Long-Term Effects of Carvedilol in Idiopathic Dilated Cardiomyopathy With Persistent Left Ventricular Dysfunction Despite Chronic Metoprolol

Andrea Di Lenarda, MD,* Gastone Sabbadini, MD,† Luca Salvatore, MD,* Gianfranco Sinagra, MD,* Luisa Mestroni, MD, FACC,‡ Bruno Pinamonti, MD,* Dario Gregori, PhD,§ Fulvio Ciani, MD,|| Aureo Muzzi, MD,* Silvio Klugmann, MD,* Fulvio Camerini, MD* and The Heart-Muscle Disease Study Group

Trieste, Italy

OBJECTIVES

The purpose of this study was to analyze whether long-term treatment with the nonselective beta-adrenergic blocking agent carvedilol may have beneficial effects in patients with dilated cardiomyopathy (DCM), who are poor responders in terms of left ventricular (LV) function and exercise tolerance to chronic treatment with the selective beta-blocker metoprolol.

BACKGROUND

Although metoprolol has been proven to be beneficial in the majority of patients with heart failure, a subset of the remaining patients shows long-term survival without satisfactory clinical improvement.

METHODS

Thirty consecutive DCM patients with persistent LV dysfunction (ejection fraction ≤40%) and reduced exercise tolerance (peak oxygen consumption <25 ml/kg/min) despite chronic (>1 year) tailored treatment with metoprolol and angiotensin-converting enzyme inhibitors were enrolled in a 12-month, open-label, parallel trial and were randomized either to continue on metoprolol (n = 16, mean dosage 142 ± 44 mg/day) or to cross over to maximum tolerated dosage of carvedilol (n = 14, mean dosage 74 ± 23 mg/day).

RESULTS

At 12 months, patients on carvedilol, compared with those continuing on metoprolol, showed a decrease in LV dimensions (end-diastolic volume -8 ± 7 vs. +7 ± 6 ml/m², p = 0.053; end-systolic volume -7 ± 5 vs. +6 ± 4 ml/m², p = 0.047), an improvement in LV ejection fraction (+7 ± 3% vs. -1 ± 2%, p = 0.045), a reduction in ventricular ectopic beats (-12 ± 9 vs. +62 ± 50 n/h, p = 0.05) and couplets (-0.5 ± 0.4 vs. +1.5 ± 0.6 n/h, p = 0.048), no significant benefit on symptoms and quality of life and a negative effect on peak oxygen consumption (-0.6 ± 0.6 vs. +1.3 ± 0.5 ml/kg/min, p = 0.03).

CONCLUSIONS

In DCM patients who were poor responders to chronic metoprolol, carvedilol treatment was associated with favorable effects on LV systolic function and remodeling as well as on ventricular arrhythmias, whereas it had a negative effect on peak oxygen consumption. (J Am Coll Cardiol 1999;33:1926–34) © 1999 by the American College of Cardiology

The progression of heart failure is mainly related to neurohormonal activation, including renin–angiotensin–aldosterone and sympathetic nervous systems (1).

It is well known that angiotensin-converting enzyme (ACE) inhibitors have beneficial effects on left ventricular (LV) remodeling (2) and reduce morbidity and mortality in patients with heart failure (3). Moreover, in the recent years several convincing demonstrations regarding the benefits of adrenergic antagonists have been provided (4–6). In fact, after a transient negative pharmacologic response (7), a time-dependent partial reversion of LV dysfunction and remodeling was demonstrated (8).

Metoprolol, a second-generation beta1-selective blocking agent, significantly improved symptoms and quality of life, LV function and hemodynamics in most patients with idiopathic dilated cardiomyopathy (DCM) (4,9). However, a subset of the others showed persistent LV dysfunction despite tailored medical therapy (9).

Carvedilol, a third-generation beta1–, beta2– and alpha1–blocker with ancillary properties was demonstrated as being able to extend the favorable effects of selective beta-blocking agents to produce a significant reduction of mortality in heart failure (5). Thus, exerting a more complete antagonism on sympathetic activation than metoprolol (10), carvedilol could have additional benefits on symptoms and LV function in heart failure.

From the *Department of Cardiology, Ospedale Maggiore; †Department of Internal Medicine and Geriatrics, University of Trieste; ‡International Center for Genetic Engineering and Biotechnologies, Area Science Park; §Department of Statistics, University of Trieste, and ¶Respiratory Physiopathology Service, Ospedale Santorio, Trieste, Italy.

Manuscript received September 25, 1998; revised manuscript received January 27, 1999, accepted February 25, 1999.
The present study was designed to evaluate the additional beneficial effects of carvedilol in highly selected patients with DCM with persistent LV dysfunction and reduced exercise tolerance despite long-term tailored treatment with digitalis, ACE inhibitors and the beta1-selective blocker metoprolol.

