Effects of Bisoprolol on Cardiac Function and Exercise in Patients with Heart Failure

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Summary

Objectives: To assess the effects of bisoprolol on exercise capacity and ventricular function in patients with heart failure.

Methods: Clinical and hemodynamic variables, ventricular function and remodeling, and ergospirometry of patients with heart failure of different etiologies were evaluated before and after the administration of bisoprolol.

Results: Twenty-two patients were analyzed; one patient did not tolerate medication and 14 patients reached the study goal. The group consisted of 9 men and 5 women, the mean age was 52 (36-64) years, and patients were followed during 551 days (238-1109). We observed an improvement in NYHA functional class, reduction in resting heart rate (78.8±8.7 vs 63±6.4 bpm, p <0.001), increase in left ventricular ejection fraction (31.3±8.5% vs 39±14.7%. p=0.043), and a tendency towards improved quality of life scores (31±20.6 vs 17.8±14.8. p=0.058). The maximum heart rate dropped during exercise (138.1±20.2 vs 116.7±27.1. p=0.01), as did peak oxygen consumption (20.9±6.8 vs 15.1±3.5. p<0.001); no change was observed on the EV/VCO2 slope. The effects were observed for all etiologies, including Chagas' disease.

Conclusion: Bisoprolol was safe and well tolerated in patients with heart failure. Bisoprolol therapy improved the symptoms, hemodynamic variables, as well as the cardiac function for all etiologies; however, it did not result in improved exercise capacity.

Key words: Bisoprolol; cardiac output, low; exercise; adrenergic beta-antagonists.

Introduction

In heart failure, neurohumoral axes are activated, including the sympathetic nervous system. Sympathetic activity is associated with the level of myocardial remodeling, cardiac dysfunction, and prognosis[1,2]. Beta-blockers may partially antagonize sympathetic and inflammatory activities, affecting cardiomyocyte apoptosis and hypertrophy, and leading to an increased ejection fraction and attenuated progression of ventricular remodeling[3]. Clinical studies have demonstrated the effect of beta-blockers in reducing mortality among patients with heart failure in different functional classes[4], and guidelines recommend that patients with left ventricular (LV) systolic dysfunction be treated with beta-blockers[5].

However, the influence of beta-blockers on exercise capacity is still controversial. Studies currently available do not characterize, in a consistent and reproducible fashion, the effects of beta-blockers on ergometric indexes[6-9]. Beta-blocker administration was found to be capable of increasing, reducing, or maintaining peak oxygen consumption levels. Most of these studies evaluated the effects of carvedilol and metoprolol[10]. There are, however, significant differences among the beta-blockers used in the treatment of heart failure, both in affinity for alpha- and beta-receptors and pharmacokinetics properties, as well as in their adverse effects and clinical benefits[11]. The effects of bisoprolol, a selective beta-1 blocker, on exercise capacity in heart failure have not been systematically evaluated in recent and significant groups of patients.

In Brazil, studies are even scarcer and data from foreign literature have been extrapolated to local populations, in spite of significant ethnical influence on the physiopathology, treatment, and prognosis of cardiovascular diseases[12]. Since the first Brazilian study on the effect of beta-blockers on heart failure[13], few others have been published[14-16]. There are no studies evaluating the effects of bisoprolol on cardiac function and exercise capacity of patients with heart failure in Brazilian clinical experience.

