β Blockers for Prevention of Exercise-Induced Left Ventricular Outflow Tract Obstruction in Patients With Hypertrophic Cardiomyopathy

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Whether treatment with β blockers (BBs) is of benefit to patients with hypertrophic cardiomyopathy (HC) and provocable outflow obstruction (with none or with only mild heart failure symptoms) is largely unresolved. Thus, we prospectively studied 27 patients with HC (age 36 ± 15 years; 81% men) with New York Heart Association class I or II, without obstruction at rest, but with exercise-induced left ventricular outflow tract (LVOT) gradient of ≥30 mm Hg. Patients underwent exercise echocardiography at baseline and after treatment with nadolol (n = 18; 40 to 80 mg/day) or bisoprolol (n = 9; 5 to 10 mg/day), according to a prespecified protocol. Without the BBs, the postexercise LVOT gradient was 87 ± 29 mm Hg and >50 mm Hg in 25 patients (93%). After a 12 ± 4-month period of BB treatment, the postexercise LVOT gradient had decreased to 36 ± 22 mm Hg (p <0.001) and was virtually abolished (to 0 or <30 mm Hg) in 14 patients (52%), substantially blunted (≥20 mm Hg reduction) in 9 (33%), and unchanged in only 4 (15%). Severe postexercise obstruction (range 58 to 80 mm Hg) persisted in 6 patients (22% compared to 93% without BBs; p <0.001). Nonresponders (residual postexercise gradient of ≥30 mm Hg with BBs) were characterized by an increased body mass index (hazard ratio 2.03/1 kg/m^2, 95% confidence interval 1.2 to 3.4; p <0.05). In conclusion, in patients with HC with mild or no symptoms, treatment with BBs can prevent the development of LVOT obstruction triggered by physiologic exercise. These findings provide a rationale for the novel strategy of early prophylactic pharmacologic treatment with standard, well-tolerated doses of BBs in physically active patients with provocable gradients, aimed at effective prevention of the hemodynamic burden associated with dynamic obstruction. **(Am J Cardiol 2012;110:715–719)**

Left ventricular outflow tract (LVOT) obstruction under resting (basal) conditions in hypertrophic cardiomyopathy (HC) is associated with adverse long-term consequences related to progressive heart failure.[1–3] In addition, a large proportion of patients without obstruction at rest develop significant LVOT gradients associated with physical exertion,[4–6] although the relevance to clinical outcomes is incompletely resolved.[7–9] However, provocable obstruction is known to cause severe functional limitation and heart failure in patients with HC, requiring therapeutic interventions with negative inotropic drugs and, occasionally, myectomy or alcohol septal ablation.[9,10] In patients with HC and advanced heart failure owing to LVOT obstruction (i.e., New York Heart Association [NYHA] functional class III-IV), β blockers (BBs) represent the standard first-line therapy recognized by international guidelines,[11,12] as originally introduced by Braunwald et al[13] in 1964. In addition to relieving the symptoms associated with obstruction, BB treatment is capable of controlling the heart rate increase during exercise and preventing rapid ventricular rates known to precipitate microvascular ischemia in HC hearts.[14] However, in patients with HC and mild or no symptoms, treatment of provocable LVOT obstruction has not been standardized and remains undefined.[11,12] In the present study, we prospectively assessed the efficacy of BB treatment on LVOT obstruction provoked by physiologic exercise in patients with HC with no or only mild symptoms related to effort.

Methods

Of the 187 patients with HC consecutively undergoing exercise echocardiography at Careggi University Hospital in 2006 to 2009, we prospectively enrolled 32 patients

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Table 1
Baseline characteristics

Variable	Value
Age (years)	36 ± 15
Men	22 (81%)
Family history of hypertrophic cardiomyopathy	10 (37%)
Height (m)	1.74 ± 0.9
Weight (kg)	75 ± 13
Body surface area (m^2)	1.83 ± 0.4
Body mass index (kg/m^2)	24.6 ± 3
Systolic blood pressure (mm Hg)	126 ± 16
Diastolic blood pressure (mm Hg)	80 ± 10
New York Heart Association functional class	1.15 ± 0.36
Left atrial diameter (mm)	42 ± 6
Left atrial volume index (ml/m^2)	42 ± 16
Left ventricular end-diastolic diameter (mm)	44 ± 5
Ventricular septal thickness (mm)	19 ± 5
Maximum left ventricular thickness (mm)	21 ± 6
Left ventricular ejection fraction (%)	67 ± 6
Left ventricular outflow gradient at rest (mm Hg)	14 ± 7
Systolic anterior motion of mitral valve	0.6 ± 0.5
0	11 (41%)
1+	15 (5%)
2+	1 (4%)
Mitral regurgitation	0.7 ± 0.5
None	10 (37%)
Mild	17 (63%)

