Effects of Carvedilol Therapy on Arrhythmia Markers in Patients With Congestive Heart Failure

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SUMMARY

The aim of this study was investigate the effects of carvedilol therapy on ventricular repolarization characteristics as assessed by QT dispersion (QTd) and heart rate variability (HRV) in patients with heart failure.

Thirty-one patients with heart failure (mean age, 63.9 years) were included in the study. Carvedilol was administered in addition to standard therapy for CHF at a dose of 6.25 mg/day and uptitrated to the maximum tolerated dose. Control group consisted of 14 patients with heart failure (mean age, 69.4 years) who could not take carvedilol due to several reasons. All patients were followed-up 6 months. QT dispersion (QTd), and corrected QTd (QTcd) values were calculated at baseline and at the end of follow-up. Time domain and frequency domain heart rate variability analysis were performed with ambulatory Holter ECG.

Mean carvedilol dose was 23.9 ± 13.9 mg. Significant reductions were observed in the QTd ($P = 0.016$) and QTcd ($P = 0.001$) with carvedilol therapy, whereas QTd ($P = 0.47$) and QTcd ($P = 0.43$) did not change significantly in the control group. The QT maximum value did not change significantly but the QT minimum value ($P = 0.03$) was significantly increased after carvedilol therapy. Although the mean SDANN value was improved ($P = 0.039$), other HRV parameters such as mean SDNN ($P = 0.32$), rMSSD ($P = 0.74$), and the LF/HF ratio ($P = 0.35$) did not change significantly after carvedilol therapy.

This prospective controlled study shows that carvedilol therapy decreased QT dispersion and improved ventricular repolarization characteristics but did not change autonomic dysfunction in patients with heart failure. (Int Heart J 2006; 47: 565-573)

Key words: Carvedilol, Heart failure, QT dispersion, Heart rate variability

CONGESTIVE heart failure has a high mortality and half of these deaths are sudden.[1)] Ventricular arrhythmias are a serious problem and major cause of mortality in patients with congestive heart failure (CHF).[2,3)] Neurohormonal activation is one of the major causes in the progression of heart failure and ventricular

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dysfunction. Impaired homogeneity of myocardial repolarization and dysregulation of autonomic nervous system function are 2 important mechanisms for the genesis of ventricular arrhythmias.[4,5] Interlead variability of the QT interval, defined as QT-interval dispersion (QTd) in 12-lead electrocardiography (ECG), reflects regional differences in myocardial repolarization and provides indirect information concerning arrhythmogenicity.[6] Decreased heart rate variability (HRV) may reflect autonomic dysfunction.[7] Increased QTd and decreased HRV have been reported in patients with CHF and are considered as potential markers for predicting mortality.[8]

Long-term treatment of patients with CHF with the new generation nonselective beta adrenergic antagonist agent carvedilol has been shown to reduce mortality in controlled clinical trials.[9-11] One plausible mechanism for the reduction in heart failure mortality attributed to carvedilol is the reduction of sudden cardiac death. The effects of carvedilol therapy on ventricular repolarization inhomogeneity and autonomic dysfunction are not clear. Some uncontrolled studies have suggested that carvedilol therapy decreased QTd and had a beneficial effect on HRV parameters.[12-14]

The aim of the present prospective, controlled study was to investigate the effects of carvedilol therapy on ventricular repolarization characteristics and autonomic dysfunction as assessed by QTd and HRV in patients with CHF.

METHODS

Population: Forty-five patients with heart failure and left ventricular systolic dysfunction (LVEF < 0.40) were included in this prospective, controlled study conducted in a university hospital setting (Dept. of Cardiology, School of Medicine, Dokuz Eylul University). Patients with atrial fibrillation, sinus node or AV node dysfunction, technically poor electrocardiograms, or taking any drugs influencing QT dispersion (ie, antihistaminic and antipsychotic drugs) and beta-blockers were excluded from the study. Thirty-one patients with CHF in a clinically stable period underwent carvedilol therapy in addition to standard medical therapy that included angiotensin converting enzyme inhibitor, diuretic, and/or digoxin administration. Carvedilol therapy was begun at a dose of 6.25 mg/day and up-titrated to the maximum tolerated dose. The control group consisted of 14 patients with heart failure who could not take carvedilol due to various reasons, such as chronic obstructive pulmonary disease, peripheral arterial disease, or prior intolerance or noncompliance to carvedilol or other beta-blocker therapy. All patients were followed-up for 6 months.

