The diagnostic value of N-terminal B-type natriuretic peptide in diastolic heart failure: comparison with echocardiographic findings

Diyastolik kalp yetersizliği tanısında N-terminal B-tipi natriüretik peptidin yeri: Ekokardiyografi bulguları ile karşılaştırma

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Objectives: We investigated the value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) to diagnose diastolic heart failure (DHF) without left ventricular (LV) hypertrophy.

Study design: The study included 33 patients (17 males, 16 females) with DHF, who had acute pulmonary congestion and LV ejection fraction (EF) >50% on admission, and were stable for at least six months of follow-up. The control group consisted of 18 hypertensive patients (9 males, 9 females) without cardiac symptoms, whose LV mass indices matched the study group, and EF was >50%. Plasma NT-proBNP levels were measured and all patients were evaluated by echocardiography, to examine the relationship between NT-proBNP levels and the ratio of peak early diastolic mitral velocity to peak early diastolic mitral annular velocity (E/E').

Results: NT-proBNP levels were significantly increased in the DHF group (293.4±52.1 pg/ml vs. 123.1±23.5 pg/ml, p=0.043). Concerning the severity of diastolic dysfunction and NT-proBNP levels, patients with delayed relaxation (n=24) did not differ from the controls, whereas those with pseudonormal (n=5) and restrictive (n=4) forms had significantly elevated NT-proBNP levels (p=011). In the ROC analysis, an NT-proBNP level of ≥490 pg/ml predicted DHF with 40% sensitivity and 94% specificity. The mean E/E' values were 5.4, 15.4, and 17.6 in patients with delayed relaxation, pseudonormal, and restrictive forms, respectively. When all the patients were examined in three groups according to the E/E' values (E/E'<8; E/E'=8-15; E/E'>15), those having E/E' >15 had significantly higher NT-proBNP levels (p=0.0001). There was a highly significant relationship between E/E' and NT-proBNP (r=0.761, p=0.001). In the ROC analysis, a threshold of 269.1 pg/ml for NT-proBNP predicted E/E' >15 with 90% sensitivity and 73% specificity. In the logistic regression analysis, left atrial diameter (p=0.018) and E/E' (p=0.05) were independent factors affecting the NT-proBNP level.

Conclusion: Plasma NT-proBNP levels are elevated in DHF independently from LV hypertrophy. NT-proBNP levels provide estimation of LV end-diastolic pressure in symptomatic hypertensive patients with preserved systolic LV function.

Key words: Echocardiography, Doppler; heart failure, diastolic/diagnosis; natriuretic peptide, brain; ventricular function, left.

Amaç: N-terminal pro-B-tipi natriüretik peptidin (NT-proBNP) sol ventrikül (SV) hipertrofisi yokluğunda diyastolik kalp yetersizliği (DKY) tanısındaki öngördürücü değeri araştırıldı.

Çalışma planı: Çalışmaya, akut pulmoner ödem ile başvuran, başvuru anında SV ejeksiyon fraksiyonu (EF) >%50 olan ve takiplerde en az altı ay stabil seyreden, DKY'li 33 hasta (17 erkek, 16 kadın) alındı. Kontrol grubunu, sol ventrikül kütle indeksleri (SVKİ) DKY grubuna eşit, EF >%50 olan ve kardiyak yakınması bulunmayan 18 hipertansif hasta (9 erkek, 9 kadın) oluşturdu. Tüm hastaların plazma NT-proBNP düzeyleri ölçüldü. Ekokardiyografide ölçülen mitral akım Doppler zirve erken diyastolik hızın, mitral anülüs seviyesindeki erken diyastolik miyokart hıza oranı (E/E') ile NT-proBNP düzeyleri arasındaki ilişki incelendi.

