Cardiomyopathy

Dilated Cardiomyopathy in Dialysis Patients—Beneficial Effects of Carvedilol: A Double-Blind, Placebo-Controlled Trial

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OBJECTIVES

The aim of this study was to investigate in dialysis patients with symptomatic heart failure New York Heart Association (NYHA) functional class II or III whether the addition of carvedilol to conventional therapy is associated with beneficial effects on cardiac architecture, function and clinical status.

BACKGROUND

Congestive heart failure (CHF) in chronic hemodialyzed patients, particularly when associated with dilated cardiomyopathy, represents an ominous complication and is an independent risk factor for cardiac mortality.

METHODS

We enrolled 114 dialysis patients with dilated cardiomyopathy. All patients were treated with carvedilol for 12 months in a double-blind, placebo-controlled, randomized trial. The patients underwent M-mode and two-dimensional echocardiography at baseline, 1, 6 and 12 months after the randomization. Each patient's clinical status was assessed using an NYHA functional classification that was determined after 6 and 12 months of treatment.

RESULTS

Carvedilol treatment improved left ventricular (LV) function. In the active-treatment group, the increase in LV ejection fraction (from 26.3% to 34.8%, \( p < 0.05 \) vs. basal and placebo group) and the reduction of both LV end-diastolic volume (from 100 ml/m² to 94 ml/m², \( p < 0.05 \) vs. basal and placebo group) and end-systolic volume (from 74 ml/m² to 62 ml/m², \( p < 0.05 \) vs. basal and placebo group) reached statistical significance after six months of therapy, compared with baseline and corresponding placebo values, and they remained constant at one year of treatment (\( p < 0.05 \) vs. basal and placebo group). The clinical status of patients, assessed by NYHA functional classification, improved during the treatment period. Moreover, at the end of the trial, there were no patients in NYHA functional class IV in the carvedilol group, compared with 5.9% of the patients in the placebo arm.

CONCLUSIONS

One year of therapy with carvedilol in dialysis patients with CHF and dilated cardiomyopathy reduces LV volumes and improves LV function and clinical status. (J Am Coll Cardiol 2001; 37:407–11) © 2001 by the American College of Cardiology

Cardiac involvement is a common finding in dialysis patients, accounting for 40% of deaths in this patient population (1,2). In this regard, congestive heart failure (CHF) in chronic hemodialyzed patients, particularly when associated with dilated cardiomyopathy, represents an ominous complication and is an independent risk factor for cardiac mortality. Carvedilol, a third-generation beta-adrenergic blocking agent, has recently been shown to reduce mortality in patients with heart failure (3).

Thus, the poor outcome of dialysis patients with dilated cardiomyopathy on one hand—and the beneficial effects documented by several controlled studies employing carvedilol in CHF on the other hand—prompted us to evaluate the effects of carvedilol on left ventricular (LV) structure, function and clinical status in dialysis patients with CHF and dilated cardiomyopathy. Carvedilol was administered for 12 months in a double-blind, placebo-controlled fashion, in addition to the standard background therapy.

METHODS

Patients. From February 1996 to December 1998 we recruited 132 patients (89 men, 43 women, mean age 55.1 ± 7.6 years) with uremia on periodic hemodialysis treatment and dilated cardiomyopathy: 68% had a history of ischemic heart disease (defined as a documented history of myocardial infarction [MI], typical angina, an exercise electrocardiogram positive for ischemia or angiographic evidence of coronary disease), 24% had a history of arterial hypertension, while 8% had non-specified histories. All patients were symptomatic for heart failure (New York Heart Association [NYHA] functional class II to III) for at least one year, with an LV ejection fraction (LVEF) <0.35 at echocardiography. To be included in the study, patients had to be clinically stable with no change in their usual medications in the last two weeks and should not have required intravenous inotropic drug therapy nor experienced weight changes for at least 48 h before the enrollment.
Abbreviations and Acronyms

