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Time Course of Improvement in Left Ventricular Function, Mass and Geometry in Patients With Congestive Heart Failure Treated With Beta-Adrenergic Blockade

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Objectives. **We examined the time course of ventricular functional improvement in patients with dilated cardiomyopathy who received beta-blockade and the long-term effects of beta-blockade on ventricular mass and geometry in these patients.**

Background. **Previous studies have shown that beta-adrenergic blocking agents when administered long term improve ventricular function in patients with heart failure. However, the time course of improvement in ventricular function and the long-term effects of beta-blockade on ventricular mass and geometry are not known.**

Methods. **Twenty-six men with dilated cardiomyopathy underwent serial echocardiography on days 0 and 1 and months 1 and 3 of either metoprolol (n = 16) or standard therapy (n = 10). At 3 months all patients on standard therapy were crossed over to metoprolol, and late echocardiograms were obtained after 18 ± 5 (mean ± SD) months of metoprolol therapy. All echocardiograms were read in blinded manner.**

Results. **Patients treated with metoprolol had an initial decline (day 1 vs. day 0) in ventricular function (increase in end-systolic volume and decrease in ejection fraction). Ventricular function improved between months 1 and 3 (p = 0.013, metoprolol vs. standard therapy). Left ventricular mass regressed at 18 months (333 ± 85 to 275 ± 53 g, p = 0.011) but not at 3 months. Left ventricular shape became less spherical and assumed a more normal elliptical shape by 18 months (major/minor axis ratio 1.5 ± 0.2 to 1.7 ± 0.2, p = 0.0001).**

Conclusions. **Patients with heart failure treated with metoprolol do not demonstrate an improvement in systolic performance until after 1 month of therapy and may have a mild reduction in function initially. Long-term therapy with metoprolol results in a reversal of maladaptive remodeling with reduction in left ventricular volumes, regression of left ventricular mass and improved ventricular geometry by 18 months.**

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Modern therapy for congestive heart failure has focused not only on reversing hemodynamic abnormalities, such as elevated intracardiac pressures and decreased cardiac output, but also on counteracting the effects of compensatory neurohormonal activation (1,2). These neurohormonal mechanisms result in short-term hemodynamic support, but in the long term they appear to augment the progression of heart failure and may precipitate cardiovascular death (2). Thus, angiotensin-converting enzyme inhibitors, which counteract the effects of the renin-angiotensin system, have been shown to confer a survival benefit in patients with congestive heart failure (3).

The sympathetic nervous system is another neurohormonal pathway that has become the recent focus for treatment of congestive heart failure using beta-adrenergic blocking agents (1). Our laboratory (4,5) and others (1,6–10) have shown improved ventricular function in patients with heart failure treated with long-term beta-adrenergic blockade. Yet at least two short-term (<1 month) studies (11,12) reported no improvement with this therapy. It has been observed that many patients report transient worsening of their symptoms on initiation of beta-blocker therapy. Therefore, this study was performed to evaluate the time course of improvement in ventricular function in patients receiving metoprolol. We hypothesized that the negative inotropic effects of metoprolol would result in initial worsening of left ventricular function with a subsequent improvement in ejection fraction and volumes after long-term therapy. Metoprolol was chosen because it was the most widely studied beta-blocker for congestive heart failure when this study was initiated (1).

We also wanted to determine whether beta-adrenergic blockade affects left ventricular mass and geometry. An increase in left ventricular mass, often found in patients with heart failure, has been associated with an increased risk of cardiovascular events and a higher mortality rate (13,14). The failing heart also undergoes progressive changes in size and shape as well as mass (15). These changes result in a more spherical or globular ventricular geometry that may produce an

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increase in meridional wall stress (15), abnormal distribution of fiber shortening (15) and an increase in functional mitral regurgitation (16) and may be associated with worsened exercise tolerance (17) and poorer long-term survival (18). Therefore, we also analyzed the effects of long-term beta-blockade on left ventricular mass and geometry. We hypothesized that long-term metoprolol therapy would exert favorable effects on wall mass and produce a more elliptical (normal) geometry.

Methods

Patient recruitment. Between December 1, 1990 and August 30, 1993, 26 men (mean [±1 SD] age 53 ± 11 years, range 35 to 78) with congestive heart failure underwent serial echocardiography at the Dallas Veterans Administration Medical Center. All patients had an ejection fractions <0.45 before entry into the study and were in New York Heart Association functional classes II to IV.

