The relationship between echocardiographic parameters and brain natriuretic peptide levels in acute and chronic mitral regurgitation

Akut ve kronik mitral yetersizliğinde beyin natriüretik peptit düzeyinin ekokardiyografi parametreleri ile ilişkisi

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ABSTRACT

Objectives: Plasma brain natriuretic peptide (BNP) level increases with symptoms and severity of mitral regurgitation (MR). We aimed to determine the relationship between plasma BNP levels and echocardiographic parameters in patients with acute and chronic MR.

Study design: The study included 55 patients (31 males, 24 females) with isolated moderate-to-severe MR. Of these, 31 patients had acute MR, and 24 patients had chronic MR. All the patients were assessed by transthoracic, transesophageal and Doppler echocardiography and plasma BNP levels were determined.

Results: Clinical characteristics and functional capacity were similar in the two groups. Patients with acute MR had significantly higher left ventricular (LV) ejection fraction (EF) (p=0.001), and significantly lower LV end-systolic diameter (p=0.016), end-systolic volume (p=0.027), end-diastolic diameter (p=0.011), left atrial volume (LAV) (p=0.003), and plasma BNP levels (p=0.036). Effective regurgitation orifice area was also significantly higher in patients with acute MR (p=0.038). In multiple linear regression analysis, the natural logarithm of BNP was significantly correlated with E/Ea ratio (β=0.50, p=0.002) and LAV (β=0.38, p=0.015) in patients with acute MR, and with systolic pulmonary artery pressure (β=0.60, p=0.002) and EF (β=-0.36, p=0.039) in patients with chronic MR.

Conclusion: Although the echocardiographic degree of MR was more pronounced in patients with acute MR, serum BNP levels tended to be lower in this group. Correlation of serum BNP with E/Ea and LAV in this group may be an important finding.

ÖZET

Amaç: Plazma beyin natriüretik peptit (BNP) düzeyi mitral yetersizliğinin (MY) semptom ve şiddeti ile artmaktadır. Bu çalışmada akut ve kronik MY'li hastalarda plazma BNP düzeyi ile ekokardiyografik parametreler arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya orta-ileri derecede izole MY olan 55 hasta (31 erkek, 24 kadın) alındı. Otuz bir hastada akut MY, 24 hastada kronik MY vardı. Tüm hastalar transtorasik, transözofageal ve Doppler ekokardiyografi ile değerlendirildi ve plazma BNP düzeyleri belirlendi.

Bulgular: İki grupta klinik özellikler ve fonksiyonel kapasite benzer bulundu. Akut MY'li hastalarda sol ventrikül ejeksiyon fraksiyonu (EF) daha yüksek bulunurken (p=0.001), sol ventrikül sistol sonu çapı (p=0.016), sistol sonu volümü (p=0.027), diyastol sonu çapı (p=0.011), sol atriyum volümü (SAV) (p=0.003) ve plazma BNP düzeyi (p=0.036) anlamlı olarak daha düşük saptandı. Etkili yetersizlik orifis alanı da bu hasta grubunda anlamlı derecede daha yüksek idi (p=0.038). Çoklu lineer regresyon analizinde, plazma BNP'nin doğal logaritması akut MY'li grupta E/Ea oranı (β=0.50, p=0.002) ve SAV (β=0.38, p=0.015) ile, kronik MY'li grupta ise sistolik pulmoner arter basıncı (β=0.60, p=0.002) ve EF (β=-0.36. p=0.039) ile anlamlı ilişki gösterdi.

Sonuç: Akut MY'li hastalarda MY derecesi ekokardiyografik olarak daha belirgin olmasına rağmen, serum BNP düzeyi daha düşük bulunmuştur. Bu grupta serum BNP düzeyi ile E/Ea oranı ve SAV arasında gözlenen ilişki önemli bir bulgu olabilir.

