MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2013; 19: 366-372
DOI: 10.12659/MSM.883911

Received: 2013.01.28
Accepted: 2013.02.21
Published: 2013.05.15

Effects of carvedilol therapy on cardiac autonomic control, QT dispersion, and ventricular arrhythmias in children with dilated cardiomyopathy

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Source of support: Departmental sources

Background: The purpose of this study was to examine the effects of carvedilol therapy on autonomic control of the heart and QT-interval dispersion (QTd) among children with idiopathic dilated cardiomyopathy (DCM) whose symptoms were not adequately controlled with standard congestive heart failure therapy.

Material/Methods: Patients with DCM who were treated with carvedilol were enrolled in the study. All patients had undergone carvedilol therapy in addition to standard therapy for at least 6 months. Clinical, echocardiographic, and electrocardiographic parameters, and 24-h Holter records of patients were retrospectively evaluated before and after carvedilol treatment.

Results: A total 34 patients (mean age: 7.4±4.3 years) with DCM were analyzed in the study. The median follow-up period was 9.5 months. After the 6 months of carvedilol therapy the clinical score significantly improved, left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) significantly increased, and left ventricle end-diastolic dimensions and end-systolic dimensions significantly decreased. There were statistically significant increases in mean SDNN, SDANN, rMSSD, and pNN50 (p=0.002, p=0.001, p=0.008, and p=0.026, respectively). After the carvedilol therapy, SDNN was correlated with the clinical score, heart rate, LVEF, LVFS, and total premature ventricular contractions (PVCs). In addition, rMSSD and pNN50 were correlated with heart rate, LVEF and LVFS. A significant reduction was observed in QTc-minimum, QTc-maximum, and QTd values (434.9±40.7 *vs.* 416.1±36.5, 497.8±43.6 *vs.* 456.3±41.7, 58.6±17.1 *vs.* 49.3±15.6; p<0.001, p=0.001, and p=0.008, respectively). QTd was significantly related to PVCs (r=0.62, p=0.02).

Conclusions: We conclude that the addition of carvedilol to standard therapy can improve clinical symptoms and heart rate variability, and reduce in arrhythmia markers in children with DCM.

Key words: dilated cardiomyopathy • carvedilol • QT dispersion • heart rate variability • children

Full-text PDF: http://www.medscimonit.com/download/index/idArt/883911

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Background

Dilated cardiomyopathy (DCM) is a rare disease in children, with an annual incidence of 0.34/100 000 persons [1]. Recent studies have suggested that multiple neuroendocrine factors, including the reduction in parasympathetic activity and activation of sympathetic nervous and renin-angiotensin-aldosterone (RAA) system, play an important role in the genesis and progression of congestive heart failure (CHF) [2–4]. In addition, adrenergic stimulation may predispose to ventricular tachyarrhythmia and sudden cardiac death [5,6]. Such observations have led to the use of neurohormonal antagonists such as aldosterone antagonists, angiotensin-converting enzyme inhibitors (ACEI), and β-adrenergic blockers for the treatment of CHF [1,7–9]. Reduced measures of heart rate variability (HRV), considered a marker of tonic sympathetic and vagal outflow, have been shown to be related with prognosis in heart failure. Several investigators have demonstrated that measurements of HRV can be used to evaluate the effect of ACEI and β-adrenergic receptor antagonists on cardiac autonomic activity [7,10,11]. Dysregulation of autonomic nervous system function and impaired homogeneity of myocardial repolarization are 2 major mechanisms for the genesis of ventricular arrhythmias [12]. Increased QT-interval dispersion (QTd) and decreased HRV have been reported in adult patients with CHF, and are considered as potential markers for arrhythmogenicity and for use in predicting mortality [12–14].