Study patients were recruited from two sources: 1) 16 patients with nonischemic dilated cardiomyopathy who were part of a randomized double-blind invasive study of metoprolol (5) and who also participated in this study were randomized to receive metoprolol (n = 10) or placebo (n = 6); 2) 10 patients with heart failure of any etiology (5 with ischemic cardiomyopathy and 5 with nonischemic dilated cardiomyopathy) were recruited for either open-label administration of metoprolol (n = 6) or continuation of their current therapy without initiation of beta-blockers (n = 4). The "standard therapy" group consisted of those patients either randomized to receive placebo or continue on current therapy without beta-blockade. Patients were excluded for any of the following: severe renal disease (creatinine >2.5 mg/dl), hepatic disease (serum glutamate oxaloacetate transaminase or serum glutamate pyruvate transaminase >3 times normal), pulmonary disease (reactive airway disease), rheumatologic disease (systemic lupus erythematosus, polyarteritis nodosa, scleroderma or dermatomyositis) or endocrine disease (primary aldosteronism, pheochromocytoma or hyperthyroidism and hypothyroidism). Patients with recent myocardial infarction (<3 years before entry) or constrictive, restrictive, hypertrophic or primary valvular disease were excluded, as were patients with a recent (<3 months) history of ethanol abuse. Patients with technically difficult echocardiograms were also excluded.

All medications were allowed except beta-adrenergic blockers within 3 months of the study. All patients (except two who were receiving isosorbide dinitrate/hydralazine) had been on long-term angiotensin-converting enzyme inhibitor therapy before the start of the study, and the dose was not changed for the duration of the study. All other cardiac medication dosages remained constant during the study, with the exception of diuretic drugs, which were changed as clinically indicated. After 3 months of placebo therapy, patients from the randomized sample were crossed over to metoprolol for long-term therapy.

Twenty patients underwent echocardiography just before and at 18 ± 5 months (range 10.5 to 27.0) after initiation of metoprolol therapy to assess long term effects of metoprolol on left ventricular mass and geometry.

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.

Metoprolol titration. The study drug therapy was initiated after initial echocardiography in all patients. The drug was titrated weekly at the following doses: 6.25, 12.5, 25 and 50 mg twice daily. All patients tolerated the full dosage by 1 month.

Echocardiography. All patients underwent two-dimensional transthoracic echocardiography in the left lateral decubitus position (Vingmed CFM 750 instrument with a 3.25-MHz transducer). By phantom calibration, this transducer has an axial and lateral resolution of 1 and 3 mm, respectively. Measurement of vertical distance using the Vingmed analysis software was also evaluated by phantom and was highly accurate, with a 2% coefficient of variation. Gain settings were adjusted to optimize visualization of the left ventricular endocardial contours while avoiding excessive gain artifact. Images were obtained from standard echocardiographic parasternal long- and short-axis views at the midventricular level and apical four- and apical two-chamber views. All images were recorded on ½-in. VHS tape and were subsequently analyzed in a blinded manner by an echocardiographer who had no knowledge of either the study medication or the time of evaluation. Left ventricular septal and posterior wall thicknesses at end-diastole were measured from the parasternal long-axis view at the tips of the mitral leaflets according to the recommendations of the American Society of Echocardiography (19). Two-dimensional echocardiographic estimation of left ventricular mass was performed using the 5/6 area-length method (19). Accordingly, the areas encompassed by the left ventricular epicardial and endocardial borders were traced at end-diastole from the parasternal short-axis view at the midventricular level. Left ventricular length (L) at end-diastole was measured from the apical four-chamber view. Myocardial thickness (t) was calculated from the areas of the epicardial (A_1) and endocardial (A_2) contours according to the following formula (19):

$$t = \sqrt{A_1/\pi} - \sqrt{A_2/\pi}.$$

Left ventricular mass (LVM) was then calculated as follows (19):

$$LVM = 1.05\,\{[5/6\,A_1(L + t)] - [5/6\,A_2(L)]\}.$$

Left ventricular geometry was assessed by a major/minor axis ratio at end-diastole (16). As this ratio approaches 1, the ventricle becomes more spherical. As this ratio increases, the ventricle becomes more elliptical.

