B-type natriuretic peptide level in the diagnosis of asymptomatic diastolic dysfunction

Asemptomatik diyastolik kalp yetersizliğinin tanısında B-tip natriüretik peptid düzeyleri

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ABSTRACT

Objective: Brain natriuretic peptide (BNP) reflects the left ventricular pressure and volume overload. It is known that it increases in systolic dysfunction proportionally with left ventricular pressure increase. The BNP levels are well correlated with NYHA classification and prognosis. Our aim was to evaluate the predictive value of BNP in patients with diastolic dysfunction but normal systolic dysfunction demonstrated by echocardiography.

Methods: Fifty patients (mean age: 48.5±6.75 years; 29 males, 21 females) were included in this cross-sectional, case-controlled study. Systolic dysfunction was the exclusion criterion. The following parameters were used to evaluate diastolic function: isovolumetric relaxation time, transmitral early to late filling flow velocities (E/A) ratio, deceleration time E, pulmonary vein Doppler findings and color mitral flow propagation velocity. Diastolic dysfunction was determined in 30 hypertensive patients (Group 1), whereas 20 patients who had normal diastolic flow patterns on echocardiography (Group 2). Blood samples were taken for serum BNP level measurements.

Results: The BNP levels were 12.0±4.97 pg/ml in individuals with normal filling pattern and 66.17±17.56 pg/ml in individuals with abnormal filling patterns ($p<0.001$). The accuracy of BNP in detection of diastolic dysfunction was assessed with receiver-operating characteristic (ROC) analysis. The area under the ROC curve for BNP test accuracy in detection any abnormal diastolic dysfunction was 0.969 (95% CI, 0.909 to 1.029; $p<0.001$). A BNP value of 37.0 pg/ml had sensitivity of 80%, specificity of 100%, a positive predictive value of 100%, a negative predictive value of 23% and accuracy of 88% in identifying asymptomatic prolonged relaxation pattern. We found a strong correlation between left ventricular mass index and plasma BNP levels ($r=0.62$, $p<0.05$).

Conclusion: Estimation of BNP values could be accepted as a fast and reliable blood test in the diagnosis of asymptomatic diastolic dysfunction. *(Anadolu Kardiyol Derg 2007; 7: 262-7)*

Key words: B-type natriuretic peptide, diastolic dysfunction, hypertension

ÖZET

Amaç: B-tipi natriüretik peptid (BNP), ventriküler basınç yüklenmesi ve volüm artışını yansıtmaktadır. Semptomatik sol ventrikül sistolik disfonksiyonunda ventrikül basıncındaki artmaya paralel olarak yükseldiği bilinmektedir. Bu hasta grubunda BNP seviyesindeki yükselme semptom (NYHA göre) ve prognoz ile ilişkilidir. Diyastolik disfonksiyon varlığında BNP seviyelerinde yükselmeler bildirilmiş olsa da, semptomlar ile ilişkisi ve cutoff değerleri net değildir. Amacımız, ekokardiyografik olarak normal sistolik fonksiyona sahip fakat asemptomatik diyastolik disfonksiyonlu hastalarda, BNP'nin diyastolik disfonksiyonu göstermedeki öngörme değerini araştırmaktı.

Yöntemler: Bu vaka-kontrollü, kros-seksiyonel çalışmaya ekokardiyografik olarak sistolik fonksiyonları normal, fakat diyastolik disfonksiyonu olduğu gösterilen asemptomatik 30 kişi (Grup 1) ve ekokardiyografik olarak sistolik ve diyastolik fonksiyonları normal olan 20 hasta (Grup 2) kontrol grubu olarak alındı. Diyastolik fonksiyonları değerlendirmede Doppler ekokardiyografik olarak izovolümetrik relaksasyon zamanı, transmitral erken ve geç doluş akım hızlarının (E/A) oranı, E deselerasyon zamanı, pulmoner ven Doppler bulguları ve renkli Doppler mitral akım yayılma hızı kullanıldı. B-tipi natriüretik peptid ölçümleri; her hastadan 2 ml kan örneği alınarak sitratlı tüpe konuldu, 15 dk içinde Biosite marka cihaz ile, Triage BNP kiti kullanılarak kantitatif olarak ölçüldü.

