Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial

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ABSTRACT It has been suspected that the increased sympathetic activity seen in patients with chronic congestive heart failure from dilated cardiomyopathy may be harmful. We therefore tested the long-term effect of metoprolol on eight patients in a double-blind, randomized protocol and 12 patients in an unblinded, crossover protocol who were treated for 12 months (range 10 to 24), and compared them with 16 similar subjects who were treated with placebo for 10 months (range 6 to 12) in a double-blind, randomized protocol. Patients were followed by serial clinical assessment, treadmill testing, radionuclide ventriculography, and echocardiography. Metoprolol-treated patients had an improvement in mean exercise capacity by 3 mets (p < .0001) while experiencing a significant improvement in functional classification (p < .001) during both the double-blind and open-label crossover studies and had an improved ejection fraction during the double-blind study (p < .02). These improvements were not seen in matched control subjects receiving placebo. Seven of 20 patients receiving long-term metoprolol therapy had resolution of nearly all symptoms of heart failure, doubled their exercise capacity, and had progressive improvement in resting radionuclide ventricular ejection fraction (12.6 ± 3% to 26.9 ± 6%) and echocardiographic left ventricular end-diastolic dimension (7.7 ± 0.5 to 6.5 ± 0.5 cm). Only one of 21 patients treated was intolerant of metoprolol. We conclude that metoprolol can be given safely to a select group of patients with dilated cardiomyopathy in doses that substantially reduce both resting and exercise heart rates. Long-term β-blockade improved functional class and exercise capacity in 14 of 20 patients while producing an exceptional clinical response in seven that was accompanied by improved resting parameters of left ventricular function.

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DILATED CARDIOMYOPATHY is a disease of heart muscle characterized by left ventricular dilatation and congestive heart failure.1 It affects a younger population than does ischemic heart disease and frequently results in functional impairment and premature death. The reflex neurohumoral responses that accompany the syndrome of congestive heart failure are useful in maintaining short-term compensation of cardiac function.2,3 Norepinephrine is released from sympathetic nerve endings to activate myocardial β-receptors that increase both the heart rate and force of ventricular contraction.4 Stimulation of α-receptors results in peripheral vasoconstriction to help maintain critical end-organ perfusion.5 With time these compensatory mechanisms fail to prevent clinical deterioration and may actually contribute to the progressive downward course that characterizes this disease.6 Although elevated plasma norepinephrine levels may be only an indirect indicator of generalized sympathetic activation in patients with dilated cardiomyopathy, a direct correlation exists between these levels and the severity of heart failure as well as prognosis.6,7 Therapy directed at reducing these humoral alterations may be beneficial in altering the natural history of dilated cardiomyopathy. This was suggested by Waagstein et al.8,31 and Swedberg et al.,9,10 who demonstrated improved symptoms, left ventricular function, and survival in uncontrolled trials of long-term β-blockade in patients with dilated cardiomyopathy. Recent placebo-controlled studies have not confirmed the Swedish experience but differed in that heterogenous populations and only 4 week treatment periods were used.11,12

This trial was designed to evaluate the effect of

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long-term sympathetic β-blockade with metoprolol on symptoms, exercise tolerance, and noninvasive indexes of left ventricular function in prospective, double-blind, placebo-controlled, and crossover studies of dilated cardiomyopathy. Our results confirm the safety and efficacy of metoprolol when given to patients with symptoms of dilated cardiomyopathy receiving conventional medical therapy.

Materials and methods

Patient selection. Consecutive patients referred to our institution from October 1981 through September 1983 and diagnosed as having idiopathic dilated cardiomyopathy by criteria established by the WHO/ISFC task force on dilated cardiomyopathy were considered for the study. Symptomatic but not rapidly deteriorating patients with radiographic cardiomegaly (cardiothoracic ratio >0.5), radionuclide left ventricular impairment (ejection fraction <.49), or echocardiographic evidence of left ventricular enlargement and dysfunction were considered. Thirty-one patients were referred but four were not enrolled: two had postpartum cardiomyopathy, one had refractory ventricular tachycardia as the primary diagnosis, and the final patient lived too far from Chicago, making follow-up impossible. Twenty-seven were enrolled but two improved spontaneously during the 6 week observation period and were rejected. Therefore 25 patients underwent randomization. All were clinically stable but remained symptomatic despite the use of digoxin and furosemide in 24 and of vasodilators in 10. Cardiac catheterization and coronary angiography were performed in all patients over 35 years of age or in the presence of atherosclerotic risk factors. Endomyocardial biopsy was done in all patients with a clinical history compatible with myocarditis or recently acquired symptoms of heart failure. Coronary artery disease was excluded in all 24 patients studied and myocarditis was excluded in all 22 patients who underwent biopsy. Electrocardiography, chest radiography, radionuclide ventriculography, multistage treadmill testing, M mode echocardiography, and 24 hr ambulatory electrocardiography were performed before enrollment into the study. Those patients with histories of active alcoholism, obstructive lung disease, and advanced atrioventricular block were excluded from the study. After informed consent was obtained, patients were randomly assigned to receive placebo or metoprolol in blinded fashion for 1 year. After 1 year, or earlier if clinical deterioration requiring hospitalization occurred, the code was broken and both groups were to cross over to the other treatment in a single-blind study. Interruption of metoprolol therapy precipitated a marked worsening of heart failure symptoms and ventricular tachyarrhythmias in the first two patients to cross over, and all subsequent metoprolol-treated patients were continued uninterrupted on the drug.

