#### Original Article / Klinik Çalışma - Araştırma

# Effect of Carvedilol on P-Wave Duration and P-Wave Dispersion in Patients with Systolic Heart Failure

Sistolik Kalp Yetmezlikli Hastalarda Karvedilolün P Dalga Süresi ve Dispersiyonu Üzerine Etkileri

Ersan TATLI, Meryem AKTOZ, Ahmet BARUTÇU, Turhan KURUM, Armağan ALTUN

Department of Cardiology, Medical Faculty of Trakya University, Edirne

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**Objectives:** Carvedilol therapy reduces the severity of the ventricular dysfunction, increases left ventricular ejection fraction and reduces the mortality and morbidity. However, the effect of carvedilol on P-wave dispersion and P-wave duration in patients with systolic heart failure is unknown. In the present study, we aimed to evaluate the effect of carvedilol therapy on P-wave duration and P-wave dispersion in patients with heart failure.

Patients and Methods: Fifty-six patients with heart failure and a left ventricular ejection fraction less than 40% were prospectively included in the study. Carvedilol was administered in addition to standard therapy for heart failure. Clinical examination and radionuclide study and baseline maximum and minimum P-wave duration and P-wave dispersion measurements were performed for each patient at the beginning and at the end of the fourth month of carvedilol therapy.

**Results:** Maximum P-wave duration and P-wave dispersion significantly decreased, left ventricular ejection fraction and NYHA functional class improved by carvedilol therapy (Maximum P-wave duration; from 126±9 ms to 120±7ms; p=0.001, P-wave dispersion; from 51±7 ms to 46±5 ms; p=0.001).

**Conclusion:** Carvedilol therapy directly or indirectly reduces maximum P-wave duration and P-wave dispersion. This may lead to a reduction in the occurrence of atrial fibrillation in patients with heart failure.

Key words: Carvedilol; heart failure; P-wave duration; P-wave dispersion.

Amaç: Karvedilol tedavisi, sol ventrikül ejeksiyon fraksiyonunu artırır, ventriküler disfonksiyonun şiddetini, morbidite ve mortaliteyi azaltır. Ancak sistolik kalp yetmezlikli hastalarda karvedilolün P dalga dispersiyonu ve süresi üzerine etkileri bilinmemektedir. Bu çalışmada kalp yetmezliği olan hastalarda karvedilolün P dalga süresi ve dispersiyonu üzerine olan etkilerini araştırdık.

Hastalar ve Yöntemler: Sol ventrikül ejeksiyon fraksiyonu %40'ın altında olan kalp yetmezlikli 56 hasta ileriye dönük olarak çalışmaya alındı. Karvedilol kalp yetmezliğinin standart tedavisine ek olarak verildi. Başlangıçta ve karvedilol tedavisinin dördüncü ayında fizik muayene, radyonüklid çalışma ve başlangıç maksimum ve minimum P-dalga süresi ve P-dalga dispersiyonu ölçümleri yapıldı.

**Bulgular:** Karvedilol tedavisi ile maksimum P dalga süresi ve P-dalga dispersiyonu belirgin olarak azaldı. Sol ventrikül ejeksiyon fraksiyonu ve NYHA fonksiyonel sınıfı karvedilol tedavisi sonrası düzeldi. (Maksimum P-dalga süresi; 126±9 ms'den 120±7ms'ye; p=0.001, P- dalga dispersiyonu; 51±7 ms'den 46±5 ms'ye geriledi; p=0.001).

**Sonuç:** Karvedilol tedavisi maksimum P-dalga süresi ve P-dalga dispersiyonunu direkt (doğrudan) ve indirekt (dolaylı) olarak azaltır. Bu kalp yetmezliği olan hastalarda atriyal fibrilasyon görülme sıklığını azaltabilir.

Anahtar sözcükler: Karvedilol; kalp yetmezliği; P-dalga süresi; P-dalga dispersiyonu.

