

# Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: Analysis with magnetic resonance myocardial tagging

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**Background** Recent data suggest that beta-blockers can be beneficial in subgroups of patients with chronic heart failure (CHF). For metoprolol and carvedilol, an increase in ejection fraction has been shown and favorable effects on the myocardial remodeling process have been reported in some studies. We examined the effects of bisoprolol fumarate on exercise capacity and left ventricular volume with magnetic resonance imaging (MRI) and applied a novel high-resolution MRI tagging technique to determine myocardial rotation and relaxation velocity.

**Methods** Twenty-eight patients (mean age,  $57 \pm 11$  years; mean ejection fraction,  $26 \pm 6\%$ ) were randomized to bisoprolol fumarate ( $n = 13$ ) or to placebo therapy ( $n = 15$ ). The dosage of the drugs was titrated to match that of the the Cardiac Insufficiency Bisoprolol Study protocol. Hemodynamic and gas exchange responses to exercise, MRI measurements of left ventricular end-systolic and end-diastolic volumes and ejection fraction, and left ventricular rotation and relaxation velocities were measured before the administration of the drug and 6 and 12 months later.

**Results** After 1 year, heart rate was reduced in the bisoprolol fumarate group both at rest ( $81 \pm 12$  before therapy versus  $61 \pm 11$  after therapy;  $P < .01$ ) and peak exercise ( $144 \pm 20$  before therapy versus  $127 \pm 17$  after therapy;  $P < .01$ ), which indicated a reduction in sympathetic drive. No differences were observed in heart rate responses in the placebo group. No differences were observed within or between groups in peak oxygen uptake, although work rate achieved was higher ( $117.9 \pm 36$  watts versus  $146.1 \pm 33$  watts;  $P < .05$ ) and exercise time tended to be higher ( $9.1 \pm 1.7$  minutes versus  $11.4 \pm 2.8$  minutes;  $P = .06$ ) in the bisoprolol fumarate group. A trend for a reduction in left ventricular end-diastolic volume ( $-54$  mL) and left ventricular end-systolic volume ( $-62$  mL) in the bisoprolol fumarate group occurred after 1 year. Ejection fraction was higher in the bisoprolol fumarate group ( $25.0 \pm 7$  versus  $36.2 \pm 9\%$ ;  $P < .05$ ), and the placebo group remained unchanged. Most changes in volume and ejection fraction occurred during the latter 6 months of treatment. With myocardial tagging, insignificant reductions in left ventricular rotation velocity were observed in both groups, whereas relaxation velocity was reduced only after bisoprolol fumarate therapy (by 39%;  $P < .05$ ).

**Conclusion** One year of bisoprolol fumarate therapy resulted in an improvement in exercise capacity, showed trends for reductions in end-diastolic and end-systolic volumes, increased ejection fraction, and significantly reduced relaxation velocity. Although these results generally confirm the beneficial effects of beta-blockade in patients with chronic heart failure, they show differential effects on systolic and diastolic function. (*Am Heart J* 2002;143:676-83.)

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The deleterious consequences of sympathetic activation in chronic heart failure (CHF) have been recognized for nearly 2 decades.<sup>1</sup> The degree of excess neurohormonal activation in this condition correlates with disease severity, is associated with progressive deterioration of cardiac function, accelerates abnormal myocardial remodeling after an infarction, and increases mortality rates.<sup>2-4</sup> In recent years, an interest in beta-adrenergic blocking agents as a therapeutic option in heart failure

has arisen in large part because of their ability to suppress sympathetic drive.<sup>2,3,5</sup>

