Long-term $\beta$-Blockade in Dilated Cardiomyopathy

Effects of Short- and Long-term Metoprolol Treatment Followed by Withdrawal and Readministration of Metoprolol

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To evaluate the short- and long-term effects of $\beta$-adrenergic blockade (metoprolol) as well as the reaction to withdrawal and readministration of metoprolol in severe heart failure, 33 patients (25 men and eight women; mean age, 47.6±14.0 years) with dilated cardiomyopathy were studied by right and left heart catheterization, right ventricular biopsy, two-dimensional and Doppler echocardiography, and external pulse recordings. Twenty-six of 33 patients survived more than 6 months, and 24 of the 26 patients improved their functional class (from mean 3.3 to 1.8, p<0.0001). These 24 patients were subjected to withdrawal of metoprolol until the number of symptoms increased and deterioration occurred as observed noninvasively (group 1, n=16), whereas the eight patients did not deteriorate during a 12-month period (group 2). During long-term treatment with metoprolol, there was an increase in ejection fraction from 0.24 to 0.42 (p<0.0001), whereas there was a decrease in the left ventricular (LV) end-diastolic dimension (from 7.3 to 6.4 cm, p<0.0001), in the grade of mitral regurgitation (from 1.7 to 0.4, p<0.0001), and in the grade of tricuspid regurgitation (from 0.6 to 0.05, p<0.007). There was a decrease in pulmonary wedge pressure (from 23.8 to 10.7 mm Hg, p<0.0001), LV end-diastolic pressure (from 24.1 to 13.4 mm Hg, p<0.002), and systolic vascular resistance (from 1,782 to 1,499 dynes/sec/cm, p<0.04). There was an increase in systolic blood pressure (from 116 to 132 mm Hg, p<0.003), cardiac index (from 2.17 to 2.58 l/min/m², p<0.005), and LV stroke work index (from 31 to 65 g · m/m², p<0.0001). During withdrawal of metoprolol, the heart rate and left atrial dimension increased (p<0.0001), whereas ejection fraction decreased (p<0.0001). The 12 (of 16) patients in group 1 who survived the withdrawal period had metoprolol readministered, and subsequently, ejection fraction increased (from 0.23 to 0.33, p<0.002). Patients had a low number of ventricular $\beta$-adrenergic receptors compared with healthy control subjects (30.3±2.9 vs. 97.4±8.7 fmol/mg protein, p<0.001), but long-term treatment with metoprolol caused a moderate up-regulation (from 30.3±2.9 to 49.0±7.1 fmol/mg protein, p<0.05), which may facilitate a more normal response to sympathetic stimulation. We conclude that metoprolol had a beneficial clinical and hemodynamic long-term effect in patients with dilated cardiomyopathy. Withdrawal was deleterious in two thirds of the patients, and survivors benefited from readministration of the drug. (Circulation 1989;80:551–563)

The concept that long-term $\beta$-blockade may be useful in some forms of severe heart failure due to dilated cardiomyopathy was introduced by our group in 1975.1 The first report was followed by further studies confirming the original observations.2-4 A recent review supports this concept from a pathophysiologic point of view and from accumulated clinical experience.5

The concept, however, has been questioned by some investigators who were not able to reproduce our observations in controlled short-term studies.6-7 Later, other investigators confirmed our data on clinical findings, ejection fraction, and exercise tolerance in controlled long-term studies.8,9 However, systematic analyses of short- and long-term hemodynamic effects of $\beta$-blockade, clinical changes, tolerance, and survival as well as effects of $\beta$-blocker
withdrawal and readministration have been lacking in representative patient studies. The present study was undertaken to answer these questions.

Methods

Patient Population

Between June 1979 and July 1984, we placed 33 consecutive patients with idiopathic dilated cardiomyopathy in a treatment regimen with metoprolol in addition to conventional treatment regimen for heart failure. The patients were followed up until February 1987 (Figure 1). All patients had experienced at least one episode of heart failure requiring short-term hospitalization. They were all symptomatic at the start of β-blocker treatment. Sixteen patients were categorized as New York Heart Association (NYHA) functional Class IV, 15 in functional Class III, and two patients in functional Class II (Figure 2). Improvement or deterioration was assessed in each patient in an unblinded fashion; however, all patients were evaluated by at least two independent cardiologists. In most cases, however, improvement or deterioration was obvious because of the observed dramatic clinical changes.

All patients above 35 years of age had coronary angiography performed that showed normal coronary arteries in all patients except one in whom a 40% stenosis was seen in an obtuse marginal branch. This patient was included in the study because the minor coronary obstruction was not considered to be the probable cause of the diffuse hypokinesia that was found. In addition to the 33 studied patients, the intention was to treat another two patients having diffuse cardiomyopathy. They were, however, excluded because of three-vessel disease. Included were, thus, 25 men and eight women ranging in age from 17 to 65 years (mean, 47.6±14.0 years). In all patients, acute or chronic myocarditis was excluded by the findings of right ventricular endomyocardial biopsy. In nine of the patients, endomyocardial biopsies were repeated after long-term metoprolol treatment for determination of β-adrenergic receptor density. In 16 patients, repeated morphometric measurements were performed after long-term metoprolol treatment (data not given here).

