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Clinical Investigations

The Effects of Metoprolol and Captopril on Heart Rate Variability in Patients with Idiopathic Dilated Cardiomyopathy

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Summary

Background: The effects of treatment with captopril or metoprolol on heart rate variability (HRV) were investigated in 38 patients (29 men and 9 women) with mild to moderate symptoms of heart failure due to idiopathic dilated cardiomyopathy (DCM).

Hypothesis: The aim of the study was to investigate and compare the effects of the angiotensin-converting enzyme inhibitor captopril with those of the selective beta-adrenergic receptor blocker metoprolol on HRV in patients with idiopathic DCM.

Methods: Heart rate variability was analyzed in the time and frequency domains from 18 h of Holter monitoring before randomized treatment was started, after 6 months of therapy, and 1 month after therapy was stopped.

Results: Captopril treatment increased HRV expressed as total power and low-frequency power in the frequency domain. There was no change in the time domain. In the metoprolol group, there was a pronounced increase in both time- and frequency-domain indices of HRV. The increase in total power was partly maintained 1 month after therapy was stopped in both treatment groups.

Conclusion: Treatment with captopril and metoprolol increases HRV in patients with DCM. This effect seems to be maintained for at least 1 month after therapy is stopped. The increase in HRV seems to be more pronounced with metoprolol, and the two different pharmacologic approaches may have additive effects that are of prognostic importance in patients with heart failure.

Key words: heart rate variability, dilated cardiomyopathy, treatment, beta blocker, angiotensin-converting enzyme inhibitor

Introduction

Heart rate variability (HRV) has been reported to be a useful method for the assessment of cardiovascular autonomic neural inputs.[1,2] In patients with myocardial infarction, reduced HRV is associated with a poor prognosis mainly because of an increased risk for malignant ventricular arrhythmias and sudden death.[3–5] Heart rate variability has also been described as a powerful predictor of increased risk for cardiac death in patients awaiting heart transplantation.[6] However, the relationship between left ventricular (LV) ejection fraction (EF) and HRV parameters and its physiologic background has been widely discussed. A positive correlation between LVEF and these parameters has been reported by several authors,[7–9] but on the other hand Kienzle *et al.* could not find any correlations between HRV, LVEF, New York Heart Association (NYHA) functional class, or age.[10]

In patients with congestive heart failure (CHF), prognosis has been correlated to the degree of neurohormonal activation.[11] As a consequence, neurohormonal inhibiting agents such as angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic receptor blockers have favorable effects on both morbidity and mortality in patients with CHF.[11,12]

Most reports concerning HRV and prognosis in patients with CHF have dealt with patients with ischemic heart disease.[2–5] The significance of HRV in patients with cardiomyopathy is still not fully known, and in patients with hypertrophic cardiomyopathy Counihan *et al.* found no correlation between HRV and the established risk factors for sudden death.[13]

The aim of the present study was to investigate and compare the effects of an ACE inhibitor (captopril) with the effects of a selective beta-adrenergic receptor blocker (metoprolol) on HRV in patients with idiopathic dilated cardiomyopathy (DCM).

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Patients

Inclusion criteria consisted of fulfillment of the WHO/ISFC task force criteria in the definition and classification of dilated cardiomyopathy[14] and age between 18 and 65 years. Exclusion criteria were coronary artery disease (> 50% diameter reduction of a major epicardial vessel) based on coronary angiography performed in all patients over the age of 30 years, clinical signs or a history of myocarditis, obstructive lung disease requiring treatment with beta-2-agonists, excessive alcohol consumption (> 700 g per week), diabetes mellitus, history of hypothyroidism or thyreotoxicosis, hypertension or other serious disease, heart valve disease, atrioventricular (AV) block II or III, or severely depressed renal function (serum creatinine > 200 mmol/l), previous or ongoing treatment with beta blockers or ACE inhibitors, and need of heart transplantation.

Patients

The study included 38 patients (29 men and 9 women). All were classified according to the recommendations of the NYHA into functional classes, and their clinical characteristics at baseline are shown in Table I.

Medical Therapy

Ten patients with a history of previous atrial fibrillation were treated with digoxin and all patients were in stable sinus rhythm at the time of investigation. Amiodarone was used in one patient in the captopril group because of previous ventricular arrhythmias. Almost all patients (n = 34) suffered from dyspnea to some extent and they were treated with diuretics (furosemide). No patient was treated with vasodilating drugs or potassium-sparing drugs.