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Mitral regurgitation is a commonly diagnosed clinical entity that is associated with significant morbidity and mortality.[1-3] The mitral valve is composed of its annulus, mitral leaflets, chordae tendineae, and papillary muscles. Abnormalities in any of these components can lead to MR. Structural abnormality of the chordae tendineae may occur due to myxomatous degeneration, spontaneous rupture, rheumatic shortening, and infectious destruction.[4] Mitral regurgitation tends to be a progressive disease. The progression may be slow and insidious or may be abrupt as a result of chordal rupture leading to flail leaflet.[5] Acute severe MR is usually poorly tolerated and frequently requires urgent surgical correction.[4] In chronic MR, however, surgical treatment should be offered when symptoms appear due to pathologic changes in the left ventricle.[6]

Brain natriuretic peptide is a hormone released by the myocardium in response to myocardial stretching and increased LV end-diastolic pressure.[7] Plasma BNP levels increase with symptoms and severity of MR.[8] Thus, BNP may be a possible marker of LV dysfunction and symptoms in patients with MR.[8-10] Experimental induction of LV remodeling has been shown to result in rapid BNP activation.[11] Clinically, BNP activation is observed in conditions causing LV remodeling[11] and a number of studies have suggested that BNP activation reflects the degree of LV remodeling.[12-15] Although plasma BNP levels in organic and functional MR have been reported to be independently determined by the degree of LV remodeling and may play an important role in the clinical evaluation of patients with MR,[16] clinical significance of BNP in acute and chronic MR has not been fully investigated.

We aimed to determine the relationship between plasma BNP levels, echocardiographic parameters, and functional status in patients with acute and chronic MR.

PATIENTS AND METHODS

Study groups

The study consisted of 55 patients (31 males, 24 females) with isolated, organic, moderate-to-severe MR. All the patients were referred to a single cardiac center for echocardiography between September 2008 and July 2009. Exclusion criteria were the presence of any of the following: mitral stenosis (mitral valve area ≤1.5 cm^2), aortic valve disease (peak velocity across the aortic valve ≥2.5 m/sec or severity greater than mild aortic regurgitation), primary right heart disease, previous valve repair or replacement, renal failure (creatinine >1.5 mg/dl), blood pressure >160/100 mmHg, moderate or severe respiratory disease, hyperthyroidism, neoplastic disease, papillary muscle rupture, dilated cardiomyopathy, hypertrophic cardiomyopathy, ischemic heart disease, ischemic MR, and congenital heart disease.

Abbreviations:

BNP	*Brain natriuretic peptide*
EDD	*End-diastolic dimension*
EDV	*End-diastolic volume*
EF	*Ejection fraction*
ESD	*End-systolic dimension*
ESV	*End-systolic volume*
LAV	*Left atrial volume*
LV	*Left ventricle*
MR	*Mitral regurgitation*
nl	*Natural logarithm*
PAP	*Pulmonary artery pressure*

There were 31 patients with acute MR and 24 patients with chronic MR. Acute MR patients were those having chordal ruptures of various etiologies. Clinical diagnosis of acute MR was made by the increase in NYHA functional class or development of new symptoms due to chordal rupture in patients with flail mitral leaflets. Chronic MR patients were selected from patients who were followed-up for rheumatic heart disease or degenerative valvular disease. Symptoms were assessed by cardiologists blinded to BNP levels and echocardiographic findings. The study protocol was approved by the local ethics committee, and informed consent was obtained from all participants.