Bulgular: Normal sol ventrikül doluş paternine sahip olan Grup 2'de serum BNP seviyesi 12.00±4.97 pg/ml iken, anormal doluş paternine sahip Grup 1'de BNP seviyesi 66.17±17.56 pg/ml olarak bulundu. Aradaki fark istatistiksel olarak anlamlı idi ($p<0.05$). B-tipi natriüretik peptid ile diyastolik disfonksiyonun tanısını koymak için "Receiver-operating characteristic" (ROC) analizi kullanıldı. Diyastolik disfonksiyon ile BNP arasındaki ROC eğrisinin altında kalan alan 0.969 idi (CI %95; 0.909-1.029, $p<0.001$). Asemptomatik uzamış relaksasyon paterninde BNP değeri 37 pg/ml alındığında sensitivite %80, spesifisite %100, pozitif öngörme değeri %100, negatif öngörme değeri %23 ve güvenirliliği %88 olarak tanımlandı. Sol ventrikül kitle indeksi ve plazma BNP değeri arasında güçlü kolerasyon bulduk ($r=0.62$, $p<0.05$).

Sonuç: Semptomatik diyastolik disfonksiyonun tanısında BNP hızlı, güvenli bir kan testi olarak kabul edilebilir. *(Anadolu Kardiyol Derg 2007; 7: 262-7)*

Anahtar kelimeler: B-tip natriüretik peptid, diyastolik disfonksiyon, hipertansiyon

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Introduction

Diastolic dysfunction is characterized by impairment of energy-dependent active relaxation, increased stiffness and resultant pulmonary congestion and low cardiac output state. Systolic functions are normal in one third of patients with heart failure as detected by echocardiography. Diastolic dysfunction was shown as the reason for symptoms in these patients (1, 2). Diastolic dysfunction starts before symptoms development. For this reason, early diagnosis and follow up of these patients are important for prevention of irreversible structural changes (2).

B-type natriuretic peptide (BNP) is a neurohormone produced mainly by ventricular myocytes in response to increased end-diastolic pressure, or volume, of the ventricles (3-5). It produces diuresis, natriuresis, and vasodilatation, which reduce the load on the heart (5). Patients with ventricular dysfunction tend to have high levels of plasma BNP; therefore BNP has been used as a diagnostic test for systolic dysfunction (6-11). Recent studies have shown that patients with diastolic dysfunction had a high levels of plasma BNP as well (12, 13) In addition, an increase in plasma BNP has been shown to reflect the prolongation in left ventricular relaxation time, increase in left ventricular end-diastolic pressure, and the left ventricular mass index (LVMI) in patients with hypertension (HT) (14) Hypertensive patients, especially those with left ventricular hypertrophy, have greater plasma levels of BNP than normotensive subjects (15-17), and there is a positive correlation between plasma BNP levels and left ventricular mass (18).

The aim of this study was to evaluate the predictive value of serum BNP levels for asymptomatic diastolic dysfunction and to compare the serum BNP levels in asymptomatic hypertensive patients with diastolic dysfunction and normal individuals.

Methods

Patient population

This study included 30 patients who presented at Hypertension Polyclinic of Fırat University Medical School with documented hypertension for over a year duration and isolated diastolic dysfunction shown on the echocardiography (Group 1) and 20 healthy individuals, served as the controls, who had neither systolic nor diastolic dysfunction (Group 2). Twenty subjects (mean age, 44.0±4.85 years; 11 men and 9 women) who were free from any cardiovascular history (hypertension, angina, myocardial infarction, myocardial disease, valvular heart disease, cerebrovascular events, or arrhythmia) or diabetes mellitus were selected from the present cohort to determine the normal range of LVMI. In the control group, the mean±SD value of LV mass index was 103.8 ± 26.0 g/m2.