Bulgular: NT-proBNP düzeyleri DKY grubunda kontrol grubuna göre anlamlı derecede yüksek bulundu (293.4±52.1 pg/ml ve 123.1±23.5 pg/ml; p=0.043). Diyastolik fonksiyon bozukluğu (DFB) derecesi açısından, NT-proBNP düzeyi, gecikmiş gevşeme olan hastalarda (n=24) kontrollerden farklı değilken, psödonormal (n=5) ve restriktif DFB'li (n=4) hastalarda anlamlı derecede yüksekti (p=0.011). ROC analizinde, NT-proBNP'nin ≥490 pg/ml olmasının DKY'yi saptamadaki duyarlılığı %40, özgüllüğü %94 bulundu. Ortalama E/E' oranı, gecikmiş gevşeme, psödonormal ve geri dönüşümsüz restriktif DFB'li hastalarda sırasıyla 5.4, 15.4 ve 17.6 bulundu (p=0.0001). Tüm hastalar (n=51) E/E' değerlerine göre üç gruba ayrıldığında (E/E'<8; E/E'=8-15; E/E'>15) E/E' >15 olan hastalarda NT-proBNP değerleri anlamlı derecede yüksek idi (p=0.0001). E/E' ile NT-proBNP arasında ileri düzeyde anlamlı ilişki bulundu (r=0.761, p=0.001). ROC analizinde, NT-proBNP'nin 269.1 pg/ml'lik eşik değerinin E/E' >15 saptamadaki duyarlılığı %90, özgüllüğü %73 idi. Lojistik regresyon analizinde, sol atriyum çapı (p=0.018) ve E/E' (p=0.05) NT-proBNP değerini bağımsız olarak etkilemekteydi.

Sonuç: NT-proBNP düzeyleri DKY'li hastalarda, SVKİ'den bağımsız olarak, yüksektir. NT-proBNP, sistolik fonksiyonları korunmuş ve semptomatik hipertansif hastalarda SV diyastol sonu basıncı hakkında iyi bir tahmin sağlayabilir.

Anahtar sözcükler: Ekokardiyografi, Doppler; kalp yetersizliği, diyastolik/tanı; natriüretik peptit, beyin; ventrikül fonksiyonu, sol.

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It was documented by many hospital records that left ventricular (LV) systolic functions are normal in many patients with heart failure (HF).[1] Four separate epidemiological studies have also shown that nearly half of the patients with HF in the community had normal LV systolic functions.[2-5] The re-hospitalization rate of patients with diastolic heart failure (DHF) is identical with the rate of patients with systolic heart failure (SHF). It is estimated that DHF accounts for more than 25% of the total cost of HF.[6,7]

Vasan and Levy divided DHF into three groups as: definite, possible and probable.[8] Definite DHF is characterized by the presence of ≥50% ejection fraction (EF) within 72 hours following the onset of the HF symptoms in addition to a definite clinical evidence of HF and objective evidence of diastolic dysfunction (DD) during cardiac catheterization. Possible DHF is defined by the absence of objective evidence in the presence of the first two criteria, whereas probable DHF is characterized by assessment of ≥50% EF within 72 hours following the onset of HF, in the presence of the first criterion. Diagnosis is not pragmatic in clinical practices since it involves an invasive approach. Therefore, further studies investigating the value of non-invasive, new imaging techniques and laboratory tests in the diagnosis of DHF are required.

The mitral flow Doppler peak early diastolic flow rate, evaluated by conventional echocardiography shows a good relationship with the LV filling pressures compared to the peak early diastolic myocardial rate (E/E') evaluated by the tissue Doppler imaging technique (TDI).[9] E/E' >15 was found highly specific in terms of increased left atrial (LA) pressure, while E/E' <8 was considered highly sensitive in terms of normal LA pressure.[10] Sensitivity of E/E' was also confirmed in patients with sinus tachycardia, atrial fibrillation, hyperthropic cardiomyopathy and cardiac transplantation.[11-14]

In recent years, several studies have been conducted which demonstrate that B-type natriuretic peptide (BNP) may be beneficial in the diagnosis of DHF.[15,16] These studies showed a sufficient increase in the value of BNP in DHF, even if this increase was found to be lower than SHF. However, left ventricular mass indices (LVMI) of the patients were not identical in most of the studies.[17] It is important to establish whether BNP values increase independently of LVMI in DHF, since studies conducted in artificial media and living organisms revealed a close association between BNP production and myositis hypertrophy.[18,19]

Aims of our study were as follows: *(i)* to establish the value of N terminal B-type natriuretic peptide (NT-proBNP) in the diagnosis of DHF, independent from LVMI; *(ii)* to compare NT-proBNP values according to the extent of DD; *(iii)* to evaluate the relationship between E/E' rates and NT-proBNP levels since it is known that E/E' rate and mean LV end-diastolic pressure are associated and that NT-proBNP levels reflect the ventricular pressure.

PATIENTS AND METHODS

The study included 51 patients (26 males, 25 females) between age 50-88 (mean age 70±10).

