Clinical Research

Plasma N-terminal pro-brain natriuretic peptide levels in elderly patients with isolated diastolic dysfunction

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Objective To investigate plasma N-terminal pro-brain natriuretic peptide (NT-BNP) levels and to assess their clinical significance in elderly patients with isolated diastolic dysfunction. Methods Plasma NT-BNP level were measured by electrochemiluminescence immunoassay in 34 symptomatic patients (Group 1), 34 asymptomatic patients (Group 2) with isolated diastolic dysfunction, and in 16 elderly healthy subjects (control group, Group 3), serving controls. Colored Doppler echocardiography was performed to evaluate the patients’ cardiac structures and functions. Results The plasma NT-BNP level in Group 1 was significantly higher than those in Group 2 and Group 3 and increased with the severity of heart failure. There was no significant difference of plasma NT-BNP levels between Group 2 and Group 3 (p>0.05). A NT-BNP value of 102.75 pg/mL showed a sensitivity of 88.2%, a specificity of 87.5%, and an accuracy of 88.1% for diagnosing diastolic dysfunction. Patients with restrictive filling pattern on echocardiography had higher NT-BNP levels than those of impaired relaxation pattern (196.1±304.9 versus 460.1±92.7 pg/mL, p<0.001). Conclusion The elevation of plasma NT-BNP level in elderly patients with isolated diastolic dysfunction correlates with the severity of their diastolic abnormalities. The level of plasma NT-BNP has an important clinical value in the diagnosis of elderly patients with isolated diastolic dysfunction. (J Geriatr Cardiol 2005; 2(4):211-215)

Key Words elderly; isolated diastolic dysfunction; N-terminal pro-brain natriuretic peptide; echocardiography

The incidence of cardiac dysfunction rises along with the gradually increasing aging population. It has been reported that about one-third of patients with cardiac dysfunction have normal left ventricular systolic function and left ventricular diastolic dysfunction. Cardiac dysfunction is often the end-stage abnormality of various kinds of cardiac diseases and one of the main causes of high health care expenditure. Detection of early cardiac dysfunction by a simple, accurate and effective biochemical marker may help to decrease the mortality and morbidity associated with cardiac dysfunction.

B-type or brain natriuretic peptide (BNP) is a peptide isolated from porcine brain and subsequently from the heart of humans as well as pigs and rats. It is secreted mainly from the ventricles in response to ventricular volume expansion and pressure overload and is involved in the regulation of blood pressure and fluid volume. Previous studies have demonstrated that it may provide valuable information on underlying cardiac function. Once released into the plasma, a prohormone is cleaved into the active C-terminal brain natriuretic peptide and the inactive N-terminal pro-brain natriuretic peptide (NT-BNP), which is slowly cleared. In this study, we measured plasma NT-BNP levels using electrochemiluminescence immunoassay to assess their clinical significance in elderly patients with isolated diastolic dysfunction.

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Materials and methods

Study population
Sixty-eight patients were recruited between October 2003 and April 2004 at the First Hospital of Peking University. Patients were divided into two groups according to New York Heart Association (NYHA) classification. Group 1 included patients with isolated diastolic dysfunction, that is, they had symptoms of cardiac dysfunction, had abnormal diastolic function but normal systolic function assessed by visualized echocardiography. There were 34 patients in Group 1, 20 males and 14 females, their ages ranged from 60 to 85 years (mean: 74.6 years). Group 2 included patients with asymptomatic diastolic dysfunction, that is, they had no symptoms of cardiac dysfunction, had abnormal diastolic function but normal systolic function assessed by visualized echocardiography. There were 34 patients in Group 2, 22 males and 12 females. Their ages ranged from 60 to 88 years (mean age 73.1 years).

Sixteen subjects (9 males and 7 females, ages 60 to 78 years, mean age 69.9) who had no evidence of cardiovascular diseases and with normal echocardiographies were included in the control group.

Patients were not enrolled into this study if he or she had acute myocardial infarction within the past 3 months, unstable angina pectoris, moderate and severe valve regurgitation, sustained atrial fibrillation, frequent premature ventricular beats, pericardial disease, chronic obstructive pulmonary disease, pulmonary embolism, severe infection, severe renal
or hepatic dysfunction, acute cerebral vascular disease or malignancy.