METHODS

Study design. We performed a 12-month, open-label, parallel, randomized and controlled trial on clinically stable DCM patients who were poor responders to chronic treatment with metoprolol in addition to conventional therapy on the basis of a persistent moderate to severe LV dysfunction and reduced exercise tolerance.

Patients were randomized to continue either on metoprolol or to cross over to carvedilol on a 1:1 basis. End points included: 1) the completion of the study, 2) worsening heart failure not controlled by the adjustment of medical therapy, 3) life-threatening ventricular arrhythmias, 4) the inclusion on a waiting list for cardiac transplant and 5) death.

The primary objectives were to evaluate the additional beneficial effects of long-term carvedilol treatment on LV function and remodeling. The secondary objectives were to assess the effects of carvedilol on symptoms, quality of life, exercise tolerance and ventricular arrhythmias.

Study population. From April 1994 to December 1995, from among 154 DCM patients referred to, and followed up in, our Heart Failure Clinics (Department of Cardiology, Trieste, Italy), 30 patients were consecutively selected on the basis of the following inclusion criteria: 1) chronic (>12 months) tailored metoprolol plus conventional heart failure therapy (ACE inhibitors, digitalis, diuretics), 2) persistent moderate to severe LV dysfunction (LV ejection fraction [EF] by echocardiography or radionuclide angiography ≤40%) and 3) reduced exercise tolerance (peak oxygen consumption [VO₂] <25 ml/kg/min).

Patients were excluded if they had: 1) clinically unstable heart failure or changes of heart failure treatment in the last three months before randomization, 2) inclusion on waiting list for cardiac transplant, 3) sustained or symptomatic ventricular tachycardia that had not been adequately con-

trolled by amiodarone therapy, 4) atrial flutter or fibrillation or other sustained supraventricular arrhythmias or 5) second- or third-degree atrioventricular block, unless the patients had been equipped with a permanent pacemaker. Informed consent was obtained from all patients.

In all patients, previous DCM diagnosis had been based on World Health Organization criteria (11). In particular, the presence of significant coronary artery disease (stenosis >50% of at least one epicardial vessel) had been excluded by coronary angiography and active myocarditis by endomyocardial biopsy, according to the “Dallas criteria” (12).

After careful clinical stabilization with tailored dosages of ACE inhibitors (mainly enalapril), digitalis and diuretics, all selected patients had tolerated increasing dosages of metoprolol, starting from 5 mg b.i.d. up to 200 mg a day with a target rest heart rate of 60 beats/min (range 50 to 70) or systolic blood pressure of 100 mm Hg (range 90 to 110) (9). The daily dosage of ACE inhibitors was converted to captopril equivalent doses multiplying by the following correction factors: enalapril 3.75, captopril 1.0, lisinopril 3.75, quinapril 1.88 and ramipril 7.5 (13).

All cases had been followed up after diagnosis by serial noninvasive evaluations and according to the patient’s clinical needs for at least 12 months (mean 34 ± 4 months) before randomization.

Randomization, open challenge, up-titration and maintenance period. Sixteen of the 30 patients enrolled were randomized to continue on the same dosage of metoprolol, and 14 to cross over to carvedilol. After careful evaluation of heart failure stability, the transition from metoprolol to carvedilol was carried out under strict clinical observation in our Heart Failure Clinics. An open-label challenge was administered beginning the day after metoprolol withdrawal (usually 18 h after the last metoprolol administration) and continuing at 12-h intervals for 3 days. Down-titration of metoprolol was not required by our study protocol. In 11 out of 14 patients (79%), treated with >100 mg/day of metoprolol and systolic blood pressure >100 mm Hg, the test dose of carvedilol was 12.5 mg b.i.d., whereas 3 patients (21%) were initially tested with the usual 6.25 mg b.i.d. Patients were classified as “not tolerant” if they showed symptoms or signs of worsening heart failure, hypoperfusion, significant hypotension (defined as systolic blood pressure <80 mm Hg), marked sinus bradycardia (defined as rest heart rate <40 beats/min) or appearance of advanced atrioventricular block.

In patients who successfully completed the open-label challenge, carvedilol was titrated every three days up to the maximum tolerated dosage, according to the following scheme: 12.5 mg b.i.d., 12.5 mg t.i.d., 25 mg b.i.d., 25 mg t.i.d., 50 mg b.i.d. The three patients who initially tolerated a carvedilol test dose of 6.25 mg b.i.d. were titrated up according the same scheme but starting from 6.25 mg b.i.d. followed by 6.25 mg t.i.d. for three days.

In the same way as metoprolol, the dosage of carvedilol
could be modified after the end of titration to obtain a comparable degree of beta blockade with a target rest heart rate of 60 beats/min (range 50 to 70) or systolic blood pressure of 100 mm Hg (range 90 to 110).

