

Original Article

Brain Natriuretic Peptide as the long-term cause of mortality in patients with cardiovascular disease: a retrospective cohort study

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Abstract: Objective: To explore the influence of BNP (Brain Natriuretic Peptide) in plasma on the long-term cause of mortality and prognosis of patients with cardiovascular disease (CVD). Method: We performed a retrospective cohort study of 276 inpatients that enrolled in our hospital from March 2003 to December 2004 and had a history of heart disease and received a BNP test. Kaplan-Meier survival curves with Log-Rank test were used to compare the survival rates among different levels of BNP (<100 ng/L, 101~1000 ng/L, 1001~5000 ng/L and >5000 ng/L). Cox proportional hazards regression models were used to estimate HRs and 95% CIs with adjustments for other covariates. Result: After a median follow-up of 7 years, a total of 91 patients died of whom fifty were cardiogenic deaths and 41 were non-cardiogenic. The survival rates were of statistical significance ($P=0.0000$) between the different levels of BNP in the 4 groups, and the mortality rate increased gradually with the increase in BNP concentration. Multivariable Cox regression analysis showed that BNP levels were inversely associated with the survival rate in CVD patients (HR=0.24, 95% CI: 0.13~0.42). In addition, age and left ventricular ejection fraction values were also of statistical significance in the Cox regression model. Conclusion: Our findings suggested that high Plasma BNP levels may have an adverse effect on the prognosis of patients with cardiovascular disease.

Keywords: Brain natriuretic peptide, cardiovascular disease

Introduction

Physical examination and chest X-ray have limited reliability in diagnosing heart failure even with the best of clinicians. Several studies have demonstrated that BNP measurements are a sensitive and specific test to diagnose chronic heart failure (CHF) in emergency medicine and urgent-care settings. B type BNP is a peptide hormone secreted by the ventricle during dilation or increased pressure. It is synthesized as an inactive pro-hormone that is split into the active hormone BNP and the inactive N-terminal fragment (NT-pro-BNP). The prognostic importance of BNP and NT-pro-BNP has been extensively studied in patients with heart failure as well as in patients with acute coronary syndromes, and both markers have been shown to be strong predictors of morbidity and mortality [1, 2].

The introduction of testing BNP in China was comparatively late and most of the studies

regarding the effect of plasma BNP value on prognosis of cardiovascular disease (CVD) are confined to short-term or medium-term observations of less than 5 years. So it is necessary to perform a large-scale retrospective study on long-term mortality rate to improve clinical outcomes and to provide constructive advice to the patients' with high plasma BNP.

Materials & methods

Clinical data

Patients were included in this retrospective cohort if they 1) were admitted in the Beijing General Hospital between March 2003 and December 2004, 2) had ever been diagnosed with CVD, and 3) had received a BNP test. After reviewing the clinic data from the hospital, 276 patients were found to be eligible and comprised the current cohort. Consent had been obtained from each participant after fully explaining the purpose and nature of all the pro-

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cedures used in this study. All of them had been diagnosed with cardiac disease rated level I-IV by NYHA (New York Heart Association). Their ages ranged from 16-94 (68.07 ± 13.08) years. In all patients, a thorough medical history was recorded, including details of any previous myocardial infarction, previous revascularization, angina pectoris, arterial hypertension, suspected congestive heart failure (defined by symptoms of shortness of breath or leg edema), previous stroke or transient ischemic attacks, diabetes, intermittent claudication, and smoking status. Information came from medical records, directly from patients, or both. Their clinical diagnoses were predominantly coronary heart disease 142 cases (51.45%), hypertension 185 cases (67.13%), valvular disease 19 cases (6.9%), cardiomyopathy 12 cases (4%), arrhythmia 6 cases (2.2%), cardiac tumor 1 case, pericardial disease 2 cases, atrial septal defect 1 case, cardiac disease associated with diabetes 70 cases (25.6%), renal insufficiency 39 cases (14.13%) and cerebral infarction 17 cases (6.16%). Most of them had comorbidities, except those with acute myocardial infarction, pulmonary dyspnea or those without cardiac disease history. Patients were interviewed in person or through phone using a structured questionnaire to obtain additional information on demographic characteristics, lifestyle, dietary habits, and other factors.