Intraobserver and interobserver variability of our echocardiographic measurements (volumes and mass) has been tested by repeated analysis of 20 echocardiograms from patients with heart failure. The standard error of the estimate for intraobserver measurements was 23 ml for volumes ($r = 0.97$, $y = 0.919x + 7.5$, $p = 0.0001$) and 28 g for mass ($r = 0.90$, $y =$

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Table 1. Baseline Clinical Characteristics of Patients With Standard Therapy Only Versus Those With Metoprolol Plus Standard Therapy

	Standard Therapy (n = 10)	Metoprolol (n = 16)	p Value
Age (yr)	56 ± 3	52 ± 3	0.35
Body surface area (m^2)	1.87 ± 0.04	2.01 ± 0.05	0.054
Isch/NIDC	3/7	2/14	0.55
Black/white	6/4	8/8	0.93
Alcohol abuse (yes/no)	5/5	6/10	0.83
LVEF	0.24 ± 0.03	0.23 ± 0.02	0.82
LVEDV (ml)	288 ± 24	256 ± 22	0.36
LVESV (ml)	219 ± 21	196 ± 16	0.39
LVSV (ml)	69 ± 10	61 ± 8	0.52
LVM (g)	315 ± 31	338 ± 21	0.54
Major axis (cm)	9.7 ± 0.2	9.3 ± 0.3	0.35
Minor axis (cm)	6.3 ± 0.3	6.0 ± 0.2	0.50
Sphericity index	1.6 ± 0.1	1.6 ± 0.1	0.93

Data presented are mean values ± 1 SEE or number of patients. Isch = ischemic etiology for heart failure; LVEDV (LVESV) = left ventricular end-diastolic (end-systolic) volume; LVEF = left ventricular ejection fraction; LVM = left ventricular mass; LVSV = left ventricular stroke volume; NIDC = nonischemic dilated cardiomyopathy.

0.796x + 71, p = 0.0001). The standard error of the estimate for interobserver measurements was 25 ml for volumes (r = 0.93, y = 0.947x+ 19, p = 0.0001) and 27 g for mass (r = 0.91, y = 0.742x + 93, p = 0.0001).

Statistical analysis. Nominal variables were compared by a chi-square contingency table analysis. Changes in left ventricular function as reflected by ejection fraction, end-diastolic and end-systolic volumes were compared by repeated-measures analysis of variance (ANOVA). Because three metoprolol group patients missed one echocardiographic assessment (the 1-month evaluation in all patients), and one in the placebo group missed one evaluation (at 3 months), the data were assessed with BMDP subprogram 5V to perform unbalanced repeated-measures ANOVA using maximal likelihood techniques. When the repeated-measures ANOVA demonstrated a nominal interaction, within-group differences were tested by a Student paired *t* test with Bonferroni correction. For within-group comparisons, a trend was defined by $p < 0.05$ and statistical significance by a more conservative $p = 0.008$.

For assessment of long-term (18 month) changes due to beta-blockers (volumes, ejection fraction, mass and geometry), we used a Student paired *t* test. For the patients who were originally randomized to receive placebo and were then crossed over to metoprolol therapy at 3 months, the results from the 3-month echocardiogram were used as the baseline value. Results are expressed as mean value ± 1 SD, unless otherwise specified, and $p < 0.05$ was considered significant.

Results

Time course of ventricular functional improvement. *Baseline characteristics.* The standard therapy and metoprolol groups were well matched with regard to age, race and etiology of heart failure (Table 1). Although the metoprolol group patients had a slightly greater body surface area, indexed volumes were not significantly different between groups. Five patients in the standard therapy group and six in the metoprolol group had some history of alcohol abuse; however all but one patient (standard therapy group) had quit >6 months before study entry.