Methods

Casuistic - Patients were selected from a cardiology outpatient service at a tertiary-level university hospital, from June 2002 to August 2003. Inclusion criteria were: age over 18 years, presence of chronic heart failure[17] and dilated myocardiopathy with different etiologies (according to existing criteria for their diagnosis)[18], and no use of beta-blockers for the treatment of heart failure. Exclusion criteria were: patient's

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refusal, left ventricular ejection fraction over 0.40 (detected by transthoracic echocardiography), dilated myocardiopathy due to infiltrative disease, moderate or significant rheumatic or degenerative valvulopathy (mitral and/or tricuspid insufficiency secondary to ventricular dilation were not considered as exclusion criteria, regardless of their intensity), cardiogenic chock, restrictive cardiac disease, alcoholism during the past 6 months, chronic obstructive pulmonary disease, use of corticoid or immunosuppressive agents during the past 3 months, malignant neoplasm, pulmonary embolism in the last 6 months, surgery or acute infections in the past 30 days, renal insufficiency (serum creatinine > 2.5 mg/dl), depression, active acute or chronic infectious disease, and contraindication for the use of beta-blockers.

Patients were treated with angiotensin-converting enzyme inhibitors (ACEI), diuretic agents (in the presence of evidence of hypervolemia), aldosterone inhibitors, and digitalis. Angiotensin II receptor inhibitors were used in cases of intolerance to ACE inhibitors. Maximum doses of ACEI had been reached before the introduction of beta-blockers and patients' initial evaluation, and had remained constant throughout the study.

Study design - After the maximum adjustment of angiotensin-converting I enzyme inhibitor doses (or angiotensin-receptor II inhibitors), patients were submitted to anamnesis and physical examination, collection of demographic data, and determination of functional class according to New York Heart Association criteria[19]. A nurse specialized in the follow-up of heart failure patients assessed their quality of life using the Minnesota Living with Heart Failure Questionnaire. Systemic arterial blood pressure and heart rate were determined with the subject in the sitting position, after a five-minute rest. Heart rate was measured in beats per minute (counting the number of beats for 60 seconds) by auscultation, and arterial pressure was determined with a sphygmomanometer.

After the clinical assessment, patients underwent transthoracic echocardiography for ventricular function analyses (measurements of heart chamber dimensions were made according to current recommendations[20] and measurement of left ventricular ejection fraction, by Simpson's modified method) and radioisotope ventriculography at rest. Patients' functional capacity was assessed by ergospirometry on a programmable treadmill (Marquette series 2000, Marquette Electronics, USA), according to Naughton's modified protocol. Patients were encouraged to exercise to exhaustion. The level of b-type natriuretic peptide was measured in peripheral blood.

Medication was started at the 2.5 mg dose, increased every 2 weeks by 2.5 mg increments up to a target dose of 10 mg or resting heart rate of 60 bpm. Medication dose adjustments were made for up to 3 months until the maximum dose had been reached. Adverse effects attributed to the medication were recorded. Clinical and supplementary evaluations were repeated 30 days later, after the maximum dose of bisoprolol had been reached.

Statistical analysis - The statistical analysis was performed using SPSS for Windows, version 11.0. Quantitative variables are expressed as means $\pm$ standard deviations, and compared before and after the administration of bisoprolol. For variables that did not follow a normal distribution, the non-parametric Wilcoxon test was employed, whereas for normal distribution variables, the paired t-test was used. Results with descriptive levels (p values) less than 0.05 were considered statistically significant.

Results

Twenty-two patients were analyzed during the period of the study. Two patients were excluded: one for having interrupted the medication during the protocol, and one who had to undergo myocardial revascularization surgery after an acute coronary ischemic episode. Two patients were interrupted during follow-up, and 3 patients died before the target-dose of medication was reached. In one case, medication had to be discontinued after several attempts due to patient's intolerance manifested by worsening dyspnea and hypotension. For this patient, subsequent administration of carvedilol caused the same symptoms and had to be discontinued.

Fourteen patients reached the study goal: 11 patients reached the 10 mg/day dose, and 3 patients reached a resting heart rate of 60 bpm at doses lower than 10 mg/day (1 patient at 2.5 mg, and 2 patients at 5 mg). The average dose of bisoprolol during the study was 8.8 mg. These patients underwent subsequent analyses.

