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Improved Exercise Hemodynamic Status in Dilated Cardiomyopathy After Beta-Adrenergic Blockade Treatment

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Objectives. **This study was performed to investigate exercise hemodynamic status in a double-blind, placebo-controlled trial and was a substudy in the Metoprolol in Dilated Cardiomyopathy Trial.**

Background. **Previous open studies have shown beneficial effects on exercise hemodynamic status after beta-adrenergic blocking agent therapy in patients with congestive heart failure.**

Methods. **The study included 41 patients with idiopathic dilated cardiomyopathy with ejection fraction <0.40 (metoprolol, 20 patients; placebo, 21 patients) whose hemodynamic status was investigated at rest and during supine submaximal exercise, at baseline and after 6 and 12 months of treatment. Myocardial metabolism was evaluated in a subset of 19 patients.**

Results. **Metoprolol-treated patients responded favorably, as expressed by improved exercise cardiac index ([mean ± SD] placebo 4.8 ± 1.6 to 4.7 ± 1.8 liters/min per m^2, metoprolol 4.3 ± 1.1 to 5.4 ± 1.9 liters/min per m^2, p = 0.0001) and stroke work index (placebo 44 ± 20 to 41 ± 27 g·m/m^2, metoprolol 35 ± 16 to 58 ± 28 g·m/m^2, p < 0.0001). Exercise systolic arterial pressure increased (placebo 161 ± 25 to 151 ± 23 mm Hg, metoprolol 155 ± 29 to 165 ± 37 mm Hg, p = 0.0003) as well as exercise oxygen consumption index (placebo 463 ± 194 to 474 ± 232 ml/min per m^2, metoprolol 406 ± 272 to 507 ± 298 ml/min per m^2, p = 0.045). There was a significant increase in exercise duration in the metoprolol group (63 ± 38 s) compared with the placebo group (−24 ± 42 s) (p = 0.01). Net myocardial lactate extraction increased in the metoprolol group, suggesting less myocardial ischemia (placebo 17 ± 22 to 9.5 ± 6.4 mmol/min, metoprolol −32 ± 100 to 42 ± 45 mmol/min, p = 0.03). Peripheral levels of norepinephrine tended to decrease at rest and during exercise, whereas myocardial net spillover was unchanged.**

Conclusions. **Metoprolol improved hemodynamic status in patients with dilated cardiomyopathy at rest and had a more pronounced effect during exercise. These positive effects were achieved along with improved or stable myocardial metabolic data.**

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An increasing number of reports suggest improvement in cardiac function and hemodynamic status after beta-adrenergic blocking agent treatment in patients with heart failure. The original observation of this therapy was reported for metoprolol therapy (1,2). In recent years metoprolol and other beta-blockers have been used successfully (3–6). The vasodilating properties of other beta-blockers may have contributed to the observed improvements. The role of beta-blockade per se as a useful therapy in heart failure has not been established. Up to the present time (7), there have been no larger randomized trials. This study was performed to investigate whether the positive effects previously noted in an open study (6) with regard to exercise hemodynamics and myocardial metabolism could be reproduced in a long-term controlled trial.

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Methods

Patients. The Metoprolol in Dilated Cardiomyopathy Trial was completed in July 1992. The study recruited 383 patients in 33 centers in Europe and North America. The study protocol was double-blind, placebo-controlled and randomized according to center and baseline ejection fraction <0.20 or >0.20. The main results of the Metoprolol in Dilated Cardiomyopathy Trial will be published elsewhere (7). Inclusion criteria were symptomatic dilated cardiomyopathy and ejection fraction <0.40. Exclusion criteria were coronary artery disease confirmed by coronary arteriography, systemic disease, insulin-dependent diabetes mellitus, excessive alcohol consumption, hypertension, signs of active myocarditis or other serious disease that might affect the prognosis of the patient. Before entering the study, the

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Table 1. Baseline Characteristics of 41 Study Patients Randomized to Receive Metoprolol or Placebo Therapy

