Metoprolol in Dilated Cardiomyopathy: Is It Possible to Identify Factors Predictive of Improvement?

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ABSTRACT

Background: Some controlled clinical trials showed a beneficial effect of beta-blockers on symptoms, exercise tolerance, and left ventricular function in dilated cardiomyopathy. The purpose of this study was to investigate if there are clinical variables at baseline that could predict a favorable response to long-term metoprolol therapy.

Methods and Results: Since November 1987, 94 consecutive patients with dilated cardiomyopathy and left ventricular ejection fraction less than 0.40 were treated with metoprolol (mean final dosage, 136 ± 32 mg) associated with tailored medical therapy with digitalis, diuretics, and angiotensin-converting enzyme inhibitors. Eighty-four surviving patients had a complete 2-year noninvasive follow-up period. Ten patients died or were transplanted before the final assessment. Improvement was defined according to a clinical score based on left ventricular ejection fraction (increase ≥ 10 U), left ventricular end-diastolic diameter (decrease ≥ 10%), regression of restrictive filling pattern, New York Heart Association functional class, exercise tolerance (increase ≥ 2 minutes), and cardiothoracic ratio (decrease ≥ 10%). According to these criteria, 48 patients (51.1%) were classified as improved. Multivariate analysis identified a group of patients with a history of mild hypertension (blood pressure between 140/90 and 170/100 mmHg) and significantly higher probability of improvement with long-term metoprolol (odds ratio [OR], 2.22; 95% confidence interval, 1.25–3.94; P = .007). Among the 71 patients with normal blood pressure (< 140/90 mmHg), heart rate in upright position (100 vs 75 beats/min: OR, 2; 95% confidence interval, 1.38–4.94; P = .003), left ventricular ejection fraction 0.20–0.33 versus less than 0.20 (OR, 4.72; 95% confidence interval, 1.06–21.04; P = .042), and New York Heart Association class I–II versus III–IV (OR, 2.74; 95% confidence interval, 0.97–7.75; P = .05) were significantly associated with a positive response to metoprolol. At baseline, both supine and upright heart rate were significantly higher in patients who improved, but heart rate in the upright position was the most significant predictor of improvement in patients with normal blood pressure at multivariate analysis.

Conclusions: According to the authors' logit model, patients with a history of mild hypertension or with a higher resting heart rate, associated with controlled symptoms of heart failure (New York Heart Association class I–II) or moderate to severe left ventricular ejection fraction (range, 0.20–0.33) showed a remarkable probability of long-term (2-year) improvement on metoprolol.

Key Words: heart failure, beta-blockers, heart rate.

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Beta-blockers were considered for many years to be contraindicated in patients with chronic heart failure, mainly because the activation of the sympathetic nervous system was considered an essential support for the failing heart. Recently, however, there has been an increasing interest in the use of beta-blockers in the treatment of heart failure (1). Some controlled and uncontrolled clinical trials showed that, in patients with idiopathic dilated cardiomyopathy, beta-blockers can alleviate symptoms, improve exercise tolerance and left ventricular function, and probably prolong survival (2–13).

Conversely, only a few small studies (12,14–16) have been performed to systematically evaluate the possible predictors of good response to long-term beta-blockers. The purpose of this study is to investigate if there are clinical, hemodynamic, and laboratory variables that could predict a favorable response to long-term metoprolol in patients with dilated cardiomyopathy.

Materials and Methods

Patient Selection

From November 1987 to June 1993, 149 consecutive patients with a final diagnosis of dilated cardiomyopathy were systematically and prospectively enrolled in our registry and treated with metoprolol in conjunction with conventional medical therapy. The diagnosis of dilated cardiomyopathy was made according to the criteria proposed by the WHO/ISFC Task Force (17).

Causes for exclusion were the presence of coronary artery disease (coronary artery stenosis > 50%), active myocarditis (diagnosed according to the Dallas criteria) (18), alcohol intake greater than 100 g/d in the previous 6 months, or history of systemic hypertension. The sporadic detection of blood pressure between 140/90 and 170/100 mmHg, however, was not considered a contraindication to enrollment in the study.

In patients with congestive heart failure, treatment with beta-blockers was started only after stabilization and in addition to optimal therapy with digitalis, diuretics, and vasodilators (usually angiotensin-converting enzyme inhibitors).

Patients received a test dose of metoprolol (5 mg twice a day, from 2 to 7 days), followed by a titration period consisting of a stepwise increase in dosage lasting 7 weeks as follows. Week 1: 5 mg twice a day; week 2: 5 mg three times a day; week 3: 10 mg three times a day; week 4: 25 mg twice a day; week 5: 25 mg three times a day; week 6: 50 mg two times a day; week 7 and onward: 50 mg three times a day. The target of the metoprolol treatment was a resting heart rate of 60 ± 10 beats/min. A higher dosage of metoprolol was sometimes administered in the presence of a persistent higher heart rate. Seven patients (4.3%) did not tolerate the test dose, while 142 underwent long-term treatment with metoprolol.

At enrollment, all patients underwent physical examination, resting electrocardiogram, chest x-ray, electrocardiographic monitoring, M-mode, two-dimensional, Doppler and color Doppler echocardiography, hemodynamic and angiographic study, coronary angiography, and endomyocardial biopsy. Mild hypertension was defined as the detection of a blood pressure between 140/90 and 170/100 mmHg on at least two measurements before diagnosis. The heart failure score was calculated according to Lee and associates (19).

Echocardiograms were evaluated according to the recommendations of the American Society of Echocardiography (20). At the two-dimensional studies, left ventricular volume and ejection fraction were calculated from the apical four-chamber view using an area-length single-plane method. End-diastolic and end-systolic right ventricular areas and their fractional shortening and end-systolic areas of both atria were obtained from the same view. All diameters, areas, and volumes were normalized on the body surface area. At Doppler echocardiographic study, severity of mitral and tricuspid regurgitation was semiquantitatively assessed as grade 1+ to 4+ using the conventional color Doppler method. The deceleration time of the E wave was obtained by extrapolating the initial slope of E deceleration to 0 line. Beats were excluded if there was E–A fusion or a curvilinear E wave descent (21). All measurements were always performed by the same operator and calculated on three beats for patients in sinus rhythm or five beats for those in atrial fibrillation.

A bicycle ergometer exercise test with patients in an upright position was performed starting at 10 W, with increments of 10 W/min. An exercise time of 60 seconds had been arbitrarily considered for those patients (6 of 94, 6.4%) who found it impossible to cycle because of an extremely severe functional limitation.

Right heart catheterization was performed with patients in the fasting state during the morning; cardiac output was measured by thermodilution.

Patients were reevaluated at 6, 12, and 24 months (and sometimes more frequently according to the patient's clinical needs) with a complete noninvasive examination. During follow-up examination, left ventricular function was evaluated with the same noninvasive method (radionuclide ventriculography or echocardiogram) considered at baseline.

Classification of Patients

Among the 149 cases (142 long-term treated with metoprolol, 7 nontolerant), 94 consecutive patients studied between November 1987 and April 1992 (ie, all the patients with a potential follow-up period of at least 18 months) who had a baseline left ventricular ejection fraction less than 0.40 were considered for the study, with the aim to identify factors predictive of good response to metoprolol. Patients with a left ventricular ejection frac-

tion greater than or equal to 0.40, or who were enrolled later than April 1992, or both, were excluded from this analysis. The study population included 14 patients, randomized to metoprolol, who participated in the Metoprolol in Dilated Cardiomyopathy (MDC) trial (10). Only data obtained at baseline were selected for our analysis.

After a 2-year follow-up study (mean, 24 months; range, 18–30 months), the study population was divided into two groups: improved (group 1) and nonimproved (group 2). Improvement was prospectively defined as either (1) an increase in left ventricular ejection fraction of greater than or equal to 10 U combined with at least one of the following major criteria:

- A decrease in left ventricular end-diastolic diameter greater than or equal to 10%
- Regression of left ventricular restrictive filling pattern (E deceleration time < 120 to ≥ 120 ms) (20)

or with at least two of the following minor criteria;

- A decrease in at least one New York Heart Association (NYHA) functional class
- A decrease in the cardiothoracic ratio of 10%
- An increase in exercise time greater than or equal to 2 minutes

or (2) an increase in left ventricular ejection fraction of 5 U combined with at least one major and two minor criteria.

Statistical Methods

First, an exploratory data analysis was performed for the purpose of describing the differences between improved and nonimproved patients with respect to noninvasive and invasive clinical variables. Differences among patients were detected using an analysis of variance approach under standard normality assumption for continuous variables, while for nominal variables, the chi-square test with Yates' correction was performed when appropriate. Differences between baseline and assessment at 6, 12, and 24 months were determined by a standard paired Student's *t*-test or McNemar test when appropriate. All the analyses were based on missing data exclusion.