None of the patients was suspected of alcohol abuse. Concomitant treatment for heart failure is given below. There was an attempt not to change concomitant treatment during the follow-up period because it may complicate interpretation of follow-up data. Inclusion of study patients was performed between 1979 and 1984. During this period, treatment with vasodilators was relatively rare in our department compared with treatment now. During the study, the following medication (mean±SD) was administered before and at the end of β-blocker treatment, respectively: digoxin (0.26±0.03 mg, n=18; 0.26±0.03 mg, n=17), furosemide (140±91 mg, n=23; 102±64 mg, n=18), spironolactone (100±32 mg, n=6; 88±25 mg, n=4), captopril (37.5±0 mg, n=2; 37.5±0 mg, n=2), hydralazine (175±87 mg, n=3; 125±87 mg, n=3), and nitroglycerin (80 mg, n=1; 80 mg, n=1). No patient included in the present study had received long-term treatment with inotropic drugs, anthracyclines, or immunosuppressive drugs. Baseline characteristics are given in Tables 1 and 2 for survivors (n=26) and nonsurvivors (n=7). Mean values for the survivors in NYHA functional Class IV (n=9) are shown separately for comparison with nonsurvivors (all functional Class IV).

Study Protocol

An attempt was made to obtain a hemodynamically stable condition during conventional treatment before initiation of β-blockers, but this was accomplished in only five of the 16 patients of functional Class IV. Subsequently, all patients underwent right and left heart catheterization at rest and right ventricular endomyocardial biopsy; in addition, patients underwent noninvasive investigation by M-mode and two-dimensional echocardiography, pulsed or continuous wave Doppler, phonocardiography, carotid pulse tracing, and apex cardiology. The study was approved by the local Ethical Committee of the Gothenburg University, and participants were informed and gave their consent.

Catheterization

Patients were catheterized in the morning in postabsorptive state. No tranquillizer was routinely given. All medication for heart failure was given 3 hours before the catheterization procedure that included β-blocker administration at the follow-up catheterization. A Swan-Ganz thermodilution catheter was introduced through the internal jugular vein and positioned in the pulmonary artery, and an artery catheter was inserted through the femoral artery.

Pressures were measured by Statham P23 transducer (Cleveland, Ohio) and stored on tape for subsequent automatic data processing. Cardiac output was determined by the thermodilution technique (Cardiac Output Computer, WTI).

Vascular resistance was expressed as dynes·sec·cm−5. Systemic resistance was calculated as

\[ 80 \times (\text{mean arterial pressure} - \text{right atrial pressure})/\text{cardiac output}. \]

Pulmonary vascular resistance was calculated as

\[ 80 \times (\text{pulmonary artery pressure} - \text{mean pulmonary capillary wedge pressure})/\text{cardiac output}. \]

Left ventricular stroke work index was calculated at

\[ 0.0136 \times \text{stroke volume index} \times (\text{systolic blood pressure} - \text{left ventricular end-diastolic pressure}) \]

and expressed as g·m/m².

Two-Dimensional Echocardiography

Two-dimensional echocardiographic recordings of routine views were obtained by an Irex IIIIC Echoscanner equipped with a 2.25- or 3.5-MHz transducer. The recordings were stored on a videorecorder with play-back and slow-motion capa-
Doppler echocardiography was performed in 25 of the 33 patients. We applied pulsed Doppler integrated with the two-dimensional echocardiographic image, or continuous wave Doppler (Alfred/Daisy, Vingmed AS, Norway) using a hand-held 2-MHz transducer. The continuous Doppler was used to classify mitral and tricuspid regurgitation into five grades, depending on the intensity of the sound and the spectral intensity of the regurgitant flow compared with the intensity of the flow. Grade 0 denoted no regurgitation or regurgitation limited to a very small part of early systole (prosystolic). Grade 0.5 denoted unimportant regurgitation, with a sound of low intensity, audible only within part of systole (decreasing signal intensity). Grade 1 denoted mild regurgitation, audible during the whole of systole and faintly visible on a paper printout. Grade 2 (moderate regurgitation) was clearly visible on a paper printout. Grade 3 (large regurgitation, intense sound) is normally the largest degree of regurgitation in dilated cardiomyopathy. Grade 4 (severe regurgitation) is only found in mitral or tricuspid valve disease, for example, chordal rupture, with a sound of very large intensity, easily heard and recorded.

M-Mode Echocardiography
M-Mode echocardiographic recordings were obtained at a paper speed of 50 mm/sec. A hand-held 2.25-MHz transducer was used in combination with an Irex II ultrasonograph. The following measurements and calculations were obtained using leading-edge methodology as previously described.11-15 End-diastolic (electrocardiogram R wave) and end-systolic (minimum) left ventricular (LV) dimensions were measured. Fractional shortening was calculated as (end-diastolic−end-systolic)/end-diastolic dimension, and ejection fraction was calculated similarly except volumes instead of dimensions were used. Volumes were calculated by means of the Teichholtz formula.16 Mean velocity of circumferential fiber shortening (mean Vcf) was calculated as fractional shortening divided by LV ejection time, and corrected for heart rate (mean Vcf.) by dividing the used LV ejection time by the square root of the cardiac cycle length (in seconds). Left atrial dimension was measured at valvular closure. LV mass was calculated as described elsewhere,12,13 subtracting the LV cavity volume from the total LV volume including septum and posterior wall and multiplying by 1.05, which is the specific weight for muscular tissue. End-systolic wall stress and the ratio of end-systolic wall stress to end-systolic volume index (or end-systolic volume/body surface area) were calculated as described elsewhere.11,15,17,18 The end-systolic blood pressure was interpolated from the systolic and diastolic blood pressures by means of the carotid pulse tracing, where diastolic blood pressure was set to the upstroke, systolic pressure to the top, and end-systolic pressure at the level of the incisure. LV meridional end-systolic wall stress is equal to \((1.332 \times \text{pressure} \times D)/(4h \times (1+h/D))\), where \(D\) is LV end-systolic dimension, and \(h\) is the mean of the septal and posterior wall end-systolic thicknesses.