**Study protocol.** The severity of heart failure symptoms was assessed by the New York Heart Association (NYHA) functional class, Heart Failure Score (14) and the Minnesota “Living With Heart Failure” Questionnaire (15). Routine clinical laboratory tests (including complete blood count, chemistry panel and urinalysis) were performed at baseline and serially repeated throughout the study period. All patients underwent chest X ray, electrocardiogram, ambulatory 24-h Holter monitoring and echocardiogram at baseline, 6 and 12 months.

Conventional M-mode, two-dimensional and Doppler echocardiographic variables were measured in all patients. Left ventricular end-diastolic (EDV) and end-systolic (ESV) volumes were calculated from the apical four-chamber view using the ellipsoid, single-plane formula. All measurements were obtained in sinus rhythm as a mean of three consecutive beats. Chamber diameters and volumes were normalized for body surface areas. In two patients (one randomized to metoprolol, one to carvedilol), in whom the echocardiograms were not adequate for quantitative evaluations, LVEF was assessed by radionuclide angiography.

Echocardiographic studies were reviewed by two independent investigators. Reproducibility of two-dimensional and Doppler echocardiographic data in our laboratory were previously assessed in 25 patients with DCM: no rater effect was demonstrated and the observations were consistent across measurements (17). Intraobserver and interobserver variability (mean ± SEM) were respectively 7 ± 1 and 2 ± 1% for LVEF, 9 ± 4 and 4 ± 4 ml/m² for LVEDV, 7 ± 2 and 3 ± 4 ml/m² for LVESV and 0 ± 5 and 8 ± 3 ms for deceleration time of mitral E wave.

Bicycle maximal exercise tests were performed with measurements of peak VO₂ at baseline and after 12 months. The maximal protocol consisted of 1 min of free pedaling, followed by 10-W/min incremental exercise to exhaustion. Dyspnea or fatigue were the required end points to stop the exercise. Expired gas analysis was made by an infrared and paramagnetic gas analyzer using the breath by breath method. Peak VO₂ was defined as the average oxygen consumption during the last minute of maximal exercise. Anaerobic threshold was detected by the V-slope method. The cardiopulmonary exercise test was performed using an instrument which met the standards of the European Respiratory Society Task Force (18). Furthermore, all patients underwent a spirometry and a single-breath carbon monoxide diffusing capacity according to the American Thoracic Society statements (19,20).

A submaximal exercise test was then performed using the maximal one to determine the appropriate work level. During the submaximal protocol patients exercised at 10 W/min, with incremental steps up to 75% of baseline maximal workload, and then continued to exhaustion. Six- and 12-month submaximal tests were performed at the same workload of the baseline evaluation.

Clinical, echocardiographic and cardiopulmonary evaluations were performed by different investigators. Echocardiographic and cardiopulmonary operators were blind to patient allocation.

**Statistical analysis.** Data are expressed as mean ± SEM or percentages. All differences were tested using a model-based approach. This was due to the need to adjust for some potentially confounding factors, for instance mild hypertension, length of the disease and therapy with amiodarone. New York Heart Association functional class of patients at randomization was not considered as a confounder because of the very few patients in class III would have led the model to being highly unstable.

Parallel sample-like tests were based on quasi-likelihood models with link and variance function specification tailored to the form of the response (identity link and constant variance for continuous variables and logit link and binomial variance for dichotomous variables) (21). Tests for categorical ordered responses were based on a proportional odds model. Paired samples-like tests were based on the same models but fitted using the generalized estimating equations (22) approach with an autoregressive order one working correlation structure.

To interpret the data properly, all p values ≤0.25 were specified. A two-tailed p value <0.05 was considered significant.

Data were stored in the Heart-Muscle Disease Registry using Oracle (23) and the statistical analyses were carried out using S-plus (24).

**RESULTS**

**Patient characteristics.** The 30 patients with DCM enrolled in the present study were identified as poor responders to chronic metoprolol treatment on the basis of persistent moderate to severe LV dysfunction and reduced exercise tolerance.

Compared with data at diagnosis before the beginning of metoprolol treatment, patients showed at randomization a predictable lower rest heart rate (60 ± 1 vs. 86 ± 2 beats/min, p < 0.001) and an improvement of symptomatic status (NYHA class I/II/III 8/19/3 vs. 4/19/7, p = 0.02; Heart Failure Score 1.1 ± 0.2 vs. 1.8 ± 0.3, p = 0.02; exercise tolerance 788 ± 36 vs. 618 ± 37 s, p < 0.001) associated with a not clinically relevant effect on LV function (EF 29 ± 1 vs. 25 ± 1%, p = 0.007) and remodeling (EDV: 121 ± 7 vs. 133 ± 7 ml/m², p = 0.15).

Thus, at randomization, patients were characterized by mildly symptomatic chronic heart failure with a moderate to severe LV dysfunction despite long-term metoprolol treatment. In all patients concomitant therapy consisted of digitalis and maximum tolerated dosages of ACE inhibitors (captopril equivalent dosage 112 mg/day); 23 patients (77%)...
were taking diuretics (furosemide: 9 patients; thiazides: 14 patients) and 3 patients (10%) with complex symptomatic ventricular arrhythmias were receiving amiodarone.

