Does carvedilol therapy reduce QT dispersion in patients with heart failure?

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Abstract

Introduction: Carvedilol therapy increases left ventricular ejection fraction, and reduces mortality and morbidity rates. However, there are very limited data relating to the effect of carvedilol on QT dispersion (QTd). In this study, we investigated the effect of carvedilol therapy on QTd in patients with heart failure.
Material and methods: Fifty-six patients with heart failure and a left ventricular ejection fraction less than 40% were prospectively included in the study. Clinical examination, determinations of plasma levels of tumour necrosis factor-α (TNF-α), interleukin 2 (IL-2) and IL-6, electrocardiography and radionuclide study were performed at baseline and repeated at the end of the 4th month of carvedilol therapy. From standard 12-lead electrocardiograms the maximum and minimum QT intervals, corrected QT intervals and corrected QTd values were calculated at baseline, and after the 4th month of carvedilol therapy.
Results: At the end of the 4th month, IL-6 (from 9.8±6.4 to 5.4±0.7 pg/ml) and TNF-α (from 10.9±4.6 to 6.0±4.9 pg/ml) levels, QTd, corrected QTd, resting heart rate, and systolic blood pressure were significantly decreased, and left ventricular ejection fraction and NYHA functional class were improved by carvedilol therapy (QTd from 66±22 to 28±13 ms, $P<0.001$, corrected QTd from 72±23 to 30±14 ms, $P<0.001$). However, maximum corrected QT and maximum QT values did not change significantly, while minimum QT and minimum corrected QT values significantly increased.
Conclusions: Carvedilol therapy for 4 months resulted in a significant reduction in QTd.

Key words: carvedilol, heart failure, QT dispersion, cytokines.

Introduction

QT dispersion (QTd), defined as the difference between the longest and the shortest QT interval on the surface ECG, is a validated measure of dispersion of repolarization [1]. It reflects regional variations in ventricular repolarization and is associated with risk for arrhythmias. Increased QTd and corrected QTd values have been reported in patients with systolic heart failure, and are considered as potential markers for predicting drug effects on mortality [2, 3]. QT dispersion predicts sudden death and ventricular arrhythmias in patients with heart failure [4, 5]. Thirty-five to 45% of patients with heart failure die suddenly without any evidence of haemodynamic or functional deterioration, presumably as a consequence of lethal ventricular arrhythmias; therefore management of these arrhythmias is a major therapeutic target [5]. Carvedilol is

a non-selective β-blocker (β1/β2 rate of 7.3) with α-blockage, vasodilatation, and antioxidant effects [6]. Carvedilol therapy reduces the severity of ventricular dysfunction, increases left ventricular ejection fraction and reduces mortality and morbidity [7]. However, there are very limited data relating to the effect of carvedilol on QT dispersion (QTd). Therefore, in this study we investigated the effect of carvedilol therapy on QTd in patients with heart failure.

Material and methods

Patients 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 current treatment for heart failure with standard therapy including: diuretics, angiotensin-converting enzyme inhibitors and digoxin at a stable dosage for at least 6 weeks. Criteria for exclusion from the study were: chronic obstructive pulmonary disease, significant valvular heart disease, thyrotoxicosis, hypothyroidism, chronic kidney and liver diseases, malignancy, anaemia (Hb <9 g/dl), atrial fibrillation, systolic blood pressure lower than 90 mm Hg, heart rate lower than 50/min, and first or second level heart block. Patients receiving anti-arrhythmic, anti-histaminic, anti-psychotic drugs or β-blockers, patients with a permanent pacemaker and psychiatric problems were also excluded from the study. The initial dose of carvedilol was 3.125 mg *b.i.d*., which was doubled at 2-weekly intervals as tolerated up to 25 mg *b.i.d*. Patients were continued on their conventional heart failure treatment in addition to carvedilol. Standard ECG recordings, determinations of plasma levels of TNF-α, IL-2 and IL-6, NYHA functional class and ejection fraction with radionuclide ventriculography of all patients were evaluated at baseline and the end of the 4th month of carvedilol therapy. The functional class was considered to have improved if the patient's functional status increased ≥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 ventricule performance was made as described elsewhere with the automatic edge-detection algorithm for the determination of left ventricule borders [8]. All studies were interpreted by two observers blinded to the treatment assigned. The left ventricular ejection fraction rates were calculated. Radionuclide study was performed at baseline and then repeated after 4 months.

