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Effect of Metoprolol on Myocardial Function and Energetics in Patients With Nonischemic Dilated Cardiomyopathy: A Randomized, Double-Blind, Placebo-Controlled Study

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Objectives. **This study examined the effects of metoprolol on left ventricular performance, efficiency, neurohormonal activation and myocardial respiratory quotient in patients with dilated cardiomyopathy.**

Background. **The mechanism by which beta-adrenergic blockade improves ejection fraction in patients with dilated cardiomyopathy remains an enigma. Thus, we undertook an extensive hemodynamic evaluation of this mechanism. In addition, because animal models have shown that catecholamine exposure may increase relative fatty acid utilization, we hypothesized that antagonism of sympathetic stimulation may result in increased carbohydrate utilization.**

Methods. **This was a randomized, double-blind, prospective trial in which 24 men with nonischemic dilated cardiomyopathy underwent cardiac catheterization before and after 3 months of therapy with metoprolol (n = 15) or placebo (n = 9) in addition to standard therapy. Pressure–volume relations were examined using a micromanometer catheter and digital ventriculography.**

Results. **At baseline, the placebo-treated patients had somewhat more advanced left ventricular dysfunction. Ejection fraction and left ventricular performance improved only in the metoprolol-treated patients. Stroke and minute work increased without an increase in myocardial oxygen consumption, suggesting increased myocardial efficiency. Further increases in ejection fraction were seen between 3 and 6 months in the metoprolol group. The placebo group had a significant increase in ejection fraction only after crossover to metoprolol. A significant relation between the change in coronary sinus norepinephrine and myocardial respiratory quotient was seen, suggesting a possible effect of adrenergic deactivation on substrate utilization.**

Conclusions. **These data demonstrate that in patients with cardiomyopathy, metoprolol treatment improves myocardial performance and energetics, and favorably alters substrate utilization. Beta-adrenergic blocking agents, such as metoprolol, are hemodynamically and energetically beneficial in the treatment of myocardial failure.**

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Myocardial failure results in inadequate systemic perfusion, elevation of intracardiac pressures and activation of compensatory neurohormonal systems (1–6). It is well known that angiotensin converting-enzyme inhibitors, which counteract the effects of the renin–angiotensin and, to a lesser degree, the sympathetic nervous system (6), are beneficial in myocardial failure (2,7,8). Since 1975, when Waagstein et al. (9) first reported the beneficial effects of beta-adrenergic blocking agents on heart failure, several investigators (1,10–18) have focused on the use of these agents to antagonize the effects of chronic sympathetic stimulation. Despite several small studies from our laboratory (10) and others (1,11–18) demonstrating improved ejection fraction and functional status of patients with dilated cardiomyopathy treated with beta-blockers, these agents remain an enigma. It is counterintuitive that a "negative inotrope" would result in improved ventricular performance in patients with myocardial failure. Because our previous trial (10) was an open label study of bucindolol, a nonselective beta-antagonist with weak vasodilatory properties (19), it remains unclear whether such salutary hemodynamic effects would extend to a beta-blocker without direct vasodilatory properties and without direct vasodilatory properties and without beta-antagonism. Therefore, we sought to determine whether metoprolol, a pure $beta_1$-antagonist, improves myocardial performance and efficiency in patients with dilated cardiomyopathy.

Finally, the metabolic effects of beta-blockers in patients with heart failure have not been elucidated. It is well known that fatty acid oxidation by the heart uses more oxygen per unit

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Table 1. Baseline Characteristics of the 24 Male Study Patients

	Metoprolol Group (n = 15)	Placebo Group (n = 9)	p Value
Age (yr)	48 ± 11	48 ± 8	0.96
Body surface area (m^2)	2.1 ± 0.2	2.0 ± 0.3	0.25
Race (white/black)	7/8	4/5	0.75
Serum glucose (mg/dl)	129 ± 72	122 ± 68	0.82
Serum free fatty acids (mEq/liter)	2.3 ± 1.0	2.3 ± 1.3	0.99
Serum triglycerides (mg/dl)	110 ± 97	115 ± 164	0.92
Serum cholesterol (mg/dl)	183 ± 27	183 ± 57	0.98
History of alcohol abuse			
Any	8/15 (53%)	5/9 (56%)	0.75
<6 mo before entry	0/15 (0%)	2/9 (22%)	0.25
NYHA functional class	2.3 ± 0.5	2.4 ± 0.7	0.66

Data presented are mean value ± SD or number (%) of patients. NYHA = New York Heart Association.

of mechanical work performed (i.e., reduces myocardial efficiency) (20–24). Because catecholamines, which are increased in heart failure (1–6), may stimulate the release and utilization of fatty acids (20–24), beta-blockade may alter the ratio of fatty acid to carbohydrate utilization. Therefore, the present study was undertaken to determine whether metoprolol improves systolic and diastolic performance and alters substrate utilization in patients with dilated cardiomyopathy.

Methods

Between December 1, 1990 and April 14, 1993, 25 men (mean [± SD] age 48 ± 10 years, range 34 to 75) with nonischemic dilated cardiomyopathy underwent cardiac catheterization at the Dallas Veterans Administration Medical Center. All patients had a left ventricular ejection fraction ≤0.45 before study entry and were in New York Heart Association functional classes II to IV. All patients with a presumptive diagnosis of dilated cardiomyopathy were approached for entry into the study unless they had a complicating illness. Patients with severe renal (creatinine >2.5 mg/dl), hepatic (serum glutamic oxaloacetic transaminase [SGOT] or serum glutamic pyruvic transaminase [SGPT] more than three times normal), pulmonary, rheumatologic or endocrine disease were excluded. Only one patient was diabetic and was taking insulin at the time of catheterization, and he was a well controlled type II diabetic. Patients with previous myocardial infarction, constrictive, restrictive or hypertrophic cardiomyopathy or primary valvular disease were excluded, as were patients with a recent (<3 months) history of alcohol abuse. Five (56%) of 9 control patients and 8 (53%) of 15 metoprolol-treated patients had some history of alcohol abuse (Table 1) (p = NS for placebo vs. metoprolol). In addition, two of nine placebo-treated patients had stopped drinking <6 months (but >3 months) before entry into the study, whereas none of the metoprolol-treated patients had a history of drinking <6 months before entry (p = NS). All patients with <6 months of clinical heart failure of unclear etiology had endomyocardial biopsy; none had evidence of myocarditis.