Carvedilol is a nonselective β-blocker that also has β-blocker and antioxidant effects. It decreases the chronic adrenergic overstimulation of the myocardium and improves myocardial function, and has been shown to improve survival, decrease morbidity, and improve quality of life in adults with CHF [7,15]. Although some studies have suggested that carvedilol therapy decreased QTd and had a beneficial effect on HRV parameters in adult patients, the effects of carvedilol therapy on inhomogeneity of ventricular repolarization and autonomic nervous regulation are not clear [7,12,16,17]. To the best of our knowledge, there have been few published studies about the effect of carvedilol on arrhythmias in dilated cardiomyopathy in pediatric patients, and there are no published data available about the effects of carvedilol therapy on heart rate dynamics and arrhythmia markers in children. Therefore, the aim of this study was to examine the effects of carvedilol therapy on autonomic control of the heart and QT-interval dispersion as an arrhythmia marker among children with DCM whose symptoms were not adequately controlled with standard CHF therapy.

Table 1. Clinical score modified from Ross and Reithmann et al. [19,20].

	Score (points)		
	0	1	2
History			
Diaphoresis	Head only	Head and body during exercise	Head and body at rest
Tachypnea	Rare	Several times	Frequent
Physical examination			
Breathing	Normal	Retractions	Dyspnea
Respiratory rate (respirations/minute)			
0–1 year	<50	50–60	>60
1–6 year	<35	35–45	>45
7–10 year	<25	25–35	>35
11–14 year	<18	18–28	>28
Heart rate (beats/minute)			
0–1 year	<160	160–170	>170
1–6 year	<105	105–115	>115
7–10 year	<90	90–100	>100
11–14 year	<80	80–90	>90
Hepatomegaly (liver edge from right costal magrin, centimeter)	<2	2–3	>3

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Material and Methods

Patients

After obtaining approval from the institutional review board of our institution, we retrospectively reviewed the hospital records of the 34 patients who were followed-up in our pediatric cardiology clinic with DCM and treated with carvedilol in addition to standard therapy of digoxin, diuretics, and ACEI. Data collected included: age at diagnosis, therapy prior to carvedilol, time between diagnosis and initiation of carvedilol, age, weight, symptoms at carvedilol initiation and last follow-up, dosage, and adverse effects of the drug. All patients who received carvedilol in addition to standard therapy were followed-up for at least 6 months. The diagnosis of dilated cardiomyopathy was defined as a child having both left ventricular (LV) contractility 2 SD below the normal mean and LV end-diastolic dimension 2 standard deviations above the normal mean, which was not caused by dysrhythmia or any other structural heart disease [18].

Clinical assessment

We used a modified scoring system of CHF signs and symptoms described by Ross and Reithmann et al. [19,20] (Table 1). Each sign or symptom was graded on a scale of 0, 1, or 2 points according to the severity. The sum of points formed the clinical score (range 0–12 points), with a higher score corresponding to more severe heart failure.

The inclusion criteria were: patients with DCM whose symptoms were not adequately controlled with standard CHF therapy (clinical score of 5 or more), and whose systemic ventricle is morphologic left ventricle and left ventricular ejection fraction (LVEF) $\leq$0.40. The exclusion criteria were: congenital heart defect, atrial fibrillation, sustained or symptomatic ventricular dysrhythmias, sinus or AV node dysfunction, bradycardia, acute myocarditis, bronchial asthma, obstructive or severe regurgitative valvular disease, significant renal, hepatic, gastrointestinal disease, endocrine disorders, taking any drugs influencing QT dispersion, and use of antiarrhythmic drugs. Patient characteristics including age, sex, weight, height and concomitant medications were collected for all patients. Clinical, echocardiographic, electrocardiographic parameters, and 24-h Holter records of patients were retrospectively evaluated before and after carvedilol treatment.

Echocardiographic assessment

Echocardiographic data obtained before and after carvedilol therapy were retrospectively reviewed from patient medical records. For estimates of left ventricular dimension, function and shortening fraction were reported with the standard method of 2-dimensionally directed M-mode measurements [18].