Sixteen out of 30 patients were randomized to continue on the same metoprolol dosage, and 14 to cross over to carvedilol titrated up to the maximum tolerated dosage. There were no significant differences in baseline clinical findings between the two groups (Table 1). Metoprolol and carvedilol patients did not differ in concomitant therapy at baseline or during the study period.

Drug tolerability and degree of beta blockade. Beta-blocker therapy was well tolerated in all patients. During titration of carvedilol, mildly symptomatic hypotension rarely required temporary adjustment of diuretics or ACE inhibitors.

Throughout the course of the study, 24-h Holter monitoring documented a nocturnal worsening of atrioventricular conduction (first or second atrioventricular block) in four carvedilol patients (29%); the maintenance dosage of carvedilol was slightly reduced in two of these patients (14%), who had a nocturnal heart rate < 40 beats/min. One carvedilol patient (7%) showed episodes of symptomatic hypotension, and two others (14%) complained of fatigue. No other side effect was documented.

No patient reached any predefined end point, and all of them completed the 12-month study period. One patient randomized to carvedilol was hospitalized because of symptomatic paroxysmal atrial fibrillation.

A similar degree of beta blockade, expressed by 12-month heart rate at rest (respectively 61 ± 3 vs. 60 ± 2 beats/min, p = NS), 24-h Holter monitoring (68 ± 3 vs. 69 ± 2 beats/min, p = NS) and peak exercise (115 ± 5 vs. 116 ± 7 beats/min, p = NS), was obtained by carvedilol and metoprolol at a dosage ratio of approximately 1:2 (respectively 74 ± 6 vs. 142 ± 11 mg/day). Systolic blood pressure did not significantly change between the two groups, with a tendency to a mild decrease in patients on carvedilol (−1 ± 3 mm Hg at 6 months, −3 ± 3 mm Hg at 12 months; p = NS) and to a mild increase in those on metoprolol (+5 ± 3 mm Hg at 6 months, +2 ± 4 mm Hg at 12 months; p = NS).

Effects on LV function and remodeling. Compared with the absence of significant changes in those continuing on metoprolol, patients on carvedilol showed a significant time-dependent improvement of LVEF (at 6 months: +2.5 ± 2.5%, p = 0.20 vs. baseline; at 12 months: +7 ± 3%, p = 0.033 vs. baseline) (Fig. 1) (Table 2). Overall, at 12 months LVEF improved by 7.8% (95% confidence interval [CI] +3% to +12%) in the carvedilol group as compared with the metoprolol group. Nine patients on carvedilol showed an increase of LVEF ≥5%, with a remarkable improvement ≥10% in five of them (mean +17%, range +12% to +28%) (Table 3). Notably, changes in LVEF were not related to the duration of metoprolol treatment before randomization both in the carvedilol group (metoprolol therapy ≤24 months [n = 6] vs. >24 months [n = 8]: +5.9 ± 4.7 vs. +7.3 ± 3.7%, p = NS) and in the metoprolol group (metoprolol therapy ≤24 months [n = 7], vs. >24 months [n = 9]: +0.9 ± 3.2 vs. −1.7 ± 2.4%, p = NS).

Carvedilol and metoprolol showed a different effect at 12 months on LVEDV (respectively −8 ± 7 vs. +7 ± 6 ml/m², p = 0.053) and LVESV (−7 ± 5 vs. +6 ± 4 ml/m², p = 0.37).

### Table 1. Baseline Characteristics of 30 Dilated Cardiomyopathy Patients With Persistent LV Dysfunction Despite Chronic Optimal Treatment Including Angiotensin-Converting Enzyme Inhibitors and Metoprolol