TNF-α, IL-2, IL-6 levels

To measure TNF-α, IL-2, IL-6 concentrations, 15 ml of blood was withdrawn from an antecubital vein and collected into pre-chilled evacuated tubes containing EDTA. Plasma was separated by centrifugation at 2500 rpm for 12 min within 15 min of collection. Samples were stored at –70°C. TNF-α, IL-2, IL-6 measurements were performed with a commercially available enzyme-linked immuno-assay (Immulite, Los Angeles CA 90045). The average of three measurements in undiluted plasma was then calculated. TNF-α, IL-2, IL-6 plasma level determinations were performed at baseline and then repeated 4 months after carvedilol therapy.

QT interval measurements

Electrocardiographic recordings were performed at baseline and at the end of follow-up. Twelve-lead ECGs were recorded at a paper speed of 50 mm/s 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. QT dispersion 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 [9].

Statistical analysis

Continuous data are shown as mean ± SD. Fit of continuous variables with the normal distribution was examined in the first study using Kolmogorov-Smirnov test. Independent sample t test and paired sample test were used in the analysis of data with a normal distribution. Mann-Whitney U and Wilcoxon tests were used to analyze data without a normal distribution, and χ^2 or Fisher's exact test was used in analyzing

categorical data. Data were analyzed using Minitab INC (licence no: WCP 1331.00197). Significance was assumed at a 2-tailed value of P<0.05.

Results

All patients were taking angiotensin-converting enzyme inhibitor, oral diuretics and digoxin at the beginning. During the follow-up period, 12 patients' rhythms degenerated to permanent atrial fibrillation. These 12 patients were not included in the statistical analysis. The remaining 44 patients (aged 60.5±9.7 years, 30 males, 14 females) completed the follow-up period in sinus rhythm and continued the carvedilol therapy. Of them, 18 were ischaemic (demonstrated by coronary angiography), and 26 were non-ischaemic. The characteristics of patients are shown in Table I. The mean daily dose of carvedilol was 38±11 mg (range 12.5-50 mg). Statistically significant improvements were detected in systolic blood pressure, resting heart rate, ejection fraction, levels of cytokines (IL-6 and TNF-α) and NYHA functional class at the end of the 4th month after carvedilol therapy (P=0.002, P=0.001, P=0.003, P=0.020, P=0.026, P=0.001, respectively; Table II). Left ventricular ejection fraction increased from 21.4±8.8 to 27.8±10.8%, IL-6 levels decreased from 9.8±6.4 to 5.4±0.7 pg/ml and TNF-α levels decreased from 10.9±4.6 to 6.0±4.9 pg/ml after carvedilol therapy. However, IL-2 levels did not significantly change. In addition, both corrected QTd (from 72±23 to 30±14 ms; P<0.001) and QTd (from 66±22 to 28±13 ms, P<0.001) significantly decreased with carvedilol therapy. Maximum corrected QT and maximum QT values were not changed (P>0.05), while minimum QT and minimum corrected QT values significantly increased (P<0.001). Electrocardiographic and clinical variables are shown in Table II.

Table I. Patients' characteristics

Age [years]	60.5±9.7
Sex [male/female]	30/14
Ischaemic/idiopathic [n, %]	18/26
Hypertension [n, %]	24 (54%)
Diabetes mellitus [n, %]	16 (36%)
Tobacco use [n, %]	26 (59%)
Hyperlipidaemia [n, %]	12 (27%)

Table II. Results at baseline and at the end of the 4th month of carvedilol therapy

	Baseline (n=44)	4th month (n=44)	P
Systolic BP [mm Hg]	123±17	112±14	0.002
Diastolic BP [mm Hg]	74±9	71±11	NS
Heart rate [bpm]	82±9	74±7	0.001
LVEF [%]	21.4±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
IL-2 [U/ml]	697.9±458.2	717.4±426.8	NS
IL-6 [pg/ml]	9.8±6.4	5.4±0.7	0.020
TNF-α [pg/ml]	10.9±4.6	6.0±4.9	0.026
Max QT [ms]	412±39	420±37	NS
Max corrected QT [ms]	434±74	460±104	NS
Min QT [ms]	351±37	406±35	<0.001
Min corrected QT [ms]	393±67	461±70	<0.001
QT dispersion [ms]	66±22	28±13	<0.001
Corrected QT dispersion [ms]	72±23	30±14	<0.001

LVEF – left ventricular ejection fraction, Min – minimum, Max – maximum, NYHA – New York Heart Association, TNF-α – tumour necrosis factor-α, IL – interleukin, NS – non-significant

Discussion

The results of this prospective study indicate that carvedilol therapy for 4 months resulted in a significant reduction in QTd, which paralleled the improvement of LVEF and the decrease of TNF-α and IL-6 levels in patients with heart failure. Prospective studies have indicated that QTd increased in patients with heart failure and that might be a marker of electrical instability leading to an increased risk of sudden death [2, 3]. Data in recent studies suggest that QTd usually varies between 20 and 50 ms in normal subjects and between 60 and 80 ms in patients with heart failure secondary to ischaemic heart lacking [10]. Our results show QT dispersion around 66 ms (66±22) at baseline. Little is known about the mechanism of increased QT dispersion in patients with heart failure. Sympathetic tone, excitation-contraction coupling, and myocardial fibrosis may all be important. Although the efficacy of carvedilol therapy in patients with heart failure have been shown in a number of studies [11], data are limited about the effect of carvedilol on QT dispersion.

