Replacement of Carvedilol for Propranolol in Patients with Heart Failure

Fabiana Marques, Renato Barroso Pereira de Castro, Fernando Nobre, Antonio Osvaldo Pintya, Lourenço Gallo Júnior, Benedito Carlos Maciel, Marcus Vinícius Simões

Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - USP, Ribeirão Preto, SP - Brazil

Abstract

Background: Large clinical trials using the betablockers carvedilol, metoprolol, bisoprolol and nebivolol have demonstrated improvement of survival and symptoms in patients with heart failure. Despite the lack of scientific evidence, it is plausible that their beneficial effects are extensible to other betablockers.

Objective: To evaluate the impact of the replacement of carvedilol for propranolol on left ventricular function, functional capacity, quality of life, pressure levels, and cardiac autonomic control in patients with heart failure.

Methods: Twenty nine patients receiving optimized drug therapy including maximum tolerated doses of carvedilol were divided into two groups: replacement of carvedilol for propranolol (n = 15) and continued carvedilol (n = 14). At baseline and 6 months later, clinical and laboratorial assessments were carried out with radionuclide ventriculography, echocardiography, Minnesota questionnaire, walk test, APBM and Holter monitoring.

Results: The clinical and demographic characteristics were similar in the two groups at baseline. Individualized propranolol dose adjustment ensured a similar degree of beta-blockade, as assessed by resting heart rate and chronotropic reserve. The mean propranolol dose used was 109 ± 43 mg/day. Only one patient presented with intolerance to propranolol, thus carvedilol was reintroduced. One death was recorded in group propranolol. Ejection fraction significantly increased in the propranolol group. No significant change was observed in the other cardiovascular variables after betablocker replacement.

Conclusion: Our results indicate that replacement of carvedilol for propranolol in patients with heart failure is not associated with deterioration of the ejection fraction, functional capacity, quality of life, and other cardiovascular variables related to autonomic and blood pressure control. (Arq Bras Cardiol. 2010; [online]. ahead print, PP.0-0)

Key words: Heart failure; betablocker; propranolol.

Introduction

The first evidences that the adrenergic blockade has beneficial effects on the treatment of chronic heart failure (HF) emerged in the 1970's in studies with practolol and alprenolol[1,2].

Only as of the 1990's, did large randomized prospective placebo-controlled clinical trials using mortality as the primary endpoint prove a significant clinical benefit with four different types of betablockers (BB) in patients with HF: carvedilol[3,4], metoprolol[5], bisoprolol[6] and, more recently, nebivolol[7]. These evidences made the use of BB highly recommended for the treatment of this clinical syndrome.

However, the cost of the treatment using the recommended BB based on these evidences is very high for a great part of the Brazilian population. Because of this socioeconomic restriction, treatment is frequently discontinued or not even introduced. Corroborating these aspects, the Épica-Niterói study showed that drug discontinuation was the first cause of decompensated HF in patients seen in public health services, thus pointing to the socioeconomic factor as one more aggravating factor in the management of this disease in Brazil[8]. Betablocker discontinuation leads to the risk of acute cardiac decompensation in addition to a worse long-term prognosis with loss of the beneficial effects produced in cardiac remodeling[9]. Consequently, despite the lack of solid scientific evidence, in our midst we observe the use of propranolol instead of other betablockers in patients with HF who failed to comply with other treatments due to socioeconomic restrictions, since propranolol is the only BB available in the public health network in several cities in Brazil.

In this context, we should point out that propranolol has already been evaluated in clinical studies on HF in which increased ejection fraction[10], improved ventricular remodeling[11] and improved hemodynamic parameters[12] were demonstrated. The BHAT (Beta-Blocker Heart Attack Trial) study evaluated

the use of gradually increasing doses of propranolol in patients with symptomatic ventricular dysfunction after acute myocardial infarction. A reduction in overall mortality by 35% was observed after 32 months of follow-up[13].

The objective of the present study was to evaluate the effect of the use of propranolol in place of carvedilol on clinical and functional cardiac parameters of clinically stable patients with HF.