The probability of improvement was modeled following a logit approach (22), which does not need the distributional assumption (variables independently normally distributed with equal variances) (23,24) usually required by the more common linear discriminant analysis. The selection of variables obtained at baseline was done at the first stage by a forward stepwise approach and then manually polished following clinical considerations and residual diagnostics based on delta betas and Cook distances (25,26). Finally, patients with a left ventricular ejection fraction less than 0.40 and a history of normal blood pressure who were enrolled later than April 1992 were used to assess external validity of the model.

Descriptive analysis was performed with SPSS 6.1 (Chicago, IL) logit model with EGRET package (Statistics and Epidemiology Research Corporation, Seattle, WA).

Results

Entry Characteristics

From November 1987 to April 1992, 94 consecutive patients were enrolled in our study (Table 1). Symptoms of heart failure characterized the past history in 80 patients (85.1%), with a mean duration of approximately 2 years (27 ± 31 months; range, 1–158 months). A history of mild hypertension (blood pressure between 140/90 and 170/100 mmHg) was present in 23 patients (24.5%). Despite a mean left ventricular ejection fraction of 0.27 ± 0.09 with a consistent proportion of patients having left ventricular ejection fraction less than 0.20 (27 patients, 28.7%), resting hemodynamics appeared only moderately compromised, probably reflecting the stable conditions of patients obtained at enrollment with tailoring of treatment with digitalis (84 patients, 89.4%), diuretics (75 patients, 79.8%), and angiotensin-converting enzyme inhibitors (83 patients, 88.3%).

Tolerability of Metoprolol in Dilated Cardiomyopathy

Most patients (88 of 94, 93.6%) tolerated the test dose of metoprolol of 5 mg twice a day and a mean dose at the end of the titration period of 126 ± 42 mg (range, 0–150 mg/d). During the dosing phase, patients occasionally experienced mild worsening of heart failure symptoms, weakness, or fatigue that usually responded favorably to prolongation of the dose interval or, very rarely, to the temporary addition of diuretics.

Six patients (6.4%) did not tolerate metoprolol. Five of them, after showing an acute worsening of heart failure during the test dose, were characterized by the following: extremely severe symptoms and signs of heart failure (NYHA class III or IV), marked left and right ventricular dysfunction (mean left ventricular ejection fraction, 0.20; range, 0.16–0.29; mean shortening fraction of right ventricular areas, 0.19; range, 0.10–0.43), severe left ventricular dilation (mean end-diastolic diameter indexed at 46 mm/m^2; range, 42–49 mm/m^2), end-diastolic volume indexed at 168 mL/m^2 (range, 132–214 mL/m^2), mitral regurgitation (mean grade, 3; range, 2–4), and left ventricular restrictive filling pattern (mean mitral E-deceleration time, 84 ms; range, 60–110 ms) (20). In three of the five patients, metoprolol was later tolerated after the introduction of an inotropic support (in 2 patients with strophantidin and 1 with enoximone). In the sixth patient, metoprolol was withdrawn after 3 months for advanced atrioventricular block; however, the patient tolerated the drug after pacemaker implantation.

Table 1. Main Characteristics of Study Population and Factors Predictive of Improvement at Baseline

		All Population (94 patients)	Improved (48 patients)	Not Improved (46 patients)	*P*
History and physical examination	Male (%)	77.7	81.3	73.9	NS
	Age (years)	45 ± 14	47 ± 11	43 ± 17	NS
	HF history (%)	85.1	85.4	84.8	NS
	HF duration (months)	27 ± 31	19 ± 20	34 ± 39	.032
	Mild hypertension (%)	24.5	41.7	6.5	< .001
	NYHA I–II (%)	67	72.9	60.5	NS
	NYHA III–IV (%)	33	27.1	39.5	NS
	SBP (mmHg)	119 ± 14	122 ± 11	115 ± 16	.007
	DBP (mmHg)	77 ± 9	80 ± 9	74 ± 10	.007
	HF score (0–13)*	2.8 ± 2.7	2.6 ± 2.7	3.1 ± 2.7	NS
	CTR	0.55 ± 0.07	0.53 ± 0.08	0.56 ± 0.07	.032
	Na (mEq/L)	139 ± 5	138 ± 4	139 ± 6	NS
Electrocardiogram	Sinus rhythm (%)	92.6	93.8	91.3	NS
	Rest HR (beats/min)	79 ± 15	82 ± 17	75 ± 12	.017
24-hour ambulatory electrocardiogram	Mean HR (beats/min)	80 ± 13	82 ± 12	78 ± 13	NS
	VEB/h	76 ± 156	80 ± 165	72 ± 148	NS
	Couplet/h	1.9 ± 5.7	0.8 ± 2	3 ± 7.8	NS
	NSVT/h	0.2 ± 0.4	0.1 ± 0.2	0.2 ± 0.6	NS
Exercise test	Exercise time (seconds)	559 ± 236	612 ± 210	502 ± 251	.024
	Maximal SBP (mmHg)	164 ± 29	171 ± 24	156 ± 31	.012
	Rest HR (upright) (beats/min)	91 ± 19	96 ± 17	86 ± 20	.015
	Maximal HR (beats/min)	164 ± 28	169 ± 25	158 ± 31	NS
Radionuclide ventriculography	LVEF	0.25 ± 0.08	0.26 ± 0.09	0.23 ± 0.08	NS
	RVEF	0.35 ± 0.16	0.36 ± 0.15	0.34 ± 0.17	NS
Echocardiogram	LVEDDI (mm/m^2)	39 ± 6	38 ± 5	40 ± 6	NS
	LA area I (cm^2/m^2)	15 ± 6	14 ± 6	15 ± 6	NS
	RVSF of areas	0.39 ± 0.19	0.4 ± 0.18	0.37 ± 0.2	NS
	LVEDVI (mL/m^2)	125 ± 47	118 ± 45	132 ± 48	NS
	LVESVI (mL/m^2)	93 ± 42	86 ± 38	100 ± 45	NS
	LVEF	0.27 ± 0.09	0.28 ± 0.07	0.27 ± 0.11	NS
	EDT (ms)	134 ± 62	139 ± 53	130 ± 69	NS
	MR (0–4)	1.4 ± 1	1.3 ± 1	1.5 ± 1.1	NS
Hemodynamic study	HR (beats/min)	86 ± 18	89 ± 17	84 ± 19	NS
	RAP (mmHg)	4 ± 3	4 ± 3	4 ± 3	NS
	Mean PAP (mmHg)	22 ± 11	21 ± 10	23 ±12	NS
	Mean PAWP (mmHg)	14 ± 9	12 ± 9	15 ± 8	NS
	LVEDP (mmHg)	18 ± 9	18 ± 8	19 ± 10	NS
	Mean AoP (mmHg)	86 ± 12	89 ± 12	83 ± 12	NS
	CI (L/min/m^2)	3.6 ± 1.1	3.9 ± 1.2	3.3 ± 1	.014
	SV1 (mL/m^2)	44 ± 18	46 ± 18	42 ± 18	NS
	SVR (UW)	13 ± 5	12 ± 4	14 ± 5	NS
	TPVR (UW)	4 ± 3	3 ± 3	5 ± 4	NS
	LVSWI (gm/m^2)	44 ± 23	49 ± 23	38 ± 20	.032
Therapy	Metoprolol (mg)†	126 ± 42	136 ± 32	114 ± 50	.012
	Digitalis (%)	89.4	89.6	89.1	NS
	ACE inhibitors (%)	88.3	83.4	93.5	NS
	Diuretics (%)	79.8	83.3	76.1	NS

ACE, angiotensin-converting enzyme; Ao, aortic; CI, cardiac index; CTR, cardiothoracic ratio; D, diameter; DBP, diastolic blood pressure; ED, end-diastolic; EDT, deceleration time of E wave; ES, end-systolic; EF, ejection fraction; HF, heart failure; HR, heart rate; I, indexed; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; Na, serum sodium; NS, not significant; NSVT, nonsustained ventricular tachycardia; NYHA, NYHA functional class; P, pressure; RA, right atrium; PA, pulmonary artery; RV, right ventricle; SF, shortening fraction; SBP, systolic blood pressure; SV, stroke volume; SW, stroke work; S, systemic; TP, total pulmonary; V, volume; VEB, ventricular ectopic beats; VR, vascular resistence; W, wedge. *From Lee et al. (19). †Metoprolol dosage at the end of titration period.

Follow-up Results

Ten patients (8 on chronic metoprolol, 2 nontolerant) withdrew before the final assessment (24 ± 6 months): four of these patients died (3 for refractory heart failure, 1 suddenly), while six patients required heart transplants.

