The effect of carvedilol on big endothelin, atrial and brain natriuretic peptide levels in patients with congestive heart failure

Konjestif kalp yetersizliği olan hastalarda karvedilol tedavisinin büyük endotelin, atriyal ve beyin natriüretik peptid düzeyleri üzerine etkisi

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Objectives: We investigated the changes in plasma big endothelin (big ET), atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) levels during carvedilol therapy in patients with congestive heart failure (CHF).

Study design: The study included 20 patients (6 females, 14 males; mean age 57±11 years) with symptomatic CHF. All the patients had sinus rhythm and resting ejection fraction ≤40%. Carvedilol therapy was initiated with a minimum dose (2 x 3.125 mg), which was increased biweekly to reach the maximum tolerable dose. Blood samples were obtained and transthoracic echocardiography was performed before and after three months of a mean carvedilol dose of 42.5±13.6 mg. Big ET, ANP, and BNP levels were assessed and correlations were sought with left ventricular functions and the NYHA (New York Heart Association) functional class.

Results: After three months, significant decreases were detected in heart rate (p<0.001), systolic blood pressure (p<0.05), and left atrial diameter (p<0.001), accompanied by a significant increase in left ventricular ejection fraction (EF) (p<0.001), and a remarkable improvement in NYHA class (p<0.05). Significant decreases were observed in ANP, BNP, and big ET levels with carvedilol treatment (p<0.001). Big ET, ANP, and BNP levels showed significant correlations with left ventricular dimensions and systolic functions, and NYHA functional class. Among these, the best correlation was with LVEF (r= -0.498, p=0.001; r= -0.642, p<0.001; r= -0.656, p<0.001; respectively).

Conclusion: Carvedilol therapy is associated with decreased BNP, ANP, and big ET levels and with improvements in NYHA functional class and left ventricular systolic functions in patients with CHF.

Key words: Atrial natriuretic factor; biological markers; carbazoles/therapeutic use; endothelin-1; heart failure, congestive/drug therapy; natriuretic peptide, brain.

Amaç: Bu çalışmada, konjestif kalp yetersizliği olan hastalarda karvedilol tedavisinin plazma büyük endotelin (büyük ET), atriyal natriüretik peptid (ANP) ve beyin natriüretik peptid (BNP) düzeylerine etkisi değerlendirildi.

Çalışma planı: Çalışmaya semptomatik konjestif kalp yetersizliği olan 20 hasta (6 kadın, 14 erkek; ort. yaş 57±11) alındı. Tüm hastalar sinüs ritmindeydi ve dinlenme ejeksiyon fraksiyonu ≤%40 idi. Karvedilol tedavisine en düşük dozda (2 x 3.125 mg) başlandı; doz iki haftada bir artırılarak hastanın tolere edebileceği en yüksek doza çıkıldı. Üç ay süreli, ort. 42.5±13.6 mg dozda karvedilol tedavisinden önce ve sonra kan örnekleri alındı ve transtorasik ekokardiyografi yapıldı. Büyük ET, ANP ve BNP düzeyleri değerlendirildi ve bunların sol ventrikül fonksiyonları ve NYHA (New York Heart Association) fonksiyonel sınıfı ile ilişkileri araştırıldı.

Bulgular: Üç aylık karvedilol tedavisi sonunda, kalp hızı (p<0.001), sistolik kan basıncı (p<0.05) ve sol atriyum çapında (p<0.001) anlamlı düşüş; sol ventrikül ejeksiyon fraksiyonu (p<0.001) ve NYHA fonksiyonel sınıfında (p<0.05) anlamlı düzelme görüldü. Karvedilol tedavisi ANP, BNP ve büyük ET düzeylerinde anlamlı düşüşe yol açtı (p<0.001). Büyük ET, ANP ve BNP düzeyleri, sol ventrikül boyutları ve sistolik fonksiyonlarıyla ve NYHA fonksiyonel sınıfıyla anlamlı ilişki gösterdi. Bunlar içinde en iyi korelasyon sol ventrikül ejeksiyon fraksiyonu ile idi (sırasıyla, r= -0.498, p=0.001; r= -0.642, p<0.001; r= -0.656, p<0.001).

