

1.2. Hemodynamic measurements

After diagnostic coronary angiography and ventriculography, a 6F single-field conductance catheter (Webster Laboratories, Baldwin Park, CA) with a 2F micromanometer (Millar Instruments, Houston, TX) was placed in the LV apex through a femoral artery and connected to a digital stimulator microprocessor (Sigma V, Leycom [dual-field system], Zoetermeer, Netherlands) for simultaneous pressure and volume measurements. The conductance catheter technique and its principles have been fully described previously [12,17]. At the beginning of the study, a conductance catheter signal gain was calibrated using a thermodilution-derived stroke volume. A calibration offset (parallel conductance) was corrected by matching a conductance catheter signal at end-diastole with an end-diastolic volume measured by biplane ventriculography using an area–length method. Each measurement represents the mean value of at least 30 consecutive sinus beats.

Table 1
Patient characteristics

Characteristic	Low-BNP levels	High-BNP levels
Age, years	59±6	60±7
Sex, M/F	8/2	7/3
NYHA function class		
I	4	0
II	6	3
III	0	7
Plasma BNP levels, pg/ml	123±16	365±120
Treatment		
Diuretics	6	9
Digitalis	1	3
ACE inhibitor	9	10
Vasodilator	3	3
Beta-blocker	6	4

1.3. Data processing and analysis

Indexes of myocardial systolic and diastolic performance were derived from signal-averaged pressure–volume data. For evaluation of the ejection phase index of LV contractility, we calculated the slope of the linear end-systolic pressure–volume relation (end-systolic elastance) produced by caval occlusion using an 8F Fogarty catheter (Baxter) placed in the inferior vena cava [16,17]. LV relaxation rates were assessed by the time constant of the isovolumetric fall of LV pressure (Tau) which was derived using the Weiss formula [18]. Total systemic resistance was calculated as LV end-systolic pressure divided by cardiac output. Effective arterial elastance was calculated as LV end-systolic pressure divided by stroke volume [19]. Coupling of the LV and arterial system was quantified as end-systolic elastance divided by effective arterial elastance [20].

1.4. Study protocol

Patients were divided into 2 groups according to their plasma BNP levels at baseline (median, 230 pg/ml; mean, 250±160 pg/ml). Previous studies in patients with CHF showed that high plasma BNP (>200–238 pg/ml) increased the likelihood of mortality and an initial morbid event [7–9]. Accordingly, we defined patients who had plasma BNP levels <230 pg/ml as the low-BNP group and >230 pg/ml as the high-BNP group. Patient characteristics are given in Table 1.

After baseline data at steady-state and variably loaded *P–V* loops generated by transient occlusion of the inferior venae cavae were obtained, ANP (carperitide, Daiichi Suntory Pharma) was infused intravenously at a dose of 0.1 μg/kg/min for 30 min. Hemodynamic measurements were taken at the end of ANP infusion. Arterial blood samples were collected for measurement of plasma ANP, BNP, and cGMP levels at baseline and at the end of infusion. Plasma ANP, BNP, and cGMP levels were measured by specific radioimmunoassay as previously described [2,12].

1.5. Statistical analysis

The results are expressed as mean±SD. Student's paired t test was used for within-group comparisons, and Student's