All medications were allowed, except beta-blockers, within 3 months of entry. All patients were taking angiotensin-converting enzyme inhibitors during the study, and the dose was not changed between catheterizations. All medications remained constant during the study period, except for diuretic agents, which were altered as clinically indicated. The patients were all studied in an overnight fasting state, and no intravenous dextrose was given before catheterization. Written informed consent was obtained from each patient, and the protocol was approved by the Human Studies Subcommittee of the Dallas Veterans Administration and University of Texas Southwestern Medical Centers in November 1990.

Hemodynamic measurements. Each study was performed using previously published techniques (10). A 7F Wilton-Webster coronary sinus thermodilution catheter was placed in the coronary sinus for sampling blood and determining coronary flow. Using diluted contrast injections in the coronary sinus, this catheter was carefully positioned in the same place in both the first and second catheterization to minimize differences in coronary flow measurements due to catheter placement. A 7F thermodilution pulmonary artery catheter was placed in the pulmonary artery using a femoral approach. An 8F double-chip Millar micromanometer pigtail catheter was positioned in the left ventricle to record left ventricular and aortic pressure.

Before any contrast injections, two coronary sinus and two left ventricular heparinized blood samples were simultaneously drawn for blood gas determination. Additional nonheparinized blood was then sampled from the left ventricle for determination of free fatty acids, triglycerides, cholesterol and glucose concentrations.

Baseline coronary sinus thermodilution and cardiac output measurements and left heart pressure recordings were performed before initiation of overdrive atrial (coronary sinus) pacing.

Atrial pacing (to match heart rate at baseline and 3 months) was performed to eliminate alterations in contractility and relaxation due to changes in heart rate from baseline to 3 months. Ten minutes after initiation of atrial pacing at 10 to 15 beats/min above the intrinsic heart rate, left heart pressure and cardiac output measurements were repeated. This was followed by digital ventriculography using 15 to 25 ml (total volume) of diluted (60:40) nonionic contrast media (Iohexol, Winthrop-Breon Laboratories). Ventriculography was performed in the 30° right anterior oblique projection at 30 frames/s with cineradiographic equipment (Philips model Optimus M200, Eindhoven, The Netherlands) interfaced directly to a digital radiographic computer (ADAC, model DPS-4100C, Milpitas) and stored as a 512 × 512 × 8-bit image matrix. The images were stored and processed using previously published techniques (10).

After these measurements were recorded, loading conditions were altered while pacing was maintaining. Intravenous sodium nitroprusside was initiated at a dose of 0.25 to 0.50 μg/kg body weight per min and increased by 0.25 μg/kg per min every 2 to 5 min to achieve a reduction of 15 to 25 mm Hg in aortic end-systolic pressure. Care was used to avoid hypotension. Repeat simultaneous ventriculograms and hemody-

namic recordings were performed at one or two time points after aortic end-systolic pressure had been altered. Because left ventriculography may increase end-diastolic pressure transiently, there was a delay of at least 10 min between ventriculograms to allow the left ventricle to return to equilibrium.

After 3 months of therapy, the same procedure was used with care to match the original atrially paced heart rate used in the baseline study.

All patients underwent selective coronary arteriography at the end of the first catheterization to exclude significant coronary disease as a cause of their cardiomyopathy.

Drug titration. The study drug (metoprolol or placebo in a 3:2 randomization) was initiated the day after initial catheterization in all patients in a double-blind fashion. The drug was titrated weekly at the following doses: 6.25, 12.5, 25 and 50 mg twice daily. All patients initially randomized to receive metoprolol tolerated titration to full dosage.

Placebo-treated patients crossed over to open-label metoprolol after the 3-month study period. We performed a radionuclide ventriculogram 6 months after randomization (i.e., after 3 months on open-label metoprolol) to assess the change in left ventricular ejection fraction after crossover to active drug. Because we had no knowledge of who received the active drug in the initial 3 months, the drug was titrated or retitrated in all patients according to the schedule given earlier. Because clinical deterioration has been noted in patients withdrawn from beta-blockers (12,25), we chose not to cross the active patients over to placebo. In addition, this allowed us to determine whether further changes in left ventricular ejection fraction occurred between 3 and 6 months.

Hemodynamic data analysis. Left ventricular volume was measured by analysis of digital left ventriculography using a standard angiographic area-length method (10,26,27). The cardiac cycle selected was not a premature beat or postpremature beat. Simultaneous left ventricular pressure recordings were interfaced directly onto the digital volume assessment at each data point in the cardiac cycle. Intraobserver and interobserver variability of our digital ventriculogram measurements has been previously published (10).

Assessment of systolic function. To test whether performance improved in the metoprolol and placebo groups, we prospectively examined ejection fraction as well as three relatively load-independent indexes of left ventricular performance: 1) end-systolic elastance, derived from the end-systolic pressure–volume relation (10,28,29); 2) peak positive first derivative of left ventricular pressure (+dP/dt) to end-diastolic volume relation (30); and 3) preload recruitable stroke work (31). These indexes were assessed at matched paced heart rates before and after 3 months of therapy. Left ventricular stroke work index (LVSWI) was determined by the following formula (32):

$$\text{LVSWI} = (\text{MSLVP} - \text{MDP}) \times \text{SVI} \times 0.0136,$$

where MSLVP = mean systolic left ventricular pressure; MDP = mean diastolic left ventricular pressure; and SVI = stroke volume index by thermodilution (cardiac index/heart rate). Minute work index = LVSWI × Heart rate.

