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Brief communication (Original)

Clinical implications of normal B-type natriuretic peptide levels in patients with severe chronic heart failure

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Background: High plasma B-type natriuretic peptide (BNP) levels in patients with severe chronic heart failure (CHF) often indicate poor ventricular function and poor prognosis. However, in some such patients plasma BNP levels are normal.
Objective: To investigate the clinical implications of BNP levels in patients with severe CHF.
Methods: Fifty-seven patients with severe CHF were divided into group A (13 normal plasma BNP level) and 44 patients (high plasma BNP levels) group B. Diuretics, angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonist, e.g., metoprolol) and digitalis were used as conventional treatment. The clinical characteristics of all patients in two groups were analyzed and compared.
Results: At the first admission, left ventricular end diastolic diameter in group B was significantly lower than group A ($p < 0.05$), and the plasma BNP level in group B was significantly higher than group A ($p < 0.05$). When metoprolol was used, 6 and 5 patients in group A and B could not tolerate the initial dose. In other cases using metoprolol at average maximum tolerance dose of metoprolol 12.5 6.25 and 24.20 11.22 mg/day in group A and B, respectively, there was a significant difference between them ($p < 0.05$). There were no significant differences in plasma BNP levels between two groups during stable period. The plasma BNP level in group B during acute worsening stage was significantly higher than in the remission stage (962.73 165.00 ng/L *vs* 876.24 167.70 ng/L, $p < 0.05$). However, there was no significant difference between group A (74.03 11.18 ng/L) and group B (71.38 11.68 ng/L) ($p > 0.05$). The mobility of group A was higher than group B (11/12 *vs* 6/44, $p < 0.05$). Logistic regression analysis showed that, the plasma BNP level was the independent risk factor for predicting cardiac death (regression coefficient, 3.817; OR, 45.488; 95% CI, 5.322"388.791).
Conclusion: In patients with severe CHF, normal plasma BNP level suggests depletion of BNP secretion and further deterioration of cardiac function, indicating a poor prognosis.

Keywords: B-type natriuretic peptide, heart failure, prognosis

According to commonly-accepted hypotheses, B-type natriuretic peptide (BNP) and pro-inflammatory cytokines, produced in response to heart failure, contribute to progressive deterioration of cardiac performance [1]. In support of these hypotheses, poor heart failure outcomes are linked to elevated serum levels of biomarkers of myocardial stress and inflammation, including cardiac hormones and pro-inflammatory mediators [2-5]. In addition to optimal biomarkers, BNP may be one of biomarkers seen with myocardial stress in patients with HF [6, 7]. High BNP levels in patients with chronic heart failure (CHF) often indicate poor ventricular function and a worse prognosis, but studies have shown that in some patients with severe chronic heart failure the plasma BNP level is normal [8, 9]. In clinical practice, with quality laboratory resources, BNP has been introduced to diagnosis, prognosis and as a guide for treatment [10-15]. In this study, 57 patients with severe CHF seen at our hospital from December 2002 to October 2009, were studied, focusing on plasma levels of BNP, clinical features and prognosis.

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Patients and methods

Patients

The 57 severe CHF patients with grade III and IV heart function (New York Heart Association) and left ventricular ejection fraction (LVEF) <45% were enrolled in this study. They were arbitrarily divided into group A (normal BNP level, 13 cases) and group B (high BNP level, 44 cases). Group A included 6 males and 7 females, aged (66.77±5.75) years. There were 2 cases of ischemic cardiomyopathy and 11 cases of dilated cardiomyopathy. Group B included 24 males and 20 females, aged (65.75±5.57) years. There were 4 cases of ischemic cardiomyopathy and 40 cases of dilated cardiomyopathy. The exclusion criteria were as follows: heart valve disease, acute myocardial infarction, liver and kidney dysfunction, atrial fibrillation, malignancy and diastolic heart failure. This study was conducted with approval from the Ethics Committee of The Fourth People's Hospital of Wuxi City. Written informed consent was obtained from patients or their families.

Treatment protocol

After admission, a complete history, physical examination, chest X-ray radiography, standard 12-lead electrocardiograph (ECG), echocardiograph and plasma BNP determination were performed. Diuretics, angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonist, e.g., metoprolol) and digitalis were used for conventional treatment. When the condition was in a stable state (not using intravenous drugs for 4 days, no fluid retention), metoprolol was used with initial dose of 6.25 mg/day. Then, the dose was adjusted every 10 to 14 days. The first increase was 6.25 mg/day, followed by increase of 6.25 mg/times, 2 times each day. The increase was stopped when the morning resting heart rate was 55 to 60 times per min. The dose was reduced when fluid retention occurred or heart failure worsened [3].

Detection of plasma BNP

Venous blood (3 mL) were collected within 24 h after admission and stored in EDTA. The BNP level in whole blood was determended using Triage rapid quantitative heart failure diagnostic apparatus (Biosite Diagnostics Inc., San Diego, USA), and a plasma BNP level of < 100 ng/L was regard as normal.