	Metoprolol Group (n = 20)	Placebo Group (n = 21)	p Value
Men (%)	75	86	—
Age (yr)	46	51	0.14
History (wk)	74 ± 63	107 ± 106	—
New York Heart Association functional class (%)			
II	25	14	
III	70	81	—
IV	0	5	
Ejection fraction (%)	21 ± 7	23 ± 9	—
Exercise time (s)	588 ± 249	564 ± 209	—
Digitalis (%)	60	71	—
Angiotensin-converting enzyme inhibitors (%)	65	90	0.11
Nitrates (%)	20	5	—
Furosemide (mg)	56 ± 46	80 ± 75	—
Creatinine (μmol/liter)	98 ± 19	102 ± 19	—
Sodium (mmol/liter)	139 ± 4	139 ± 3	—
Norepinephrine (nmol/liter)	2.94 ± 1.7	2.76 ± 1.9	0.13
Heart rate (beats/min)	90 ± 16	84 ± 17	—
Systolic blood pressure (mm Hg)	119 ± 17	119 ± 16	—

patients received a test dose of 5 mg of metoprolol twice daily for 2 days. If this dosage was tolerated, the patients were randomly assigned to receive metoprolol or placebo for 12 months. Twenty patients were randomized to receive metoprolol, and 21 patients received placebo treatment. In the main study 4% of the patients were not included because of hemodynamic intolerance. Treatment was continued with increasing doses over 6 weeks according to the following schedule: week 1, 5 mg twice daily; week 2, 5 mg three times a day; week 3, 10 mg twice daily; week 4, 25 mg twice daily; week 5, 25 mg three times a day; week 6, 50 mg twice daily; week 7 and onward, 50 mg three times a day. The final dose was determined by the clinical status of the patient and possible adverse effects. The mean (±SD) final dose was 130 ± 26 mg in the metoprolol group and 116 ± 52 mg in the placebo group (p = NS). In this report the patients participating in an optional substudy on exercise hemodynamic status are presented. The baseline characteristics of the two groups are shown in Table 1. There were no statistically significant differences in baseline variables between the two groups.

Protocol. The test drug was stopped 24 h before the investigation. All other medications were maintained throughout the investigation. The patients were studied before inclusion and after 6 and 12 months of treatment. On day 1, the patient performed a maximal sitting bicycle exercise test starting at 20 W, with increments of 10 W/min. Radionuclide angiocardiography was performed on day 2. On day 3, right heart catheterization was performed in the morning with the patient in a fasting state and without premedication. A triple-lumen Swan-Ganz pulmonary artery catheter and a Wilton-Webster coronary sinus catheter were introduced percutaneously through the internal jugular vein. The correct position of the coronary sinus catheter was checked by fluoroscopic injection of radiopaque medium and by tracings of flow curves. An arterial line was obtained through the radial artery. Pressures, flows and blood samples were obtained at rest. The patients then performed supine bicycle exercise at a fixed load of 50% of their maximal work load as determined from the exercise test performed on day 1. After 4 min of exercise, pressures were recorded, and thereafter flow measurements and blood sampling were performed during continuous exercise. Coronary sinus catheterization was optional in the study protocol and was only performed at the coordinating center.

Measurements. Functional status was assessed according to New York Heart Association functional classification. Left ventricular ejection fraction was estimated from equilibrium radionuclide angiography. Flows were measured by a thermodilution technique. Cardiac output was measured in the pulmonary artery and was calculated by computers. The coronary sinus catheter was attached to a Wheatstone bridge, and changes in thermistor resistance caused by temperature changes were recorded on a Siemens-Elema mingograph. Coronary sinus blood flow was calculated with a standard formula (8). Blood samples were obtained for analysis of oxygen content and catecholamine and lactate concentration levels. Norepinephrine and epinephrine levels in plasma were measured by high performance liquid chromatography with electrochemical detection (9). Lactate was analyzed with an enzymatic method (Lactate Analyzer 640, Roche Bio-Electronics).

Derived variables. The following variables were derived: Cardiac index (Cardiac output/Body surface area; stroke volume index (Stroke volume/Body surface area); stroke work index [(Mean artery pressure − Pulmonary capillary wedge pressure) × Stroke volume index × 0.0136]; oxygen consumption index (Cardiac index × Arteriovenous oxygen difference); rate-pressure product (Mean artery pressure × Heart rate); systemic vascular resistance [(Mean artery pressure − Right atrial pressure)/Cardiac output]; and myocardial oxygen consumption [Coronary sinus flow × (Arterial oxygen content − Coronary sinus oxygen content)]. Net myocardial extraction of lactate and catecholamines = Coronary sinus flow × (Arterial concentration − Coronary sinus concentration). Coronary sinus flow tracings could not be obtained in all patients because of difficulties with positioning the catheter.

