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Systolic and diastolic heart failure are associated with different plasma levels of B-type natriuretic peptide

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SUMMARY

Previous studies have found that plasma B-type natriuretic peptide (BNP) is elevated during left ventricular systolic or diastolic dysfunction. It is unclear whether the ventricular systolic and diastolic function is associated with different levels of plasma BNP. Plasma BNP was measured in 149 heart failure patients by a rapid point-of-care assay. The patients were divided into left ventricular diastolic dysfunction ($n = 48$), left ventricular systolic dysfunction ($n = 62$) and right ventricular systolic dysfunction group ($n = 39$). The mean BNP level in the left ventricular diastolic dysfunction, left ventricular systolic dysfunction and right ventricular systolic dysfunction was 115 ± 80 pg/ml, 516 ± 445 pg/ml and 345 ± 184 pg/ml, respectively ($p < 0.05$). We concluded that ventricular systolic and diastolic dysfunction increases plasma BNP levels to a different extent. Left and right ventricular systolic dysfunction is associated with a higher level of plasma BNP than left ventricular diastolic dysfunction.

Keywords: B-type natriuretic peptide; diastolic heart failure; systolic heart failure

INTRODUCTION

B-type natriuretic peptide (BNP) is a 32-amino acid neurohomone synthesised mainly by ventricular myocytes in response to increased end-diastolic pressure or volume of the ventricles (1–3). The main biological effects of BNP are diuresis, natriuresis and vasodilation which reduce the load on the heart (3). Patients with left ventricular systolic dysfunction have an increased level of plasma BNP, which has become a diagnostic maker and a predictor of long-term prognosis of congestive heart failure (4–6). BNP is also elevated in patients with diastolic heart failure and in patients with only right-sided ventricular dysfunction (7,8). However, whether ventricular systolic and diastolic dysfunction is associated with the same level of plasma BNP is unclear.

The primary purpose of this study was to investigate the plasma BNP levels in different types of ventricular dysfunction in consecutive patients from a single cardiology unit.

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PATIENTS AND METHODS

Patient Selection

The investigation was approved by the Human Ethics Committee of Lishui Central Hospital, and conforms to the principles outlined in the Declaration of Helsinki. All patients gave written informed consent to participate in the study.

Between September 2002 and January 2004, 149 consecutive patients (94 males, average age 69 ± 12 years, ranged 32–86 years), *who* presented to the Cardiology Department of Lishui Central Hospital with a diagnosis of heart failure, were selected for the study. None of these patients had received any pharmacological management for heart failure at the time of the study. The aetiology of heart failure in these patients included coronary heart disease, rheumatic heart disease, cardiomyopathy and hypertension. Thirty-five other heart failure patients who presented to the Department in the same period were excluded from the study because of renal dysfunction and pericardial effusions.

A thorough physical examination, blood biochemistry profile, chest X-ray and 12-lead electrocardiograph was performed in each patient. Ventricular function was assessed by echocardiography.

Assessment of Ventricular Function

The left ventricular function was assessed by two-dimensional and Doppler echocardiography (Acuson Sequoia 512, transducer frequency 2.5–3.5 MHz) by two experienced cardiologists. Standard two-dimensional images were obtained in the parasternal long and short axes, and in the apical four and two-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 presence of clinical symptoms and both of the following two criteria (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 50%.

The diastolic function was assessed by Doppler echocardiography of transmitral flow, where the E and A peaks, the diastolic time and the isovolumic relaxation time were measured. The definition of diastolic heart failure was based on the presence of all three criteria: (i) the presence of signs or symptoms of congestive heart failure; (ii) the echocardiographically measured left ventricular ejection fraction was more than 50%; and (iii) echocardiographic evidence of abnormalities of left ventricular relaxation: E/A ratio < 1.0 (<55 years old) or <0.8 (>55 years old); E peak deceleration time of more than 240 ms or isovolumic relaxation time of less than 90 ms (9).

The thickness of the ventricular walls and the interventricular septum and the diameter of the left ventricle were measured by M-mode echocardiography. The left ventricular mass (LVM) and mass index (LVMI) was also calculated. LNM index (LVMI) was calculated using the equation described by Devereux et al. (10): $\{1.04\ [(IVST + LVIDd + LVPWT) - LVIDd] - 13.6\}$; where IVST is the interventricular septal thickness, LVIDd is the left ventricular internal diastolic diameter and LVPWT is the left ventricular posterior wall thickness. Left ventricular hypertrophy was defined as LVMI > 116 g/m^2 (male) or >104 g/m^2 (female) (10,11).

