

PROGNOSTIC ROLE OF HEART RATE REDUCTION UNDER CARVEDILOL THERAPY IN CHRONIC HEART FAILURE

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REZUMAT

Obiectiv: Scopul nostru a fost de a stabili dacă reducerea frecvenței cardiace sub tratament cu carvedilol în insuficiența cardiacă cronică sistolică reprezintă un indicator al ameliorării prognosticului și a statusului neurohormonal. **Material și metode:** Am inclus în mod prospectiv 100 pacienți consecutivi cu insuficiență cardiacă cronică sistolică sub tratament cu inhibitori de enzimă de conversie și diuretice, adresați pentru introducerea terapiei betablocante. Am utilizat carvedilol în doza inițială de 6,25mg, cu creștere progresivă la doza recomandată. End-point-ul la 1 an a fost reprezentat de decese și spitalizări pentru insuficiența cardiacă. Prognosticul a fost estimat în funcție de frecvența cardiacă medie inițială, frecvența cardiacă medie realizată și variația medie a frecvenței cardiace sub terapie. **Rezultate:** Vârsta pacienților a fost cuprinsă între 28 și 80 ani. Etiologia insuficienței cardiace a fost ischemică în 51% din cazuri. Sub tratament cu carvedilol, fracția de ejeție ventriculară stângă și capacitatea funcțională s-au îmbunătățit, în timp ce frecvența cardiacă și concentrația plasmatică a peptidului natriuretic B au scăzut. Frecvența cardiacă inițială a influențat prognosticul la 1 an (18% evenimente în grupul cu frecvență cardiacă inițială crescută, 25% evenimente în grupul cu frecvență cardiacă inițială joasă, $p < 0,05$). În ciuda unui status neurohormonal mai bun, pacienții cu o frecvență cardiacă realizată joasă sub betablocant nu au prezentat o supraviețuire mai bună. **Concluzii:** Frecvența cardiacă realizată și variația frecvenței cardiace sub tratament cu carvedilol nu reprezintă factori predictivi de supraviețuire la 1 an pentru pacienții cu insuficiență cardiacă. Frecvența cardiacă inițială rămâne un factor prognostic semnificativ sub tratament cu carvedilol.

Cuvinte cheie: Frecvență cardiacă, insuficiență cardiacă cronică, betablocante

ABSTRACT

Objective: Our purpose was to determine whether heart rate reduction under carvedilol therapy in patients with chronic systolic heart failure is an indicator of improved outcome and neurohormonal status. **Material and methods:** We prospectively included 100 consecutive patients with chronic systolic heart failure under ACE-inhibitors and diuretics referred for starting beta-blocker therapy. We used carvedilol at an initial 6.25 mg dose, with progressive increase to the recommended dose. The 1-year end-point was represented by death and hospitalization for heart failure. Outcome was assessed according to the initial mean heart rate, mean achieved heart rate and mean heart rate variation under therapy. **Results:** The age of included patients ranged between 28 and 80 years. An ischemic aetiology was identified in 51% of cases. Under carvedilol therapy, left ventricular ejection fraction and functional capacity increased, while heart rate and B-type natriuretic peptide plasma concentration decreased. Initial heart rate had an impact on the event-free survival (18% events in patients with high initial heart rate vs. 25% in patients with low initial heart rate, $p < 0.05$). Despite an improved neurohormonal status, patients with low achieved heart rate under beta-blocker did not have a better 1-year outcome. **Conclusions:** In patients with chronic heart failure, receiving optimal doses of carvedilol, the achieved heart rate and the heart variation are not predictors of a better outcome. Initial heart rate is a significant prognostic marker under carvedilol therapy.