The average age was 52 (36-64) years, 9 patients were men, and 5 were women. The follow-up period lasted 551 (238-1109) days. Table 1 shows patients' baseline clinical characteristics. At the end of the study, none of the 14 patients had to have ACE inhibitor use interrupted or doses modified; 1 patient had digitalis therapy interrupted due to clinical improvement, and 8 patients were no longer on diuretics. Before starting on bisoprolol, 2 patients were classified as NYHA functional class I, 9 were class II and 3 were class III. After administration of bisoprolol, 10 patients were classified as NYHA functional class I, 4 were class II, and none was class III.

Hemodynamics - With bisoprolol, the resting heart rate was reduced, with a non-significant reduction in systolic and diastolic arterial pressures. Despite the reduction in b-type natriuretic peptide plasma levels, the variance did not reach statistical significance (Table 2).

Quality of life - Quality of life assessed before and after the bisoprolol therapy showed a trend towards improvement, indicated by a drop in the scores of the different dimensions evaluated. Differences observed did not reach statistical value: the physical dimension ranged from 14.7 ± 10.9 to 9.9 ± 9.4 ($p=0.29$); the emotional dimension ranged from 8.9 ± 7.3 to 5.9 ± 14.9 ($p=0.18$); and the final results ranged from 31 ± 20.6 to 17.8 ± 14.8 ($p=0.058$).

Ventricular function and remodeling - On bidimensional echocardiography, no statistically significant reduction in end-diastolic diameter of the left ventricle was detected.

On radioisotope ventriculography, an increase in left ventricular ejection fraction was detected. The increase in the right ventricular ejection fraction was not statistically significant (Table 1).

Table 1 - Patient characteristics

	n	%
Age	52 ± 9.6	
Gender		
Male	9	64.3
Female	5	35.7
Duration of symptoms (months)	37.7(4-189)	
Etiology		
Ischemic	4	28.5
Idiopathic	5	35.8
Hypertensive	4	28.5
Chagas' disease	1	7.2
Diabetes mellitus	3	21.4
Previous MI	2	14.3
Previous myocardial revascularization	1	7.2
Functional class (NYHA)		
I	2	14.3
II	9	64.3
III	3	21.4
Initial treatment		
ACE inhibitor	13	92.8
ATII inhibitor	1	7.2
Spironolactone	10	71.4
Digitalis	9	64.3
Diuretics	14	100
Sodium	138±3.5	
Hemoglobin	13.9±0.9	
Uric acid	9.9±3.2	
Cholesterol/LDL	209±33	
Triglycerides	92.1±36.2	
Creatinine	1.1±0.2	

ACE: angiotensin-converting enzyme; AT II: angiotensin II; LDL: low-density lipoprotein.

Exercise capacity - Table 1 and Figure 1 show the maximum heart rate reached with exercise, peak oxygen consumption, and slope inclination given by the ratio of the exhaled volume to the carbon dioxide consumption.

Chagasic etiology - One patient with Chagas' disease tolerated 10 mg doses of bisoprolol. Upon drug dosing, the functional class shifted from III to II, resting heart rate from 72 bpm to 60 bpm, arterial pressure from 90x60 mmHg to 100x60 mmHg, BNP level from 1090 to 863, left ventricular end-diastolic diameter from 67 mm to 61 mm, ejection fraction of the left ventricule went from 29% to 36% and of the right ventricle from 25% to 31%. Peak oxygen consumption ranged from 13 mL/Kg/min to 10.8 mL/Kg/min, maximum

