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Carvedilol Improves Left Ventricular Function and Symptoms in Chronic Heart Failure: A Double-Blind Randomized Study

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Objectives. **This study assessed the safety and efficacy of carvedilol in patients with heart failure caused by idiopathic or ischemic cardiomyopathy.**

Background. **Carvedilol is a mildly beta$_1$-selective beta-adrenergic blocking agent with vasodilator properties. Beta-blockade may be beneficial in patients with heart failure, but the effects of carvedilol are not known.**

Methods. **Sixty patients with heart failure (New York Heart Association functional classes II to IV) and left ventricular ejection fraction ≤0.35 were enrolled in the study. All patients tolerated challenge with carvedilol, 3.125 mg twice a day, and were randomized to receive carvedilol (n = 36) versus placebo (n = 24). Study medication was titrated over 1 month from 6.25 to 25 mg twice a day (<75 kg) or 50 mg twice a day (>75 kg) and continued for 3 months. One placebo-treated and two carvedilol-treated patients did not complete the study.**

Results. **Carvedilol therapy resulted in a significant reduction in heart rate and mean pulmonary artery and pulmonary capillary wedge pressures and a significant increase in stroke volume and left ventricular stroke work. Left ventricular ejection fraction increased 52% in the carvedilol group (from 0.21 to 0.32, $p < 0.0001$ vs. placebo group). Carvedilol-treated patients also reported a significant lessening of heart failure symptoms ($p < 0.05$ vs. placebo group). Submaximal exercise duration tended to increase with carvedilol therapy (from 688 ± 31 s to 871 ± 32 s), but this change was not significantly different from that with placebo therapy by between-group analysis. Peak oxygen consumption during maximal exercise did not change.**

Conclusions. **Long-term carvedilol therapy improves rest cardiac function and lessens symptoms in patients with heart failure.**

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Adrenergic activation in heart failure appears to have adverse effects on myocardial function (1,2) and signal transduction (3,4). This finding has led to renewed interest in the therapeutic use of beta-adrenergic blocking agents in patients with heart failure. Early reports (5,6) suggested that beta-blockade may improve hemodynamic function in patients with heart failure caused by idiopathic dilated cardiomyopathy. Subsequent reports (7–17) have mostly supported this finding, but available data from long-term placebo-controlled trials are limited. We recently reported (12) that long-term therapy with bucindolol, a nonselective beta-blocker with weak vasodilator activity, improves rest cardiac function and lessens symptoms of heart failure in patients with idiopathic dilated cardiomyopathy. The improvement in left ventricular dysfunction with bucindolol appears to be dose dependent (16). Few trials have included patients with heart failure caused by ischemic cardiomyopathy, but the initial experience suggested that these patients may also benefit from beta-blockade (13,15–17).

The effect of beta-blockade on exercise tolerance in patients with heart failure remains unclear. This uncertainty is due in part to the finding that maximal exercise tolerance is heart rate-dependent, and the use of beta-adrenergic blockers may significantly lower maximal exercise heart rate (12,15,16). Thus, standard maximal exercise protocols used in previous trials may not adequately assess clinically relevant changes in exercise tolerance in patients with heart failure treated with beta-blockade. The ideal method for evaluating changes in exercise tolerance during beta-blocker therapy would not be dependent on maximal heart rate but would reflect improvement in submaximal exercise tolerance.

Carvedilol is a potent, mildly beta$_1$-selective beta-blocking agent with vasodilator properties related to alpha$_1$-receptor blockade (18–21). These complementary pharmacologic actions occur within the same dose range. Although the beta-blocking action of the drug may provide therapeutic benefit as described earlier, the vasodilating properties may attenuate the worsening of hemodynamic function that often accompanies initiation of beta-blockade in patients with heart failure. A

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small uncontrolled trial (22) of carvedilol suggested that this agent was well tolerated and improved left ventricular function and exercise tolerance. We report the results of a controlled trial of carvedilol in patients with heart failure.

