Effects of Carvedilol on Heart Rate Dynamics in Patients with Congestive Heart Failure

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Background: Patients with congestive heart failure (CHF) have alterations in the traditional and nonlinear indices of heart rate (HR) dynamics, which have been associated with an increased risk of mortality. This study was designed to test the effects of carvedilol, a nonselective beta-blocker with alpha-1 blocking properties, on HR dynamics in patients with CHF.

Methods: We studied 15 patients with CHF secondary to ischemic or idiopathic cardiomyopathy who met the following inclusion criteria: NYHA functional class II-III, optimal conventional medical therapy, normal sinus rhythm, left ventricular ejection fraction (LVEF) of $< 40\%$, and resting systolic blood pressure greater than 100 mmHg. The 6-minute corridor walk test, estimation of LVEF, and 24-hour Holter recording were performed at baseline and after 12 weeks of therapy with carvedilol. Traditional time and frequency domain measures and short-term fractal scaling exponent of HR dynamics were analyzed.

Results: After 12 weeks of therapy with carvedilol, the mean LVEF improved significantly (from 0.27 ± 0.08 to 0.38 ± 0.08, $P < 0.001$). The average HR decreased significantly (from 86 ± 11 to 70 ± 8 beats/min, $P < 0.001$). The mean distance traveled in the 6-minute walk test increased significantly (from 177 ± 44 to 273 ± 55 m, $P < 0.01$). The frequency-domain indices (HF and LF), the time domain indices (rMSSD and PNN5), and the short-term fractal scaling exponent increased significantly. The scaling exponent increased particularly among the patients with the lowest initial values (< 1.0), and the change in the fractal scaling exponent correlated with the change in ejection fraction ($r = 0.63$, $P < 0.01$).

Conclusion: Carvedilol improves time and frequency domain indices of HR variability and corrects the altered scaling properties of HR dynamics in patients with CHF. It also improves LVEF and functional capacity. These specific changes in HR behavior caused by carvedilol treatment may reflect the normalization of impaired cardiovascular neural regulation of patients with CHF.

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carvedilol; heart rate variability; congestive heart failure.

Congestive heart failure (CHF) is accompanied by alterations in both traditional time and frequency measures and nonlinear indices of heart rate (HR) dynamics.[1-4] Recent studies have shown that these alterations in the indices of HR variability are associated with an increased risk of mortality, particularly in patients with depressed left ventricular ejection fraction (LVEF).[1-4] Therefore, there is a

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need to understand the pathophysiologic mechanisms of these abnormalities in HR behavior in patients with CHF, in order to achieve better profiling of risk and to design more specific therapeutic modalities.

Therapy with beta-blockers increases the traditional time and frequency domain measures of HR variability.[5-7] A recent clinical study also demonstrated that atenolol exerts a beneficial effect on nonlinear indices of HR dynamics in CHF.[8] Carvedilol, a nonselective beta-blocker and a selective alpha-1 blocker decreases morbidity and mortality in CHF.[9] There is limited data reported in the literature about the effect of carvedilol on HR variability.[10] The purpose of this study was to evaluate the effect of carvedilol on traditional and nonlinear indices of HR variability in patients with CHF.

METHODS

We studied 15 patients with CHF followed in the cardiology clinic at the VA Medical Center. The inclusion criteria were: 1) cardiomyopathy (ischemic or nonischemic) with LVEF of < 40%, determined by echocardiography or nuclear scintigraphy; 2) NYHA functional class II or III; 3) systolic blood pressure > 100 mmHg; and 4) maximal therapy with diuretics, digoxin, and ACE inhibitors. A written informed consent was obtained from the patients. The exclusion criteria were: 1) any contraindication to beta-blocker therapy; 2) rhythm other than sinus; 3) diabetes mellitus; 4) inability to perform 6-minute walk test; and 5) use of antiarrythmic drugs.

All patients had a baseline 12-lead EKG, 24-hour Holter, 6-minute corridor walk test, and echocardiogram or nuclear scintigraphy for assessment of LVEF. These were repeated after 12 weeks of carvedilol therapy. All patients received a test dose of carvedilol 3.125 mg and were monitored for 1 hour for any signs of intolerance. All 15 patients tolerated the test dose, and were started on carvedilol 3.125 mg twice a day. This dose was increased weekly, until a maximum dose of 100 mg/day was achieved or adverse effects appeared.