Inclusion criteria:

1. Being over 18 years of age
2. Not having left ventricular systolic dysfunction (ejection fraction > 55%)
3. Exclusion of secondary HT causes in hypertensive patients
4. Accepting to take part in the study

Exclusion criteria:

1. Patients over 80 years of age
2. Patients with secondary HT
3. Patients using anti-diabetic drugs or having fasting blood glucose level above 126 mg/dl
4. Patients who had known coronary artery disease (those who had myocardial infarction, history of coronary artery bypass graft operation or percutaneous transluminal coronary angioplasty, those who were found to have lesions on coronary angiography or had positive effort test)
5. Patients with impaired left ventricular systolic function (with ejection fraction <55%)
6. Patients with significant heart valve disease (those with valvular regurgitation over grade 1 as established by echocardiography or with mild-moderate and severe valvular stenosis)
7. Patients with renal dysfunction
8. Patients with hyperthyroidism or hypothyroidism
9. Patients having anemia with hematocrit value below 30%
10. Pregnancy
11. Patients with unsatisfying echocardiographic images

All patients were informed before the study and their consents were taken. The study protocol was approved by the "Fırat University Medical School Research Ethics Committee".

Study design

The study design was cross-sectional and case-controlled. The sample size was determined with significance level at 5% and power of the study of 80%.

Echocardiography

Echocardiographic examination was performed in all study subjects by using a commercially available system (Acuson Sequa 512 machine with a 3-MHz transducer). Measurements were made during normal breathing at end of expiration. M-Mode echocardiographic measurements were obtained on the basis of the standards of the American Society of Echocardiography. Left atrial (LA) diameter, left ventricular (LV) end-systolic and end-diastolic diameters, end-diastolic interventricular septal thickness (IVST), and end-diastolic LV posterior wall thickness (PWT) were measured. Left ventricular ejection fraction (EF) was determined by the Simpson method (19). Systolic dysfunction was recognized, when ejection fraction was below 55% and fractional shortening was below 30%. Diastolic transmitral Doppler parameters were measured by pulsed Doppler transducer: peak of early diastolic (E) and late diastolic (A) mitral flow velocities, E/A ratio, deceleration time E (DT) and isovolumetric relaxation time (IVRT). The left ventricular flow propagation velocity (FPV) was measured by color Doppler echocardiography from the apical four-chamber view and was expressed as cm/sec. Pulmonary veins were viewed from the apical four- and two-chamber views and the pulmonary vein velocities during systole, diastole and atrial retrograde flow velocity (PVs, PVd, Pva) were recorded using pulse Doppler examination and were expressed as cm/sec.

Evaluation of diastolic functions

The definition of diastolic heart failure was based on two criteria: (1) the echocardiographically measured LVEF of >55%; and (2) echocardiographic evidence of abnormalities of left ventricular relaxation: E/A ratio <1.0 (in patients <55 years old) or <0.8 (in patients >55 years old); DT > 240 ms or IVRT<100 ms (20), FPV<45 cm/sec and pulmonary vein velocities PVs>PVd (21-25).

Evaluation of left ventricular hypertrophy

Left ventricular mass index was calculated using Devereux method (26).

LVMI = 1.04 [(IVST+LVEDD+PWT)3-LVEDD3]-13.6 / body surface area (gr/m^2)

The upper limit of LVMI was accepted to be 134 g/m^2 in men and 110 g/m^2 in women (27). The values above these were regarded as "left ventricular hypertrophy".

BNP measurements

Two ml of venous blood samples were collected from the antecubital vein using Angiokit in all patients and controls, and the samples were put in citrated tubes. The BNP levels were measured quantitatively using fluorescence immunoassay method within 15 minutes after the collection of samples using BNP triage kit (Triage BNP, BIOSITE-San Diego, CA, U.S.A.).

Statistical analysis

The statistical data were evaluated using SPSS 11.00 (Chicago, IL, USA) package software. General descriptive characteristics were assessed as mean± SD and percentage (%). The normality of data distributions were determined by Kolmogorov - Smirnov test. Normally distributed continuous variables were compared made by independent samples Student t test and discrete variables were compared using Chi-square test. Group comparisons of BNP values were made by use of Mann-Whitney test because BNP values were not normally distributed. The significance level was accepted as p<0.05. Sensitivity, specificity, and accuracy were computed for BNP by use of a selection of possible cut points. The diagnostic utility of BNP in prediction of echocardiographic probability of LV diastolic dysfunction was preformed using of receiver-operating characteristic (ROC) curve analysis. Results are expressed in terms of the area under the curve (AUC) and 95% CI for this area. The relationship of plasma BNP values with LVMI was assessed using Pearson correlation analysis.