Methods

Study objectives. The primary objective of the present study was to assess the safety and tolerability of carvedilol in patients with chronic heart failure caused by either ischemic or idiopathic dilated cardiomyopathy. Secondary objectives were to assess the effects of long-term carvedilol therapy on left ventricular function, symptoms of heart failure and exercise tolerance.

Study design. This study was a 4-month prospective, randomized, double-blind, placebo-controlled trial. The trial consisted of four phases: a 2- to 4-week baseline period, a 1-week challenge period, an up-titration period and a double-blind treatment phase. Patients were randomized to receive carvedilol or placebo on a 3:2 basis with a block size of 5. End points of the study included completion of the study, significantly worsening heart failure not improved with adjustments in conventional medications, cardiac transplantation or death.

Patient eligibility. Patients 18 to 80 years old were eligible for study entry if they had symptomatic but stable heart failure (New York Heart Association functional class II or III) caused by ischemic or idiopathic dilated cardiomyopathy and a radionuclide left ventricular ejection fraction <0.35. Patients were excluded if they had valvular heart disease as the etiology of left ventricular dysfunction, active myocarditis, active angina, a documented history of sustained (>15 s) ventricular tachycardia or symptomatic nonsustained ventricular tachycardia not adequately controlled by antiarrhythmic drugs or second- or third-degree atrioventricular block unless equipped with a permanent pacemaker. Patients were also excluded if their exercise duration was <3 or >30 min on the maximal exercise protocol. Patients with symptomatic peripheral vascular disease; chronic obstructive lung disease; bronchial asthma; insulin-dependent diabetes mellitus; long-term alcohol or drug abuse; or chronic renal, hepatic, hematologic, neurologic or collagen vascular disease were excluded. All subjects gave written informed consent approved by the Human Subjects Committee of the Institutional Review Board of the University of Utah.

Concomitant medications. Permissible concomitant medications included digitalis, diuretic drugs, digoxin, class I antiarrhythmic drugs, angiotensin-converting enzyme inhibitors, anticoagulant agents, nitrates (given for heart failure therapy but not for angina) and hydralazine. Adjustment of cardiac medication doses was not permitted during the screening or baseline phases but was permitted when clinically indicated during the remainder of the study. Patients received anticoagulation when clinically appropriate, generally for left ventricular ejection fraction <0.25 or atrial fibrillation. Excluded medications were other beta-blockers, amiodarone, calcium channel blockers, monoamine oxidase inhibitors, tricyclic antidepressant agents, beta-agonists, reserpine, guanethidine and antihypertensive medications. Other noncardiac medications were administered when appropriate.

Study measures. Two graded maximal bicycle ergometeric exercise tolerance tests were performed with measurement of peak oxygen consumption. The maximal protocol consisted of 2 min of free pedaling followed by incremental exercise to exhaustion, with work load ramped at either 5 or 10 W/min so that the total duration of exercise would be between 8 and 15 min. Dyspnea and fatigue were the required end points to terminate exercise. Any alternative reasons for terminating exercise excluded the patient from further participation. Expired gas analysis was performed by mass spectrometry (23). Peak oxygen consumption was defined as the average oxygen consumption during the last minute of maximal exercise. For study entry, it was required that the two consecutive values for total exercise duration or peak oxygen consumption not vary >30%. The values of the two tests were then averaged to obtain the baseline maximal exercise values. A submaximal bicycle exercise tolerance test was then performed using the average maximal peak oxygen consumption from the tests to determine the appropriate work level (24). During the submaximal protocol, the patient exercised at a work load equal to 66% of the peak oxygen consumption of the maximal exercise test for 6 min, after which the work load was increased to 85% of the maximal peak oxygen consumption of the maximal exercise test. Exercise was then continued to exhaustion. Total exercise duration was the end point for the submaximal test.