Research method

All of the inpatients received UCG (Ultrasound Cardiogram) examination following enrollment. Meanwhile, venous blood sample was obtained from all patients either in the morning or when they were enrolled in the hospital. Blood specimens were immediately sent for examination without delay. BNP was measured with use of BIOSITE Dry's Rapid Heart Failure/Myocardial Infarction diagnostic unit by IFA (Immunofluorescence Assay). Its results are obtained in 0.5 hour and the detection range is 5~5000 ng/L. On the basis of BNP test result, the patients were divided into 4 groups, which were BNP<100 ng/L n=123; BNP 101~1000 ng/L n=104; BNP 1001~5000 ng/L n=34; BNP>5000 ng/L n=13.

Follow-up

Subjects were followed up with phone or in person during reexamination at the hospital every 2-3 months to ascertain deaths from all causes.

Outcome data until 31 December 2011 for all patients were used for the present analysis, with median follow-up time of 7 years. The underlying causes of death were coded according to the 10th International Classification of Disease (ICD-10).

Statistical treatment

The measurement data were expressed in terms of the error's average and standard deviation ($X \pm s$). The variance analysis was applied in the comparison of AGE, EF (Left ventricular ejection fraction) value between groups. Kaplan-Meier survival curves with the Log-Rank test were used to compare the survival rates among different levels of BNP (<100 ng/L, 101-1000 ng/L, 1001-5000 ng/L and >5000 ng/L). Multi-variable Cox proportional hazards regression models were fitted to estimate HRs and 95% CIs for BNP and other potential risk factors including age and EF value. Covariates were selected based on their potential to confound or modify the association between BNP and mortality in CVD patients. All covariates were modeled using baseline values. The covariates included in the multivariate adjusted models were gender (male and female), age (continuous variable), smoking (yes and no), EF value (continuous variable), and NYHA functional class (I-IV). All the aforementioned calculations were generated by SAS software, version 7.2.

Results

Comparison of gender, age and RVEF (EF, %) between groups

Among the 276 selected cases, 2 cases were lost in the follow-up and so 274 cases were selected. Of these 140 cases were male and 134 were female. The gender comparison was not statistically significant. In the age comparison between the groups, the difference in age between the first group and the other groups were of statistical significance ($P < 0.05$). The comparison of EF value between the groups was also statistically significant and the BNP value increased with a decrease in EF value (**Table 1**).

Comparison of mortality rate between groups during the 7-year follow-up

There were 91 cases of death of which 41 were ruled to be due to non-cardiogenic causes and

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Table 1. Comparisons of gender, age, EF value, and NYHA functional class by different BNP levels

Group	BNP<100 ng/L	101-1000 ng/L	1001-5000 ng/L	>5000 ng/L	P value
Gender (Male/Female)	72/51	43/61	18/16	7/6	0.0768
Age (mean ± SD)	63.5±13.3	71.5±12.3	72.7±11.1	71.9±8.7	0.0000
EF (%)	62.2±7.8	55.9±11.3	39.5±13.6	42.7±13.4	0.0000
NYHA (I-IV)	107/5/7/4	23/31/28/22	3/7/10/14	1/2/4/6	0.000 ¹

¹Chi-square test.

Table 2. Statistical analysis of survival rates and death of each group

Group (BNPng/L)	Total cases	Death cases	Cardiogenic death	Survival rate (%)	P value
<100	123	13	2	89.43	
101-1000	104	39	21	62.5	
1001-5000	34	26	20	23.53	
>5000	13	13	7	0	
Total	274	91	50	66.29	0.0000

50 due to cardiogenic causes. Death in the 1st group totaled 13 cases, the 2nd group was 39 cases (39/104), and the 3rd group was 26 cases (26/34). However, members of the 4th group all died in the first 5 years of the follow-up (13/13) (Table 2). As can be seen from the table, the ratio of cardiogenic death gradually increased with an increase in the BNP value. The Kaplan-Meier survival graph shows that the survival rate gradually decreases with an increase in BNP value (Figure 1) and the comparison of survival rate between groups was statistically significant ($X^2=137.45$, $P=0.0000$).