The study was approved by the Ethics Committee of the Medical Faculty, University of Göteborg. Participating patients gave informed consent before inclusion in the study.

Statistical methods. Data were analyzed with an IBM 3081 minicomputer-based SAS statistical software (SAS Inc.). Analysis of variance of repeated measures with

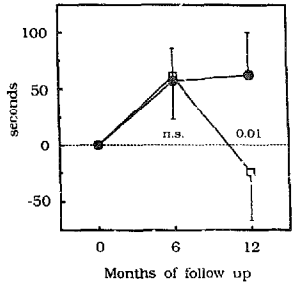


Figure 1. Effects on changes in exercise time from baseline investigation; p values denote intergroup comparison by analysis of variance from baseline to 6 and 12 months of follow-up. Data are mean values ± SEM. Circles = metoprolol; squares = placebo.

unbalanced data (10) was used. All p values were two-tailed. All values are expressed as mean values ± 1 SD and in figures as mean values ± 1 SEM.

Results

One patient in the placebo group, who was withdrawn from the study after 6 months of follow-up because of clinical deterioration and noncompliance, died of congestive heart failure before the end of the study. Another patient in the placebo group died of congestive heart failure after 6 months of treatment, and one patient in the metoprolol group died suddenly after 6 months of treatment. One patient in the placebo group reached a nonfatal end point (need for heart transplantation) but maintained therapy and was studied at 12 months of follow-up. Hemodynamic evaluation at 6 months was not performed in all patients because of administrative reasons. Furthermore, in the metoprolol group, one patient's clinical condition was too poor to allow supine exercise on the catheterization table, and one patient was unable to exercise because of knee pain.

Functional classification did not change significantly during the study period. Maximal exercise time increased significantly in the metoprolol group by 12 months of treatment (Fig. 1). Ejection fraction increased significantly more in the metoprolol group (21% ± 7, 30% ± 11, 34% ± 13 at baseline and at 6 and 12 months, respectively) compared with the

Table 2. Hemodynamic Variables at Rest, at Baseline Investigation and at 6 and 12 Months of Follow-Up

	Baseline	6 mo	p Value*	12 mo	p Value*
No. of pts					
Placebo	21	16		18	
Metoprolol	20	15		17	
Heart rate (beats/min)					
Placebo	84 ± 17	83 ± 19	0.05	85 ± 12	0.01
Metoprolol	90 ± 16	75 ± 15		80 ± 18	
Right atrial pressure (mm Hg)					
Placebo	4 ± 3.7	4 ± 4.4	—	3 ± 3.1	—
Metoprolol	4 ± 3.9	2 ± 3.1		3 ± 2.4	
Pulmonary capillary wedge pressure (mm Hg)					
Placebo	15 ± 10	12 ± 10	0.09	13 ± 10	0.20
Metoprolol	15 ± 8.2	8 ± 6.4		9 ± 5.0	
Systolic arterial pressure (mm Hg)					
Placebo	121 ± 17	112 ± 17	0.02	115 ± 18	0.005
Metoprolol	119 ± 23	124 ± 26		132 ± 26	
Cardiac index (liters/min per m^2)					
Placebo	2.5 ± 0.6	2.5 ± 0.5	0.17	2.5 ± 0.6	0.01
Metoprolol	2.4 ± 0.5	2.6 ± 0.7		2.8 ± 0.7	
Stroke volume index (ml/m^2)					
Placebo	30 ± 10	28 ± 12	0.04	29 ± 12	0.0006
Metoprolol	27 ± 8	36 ± 12		37 ± 10	
Stroke work index (g·m/m^2)					
Placebo	36 ± 10	28 ± 12	0.004	29 ± 12	< 0.0001
Metoprolol	27 ± 12	38 ± 16		42 ± 15	
Systemic vascular resistance (dynes·s·cm^{-5})					
Placebo	1,431 ± 445	1,302 ± 405	—	1,376 ± 380	—
Metoprolol	1,489 ± 414	1,423 ± 580		1,312 ± 460	
Oxygen consumption index (ml/min per m^2)					
Placebo	127 ± 49	130 ± 29	0.10	118 ± 48	0.08
Metoprolol	103 ± 59	124 ± 32		106 ± 61	

*Changes from baseline in intergroup comparison by analysis of variance. pts = patients.

