Effects of Carvedilol on Functional Capacity, Left Ventricular Function, Catecholamines, and Oxidative Stress in Patients With Chronic Heart Failure

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Introduction and objective. Carvedilol is an antioxidant and adrenergic antagonist with demonstrated benefits in terms of mortality from heart failure (HF). The aim of the present study was to evaluate clinical parameters, left ventricular function, oxidative stress levels, and neurohumoral status at baseline and after 6 months of treatment with carvedilol in patients with chronic HF.

Patients and method. Thirty patients with chronic HF that was stable without beta-blocker treatment were included. Functional class was II or III, and left ventricular ejection fraction (LVEF) was <40%. Mahler score, distance walked in 6 min, peak oxygen consumption, LVEF, plasma catecholamine (norepinephrine) concentration, and oxidative stress parameters were evaluated at baseline and after 6 months of treatment with carvedilol.

Results. Mean age was 59 (2) years, and 23 patients were men. After 6 months of treatment there were clinical improvements as measured by the Mahler score (from 6.8 to 11.0 points; *P*=.001) and the 6-min walk distance (from 499 [18] to 534 [17] m; *P* =.032), but no changes in peak oxygen consumption. The LVEF increased from 24 (1) to 31 (2)% (*P*=.003). In patients with chronic HF, plasma malondialdehyde concentration was significantly lower after 6 months (decrease from 2.4 [0.2] to 1.1 [0.2] μmol/L; *P*<.001). No significant changes were observed in plasma catecholamine levels or antioxidant enzyme activities.

Conclusions. In patients with chronic HF, carvedilol treatment for 6 months was associated with clinical improvements, increased left ventricular function and decreased plasma concentrations of malondialdehyde, with no changes in plasma catecholamine levels.

Key words: *Heart failure. Beta-blockers. Oxidative stress. Catecholamines.*

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Efectos del carvedilol en la capacidad funcional, función ventricular izquierda, catecolaminas y estrés oxidativo en pacientes con insuficiencia cardíaca crónica

Introducción y objetivo. El carvedilol es un antagonista adrenérgico con acción antioxidante y un demostrado beneficio sobre la mortalidad en insuficiencia cardíaca. El objetivo de este estudio es evaluar, en pacientes con insuficiencia cardíaca, diversos parámetros clínicos y de la función ventricular izquierda, así como el grado de estrés oxidativo y el estado neurohormonal, antes y después de 6 meses de tratamiento con carvedilol.

Pacientes y método. Se incluyó a 30 pacientes con insuficiencia cardíaca crónica estable sin tratamiento con bloqueadores beta, con capacidad funcional II-III y fracción de eyección ventricular izquierda (FEVI) < 40%. Se midió el índice de Mahler, la distancia recorrida en 6 min, el consumo de oxígeno *peak,* la FEVI y las concentraciones circulantes de noradrenalina y estrés oxidativo basales y tras 6 meses de tratamiento con carvedilol.

Resultados. La edad promedio fue de 59 ± 2 años y 23 eran varones. Se observó una mejoría clínica según el índice de Mahler (basal de 6,8 frente a 11,0 puntos; p = 0,001) y un aumento en la distancia recorrida en 6 min (499 ± 18 a 534 ± 17 m; p = 0,032), sin cambios en el consumo de oxígeno pico. La FEVI aumentó del 24 ± 1 al 31 ± 2% (p = 0,003). El malondialdehído plasmático disminuyó a los 6 meses (2,4 ± 0,2 a 1,1 ± 0,2 μmol/l; p < 0,001). No se observaron cambios significativos en los valores plasmáticos de catecolaminas ni en las actividades enzimáticas antioxidantes.

Conclusiones. El tratamiento con carvedilol durante 6 meses en pacientes con insuficiencia cardíaca crónica se asoció a una mejoría clínica, un aumento de la función ventricular izquierda y una disminución del malondialdehído plasmático, sin cambios en los valores de catecolaminas circulantes.

