Carvedilol therapy is associated with improvement in QT dispersion in patients with congestive heart failure

Konjestif kalp yetersizliği olan hastalarda karvedilol tedavisi QT dispersiyonunda düzelme sağlamaktadır

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Objectives: We investigated the effect of carvedilol on corrected QT dispersion (QTd) in patients with congestive heart failure (CHF).

Study design: The study included 20 patients (6 females, 14 males; mean age 57±11 years) who had symptomatic CHF with sinus rhythm, resting ejection fraction ≤%40, and no contraindications for beta-blockers. Coronary angiography showed 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 inhibitors for one year. Carvedilol was initiated with a minimum dose of 3.125 mg twice daily, to be increased biweekly to reach the maximum tolerable dose (mean daily dose 42.5±13.6 mg). All the patients were assessed by electrocardiography and transthoracic echocardiography before and three months after treatment.

Results: Significant decreases were observed in the following clinical and echocardiographic parameters: heart rate (p=0.001), systolic blood pressure (p=0.002), left atrial diameter (p<0.001), and left ventricular end-systolic (p<0.001) and end-diastolic (p=0.04) diameters. Left ventricular ejection fraction showed a significant increase (p<0.001). There was also a remarkable improvement in NYHA functional capacity in all the patients (p<0.05). Both corrected QTd (p=0.001) and QTd (p<0.001) significantly decreased. Maximum corrected QT and maximum QT did not change significantly (p>0.05), while minimum QT and minimum corrected QT significantly increased (p<0.001). No significant correlation was found between the carvedilol dose and the percent decrease in QTd (p>0.05).

Conclusion: Carvedilol is associated with significant decreases in corrected QTd in patients with CHF.

Key words: Adrenergic beta-antagonists/therapeutic use; cardiomyopathies; electrocardiography; heart failure, congestive/drug therapy.

Amaç: Bu çalışmada, konjestif kalp yetersizliği (KHY) olan hastalarda karvedilol tedavisinin düzeltilmiş QT dispersiyonu (QTd) üzerine etkisi araştırıldı.

Çalışma planı: Çalışmaya semptomatik (KHY) olan 20 hasta alındı (6 kadın, 14 erkek; ort. yaş 57±11). Tüm hastalar sinus ritminde idi, dinlenme ejeksiyon fraksiyonu ≤%40 idi ve beta-bloker için herhangi bir kontrendikasyon yoktu. Koroner anjiyografide dokuz olguda koroner arter hastalığı, 11 olguda dilate kardiyomiyopati saptandı. Sekiz hasta daha önce miyokard infarktüsü geçirmişti. Tüm hastalar en az bir yıl süreyle diüretik ve anjiyotensin dönüştürücü enzim inhibitörü kullanmaktaydı. Karvedilol tedavisine minimum dozda (3.125 mg x 2) başlandı; doz 15 günde bir artırılarak, hastanın tolere edeceği maksimum doza çıkıldı (günlük ort. 42.5±13.6 mg). Tüm hastalar tedaviden önce ve üç ay sonra elektrokardiyografi ve transtorasik ekokardiyografi ile değerlendirildi.

Bulgular: Klinik ve ekokardiyografik parametrelerden anlamlı düşüş gözlenenler şunlardı: kalp hızı (p=0.001), sistolik kan basıncı (p=0.002), sol atriyum çapı (p<0.001), sol ventrikül sistol sonu (p<0.001) ve diyastol sonu (p=0.04) çapları. Sol ventrikül ejeksiyon fraksiyonu anlamlı artış gösterdi (p<0.001). Tüm hastaların NYHA fonksiyonel kapasitesinde anlamlı iyileşme görüldü (p<0.05). Hem düzeltilmiş QTd (p=0.001), hem de QTd'deki (p<0.001) düşme anlamlı idi. Maksimum düzeltilmiş QT ve maksimum QT'de anlamlı değişiklik olmadı (p>0.05); minimum QT ve minimum düzeltilmiş QT ise anlamlı artış gösterdi (p<0.001). Karvedilol dozu ile QTd'deki yüzdelik düşüş arasında anlamlı ilişki görülmedi (p>0.05).

Sonuç: Karvedilol, KHY'li hastalarda düzeltilmiş QTd'yi anlamlı derecede düşürmektedir.

Anahtar sözcükler: Adrenerjik beta-antagonisti/törapötik kullanım; kardiyomiyopati; elektrokardiyografi; kalp yetersizliği, konjestif/ilaç tedavisi.

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Increased QT dispersion (QTd) on the surface electrocardiogram (ECG) in patients with congestive heart failure (CHF) is a noninvasive marker of susceptibility to malignant ventricular arrhythmias.[1] It is generally attributed to heterogeneity of ventricular repolarization and provides indirect information on arrhythmogenicity.[2,3] Carvedilol, a new generation beta-adrenergic antagonist with alpha-adrenergic receptor blocking effect, has been shown to reduce mortality by 65% in CHF patients compared to those receiving a placebo.[4] Plausible results obtained with carvedilol are associated with B1 and B2 receptor antagonism, blockage of alpha-1 adrenergic receptors, anti-ischemic effect, inhibition of apoptosis, antioxidative and electrophysiological characteristics.[5] There are very limited data relating to the effect of carvedilol on QTd. In this study, we investigated the effect of carvedilol therapy at the end of the third month on corrected QTd in patients with CHF.