according to the following entry criteria: sinus rhythm, LVOT gradient <30 mm Hg under basal conditions in the supine position and erect on a cycle ergometer and ≥30 mm Hg after a maximum symptom-limited exercise test, in the absence of treatment with cardioactive medications (including BB, disopyramide, or verapamil); and no or only mild heart failure-related symptoms (i.e., NYHA functional class I or II). Patients in NYHA class III-IV were excluded because, by convention, they were already receiving BBs to control advanced heart failure symptoms related to LVOT obstruction. Furthermore, patients with previous surgical myectomy or percutaneous alcohol septal ablation and those with medical conditions precluding maximum exercise stress testing[15] were excluded from the study group. Of the 32 patients who met the entry criteria, 5 refused enrollment. Thus, the remaining 27 patients with HC constituted the study cohort (Table 1). Of the 27 patients, 4 (15%) had mild pharmacologically controlled systemic hypertension, and none had previously been treated with BBs.

Standard echocardiographic studies were performed with the patient in the left lateral supine decubitus using commercially available instruments according to current guidelines.[16] Subaortic obstruction was defined as mechanical impedance to outflow due to systolic anterior motion and midsystolic mitral–septal contact and was graded semiquantitatively.[4,8] The peak instantaneous LVOT gradient was measured at rest (and with the Valsalva maneuver) with the patient in the left lateral position with continuous-wave Doppler interrogation in the apical 5-chamber view, taking care to avoid contamination of the waveform by the mitral regurgitation jet.[4,8] Mitral regurgitation was graded as none or trivial (score 0), mild (score 1+), moderate (score 2+), or severe (score 3+).[3,6]

Table 2
Exercise data with and without β-blocker (BB) treatment

Variable	BB Treatment		p Value
	Off	On	
Heart rate at rest (beats/min)	77 ± 11	67 ± 17	0.02
Heart rate with Valsalva (beats/min)	80 ± 16	71 ± 17	0.007
Heart rate at peak exercise (beats/min)	157 ± 18	131 ± 20	<0.001
Heart rate attained (%)	86 ± 8	72 ± 10	<0.001
Systolic blood pressure at rest (mm Hg)	126 ± 16	117 ± 15	0.008
Diastolic blood pressure at rest (mm Hg)	80 ± 10	73 ± 9	<0.001
Systolic blood pressure at peak exercise (mm Hg)	170 ± 27	157 ± 27	0.005
Diastolic blood pressure at peak exercise (mm Hg)	94 ± 13	92 ± 14	0.46
Exercise performance*			
Exercise time (min)	10.0 ± 2.8	10.6 ± 2.6	0.13
Maximum Watt	131 ± 36	131 ± 31	0.84
Maximum METs	7.0 ± 1.7	6.9 ± 1.4	0.55
Left ventricular outflow tract peak velocity (m/s)			
At rest	1.8 ± 0.5	1.8 ± 0.5	0.27
With Valsalva maneuver	2.5 ± 1.0	2.0 ± 0.7	0.006
Peak exercise	4.3 ± 0.8	2.8 ± 0.9	<0.001
After exercise	4.6 ± 0.8	2.9 ± 0.9	<0.001
Left ventricular outflow tract gradient (mm Hg)			
With Valsalva maneuver	30 ± 25	18 ± 14	0.018
At peak exercise	77 ± 28	35 ± 22	<0.001
≥30 mm Hg	27 (100%)	12 (44%)	<0.001
≥50 mm Hg	24 (89%)	8 (30%)	<0.001
After exercise	87 ± 29	36 ± 22	<0.001
≥30 mm Hg	27 (100%)	13 (48%)	<0.001
≥50 mm Hg	25 (93%)	8 (30%)	<0.001
Mitral valve			
Systolic anterior motion			
Baseline	0.6 ± 0.6	0.6 ± 0.5	0.49
At peak exercise	2.8 ± 0.4	1.1 ± 1.1	<0.001
After exercise	2.7 ± 0.5	1.3 ± 1.1	<0.001
Mitral regurgitation			
Baseline	0.6 ± 0.7	0.6 ± 0.5	0.48
At peak exercise	1.3 ± 0.7	0.9 ± 0.8	0.008
After exercise	1.4 ± 0.6	0.9 ± 0.9	<0.001

* In accordance with the study protocol, exercise echocardiography with BB treatment was interrupted at the same exercise work load and time as in the baseline study for each patient.