The remaining 84 patients (89.4%) were followed by a serial complete, noninvasive assessment at 6, 12, and 24 months (Table 2). A highly significant improvement was evident in most of the analyzed variables. At 6 months, heart failure symptoms, left ventricular function and dimension, and exercise tolerance were significantly better and often continued to improve in the second year (Table 2, Fig. 1). Only three patients who showed a good response to metoprolol in the first year did not maintain the improvement in subsequent evaluations.

Table 2. Main Clinical Data at Baseline, 6, 12, and 24 Months

			Baseline	6 Months	*P* (vs Baseline)	12 Months	*P* (vs Baseline)	24 Months	*P* (vs Baseline)
History and physical examination	NYHA class I–II (%)	All population	67	82.4	<.001	83.9	<.001	86.8*	<.001
		Improved	72.9	95.8		93.8		95.8	
		Nonimproved	60.5	69.8		71.8		74.3	
	SBP (mmHg)	All population	119 ± 14	124 ± 17	.02	126 ± 17	.001	123 ± 16	NS
		Improved	122 ± 11	131 ± 16		132 ± 16		124 ± 16	
		Nonimproved	115 ± 16	117 ± 14		118 ± 13		122 ± 16	
	DBP (mmHg)	All population	77 ± 9	78 ± 9	NS	80 ± 10	.043	78 ± 9*	NS
		Improved	80 ± 9	80 ± 9		82 ± 10		78 ± 9	
		Nonimproved	74 ± 10	75 ± 9		77 ± 8		77 ± 8	
	HF score (0–13)*	All population	2.8 ± 2.7	1.4 ± 2.5	<.001	1.2 ± 2.2	<.001	0.8 ± 1.7	<.001
		Improved	2.6 ± 2.7	0.4 ± 0.8		0.6 ± 0.8		0.2 ± 0.7	
		Nonimproved	3.1 ± 2.7	2.4 ± 3.2		1.9 ± 3.1		1.6 ± 2.4	
	CTR	All population	0.55 ± 0.07	0.53 ± 0.07	.002	0.52 ± 0.07	.002	0.51 ± 0.06	<.001
		Improved	0.53 ± 0.08	0.5 ± 0.06		0.51 ± 0.06		0.5 ± 0.06	
		Nonimproved	0.56 ± 0.07	0.56 ± 0.07		0.54 ± 0.07		0.54 ± 0.06	
	Serum sodium (mEq/L)	All population	139 ± 5	141 ± 4	.002	141 ± 4	.016	141 ± 4	.001
		Improved	138 ± 4	141 ± 4		141 ± 4		142 ± 5	
		Nonimproved	139 ± 6	140 ± 4		140 ± 4		140 ± 5	
Electrocardiogram	Resting heart rate (beats/min)	All population	79 ± 15	67 ± 7	<.001	63 ± 6	<.001	61 ± 7	<.001
		Improved	82 ± 17	69 ± 8		63 ± 7		61 ± 7	
		Nonimproved	75 ± 12	66 ± 7		62 ± 6		61 ± 7	
24-hour ambulatory electrocardiogram	Mean heart rate (beats/min)	All population	80 ± 13	73 ± 12	<.001	73 ± 12	<.001	73 ± 12	<.001
		Improved	82 ± 12	72 ± 11		74 ± 13		75 ± 12	
		Nonimproved	78 ± 13	74 ± 13		72 ± 11		70 ± 12	
Exercise test	Exercise time (seconds)	All population	559 ± 236	631 ± 222	<.001	642 ± 217	.002	669 ± 220	<.001
		Improved	612 ± 210	691 ± 212		707 ± 194		726 ± 195	
		Nonimproved	502 ± 251	553 ± 213		557 ± 219		586 ± 232	
	Maximal SBP (mmHg)	All population	164 ± 29	175 ± 28	<.001	178 ± 31	.002	176 ± 29	.002
		Improved	171 ± 24	183 ± 26		188 ± 27		187 ± 19	
		Nonimproved	156 ± 31	165 ± 27		164 ± 31		161 ± 34	
	Resting heart rate (upright) (beats/min)	All population	91 ± 19	79 ± 20	<.001	76 ± 19	<.001	71 ± 17*	<.001
		Improved	96 ± 17	79 ± 19		80 ± 20		75 ± 17	
		Nonimproved	86 ± 20	78 ± 21		70 ± 17		68 ± 18	
	Maximal heart rate (beats/min)	All population	164 ± 28	150 ± 30	<.001	144 ± 29	<.001	134 ± 25*	<.001
		Improved	169 ± 25	156 ± 28		149 ± 28		140 ± 22	
		Nonimproved	158 ± 31	142 ± 30		137 ± 30		128 ± 27	
Echocardiogram	LVEDDI (mm/m^2)	All population	39 ± 6	37 ± 7	<.001	36 ± 6†	<.001	35 ± 6	<.001
		Improved	38 ± 5	35 ± 5		34 ± 5		32 ± 4	
		Nonimproved	40 ± 6	40 ± 7		39 ± 6		38 ± 6	
	LA area I (cm^2/m^2)	All population	15 ± 6	13 ± 5	.003	12 ± 4	<.001	12 ± 4	.007
		Improved	14 ± 6	11 ± 3		11 ± 3		11 ± 3	
		Nonimproved	15 ± 6	15 ± 6		14 ± 5		12 ± 5	
	SFRV of areas	All population	0.39 ± 0.19	0.46 ± 0.16	.002	0.48 ± 0.14	<.001	0.5 ± 0.15	<.001
		Improved	0.4 ± 0.18	0.51 ± 0.13		0.5 ± 0.1		0.52 ± 0.11	
		Nonimproved	0.37 ± 0.2	0.41 ± 0.19		0.46 ± 0.18		0.47 ± 0.19	
	LVEDVI (mL/m^2)	All population	125 ± 47	108 ± 45	<.001	102 ± 45	<.001	93 ± 44*	<.001
		Improved	118 ± 45	91 ± 32		86 ± 32		74 ± 26	
		Nonimproved	132 ± 48	126 ± 51		122 ± 51		118 ± 51	
	LVEF§	All population	0.25 ± 0.08	0.33 ± 0.11	<.001	0.36 ± 0.13†	<.001	0.4 ± 0.13*	<.001
		Improved	0.27 ± 0.08	0.36 ± 0.1		0.42 ± 0.11		0.47 ± 0.1	
		Nonimproved	0.24 ± 0.08	0.29 ± 0.11		0.29 ± 0.11		10.3 ± 0.11	
	EDT (ms)	All population	134 ± 62	188 ± 79	<.001	205 ± 70	<.001	209 ± 73	<.001
		Improved	139 ± 53	205 ± 52		212 ± 44		223 ± 63	
		Nonimproved	130 ± 69	171 ± 97		198 ± 93		190 ± 83	
	MR (0–4)	All population	1.4 ± 1	0.9 ± 1	<.001	0.9 ± 1	<.001	0.9 ± 0.8	<.001
		Improved	1.3 ± 1	0.6 ± 0.7		0.6 ± 0.7		0.6 ± 0.7	
		Nonimproved	1.5 ± 1.1	1.2 ± 1.1		1.3 ± 1.1		1.2 ± 0.8	
Therapy	Metoprolol (mg)	All population	126 ± 42‡	131 ± 45	NS	147 ± 53	<.001	136 ± 32	<.001
		Improved	136 ± 32‡	140 ± 34		156 ± 48		162 ± 54	
		Nonimproved	114 ± 49‡	120 ± 54		133 ± 57		139 ± 57	
	Digitalis (%)	All population	89.4	88.9	NS	88.5	NS	84.3	NS
		Improved	89.6	91.7		89.6		83.3	
		Nonimproved	89.1	85.7		87.2		85.7	
	ACE inhibitors (%)	All population	88.3	89	NS	90.8	NS	95.2	.007
		Improved	83.3	85.4		87.5		95.8	
		Nonimproved	93.5	93		94.9		94.3	
	Diuretics (%)	All population	79.8	72.2	NS	69.3	NS	60.5	.004
		Improved	83.3	70.8		62.5		45.8	
		Nonimproved	76.1	73.8		77.5		78.9	

*$P < .05$, 24 months versus 12 months. †$P < .05$, 12 months versus 6 months. ‡Metoprolol dosage at the end of titration period. §LVEF was evaluated with the same noninvasive method (radionuclide ventriculography or echocardiogram) considered at baseline. All population: n = 94 at baseline, n = 91 at 6 months, n = 88 at 12 months, n = 84 at 24 months. Improved: n = 48 at baseline, 6, 12, and 24 months. Nonimproved: n = 46 at baseline, n = 43 at 6 months, n = 40 at 12 months, n = 36 at 24 months. ACE, angiotensin-converting enzyme; CTR, cardiothoracic ratio; D, diameter; DBP, diastolic blood pressure; EDT, deceleration time of E wave; ED, end diastolic; EF, ejection fraction; HF, heart failure; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; NYHA, New York Heart Association; RV, right ventricle; SBP, systolic blood pressure; SF, shortening fraction; V, volume. *From Lee et al. (19).