PATIENTS AND METHODS

Study population. The study included 20 patients (6 females, 14 males; mean age 57±11 years) who had symptomatic CHF with sinus rhythm, resting ejection fraction ≤%40, and no contraindications for beta-blockers. All the patients had symptoms of CHF for more than one year. In order to determine the etiology of heart failure, coronary angiography was performed in all the patients, which revealed 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 one year. Patients with atrial fibrillation, primary obstructive or severe regurgitant valvular disease, uncontrolled ventricular arrhythmias, chronic obstructive pulmonary disease, active myocarditis, sick sinus syndrome, atrioventricular block, bradycardia (<60 bpm), and hypotension (systolic blood pressure <90 mmHg) were excluded from the study.

For echocardiographic examination, a Vingmed System 5 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 ventricular end-diastolic and left ventricular end-systolic diameters were measured in the parasternal long-axis view. Left ventricular ejection fraction was calculated by the Teichholz method.[6]

Carvedilol was initiated with a minimum dose of 3.125 mg twice daily, to be increased biweekly to reach the maximum tolerable dose for each patient. All the patients had standard ECG recordings obtained at the same paper speed and gain setting of 50 mm/ms and 10 mm/mV, respectively, before the treatment and at the end of the third month. At the end of three-month treatment, a second transthoracic echocardiography was performed.

All the ECGs were evaluated manually by a single observer, blinded to the clinical status of the patient. QT intervals were measured in each lead of the 12-lead surface ECG for two consecutive cycles. The QT interval was measured from the onset of the QRS to the end of T-wave.[7] In case the T-wave could not be identified, the lead was not included. The values were then expressed as both uncorrected and rate-corrected QT intervals and QTd (QTcd) using Bazett's formula (QTc= QT/square root of the RR interval). QT dispersion was defined as the difference between the maximal and minimal QT intervals occurring in any of the 12 ECG leads. The measurements were performed manually. QT intervals were measured in all leads if technically possible. Ethics committee of our institute approved The study protocol was approved by the ethics committee of our institute and all patients gave written informed consent for the study.

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using paired t-test. A p value of less than 0.05 was considered significant.

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	0.04
Left ventricular end-systolic diameter (cm)	5.46±0.60	5.11±0.73	<0.001
Left ventricular ejection fraction (%)	33±5	39±8	<0.001
Left atrium diameter (cm)	4.8±0.5	4.41±0.4	<0.001
Systolic blood pressure (mmHg)	128±17	116±12	0.002
Diastolic blood pressure (mmHg)	81±8	75±7	NS

NS: Not significant.

Table 2. NYHA functional class before and after carvedilol therapy

NYHA class	Before No. of patients	After No. of patients
I	0	9*
II	4	11*
III	15	0*
IV	1	0*

NYHA: New York Heart Association; *p<0.05.

Table 3. The QT intervals and QT dispersion values at baseline and after three months of carvedilol therapy

	Before	After	*p*
Maximum QT (msn)	410±41	423±34	NS
Maximum corrected QT (msn)	439±74	462±113	NS
Minimum QT (msn)	364±37	402±35	<0.001
Minimum corrected QT (msn)	391±68	464±62	<0.001
QT dispersion (msn)	45±21	21±14	<0.001
Corrected QT dispersion (msn)	49±23	25±17	0.001
Heart rate (beat/min)	85±16	72±12	0.001

NS: Not significant.

RESULTS

At the end of three months, the following improvements were observed with carvedilol therapy: heart rate decreased from 85±16 beat/min to 72±12 beat/min (p=0.001), systolic blood pressure decreased from 128±17 mmHg to 116±12 mmHg (p=0.002), and left atrial diameter decreased from 4.8±0.5 cm to 4.41±0.4 cm (p<0.001). Left ventricular end-systolic (p<0.001) and end-diastolic (p=0.04) diameters showed significant decreases, and left ventricular ejection fraction showed a significant increase (p<0.001) (Table 1). There was also a remarkable improvement in NYHA (New York Heart Association) functional capacity in all the patients (p<0.05) (Table 2).

Both QTcd and QTd significantly decreased with carvedilol treatment (p=0.001 and p<0.001, respectively; Table 3). Maximum QTc and maximum QT values were similar (p>0.05), while minimum QT and minimum QTc significantly increased (p<0.001).

The mean daily dose of carvedilol was 42.5±13.6 mg. No significant correlation was found between the carvedilol dose and the percent decrease in QTd (p>0.05).

When the patients were analyzed according to the etiology of CHF, namely, ischemic *vs* nonischemic dilated cardiomyopathy, all QT parameters evaluated showed the same trend.