NT-BNP level measurement

A 2ml blood sample was drawn by venipuncture after 30 min of recumbent rest, and collected into a tube that contained no anticoagulants. Then the sample was centrifuged at 3000 rpm, and the separated plasma was stored at -20°. NT-BNP level was measured by electrochemiluminescence immunoassay. The detectable plasma concentration of NT-BNP ranged from 5 to 35000 pg/ml (0.6 to 4130 pmol/l). The intra-assay precision had a coefficient of variation (CV) of 2.7% at 175 pg/ml, 2.4% at 355 pg/ml and 1.9% at 1068 pg/ml.

Echocardiography

Echocardiography was performed within 3 days before or after blood sample collection. Echocardiograms were obtained with an HP 5500 echocardiographic instrument operating at 1.0-3.0 MHz. All data were copied to videotape for subsequent analysis and measurement. Data were the mean values of 3 consecutive cardiac cycles.

Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV systolic and diastolic volumes and ejection fractions were derived from the apical 4-chamber view with a modified Simpson’s rule algorithm.

Pulsed Doppler spectral recordings were obtained in the apical 4-chamber view from a sample volume positioned at the tips of the mitral leaflets and in the right upper paraseptal pulmonary vein by which the maximal amplitude velocity signals are produced. The transmittal pulsmod Doppler velocity recordings were used to derive measurements as follows: E and A velocities were the peak values reached in early diastole and after atrial contraction respectively, while deceleration velocity (DV) was the velocity from the E-wave peak to the baseline. In addition, pulmonary venous systolic (PVs) and diastolic (PVd) flow velocities were obtained as the maximal values reached during the respective phase of the cardiac cycle, and the pulmonary venous “A” reversal (PVa) was the maximal velocity of retrograde flow into the vein after the P wave of the ECG. Finally, the LV isovolumetric relaxation time (IVRT) was obtained in the apical 5-chamber view with a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to obtain signals from aortic valve closure, the termination of ejection and mitral valve opening, or the onset of transmural flow. IVRT was taken as the time from the end of ejection to the onset of LV filling.

M-mode imaging examination was performed in the standard fashion in the parasternal left ventricular long-axis view. According to standard criteria, we measured left atrial diameter (LAD), left ventricular end systolic diameter (LVEDD), left ventricular end systolic diameter (LVEDD), interventricular septum (IVS) thickness, left ventricular posterior wall (LVPW) thickness, and right ventricular end diastolic diameter (RVD). All echocardiograms were interpreted by experienced cardiologists who were blinded to the NT-BNP levels.

Echocardiographic classifications

Normal ventricular function was defined by an ejection fraction >50%, normal LVEDD and LVEDD, and no evidence of relaxation abnormalities. Systolic dysfunction was defined by an ejection fraction <50%. Diastolic dysfunction was defined by an ejection fraction >50%. Abnormal diastolic function, and was classified into 3 patterns as defined below:

1. Impaired relaxation: E/A <1.0, EDV<355cm/s², IVRT>90ms and PVs/PVd>1.0.
2. Pseudonormal filling: E/A>1.0, EDV<355cm/s², IVRT<90ms and PVs/PVd<1.0.
3. Restrictive filling: E/A>2.0, EDV<355cm/s², IVRT<70ms and PVs/PVd<1.0.

Left atrial enlargement was defined as LAD>4.0cm or LAD/AoD>1.17. Left ventricular enlargement was defined as LVEDD>5.5cm in males or LVEDD>5.0cm in females. Left ventricular hypertrophy was defined as IVS>1.1cm or LVPW>1.1cm.

Statistical Analysis

Results were presented as mean ± SD. Comparisons of NT-BNP values between groups were made with t tests for independent samples and ANOVA with post hoc Tukey tests when indicated. The chi-square test was applied when frequencies were compared. Partial correlation and linear regression analysis were employed to assess the relation between NT-BNP and clinical variables. The diagnostic utility of NT-BNP alone was compared with the echocardiographic probability of diastolic dysfunction through the use of receiver-operating characteristic (ROC) curves. Results were expressed in terms of the area under the curve (AUC) and 95% confidence interval for this area. A value of p<0.05 was considered as significant.

Results

We selected eight indices including LAD, LVEDD, E, A, EDV, PVs, PVd, IVRT to evaluate the echocardiographic measurements. The results showed that the difference of measurements in different times performed by the same operator was not significant (p>0.05), neither was the difference between two different operators (p>0.05) (Table 1).
Among clinical variables such as age, gender, concomitant diseases and cardiac function, multiple linear-regression analysis showed that the NYHA class was the main factor that affects NT-BNP level.

The utility of NT-BNP to detect abnormal diastolic function in patients was assessed with a ROC curve analysis. The area under the curve was 0.960 (95% confidence interval: 0.916-1.003, p<0.001) (Figure 2).