Table 1. Hemodynamic and clinical characteristics of patients and controls

Parameters	Group 1 (n=30)	Group 2 (n=20)	p *
Age, years	53.0±9.2	44.0±4.8	<0.05
Sex, male/female, %	60/40	55/45	>0.05
Body mass index, kg/m^2	28.3±3.3	27.3±5.6	>0.05
Diastolic blood pressure, mmHg	98.0±11.2	70.0±8.25	<0.05
Systolic blood pressure, mmHg	149.0±17.6	108.0±10.40	<0.05
Mean blood pressure, mmHg	116.0±9.6	82.0±8.9	<0.05

*-p values for Student t test and Chi-square test

Table 2. Diastolic functions in patients and controls

Parameters	Group 1 (n=30)	Group 2 (n=20)	p*
E/A ratio	0.64±0.16	1.38±0.15	<0.05
DT, ms	252.8±12.5	181.7±33.9	<0.05
IVRT, ms	138.7±14.4	87.6±6.1	<0.05
PVs, m/s	0.668±0.179	0.740±0.132	>0.05
PVd, m/s	0.496±0.178	0.551±0.183	>0.05
PVa, m/s	0.162±0.047	0.159±0.038	>0.05
FPV, m/s	35.27±52.40	5.26±4.76	<0.05

*- p values for Student t test

DT- deceleration time E, FPV- mitral flow propagation velocity, IVRT- isovolumetric relaxation time, PVa- A wave velocity of pulmonary veins (retrograde), PVd- diastolic wave velocity of pulmonary veins (antegrade), PVs- systolic wave velocity of pulmonary veins (antegrade)

Results

Demographical data Groups 1 and 2 are presented in Table 1.

Significant differences were found in age, systolic and diastolic blood pressures between patient`s and control groups (p<0.05). The groups did not differ in terms of sex and body mass index.

Evaluation of systolic functions showed that EF was 62.3±4.0% in Group 1 and 62.7±4.0% in Group 2 (p>0.05).

Diastolic function indicators calculated by echocardiography for both groups are shown in Table 2. Diastolic functions as evaluated according to E/A ratio, IVRT, DT, and pulmonary venous Doppler findings were found impaired Group 1 patients as compared with Group 2 control subjects. All patients with HT were diagnosed as having prolonged relaxation pattern according to diastolic function classification, while control had normal diastolic pattern (Table 2).

Comparison of cases in Group 1 and Group 2 in terms of plasma BNP levels demonstrated that plasma BNP level in Group 1 was statistically significantly higher than that of Group 2 (66.17±17.56 pg/ml vs 12.0±4.97 pg/ml, p<0.001). The BNP values correlated positively and significantly with IVRT, DT, and pulmonary vein velocities (r-0.42 p<0.05, r-0.46 p<0.05, r-0.55, p<0.05, respectively). There was a negative correlation between BNP and E/A ratio (r=-0.27, p<0.01).