Selection of patients: Medical records of the 1211 patients with definite pulmonary edema confirmed by teleradiography, which was performed in our emergency room between January 2000 and June 2004 were assessed. Inclusion criteria were; baseline ejection fraction (EF) ≥50% and heart-thorax index <50%, and the correction of HF symptoms with diuretics and/or vasodilator agents, whereas exclusion criteria included acute coronary syndrome, atrial fibrillation, congenital heart disease, severe valvular lesions, serum creatinine >2 mg/dL, chronic obstructive pulmonary disease, right ventricular dysfunction and a history of acute pulmonary edema in the previous 6 months. 33 patients (17 males, 16 females) who met these criteria made up the DHF arm.

Medical records of the 953 patients referred to our hospital for routine echocardiographic assessment during the same period were evaluated to set a control group. 18 of these patients (9 males, 9 females) with EF ≥50%, age >50 and with LVMI equal to the DHF group were selected for the control group. Exclusion criteria for control group were HF symptoms and the presence of exclusion criteria in DD and DHF group as assessed by echocardiograms.

The study was approved by the ethical committee and written informed consents of all the patients were obtained following necessary information.

General demographic characteristics of the patients and risk factors were assessed. HF functional classification of the patients were subjectively evaluated according to the New York Heart Association (NYHA) criteria.[20] Diabetes mellitus was defined as fasting blood glucose of >126 mg/dL measured randomly and 2nd hour plasma glucose level of ≥200 mg/dL during the oral glucose tolerance test, according to the American Diabetes Association (ADA) criteria.[21] Hypercholesterolemia was defined according to the Adult Treatment Panel III (ATP III) guidelines as total cholesterol ≥200 mg/dL or LDL cholesterol ≥100 mg/dL, or patients using lipid lowering drugs.[22] In addition, hypertension was defined according to the Joint National Committee VII (JNC VII) guidelines as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg or patients using antihypertensive drugs.[23] Family history was defined as a history of coronary artery disease in first degree relatives, of male patients less than 55 years old and female patients less than 65 years old.[22] Medication used by the patients were also recorded.

Echocardiographic measurements: All patients were evaluated in the left lateral position at 45≥ while resting. 2.5-3.5 MHz transducers on the Acuson Sequoia C256 echocardiography device (Siemens Medical Solutions, Mountain View, CA, USA) were used to obtain the M-mode, two-dimensional and the color-flow Doppler records. Harmonic imaging was used when necessary. Double planned imaging was performed at the four apical spaces and two spaces with parasternal short and long axial imagings.[24] Pulsed wave Doppler spectral records were obtained by placing the 4x4 mm sample volume to the mitral valvular ends and right upper pulmonary vein in the 4 apical space images. Regional wall movements were closely monitored. Fractional shortening (FS) and LVMI were calculated by measuring LV wall thickness in M-mode and the end-diastolic and end-systolic diameters.[25] The left ventricular systolic volumes, diastolic volumes and EF were calculated by the modified Simpson method in two planned apical (2 and 4 spaces) images.[26] The mitral pulse Doppler flow obtained from three cardiac cycles were used to measure, early diastolic flow (E), late diastolic flow (A), deceleration time (DT) and isovolumetric relaxation time (IVRT). The highest systolic (PVs) and diastolic (PVd) velocities of the pulmonary venous flow during cardiac cycle were obtained. The pulmonary venous atrial backward flow (BF) was considered as the highest value of backward flow to pulmonary vein following P wave of electrocardiography. DDI was obtained at the mitral annulus level in the apical four chamber view after making adjustments regardless of high frequency signals. A 5 mm sample volume was placed at the lateral and medial annulus level, and the peak systolic velocity (S'), early diastolic velocity (E') and late diastolic velocity (A') were measured during the course of the following three cardiac cycles.[27] Diastolic dysfunctions were classified in three categories:[28] *(i)* impaired relaxation: for <55 years-old, E/A <1 or DT >220 msc and for >55 years-old E/A <0.8 and DT >220 msc; *(ii)* pseudonormal DD: E/A = 1-2 and DT = 150-200 msc and in addition PVd/PVs >1.5 or BF ≥35 cm/sc or BF time >A time + 30 msc or conversion of E/A rate to E/A <1 with Valsalva maneuver or one of the E/E' parameters >10 in TDI; *(iii)* restrictive DD: the presence of one of those following plus DT <150 msc: E/A >2, IVRT <60 msn, PVd/PVs >1.5, BF ≥35 cm/sc or BF time >A time + 30 msc. Restrictive DD was also divided into two groups according to the change in E/A rate with Valsalva maneuver: *(i)* reversible restrictive DD if the rate of E/A decreased with Valsalva maneuver and *(ii)* irreversible restrictive DD if the rate of E/A remained stable.