Maximum, symptom-limited exercise tests were performed on a bicycle ergometer in the upright position. Exercise began at an initial workload of 25 W, with stepwise 25-W increments every 2 minutes. A 12-lead electrocardiogram was monitored continuously and recorded at baseline, at each minute during exercise, and after exercise. The arterial blood pressure was measured using a mercury sphygmomanometer at baseline and every 2 minutes during exercise and in the postexercise phase.

Patients were encouraged to perform maximally to achieve their expected heart rate. The maximum predicted heart rate was calculated as 220 minus the patient's age, and the percentage of the predicted heart rate was calculated as

the maximum heart rate attained divided by the maximum predicted heart rate multiplied by 100. Exercise was terminated when the predicted heart rate was achieved or when fatigue, dyspnea, chest pain, or hypotension intervened. Peak exercise was defined as the maximum attained workload before discontinuation. Peak functional capacity was estimated in METs, with 1 MET defined as the energy expended at rest, equivalent to oxygen consumption of 3.5 ml/kg of body weight/min, as recommended.[15] No adverse events or clinically relevant arrhythmias occurred during exercise testing.

Exercise echocardiography was performed with the patients sitting upright on the bicycle ergometer under basal conditions and serially every 2 minutes during exercise at each 25-W workload increment. The left ventricle was imaged in the apical and parasternal long-axis views to identify and grade systolic anterior motion and mitral regurgitation and estimate the LVOT gradient with continuous-wave Doppler. After termination of exercise, the patients were immediately placed in the left lateral decubitus position, and the LVOT velocities were measured again in the apical view using continuous-wave Doppler.[8]

After baseline exercise echocardiography, BB treatment was initiated and titrated to a tolerable target dose (heart rate at rest of ≤60 beats/min, without symptoms of hypotension or bradycardia or the appearance of second-degree or greater atrioventricular block). Using the standard treatment strategy followed at our center for >20 years, the initial 18 patients enrolled in the study were administered nadolol (starting dose 20 mg/day titrated up to 40 to 80 mg/day; mode 40 mg, once daily). After nadolol became commercially unavailable in Italy in 2009, 9 subsequent study patients were treated with bisoprolol (starting dose 2.5 mg/day, titrated up to 5 to 10 mg/day; mode 5 mg once daily). With the target doses of the BB, an average decrease of 10 beats/min (or 13%) was achieved compared to baseline (67 ± 17 vs 77 ± 11 beats/min, respectively; p = 0.02). The heart rate at rest at the last evaluation was ≤60 beats/min in 11 patients (41%), 61 to 70 beats/min in 7 (26%), and >70 beats/min in 9 (33%; Table 2). No exclusions were necessary because of side effects, and treatment was well tolerated. According to a prespecified design, follow-up exercise echocardiography was performed after ≥6 months (range 8 to 32) of treatment at the target BB dose. The LVOT gradient was compared at the same workload in the 2 studies, with the second test interrupted at the same exercise point and level as in the baseline study.

Data are expressed as the mean ± SD. Paired Student's *t* test or 1-way analysis of variance was used to compare the normally distributed data. The chi-square test was used to compare categorical variables expressed as proportions. The predictors of persistent provocable obstruction after introduction of BB were assessed by logistic regression analysis, using the forward conditional method. p Values <0.05 were considered significant. The calculations were performed using SPSS, version 12.0 (SPSS, Chicago, Illinois).

Results

Off β Blockers. Each of the 27 study patients had an absence of the LVOT gradient at rest, associated with no or mild mitral regurgitation. In the 27 patients, the peak LVOT gradient measured with the patients supine immediately after exercise was 87 ± 29 mm Hg (range 36 to 140). In 25 patients, provocable LVOT obstruction was marked (LVOT gradient >50 up to 140 mm Hg; Figure 1).