Pulse Curves
Carotid and apex pulse curves were obtained on a Mingograph 81 or 82 (Siemens-Elema AB, Copenhagen, Denmark) at a paper speed of 100 mm/sec together with an electrocardiogram (lead II) and a phonocardiogram as previously described.19 Rapid filling wave was measured from the apexcardiogram, and its height was calculated as percentage of the total apexcardiographic height.20 LV ejection time was measured from the carotid pulse upstroke to the incisure and was adjusted for heart rate as percentage of expected normal (LV ejection time percentage).14

Receptor Binding Studies
In nine patients, \(\beta\)-adrenergic receptor density before and after long-term \(\beta\)-blocker therapy was determined in right ventricular endomyocardial biopsies and compared with five donor hearts not used for transplantation. These donors were known to be previously healthy, and macroscopic and microscopic evaluation of the hearts revealed no heart disease. Biopsies containing macroscopic connective tissue were not included in the receptor assay. \(\beta\)-Adrenergic receptors were determined in homogenate of myocardial biopsies (total weight, about 20 mg) with \([^{125}\text{I}]\)iodocyanopindolol (\([^{125}\text{I}]\)ICYP) as radioligand as described earlier.20 The incubation buffer had the following composition (mM): 10 Tris HCl, 2 MgCl\(_2\)/150 NaCl, and 1 ascorbic acid (pH 7.4). Nonspecific binding was determined by the inclusion of radioligand plus 1 \(\mu\)M propranolol. Specific binding represents the difference between total and nonspecific bindings and was greater than 90% at low \([^{125}\text{I}]\)ICYP concentrations (<70 pM). Maximum binding (\(B_{\text{max}}\)) and equilibrium dissociation constant (\(K_d\)) were determined according to Scatchard.21 Protein content was measured by the Lowry technique.22 \([^{125}\text{I}]\)ICYP was obtained from New England Nuclear (Boston, Massachusetts). All other chemicals were of reagent grade and obtained from Sigma Chemical (St. Louis, Missouri).

Metoprolol Administration
Intravenous administration. In the first 19 of the 33 patients, the tolerance of metoprolol injected intravenously was tested during the first catheterization procedure. A maximal dose of 15 mg was given to 19 patients. Hemodynamic measurements were repeated 10–15 minutes after the intravenous injection of metoprolol.

Long-term treatment. After heart catheterization, all patients were given oral metoprolol. Patients in NYHA functional Class IV received titrated
doses beginning with an extremely low, but increasing, dose of metoprolol: days 1–7 (5 mg bid), 8–14 (5 mg tid), 15–21 (10 mg tid), 22–28 (25 mg bid), 29–35 (25 mg tid), 36–42 (50 mg bid), and days 43 and onward (50 mg tid). In the remaining Class II and Class III patients, the initial dose was 25 mg bid and increased to 50 mg tid or 100 mg bid. The aim was a heart rate of 50–70 beats/min. Treatment with vasodilators was never initiated after starting β-blocker therapy. Temporary increase in the dose of diuretics was permitted. Antiarrhythmics were not given to any patient because patients with major ventricular arrhythmias were not included in the study, with one exception.

Metoprolol was given to most patients for 6–20 months (average, 15.9±9.5 months). Three patients received longer treatment (27, 41, and 46 months). Clinical response and noninvasive investigations were used as guidelines when deciding on the time for follow-up investigations. We used different follow-up times because our experience from earlier studies with β-blockers in dilated cardiomyopathy, show a continuous improvement in some patients during a 24-month follow-up.2

At the end of the metoprolol treatment, 22 patients were recatheterized, whereas noninvasive follow-up investigations were performed 2 weeks, 1, 3, and 6 months after initiation of treatment in most patients. In some patients, there were additional 9-, 12-, and 18-month follow-up studies. After catheterization, systematic follow-up by noninvasive investigations was performed before withdrawal of metoprolol and at 2 weeks, 1, 3, 6, 9, and 12 months after medication was withheld. When deterioration was observed, metoprolol was readministered. Deterioration after withdrawal of metoprolol was defined as clinical deterioration by at least one NYHA functional class plus at least two of the following alternatives: 1) decrease of ejection fraction of 0.05 or more, 2) increase of left atrial diameter by 3 mm or more, 3) reappearance or increase in grade of mitral or tricuspid regurgitation, 4) increase of rapid filling wave ratio by 25% or more. When there was no deterioration after 12 months, metoprolol was permanently withdrawn, and these patients had only occasional further follow-up studies. In patients who deteriorated after withdrawal of metoprolol, medication was readministered with a follow-up of 6–12 months, and the patients were monitored noninvasively at 3-month intervals.

Metoprolol was withdrawn in 24 of 26 patients (mean observation time, 7.7±4.9 months; range, 1–18 months). One patient moved out of the catchment area and was therefore not eligible for withdrawal. One patient who suffered from paroxysmal ventricular tachycardia before metoprolol treatment was free of arrhythmias while on long-term metoprolol treatment and was excluded from withdrawal because of risk of recurrent ventricular tachycardia. Withdrawal was continued until increased symptoms occurred in addition to deterioration of noninvasive hemodynamic variables. Patients were grouped according to results of withdrawal: group 1 (n=16), those who died or deteriorated within 18 months; and group 2 (n=8), those who did not deteriorate.

Data Analysis and Statistical Methods

Mann-Whitney's nonparametric U test was used for group comparisons. Hemodynamic baseline variables were compared: 1) between those who tolerated metoprolol and survived for more than 6 months and those who did not tolerate metoprolol and died within 3 months or had heart transplantation; 2) between those patients of functional Class IV who died and those who survived.