QTd analysis: ECG and ambulatory ECG recordings were performed at baseline and at the end of follow-up. Twelve-lead ECGs were recorded at a paper speed of

50 mm/sec using a 12-channel recorder (Nihon Kohden). QT dispersions were measured in all patients manually by the same investigator. All measurements were repeated by a second investigator who was blinded to the demographic information and therapy. QT intervals were measured from the beginning of the QRS complex to the end of the T wave, which was defined as return to baseline in each ECG lead. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U waves. QT intervals were measured in all leads if technically applicable. For each lead, 2 or more consecutive cycles were measured and the arithmetic mean of the QT interval for that lead was used in all calculations for QTd. QTd was calculated according to the difference between the longest and shortest QT interval measured in each individual ECG lead. The measured values were then expressed as both uncorrected and corrected heart rate using Bazett's formula.[15)]

HRV analysis: We also performed HRV analysis in patients taking carvedilol by using 24-hour Holter ECG recordings (Reynolds Medical USA). All recordings were visually monitored after computer-supported analysis. Time domain analysis was performed with the standard deviations of mean RR intervals (SDDN), root mean square of successive differences (rMSSD), and standard deviation of the average NN intervals (SDANN).[7)] Frequency domain analysis was performed in the first 5-minute segments of the 24-hour ECG recordings. The spectral analysis showed different frequency bands. The frequency domain analysis of HRV was based on the Fast Fourier transformation. High frequency (HF, 0.15 - 0.40 Hz) and low frequency (0.04 - 0.15 Hz) bands were used.

Statistics: Continuous variables are reported as the mean ± SD. Comparisons between groups at baseline were performed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Analysis before and after the follow-up period were performed using Student's *t* test for repeated measures in the carvedilol group and Wilcoxon's signed-rank test for the control group. Kendall's correlation tests were used when assessing the correlation between the delta QTcd and carvedilol dose and the Pearson correlation test when assessing the correlation to left ventricular (LV) ejection fraction and LV diastolic diameter. All tests were 2-sided and a P value < 0.05 was considered significant. All statistical tests were performed using SPSS 11 software.

RESULTS

The majority of the study population (80.6%) had ischemic heart failure and were male (75.6%). The mean age of the study group was 65.6 ± 11 years (range, 38 - 81 years). The distribution of heart failure according to the New York Heart Association (NYHA) classification was as follows: class I, 1 patient; class II, 14

Table I. Baseline Clinical Characteristics in Carvedilol and Control Groups

	Carvedilol (n = 27)	Control group (n = 12)	P
Clinical characteristics			
Age (years)	63.9 ± 9.3	69.4 ± 13.7	0.07
Sex (male) (%)	77.4	71.4	0.46
Diabetes (%)	38.7	58.3	0.25
Coronary heart disease (%)	80.6	78.6	0.58
Previous MI (%)	48.4	64.3	0.32
CHF NYHA class: I-II (%)	35.5	28.5	0.46
III-IV (%)	64.5	72.5	
Echocardiographic characteristics			
Ejection fraction (%)	27.9 ± 5.9	29.7 ± 6.4	0.44
Left ventricular diastolic diameter (mm)	64.3 ± 9.9	57.5 ± 6.9	0.02
Medications			
ACE inhibitors /ARB (%)	90.3	92.2	0.63
Nitrates (%)	30	21.4	0.41
Digoxin (%)	29	30.8	0.58
Furosemide (%)	87.1	76.7	0.37
Spironolactone (%)	50	42.9	0.65

Table II. Comparison of QT and QT Dispersion at Baseline and at End of the Follow-up Period in Both Groups

	Carvedilol			Control group		
	Baseline	After treatment	P	Baseline	After treatment	P
Heart rate (bpm)	80.7 ± 13.6	72.1 ± 11.8	0.022	85.9 ± 12.7	88.5 ± 12.2	0.67
QT max	430.4 ± 49.6	433.5 ± 48.6	0.680	413.6 ± 37.5	390.0 ± 43.0	0.035
QT min	378.0 ± 44.0	388.7 ± 46.0	0.003	363.6 ± 39.3	341.4 ± 43.2	0.026
QTc max	495.6 ± 42.9	469.7 ± 40.5	< 0.001	494.4 ± 34.5	472.9 ± 45.5	0.15
QTc min	435.5 ± 34.8	419.8 ± 38.1	< 0.001	433.9 ± 32.3	413.8 ± 43.5	0.026
QT d	52.4 ± 14.1	46.1 ± 14.3	0.016	50.0 ± 14.1	48.6 ± 22.1	0.47
QT cd	60.9 ± 16.9	50.3 ± 13.9	0.001	60.3 ± 20.1	58.1 ± 31.3	0.43