Echocardiographic evaluation

Transthoracic, transesophageal and Doppler echocardiographic examinations were performed by a 3.25-MHz transthoracic transducer and a 5-MHz multiplane transesophageal probe connected to a Vivid 5 System (GE Vingmed Ultrasound AS, Horten, Norway). Transesophageal echocardiography was performed after four hours of fasting, under topical anesthesia with 10% lidocaine and conscious sedation with intravenous midazolam. Chordal rupture was defined as the presence of free and highly mobile, linear echoes associated with flail mitral leaflet(s).[17-19] Transesophageal echocardiography was considered the reference method in diagnosing chordal rupture and vegetation.[18] Left ventricular end-systolic dimension, end-diastolic dimension, wall thickness, and left atrial volume were measured according to the guidelines of the American Society of Echocardiography.[20] Left atrial volume was measured by carefully tracing left atrial margins in the apical four-chamber and apical two-chamber views in atrial diastole.[21] All measurements were

averaged from three to five cardiac cycles. Left ventricular end-systolic and end-diastolic volumes and ejection fraction were measured from the apical four-chamber view and two-chamber views using the modified Simpson's method.[20] Regurgitant fraction, vena contracta width, regurgitant volume, effective regurgitant orifice area were measured according to the guidelines of the American Society of Echocardiography.[22] Systolic pulmonary artery pressure was estimated from the systolic transtricuspid pressure gradient (in mmHg) using the simplified Bernoulli equation. Left ventricular peak early diastolic transmitral flow velocity (E), early diastolic velocity of the lateral mitral annulus (Ea) and E/Ea ratio were measured.[23] Tissue Doppler imaging was obtained with the sample volume placed at the lateral corner of the mitral annulus from the apical four-chamber view. Doppler echocardiographic recording and

Table 1. Clinical and echocardiographic characteristics of patients with acute and chronic mitral regurgitation

	Acute (n=31)			Chronic (n=24)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			60±15			57±14	N S
Sex							N S
Male	20	64.5		14	58.3		
Female	11	35.5		10	41.7		
Heart rate (bpm)			87±21			93±21	N S
Systolic blood pressure (mmHg)			119±23			127±28	N S
Diastolic blood pressure (mmHg)			73±11			79±17	N S
Body mass index (kg/m^2)			26±4			25±3	N S
Diabetes mellitus	1	3.2		5	20.8		N S
Atrial fibrillation	9	29.0		12	50.0		N S
NYHA class							N S
II	11	35.5		8	33.3		
III	13	41.9		12	50.0		
IV	7	22.6		4	16.7		
Left ventricle							
Ejection fraction (%)			70±5			59±5	**0.001**
End-diastolic volume (ml)			158±40			184±41	N S
End-systolic volume (ml)			40±24			65±30	**0.027**
End-systolic dimension (cm)			3.4±0.7			3.9±0.8	**0.016**
End-diastolic dimension (cm)			5.0±0.6			5.9±0.6	**0.011**
Posterior wall thickness (cm)			1.03±0.04			1.10±0.12	N S
Ventricular septum thickness (cm)			1.05±0.02			1.10±0.11	N S
Left atrial volume (ml)			90±32			114±38	**0.003**
Vena contracta width (mm)			0.59±0.15			0.56±0.13	N S
Effective regurgitant orifice area (cm^2)			0.51±0.13			0.44±0.12	**0.038**
Regurgitant volume (ml)			71±19			64±17	N S
Regurgitant fraction (%)			0.59±0.08			0.59±0.09	N S
Systolic pulmonary artery pressure (mmHg)			52±11			54±14	N S
E/Ea ratio			17±5			18±7	N S
Brain natriuretic peptide (pg/ml)			185±122			279±124	**0.036**
Ln-brain natriuretic peptide (pg/ml)			4.9±0.4			5.5±0 .5	**0.012**

NS: Not significant; NYHA: New York Heart Association; Ln: Natural logarithm.

blood sampling were conducted simultaneously, but were processed independently.

Measurement of BNP

Venous blood samples were taken with the patient resting at the semirecumbent position and while on usual medications. Blood samples were collected in EDTA-containing tubes and stored at 2 to 8 °C. Particulates were removed by centrifugation at 1000 g for 15 to 20 minutes. Quantitative determination of BNP in plasma was made using the ADVIA Centaur BNP assay (Bayer HealthCare LLC, Germany). This system is a fully automated two-site sandwich immunoassay using direct chemiluminescent technology, in which constant amounts of two monoclonal antibodies are used. The assay is linear for BNP concentrations from 2.0 to 5,000 pg/ml (0.58-1445 pmol/l), which allows estimation of the minimum detectable concentration with 95% confidence.