Table 2 and Figure 1 demonstrate changes in end-diastolic and end-systolic volumes and ejection fraction for the two

Table 2. Mean (±SD) Changes in Volumetric and Ejection Fraction Indexes Over Time

					p Value	
	Baseline	Day 1	Month 1	Month 3	Over Time	Versus Standard Therapy
Metoprolol group (n = 16)						
LVEDV (ml)	256 ± 88	273 ± 84	268 ± 87	243 ± 88	0.19	0.801
LVESV (ml)	196 ± 66	217 ± 68*	206 ± 74	170 ± 81	0.0017	0.072
LVEF	0.23 ± 0.07	0.21 ± 0.07†	0.24 ± 0.08	0.32 ± 0.10*	0.0001	0.013
Standard therapy group (n = 10)						
LVEDV (ml)	288 ± 76	300 ± 64	309 ± 55	262 ± 69‡	0.0032	
LVESV (ml)	219 ± 65	225 ± 57	232 ± 55	204 ± 68	0.16	
LVEF	0.24 ± 0.08	0.25 ± 0.08	0.25 ± 0.09	0.25 ± 0.08	0.93	

* $p < 0.0001$, † $p < 0.05$ versus baseline. ‡ $p < 0.02$ versus day 1 and month 1. Abbreviations as in Table 1.

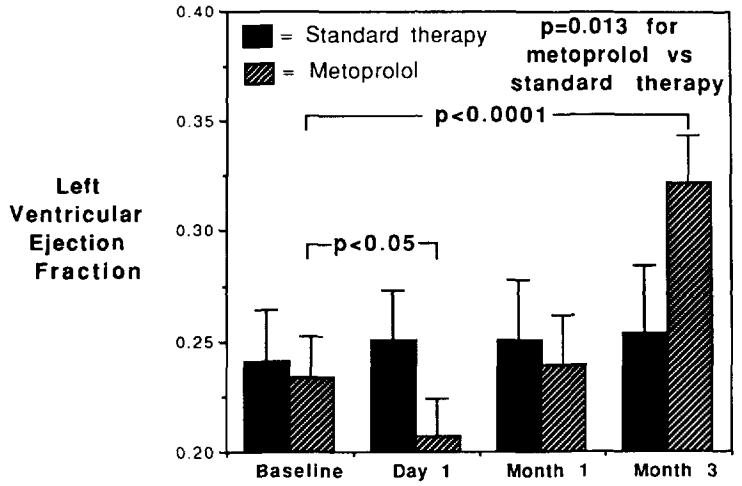

Figure 1. Changes in left ventricular ejection fraction from baseline to day 1, month 1 and month 3 in the metoprolol and standard therapy groups. Ejection fraction decreased at day 1 and increased only after 1 month of metoprolol therapy. In the placebo group, ejection fraction did not change significantly.

groups at baseline and at day 1 and months 1 and 3 of drug therapy. There were no significant differences between the standard therapy and metoprolol groups at baseline. In the metoprolol group there was an increase in end-systolic volume ($p < 0.0001$) and a trend toward an increase in end-diastolic volume ($p = 0.018$) at day 1. Left ventricular ejection fraction at day 1 was depressed ($p = 0.021$) but returned to baseline by month 1 and improved between months 1 and 3. By 3 months of therapy there was a significant increase in left ventricular ejection fraction in the metoprolol group patients compared with those in the standard therapy group ($p = 0.0001$ for metoprolol therapy at 3 months vs. baseline; $p = 0.013$ for metoprolol vs. standard therapy). This improvement in left ventricular ejection fraction was due primarily to a late decrease in end-systolic volume. End-diastolic and end-systolic volumes in the standard therapy group increased nonsignificantly at day 1 and month 1 but returned to baseline by month 3. There was no change in left ventricular ejection fraction in the standard therapy group ($p = 0.63$ for standard therapy at 3 months vs. baseline).

Long-term (18 month) effects of metoprolol on ventricular size, shape and mass. Long-term changes in heart rate, systolic blood pressure and left ventricular volume, ejection fraction, mass and geometry are presented in Table 3. Metoprolol therapy reduced heart rate (88 ± 13 vs. 74 ± 11 beats/min, $p = 0.0006$) and increased systolic blood pressure (117 ± 26 vs. 129 ± 22 mm Hg, $p = 0.022$) by 18 months of therapy (vs. baseline). Left ventricular end-diastolic volume (247 ± 76 vs. 186 ± 48 ml, $p = 0.0067$) and end-systolic volume (188 ± 57 vs. 111 ± 44, $p = 0.0006$) decreased with long-term metoprolol therapy, and left ventricular ejection fraction (0.24 ± 0.07 vs. 0.41 ± 0.13, $p = 0.0002$) continued to improve from baseline at late echocardiography.