Palabras clave: *Insuficiencia cardíaca. Bloqueadores beta. Estrés oxidativo. Catecolaminas.*

ABBREVIATIONS

GSH-Px: glutathione peroxidase.
MDA: malondialdehyde.
CAT: catalase.
SOD: superoxide dismutase.
LVEF: left ventricular ejection fraction.
SBP: systolic blood pressure.
DBP: diastolic blood pressure.

INTRODUCTION

Despite advances in treatment, the prognosis for patients with heart failure remains poor.[1-3] It is essential to understand the mechanisms that contribute to the progression of this disease in order to implement new therapeutic strategies that can modify its course.

Numerous studies have shown the efficacy of beta-adrenergic blockers in the treatment of patients with heart failure.[4,5] Treatment with these agents can lead to improvement in functional capacity, left ventricular function and survival in patients whose functional capacity has become compromised to different degrees.[6-8] Heart failure is associated with an increase in adrenergic activity and in that of the renin-angiotensin-aldosterone system.[9,10] Further, plasma levels of markers of oxidative stress are also increased.[11-13]

Of the beta-blockers currently available, carvedilol is particularly attractive since, in addition to its vasodilatory action, it acts as a direct antioxidant. This latter quality, along with a reduction in sympathetic activity, might reduce oxidative stress levels.[14,15] However, contradictory results have been reported with respect to the effects of carvedilol on circulating catecholamines.[14]

The aim of this study was to determine, in patients with heart failure, the effect of carvedilol treatment over 6 months on a number of clinical variables, left ventricular function, oxidative stress levels, and neurohormonal status.

PATIENTS AND METHODS

The patients enrolled all suffered from chronic heart failure and had a New York Heart Association (NYHA) functional capacity of II-III. To be included, all patients had: *a)* to show a left ventricular ejection fraction (LVEF) of <40% as determined by radioventriculography; *b)* to have received conventional medical treatment with digitalic drugs, diuretics and inhibitors of angiotensin converting enzyme (IACE) or angiotensin receptor antagonists; and *c)* to have been clinically stable for the previous four months. The exclusion criteria were: *a)* unstable angina or having suffered a myocardial infarction in the previous 6 months; *b)* having undergone coronary surgery or angioplasty in the previous 6 months; *c)* uncontrolled high blood pressure, defined as a systolic blood pressure (SBP) of >160 mm Hg or a diastolic blood pressure (DBP) of >100 mm Hg; *d)* hypertrophic cardiomyopathy, congenital cardiomyopathy or significant valve disease; and *e)* concomitant systemic disease affecting the metabolism of malondialdehyde (MDA), creatinine levels of >2 mg/dL, autoimmune disease, neoplasia, liver disease, chronic obstructive pulmonary disease, or acute or chronic inflammation. No modifications to treatment were made during the study period that might alter oxidative stress levels. The trial was approved by the Ethics Committee of our institution and all patients gave their signed informed consent.

Carvedilol Treatment

All patients were treated with carvedilol for 6 months. The initial dose administered was 3.125 mg twice per day, increasing every 2 weeks, depending on tolerance, to 6.25 mg, 12.5 mg, and to a maximum of 25 mg twice per day.

Assessment

The following assessments were made at baseline and after 6 months of treatment:

– Clinical assessment: NYHA functional capacity and Mahler index.[16] The Mahler index assess the magnitude of dyspnea (on a scale of 0-4; 4=normal, 0=serious dyspnea) with respect to 3 variables: functional impairment, magnitude of task and magnitude of effort. The sum of the scores for these 3 factors provides the final score.

– Ventricular function: LVEF was determined by injecting ^{99}Tc-sestamibi and obtaining images by single-photon emission computerized tomography (SPECT) using a gamma camera (Genesys, ADAC, Milpitas, California) equipped with a high resolution collimator. The images were acquired taking 64 projections over 20 s.

– Exercise capacity: this involved measuring the distance covered in a 6-min walk test, and recording the peak mean oxygen consumption in a cardiopulmonary test. In the 6-min walk test, patients had to walk on a hard surface 20 m in length (in the hospital), while being monitored and encouraged by a trained kinesiologist. Oxygen saturation before and after the test was recorded. The cardiopulmonary test was a symptom-limited maximum stress test, performed using the 3 min Naughton (Treadmill Marquette) protocol. Gases were measured during this test using a buccal pneumotachograph. Oxygen saturation was measured non-invasively.