The E/E rate obtained from the level of the lateral mitral annulus by tissue Doppler imaging technique was used to calculate the LV filling pressure. Patients were divided into three groups according to their E/E' rates: E/E' <8; E/E'=8-15; E/E' >15.

All echocardiographic assessments were performed by an experienced cardiologist, blinded for NT-proBNP levels.

Laboratory methods: Among the biochemical parameters necessary for the evaluation of glomerular filtration rate (GFR), albumin (Alb) was measured by *bromcresol green* method, creatinine (Cr) was measured by *compensated Jaffe* method, while blood urea nitrogen (BUN) was measured by urease test.

10 mL of blood sample was collected from the peripheral vein of the patient who had rested for minimum 20 minutes in the supine position before the echocardiography procedure. Collected samples were placed in EDTA tubes containing 500 IU/mL aprotinin and centrifuged at 4^0C. They were then stored at -30^0C until the analysis following separation of plasma from the blood cells. Plasma NT-proBNP level was measured by the electrochemiluminescent method using the Elecsys 2010 kit (Roche Diagnostics, Basel, Switzerland). In our study NT-proBNP level was decided to be measured since it was more specific, sensitive and stable than BNP.[29]

Evaluation of renal functions: The GFR of all patients was measured and calculated by the MDRD formula (Modification of Diet in Renal Disease) since NT-proBNP level was found to be affected by GFR.[30]

Statistical analysis: In the evaluation of the study data descriptive statistical methods were used (mean, standard deviation). The Student t-test was also used to compare quantitative data and comparison of two groups with parameters having normal distribution, whereas the one-way ANOVA test was used to compare more than two groups (assessment of NT-proBNP levels according to DD, E/E', E/A) and the Tukey HDS test was used to identify the group with a difference. The Mann-Whitney U-test was also used to compare parameters with abnormal distribution of two

Table 1. Characteristics of the study groups

	Control group (n=18)			Diastolic heart failure (n=33)			
	Number	Percentage	Mean±SD	Number	Percentage	Mean±SD	*P*
Age			66±10			71±8	0.100
Sex							0.918
Male	9	50.0		16	48.5		
Female	9	50.0		17	51.5		
Heart rate (beats/min)			73±18			75±15	0.634
Body mass index (kg/m²)			29.6±4.8			29.9±4.4	0.958
Glomerular filtration rate (%)			70±12			66±14	0.696
Plasma NT-proBNP (pg/mL)			123.1±23.5			293.4±52.1	**0.043**
Drug use							
Beta-blockers	9	50.0		13	39.4		0.465
Angiotensin converting enzyme inhibitors	10	55.6		14	42.4		0.369
Angiotensin receptor blockers	4	22.2		10	30.3		0.537
Calcium channel blockers	8	44.4		17	51.5		0.629
Diuretics	5	27.8		10	30.3		0.850
Clinical history							
Hypertension	18	100.0		33	100.0		1.000
Diabetes mellitus	2	11.1		4	12.1		0.915
Hyperlipidemia	9	50.0		17	51.5		0.918
Cigarette smoking	3	16.7		8	24.2		0.530
Familial history	1	5.6		3	9.1		0.558
NYHA class							
I	18	100.0		11	33.3		
II	-			6	18.2		**0.001**
III	-			16	48.5		
Systolic blood pressure (mmHg)			158±16			162±25	0.571
Diastolic blood pressure (mmHg)			92±9			91±12	0.827

groups. On the other hand, the Chi-square test and Fischer's exact test were used to compare qualitative data. The Pearson correlation analysis was used to establish the relationship between parameters. Although the NT-proBNP levels were presented with real concentration values, analyses were conducted by algorithmic transformation values since NT-proBNP levels did not show normal distribution. The Receiver Operating Characteristic (ROC) analysis was used to determine the threshold value of NT-proBNP levels. The value of using NT-proBNP level alone in diagnosis was compared to DHF and rate of E/E' obtained from echocardiograms by ROC analysis. These results were established as area under the curve (AUC) and 95% confidence interval. The backward stepwise logistic regression analysis was implemented and the EF, LA size, DT, IVRT, BF time and E/E' parameters were used to investigate echocardiographic parameters independently affecting the NT-proBNP value. Results of the model were evaluated in the 95% confidence interval and p value <0.05 significance level. All analyses were made by SPSS 11.5 statistical program.