Table 3. Hemodynamic Variables During Supine Submaximal Exercise, at Baseline Investigation and at 6 and 12 Months of Follow-Up

	Baseline	6 mo	p Value*	12 mo	p Value*
No. of pts					
Placebo	21	16		18	
Metoprolol	20	15		17	
Work load (W)					
Placebo	56 ± 22	58 ± 24	0.14	57 ± 26	0.14
Metoprolol	54 ± 21	63 ± 26		58 ± 23	
Heart rate (beats/min)					
Placebo	126 ± 16	129 ± 16	0.07	128 ± 11	0.02
Metoprolol	136 ± 20	123 ± 22		124 ± 26	
Right atrial pressure (mm Hg)					
Placebo	8 ± 4.5	9 ± 6.5	—	9 ± 7.3	0.13
Metoprolol	9 ± 4.6	7 ± 5.9		8 ± 4.5	
Pulmonary capillary wedge pressure (mm Hg)					
Placebo	27 ± 11	23 ± 12	0.09	25 ± 12	0.047
Metoprolol	28 ± 7.9	19 ± 7.6		21 ± 12	
Systolic arterial pressure (mm Hg)					
Placebo	161 ± 25	149 ± 31	0.10	151 ± 23	0.0003
Metoprolol	155 ± 29	151 ± 35		165 ± 37	
Cardiac index (liters/min per m^2)					
Placebo	4.8 ± 1.6	4.9 ± 1.7	0.01	4.7 ± 1.8	0.0001
Metoprolol	4.3 ± 1.1	5.1 ± 1.8		5.4 ± 1.9	
Stroke volume index (ml/m^2)					
Placebo	39 ± 15	37 ± 14	0.001	38 ± 15	< 0.0001
Metoprolol	32 ± 9	42 ± 14		46 ± 17	
Stroke work index (gm/m^2)					
Placebo	44 ± 20	37 ± 19	< 0.0001	41 ± 27	< 0.0001
Metoprolol	35 ± 16	49 ± 27		58 ± 28	
Systemic vascular resistance (dynes·s·cm^{-5})					
Placebo	991 ± 469	897 ± 508	—	875 ± 348	0.19
Metoprolol	917 ± 276	820 ± 356		854 ± 406	
Oxygen consumption index (ml/min per m^2)					
Placebo	463 ± 194	539 ± 186	0.04	474 ± 232	0.045
Metoprolol	406 ± 272	571 ± 205		507 ± 298	

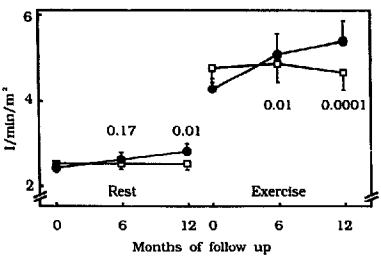
*Changes from baseline in intergroup comparison by analysis of variance. pts = patients.

placebo group (23% ± 9, 24% ± 9, 28% ± 12 at baseline and at 6 and 12 months, respectively). The corresponding p values in intergroup comparison of changes from baseline were p = 0.02 at 6 months and p = 0.03 at 12 months.

Hemodynamic data. At rest, metoprolol treatment was associated with a significantly lower heart rate and an increase in systolic arterial pressure and cardiac, stroke volume and stroke work indexes (Tables 2 and 3). There were similar trends during exercise, although the increase in cardiac, stroke volume and stroke work indexes in the metoprolol group seemed to be more pronounced (Fig. 2). Individual data points on stroke work index at baseline and after 12 months of treatment are shown in Figure 3. There was a trend toward lower pulmonary capillary wedge pressure in the metoprolol group at rest as well as during exercise (Fig. 4). Exercise oxygen consumption index increased significantly in the metoprolol group compared with the placebo group.

