The predictive value of plasma brain natriuretic peptide for the recurrence of atrial fibrillation six months after external cardioversion

Plazma beyin natriüretik peptid düzeyinin kardiyoversiyon sonrası altıncı aydaki atriyal fibrilasyon nüksünü öngörmedeki değeri

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Objectives: The aim of this study was to assess the predictive value of plasma brain natriuretic peptide (BNP) level for the recurrence of atrial fibrillation (AF) after successful cardioversion in patients with persistent AF.

Study design: The study included 58 patients (36 females, 22 males; mean age 59 years) with preserved left ventricular function, who underwent successful electrical cardioversion for persistent AF. Plasma BNP levels were measured before, 30 minutes and six months after cardioversion and electrocardiography was performed to assess AF recurrence. Echocardiography was performed in all the patients before cardioversion.

Results: At six months, 38 patients (65.5%) were in sinus rhythm (SR), whereas 20 patients (34.5%) reverted to AF. The mean baseline BNP level was significantly higher than that measured 30 minutes after cardioversion (255.6±159.6 pg/ml *vs* 70.5±57.0 pg/ml; p=0.00006). Patients who reverted to AF had significantly higher baseline (p=0.035) and six-month (p=0.001) BNP levels. In addition, they had a significantly greater decrease in BNP levels 30 minutes after cardioversion than patients who remained in SR (-271.9±42.4 pg/ml *vs* -139.4±25.3 pg/ml; p=0.008). ROC analysis of this drop with the cutoff value of 200 pg/ml predicted AF recurrence at six months with 80% sensitivity and 86% specificity. There were no correlations between baseline BNP level and duration of AF. However, left atrium diameter showed a significant negative correlation with the baseline BNP level (for ≤40 mm, 41-45 mm, and ≥45 mm: 394.6 pg/ml, 206.5 pg/ml, and 198.5 pg/ml, respectively; p=0.02).

Conclusion: In patients with persistent AF, baseline plasma BNP level and the magnitude of its decrease after successful cardioversion may predict AF recurrence.

Key words: Atrial fibrillation/therapy; biological markers; electric countershock; electrocardiography; natriuretic peptide, brain/blood; recurrence.

Amaç: Bu çalışmada dirençli atriyal fibrilasyonlu (AF) hastalarda başarılı kardiyoversiyon sonrası AF nüksünü öngörmede plazma beyin natriüretik peptid (BNP) düzeyinin değeri araştırıldı.

Çalışma planı: Çalışmaya, dirençli AF nedeniyle başarılı elektriksel kardiyoversiyon uygulanan, sol ventrikül fonksiyonu korunmuş 58 hasta (36 kadın, 22 erkek; ort. yaş 59) alındı. Hastaların kardiyoversiyon öncesi, kardiyoversiyon sonrası 30. dakika ve kardiyoversiyon sonrası altıncı aydaki plazma BNP düzeyleri ölçüldü ve AF nüksünü değerlendirmek için elektrokardiyografileri çekildi. Tüm hastalara işlem öncesinde ekokardiyografi yapıldı.

Bulgular: Altıncı ayda 38 hasta (%65.5) sinüs ritminde (SR) kalırken, 20 hastada (%34.5) AF görüldü. Tüm hasta grubunda işlem öncesindeki ortalama BNP düzeyi (255.6±159.6 pg/ml), kardiyoversiyon sonrası 30. dakikadaki BNP değerine (70.5±57.0 pg/ml) göre anlamlı derecede yüksek bulundu (p=0.00006). Altıncı ayda AF görülen hastalarda başlangıç (p=0.035) ve altıncı aydaki (p=0.001) BNP değerleri sinüs ritmindeki hastalardan anlamlı derecede yüksek idi. Ayrıca, bu grupta kardiyoversiyondan 30 dakika sonra BNP düzeyinde görülen düşme miktarı anlamlıydı (-271.9±42.4 pg/ml ve -139.4±25.3 pg/ml; p=0.008). Kesim değeri 200 pg/ml alınarak yapılan ROC analizinde, BNP düzeyindeki bu düşüşün altıncı aydaki AF nüksünü öngörmedeki duyarlılığı %80, özgüllüğü %86 bulundu. Başlangıç BNP düzeyi AF süresiyle ilişkili bulunmadı; sol atriyum çapı ise BNP düzeyi ile anlamlı ters ilişki gösterdi (≤40 mm, 41-45 mm ve ≥45 mm için sırasıyla 394.6 pg/ml: 206.5 pg/ml ve 198.5 pg/ml; p=0.02).

Sonuç: Başlangıçtaki plazma BNP düzeyi ve başarılı kardiyoversiyon sonrası BNP düzeyindeki düşme miktarı, dirençli AF'li hastalarda AF nüksünü öngörebilir.