Influences of multi-factor analysis (Cox regression) on survival rate

In the multi-factor analysis of survival, age, BNP and EF were independent risk factors for death (Table 3) and BNP level was a protective factor in the survival of patients. The lower the BNP value was, the longer the survival rate was and the lower the risk of death. With an increase in the age, the mortality rate also gradually increased. Among the 3 factors, the influence of BNP and age on survival was greater than EF.

Influence of extremely high BNP on mortality rate

In this study, we found that extremely high BNP value (>5000 ng/L) had a serious influence on both the short-term and long-term mortality rate. The mortality rate of 13 cases in 3 months was 53.8% (7/13), in 2 years was 69.2% (9/13)

and in 5 years all patients died (13/13). The survival rate was 0 and prognosis 111 was seriously adverse.

Discussion

As an important indicator or a potent marker for diagnosis of heart failure, BNP has been a hot topic in the recent years. It is also becoming a potent marker [3] to estimate the seriousness of heart failure for its linear correlation with the symptoms. Many studies have proved that BNP is an independent risk factor for cardiovascular incidents and deaths from cardiovascular disease. For patients with coronary heart disease, BNP is a potent predicting factor [4] for death in 6 months or re-admission. For patients with chronic heart failure (CHF), high BNP value is related to repeatedly being hospitalized and the risk of sudden death. Thus, BNP testing in the course of CHF is helpful [5] in estimating risk level clinically.

In this study we used BNP to predict the long-term cause for mortality in patients and this work had two important characteristics, one was the wide range in age (16~94 years old), and the other is the average time of follow-up was 7 years, which is the longest follow-up time among domestic reports. As can be seen from the Kaplan-Meier survival graph, the survival rate decreased with the increase in BNP values. The survival rate for 7 years was 89.43% for the group with BNP>100 ng/L while it was only 23.53% for the group with BNP>1000 ng/L. The surprising thing is that the short-term and long-term risk of death at an extremely high BNP value were significantly increased: 53.8% mortality in 3 months, 69.2% in 2 years and all patients died in 5 years, which was observably higher than the other groups. The probable reasons are: (1) advanced age; (2) the advanced nature of the disease; (3) the complexity of the disease: mostly accompanied by multi-organ failure (MOF) and comorbidities and (4) terminally ill patients.

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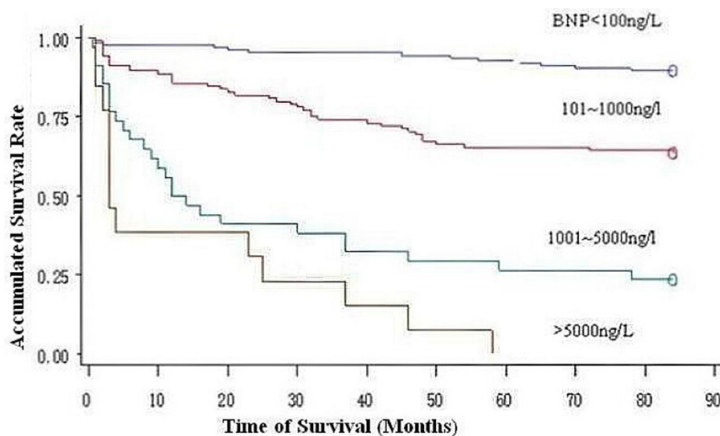


Figure 1. The study design and results in patients with SVT.