Myocardial metabolism. Although the average myocardial lactate extraction at baseline rest investigation was negative in the metoprolol group, suggesting myocardial ischemia, there was no statistical difference between the two groups (Tables 4 and 5). The negative extraction turned to positive after 6 and 12 months of treatment (Fig. 5). The

Figure 2. Effects on cardiac index at rest and during supine bicycle submaximal exercise; p values and symbols as in Figure 1.



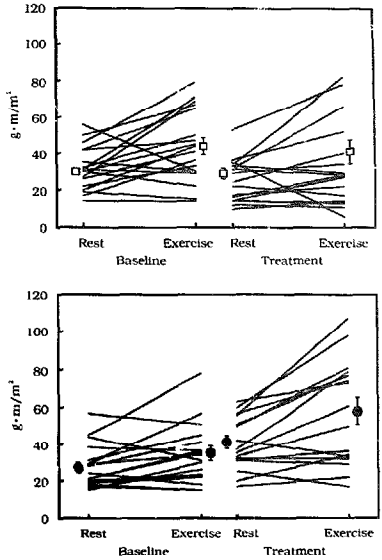


Figure 3. Stroke work index represented by individual data points in the placebo **(top)** and metoprolol **(bottom)** groups at baseline and after 12 months of treatment. Patients were investigated at rest and during supine submaximal exercise. Mean values ± SEM are also shown.

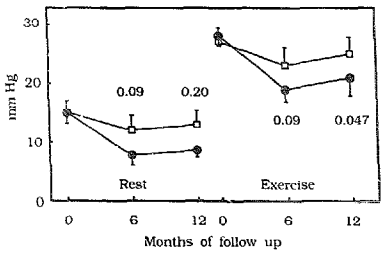


Figure 4. Effects on pulmonary capillary wedge pressure at rest and during supine bicycle submaximal exercise; p values and symbols as in Figure 1.

placebo group had positive extraction at baseline that was unaltered by therapy. The trends were similar during exercise, but were not statistically different in group comparisons. Coronary sinus flow and myocardial oxygen consumption did not change during the study. By analysis of variance the arterial norepinephrine concentration decreased significantly more in the metoprolol group than in the placebo group during follow-up ($p = 0.03$). Myocardial metabolism of norepinephrine and epinephrine was unaltered by metoprolol and placebo treatment.

Discussion

The patients receiving metoprolol treatment responded favorably, as expressed by improved hemodynamic status, improved ejection fraction, increased myocardial lactate extraction and lower arterial norepinephrine levels, whereas the placebo-treated patients did not show any such improvement. Hemodynamic improvement seemed more accentuated during exercise, suggesting improved cardiovascular reserve.

Hemodynamic variables. Both rest and exercise hemodynamic variables suggested improvement in the metoprolol group, whereas the placebo group was unchanged. Lower heart rate and filling pressures, accompanied by increased stroke volume, stroke work and cardiac indexes are in accordance with most previous trials (4,11–13). The difference between the groups tended to be more accentuated during exercise, possibly reflecting an improved myocardial reserve. Although the patients in our previous open study had worse myocardial function compared with the patients in this study, the magnitude of improvement was very similar (6). In the present study there was an increase in maximal exercise time in the metoprolol group, but the derived supine submaximal exercise load was very similar in the two groups during the study investigations. In consideration of the latter, and the marked improvement in exercise hemodynamic variables found in this study, it might be that submaximal performance is a better measure of treatment effect. It is also likely that a submaximal performance would better reflect everyday activities than the ordinary maximal exercise test.

Myocardial metabolism and catecholamine levels. After intravenous beta-blocker administration, myocardial energy demand is reduced (14). During long-term therapy, metoprolol tended to improve ventricular energetics, as reflected by increase in stroke work index, ejection fraction and arterial pressure. However, the improvement in cardiac function is not accompanied by increased energy demand, as expressed by unchanged myocardial oxygen consumption and norepinephrine spillover. Peripheral norepinephrine values decreased by 42% in the metoprolol group at rest and by 17% during exercise, which is in accordance with our previous study (6). Two other studies have suggested a

Table 4. Catecholamine Levels and Myocardial Metabolic Data at Rest, at Baseline Investigation and at 6 and 12 Months of Follow-Up