Anahtar sözcükler: Atriyal fibrilasyon/tedavi; biyolojik belirteç; elektrik şoku; elektrokardiyografi; natriüretik peptid, beyin/kan; nüks.

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia especially in the elderly. After cardioversion and despite the use of pharmacologic therapy, the recurrence rate of AF is high, approximately 50% at one year.[1] Two clinical trials have shown that a rhythm control approach offers no survival benefit over a rate control approach.[1,2] The benefit of an aggressive conversion strategy compared to pharmacologic heart rate control is still controversial.[1] Since atrial fibrillation is a heterogenous disease, identification of patients at risk for recurrence with the use of simple and objective parameters may be helpful in tailoring the treatment. Age, history of AF, left ventricular dysfunction, left atrial (LA) dilatation, LA appendage functions, and hyperthyroidism have been associated with increased recurrence rates of AF.[3-7] Brain natriuretic peptide (BNP) is synthesized mainly by cardiac ventricles and to a lesser degree by cardiac atrias.[8] Recently, it has been reported that plasma BNP is mainly produced in the atria and not in the ventricles in patients with lone AF.[9] Its synthesis is triggered by elevated endocavitary pressure, and its diagnostic and prognostic usefulness has been shown in patients with heart failure.[8,10,11]

The present study aimed to investigate whether BNP levels measured before and after cardioversion in patients with preserved left ventricular function and persistent AF would predict the recurrence of AF six months after cardioversion.

PATIENTS AND METHODS

Seventy-three consecutive patients (45 females, 28 males; range 34 to 76 years) volunteered to participate in the study and underwent elective cardioversion for persistent AF as clinically indicated. Exclusion criteria were significant valvular heart disease, history of previous valve surgery, significant left ventricular dysfunction (EF <40%), severe LA enlargement (>5 cm), and paroxysmal AF. Eight patients were excluded because of significant valvular heart disease and five patients were excluded because of left ventricular dysfunction. The remaining 60 patients with persistent AF were studied.

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed in all the patients before cardioversion using the Vivid 7 Pro Doppler echocardiography system (TTE: 3.5 MHz probe,; TEE: 6 MHz probe).

Peripheral blood samples for BNP were obtained 5 min before cardioversion and sedation, and 30 minutes and 6 months after cardioversion, during which electrocardiographic monitoring of heart rate was performed. All specimens were collected in tubes containing EDTA.

A point-of-care fluorescence immunoassay kit (Triage BNP Test, Biosite, San Diego, CA, USA) was used to measure BNP. Values of peptides were expressed in pg/ml. The measuring range for the assay was 15 to 5,000 pg/ml.

Intravenous unfractionated heparin was given to all patients before cardioversion under monitoring of target activated partial thromboplastin time (aPTT) of 1.5-2 times of normal. All patients had effective anticoagulation (with international normalized ratio higher than 2.0) with warfarin after cardioversion.

An experienced anesthesiologist gave a brief general anesthetic with intravenous midazolam for direct current (DC) cardioversion. DC external monophasic shocks were used at the physician's discretion, starting with 150 J and followed by 200 J, 300 J and 360 J. The procedure was discontinued upon failure of achieving sinus rhythm (SR) despite two shocks with the highest energy (360 J).

The study protocol was approved by the ethical committee of Bursa Yüksek İhtisas Hospital and was explained to each patient. Written informed consent was obtained from all the patients.

Statistical analysis. The results were expressed as mean ± standard deviation (SD). Comparisons of parametric data were made using the Student's t-test or Mann-Whitney U-test and nonparametric data were analyzed using the chi-square test or Fisher's exact test. Kruskall-Wallis test was used for subgroup analysis. Receiver operator characteristic (ROC) analysis was performed to determine sensitivity and specificity of BNP in detecting AF recurrence.

RESULTS

In 58 patients (96.7%), SR was restored immediately after cardioversion and maintained 30 minutes after cardioversion. In two patients (3.3%) in whom cardioversion was unsuccessful after two shocks with 360 J, no further cardioversion was attempted. There were no adverse events related to cardioversion or anesthesia.

Fifty-eight patients were followed-up for six months and divided into two groups depending on the presence or absence of AF recurrence. Thirty-eight patients (65.5%) were still in SR, whereas 20 patients (34.5%) reverted to AF after six months.