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Correspondence (İletişim adresi): Dr. Ersan Tatlı. Trakya Üniversitesi Tıp Fakültesi Kardiyoloji Anabilim Dalı, 22030 Edirne. Tel: 0284 - 235 76 41 Fax (Faks): 0284 - 235 50 35 e-mail (e-posta): ersantatli@yahoo.com

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P-wave dispersion is a new and simple electrocardiographic marker that has been reported to be associated with inhomogeneous and discontinuous propagation of sinus impulses.<sup>[1,2]</sup> It has been defined as the difference between shortest and longest P-wave durations.<sup>[1]</sup> Prolonged P-wave duration and increased P-wave dispersion have been reported to carry an increased risk for atrial fibrillation.<sup>[1,3]</sup> Dilated cardiomyopathy imposes the greatest risk for the development of atrial fibrillation.[4] Recently, it has been reported that patients with heart failure have prolonged P-wave duration and increased P-wave dispersion compared to healthy population.<sup>[5]</sup> Carvedilol is a non-selective beta-blocker  $(\beta 1/\beta 2 \text{ rate of } 7.3)$  with  $\alpha$ -blockage, vasodilatation, and antioxidant effects.<sup>[6]</sup> Recent literature indicated that carvedilol use in patients with heart failure reduced the severity of the ventricular dysfunction, increased ejection fraction and consequently reduced the mortality and morbidity rates.<sup>[7]</sup> However, to the best of our knowledge, the effect of carvedilol on P-wave dispersion and P-wave duration in patients with systolic heart failure has not been investigated so far. We aimed to evaluate the effect of carvedilol therapy on P-wave dispersion and P-wave duration in patients with systolic heart failure.

## PATIENTS AND METHODS

Patients who admitted to the department of cardiology of our institution with a diagnosis of heart failure were screened and 56 of them were prospectively included in the study. The inclusion criteria were the presence of NYHA class II-IV heart failure, left ventricular ejection fraction less than 40%, and the current treatment for heart failure with standard therapy including: diuretics, angiotensin-converting enzyme inhibitors and digoxin at a stable dosage for at least six weeks. Criteria for exclusion from the study were: chronic obstructive pulmonary disease, significant valvular heart disease, thyrotoxicosis, hypothyroidism, chronic kidney and liver diseases, malignancy, anemia (Hb<9gr/dl), systolic blood pressure lower than 90 mmHg, heart rate lower than 50/min, and first- or second-degree heart block. Patients receiving anti-

arrhythmic drugs or beta-blockers, patients with a permanent pacemaker, indiscernible P-waves in greater than 4 leads on a baseline 12-lead ECG and psychiatric problems were also excluded from the study. The initial dose of carvedilol was 3.125 mg bid, which was doubled at 2-week intervals and tolerated up to 25 mg bid. Patients were continued on their conventional heart failure treatment in addition to carvedilol. Standard ECG recordings, NYHA functional class and ejection fraction with radionuclide ventriculography of all patients were evaluated at baseline and the end of the fourth months of carvedilol therapy. The functional class was considered to have improved if the patient's functional status increased  $\geq 1$  grade of the NYHA classification.

### **Radionuclide study**

We used a multiple-gated equilibrium cardiac-blood-pool scintigraphic technique to measure left ventricular ejection fraction (Siemens, Erlangen). Imaging was performed in the left anterior oblique projection, which provided the best septal separation of the ventricles with a 0° to 10° caudal tilt. Calculation of left ventricular performance was made as described elsewhere with the automatic edge-detection algorithm for the determination of left ventricular borders.[8] All studies were interpreted by two observers (ET, MA) who were blinded to the treatment assigned. The left ventricular ejection fraction rates were calculated. Radionuclide study was performed at baseline and then repeated at the fourth months.

# Measurement of P-wave duration and dispersion

Basal simultaneous 12-lead electrocardiogram was recorded for each patient at a rate of 50 mm/s (Hewlett Packard page writer, Model M 1772A, USA). The measurement of the P-wave duration were performed manually by two of the investigators without knowledge of the clinical status of the patients. To improve accuracy, measurements were performed with calipers and magnifying lens. The onset of the P-wave was defined as the junction between the isoelectric line and the begin of the P-wave deflection and the offset of the P-wave as the junction between

Tuble 1. Tutlents characteristics					
Age (years)	60.5±9.7				
Sex (male/female)	30 /14				
Ischemic/idiopathic (n, %)	18/26				
Hypertension (n, %)	24 (54%)				
Diabetes mellitus (n, %)	16 (36%)				
Tobacco use (n, %)	26 (59%)				
Hyperlipidemia (n, %)	12 (27%)				

Table 1. Patients' characteristics

the end of the P-wave deflection and the isoelectric line.<sup>[1,9,10]</sup> Maximum and minimum P-wave durations were measured from the 12-lead surface electrocardiogram. P-wave dispersion was calculated as the difference between maximum P-wave duration and minimum P-wave duration (P-wave dispersion = maximum P-wave duration – minimum P-wave duration).