The potential mechanisms by which inhibition of sympathetic activation may benefit patients with CHF include the prevention of beta-receptor down-regulation, improved relaxation and contraction as the result of improved myocardial energetic balance, improved mortality rate through inhibition of excessive catecholamine levels, and antiarrhythmic effects.<sup>2,5-7</sup> As a consequence of these effects, some studies have shown improvements in hemodynamic indices, ventricular function, exercise tolerance, and left ventricular remodeling.<sup>2,5,8-10</sup> However, the effects of beta-blockade therapy on exercise capacity have been mixed, with most studies showing no significant improvement.<sup>8,10</sup> Moreover, the influence of beta-blockade therapy on left ventricular size is unclear, and there are few controlled studies that have evaluated the effects of these agents on left ventricular mass, volume, and function. Most previous studies have been performed with metoprolol and carvedilol, but it is also unclear whether their effects can be generalized to all beta-blockers in patients with CHF. In addition, little is known about the effects of these agents on the hemodynamic and ventilatory gas exchange response to exercise in patients with CHF.

Previous studies have assessed changes in left ventricular function after beta-blockade therapy with echocardiographic or radionuclide techniques. Although these techniques provide an assessment of cardiac motion in terms of radial displacement or systolic shortening, rotational movements during systole and diastole cannot be easily imaged with these techniques. Because different points of the myocardium are analyzed during the cardiac cycle, significant errors can occur in the determination of radial displacement. Recently, novel myocardial tagging techniques with magnetic resonance imaging (MRI) have been developed, which make it possible to label specific myocardial regions and quantify torsional motion of the ventricle during contraction (“twisting”) and filling (“untwisting”).<sup>11,12</sup> To our knowledge, no previous studies have assessed the effects of beta-blockade with MRI or tagging techniques in patients with reduced ventricular function.

This study is a detailed analysis of the effects of bisoprolol fumarate on the hemodynamic and gas exchange response to exercise in patients with CHF. To our knowledge, this is the first study to assess left ventricular volumes and function with MRI and to use myocardial tagging techniques to analyze rotation and relaxation velocities in patients with reduced ventricular function after beta-blockade therapy.

## Methods

### Patients

Twenty-eight patients with stable CHF were randomized to either bisoprolol fumarate (n = 13) or placebo (n = 15) ther-

**Table I.** Demographic and clinical characteristics at baseline

Patient characteristics	Bisoprolol fumarate (n = 13)	Placebo (n = 15)
Age (years)	55.4 ± 12	59.4 ± 10
Height (cm)	173.5 ± 5.1	171.0 ± 7.5
Weight (kg)	75.6 ± 8	69.9 ± 13
Maximal oxygen uptake (mL/kg/min)	18.3 ± 5	18.9 ± 3
Ejection fraction (%)	26.7 ± 6.2	25.1 ± 5.1
Pulmonary function		
Forced expiratory volume, in 1 second (L)	2.81 ± 0.72	2.93 ± 0.65
Forced expiratory volume (% of healthy)	83.3 ± 18	94.8 ± 14
Forced vital capacity (L)	3.78 ± 0.74	3.52 ± 0.78
Forced vital capacity (% of healthy)	88.1 ± 15	91.9 ± 14
Peak expiratory flow (% of healthy)	77.8 ± 21	86.4 ± 23
Etiology of CHF		
Coronary artery disease	8	8
Idiopathic	5	7
Medications		
Digoxin	5	9
ACE inhibitor	13	15
Diuretics	10	14
Others	13	10
Risk factors		
Smoking	8	7
Diabetes mellitus	1	0
Hyperlipidemia	5	3
Hypertension	5	7
Family history of CAD	6	4

CHF, Chronic heart failure; ACE, angiotensin-converting enzyme; CAD, coronary artery disease

apy. Clinical characteristics of the 2 groups at randomization are presented in Table I. Eight patients in the bisoprolol fumarate group and 8 in the placebo group had an underlying etiology of coronary artery disease; in all others, the etiology was idiopathic cardiomyopathy. Inclusion criteria and the study protocol were in accordance with those of the Cardiac Insufficiency Bisoprolol Study (CIBIS).<sup>13</sup> To be considered for the study, patients had to meet the following criteria: 1, dyspnea or fatigue corresponding to New York Heart Association functional classification II or III; 2, ambulatory and not awaiting transplantation; 3, diuretic and angiotensin-converting enzyme-inhibitor therapy; 4, nuclear or angiographic ejection fraction of less than 40%, performed within 4 weeks of randomization; 5, clinical stability defined as absence of any episode of heart failure decompensation during the 6-week period before study entry; and 6, the absence of any major changes in therapy during the previous 3 weeks.