Patients meeting the exercise eligibility requirements then underwent *radionuclide ventriculography* at rest and during maximal supine bicycle exercise to determine left ventricular ejection fraction. *Echocardiography* was performed to determine left ventricular diastolic and systolic dimensions using standard M-mode measurements. A 24-h Holter recording was obtained. Cardiac function was assessed using a questionnaire modified from that of Lee et al. (25) with a composite symptom score. Scores ranged from 0 or no symptoms to 13 or most severe heart failure symptoms. Functional class was assessed by two investigators in a blinded manner.

Routine clinical laboratory testing, including chest radiography, electrocardiography, complete blood count, multichannel chemistry panel and urinalysis, was performed during the baseline period and repeated routinely throughout the study for safety monitoring.

On completion of these tests, eligible patients were admitted to the hospital for *hemodynamic measurements by right heart catheterization*. Patients were studied in the morning several hours after an overnight fast. Cardiovascular medications with the exception of class I antiarrhythmic agents, were withheld before the procedure. Right atrial, pulmonary artery and pulmonary capillary wedge pressures were measured. Cardiac output was determined by the Fick method. Systemic arterial pressures were measured by an arterial line placed in either a radial or femoral arterial catheter and heart rate was determined by electrocardiographic (ECG) telemetry monitoring during the procedure. Left ventricular stroke work was calculated using the formula: Stroke work = (Stroke volume

index) × (Mean arterial pressure − Mean wedge pressure) × 0.0136.

Open-label challenge period. After baseline measurements, an open-label carvedilol challenge was administered at 3.125 mg every 12 h for 7 days.

Up-titration and double-blind treatment phases. Patients who successfully completed the open-label challenge were then randomized to the blinded treatment phase in a ratio of 3:2 for carvedilol versus placebo treatment, respectively. Study medication was initiated at a dose equivalent to 6.25 mg orally every 12 h. For each new dose of study medication, vital signs were monitored for at least 2 h after the first dose was administered. At each weekly clinic visit, patients were evaluated for symptoms and signs of worsening heart failure, hypoperfusion or other adverse effects possibly related to beta-blocker therapy. If no adverse effects were observed, doses of carvedilol versus matched placebo were then titrated upward in weekly intervals until either a maximal tolerated dose or the maximal allowed dose was reached. The maximal allowed dose was 25 mg twice a day for patients weighing <75 kg and 50 mg twice a day for those weighing >75 kg. The maximal attained dose of study medication was then continued for a fixed-dose maintenance period of 3 months.

During the final week of the fixed-dose maintenance period, noninvasive and invasive variables were measured again. Carvedilol was administered on the morning of repeat right heart catheterization, which was then performed in the late morning.

Statistical analysis. The tolerability and safety of carvedilol were assessed by determining the proportion of patients tolerating the open-label challenge and by comparing the occurrence of adverse events in the carvedilol versus placebo groups during the double-blind treatment phase. Differences between the carvedilol and placebo groups were evaluated by repeated-measures analysis of variance for continuous variables and by chi-square test for discrete variables. Results are expressed as mean value ± SEM. Differences were considered significant at $p < 0.05$.

Results

Patient characteristics. Sixty subjects were enrolled in the study, 43 with idiopathic dilated cardiomyopathy and 17 with ischemic cardiomyopathy. All 60 patients tolerated the open-label challenge and were randomized to receive carvedilol (n = 36) or placebo (n = 24). Of the patients assigned to receive carvedilol, 23 had heart failure caused by idiopathic dilated cardiomyopathy, and 13 had ischemic cardiomyopathy. In the placebo group, 20 patients had idiopathic dilated cardiomyopathy, and 4 had ischemic cardiomyopathy.

Baseline characteristics are shown in Table 1. The treatment groups did not differ with respect to age, male/female ratio, left ventricular ejection fraction, pulmonary capillary wedge pressure, cardiac index or peak oxygen consumption. There was a trend for more patients with functional class III heart failure symptoms in the carvedilol group, but the difference compared with the placebo group was not significant. Plasma venous norepinephrine concentrations were higher in the carvedilol group. Concurrent medical therapy did not differ significantly between the treatment groups. There were no intergroup differences in changes to concomitant medications during the maintenance period.