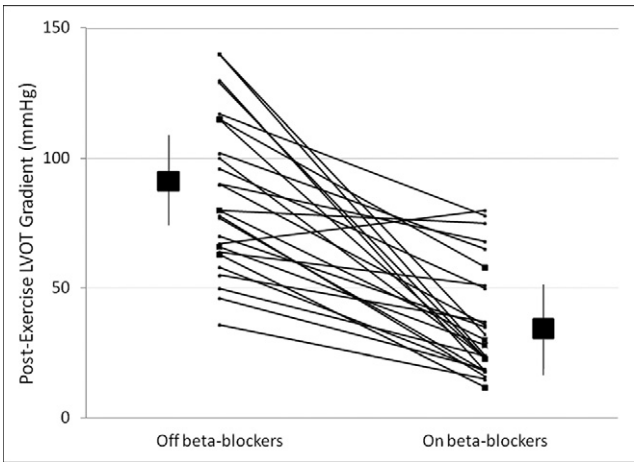

Figure 1. Effect of treatment with BBs on postexercise LVOT gradient in 27 patients with HC. Each patient is depicted by a line connecting the 2 measurements of a gradient. *Rectangles* and *vertical bars* represent mean and SD, respectively.

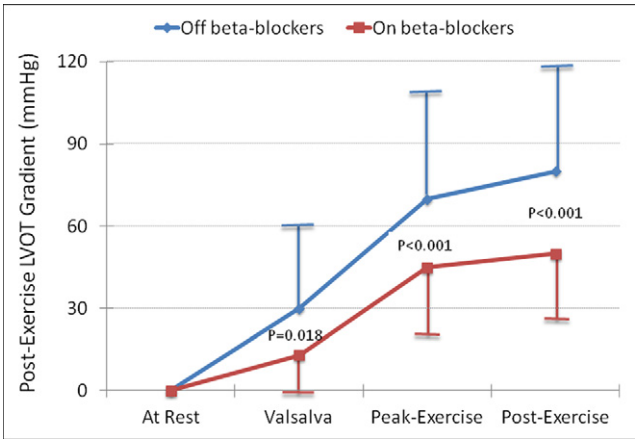

Figure 2. LVOT gradients at rest, with Valsalva maneuver, at peak exercise, and after exercise at initial exercise echocardiogram *(solid blue line)* and with BB treatment *(dotted red line). Squares* and *vertical lines* indicate mean and SD, respectively, at each step for the 27 study patients.

On β Blockers. Follow-up exercise echocardiograms were performed 12 ± 4 months after the initial test. The BBs effectively blunted the LVOT gradients at peak exercise, after exercise, and also with the Valsalva maneuver (Table 2 and Figure 2). The postexercise LVOT gradient was markedly reduced by BB treatment, by 51 ± 34 mm Hg (range +13 to −116). No significant difference in the magnitude of this reduction was evident between bisoprolol and nadolol (p = 0.23). The postexercise LVOT gradient was abolished (to 0 or <30 mm Hg) in 14 patients (52%), significantly blunted (≥20 mm Hg reduction) in 9 patients (33%), and remained unchanged in 4 patients (<20 mm Hg reduction). Marked postexercise gradients >50 mm Hg (range 58 to 80) persisted with BB treatment in 6 of these patients (Figure 1). Moreover, in those patients who devel-

oped obstruction with exercise during BB treatment, the gradients occurred early during exercise (≤5 METs) in 8 patients (29%) compared to in 17 patients (63%) without BB treatment ($p = 0.029$). Without BBs, postexercise mitral regurgitation was 1.4 ± 0.6 (Table 2), including 13 patients in whom it was moderate to severe. With BB treatment after exercise, mitral regurgitation was significantly reduced to 0.9 ± 0.9 and was moderate-to-severe in only 6.

The 23 patients in NYHA class I at the initial evaluation remained asymptomatic after the introduction of BB treatment. Of the 4 patients in NYHA class II, 2 improved to class I and the other 2 remained in class II. The only predictor of a lack of hemodynamic response to BBs (i.e., persistent provocable obstruction of ≥30 mm Hg) was an increased body mass index (hazard ratio 2.03 per 1 kg/m^2 increase; 95% confidence interval 1.2 to 3.4; $p < 0.05$). Specifically, only 2 of 12 patients with a body mass index >25 kg/m^2 (17%) had abolition of the postexercise gradient with BBs compared to 10 of 15 patients with a body mass index of ≤25 kg/m^2 (67%; $p < 0.01$).

