The value of blood brain natriuretic peptide for predicting clinical severity and prognosis in patients with acute coronary syndromes

Tong-wen Sun [1], Shu-xiang Zhang[2], Qing-yan Xu [1], Xiao-juan Zhang [1], Ling Li [3], Jin-ying Zhang [3]

1. Department of Emergency Medicine , The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
2. Department of International Exchange and Coorperation, Zhengzhou University, 100 Science Road ,Zhengzhou, Henan 450001, China
3. Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China

E-mial:suntongwen@163.com

ABSTRACT: **Background:** B-type/brain natriuretic peptide (BNP) is a neurohormone synthesized predominantly in ventricular myocardium. Although the circulating level of this neurohormone has been shown to provide independent prognostic information in patients with heart failure, few data are available for Chinese patients with acute coronary syndromes (ACS). This study was designed to investigate the value of blood BNP for predicting clinical severity and prognosis in patients with ACS. **Methods:** Blood BNP concentration was measured in 106 ACS patients, 1-3 days after onset of ischemic symptoms. Patients were followed up for six months. The end-point were cardiac death, non-fetal myocardial infarction and readmission. **Results:** (1) The concentration of circulating BNP in patients with ACS were increased. (2) 1 month follow-up demonstrated that, levels of BNP in non- survivals were much higher than that in survivals (P<0.0005); step-wise logistic regression analysis demonstrated that ST segment deviation ≥ 1 mm and BNP ≥ 596 ng/L were independent predictors of short-term cardiac death in patients with ACS [OR=3.467, 95% confidence interval (CI) 1.336-32.836, P=0.002; OR=21.168, 95% CI 4.419-107.990, P<0.0005]. (3) area under the curve（AUC） of the receiver-operating-characteristic (ROC) of BNP to predict short-term cardiac death in patients with ACS was 0.878（95% CI 0.781-0.974, P<0.0005）. (4) Kaplan-Meier survival curve showed that the survival curve of patients with BNP above 596 ng/L was significantly lower than that of patients with BNP below 596 ng/L（Log-rank test, P<0.0005）. Cox proportional hazards regression models demonstrated that BNP and cardiac troponin I were risk factors which related to ACS prognosis (RR = 2.507, 95% CI 1.081-3.914, P =0.028; RR =2.208, 95% CI 1.609-3.874, P=0.030). **Conclusions:** (1) The circulating levels of BNP are significantly increased in patients with ACS. Myocardial ischemia and / or left ventricular systolic dysfunction are the main cause of stimulating BNP secretion. (2) BNP could provide important clinical value for predicting clinical severity and prognosis. It could be used for risk stratification in patients with ACS, especially when there is only ischemia without infarction and when blood is sampled very early after the onset of ischemia that would be missed by markers of myocyte necrosis.

[Tong-wen Sun, Shu-xiang Zhang, Qing-yan Xu, Xiao-juan Zhang, Ling Li, Jin-ying Zhang. The value of blood brain natriuretic peptide for predicting clinical severity and prognosis in patients with acute coronary syndromes. Life Science Journal 2010;7(4):119-123]. (ISSN: 1097-8135).

Keywords: B-type / brain natriuretic peptide; Acute coronary syndromes; Prognosis

1. Introduction

B-type/brain natriuretic peptide (BNP) is a neurohormone synthesized predominantly in ventricular myocardium. Although the circulating level of this neurohormone has been shown to provide independent prognostic information in patients with heart failure (Sun et al 2007), few data are available for Chinese patients with acute coronary syndromes (ACS). This study was designed to investigate the values of circulating BNP for predicting clinical severity and prognosis in Chinese patients with ACS.

2. Material and Methods

Patient selection

This study was approved by the institutional review board and consent was obtained from all participants. Between September 2003 and May 2004, total of 106 ACS patients (71 males, mean age 62±11 years, range 37-85) admitted to the coronary care unit and ordinary ward at the First Affiliated Hospital of Zhengzhou University were enrolled in the study.20 inpatients or outpatients (13 males, mean age 58±10 years, range 39-75) with stable angina pectoris were considered control group. Patients were followed up for up to six months after hospital

discharge. Events, including death, readmission to hospital with heart failure and non-fetal myocardial infarction were recorded.