A Marquette 8000 Holter system was used for ambulatory 24-hour recordings. All recordings were manually edited to exclude ectopic beats and artefact. Mean HR, standard deviation of normal-to-normal R-R intervals (SDNN), proportion of adjacent RR more than 50 ms different (PNN50), and root mean square of difference of successive RR (rMSSD) were used as a time-domain indices. Spectral analysis was done by fast Fourier transformation of 24-hour data. Low frequency power (LF) was measured in the 0.04-0.15 Hz band, and the high frequency power (HF) was measured in the 0.15-0.40 Hz band as recommended by ESC/NASPE task force on heart rate variability.[11] For short-term fractal scaling analysis, the detrended fluctuation analysis (DFA) technique was used.[12-14] This method quantifies the presence or absence of fractal correlation properties, and has been validated for HR data. In this method, the root-mean-square fluctuation of integrated and detrended time series is measured in each observation window and plotted against the size of the window on a log-log scale. In our study HR correlations were defined for short-term (< 11 beats) fluctuations in the R-R interval data (short-term scaling exponent α_1).

A commercial software program (SPSS 9.0 program for Windows) was used for statistical analysis. Data are presented as the mean ± SD, unless otherwise indicated. Measurements before and after carvedilol therapy were compared using the paired Student's *t*-test. A P value < 0.05 was considered significant. In addition to absolute values, a logarithmic transformation to the natural base was performed on the spectral components of HR variability. Pearson correlation coefficient was used to estimate the correlations between different variables.

RESULTS

The demographic and clinical characteristics of the patients are presented in Table 1. All 15 patients, 8 with ischemic cardiomyopathy, and 7 with nonischemic cardiomyopathy, completed the study. The effect of carvedilol on HR dynamics, LVEF, and functional capacity as measured by the 6-minute walk test, are shown in Table 2. The mean LVEF improved from 0.27 ± 0.08 at baseline to 0.38 ± 0.08 after 3 months of therapy (P < 0.001). The mean distance traveled in the 6-minute walk test increased significantly (from 177 ± 44 to 273 ± 55 m, P < 0.01). The average HR decreased significantly (P < 0.001). The frequency-domain indices (HF and LF, P < 0.05 and P < 0.01, respectively), as well as the time domain indices (rMSSD and PNN50, P < 0.05 for both), increased signifi-

Table 1. Demographic and Clinical Characteristics of Study Patients (n = 15)

Demographics:	
Mean age (years)	62 ± 11
Gender (men/women)	15/0
White/African-American	13/2
Clinical Characteristics:	
Coronary artery disease	8
Hypertension	8
Mean blood pressure	94 ± 14
LVEF	0.27 ± 0.08
ACE inhibitors	15
Diuretics	15
Digoxin	15
Carvedilol (mean dose, mg)	32 ± 8

ACE = angiotensin converting enzyme; CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

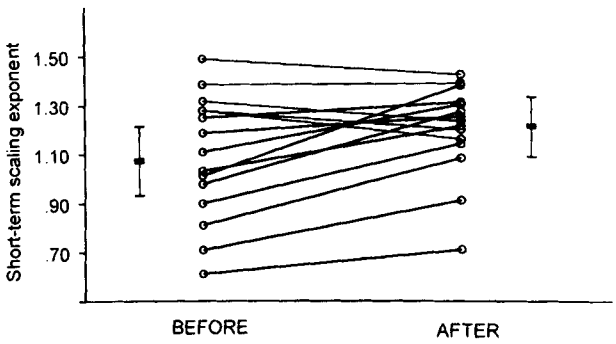

Figure 1. Individual changes of short-term scaling exponent after 12 weeks carvedilol treatment among patients with CHF.

cantly. In scaling analysis of HR behavior, a significant change in short-term fractal scaling exponent (from 1.08 ± 0.24 to 1.19 ± 0.19, $P < 0.05$) toward more correlated short-term HR dynamics was seen after 12 weeks therapy with carvedilol. The exponent increased particularly in the patients with the lowest initial values (Fig. 1.).