Electrocardiography and QTd analysis

Standard 12-lead electrocardiography was obtained simultaneously using a recorder set at 50 mm/s paper speed and calibration of 1milivolt/centimeter, in a comfortable supine position. QT intervals (QTc=QT/$\sqrt{RR}$, maximum and minimum QTc intervals) were also measured. QT dispersions were manually measured in all electrocardiograms (ECG) 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 [12,21]. 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 as the difference between the longest and shortest QT interval measured in each individual ECG lead [13,14]. Premature ventricular contractions (PVCs) were characterized by the following: ectopic, premature, and bizarrely shaped QRS complexes, usually wider than 120 msec; absence of P waves preceding a QRS complex; the T wave is usually large, and its direction is opposite the major deflection of the QRS. Couplets were characterized by 2 consecutive premature ventricular contractions. Nonsustained ventricular tachycardia (VT) was characterized by 3 or more consecutive beats lasting less than 30 seconds, at a rate >100/min.

HRV analysis

All records of the 24-Holter monitoring before and after carvedilol therapy were obtained from the computer-based electronic Holter archive of our institution. Holter studies were considered adequate for interpretation if there was greater than 16 hours of analyzable data for the 24-hour recording. The tapes were manually reviewed by an independent observer who was blinded to the patient's identity and study treatment. Total numbers of PVC and number of episodes of VT were calculated. We also performed HRV analysis by using 24-hour Holter ECG monitoring (DMS 300 Holter recorder; DMS Inc., New York, NY, USA). Abnormal beats and areas of artifact were automatically and manually identified and excluded from the analysis. We analyzed HRV in the time domain by the following 5 standard 24-hour time-domain measures: SDNN (standard deviation of all normal sinus R-R intervals during 24 hours), SDNNi (mean of the standard deviation of all normal sinus R-R intervals for all 5-minute segments), SDANN (standard deviation of the average normal sinus R-R intervals for all 5-minute segments), rMSSD (root mean square of the successive

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Table 2. Initial characteristics of patients (n=34).

Age (mean, [range]) (years)	7.4±4.3 [32 months–14 years]
Gender (male/female)	18 male/16 female
Body weight (kg)	39.6±10.4
ACEI	32/34 (94.1%)
Diuretics	32/34 (94.1%)
Digoxin	34/34 (100%)
Carvedilol (mean dose, mg/kg)	0.46±0.28

Data are expressed as mean ± standard deviation or number (%) of patients. ACEI, angiotensin-converting enzyme inhibitors.

normal sinus R-R interval difference), and pNN50 (percentage of successive normal sinus R-R intervals longer than 50 ms).

Statistical analysis

Descriptive analysis was performed for demographic and clinical characteristics of the patients. Continuous variables were reported as the mean ± standard deviations. The Kolmogorov-Smirnov test was used to assess evidence of deviation from normality. Changes from pre- to post-carvedilol therapy were assessed using paired t-tests for continuous variables when the differences were approximately normally distributed, and by using Wilcoxon signed rank tests for differences with skewed distributions. The relationship among variables was evaluated by Pearson's correlation coefficient. A p-value <0.05 was considered to be significant. Analyses were performed with the software package SPSS 11.0 (SPSS, Inc, Chicago, IL, USA).

Results

A total 34 patients (18 male, 16 female, mean age: 7.4±4.3 years, range 32 months to 14 years) with DCM were analyzed in the study. All patients had undergone carvedilol therapy in addition to standard therapy for at least 6 months. The median follow-up period was 9.5 months (range 6.4–13.7 months) after the initiation of carvedilol therapy. Baseline patient characteristics are shown in Table 2.

Clinical characteristics

The initial mean carvedilol dose was 0.14±0.07 mg/kg/day, and 0.46±0.28 mg/kg/day at 6 months. All patients tolerated the highest dose of carvedilol. As standard treatment, 34/34 (100%) were on digoxin, 32/34 (94.1%) were on furosemide, and 32/34 (94.1%) were on ACEI. The average heart rate was significantly reduced after carvedilol treatment (114±23 *vs.* 89±21 beat/min, p=0.008). Systolic blood pressure tended to decrease after carvedilol therapy, but did not reach statistical significance. After 6 months of carvedilol treatment, the Ross clinical score significantly improved from 6 to 3 (p=0.03) (Table 3). The most common adverse events were dizziness (22%), vomiting (13%), hypotension (8%), and headache (5%). No serious adverse effects were observed that necessitated discontinuation of carvedilol therapy.