Statistical analysis

The results are presented as mean±standard deviation or percentages. Comparison of continuous variables between groups were tested by the unpaired Student's t-test and categorical variables were compared using the chi-square test. The Fisher's exact test was used to compare categorical variables, as more than 25% of the classes had frequencies less than 5. The distribution of BNP was skewed, but the levels were normal after natural logarithm transformation. The relationship between plasma BNP and echocardiographic variables was assessed by a bivariate correlation method (Pearson correlation). Significantly correlated variables were further analyzed by a stepwise multiple linear regression analysis. A *P* value of less than 0.05 was considered significant. All tests were done with the SPSS for Windows 11.5 statistical package.

RESULTS

Table 1 summarizes the clinical and echocardiographic characteristics of the patients with acute and chronic MR. Clinical characteristics were similar in the two groups. Patients with acute MR had significantly higher EF (p=0.001), and significantly lower ESV (p=0.027), ESD (p=0.016), EDD (p=0.011), LAV (p=0.003), BNP (p=0.036) and ln-BNP values (p=0.012). Effective regurgitant orifice area was also significantly higher in patients with acute MR (p=0.038). Other parameters used for MR grading (regurgitant volume, vena contracta width) were higher in patients with acute MR, but these did not reach significance. The remaining echocardiographic parameters were similar in the two groups.

Table 2 summarizes the results of univariate and multivariate analyses between plasma ln-BNP levels and echocardiographic parameters. In patients with acute MR, plasma ln-BNP level showed significant correlations with the following echocardiographic parameters: E/Ea (r=0.58), LAV (r=0.48), EDV (r=0.43), EDD (r=0.41), and ESV (r=0.37). In patients with chronic MR, plasma ln-BNP level was positively correlated with systolic PAP (r=0.65), EDV (r=0.38), EDD (r=0.34), ESV (r=0.32), and negatively correlated with EF (r= -0.46). In multivariate analysis, significant correlations with plasma ln-BNP level remained only

Table 2. Univariate and multivariate correlates of plasma Ln-brain natriuretic peptide levels in patients with acute and chronic mitral regurgitation

		Univariate analysis		Multivariate analysis	
		r	*p*	β	*p*
Acute mitral regurgitation	E/Ea ratio	0.58	**0.001**	0.50	**0.002**
	Left atrial volume	0.48	**0.007**	0.38	**0.015**
	LV end-systolic volume	0.37	**0.044**		
	LV end-diastolic volume	0.43	**0.017**		
	LV end-diastolic dimension	0.41	**0.026**		
Chronic mitral regurgitation	Systolic pulmonary artery pressure	0.65	**0.001**	0.60	**0.002**
	LV ejection fraction	-0.46	**0.038**	-0.36	**0.039**
	LV end-diastolic volume	0.38	**0.041**		
	LV end-diastolic dimension	0.34	**0.029**		
	LV end-systolic volume	0.32	0.42		

Ln: Natural logarithm; LV: Left ventricle.