Arterial elastance (Ea) was determined by a previously validated formula (33,34): Ea = Pes/SV, where Pes = end-systolic pressure; and SV = stroke volume.

Assessment of diastolic performance. Isovolumic relaxation. Left ventricular relaxation was assessed by analyzing changes in the time constant of exponential isovolumetric pressure decrease (tau) uncorrected for afterload (35,36) and the slope of the tau–end-systolic pressure relation (36,37), both before and after long-term beta-adrenergic blockade.

The time constant of exponential isovolumetric pressure decrease (tau) was determined by a previously described method (10,35,36) and was calculated using a linear regression of dP/dt versus ($P - P_B$) from maximal negative dP/dt to left ventricular end-diastolic pressure, where P_B = nonzero asymptotic pressure (35,36). Beats with a correlation coefficient (r value) <0.95 for this linear regression were discarded, and 20 to 30 beats were analyzed and averaged.

Chamber and myocardial stiffness. Chamber stiffness was analyzed by the constant of chamber stiffness (38) and myocardial stiffness was determined as the slope of the relation of V dP/dV to left ventricular pressure (P) (39). The constant of chamber stiffness was determined by solving a nonlinear, best fit analysis of the diastolic pressure–volume points from mitral opening to the peak of the R wave on the electrocardiogram (ECG). A nonlinear equation-fitting program (NFIT, Island Products) was used to solve the equation $P = a + be^{kV}$, where coefficients a, b and k were determined from a best fit of this equation; coefficient k = the constant of chamber stiffness; coefficient a = the upward or downward displacement (shift) of the pressure–volume relation. On the basis of this equation, a linear regression of V dP/dV versus P was determined, with a slope K_N, where K_N = a measure of myocardial stiffness (39).

Determination of myocardial efficiency. Myocardial oxygen consumption (MOC) was determined by the following formula (10):

$$\text{MOC} = \text{Coronary sinus blood flow} \times (\text{Left ventricular} - \text{Coronary sinus } O_2 \text{ difference});$$

and myocardial efficiency by (10),

$$\text{Efficiency (\%)} = (\text{Stroke work} \times \text{Heart rate}/k \times \text{MOC}),$$

where k = conversion constant 2.059 (kg-m/ml O_2 consumed).

Because our determination of mechanical efficiency is calculated by this ratio of external mechanical work to myocardial oxygen consumption (as just shown), and because total mechanical energy actually represents both external mechanical work and potential energy changes, we also calculated potential energy changes before and after therapy. We calculated potential energy by a calculation based on end-systolic pressure (V_0), and end-systolic volume (ESV) using the following formula (40):

$$\text{Potential energy} = \{[(\text{End-systolic pressure}) \times (\text{ESV} - V_0)]/2\} \times (1.33 \times 10^{-4} \text{ J/mm Hg-ml}).$$

Because the volume intercept V_0 changed between catheterizations, we used the calculated V_0 from each study to calculate potential energy.

Determination of myocardial respiratory quotient. Myocardial respiratory quotient, a reflection of myocardial substrate utilization (41), was determined using left ventricular and coronary sinus blood gas determinations. Oxygen and carbon dioxide content was measured, and myocardial respiratory quotient (RQ) was calculated as follows:

$$RQ = (CSco_2 - Aco_2)/(Ao_2 - CSo_2),$$

where Aco_2, Ao_2, $CSco_2$ and CSo_2 = arterial and coronary sinus carbon dioxide and oxygen content, respectively. The carbon dioxide content of the blood specimens was calculated by the following equation (42):

CO_2 content (mmol/liter)

$$= (Pco_2 \text{ mm Hg})\ (0.0301 \text{ mmol/liter per mm Hg}) + HCO_3^- \text{ (mmol/liter)}.$$

This formula assumes a negligible amount of carbon dioxide bound to hemoglobin (Hgb). Oxygen content was calculated as follows:

O_2 content (ml/dl) = (O_2 sat %) (1.36 ml O_2/g Hgb) (Hgb g/dl);

O_2 content (mmol/liter)

$$= \{[O_2 \text{ content (ml/dl)}](10 \text{ dl/liter})\}/(22.4 \text{ ml/mmol}),$$

where sat = saturation. Variability of our myocardial respiratory quotient measurements has been tested by repeated analysis of measurements from seven patient studies of myocardial respiratory quotient taken 30 s apart (14 samples) ($r = 0.68$, SEE 0.14, $p = 0.0072$).

Radionuclide scan at 6 months. After completion of the hemodynamic analysis at 3 months after randomization, all patients crossed over by titration to open-label metoprolol. All patients were then asked to undergo a radionuclide ventriculogram at 6 months after randomization. One patient did not receive a 6-month scan because of sudden death before the scan; another patient from the placebo group was intolerant to metoprolol titration because of severe heart failure and did not undergo a 6-month scan. Radionuclide ventriculography was performed and analyzed as previously described (43,44). All radionuclide studies were analyzed in blinded manner.

Statistical analysis. Changes in hemodynamic variables and ventricular function were compared by two-way (group effect and time effect) repeated measures analysis of variance. Statistical differences between groups were then tested by a Scheffé F test. Differences within groups were tested by a Student paired *t* test only if the repeated measures analysis demonstrated an intragroup time effect. Baseline characteristics were compared by an unpaired *t* test. For the peak +dP/dt–end-diastolic volume relation, a repeated measures analysis of covariance (with end-diastolic volume as the covariate) was used with 1) intergroup (metoprolol vs. placebo) and 2) intragroup (time effect and nitroprusside effect) factors examined. For end-systolic elastance, the slopes and intercepts of each individual patient before and after therapy were compared by a two-way repeated measures analysis of variance. For preload recruitable stroke work, the slopes of the stroke work–end-diastolic volume relation was compared by a two-way repeated measures analysis of variance. Nominal variables were compared by a chi-square contingency table analysis. All results are expressed as mean value ± 1 SD, unless otherwise specified; $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics. One of the 25 original patients refused a second cardiac catheterization and was excluded from analysis. As demonstrated in Table 1, both the metoprolol and placebo groups were well matched with regard to age, body habitus, race, functional class and available substrates (glucose, free fatty acids, triglycerides and cholesterol).