Echocardiography

LVEF significantly increased from 34.7±7.6% (range 22–40%) to 45.2±9.6% (range 29–61%) following carvedilol treatment (p=0.002). After carvedilol treatment, the left ventricular fractional shortening (LVFS) significantly increased from 16.4±9.7% (range 10–33%) to 23.9±7.7% (range 16–37%) (p=0.016), left ventricle end-diastolic dimensions (LVEDd) significantly decreased from 45.7±8.1 mm (range 31–60 mm) to 41.4±6.5 mm (range 26–58 mm) (p=0.026) and the left ventricle end-systolic dimensions (LVEDs) significantly decreased from 39.4±6.9 mm (range 24–47 mm) to 34.2±6.0 mm (range 20–43 mm) (p=0.047) (Table 3).

Heart rate variability parameters

There were significant increases in mean SDNN, SDANN, rMSSD, and pNN50 after carvedilol therapy (p=0.002, p=0.001, p=0.008, and p=0.026, respectively). A trend toward an increase in SDNNi did not achieve statistical significance after 6 months. Baseline SDNN was significantly correlated with baseline heart rate and total PVCs. After carvedilol therapy, SDNN was correlated with the clinical score of CHF, heart rate, LVEF, LVSF, and total PVCs. In addition, rMSSD and pNN50 were correlated with heart rate, LVEF, and LVSF after carvedilol therapy. The comparison of clinical, hemodynamic, heart rate variability, and ventricular arrhythmia parameters of patients receiving carvedilol therapy at baseline and after the treatment are shown in Table 3, and the correlation between changes in HRV in the time domains and changes in hemodynamic parameters are presented in Table 4.

QT interval and ventricular arrhythmias

Intra- and interobserver variability were assessed in 18 randomly chosen patients; all intra- and interobserver variability for ECG parameters ranged from 3.1 to 4.8%. A significant reduction was observed in maximum and minimum QTc interval, QTc, and QTd values after carvedilol treatment. QTd was slightly higher in patients with a lower clinical score than in those with a higher clinical score, but the difference was not statistically significant. QTd was significantly related to total PVCs, but QTd was not related to age, sex, clinical score of CHF, heart rate, LVEF, LVSF, or LVEDd (Table 4). No patient had a history of a previous abnormal heart rhythm. Although 8 patients (23.5%) had PVCs before treatment, they disappeared

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Table 3. Comparison of clinical, hemodynamic, heart rate variability and ventricular arrhythmia parameters of patients receiving carvedilol at baseline and after the treatment.

	Baseline	After carvedilol therapy	p value
Mean heart rate (beats/min)	114±23	83±21	0.008
Clinical score of CHF	**6 (5–10)**	**3 (2–7)**	0.030
Systolic BP (mmHg)	102.3±24.4	89.4±21.5	0.188
LVEDd (mm)	45.7±8.1	41.4±6.5	0.026
LVEDs (mm)	39.4±6.9	36.2±6.0	0.047
LVEF (%)	34.7±7.6	45.2±9.6	0.002
LVSF (%)	16.4±9.7	23.9±7.7	0.016
SDNN (ms)	98.7±35.6	133.4±39.2	0.002
SDANN (ms)	81.3±38.2	108.6±27.4	0.001
SDNNi (ms)	34.2±10.3	39.5±14.7	0.060
rMSSD (ms)	23.6±15.2	32.6±19.4	0.008
pNN50 (%)	4.7±2.9	5.5±3.0	0.026
QTc minimum	434.9±40.7	416.1±36.5	<0.001
QTc maximum	497.8±43.6	456.3±41.7	0.001
QT dispersion	58.6±17.1	49.3±15.6	0.008
Ventricular ectopic beats (n/h)	62.4±19.6	48.6±17.1	0.016
Ventricular couplets (n/h)	1.3±0.9	1.1±0.6	0.190
Nonsustained VT (n/h)	0.19±0.04	0.16±0.02	0.220