### Statistical analysis

Data were analyzed using Minitab (Minitab Inc.; State College, PA, USA). Continuous data were shown as mean  $\pm$  SD and categorical data were shown as percentage. The relation of ejection fraction with P-wave values at baseline and at the fourth month was investigated with Pearson's correlation test. The same test was used to analyze the relationship between baseline maximum P-wave duration and P-wave dispersion, between fourth month measurements and between change in maximum P-wave duration and change in P-wave dispersion. Paired t-test for continuous variables was used to compare baseline and fourth month measurements in patients. All hypothesis testing was two-tailed. A P value of <.05 was considered significant.

### RESULTS

All patients were taking angiotensin-converting enzyme inhibitor, oral diuretics and digoxin at the beginning. During follow-up period, six patients died, six patients' rhythms were degenerated to permanent atrial fibrillation. These 12 patients were not included to statistical analysis about P-wave duration and P-wave dispersion. The remaining 44 patients (30 males, 14 females; mean age 60.5±9.7 years) completed the follow-up period in sinus rhythm and continued the carvedilol therapy. Of them, 18 were ischemic (proved by coronary angiography), and 26 were nonischemic. The characteristics of the patients are shown in Table 1. The mean daily dose of carvedilol was 38±11 mg (range 12.5-50 mg). Statistically significant improvement was detected on systolic blood pressure, resting heart rate, ejection fraction and NYHA functional class at the end of the fourth month after initiation of carvedilol therapy (p=0.002, 0.001, 0.003, 0.001, respectively). Maximum P-wave duration and P-wave dispersion were significantly decreased by carvedilol therapy (maximum P-wave duration; from 126±9 ms to 120±7 ms; p=0.001, P-wave dispersion; from  $51\pm7$  ms to  $46\pm5$  ms; p=0.001). However, there was no significant difference between the values of minimum P-wave duration measured before and at the end of the fourth month of carvedilol therapy (from 74±4 ms to 73±4 ms; p=0.600). In addition, ejection fraction was negatively correlated with maximum P-wave duration and P-wave dispersion at the baseline and at the end of the fourth month of carvedilol therapy. Electrocardiographic and clinical variables were shown in Table 2.

Table 2.	Results at	baseline and	l at the	end of	the fourth	n month c	of carvedilol	therapy
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	Baseline (n=44)	Fourth month (n=44)	р
Systolic BP (mmHg)	123±17	112±14	0.002
Diastolic BP (mmHg)	74±9	71±11	0.270
Heart rate (bpm)	82±9	74±7	0.001
LVEF (%)	$21.4 \pm 8.8$	27.8±10.8	0.003
NYHA class (I/II/III/IV, n)	0,20,24,0	16,22,6,0	0.001
Max. P-wave duration (ms)	126±9	120±7	0.001
Min. P-wave duration (ms)	74±4	73±4	0.600
P-wave dispersion (ms)	51±7	46±5	0.001

LVEF: Left ventricular ejection fraction; Min: minimum; Max: maximum; NYHA: New York Heart Association.

