Low Level of B-type Natriuretic Peptide in Relation to Poor Prognosis in Patients with Advanced Left Ventricular Systolic Dysfunction

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Abstract: Background. B-type/brain natriuretic peptide (BNP) is released from the cardiac ventricles in response to increased wall tension. Elevated circulating BNP in heart failure (HF) usually indicates poor outcome and compensation. In advanced chronic HF, however, low level of BNP may reflect an impaired neurohormonal response. The primary aim of present study was to investigate the prognostic value of low BNP level in advanced heart failure patients. **Materials and Methods.** 50 advanced HF patients with New York Heart Association (NYHA) functional class Ⅲ and Ⅳ were enrolled in this study. Their blood BNP level were measured by Biosite Triage BNP test on admission and they were followed-up for 12±2 month after hospital discharge. **Results.** Cardiovascular mortality during follow-up was 24%. BNP levels were lower in patients who died (501±72 vs. 877 ± 89 ng/L, $P<0.01$). After adjusted for age, sex, duration of HF, left ventricular ejection fraction, serum creatinine level and drug therapy (including β-blocker, angiotensin-converting enzyme inhibitor, digoxin, diuretics and intravenous vasoactive medications), logistic stepwise regression analysis showed that lower BNP level (<520 ng/L) on admission was an independent predictor of cardiovascular mortality in advanced HF patients (OR = 1.21, 95% confidence interval 0.56−2.32, $P<0.01$). **Conclusions.** Cardiac natriuretic peptide system can no longer contribute adequately to neurohormonal compensation and that paradoxically low BNP level is an adverse prognostic marker in advanced HF. [Life Science Journal. 2006;3(1):5−8] (ISSN: 1097−8135).

Keywords: B-type /brain natriuretic peptide; heart failure; prognosis; mortality

1 Introduction

B-type/brain natriuretic peptide (BNP) is a peptide hormone released from cardiac ventricles in response to myocardial stretch or increased wall tension (Sun, 2005). Circulating levels of BNP are elevated in patients with heart failure (HF) and represent the activation of initially beneficial compensatory mechanisms (Sun, 2005). In addition, levels of BNP can be used to confirm the diagnosis and to aid in the assessment of prognoses in patients with HF (Sun, 2005; Lainchbury, 2003; Multinational, 2002; Anand, 2003; Anand, 2003; Tsutamoto, 1997). It is generally accepted that high level of BNP indicates an increased risk for a poor prognosis and that low circulating level reflect more stable compensation or effective treatment (Sun, 2005; Anand, 2003; Anand, 2003; Tsutamoto, 1997). However, some patients with symptomatic chronic HF can have "normal level" (<100 ng/L) of BNP (McGeoch, 2002; Tang, 2003). Recently, a small sample study suggested that lower BNP level could predict higher mortality in advanced HF patients because their neurohormonal systems can no longer maintain the higher levels needed for hemodynamic compensation (Miller, 2005; Packer, 2003). The primary objective of this study was to assess the association between BNP level and clinical outcomes in advanced HF patients with New York Heart Association (NYHA) class Ⅲ and Ⅳ.

2 Materials and Methods

2.1 Patients

A total of 50 patients with NYHA class Ⅲ and Ⅳ hospitalized for management of decompensated

chronic HF from August 2003 to December 2004 were enrolled in this study. Male 34, female 16, age 65 ± 9 (range from 24 to 78). The inclusion criteriaes were a history of HF more than 2 years and left ventricular ejection fraction (LVEF) less than 40%. The exclusion criteriaes were severe renal dysfunction, cancer and died during hospitalision. All the patients received intravenous diuretics and vasoactive agent during hospitalision. The discharged from hospital when symptoms were relief and stabilization. We followed up once every month during the first three months and then once every quarter. The total follow-up time was 12 ± 2 (range from 2 to 24) months. They were divided into two groups according to the results of follow-up.

2.2 Measurement of circulating BNP level

A point-of-care test of fluorescence immunoassay for the quantification of BNP was used (Biosite Diagnostics Inc, USA), 2 ml of intravenous blood was collected within 24 h of admission and BNP was determined within 20 minutes. The range of measurement was 5 – 5 000 ng/L.

2.3 Echocardiogram examination

A GE VIVID-7 echocardiograph (GE company, USA) were used. All the enrolled patients accepted echocardiograph examination by the same echocardiographer. Left ventricular ejection fraction (LVEF) and left ventricular end-diastolic dimension (LVEDd) were measured from the apical four-chamber view.

2.4 Statistical analysis

Numerical variable were presented by mean ± standard deviation (SD) and analyzed with student t test. Categorical variable were tested with χ^2 test analysis. All data were analyzed by SPSS 10.0 and a value of $P<0.05$ was considered statistically significant.

3 Results

The BNP levels and the LVEF of all the patients were 520 ± 270 ng/L (range from 78 to 3400 ng/L) and 26% ± 2% (range from 15% to 35%), respectively. The cardiovascular mortality rate was 24% during follow-up (12 patients died). There were no statistical difference about the clinical characteristics and therapy between the non-survival and the survival except for diastolic blood pressure (lower in the non-survival) and serum creatinine (higher in the non-survival) (Table 1). The BNP level was significantly lower in the non-survival than that in the survival (501 ± 72 ng/L vs. 877 ± 89 ng/L, $P<0.01$). After adjusted for age, sex, duration of HF, left ventricular ejection fraction, serum creatinine level and drug therapy (including β-blocker, angiotensin-converting enzyme inhibitor, digoxin , diuretics and intravenous vasoactive medications), logistic stepwise regression analysis showed that lower BNP level (< 520 ng/L) on admission was an independent predictor of cardiovascular mortality in advanced HF patients (OR = 1.21, 95% confidence interval 0.56 – 2.32, $P<0.01$).