<table>
<thead>
<tr>
<th></th>
<th>All Population (n = 30)</th>
<th>Metoprolol (n = 16)</th>
<th>Carvedilol (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of heart failure symptoms (mo)</td>
<td>60 ± 10</td>
<td>70 ± 16</td>
<td>50 ± 11</td>
<td>0.13</td>
</tr>
<tr>
<td>Duration of metoprolol therapy (mo)</td>
<td>34 ± 4</td>
<td>40 ± 8</td>
<td>29 ± 4</td>
<td>0.11</td>
</tr>
<tr>
<td>Mild hypertension (n, %)</td>
<td>6 (20)</td>
<td>4 (25)</td>
<td>2 (14)</td>
<td>0.15</td>
</tr>
<tr>
<td>NYHA functional class (I/II/III) (n)</td>
<td>8/19/3</td>
<td>3/10/3</td>
<td>5/9/0</td>
<td>0.17</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>121 ± 2/75 ± 2</td>
<td>118 ± 3/73 ± 3</td>
<td>124 ± 3/78 ± 3</td>
<td>0.14/0.13</td>
</tr>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>60 ± 1</td>
<td>59 ± 2</td>
<td>60 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Left bundle branch block (n, %)</td>
<td>19 (63)</td>
<td>12 (73)</td>
<td>7 (50)</td>
<td>0.21</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm/m²)</td>
<td>38 ± 1</td>
<td>38 ± 1</td>
<td>37 ± 1</td>
<td>0.17</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml/m²)</td>
<td>121 ± 7</td>
<td>126 ± 12</td>
<td>115 ± 9</td>
<td>0.16</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29 ± 1</td>
<td>29 ± 2</td>
<td>29 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral regurgitation (0–4)</td>
<td>1.3 ± 0.1</td>
<td>1.4 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>0.18</td>
</tr>
<tr>
<td>E-wave deceleration time (ms)</td>
<td>232 ± 14</td>
<td>252 ± 16</td>
<td>210 ± 24</td>
<td>0.07</td>
</tr>
<tr>
<td>Ventricular ectopic beats (n/h)</td>
<td>68 ± 23</td>
<td>67 ± 40</td>
<td>68 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Ventricular couplets (n/h)</td>
<td>1.2 ± 0.5</td>
<td>0.1 ± 0.05</td>
<td>2.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia (n/h)</td>
<td>0.05 ± 0.02</td>
<td>0.01 ± 0.01</td>
<td>0.1 ± 0.06</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal exercise tolerance (s)</td>
<td>788 ± 36</td>
<td>776 ± 58</td>
<td>802 ± 41</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>126 ± 3</td>
<td>121 ± 5</td>
<td>131 ± 3</td>
<td>0.09</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg/min)</td>
<td>18 ± 1</td>
<td>17 ± 1</td>
<td>18 ± 1</td>
<td>0.18</td>
</tr>
<tr>
<td>Submaximal exercise tolerance (s)</td>
<td>862 ± 65</td>
<td>906 ± 119</td>
<td>815 ± 46</td>
<td>0.13</td>
</tr>
</tbody>
</table>

LV = left ventricular; NYHA = New York Heart Association; VO₂ = volume of oxygen consumption.
LVEDV and of 13 ml/m² (95% CI LV5, *p = 0.033, 12 months vs. baseline carvedilol; †p = 0.046, Δ 12 months carvedilol vs. metoprolol.

Figure 1. Time-dependent improvement of left ventricular ejection fraction (LVEF) with carvedilol (n = 14, black circles) or metoprolol (n = 16, open circles) in dilated cardiomyopathy patients with persistent left ventricular dysfunction despite chronic optimum treatment including angiotensin-converting enzyme inhibitors and metoprolol. *p = 0.033, 12 months vs. baseline carvedilol; †p = 0.046, Δ 12 months carvedilol vs. metoprolol.

p = 0.047) (Fig. 2). There was therefore an overall difference of 15 ml/m² (95% CI −3 to −27 ml/m²) in LVEDV and of 13 ml/m² (95% CI −4 to −22 ml/m²) in LVESV between the carvedilol and metoprolol groups.

Effects on symptoms, quality of life and exercise tolerance. The NYHA class, the Heart Failure Score, the Minnesota “Living With Heart Failure” Questionnaire and submaximal exercise tolerance did not significantly change between the two groups (Table 4). At 12 months, the maximal exercise tolerance was slightly reduced in both groups but to a greater, although not significant, extent in carvedilol (−47 ± 31 vs. −14 ± 16 s, p = 0.19). Notably, seven patients (54%) treated with carvedilol, compared with one on metoprolol, worsened their maximal exercise time by at least 2 min (p = 0.003) (Table 3). Moreover, the two study drugs showed a different effect on peak VO₂ at 12 months (−0.6 ± 0.6 vs. +1.3 ± 0.5 ml/kg/min, p = 0.03). Overall, peak VO₂ was reduced by 1.9 ml/kg/min (95% CI −0.9 to −2.9) in the carvedilol compared with the metoprolol group. Compared with metoprolol, at 12 months the negative effect of carvedilol on exercise capacity was associated with a more evident, although not significant, reduction of maximum heart rate (−16 ± 5 vs. −7 ± 4 beats/min, p = 0.13).

Effects on ventricular arrhythmias. Compared with metoprolol patients, those on carvedilol showed a positive effect on ventricular ectopic beats (−12 ± 9 vs. +62 ± 50 n/h, p = 0.05) and couplets (−0.5 ± 0.4 vs. +1.5 ± 0.6 n/h, p = 0.048) but not a significant effect on episodes of nonsustained ventricular tachycardia (Table 4). Similarly, the distribution of patients with an increase or a reduction of ventricular extrasystoles (≥30/h) or couplets was significantly different in favor of carvedilol (Table 3).