DISCUSSION

Previous studies have demonstrated significantly increased QTd values in patients with CHF.[8] QT dispersion may represent dispersion of ventricular repolarization, and therefore, be a potential measure of substrates for re-entry tachycardia. Evidence from several studies supports the role of increased repolarization heterogeneity in the genesis of re-entry and malignant ventricular arrhythmias.[9] Previous studies pointed out the importance of QT dispersion in the prediction of sudden death in patients with CHF, and ventricular arrhythmias in patients with hypertrophic cardiomyopathy.[10,11]

Although the efficacy of carvedilol therapy in patients with heart failure have been shown in a number of studies,[4,12] data are limited about the effect of carvedilol on QT dispersion. Yildirir et al.[13] investigated the effect of carvedilol therapy on QTd in 19 patients with CHF. In addition to conventional therapy for CHF, the patients received carvedilol at a dose of up to 25 mg twice daily as tolerated and QTd and QTcd values were evaluated at baseline and after two and 16 months of the study. Carvedilol treatment resulted in significant reductions in QTd and QTcd values at the end of 16 months. They noted no decrease in QTd values at the end of the second month. However, there was a significant increase in minimum QTc, whereas maximum QTc remained unchanged. They attributed significant decreases in QTd at the end of 16 months to low-dose carvedilol. Their study was significant for demonstrating the effect of long-term carvedilol use on QTd.

Jepsen et al.[14] obtained similar results about the effect of carvedilol on QTd in patients with heart failure. They evaluated QTd and QTcd at baseline and at the end of four weeks of treatment. While no changes were observed in maximum QT and maximum QTc, minimum QT and minimum QTc increased significantly.

In our study, QTc significantly improved, and maximum QT and maximum QTc did not change. On the other hand, minimum QT and minimum QTc significantly reduced. We concluded that decreases in QTd and QTcd were associated with increases in minimum QT and minimum QTc. In earlier studies, the effect of carvedilol was evaluated at the end of the first and second months. We used the highest dose in almost all the patients (25x2 mg). Considering the dose increase interval of carvedilol (every 15 days), the maximum dose could be reached

only in two months. We believe that, with use of the drug for an additional month at the maximum dose, the effect of carvedilol may be more clearly observed.

Concerning the effect of carvedilol dose on QTd decrease, Pittenger et al.[15] suggested that carvedilol decreased QTd in a dose-dependent fashion. Yildirir et al.,[13] however, found no significant correlation between the dose of carvedilol and decreases in QTd. In our study, decreases in QTd and QTcd were not dose-dependent.

To our knowledge, there is only one study comparing the effects of other beta-blockers and carvedilol on QTd. Fesmire et al.[16] examined the ECGs of 35 patients with nonischemic dilated cardiomyopathy and compared the effects of selective *vs* nonselective beta blockade on QTd. Of these patients, 12 patients were on metoprolol, eight patients were on bucindolol, and six patients were on carvedilol for at least three months, and nine patients did not receive any beta-blockers. This study indicated no differences between beta-1 selective metoprolol and the nonselective agents, bucindolol and carvedilol in reducing QTd, implying that the effect of carvedilol on QTd may be group effect. However, such an observation needs to be confirmed with further studies before a general conclusion can be derived.

Several mechanisms might be responsible for prolonged QTd in CHF and its reduction with carvedilol therapy. The etiology of increased QTd in patients with CHF includes sympathetic overactivity, alterations in excitation contraction coupling, and myocardial fibrosis.[17] Decreases in QTd under carvedilol treatment may be partly due to adrenergic blocking effects of this agent. It has been demonstrated that chronic ACE inhibitory therapies decrease QTd in patients with heart failure.[18] As the patients in our study were receiving conventional therapies such as ACE inhibitors and diuretics, it is likely that the favorable results in QTcd might be due to the adjuvant effect of carvedilol, in that blockade of sympathetic activity may be incomplete by ACE inhibitors whereas carvedilol provides a more complete blockade.[13]

In our study, carvedilol exhibited a decreasing effect on QTcd in patients with heart failure. Three-month therapy with carvedilol was associated with marked improvements in both left ventricular functions and functional capacities of the patients. Moreover, significant decreases in left ventricular diameters and significant increases in left ventricular ejection fraction were observed echocardiographically. Decreases in QTd and QTcd may be attributed to improvement in neurohumoral mechanisms, beta receptor upregulation, increased left ventricular performance as a result of carvedilol therapy, and antiarrhythmic effect of carvedilol.

Limitations. The study has some limitations. The main one is the small size of the patient group. For electrocardiographic and echocardiographic measurements, interobserver and intraobserver variability were not determined. Another significant limitation is the short duration of the study, which might have limited the statistical strength of prognostic findings.

In conclusion, our findings support the idea that carvedilol therapy decreases QTcd in the early phase of heart failure. This decrease in QTc may be due to antiarrhythmic effects of carvedilol as well as to the improvement in left ventricular function provided by carvedilol.

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