### Study protocol

The study was double-blinded and randomized with a list of random numbers. The treatment period was 1 year. Bisoprolol fumarate is a beta<sub>1</sub>-selective adrenoceptor antagonist without any partial agonist or vasodilatory effects, with a half life of 10

to 12 hours. Treatment was titrated and administered with divisible 2.5-mg pills and matched placebo. The initial dose was 1.25 mg/day, increased 48 hours later to 2.5 mg/day and by 1 month to as high as 10 mg/day according to tolerance and clinical status of the patient. After individual titration, the mean bisoprolol fumarate dose was 7.19 mg for the duration of the study.

### Exercise testing

On the day of testing, patients in both groups were requested to abstain from food, coffee, and cigarettes for 3 hours before the test. Standard pulmonary function tests were performed. Maximal exercise testing was performed on an electrically braked cycle ergometer with an individualized ramp protocol.<sup>14</sup> Briefly, this test entailed choosing an individualized ramp rate to yield a test duration of approximately 10 minutes. The patient's subjective level of exertion was quantified every minute with the Borg 6-20 scale.<sup>15</sup> All the tests were continued to volitional fatigue/dyspnea. Respiratory gas exchange variables were acquired continuously throughout exercise with the Schiller CS-100 metabolic system. Gas exchange variables analyzed included oxygen uptake, carbon dioxide production, minute ventilation, respiratory rate, tidal volume, oxygen pulse, and respiratory exchange ratio.

### Magnetic resonance imaging

Cine-MRI was performed with a commercially available 1.5-T MRI scanner (Gyrosan ACS/NT, Best, The Netherlands). Patients were positioned into a circular surface coil in the prone position. Instructions were given to each patient regarding breath holding during imaging and specifically avoiding the Valsalva maneuver; each patient performed several practice procedures before imaging. Electrodes were placed on the chest to synchronize the images with the electrocardiogram signal. Determination of the short axis geometry was carried out with bright blood turbo-field-echo sequences. Two short localizer scans were applied: a first multiple slice scan in the transverse plane and a second scan along a line extending from the apex of the left ventricle to the center of the mitral valve (vertical long axis scan). The left ventricular short axis view was defined as imaging planes perpendicular to the left ventricular long axis.

To obtain images with uniform signal intensity and contrast, a homogeneity correction algorithm was applied to all the images acquired with the surface coil immediately during image reconstruction. This step also minimized differences in image intensities and contrast over the patient population. Image quality permitted the left ventricles of all patients to be evaluated. All images were analyzed by the same investigator (T.S.) who was blinded to patient group. Myocardial contours were marked manually for end-diastolic and end-systolic images for both the left and the right ventricle with the system software. End-diastole was defined as the image acquired directly after the R-wave of the electrocardiogram. End-systole was defined as the image with the smallest left ventricular cavity area in an equatorial plane. For each slice image, the following 5 contours were drawn manually: left ventricular epicardial border, left ventricular endocardial border, left

ventricular endocardial border excluding papillary muscles, right ventricular epicardial border, and right ventricular endocardial border. The long axis extension of the left ventricle from apex to base was measured in the vertical long axis images acquired for planing. This information was used to determine the most basal slice within the chamber to draw endocardial contours. Ventricular volumes were calculated as the sum of the measured cavity area with exclusion of the visible papillary muscles multiplied by the slice thickness plus the slice gap (volumetric method). The volumes obtained were used to calculate left and right ventricular ejection fraction and stroke volume. Cardiac output in liters per minute was obtained from the product of stroke volume and heart rate. Peripheral resistance was calculated with  $[80 \times (\text{mean arterial pressure}/\text{cardiac output})]$ .