Follow-up

Clinic or telephone follow-up was conducted once a month, and the plasma BNP concentration was monitored once every two months. For acute onset of CHF, the plasma BNP level was measured in the acute onset stage and stable stage. Cardiac death modes included pump failure and sudden cardiac death. The sudden cardiac death referred to the death with ECG evidence of cardiac arrest, death with acute onset within 1 hour, death with stable symptoms 24 hours previously.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 statistical software. Measurements were expressed as mean±SD, and enumeration data were expressed as frequency distribution. *t*-test and chi-square test were performed for analyzing the measurement data and enumeration data, respectively. Logistic regression analysis (backward method) was used to analysis of the risk factor for cardiac death. $p < 0.05$ was considered as statistically significant.

Results

Baseline data

As shown in **Table 1**, there was no significance in age, gender, cause of disease, hypertension, heart rate and creatinine between the two groups ($p > 0.05$).

Results of echocardiography and plasma BNP detection

Results of echocardiography and plasma BNP detection are shown in **Table 2**. Compared with group A, left ventricular end diastolic diameter (LVEDd) in group B was significantly lower ($p < 0.05$), and LVEF in group B was significantly higher ($p < 0.05$). At the same time, the plasma BNP level in group B was significantly higher than group A ($p < 0.05$).

Table 1. Baseline data in patients

Group	Age (years)	Gender		Disease cause		Hypertension (cases)	Heart rate (beats/min)	Creatinine (μmol/L)
		male	female	DCM	ICM			
A	66.77 ± 5.75	7	6	11	2	2	81.24 ± 5.74	112.41±10.29
B	65.77 ± 5.55	20	24	40	4	5	77.12 ± 3.23	108.52±9.57

Group B compared within group A, $P < 0.05$, DCM = dilated cardiomyopathy, ICM = ischemic cardiomyopathy

Table 2. Echocardiography results and plasma BNP levels in two groups

Group	LVEDd (mm)	LVEF (%)	Plasma BNP level (ng/L)
A	70.56 ± 4.33	24.16 ± 2.50 (22–27)	77.85 ± 9.67
B	63.73 ± 3.75[a]	28.49 ± 2.63[a] (26–33)	950 (728–1525)[a]

[a]$P < 0.05$ compared with group A; LVEDd = left ventricular end diastolic diameter, LVEF = left ventricular ejection fraction

Clinical use of metoprolol

All patients received conventional treatment using diuretics, angiotensin-converting enzyme inhibitors (or angiotensin II receptor antagonist) and digitalis. When metoprolol was used, 6 and 5 patients in group A and B could not tolerate the initial dose and use of metoprolol was stopped. In another 7 (group A) and 39 (group B) cases using metoprolol, the average maximum tolerance dose of metoprolol was 12.5±6.25 mg/day and 24.20±11.22 mg/day, respectively, with significant difference between them ($p < 0.05$).

Follow-up results

Patients in group A were followed up for 19.62±14.71 months, with no significant difference in plasma BNP levels during the stable periods. The plasma BNP levels at the 2nd, 6th, 12th and 16th month were 76.85±10.69, 77.07±11.55, 77.15±13.09, and 75.50±11.37 ng/L, respectively. There were a total of 29 times of acute failure onset stages. The average plasma BNP levels at the acute onset stage and remission stage were 74.03±11.18 and 71.38±1.68 ng/L, respectively, with no significant difference between them ($p > 0.05$). In group B, the follow-up was performed for 72.5±17.08 months. The plasma BNP levels at the 6th, 12th, 24th and 48th month were 897.20±175.40, 896.45±161.53, 889.34±167.81 and 900.59±154.40 ng/L which indicated no significant difference of plasma BNP levels during the stable periods. There were a total 89 times of acute onset failure. The average plasma BNP levels at acute onset and remission were 962.73±165.00 and 876.24±167.70 ng/L, respectively, with significant difference between them ($p < 0.05$).

There were 11 cases of cardiac deaths in group A, including 6 cases of pump failure, 2 cases of ventricular fibrillation, and 3 cases of sudden death. In group B, there were 6 cases of death, accounting for 13.63% (6/44), including 1 cases of pump failure and 5 cases of sudden death. There were significant differences between two groups ($p < 0.05$). The survival time prior to death in group A and B was 13.80±4.29 and 38.42±8.31 months, respectively, with significant difference between the two groups ($p < 0.05$). In 11 cases of cardiac death in group A, the plasma BNP level at the first admission was 77.91±11.16 ng/L, and at approaching death it was 76.82±8.26 ng/L, with no significant difference between two time points ($p > 0.05$). In 6 cases of cardiac death in group B, the plasma BNP level at the first admission was 1143.50±173.10 ng/L, and at approaching death it was 924.43±183.10 ng/L, indicating decrease from before ($p < 0.05$).