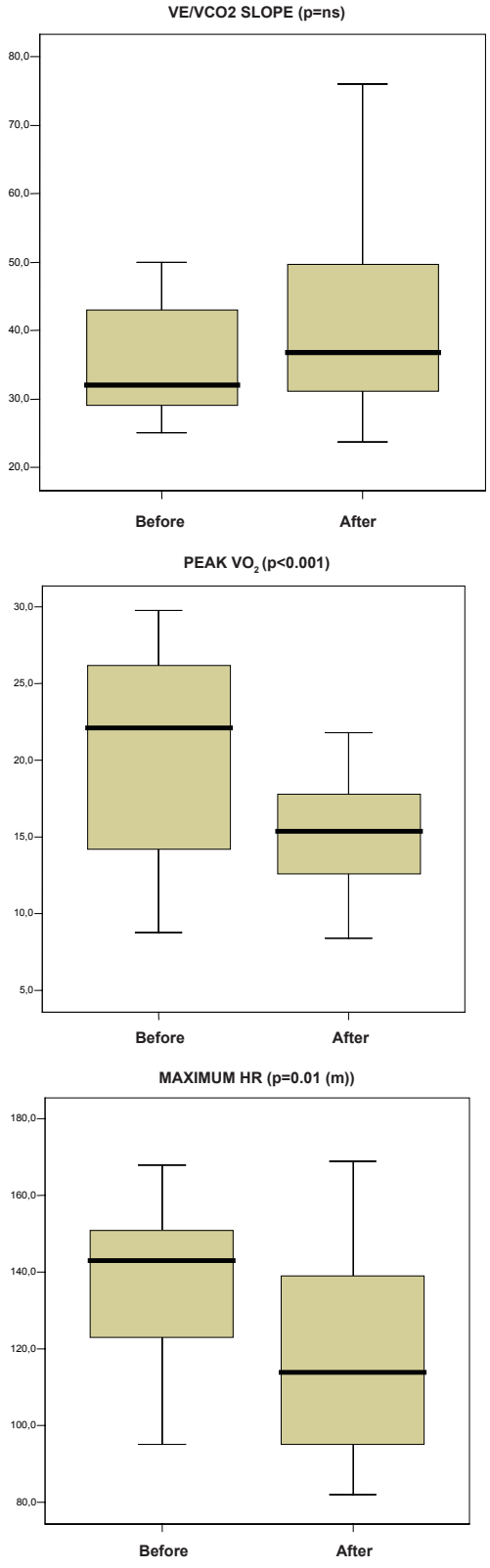

Fig. 1 - *Maximum heart rate attained with exercise (HR Max), maximum oxygen consumption (VO_2 max) and inclination of the slope produced by the peak exhaled volume by carbon dioxide consumption ration (EV/VCO_2 slope) before and after bisoprolol dosing.*

Table 2 - Variables analyzed before and after the administration of bisoprolol

Variable	Before (mean ± sd)	After (mean ± sd)	p value
HR	78.8±8.7	63.0±6.4	<0.001
Systolic arterial pressure	119.1±20.8	110.0±23.8	Ns
Diastolic arterial pressure	75.6±11.5	70.4±11.8	Ns
BNP	368±410.9	211±238.6	Ns
LVDD	6.8±0.8	6.5±1.3	Ns
LVEF	31.3±8.5	39.6±14.7	0.043
RVEF	37.2±9.2	42.2±9.5	ns
Peak VO_2	20.9±6.8	15.1±3.5	<0.001
Max. HR	138.1±20.2	116.7±27.1	0.01
VE/VCO_2 Slope	35.3±8.5	40.7±14.5	ns

heart rate from 130 bpm to 102 bpm, and the VE/VCO_2 slope from 49 to 52.

Discussion

Bisoprolol therapy improved the clinical and hemodynamic status, as well as the cardiac function of patients with heart failure of different etiologies, including those with Chagas' disease; however, it did not result in improved exercise capacity.

Bisoprolol was safe and well tolerated by patients in different etiologies, which is in agreement with other studies[21]; up to 76.5% of the patients tolerated the medication and this rate was not different from that of placebo-controlled studies. The patient with Chagas' disease tolerated the medication well up to the 10 mg dose, and experienced improvement of the symptoms and ventricular function comparable to patients from other etiologies. This is the first report on the use of bisoprolol in patients with Chagas' disease, and it draws attention to the possibility of using bisoprolol in this type of myocardiopathy, too.