### Myocardial tagging

All the subjects underwent imaging with a conventional 1.5-T magnetic resonance system (Gyrosan ACS II; Philips, Best, The Netherlands) while they lay prone, with a cardiac surface coil (16 cm diameter). An electrocardiogram was recorded, and respiratory motion was monitored with a strain gauge. After 2 short scans to localize the longitudinal heart axis, 3 short-axis planes (basal 1 cm below the valvular annulus, equatorial at mid-distance between basal and apical planes, and apical 1 cm caudal to the endocardium of the apex) were imaged and labeled with a rectangular grid (spacing 8 mm) with the Complementary Spatial Modulation of Magnetization (CSPAMM) technique. A total of 16 images was acquired for each imaging plane beginning at end-diastole and ending during the next diastole. Temporal resolution was 35 ms, and spatial resolution was 1.4 mm  $\times$  1.4 mm with slice thicknesses of 6 mm at the apex, 7 mm at the equator, and 8 mm at the base. Motion artefacts were reduced with implementation of a breathing scheme in which the patient was asked to breathe regularly and every 4th and 5th heartbeat was used for acquisition and images during a short period of apnea. One set of images was acquired for tagging of the horizontal lines, and one set of images for the vertical lines. A rectangular grid was achieved with multiplication of the 2 images. Acquisition time was 8 to 12 minutes per slice.

The intersection points of the tagging lines were marked and traced semiautomatically in each image with a custom-written evaluation program. Epicardial and endocardial borders were defined manually in the first image. The position of the border relative to the intramyocardial grid-crossing points was calculated and then automatically determined in all other images with the motion of the grid-crossing points. From the intersection points of the lines, 72 endocardial, midmyocardial, and epicardial points were calculated with the centerline method. End-diastole was defined as the first image after the R wave, and end-systolic as the image with the smallest cavity volume. The left ventricle was divided into 8 segments with the septal insertion point of the right ventricle and the center of gravity of left ventricle as reference points. We compensated for translational motion with the slice-monitoring technique.

Systolic rotation (degrees) was defined as the systolic component of circular motion of a midmyocardial region around the center of gravity. Clockwise rotation was described as negative, and counterclockwise rotation as positive. Diastolic

**Table II.** Exercise and gas exchange data

	Bisoprolol fumarate group			Placebo group			P value between groups
	Baseline	6 Months	1 Year	Baseline	6 Months	1 Year	
<b>Rest</b>							
Heart rate (bpm)	81 ± 12	64 ± 13*	61 ± 11*	84 ± 13	80 ± 9	68 ± 7	<.001
Systolic BP (mm Hg)	125 ± 15	130 ± 15	138 ± 18	129 ± 15	133 ± 18	144 ± 18	.59
Diastolic BP (mm Hg)	82 ± 13	79 ± 10	85 ± 11	90 ± 7	86 ± 14	81 ± 11	.11
<b>Maximal exercise</b>							
Heart rate (bpm)	144 ± 20	126 ± 24†	127 ± 17*	146 ± 17	148 ± 17	150 ± 19	.03
Systolic BP (mm Hg)	166 ± 22	179 ± 27	199 ± 18†	162 ± 31	166 ± 34	179 ± 25	.51
Diastolic BP (mm Hg)	97 ± 12	95 ± 15	104 ± 18	100 ± 10	97 ± 19	99 ± 11	.83
Oxygen uptake (mL/min)	1391 ± 411	1526 ± 361	1672 ± 314	1335 ± 382	1357 ± 375	1420 ± 328	.62
Oxygen uptake (mL/kg/min)	18.3 ± 5	19.9 ± 4.0	21.0 ± 3.3	18.9 ± 3.6	19.4 ± 3.6	20.4 ± 3.0	.78
Minute ventilation (L/min)	54.8 ± 12.7	62.7 ± 14.5	64.9 ± 14.0	53.4 ± 13.5	55.5 ± 14.1	56.6 ± 14.7	.37
CO <sub>2</sub> production (L/min)	1.61 ± 0.45	1.85 ± 0.38	1.973 ± 0.338‡	1.56 ± 0.38	1.64 ± 0.43	1.687 ± 0.389	.33
Respiratory exchange ratio	1.17 ± 0.08	1.23 ± 0.10	1.19 ± 0.11	1.19 ± 0.14	1.22 ± 0.15	1.19 ± 0.09	.62
Lactate (mmol/L)	2.45 ± 0.72	2.81 ± 0.73	3.66 ± 1.2*	2.26 ± 0.78	2.74 ± 1.13	2.46 ± 0.52	.37
Exercise time (minutes)	9.1 ± 1.7	10.5 ± 2.3	11.35 ± 2.8†	9.2 ± 2.0	9.64 ± 2.7	9.9 ± 2.3	.43
Perceived exertion	19.6 ± 0.5	19.8 ± 0.6	19.6 ± 0.95	19.5 ± 0.6	19.8 ± 0.4	19.5 ± 0.71	.37
Watts	117.9 ± 36	135.6 ± 34	146.1 ± 33†	116.2 ± 31	116.6 ± 33	127.0 ± 25	.44