– Oxidative stress: the levels of MDA and enzymatic antioxidants were measured, as was the activity of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Twenty milliliters of peripheral venous blood were obtained from every patient. After centrifuging at 3000 rpm for 10 min at 4°C, the plasma was stored at –20°C. The erythrocytes were washed 3 times with a saline solution and lysed by adding 0.1 mL of distilled water. The resulting product was then stored at –20°C. Plasma MDA levels were determined by measuring the content of thiobarbituric acid reactive substances (TBARS)[17]; values were expressed in μmol/L. Superoxide dismutase activity was measured according to the method described by Misra et al.[18] The degree of oxidation was determined photocolorimetrically at 480 nm and expressed as units (U) per mg of hemoglobin (Hb). Catalase activity was determined using the method described by Beers et al[19] and expressed as U (nM H_2O_2/min) per g Hb. Glutathione peroxidase activity was determined using the method of Paglia et al[20] and expressed as U (nmoles NADPH oxidized/min) per g Hb.

– Neurohormonal profile. Levels of circulating adrenaline and noradrenaline were determined in peripheral venous blood samples obtained after the patient had reclined supine for 30 min, and then again during the stress test, according to the Naughton protocol. Catecholamine levels were determined by HPLC and via the use of a commercial kit (Chromosystems Instruments and Chemical GmbH, Munich, Germany). Inter-assay and intra-assay variations were 6% and 5% respectively.

Statistical Analysis

Results were recorded as means±standard error. The Student *t* test for paired samples was used to compare the baseline and 6-month results, and to compare neurohormonal results before and after the stress test. Changes in the LVEF were correlated to those in MDA values using the Pearson linear correlation test. Significance was set at $P<.05$.

RESULTS

Of the 32 patients originally included in the study, 2 could not tolerate the carvedilol treatment; the total sample was therefore reduced to 30. Table 1 shows the baseline characteristics of the patients. Their mean age was 59±2 years (range, 47-71 years); 23 were men, 7 were women. The etiology of the heart failure of 16 patients (53%) was ischemic; in the remaining 14 (47%) it was due to non-ischemic dilated cardiomyopathy. Twenty five patients showed sinusoidal rhythm; 5 showed atrial fibrillation.

Ten patients showed right bundle block and another ten showed left bundle block. All patients were treated with carvedilol, with a mean dose of 25 mg/day (range, 6.25-50 mg/day). In 58.8% of patients, the dose administered was ≥25 mg.

TABLE 1. **Patient Baseline Characteristics***

n	30
Age, years	59±2
Men/women, n	23/7
Etiology	
Ischemic, n (%)	16 (53)
Non-ischemic, n (%)	14 (47)
NYHA II/III functional capacity 16/14	
Blood pressure, n (%)	17 (57)
Diabetes mellitus, n (%)	5 (17)
Hypercholesterolemia, n (%)	7 (23)
Use of tobacco, n (%)	7 (23)
Atrial fibrillation, n (%)	5 (17)
LV diastolic diameter, mean ±SE (mm)	69±2
LV systolic diameter, mean ±SE (mm)	58±2
LV ejection fraction, (%)	24±1
IACE, n (%)	24 (80)
Furosemide, n (%)	23 (77)
Digoxin, n (%)	16 (53)
Spironolactone, n (%)	18 (62)
Statins, n (%)	6 (20)

*LV indicates left ventricle; SE, standard error; IACE, angiotensin converting enzyme inhibitors.