	Baseline	6 mo	p Value*	12 mo	p Value*
No. of pts					
Placebo	11	11		11	
Metoprolol	10	10		10	
Coronary sinus flow (ml/min)					
Placebo	164 ± 101	245 ± 123	—	115 ± 58	0.12
Metoprolol	143 ± 89	131 ± 58		177 ± 102	
Myocardial oxygen consumption (ml/min)					
Placebo	22 ± 15	33 ± 16	—	15 ± 7.5	0.12
Metoprolol	20 ± 16	17 ± 8.6		24 ± 18	
Arterial lactate (mmol/liter)					
Placebo	0.55 ± 0.25	0.63 ± 0.33	—	0.62 ± 0.24	—
Metoprolol	0.55 ± 0.18	0.59 ± 0.28		0.85 ± 0.17	
Net lactate extraction (mmol/min)					
Placebo	17 ± 22	22 ± 25	—	9.5 ± 6.4	0.03
Metoprolol	−32 ± 100	22 ± 18		42 ± 45	
Arterial norepinephrine (nmol/liter)					
Placebo	2.76 ± 3.3	3.20 ± 2.3	0.03	2.46 ± 1.5	0.16
Metoprolol	2.94 ± 1.7	1.72 ± 2.3		1.70 ± 0.65	
Net norepinephrine extraction (nmol/min)					
Placebo	−288 ± 455	−733 ± 833	0.17	−233 ± 144	—
Metoprolol	−286 ± 269	−91 ± 112		−145 ± 228	
Arterial epinephrine (nmol/liter)					
Placebo	0.97 ± 0.47	1.14 ± 1.0	—	0.60 ± 0.47	—
Metoprolol	0.84 ± 0.37	0.52 ± 0.30		0.37 ± 0.16	
Net epinephrine extraction (nmol/min)					
Placebo	35 ± 31	11 ± 86	—	17 ± 13	—
Metoprolol	32 ± 38	37 ± 37		24 ± 25	

*Changes from baseline in intergroup comparison by analysis of variance. pts = patients.

reduction in norepinephrine levels after beta-blockade in patients with dilated cardiomyopathy, whereas there was no effect in patients with ischemic cardiomyopathy (3,15).

Beta-blocker therapy. From the results of previous studies we have suggested that the primary short-term effect of beta-blockade in heart failure is a reduction in metabolic demand (11,16). Heart rate, myocardial oxygen consumption and coronary sinus flow decreased, whereas filling pressure, ventricular volume and ejection fraction were maintained (14). The main achievement of beta-blockade may be to induce this state of low oxygen demand, whereas systemic circulation is maintained on an acceptable level, pending recovery of myocardial function. The beneficial effect on myocardial function is supported by the findings of relieved ischemia, expressed by increased lactate utilization. Along with improved myocardial function, higher dosages of beta-blockade are tolerated with maintained systemic circulation. This could explain why long-term studies could yield different results than short-term studies (17,18), as well as why patients with very poor ventricular function may be unable to recover (19). Furthermore, it would explain why beta-blockade therapy must be instituted at low doses and gradually increased over several weeks. In contrast with inotropic agents (20,21), the inotropic recovery after beta-blockade is not accompanied by an increase in myocardial oxygen consumption. Increased beta-receptor density and function have been proposed as one reason for improved ventricular function (11,12). In a recent report, however, it was suggested that improvement in cardiac function was not related to increment in beta-adrenoreceptor activity (22). Modern adrenergic beta-blockers have been used successfully in recent trials (3,13,22,23). Bucindolol and carvedilol are beta-blockers with vasodilating properties. The vasodilatory effect should be of benefit but makes interpretation of the results more difficult with respect to whether the hemodynamic effect is due to beta-blockade or vasodilation. From the Metoprolol in Dilated Cardiomyopathy Trial (7) it was suggested that only 4% of the patients showed intolerance to metoprolol. However, in severely decompensated patients, the intolerance may be as great as 50% (11). This study was performed in patients with pure idiopathic dilated cardiomyopathy. Most previous studies reporting beneficial effects of beta-blockade treatment have been performed in patients with dilated cardiomyopathy. There are more controversies with respect to beta-blockade treatment in congestive heart failure of other etiologies. Some results suggest less positive effects in ischemic cardiomyopathy (3,6,15), but recent reports also suggest positive effects in ischemic patients (24).