![Figure 2. ROC curve comparing sensitivity and specificity of NT-BNP and echocardiographic diagnosis of LV diastolic dysfunction](image)

Table 2. Subjects characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=34)</th>
<th>Group 2 (n=34)</th>
<th>Controls (n=16)</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>74.6±6.34</td>
<td>73.1±6.9</td>
<td>69.9±6.4</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/14</td>
<td>22/12</td>
<td>9/7</td>
</tr>
<tr>
<td>History of CAD (%)</td>
<td>73.5</td>
<td>64.7</td>
<td>0.0</td>
</tr>
<tr>
<td>History of hypertension (%)</td>
<td>64.7</td>
<td>61.8</td>
<td>0.0</td>
</tr>
<tr>
<td>History of diabetes mellitus (%)</td>
<td>26.5</td>
<td>26.5</td>
<td>0.0</td>
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</table>

The NT-BNP levels in the 3 groups are presented in Figure 1. Patients with symptomatic diastolic heart failure had higher NT-BNP levels (1232.9±209.1 pg/ml) than those with asymptomatic diastolic dysfunction (148.9±45.2 pg/ml) and the controls (63.2±27.3 pg/ml) (p=0.000). There was no significant difference between patients with asymptomatic diastolic dysfunction and the controls (p>0.05).

![Figure 1. NT-BNP levels in the normal and abnormal diastolic function groups](image)

Plasma NT-BNP concentration increased along with the severity of congestive heart failure (CHF) according to the NYHA system (Table 3). There was a positive correlation between the plasma NT-BNP and NYHA class (r=0.735, p=0.000) after adjustment for age and sex.

Table 3. NT-BNP levels for different NYHA classes

<table>
<thead>
<tr>
<th></th>
<th>Control (n=16)</th>
<th>NYHA I (n=34)</th>
<th>NYHA II (n=16)</th>
<th>NYHA III~IV (n=18)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>NT-BNP levels (pg/ml)</td>
<td>63.2±27.3</td>
<td>148.9±45.2</td>
<td>487.9±159.2</td>
<td>1895.3±326.6</td>
<td>0.000</td>
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Table 4. Value of NT-BNP in diagnosing diastolic dysfunction

<table>
<thead>
<tr>
<th>NYHA class</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive (%)</th>
<th>Negative predictive (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I~IV</td>
<td>0.960</td>
<td>88.2</td>
<td>87.5</td>
<td>96.8</td>
<td>63.6</td>
<td>88.1</td>
</tr>
<tr>
<td>II~IV</td>
<td>1.000</td>
<td>100</td>
<td>87.5</td>
<td>94.4</td>
<td>100</td>
<td>96.0</td>
</tr>
</tbody>
</table>
Patients with the restrictive filling pattern had significantly higher NT-BNP levels than those with impaired relaxation (196±1.2±304.9 vs 460.1±92.7pg/ml, p<0.001).

Plasma NT-BNP concentration was positively correlated with LAD (r=0.251, p=0.023), LVEDD (r=0.268, p=0.015), LVESD (r=0.368, p=0.001). A NT-BNP value of 102.75pg/ml detected most abnormal atrial and ventricular structure (Table 5).

Discussion

Cardiac dysfunction is a common and disabling disorder with high mortality and morbidity. Currently, echocardiography is the most commonly used non-invasive method for the assessment of cardiac function. However, the technique requires the cooperation of patients and depends on the cardiologist’s experience. Both the limited availability in community settings and the high cost restrict its use. Thus, a less expensive and more accessible and accurate diagnostic approach is required. As the world population is aging, the elderly patients are often accompanied with multiple organ dysfunction, which makes the clinical features atypical and increases the diagnostic difficulty, especially in the intensive care unit and the emergency department. Therefore, rapid and accurate differentiation of cardiac dysfunction in elderly people from other diseases, such as pulmonary disease, is extremely important.

Brain natriuretic peptide is a 32 amino acid polypeptide containing a 17 amino acid ring structure common to natriuretic peptides. The source of plasma BNP is mainly the ventricles, which suggests that it may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides. The nucleic acid sequence of the gene contains the unstable sequence “TAATTAT”, which can accelerate the transcription of BNP mRNA, so that BNP synthesis is increased.7 The release of BNP appears to be directly proportional to ventricular volume expansion and pressure overload. The natriuretic peptides play an important role in the body’s defense against excess salt and water retention. The elevation of BNP in CHF can be considered as a compensatory mechanism against ventricular overload, since BNP serves to reduce both cardiac preload and afterload with a wide range of potent biological effects, including natriuresis, diuresis, vasodilatation, and inhibition of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS).