Time and frequency domain measures of HR variability, i.e., mean HR, SDNN, and spectral indices had relatively high mutual correlation with each other ($r = 0.5$ to 0.9, $P < 0.001$ for all) in baseline as well as after treatment with carvedilol, but short-term scaling exponent had only a weak negative or no correlation with mean HR ($r < -0.3$, P = NS). None of the HR variability indices showed a significant correlation with the LVEF measured at baseline ($r < 0.4$, P = NS for all). However, the change in the short-term scaling exponent value and change in high frequency spectral power had a significant mutual correlation with the change in LVEF during carvedilol treatment ($r = 0.6$, $P < 0.01$ and $r = -0.5$, $P < 0.05$, respectively, Fig. 2.). Change in the LVEF value did not correlate significantly with the change in mean HR or standard deviation of all RR intervals.

DISCUSSION

The main finding of this study is that carvedilol therapy increases time and frequency domain mea-

Table 2. Effect of Carvedilol on Heart Rate Variability and Clinical Parameters

	Baseline	Carvedilol Therapy	P Value
Mean heart rate (beats/min)	86 ± 11	70 ± 8	<0.001
Short-term fractal exponent (α_1)	1.08 ± 0.24	1.19 ± 0.19	<0.05
Frequency domain:			
lnLF (0.04–0.15 Hz)	5.0 ± 1.0	5.7 ± 0.9	<0.01
lnHF (0.15–0.40 Hz)	4.7 ± 0.7	5.1 ± 0.7	<0.05
Time domain:			
SDNN (ms)	106 ± 47	109 ± 28	NS
SDANN (ms)	58 ± 22	68 ± 24	NS
rMSSD	22 ± 8	27 ± 9	<0.05
PNN50 (%)	3.9 ± 3.2	5.2 ± 3.5	<0.05
Mean blood pressure (mmHg)	94 ± 14	83 ± 8	<0.01
LVEF	0.27 ± 0.08	0.38 ± 0.08	<0.001
6 minute walk distance (m)	177 ± 44	273 ± 55	<0.01

HF = high frequency spectral component; LF = low frequency spectral component; ln = natural logarithm; LVEF = left ventricular ejection fraction; p values determined in T-test analysis. NS = Not significant; PNN50 = proportion of adjacent R-R interval more than 50 msec difference; rMSSD = root mean square of difference of successive R-R intervals; SDANN = standard deviation of all N-N intervals of 5 minute epocs; SDNN = standard deviation of all N-N intervals.

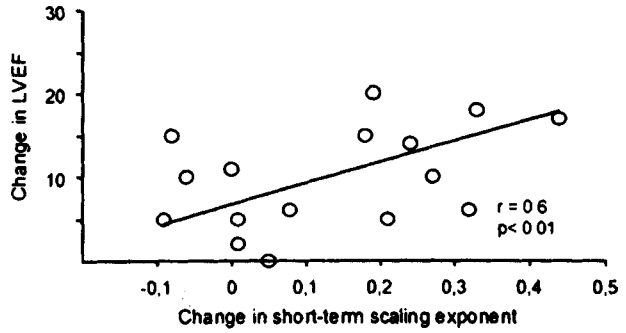

Figure 2. Correlation between a change in short-term scaling exponent and a change in left ventricular systolic function among patients treated with carvedilol.

sures and corrects the abnormal short-term scaling patterns of HR dynamics in patients with CHF. The increase in short-term scaling exponent of HR dynamics was greatest among those patients with an abnormal value at the baseline and it was correlated to an improvement of the LVEF.