Bonnar et al. [2] compared the QTd and corrected QTd values in 25 patients with heart failure to the healthy population. A significant increase was noted in QTd and corrected QTd values in patients with heart failure. In addition, those using β-blocker agents had lower QTd values than non-users. Jepson et al. [12] investigated the effects of carvedilol therapy on QTd in 35 patients with heart failure. In addition to the conventional therapy for heart failure, the patients received carvedilol at a dose

of 25 mg *b.i.d.* and QTd and corrected QTd values were evaluated at study entry and after 4 weeks. Carvedilol resulted in a significant reduction in QTd and corrected QTd values in addition to the significant decrease in heart rate. They noted a significant increase in minimum QT values, whereas the maximum QT values remained unaltered. Yildirir et al. [13] investigated the effect of carvedilol therapy on QTd in 19 patients with heart failure. Carvedilol treatment resulted in significant reductions in QTd and corrected QTd values at the end of 16 months. However, there was a significant increase in minimum QT values, whereas maximum QT values remained unchanged. These studies were important for demonstrating the effect of carvedilol therapy on QTd. In addition, Akdeniz et al. [14] obtained similar results about the effect of carvedilol on QTd in patients with heart failure. Our findings were consistent with the results of these studies.

Various pharmacodynamic mechanisms of carvedilol may lead to reduction in QTd. The reduction in QTd may be partly due to adrenergic blocking effects of carvedilol. Another possible explanation is that the reduction in QTd may be related to its antiarrhythmic effects. Two major mechanisms for the antiarrhythmic effects of carvedilol were cited [15]. One mechanism is the ability of carvedilol to reverse negative remodelling with improvement of overall left ventricular function, which can indirectly decrease the incidence of both atrial and ventricular tachyarrhythmias. A more recent double-blind placebo controlled study [16] showed that the antiarrhythmic efficacy of carvedilol in patients with dilated cardiomyopathy was paralleled by an improvement in ejection fraction independent of the aetiology of heart failure, as in our study. The second mechanism may be related to some additional properties of carvedilol besides its beta blocking effects. Carvedilol effectively blocks the renin-angiotensin system *via* β-adrenoreceptors, and blocks almost completely the sympathetic nervous system activity *via* β-1, β-2 and α-1 adrenoreceptors [17]. Moreover, anti-ischaemic and anti-apoptotic effects indirectly may contribute to the observed homogenization of the ventricular repolarization process and prevention of induction of arrhythmia in patients with heart failure [18].

Kowalewski et al. [19] showed that TNF-α and IL-6 levels significantly increased in young patients with ventricular arrhythmias. Mizuochi et al. [20] showed that carvedilol therapy reduced TNF-α levels of human monocytes *in vitro*. We previously reported that carvedilol therapy increased left ventricular ejection fraction by decreasing TNF-α and IL-6 levels in patients with dilated cardiomyopathy [21].

In our study, the reduction in QTd after carvedilol therapy was associated with decreased TNF-α and IL-6 levels. However, in studies done previously, which investigated effects of carvedilol therapy on QTd in patients with heart failure, cytokine levels were not investigated. Based on the results of our study, the reduction in QTd may be caused by the suppressor effect of carvedilol on plasma cytokine levels. Maybe it is not caused by carvedilol increasing left ventricular ejection fraction. Or, carvedilol may reduce QTd both by increasing ejection fraction and by decreasing cytokine levels in these patients.

The major limitations of our study are the small sample size and the lack of a control group. However, with this design everyone served as his/her own control with stable concomitant medications throughout the study.

In conclusion, our study suggests that carvedilol therapy in patients with heart failure considerably reduces QTd, which is a potent predictor of susceptibility to ventricular arrhythmias. This antiarrhythmic effect of carvedilol, in addition to the improvement in left ventricular ejection fraction, may be caused by the suppressor effect of carvedilol on plasma cytokine (TNF-α and IL-6) levels. However, the mechanisms underlying the reduction in QTd by carvedilol need to be clarified with more powerful studies.

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