Paired Student's t test was used to evaluate intraindividual changes. Noninvasive follow-up data at varying intervals during long-term treatment with metoprolol were compared with entry variables. A similar analysis was carried out during the withdrawal phase of metoprolol, comparing the corresponding variables before withdrawal. After readministration, the various variables were compared with the corresponding variables before readministration. In a separate analysis, using Mann-Whitney's nonparametric U test, patients who deteriorated after withdrawal were compared with patients who did not deteriorate.

Invasive hemodynamic data at entry were compared with follow-up data using Student's paired two-tailed t test, and finally, the effect of short-term metoprolol treatment was compared with long-term treatment in the same individuals.

Results

Clinical Findings

Twenty-six of 33 patients survived more than 6 months, and seven died within 3 months (Figure 1). One patient had heart transplantation but died later from sepsis. Five of the nonsurviving patients did not tolerate oral metoprolol even in small doses (5 mg bid). Two patients initially tolerated a low dose of metoprolol but died during the titration period; they died of right ventricular failure after massive pulmonary embolism that had necessitated the withdrawal of metoprolol. Univariate analyses of hemodynamic variables are given in Table 1.

Survivors tended to be older than nonsurvivors (50.1±10.4 vs. 38.3±11.5 years, p=NS), and their weight was significantly higher (77.5±15.2 vs. 62.2±8.8 kg, p=0.016). Nonsurvivors were all in NYHA functional Class IV (Figure 2) and had low baseline systolic and diastolic blood pressures in comparison with survivors and even with those in functional Class IV (Table 1). This may be due to the poorer systolic function in nonsurvivors evidenced by lower ejection fraction and stroke work index and by LV ejection time being significantly shorter even in comparison with survivors in functional Class IV. Except for the lower systolic func-
tion and inability to maintain a systolic blood pressure in nonsurvivors, only right atrial pressure at rest was higher than that in survivors; otherwise, differences in variables between the groups were not significant.

When surviving Class IV patients were compared with nonsurviving Class IV patients, systolic and diastolic blood pressures and LV ejection time percentage were found to be significantly lower in the latter group, possibly explaining the lack of tolerance for metoprolol in that group. Improvement in functional class was seen in 24 of the surviving 26 patients (from functional Class 3.3 to functional Class 1.8, *p*<0.0001), the seven nonsurvivors all died of progressive heart failure (Figure 2).

Generally, only small changes in clinical condition were seen during the first month on β-blocker treatment. As a rule, all patients in Class IV suffered from temporary systemic arterial hypotension and fatigue. However, very few complained of increased dyspnea. Temporary increase in diuretics was most commonly found in patients with increased right heart failure. In those patients, reduction of diuretics was possible at a later stage. Patients with a marked degree of right heart failure and tricuspid regurgitation had a slower improvement rate compared with patients without. Most of those requiring more than 6 months of follow-up on metoprolol treatment had right heart failure at entry. Functional Class III patients, with no signs of right heart failure and mitral regurgitation of grade 1 or less, showed the highest rate of improvement. After 3 months of metoprolol treatment, clinical improvement was obvious in all Class III patients and likewise in about half of those belonging to Class IV at entry. Consequently, diuretics could be withdrawn or the dose reduced in some patients. The final metoprolol dose varied from 25 tid to 100 mg bid with a mean dose of 154±43 mg.

**Invasive Hemodynamic Findings**

**Short-term intravenous metoprolol administration.** Short-term administration of 15 mg metoprolol

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**Table 1.** Comparison Between Baseline Invasive and Noninvasive Hemodynamic Variables in Survivors and Nonsurvivors

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>HR (beats/min)</td>
<td>94±15</td>
<td>NS</td>
<td>101±23</td>
<td>NS</td>
<td>96±14</td>
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<td>Systolic BP (mm Hg)</td>
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<td>0.001</td>
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<td>Diastolic BP (mm Hg)</td>
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<td>0.024</td>
<td>67±7</td>
<td>0.049</td>
<td>80±13</td>
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<td>CI (l/min/m²)</td>
<td>2.25±0.50</td>
<td>0.047</td>
<td>1.77±0.49</td>
<td>NS</td>
<td>1.79±0.33</td>
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<td>RAP (mm Hg)</td>
<td>5.8±5.6</td>
<td>0.018</td>
<td>11.3±3.9</td>
<td>NS</td>
<td>9.2±7.7</td>
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<td>PCWP (mm Hg)</td>
<td>22.6±9.7</td>
<td>NS</td>
<td>26.6±8.8</td>
<td>NS</td>
<td>28.6±7.0</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>21.6±8.6</td>
<td>NS</td>
<td>23.8±5.9</td>
<td>NS</td>
<td>26.2±6.4</td>
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<tr>
<td>PAP (mm Hg)</td>
<td>31.8±10.1</td>
<td>NS</td>
<td>37.7±6.7</td>
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<td>37.8±8.0</td>
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<td>LVSWI (g · m/m²)</td>
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<td>18.5±5.3</td>
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<td>23.2±8.9</td>
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<td>LVEDD (cm)</td>
<td>7.25±0.88</td>
<td>NS</td>
<td>7.37±0.76</td>
<td>NS</td>
<td>7.13±0.70</td>
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<td>FS (%)</td>
<td>11.6±2.6</td>
<td>0.006</td>
<td>7.9±3.3</td>
<td>NS</td>
<td>9.9±2.0</td>
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<tr>
<td>EF</td>
<td>0.24±0.05</td>
<td>0.008</td>
<td>0.17±0.07</td>
<td>NS</td>
<td>0.21±0.04</td>
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<td>Mean Vcf (circumference/sec)</td>
<td>0.50±0.13</td>
<td>0.074</td>
<td>0.41±0.18</td>
<td>NS</td>
<td>0.45±0.14</td>
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<td>LVET (%)</td>
<td>91±7</td>
<td>0.0008</td>
<td>78±8</td>
<td>0.020</td>
<td>89±9</td>
</tr>
</tbody>
</table>

All values are mean±SD.