Hence, the crossover group consisted of patients initially assigned to receive placebo who either remained stable for 1 year or deteriorated early and were then treated with metoprolol. All three groups were similar in baseline demographic, clinical, hemodynamic, and noninvasive parameters (Table 1).

Study design

Double-blind, randomized study. Written informed consent was obtained from each patient before enrollment. After a 6 week stabilization and observation period, all patients were randomly assigned to receive placebo or metoprolol in a double-blind fashion. Patients were started on 6.25 mg (one-quarter tablet) once daily and then were given 6.25 to 12.5 mg increments of placebo or metoprolol (Lopressor 25 mg tablets, kindly supplied by Ciba-Geigy, Summit, NJ) that were increased once or twice weekly for 4 to 6 weeks. They were evaluated before each dose increase and then observed for bradycardia, hypotension, or clinical decompensation for 2 hr after administration of the drug. The therapeutic end point was 100 mg. Patients received less than 100 mg if their systolic blood pressure was less than 90 mm Hg or if their resting heart rate was less than 60 beats/min.

During drug maintenance, patients were reevaluated every 3 months. The NYHA guidelines were used for functional classification, which was aided by a questionnaire filled out at each visit that requested information regarding the patient’s ability to perform routine daily activities. Compliance was ensured by careful questioning and tablet counts. Serial noninvasive testing included left ventricular radionuclide ejection fraction and echocardiographic left ventricular end-diastolic determinations every 3 months, and maximal oxygen consumption estimated by multistage exercise treadmill testing (met score) every 6 months. Clinically stable patients were to remain blinded to the medication for 1 year. All practical attempts were made to prevent biasing of follow-up studies, which could be affected by knowledge of heart rate responses during titration of the study drug. These efforts included having treadmill tests, radionuclide ventriculography, and echocardiography supervised and interpreted as data were generated by blinded physicians not associated with the study. Functional classification and management decisions were usually made by a blinded study physician who did not participate in the drug titration.

Crossover study. The second part of the trial was a crossover study designed to evaluate the effects of metoprolol on the symptoms, exercise tolerance, and noninvasive parameters of left ventricular function of patients initially assigned to receive placebo. During this phase, neither the patients nor investigators were blinded. Metoprolol was administered and patients were serially investigated as previously described. Treadmill

<table>
<thead>
<tr>
<th>TABLE 1 Baseline clinical and hemodynamic features of patients in placebo and metoprolol groups</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Sex, n (%), male</td>
</tr>
<tr>
<td>Symptomatic period (mo)</td>
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<tr>
<td>Functional class (NYHA)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
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<tr>
<td>Cardiothoracic ratio by x-ray &gt;0.5, n (%)</td>
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<tr>
<td>Cardiac index (l/min/m²)</td>
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<tr>
<td>Pulmonary capillary wedge (mm Hg)</td>
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<tr>
<td>RNV EF (%)</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
</tr>
<tr>
<td>Exercise tolerance (met score)</td>
</tr>
</tbody>
</table>

LVEDD = left ventricular end-diastolic dimension; met score = metabolic equivalent utilization units from multistage treadmill testing; RNV EF = radionuclide left ventricular ejection fraction.

*p = NS in all categories.
tests, radionuclide ventriculograms, and echocardiograms were interpreted as data were generated by blinded physicians not associated with the study. Twelve patients have been followed for 12 months on metoprolol (range 10 to 24 months) after crossing over from placebo and comprise the crossover group. Four patients did not cross over from placebo: two died, one improved significantly, and the other experienced normalization of ejection fraction, although his other clinical, treadmill, and noninvasive parameters did not change.

This study was approved by the Institutional Review Board for the Protection of Human Subjects of Loyola University Medical Center.

Noninvasive and treadmill testing. Radionuclide ventricular ejection fraction was obtained by the electrocardiogram-gated equilibrium method, 15, 25 mCi of 99m-technetium-labeled red blood cells were used after labeling in vivo. Imaging was performed in multiple views by an Anger scintillation gamma camera and collected at 20 frames/cycle. Left ventricular ejection fraction was calculated from a MDS A-3 computer-derived, background-corrected time-activity curve, using the left anterior oblique projection. An arrhythmia filtration technique was used in the two patients with atrial fibrillation and in 18 patients with repetitive ventricular arrhythmias (Lown grade 4). A wide individual variability in ejection fraction was attributed to the high frequency of arrhythmias in all groups. A significant change in ejection fraction was therefore defined as a progressive increase or decrease terminating at least seven percentage points above or below the pretreatment control value.