Table 1. Clinical Characteristics of 60 Study Patients

	Carvedilol Group (n = 36)	Placebo Group (n = 24)
Age (yr)	54 ± 2	50 ± 3
Range	29–73	24–68
Gender (male/female)	34/2	22/2
NYHA functional class		
II	16	14
III	20	10
LVEF	0.20 ± 0.01	0.19 ± 0.01
CI (liters/min per m^2)	2.2 ± 0.1	2.2 ± 0.1
PCWP (mm Hg)	17 ± 2	15 ± 2
Norepinephrine (pg/ml)	558 ± 75*	337 ± 43*
Concomitant medications		
Diuretic drugs	30 (83%)	19 (79%)
Digoxin	33 (92%)	17 (71%)
ACE inhibitors	32 (89%)	24 (100%)
Vasodilator drugs	3 (8%)	3 (12%)
Antiarrhythmic agents	6 (17%)	5 (21%)
Warfarin	28 (78%)	18 (75%)
Dose of study drug (mg/day)	80 ± 9	83 ± 5

*p = 0.02. Data presented are mean value ± SEM or number (%) of patients. ACE = angiotensin-converting enzyme; CI = cardiac index; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

Three patients did not complete the protocol. One patient with ischemic cardiomyopathy who was randomized to receive carvedilol withdrew because of significantly worsening heart failure during up-titration. A second patient with ischemic cardiomyopathy randomized to receive carvedilol died suddenly during up-titration 4 days after reaching a dosage of 12.5 mg twice a day. In the placebo group, one patient with clinically stable ischemic cardiomyopathy in the absence of worsening heart failure was electively withdrawn for cardiac transplantation when a suitable donor became available.

One patient with idiopathic dilated cardiomyopathy in the carvedilol group had an embolic cerebrovascular accident during the study period, which was not thought to be related to the study medication. One patient with idiopathic dilated cardiomyopathy in the placebo group sustained a non-Q wave myocardial infarction after one dose of carvedilol during the open-label challenge. Cardiac catheterization revealed normal coronary arteries, and an ergonovine stimulation test failed to induce vasospasm; therefore, the event was thought to be embolic. This patient completed the open-label challenge without further incident. Another patient with idiopathic dilated cardiomyopathy in the placebo group reached the end point 4 weeks before completion of the maintenance period, because of clinical deterioration refractory to adjustments in

Table 2. Response to Carvedilol Therapy: Noninvasive Variables

	Carvedilol Group (n = 34)		Placebo Group (n = 23)		
	Baseline	4 mo	Baseline	4 mo	p Value
Symptom score	4.9 ± 0.6	2.6 ± 0.4	4.2 ± 0.1	4.0 ± 0.7	0.0277
NYHA functional class					
I	0	4	0	0	
II	16	27	14	16	
III	18	3	10	6	0.0170
IV	0	0	0	1	
LVIDD (mm)	73 ± 9	70 ± 9	79 ± 14	76 ± 15	0.7200
FS (%)	15 ± 0.6	20 ± 1	17 ± 3	20 ± 3	0.0037
Rest LVEF (%)	20 ± 1	31 ± 2	19 ± 1	20 ± 2	0.0001
Exercise LVEF (%)	21 ± 1	29 ± 2	20 ± 2	21 ± 2	0.0001

Data presented are mean value ± SEM or number of patients. FS = fractional shortening; LVIDD = left ventricular internal diastolic dimension; other abbreviations as in Table 1.

conventional medications. This patient completed the end-of-study variables, and the data are included in the analysis.

Noninvasive variables. Results of the noninvasive tests, with the exception of exercise and Holter monitoring, are shown in Table 2. Patients treated with carvedilol reported a significant improvement in heart failure symptoms as rated by responses to the symptom questionnaire. This self-assessed clinical improvement in the carvedilol-treated patients was accompanied by an improvement in functional class assigned by the clinician. Symptom score and functional class did not improve significantly in the placebo group during the study. Left ventricular end-diastolic dimension tended to decrease in both the carvedilol and placebo groups, but the change was not significant in either group. Left ventricular end-systolic dimension was also reduced in both groups but to a greater degree in the carvedilol group. This resulted in a significant improvement in percent fractional shortening in the carvedilol group.