Methods

Patients

A total of 29 patients with heart failure (HF), defined according to Framingham's criteria[14], were prospectively studied in a clinical follow-up at the Heart Failure Clinic of *Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - USP.*

The inclusion criteria were: use of optimized clinical treatment with carvedilol at the maximum tolerated dose for more than six months, and systolic ventricular dysfunction with EF lower than 40% on resting radionuclide ventriculography before and after the beginning of treatment with carvedilol. Patients in functional class IV, with HF decompensation within 30 days prior to admission in the study, ischemic etiology, advanced chronic obstructive pulmonary disease, pacemakers, and grade II and III atrioventricular block were excluded from the study.

The study was approved by the Research Ethics Committee of *Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - USP.* A written informed consent was obtained from all participants.

Methods

The patients were prospectively included and underwent clinical and laboratory assessment at baseline, with the methods described below.

Clinical history and physical examination

Detailed clinical history was taken from and physical examination was performed in all participants, including assessment of New York Heart Association functional class (FC) and duration of HF.

Left ventricular remodeling

The patients underwent resting radionuclide ventriculography with the steady-state technique by using stannous agent and technetium-99m (25 mCi) to label the blood pool. Electrocardiogram-gated images were acquired in left anterior oblique view, for better septal separation. A digital DST SMV gamma camera (Sopha Medical Vision - Twinsburg, Ohio-USA) and frame method, 32 frames/cardiac cycle, 400 Kcounts per frame, were used. Left ventricular ejection fraction (LVEF) was calculated from the automatic construction of the time-activity curve.

Two-dimensional transthoracic Doppler echocardiography with color-flow mapping was performed with digital equipment coupled to 3 to 4 MHz transducers with second-harmonic capability (Sonos 5500 - Hewlett Packard, Andover, Mass, USA, and Acuson Cypress - Siemens, Malvern, Pa, USA), by experienced observers blind to the investigation group which the patient had been assigned to. Measurement of the left ventricular end-diastolic diameter (VLEDD) was considered for the analysis of remodeling.

Quality of life

Quality of life was assessed by means of a specific questionnaire (Minnesota Living with Heart Failure Questionnaire), comprising 21 questions regarding physical and psychological limitations found in HF. The total sum of the questionnaire can range from 0 to 105; the lower the value the better the quality of life.

Functional capacity and chronotropic reserve

The distance walked during the 6-minute walk test was used to evaluate the functional capacity. The tests were conducted by physical therapists blind to the study group which the patient had been assigned to, according to the guidelines of the American Thoracic Society[15]. Heart rate (HR) was monitored by using a Polar™ heart rate meter model S 810 (Polar Electro Co. Ltd, Kempele, Finland) 15 minutes before, during, and 15 minutes after the walk test. The chronotropic reserve was calculated by the difference between peak HR during exercise and the pre-test resting HR.

24-hour blood pressure

The patients underwent 24-hour ambulatory blood pressure monitoring (ABPM) through the oscilometric method with monitors Spacelabs 90207 (Spacelabs, Redmond, Washington, USA) and Dyna-MAPA (*Cardio Sistemas*, Sao Paulo, Brazil). Analysis of the data collected included the means of systolic (SBP) and diastolic blood pressure (DBP) measurements.

Cardiac autonomic control

All participants underwent a 24-hour ambulatory electrocardiographic monitoring (Holter monitoring). A recording system of two simultaneous leads (CM5 and CM1) was used. The recording was analyzed in a microcomputer with a Spacelabs analysis module (Issaquah, Washington, USA). Mean 24-hour heart rate and SDNN (standard deviation of normal RR intervals) were extracted and computed from data processing. Patients with chronic or persistent atrial fibrillation were excluded from the analysis of HR variability.

Clinical follow-up

After baseline assessment with the laboratory tests described, the patients were randomly assigned to one of two groups: group of replacement of carvedilol for propranolol (group propranolol, n = 15), and group with continued carvedilol (group carvedilol, n = 14).

Patients randomized for the propranolol group received an initial propranolol dose of 80mg/day bid. Other medications used for the treatment of HF were maintained in both groups.