A, comparison between 26 survivors (all) and seven nonsurvivors; B, comparison between nine survivors (NYHA Class IV) and seven nonsurvivors; HR, heart rate; NYHA, New York Heart Association; BP, blood pressure; CI, cardiac index; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary arterial pressure; LVSWI, left ventricular stroke work index; LVEDD, left ventricular end-diastolic dimension; FS, fractional shortening; EF, ejection fraction; Vcf, velocity of circumferential fiber shortening; LVET, left ventricular ejection time, as percentage of that expected from heart rate.
was studied in 19 patients and compared with the long-term effect (Figure 3). The administration of metoprolol caused a decrease in heart rate and arterial systolic blood pressure, whereas LV end-diastolic pressure did not change.

**Long-term treatment.** Intra-arterial systolic pressure increased during long-term metoprolol treatment (Table 2). Pulmonary wedge pressure decreased from 23.8 to 10.7 mm Hg \((p<0.0001)\) and LV end-diastolic pressure from 24.1 to 13.4 mm Hg \((p<0.002)\). Systolic blood pressure increased from 116 to 132 mm Hg \((p<0.003)\), cardiac index increased from 2.17 to 2.58 l/min/m² \((p<0.005)\), and stroke volume index increased from 24.2 to 39.7 ml/m² \((p<0.0001)\). Calculated systemic vascular resistance decreased from 1,782 to 1,499 dynes * sec/ cm² \((p<0.003)\), whereas pulmonary vascular resistance did not change. An increase in body weight from 77.5 to 81.7 kg \((p<0.008)\) may reflect an increase in muscle mass because less severe edema was present at follow-up (Table 2).

**Noninvasive Hemodynamic Findings**

**Long-term treatment.** During long-term treatment with metoprolol (Table 3), heart rate decreased, whereas blood pressure did not change significantly after 45 minutes of supine rest, which is in contrast to intra-arterial pressures during catheterization. There was an improvement of systolic LV function with increased fractional shortening, ejection fraction, and mean Vcf. End-diastolic and end-systolic LV dimension decreased, whereas end-systolic wall stress decreased (from 151±39 to 114±45 10³ dynes/cm², \(p=0.0001)\), and end-systolic wall stress/volume index increased (from 1.4±0.3 to 1.8±0.3 10⁷ dynes/ml, \(p=0.0001)\), also indicating an improved contractility. LV mass tended to become reduced after treatment. Although measurements at end diastole and end systole were not reported, the improvement in contractility suggests a reduction in LV mass.

**FIGURE 2.** Flow chart of New York Heart Association (NYHA) functional classification and mortality during long-term treatment, withdrawal, and readministration of metoprolol. ***p<0.001.

**FIGURE 3.** Bar graphs of comparison of the effect of intravenous administration of 15 mg metoprolol and long-term oral administration of metoprolol in 19 patients on heart rate, systolic blood pressure (SBP), left ventricular end-diastolic pressure (LVEDP), and cardiac index. **p<0.01; ***p<0.001.
TABLE 2. Invasive Hemodynamic Variables Before and After
Long-term Metoprolol Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=22)</th>
<th>Long-term treatment (n=22)</th>
<th>p</th>
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</thead>
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<tr>
<td>HR (beats/min)</td>
<td>93±13</td>
<td>68±12</td>
<td>0.0001</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>116±20</td>
<td>132±17</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79±12</td>
<td>75±10</td>
<td>NS</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>98±18</td>
<td>101±17</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>2.17±0.51</td>
<td>2.58±0.43</td>
<td>0.005</td>
</tr>
<tr>
<td>SVI (ml/m²)</td>
<td>24.2±8.1</td>
<td>39.7±9.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>SVR (dynes. · sec/cm²)</td>
<td>1,782±443</td>
<td>1,499±318</td>
<td>0.035</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5.9±5.8</td>
<td>2.5±3.0</td>
<td>0.002</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>23.8±9.4</td>
<td>10.7±6.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>24.1±7.3</td>
<td>13.4±9.0</td>
<td>0.002</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>34.6±8.1</td>
<td>20.7±6.7</td>
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<td>PVR (dynes · sec/cm²)</td>
<td>201±59</td>
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<td>LVSWI (g · m²)</td>
<td>31.0±13.0</td>
<td>64.9±20.1</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

All values are mean±SD.

HR, heart rate; BP, blood pressure; MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; SVR, stroke volume resistance; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; LVSWI, left ventricular stroke work index.

An improvement of diastolic function was evidenced by reduced left atrial dimension and decreased rapid filling wave. An important decrease of mitral regurgitation probably contributed to the reduction of atrial dimension. Also, the degree of tricuspid leakage was reduced after treatment.

The time course of the changes in ejection fraction, left atrial diameter, and rapid filling wave was analyzed. Only minor changes in left atrial size were observed until 3 months of follow-up, and maximum changes were observed after 6 months. Only minor changes in ejection fraction were seen after 1 month, and about 50% of the improvement occurred after 3 months. In contrast, the changes in rapid filling were observed already after 1 month, with only small additional changes during the following 5–12 months. When rapid filling wave ratio in all patients, in whom an apex curve could be obtained, was plotted against pulmonary wedge pressure, it was found that a fall in pulmonary wedge pressure was accompanied by a decrease in rapid filling wave ratio (Figure 4).