RESULTS

Characteristics of control group and patients with DHF are shown in Table 1 and echocardiographic data are given in Table 2. DD, evaluated by echocardiography was observed in all patients in the diastolic heart failure group. The classification of diastolic dysfunction was as follows: impaired relaxation in 24 patients (72.7%), pseudonormal DD in 5 patients (15.2%); reversible restrictive DD in 1 patient (3%), and irreversible restrictive DD in 3 patients (9.1%).

Plasma NT-proBNP levels were found to be significantly higher in the DHF group compared to the control group (293.4±52.1 pg/mL and 123.1±23.5 pg/mL, respectively; p=0.043). Evaluation according to the degree of diastolic dysfunction demonstrated that the NT-proBNP concentration was 147.9±3.3 pg/mL in patients with delayed relaxation; 1348.9±0.7 pg/mL in patients with pseudonormal DD; 2137 pg/mL in patients with reversible restrictive DD and 2754.2±1.6 pg/mL in patients with irreversible restrictive DD. NT-proBNP levels were significantly higher in patients

Table 2. Comparison of echocardiographic data

	Control group (n=18)	Diastolic heart failure (n=33)	*P*
Left ventricular ejection fraction (%)	64±5	60±5	**0.011**
Interventricular septal thickness (mm)	13.0±1.0	14.1±1.0	0.234
Left ventricular posterior wall thickness (mm)	13.6±0.6	13.9±1.2	0.292
Left atrial size (mm)	37.6±3.6	40.5±4.2	**0.016**
Left ventricular mass index (g/m^2)	315.5±52.0	359.3±95.1	0.077
E/A rate	1.01±0.07	1.02±0.64	0.942
Deceleration time (msc)	194.8±43.3	258.1±69.4	**0.0001**
Isovolumic relaxation time (msc)	80.3±11.0	107.9±27.0	**0.0001**
BF time (msc)	13.00±13.21	53.64±19.77	**0.0001**
E/E'	5.61±2.06	8.33±5.31	**0.042**

BF: Pulmonary venous atrial backward flow; E/A: ratio of the peak early diastolic mitral flow to the peak late diastolic mitral flow; E/E': ratio of the peak early lateral mitral annular myocardial velocity to the peak early diastolic mitral flow

with pseudonormal DD and restrictive DD compared to controls (p=0.011). No significant difference was found between patients with delayed relaxation and controls in terms of NT-proBNP levels (p>0.05).

The specificity and sensitivity of NT-proBNP levels in the identification of DHF was evaluated by the ROC curve (Figure 1). AUC was estimated as 0.623 in the detection of diastolic heart failure (p=0.03). When the NT-proBNP concentration was ≥490 pg/mL, a 40% sensitivity, 94% specificity, 93% positive predictive value, 46% negative predictive value and a 59% accuracy ratio was demonstrated in the detection of DHF.

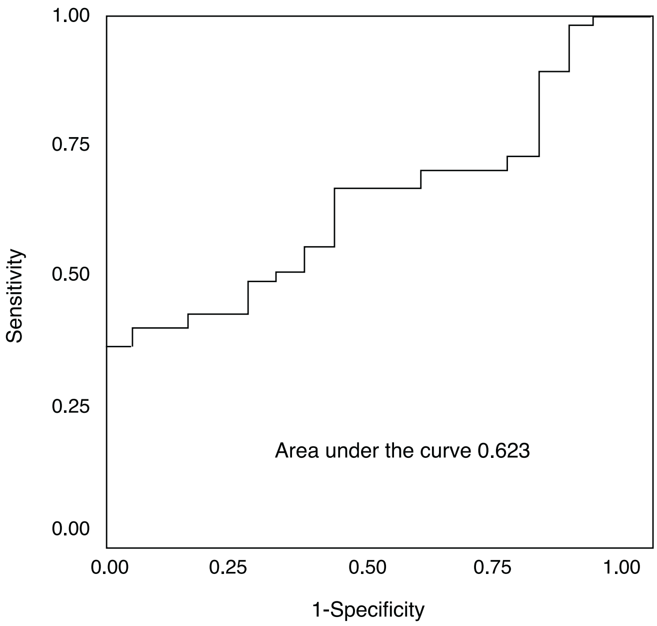

Figure 1. Specificity and sensitivity at different levels of the predictive effect of NT-proBNP on the detection of diastolic heart failure.

According to the threshold value of 490 pg/mL estimated by the ROC curve, 94.4% (17/18) of the patients in the control group and 79.2% (19/24) of the patients with impaired relaxation in the DHF group were found to have NT-proBNP levels below 490 pg/dL. 80% (4/5) of the patients with pseudonormal DD and all of the patients with restrictive DD had NT-proBNP levels of ≥490 pg/mL. The degree of DD increased with an increase in NT-proBNP levels (p=0.0001).