Propranolol doses were titrated according to the HR observed on clinical examination performed during outpatient follow-up visits, with the goal of reaching a HR similar to that observed prior to the introduction of propranolol. Next, the degree of beta-blockade was assessed with base on the maximum HR in the 6-minute walk test, with the aim of keeping the HR equal to that observed prior to randomization or with a maximum variation of 5 beats. Six months after the end of propranolol titration, the patients of both groups underwent a final assessment by means of the same methods used at baseline.

Statistical analysis

For variables normally distributed, the Student's t test was applied for comparison of the means of the two groups investigated; the paired Student's t test was used for comparison of the means in the same group at baseline and final assessment. Variables non-normally distributed were analyzed using the non-parametric Mann-Whitney test in the non-paired analysis, and the Wilcoxon test in the paired analysis. Fisher's exact test was used for the analysis of the association between categorical variables. The level of significance was set at 5% for all statistical tests used.

Results

The general and clinical baseline laboratorial characteristics of the individuals from the two groups formed are shown in Table 1. The statistical analysis of the clinical laboratorial variables obtained at baseline did not show significant differences between the groups, except for the presence of hyperuricemia, which was significantly greater in the propranolol group. There was a predominance of women in the carvedilol group, although this difference was not statistically significant. Medication doses used for the specific treatment of HF were not significantly different between the two study groups (Table 2).

Clinical course

The propranolol dose required to keep the degree of β-adrenergic blockade in the propranolol group ranged from 80 to 240 mg/day, with a mean of 109 ± 43 mg/day.

Table 1 - General, clinical and laboratorial characteristics of the patients included in the two study groups

	Propranolol (n=15)	Carvedilol (n=14)	P
Age (years)	54 ± 8.0	51.8 ± 9.2	0.51
Female gender	3 (20%)	8 (57%)	0.13
Duration of HF (years)	5.7	5.4	0.79
Use of carvedilol (months)	16.5±11.5	19±13.0	0.59
LVEF (%)	34.4 ± 10.3	38.5 ± 10.4	0.30
Cardiac rhythm			
Sinus rhythm	14 (93.3%)	13 (92.8%)	1
Atrial fibrillation	1 (6.7%)	1 (7.2%)	1
FC (NYHA)			
I	8 (53.3%)	8 (57.1%)	1
II	5 (33.3%)	5 (35.7%)	1
III	2 (13.3%)	1 (7.1%)	1
Cause			
Idiopathic	9 (60%)	10 (71.4%)	0.69
Hypertension	3 (20%)	2 (14.2%)	1
Chagas disease	1 (6.6%)	1 (7.1%)	1
Alcohol	2 (13.3%)	0 (0%)	0.48
Myocarditis	0 (0%)	1 (7.1%)	0.48
Chemotherapics	0 (0%)	1 (7.1%)	0.48
Comorbidities			
SH	5 (33.3%)	6 (42.8%)	0.74
DM	3 (20%)	6 (42.8%)	0.24
Dyslipidemia	2 (20%)	4 (28.5)	0.38
CRF	1 (6.6%)	0 (0%)	1
Obesity	3 (20%)	3 (21.4%)	1
Hyperuricemia	7 (46.6%)	1 (7.1%)	0.03

LVEF - left ventricular ejection fraction, FC (NYHA) - New York Heart Association functional class, SH - systemic hypertension, CRF - chronic renal failure, DM - diabetes mellitus.

Table 2 - Doses of medications used for the treatment of heart failure

Medication (mg/day)	Group Propranolol			Group Carvedilol		
	Baseline	Final	p	Baseline	Final	P
Carvedilol	52 ± 9.8	0		55.3 ± 14.4	54.4±15.19	0.99
Captopril	125 ± 39	119 ± 52	0.99	121.8 ± 4	120.3± 44.2	0.99
Enalapril	23.3 ± 14.0	23.3 ± 14.0		30 ± 14.1	32.5±15	0.39
Digoxin	0.10 ±0.09	0.11 ± 0.09	0.21	0.12± 0.12	0.13± 0.11	0.75
Furosemide	45.3 ± 41.7	42.6 ± 38.4	0.56	30.0 ± 23.20	30.0 ±23.20	0.99
Aldactone	14.1 ± 12.3	11.6 ± 12.9	0.62	16.0 ±12.43	17.8 ± 11.72	0.75

Three patients required transient increase of the diuretic dose after BB replacement; in only one of them propranolol had to be discontinued due to clinical decompensation with worsening of the functional class irresponsive to increase in the diuretic dose accompanied by decompensation of diabetes mellitus. Hospitalization was not necessary. Propranolol was discontinued on the third week after its introduction, and carvedilol was restarted with improvement of the symptoms.