patients; class III, 28 patients; and class IV, 2 patients. The baseline clinical and echocardiographic characteristics and medications of both groups are shown in Table I. There were no significant differences between the groups other than the larger left ventricular diastolic diameter in the carvedilol group. The mean daily carvedilol dose was 23.9 ± 13.9 mg (range, 6.25 - 50 mg) in the carvedilol group.

Mean heart rate was significantly reduced (80.7 bpm - 72.1 bpm) after carvedilol treatment but it was not changed in the control group. The QTd and QTcd values in both groups at baseline and at 6th months of the follow-up are summarized in Table II. A significant reduction was observed in the QTd (P = 0.016) and QTcd (P = 0.001) values after carvedilol therapy. However, QTd (P = 0.47) and QTcd (P = 0.43) did not change after the follow-up period in the control

Table III. Outcomes of Ambulatory ECG Monitoring. Time Domain and Frequency Domain Parameters of Heart Rate Variability in Patients Receiving Carvedilol at Baseline and After the Treatment

	Baseline	After treatment	*P*
VPS (*n*)	1919.8 ± 2590.2	1428.9 ± 1708.7	0.56
SDNN	77 ± 31.5	96.3 ± 44.1	0.32
SDANN	65.7 ± 26.4	93 ± 32.2	0.039
rMSSD	25 ± 18.2	31.1 ± 36.3	0.74
VLF	495.6 ± 964.5	733.3 ± 1570.7	0.59
LF/HF	3.2 ± 2.9	3.9 ± 3.7	0.35

VPS indicates ventricular premature systole; SDNN, standard deviation of mean RR intervals; rMSSD, root mean square of successive differences; SDANN, standard deviation of the average NN intervals; LF, low frequency power bands; HF, high frequency power bands; and VLF, very low frequency bands.

group. The QT max value did change not significantly while the QT min value increased significantly after carvedilol therapy.

The mean reduction in QTcd (Δ QTcd) after treatment in the carvedilol group was 10.67 ms. There was no correlation between the reduction in QTcd and dose of carvedilol (r = 0.015; $P = 0.92$, Δ QTcd was 11.5 and 10.1 ms in patients receiving a carvedilol dose higher and lower than 25 mg, respectively). A reduction in QTcd was also not related to age (r = 0.19; $P = 0.21$), baseline LVEF (r = –0.1; $P = 0.95$), or left ventricular end diastolic diameter (r = 0.18; $P = 0.41$). When the patients taking carvedilol were classified according to NYHA functional class (class I-II versus class III-IV), Δ Qtcd was slightly higher in patients with a lower NYHA class (19 ± 19.1) than in those with a higher NYHA class (6.1 ± 13.3), however, the difference was not statistically significant ($P = 0.09$).

The changes in HRV parameters after carvedilol therapy are summarized in Table III. In the carvedilol group, the mean SDANN value was significantly increased ($P = 0.039$), and the mean SDNN value was increased but did not reach statistical significance ($P = 0.32$). Neither the LF/HF ratio nor rMSSD ($P = 0.7$) changed significantly after carvedilol therapy.

DISCUSSION

The results of this prospective, controlled study indicate that carvedilol therapy decreased QT dispersion and improved ventricular repolarization characteristics in patients with congestive heart failure. After 6 months of follow-up,

patients who had taken carvedilol therapy had a significant reduction in QTd and corrected QTd.