The improvement in different clinical parameters (functional class, reduced heart rate at rest, improved quality of life scores, and drop in B-type natriuretic peptide levels) concurs with results reported by other authors[4,22], showing that, by promoting a reduction in sympathetic nervous activity, bisoprolol leads to an improvement in clinical status and ventricular function. This improvement is reflected in the best prognosis found in literature.

The drop in peak oxygen consumption reported in this study, associated with an increase in the VE/VCO_2 slope and the drop in maximum heart rate during exercise, are in agreement with the findings in the CIBIS[16] study that reported a decline in peak oxygen consumption and an increased VE/VCO_2 slope. Different results, however, were found by other authors: a recent study[6] evaluated the effect of chronic use of beta-blockers on exercise capacity measured by ergospirometry in 35 patients with chronic heart failure, 24 of whom received carvedilol and 11 received bisoprolol. The average bisoprolol dose administered to each patient was 6.2 mg. The authors found that both resting and peak heart rates were reduced, without any changes in arterial pressure. A reduction in left ventricular diastolic volume and an increase in ejection fraction were observed. No changes in peak oxygen consumption or VE/VCO_2 slope values were observed with any of the beta-blockers.

In another study[9], the effect of bisoprolol (mean dose of 7.2 mg) was assessed in 21 patients with heart failure, and reductions in heart rate at rest and during peak exercise were noticed. Peak oxygen consumption increased by 15%, but the difference was not statistically significant and the duration of exercise tended to increase. The ejection fraction increased, with a tendency for reduction of the left ventricular volume.

Moreover, in a study conducted with 201 patients[8] treated with bisoprolol at a mean dose of 8.8 mg, the peak oxygen consumption was improved. Despite being statistically significant, improvement in absolute terms was small. Improvements in NYHA functional class, ejection fraction, and a reduction of the ventricular diastolic diameter were also noticed.

Taken as a whole, currently available data indicate that despite being capable of improving the capacity for daily activities (as indicated by the improvement of functional class and quality of life scores), reducing sympathetic activity and improving ventricular function, bisoprolol has no significant effect on the improvement of exercise capacity as measured by ergospirometry. The absence of a relationship between the hemodynamic effects and exercise capacity has been also described for other forms of heart failure therapies, including the use of vasodilators[23], inotropic agents[24], and heart transplantation[25]. It is believed that measurements such as functional class, 6-minute walk test, or quality of life scores may reflect physical capacity during daily activities better than ergospirometry[7]. From a physiopathological point of view, one can think of bisoprolol as having a protective effect that prevents the cardiovascular system from reaching its maximum limits induced by sympathetic hyperactivation during physical exercising. Probably, these limits would not need to be attained during routine physical activities. It is also worth mentioning that patients whose initial peak oxygen consumption may be considered high for a person with heart

failure are likely to experience a drop in oxygen consumption due to the loss of chronotropism caused by the beta-blocker agent. On the other hand, patients whose initial peak oxygen consumption is low, indicating a more advanced stage of the disease, are likely to have an initial chronotropic deficit due to the disease; in this situation, the tendency is increased oxygen consumption during exercise due to improvement of function induced by beta-blocker use. Therefore, the initial value of oxygen consumption may influence the ergospirometry results obtained with the administration of a beta-blocker.

Limitations - Despite the positive results, this study has a limited number of patients. One cannot rule out the possibility that differences in the variables that did not reach statistical significance in this study may be verified in larger groups of patients with longer follow-up periods. Moreover, in view of current results on the beneficial effects of bisoprolol for patients with heart failure, the inclusion of a control group was not considered ethically sound.

Conclusion

Despite being a safe and well-tolerated medication for patients with chronic heart failure of different etiologies and promoting clinical and ventricular function improvement, bisoprolol did not show any significant effects for enhancing exercise capacity measured by ergospirometry.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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