Discussion

The present study prospectively assessed the effects of BB therapy on the exercise-induced LVOT gradient in patients with HC with no or only mild self-reported symptoms. We found that relatively low, well-tolerated doses of BBs were capable of blunting exercise-induced obstruction, including marked gradients >50 mm Hg. The postexercise LVOT gradient decreased from a pretreatment value of 87 ± 29 to 36 ± 22 mm Hg after the administration of BBs (i.e., average reduction of >50 mm Hg), paralleled by a decrease in the degree of functional mitral regurgitation. The exercise-induced gradients were greatly diminished or abolished (to <30 mm Hg) in 52% of the patients and substantially reduced (≥20 mm Hg reduction) in another 33%. Of those patients with an initial gradient >50 mm Hg with exercise, consistent with the established threshold for invasive septal reduction intervention in symptomatic patients,[11,12] only 24% had persistent gradients in this range with BB treatment.

The present study was specifically designed to assess the effects of BBs on provocable outflow gradients, rather than exercise duration or capacity. Most enrolled patients had no or only mild symptoms, and, consequently, major and detectable improvement in symptoms could not be expected in the overall study cohort. Nevertheless, of the 4 patients in NYHA class II, 2 were judged to have improved to class I, suggesting that subjective improvement is achievable with BB treatment even in patients with mildly symptomatic HC. Furthermore, the time course of exercise-inducible obstruction was significantly delayed by BB treatment. Outflow gradients occurred early during effort (<5 METs) in only about 30% of patients during BB treatment compared to >60% without BB treatment. This observation has potential clinical relevance, because the timing of LVOT gradient onset has been reported to dictate the degree to which exercise capacity is impaired in patients with HC, with an earlier appearance of gradients during exercise predicting reduced performance.[8]

The data from large patient cohorts have consistently identified LVOT obstruction occurring under basal (at rest) conditions as an important determinant of cardiovascular morbidity and mortality in patients with HC, thereby underscoring the importance of abolishing subaortic gradients in severely symptomatic patients.[1–6] The present data support a rationale for BB administration in patients with HC who develop LVOT obstruction with physiologic exercise, even in the absence of disabling heart failure symptoms. Of note, effective control of the obstructive pathophysiology in our patients could be achieved with low BB doses, which were well tolerated after prudent titration. This is a relevant issue for the long-term treatment of patients with HC with mild or no symptoms, who are frequently young and active and otherwise might not require treatment.[5,6]

In patients with HC without obstruction at rest, substantial LVOT gradients are commonly elicited by exercise[4] and might represent a detrimental pathophysiologic feature exerting considerable effect on long-term functional capacity and prognosis.[4–8] In the large Mayo Clinic cohort, about 20% of patients with HC and provocable obstruction progressed to class III or IV symptoms, requiring surgical myectomy (or percutaneous septal reduction).[7] Severely symptomatic drug-refractory patients with obstruction confined to provocable conditions have undergone surgical myectomy with favorable results similar to those obtained in patients with obstruction at rest.[7,9,17,18] The present data, consistent with data from previous studies,[7,9,10,17,18] have shown that a reduction in intraventricular gradients elicited with physiologic provocation benefits patients in the long term and suggests the potential value of more routine use of exercise echocardiography in physically active patients with HC without LVOT gradients at rest. Furthermore, should a substantial LVOT gradient be demonstrated during physical effort, our findings support the consideration for the initiation of BB treatment.[6]

Although most of our patients with HC exhibited a reduction in LVOT obstruction with BB treatment, the individual variability was considerable, including a subset of nonresponders with a persistent provocable LVOT gradient of ≥30 mm Hg at the final evaluation despite BB treatment during an average of 12 months. Also owing to the lack of a placebo-treated control group, representing a potential limitation of the present study, the determinants of such variability remain incompletely resolved. However, we found that an inadequate response to BB treatment was predicted by an increased body mass index. Thus, the role of obesity in promoting LVOT gradients deserves additional investigation in patients with HC, although alternative explanations exist, such as insufficient drug dosage in patients with the greatest body weight.

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