Table 1. The comparison of clinical characteristics, therapy and BNP level between the non-survival and the survival

Group	Age	Male	Cause of HF		Duration of HF (m)	BP (mmHg)		HR (bpm)	LVEF
			DCM	ICM		SBP	DBP		
Non-survival (n=12)	67 ± 6	7	5	7	60 ± 10	121 ± 5	58 ± 2	78 ± 3	24 ± 2
Survival (n=38)	66 ± 5	25	13	25	54 ± 9	116 ± 6	65 ± 3▲	88 ± 4	25 ± 2

Group	BNP (ng/L)	Urine output (ml)	Serum creatinine (mg/dl)	Therapy				
				β-bolcker	ACEI	Nitrates	Digosin	Frusemide
Non-survival (n=12)	501 ± 72	1400 ± 360	2.1 ± 0.20	9	10	12	8	12
Survival (n=38)	877 ± 89▲	1300 ± 350	1.7 ± 0.13▲	27	29	38	25	38

▲$P<0.01$. BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor

4 Discussion

The physiological mechanism of HF is excessively activation of neuroendocine systems such as sympathetic nerve system (SNS), rennin-angiotensin-aldosterone-system (RAAS) and endothelin system(Sun, 2005). The physiological function of BNP includes vasodilation, natriuresis, diuresis, and inhibits both RAAS and SNS (Sun, 2005). The activation of natriuretic peptides system is a rational compensation (Sun, 2005; Lainchbury, 2003; Multinational Study Investigators, 2002; Anand, 2003; Tsutamoto, 1997). Recombined human BNP-nesiritide had been used for treatment in HF patients and had a better effect than positive inotropic therapy (Coclucci, 2000; The UMAC Invetigators, 2002; Abraham, 2005). Numerous clinical studies revealed that circulating BNP increased in HF patients and were positively related to mortality (Lainchbury, 2003; Multinational Study Investigators, 2002; Anand, 2003; Tsutamoto, 1997). It served as independent predictor of poor prognosis in cardiovascular disease (Anand, 2003; Tsutamoto, 1997). But we followed up 50 NYHA Ⅲ-Ⅳ patients with a HF history of more than 2 years for 12 months. Finally we concluded that the BNP level of non-survivals were significantly lower than that of survivals. Multiple variable analysis demonstrated that lower BNP level on admission was an independent risk factor of mortality. This was contrary to many previous studies (Anand, 2003; Tsutamoto, 1997).

In 2002, McGeoch and his coworkers (2002) found that among patients with LVEF of below 45% and receiving long-term treatment, 19% of them had a BNP level below 35 pmol/L (= 128 ng/L). In 2003, Tang and his coworkers (2003) studied 558 ambulatory patients with chronic, stable systolic HF (LVEF < 50%). They finally found that among the 498 symptomatic (NYHA functional class Ⅱ-Ⅲ) patients, 106 (21.3%) had plasma BNP levels in the "normal" diagnostic range (<100 ng/L); 60 patients were considered asymptomatic, and their plasma BNP levels ranged from 5 to 572 ng/L (median, 147 ng/L) (Tang, 2003). This suggested that natriuretic peptides system has been activated during the compensation stage of HF. However, in the decompensation stage of HF, a part of patients had "normal" BNP level (Tang, 2003). The author believed that it was the result of aggressive therapy. They did not follow-up for prognosis, but the author accepted the opinion of lower BNP level with a better clinical outcome (Tang, 2003). In 2005, Miller's study (2005) indicated that end-stage HF patients were treated with nesiritide, and the BNP level before and after nesiritide treatment were much lower in the non-survival than that in the survival. All the patients' BNP level were significantly increased after nesiritide treatment. Present study was partly coincidence with Miller' study.

The lower concentration of BNP may reflect a loss of the ability to synthesize and release BNP in amounts of sufficiency and maintain effective neurohormonal compensation; or the BNP clearance and/or degradation is up regulated in end-stage HF (Packer, 2003; Andreassi, 2001; Alimirez, 1999; Deschodt-Lanckman, 1989). Increased levels of the neutral endopeptidases that degrade BNP have been described in patients with end-stage renal dysfunction (Deschodt-Lanckman, 1989) and may be a common mechanism in patients with HF, given the relative severity of renal dysfunction observed in the patients in this study.

These observations support the hypothesis that at some point in the progression of advanced HF, neurohormonal systems in HF are unable to provide adequate levels of the natriuretic hormones to maintain hemodynamic compensation. This could be due to reduced synthesis and secretion, increased degradation, and/or clearance or other additional factors not yet clearly understood (Packer, 2003). Regardless of the cause, it suggests that the inability to maintain high cardiac natriuretic peptide levels in the setting of hemodynamic compromise is an adverse prognostic indicator (Packer, 2003).

The clinical value of present study is that, with the dramatically clinical use and study of measuring BNP, the clinical cardiologists should not over-depend on the results of BNP measurement in the diagnosis, monitoring therapy and risk stratification in patients with HF. They should evaluate the disorder comprehensively and tightly integrate with clinical findings. End-stage HF patients with lower BNP level reflects exhausion of natriuretic peptides. This also provides theoretical foundation for human recombined BNP-nesiritide used as an agent for HF treatment.

The samples of this study were relatively small, so the selection bias may exist. Furthermore, We did not measure atrial natriuretic peptide in this group of patients. So, the result of this study need large samples, multi-center, double blind clinical trials to confirm. The relationship between natriuretic peptides and pathogenesis, progression and prognosis of HF need further research to elucidate.

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