Table 5. Catecholamine Levels and Myocardial Metabolic Data During Supine Submaximal Exercise, at Baseline Investigation and 6 and 12 Months of Follow-Up

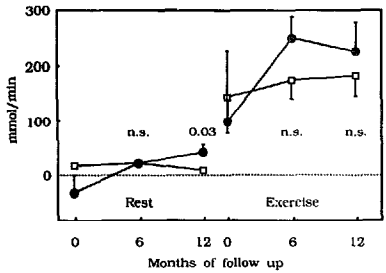
	Baseline	6 mo	p Value*	12 mo	p Value*
No. of pts					
Placebo	10	10		9	
Metoprolol	9	9		5	
Coronary sinus flow (ml/min)					
Placebo	304 ± 234	299 ± 110	—	275 ± 167	—
Metoprolol	286 ± 128	248 ± 82		316 ± 71	
Myocardial oxygen consumption (ml/min)					
Placebo	45 ± 37	40 ± 13	—	39 ± 24	—
Metoprolol	44 ± 25	33 ± 13		42 ± 7.1	
Arterial lactate (mmol/liter)					
Placebo	2.38 ± 1.3	2.77 ± 0.88	—	2.44 ± 0.90	—
Metoprolol	2.23 ± 1.5	3.13 ± 1.3		2.61 ± 1.2	
Net lactate extraction (mmol/min)					
Placebo	145 ± 210	176 ± 108	—	184 ± 110	—
Metoprolol	99 ± 383	249 ± 121		226 ± 117	
Arterial norepinephrine (nmol/liter)					
Placebo	10.5 ± 8.4	8.25 ± 5.3	—	11.8 ± 6.9	0.04
Metoprolol	11.0 ± 4.1	7.68 ± 4.4		9.16 ± 5.8	
Net norepinephrine extraction (nmol/min)					
Placebo	−1,382 ± 2,199	−1,351 ± 1,019	—	−2,148 ± 1,045	—
Metoprolol	−403 ± 1,064	−884 ± 1,005		−1,186 ± 581	
Arterial epinephrine (nmol/liter)					
Placebo	3.95 ± 9.1	1.48 ± 1.3	0.02	1.38 ± 0.96	—
Metoprolol	1.61 ± 1.1	0.99 ± 0.84		0.78 ± 0.23	
Net epinephrine extraction (nmol/min)					
Placebo	56.6 ± 162	−12.0 ± 60	—	10.1 ± 31	—
Metoprolol	10.9 ± 95	47.6 ± 97		−32.4 ± 10	

*Changes from baseline in intergroup comparison by analysis of variance. pts = patients.

This study adds further support to the theory that long-term beta-blockade treatment constitutes a therapeutic alternative in patients with dilated cardiomyopathy.

Study limitations. In the present study the test drug was withheld before investigations to assess the long-term effects of beta-blockade treatment apart from ongoing drug effects. To avoid a rebound phenomenon the drug was not withheld >2 days (25,26). The present data support that this approach did not cause any increase in sympathetic drive, as expressed by alterations in heart rate or catecholamine levels. On the contrary, a lower beta-blockade level may influence hemodynamic status, resulting in impairment of diastolic function and filling pressures in particular, which in turn might influence exercise tolerance (27,28). Assessment of myocardial metabolism by the present method has some limitations. A more precise isotope tracer technique was not available in our department at the time of the study (29). Further, there were only myocardial metabolic data from five patients during exercise in the metoprolol group at 12 month follow-up.

Figure 5. Effects on net myocardial lactate release at rest and during supine bicycle submaximal exercise; p values and symbols as in Figure 1.



Conclusions. There is accumulated evidence that long-term treatment with beta-blockers is useful in congestive heart failure, especially that due to dilated cardiomyopathy. The present study further supports the unique therapeutic effects of beta-blockers, which are totally different from other pharmacologic therapies in heart failure. Protection from sympathetic overstimulation is in accordance with the fundamentals of contemporary heart failure therapy, with internal unloading instead of increased inotropic stimulation.

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