Echocardiographic left ventricular end-diastolic dimension was determined on a commercially available ATL recorder and a 2.25 MHz transducer. Measurements were obtained at end-diastole on the R wave of the electrocardiogram-derived QRS complex, just below the mitral leaflets, by means of the standard left parasternal or subcostal windows. 16 Transducer position was aided by cross-sectional echocardiographic analysis. Good-quality echocardiograms were obtained in 24 of 25 patients. Less individual variability was observed in left ventricular end-diastolic dimension than in ejection fraction. A significant change was defined as a progressive increase or decrease in left ventricular end-diastolic dimension, terminating at least 0.5 cm above or below the pretreatment control value. All calculations of left ventricular end-diastolic dimension were made as data were generated by a blinded cardiologist not associated with the study.

Maximal oxygen consumption (met score) was estimated with patients in the postabsorptive state by multistage exercise testing carried out according to a standard Naughton or Bruce protocol. 17, 18 The procedure was selected by a cardiologist blinded to the treatment group after a preliminary assessment of the patient’s exercise capability. Both exercise protocols used 3 min stages and continuous three-channel electrocardiographic monitoring. Blood pressure was obtained after 2 min of each stage. Patients exercised to exhaustion and usually terminated exercise because of leg symptoms, fatigue, or dyspnea. No test was terminated for chest pain, heart rate criteria, ST segment abnormalities, or exercise-induced hypotension. One patient had exercise terminated before exhaustion because of nonsustained ventricular tachycardia that occurred before and after metoprolol was started. Exercise-induced arrhythmias were common but no patient experienced morbidity or mortality as a result of the exercise test. Because two exercise protocols of differing grades and speeds were used, duration of exercise was converted to metabolic energy utilization units (met score) based on a nomogram described by Fox et al., 19 enabling comparison of exercise capacity for both protocols. A change in met score greater than 2 was considered significant, which was based on our experience with patients with dilated cardiomyopathy who performed both treadmill protocols as part of an independent study.

Statistical analysis. Comparison of change in NYHA functional class from the pretreatment control to serial evaluations was made by Friedman’s two-way analysis of variance. Comparison of change in met score, ejection fraction, and left ventricular end-diastolic dimension from pretreatment control to serial investigations was made by analysis of variance for multiple observations. Comparison of percent change was made by Student’s t test for unpaired variables. Heart rate response to exercise at the last follow-up on metoprolol compared with the pretreatment control value was evaluated for significance by covariance. Stepwise discriminant analysis was performed on data from all metoprolol-treated patients to analyze parameters predictive of a favorable response to the drug. Results are expressed as mean ± SD unless otherwise specified; p < .05 rejected the null hypothesis.

Results

Double-blind, randomized study

Changes in clinical status and functional class with placebo

Sixteen patients were randomly assigned to receive placebo. Ten clinically stable patients remained blinded for 12 months while another crossed over at 6 months after no improvement on the blinded protocol at the request of the referring physician. Four deteriorating patients were hospitalized for progressive heart failure at 6 months, with one of the four succumbing to refractory congestive heart failure. The three survivors were stabilized on intravenous diuretic therapy. The final patient died suddenly at 3 months. The clinically stable patients had no changes in medications.

Functional classification was assessed quarterly. The mean NYHA functional class did not change significantly during the first 6 months or at the last follow-up of patients on placebo when compared with the pretreatment control. The minor improvement at 9 months reflects the drop-out of the deteriorating patients. Thirteen individuals had the same or worse functional class at all follow-up intervals. Three had minor amelioration of symptoms that represented less than one full class improvement (table 2, figure 1).

Serial treadmill tests and noninvasive studies with placebo

Thirteen patients had at least one and eight had two follow-up treadmill tests while on placebo. Reasons for failure of a 6 month study included one death, one case of severe incapacitation from progressive heart failure, and one refusal. Five additional patients did not have a 12 months study because of one death, three cases of deterioration and removal from placebo, and one refusal. There was no significant difference in mean met score at the 6 month and last follow-up interval when compared with the pretreatment control value. Two individuals showed improvement in met score at 6 and 12 months. One of these experienced
normalization of her mildly abnormal ejection fraction and left ventricular end-diastolic dimension, while the other probably benefited from a self-motivated conditioning regimen undertaken without change in noninvasive parameters of left ventricular function. Four individuals had decreases in met score at the 6 month study that persisted in the two undergoing a 12 month study. Seven individuals had no change noted at 6 months as well as four individuals at 12 months (table 2, figure 2).

Mean ejection fraction and left ventricular end-diastolic dimension did not change significantly at the quarterly evaluations of patients on placebo when compared with the pretreatment control values. Only one patient had an improvement in both parameters (ejection fraction 32% to 56%, left ventricular end-diastolic dimension 5.7 to 4.8 cm), which accompanied improved symptoms and met score. Another patient had an improvement in ejection fraction (23% to 53%) that was not accompanied by change in symptoms, exercise capacity, or left ventricular end-diastolic dimension. Three patients had echocardiographic progression of left ventricular enlargement: one died, one had decompensation from heart failure, and the third was stable (table 2, figures 3 and 4).