DISCUSSION

Previous data reported a progressive and sustained improvement of heart failure symptoms and LV function (4–9) in most DCM patients treated with metoprolol. Nevertheless, a consistent proportion of remaining patients survived with a persistent moderate to severe LV dysfunction, even though an improvement of symptoms was often detectable. During long-term follow-up, these patients may be at higher risk of worsening heart failure, heart transplantation or death (25).

Carvedilol, a third-generation mildly beta1-selective antagonist (26,27) with a vasodilator action related to alpha1-receptor blockade (26–29) and potentially relevant antioxidant (30) and antiproliferative (31) properties, might produce different and more favorable clinical effects in chronic heart failure compared with the second-generation beta1-selective antagonist metoprolol.

We tested this hypothesis in strictly selected DCM patients characterized by stable heart failure symptoms but no clinically relevant improvement of LV function despite tailored long-term treatment (three years on average) with ACE inhibitors, digitalis and metoprolol. Thus, we randomized in our open-label, parallel trial, 30 consecutive patients either to continue on metoprolol or to cross over to carvedilol for 12 months.

At the end of the study period, compared with metoprolol, carvedilol was associated with a positive effect on LV

### Table 2. Effect of Carvedilol Versus Metoprolol on LV Function and Remodeling in 30 Dilated Cardiomyopathy Patients

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol (n = 16, 142 ± 11 mg/day)</th>
<th>Carvedilol (n = 14, 74 ± 6 mg/dl)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Δ 6 Months</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm/m²)</td>
<td>38 ± 1.3</td>
<td>−0.6 ± 0.6</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml/m²)</td>
<td>126 ± 12</td>
<td>+11 ± 6*</td>
</tr>
<tr>
<td>LV end-systolic volume (ml/m²)</td>
<td>91 ± 10</td>
<td>+9 ± 4*</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29 ± 2</td>
<td>−0.3 ± 2</td>
</tr>
<tr>
<td>E-wave deceleration time (ms)</td>
<td>252 ± 16</td>
<td>−19 ± 19</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1 ± 0.1</td>
<td>−0.04 ± 0.1</td>
</tr>
<tr>
<td>Mitral regurgitation (0–4)</td>
<td>1.4 ± 0.2</td>
<td>+0.1 ± 0.2</td>
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</table>

*p < 0.10, Δ 6 or Δ 12 months carvedilol vs. metoprolol; †p < 0.05, Δ 6 or Δ 12 months carvedilol vs. metoprolol; ‡p < 0.05, Δ 12 months vs. baseline carvedilol or metoprolol.

LV = left ventricular.
systolic function and remodeling, and a reduction of ventricular arrhythmias. Conversely, a neutral effect on heart failure symptoms and a worsening of maximal exercise capacity were observed in patients on carvedilol.

Drug tolerability and degree of beta blockade. Although down-titration has been shown to reduce the rebound effects of beta blockade discontinuation (32), nevertheless the withdrawal of metoprolol may lead to worsening heart failure and arrhythmias (33,34). So, to avoid leaving patients without beta-blocker treatment, we administered carvedilol under strict clinical observation beginning the day after metoprolol withdrawal. This strategy was well tolerated in all cases without worsening heart failure. Furthermore, the long-term treatment with tailored dosages of metoprolol, combined with the optimum clinical stability of the patients enrolled, favored the good tolerability of a higher than usual test dose of carvedilol (12.5 mg b.i.d.), rapidly titrated (every 3 days) up to the maximum tolerated dosages.

Our experience would suggest that, in clinically stable patients with LV dysfunction, the transition from metoprolol to carvedilol is a practical and safe method.

![Figure 2. Effects of 12-month carvedilol (n = 14, black bars) or metoprolol (n = 16, open bars) treatment on left ventricular (LV) remodeling in dilated cardiomyopathy patients with persistent LV dysfunction despite chronic optimum treatment including angiotensin-converting enzyme inhibitors and metoprolol. *p = 0.053, Δ 12 months carvedilol vs. metoprolol; †p = 0.047, Δ 12 months carvedilol vs. metoprolol. LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume.](image)

**Table 3.** Effect of Carvedilol Versus Metoprolol at 12 Months on Categorical Measures of Clinical Status, LV Function and Ventricular Arrhythmias in 30 Dilated Cardiomyopathy Patients