A marked improvement of symptoms was evident in most of the cases (NYHA classes I–II: from 67.0% at baseline to 86.8% at 2 years, $P < .001$; heart failure score from 2.8 ± 2.7 to 0.8 ± 1.7, $P < .001$), and 57 patients (67.8%) were asymptomatic at last assessment on metoprolol; consequently, diuretics could be withdrawn or the dose reduced in 39 of 75 patients (52.0%) ($P < .001$).

As expected, the mean heart rate decreased by about 20 beats/min (in the supine position: from 79 ± 15 to 61 ± 7 beats/min, $P < .001$; in the upright position: from 91 ± 19 to 71 ± 17 beats/min, $P < .001$), while systolic blood pressure showed a tendency to increase in the first year (from 119 ± 14 to 126 ± 17 mmHg, $P = .001$). Despite a large reduction in peak exercise heart rate (by an average of 30 beats/min, from 164 ± 28 to 134 ± 25 beats/min, $P < .001$), both maximal exercise time (Fig. 1) and blood pressure increased significantly (from 559 ± 236 to 669 ± 220 seconds, $P < .001$ and from 164 ± 29 to 176 ± 29 mmHg, $P = .002$, respectively).

Furthermore, an improvement in left ventricular systolic function was evidenced by the increase of 15 U in ejection fraction (from 0.25 ± 0.08 to 0.40 ± 0.13, $P < .001$) (Fig. 1) and by the high proportion of patients (43 of 84, 51.2%) with ejection fraction greater than 0.40 at the end of the study period. These changes were associated with a decrease of left ventricular dimension (end-diastolic diameter indexed from 39 ± 6 to 35 ± 6 mm/m^2, $P < .001$; end-diastolic volume indexed from 125 ± 47 to 93 ± 44 mL/m^2, $P < .001$) (Fig. 1) and a decrease in the severity of mitral regurgitation (from 1.4 ± 1.0 to 0.9 ± 0.8, $P < .001$). Finally, an improvement in diastolic function was documented by a prolonged E-deceleration time (from 134 ± 32 to 209 ± 73 ms, $P < .001$) and reduced left atrial area (from 15 ± 6 to 12 ± 4 cm^2/m^2, $P = .007$), probably related also to the reduction of mitral regurgitation.

After 2 years, 48 patients (51.1% of the total population, 54.5% of tolerant subjects) were classified as improved according to our clinical score (group 1), while 36 (38.3%) survived without satisfying our clinical criteria of improvement, and 10 (10.6%), who died or underwent a heart transplant, were classified as nonimproved (group 2).

At last assessment, most of the improved patients were asymptomatic (41 of 48, 85.4%), and mean left and right ventricular functions and dimensions were close to normal (left ventricular ejection fraction, 0.47 ± 0.10; right ventricular shortening fraction, 0.52 ± 0.11; left ventricular end-diastolic diameter indexed at 32 ± 4 mm/m^2; left ventricular end-diastolic volume indexed at 74 ± 26 mL/m^2). Mean final dosage of metoprolol was 162 ± 54 mg (range, 50–300 mg). Ten patients (10.6%) showed a complete normalization of clinical signs and cardiac function.

Conversely, despite the stable or often improved symptoms of heart failure (NYHA class, 1.9 ± 0.9; heart failure score, 1.6 ± 2.4), a persistent functional limitation (exercise time, 586 ± 232 seconds), left ventricular dysfunction (ejection fraction, 0.30 ± 0.11), and dilation (end-diastolic diameter indexed at 38 ± 6 mm/m^2, end-diastolic volume indexed at 118 ± 51 mL/m^2) were evident in the surviving patients of group 2. Notably, with the exception of the 10 patients who died or underwent a heart transplant, only 4 patients (4.3%) experienced a worsening of functional class and heart failure score during the follow-up study.

Among the five patients nontolerant for acute hemodynamic deterioration, three subsequently tolerated a second attempt of metoprolol during inotropic support. One markedly improved, one remained stable in severe heart failure, and the third underwent a heart transplant during the titration period. The two remaining patients died of refractory heart failure 18 and 36 months after enrollment.

Factors Predictive of Improvement

Improved patients (group 1) more frequently had a history of mild hypertension (20 of 48, 41.7% vs 3 of 46, 6.5%; $P < .001$), a significantly higher blood pressure at baseline (systolic: 122 ± 11 vs 115 ± 16 mmHg; $P = .007$; diastolic: 80 ± 9 vs 74 ± 10 mmHg, $P = .007$), and a shorter duration of heart failure symptoms (19 ± 20 vs 34 ± 39 months, $P = .032$). Moreover, in group 1, resting heart rate (in the supine position: 82 ± 17 vs 75 ± 12 beats/min, $P = .017$; in the upright position: 96 ± 17 vs 86 ± 20 beats/min, $P = .015$) was significantly higher, as was mean aortic pressure (89 ± 12 vs 83 ± 12 mmHg, $P = .011$), cardiac index (3.9 ± 1.2 vs 3.3 ± 1 L/min/m^2, $P = .014$), and left ventricular stroke work index (49 ± 23 vs 38 ± 20 gm/m^2, $P = .032$).

A progressively higher incidence of improvement was related to the maximal tolerated dose of metoprolol (136 ± 32 vs 114 ± 50, $P = .012$) and an absolute decrease of heart rate on treatment (Fig. 2), while digitalis (89.6 vs 89.1, P = NS), diuretics (83.3 vs 76.1, P = NS), and angiotensin-converting enzyme inhibitors (83.4% vs 93.5%, P = NS) were given to a similar percentage of patients at baseline.

Stepwise linear logistic regression analysis on baseline data identified a group of 23 patients with a history of mild hypertension who presented an exceptionally good response to metoprolol (Tables 3, 4). Twenty patients (87%) improved on metoprolol, with a mean absolute increase of left ventricular ejection fraction of 0.20 ± 0.13 ($P < .001$). Interestingly, with the exception of blood pressure, patients with history of mild hypertension showed, at baseline, similar clinical characteristics in comparison with patients with normal blood pressure (Table 4). Table 3 gives an estimation of the relative chance of improvement in the two groups of patients, showing a 2.2 times higher (95% confidence interval