### DISCUSSION

To the best of our knowledge, this is the first report to evaluate the effect of carvedilol therapy on-P wave duration and P-wave dispersion in patients with heart failure. The major finding of our study is that carvedilol therapy leads to a significant decrease in maximum P-wave duration and P-wave dispersion in patients with systolic heart failure. P-wave dispersion first described by Dilaveris et al.<sup>[1]</sup> in 1998 as the difference between maximum and minimum P-wave duration measured on the standard 12-lead surface electrocardiogram. It has been reported to be associated with inhomogeneous and discontinuous propagation of sinus impulses.<sup>[1,2]</sup> Prolonged P-wave duration and increased P-wave dispersion have been reported to carry an increased risk for atrial fibrillation.<sup>[1,3]</sup> Moreover, the correlation between inter-atrial and intra-atrial conduction abnormalities and the induction of paroxysmal atrial fibrillation has been well documented.<sup>[3]</sup> Senen et al.<sup>[5]</sup> showed that maximum P-wave duration and P-wave dispersion were significantly higher in patients with systolic heart failure than normal population. Atrial fibrillation affects approximately 2 million people in the United States and is a common comorbidity among patients with heart failure.<sup>[11]</sup> Furthermore, 13% to 27% of atrial fibrillation patients have chronic heart failure and left ventricular dysfunction.<sup>[12,13]</sup> The mortality and morbidity of atrial fibrillation is mainly related to thromboembolic consequences.<sup>[14,15]</sup> The mortality rate is approximately doubled in patients with atrial fibrillation compared with patients in normal sinus rhythm and is linked to the severity of heart disease.<sup>[16]</sup> Atrial fibrillation is also associated with loss of atrial contractile functioning and may result in hemodynamic deterioration. This hemodynamic deterioration may result in exacerbation of chronic heart failure symptoms and impaired exercise tolerance.<sup>[14,15]</sup>

We have shown a statistically significant increase in ejection fraction and NYHA functional class by adding carvedilol to the treatment. Carvedilol is known to reduce morbidity and

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mortality and to improve hemodynamic status in patients with heart failure across a broad spectrum of clinical severity. Recent data indicate that these benefits extend to patients with chronic heart failure complicated by atrial fibrillation.<sup>[17]</sup> Carvedilol provides incremental benefits in the rate control when used in combination with digoxin, the standard therapy for heart failure patients with persistent atrial fibrillation.<sup>[18]</sup> Carvedilol was also shown to reduce the incidence of recurrent atrial fibrillation recurrence after cardioversion.[19,20] Moreover, in a recent prospective study of patients undergoing coronary artery bypass graft or cardiac valve surgery, carvedilol demonstrated a marked reduction in the incidence of postoperative atrial fibrillation, when compared to metoprolol or atenolol.<sup>[21]</sup> Carvedilol's antiarrhythmic potential was also shown in the Carvedilol Post-Infarct Survival Control in the Left Ventricular Dysfunction (CAPRICORN) study<sup>[22]</sup> and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.<sup>[23]</sup> A 59% risk reduction in the development of atrial flutter/fibrillation identified as an adverse event was seen with carvedilol versus placebo in the CAPRICORN trial. Likewise in COPERNICUS, atrial fibrillation was more commonly reported as an adverse event in the placebo group versus the carvedilol group.

In our study, P-wave dispersion and maximum P-wave duration were significantly decreased with adding carvedilol to the heart failure patients' medication. Camsari et al.[24] showed that metoprolol treatment was associated with a decreased maximum P-wave duration and P-wave dispersion in patients with congestive heart failure. The results of their study were similar to the results of our study. Decreasing in maximum P-wave duration and P-wave dispersion can be thought to be the result of carvedilol's positive hemodynamic effects. Because, the ejection fraction was significantly correlated with maximum P-wave duration and P-wave dispersion at the baseline and at the fourth month. Cice et al.[25] showed that the antiarrhythmic efficacy of carvedilol in patients with heart failure was paralleled by an improvement

in ejection fraction. Thus, it can be concluded that P-wave changes depend on improvement in ejection fraction. Decreasing in maximum P-wave duration and P-wave dispersion may also be related to the electrophysiologic effects of carvedilol. Because Workman et al.<sup>[26]</sup> showed that the action potential duration and effective refractory period were significantly longer in myocytes in the right atrium of patients treated chronically with beta blockers than in myocytes from non-beta blocked patients. They found mechanistic evidence that supported the antiarrhythmic actions of beta blockade. Moreover, decrease in maximum P-wave duration and P-wave dispersion may be related to some of the additional properties of carvedilol besides its beta blocking effects.

In conclusion, carvedilol therapy directly or indirectly reduces maximum P-wave duration and P-wave dispersion. This may lead to a reduction in the occurrence of atrial fibrillation in patients with heart failure.

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