The inclusion criteria were as follows: older than 18 years old; electrocardiographic changes (ST-segment depression or elevation of at least 0.5 mm, T-wave inversion of at least 3 mm in at least three leads, or left bundle-branch block), elevated levels of cardiac markers (CK-MB and troponin I), absence of immediate heart failure or cardiogenic shock, ischemic symptoms less than 72 hours, and survival for at least 24 hours after onset of ischemic symptoms. The exclusion criteria were as follows: chronic renal dysfunction (blood creatinine >133μmol/L); primary pulmonary hypertension and cor pulmonale; primary cardiomyopathy and severe valve disease.

Measurement of circulating BNP level

A point-of-care test of fluorescence immunoassay for the quantification of BNP was used (Biosite Diagnostics Inc, USA), 2ml of intravenous blood was collected at the early morning after 1-3days of admission and BNP was determined within 20 minutes. The range of measurement was 5ng/L-5000ng/L.

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 using modified Simpson method.

Statistical analysis

Data were presented by mean±standard deviation (SD) and median. The difference of circulating BNP between the survival and the non-survival groups were compared using Wilcoxon signed rank test. Spearman rank correlation analysis was used to determine the factors that influence the circulating BNP level. Stepwise logistic forward regression analysis and Cox proportional hazards regression model were used to determine the factors related to prognosis. The accuracy of blood BNP in predicting cardiac death was assessed by a receiver-operator characteristic curve (ROC). $P<0.05$ was considered to be statistically significant. All data analysis was performed using the Statistical Package for Social Sciences (SPSS 11.0).

3. Results

After hospital admission, ST elevation myocardial infarction (STEMI) was diagnosed in 33, non- ST elevation myocardial infarction (NSTEMI) in 7 and unstable angina pectoris (UAP) in 66.

The changes of circulating BNP between ACS group and SAP group

1. The median of circulating BNP in ACS group and SAP group were 172ng/L and 18 ng/L, respectively. Wilcoxon signed rank test for two independent samples showed that the difference was statistically significant (U=136, P<0.0005). There were statistically significant difference between 2 groups about left ventricular ejection fraction (50.12 %±12.81% *vs.* 56.31%±9.60%, P＝0.031), leads number of ST segment deviation (2.75±3.43 *vs.* 0.53 ± 1.13, P＝0.015) and the degree of ST segment deviation (0.76±1.03 mm *vs.* 0.23±0.71mm, P＝0.042)".

2. Spearman rank correlation analysis showed that age, gender, blood pressure, smoking, drinking, history of diabetes mellitus, history of essential hypertension, serum C-reactive protein (CRP) were not related to blood BNP concentration. The BNP level were positively correlated with heart rate (r =0.229, P＝0.035), leads number of ST segment deviation (r =0.281, P＝0.009), the degree of ST segment deviation (r=0.284, P ＝ 0.008), left ventricular end-diastolic dimension (r=0.429, P<0.0005), history of heart failure (r=0.372, P<0.0005), history of myocardial infarction (r =0.220, P ＝ 0.043) and negatively correlated with left ventricular ejection fraction (r=－0.625, P <0.0005).

The relationship between circulating BNP levels and clinical condition and prognosis

After 1 month follow-up, 13 patients died, 2 patient experienced non-fatal myocardial infarction in ACS group. There were no end events in the SAP group at the end of 1 month follow-up. Among the 13 died patients, 12 patients' BNP levels were above 172ng/L (median) and 10 patients' BNP levels were above 596 ng/L (75% percentile). Those with a circulating BNP above 172 ng/L and 596 ng/L had a mortality of 23.6% (12/53) and 38.5% (10/26), respectively.