Data are expressed as mean ± standard deviation **and median (range)**; *p* value is given for comparison between baseline and after carvedilol therapy. CHF – congestive heart failure; BP – blood pressure; LVEDd – left ventricular end diastolic diameter; LVEDs – left ventricular end systolic diameter; LVEF – left ventricular ejection fraction; LVSF – left ventricular fractional shortening; SDNN – standard deviation of all normal RR intervals during 24 h; SDANN – standard deviation of 5-minute mean RR intervals; SDNNi – mean of all 5-minute standard deviation of RR intervals; rMSSD – root-mean-square of difference of successive RR intervals; pNN50 – percentage of adjacent RR intervals >50 ms different; QTc – corrected QT interval; VT – ventricular tachycardia.

in 4 patients and PVC decreased in 2 patients after treatment. Sustained ventricular tachycardia was not observed in any patients. Before carvedilol therapy, 5 patients (14.7%) had ventricular couplets and 2 patients (5.8%) had nonsustained ventricular tachycardia. A trend toward a decrease in ventricular couplets and nonsustained ventricular tachycardia did not reach statistical significance after 6 months. Patients with DCM who had arrhythmic events during follow-up had significantly greater QTd than those without arrhythmic events (59.7±16.8 *vs.* 51.4±15.6, *p*=0.026).

Discussion

The neurohumoral mechanisms of CHF involve activation of the sympathetic nervous system and the RAA system, leading to intrinsic myocardial dysfunction, apoptosis, and remodeling [22,23]. Stimulation of α-receptors increases oxygen consumption of the myocardium by increasing the afterload, which causes peripheral and coronary vasoconstriction that results in accumulation of calcium in the myocyte, leading to cell death, and contributes to remodeling of the heart with fibrosis and hypertrophy [4,24]. Carvedilol is a third-generation β-blocking agent that at therapeutic target doses blocks all 3 adrenergic receptors that decrease the chronic adrenergic overstimulation of the myocardium and improve myocardial function, and it has been shown to inhibit free radical induced cardiac contractile dysfunction [25,26]. Therefore, it is important to examine the clinical effect of a β-adrenergic blocker therapy on DCM (e.g., carvedilol) to verify its efficacy in children. There are limited data concerning the use of carvedilol in children with ventricular dysfunction [22,27]. We have shown that oral carvedilol added to standard drug therapy improved ventricular function and clinical symptom scores in children with DCM, and we also found

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Table 4. Correlation between HRV-QT parameters and clinical-hemodynamic-PVC parameters at before and after carvedilol treatment.

Correlation (R) before/after	Clinical score of CHF	HR	LVEF	LVSF	Total PVCs#
SDNN	–0.20/–0.58*	–0.52*/–0.48*	0.46/0.52*	0.34/0.48*	–0.34*/–0.69*
SDANN	–0.36/–0.40	–0.14/–0.26	0.34/0.41	0.28/0.32	–0.26/–0.52
rMSSD	–0.04/–0.17	–0.39/–0.41*	0.32/0.55*	0.18/0.47*	–0.24/–0.49
pNN50	–0.21/–0.26	–0.28/–0.34*	0.36/0.58*	0.21/0.38*	–0.11/–0.37
QTc minimum	0.15/0.20	–0.12/–0.26	–0.28/–0.34	–0.31/–0.34	0.12/0.28
QTc maximum	0.19/0.33	–0.34/–0.41	–0.17/–0.46*	–0.19/–0.29	0.33/0.41
QT dispersion	0.23/0.37	0.36/0.52	–0.09/–0.38	–0.11/–0.44	0.42*/0.62*