Patients were divided into three groups: left ventricular systolic failure, left ventricular diastolic failure and the right ventricular systolic failure.

Measurement of Plasma BNP

BNP was tested in all patients immediately after the clinical and echocardiographic examinations. Plasma BNP was measured by the previously reported methods (8,11). Venous blood samples were kept in EDTA tubes at room temperature and analysed within 4 h of the collection. The whole blood was then analysed in triplicate with the Triage BNP assay, a sandwich immunoassay that consists of a disposable device to which 250 μl of EDTA-anti-coagulated whole blood was added. The Triage meter was used to measure the BNP concentrations by detecting a fluorescent signal that reflects the amount of BNP in the sample.

Once 250 μl of whole blood was added to the device, the cells were separated from the plasma by a filter, and the plasma containing BNP was put in a reaction chamber containing fluorescent-tagged BNP antibodies to form a reaction mixture. The reaction mixture was incubated for about 2 min and then migrated through the diagnostic lane by capillary action to a zone of immobilised antibody that would bind the desired BNP-fluorescent antibody complex. After about 15 min, the device was placed into the Triage meter, and the fluorescence intensity of the BNP assay zone was measured. An internal calibration curve was used to correlate the Triage meter and the fluorescence measurement to the BNP concentration. The assay was completed in approximately 15 min.

Statistical Analysis

Data were expressed as means $\pm$ SD. ANOVA test was used to analyse the difference in clinical parameters between groups. Chi-square test was used to assess the differences in percentage data. The correlations between BNP and the left ventricular anatomy or function were also assessed with Spearman analysis. The value $p < 0.05$ was considered to be statistically significant.

RESULTS

Comparison of Plasma BNP between Different Types of Ventricular Dysfunction

The left diastolic heart failure was mainly found in patients with hypertension and left ventricular hypertrophy. Patients with right ventricular systolic dysfunction only were those who either suffered from chronic obstructive pulmonary disease or had only mitral stenosis due to rheumatic heart disease. All patients with right-sided systolic dysfunction had enlarged right ventricle, increased pulmonary pressure on echocardiography, and clinical symptoms of right-sided heart failure.

Patients in the diastolic dysfunction group and in the right ventricular systolic failure group had no echocardiographic or clinical evidence of left ventricular dysfunction.

There were no significant differences in age and sex among the three groups (Table 1). The left ventricular end-diastolic diameter was the greatest, and the ejection fraction was the lowest in the left ventricular systolic dysfunction group (Table 1).

The plasma BNP level in the left ventricular systolic dysfunction group was higher than that of the right ventricular systolic dysfunction and the left ventricular diastolic dysfunction group (Table 1).

Within the same New York Heart Association functional class, patients with left ventricular systolic dysfunction had a higher BNP level than that from patients of left ventricular diastolic dysfunction (Fig. 1).

Table 1 Comparison of clinical data and BNP levels among three study groups

	LV systolic dysfunction (62)	*LV diastolic dysfunction* (48)	*RV systolic dysfunction* (39)	*p-value*
Age	67 ± 12	71 ± 9	61 ± 15	NS
Male	40 (65%)	29 (60%)	25 (64%)	NS
LV (mm)	64 ± 6	43 ± 5	45 ± 6	0.01
EF (%)	42 ± 6	56 ± 7	54 ± 6	0.004
BNP (pg/ml)	516 ± 445	115 ± 80	345 ± 184	0.001

BNP, B-type diuretic peptide; EF, ejection fraction; LV and RV, left and right ventricle.

Correlations between Plasma BNP and Ventricular Ejection Fraction or Mass Index

In patients with left ventricular systolic dysfunction, there was a significant inverse correlation between the plasma BNP levels and the ejection fraction ($r = -0.746$, $p = 0.001$) (Fig. 2).

In patients with left ventricular diastolic dysfunction, no significant correlation was found between the plasma BNP levels and the ejection fraction ($p = 0.12$), but a significant correlation between the BNP levels and the LVMI was identified ($r = 0.371$, $p = 0.001$). Significant increases in BNP were found when the LVMI was above 140 g/m^2 (Fig. 3).