In 14 patients who took metoprolol from the start of the study, the 18-month follow-up echocardiogram showed no change in baseline left ventricular mass and that after 3 months of therapy (327 ± 79 vs. 327 ± 76, respectively, p = NS); however, by 18 months of metoprolol therapy, left ventricular mass had regressed significantly (269 ± 57 g, $p = 0.029$). In addition, when all patients were considered, including those who crossed over to metoprolol therapy ($n = 20$), left ventricular mass had regressed by 18 months (333 ± 85 vs. 275 ± 53 g, $p = 0.011$).

In 14 patients who took metoprolol from the start of the study, the 18-month follow-up echocardiogram showed no change between baseline left ventricular geometry (as manifest by major/minor axis ratio at end-diastole) and that after 3 months of therapy (1.6 ± 0.2 vs. 1.6 ± 0.2, respectively, $p = 0.63$); however, by 18 months of metoprolol therapy, the left ventricle had undergone remodeling and had become less spherical and more elliptical (1.8 ± 0.2, $p = 0.01$). The standard therapy group also had no change in left ventricular geometry (1.6 ± 0.2 to 1.4 ± 0.2, $p = 0.092$ vs. baseline; $p = 0.095$ vs. metoprolol). In addition, when all patients were considered, including those who were crossed over to metoprolol therapy ($n = 20$), left ventricular geometry had improved by 18 months (1.5 ± 0.2 to 1.7 ± 0.2, $p = 0.0001$).

Discussion

The present study demonstrates that long-term metoprolol therapy for dilated cardiomyopathy leads to time-dependent improvement in left ventricular volumes and ejection fraction, regression of left ventricular hypertrophy and restoration of elliptical left ventricular geometry. The reduction in ventricular volumes does not occur within the first month of beta-blocker therapy. In fact, there was a trend toward larger volumes and reduced ejection fraction on initiation of metoprolol therapy. However, beta-adrenergic blockade improved left ventricular function, as evidenced by an increase in left ventricular ejection fraction by 3 months of therapy. Thus, it is not surprising that the only two studies of beta-blockade in heart failure that failed to show improvement in left ventricular performance or lessening of symptoms (11,12) were both <1 month in duration. These data reflect the clinical observation that some patients report worsening of symptoms (short-

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Table 3. Long-Term (18 mo) Effects of Metoprolol on Ventricular Size, Shape and Mass (mean ± SD)

	Baseline	3 mo	18 mo	p Value
Patients Initially Taking Metoprolol (n = 14)				
Heart rate (beats/min)	91 ± 13	81 ± 14	78 ± 13	0.012
Systolic BP (mm Hg)	122 ± 27	125 ± 21	134 ± 21	0.067
EDV (ml)	252 ± 83	237 ± 78	177 ± 36	0.0039
ESV (ml)	192 ± 60	162 ± 73	100 ± 36	0.0005
EF	0.24 ± 0.08	0.33 ± 0.10	0.44 ± 0.13	0.0004
LVM (g)	327 ± 79	327 ± 76	269 ± 57	0.029
Sphericity	1.6 ± 0.2	1.6 ± 0.2	1.8 ± 0.2	0.01
Patients Initially Taking Standard Therapy (n = 10)				
Heart rate (beats/min)	87 ± 12	86 ± 13		0.84
Systolic BP (mm Hg)	110 ± 16	109 ± 17		0.84
EDV (ml)	288 ± 76	263 ± 69		0.14
ESV (ml)	219 ± 65	204 ± 68		0.083
EF	0.24 ± 0.08	0.25 ± 0.08		0.50
LVM (g)	303 ± 95	318 ± 98		0.41
Sphericity	1.6 ± 0.2	1.4 ± 0.2		0.092
All Patients Studied at 18 mo of Metoprolol Therapy (n = 20)				
Heart rate (beats/min)	88 ± 13		74 ± 11	0.0006
Systolic BP (mm Hg)	117 ± 26		129 ± 22	0.022
EDV (ml)	247 ± 76		186 ± 48	0.0067
ESV (ml)	188 ± 57		111 ± 44	0.0006
EF	0.24 ± 0.07		0.41 ± 0.13	0.0002
LVM (g)	333 ± 85		275 ± 53	0.011
Sphericity	1.5 ± 0.2		1.7 ± 0.2	0.0001

BP = blood pressure; sphericity = major/minor axis ratio (see text); other abbreviations as in Table 1.

ness of breath and edema) in the first few weeks of beta-blocker titration. Previous trials (5,20) have shown that left ventricular function continues to improve even beyond 3 months of therapy. To our knowledge, our study is the first to demonstrate that this continued improvement is associated with regression of hypertrophy and favorable left ventricular remodeling at 18 months.