One patient in the propranolol group presented with decompensation and died during the final study phase. Several clinical and laboratorial evidences showed that this patient had advanced HF and a poor prognosis. At the baseline assessment, he had the lowest EF value among all participants (15%), and the shortest distance walked in the 6-minute walk test among all men in the sample. He was the only patient with chronic renal failure in this case series. Additionally, he had other criteria of severity such as a significantly enlarged left ventricle (LVDD = 81 mm), persistently reduced functional capacity (FC III), and severely reduced RR variability (SDNN = 52 ms).

In the carvedilol group, two patients required transient increase in the diuretic dose due to signs of decompensation during the follow-up period. No deaths or hospitalizations occurred in this group.

Heart rate and degree of beta-adrenergic blockade

Resting HR and maximum HR values during the walk test, as well as HR variation between exercise and rest (chronotropic reserve) were not significantly different (Table 3). The resting HR observed in the two groups during baseline assessment showed similar values: 63.64 ± 8.63 bpm (propranolol group) and 65.83 ± 7.2 bpm (carvedilol group), p= 0.49. Patients assigned to the propranolol group showed a resting HR of 61.08 ± 8.35 at the end of the study, with a mean reduction of 2.56 bpm, which was not statistically significant.

HR variation between peak exercise and rest (chronotropic reserve) throughout the study showed values practically identical in the propranolol group (baseline assessment = 49.57 ± 14.78; and final assessment = 49.41 ± 11.79; p= 0.71) and in the carvedilol group (baseline assessment = 48 ± 15.47; and final assessment = 48.16 ± 15.60; p= 0.97). These results show that the degree of beta-blockade was similar between the groups throughout the study.

Left ventricular systolic performance

Baseline LVEF was not significantly different between the groups studied (p = 0.30). In the propranolol group, LVEF showed significant increase throughout the follow-up period, with mean baseline values of 34.4 ± 10.0 and final values of 39.5 ± 11.7 (p = 0.048). The statistical analysis of LVEF in the carvedilol group did not show a significant difference between the baseline and final assessments.

LVDD values obtained by echocardiographic study at baseline and final assessments from individuals of the two groups proved statistically similar with p > 0.05, both in the analysis between the two groups and in the intra-group analysis between the baseline and final assessments.

Functional capacity and quality of life

Both the scores obtained in the quality of life assessment questionnaire and the distance walked in the walk test did not show significant changes throughout the study in the two groups (Table 4).

Autonomic and blood pressure controls

The results of blood pressure assessments did not show significant differences between the groups at baseline as regards the mean 24-hour systolic blood pressure. On the other hand, the mean 24-hour diastolic blood pressure was significantly lower in the carvedilol group (p = 0.018, Table 4). These results remained similar at the final assessment: the mean systolic blood pressure did not show a significant difference between the two groups and no significant variation was observed in the intra-group analysis (baseline and final). Diastolic blood pressure maintained a significant difference at the final assessment between the two groups (p = 0.015), however with no significant change in the analysis between baseline and final assessments in each group (p = 0.61).

HR variability in the time domain was assessed using the mean 24-hour HR and SDNN. These variables did not show significant changes in the two groups studied.

Discussion

The results of the present study show that the replacement of carvedilol for propranolol in patients with stable chronic HF provides a favorable clinical outcome in most of the patients without causing deterioration of the left ventricular systolic function, change in quality of life, or functional capacity.

One of the key points in the design of this study was to keep the same degree of adrenergic blockade after replacement of carvedilol for propranolol. This methodological detail took into consideration the concept that the degree of HR reduction obtained with the betablocker therapy is quite relevant for a clinical response to HF treatment to be obtained.