Tables 2 and 3 show the characteristics of the two groups at baseline and after 3 months of therapy. The placebo group had more ventricular dysfunction at baseline, as evidenced by a lower ejection fraction, larger end-systolic and end-diastolic volumes, higher end-diastolic pressure and more prolonged relaxation.

Drug titration. Fifteen patients were randomized to receive metoprolol and 9 to receive placebo. All patients tolerated full titration to 50 mg twice daily without difficulty. All patients were outpatients during titration, and no patient required repeat hospital admission for worsening congestive failure during the titration phase.

Effect of metoprolol on hemodynamic variables in the absence of pacing. The changes in hemodynamic variables in the two groups are summarized in Table 2. Heart rate was reduced by metoprolol, thus accounting for a lack of increase in cardiac output despite an increase in stroke volume. Left ventricular end-diastolic pressure at rest was not reduced by metoprolol. However, peak systolic and end-systolic pressures were increased by beta-blockade.

Both stroke and minute work were increased by metoprolol, whereas potential energy did not change (Tables 2 and 3). Despite this increase in mechanical work, coronary flow and myocardial oxygen consumption decreased. This resulted in an increase in myocardial efficiency in the metoprolol group only (from 8.5 ± 5.6% to 18.5 ± 10.9%, $p = 0.01$ vs. pretherapy, $p = 0.10$ vs. placebo).

Despite improvement in ventricular performance and myocardial efficiency, coronary sinus norepinephrine did not decrease. However, compared with the placebo group, metoprolol attenuated progressive increases in coronary sinus norepinephrine and epinephrine.

Systolic assessment. At matched paced heart rates, metoprolol increased end-systolic and reduced left ventricular end-diastolic pressures (Table 3). Despite these changes, end-systolic volume decreased, and ejection fraction increased, in the metoprolol group (Table 3, Fig. 1). Stroke work increased

Table 2. Baseline Left Ventricular Characteristics Before and After Metoprolol or Placebo Therapy

	Before Treatment	After Treatment	p Value (metoprolol vs. placebo)
Heart rate (min^{-1})			
Placebo	84 ± 10	83 ± 19	
Metoprolol	83 ± 17	68 ± 17*	0.014
Cardiac output (liters/min)			
Placebo	4.2 ± 1.4	4.4 ± 1.2	
Metoprolol	4.7 ± 1.2	4.8 ± 1.0	0.76
Stroke volume (ml)			
Placebo	52 ± 20	56 ± 22	
Metoprolol	59 ± 19	74 ± 24†	0.19
LVEDP (mm Hg)			
Placebo	28.6 ± 5.7	26.8 ± 7.8	
Metoprolol	19.1 ± 9.4‡	16.8 ± 7.3	0.91
Peak systolic pressure (mm Hg)			
Placebo	100 ± 8	102 ± 6	
Metoprolol	105 ± 21	124 ± 29†	0.077
End-systolic pressure (mm Hg)			
Placebo	61 ± 6	60 ± 7	
Metoprolol	62 ± 14	77 ± 19†	0.023
Stroke work index ($g\text{-}m/m^2$)			
Placebo	17.0 ± 5.0	20.7 ± 10.9	
Metoprolol	18.7 ± 7.8	32.9 ± 17.5*	0.064
Minute work index ($kg\text{-}m/m^2$)			
Placebo	1.4 ± 0.4	1.6 ± 0.7	
Metoprolol	1.5 ± 0.6	2.1 ± 0.8†	0.25
Coronary sinus blood flow (ml/min)			
Placebo	146 ± 102	201 ± 136	
Metoprolol	178 ± 88	115 ± 71	0.026
Myocardial oxygen difference (vol %)			
Placebo	12.2 ± 1.7	11.5 ± 2.3	
Metoprolol	12.4 ± 1.3	11.7 ± 1.2†	0.95
Myocardial oxygen consumption (ml/min)			
Placebo	16.8 ± 9.2	22.1 ± 12.5	
Metoprolol	22.3 ± 11.3	13.1 ± 7.6	0.035
Myocardial efficiency (%)			
Placebo	7.9 ± 3.8	9.2 ± 6.7	
Metoprolol	8.5 ± 5.6	18.5 ± 10.9†	0.10
Coronary sinus norepinephrine (pg/ml)			
Placebo	730 ± 445	1,114 ± 727	
Metoprolol	569 ± 426	433 ± 357	0.025
Coronary sinus epinephrine (pg/ml)			
Placebo	86 ± 88	135 ± 174	
Metoprolol	65 ± 55	46 ± 36	0.09
Respiratory quotient			
Placebo	0.88 ± 0.25	0.68 ± 0.15	
Metoprolol	0.70 ± 0.27	0.78 ± 0.25	0.054

*$p < 0.005$ versus before treatment. †$p < 0.05$ versus before treatment. ‡$p < 0.05$ versus before treatment with placebo. Data presented are mean value ± SD. LVEDP = left ventricular end-diastolic pressure.

only in the metoprolol group despite the finding that preload, reflected by end-diastolic volume, decreased.