- ACE = angiotensin-converting enzyme
- BP = blood pressure
- CHF = congestive heart failure
- HR = heart rate
- LV = left ventricle, left ventricular
- LVEDV = left ventricular end-diastolic volume
- LVEF = left ventricular ejection fraction
- LVESV = left ventricular end-systolic volume
- MI = myocardial infarction
- NYHA = New York Heart Association

(>2.5 kg compared with the “dry weight”). Exclusion criteria included: current NYHA functional class IV; heart rate (HR) <50 beats/min; sick sinus syndrome; first degree atrioventricular block with a PQ interval >0.24 s; second- or third-degree heart block (unless controlled by a pacemaker); documented episodes of sustained ventricular tachycardia (>30 s, >120 beats/min); systolic blood pressure (BP) <90 mm Hg; stroke; acute MI; unstable angina; coronary angioplasty or aortocoronary bypass surgery in the three previous months; uncorrected valvular heart disease; active myocarditis; obstructive and restrictive cardiomyopathy; current treatment with verapamil, alpha/beta adrenergic agonists or antagonists; chronic obstructive Airways disease; hepatic disease (serum transaminase >3 times normal); drug or alcohol abuse; or any other life-threatening noncardiac disease.

All patients were on digitalis; 128 patients (96.9%) were also receiving angiotensin-converting enzyme (ACE) inhibitors; four patients (3.1%) who were intolerant of the ACE-inhibitors received angiotensin II receptor antagonists; 32 (25%) patients were taking nitrates.

All patients were dialyzed four times a week for a mean time of 210 ± 30 min, with a middle quote blood of 260 ± 20 ml/min, using a cuprophan hollow-fiber hemodialyzer by 1.3 to 1.8 m² of surface and 7.5 µ of thickness. A personalized bath of dialysis was used, with variable concentration of potassium between 2 and 3.5 mEq/L. The concentration of sodium was variable between 144 and 150 mEq/L in relation to the BP. Monitors were used for computerized checking of ultrafiltration and real-time monitoring of the loss of the weight, so as to have an exact and constant control of the weight reduction per hour. Furthermore, HR and BP were checked. The “dry-weight” of all patients was stable for at least one month.

**Design and study treatment.** Potentially eligible patients were enrolled in a parallel, double-blind, placebo-controlled, randomized treatment protocol. During a preliminary “run-in” phase, all patients received carvedilol (3.125 mg twice a day) for two weeks in order to determine, before randomization, which patients were unable to tolerate low doses of carvedilol. Patients able to tolerate the initial dose were then randomly assigned to receive either placebo or carvedilol (1:1 randomization) in double-blind fashion, while maintaining their background therapy unchanged. During the titration period, the dose of carvedilol was doubled at two-week intervals and then increased to a target dose of 25 mg twice a day. When the dose increase was not tolerated for the appearance of adverse reactions such as HR <50 beats/min or arterial hypotension (BP <90/60 mm Hg), it was temporarily halved, then again increased the following week. The same protocol was followed for patients randomized to the placebo treatment; it was administered in tablets similar to the study drug. At the end of the up-titration phase, the therapy with carvedilol or placebo was maintained for 12 months (maintenance phase), during which time carvedilol was administered at the maximum dose of 25 mg twice a day or to the highest dose tolerated. Concomitant therapy with digitals, ACE inhibitors, angiotensin II receptor antagonists and nitrates was maintained, although the dosage was adjusted according to the clinical conditions of the patient or to the appearance of side effects possibly related to these drugs.

**End points and assessment.** The patients were checked with daily medical examinations during titration and every other day during the maintenance phase in concomitance with dialysis.

The end points considered were as follows: 1) changes in LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) and LVEF at 1, 6 and 12 months after randomization and 2) changes in symptoms of heart failure 6 and 12 months after the randomization.