Table 3 - Results of heart rate assessment

	Propranolol			Carvedilol		
	Baseline	Final	P	BaselineHR	Final HR	p
Resting HR (bpm)	63.6±8.6	61.0±8.3	0.09	65.8±7.2	65.91±6.0	0.97
Exercise HR (bpm)	113.2±13.4	110.5±12.3	0.27	113.8±17.9	114.0±17.0	0.96
HR variation (bpm)	49.5±14.7	49.4±11.7	0.71	48±15.4	48.1±15.6	0.97

HR - heart rate in beats per minute (bpm). p > 0.05 for all comparisons between the carvedilol and propranolol groups.

Table 4 - Laboratory test results at baseline and final assessments in both groups studied

	Propranolol			Carvedilol		
	Baseline	Final	P	Baseline	Final	P
LVEF%	34.4 ±10.0	39.5 ±11.7	0.048	38.5±10.4	36.7±11.4	0.36
LVDD mm	68.2±8.9	66.0±10.0	0.11	67.4±10.4	67.5±12.2	0.91
Distance m	570.4±65.4	554.8±85.5	0.25	524.4±72.7	517.2±71.3	0.46
Minnesota score	18.7±10.9	24.0±16.3	0.17	20.5±16.4	24.2±23.2	0.30
24-h MSBP (mmHg)	119.3±10.9	122.4±13.5	0.81	113.6±17.4	113.0±16.9	0.86
24-h MDBP (mmHg)	73.6±9.4	74.3±12.2	0.61	65.7±6.7	65.2±9.0	0.84
Mean 24-h HR (bpm)	71.9±7.7	73.0±11.2	0.87	73.2±10.6	71.7±7.8	0.35
SDNN (ms)	109.9±35.7	99.9±24.5	0.11	94.7±24.5	96.3±26.3	0.60

LVEF% - left ventricular ejection fraction, LVDD - left ventricular diastolic diameter, MSBP - mean systolic blood pressure, MDBP - mean diastolic blood pressure, HR - heart rate, SDNN - standard deviation of the RR intervals.

A retrospective analysis of large clinical trials found a strong correlation between HR reduction, LVEF improvement and mortality reduction[16].

In this sense, the betablocker dose used influences the clinical outcome as well. The MDC and CIBIS I studies showed that metoprolol and bisoprolol doses lower than those currently recommended do not have an impact on morbidity and mortality[17,18]. Therefore, we can state that both the BB dose and the magnitude of HR reduction have great importance in the deriving of a clinical benefit.

The HR observed during outpatient visits was the initial parameter for the propranolol dose adjustment. For a fine dose adjustment and confirmation that the degree of beta-blockade was maintained, the maximum HR and chronotropic reserve during the walk test were evaluated. Thus, we showed that resting HR, peak exercise HR, and HR variation during exercise did not show significant differences.

Since the peak exercise HR is the most relevant clinical indicator of the extent of adrenergic blockade[19], the finding of very similar values of HR variation between rest and exercise in the two study groups seems to demonstrate equivalent potency of BB doses and a similar degree of adrenergic blockade.

There was a wide variation in the doses required to achieve the degree of adrenergic blockade in group propranolol - with values ranging between 80 and 240 mg/day - which is consistent with data from the literature showing wide interindividual variability in propranolol plasma concentrations[20].

The present results show that, in clinically stable patients using the maximum tolerated carvedilol dose, transition to propranolol at an initial dose of 80 mg/day is associated with a high success rate. Three patients required transient increase of the diuretic dose after BB replacement; only one of them required discontinuation and reintroduction of carvedilol. In the carvedilol group, two patients also required transient increase in the loop-diuretic dose due to worsening of congestive symptoms. On the other hand, the only death recorded in the cohort occurred in a patient using propranolol. However, at baseline, this patient presented with several clinical and laboratorial evidences of a very severe heart disease and poor prognosis, and was randomly assigned to the propranolol group.