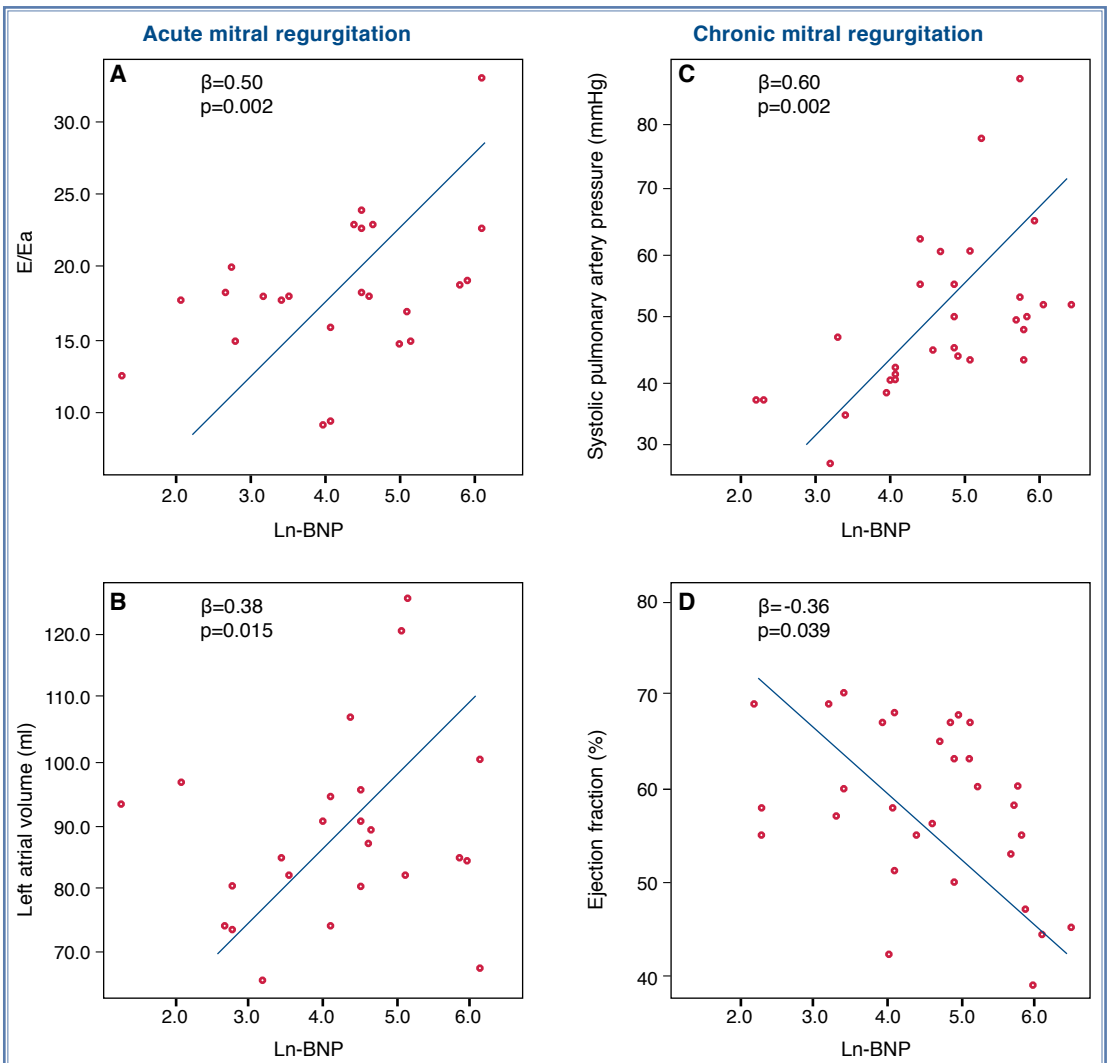

Figure 1. The results of multivariate correlation analysis between plasma ln-BNP levels and **(A)** E/Ea ratio, **(B)** left atrial volume for acute mitral regurgitation, and **(C)** systolic pulmonary artery pressure, and **(D)** left ventricular ejection fraction for chronic mitral regurgitation. Ln-BNP: Natural logarithm brain natriuretic peptide.

for E/Ea ratio (β=0.50, p=0.002) and LAV (β=0.38, p=0.015) in patients with acute MR, and for systolic PAP (β=0.60, p=0.002) and EF (β=-0.36, p=0.039) in patients with chronic MR (Fig. 1).