Changes in clinical status and functional class with metoprolol. Nine patients were randomly assigned to metoprolol therapy. One with atrial fibrillation acquired a slow ventricular response during low-dose titration and was removed from the study within 4 weeks. Because he lacked follow-up studies, he was not evaluated with the metoprolol treatment group. Therefore only patients tolerant of 100 mg of metoprolol or whose heart rates were limited to less than 60 beats/min or systolic blood pressures to less than 90 mm Hg by β-blockade are considered in the subsequent discussion. Eight patients tolerated an average metoprolol dose of 92 mg (range 63 to 100). Seven clinically stable patients re-

FIGURE 1. Individual and mean changes in functional classification (NYHA FC) in placebo and metoprolol groups, comparing baseline (Control) with completion of the blinded trial (Treatment).

FIGURE 2. Individual and mean changes in exercise capacity (met score) in placebo and metoprolol groups, comparing baseline (Control) with completion of the blinded trial (Treatment).
TABLE 2
Serial changes in mean functional class, treadmill results, and noninvasive studies with placebo and metoprolol: double-blind, randomized study

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>Last F/U 8</th>
<th></th>
<th>Control</th>
<th>3 mo</th>
</tr>
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<td>NYHA FC</td>
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<td>2.34±0.7</td>
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<td>2.1±0.9</td>
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<tr>
<td></td>
<td>(16)</td>
<td>(16)</td>
<td>(14)</td>
<td>(13)</td>
<td>(16)</td>
<td></td>
<td>(8)</td>
<td>(8)</td>
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<tr>
<td>Exercise tolerance</td>
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<td>6.9±5</td>
<td>4.4±2.3</td>
<td></td>
<td>13.1±6</td>
<td>18.2±5E</td>
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<tr>
<td>(met score)</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
<td>(8)</td>
<td></td>
<td>(8)</td>
<td>(8)</td>
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<tr>
<td>RNV EF</td>
<td>18.2±10</td>
<td>19.6±9</td>
<td>21.6±11</td>
<td>21.6±13</td>
<td>21.9±14</td>
<td></td>
<td>7.3±0.6</td>
<td>7.2±0.6</td>
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<tr>
<td>(%)</td>
<td>(16)</td>
<td>(16)</td>
<td>(12)</td>
<td>(8)</td>
<td>(16)</td>
<td></td>
<td>(8)</td>
<td>(8)</td>
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<tr>
<td>LVEDD</td>
<td>6.7±0.9</td>
<td>6.9±1</td>
<td>7.2±1.2</td>
<td>7.0±1.4</td>
<td>6.9±1.1</td>
<td></td>
<td>7.3±0.6</td>
<td>7.2±0.6</td>
</tr>
<tr>
<td>(cm)</td>
<td>(15)</td>
<td>(14)</td>
<td>(14)</td>
<td>(8)</td>
<td>(15)</td>
<td></td>
<td>(8)</td>
<td>(7)</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD, with number of tests averaged in parentheses.
LVEDD = echocardiographic left ventricular end-diastolic diameter; met score = maximal oxygen consumption estimated by treadmill test; NYHA FC = New York Heart Association functional classification; RNV EF = radionuclide left ventricular ejection fraction.

8Last follow-up on placebo: 10±3 months.
9Last follow-up on metoprolol: 12±0.7 months.

Comparing serial investigations to pretreatment control: 5p < .0001; 6p < .001; 7p < .02.

remained blinded to the medication for 12 months, and the final patient was unblinded after 7 months because of progressive heart failure. Diuretic dosage was increased but he continued to deteriorate and required hospitalization, where metoprolol was discontinued. He died 2 weeks later from refractory heart failure. No other metoprolol-treated patient received additional medication during the blinded period.

Mean functional class was assessed quarterly. By 3 months the mean was significantly improved and continued to improve in subsequent evaluations when compared with the pretreatment control (p < .001). Four individuals had a full class improvement by 3 months, with three of four showing sustained improvement for the subsequent 9 months. The fourth patient had decompensation at 6 months, requiring hospitalization for congestive heart failure at 9 months and died 2 weeks later while off metoprolol. One patient improved one full class at 9 months, and the remaining three patients had less than one full class improvement (table 2, figure 1).

Serial treadmill tests and noninvasive studies with metoprolol. All eight patients had 6 month treadmill tests and all seven survivors had 12 month treadmill tests. Mean met score improved significantly at 6 months (4.4 to 7.4 mets; p < .0001) and at 12 months (8.4 mets; p < .0001) in the seven survivors when compared with the pretreatment control values. The last follow-up mean result in all eight patients likewise was significantly improved (7.9 mets; p < .0001). Six individuals improved with three of them doubling their exercise capacity by 6 months, which was sustained through 12

![FIGURE 3](http://circ.ahajournals.org/)

FIGURE 3. Individual and mean changes in radionuclide left ventricular ejection fraction (RNV EF) in placebo and metoprolol groups, comparing baseline (Control) with completion of the blinded trial (Treatment).
months. Of the two who did not by definition improve, one had increased exercise capacity from 1.6 to 3 mets and the other had no change at 6 months and ultimately died from progressive heart failure (table 2, figure 2).