Left ventricular ejection fraction increased in 13 of 15 patients randomized to metoprolol treatment by 3 months of therapy. One of the remaining two patients had an improvement in ejection fraction by 6 months compared with baseline. Thus, 14 (93%) of 15 patients had some improvement in ejection fraction by 6 months. By 3 months of metoprolol therapy, 10 (67%) of 15 patients experienced an increase of 0.05 in ejection fraction, 6 (40%) of 15 had an increase of 0.10; and 3 (20%) of 15 had an increase of 0.20. By 6 months of metoprolol therapy, 11 (79%) of 14 patients assessed experienced an increase of 0.05 in ejection fraction; 10 (71%) of 14 had an increase of 0.10; and 6 (43%) of 14 had an increase of 0.20.

Although end-systolic elastance did not increase in the placebo and metoprolol groups, the y intercept of the end-systolic pressure–volume relation was increased in the metoprolol group (Table 3). This suggests that a parallel

Table 3. Left Ventricular Characteristics During Atrial Pacing Before and After Study Drug Therapy

Measurement	Before Treatment	After Treatment	p Value (metoprolol vs. placebo)
Heart Rate and Pressures			
Heart rate (min^{-1})			
Placebo	95 ± 8	97 ± 9	
Metoprolol	94 ± 13	93 ± 13	0.11
LVEDP (mm Hg)			
Placebo	26.2 ± 5.9	25.8 ± 9.5	
Metoprolol	19.2 ± 10.6*	12.5 ± 7.4†	0.15
End-systolic pressure (mm Hg)			
Placebo	62 ± 4	59 ± 9	
Metoprolol	62 ± 13	72 ± 17†	0.053
Aortic end-diastolic pressure (mm Hg)			
Placebo	79 ± 5	77 ± 6	
Metoprolol	79 ± 15	78 ± 14	0.85
Potential energy (J)			
Placebo	1.49 ± 1.08	1.25 ± 0.68	
Metoprolol	1.17 ± 1.14	1.26 ± 1.26	0.57
Volumes and Systolic Properties			
EDVI (ml/m^2)			
Placebo	177 ± 56	159 ± 63	
Metoprolol	137 ± 36‡	116 ± 37†	0.84
ESVI (ml/m^2)			
Placebo	154 ± 54	134 ± 56	
Metoprolol	108 ± 36‡	80 ± 37§	0.44
LVEF			
Placebo	0.14 ± 0.07	0.17 ± 0.08	
Metoprolol	0.22 ± 0.10‡	0.33 ± 0.13§	0.05
Ees (mm Hg/ml)			
Placebo	0.63 ± 0.48	0.53 ± 0.19	
Metoprolol	0.82 ± 0.48	0.84 ± 0.39	0.66
Ees y intercept (mm Hg)			
Placebo	−82 ± 154	−48 ± 52	
Metoprolol	−84 ± 116	−11 ± 34†	0.49
Ea (mm Hg/ml)			
Placebo	2.9 ± 2.2	2.6 ± 1.7	
Metoprolol	1.8 ± 0.8	1.7 ± 0.8	0.83
Stroke work index ($g\text{-}m/m^2$)			
Placebo	16.4 ± 5.4	17.1 ± 6.2	
Metoprolol	16.9 ± 7.0	27.0 ± 15.1†	0.11
Peak +dP/dt (mm Hg/s)			
Placebo	774 ± 101	799 ± 55	
Metoprolol	875 ± 232	1,073 ± 295§	0.04
PRSW (g-m/ml)			
Placebo	0.12 ± 0.08	0.06 ± 0.04	
Metoprolol	0.18 ± 0.16	0.35 ± 0.24†	0.08
Diastolic Properties			
Peak −dP/dt (mm Hg/s)			
Placebo	787 ± 76	808 ± 104	
Metoprolol	922 ± 254*	1,106 ± 331†	0.097
Tau (ms)			
Placebo	123 ± 25	104 ± 32‖	
Metoprolol	89 ± 25‡	78 ± 24‖	0.41
R (ms/mm Hg)			
Placebo	3.5 ± 1.7	2.5 ± 1.5‖	
Metoprolol	1.5 ± 1.0‡	0.8 ± 0.8§	0.58
K_N			
Placebo	9.8 ± 5.0	11.0 ± 8.0	
Metoprolol	3.7 ± 3.0‡	3.4 ± 2.6	0.67
k			
Placebo	0.031 ± 0.021	0.042 ± 0.036	
Metoprolol	0.031 ± 0.035	0.031 ± 0.040	0.64
a			
Placebo	4.46 ± 15.80	−1.38 ± 17.57	
Metoprolol	−5.16 ± 25.11	0.13 ± 10.68	0.37

*$p < 0.1$, ‡$p < 0.05$ versus placebo pretreatment. †$p < 0.05$, §$p < 0.01$, ‖$p < 0.1$ versus pretreatment. Data presented are mean value ± SD. a = diastolic pressure–volume shift coefficient; Ea = arterial elastance; Ees = end-systolic elastance; EDVI (ESVI) = end-diastolic (end-systolic) volume index; k = constant of chamber stiffness; K_N = myocardial stiffness; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; Peak +dP/dt (−dP/dt) = peak positive (negative) first derivative of left ventricular pressure; PRSW = preload recruitable stroke work; R = end-systolic pressure relation; Tau = time constant of exponential isovolumetric pressure decrease.

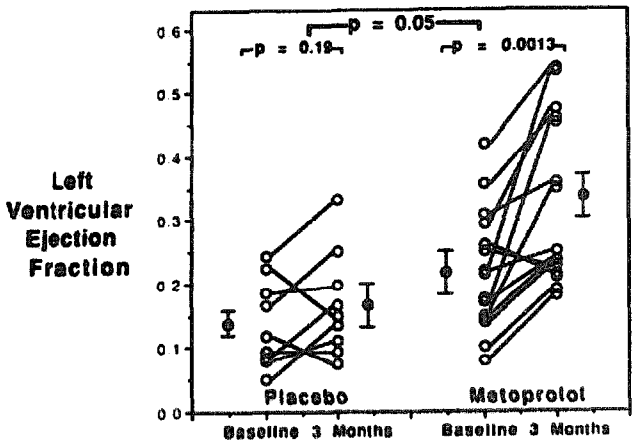

Figure 1. Changes in left ventricular ejection fraction between baseline and 3 months for the placebo and metoprolol groups. A significant increase in ejection fraction was seen only in the metoprolol group. **Vertical bars** are group mean value and standard error.