\*P < .01 versus baseline within group.  
†P < .05 versus baseline within group.  
‡P = .06 versus baseline within group.

rotation (degrees) was defined as the diastolic component of circular motion around the center of gravity. Velocity of rotation (degrees/s) was calculated as the angle of rotation between 2 cardiac phases divided by the time between those phases. Velocity of rotation was also normalized for maximal systolic rotation (s<sup>-1</sup>).

### Statistical analysis

Statistical Graphics Corporation software (Bethesda, Md) was used to perform multivariate analysis of variance procedures between patients randomized to bisoprolol fumarate or placebo. Post hoc procedures were performed with the Scheffé test. Data are presented as mean ± standard deviation. Sample size estimates were on the basis of variance obtained from our previous studies of ventricular volumes with MRI, in which the standard deviation of left ventricular end-diastolic volume was roughly 40 mL. With an alpha of 0.05 and 80% power, the sample size needed to detect a 20% difference was calculated as: [(2 × standard deviation<sup>2</sup>)/(180 - 142) × 7.9], or approximately 17 subjects per group.

### Results

At randomization, the 2 groups were similar in terms of clinical and demographic data, including age, height, weight, resting ejection fraction, pulmonary function, medication use, extent of coronary artery disease, and peak oxygen uptake (Table I). At baseline with angiographic measurements, 5 patients for bisoprolol fumarate and 6 patients for placebo had mild mitral regurgitation, and 3 patients for bisoprolol fumarate and 2 patients for

placebo had moderate mitral regurgitation. One patient in the bisoprolol fumarate group died 5 months into the study because of worsening heart failure. No other cardiac events or episodes of decompensation occurred in either group during the course of the study.

### Exercise testing

Hemodynamic and gas exchange responses to exercise are presented in Table II. Resting heart rate was significantly reduced after bisoprolol fumarate treatment (81 ± 12, 64 ± 13, and 61 ± 11 beats/min, at baseline, 6 months, and 1 year respectively; P < .01), and heart rate did not change among controls. No differences were observed within or between groups in resting systolic or diastolic blood pressures.

At maximal exercise, both groups achieved respiratory exchange ratios of more than 1.15 and perceived exertion levels of 19.5 or more on each test, which suggests that maximal efforts were generally achieved. After 1 year, heart rate was reduced after bisoprolol fumarate therapy at maximal exercise (144 ± 20 to 127 ± 17 beats/min; P < .01). Maximal systolic blood pressure was higher only in the bisoprolol fumarate group (by 33 mm Hg; P < .05). Peak oxygen uptake increased modestly (15%) but insignificantly in the bisoprolol fumarate group, and it was unchanged in the placebo group. In the bisoprolol fumarate group, maximal work rate achieved was higher after the study period (118 ± 36 watts versus 146 ± 33 watts; P < .05), and a trend was observed for higher