Treatment was started with either metoprolol 5 mg twice daily, or captopril 6.25 mg twice daily, respectively. The daily dose was increased over 6 weeks. The target dose for metoprolol was 150 mg daily and for captopril 100 mg daily. Drugs were administered on a double-blind basis.

All patients gave their informed consent to the trial, which was approved by the local Committee of Ethics at the University Hospitals of Linköping (L) and Huddinge (H).

TABLE I Clinical characteristics at baseline of the captopril- and the metoprolol-treated patients

	Captopril	Metoprolol	p Value
No. of patients	21	17	
Mean age (years)	49, 26–60[a]	49, 35–61[a]	NS
Sex (male/female)	15/6	14/3	NS
NYHA class			
I	2	1	
II	13	9	
III	6	7	
Treatment			
Digitalis (n)	4	6	NS
Furosemide (n)	19	15	NS
Mean dose (mg)	59, 0–160[a]	54, 0-240[a]	NS
Heart rate (rest) (/min)	76 ± 10	85 ± 9	p<0.05
Maximum exercise capacity (Watt)	124 ± 60	117 ± 47	NS
LVID ed (mm)	68 ± 10	71 ± 9	NS
LVID es (mm)	58 ± 10	63 ± 10	NS
Fractional shortening	0.16 ± 0.06	0.12 ± 0.05	p<0.05

Figures are the mean ± standard deviation (SD).
Figures refer to number unless otherwise stated.
[a] Gives the range.
Abbreviations: NYHA = New York Heart Assoication, LVID ed = left ventricular inner dimension at end diastole, LVID es = left ventricular inner dimension at end systole.

Study Protocol

The study was designed as a prospective, double-blind, controlled parallel-group study. Patients were randomized to active treatment with either captopril or metoprolol. Prior to randomization, patients were also stratified according to their exercise capacity. The rationale for this strategy was to distribute the patients with more severe disease more evenly between the two groups. All patients were investigated with 18 h Holter monitoring at baseline, after 6 months of therapy, and 1 month after therapy was stopped.

Methods

This report is a part of a study investigating therapy with either metoprolol or captopril in patients with DCM.[15] The diagnosis of DCM was based on echocardiography and the measurements were taken according to the recommendations of the American Society of Echocardiography.[16] Left ventricular dilatation was defined as LV end-diastolic dimension > 2 mm above the reference for age and body weight.[17] Systolic dysfunction was defined as a fractional shortening < 24%. Echocardiography also excluded significant heart valve disease in all cases.

Heart rate variability was analyzed in the time and frequency domains from 18 h of Holter monitoring before treatment, after 6 months of therapy (captopril vs. metoprolol), and 1 month after therapy was stopped. Recordings with < 13.5 h of technically acceptable quality were excluded from analysis. The RR intervals and their corresponding classification of QRS complexes were exported as an ASCII-text file from the commercially available electrocardiographic (ECG) analyzer in the Aspect Holter System (Daltek Biomedical, Sweden). The RR intervals were expressed as centisec (cs) with an accuracy of ± one cs. The exported text files were fed into a custom made software running under MS-Windows. Data were presented in segments of 5 min. The RR intervals were checked for the occurrence of non-normal beats. Such beats were deleted and interpolated using cubic spline interpolation. In addition, sudden long RR intervals, that is, dropped beats, were interpolated. The periods of raw RR data were corrected for

linear trend using linear regression and subtraction of the mean of all RR intervals in the same segment. Segments containing > 10% non-normal beats were excluded. If more than 25% of the segments had to be excluded for this reason, the whole time period was withdrawn from analysis. The following time domain indices were used:

SDNN: Standard deviation of all RR intervals (ms)
SDANN: Standard deviation of the average of RR intervals in all 5-min segments of the entire record recording (ms)
SDNNindex: Mean of the standard deviations of all RR intervals for all 5-min segments of the entire record recording (ms).