In the carvedilol group, rest left ventricular ejection fraction increased by 52%; there was no change in the placebo group. There was a corresponding increase in exercise left ventricular ejection fraction for the carvedilol group, but this change did not appear to be independent of the improvement in rest ejection fraction.

Invasive hemodynamic variables. Table 3 presents the hemodynamic measurements at baseline and at the end of the 4-month trial for both treatment arms. There were no significant differences between the groups at baseline, although the pulmonary capillary wedge pressure tended to be higher in the carvedilol group. As would be expected, therapy with carvedilol significantly reduced rest heart rate by 23%. No significant changes in systemic arterial or systemic venous pressures were observed in either group. A significant decrease in both pulmonary artery and pulmonary capillary wedge pressures occurred in the carvedilol but not the placebo group. Cardiac index did not increase significantly with carvedilol, most likely reflecting the drug's effect on rest heart rate. However, both stroke volume and left ventricular stroke work index were markedly improved with carvedilol therapy compared with placebo therapy.

In Figure 1, stroke volume index is plotted as a function of pulmonary artery wedge pressure at baseline and at the end of study (4 months) for each treatment group. There was a

Table 3. Response to Carvedilol Therapy: Hemodynamic Variables

	Carvedilol Group (n = 34)		Placebo Group (n = 23)		p
	Baseline	4 mo	Baseline	4 mo	Value
HR (beats/min)	87 ± 3	67 ± 3	83 ± 3	84 ± 3	0.0001
SAP (mm Hg)	84 ± 2	84 ± 2	85 ± 1	84 ± 2	0.7182
RAP (mm Hg)	5 ± 1	4 ± 1	5 ± 1	5 ± 1	0.7480
PAP (mm Hg)	28 ± 2	22 ± 2	25 ± 3	25 ± 2	0.0205
PCWP (mm Hg)	17 ± 2	12 ± 1	15 ± 2	15 ± 1	0.0213
CI (liters/min per m^2)	2.2 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.2 ± 0.1	0.4000
SVI (ml/beats per min)	26 ± 2	38 ± 2	26 ± 1	27 ± 2	0.0004
SVR (Wood U)	20 ± 1	18 ± 1	19 ± 1	18 ± 1	0.4826
PVR (Wood U)	2.9 ± 0.3	2.1 ± 0.2	3.1 ± 0.5	2.3 ± 0.3	0.8959
LVSWI ($g \cdot m/m^2$)	26 ± 3	38 ± 3	29 ± 4	27 ± 2	0.0033

Data presented are mean value ± SEM. HR = heart rate; LVSWI = left ventricular stroke work index; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SAP = mean systemic arterial pressure; SVI = stroke volume index; SVR = systemic vascular resistance; other abbreviations as in Table 1.

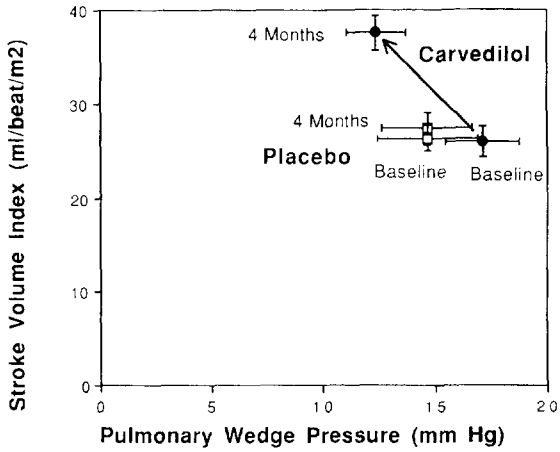

Figure 1. Relation between pulmonary wedge pressure and stroke volume index at baseline and at the end of study for the carvedilol (**circles**) and placebo (**squares**) groups. Results are mean value ± SEM.