One, 6 and 12 months after the beginning of the maintenance phase, a clinical-instrumental assessment was performed in all patients, including a complete M-mode and two-dimensional echocardiography. The clinical status of the patients was also assessed using an NYHA functional classification that was determined at 6 and 12 months of treatment.

**Echocardiographic assessment.** The patients admitted to the randomization phase were subjected to baseline M-mode and two-dimensional echocardiography upon admission and at 1, 6 and 12 months after the randomization.

The assessment was performed in all patients on the day after dialysis, between 24 and 30 h after completion of the dialysis session, by operators who were not aware of the clinical conditions of the patients. The assessment was performed after 5 min of rest, with the subject in left lateral decubitus using a Hewlett Packard Sonos 1000 machine equipped with a 2.5 MHz probe. As an index of systolic function, LVEF, LVEDV and LVESV were measured according to the Simpson’s rule (4). The echocardiographic exams were made on videotapes and controlled by medical doctors not aware of the clinical conditions of patients.

The patients were informed in detail of the formalities and finality of the study. All patients provided written informed consent to participate. The institutional committee on human research approved the study protocol.

Among the 132 patients eligible for the inclusion in the trial, 18 were excluded during the run-in phase. Thus, 114
patients, whose clinical characteristics are displayed in Table 1, started the maintenance phase.

Statistics. All values are given as mean ± standard deviation. Statistical analysis was performed using a PC computer. Between-group comparisons were performed using the two-way analysis of variance with treatment as one factor and time as the other factor. One-way analysis of variance was used for the other comparisons. When appropriate, comparisons to determine the significance of changes within the same group over time and between groups at each time point were performed with the Newman-Keul test after the samples were tested for normal distribution. Noncontinuous variables, like NYHA class, were analyzed with the chi-square test. A value of p < 0.05 was considered significant.

RESULTS

Dropout patients. Of the 132 patients entering the run-in phase, 18 (13.6%) were excluded due to side effects: hypotension (n = 3), dizziness (n = 1), bronchospasm (n = 5), bradycardia (n = 4), worsening heart failure (n = 4) and protocol violation (n = 1). Of the 114 patients starting the titration phase, no one was excluded. Of the 114 patients entering the maintenance phase, 11 (9.6%) dropped out of the study: four patients in the carvedilol group dropped out—one for the appearance of hypotension, one for bradycardia, one for second-degree heart block and one because of acute MI; seven patients in the placebo group dropped out—three for worsening heart failure, two because of sudden death, one because of acute MI and one because of death from refractory hyperpotassiemia. One hundred and three patients completed the study.

Mortality was not significantly different between the two groups at one year (0/58 in carvedilol group vs. 3/56 in placebo group; p > 0.05).

Clinical and echocardiographic parameters. The principal clinical and echocardiographic parameters in the placebo and carvedilol groups are summarized in Table 2. Heart rate decreased significantly after one month of treatment compared with baseline and corresponding placebo values; such reduction was sustained at 6 and 12 months. Systolic and diastolic systemic BP decreased significantly after one month of treatment compared with baseline and corresponding placebo values, and such reduction remained significant until the end of the trial. A new statistical significance was reached at 6 and at 12 months, compared with the control at one month and corresponding placebo values.

The increase in LVEF and the reduction of both LVEDV and LVESV reached statistical significance after six months of therapy, compared with baseline, compared with control at one month and compared with corresponding placebo values, and remained constant at one year of treatment.