The regression line of the relation between mean Vcf, and end-systolic wall stress was significantly changed (p<0.01) by metoprolol treatment, and for most patients, this relation was shifted to the left and upward (Figure 5).

Withdrawal of metoprolol. After withdrawal of metoprolol in 24 patients, four died (Figure 1). These four patients were in functional Class III before β-blocker treatment, and they had progressed to functional Class II (three patients) and

TABLE 3. Comparison of Noninvasive Variables During Treatment, Withdrawal and Readministration of Metoprolol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (n=26)</th>
<th>Treatment (n=26)</th>
<th>Before withdrawal (n=24)</th>
<th>No treatment (n=24)</th>
<th>Before readministration (n=12)</th>
<th>Treatment (n=12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (mo)</td>
<td>15.9±9.5</td>
<td></td>
<td></td>
<td>7.7±4.9</td>
<td>6.3±3.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA Class</td>
<td>3.3±0.6</td>
<td>1.8±0.7</td>
<td></td>
<td>2.8±1.1</td>
<td>3.3±0.8</td>
<td>2.0±0.6</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>80±16</td>
<td>57±10</td>
<td></td>
<td>77±14</td>
<td>84±21</td>
<td>54±8</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122±17</td>
<td>128±16</td>
<td></td>
<td>125±15</td>
<td>119±20</td>
<td>129±15</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>79±13</td>
<td>81±10</td>
<td></td>
<td>84±12</td>
<td>84±14</td>
<td>83±13</td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>7.26±0.86</td>
<td>6.44±1.11</td>
<td></td>
<td>6.81±1.19</td>
<td>7.28±0.79</td>
<td>6.91±0.77</td>
<td></td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>6.40±0.83</td>
<td>5.14±1.12</td>
<td></td>
<td>5.77±1.35</td>
<td>6.48±0.81</td>
<td>5.81±0.80</td>
<td></td>
</tr>
<tr>
<td>FS (%)</td>
<td>12.0±3.2</td>
<td>21.0±7.5</td>
<td></td>
<td>16.1±7.4</td>
<td>11.0±3.4</td>
<td>16.1±3.5</td>
<td></td>
</tr>
<tr>
<td>EF</td>
<td>0.25±0.06</td>
<td>0.41±0.13</td>
<td></td>
<td>0.32±0.13</td>
<td>0.23±0.06</td>
<td>0.33±0.07</td>
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</tr>
<tr>
<td>Mean Vcf</td>
<td>0.51±0.13</td>
<td>0.73±0.22</td>
<td></td>
<td>0.61±0.25</td>
<td>0.45±0.12</td>
<td>0.58±0.10</td>
<td></td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>5.16±0.93</td>
<td>4.52±0.76</td>
<td></td>
<td>4.80±0.83</td>
<td>5.24±0.40</td>
<td>4.94±0.49</td>
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</tr>
<tr>
<td>MR (grade)</td>
<td>1.7±0.9</td>
<td>0.4±0.6</td>
<td></td>
<td>1.4±1.2</td>
<td>2.2±1.0</td>
<td>0.6±0.9</td>
<td></td>
</tr>
<tr>
<td>TR (grade)</td>
<td>0.6±0.9</td>
<td>0.1±0.3</td>
<td></td>
<td>0.4±0.8</td>
<td>0.5±0.9</td>
<td>0.2±0.4</td>
<td></td>
</tr>
<tr>
<td>RFW (%)</td>
<td>12.0±4.5</td>
<td>6.1±3.5</td>
<td></td>
<td>11.3±13.4</td>
<td>17.7±17.7</td>
<td>5.5±4.2</td>
<td></td>
</tr>
<tr>
<td>LVET (%)</td>
<td>87±6</td>
<td>92±8</td>
<td></td>
<td>91±8</td>
<td>89±9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are mean±SD.

NYHA, New York Heart Association; HR, heart rate; BP, blood pressure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; FS, fractional shortening; EF, ejection fraction; Vcf, velocity of circumferential shortening; LAD, left atrial diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; RFW, rapid filling wave; LVET, left ventricular ejection time.
ministration of metoprolol (range of follow-up, 2.5–6.5 years).

All variables but blood pressure, degree of tricuspid regurgitation, and rapid filling wave ratio worsened during the withdrawal period (Table 3). When the temporary changes in noninvasive variables were followed up during withdrawal of long-term metoprolol treatment, the pattern of effect was reversed compared with the metoprolol treatment period. Ejection fraction decreased within 2 weeks (from 0.41 to 0.37, \( p<0.01 \)) and remained significantly lower than the baseline level. Left atrial dimension increased slowly (a significant increase by 1.9 mm, \( p<0.05 \), was noted 6 months after withdrawal), and the rapid filling wave did not deviate significantly for the whole group during withdrawal, although there was a tendency toward an increase (\( p=0.067 \)). Patients who deteriorated (group 1) displayed a pattern more obviously congruent to that seen during the long-term metoprolol treatment period than did the whole group and particularly the patients of group 2 (Figure 6). At baseline, before withdrawal of metoprolol, there was a significantly lower ejection fraction (Figure 6A) and a larger left atrial dimension (Figure 6B) in group 1 than in group 2. An increase in rapid filling wave ratio was a late phenomenon that indicated severe heart failure (Figure 6C). Further withdrawal of metoprolol caused an increase or reappearance of mitral and tricuspid regurgitation in some patients.

The patients who died during the withdrawal period all deteriorated at least one NYHA functional class. In addition, deterioration was seen in the hemodynamic variables. Another three patients were severely decompensated and required hospitalization.

**Readministration of metoprolol.** Metoprolol was given to all 12 patients in group 1 who survived the

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**Figure 4.** Plot of comparison between pulmonary capillary wedge pressure in millimeters of mercury and rapid filling wave ratio in percent before and after long-term metoprolol treatment.