SDNN is a measure of the total variability, SDANN of the long-term variability, and SDNNindex of the short-term variability.[18]

In the frequency domain analysis, the power at different frequencies was determined using an autoregressive spectral analysis method.[19] The model order of the autoregressive spectral analysis (number of coefficients in the polynominal describing the time series) was constantly set at 18. The following frequency domain indices were used:

TP (total power): Variance of all RR intervals (ms^2), <0.4 Hz
HF (high frequency): Power in the high-frequency range (ms^2), 0.15–0.4 Hz
LF (low frequency): Power in the low-frequency range (ms^2), 0.04–0.15 Hz
VLF (very low frequency): Power in the very low-frequency range (ms^2), 0.003–0.04 Hz

The values for HF, LF, and VLF were calculated as absolute and normalized values.[18]

Statistical Methods

All data are presented as mean ± standard deviation (SD) and were subjected to one-way analysis of variance (ANOVA) for repeated measurements within treatment groups. Group differences were tested with two-tailed Student's *t*-test for unpaired samples. A p value of < 0.05 was required for statistical significance.

Results

Baseline characteristics of the 38 patients included are described in Table I. There were only minor differences with regard to clinical characteristics between the groups at baseline. Both drugs were well tolerated,[15] and only 2 of the 38 patients (both in the captopril group) did not reach the target dose. The mean daily dose for metoprolol was 150 mg and for captopril 99 mg per day.

Heart Rate Variability and Power Spectrum Analysis

Captopril: The time- and frequency-domain analysis results for the captopril group are shown in Table II. Heart rate did not change during captopril therapy. As can be seen, there

TABLE II Heart rate, heart rate variability, and power spectrum analysis before, after 6 months of therapy, and 1 month after stopping therapy with captopril (n = 21)

	Before	6 Months	After	p Value
Heart rate rest (beats/min)	76 ± 10	75 ± 10	74 ± 10	NS
Heart rate variability				
SDNN	130 ± 40	139 ± 46	136 ± 29	NS
SDNNindex	38 ± 9	44 ± 13	45 ± 12	0.07
SDNN/mean RR	0.16 ± 0.03	0.17 ± 0.03	0.17 ± 0.03	NS
SDNNindex/mean RR	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.009	NS
Frequency domain analysis				
TP	914 ± 445	1519 ± 1117	1532 ± 1063	<0.05
HF	157 ± 92	318 ± 409	312 ± 453	NS
HF/TP	0.17 ± 0.04	0.18 ± 0.07	0.18 ± 0.09	NS
LF	249 ± 142	550 ± 502	483 ± 360	<0.05
LF/TP	0.265 ± 0.03	0.33 ± 0.06	0.31 ± 0.05	<0.01
VLF	470 ± 221	583 ± 307	663 ± 421	NS
VLF/TP	0.47 ± 0.05	0.42 ± 0.07	0.43 ± 0.08	<0.01

Values are expressed as mean ± standard deviation (SD).
Abbreviations: SDNN = standard deviation of all RR-intervals (ms); SDNN index = mean for the standard deviations of all RR intervals for all 5-min segments of the entire recording (ms); TP, total power = variancy of all RR-intervals, < 0.4 Hz; HF, high frequency = power in the high frequency range, 0.15–0.4 Hz; LF, low frequency = power in the low frequency range, 0.04–0.15 Hz; VLF, very low frequency = power in the very low frequency range, 0.003–0.04 Hz.

TABLE III Heart rate variability and power spectrum analysis before, after 6 months of therapy, and 1 month after stopping therapy with metoprolol (n = 17)

	Before	6 Months	After	p Value
Heart rate rest (beats/min)	85 ± 9	65 ± 7	79 ± 10	<0.001
Heart rate variability				
SDNN	115 ± 26	152 ± 38	138 ± 29	<0.001
SDNNindex	41 ± 11	62 ± 15	52 ± 15	<0.001
SDNN/mean RR	0.16 ± 0.03	0.16 ± 0.03	0.18 ± 0.03	NS
SDNNindex/ mean RR	0.06 ± 0.01	0.07 ± 0.014	0.07 ± 0.014	NS
Frequency domain analysis				
TP	1370 ± 806	3051 ± 1940	2165 ± 1124	<0.01
HF	188 ± 127	476 ± 206	351 ± 250	<0.001
HF/TP	0.14 ± 0.05	0.18 ± 0.05	0.16 ± 0.05	<0.05
LF	426 ± 363	1089 ± 958	720 ± 434	<0.01
LF/TP	0.30 ± 0.07	0.33 ± 0.06	0.33 ± 0.09	NS
VLF	695 ± 375	1343 ± 757	992 ± 566	<0.01
VLF/TP	0.47 ± 0.06	0.42 ± 0.04	0.43 ± 0.07	<0.01

Values are expressed as mean ± standard deviation (SD).
Abbreviations as in Table II.

was no statistically significant difference in SD or SDNNindex even if there was a tendency toward an increase in SDNNindex (p = 0.07). In the frequency-domain analyses, there was an increase in TP and in the LF domain both for absolute and normalized values. Power in the HF was unchanged, as was the absolute value for VLF, while the normalized values decreased. Low frequency/HF increased significantly.