Table 1. Baseline characteristics of the two groups with and without recurrent atrial fibrillation (AF) after cardioversion

	Sinus rhythm (n=38)			Recurrent AF (n=20)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			60.3±1.8			57.6±4.3	0.51
Sex							
Female	22	57.9		14	70.0		0.36
Male	16	42.1		6	30.0		
Ejection fraction (%)			54.6±2.2			57.2±4.1	0.55
Left atrium (LA) diameter (cm)			4.3±0.1			4.3±0.1	0.93
LA diameter/body surface area (cm/m^2)			2.4±0.4			2.4±0.2	0.87
Duration of atrial fibrillation (months)			20.4±6.0			28.4±7.5	0.42
Heart rate (beat/min)			89.0±12.3			94.6±8.7	0.47
Diabetes mellitus	1	2.6		–			0.46
Hypertension	9	23.7		6	30.0		0.60
Systolic blood pressure (mmHg)			124.7±16.3			129.0±11.7	0.50
Diastolic blood pressure (mmHg)			76.8±7.3			81.0±9.4	0.34
Body mass index (kg/m^2)			25.2±1.5			24.7±1.4	0.24
Cardioversion energy (J)			250.5±76.4			296.0±64.6	0.15
Biochemical parameters							
Glucose (mg/dl)			92.3±21.8			90.5±13.4	0.42
Urea (mg/dl)			37.3±6.6			44.2±15.4	0.37
Creatinine (mg/dl)			0.9±0.1			1.0±0.2	0.52
Medical treatment							
Acetylsalicylic acid	38	100.0		20	100.0		1.00
Beta-blockers	19	50.0		13	65.0		0.27
Amiodarone	19	50.0		7	35.0		0.27
Ia or Ic antiarrhythmic drugs	3	7.9		3	15.0		0.39
Angiotensin-converting enzyme inhibitors	5	13.2		4	20.0		0.49
Angiotensin receptor blocker	4	10.5		3	15.0		0.61

Baseline characteristics of the patients are listed in Table 1. Demographic characteristics, biochemical parameters, cardioversion energy used, and medications were similar between the two groups. Heart rates were also similar before (89.0±12.3 *vs* 94.6±8.7 beat/min; p=0.47) and 30 minutes after cardioversion (74.8±7.8 *vs* 78.2±6.6 beat/min; p=0.25), but patients with recurrent AF had a higher heart rate six months after cardioversion (69.7±12.8 *vs* 86.6±14.6; p<0.001).

The frequency of coronary artery disease, which is a confounding factor for BNP levels, did not differ significantly between the two groups. There were six patients (15.8%) in the SR group, compared to four patients (20%) with recurrent AF (p=0.77). No cardiac events occurred following six months of cardioversion.

The mean baseline BNP level was significantly higher compared to that measured 30 minutes after cardioversion (255.6±159.6 pg/ml *vs* 70.5±57.0 pg/ml; p=0.00006). Patients who reverted to AF after six months had significantly higher baseline (p=0.035) and six- month (p=0.001) BNP levels than patients who maintained SR (Fig. 1).

The amount of decrease in baseline BNP levels after 30 minutes of cardioversion was associated with the type of the rhythm at six months. Patients who reverted to AF after six months had a significantly greater decrease in BNP levels after cardioversion than patients who remained in SR (-271.9±42.4 pg/ml *vs* -139.4±25.3 pg/ml; p=0.008). The change in BNP levels from baseline to that found 30 minutes after cardioversion was evaluated with ROC analysis to predict AF recurrence at six months. The area under the curve was measured as 86% (Fig. 2). Assuming the cutoff value as 200 pg/

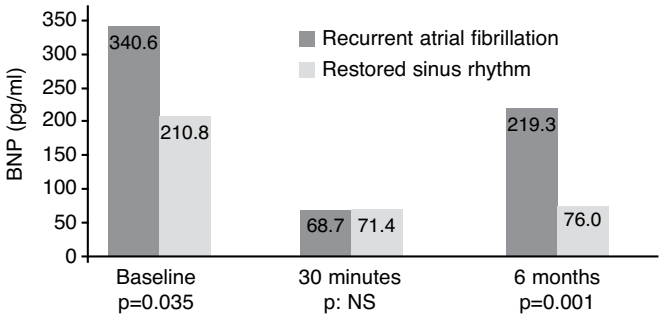

Figure 1. Comparison of BNP levels before and after cardioversion in patients with restored sinus rhythm and recurrent atrial fibrillation at six months. NS: Not significant.

