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**Abstract:** An increase in circulating BNP is associated with a poor outcome in patients with acute heart failure. The primary aim of study was to investigate the prognostic value of BNP levels in patients with chronic and advanced heart failure. Fifty patients with New York Heart Association (NYHA) functional class III and IV were enrolled in this study. Their blood BNP levels at admission were measured and patients were followed-up for  $12 \pm 2$  months. There was no significant correlation between BNP levels on admission and LVEF ( $r=0.12$ ,  $p>0.05$ ). Twelve patients (24%) died during follow-up. BNP levels were lower in patients who died ( $501 \pm 72$  vs.  $877 \pm 89$  ng/L,  $P<0.01$ ). Logistic stepwise regression analysis showed that lower BNP level ( $<520$  ng/L) on admission was an independent predictor of cardiovascular mortality in these patients (OR=1.21, 95% CI 1.06-2.32,  $P<0.01$ ). We conclude that patients with chronic and advanced heart failure have a lower circulating BNP level than those who survive. The paradoxically low BNP level is an adverse prognostic marker in advanced heart failure.

**Prognostic Value of B-type Natriuretic Peptide in Patients with Chronic and  
Advanced Heart Failure**

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## **Abstract**

An increase in circulating BNP is associated with a poor outcome in patients with acute heart failure. The primary aim of study was to investigate the prognostic value of BNP levels in patients with chronic and advanced heart failure. Fifty patients with New York Heart Association (NYHA) functional class III and IV were enrolled in this study. Their blood BNP levels at admission were measured and patients were followed-up for  $12 \pm 2$  months. There was no significant correlation between BNP levels on admission and LVEF ( $r=0.12$ ,  $p>0.05$ ). Twelve patients (24%) died during follow-up. BNP levels were lower in patients who died ( $501 \pm 72$  vs.  $877 \pm 89$  ng/L,  $P<0.01$ ). Logistic stepwise regression analysis showed that lower BNP level ( $<520$  ng/L) on admission was an independent predictor of cardiovascular mortality in these patients (OR=1.21, 95% CI 1.06-2.32,  $P<0.01$ ). We conclude that patients with chronic and advanced heart failure have a lower circulating BNP level than those who survive. The paradoxically low BNP level is an adverse prognostic marker in advanced heart failure.

**Key words:** B-type natriuretic peptide; heart failure; prognosis; mortality

## **Introduction**

B-type natriuretic peptide (BNP) is a peptide hormone released from cardiac ventricles in response to myocardial stretch or increased wall tension (1). Circulating levels of BNP are elevated in patients with heart failure, representing the activation of initially beneficial compensatory mechanisms (1). Levels of BNP can be used to confirm the diagnosis and to aid in the assessment of prognoses in patients with acute heart failure (1-6). During acute heart failure, a higher level of BNP usually indicates an increased risk for a poor prognosis and that lower circulating level reflects a more stable compensated or effectively treated status (1, 4-6). However, up to 20% of patients with symptomatic chronic heart failure may have “normal level” (<100ng/L) of BNP (7, 8). Recently, a relatively small study suggests that patients with end-stage heart failure and a poor prognosis may actually have a lower level of circulating BNP (9). Therefore, whether the prognostic values of BNP observed from acute decompensated heart can be applied to chronic heart failure requires further investigation (10). The primary objective of this study is to assess the association between BNP levels and clinical outcomes in patients with chronic and advanced heart failure.

## **Patients and Methods**

### **Patients**

This study was approved by the institutional review board of the first Affiliated Hospital of Zhengzhou University. Between August 2003 to December 2004, 50 patients who were admitted to the Department of Cardiology at the first Affiliated Hospital of

Zhengzhou University for severe heart failure were selected for the study. There were 34 males and 16 females with an average age of  $65 \pm 9$  (24-78) years. The selection criteria were: 1) an established diagnosis of heart failure 2 years before the study; 2) NYHA functional class III and IV at admission; 3) left ventricular ejection fraction (LVEF) less than 40%. Patients with severe renal dysfunction, pulmonary disease, terminal cancer or other concurrent illnesses were excluded from the study.