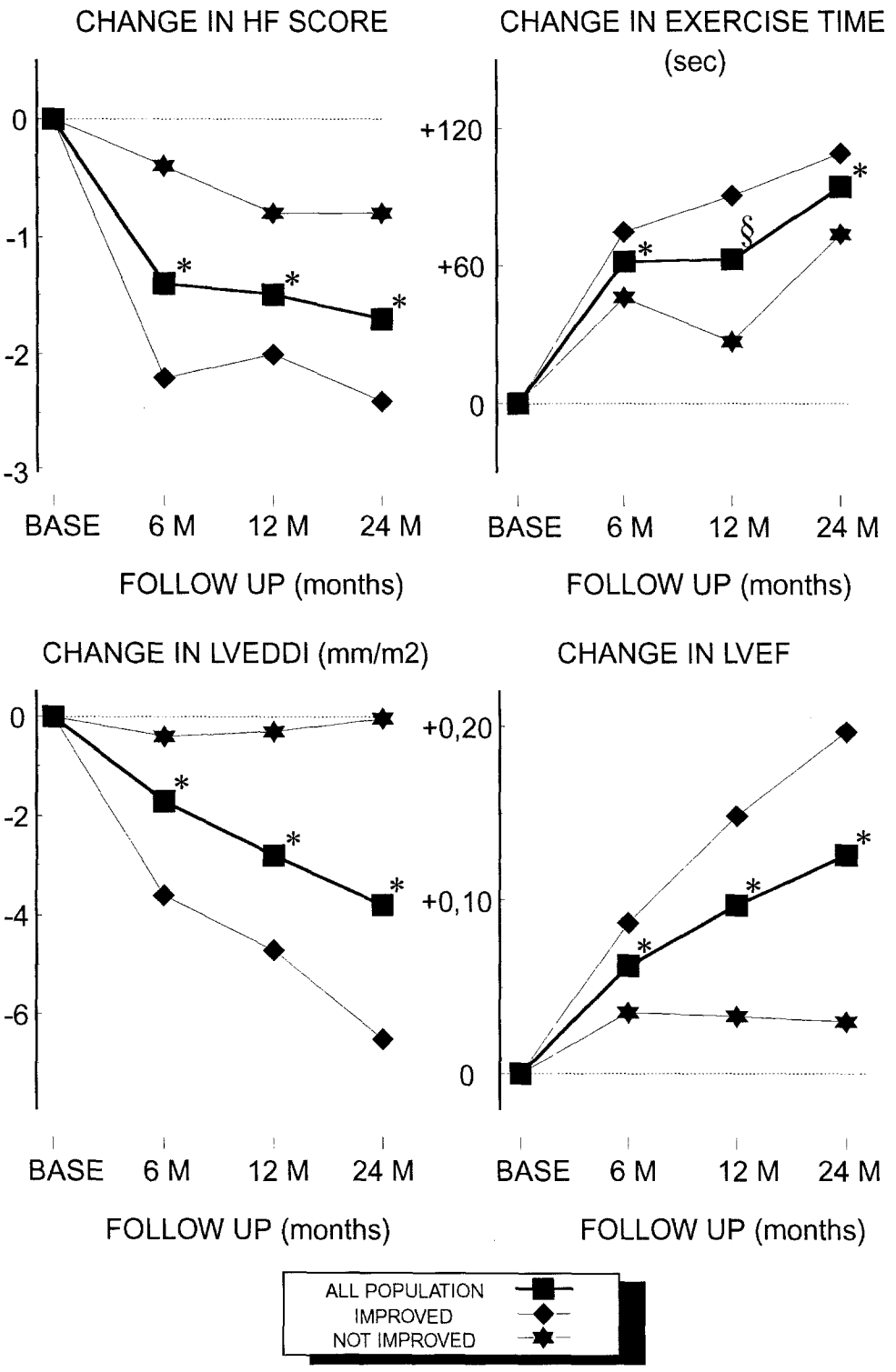

Fig. 1. Heart failure score (19), left ventricular function and dimension, and exercise tolerance at baseline and during the follow-up period in 94 patients with dilated cardiomyopathy treated with metoprolol and classified as improved or not improved according to our clinical criteria. *$P < .001$ versus baseline; §$P = .002$ versus baseline. HF, heart failure; LVEDDI, left ventricular end-diastolic diameter indexed; LVEF, left ventricular ejection fraction.

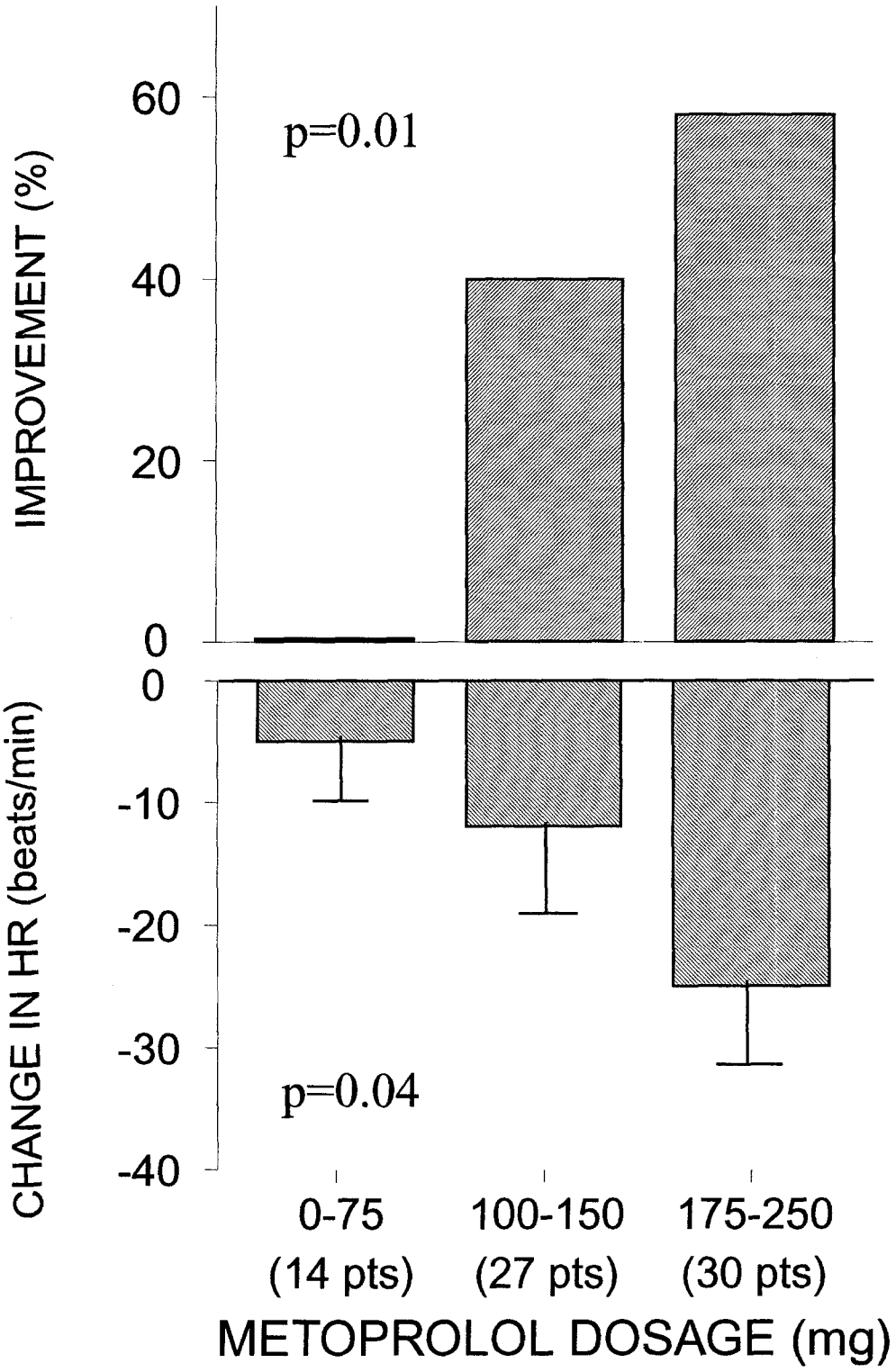

Fig. 2. Relationship among maximal tolerated dosage of metoprolol, absolute decrease of heart rate on treatment, and improvement in 71 patients with dilated cardiomyopathy and normal blood pressure. HR, heart rate; pts, patients.

Table 3. Variables Predictive of Improvement at Stepwise Logistic Regression Analysis

	Beta Coefficient	*P* Value	Odds Ratio	95% Confidence Interval
All population: n = 94				
Constant	–5.5			
Mild hypertension (0.1)	0.7958	.007	2.216	1.246–3.942
Patients with normal blood pressure: n = 71				
Constant	–5.6			
Resting heart rate (beats/min)	0.039	.003	1.039	1.013–1.066
LVEF (0.20–0.33 vs < 0.20)	1.552	.042	4.719	1.059–21.04
LVEF (> 0.33 vs < 0.20)	1.052	.222	2.863	0.529–15.49
NYHA class (I–II vs III–IV)	1.009	.05	2.742	0.971–7.751
Age (years)	–0.027	.071	1.027	0.998–1.057

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

1.2–3.9) chance of getting better in patients with mild hypertension.

A second stepwise linear regression analysis was then performed with the aim of predicting a good response to metoprolol in the subgroup of patients with normal blood pressure (28 of 71 patients improved, 39.4%). Heart rate during the resting phase of exercise testing in the upright position ($P = .003$), left ventricular ejection fraction ($P = .042$), and NYHA class ($P = .05$) could be related to improvement, as shown in Table 3.

Heart Rate. In patients with normal blood pressure, heart rates in the supine and upright positions were strictly related to the clinical response to chronic metoprolol (Table 4), but the most significant predictor of improvement at multivariate analysis was heart rate in the upright position ($P = .003$) (Table 3). The estimated chance of improvement was twofold higher in a patient with a heart rate in the upright position of 100 beats/min than in a patient with a heart rate of 75 beats/min. Moreover, patients with a heart rate greater than or equal to 90 beats/min (42 of 71, 59.2%) showed a significantly higher change in left ventricular function and dimension (0.12 ± 0.13 vs 0.06 ± 0.12, $P = .049$ and –4.2 ± 5.9 vs –1.1 ± 3.1 mm/m^2, $P = .017$, respectively), while no patients with a heart rate less than 90 beats/min and a left ventricular ejection fraction less than 0.20 or in NYHA classes III–IV at baseline improved on metoprolol.