The mean ejection fraction improved by 3 months and was sustained at all subsequent follow-up intervals when compared with the pretreatment control value (p < .02). Mean left ventricular end-diastolic dimension did not change significantly with metoprolol from the pretreatment control value. Three patients had progressive, simultaneous improvements in ejection fraction (12.4% to 29 ± 7%) and left ventricular end-diastolic dimension (7.7 ± 0.6 to 6.6 ± 0.7 cm) while returning to functional class I and II and doubling their exercise capacity over the 12 month blinded period. One patient who died had progressive deterioration of ejection fraction beginning at 3 months, and another stable patient had progressive enlargement of left ventricular end-diastolic dimension. Two other patients had no changes (table 2, figures 3 and 4).

Changes in mean functional class, met score, and results of noninvasive studies. Percent change in mean NYHA functional class, met score, ejection fraction, and left ventricular end-diastolic dimension at the last follow-up compared with the pretreatment control values was evaluated in the placebo and metoprolol groups. The percent change in functional class and met score was significantly better (p < .001) in the metoprolol group, whereas the percent change in ejection fraction and left ventricular end-diastolic dimension favored neither group (figure 5).

**Crossover trial (table 3)**

Changes in clinical status and functional class with placebo and metoprolol. Twelve patients randomly assigned to receive placebo crossed over and received open-label metoprolol. Eight clinically stable patients remained blinded on placebo for 1 year, and one crossed over at 6 months at the request of the referring physician because she showed no improvement on the blinded drug. Three patients experienced acute decompensation from congestive heart failure while on placebo, requiring hospitalization, and were stabilized on intravenous diuretics. All 12 patients were stable and have been followed for at least 10 months on metoprolol (range 10 to 24 months). One was hospitalized for syncope and newly diagnosed diabetes mellitus, and another died at 15 months from metabolic acidosis and respiratory failure of unknown cause. Diuretic dosages were increased in one patient, and vasodilator and digitalis therapy was discontinued in two patients receiving metoprolol.

Mean functional classification did not change in patients on placebo at quarterly evaluations but did improve at 3 months in patients on metoprolol; this improvement was sustained through the last follow-up.

![FIGURE 4. Individual and mean changes in echocardiographic end-diastolic dimension (LVEDD) in placebo and metoprolol groups, comparing baseline (Control) with completion of the blinded trial (Treatment).](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.72.3.541?journalCode=circ)
when compared with the last follow-up value in placebo-treated patients (p < .001). No patient had a full class improvement on placebo, but two at 3 months, three at 6 months, and one at 9 months improved while on metoprolol.

Treadmill tests and noninvasive studies with placebo and metoprolol. The mean met score did not change at 6 months or at last follow-up in 10 patients who underwent serial studies while on placebo. After 6 months, the 12 patients on metoprolol showed an improvement in mean met score (6.7 to 9.3 mets; p < .05) that was sustained through the last follow-up (9.6 mets; p < .05) when compared with the last follow-up value in placebo-treated patients. Seven individuals improved by 6 months, and six had sustained improvement in met score at 12 months. Three of six doubled their exercise capacity while on metoprolol.

The mean ejection fraction and left ventricular end-diastolic dimension did not change significantly with placebo but the mean change in ejection fraction bordered on significance with metoprolol at 3 months; this value was sustained through the last follow-up (p < .06). Four individuals had progressive simultaneous improvement in ejection fraction (13 ± 2% to 25 ± 2%) and left ventricular end-diastolic dimension (7.6 ± 0.3 to 6.5 ± 0.4 cm) with metoprolol. These changes were accompanied by a return to NYHA functional class I and II, a doubling of exercise capacity in three, and an improvement by 5 mets in the fourth.

Changes in mean functional class, met score, and results of noninvasive studies. Percent change in mean NYHA functional class, met score, ejection fraction, and left ventricular end-diastolic dimension at last follow-up compared with control was evaluated during placebo and metoprolol therapy. The percent changes in NYHA functional class and met score were significantly better (p < .01, p < .05) with metoprolol in these 12 patients as compared with placebo. No difference was observed in percent change in noninvasive parameters with placebo or metoprolol (figure 6).