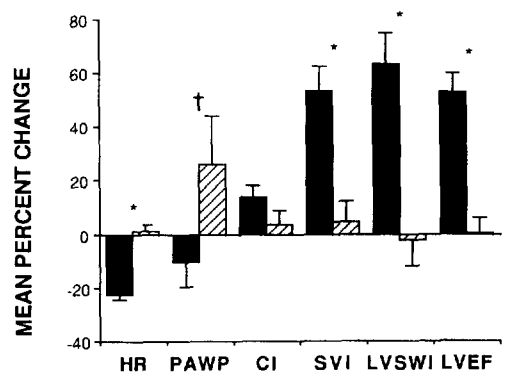

Figure 2. Percent changes in heart rate (HR), pulmonary artery wedge pressure (PAWP), cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI) and left ventricular ejection fraction (LVEF) in the carvedilol (**solid bars**) and placebo (**hatched bars**) group. Results are mean value ± SEM. *p < 0.001, †p < 0.02, change in carvedilol vs. placebo group.

significant shift upward and to the left of the stroke volume index–pulmonary wedge pressure relation after treatment with carvedilol; no significant change in this relation was seen in the placebo group.

Figure 2 illustrates the magnitude of relative changes for selected variables in the two groups. The difference in percent response to carvedilol relative to placebo, obtained by subtracting the percent change from baseline in the carvedilol group from that in the placebo group, was 52% for left ventricular ejection fraction and 66% for left ventricular stroke work.

Exercise tolerance testing. Table 4 presents the maximal and submaximal exercise data obtained at baseline and at the end of study for both treatment groups. Two patients in the carvedilol group were excluded from exercise data analysis, one because of inability to exercise after a stroke and the second because of an exercise time at baseline >30 min. Despite the lessening of symptoms and improvement in functional class and left ventricular ejection fraction, maximal exercise duration and peak oxygen consumption did not improve with carvedilol therapy. There was a significant decrease in maximal exercise heart rate in the carvedilol group. Thus, patients receiving carvedilol achieved a comparable level of exercise at the end of the study, with a reduced rate-pressure product, compared with that at baseline.

Submaximal exercise duration tended to increase after 4 months of therapy with carvedilol. However, the magnitude of the change was not significantly different from that achieved with placebo by between-group analysis.

Ambulatory ECG monitoring. Analyzable 24-h ambulatory Holter monitoring was obtained at both baseline and the end of study in 33 patients in the carvedilol group and 21 in the placebo group. Mean and maximal heart rates (from 87 ± 3 to 69 ± 2 and from 129 ± 4 to 103 ± 3 beats/min, respectively) were significantly reduced in the carvedilol group but were unchanged in the placebo group ($p = 0.0005$ for mean and $p = 0.05$ for maximal heart rate by analysis of variance). The carvedilol group showed a tendency for a reduction in the total number of premature ventricular complexes per hour (from 186 ± 56 to 51 ± 14 beats/h) and number of runs of ventricular tachycardia (from 2.4 ± 1.1 to 0.1 ± 0.04 runs/h). However, these changes failed to achieve statistical significance by between-group analysis.

Discussion

Carvedilol is a mildly $beta_1$-selective beta-blocking agent with direct vasodilator action as a result of $alpha_1$-receptor blockade (18–21). In the present study we evaluated the effects of long-term administration of carvedilol compared with those of placebo therapy in patients with symptomatic heart failure caused by either idiopathic or ischemic cardiomyopathy. In both types of symptomatic cardiomyopathy, beta-blockade with carvedilol appears to be safe and well tolerated.

Effects of carvedilol on cardiac function. Long-term administration of carvedilol in the present study was associated with a marked improvement in left ventricular ejection fraction and stroke work. Left ventricular stroke volume index increased significantly with carvedilol therapy, but because of the significant decrease in heart rate, rest cardiac output did not change. The upward and leftward shift of the stroke volume index–pulmonary wedge pressure relation suggests improvement in intrinsic ventricular performance, not merely changes in loading conditions. Similar findings have been reported for bucindolol and nebivolol using both load-dependent (12) and load-independent (left ventricular pressure-volume loops) measures of left ventricular function (26,27).