The rate of E/E' assessed by the tissue Doppler imaging technique was also found to increase when the degree of DD increased. Mean rate of E/E' was 5.4 in patients with delayed relaxation, 15.4 in patients with pseudonormal DD, 15.0 in patients with reversible restrictive DD, and 17.6 in patients with irreversible restrictive DD (p=0.0001).

Evaluation of the NT-proBNP levels of patients (n=51) in three groups categorized according to their rates of E/E' (E/E'<8; E/E'=8-15; E/E'>15) demonstrated that the group with rate of E/E'>15 had significantly higher NT-proBNP levels compared to the other two groups (p=0.0001; Table 3).

The relationship between the rate of E/E' and NT-proBNP level was assessed in both DHF group and control group. No relationship was found between the rate of E/E' and NT-proBNP level in the control group.

Table 3. Distribution values of NT-proBNP based on rates of E/E'

E/E'	Number	NT-proBNP (pg/mL)	*P*
<8	32	104.71±2.51	
8-15	11	309.02±3.09	
>15	8	2344.2±2.81	0.0001

E/E': ratio of the peak early lateral mitral annular myocardial velocity to the peak early diastolic mitral flow

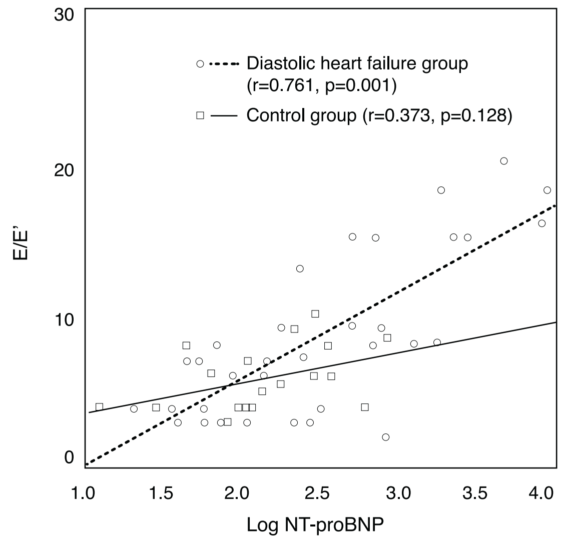

Figure 2. Relationship between the rate of E/E' and NT-proBNP values in the control and diastolic heart failure groups.

(r=0.373; p=0.128), whereas a positive and highly significant relationship was observed between the rate of E/E' and NT-proBNP level in DHF group (r=0.761, p=0.001; Figure 2).

The specificity and sensitivity of NT-proBNP level in the detection of E/E' >15 was assessed by the ROC curve. ROC AUC was found to be 0.927 of NT-proBNP level in detection of E/E' >15 (p<0.001; Figure 3). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy ratio of the 269.1 pg/mL threshold value of NT-proBNP was, 90%, 73%, 45%, 97% and 76%, respectively.

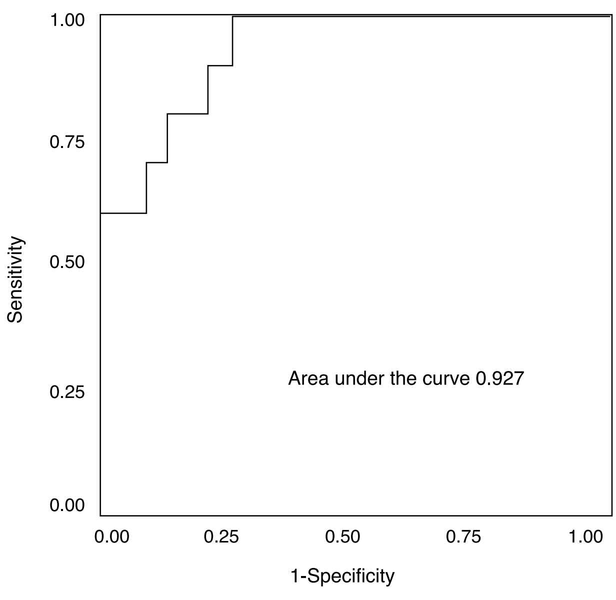

Figure 3. Specificity and sensitivity at different levels of the predictive effect of NT-proBNP on the detection of E/E' >15.