Stepwise discriminant analysis. Stepwise discriminant analysis was used to evaluate which clinical parameters would predict a favorable response to metoprolol in patients with dilated cardiomyopathy. The following baseline variables times the corresponding coefficient was 78% accurate in predicting a favorable clinical response if the sum was greater than zero: −1.33

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3 mo</th>
<th>Placebo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>Last F/Ua</th>
<th>Metoprolol</th>
<th>Control</th>
<th>3 mo</th>
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<tbody>
<tr>
<td>NYHA FC</td>
<td>2.38 ± 0.7</td>
<td>2.33 ± 0.7</td>
<td>2.36 ± 0.7</td>
<td>2.1 ± 0.8</td>
<td>2.42 ± 0.9</td>
<td>2.42 ± 0.9</td>
<td>1.92 ± 0.7c</td>
<td>2.38 ± 0.7</td>
<td>2.33 ± 0.7</td>
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<tr>
<td>Exercise tolerance</td>
<td>7.3 ± 2.5</td>
<td>7.0 ± 3.5</td>
<td>7.0 ± 3.5</td>
<td>7.3 ± 3.8</td>
<td>6.7 ± 3.8</td>
<td>7.2 ± 3.8</td>
<td>22.8 ± 11E</td>
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<tr>
<td>(met score)</td>
<td>(10)</td>
<td>(10)</td>
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<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
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<td>RNV EF</td>
<td>17.5 ± 11</td>
<td>17.3 ± 7</td>
<td>17.9 ± 8</td>
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<td>LVEDD (cm)</td>
<td>6.9 ± 1.0</td>
<td>7.1 ± 1.0</td>
<td>7.5 ± 1.0</td>
<td>7.2 ± 1.0</td>
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<td>7.2 ± 1.0</td>
<td>7.1 ± 1.0</td>
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</table>

Results are expressed as mean ± SD, with number of tests averaged in parentheses. Abbreviations as in table 2.

*Last follow-up on placebo: 10 ± 3 months.
*p < .001; **p < .05; ***p < .06.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>Last F/Ua</th>
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</tr>
<tr>
<td>(met score)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
</tr>
<tr>
<td>RNV EF</td>
<td>17.5 ± 11</td>
<td>17.3 ± 7</td>
<td>17.9 ± 8</td>
<td>19.3 ± 12</td>
<td>17.3 ± 8</td>
<td>17.2 ± 8</td>
<td>22.8 ± 11E</td>
</tr>
<tr>
<td>(%)</td>
<td>(12)</td>
<td>(12)</td>
<td>(10)</td>
<td>(7)</td>
<td>(12)</td>
<td>(12)</td>
<td>(11)</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.9 ± 1.0</td>
<td>7.1 ± 1.0</td>
<td>7.5 ± 1.0</td>
<td>7.2 ± 1.0</td>
<td>7.2 ± 1.0</td>
<td>7.2 ± 1.0</td>
<td>7.0 ± 1.0</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SD, with number of tests averaged in parentheses. Abbreviations as in table 2.

*Last follow-up on placebo: 10 ± 3 months.
*p < .001; **p < .05; ***p < .06.

### FIGURE 5

Percent improvement in mean functional class, exercise capacity, and noninvasive studies in placebo and metoprolol groups. The last follow-up study was expressed as a percent improvement of the pretreatment control value for each patient and then averaged in the placebo and metoprolol groups. Results expressed as mean ± SE. LVEDD = left ventricular end-diastolic dimension; MET Score = maximal oxygen consumption estimated by treadmill test; NYHA FC = New York Heart Association functional classification; RNV EF = radionuclide left ventricular ejection fraction. ***p < .001.
TABLE 3 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Metoprolol</th>
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<tr>
<td></td>
<td>6 mo</td>
<td>9 mo</td>
</tr>
<tr>
<td>1.67 ± 0.6^C</td>
<td>1.59 ± 0.5^C</td>
<td>1.42 ± 0.4^C</td>
</tr>
<tr>
<td>(12)</td>
<td>(11)</td>
<td>(12)</td>
</tr>
<tr>
<td>9.3 ± 2.8^D</td>
<td>9.6 ± 2.9^D</td>
<td></td>
</tr>
<tr>
<td>(12)</td>
<td>(12)</td>
<td></td>
</tr>
<tr>
<td>21.4 ± 10^E</td>
<td>21.4 ± 10^E</td>
<td>23.4 ± 10^E</td>
</tr>
<tr>
<td>(12)</td>
<td>(11)</td>
<td>(12)</td>
</tr>
<tr>
<td>7.0 ± 1.0</td>
<td>6.7 ± 0.7</td>
<td>6.7 ± 0.9</td>
</tr>
<tr>
<td>(12)</td>
<td>(10)</td>
<td>(12)</td>
</tr>
</tbody>
</table>

+ (HR × .04) + (sex × .84) + (DOS × (−.001)) + (RNV EF × (−.01)), where HR = heart rate, male sex = 0, female sex = 1, DOS = duration of symptoms (in months), and RNV EF = radionuclide left ventricular ejection fraction.