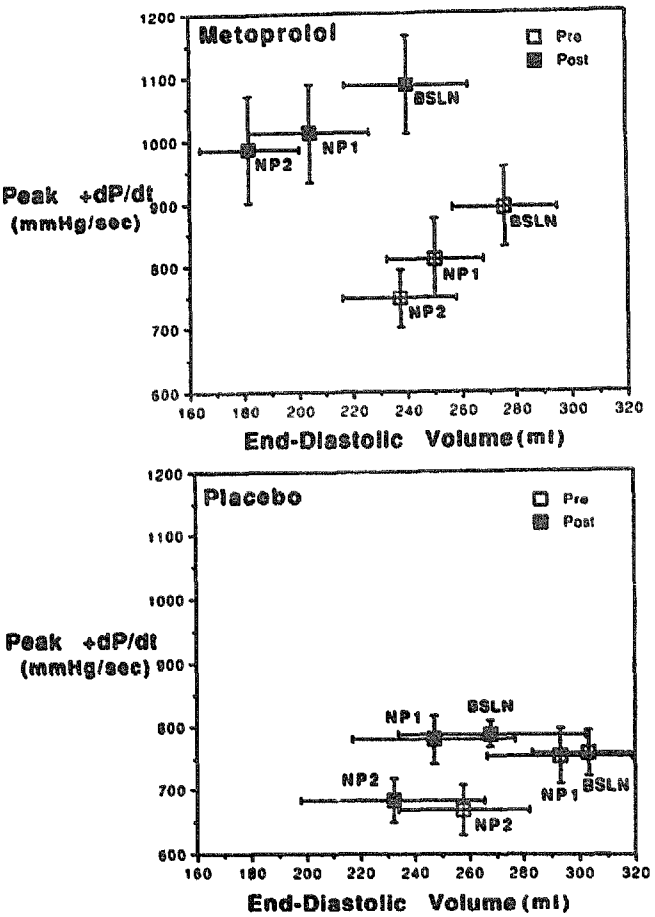

Figure 2. Changes in the peak positive first derivative of left ventricular pressure (+dP/dt)–end-diastolic volume relation at paced baseline (BSLN) and after two doses of nitroprusside (NP1 and NP2) for the metoprolol (**top**) and placebo (**bottom**) groups. Both pretherapy and postherapy group mean values are shown with the standard error of the estimate (**vertical bars**). Analysis demonstrated significant improvement in peak +dP/dt in the metoprolol group compared with the placebo group ($p = 0.04$). This suggests that metoprolol increases contractility compared with placebo.

leftward shift (upward shift) occurred in the end-systolic pressure–volume relation consistent with either an increase in chamber contractility or a reduction in ventricular volume, or both.

Peak +dP/dt at matched paced heart rates increased with beta-blockade ($p = 0.023$), an effect that is not explained by an increase in preload (Fig. 2). The slope of the stroke work–end diastolic volume relation demonstrated an increase in preload recruitable stroke work in the metoprolol group only (Table 3). Taken together, these data suggest that long-term metoprolol therapy may increase contractility in patients with dilated cardiomyopathy.

Diastolic assessment. Although isovolumic relaxation improved slightly with metoprolol (as reflected by a decrease in the time constant of exponential isovolumetric decrease [tau], the tau–end-systolic pressure relation [R] and an increase in peak −dP/dt) (Table 3), the placebo group likewise had a small improvement in relaxation. Thus, the metoprolol group did not differ significantly from the placebo group. The reduction in the time constant of exponential isovolumetric decrease (tau) in the metoprolol group probably would have been more prominent had end-systolic pressure not increased in this group (36,37).

End-diastolic volume and pressure decreased in the metoprolol group (Table 3). However, myocardial stiffness and chamber stiffness did not change with therapy. In addition, the diastolic pressure–volume relation was not shifted upward or downward with administration of metoprolol or placebo, as reflected by lack of change in coefficient "a." Thus, metoprolol did not significantly improve diastolic function compared with placebo.

Myocardial energetics and neurohormonal activation. Myocardial oxygen consumption decreased despite an increase in left ventricular minute work (Table 2), suggesting improved myocardial efficiency with beta-blockade.

Myocardial respiratory quotient tended to increase in the metoprolol-treated patients, whereas it tended to decrease in the placebo-treated patients (Table 2). These data suggest that beta-blockade alters substrate utilization by increasing carbohydrate utilization (increased myocardial respiratory quotient). By comparison, placebo-treated patients had a progressive increase in noncarbohydrate utilization (reduction in respiratory quotient). Although the intragroup changes in respiratory quotient did not reach statistical significance ($p = 0.36$ for the metoprolol group vs. pretherapy and $p = 0.12$ for the placebo group vs. pretherapy), the intergroup comparison suggests that metoprolol at least may inhibit progressive changes in the respiratory quotient ($p = 0.054$).