Key Words: Heart rate, chronic heart failure, beta-blockers

INTRODUCTION

Beta-blocker (BB) therapy is highly recommended in all chronic heart failure (CHF) guidelines.^{1,2} Heart rate (HR) reduction under BB therapy in CHF has beneficial effects, mainly as a consequence of improved myocardial energetic balance, subendocardial perfusion and lengthening of the diastolic phase.³⁻⁵

Experimental data in a valvular left ventricular (LV) dysfunction model have shown that the improvement of the LV function under BB therapy may depend solely on HR reduction.⁶ However, under BB therapy an improvement in myocardial function was observed even in patients with high HR.⁷

HR represents an independent cardiovascular risk factor in patients with hypertension and myocardial infarction.^{8,9} Data supporting such a relation in patients with CHF are less convincing. The relation between HR reduction and the beneficial effect of beta-blockers was used to explain differences between BB in the COMET study.¹⁰⁻¹² However this relation has not been demonstrated for carvedilol.

The purpose of our study was to determine whether initial HR, achieved HR under therapy with

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carvedilol and HR variation have an independent prognostic role in patients with CHF.

MATERIALS AND METHODS

Study population

We have prospectively included 100 consecutive patients with systolic CHF referred between November 2004 and November 2005, for starting BB treatment.

The study was in accordance with good clinical practice guidelines and followed the recommendations of the Declaration of Helsinki. All patients have signed the informed consent and the study protocol was approved by the Ethics Committee.

The inclusion criteria were:

- Symptomatic CHF > 1 month;
- Stable patients in New York Heart Association (NYHA) class I to III;
- Echocardiographic LV ejection fraction (EF) < 45%;
- Previous treatment with ACE inhibitors for at least 4 weeks unless contraindicated, and diuretics for at least 2 weeks at optimal doses.

The exclusion criteria were:

- Systolic blood pressure (BP) < 85 mmHg;
- Initial HR < 50/min;
- Sick sinus syndrome, second or third degree atrio-ventricular block;
- History of asthma or severe chronic obstructive pulmonary disease;
- Peripheral arterial disease with symptoms at rest;
- Unstable insulin-dependent diabetes mellitus;
- Unstable angina, myocardial infarction, coronary revascularization, stroke or symptomatic sustained ventricular arrhythmias not adequately treated with anti arrhythmic drugs in the 2 months preceding inclusion;
- Treatment with β -adrenergic or α -adrenergic receptor blockers in the 2 weeks before inclusion;
- Use of inotropic agents other than digitalis;
- Paced rhythm;
- Permanent atrial fibrillation.

Carvedilol administration

Carvedilol was administered at a starting dose of 3.125 mg bid, and increased (if tolerated) at fortnightly intervals to 6.25 mg, 12.5 mg and finally to a target dose of 25 mg bid (50 mg bid in patients > 80 kg). Up-titration was slowed down if deemed appropriate.

Data collection and follow-up

A clinical evaluation was performed at baseline and after reaching the target dose of carvedilol. Patients were examined and classified according to the NYHA classification. At each visit, HR, BP, natremia, creatininemia and B-type natriuretic peptide (BNP) plasma levels were measured.

HR was measured by pulse rate measurement or/and ECG recordings at rest in supine position. Each recorded HR and BP value represented the mean of three measurements at each visit.

To appreciate the functional capacity, a 6-minute walk test on flat ground was carried out. The patient was asked to walk the longest possible distance during the 6-minute test.¹³ The patient could decide to stop or to slow down during the test, according to his state.

Echocardiography was performed using an Agilent Technologies SONOS 5500 device equipped with a 'second harmonic' function at the enrolment visit and after reaching the target dose of carvedilol. EF was measured according to Simpson's biplane method, as recommended by the American Society of Echocardiography.¹⁴

For assessment of BNP levels, a sample of whole blood (5 ml) was collected via a peripheral venous catheter after 15 min of dorsal decubitus. Blood was collected in tubes containing potassium ethylenediamine-tetraacetic acid EDTA (1mg/ml). 2.5ml of whole blood were immediately analyzed using the triage BNP test (Biosite Diagnostics Inc. San Diego, CA). The average confidence limit of the analytical sensitivity was less than 5pg/ml (95% confidence interval of 0.2 - 4.8 pg/ml).