Heart rate responses to metoprolol. The resting heart rate did not change with placebo, remaining at 92 ± 14 beats/min. With metoprol, however, it decreased from 91 ± 16 to 75 ± 14 beats/min (p < .001). The mean heart rate response to exercise with placebo did not change from the pretreatment control value, but with metoprol it was suppressed at all levels of exercise compared with the pretreatment control value (figure 7) (p < .001). The mean peak heart rate with metoprolol was identical to that at baseline control or with placebo, with the major difference being that it occurred after significantly more exercise in the metoprolol-treated patients.

Adverse effects of metoprolol. Twenty patients received an average maintenance dose of 92 ± 21 mg/day metoprolol. During the dosing phase, patients occasionally experienced mild worsening of heart failure symptoms, weakness, fatigue, mild nausea, and depression that usually responded favorably to prolongation of the dosing interval or rarely to intermittent addition of diuretics. Only one patient had a serious side effect requiring dismissal from the study (bradycardia). During the maintenance phase, one patient with a history of bipolar illness suffered an episode of severe depression that improved when atenolol replaced metoprolol. Another with peripheral vascular disease had worsening of claudication during maximal treadmill exercise, although his functional classification actually improved. Serious exacerbation of heart failure or cardiovascular collapse did not result from our protocol of metoprolol administration and patient selection.

Discussion

The rationale for treating patients with severe chronic congestive heart failure from dilated cardiomyopathy with metoprolol, a β<sub>1</sub> selective blocking agent, may appear misguided and likely to worsen heart failure. The latter may occur if this agent is administered in standard dosage or during acute cardiac decompensation. We administered metoprolol in an ambulatory

FIGURE 6. Percent improvement in mean functional class, exercise capacity, and noninvasive studies with placebo or metoprolol in crossover study. The last follow-up study was expressed as a percent improvement of the pretreatment control value for each patient and then averaged for placebo and metoprolol. Results expressed as mean ± SE. Abbreviations as in figure 5. **p < .01; *p < .05.

FIGURE 7. Heart rate response to exercise before and after metoprolol. The heart rates were averaged for all patients (number under line) at each level of exercise (line A) before administration of metoprolol and were then compared with the same patients' averaged heart rates at similar levels of exercise with metoprolol (line B). Significant suppression of heart rate response was observed at all levels of exercise.
setting to relatively stable, incapacitated patients with dilated cardiomyopathy, beginning with small doses and increasing the dose only after prolonged intervals under close supervision. This dosing phase frequently required 6 weeks, since patients occasionally experienced mild worsening of heart failure symptoms after each increment. Only one of 21 patients was intolerant of metoprolol, which was obvious during the first few weeks, and he was quickly removed without serious consequence. Once reaching a stable dose of 100 mg or having heart rates of 60 beats/min or systolic blood pressure of 90 mm Hg after β-blockade, 14 out of 20 had improved exercise tolerance and less symptomatic impairment, usually noted within 3 months. Seven of 20 patients had an exceptional response to the drug, which was characterized by returning to functional class I or II, doubling exercise tolerance, and progressively improving ejection fraction and left ventricular end-diastolic dimension.

The only plausible explanation for the improvements seen was the addition of long-term sympathetic β-blockade. There were minimal changes in other medications with doses of diuretics more frequently increased in the placebo group. Vasodilators and inotropic agents were not added after randomization. Alcohol consumption was carefully scrutinized at all follow-up visits and was not a factor. Ischemic cardiomyopathy and myocarditis were ruled out by invasive procedures in all 18 of 20 metoprolol-treated patients that were studied. Spontaneous improvement of myocardial function is also an unlikely explanation because the metoprolol patients were asymptomatic for an average of 2 years and the exceptional responders were symptomatic for 37 months (range 3 to 108) before randomization. Additionally, only one of 16 patients randomly assigned to receive placebo improved spontaneously. This patient was minimally symptomatic for 12 months with mild left ventricular impairment at entry (ejection fraction 32%, left ventricular end-diastolic dimension 5.7 cm), which contrasts sharply with 20 of 25 of our study patients, including all eight who were tolerant of metoprolol and all seven exceptional responders who had an ejection fraction less than 20% and a left ventricular end-diastolic dimension greater than 6.3 cm. These patients undoubtedly had end-stage dilated cardiomyopathy that did not improve spontaneously, nor did they receive other medications that could account for their status changes.

There was no degree of left ventricular impairment that prevented the safe administration of metoprolol as long as patients were clinically stable. The three patients who required hospitalization for progressive heart failure were stabilized with intravenous diuretics before receiving metoprolol. The most favorable response occurred in patients with higher resting heart rates and poorer noninvasive indexes of left ventricular function. With these parameters, stepwise discriminant analysis was 78% accurate in predicting a favorable clinical response to metoprolol.

Significant changes in resting ejection fraction and left ventricular end-diastolic dimension correlated well with the clinical outcome in all groups and frequently preceded overt clinical changes. Seven of eight patients with improved ejection fraction and left ventricular end-diastolic dimension had the greatest symptomatic and exercise responses, while both patients with worsened ejection fraction died, and two of four with worsened left ventricular end-diastolic dimension developed more severe congestive heart failure with one dying. These results demonstrate the utility of serial noninvasive studies in patients with dilated cardiomyopathy in defining prognosis and may allow consideration of earlier interventions, such as transplantation, that may not be indicated solely on clinical grounds.