1. There were no significant differences in patient's age, gender, smoking or alcohol drinking, lipid profile, systolic blood pressure and the left ventricular ejection fraction （ 56.9±14.1% *vs.*56.9±14.1%, P=0.792）between the survival and non-survival groups.

The average and the median BNP levels in the non-survival group were significantly higher than that of the survival group (P<0.0005, Table 1). Univariate analysis indicated that the degree of ST segment deviation (r=0.289, P = 0.007), leads number of ST segment deviation (r =0.415, P<0.0005), BNP levels (r =0.469, P<0.0005) and Killip class (r =0.316, P =0.001) were risk factors of short-term prognosis. Step-wise logistic regression demonstrated that ST segment deviation ≥0.1 mV and BNP ≥596 ng/L were independent predictors of short-term death in patients with ACS (OR=3.467, 95% confidence interval 1.366-32.836, P=0.002; OR=21.168, 95% confidence interval 4.419-107.990, P<0.0005; [covariate were age, sex ,history of heart failure, history of myocardial infarction, diabetes mellitus, ST segment deviation ≥ 0.1mV, Killip class (Ⅰ/Ⅱ-Ⅳ), LVEF(≥50%/<50%), circulating BNP (≥596 ng/L/<596ng/L) and cTn I (positive/negative)]. Area under the curve of the receiver-operating-characteristic (ROC) of BNP to predict short-term death in patients with ACS was 0.878, 95% confidence interval 0.781-0.974, P<0.0005 (Figure 1). A circulating BNP cut-off value of 596 ng/L had a sensitivity of 76.9 percent, a specificity of 86.2 percent for predicting death at 1 month.

2. Kaplan-Meier survival curve showed that the survival curve of patients with BNP above 596 ng/L was significantly lower than that of patients with BNP below 596 ng/L (Log-rank test, P<0.0005, seen in Figure 2). Cox proportional hazards regression models demonstrated that BNP ≥ 596 ng/L and myocardial infarction were risk factors which related to ACS prognosis (RR=2.507, 95% confidence interval 1.081-3.914, P=0.028; RR =2.208, 95% confidence interval 1.069-3.874, P =0.030).

4. Discussions

This study indicates that the circulating BNP in patients with ACS are significantly higher , the degree of ST segment deviation are more severe, the number of ST segment deviation are more , but LVEF are lower than those in patients with SAP. These reveal that the increase of circulating BNP in patients with ACS are related to myocardial ischemia and left ventricular dysfunction, according with previous study (Wiviott 2004, Galvani 2004, de Lemos 2001, Morrow 2003, Sun 2006)

The release of BNP from myocardial cells is provoked by a variety of stimuli, including hypoxia, ischemia, increased wall stress, and dilation of ventricles. Early animal studies of experimental infarction in rats demonstrated rapid induction of ventricular BNP gene expression and BNP production not only in the infarct and the perinfarct regions but also in the nonischemic surrounding myocardium (Hama 1995). These changes in gene expression were seen as early as four hours postinfarction (Hama 1995). Clinically, there was transient increase in cardiac BNP secretion after percutaneous transluminal coronary angioplasty (Tateishi 2000). These results indicate that myocardial ischemia induces synthesis and secretion of BNP, even before myocyte necrosis and overt left ventricular dysfunction taking place. But the exact mechanism of stimulating BNP release in myocardial ischaemia is unclear (Talwar 2000). Cardiotrophin 1 is reased in myocardial ischaemia. It stimulates BNP production at a transcriptional level in vitro, suggesting that it may be involved in BNP secretion in vivo. This should be validated by basic and clinical studies (Talwar 2000).