**Figure 5.** Plot of relation between end-systolic wall stress and rate-corrected mean velocity of circumferential fiber shortening (mean Vcf). Panel A: Comparison of regression lines between patients before metoprolol treatment (A) and after metoprolol treatment (B) in relation to reference group (C) (with 95% confidence intervals). The regression equations were A: \( y=0.547-0.000832x \); B: \( y=1.17-0.00357x \) (\( p<0.01 \), A vs. B); C: \( y=1.53-0.00713x \) (\( p=NS \), B vs. C) (\( p<0.001 \), \( p<0.01 \) vs. NS). Panel B: Individual patients before and after long-term \( \beta \)-blockade.
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Figure 6. Bar graphs of comparison of ejection fraction, left atrial diameter, and rapid filling ratio after long-term metoprolol treatment and during withdrawal of metoprolol. Comparisons were made between the patients who died or deteriorated (group 1) and those who remained unchanged (group 2) after withdrawal of metoprolol (up to 6 months), and finally the mean withdrawal time for group 1 (5.8±5.0 months) and mean follow-up time for group 2 (11.0±1.9 months), respectively.

withdrawal period. The changes observed during 6–12 months (average, 6.3 months) of follow-up were similar to those observed during the first metoprolol treatment period (Table 3). The increase in ejection fraction from 0.23 to 0.33 (p<0.002) and the decrease in left atrial diameter from 5.24 to 4.94
cm (p<0.040) were less pronounced. However, the decrease in rapid filling wave ratio was of the same magnitude as during the initial treatment period (from 17.7% to 5.5%, p<0.028).

**β-Receptor Binding Studies**

Total β-adrenergic receptor density in ventricular myocardium before the start of β-blocker therapy was 30.3±2.9 fmol/mg protein. This was compared with the density of healthy donor hearts (97.4±8.7 fmol/mg of protein), and the difference was highly significant (p<0.001, Table 4) After long-term treatment with metoprolol, the receptor density amounted to 49±7.1 fmol/mg of protein, that is, a value that is about 60% higher than before treatment (p<0.05).

**Discussion**

The present data indicate that improvement after long-term metoprolol treatment is a slow process that takes from 3 to 12 months depending on the severity of the myocardial dysfunction. The findings are in general agreement with earlier reports from our group and others.1,2,4,8,9 Ikram and Fitzpatrick6 and Currie et al7 did not see effects in 1 month. The improvement after withdrawal of metoprolol therapy seems to be long-lasting, in contrast to withdrawal of treatment of most vasodilators and inotropic drugs, during which time hemodynamic variables often quickly return to baseline values.23 The improvement in exercise tolerance also seems to be of greater magnitude8 than after treatment with vasodilators or inotropic drugs.24 For example, after long-term treatment with inotropic drugs, deterioration occurs in comparison to baseline, indicating that the underlying disease continues despite treatment.24 The reason for this difference may be a more profound change in myocardial function, induced by long-term β-blockade. The fall in systemic vascular resistance, the fall in filling pressures, and the increase in cardiac index, secondary to treatment with vasodilators, do not necessarily imply improved myocardial contractility. In the present study with metoprolol, only a modest decrease in calculated systemic resistance was seen. This fall in resistance is probably an indirect effect of metoprolol because metoprolol lacks vasodilating properties and because the dose of vasodilators was unchanged between the two measurements. The fall in systemic vascular resistance may be secondary to a decrease in circulating norepinephrine or to a decrease in renin and angiotensin levels secondary to β-blockade, as could be seen after long-term treatment with β-blockade in hypertensive patients.25 Systolic blood pressure measured invasively at follow-up increased significantly, whereas the rise in systolic blood pressure measured noninvasively was not significant (Tables 2 and 3). The reason for these findings may be that the invasive procedure per se causes sympathetic stimulation in contrast to the less stressful noninvasive procedure. A more vigorous systolic contraction at the follow-up catheterization due to up-regulation of β-adrenergic receptors26 may result in a higher resting systolic blood pressure. A stronger sympathetic activity may also be reflected in the tendency to higher heart rate at follow-up catheterization compared with follow-up noninvasive investigations.

There is a contrasting effect between short- and long-term administration of metoprolol; the former produces an acute depression of systolic function, and the latter produces a marked improvement of systolic function. These findings are in contrast with the hemodynamic effects observed with short- and long-term administration of vasodilators, although they are in agreement with the improvement after long-term treatment with angiotensin converting enzyme inhibitors.23 The reason why metoprolol did not change left ventricular filling pressure remains obscure, but the phenomenon may be due to a prolonged filling period and improvement in compliance. Ikram et al27 showed that the decrease in stiffness is constant after short-term administration of acebutalol to patients with dilated cardiomyopathy. This finding may explain a greater ventricular diastolic volume without an increase in filling pressure.28 A decrease in systolic shortening after short-term administration of β-blockade may therefore not cause a marked fall in stroke volume because the ventricle with a greater end-diasstolic volume could produce a similar stroke volume with less systolic shortening.

Among the most important variables discriminating between survivors and nonsurvivors were fractional shortening or ejection fraction, LV ejection time percentage, right atrial mean pressure, systemic blood pressure, and stroke work index. We also used heart function variables that are claimed to be load independent.17 End-systolic wall stress/volume index increased during long-term treatment, indicating an improved systolic function.18
values for mean Vcf were plotted against end-systolic wall stress, there was a significant upward shift in the regression line obtained after treatment compared with pretreatment, indicating improved contractility after long-term treatment with metoprolol (Figure 5A). With treatment, the myocardium could use less of preload reserve, as indicated by an unchanged (left upward shift) or improved (upward shift) relation between Vcf and wall stress (Figure 5B).