This study was not designed to explain how patients with moderate-to-severe heart failure from dilated cardiomyopathy improve after metoprolol. We suspect that several mechanisms may be responsible, including blocking the cardiotoxic effect of catecholamines, restoring the down-regulated β-adrenergic pathway to normal, suppressing an inappropriate exercise-induced tachycardia, inhibiting ventricular tachyarrhythmias, or altering renin-angiotensin activity. These mechanisms need to be addressed by a multicenter study designed to explore the cardiovascular sympathetic response to long-term sympathetic β-blockade in patients with dilated cardiomyopathy.

Our results are in agreement with those of the Swedish group. The patients in both studies were comparable except that ours had better functional classification at entry (2.6 ± 0.9 vs. 3.2 ± 0.5), which may be a result of improved conventional therapy and use of vasodilators. Eighteen of 23 patients with hemodynamic measurements had a pretreatment pulmonary capillary wedge pressure below 20 mm Hg, with a mean of 11.5 ± 4.9 mm Hg. Most of our patients achieved symptomatic improvement by 3 months, with the maximal improvement noted at 5.6 ± 3.8 months. Sixty percent of the patients studied by Swedberg and colleagues improved by 3 months, with their maximal improvement occurring at 7.4 ± 5.9 months. We discontinued metoprolol in only the first two pa-
patients completing 1 year. Similar to the Swedish experience, both had profound worsening of symptoms and ventricular tachyarrhythmias within 2 weeks. We therefore did not discontinue metoprolol in any other patients. There were similar numbers of patients experiencing improvements in exercise capacity in our study (14 of 20) compared with theirs (13 of 22).

Anderson et al. demonstrated improved survival and functional class in a randomized study of 25 patients treated with long-term, low-dose β-blockade. They did not, however, document the improved exercise tolerance that was seen in our study. Possible explanations for this lack of improvement include a lower dose of metoprolol (61 vs 92 mg) used in patients with less left ventricular impairment (ejection fraction 27% vs 16%) with lower baseline resting heart rates (82 vs 91 beats/min). Only one-half of their patients underwent treadmill exercise testing. The best response in our study occurred in patients with higher resting heart rates and poorer left ventricular function.

Two placebo-controlled trials have shown no benefit from β-blocker therapy. In one study, 40% of subjects had significant double- or triple-vessel coronary artery disease, and in the other 70% of subjects had alcoholic heart disease. Both studies followed patients for only 4 weeks. Although we did not systematically reassess our patients at 4 weeks, only six of 15 patients improved in the series of Swedberg and associates by 1 month. Three of these improved further several months later, implying that benefit from β-blockade is delayed and usually occurs after 1 month of therapy. These studies are therefore limited by heterogeneous patient populations and short follow-up periods, and the findings must be interpreted with caution.

Our study was limited by insufficient patient numbers and a relatively short follow-up in any single treatment group, making it impossible to predict the effect of metoprolol on survival in patients with moderate-to-severe degrees of dilated cardiomyopathy. Our experience is limited only to metoprolol, and the favorable results cannot be extrapolated to other β1-blocking agents with varying degrees of β2-blockade, and β2-agonist, or α-antagonist properties. An explanation for the clinical improvement, effects on survival, and efficacy in other forms of heart failure are unknown and need to be addressed by a larger, multicenter trial.

In summary, metoprolol improves the symptoms and exercise tolerance of most patients with dilated cardiomyopathy. A subset of these patients will become nearly free of symptoms and have improved non-invasive indexes of resting left ventricular function. Most patients will tolerate the drug when selected and treated by our protocol. We suggest that metoprolol be considered as a therapeutic option for patients with dilated cardiomyopathy who remain symptomatic despite conventional therapy. Metoprolol must be administered cautiously and patients selected carefully to avoid worsening of already impaired left ventricular function. Further studies are necessary to evaluate the effect of metoprolol on survival and determine its mechanism of action.

We are indebted to Kimberly Treckler for help in preparing the manuscript.

References


Vol. 72, No. 3, September 1985

Retraction
The authors of the following manuscript have requested that it be retracted. An excerpt from the authors’ letter requesting the retraction follows:

We wish to retract our paper previously published in Circulation entitled “Increased circulating bradykinin during hypothermia and cardiopulmonary bypass in children” (Circulation 60: 1503, 1979). We have been unable to repeat the results with respect to bradykinin.

Leila M. Pang, M.D.
S. Alex Stalcup, M.D.
Joel S. Lipset, M.S.
Constance J. Hayes, M.D.
Frederick O. Bowman, Jr., M.D.
Robert B. Mellins, M.D.
Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial.
R S Engelmeier, J B O'Connell, R Walsh, N Rad, P J Scanlon and R M Gunnar

Circulation. 1985;72:536-546
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