De Lemos and his coworkers (de Lemos 2001) measured the blood BNP level of 2,525 patients with ACS and followed up for 10 months. They found that the base-line levels of BNP were correlated with the risk of death, heart failure, and myocardial infarction at 30 days and 10 months. After adjustment for independent predictors of the long-term risk of death, patients with blood BNP level in the second, third, and fourth quartiles had a risk of death in 10 months of 3.8 times, 4.0 times, 5.8 times higher than those with blood BNP level in the first quartile. Subgroups analysis showed similar results. Marrow （Morrow 2003） observed 1,676 patients with non-ST elevation ACS and found that the mortality of seven day and six month increased significantly in patients with elevated BNP (above 80 ng/L). Wang studied 110 AMI patients and founded that circulating BNP were related to cardiac events, heart failure and death （Wang 2005）. The present study demonstrated that the risk of death in patients with circulating BNP level above 596ng/Lwas 21 times higher than those with circulating BNP level under 596ng/L. A circulating BNP cut-off value of 596 ng/L had a sensitivity of 76.9 percent, a specificity of 86.2 percent for predicting death at 1 month.

The potential mechanisms of circulating BNP for evaluating prognosis in patients with ACS is unknown (Wiviott 2004, Galvani 2004, de Lemos 2001, Morrow 2003). Traditional biomarkers for the evaluation of myocardial infarction, such as CK-MB and cardiac troponins, are released when there is irreversible injury to cardiac myocytes. In contrast, BNP is released by intact cells, including those that are not ischemic. The functions of BNP, such as natriuresis , diuresis, vasodilatation, inhibition of the renin-angiotensin-aldosterone axis, and inhibition of sympathemic nerve activity, are beneficial to the heart. Accordingly, the magnitude of the increase in

BNP concentrations may reflect the size of the ischemic territory（Sun 2006, Talwar 2000）. Secondly, the present study and previous studies demonstrate that the increase of BNP are related to cardiac dysfunction （Sun 2006）. Thirdly, the increase BNP at the early time of MI can predict left ventricular remodling (Yoshitomi 1998). Finally, the increase of BNP is related to elder, renal dysfunction, heart failure, and arrhythmia. These also influence the prognosis of ACS (Sun 2006, Wiviott 2004, Galvani 2004, Sun 2006). In aggregate, we concluded that ischemia and cardiac dysfunction contributed to the adverse prognosis of ACS.

In conclusion, in patients with ACS, high levels of blood BNP levels are associated with a significantly increased risk of cardiac death in short term. BNP should be used, together with other biomedical markers for ischemia, as a prime factor for risk stratification in patients with ACS.