The mechanism by which beta-adrenergic blockade improves left ventricular systolic function is not yet clear. For many years the predominant theory was based on the observation that $beta_1$-cell surface receptors are downregulated in heart failure (6,21,22). This downregulation probably occurs as a protective mechanism against the long-term sympathetic stimulation and its possible toxic effects (22,23). Upregulation of these receptors and renewed responsiveness to beta-agonist stimulation have been demonstrated after beta-blockade with metoprolol (6). However, although upregulation may play a role in exercise and stress responsiveness (23) it cannot explain the improvement in rest left ventricular function, for several reasons. First, if improved left ventricular systolic function is to be attributed to an increased sensitivity to sympathetic stimulation, heart rate should increase along with the increased contractility (1,4,5,10). Instead, heart rate decreases with beta-blocker therapy. Second, if improved function is to be attributed to an increase in beta-receptor density, a direct relation between receptor density and systolic function should exist. However, beta-receptor density increases rapidly within a few days of beta-blockade, but, as shown in the present study, left ventricular function does not improve significantly until after 1 month of therapy (1,23). Finally, some beta-blocking agents have been shown to improve left ventricular function without receptor upregulation (23,24). Thus, other secondary mechanisms must be at work, including alterations in myocardial metabolism (1,5), inhibitory actions on the renin-angiotensin system (1), inhibition of endothelin and cytokine release (1,25), improved calcium transport within the myocyte (26) or cellular effects on protein synthesis, message expression and function of the mitochondria or sarcoplasmic reticulum.

Thus, the initial mild depression of ventricular function may be due to the negative inotropic properties of beta-receptor blockade. During initial titration to larger doses, the left ventricle may actually be more depressed, although we did not perform echocardiography at 1 to 2 weeks of therapy to examine this. Secondary effects of beta-adrenergic blocking agents may then occur after a few weeks of therapy. These secondary effects, which probably represent healing and improvement in myocyte function, begin to offset the negative inotropic effect of beta-receptor blockade, making the heart more efficient and improving its contractility and relaxation. Further research will help to elucidate these secondary mechanisms of action of beta-blockade in patients with heart failure.

Effect of metoprolol on left ventricular mass. The results of the present study demonstrate that long-term therapy with the beta-antagonist metoprolol results in regression of left ventricular hypertrophy. In previous studies left ventricular hypertrophy has been shown to be an independent risk factor for cardiovascular events and increased mortality (13,14). Left ventricular hypertrophy also is associated with decreased coronary flow reserve (27), decreased subendocardial perfusion (27), reduced coronary flow/g of tissue (28) and increased myocardial oxygen consumption (29), factors that may favor the development of myocardial ischemia. Thus, it is attractive to speculate that regression of hypertrophy might reduce cardiovascular risk and ischemia (30).

Key factors producing myocardial hypertrophy include pressure or volume overload and myocardial stimulation by angiotensin II, which acts through such local growth factors as transforming growth factor-beta to produce growth (31–35). Endothelin also has been postulated to have a possible role in promoting ventricular hypertrophy (32,33). Some vasodilator agents (hydralazine or hydralazine plus isosorbide dinitrate) have been shown to reduce load and regress hypertrophy in patients with idiopathic dilated cardiomyopathy (36). In addition, angiotensin-converting enzyme inhibitors have been shown to regress hypertrophy in spontaneously hypertensive rats (31,37) and in humans (33).