Changes in coronary sinus norepinephrine closely correlated with changes in myocardial respiratory quotient (Fig. 3). These data suggest that a relation may exist between neurohormonal activation and substrate utilization in patients with heart failure. Despite this correlation, no relation was seen

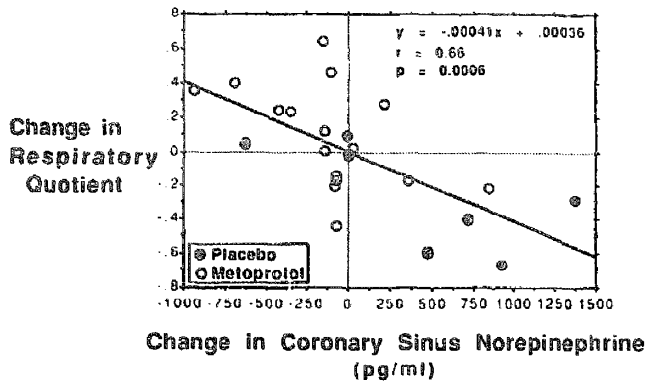

Figure 3. Linear relation between changes in transmyocardial respiratory quotient and coronary sinus norepinephrine ($p = 0.0006$). These data suggest that a significant relation may exist between adrenergic activation of the heart and substrate utilization in patients with congestive heart failure.

between changes in respiratory quotient and myocardial efficiency or ejection fraction.

Six-month follow-up. Of the 14 patients randomized to receive metoprolol who underwent both catheterizations and the 6-month radionuclide ventriculogram, the left ventricular ejection fraction increased from 0.22 ± 0.10 at baseline to 0.32 ± 0.13 at 3 months ($p = 0.0013$ vs. baseline) to 0.41 ± 0.13 at 6 months ($p = 0.017$, 6 months vs. 3 months). In the seven placebo patients who had all three assessments, ejection fraction went from 0.13 ± 0.07 to 0.17 ± 0.09 at 3 months ($p = 0.19$ vs. baseline) and increased to 0.28 ± 0.09 3 months after crossover to metoprolol ($p = 0.011$ vs. 3 months). Functional class improved over the 6 months of follow-up in the 15 metoprolol-treated patients. Functional class was 2.3 ± 0.5 at baseline, 2.1 ± 0.7 at 3 months ($p = 0.08$ vs. baseline) and improved to 1.5 ± 0.7 by 6 months of therapy ($p < 0.05$ vs. baseline and vs. 3 months). Functional class did not change in the placebo-treated group over the 3 months of double-blind therapy.

Discussion

The use of beta-adrenergic blockade to treat patients with heart failure remains an enigma. Improvements in ventricular function in the presence of a "negative" inotropic agent is counterintuitive and remains controversial despite a considerable number of published reports (1,9–18) that demonstrate a salutary effect of these agents in these patients. Our study demonstrates improved left ventricular function and a reduction in left ventricular chamber size in patients with dilated cardiomyopathy randomized to metoprolol therapy. Additionally, improvement in three relatively load independent indexes of performance, the end-systolic pressure–volume relation, peak +dP/dt–end-diastolic volume relation and slope of the stroke work–end-diastolic volume relation suggests that left ventricular contractility may have increased, although the long-term changes in heart size precludes our ability to state this definitively.

The increase in myocardial work, as expressed by left ventricular minute work, did not occur at the expense of oxygen delivery or myocardial efficiency. Because the failing heart may be energy depleted (45), improvement in cardiac efficiency may be a beneficial effect of these agents.

Although metoprolol did not significantly improve either relaxation or chamber stiffness, when the heart was paced above baseline, end-diastolic pressure decreased, an effect not seen in the placebo-treated patients. Such a reduction in end-diastolic pressure may represent one beneficial effect of beta-blocking agents on these patients when they exercise (16,17,46). As heart rate increases, beta-blockers may blunt the increase in end-diastolic pressure with exercise. As with our previous study with bucindolol (10), there was an intragroup improvement in relaxation (reduction in the tau–end-systolic pressure relation). However, no intergroup effect was seen because of some spontaneous improvement in the placebo group and an increase in end-systolic pressure in the metoprolol group, which can mask improvement in relaxation times (36,37).

Despite hemodynamic improvement, metoprolol did not significantly reduce coronary sinus norepinephrine. This may have been due to the fact that metoprolol reduces the clearance of norepinephrine (47). By contrast, metoprolol did retard the progressive increase in norepinephrine seen in the placebo group ($p = 0.025$ vs. placebo) and also reduced rest heart rate ($p = 0.014$ vs. placebo), a marker of receptor blockade and adrenergic antagonism.

Although myocardial respiratory quotient did not significantly increase with beta-blockade, metoprolol blunted the progressive decrease in respiratory quotient seen in the placebo group ($p = 0.054$ vs. placebo). Thus, metoprolol may have resulted in preferential carbohydrate utilization. We believe that this is the first study to suggest an in vivo relation between substrate utilization and adrenergic activation in patients with heart failure. This finding is not surprising in view of previous animal studies demonstrating increased lipolysis (21,24) and reduced insulin-induced glucose transport (48) in the presence of catecholamines. In addition, previous data in patients with heart failure have shown enhanced insulin-mediated suppression of hepatic glucose output, increased glucose and lactate uptake and a decline in basal free fatty acids with the long-term administration of metoprolol (49,50). Because congestive heart failure is a state of increased adrenergic stimulation, with elevated sympathetic nerve traffic and increased plasma norepinephrine levels (2–6), lipolysis and glycogenolysis may be stimulated (21,24). Beta-blockers may act to reduce effective postsynaptic norepinephrine and shift the balance of substrate selection in favor of carbohydrate.

Several experimental observations suggest that fatty acid metabolism by the heart is less efficient than carbohydrate metabolism, a factor which may be hemodynamically relevant in the setting of catecholamine excess and limited oxygen delivery (20,24). Although fatty acid utilization in the presence of this stress may serve to decrease myocardial efficiency, the lack of a direct relation between changes in respiratory quotient and changes in efficiency in this study suggest that this is

either not a factor or not the only factor resulting in improved efficiency. Further investigation into the mechanism(s) whereby beta-blockade improves myocardial efficiency is warranted using more sophisticated methods, such as magnetic resonance spectroscopy, proton emission tomography and molecular techniques.