We used a composite end-point represented by death or hospitalization for heart failure. The length of the follow-up was one year. Study patients were divided in two groups, above and below the mean initial HR. One-year outcome and neurohormonal status were determined for the two groups. A possible relation between the composite end-point and the achieved HR and HR variation under carvedilol treatment was also studied. The HR variation was computed as difference between the initial HR and achieved HR at the end of up-titration.

Statistical analysis

Comparisons of variables between groups were performed with a Student t test for continuous variables and a χ^2 test for categorical variables. The level of significance on these univariate analyses was set at less than 0.05. All statistical analyses were performed with SPSS 11.0 software (SPSS Inc, Chicago, IL, USA).

RESULTS

Study patients were divided in two groups: above and below the mean initial HR of 75/min. Their baseline characteristics are summarized in Table 1. There were no significant differences between the two groups in terms of ischemic aetiology of heart failure and clinical status. There was a significantly higher prevalence of women and hypertension in the high initial HR group. A higher prevalence of renal insufficiency, higher levels of BNP and a lower EF were also recorded in the high initial HR group, although the differences weren't statistically significant. ACE inhibitors were administered in 99% of patients, diuretics in 100% of patients. Few patients received amiodarone (10 %, n = 12) and digoxin (5%, n = 11), as patients with arrhythmias and pacemakers were excluded.

Table 1. Baseline characteristics and one year outcome of patients stratified into groups above and below the mean initial HR (75/min).

Variable	All patients (n=100)	Low initial HR (n=42)	High initial HR (n=58)	p value
HR (/min)	76 ± 18	61 ± 9	90 ± 12	<0.001
Age(years)	62 ± 19	58 ± 10	63 ± 11	ns
Male gender (%)	72	80	67	<0.05
Weight (kg)	74 ± 17	71 ± 12	77 ± 20	ns
NYHA class II / III (%)	78 / 22	83 / 18	75 / 25	ns
6 minute walk test (m)	420 ± 123	394 ± 146	442 ± 93	ns
Ischemic aetiology (%)	51	53	50	ns
Hypertension history (%)	55	45	62	<0.05
Diabetes history (%)	25	25	25	ns
Smoking habits (%)	44	43	45	ns
Renal failure (%)	17	7	10	ns
EF (%)	35	38	34	ns
Systolic BP (mmHg)	125 ± 27	123 ± 22	127 ± 31	ns
Creatinine (µmol/l)	118 ± 117	100 ± 67	136 ± 153	ns
Natremia (mmol/l)	138 ± 4	138 ± 3	138 ± 4	ns
BNP (pg/ml)	180 ± 255	116 ± 165	243 ± 310	ns
End point (%)	21	25	18	<0.05

In terms of clinical outcome (cardio-vascular death and hospitalization for heart failure) patients with low initial HR had a significantly poorer one year outcome. (Fig. 1)

Carvedilol therapy was well tolerated in 95% of patients. The mean daily dose of carvedilol at the end of follow-up was 31 mg. A significant reduction of HR was observed under carvedilol treatment. Significant improvement of the neurohormonal status (reduction

of the BNP levels) and of the EF were also observed. These data are revealed in Table 2. Carvedilol daily dose was significantly correlated with BNP variations ($p = 0.005$).