Table 3. Influence of each index on survival rate

Factor	Regression Coefficient	Standard Deviation	P value	Risk Ratio	95% CI
BNP	-1.617	0.313	<0.0001	0.235	0.13-0.42
AGE	0.638	0.124	<0.0001	1.894	1.48-2.42
EF	-0.118	0.042	0.0053	0.889	0.82-0.96

According to our results BNP is a valuable biochemical indicator for long-term cause for mortality, so repeatedly testing BNP levels in blood plasma might be of significance. It can monitor the progression of the disease and help estimating the clinical effect of drug therapy [6, 7]. Some scholars even suggest a dynamic monitoring of BNP value to guide clinic judgment and treatment [8, 9]. In our study, we also observed that part of the patients have a decreased BNP following drug therapy and their long-term survival rate was higher than those with an increased BNP. Hence, the decrease in BNP following drug therapy does indicate that conditions improve with treatment.

The Triage BNP Test diagnostic level to exclude heart failure is BNP<100 pg/ml (negative). A level of >100 pg/ml is considered positive and indicative of heart failure. In our study, the minimum BNP value was <100 ng/ml and the highest reached 5000 ng/ml. This could be due to the fact that a different measurement method was used. So hospitals should choose accurate as well as a simple and economic method to fit the specific symptoms. When it comes to the ELISA test we should be more careful. The latest study indicates that activated BNP is not the main component of blood and that there

are also BNP (3-32), BNP (4-32) and a large amount of proBNP. Sometimes activated BNP cannot be detected even in some seriously ill patients with heart disease, partially because BNP1-32 has very short half live and is easy to degrade. The other reason is the glycosylation of the middle portion of the peptide so the antigen is invisible when we use the antibody specific to this region. After the amino acids on the 8 binding sites of the proBNP are glycosylated, especially on Thr71 site, degradation of proBNP will be blocked to generated activated BNP (1-32). People begin to think the ability of proBNP glycosylation and avoidance to generate activated BNP (1-32) is authentically reflecting the potential of the damaged heart to withstand failure [10]. Future studies should focus on the degree of glycosylation of proBNP in heart failure

and the ratio of glycosylated BNP to non-glycosylated BNP, which may be the pertinent indicator to reflect the degree of heart failure, monitor the development of the disease and assess the effect of drug therapy more accurately.

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Disclosure of conflict of interest

None.

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References

- [1] Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, Luchner A, McDonagh T, Mair J, Nieminen M and Francis G. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003; 24: 1710-1718.
- [2] Daniels LB and Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007; 50: 2357-2368.

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- [3] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008; 10: 933-989.
- [4] Aspromonte N, Valle R, Peacock WF, Vanderheyden M and Maisel A. Inpatient monitoring and prognostic importance of B-type natriuretic peptide. *Congest Heart Fail* 2008; 14 Suppl 1: 30-34.
- [5] Tsuchida K and Tanabe K. Plasma brain natriuretic peptide concentrations and the risk of cardiovascular events and death in general practice. *J Cardiol* 2008; 52: 212-223.
- [6] Mohammed AA and Januzzi JL. Natriuretic Peptide guided heart failure management. *Curr Clin Pharmacol* 2009; 4: 87-94.
- [7] Masson S, Latini R, Anand IS, Vago T, Angelici L, Bariera S, Missov ED, Clerico A, Tognoni G and Cohn JN. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem* 2006; 52: 1528-1538.
- [8] Faggiano P, Valle R, Aspromonte N, D'Aloia A, Di Tano G, Barro S, Giovinazzo P, Milani L, Lorusso R and Dei Cas L. How often we need to measure brain natriuretic peptide (BNP) blood levels in patients admitted to the hospital for acute severe heart failure? Role of serial measurements to improve short-term prognostic stratification. *Int J Cardiol* 2010; 140: 88-94.
- [9] Porapakkham P, Porapakkham P, Zimmet H, Billah B and Krum H. B-type natriuretic peptide-guided heart failure therapy: A meta-analysis. *Arch Intern Med* 2010; 170: 507-514.
- [10] Semenov AG and Sefrian KR. Biochemistry of the human B-type natriuretic peptide precursor and molecular aspects of its processing. *Clin Chim Acta* 2011; 412: 850-860.