Clinical Response

Following treatment with carvedilol, mean SBP was reduced from 127±4 mm Hg to 115±4 mm Hg ($P=.24$), mean DBP was reduced from 75±2 mm Hg to 65±2 mm Hg ($P=.72$) and mean heart rate was reduced from 78±2 beats/min to 65±2 beats/min ($P=.001$). At the beginning of the study, 16 patients showed grade II functional capacity and 14 showed grade III. After 6 months of treatment with carvedilol, 8 patients were in class I, 13 in class II, and 9 in class III. The Mahler index increased significantly from 6.8±1.6 to 11.0±3.0 ($P=.001$). The LVEF increased significantly from 24±1% to 31±2% ($P=.003$) and a significant increase was seen in the distance covered in the 6-min walk test (499±8 m to 534±17 m; $P=.03$). The results of the cardiopulmonary test showed a reduction in the maximum heart rate reached from 143±4 beats/min to 125±7 beats/min ($P<.001$), a reduction in maximum SBP from 143±6 mm Hg to 133±6 mm Hg ($P=.01$), and a reduction in maximum DBP from 88±3 mm Hg to 80±4 mm Hg ($P=.04$). The product of the SBP and maximum heart rate was significantly reduced from 21.879±1.137 to 16.625±1.363 ($P<.001$). No significant changes were seen in peak oxygen consumption (17±1 mL/kg/min before and after treatment), nor in the anaerobic threshold (14±1 mL/kg/min) before and after treatment).

TABLE 2. **Plasma Noradrenaline Levels at Baseline and After 6 Months of Treatment With Carvedilol**

Catecholamines (pg/mL)	Normal Value	Baseline	6 Months	*P**
Pre-exercise noradrenaline	95-446	659±571	578±556	.72
Post-exercise noradrenaline		2.445±1.213	2.436±1.584	.91

* *P*=baseline vs level at 6 months.

TABLE 3. **Oxidative Stress Variables at Baseline and After 6 Months of Treatment With Carvedilol***

	Normal Value	Baseline	6 Months	*P**
MDA, μmol/L	0.91±0.1	2.4±0.2	1.1±0.2	<.001
CAT, U/g Hb	192.9±7.7	84±9	116±12	.06
SOD, U/g Hb	1.33± 0.1	1.0±0.1	0.8±0.2	.51
GSH-Px, U/g Hb	33±1	65±4	64±5	.68

*MDA indicates malondialdehyde; CAT, catalase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase. Values are mean ± standard error.
P=baseline vs activity at 6 months.

Catecholamine and Oxidative Stress Responses

The patients' baseline and post-exercise noradrenaline levels were higher than those of healthy subjects. These levels did not change after 6 months of carvedilol treatment (Table 2).

Baseline MDA levels were higher than those of healthy subjects (2.4±0.2 μmol compared to 0.9±0.1 μmol) but were significantly reduced after 6 months of treatment with carvedilol (1.1±0.2 μmol/L; *P*<.001). The activities of the enzymatic antioxidant systems (SOD, CAT, and GSH-Px) at baseline were below normal, and did not change with carvedilol treatment (Table 3). No correlation was seen between the reduction in oxidative stress and improvement in left ventricular function (r=0.22; *P*=.42).

DISCUSSION

This study shows that the treatment of chronic heart failure with carvedilol leads to improvements in functional capacity and left ventricular function, and to a reduction in oxidative stress. Although the distance covered in the 6-min walk test improved, peak oxygen consumption did not change.

Carvedilol was well tolerated; this agrees with other studies on the use of beta-blockers in heart failure.[21] Only 2 of the original patients (6.3%) could not be included because of hypotension and bradycardia. Tolerance to carvedilol might be facilitated by its vasodilatory effect, brought about via the agents' alpha-blocking function. However, Kukin et al[22] compared the tolerance of carvedilol and metaprolol, a beta-blocker with no alpha-adrenergic blocking properties, and found no differences.[22] The mean daily dose of carvedilol received was 25 mg. This dose has been described beneficial in terms of left ventricular function and patient mortality, although the greatest benefit was obtained with 50 mg/day.[4]

Previous studies have consistently shown that carvedilol improves functional capacity as well as the symptoms of heart failure.[23] This agrees with the results of the present study. It is also thought to slow disease progression.[24] Our patient population showed an improvement in NYHA functional capacity and in the degree of dyspnea suffered (as reflected by the Mahler index). The distance covered in the 6-min walk test increased but peak oxygen consumption remained unchanged. In an earlier study it was reported that peak oxygen content increased significantly with cardevilol.[22] However, these patients showed lower baseline levels of oxygen consumption. It is possible that with a larger sample, or the inclusion of patients with poorer oxygen consumption levels, the magnitude of the benefit obtained in the present study would have reached statistical significance.