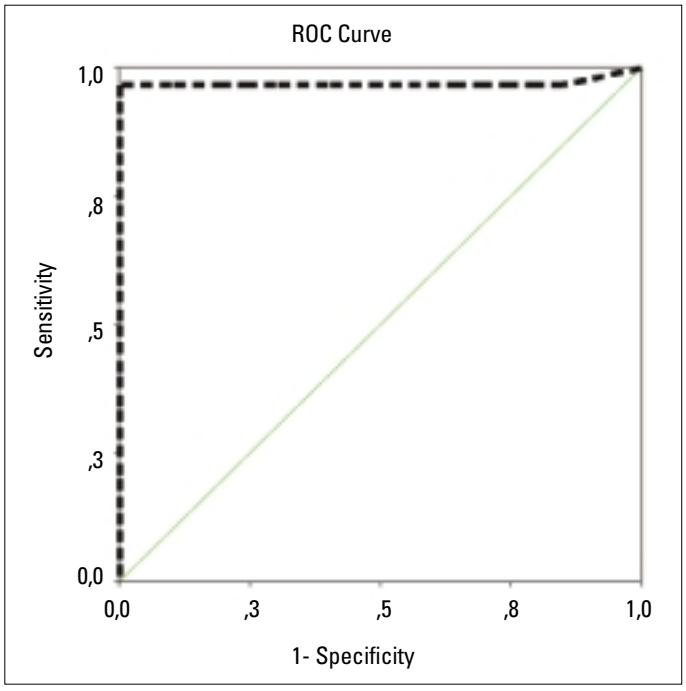

Figure 1. ROC curve for BNP test accuracy in diagnosis of asymptomatic left ventricular diastolic dysfunction The AUC for the ROC curve - 0.969 (95% CI, 0.909 to 1.029; p <0.001). BNP at cut-off value of 37 pg/ml had sensitivity 80%, specificity 100% in predicting diastolic dysfunction

AUC- area under the curve, BNP- b-type natriuretic peptide, CI- confidence interval, ROC- receiver-operating characteristic analysis

The ability of BNP to detect abnormal diastolic function was assessed with ROC analysis (Fig. 1). The AUC for the ROC curve of BNP test ability to detect any abnormal diastolic dysfunction was 0.969 (95% CI, 0.909 to 1.029; p<0.001). A BNP value of 37.0 pg/ml had sensitivity of 80%, specificity of 100%, a positive predictive value of 100%, a negative predictive value of 23% and accuracy of 88% in identifying asymptomatic prolonged relaxation pattern.

The LVMI was 143.7±48.0 g/m^2 in hypertensive patients and 103.8±26.0 g/m2 in the healthy subjects control group. We found a strong significant correlation between LVMI and plasma BNP (r=0.62, p<0.05).

Discussion

In our study, plasma BNP levels in hypertension dependent asymptomatic diastolic dysfunction group were found meaningfully high compared with those of control group having normal filling pattern. The BNP cut-off value was found as 37 pg/ml for asymptomatic diastolic dysfunction (sensitivity of 80% and specificity of 100%).

The major sources of BNP in the plasma are cardiac ventricles (3, 4). It was shown by previous studies, to be more sensitive than other natriuretic peptides (C-type natriuretic peptide, A-type natriuretic peptide) in determining ventricle disorders (4-6, 28). The BNP is a vasodilator and an important mediator playing an important role in reverse remodeling, which is directly released from the ventricles when they are overloaded with volume and pressure (3, 18). It is widely used in the follow-up of patients with systolic dysfunction and diagnosed as having chronic heart failure. It was demonstrated to be more sensitive than norepinephrine and atrial natriuretic peptide in determining follow-up mortality and showing the efficiency of the treatments used (4-6, 28). For the time being, increase in plasma BNP is acknowledged as an independent determinant of the increase in LV end-diastolic pressure (29).

Systolic functions are normal on echocardiography in one third of patients with heart failure. In these patients diastolic dysfunction was shown to underlie the symptoms development (1, 2). Impairment of the diastolic filling of blood in the left ventricle leads to an increase in left atrial-pulmonary veins and pulmonary wedge pressure, causing the symptoms of cardiac failure. It is known that the prevalence of diastolic dysfunction increases with age. Its incidence is reported to be 15-25% in patients less than 60 years of age, 35-40% - between 60 and 70 years and above 50% - over 70 years (30, 31). In our study, mean age in the healthy control group was significantly lower than that in the patients with diastolic dysfunction.

It is not possible to differentiate between diastolic and systolic heart failure with physical examination, radiological examination, and electrocardiogram under emergency conditions (32-34). In emergent cases, diastolic dysfunction is diagnosed upon recognizing normal systolic functions in patients with heart failure symptoms. The data we obtained in this study indicate that BNP can be a determining marker of diastolic dysfunction.