<table>
<thead>
<tr>
<th>Parameters and Changes</th>
<th>Metoprolol (n = 16, 142 ± 11 mg/day)</th>
<th>Carvedilol (n = 14, 74 ± 6 mg/day)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved ≥1 class</td>
<td>1 (6%)</td>
<td>4 (28.5%)</td>
<td>NS</td>
</tr>
<tr>
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<td>13 (82%)</td>
<td>9 (64.5%)</td>
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<tr>
<td>Worsened ≥1 class</td>
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<td>1 (7%)</td>
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<tr>
<td>Maximal exercise tolerance*</td>
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</tr>
<tr>
<td>Increased ≥2 min</td>
<td>0</td>
<td>2 (15%)</td>
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<tr>
<td>Unchanged</td>
<td>13 (87%)</td>
<td>4 (31%)</td>
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<tr>
<td>Decreased ≥2 min</td>
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<td>7 (54%)</td>
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<tr>
<td>LV ejection fraction</td>
<td></td>
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</tr>
<tr>
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<td>2 (13%)</td>
<td>5 (36%)</td>
<td></td>
</tr>
<tr>
<td>≥5 and &lt;10%</td>
<td>2 (13%)</td>
<td>4 (29%)</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>9 (56%)</td>
<td>2 (14%)</td>
<td></td>
</tr>
<tr>
<td>Decreased ≥5 and &lt;10%</td>
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<td>3 (22%)</td>
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</tr>
<tr>
<td>≥10%</td>
<td>2 (13%)</td>
<td>0</td>
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</tr>
<tr>
<td>Ventricular ectopic beats</td>
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<td>0.03</td>
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<tr>
<td>Increased ≥30/h</td>
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<td>2 (14%)</td>
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<tr>
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<td>6 (38%)</td>
<td>7 (50%)</td>
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<tr>
<td>Ventricular couplets</td>
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<td>2 (14%)</td>
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</tr>
<tr>
<td>Decreased</td>
<td>2 (12%)</td>
<td>8 (57%)</td>
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*Maximal exercise test was not performed in two patients (one on metoprolol, one on carvedilol). LV = left ventricular; NYHA = New York Heart Association.

Figure 2. Effects of 12-month carvedilol (n = 14, black bars) or metoprolol (n = 16, open bars) treatment on left ventricular (LV) remodeling in dilated cardiomyopathy patients with persistent LV dysfunction despite chronic optimum treatment including angiotensin-converting enzyme inhibitors and metoprolol. *p = 0.053, Δ 12 months carvedilol vs. metoprolol; †p = 0.047, Δ 12 months carvedilol vs. metoprolol. LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume.
energy consumption and the modification in force–frequency relation are undoubtedly part of the mechanisms of improvement with beta-blockers (39). On the contrary, in this study the response to carvedilol in the absence of any significant further change in heart rate suggests that there are other contributory factors.

A relevant effect of alpha blockade seems unlikely, since a previous trial showed the development of tolerance to alpha blockade after a few months of therapy (35). Otherwise, the vasodilator action of carvedilol could improve the short-term low tolerability of nonselective beta-blockers in more compromised patients (27,40). In fact, previous trials showed an acute significant reduction of LV filling pressure compared with those treated with metoprolol (35,41,42).

Gilbert et al. (10) recently reported that carvedilol and metoprolol significantly differ in their effects on adrenergic activity and on cardiac beta-adrenergic receptors. In that study, metoprolol was associated with an increased level of central venous norepinephrine with no apparent effect on transmyocardial balance and with an up-regulation of beta1-receptor subpopulation, down-regulated in the failing human heart. Conversely, carvedilol reduced two indexes of cardiac adrenergic activity, central venous norepinephrine and transmyocardial norepinephrine balance, without affecting systemic norepinephrine levels, and showed no effect on beta-adrenergic receptor density, although it was associated with effects on hemodynamics, LV function and heart failure symptoms at least as favorable as those produced by metoprolol.

Compared with the expected lack of further significant changes in patients randomized to continue on metoprolol, patients who crossed over to carvedilol showed a significant effect on LV systolic function with a net increase in LVEF of 7.8% after 12 months and, impressively, an improvement of ≥10% in five of them (35.7%).

These data seem to agree with the results of previous 4- to 6-month placebo-controlled trials showing a tendency to a greater improvement of LVEF on carvedilol (+9/+11%) (10,35,36,43), with respect to metoprolol (+6%) (4). In our study, the effect of carvedilol on LVEF was favored by a longer study period but seems particularly relevant considering the strictly selected characteristics of our DCM patients.

Notably, the improvement of LV systolic function in patients treated with carvedilol was associated with a slight decrease of LV volumes compared with those continuing on metoprolol. It is well known that ACE inhibitors have beneficial effects on ventricular remodeling by slowing the progression of chamber dilation in patients with myocardial infarction and LV dysfunction (2). More recently, Doughty et al. (44) provided evidence of the benefits of carvedilol in addition to ACE inhibitors on LV remodeling in ischemic cardiomyopathy patients. Our data on DCM patients are consistent with those of Doughty et al. (44) and suggest the possibility that carvedilol, compared with metoprolol, could influence a partial reversion of ventricular remodeling more efficiently, as also hypothesized by Eichhorn and Bristow (8).

**Effects on symptoms, quality of life and exercise tolerance.** In most studies (35,36,43,45) both carvedilol and metoprolol showed a favorable effect on symptoms and quality of life, with some advantages for carvedilol (10). It is conceivable that the mild functional impairment of our study population at enrollment could have reduced the margins of improvement with treatment.