Metoprolol: The time and frequency-domain analysis results for the metoprolol group are shown in Table III. Heart rate was reduced during metoprolol therapy. Heart rate variability increased for all indices tested, both in the time and frequency domain, except for LF/TP which was unchanged and VLF/TP which decreased.

Captopril versus Metoprolol

The effects of the different pharmacologic approaches on HRV are shown in Figures 1–3. As can be seen, heart rate and SDNNindex were higher in the metoprolol group than in the captopril group at baseline. The SDNNindex increased in both groups during therapy, but metoprolol reduced heart rate and increased SDNNindex more than did captopril. There was a tendency toward a higher TP at baseline in the metoprolol group compared with the captopril group (p = 0.055), but TP increased in both groups during therapy. However, metoprolol increased TP more than captopril did. Metoprolol also increased the LF and the VLF domains significantly more than did captopril.

Discussion

Heart rate variability is depressed in patients with CHF.[10,20] In the present study, we have demonstrated an overall increase in HRV during treatment with captopril or metoprolol in patients with DCM, which is in accordance with previous studies on CHF.[21–23] The two different pharmacologic approaches compared in the present study are well documented in the

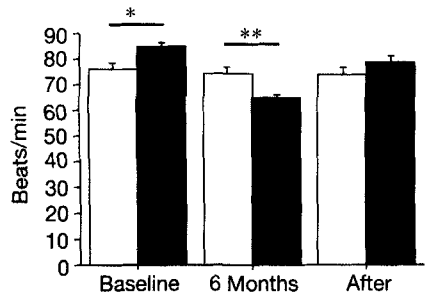

FIG. 1 Heart rate at baseline, at 6 months of therapy, and 1 month after therapy was stopped. □ = Captopril, ■ = metoprolol, *p > 0.05, **p < 0.01.

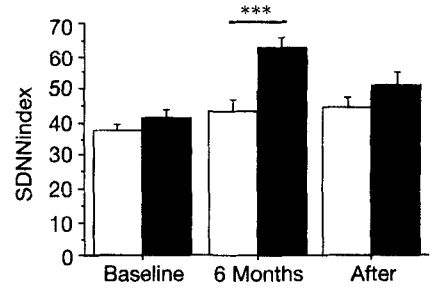

FIG. 2 SDNNindex at baseline, at 6 months of therapy, and 1 month after therapy was stopped. □ = Captopril, ■ = metoprolol, ***p < 0.001.

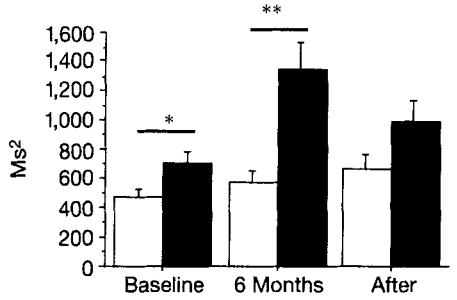

FIG. 3 Very low frequency (VLF) at baseline, at 6 months of therapy, and 1 month after therapy was stopped. □ = Captopril, ■ = metoprolol, *$p > 0.05$, **$p < 0.01$.

treatment of patients with CHF,[11, 24] and both have effects on neurohumoral activation, which is linked to the prognosis.[25]

Treatment with ACE inhibitors is known not only to increase the parasympathetic activity,[26] but also to decrease the augmented sympathetic activity in patients with CHF.[27] In the present study, there was an increase in TP and LF power, reflecting modulation of both sympathetic and parasympathetic tone. In contrast, power in the HF band, reflecting parasympathetic modulation alone, remained unchanged. Zhang *et al.*,[28] however, reported an increase in HF, but in that study 6 of the 12 patients had ischemic cardiomyopathy, which may contribute to the fact that the results differed. The long-term recordings analyzed by the time domain methods should contain at least 18 h of analyzable ECG data that include the whole night. In this study, 47% of recorded ECG contained 13.5 to 18 h and 53% more than 18 h of analyzable material (in all patients a whole night was included). This might have influenced the results of the time domain indices, especially in the captopril group.