Left Ventricular Ejection Fraction. The relation between left ventricular ejection fraction and improvement was not linear. Cutoff points were defined by the lower and upper quartiles of the distribution, and three subgroups resulted (left ventricular ejection fraction < 0.20, 0.20–0.33, and > 0.33). The observed incidence of improvement for the three subgroups was 4 of 22 patients (18.8%), 19 of 38 patients (50%), and 5 of 11 patients (45.5%), respectively. The highest estimated chance of improvement was present in patients with left ventricular ejection fractions of 0.20–0.33 (left ventricular ejection fraction, 0.20–0.33 vs < 0.20: OR 4.7, $P = .042$) (Table 3).

Patients with left ventricular ejection fractions less than 0.20 and heart rates less than 90 beats/min frequently showed a long duration of heart failure symptoms and a low probability of response to metoprolol (Fig. 3). Conversely, four cases with severe left ventricular dysfunction, heart rate greater than or equal to 90 beats/min, and a relatively short history of heart failure showed a remarkable improvement, with mean increases in ejection fraction and exercise time of 0.26 ± 0.17 and 311 ± 268 seconds, respectively.

Functional Class. In the adjusted model, NYHA functional class entered as the third predictor of improvement on metoprolol with a borderline significance ($P = .05$). Twenty-two patients (46.8%) classified in class I or II had improved at the end of the study period compared with only six patients (25.0%) in class III or IV ($P = .07$); no improvement was found among patients in NYHA classes III–IV associated with a heart rate less than 90 beats/min (Fig. 3).

Age at Entry. Despite not being strictly significant, age played a key role in stabilizing the model.

Based on these data, the individual patient's characteristics can be entered into the following equation and their probability of being improved after 2 years on metoprolol calculated:

$$(1)\quad P = \frac{\begin{array}{l}(\mathrm{EXP}(-5.6 + (0.03863 \times \mathrm{HR}) + (1.552 \times \\ (\mathrm{EF}\ 0.20 - 0.33)) + (1.052 \times (\mathrm{EF} > 0.33)) \\ + (1.009 \times \mathrm{NYHA}) - (0.02668 \times \mathrm{AGE})))\end{array}}{\begin{array}{l}1 + (\mathrm{EXP}(-5.6 + (0.03863 \times \mathrm{HR}) + (1.552 \\ \times (\mathrm{EF}\ 0.20 - 0.33)) + (1.052 \times (\mathrm{EF} > 0.33)) \\ + (1.009 \times \mathrm{NYHA}) - (0.02668 \times \mathrm{AGE})))\end{array}}$$

where EXP, exponential; HR, resting heart rate in the upright position expressed in beats/min; EF 0.20–0.33, left ventricular ejection fraction graded as 0 if < 0.20 or 1 if 0.20–0.33; EF > 0.33, left ventricular ejection fraction graded as 0 if ≤ 0.33 and 1 if > 0.33;

Table 4. Main Characteristics of Study Population at Baseline and Factors Predictive of Improvement in Patients With Normal Blood Pressure

					Normal Blood Pressure		
		Mild Hypertension (n = 23)	Normal Blood Pressure (n = 71)	*P*	Improved (n = 48)	Not Improved (n = 46)	*P*
History and physical examination	Male (%)	87	74.6	NS	75	74.4	NS
	Age (years)	49.2 ± 8.5	43.7 ± 15	NS	46 ± 13	42 ± 17	NS
	HF history (%)	82.6	85.9	NS	82.1	88.4	NS
	HF duration (months)	19 ± 21	29 ± 34	NS	20 ± 19	35 ± 40	NS
	NYHA I–II (%)	65.2	66.2	NS	78.6	58.1	NS
	NYHA III–IV (%)	34.8	33.8	NS	21.4	41.9	NS
	SBP (mmHg)	130 ± 11	115 ± 13	<.0001	118 ± 11	113 ± 14	NS
	DBP (mmHg)	83 ± 10	75 ± 9	.0011	78 ± 7	73 ± 9	.024
	HF score (0–13)*	2.7 ± 3	2.9 ± 2.6	NS	2.3 ± 2.4	3.2 ± 2.7	NS
	CTR	0.54 ± 0.07	0.54 ± 0.08	NS	0.52 ± 0.090	.56 ± 0.08	NS
	Na (mEq/L)	138 ± 5	139 ± 5	NS	138 ± 4	140 ± 6	NS
Electrocardiogram	Sinus rhythm (%)	87	94.4	NS	96.4	93	NS
	Rest HR (beats/min)	75 ± 12	80 ± 16	NS	85 ± 17	77 ± 12	.0326
24-hour ambulatory electrocardiogram	Mean HR (beats/min)	81 ± 11	80 ± 13	NS	84 ± 12	78 ± 14	NS
	VEB/h	21 ± 21	94 ± 176	NS	121 ± 207	77 ± 152	NS
	Couplet/h	0.2 ± 0.2	2.4 ± 6.5	NS	1.2 ± 2.6	3.2 ± 8	NS
	NSVT/h	0.1 ± 0.1	0.2 ± 0.4	NS	0.1 ± 0.2	0.2 ± 0.5	NS
Exercise test	Exercise time (seconds)	621 ± 206	540 ± 243	NS	591 ± 236	506 ± 244	NS
	Maximal SBP (mmHg)	174 ± 24	161 ± 29	NS	169 ± 24	156 ± 32	NS
	Rest HR (upright) (beats/min)	90 ± 20	92 ± 19	NS	100 ± 13	86 ± 20	.0024
	Maximal HR (beats/min)	164 ± 26	164 ± 29	NS	174 ± 23	158 ± 31	.0296
Radionuclide ventriculography	LVEF	0.26 ± 0.08	0.24 ± 0.08	NS	0.26 ± 0.09	0.23 ± 0.08	NS
	RVEF	0.39 ± 0.17	0.34 ± 0.15	NS	0.36 ± 0.1	0.33 ± 0.17	NS
Echocardiogram	LVEDDI (mm/m^2)	37 ± 5	40 ± 6	NS	39 ± 5	40 ± 6	NS
	LA area I (cm^2/m^2)	13 ± 4	15 ± 6	NS	14 ± 7	15 ± 6	NS
	RVSF of areas	0.42 ± 0.18	0.38 ± 0.19	NS	0.41 ± 0.18	0.36 ± 0.2	NS
	LVEDVI (mL/m^2)	115 ± 48	128 ± 47	NS	119 ± 43	183 ± 49	NS
	LVESVI (mL/m^2)	84 ± 40	95 ± 42	NS	86 ± 36	101 ± 45	NS
	LVEF	0.28 ± 0.07	0.27 ± 0.1	NS	0.29 ± 0.07	0.26 ± 0.11	NS
	EDT (ms)	161 ± 63	127 ± 60	.0357	129 ± 53	125 ± 64	NS
	MR (0–4)	1.2 ± 1	1.5 ± 1.1	NS	1.3 ± 1	1.6 ± 1.1	NS
Hemodynamic study	HR (beats/min)	83 ± 16	87 ± 19	NS	92 ± 17	84 ± 20	NS
	RAP (mmHg)	4 ± 2	4 ± 3	NS	5 ± 3	4 ± 3	NS
	Mean PAP (mmHg)	19 ± 9	23 ± 11	NS	22 ± 11	23 ± 11	NS
	Mean PAWP (mmHg)	10 ± 7	15 ± 9	.024	14 ± 11	16 ± 8	NS
	LVEDP (mmHg)	16 ± 7	20 ± 9	NS	20 ± 9	19 ± 10	NS
	Mean AoP (mmHg)	93 ± 12	84 ± 12	.0014	87 ± 11	82 ± 12	NS
	CI (L/min/m^2)	3.9 ± 1.2	3.5 ± 1.1	NS	4 ± 1.3	3.2 ± 0.9	.009
	SVI (mL/m^2)	48 ± 18	43 ± 18	NS	46 ± 20	40 ± 17	NS
	SVR (UW)	12 ± 3	14 ± 5	NS	12 ± 5	14 ± 5	NS
	TPVR (UW)	3 ± 2	4 ± 4	.04	4 ± 3	5 ± 4	NS
	LVSWI (gm/m^2)	53 ± 22	41 ± 22	.044	47 ± 25	37 ± 20	NS
Therapy	Metoprolol (mg)†	127 ± 43	126 ± 42	NS	142 ± 24	114 ± 48	.006
	Digitalis (%)	95.7	87.3	NS	85.7	88.4	NS
	ACE inhibitors (%)	95.7	87.3	NS	78.6	93	NS
	Diuretics (%)	78.3	80.3	NS	78.6	81.4	NS

*From Lee et al. (19). †Metoprolol dosage at the end of the titration period. ACE, angiotensin-converting enzyme; Ao, aortic; CI, cardiac index; CTR, cardiothoracic ratio; D, diameter; DBP, diastolic blood pressure; ED, end-diastolic; EDT, deceleration time of E wave; ES, end-systolic; EF, ejection fraction; HF, heart failure; HR, heart rate; I, indexed; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; Na, serum sodium; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; P, pressure; RA, right atrium; PA, pulmonary artery; RV, right ventricle; SF, shortening fraction; SBP, systolic blood pressure; SV, stroke volume; SW, stroke work; S, systemic; TP, total pulmonary; V, volume; VEB, ventricular ectopic beats; VR, vascular resistance; W, wedge.