In patients with right ventricular dysfunction, mitral stenosis and chronic obstructive pulmonary disease was identified in 12 and 21, respectively. Patients in the mitral stenosis group were younger, had more females and a larger left atrium than those in the pulmonary disease group (Table 2). There was no significant difference in the BNP levels between these two groups (Table 2).

DISCUSSION

Numerous studies have shown an increased level of plasma BNP in patients with left ventricular systolic dysfunction and a clear relationship between New York Heart Association functional class and levels of BNP (5–7). Results from different investigators suggest that the values of plasma BNP during systolic heart failure was higher than that of the diastolic dysfunction; the highest BNP was found in patients with combined systolic and diastolic failure (12). BNP was also elevated in patients with primary pulmonary hypertension, chronic obstructive pulmonary disease and pulmonary embolism (8,13). Plasma BNP correlated positively with mean pulmonary artery pressure; it correlated negatively with cardiac output and RV ejection fraction (8). Although plasma BNP increases during right heart failure is in proportion to the extent of right ventricular dysfunction and pulmonary hypertension, the average BNP levels appear lower than that in left ventricular systolic dysfunction (5–8).

However, it is difficult to interpret the differences in BNP levels between the systolic and diastolic heart failure from the previous studies, because the methodologies for BNP measurements and the criteria for patient selection vary among the individual studies (5–8,12–15). Our observation in consecutive patients from a single cardiology unit has demonstrated a clear difference in the plasma BNP levels between systolic and diastolic dysfunction and between left and right systolic dysfunction.

Increases in left ventricular volume and overload are the primary causes of enhanced BNP synthesis and secretion from ventricular myocytes (5). In our patients, left ventricular dysfunction group had the most significant alterations in left ventricular diameter and ejection fraction, which explains the highest plasma level of BNP. There was a gradual increase in

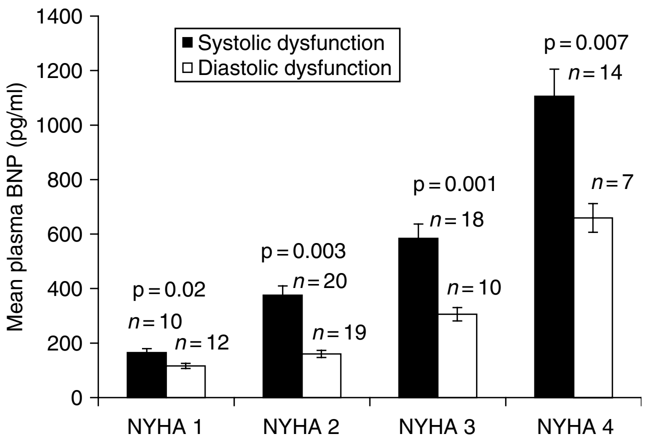

Figure 1 Comparison of B-type natriuretic peptide (BNP) within the same New York Heart Association functional class

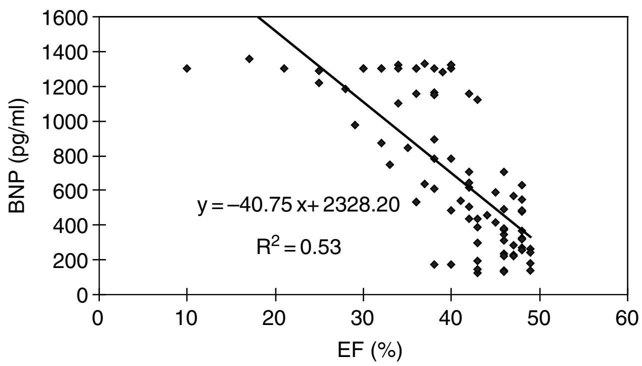

Figure 2 Correlation between plasma BNP levels and ejection fraction. EF: ejection fraction. BNP: B-type natriuretic peptide

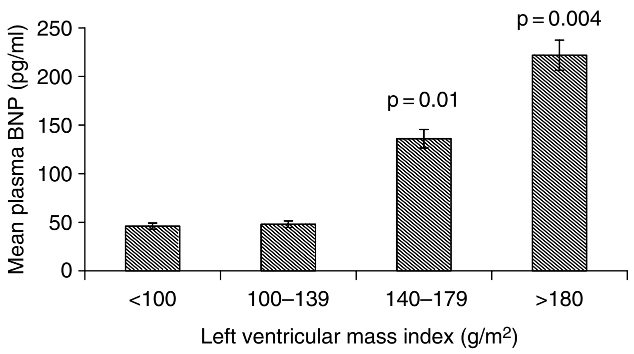

Figure 3 Relationships between left ventricular mass index (LVMI) and plasma B-type natriuretic peptide (BNP) levels

along with the advance in New York Heart Association functional class. A significant correlation between the plasma BNP values and the left ventricular end-diastolic parameter or left ventricular ejection fraction was also identified.