Regression analysis results

Logistic regression model was used to analyze the effects of gender, age, hypertension, heart failure duration, LVEF, low plasma BNP and drug use on cardiac death. Results found that, plasma BNP was the independent risk factor for predicting cardiac death (regression coefficient, 3.817; OR, 45.488; 95% CI, 5.322-388.791; $p < 0.05$).

Discussion

BNP secretion is an important neuro-humoral compensatory mechanism caused by ventricular expansion and pressure overload in CHF. BNP can cause vasodilatation and reduce blood volume to increase the ventricular preload, while BNP acts with renal tubules and renal vessel to increase urinary sodium excretion [16]. In the clinic, the plasma concentration of BNP increases with the increase of LVEDd and severity of CHF, which leads to enhancement of compensation [17]. However, in some patients with CHF, the plasma BNP levels were normal. McGeoch et al [8] found that, in approximate 19% of patients with CHF (LVEF < 45%), the serum BNP level is below 128 ng/L. Tang et al study showed that, in 558 asymptomatic patients with CHF (LVEF < 50%) and 498 symptomatic CHF patients, 106 cases had normal plasma BNP levels (< 128 ng/L) [9]. Results of this study found that, in patients with severe CHF, about 23% (13/57) have normal plasma BNP level.

Severe CHF with normal BNP levels indicates a poor prognosis. Miller et al [18] have used nesiritide to treat 40 patients with severe CHF and found that, compared with patients with elevated plasma BNP level, the mortality in patients with normal plasma BNP levels is significantly increased in spite of the treatment. It is reported that, in follow-up of patients with chronic advanced heart failure who died cardiac deaths, the plasma BNP level in cases with cardiogenic death (501±72 ng/L) is significantly lower than those that survived (877±89 ng/L). There were 3 patients with cardiogenic deaths and plasma BNP level was normal [19]. Niederkofler et al [20] believe that, for CHF with aggravated symptoms, a normal plasma BNP level indicates an elevated cardiac readmission and death rate as well as worse prognosis. This is consistent with the results of our study. In group A with 13 CHF patients, the plasma BNP level was normal on admission, but the LVEF (24.16±2.50 %), LVEDd (70.56±4.33 mm), survival time of the died patients (13.8±4.2 months) was significantly shorter than group B. There were 11 cases of death, accounting for 84.62% (11/13) and included 6 cases of pump failure, 2 cases of ventricular fibrillation and 3 cases of sudden death. In group B, there are 6 cases of death, accounting for 13.63% (6/44), including 1 cases of pump failure and 5 cases of sudden death. This indicates that, patients in group A are in a further deteriorated status of heart failure, and the prognosis is worse than in group B. Logistic regression analysis shows that, lower plasma BNP is the independent risk factor to predict cardiac deaths in patients with heart failure.

The mechanism for severe CHF with normal plasma BNP levels was discussed in several previous papers. Miller et al [18] speculated that, due to long or heavy heart failure compensation BNP secretion needs to be maintained at a higher level. Long-term excessive secretion leads to depletion of BNP. Our study found that, there is no significant difference in plasma BNP level in the stable period between two groups. In the acute onset failure stage, the BNP level in group B is significantly increased, but there is no obvious change in group A. This suggests that there is BNP depletion in group A. The ventricle further expands in patients with severe CHF and the cardiac function further deteriorates which leads to reduction of BNP secretion [21]. In this study, further ventricular expansion appears in patients with normal serum BNP level (group A), compared with group B, indicating further thinning of ventricular wall.

The sympathetic nervous system (SNS) is another important compensatory mechanism in heart failure, but continued over-excitement of SNS can lead to ventricular remodeling and cardiac toxicity. Angiotensin II receptor antagonists can inhibit the action of the SNS to myocardium, thus improve the prognosis [22], but it also can cause dissociation of myocardium from β-adrenergic support, leading to negative negative inotropic effect and aggravate heart failure. With the development of research on heart failure, SNS excitement for maintenance of hemodynamic balance becomes more and more important, especially for patients with severe CHF, of whom tolerance of β-blockers is decreased. So the decreased tolerance of patients to β-blockers may prompt further deterioration of cardiac function [23]. In this study, after use of metoprolol, the heart failure becomes worse in two groups, and the drug was discontinued in some patients. Tolerance to metoprolol in group A is less than in group B. This indicates that, with the reduction of plasma BNP level, the dependence of patients to SNS excitement is increased. So the cardiac function in group A deteriorates more than in group B. This paper is a further research of previous study [24].

Conclusions

In patients with severe CHF, a normal plasma BNP level suggests depletion of BNP secretion and a further deterioration of cardiac function. This indicates poor prognosis. However, there are limitations of this study, including small sample size and short duration of follow-up. In addition, the specific time points and condition of BNP change from high to low have not been observed. These need to be further investigated.

The authors have no conflict of interest to declare.

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