DISCUSSION

In this study, serum BNP levels were found to be lower in patients with acute MR, where LV remodeling is less than that in chronic MR. Multivariate analysis showed that serum BNP level was correlated with LAV and E/Ea ratio in acute MR, and with systolic PAP and EF in chronic MR.

Brain natriuretic peptide is produced by ventricular myocytes in response to increases in wall stress and studies have shown that plasma BNP levels increase with symptoms and severity in patients with MR.[4,8,24] In our study, symptoms were similar in acute and chronic MR groups, but the frequency of NYHA class IV was higher in patients with acute MR. Although the severity of symptoms were similar, BNP levels were lower in patients with acute MR and a positive correlation was present with LAV and E/Ea. This may be explained by the acute effects of volume loading on the left atrium and LV, in which circumstance EF is still preserved and LV remodeling has not yet taken place. Similarly, LV dimensions were smaller in patients with acute MR, showing the lack of significant remodeling. Left ventricular pressure or volume overload is accompanied by myocardial remodeling in both acute and chronic MR.[4,5,25] However, in acute

MR, the regurgitant volume that returns from the left atrium causes a sudden increase in LV end-diastolic volume. The LV compensates for this by means of the Frank-Starling mechanism; increased sarcomere length enhances LV contractility. Because acute MR reduces both late systolic ventricular pressure and radius, LV wall tension declines markedly permitting a reciprocal increase in both the extent and velocity of myocardial fiber shortening, leading to a reduced ESV and resulting in a more complete LV emptying.[4] Moreover, in acute MR, hyperdynamic state such as increased inotropy and reduced afterload may account for the relatively better overall LV function. Similar to our findings, Sutton et al.[8] reported that BNP secretion was closely related to increases in left atrial dimensions rather than the remodeling of the LV or EF. In their study, there was no significant LV remodeling and sudden volume overload due to acute MR. Studies have shown that BNP is also produced in the atrium in addition to the main production site, ventricles.[26,27]

On the other hand, there is dilatation of the LV with eccentric hypertrophy in chronic MR. Wall stress is normalized with the development of hypertrophy. Left ventricular function is not hyperdynamic as in the acute state, but is in a high-normal range. In chronic MR, diastolic wall stress increases, resulting in LV chamber enlargement. As the LV dilates, it becomes more spherical, and this change may reduce its efficiency, particularly compromising its longitudinal (base-apex) piston function. As a result, left atrial pressure and systolic PAP are increased in chronic MR. We found that LV remodeling parameters were significantly higher in chronic MR. This explains the higher levels of serum BNP and its positive correlation with systolic PAP and negative correlation with EF. Studies have shown that BNP reflects the impact of MR on the heart, regardless of the degree of valve regurgitation.[7,28] Yusoff et al.[28] proposed that altered BNP and normal EF at rest might reflect subclinical ventricular dysfunction in patients with MR.

A recent study involving children and adolescents found significant correlations between N-terminal pro-BNP and echocardiographic indices of MR.[29] The correlations were significant and strong with the dimension and volume of the left atrium, and EDD and ESD of the LV, indexed for body surface area.

Study limitations

The study had two limitations. Firstly, we classified our patients on the basis of noninvasive data and compared plasma BNP levels with noninvasive echocardiographic parameters. Secondly, our study groups were relatively small. Studies with larger sample sizes are needed to elucidate the clinical role of plasma BNP levels rather than its statistical significance. In addition, the lack of a significant difference between the two groups with respect to functional class was attributed to small sample size.

In conclusion, serum BNP levels tended to be lower in patients with acute MR, despite the higher degree of echocardiographic MR. In this group, serum BNP levels correlated significantly with E/Ea and LAV, which can be an important finding in understanding and interpreting plasma BNP levels in acute MR.

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Key words: Echocardiography; mitral valve insufficiency; natriuretic peptide, brain; ventricular function, left.

Anahtar sözcükler: Ekokardiyografi; mitral kapağı yetersizliği; natriüretik peptit, beyin; ventrikül fonksiyonu, sol.