Therapy with beta blockers is reported to increase HRV both in time and frequency domains.[22, 23] Beta-adrenergic blockers are known to act by reducing the sympathetic activity and can be regarded as restoring the autonomic balance in patients with CHF.[23] As expected, treatment with metoprolol decreased heart rate and increased the mean sinus cycle length. For simple time domain indices, total variance of the RR intervals may be dependent on the duration of the mean RR interval. This is avoided if the variability is calculated on the basis of beats/min (instantaneous heart rate) which was done in the frequency analysis. Correcting the time domain indices for mean RR did not alter the results in this study (Tables II and III). Similar results were obtained treating patients with acute myocardial infarction with beta blockers.[29] We found an increase in LF and HF power (for HF in both absolute and normalized values), while normalized LF was on the borderline of significance, indicating a shift to an augmented parasympathetic influence during beta-blocker therapy. Heart rate variability was analyzed from long-term recordings, which raises the question of stationary components in the data sets. The physiologic mechanisms that affect the different frequency components are in themselves nonstationary. These long-term recordings therefore constitute averages of modulations of autonomic tone.[18] This study focuses on patients with mild to moderate symptoms of heart failure and with normal levels of angiotensin II (Jansson *et al.*, *J Int Med* 1999, in press) as an indication of only partial neurohumoral activation. In patients with severe heart failure, the LF component is depressed despite a marked sympathetic activation.[10] In our study, the LF component increased with time in both treatment groups and did not return to baseline after 1 month without treatment, probably due to an increase in the responsiveness of the sinus node to neural inputs during long-term treatment. Such an effect would probably be observed in the LF band during long-term recordings in the nonstationary condition.

Normalized power in the VLF range decreased significantly in both groups. The physiologic background to these long cycle length fluctuations is not completely understood, but they may be influenced by diurnal variations in hormonal systems such as the renin-angiotensin system. If so, the changes in the VLF band may reflect a neurohumoral influence on HRV.

Heart rate was higher in the metoprolol group at baseline and was, not unexpectedly, lower at 6 months. The difference between the groups in the basal state was surprising, as the patients were randomly selected (and also stratified according to exercise capacity) and the groups did not differ in any other respect.

Heart rate variability is claimed to be a more reliable prognostic index than heart rate.[30, 31] The normal physiologic modulation of autonomic nervous functions reflected by heart rate and HRV correlations might be influenced in patients with CHF by the downregulation of beta adrenergic receptors. Furthermore, in long-term recordings, the effect of heart rate on HRV has less impact, especially when normalized with total power.[32]

In the present study, metoprolol was superior to captopril in increasing HRV in both time and frequency domains. In the Metoprolol in Dilated Cardiomyopathy (MDC) trial,[24] there were favorable effects on LV function and exercise capacity when metoprolol was added to already ongoing therapy with an ACE inhibitor in patients with DCM. There was also a tendency toward a better outcome in the combined endpoint death and need of heart transplantation. Adding a nonselective beta blocker (carvedilol) to patients with CHF already on therapy with digitalis, diuretics, and an ACE inhibitor reduced the risk for sudden death and death due to progressive heart failure.[33] The role of digitalis is noteworthy since digitalis has itself a vagotonic effect and is reported to increase parasympathetic activity in patients with CHF,[34] but in the present study most patients were not treated with digitalis. Fauchier *et al.*[36] have recently reported that depressed HRV in patients with idiopathic DCM was significantly related to LV shortening and peak oxygen uptake and that an increased risk for cardiac death was predicted by reduced HRV. In view of these results, the results of the present study may indicate that there would be additive and beneficial effects on HRV and prognosis when adding a beta-adrenergic receptor blocker in patients with heart failure due to DCM already being treated with an ACE inhibitor.

Conclusions

In patients with mild to moderate symptoms of heart failure due to idiopathic dilated cardiomyopathy, treatment with captopril and metoprolol increases heart rate variability. Metoprolol was superior to captopril especially in the low-frequency domains, which reflects both sympathetic and parasympathetic activity. Combining the drugs may have additive effects on the modulation of heart rate variability, which may have prognostic importance.

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