NYHA, NYHA class graded as 1 = I or II and 0 = III or IV; and AGE, age at entry expressed in years.

Figure 4 plots the relation between the probability of improvement and resting heart rate in patients with different degrees of functional impairment and left ventricular dysfunction.

The sensitivity and specificity of this model was 75.0% and 81.4%, respectively (Table 5). The other 24 patients (mean age, 42 ± 12 years; 19 men; left ventricular ejection fraction, 0.29 ± 0.08) with normal blood pressure, who were enrolled later than April 1992, have been considered in order to estimate the probabilities of

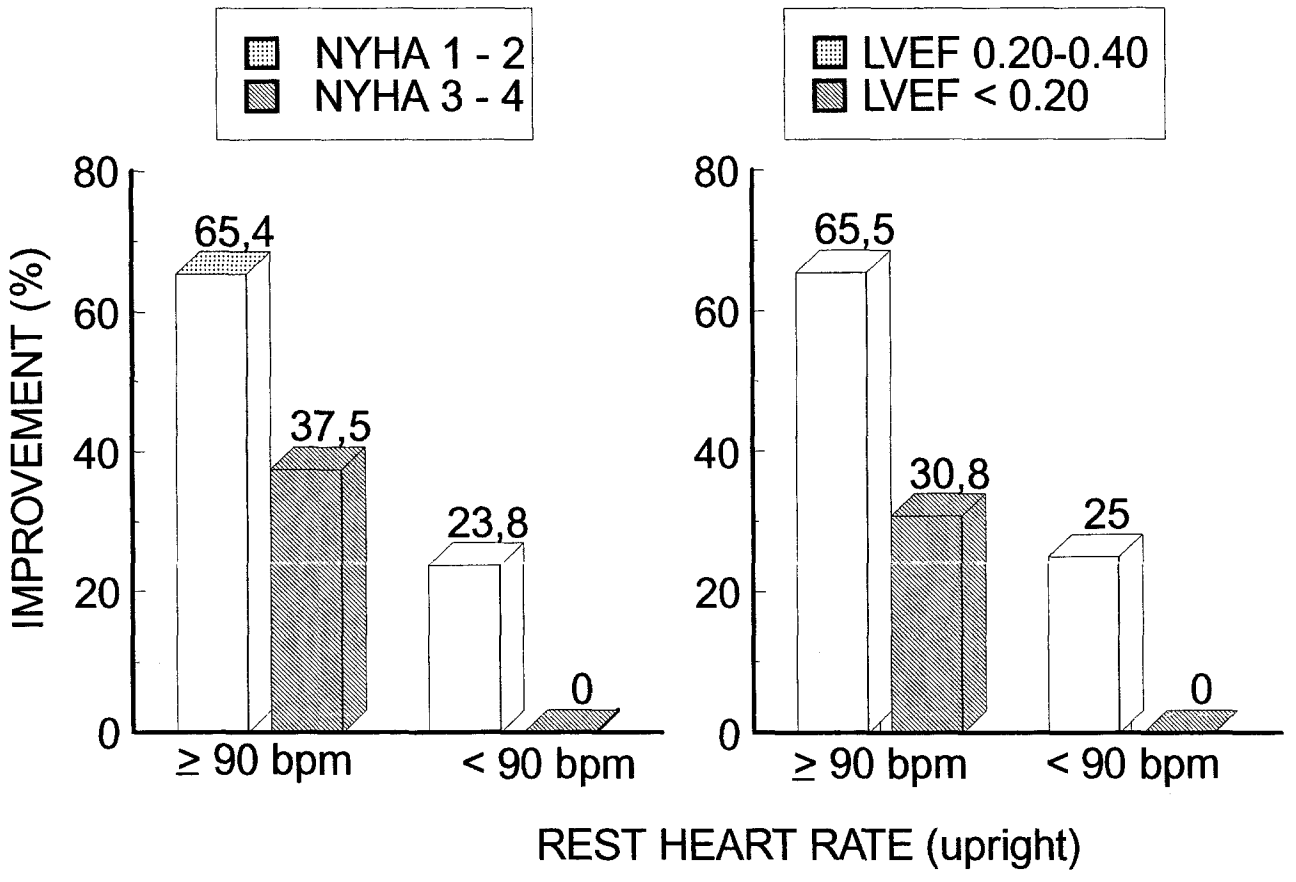

Fig. 3. Predictive value of resting heart rate (upright), symptoms, and left ventricular function in patients with dilated cardiomyopathy and normal blood pressure treated with metoprolol. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

improvement and for assessing external validity of the model (Table 5).

Discussion

Improvement With Beta-blockers in Dilated Cardiomyopathy

Since 1975, when Waagstein and co-workers (2) first introduced beta-blockers into the treatment of dilated cardiomyopathy, several clinical investigations suggested or demonstrated positive clinical responses to chronic therapy with beta-adrenergic-blocking drugs (3,4,8,9,27–31), while some recent randomized trials also evaluated the efficacy on hemodynamics and survival in patients with dilated cardiomyopathy (5–7, 10–12,32).

In the MDC trial (10), 383 subjects with symptomatic dilated cardiomyopathy and ejection fractions less than 0.40 were randomized to metoprolol or placebo. In the metaprolol group, 34% fewer primary events (death or the need for heart transplantation) (P = .058), a significant increase in ejection fraction and exercise capacity, and an improvement in hemodynamics were seen. Moreover, in the Cardiac Insufficiency Bisoprolol Study trial (11), a large reduction in mortality (50%) in the subgroup of patients with heart failure and no history of myocardial infarction was shown on bisoprolol.

Our study of 94 consecutive patients affected by dilated cardiomyopathy, despite not being controlled, confirms the long-term progressive improvement of symptoms, exercise tolerance, and left ventricular function obtained with metoprolol and gives a contribution to the identification of a subgroup of patients with a high probability of improvement while on treatment.

Although dilated cardiomyopathy is usually considered a progressive disease (33), improvement may occur spontaneously in about one quarter of patients (10, 33–38), especially in subjects with a short history of heart failure (34). Spontaneous improvement is also possible in active myocarditis (39), but it was excluded by left or right endomyocardial biopsy in all our cases. Moreover, the significant increase of ejection fraction with metoprolol contrasts with the slight changes observed during

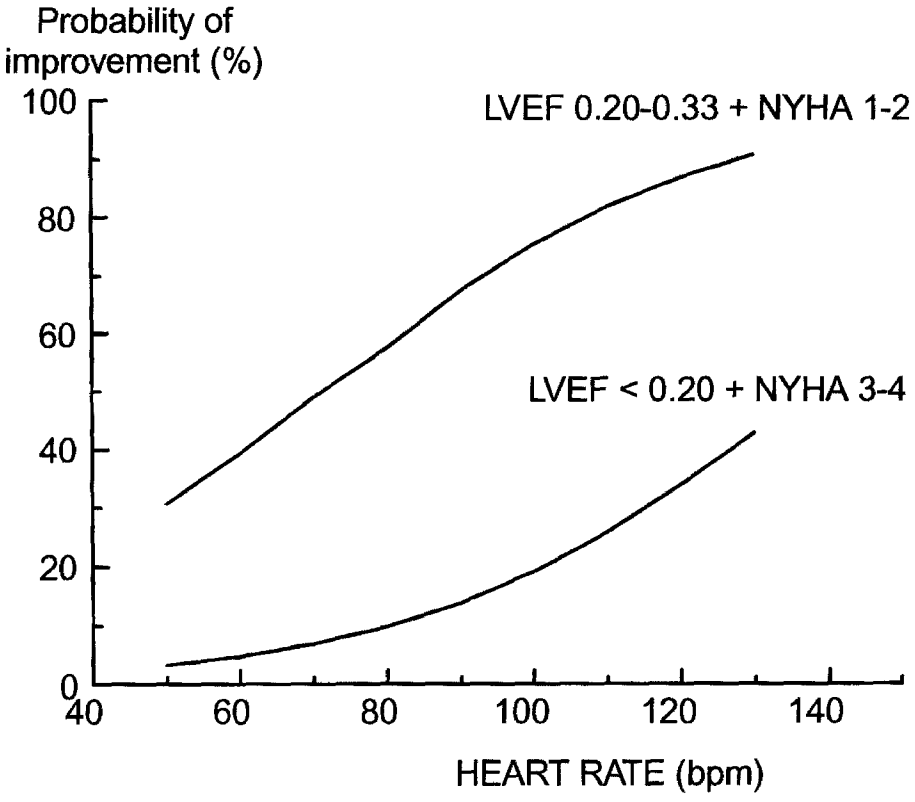

Fig. 4. Relation between probability of improvement and upright resting heart rate in normotensive patients with different degrees of functional impairment and left ventricular dysfunction according to our logit model. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class.

placebo administration (10,40,41), angiotensin-converting enzyme inhibitors, or digitalis (41,42).