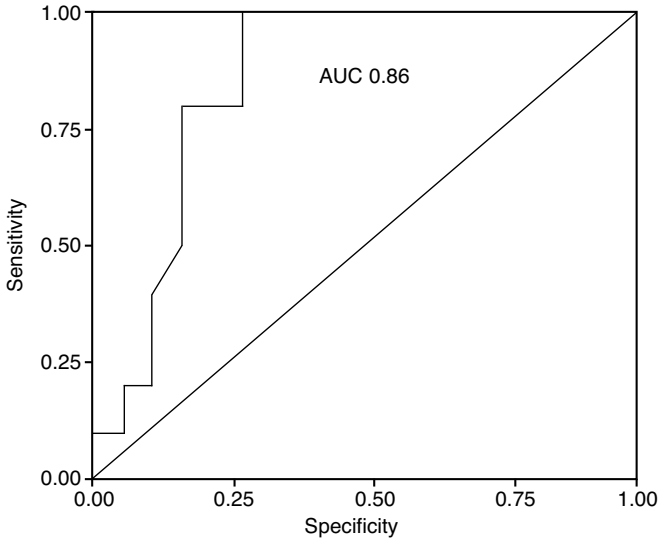

Figure 2. ROC curve analysis to predict the type of rhythm at six months. AUC: Area under curve.

ml for BNP change, we found that change in BNP level predicted AF recurrence with 80% sensitivity and 86% specificity at six months.

Subgroup analysis showed no correlation between baseline BNP level and duration of AF (for durations of <1 month, ≤12 months and >12 months: 221.2 pg/ml: 265.2 pg/ml and 264.4 pg/ml, respectively, p=0.86). However, LA diameter showed a significant negative correlation with the BNP level (for ≤40 mm, 41-45 mm, and ≥45 mm: 394.6 pg/ml, 206.5 pg/ml, and 198.5 pg/ml, respectively, p=0.02).

DISCUSSION

Our findings showed that elevated baseline plasma BNP levels and the amount of decrease in baseline BNP levels 30 minutes after cardioversion predicted AF recurrence at six months in patients with persistent AF and preserved left ventricular function. This may suggest that patients who show greater decrease in BNP levels after cardioversion are hemodynamically more unstable at baseline, and consequently, they are more likely to revert to AF. Our findings were consistent with previous studies which demonstrated that BNP levels predicted AF recurrence at two weeks[12] and at one year[13] after cardioversion in patients with preserved left ventricular function.

The mechanism of the immediate drop in plasma BNP levels after DC cardioversion may be related to conversion from AF to SR, reduction in heart rate, and to changes in cardiac condition. Ohta et al.[14] compared BNP levels after DC cardioversion in AF patients with or without underlying heart disease and found that the former had a greater decrease in BNP levels after cardioversion.

Although the elimination half-time of BNP is nearly 20 minutes in healthy population, it may decrease to 10-12 minutes in patients with volume overload, congestion, hemodynamic instability, high renin-angiotensin system activity, and increased neutral endopeptidase activity.[15,16] Hemodynamic instability of the patients may account for the immediate drop in plasma BNP levels; however, the effect of other factors such as DC shock and anesthetics on BNP levels cannot be excluded. Previous studies evaluated the natriuretic peptide response to cardioversion methods and found that neither mode of cardioversion (DC shock or pharmacological) influenced the natriuretic peptide response.[17,18]

The association between BNP and myocardial stretch and intra-atrial pressures is well established.[10,19] It is also known that patients with overt congestion, significant atrial dilatation, and high atrial pressures have a higher incidence of relapse after electrical cardioversion for AF.[20,21] On the other hand, patients with normal left ventricular function and no significant atrial dilation would be expected to respond better; however, other factors may play role in the development of AF recurrence in these patients. Left ventricular hypertrophy, diastolic dysfunction, atrial stunning, and rapid ventricular rate are some factors that may contribute to increased atrial pressure, resulting in AF.[22] In subgroup analysis, we did not find any association between BNP levels and duration of AF, but BNP levels showed a significant association with LA diameter. Patients with a smaller LA diameter had a higher BNP level. This suggests that BNP level is related with volume overload of the atrium and atrial stretch rather than electrical or structural remodeling.

In patients with diastolic dysfunction, increased BNP levels have been shown to be associated with higher left ventricular end-diastolic pressures.[23,24] Because BNP is a surrogate marker of myocardial stretch, elevated BNP levels may be expected if any of these abnormalities are present and, thus, predict the likelihood of AF recurrence. The present study raises the possibility that patients with elevated BNP levels and having a greater fall in plasma BNP levels after cardioversion are more likely to revert to AF. Further studies are needed to determine whether BNP level would still be predictive of AF recurrence when other factors are controlled.

In conclusion, despite preserved left ventricular function, patients with AF have increased BNP lev-

els. This study suggests that baseline BNP levels and the extent of decrease in plasma BNP levels after cardioversion may predict AF recurrence in patients with persistent AF and preserved left ventricular function. These findings may make BNP measurement a useful noninvasive tool in selecting which patients should undergo elective DC cardioversion for persistent AF.

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