Echocardiographic parameters affecting NT-proBNP levels independently were assessed by logistic regression analysis. Logistic regression model was found highly significant (p<0.01, Negelkerde R square value 0.650). The results showed that diameter of LA (p=0.018, 95% confidence interval, 0.001-0.498) and rate of E/E' (p=0.05, 95% confidence interval, 0.643-1.008) affected NT-proBNP level independently.

Intraobserver variable was found <6% for echocardiographic measurements.

DISCUSSION

Heart failure is generally accepted to be associated with increased cardiothoracic index and decreased systolic function. However, there are a few evidences suggesting that nearly 50% of the patients with HF syndrome have normal or mild impaired systolic functions.[31] Diagnosis in these patients is based on exclusion criteria, rather than definite criteria. The prevalence of diastolic heart failure increases with age and is higher in females than in males.[32] Hypertension and LV hypertrophy are the most common pathologies accompanying DHF. Although the prognosis of the disease is still unknown compared to left heart failure, the long term mortality rate, particularly in elderly is similar to the rate of LHF.[33]

Cardiac catheterization is the standard for the diagnosis of diastolic heart failure. On the other hand, echocardiography is another more practical and alternative method to cardiac catheterization. It is also possible to obtain information about intracardiac pressure with Doppler flows by evaluating intracardiac flows. Of these, mitral flow Doppler is the most commonly used technique. However, due to its limitations, procedures such as pulmonary venous flow and TDI are also used while evaluating DD. In our study, degree of DD was examined by all three methods.

Despite all these methods, additional methods are still required to diagnose DHF. Assessment of plasma BNP levels is one of the latest approaches. There are several studies showing high specificity and sensitivity of BNP and NT-proBNP in LHF diagnosis.[34-37] However, there are also several controversial publications about its role in the diagnosis of DHF. Plasma BNP levels were found to be high in hypertensive patients. This increase in BNP levels was thought to be associated with the increase in LVMI.[38,39]

Almeida et al.[40] found a relationship between LVMI and BNP levels in hypertensive patients, however it was concluded that LVMI was not the only variable leading to an increase in BNP level. The study also showed that normotensive athletes had normal BNP levels with LVMI similar to hypertensive patients.[40] Although Wei et al[41] also found similar relationship between plasma BNP levels and LVMI, 15 patients who were found to have increased LVMI and normal diastolic functions assessed by echocardiography had normal BNP levels. On the other hand, Talwar et at.[42] could not demonstrate any relationship between LVMI and NT-proBNP levels. We matched LVMI in the DHF group and controls to decrease these contradictions. Our findings supported the study conducted by Yamaguchi et al[43] suggesting that patients in the DHF group with matched LVMI and DHF had higher BNP levels. However, the patients were not assessed according to their degree of DD in this study neglecting the possible differences in the degree of DD among patients, with regard to DHF and the fact that increase in BNP levels paralleled increase in the degree of DD.[44] As seen in our study, NT-proBNP levels were within normal range in most patients with delayed relaxation, despite a DHF history. As a reslut, it is important to assess patients based on their degree of DD.

Since the plasma level of both BNP and NT-proBNP may be affected in chronic renal failure, we estimated GFR of the control group and the DHF group using the MDRD formula in our study.[45] No significant difference was found between the control and study groups in terms of GFR values. Although there was no difference between the groups regarding LVMI, GFR and blood pressure patients in the DHF group were found to have significantly higher plasma NT-proBNP levels.

Another interesting finding in our study was the persistently high NT-proBNP levels after a long period of time (>6 months) following regression of the symptoms of acute pulmonary edema in the DHF group. High NT-proBNP levels in patients with preserved EF and at DHF risk may be specific for this clinical presentation. The ROC curve which was performed to determine the specificity and sensitivity of NT-proBNP levels in the detection of DHF demonstrated that NT-proBNP levels ≥490 pg/mL had low sensitivity (40%) and high specificity (94%) in the detection of DHF. This led us to consider that NT-proBNP cannot be used as an ideal screening test for DHF in clinical practice; however, it can be more helpful to confirm the diagnosis when used together with other procedures such as echocardiography. Apart from the high sensitivity, low specificity and high predictive value of NT-proBNP in the classical diagnosis of heart failure,[46] the low sensitivity, high specificity and low predictive value of NT-proBNP seen in our study may be due to the characteristics of the patients. In our study, the fact that assessment of NT-proBNP levels was based on evaluation during a stable period lasting at least for 6 months, and not at the time of decompensated HF, unlike in previous studies where patients with particular LVMI were included in control group, may have led to such results. Following the comparison of NT-proBNP values based on the degree of DD assessed by echocardiographic examination, which was the second aim of our study, we observed that NT-proBNP levels significantly increased in the patients with pseudonormal and restrictive DD. On the other hand, the difference in the increase of NT-proBNP levels in the patients with delayed relaxation was not found to be significant when compared to controls. This result was consistent with the study conducted by Maisel et al,[47] which investigated the association between BNP level and DD in hypertensive patients. In a small scale study, Mottram et al[48] found higher BNP levels in patients with DD associated with hypertension compared to the patients with normal diastolic functions. However, more than 70% of the patients with DD had normal BNP levels in the study.[48]