Study limitations. The main limitation of this study was the failure of the randomization to achieve identical patients in the metoprolol and placebo groups. Despite this limitation, the metoprolol group clearly responded more favorably to therapy both clinically and in terms of left ventricular systolic function. Even the more impaired placebo group was capable of responding to therapy, as manifested by improved ejection fraction after crossover to open-label metoprolol. In addition to baseline differences, there was some spontaneous improvement in ejection fraction in four of the nine placebo-treated patients, which reduces the statistical significance of our findings. However, spontaneous improvement in ejection fraction in a substantial proportion of placebo-treated patients with dilated cardiomyopathy is not unique to our trial and has been seen in other large randomized trials (17,18). That we reached statistical significance despite these baseline differences and some spontaneous improvement in the placebo group attests to the very consistent improvement seen with metoprolol.

Another limitation of this study is our limited ability to measure myocardial metabolism in vivo. Myocardial respiratory quotient has a relatively large standard error and may be insensitive to small changes in substrate utilization. We thus believe that our results are suggestive but require further investigation.

Nitroprusside may result in geometric alterations as ventricular volumes decrease, and could introduce an error into the volume calculations. In addition, in certain circumstances of large volumes constrained by the pericardium, application of nitroprusside (or drugs that reduce ventricular volumes over time) can result in a downward shift of the diastolic pressure–volume relation as the constraint is relieved (51). In circumstances where there was a clear downward shift of a pressure–volume loop with nitroprusside, the pressure–volume diastolic points before that application of nitroprusside were used.

The use of nitroprusside may also result in some baroreflex-mediated changes in contractility (52). However, because patients with congestive heart failure have high neurosympathetic tone at baseline (2,4–6,52), baroreflex stimulation from nitroprusside should be of minimal significance. In addition, the small range of pressure reduction (15 to 25 mm Hg) induced by nitroprusside may have affected the accuracy of measuring the end-systolic pressure volume relation, especially because this relation may be somewhat curvilinear (53,54).

The comparison of left ventricular ejection fraction at 6 and 3 months involves use of two different techniques: angiographic left ventriculography and radionuclide ventriculography. The former makes geometric assumptions to assess ejection fraction (26,27); the latter makes no geometric assumptions (43,44). Despite these differences, these two techniques have been shown to correlate well with each other (44). In addition, comparison of 36 studies of patients with dilated cardiomyopathy by radionuclide and angiographic techniques in our institution have shown excellent correlation ($r = 0.78$, SEE 0.06, $p < 0.0001$). Although previous studies (55) have demonstrated no differences in ejection fraction with atrial pacing, because the ejection fraction at 3 months was determined with atrial pacing and that at 6 months was determined at rest, some slight overestimation of ejection fraction at 3 months may have occurred. However, this makes the improvement seen from 3 to 6 months that much more significant.

Measurement of left ventricular performance in vivo during a long-term intervention is difficult. No perfect measurement of left ventricular function is available, and it is possible for left ventricular performance to improve without an increase in intrinsic myocardial function (56). Our study demonstrates that chamber performance improved. This is suggested by 1) a parallel leftward shift in the end-systolic pressure–volume relation, 2) an increase in left ventricular ejection fraction in the setting of reduced preload and increased end-systolic pressure, 3) an upward shift of the peak +dP/dt–end-diastolic volume relation, and 4) an increase in preload recruitable stroke work. Although long-term changes in ventricular size and geometry could explain our data, it is likely that such changes in the ventricle reflect improvement in contractile performance. Indeed, reduction in ventricular volumes by itself suggests that cardiac function has improved.

Because previous studies (57) have shown that the peak +dP/dt–end-diastolic volume relation is more sensitive than the end-systolic pressure–volume relation for detecting changes in inotropic state, it is not inconsistent to have a parallel shift in elastance with an increase in the peak +dP/dt–end-diastolic volume relation. In addition, the upward shift in the peak +dP/dt–end-diastolic volume relation in this case cannot be due to a change in aortic pressure because aortic end-diastolic pressure (aortic valve opening pressure) was unchanged after administration of metoprolol.

We recognize that coronary sinus thermodilution determination of coronary sinus blood flow is limited by changes in catheter position within the coronary sinus, patterns in coronary venous drainage and coronary sinus reflux (58,59). We attempted to minimize these problems by meticulous examination of catheter position during each procedure. In addition, the presence of a placebo-treated group in this study helps to assess the significance of any random measurement errors.

Finally, it is clear that the analysis of myocardial energetics is complex. Myocardial efficiency can be defined as the relation between myocardial oxygen consumption and its covariate, the pressure–volume area (total mechanical energy) (40). Total mechanical energy may further be defined as the sum of external mechanical work plus potential energy produced during a cardiac cycle. Because external mechanical work (stroke work) increased, potential energy was unchanged, and myocardial oxygen consumption decreased, it is likely that myocardial efficiency increased. This increase is most likely due to an increase in shortening work as opposed to pressure work because potential energy did not increase substantially and

stroke volume increased significantly. Because systolic pressure increased in the metoprolol-treated patients, there may have been an associated thermodynamic energy expenditure.

Conclusions. Treatment of patients with nonischemic dilated cardiomyopathy with metoprolol results in increased left ventricular performance and ejection fraction, augmented stroke work and an increase in myocardial efficiency. Continued improvement in left ventricular ejection fraction was seen between 3 and 6 months. The improvement seen in the metoprolol-treated patients occurred in the presence of angiotensin converting-enzyme inhibitor therapy. Thus, although angiotensin converting-enzyme inhibitors have been shown to slow the progression of left ventricular dysfunction and improve survival, they make only modest improvements in ejection fraction in patients with heart failure (60). In contrast, beta-blockade with metoprolol appears to reverse left ventricular dysfunction in a majority of patients with nonischemic cardiomyopathy. Improved left ventricular performance in the setting of decreased myocardial oxygen utilization may be related to the effects of beta-blockade on neuroendocrine activation and myocardial substrate utilization in the failing heart. However, this hypothesis merits further investigation with more sophisticated techniques.

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