Absence of an increase in left ventricular filling pressure after short-term administration of metoprolol may explain the lack of increase of dyspnea in most patients during titration of metoprolol. The very early decrease in rapid filling wave ratio, seen already after 1 month of treatment with metoprolol, may indicate a fall in left ventricular end-diastolic pressure. Clinically, we observed that relief of exertional dyspnea during daily activity was an early finding during long-term treatment with metoprolol. This finding was, however, not evaluated systematically in the present study, nor were left ventricular filling pressures measured in the early follow-up period.

How strong is the evidence that improvement was caused by the metoprolol treatment? Spontaneous improvement has been reported to occur in patients with dilated cardiomyopathy. Regardless of cause, heart failure may worsen or improve progressively. To minimize the influence from spontaneous improvement on the interpretation, only patients who had a stable, poor clinical and hemodynamic condition or had had an exacerbation ongoing for 1 month or more were included. Myocarditis has been proposed as a major cause of dilated cardiomyopathy. Chronic active myocarditis was excluded by right ventricular endomyocardial biopsy. However, because some patients may have been in the healing phase after myocarditis at the time of the first biopsy, improvement could be the result of an ongoing healing process.

In 16 of the 24 patients in whom long-term metoprolol treatment was withdrawn, the findings indicate that spontaneous improvement due to healing myocarditis or improvement due to concomitant treatment could not be the only causes of improvement. The slow improvement during the first treatment period, followed by a relatively slow onset of deterioration during the withdrawal period, followed by new improvement during the second treatment period, indicate a cause and effect relation between improvement and metoprolol treatment in these patients.

Mode of Action of Long-term β-Blockade

The knowledge of how β-blockers exert their possible beneficial effect is limited. The following mechanisms could be hypothesized:

1) During chronic heart failure, there is a high metabolic load on the myocardium despite a low mechanical output. Recent data indicate limitation of aerobic function of the myocardium with limitation of production of ATP in the mitochondria. Short-term β-blockade decreases MVO₂ by decreasing heart rate and systolic blood pressure, and possibly also by a direct reduction of heat production. All these effects are mediated through β-receptor blockade, which is the dominating property of metoprolol. Shortage of energy production in the myocardium may cause a catabolic state with a negative protein synthesis that may be unfavorable because there is a need for compensatory hypertrophy to develop in patients with severe dilatation. Morphometric studies on endomyocardial biopsies before and after long-term metoprolol treatment showed an increase in myocardial diameter (unpublished observation), suggesting that metoprolol may have an advantageous metabolic effect.

2) Chronically elevated levels of circulating catecholamines and a high local release of norepinephrine may worsen heart failure due to direct toxic effects on the myocytes.

3) There is a marked down-regulation of β-receptor density in severe heart failure. Down-regulation is thought to be a secondary phenomenon to overstimulation of the β₁-adrenergic receptor. Our group and others have shown that in patients after long-term treatment with metoprolol there is a receptor up-regulation to a level somewhat below the value seen in normal individuals. An increased number of β-receptors after long-term treatment with metoprolol may explain the increase in exercise capacity, described in some studies after long-term β-blockade because a higher number of receptors may exert a stronger response to sympathetic stimulation during exercise. These results in humans agree well with previous data from animal experiments. Because of lack of tissue samples, we have not been able to determine the β₁/β₂-receptor subpopulations and the relative changes in these. However, Bristow et al showed that mainly the β₁-receptor subpopulation is affected in myocardial failure. Recent data also indicate a role for G proteins in cardiovascular disease. These are the proteins that couple the signal generated by receptor occupancy by an agonist to the activation of second messenger effector systems. Minor quantitative changes in stimulatory G proteins (G_s) in dilated cardiomyopathy may be associated with prominent changes in functional activity. Also, the recent findings that G_s not only stimulates adenyl cyclase but also modulates calcium conductance in the heart may indicate that the beneficial influence of β-adrenergic blockade does not only affect adenyl cyclase activity but also calcium conductance. These effector systems may be differently affected by β-blockade.

4) An important reason for secondary prevention with β-blockers after acute myocardial infarction is prevention of sudden death. A large proportion of patients with dilated cardiomyopathy die suddenly because of embolic complications, ventricu-
lar fibrillation, or conduction disturbances. None of the patients died suddenly during long-term treatment, whereas two of four deaths during the withdrawal period were probably due to arrhythmia according to autopsy. The absence of sudden death during long-term β-blockade in the present study is not in accordance with our previous study. However, the follow-up in the present study is much shorter, and patients with problems associated with known severe arrhythmia were, with one exception, not included in the study.

The findings in the present study are encouraging, and they support earlier studies of functional improvement after long-term β-blocker treatment. The deterioration during β-blocker withdrawal in most patients and improvement after reinstitution strongly support a treatment effect and exclude spontaneous improvement. Survival data from our previous studies and from that of Anderson et al indicate that long-term metoprolol treatment may prolong survival, but this is not yet proven in a large prospective randomized trial. A large multicenter and international trial is now in progress.

Limitations of the Study

The present study was nonrandomized and unblinded. This may create bias when classifying a patient according to NYHA functional classes. This classification was, however, performed by two independent cardiologists who were not aware of the hemodynamic measurements. Furthermore, there was a good correlation between the changes in NYHA classes and those of the hemodynamic variables. Even though there was only a limited number of patients available for randomization, we believed that the present design was acceptable because patients act as their own controls.

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**Key Words:** cardiomyopathies • heart failure, congestive • beta-adrenergic receptor blockers • hemodynamics

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