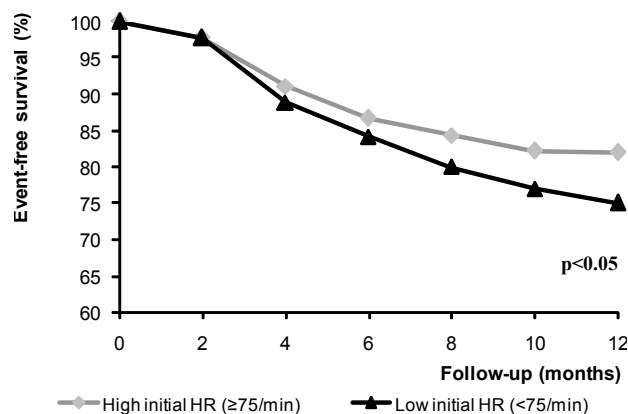


Figure 1. Event-free survival in patients with low initial HR and high initial HR under Carvedilol therapy.

Table 2. Characteristics of all studied patients before and after Carvedilol up-titration.

Variable	Baseline	After Carvedilol up-titration	p value
HR (/min)	76 ± 18	68 ± 12	<0.05
Weight (kg)	74 ± 17	74 ± 16	ns
NYHA class I / II / III (%)	0 / 78 / 22	26 / 61 / 13	<0.05
6 minute walk test (m)	420 ± 123	472 ± 203	<0.05
EF (%)	35	48	<0.05
Systolic BP(mmHg)	125 ± 27	124 ± 24	ns
Natremia (mmol/l)	138 ± 4	139 ± 4	ns
Creatinine (µmol/l)	118 ± 117	101 ± 68	ns
BNP (pg/ml)	180 ± 255	124 ± 163	<0.05

In a second analysis we divided our population according to the mean achieved HR at the end of up-titration (68/min). The two groups of patients did not differ in terms of clinical and biological parameters, like NYHA class, systolic BP, weight, natremia and creatinine. The final EF was significantly higher in the low achieved HR group and the BNP levels lower in the same group. (Table 3) In terms of hospitalization or death related to heart failure, no significant differences were observed between the two groups.

Finally, we analyzed HR variations under carvedilol therapy and studied our population according to the mean HR variation (5/min). Patients with an important reduction of HR under therapy did not exhibit a better 1-year outcome. (Table 3)

Table 3. Patients' characteristics after Carvedilol up-titration according to the mean achieved HR (68/min) and HR variation (5/min).

Variable	LAHR	HAHR	p	HR variation ≤ 5/min	HR variation > 5/min	p
HR (/min)	58 ± 7	78 ± 8	< 0.05			
HR variation (/min)				-3.2 ± 7.5	18.2 ± 8.9	< 0.05
NYHA class I / II / III (%)	28 / 58 / 13	24 / 63 / 13	ns	29 / 56 / 15	23 / 65 / 9	ns
EF (%)	51 ± 8	46 ± 7	< 0.05	49 ± 11	52 ± 9	ns
6 minute walk test	394 ± 190	442 ± 215	< 0.05	402 ± 197	493 ± 220	< 0.05
Systolic BP (mmHg)	129 ± 23	121 ± 24	ns	130 ± 15	125 ± 22	ns
Creatinine (μmol/l)	112 ± 85	92 ± 44	ns	97 ± 46	108.5 ± 92.3	ns
Natremia (mmol/l)	139 ± 3	137 ± 4	ns	138 ± 4	139 ± 3	ns
BNP (pg/ml)	100 ± 140	145 ± 180	< 0.05	108 ± 154	147 ± 176	< 0.05
End point (%)	19.5	22	ns	21.4	18.2	ns

LAHR - low achieved heart rate; HAHR - high achieved heart rate.

DISCUSSIONS

Our study demonstrates that carvedilol significantly improved clinical and neurohormonal status in patients with CHF. The outcome (death or hospitalization for heart failure) was significantly poorer in patients with low initial HR. One-year prognosis did not appear to be influenced by the achieved HR or the HR variation under carvedilol therapy.