Conversely, beta-adrenergic receptor down-regulation of failing heart appears to contribute to the decline in maximal exercise response (46). In this case, it is interesting to note that metoprolol, which has been shown to up-regulate beta1 receptors, was demonstrated as improving maximal exercise response (4) in contrast to carvedilol (2,35,36,45). In our study, the unfavorable effect of carvedilol on maximal exercise capacity was associated to a greater, but not significant, decrease of maximum heart rate in comparison with
metoprolol. Nevertheless, the blunting of maximal vasodilating response mediated by peripheral beta1 antagonism could contribute to explaining the negative effect of carvedilol on maximal exercise.

Effects on ventricular arrhythmias. A previous randomized trial in patients with DCM showed a significant effect of carvedilol in reducing ventricular arrhythmias (36). Similarly, our patients treated with carvedilol, in comparison with those on metoprolol, showed an additional beneficial effect on the reduction of ventricular arrhythmias evaluated by 24-h Holter monitoring. Whereas previous trials with beta1-selective antagonists in DCM failed to show a reduction of arrhythmic deaths (4,47), our data seem to be in accordance with the possibility of a significant prevention of sudden cardiac death with carvedilol (5).

Study limitations. A recognized limitation of the present study is that it was open-label. This lack of blinding is particularly relevant for more subjective parameters. For this reason we avoided considering symptoms as the selection criteria or NYHA functional class evaluation as a primary objective of the present study. However, it must be pointed out that all instrument readings were done by blinded operators. Thus the potential impact of investigator subjectivity was greatly limited.

Another limitation is the relatively small number of study patients. Yet, it deserves to be pointed out how enrollment was strongly affected by the strict selection criteria, requiring DCM patients with stable heart failure who were poor responders in terms of LV systolic function and reduced exercise tolerance to optimum medical therapy including long-term metoprolol. Even though we are aware that a larger number of subjects could have improved the power of our results, nevertheless the size of our study population did not hinder the identification of significant differences between carvedilol and metoprolol patients using a conservative statistical approach.

Finally, although the carvedilol and metoprolol groups did not significantly differ in their baseline characteristics, we recognize that some randomization imbalances may exist. In particular, being aware that more chronic patients might be sicker, we performed all our analyses considering the duration of heart failure as a confounder. These considerations make us confident about our conclusions.

The results of this study might not be applicable to patients with ischemic cardiomyopathy. However, previous trials (4-6) suggest the possibility of an additive effect of carvedilol compared with metoprolol also in ischemic patients.

Conclusions. The results of the present study on a selected population of DCM patients, who were poor responders to long-term optimum treatment for heart failure including metoprolol, suggest a benefit of carvedilol on LV function, remodeling and arrhythmias, and a negative effect on peak exercise compared with metoprolol.

These effects may be secondary to a greater cardioprotection from sympathetic activation (10) due to the nonselective blockade of adrenergic receptors, lowering cardiac adrenergic activity and not sensitizing to adrenergic stimulation the down-regulated beta1-adrenergic pathway.

Whether the different effects of these two beta-blockers on relevant prognostic markers such as LV function and arrhythmias could influence cardiac mortality will be analyzed by the ongoing multicenter Carvedilol or Metoprolol European Trial (48).

Acknowledgments

We are indebted to Prof. Peter Brown, Dorita Chesevani, MD and Luigi Salvatore, MD for help in writing this report.

APPENDIX

Heart-Muscle Disease Study Group

Department of Cardiology, Ospedale Maggiore, Trieste, Italy: L. Barbieri, MD, F. Camerini, MD, A. Cherubini, MD, M. Davanzo, RN, C. Di Chiara, RN, A. Di Lenarda, MD, R. Gorton, MD, F. Longaro, MD, A. Perkan, MD, B. Pinamonti, MD, A. Poletti, MD, S. Rakar, MD, C. Rocco, MD, L. Salvatore, MD, G. Scherl, G. Scolari, MD, G. Sinagra, MD, C. Zanchi, RN, M. Zecchin, MD.

Department of Internal Medicine and Geriatrics, University of Trieste, Italy: G. Sabbadini, MD.

International Center for Genetic Engineering and Biotechnologies (ICGEB), Trieste, Italy: A. Falaschi, MD, PhD, M. Giacca, MD, PhD, L. Mestroni, MD, FACC, S. Miocic, MD, M. Vatta, PhD.

Department of Morbid Anatomy, University of Trieste, Trieste, Italy: R. Bussani, MD, F. Silvestri, MD.

Reprint requests and correspondence: Dr. Andrea Di Lenarda, MD, Department of Cardiology, Ospedale Maggiore, Piazza Ospedale 1, 34100 Trieste, Italy. E-mail: dilenar@uts.univ.trieste.it.

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6. Australia/New Zealand Heart Failure Research Collaborative Group.