Several studies have shown that traditional time and frequency domain measures of HR variability are reduced in patients with CHF, and this finding is associated with increased mortality.[1,2] Particularly, a specific spectral pattern with a marked reduction or even an absence of low frequency oscillations of HR have been described in severe CHF.[15] A change in HR dynamics caused by increased sympathetic activation seems to be clearly different among patients with CHF than among normal healthy humans. Among patients with CHF, HR fluctuations are most prominently decreased in low frequency area and rather no reduction or a slight increase in high frequency area.[15,16] On the contrary, during sympathoexcitation of healthy humans, low frequency component is increased relative to the high frequency component. This absence of low frequency fluctuation of HR in CHF is associated to unfavorable outcome of heart failure patients.[15,16]

Among patients with depressed LVEF, decreased short-term scaling exponent values are frequently observed. Alterations from this normal "fractal-like" HR dynamics seem to reflect a specific perturbation in cardiovascular regulation system, which might at least partially explain the increased cardiac mortality in CHF.[4,16] The reasons for reduced short-term fractal scaling exponent and reduced low frequency oscillations are not completely established. However, recent experiments in healthy volunteers showed that high levels of circulating norepinephrin decrease the short-term fractal scaling exponent value,[17] and results in reduced low frequency oscillations of HR. These data support the concept that sympathoexcitation caused by CHF well explain the observed alterations in HR dynamics. The present data show that carvedilol partly corrects these abnormalities in HR behavior by reducing the sympathetic outflow.

Therapy with metoprolol results in a significant increase in time and frequency domain measures of HR variability.[7] Atenolol has been reported to produce a significant improvement in the scaling indices of HR dynamics among patients with CHF.[8] This suggests more organized short-term properties of HR behavior. Although carvedilol has been demonstrated to improve morbidity and mortality in CHF,[9] its effect on heart rate variability has not been studied extensively. In a recent study, carvedilol was reported to improve baroreflex sensitivity, SDNN, and rMSDD.[10] In the present study, improvements in rMSSD and PNN50 were noted. SDNN as well as SDANN demonstrated a trend of increasing values but the change was not statistically significant. There are at least two possible explanations for this. The study group is relatively small and with larger numbers this change probably would have reached statistical significance. Among patients with CHF, the major abnormality in HR dynamics is the lack of oscillation in LF area with less marked alterations in ULF spectral power. Therefore the changes caused by beta-blockers are more prominent in specific spectral bands than in SDNN where changes partially "drown" to the very low fluctuation of HR. Therefore it is not surprising that changes are more evident in other parameters rather than in SDNN. In addition, carvedilol was associated with a significant increase in the short-term fractal scaling exponent. Carvedilol seemed to improve the HR fluctuation properties of patients with clearly altered scaling characteristics at baseline, while it did not affect HR fluctuation properties of the patients with well preserved short-term scaling qualities (Fig. 1). These improvements in traditional and nonlinear indices of HR dynamics might explain some of the beneficial effects of carvedilol on the survival of patients with CHF.[9,18] Therapy with carvedilol was also associated with significant improvement in LVEF and functional capacity, con-

sistent with the findings of previous clinical studies.[19,20]

ACE inhibitors are first line therapy in CHF due to their beneficial effects on survival. Captopril and enalapril have also demonstrated effects on HR variability indices.[21,22] Additionally, spironolactone and digoxin have shown beneficial effects on HR variability indices in patients with CHF.[23,24] The mechanism of altered HR variability in patients with CHF might be due to direct influences of the increased neurohormonal activation that characterizes CHF.[25] The beneficial effects of beta-blockers, ACE inhibitors, and spironolactone on HR variability measurements in CHF reinforces this concept, since all of these drugs exert an inhibitory effect on different arms of the increased neurohormonal activation in CHF and have been associated with improvement in survival. This suggests that HR variability measurements could be utilized to quantify the degree of neurohormonal derangement among patients with CHF, and perhaps to assess the potential benefit of different pharmacological agents.[21-24]

A relatively small study group and the lack of a placebo control group are obvious limitations of the present study. However, since the beneficial effect of beta-blockers, particularly of carvedilol, on survival among patients with heart failure is well proven, a placebo group may not be appropriate.

In addition to improvements in left ventricular systolic function and functional capacity, carvedilol exerts clear effects on nonlinear scaling indices as well as conventional time and frequency domain measures of HR variability in patients with CHF. These specific changes in HR behavior caused by carvedilol treatment may reflect the normalization of impaired cardiovascular neural regulation in patients with CHF and explain some of its beneficial effects on survival.

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