Left ventricular hypertrophy also leads to an increased myocardial secretion of BNP (14,15). In our patients who had left ventricular hypertrophy as well as diastolic dysfunction but a relatively normal left ventricular diameter and ejection fraction, a modest increase in plasma BNP was demonstrated. The increase in plasma BNP was closely associated with LVMI. Within the same New York Heart Association functional class, however, the elevation in BNP in the diastolic dysfunction group was consistently lower than that of the systolic dysfunction patients, indicating that systolic heart failure has a greater effect than diastolic failure on the myocardial production of BNP.

Atria appear to make very limited contribution to the plasma level of BNP during congestive heart failure. In the present study, enlarged left atrium was found in all patients with mitral stenosis and right ventricular dysfunction. The plasma BNP level in the patients of mitral stenosis was similar to that in patients with right heart failure but a normal left atrial diameter.

In conclusion, ventricular dysfunction is associated with a higher level of plasma BNP than diastolic dysfunction. The most significant BNP elevation occurs in those with left ventricular systolic dysfunction, followed by right-sided systolic dysfunction and left ventricular diastolic dysfunction.

Table 2 Clinical data and plasma BNP levels in patients with right ventricular dysfunction

	Mitral stenosis (n = 12)	*COPD (n = 27)*	*p-values*
Male	1(8%)	17(63%)	0.02
Age (year)	38 ± 18	71 ± 14	0.01
LA (mm)	42 ± 6	31 ± 3	0.002
BNP (pg/ml)	312 ± 213	340 ± 171	NS

BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; LA, left atrial diameter.

REFERENCES

1 Maeda K, Tsutamota T, Wada A et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; **135**: 825–32.
2 Nakamura S, Naruse M, Naruse K et al. Atrial natriuretic peptide and brain natriuretic peptide coexist in the secretory granules of human cardiac myocytes. *Am J Hypertens* 1991; **4**: 909–12.
3 Nakagawa O, Ogawa Y, Itoh H et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy; evidence for brain natriuretic peptide as an 'emergency' cardiac hormone against ventricular overload. *J Clin Invest* 1995; **96**: 1280–7.
4 Maisel A. B-type natriuretic peptide levels: a potential novel 'white count' for congestive heart failure. *J Cardiac Failure* 2001; 7: 183–93.
5 Maisel A, Krishnaswamy P, Nowak R et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; **347**: 161–7.
6 Berger R, Huelsman M, Strecker K et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; **105**: 2392–7.
7 Maisel AS, Koon J, Krishnaswamy P et al. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J* 2001; **141**: 367–74.
8 Nagaya N, Nishikimi T, Okano Y et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. *J Am Coll Cardiol* 1998; **31**: 202–8.
9 European Study Group on Diastolic Heart Failure. How to diagnose diastolic heart failure. *Eur Heart J* 1998; **19**: 990–1003.
10 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. *Circulation* 1977; **55**: 613–8.
11 Wei TM, Zeng CL, Chen LP et al. Role of brain natriuretic peptide in the diagnosis of left ventricular diastolic dysfunction in patients with hypertension. *Eur J Heart Fail* 2005; **7**: 75–9.
12 Matsuo K, Nishikimi T, Yutani C et al. Diagnostic value of plasma levels of brain natriuretic peptide in arrhythmogenic right ventricular dysplasia. *Circulation* 1998; **98**: 2433–40.
13 Morrison LK, Harrison A, Krishnaswamy P et al. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002; **39**: 202–9.
14 Nishikimi T, Yoshihara F, Morimoto A et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996; **28**: 22–30.
15 Bettencourt P, Ferreira A, Sousa T et al. Brain natriuretic peptide as a marker of cardiac involvement in hypertension. *Int J Cardiol* 1999; **69**: 169–77.

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