Several studies have shown that, compared to a placebo, carvedilol causes a significant increase (5%-11%) in LVEF.[25,26] This has been reported to occur within the first 4 months of treatment and to be maintained for at least 2 years.[27] In the present study, a significant increase (7%, i.e., 24%-31%) was seen in LVEF after 6 months of carvedilol treatment. The improvements seen in functional class and left ventricular function may be partly explained by the reduction in cardiac work, as shown by the significant reduction in heart rate and blood pressure.

Heart failure is associated with an exaggerated activation of the sympathetic nervous system.[10] This is reflected in a two or three-fold increase in circulating noradrenaline levels, plus higher concentrations of dopamine and adrenaline.[9] This neurohormonal activation even occurs in patients with asymptomatic left ventricular dysfunction and it increases with the severity of heart failure.[10]

For similar levels of exercise, patients with heart failure have higher levels of circulating noradrenaline than normal subjects.[28] This increase in plasma adrenaline levels has been related to increased cardiac mortality.[29] It has recently been proposed that part of the harmful effect of this neurohormonal activation, especially that of catecholamines, might be mediated by an increase in oxidative stress.[22,30] Experimental studies have shown that oxygen free radicals are produced in the dysfunctional myocardium and that they can cause damage to cardiomyocytes.[31,32] Free radicals also mediate the apoptotic and hypertrophic effects of cytokines in the myocardium.[33,34] The degree of oxidative stress correlates with the severity of symptoms suffered by heart failure patients.[35]

The favorable effects of beta-blockers in the treatment of heart failure may be attributable to their ability to modulate presynaptic release of noradrenaline,[36] reduce heart rate, antagonize the direct toxic effect of catecholamines on the myocardium, and modulate regional energetics.[15] Under this perspective, Kaye et al[15] found no reduction in regional sympathetic activity in patients with heart failure treated with carvedilol.[15] Similarly, in the present study, no differences in catecholamine levels were recorded either before or after exercise following 6 months of treatment with carvedilol. It may be that the benefit provided by this agent should mainly be explained in terms of protection of adrenergic receptors from the cardiotoxic effects of catecholamines.

Using biopsies obtained from 23 patients with heart failure, Nakamura et al[15] showed oxidative stress (determined by measuring the levels of the modified cytosolic protein 4-hydroxy-2-nonenal) to be higher than that in healthy subjects.[14] In addition, these authors found that 9 months of carvedilol treatment reduced this oxidative stress. In the present work, a significant reduction in plasma MDA was seen after 6 months of carvedilol treatment, although the activities of the enzymatic antioxidant systems experienced no variation. Carvedilol might exert its antioxidant effect via an intrinsic mechanism different to that used by these enzyme systems. No correlation was found between the reduction in oxidative stress and the improvement in left ventricular function; other mechanisms of action not related to the antioxidant effect must therefore participate in ventricular remodeling.

The main limitation of this study is its small number of patients. Although most of the results obtained agree with those reported by other authors, it cannot be inferred that the significant reduction in oxidative stress observed contributes to the improvements noticed in functional capacity and left ventricular function, nor that it is a consequence of these improvements. A wider range of possible causes need to be studied to clarify the interpretations made, and investigations should be undertaken to determine whether there is a temporal relationship between improvement in oxidative stress, LVEF and clinical symptoms. A further limitation of the study lies in the use of peripheral blood rather than myocardial determinations to measure the effect of carvedilol on oxidative stress markers and cardiac remodeling. Other techniques for measuring oxidative stress are currently being investigated. Finally, this study had no control group since beta-blockers are clearly beneficial in patients with heart failure; however, the patients did not modify their regular treatment during the study period.

In conclusion, in patients with stable heart failure and with an NYHA functional capacity of II-III, 6 months of treatment with carvedilol led to improvements in functional capacity and left ventricular function, as well as a reduction in oxidative stress. No changes were observed in plasma catecholamine levels nor in the activity of the major enzymatic antioxidant systems. The reduction in oxidative stress observed was not correlated to the improvement in left ventricular function.

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