In our study, mean NT-proBNP levels were 10-fold higher in patients with pseudonormal DD and 20-fold higher in patients with restrictive DD compared to the control group. These values were markedly higher than the plasma NT-proBNP levels of the control group and of patients with delayed relaxation. This may be due to the inclusion of patients with DD associated with hypertension in other studies. On the contrary, our study included patients with DD associated with DHF.

Based on our assessment of patients with DD with a threshold value of 490 pg/mL established by ROC curve, we found that most of the patients with NT-proBNP levels below 490 pg/mL had delayed relaxation DD. 80% of the patients with delayed relaxation had NT-proBNP levels below 490 pg/mL, while 80% of the patients with pseudonormal DD and all patients with restrictive DD had NT-proBNP levels above 490 pg/mL. These findings suggest that NT-proBNP levels above 490 pg/mL, could be predictive particularly in advanced DD. On the other hand, the role of NT-proBNP in the diagnosis of patients with mild DD (delayed relaxation) assessed by echocardiography, in spite of a medical history of heart failure, is still controversial. Given the fact that the cost of the NT-proBNP level test is approximately twice as expensive as echocardiography in Turkey, echocardiography alone can be used to assess these patients.

The rate of E/E' assessed by tissue Doppler imaging technique is one of the non-invasive approaches in the assessment of characteristics of LV filling. Ommen *et al*[9] reported that when E/E' >15, a mean SV pressure of

>15 mmHg had a predictive sensitivity of 86% (64% positive predictive value). They also observed normal filling pressures in 85% of the patients with E/E' <8 and an increased LV pressure in all patients with E/E' >15. Mak et al[49] investigated the role of BNP in DD, using TDI in the patients who were consulted for echocardiographic examination and found an 88% sensitivity and 82% specificity of BNP in the detection of E/E' >15.

In our study we demonstrated a good relation between NT-proBNP levels and the rates of E/E'. Comparison of patients with E/E' <8 demonstrated that, NT-proBNP levels were 3-fold higher in patients with E/E' of 8-15, whereas they were 20-fold higher in patients with E/E' >15. Following the investigation of the role of NT-proBNP levels in the detection of increased filling pressure by ROC curve, we found a 90% sensitivity and a 73% specificity of NT-proBNP levels in the prediction of E/E' >15. We also found that the best NT-proBNP level to show left ventricular filling pressure was 269.1 pg/mL. The reason why higher sensitivity levels were obtained in our study compared to Mak et al[49] may be explained by the different characteristics of the patients or our preference of NT-proBNP instead of BNP.

The small sample size was one of the most important limitations in our study. Diastolic heart failure group consisted of patients who were diagnosed with definitive pulmonary edema at submission to hospital, patients with EF >50% at diagnosis and those who were followed up at least 6 months in our clinic and found to be stable. The reason for evaluating this limitation was due to increased NT-proBNP levels in HF presentation and the gradual decline following the regression of symptoms. Thus the fluctuations in NT-proBNP levels would have been prevented. On the other hand, the reason for the small sample size in the control group was the rare presentation of the patients with LVMI matched to DHF group, with a history of hypertension and having no cardiac symptoms and no DD. In addition to the small sample size, findings were not representative for all patients with DHF since they were only available for a selected patient group. Insufficient findings concerning the role of NT-proBNP in the diagnosis of patients with mild DD was the second limitation of our study.

In conclusion, we found that NT-proBNP levels were significantly high in patients with DHF regardless LVMI. NT-proBNP levels increased significantly particularly in patients with pseudonormal and restrictive DD compared to controls, with an increase in DD, in the diastolic heart failure group. We also found a marked significant positive relation between the rate of E/E' obtained by tissue Doppler imaging technique and NT-proBNP levels. These findings may support the idea that NT-proBNP is an appropriate biochemical parameter in the diagnosis of DHF, particularly in the assessment of DD.

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