Sonuç: Konjestif kalp yetersizliği olan hastalarda karvedilol tedavisi, BNP, ANP ve büyük ET düzeylerini düşürmekte, NYHA fonksiyonel sınıfı ve sol ventrikül sistolik fonksiyonlarında düzelmeye yol açmaktadır.

Anahtar sözcükler: Atriyal natriüretik faktör; biyolojik belirteç; karbazol/terapötik kullanım; endotelin-1; kalp yetersizliği, konjestif/ilaç tedavisi; natriüretik peptid, beyin.

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Congestive heart failure (CHF) is a major cause of death worldwide.[1] Carvedilol improves symptoms, left ventricular ejection fraction (LVEF), and survival in patients with CHF.[2] Neurohumoral activation is increased in patients with CHF and correlates with the severity of the disease. Various neurohumoral markers such as brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP), and big endothelin (big ET) have been associated with prognosis in CHF.[3-5] However, the effect of beta-blockade on neurohumoral markers has not been extensively studied in CHF.

This study was designed to investigate the changes in plasma ANP, BNP, and big ET levels during carvedilol therapy in patients with CHF over three months of follow-up, and to determine whether ANP, BNP and big ET concentrations correlate with cardiac function.

PATIENTS AND METHODS

Patients. The study included 20 patients (6 females, 14 males; mean age 57±11 years) who had symptomatic CHF for more than a year. All the patients had sinus rhythm and resting ejection fraction ≤40%, and no contraindications for beta-blockers. Coronary angiography was performed in all the patients. The reason of heart failure was coronary artery disease in nine patients and dilated cardiomyopathy in 11 patients. Eight patients had myocardial infarction previously. All the patients had been receiving diuretics and angiotensin-converting enzyme (ACE) inhibitors for a long time. Patients with atrial fibrillation, primary obstructive or severe regurgitative valvular disease, uncontrolled ventricular arrhythmias, chronic obstructive pulmonary disease, active myocarditis, atrioventricular block, bradycardia (<60 bpm), or severe hypotension (systolic blood pressure <90 mmHg) were excluded. The study protocol was approved by the institutional ethics committee and all the subjects gave written informed consent for the study.

Echocardiography. A Vingmed System Five Doppler echocardiographic unit (GE Vingmed Ultrasound, Horten, Norway) with a 2.5-MHz flat phased-array probe was used. Echocardiography was performed with subjects in the left lateral decubitus position. Left atrial, left ventricular end-diastolic, and end-systolic diameters were measured in the parasternal long-axis view. Left ventricular ejection fraction was determined from the apical two- and four-chamber views with the modified Simpson's rule.

After the first blood samples were obtained and transthoracic echocardiography was performed, carvedilol therapy was initiated with a minimum dose (2 x 3.125 mg). The dose was increased biweekly to reach the maximum tolerable dose for each patient. After three months of administering the maximum tolerable dose, blood samples were drawn again and transthoracic echocardiography was performed.

Assessment of neurohumoral markers. Venous blood samples were collected in tubes containing EDTA and centrifuged at 1500 x g for 15 minutes. Plasma aliquots were stored at -80 °C until being tested. Levels of ANP and BNP were determined with the ELISA assay protocol and using commercial kits (ANP: Lot no EK-005-06; BNP: Lot no EK-011-03, Phoenix Pharmaceuticals, Germany). Big ET levels were determined using the RIA assay protocol and a commercial kit (Endothelin-1: Lot no RK- 023-12, Phoenix Pharmaceuticals).