The role of the adrenergic nervous system in the development of left ventricular hypertrophy is less well defined (33). Some evidence suggests a role for the adrenergic nervous system in the development of hypertrophy: 1) Norepinephrine has been shown in vitro to stimulate protein synthesis and hypertrophy (38); 2) long-term norepinephrine administration induces left ventricular hypertrophy in dogs (39); 3) heart weight/body weight has been shown to be proportional to myocardial catecholamine concentrations in spontaneously hypertensive rats (40); and 4) left ventricular hypertrophy has been associated with a reduced inotropic response to catecholamine levels (41), suggesting possible beta-receptor downregulation or uncoupling, a long-term response to norepinephrine (21–23). Despite these data, it is not clear that norepinephrine is a major contributor to the development of hypertrophy in humans. It is also unclear whether the regression of hypertrophy seen in this study was a primary effect of adrenergic blockade or was due to an indirect effect of the therapy. The response to beta-blockade in patients with hypertrophy due to hypertension has been variable despite reductions in blood pressure (40,42). Thus, indirect effects, such as inhibition of renin-angiotensin (1,32,43), inhibition of cytokine and endothelin release (25,32,33), production of bradykinin (43) or reduction in left ventricular wall stress (1,4,5,10,34,35,44), may have played a role in reducing left ventricular mass in our study patients. Indeed, the reduction in volumes by 3 months of therapy preceded the reduction in mass seen at 18 months. This suggests that reduction in wall stress may play some role in reducing mass. Finally, recent studies have elucidated a biochemical pathway connecting changes in cyclic adenosine monophosphate, the second messenger for beta-adrenergic stimulation, to changes in the *ras* oncogene mitogen-activated protein (RAS-MAP) kinase system, which stimulates several proto-oncogenes. This is an attractive additional theoretic mechanism by which beta-adrenergic blockade could result in alterations in left ventricular mass (45,46). The importance of regression of hypertrophy in these patients with regard to morbidity and mortality and the mechanism by which this occurs deserve further investigation.

Effect of metoprolol on left ventricular geometry. Previous investigators (15,37) have shown that the left ventricle undergoes global changes in size, shape and mass after myocardial infarction, a process known as remodeling. Noninfarcted failing myocardium undergoes similar time-dependent changes (15,18) that have been attributed to side-to-side slippage, increased myocyte length and hypertrophy (15). The result is a shift in left ventricular geometry from a prolate ellipse to a more spherical shape. A spherical ventricle exhibits increased meridional wall stress (15), abnormal distribution of fiber shortening (15), functional mitral regurgitation (16), lessened exercise tolerance (17) and poorer long-term survival (18).

Angiotensin-converting enzyme inhibitors have been shown to slow ventricular enlargement and remodeling after myocardial infarction (15,17,37) and chronic heart failure (47). The present study demonstrates that the addition of long-term beta-blockade with metoprolol to background therapy with angiotensin-converting enzyme inhibitors confers additional benefit by reducing left ventricular volumes and restoring a more normal ventricular geometry. Thus, the present study suggests that beta-blocking agents may not simply slow remodeling, but may actually produce a reversal of maladaptive remodeling, or "reverse remodeling."

Study limitations. Although the first 16 patients entered into this study were randomized in a placebo-controlled, double-blind manner, the remaining 10 patients were not randomized in a similar way. Thus this study is not a randomized investigation. However, the echocardiograms were interpreted in a blinded manner with regard to study medication and time of echocardiography. In addition, the 18-month data were not controlled as patients were crossed over to active drug after 3 months. There was therefore no placebo group for intergroup comparison at 18 months.

We used two-dimensional echocardiography to assess wall mass and volumes. Although this methodology is standard (19,48), use of three-dimensional echocardiography (49,50) or magnetic resonance imaging (51) may be more accurate. However, any errors in measurement would be random, so the use of two-dimensional echocardiography cannot account for statistically significant changes in left ventricular mass and dimensions.

Because five patients in the standard therapy group and six in the metoprolol group had some history of alcohol abuse, it is possible that previous use may have influenced long-term changes. However, this is unlikely because the standard therapy group showed no changes in left ventricular mass, geometry or volumes at 3 months after entry (i.e., at least 6 months since previous alcohol use). All of the metoprolol group

patients had ceased alcohol use at least 6 months before study entry, and most had quit years before entry. These data suggest that alcohol use is probably not a significant factor.

Conclusions. Long-term therapy of dilated cardiomyopathy with beta-adrenergic blockade results in time-dependent improvement in left ventricular ejection fraction, hypertrophy and geometry. Left ventricular volumes and ejection fraction may worsen after initiation of metoprolol but show improvement by 3 months. Regression of left ventricular hypertrophy and restoration of ventricular geometry are apparent by 18 months, suggesting that reverse remodeling of the failing left ventricle is possible. Further studies are needed to define the mechanism by which these favorable changes occur.

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