NYHA classification. The clinical status of patients, assessed by NYHA functional classification, improved significantly during the treatment period (p < 0.05) (Table 3): three (5.6%) patients treated with carvedilol were in NYHA functional class I after six months, increasing to four (7.4%) after 12 months; patients in NYHA functional class II increased from 18 (33.3%) at baseline to 34 (63%) at six months and to 35 (64.8%) at 12 months. Conversely,

### Table 1. Clinical Characteristics of 114 Study Patients

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol (n = 58)</th>
<th>Placebo (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54.9 ± 8.1</td>
<td>55.2 ± 7.1</td>
</tr>
<tr>
<td>Men/women</td>
<td>32/26</td>
<td>37/19</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.80 ± 0.25</td>
<td>1.84 ± 0.22</td>
</tr>
<tr>
<td>Duration of dialysis (months)</td>
<td>85.6 ± 14.9</td>
<td>81.7 ± 14.2</td>
</tr>
<tr>
<td>Interdialytic weight increase (kg)</td>
<td>2.5 ± 0.7</td>
<td>2.8 ± 0.8</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>93.3 ± 10.9</td>
<td>92.6 ± 11.8</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>133.9 ± 7.7</td>
<td>134.5 ± 9.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75.4 ± 5.8</td>
<td>74.7 ± 6.3</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>Current treatment:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists (%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Digitalis (%)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>NYHA classification I (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II (%)</td>
<td>34.5</td>
<td>42.9</td>
</tr>
<tr>
<td>III (%)</td>
<td>65.5</td>
<td>57.1</td>
</tr>
<tr>
<td>IV (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LVEDV (ml/m²)</td>
<td>100 ± 9</td>
<td>97 ± 8</td>
</tr>
<tr>
<td>LVESV (ml/m²)</td>
<td>74 ± 8</td>
<td>72 ± 9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26 ± 8</td>
<td>26 ± 8</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

### Table 2. Blood Pressure and Echocardiographic Parameters in the Carvedilol and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Carvedilol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>1 Month</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>93 ± 11</td>
<td>69 ± 7†</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>134 ± 8</td>
<td>124 ± 7†</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>75 ± 6</td>
<td>68 ± 6†</td>
</tr>
<tr>
<td>LVEDV (ml/m²)</td>
<td>100 ± 9</td>
<td>99 ± 8</td>
</tr>
<tr>
<td>LVESV (ml/m²)</td>
<td>74 ± 8</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26 ± 8</td>
<td>27 ± 7</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. basal; †p < 0.05 vs. placebo; ‡p < 0.05 vs. control at 1 month.

DBP = diastolic blood pressure; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; SBP = systolic blood pressure.
patients in NYHA functional class III decreased from 36 (66.7%) at baseline to 17 (31.4%) at six months and to 15 (27.8%) at 12 months of treatment; there were no patients in NYHA functional class IV in the placebo group. By contrast, in the placebo group there was a worsening of the NYHA functional classification; there was no patient in NYHA functional class I, and patients in NYHA functional class II decreased from 22 (44.9%) at baseline to 19 (38.8%) at six months, with no change at 12 months. Patients in NYHA functional class III increased from 27 (55.1%) at baseline to 28 (57.1%) at six months and to 27 (55.1%) at 12 months. Patients in NYHA functional class IV increased from two (4.1%) at six months to three (6.1%) at 12 months.

### DISCUSSION

The current data demonstrate for the first time that a 12-month therapy with carvedilol reduces LV volumes and improves cardiac function and the clinical status of dialysis patients with dilated cardiomyopathy. Such beneficial effects were significant after six months of therapy, persisted until the end of the trial, and were independent of the genesis of heart failure.

### Use of beta-blockers in dialysis patients

Although the use of beta-blockers in dialysis patients with CHF is justified in view of the peculiar neurohumoral status of these patients (5–7), no controlled study has yet addressed their safety and potential usefulness in such a clinical setting. Previous studies from our group have recently documented the efficacy and safety of carvedilol in CHF patients (8) and in the management of systemic hypertension and “silent” angina in chronic hemodialyzed patients (9–11). Among other beta-blocking agents, carvedilol possesses a favorable profile, considering its prevalent hepatic metabolism that does not require dose adjustment in the case of impaired renal function (12).