Overall, our results are consistent with those of other studies in the literature using propranolol for the treatment of chronic HF. A previous study of 56 patients with HF due to dilated cardiomyopathy started betablocker therapy with propranolol at gradually increasing doses and found an intolerance rate of 21%[21]. In a similar study of 20 patients with HF, Maia et al[11] did not observe the need for propranolol discontinuation in any patient; however, 63% of the participants showed transient side effects during the use of propranolol, including worsening of exercise capacity and/or signs of congestion, all controlled with a diuretic dose adjustment. In our study, we obtained a low intolerance rate (6.6%). This result is probably associated with the design of the present study, which investigated patients already in chronic and stable use of carvedilol for at least six months. On the other hand, the case series predominantly comprised individuals with not severe HF, which justifies the good tolerance observed.

Left ventricular ejection fraction (LVEF) as assessed by radionuclide ventriculography showed a significant difference between the two groups at the end of the study. A 4.4% increase in LVEF was observed in the group in which propranolol was introduced in the period between the two assessments (p = 0.048). No significant differences in LVEF occurred in the carvedilol group. It is plausible to presume that this intriguing result showing LVEF increase exclusively in the propranolol group may have occurred because of the randomization linked to the reduced number of subjects in the sample. Anyway, this finding clearly underscores that the use of propranolol was not associated with any deleterious effect on the left ventricular systolic function, an information which is consistent with the favorable clinical outcomes obtained.

We should also point out that, in consistency with the results obtained in the sequential LV systolic function assessment, the quality of life was also not significantly changed after replacement of carvedilol for propranolol, thus corroborating data of good clinical tolerance to propranolol in these patients.

Likewise, the functional capacity as assessed by the distance walked in the 6-minute walk test did not significantly change

throughout the follow-up period. The mean distance walked in both groups was longer than 500 m, which is consistent with other features of the sample studied, characterizing it as a sample of patients with mild HF and low risk.

One of the relevant aspects when the differences in the pharmacological actions between carvedilol and propranolol are addressed is related to the alpha-1 receptor blockade effect produced only by carvedilol. The peripheral arteriolar vasodilating action and consequent reduction in left ventricular afterload mediated by alpha-1 blockade seems to be important to induce better tolerance to carvedilol in the introduction and titration phase in patients with advanced HF. However, there are evidences that the alpha-1 blockade has no relevant effect or contributes to the benefits of the long-term therapy[22]. Our findings showed a null effect on systolic and diastolic blood pressure levels after replacement of carvedilol for propranolol, thus reinforcing previous evidence that alpha-1 blockade has little effect on blood pressure control in the long-term therapy with carvedilol.

The cardiac autonomic control was assessed by means of the SDNN, a global index of HR variability, which represents the standard deviation of all RR intervals. Reduction in SDNN values reflects the increase in the adrenergic tone and implicates more severe HF. SDNN values lower than 70 ms are independent predictors of mortality[23,24].

Mean SDNN values found in both groups of this study were higher than 70ms. This favorable profile of HR variability may have resulted from the previous use of BB, since it has been demonstrated that the chronic use of carvedilol favorably acts on the autonomic tone of patients with HF[25,26]. After replacement of carvedilol, no significant changes were observed in SDNN values, and this suggests that propranolol maintained an effect similar to that of carvedilol on the adrenergic tone modulation.

Study limitations

We should point out that the number of patients was relatively small, and this may have affected the identification of differences between the two groups.

The fact that this was not a double-blind study may have influenced the assessment of quality of life by the Minnesota questionnaire. However, although the patients knew which their study group was, the operators that performed the ancillary tests were blind to each individual's assignment in the study.

Conclusions

Replacement of carvedilol for propranolol in clinically stable patients with non-ischemic HF receiving optimized medication therapy including chronic use of the maximum tolerated carvedilol dose showed a low intolerance rate and was not associated with deterioration of the left ventricular systolic function, quality of life, functional capacity, or autonomic and blood pressure controls.

Our findings suggest that in patients with HF showing low compliance to carvedilol due to financial limitations, propranolol may be an alternative with a good chance of short-term therapeutic success. These results point to the need for further broader clinical trials with the purpose of confirming the beneficial role of propranolol in the treatment of chronic systolic HF.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Fabiana Marques, from Faculdade de Medicina de Ribeirão Preto-USP.

References

1. Waagstein F, Hjalmarson A C, Wasir HS. Apex cardiogram and sistolic time intervals in acute myocardial infarction and effects of practolol. Br Heart J. 1974; 36 (11): 1109-21.

2. Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J. 1975; 37 (10): 1022-36.

3. Packer M, Bristow MR, Cohn JN, Collucci W, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U S Carvedilol Heart Failure Study Group. N Engl J Med. 1996; 334 (21): 1349-55.

4. Packer M, Coats AJS, Fowler MB, katus HA, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344 (22): 1651-8.

5. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999; 353 (9169): 2001-7.

6. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet. 1999; 353 (9146): 9-13.

7. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005; 26 (3): 215-25.

8. Tavares LR, Victer H, Linhares JM, Barros CM, Oliveira MV, Pacheco LC, et al. Epidemiology of decompensated heart failure in the city of Niterói - EPICA - Niterói Project. Arq Bras Cardiol. 2001; 82 (2): 125-8.

9. Waagstein F, Caidahl K, Wallentin I, Berg C, Hjalmaroson A. Long-term beta-blockade in dilated cardiomyopathy: effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. Circulation. 1989; 80 (3): 551-63.

10. van Campen LCMC, Visser F, Visser CA. Ejection fraction improvement by β-blocker treatment in patients with heart failure: an analysis of studies published in the literature. J Cardiovasc Pharmacol. 1998; 32 (1): S31-5.

11. Maia ER, Villacorta H, Subietta GC, Munhoz C, Romeu-Filho LJM, Mesquita ET. Use of propranolol in heart failure patients: safety, tolerability, and effects on left ventricular function. Rev Port Cardiol. 2001; 20 (4): 383-99.

12. Talwar KK, Bhargava B, Upasani PT, Verma S, Kamlakar T, Chopra P. Hemodynamic predictors of early intolerance and long-term effects of propranolol in dilated cardiomyopathy. J Card Fail. 1996; 2 (4): 273-7.

13. Chadda KK, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. Circulation. 1986; 73 (3): 503-10.

14. Mckee PA, Castelli WP, Mcnamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. N Engl J Med. 1971; 285: 1441-6.

15. ATS Committe on proficiency standards for clinical pulmonary function laboratories. ATS statement: guidelines for the six-minute walk test. Am J Crit Car Med. 2002; 166 (1): 111-7.

16. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol. 2008; 101 (6): 865-9.

17. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet. 1993; 342 (8885): 1441-6.

18. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994; 90 (4): 1765 -73.

19. De Mey C, Breithaupt-Grogler K, Schloos J, Palm D, Belz GG. Reproducibility and consistency of the responses to supine bicycle ergometry: evaluation in conjunction with β-1 adrenoreceptor occupancies. Br J Clin Pharm. 1994; 38 (5): 480-3.

20. Chidsey CA, Morselli P, Bianchetti G, Marganti A, Leonetti G, Zanchetti A. Studies of the absorption and removal of propranolol in hypertensive patients during therapy. Circulation. 1975; 52 (2): 313-8.

21. Talwar KK, Bhargava B, Upasani PT, Verma S, Kamlakar T, Chopra P. Hemodynamic predictors of early intolerance and long-term effects of propranolol in dilated cardiomyopathy. J Card Fail. 1996; 2 (4): 273-7.

22. Gilbert EM, Abraham WT, Olsen S, Hattler B, White M Mealy P, Larrabee P, et al. Comparative hemodynamic, left ventricular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. Circulation. 1996; 94 (11): 2817-25.

23. Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, et al. Prognostic values of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol. 2002; 90 (1): 24-8.

24. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J. 2000; 21 (6): 475-82.

25. Malfatto G, Facchini M, Branzi G, Riva B, Sala L, Perego GB. Long-term treatment with the beta-blocker carvedilol restores autonomic tone and responsiveness in patients with moderate heart failure. J Cardiovasc Pharmacol. 2003; 42 (1): 125-31.

26. Mortara A, La Rovere MT, Pinna GD, Maestri R, Capomolla S, Cobelli F. Nonselective beta adrenergic blocking agent carvedilol, improves arterial baroflex gain and heart rate variability in patients with stable chronic heart failure. J Am Coll Cardiol. 2000; 36: 1612 -8.