Effects of carvedilol on symptoms and exercise. Carvedilol significantly lessened symptoms of heart failure as assessed by the patient using a symptom questionnaire and by the clinician according to functional class. Although peak oxygen consumption during exercise did not change with carvedilol therapy, the same peak oxygen consumption was achieved at a significantly

Table 4. Response to Carvedilol Therapy: Maximal and Submaximal Exercise Tolerance

	Carvedilol Group (n = 32)		Placebo Group (n = 23)		p Value
	Baseline	4 mo	Baseline	4 mo	
Rest HR (beats/min)	96 ± 3	72 ± 3	97 ± 3	94 ± 4	0.0047
Exercise HR (beats/min)	152 ± 4	120 ± 5	158 ± 5	153 ± 6	0.0003
Exercise SAP (mm Hg)	147 ± 4	144 ± 4	150 ± 6	149 ± 5	0.7890
Rate-pressure product (mm Hg beats/min)	22,548 ± 1,037	17,559 ± 924	24,021 ± 1,593	23,283 ± 1,669	0.0001
Exercise duration, max ETT (s)	614 ± 35	624 ± 29	640 ± 37	660 ± 37	0.5790
Peak oxygen consumption (ml O_2/kg per min)	17.5 ± 0.8	17.5 ± 0.9	17.3 ± 0.8	17.8 ± 0.9	0.8842
Exercise duration, submax ETT (s)	688 ± 31	871 ± 82	816 ± 67	893 ± 111	0.5542

Data presented are mean value ± SEM. max (submax) ETT = maximal (submaximal) exercise tolerance test; other abbreviations as in Table 3.

lower rate-pressure product. Failure to increase maximal exercise capacity is not unexpected because carvedilol therapy significantly lowered maximal exercise heart rate, and the exercise capacity of patients with heart failure is dependent on maximal exercise heart rate (28). This attenuation of heart rate response to exercise has been reported to occur with beta-blocker therapy in patients with normal left ventricular function (29). However, Engelmeier et al. (11) and the Metoprolol in Dilated Cardiomyopathy study investigators (13) observed improved maximal exercise capacity in patients with heart failure treated with metoprolol, although maximal exercise heart rate was not reduced in their patients. Maximal exercise heart rate was significantly reduced with bucindolol therapy (16) and peak oxygen consumption did not change, similar to our findings with carvedilol. Thus, maximal exercise tolerance testing may be an inadequate method for measuring improved exercise capacity in patients with heart failure treated with some, but not all dosages or types of beta-blocking agents.

In the present study, submaximal exercise duration tended to increase with carvedilol therapy. However, submaximal exercise duration also tended to increase in the placebo group, and the between-group change was not statistically significant. Neither maximal exercise time nor peak oxygen consumption correlated significantly with the change in left ventricular function, in agreement with previous observations (30) on the lack of a relation between maximal exercise capacity and indexes of rest left ventricular function. Similar results have been obtained with bucindolol; submaximal but not maximal exercise tended to improve on beta-blockade (16). As noted by others (31,32), the level of effort required in a submaximal exercise test is probably a better approximation of normal daily activity in patients with chronic heart failure. Thus, submaximal exercise testing as performed in the present study appears to be a more appropriate method to assess changes in exercise capacity in patients with heart failure treated with beta-blockade.

Conclusions. Long-term treatment with carvedilol in patients with heart failure as a result of ischemic or idiopathic dilated cardiomyopathy results in a significant improvement in rest left ventricular function and lessening of symptoms of heart failure. Additional trials with larger numbers of patients will be needed to determine whether carvedilol improves submaximal exercise. Further studies are also needed to determine the optimal dosage of carvedilol and the effect of carvedilol therapy in patients with functional class IV symptoms and to clarify further the response of patients with ischemic cardiomyopathy. Several multicenter trials are currently under way to address these issues.

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