All the patients received standard care for heart failure, including angiotensin-converting enzyme inhibitors, diuretics,  $\beta$ -blockers and digoxin, during the hospitalization. They were discharged from the hospital when symptoms were relieved and the cardiac function was improved.

Patients were followed-up in our hospital clinic monthly for the first three months, and quarterly in the following months. The average of duration of follow up was  $12 \pm 2$  (8-24) months. The cardiac function was assessed by physical examination and echocardiography if necessary, and heart failure medications were adjusted according to patient's clinical symptoms and results from the physical or laboratory examination.

### **Measurement of circulating BNP level**

Plasma BNP was measured by a previously reported method (5, 11), using a Triage BNP assay kit (Biosite, San Diego, CA). Intravenous blood was collected within 24 h of admission and BNP was determined within 20 minutes after blood collection.

### **Echocardiogram examination**

On admission, the left ventricular function was assessed by two-dimensional and Doppler

echocardiography (GE VIVID-7, transducer frequency 2.5-3.5 MHz) by an experienced cardiologist who was unaware of the BNP results. Standard two-dimensional images were obtained in the parasternal long and short axes, and in the apical 4- and 2-chamber views. Pulsed-wave Doppler tracings of mitral valve inflow were recorded at the leaflet tips. Left ventricular volumes and Doppler tracings were analysed using a digital echocardiography workstation.

Left ventricular systolic dysfunction was defined as, apart from clinical symptoms: 1) enlargement of the left ventricle with a diameter of more than 55 mm on echocardiography; 2) left ventricular ejection fraction measured by echocardiography was less than 45% (6).

### **Statistical analysis**

Numerical variable were presented by mean  $\pm$  standard deviation (SD) and analyzed with ANOVA. Comparison of BNP values in subgroups was performed with Wilcoxon rank sum test. Categorical variable were analyzed with Chi-square analysis. All analysis was conducted with SPSS10.0.  $P < 0.05$  was considered to be statistically significant.

### **Results**

At admission, the average LVEF of all patients was  $26\% \pm 2\%$  (15%- 35%). The average BNP levels were  $520 \pm 270$  (range, 78-3400, median, 780) ng/L. There were 3 patients (6.0%) whose BNP was less than 100 ng/L, and the LVEF in these patients were 30%, 31%, 35%, respectively. There was no significant correlation between BNP levels and LVEF in the 50 patients ( $r=0.12$ ,  $p>0.05$ ).

During the follow up, 12 patients (24%) died of heart failure. There were no significant differences in the clinical characteristics (Table 1) and therapies for heart failure (Table 2) between the non-survival and the survival groups, except for diastolic blood pressure which was lower in the non-survival group, and the serum creatinine, which was higher in the non-survival group ( $p < 0.01$ ).

The average BNP level in the non-survival group was significantly lower than that in the survival group ( $501 \pm 72$  vs.  $877 \pm 89$  ng/L,  $P < 0.01$ ). The three patients whose BNP was less than 100 pg/L were from the non-survival group.

Logistic stepwise regression analysis, taking into consideration of age, sex, duration of heart failure, LVEF, serum creatinine levels, showed that lower BNP level ( $< 520$  ng/L) on admission was an independent predictor of mortality in these patients (OR=1.21, 95% CI 1.06-2.32,  $P < 0.01$ ).

## Discussion

BNP is synthesized in response to ventricular stretch and pressure overload (1). BNP reduces cardiac preload by causing vasodilatation and increasing vascular capacitance (2). It also diminishes sympathetic nervous tone and induces natriuresis by its action on the renal vasculature and tubules (2).

Plasma BNP concentration is increased in patients with ventricular systolic dysfunction; the plasma level of BNP correlates well with pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, and left ventricular ejection fraction in patients with systolic dysfunction. In patients with ventricular systolic dysfunction, BNP concentration increases with the clinical severity of the disease, as assessed by New

York Heart Association classification (3).