Statistical analysis. The data were expressed as mean ± standard deviation or as percentages. Differences between parameters before and after carvedilol therapy were assessed by the Wilcoxon signed-rank test. Pearson's correlation analysis was used to demonstrate correlations between left ventricular functions and ANP, BNP, and big ET levels. Spearman's correlation test was used for correlations between the NYHA (New York Heart Association) class and ANP, BNP,

Table 1. Echocardiographic and hemodynamic parameters before and after carvedilol therapy

	Before	After	*p*
Left ventricular end-diastolic diameter (cm)	6.47±0.62	6.32±0.65	<0.001
Left ventricular end-systolic diameter (cm)	5.46±0.60	5.11±0.73	<0.001
Left ventricular ejection fraction (%)	32±5	38±7	<0.001
Left atrium (cm)	4.8±0.5	4.4±0.4	<0.001
Systolic blood pressure (mmHg)	128±17	116±12	<0.05
Diastolic blood pressure (mmHg)	81±8	75 ±7	NS
Heart rate (beat/min)	84±1	71±9	<0.001

NS: Not significant.

Table 2. NYHA functional class of patients before and after carvedilol therapy

NYHA class	Before	After	*p*
Class I	0	9	<0.05
Class II	4	11	<0.05
Class III	15	0	<0.05
Class IV	1	0	<0.05

Table 3. Atrial and brain natriuretic peptide and big endothelin levels before and after carvedilol therapy

	Before	After	*p*
Atrial natriuretic peptide (ng/ml)	2.8±1.6	1.1±0.6	<0.001
Brain natriuretic peptide (ng/ml)	41±14	17±7	<0.001
Big endothelin (pg/tube)	232±122	55±34	<0.001

and big ET. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

The mean total daily carvedilol dose was 42.5±13.6 mg. At the end of three months of maximum tolerable dose of carvedilol, significant decreases were detected in heart rate (84±1 beat/min *vs* 71±9 beat/min; p<0.001), systolic blood pressure (128±17 mmHg *vs* 116±12 mmHg; p<0.05), and left atrial diameter (4.8±0.5 cm *vs* 4.4±0.4 cm; p<0.001). Decreases in left ventricular systolic and diastolic diameters were significant (p<0.001). Left ventricular ejection fraction showed a significant increase after carvedilol administration (32±5% *vs* 38±7%; p<0.001) (Table 1). There was also a remarkable improvement in NYHA functional capacity of all the patients (p<0.05; Table 2).

Compared to baseline values, significant decreases were observed in ANP, BNP, and big ET levels with carvedilol treatment (p<0.001; Table 3).

The three neurohumoral parameters (ANP, BNP, and big ET) showed strong correlations with left ventricular dimensions and systolic functions. Among these, the best significant correlation was with LVEF (r= -0.642, p<0.001; r= -0.656, p<0.001; r= -0.498, p=0.001, respectively). The dimensions of the left ventricle and left atrium showed positive correlations with the neurohumoral parameters. In addition, improvement in NYHA functional capacity was correlated with decreases in these markers (Table 4).

DISCUSSION

This study demonstrated that carvedilol had a favorable effect in lowering big ET, ANP, and BNP levels in patients with heart failure. Following a three-month therapy with carvedilol, marked improvements were noted in left ventricular functions and functional capacity of the patients. The three neurohumoral parameters were negatively correlated with improvement in LVEF , and positively correlated with cardiac diameters and functional capacity. The strongest correlations were with BNP levels.

A number of studies have demonstrated the effect of carvedilol on the neurohumoral system in patients with heart failure. Fujimura et al.[6] evaluated BNP, ANP, and norepinephrine (NE) levels before and three to five months after initiation of carvedilol in 42 patients with idiopathic dilated cardiomyopathy and demonstrated declined BNP levels in patients who had improved LVEF. They also observed a decline in ANP levels in responders, but no change in non-responders. Norepinephrine levels, however, remained unchanged. Kawai et al.[7] measured BNP levels before and two and six months after initiation of carvedilol in 21 patients with dilated cardiomyopathy. They found that BNP levels declined and this decline was in inverse correlation with LVEF after six months of therapy. Our findings were consistent with carvedilol-induced effects on neurohumoral markers and their correlation with LVEF. In addition, we also showed that these neurohumoral markers were correlated with clinical and other echocardiographic findings.