Increased repolarization inhomogeneity has been shown to play a role in the genesis of reentrant ventricular arrhythmias.[16] QTd has been recognized as a significant prognostic, noninvasive marker of inhomogeneity of myocardial repolarization in several disease settings, especially those involving ischemic heart disease.[17,18] Previous studies have demonstrated increased QTd values in congestive heart failure.[8] However, only limited data is available regarding the effects of carvedilol on QTd in patients with CHF. One retrospective study reported significant increases in QTd values in patients with left ventricular systolic dysfunction.[8] However, the study did not specifically investigate the effect of a beta-blocker on QTd in the same patient. Although contradictory results were reported in children,[19] several prospective studies have found a reduction in QTd by carvedilol therapy in addition to standard therapy for CHF.[12,20] Jepson, *et al* administered carvedilol (25 mg bid) to 35 patients for 4 weeks.[20] Yildirir, *et al*, who followed-up their patients for 16 months, reported that reductions in QTd and QTcd were seen only after the 2nd month.[12] However, neither study had a control group. We evaluated the effect of carvedilol on QTd in patients with CHF with respect to a control group who could not take carvedilol. A reduction in QTd was not observed after the follow-up in the control group. The control group was not exactly matched to the carvedilol group. The control group consisted of patients who could not receive carvedilol therapy (this group had a larger left ventricular diameter). Moreover, our analysis showed that neither baseline left ventricular diameter nor ejection fraction influenced the reduction in QTd.

Although in heart failure improvements of left ventricular ejection fraction and survival are related to carvedilol dose, it is unclear whether a reduction in QTd is dose-related. Pittenger, *et al* analyzed the effect of carvedilol dose on reduction of QTcd in a larger series, the MOCHA trial, and reported that carvedilol dose was inversely correlated with a reduction in QTcd.[21] Interestingly, we could not find any relationship between a reduction in QTcd and carvedilol dose. Our study group may have been too small for such an analysis.

An increased QT minimum interval appears to be responsible for the reduction in QTd, a finding that was consistent with those of 2 other studies.[12,19] Another study reported that carvedilol therapy significantly decreased QT interval dispersion in both elderly and younger patients.[22] Our findings confirm this finding. In our study, the reduction in QTd was not related to the age of the patient, baseline left ventricular diameter, or left ventricular ejection fraction. However, QTd reduction seemed to be more prominent in patients with a better functional NYHA class.

There are several mechanisms that may be responsible for increased QTd in

patients with CHF. These include sympathetic over-activity, alterations in the excitation-coupling interval, and myocardial fibrosis.[23] The reduction in QTd under carvedilol treatment may be partly due to an adrenergic blocking effect. Carvedilol blocks the sympathetic nervous system completely via beta-1, beta-2, and alpha adreno-receptors, as well as the renin-angiotensin system. Moreover, anti-ischemic and antiapoptotic effects and inhibition of chronic remodeling of the myocardium indirectly may contribute to the observed homogenization of the ventricular repolarization process and prevention of induction of arrhythmia in patients with CHF.[23,24] A reduced QTd with beta-blockers other than carvedilol was also reported in patients with CHF.[8,25,26]

Autonomic system integrity may be quantified noninvasively by analysis of HRV.[7] HRV is believed to mirror sympathovagal balance and has been shown to be decreased early after acute myocardial infarction, and the use of HRV by nominal 24-hour recordings is recommended for risk stratification.[7] A reduced HRV has been observed consistently in patients with CHF characterized by sympathetic activation and high levels of circulating catecholamines.[27] Previous evidence suggests that beta-blockers modulate HRV and vagal reflex in normal as well as hypertensive subjects, but sparse and inconsistent data have been reported for postmyocardial infarction[28,29] and heart failure patients.[30-32] Mortara, *et al* investigated to effect of carvedilol therapy on HRV parameters in mild to severe stable patients with CHF in a case-controlled study. Carvedilol therapy given in addition to standard therapy was shown to significantly improve SDNN and rMSSD values 6 months after treatment.[14]

We observed a significant increase in only SDANN. The other parameters of HRV analysis were not changed significantly after carvedilol therapy. The higher standard deviation may be responsible for the nonsignificance of the SDDN value. Moreover, our study group consisted of patients with moderately depressed HRV. The baseline mean SDNN value (77 ms) was higher in our subjects than in those of Mortara, *et al*[14] (56 ms). Finally, the carvedilol dose used (mean dose, 23 mg) was lower in our study compared to previous study (40 mg). This dose may be too low to have a detectable effect in the 24-hour analysis of HRV testing. Nevertheless, we did not observe a clear benefit with carvedilol therapy on autonomic dysfunction in patients with CHF.

Limitations: Our study was not designed to compare long-term mortality and morbidity parameters. Studies designed to obtain data proving the beneficial effect of reducing QTcd on clinical arrhythmic events and sudden cardiac death should be performed.

Conclusion: These data show that carvedilol therapy decreased QT dispersion, although it seems to have no effects on autonomic nervous function parameters in patients with heart failure. Improved ventricular repolarization characteristics

with carvedilol may contribute significantly to reducing mortality associated with CHF.

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