**Table III.** Magnetic resonance imaging measurements of ventricular function

	Bisoprolol fumarate			Placebo			P value between groups
	Baseline	6 Months	1 Year	Baseline	6 Months	1 year	
LVEDV (mL)	252.1 ± 78	231.4 ± 85	197.8 ± 105	200.9 ± 55	202.6 ± 64	202.8 ± 55	.14
LVESV (mL)	190.9 ± 68	191.2 ± 94	129.2 ± 85	147.7 ± 51	149.7 ± 59	152.0 ± 54	.25
EF (%)	25.0 ± 7	29.2 ± 8	36.2 ± 9*	27.0 ± 13	27.8 ± 10	26.2 ± 11	.33
LVSV (mL/beat)	61.1 ± 17	62.8 ± 6	68.7 ± 26	53.4 ± 27	52.9 ± 18	50.9 ± 19	.74
CO (L/min)	4.82 ± 1.8	3.66 ± 0.44	4.11 ± 1.4	3.97 ± 2.1	3.82 ± 1.7	3.36 ± 1.0	.13
PR	1772 ± 547	2127 ± 464	2289 ± 794	2728 ± 1462	2415 ± 653	2563 ± 581	.20

LVEDV, Left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; EF, ejection fraction; LVSV, left ventricular stroke volume; CO, cardiac output; PR, peripheral resistance.

\* $P < .05$  versus baseline within group.

**Table IV.** Magnetic resonance tagging measures of rotation and relaxation velocity (degrees/s; mean ± standard deviation)

	Bisoprolol fumarate			Placebo			P value between groups
	Baseline	6 Months	1 Year	Baseline	6 Months	1 Year	
Rotation	41.4 ± 17.3	40.4 ± 19.5	31.7 ± 15.8	35.6 ± 17.0	35.2 ± 12.9	27.9 ± 12.8	.98
Relaxation	-28.7 ± 12.0	-19.5 ± 11.8*	-17.4 ± 8.3†	-21.6 ± 11.9	-20.8 ± 18.1	-16.6 ± 12.7	.49

\* $P = .08$  versus baseline within group.

† $P < .05$  versus baseline within group.

exercise time ( $P = .06$ ). For these measures of exercise tolerance, the group/test interactions were not significant.

### Left ventricular volume and function

Left ventricular volumes and function data are presented in Table III. Left ventricular volumes at end-systole and end-diastole were reduced in the bisoprolol fumarate group and unchanged in the control group, although the differences were not significant within or between groups. Ejection fraction was higher after 1 year in the bisoprolol fumarate group ( $25.0 \pm 7\%$  versus  $36.2 \pm 9\%$ ;  $P < .05$ ), whereas ejection fraction did not change in the placebo group. Most of these changes occurred during the final 6 months of observation. Stroke volume, cardiac output, and peripheral resistance did not change in either group.

Magnetic resonance tagging measures of left ventricular rotation and relaxation velocity are presented in Table IV. Rotation velocity decreased in both groups (by 23% and 22% in the bisoprolol fumarate and placebo groups, respectively), but these differences were not significant within or between groups. Relaxation velocity decreased significantly after 1 year in the bisoprolol fumarate group

( $-28.7 \pm 12$  to  $-17.4 \pm 8$  degrees/s;  $P < .05$ ) but did not change among patients for placebo.

### Discussion

Despite 20% to 30% improvements in left ventricular end-diastolic volume, left ventricular end-systolic volume, ejection fraction, and measures of exercise capacity after 1 year of bisoprolol fumarate therapy, these changes were not statistically significant between groups, which suggests that the study was underpowered. Beta-blockade significantly reduced resting and exercise heart rates, showing the expected diminution of sympathetic drive. Although the between-group differences were not significant, the magnitude of our observations on left ventricular size and function are similar to a number of studies with the beta-blockers metoprolol and carvedilol.<sup>9,16-21</sup> Although the CIBIS trial, from which we based our study criteria and treatment regimen, did not measure exercise tolerance, improvements in New York Heart Association functional classification, fewer hospitalizations, and an improvement in left ventricular fractional shortening was observed.<sup>13</sup> Although our study was comparatively

small, we based our sample size estimates on volume measurements with MRI, whereas several recent multicenter studies used mortality as the primary endpoint and were therefore much larger.<sup>6,22-24</sup>