In quantifying total PVCs, each of the complexes occurring in clusters as couplets or runs of ventricular tachycardia was counted individually and contributed to the total PVC count. * $p<0.05$. SDNN – standard deviation of all normal RR intervals during 24 h; SDANN – standard deviation of 5-minute mean RR intervals; rMSSD – root-mean-square of difference of successive RR intervals; pNN50 – percentage of adjacent RR intervals >50 ms different; QTc – corrected QT interval; HR – heart rate; LVEF – left ventricular ejection fraction; LVSF – left ventricular fractional shortening; PVCs – premature ventricular contractions.

a significant correlation between changes in LVEF and time domain parameters of HRV, including SDNN, rMSSD, and pNN50. In accordance with the results obtained from adults, the improvement of the autonomic function seen after the initiation of carvedilol therapy is likely to play an important role in children with DCM. Recently, some authors have observed a statistically significant association between sudden cardiac death and depressed SDNN in patients with DCM. However, Bilchick et al. [28] demonstrated that SDNN has a strong and independent association with mortality in patients with moderate-to-severe CHF [29]. In this context, the UK-Heart prospective study [10] has recently demonstrated that reduced SDNN was the best noninvasive independent predictor of cardiac death in patients with CHF. In our study, SDNN and SDANN were found to be increased after the addition of carvedilol to standard medical therapy; these results may have important clinical implications. The pNN50 and rMSSD predominantly reflect parasympathetic activity and are independent of long-term trends [30]. In the present study, improvements in rMSSD and pNN50 were noted, and pNN50 and rMSSD correlated to improvement in LVEF. Our findings confirm that carvedilol treatment has a beneficial effect on the mechanisms that sustain the harmful hyperadrenergic state and may improve prognosis in children with DCM.

QTd has been found to be a significant, noninvasive prognostic marker of inhomogeneity of myocardial repolarization in several disease settings, and increased QTd may predispose to arrhythmic events [12,31]. In a retrospective study of adult patients with CHF, Fu et al. [32] found a larger QTd in patients who died suddenly or had spontaneous ventricular tachycardia than in survivors. However, only limited data is available regarding the effects of carvedilol on QTd in children with DCM. One retrospective study reported significant increases in QTd values in patients with LV systolic dysfunction [13]. Our study showed that carvedilol therapy decreased QT dispersion and QTc parameters, and improved ventricular repolarization characteristics in children with DCM after 6 months of follow-up.

A randomized trial in adult patients with DCM showed a significant effect of carvedilol in reducing ventricular arrhythmias [9]. SDNN and SDANN could predict ventricular tachycardia on Holter monitoring of patients with CHF [30]. Our study results suggest that the increase in SDNN and reduction in QTd are related with decrease in total PVCs. The increase in SDNN and reduction in QTd under carvedilol treatment may be partly due to an adrenergic blocking effect. Moreover, antiapoptotic effects and inhibition of chronic remodeling of the myocardium may indirectly contribute to the observed homogenization of the ventricular repolarization process and prevention of induction of arrhythmia in patients with CHF [12]. We observed that ventricular ectopic beats disappeared in 4 patients and decreased in 2 patients with carvedilol treatment. Reduced heart rate at rest may lead to better oxygen supply, lower the risk for life-threatening arrhythmia, and slow the myocardial remodeling process; thus, carvedilol may have also been effective in the control of ventricular ectopic beats [33,34]. Our data support the evidence that the increase in heart rate variability reflects improved autonomic regulation of heart rate, and show a significant correlation between heart rate variability changes and hemodynamic improvement with carvedilol therapy in children with DCM.

Conclusions

We conclude that the addition of carvedilol to standard medical regimens can improve clinical symptoms and heart rate

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variability in association with improved left ventricular function, and reduce arrhythmia markers in children with DCM. A randomized, controlled, prospective trial is required to determine the true efficacy of carvedilol on the progression of congestive heart failure and to more clearly define its role in the cardiac autonomic dysfunction and rhythm disorders of children with DCM.

Conflict of interest

None.

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