On secretion, pro-BNP, the storage form of BNP, is cleaved into the inactive N-terminal pro-BNP (NT-BNP) and the active C-terminal BNP. NT-BNP, with a longer half-life than BNP, can be rapidly measured by electrochemiluminescence immunoassay.

As many as 30% to 40% of patients with a diagnosis of heart failure have normal systolic function, which implicates diastolic dysfunction as the most likely potential abnormality responsible for this disorder. The prevalence of diastolic dysfunction increases with the aging of the world population. Diastolic dysfunction is often seen in patients with hypertension, myocardial ischemia and in hypertrophic cardiomyopathy. Epidemiological surveys show the prognosis of diastolic dysfunction is similar to that of systolic dysfunction in the elderly patients.3 It is difficult to distinguish diastolic dysfunction from systolic dysfunction on the basis of history, symptom, physical examination, chest x-ray, and ECG alone, while its treatment is different with systolic dysfunction. Early recognition is favorable for an early diagnosis and initiation of treatment, which leads to improved survival.

It has been previously demonstrated that BNP would elevate in the presence of cardiac dysfunction.8,9 This study confirms those findings in elderly patients with normal systolic function. We examined the utility of a rapid test for NT-BNP to predict LV diastolic dysfunction determined by echocardiography in the elderly people. The result indicates that plasma NT-BNP levels significantly increase in the patients with diastolic dysfunction compared with controls, and positively correlate with the severity of diastolic abnormalities, according to the NYHA classification.

Asymptomatic cardiac dysfunction is the early stage of heart failure. In this pre-clinical stage, the neurohormonal system is activated and cardiac function decreases. In our study, the difference between asymptomatic diastolic dysfunction

<table>
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<th>Table 5. NT-BNP levels in abnormal ventricular structure</th>
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<tr>
<td><strong>NT-BNP levels</strong></td>
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<tr>
<td>-------------------</td>
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<tr>
<td>LA enlargement (n=39)</td>
</tr>
<tr>
<td>LV enlargement (n=8)</td>
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<tr>
<td>LV hypertrophy (n=19)</td>
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patients and the controls was not significant, suggesting that the body was still in a compensatory state.

In the present study, the optimal NT-BNP level for detecting diastolic dysfunction (NYHA class I-IV) was 102.75 pg/mL. With this threshold, the area under the ROC curve was 0.960. The identification of isolated diastolic dysfunction by this diagnostic threshold was beneficial with the sensitivity, specificity and accuracy of 88.2%, 87.5% and 88.1%, respectively, and up to 100%, 87.5% and 96.0% for patients with NYHA class II-IV. Plasma NT-BNP concentrations <105.75 pg/mL had a negative predictive value of 100% for patients with NYHA class II-IV. The results indicate that plasma level of NT-BNP is a sensitive indicator of diastolic dysfunction.

Previous studies have shown that the transcription of BNP mRNA is strongly enhanced when the ventricular wall is stretched. The synthesis and secretion of NT-BNP are stimulated with the change of ventricular structure and function. In our study, there were positive correlations between NT-BNP and LAD, LVEDD as well as LVEF. Most patients with abnormal cardiac structure had NT-BNP greater than 105.75 pg/mL.

Diastolic dysfunction was classified into three patterns: impaired relaxation, pseudonormal filling and restrictive filling through the transmural and pulmonary venous pulsed Doppler velocity recordings. Patients with restrictive filling pattern on echocardiography had higher NT-BNP levels than those with impaired relaxation pattern. Our results are similar to those of Lubien et al,10 who studied 294 patients with normal systolic function and found that BNP levels were highest in those with restrictive filling pattern.

In conclusion, an easy and rapid test for NT-BNP, which can be performed at the bedside or clinic, may reliably predict the presence of LV diastolic abnormalities in the elderly patients, which could guide further cardiac examination. It is quite possible that measuring NT-BNP concentrations might also be an effective way to monitor therapy and disease course and to estimate prognosis, thus to enhance the quality of life in elderly patients with diastolic dysfunction.

We believe that NT-BNP should prove to be useful in the emergency department, the intensive care unit, as well as in the community where the greatest burden of disease exists and the accessibility of echocardiography is limited. It is likely that NT-BNP analysis would greatly assist in assessing cardiac function and guiding optimal therapy and would be of significant clinical benefit.

References