The activation of natriuretic peptides system is considered as a compensation mechanism in response to the failing heart (10). The level of BNP is usually less than 20 ng/L in young and healthy subjects (10). An increase in BNP has been reported in elderly individuals, in those with chronic pulmonary disease, pulmonary embolism and renal insufficiency (10). Our previous studies and reports from other institutions all suggest that in patients with acutely decompensated heart, circulating BNP levels are often above 100 ng/L (1-13), and are closely correlated LVEF. Numerous clinical studies revealed that increased circulating BNP in heart failure patients are associated with an increase in mortality and BNP is an independent predictor of poor prognosis in such patients (4-6).

In 2002 , McGeoch and his coworkers (7) found that among patients with LVEF below 45% and receiving long-term treatment, 19% of them had a BNP level below 35 pmol /L (128ng/L). Tang and associates (8) studied 558 ambulatory patients with chronic, stable systolic hear failure (LVEF<50%) and found that among the 498 symptomatic (NYHA functional class II–III) patients, 106 (21.3%) had plasma BNP levels in the “normal” diagnostic range (<100ng/L). Sixty patients were considered asymptomatic, and their plasma BNP levels ranged from 5 to 572 ng/L (median, 147ng/L) (8). A more recent study on 40 patients with chronic end-stage heart failure has found that BNP levels were significantly increased after nesiritide treatment (9). However, the BNP levels before and after nesiritide treatment were lower in patients who died during a 10-month follow up (9).

Patients in the present study had a chronic heart failure history of more than 2 years,



and III-IV NYHA classification at the time of the study. On admission, 3 had a BNP level less than 100 pg/L although their left ventricular ejection fraction was less than 35% and heart failure symptoms were evident on clinical examination. After an average follow up of 12 months, 24% of the 50 patients died, including those with an initial BNP levels of less than 100 pg/L. The average admission BNP was lower in the non-survival group than in the survival group. Multiple variable regression analysis demonstrated that lower BNP level on admission was an independent risk factor for mortality.

Although this study is based on a relatively small number of patients, the results support the hypothesis that at some point during the progression of advanced heart failure, the neurohormonal systems is unable to provide adequate levels of the natriuretic hormones as compensation. This could be due to reduced synthesis or secretion, increased degradation or clearance, or additional factors not yet clearly understood (10). Regardless of the causes, the paradoxically low circulating BNP levels appear to be an adverse prognostic marker in advanced heart failure. It is also important to note that the correlation between the level of BNP and LVEF, which is evident in acutely decompensated heart failure, is lost in our patients with chronic severe heart failure.

In conclusion, although elevated circulating BNP levels can be used to predict the severity of ventricular dysfunction and the short-term prognosis of patients with acute heart failure, the same cannot be assumed with chronic heart failure. A proportion of patients with chronic and advanced heart failure may have a relatively low or even normal circulating BNP level due to diminished neurohormonal compensation. A lower level of circulating BNP in advanced heart failure may be used as a marker of poor prognosis.

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Table1. The comparison of clinical characteristics, therapy and BNP level between the non-survival and the survival groups.

	Non-Survival (n=12)	Survival (n=38)	P
Age	67±6	66±5	NS
Male	7 (58.3%)	25 (65.8%)	NS
Causes of HF			
DCM	5 (41.7%)	13 (34.2%)	NS
ICM	7 (58.3%)	25 (65.8%)	NS
Duration of HF (months)	60±10	54±9	NS
SBP (mm Hg)	121±5	116±6	NS
DBP (mm Hg)	58±2	65±3	<0.01
HR (bpm)	78±3	88±4	NS
LVEF (%)	24±2	25±2	NS
BNP (ng/L)	501±72	877±89	<0.01
Serum creatinine (mg/dl)	2.1±0.20	1.7±0.13	NS
Urine output (ml/day)	1400±360	1300±350	NS

SBP and DBP: Systolic and diastolic blood pressure; LVEF: left ventricular ejection fraction.

Table 2. Type of medications for heart failure.

	Non-Survival group (n=12)	Survival group (n=38)	p
B-blocker	9 (75.0%)	27 (71.1%)	NS
ACEI	10 (83.3%)	29 (76.3%)	NS
Nitrates	12 (100.0%)	38 (100.0%)	NS
Digoxin	8 (39.6%)	25 (65.8%)	NS
Furosemide	12 (100.0%)	38 (100.0%)	NS

ACEI: Angiotensin-converting enzyme inhibitor.