Table 4. The correlations of ANP, BNP, and big ET levels with left ventricular functions and functional capacity

	ANP		BNP		Big ET	
	r	*p*	r	*p*	r	*p*
Left ventricular ejection fraction	-0.642	<0.001	-0.656	<0.001	-0.498	0.001
Left ventricular end-diastolic diameter	0.278	NS	0.319	0.04	0.324	0.04
Left ventricular end-systolic diameter	0.482	0.002	0.529	<0.001	0.450	0.004
Left atrium	0.367	0.02	0.521	0.001	0.465	0.003
NYHA class	0.508	0.001	0.693	<0.001	0.627	<0.001

NS: Not significant; ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide; Big ET: Big endothelin.

Fung et al.[8] compared the effects of carvedilol and metoprolol on ANP and amino-terminal BNP (N-BNP) levels and found that both had similar efficacy in causing significant decreases in ANP and N-BNP, suggesting that a group effect of beta-blockers might account for these neurohumoral decreases.

Morooka et al.[9] evaluated the effect of carvedilol in patients with dilated cardiomyopathy and found that patients who did not benefit from carvedilol therapy continued to have high ANP and BNP levels. All these data suggest that ANP and BNP levels can be used as a marker for therapeutic response.

Big endothelin, which is a precursor of endothelin-1, reflects endothelin overproduction more accurately than circulating endothelin-1 itself,[10] and shows better correlation with functional NYHA class and long-term prognosis of patients with chronic heart failure. Previous studies showed that big ET level was a better prognostic marker than atrial and brain natriuretic peptides or their pro-peptides.[11,12] Spinarova et al.[10] demonstrated that increased plasma levels of big ET was a highly sensitive tool for the diagnosis of chronic heart failure, and that normal values might be used for exclusion of this syndrome with very high probability.

Ohlstein et al.[13] showed that, unlike other beta-blockers, carvedilol inhibited ET-1 biosynthesis in cultured endothelial cells, and this effect seemed to be related to its potent antioxidant properties. The authors suggested that this effect may contribute to clinical improvement in CHF patients. Massart et al.[14] showed that carvedilol and lacidipine had cardiac antihypertrophic properties that were partially independent of their antihypertensive effect and appeared to be related to their capacity to decrease myocardial prepro-endothelin-1 overexpression induced by pressure overload. However, the effect of carvedilol on big ET levels has been assessed in only one study. Frantz et al.[15] found that carvedilol therapy lowered amino-terminal ANP and BNP levels in patients with heart failure, but did not affect big ET levels, which did not change within six months of carvedilol therapy, and showed an insignificant decrease at the end of a year, without exhibiting any correlation with LVEF. In contrast to the finding of Frantz et al.,[15] carvedilol treatment significantly decreased big ET levels in our patients (from 232±122 pg/tube to 55±34 pg/tube; $p<0.001$). Moreover, there was a significant negative correlation between big ET and clinical and echocardiographic parameters. However, among the three markers, BNP levels showed the strongest correlation with clinical and echocardiographic findings. As there is no other evidence for the effect of carvedilol on big ET levels, further studies are needed to clarify this relationship.

Limitations. One limitation to this study is the small size of the patient group. Another significant limitation is the short duration of the study, which might have limited the statistical power of prognostic findings. Due to the absence of control groups, all therapeutic results cannot solely be attributed to the effect of carvedilol because the patients were already receiving conventional therapies such as ACE inhibitors and diuretics.

In conclusion, carvedilol therapy is associated with declines in BNP, ANP, and big ET levels and with improvements in NYHA functional class and left ventricular systolic functions in patients with CHF. In this patient group, plasma BNP, ANP, and big ET levels correlate well with echocardiographic findings, suggesting that these neurohumoral markers, especially BNP may be instrumental in the diagnosis, management, and prognosis of heart failure.

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