### Exercise tolerance

Several studies that evaluated beta-blockade in heart failure have shown increases in exercise capacity,<sup>9,17-20,25,26</sup> but numerous other studies have reported no change.<sup>19,24,27-31</sup> Few studies have evaluated the gas exchange response to exercise in a controlled fashion after beta-blockade. Metra and colleagues<sup>9</sup> did not observe any difference in peak oxygen uptake ( $\text{VO}_2$ ) despite marked hemodynamic benefits after 3 months of carvedilol therapy. In a more recent study from these investigators, neither carvedilol nor metoprolol had any effect on peak  $\text{VO}_2$ , although carvedilol resulted in a greater increase in exercise time.<sup>21</sup> The latter studies support our findings in that beta-blockade has minimal effects on peak  $\text{VO}_2$  in patients with heart failure, although we did observe a 24% increase in peak watts achieved ( $P < .05$ ) and a 25% increase in exercise time ( $P = .06$ ). Given these results and the mixed observations of others,<sup>2,8,10</sup> the benefits of beta-blockade on exercise capacity appear to be positive but relatively small. A noteworthy finding from this study, however, was the 28% improvement in  $\text{VO}_2$  at the lactate threshold. Why beta blockade would delay the lactate threshold specifically is unclear, but this observation concurs with several studies that show improvements in submaximal measures of exercise tolerance (eg, 6-minute walk test) after beta-blockade in patients with CHF.<sup>21,28</sup>

### Ventricular volume measurements

Most studies that evaluate the hemodynamic response to 3 to 6 months of beta-blockade therapy have reported benefits, including improvements in left ventricular ejection fraction, stroke work index, reduced ventricular volumes, and reduced pulmonary capillary wedge pressure.<sup>9,18-21,24,26,27,32-34</sup> Our findings confirm most of these studies in that measures of left ventricular end-diastolic volume, left ventricular end-systolic volume, and ejection fraction tended to improve in the treatment group. Although the reductions in end-diastolic and end-systolic volumes did not reach statistical significance, these changes were substantial (22% and 32% reductions in end-diastolic and end-systolic volumes, respectively). Importantly, most of these hemodynamic changes occurred during the latter 6 months of the study, which suggests that previous studies of 3 to 6 months duration may not have been carried out long enough to observe the full extent of the effects of beta blockade.

The hemodynamic effects of bisoprolol fumarate have previously been studied in a subset of patients in the CIBIS trial<sup>22</sup>; 5 months of bisoprolol fumarate therapy

had no significant effects on end-diastolic or end-systolic dimensions. Although left ventricular fractional shortening increased with bisoprolol fumarate and this improvement was related to improved survival rate, the effect of therapy was small (0.05% increase in fractional shortening). The differences in our findings and those of the CIBIS trial may be the result of differences in study duration (5 months versus 1 year) or measurement techniques. Our results concur with recent observations with carvedilol, which was recently shown to have beneficial effects on myocardial remodeling (abnormal volume expansion) in patients with ischemic heart failure.<sup>34</sup>

A concern with the trend for improved hemodynamics noted in the beta blocker-treated group in our study is that the improved ejection fraction could be entirely the result of the decrease in heart rate. Normally with a decrease in heart rate, ventricular volumes and ejection fraction increase to maintain cardiac output. However, the improved ejection fraction we observed at 1 year was accompanied by decreases in ventricular volumes and was preceded at 6 months by the expected decrease in heart rate. Whether the decrease in heart rate allows the ventricle to function better or whether there are heart rate-independent changes that follow the decrease in heart rate can only be speculated. Both the temporal sequence of the change in heart rate (at 6 months) and hemodynamic changes (occurring later at 1 year) support a direct benefit to myocardial function from beta-blockade and may help explain the survival benefit associated with beta-blocker treatment.