The presence of dilated cardiomyopathy in our patient population represents a further indication for the use of a beta-blocker (13,14). In fact, LV dilation is an independent predictor of mortality in chronic hemodialyzed patients that exhibits a two-year survival rate of 67% when an echocardiographic diagnosis of dilated cardiomyopathy is made, compared with a 90% survival rate observed in the control population with a normal echocardiogram.

On the other hand, carvedilol is the only beta-blocker approved for treatment of chronic heart failure in the U.S. and most other countries (3).

Our patient population consisted of subjects with moderate-to-severe heart failure (EF 26.3 ± 7.6% in the carvedilol group; 26.1 ± 7.9% in the placebo group) and symptomatic NYHA functional class II to III, with prevalent ischemic etiology. There were no patients in NYHA functional class IV, except at the end of the trial in the placebo group.

### Dropout patients

There were 18/132 patients during the run-in phase and 4/58 patients during the maintenance phase who were unable to tolerate the drug (20.5%), compared with 7/56 placebo patients (12.5%). Although the incidence of dropout was considerable in this study, most of them occurred during the run-in phase. Once the patients entered the titration phase, there were no dropouts. During the maintenance phase, there were only four dropouts (6.9%) in the carvedilol group, compared with seven dropouts (12.5%) in the placebo group.

### Effects of carvedilol on cardiac function and on NYHA classification

The time-course of LV structural and functional changes in this study was evaluated by means of two-dimensional echocardiography (15). Significant reduction of LV volumes and improvement in LVEF were evident after six-month carvedilol treatment and persisted until the end of the trial.

The magnitude of change in LVEF, LVEDV and LVESV observed in this study is reminiscent of that described in previous trials using beta-blockers for patients with CHF (16–21). The change in volumes and EF are generally higher than those achieved with ACE inhibitor drugs (22) that are known to stabilize rather than reduce LV volumes in the setting of CHF (23).

It should be stressed that the structural and functional changes observed with noninvasive techniques were associated with significant improvements in the clinical status in this study. In fact, almost 30% of the patients on carvedilol shifted from NYHA class III to NYHA class II, and no patient progressed to NYHA class IV, compared with 6.1% of the patients on placebo in NYHA class IV after 12 months of treatment. This finding is congruent with previous clinical trials in nonuremic patients with CHF, in whom beta-blockers were able to slow the disease progression (16–21).

A potential limitation of this study was the lack of an

### Table 3. Assessment of NYHA Class Over the Treatment Period

<table>
<thead>
<tr>
<th>Class</th>
<th>Basal</th>
<th>6 Months</th>
<th>12 Months</th>
<th>Basal</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>0 (0%)</td>
<td>3 (5.6%)*</td>
<td>4 (7.4%)*</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Class II</td>
<td>18 (33.3%)</td>
<td>34 (63%)*</td>
<td>35 (64.9%)*</td>
<td>22 (44.9%)</td>
<td>19 (38.8%)</td>
<td>19 (38.8%)</td>
</tr>
<tr>
<td>Class III</td>
<td>36 (66.7%)</td>
<td>17 (31.4%)*</td>
<td>15 (27.8%)*</td>
<td>27 (55.1%)</td>
<td>28 (57.1%)</td>
<td>27 (55.1%)</td>
</tr>
<tr>
<td>Class IV</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (4.1%)</td>
<td>3 (6.1%)</td>
</tr>
</tbody>
</table>

*P < 0.05 versus basal.

NYHA = New York Heart Association.
accurate assessment of the exercise capacity and the subjective nature of the NYHA class assignment. However, in all the study participants we assessed the NYHA functional class, which in several previous studies has been successfully employed to monitor the clinical status in CHF clinical trials.

**Conclusions.** In conclusion, one year of therapy with carvedilol in dialysis patients with CHF and dilated cardiomyopathy reduced LV volumes and improved LV function and clinical status. Future survival studies are needed to evaluate whether the beneficial effects observed with one year of carvedilol therapy will eventually translate into decreased mortality in dialysis patients with CHF and dilated cardiomyopathy (24).

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**REFERENCES**