Wei et al. (35) reported that BNP at cut off value >40 pg/ml had the79% sensitivity and 92% specificity in diagnosing LV diastolic dysfunction in 61 patients. Suziki et al (36) reported cut off value for BNP as 41 pg/ml. We found the 100% specificity and 80% sensitivity of BNP value>37 pg/ml in predicting asymptomatic diastolic dysfunction. Lubien et. al. (37) demonstrated that BNP at cut-off value of 62 pg/ml could be a predictive marker in showing diastolic dysfunction in patients with heart failure. They reported that levels of BNP above that value had 85% specificity and 82% sensitivity in showing diastolic dysfunction. This value is above the cut-off value of 37 pg/ml established in our study. The difference between these two cut-off values resulted from the fact that mean BNP level in our cases was lower. Lubien et al. (37) found BNP levels to be 202±30 pg/ml in their series consisting of patients with heart failure and impaired relaxation pattern, whereas the mean BNP level in our hypertensive patients with impaired relaxation pattern was 66.17±17.56 pg/ml. We attributed the difference therein to our patients' being asymptomatic. The mean BNP level in the study carried out by Lubien et al. (37) was 300 pg/ml in symptomatic patients, and 120 pg/ml in asymptomatic patients with diastolic dysfunction. We attributed these high differences to the difference between mean ages of the groups (71±1 years in Lubien series versus 53.0±9.24 years in our series). The same difference between these two series persisted in groups without diastolic dysfunction as well. Mean age of the group without diastolic dysfunction was 60±1 years, and mean BNP level was 33.3±3 pg/ml in the Lubien series, whereas mean age of the group with normal diastolic function was 44.0±4.85 years and mean BNP level was 12.0±4.97 pg/ml in our series. Plasma BNP levels may exhibit an increase within normal limits due to diastolic dysfunction increasing with age. We think that further studies are needed to show distribution of mean BNP levels by age in the normal population.

Literature studies demonstrated that serum BNP levels changed in association with not only the patients' being either symptomatic or asymptomatic, but also the severity of diastolic dysfunction (37, 38). The highest BNP levels were reported in restrictive filling patterns (37). The lowest BNP levels, on the other hand, were reported in the patients with asymptomatic, prolonged relaxation pattern (37), the similar group of patients were included in our study. We think this difference can explain the fact that the mean BNP level in our series comprising asymptomatic patients with diastolic dysfunction was relatively lower than the BNP levels of patients with diastolic dysfunction reported in the literature (39-41).

Various studies recommend using >100 pg/ml as the cut-off plasma BNP value in the diagnosis of symptomatic diastolic dysfunction. Depending on the data we obtained from patients with asymptomatic diastolic dysfunction, we think it is necessary to determine new cut-off values for patients with increased LVMI, as we found LVMI was markedly higher in our patient group with diastolic dysfunction. It is known that increased LVMI is associated with increased cardiovascular risk (40). We showed the significant positive relationship between LVMI and plasma BNP values. Several studies described the relationship between left ventricular hypertrophy and BNP in hypertensive population (35, 36, 42). In athletic healthy individuals, no correlations have been found between mass index and BNP in the various studies (43). In hypertensive population, probably diastolic dysfunction as a result of the increase in pressure in end- diastole end increases BNP level independently of mass. In our patient group, the reason for the increase in BNP level is multifunctional.

Definitive diagnosis of diastolic dysfunction requires measuring left ventricular pressure and showing the pressure-volume relation. However, invasive and time-consuming nature of these methods hinders its use for the diagnosis of diastolic dysfunction in emergency clinics. Evaluation of left ventricle filling through indirect, non-invasive tests is the approach preferred in emergency clinics for the diagnosis of LV diastolic dysfunction (44-46). Changes in heart rate, valvular deficiencies and contractility differences can bring out differences in echocardiography-Doppler results used for the diagnosis of diastolic dysfunction (47). Our data demonstrate that serum BNP measurement is a useful test that gives rapid results and has a positive predictive value.

Study limitations

There are some limitations of this study; the number of study subjects is not large. Control patients were younger than patients with hypertension.

Conclusion

Brain natriuretic peptide levels are increased in hypertensive patients with asymptomatic diastolic dysfunction and the BNP levels are related with the degree of diastolic dysfunction. The BNP test could be used for prediction of asymptomatic diastolic dysfunction in hypertensive patients with sensitivity of 80% and specificity of 100%.

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