### Measurement techniques

Because the CIBIS trial measured left ventricular dimensions in a subgroup of patients, the effects of bisoprolol fumarate specifically on ventricular function are largely unknown, and because mixed results have previously been reported on the effects of beta-blockade on ventricular volumes and function with echocardiography, we used MRI in this study. MRI is unique among the available technologies for measuring ventricular size and function in that it can image the entire left ventricle without depending on geometric assumptions, it provides superior contrast between the heart and blood pool, and it is considered the most accurate and reproducible method for quantifying left ventricular morphology.<sup>35,36</sup>

We also used a novel myocardial tagging technique to assess left ventricular contraction and relaxation. This technique is on the basis of MRI and permits the labeling of specific myocardial regions for imaging cardiac motion. Echocardiography, radionuclide ventriculography, and standard MRI assess cardiac motion only in terms of radial displacement or systolic shortening, which can lead to errors because the base of the ventri-

cle moves toward the apex during systole (translational motion) and shows rotational movement during systole and diastole that cannot easily be imaged with previous techniques. In patients with hypertrophic or dilated cardiomyopathy and aortic stenosis, a prolonged systolic rotation with an enhanced torsional motion has been observed and diastolic “untwisting” is prolonged.<sup>37</sup>

The changes in rotation velocities during the year in the bisoprolol fumarate group in this study paralleled those in controls. Although the trend for a lessening of rotation velocity suggests a reduction in contractility, the changes were similar in the 2 groups. At the same time, diastolic relaxation velocity (untwisting) was significantly reduced in the bisoprolol fumarate group. A reduction of relaxation velocity has been associated with diastolic dysfunction, including hypertrophic cardiomyopathy, ischemic heart disease, and aortic stenosis.<sup>37-39</sup> Each of these conditions has been associated with a prolongation of the untwisting process, a reduced rate of relaxation, a diminution of early diastolic filling, or their combination. Thus, these results suggest that beta-blockade may have a negative effect on diastolic filling. These findings also suggest an uncoupling between systolic shortening (which improved) and rotation and relaxation velocities (which worsened), suggesting a rate, rather than an inotropic-mediated effect of bisoprolol fumarate on systolic function. This could contribute to the failure of peak  $\text{VO}_2$  to increase significantly after beta-blockade.

### Limitations

The effects of beta-blockade have been specific to the etiology of heart failure in some studies.<sup>10,40</sup> The fact that our population was a mixture of ischemic and idiopathic dilated etiologies in accordance with the CIBIS trial<sup>13</sup> may have influenced our findings. The absence of statistical differences in exercise capacity and ventricular volumes after bisoprolol fumarate therapy, despite benefits in the order of 20% to 30%, clearly suggests that our study was underpowered, and our sample size was small relative to recent multicenter trials of beta-blockade. However, although the novel myocardial tagging techniques and volume measurements with MRI provide greater precision, the greater expense and time required with this technique limited our sample size.

### Summary

Beta-blockade is gaining momentum as a therapeutic option for many patients with stable CHF. Neurohumoral alterations that occur in heart failure and the need to inhibit these alterations are now well appreciated. Clinical trials have shown that beta-blockade can improve hemodynamic status and generally does not worsen symptoms, and some studies have shown improvements in survival rates. However, most trials

have only been performed in patients with mild heart failure, have been of short duration, and have mainly been performed in patients with an idiopathic dilated etiology. In this study, 1 year of bisoprolol fumarate therapy tended to improve ventricular volumes and exercise capacity and markedly delayed the lactate threshold. However, the influence of bisoprolol fumarate on left ventricular function was mixed; although ejection fraction improved, rotation and relaxation velocities were negatively influenced. This uncoupling between volume changes, ejection fraction, and rotation and relaxation velocities could explain the failure of peak  $\text{VO}_2$  to increase to a greater extent after beta-blockade. These findings generally confirm the results of studies with carvedilol and metoprolol while adding new insight to the influence of beta-blockade on systolic and diastolic function.

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