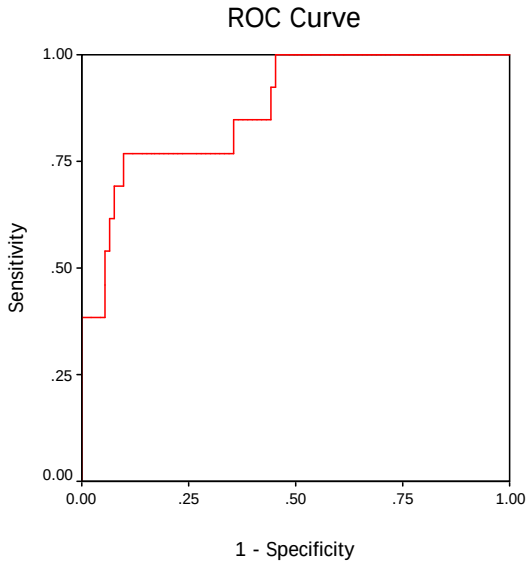

Fig 1. The ROC curve in assessing the predicting value of BNP for cardiac death

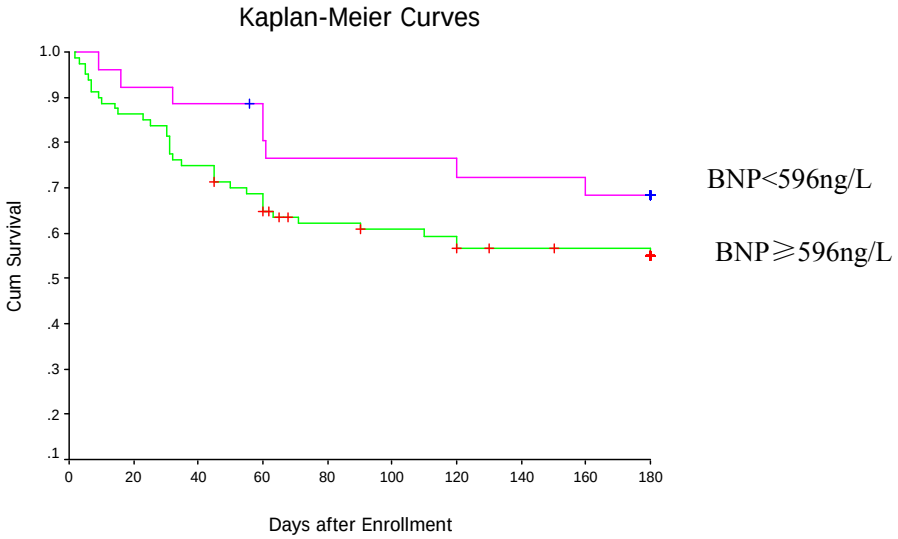

Fig 2. Kaplan-Meier survival curve

Table1: Comparison of BNP levels between survival group and non-survival group (ng/L)

group	BNP	LogBNP	Median
Survival (n=93)	320.87±425.54	2.10±0.68	116
Non-survival (n=13)	1762.31±1415.10	3.06±0.48	1132
Statistical value	*t* =-7.175	*t* =-4.879	*U*=149*
P value	<0.0005	<0.0005	<0.0005

*Wilcoxon signed rank test for 2 independent samples

Acknowledgment: This study was support by the program of tackle key problems in science and technology (No.200803024).

Corresponding Author:
Prof. Ling Li or Prof. Jing-ying Zhang
Department of cardiology,
The First Affiliated Hospital of Zhengzhou University
Zhengzhou, Henan 450052, China
Tel: 86-138-3851-6916
E-mail: suntongwen@163.com

REFERENCES

1 Sun T, Wang L , Zhang Y . Prognostic value of B-type natriuretic peptide in patients with chronic and advanced heart failure.Intern Med J 2007;37:168-71.
2 Wiviott SD, de Lemos JA, Morrow DA. Pathophysiology, prognostic significance and clinical utility of B-type natriuretic peptide in acute coronary syndromes. Clin Chim Acta 2004;346:119-128.
3 Galvani M, Ferrini D, Ottani F. Natriuretic peptide for risk stratification of patients with acute coronary syndrome. Euro J Heart Fail 2004; 6:327-333.
4 de Lemos JA, Marrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med 2001;345:1014-1021.
5 Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina /non –ST – elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS–TIMI 18. J Am Coll Cardiol 2003; 41:1264- 1272.
6 Sun TW, Zhang SX, Su GY, et al. Low level of B-type natriuretic peptide in relation to poor prognosis in patients with advanced left ventricular systolic dysfunction. Life Science Journal-Acta of Zhengzhou University Oversea Version 2006; 3: 5-8.
7 Hama N, Itoh H, Shirakami G, et al. Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. Circulation 1995;92:1558-1564.
8 Tateishi J, Masutani M, Ohyanagi M, et al . Transient increase in plasma brain(B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. Clin Cardio 2000; 23:776-780.
9 Talwar S, Squire IB, Downie PF, et al. Plasma N terminal probrain natriuretic peptide and cardiotrophin I are raised in unstable angina. Heart 2000; 84:421-424.
10 Wang LF, Wu S, Guan XR,et al. Relationship between plasma brain natriuretic peptide concentration and clinical prognosis in patients of acute myocardial infarction. Chin J Cardio 2005;33:234-237.
11 Yoshitomi Y, Nishikimi T, Kojima S, et al. Plasma natriuretic peptide as indicators of left ventricular remodeling after myocardial infarction. Int J Cardio 1998; 64:153-160.
12 Sun T, Wang L, Zhang Y.Prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. Arch Med Res 2006; 37:502-5.

9/29/2010