In the last few years, some authors (5,8,10,12, 14,29,43–45) analyzed the possibility of improvement in patients with dilated cardiomyopathy on metoprolol, but different and not comparable criteria of improvement were used. While in the MDC study (10) classification of patients was based on a combination of clinical and hemodynamic parameters, in others (44,45) improvement was simply defined according to heart failure symptoms, NYHA classification, left ventricular function, or a combination of these. Conversely, we applied a complex clinical score based on relevant changes of left ventricular systolic (ejection fraction) and diastolic (filling pattern) function, left ventricular dimension (end-diastolic diameter, cardiothoracic ratio), and functional capacity (NYHA class exercise tolerance).

According to our index, 48 patients (51.1% of the total population, 54.5% of tolerant subjects) were classified as improved. This is consistent with the 60% improvement in the MDC trial (10) and other reports (2–5,8,27,46,47).

The identification of predictors of a good response to beta-blockers in dilated cardiomyopathy still remains an unresolved issue. In the study by Swedberg and co-workers (4), "the patients responding best to beta-blockade could not be predicted." On the other hand, patients in NYHA functional class III, with no signs of right heart failure, and with minimal or absent mitral regurgitation showed the highest rate of improvement with metoprolol in the analysis by Waagstein and associates (8). Moreover, in the study by Eichhorn and associates (12), only a higher peak systolic pressure was significantly related to the degree of improvement of ventricular function.

Other investigators reported that the most favorable response occurs in patients with a high heart rate at rest (2,5,14,15,47), shorter duration of symptoms, and more severe impairment of left ventricular function (5). Using these parameters, the multivariate model proposed by Engelmeier and co-workers (5) by a linear discriminant analysis was 78% accurate in predicting a favorable response to metoprolol.

It was also reported (47) that the tolerability to beta-blockers in dilated cardiomyopathy might be at least partially predicted by the severity of structural abnormalities, which was qualitatively estimated from the extent of fibrosis, myocite hypertrophy, and nuclear abnormalities in endomyocardial biopsy samples. Furthermore, in the

Table 5. Internal and External Validation of Our Logit Model on Improvement in Patients With Dilated Cardiomyopathy and Normal Blood Pressure Treated With Metoprolol

Observed Group Membership	No. of Cases*	Predicted Group Membership		
		Improved†	Nonimproved	Correctly Classified (%)
Internal validation				
Improved	28	21	7	75
Nonimproved	43	8	35	81.4
Total	71			78.9
External validation				
Improved	17	12	5	70.6
Nonimproved	7	1	6	85.7
Total	24			75

*The cutoff value for the model predicted probability used to define group membership was 0.50.
†Patients with a model predicted probability of improvement >.50 were classified as improved.

study of Yamada and associates (44), histologic findings, such as the dominant type (pericellular vs focal) and extent of fibrosis were significant predictors of the efficacy of long-term beta-blocker therapy in patients who were able to tolerate the drug. On the other hand, a recent analysis (48) of our histologic data using our strict improvement index could not confirm the results of Yamada and associates (44). Thus, the utility of clinical and histologic variables to predict the response to beta-blocker therapy still remains controversial in patients with dilated cardiomyopathy.

As recently reported by Eichhorn and associates (12), actual analyses indicate that patients with a history of mild hypertension (blood pressure between 140/90 and 170/100 mmHg) are more likely to benefit from long-term metoprolol therapy. Hypertension increases the risk of heart failure about threefold (49), and mild hypertension frequently exacerbates heart failure in dilated cardiomyopathy. In such patients, cardiac performance and clinical symptoms often dramatically improve with tailored medical therapy (50). In our patients, a history of mild hypertension was associated with a high probability of improvement not related to other baseline clinical conditions and to an impressive 20 U mean increase of left ventricular ejection fraction.

On the contrary, a significantly lower probability of improvement was observed among patients without such a history. In these patients, a higher heart rate was significantly associated with a positive, and sometimes exceptional, response to metoprolol.

As reported by Gilbert and co-workers (16), a higher sympathetic activation, or perhaps a more pronounced response to it (in our study expressed by a higher heart rate), might explain the improvement with metoprolol. Despite the strict relationship between the supine and upright heart rates, the higher predictive value of the heart rate during the resting phase of exercise in the upright position might be related to a more preserved baroreflex sensitivity and sympathetic responsiveness, which could characterize responses to beta-blocker treatment.

For optimal cardioprotection, a higher dose of beta-blockers might be preferable, since undesirable adrenergic stimulation would be prevented (45). Furthermore, a reduction in heart rate with metoprolol may be favorable from a bioenergetic standpoint. In a previous report, Bristow and associates (45) showed a dose-related improvement in ventricular function and dimension, with the highest dosage of bucindolol producing a more beneficial effect than a lower dosage. Accordingly, in our study, patients who tolerated the highest dosage of metoprolol and experienced the highest reduction of heart rate, showed the greatest probability of improvement (Fig. 3). Since patients were not randomized but titrated to the maximal tolerated dose, we cannot exclude that patients receiving high doses of metoprolol were the same as those who had the best prognosis.

In the absence of mild hypertension, a higher probability of improvement was present in patients with a high heart rate associated with a left ventricular ejection fraction between 0.20 and 0.33 or with mild symptoms of heart failure (NYHA classes I–II) after stabilization with tailored medical therapy (Fig. 3).

A progressively higher degree of sympathetic activation was also expected in patients with more severe left ventricular dysfunction (51). A lower left ventricular ejection fraction was found by Engelmeier and co-workers (5) to be associated with a positive response to metoprolol, and Erlebacher and co-workers (52) demonstrated that beta-blocking agents can be given to patients with ejection fractions less than 0.20 under close observation without causing a significant hemodynamic deterioration. In our study, a consistent proportion of patients with ejection fraction less than 0.20 and a longer duration of heart failure symptoms showed a resting heart rate less than 90 beats/min, which was probably an expression of progressive down-regulation of beta-recep-

tors (53). According to our strict criteria, these few patients with end-stage cardiomyopathy were characterized by a lower probability of improvement. The beneficial effect on symptoms associated with a low mortality, however, and the impressive improvement observed in some of these patients justifies this therapeutic approach, particularly in patients with higher resting heart rates and short histories of heart failure.

Further investigations are necessary to clarify the response to beta-blockers in patients with mild left ventricular dysfunction, which usually shows a lower sympathetic activation (51).

Clinical Implications

Despite the limitation of a noncontrolled study, this trial on metoprolol in dilated cardiomyopathy supports the possibility of predicting a significant improvement of symptoms, left ventricular function and dimension, and exercise capacity during long-term treatment.

According to our logit model, a probability of good response to metoprolol can be calculated with high accuracy. Patients with a history of mild hypertension or with a high resting heart rate associated with controlled heart failure (NYHA classes I–II) or moderate to severe left ventricular dysfunction (left ventricular ejection fraction between 0.20 and 0.33) show a remarkable probability of improvement on metoprolol.

Sometimes an exceptional improvement can also be observed in patients with more severe heart failure symptoms and left ventricular dysfunction associated to a high heart rate, but an extremely poor response was seen in patients with end-stage dilated cardiomyopathy when a lower heart rate associated with a long history of heart failure indicated a lower probability of reversible left ventricular dysfunction. Our analysis, however, does not allow any conclusion regarding survival. Indeed, beta-blocking agents potentially could also have a survival benefit in patients with little or absent hemodynamic or clinical improvement.

The favorable effects of beta-blockade in our and other studies (2–13) are consistent with the general hypothesis that excessive neuroendocrine activation may be detrimental (54). Since the degree of neuroendocrine activation is a strong predictor of mortality (55), the combination of digitalis, an angiotensin-converting enzyme inhibitor and a beta-receptor blocking agent may, at present, provide the best treatment for heart failure in dilated cardiomyopathy.

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Appendix

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