In studies focusing on patients with ischemic or hypertensive heart disease, the mortality rate was linearly correlated with HR, an achieved HR < 60/min representing a target for BB treatment.^{8,9} An autonomic imbalance may be responsible for increased myocardial metabolic needs.¹⁵ Dominant sympathetic activity leads to an increase in oxygen needs, causing a relative hypoxemia in under-perfused tissues. HR reduction may influence hypoxemia, increasing the duration of the diastolic phase and reducing oxidative stress.^{3,16}

Studies performed in CHF with BB like metoprolol or bisoprolol have focused on the influence of HR on the event-free survival but their results are still subject of debate. In the CIBIS II study with bisoprolol, Lechat et al support the existence of a relation between initial HR and the beneficial effect of BB therapy.^{10,11} The major limiting factors in the CIBIS II trial were the inclusion of patients with arrhythmia and pacemakers and the lack of effect of bisoprolol on patients with supraventricular arrhythmias.^{10,11} Carvedilol shows a beneficial effect in this particular population. In a post-hoc analysis of the MERIT-HF trial, Gullestad demonstrated that metoprolol significantly reduced hospitalization and CHF-related mortality independently of initial and final HR.¹⁵

Data regarding the relation between HR and carvedilol effectiveness are still lacking. In various studies, BB showed a comparable capacity of reducing HR.³ One confounding factor in these studies is represented by significant differences in achieved HR after up-titration. In animal models of heart failure, bisoprolol and metoprolol significantly increased the density of β₂ receptors on the cardiomyocytes.¹⁶ Carvedilol does not have this effect but proves a comparable effect on hospitalizations and mortality related to CHF.¹⁷⁻²⁰ The COMET study concluded that carvedilol was superior to metoprolol therapy in CHF.¹² Some authors explain this finding by different degrees of beta-blockade. However, HR at the end of the study was comparable between the metoprolol and carvedilol group. Our findings are in accordance with these data, achieved HR under carvedilol therapy not being correlated with the beneficial effect of BB therapy in terms of reducing death and hospitalizations for CHF.

BNP levels were significantly lower in patients with low initial HR but also in patients with low achieved HR. BNP is known as a major prognostic factor in acute and CHF.²¹ It has been reported that an important initial neurohormonal activation reflected by high BNP levels accurately estimates the beneficial effect of carvedilol in CHF.²² In our study, patients with high initial BNP levels had a significantly better outcome.

The beneficial effect of carvedilol and the reduction in BNP levels are correlated with the daily dose. Our study was too small to analyze the effect of each daily dose of carvedilol on BNP levels and event-free survival. Throughon suggested that a BNP monitoring strategy may be more effective than a “clinical based”

strategy in the up-titration of BB in CHF.²³ In a recent study by Frantz et al, carvedilol therapy was associated with a sustained decline in BNP levels in patients with systolic CHF.²⁴ In this study long-term improvement in EF was inversely correlated with BNP levels, but the relationship was not strong enough for BNP levels to supplant EF measurement. Concerning the lack of correlation between the improvement of EF and HR reduction under BB therapy, the available data are controversial. We have observed significantly higher EF in patients with low achieved HR under carvedilol therapy. In the CIBIS II study, there was no correlation between LV systolic function and the achieved HR under bisoprolol therapy.¹⁰ It was the same for bucindolol in a report by Bristow et al.²⁵

CONCLUSIONS

In large multicentric studies, carvedilol had a beneficial effect on hospitalizations and mortality related to CHF, therefore being recommended as an essential treatment in systolic CHF. Despite these facts, BB remain under-prescribed, as reported in the EuroHeart Failure Survey with daily prescribed doses much lower than doses recommended in international guidelines.²⁶ The aim of our study was to determine whether achieved HR should be a target for carvedilol therapy in patients with CHF. According to our results, HR should not guide carvedilol therapy, a HR target not being recommended. Clinical tolerance remains the main indicator of an optimal dose of carvedilol.

We conclude that the beneficial effect of carvedilol cannot be determined using the achieved HR at the end of up-titration. The principle of the best tolerated daily dose should be the rule for carvedilol treatment monitoring in patients with systolic CHF.

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