Effects of Metoprolol Tartrate Therapy in Patients with Heart Failure

José Albuquerque de Figueiredo Neto, Charles Mady, César Grupi
Universidade Federal do Maranhão e Instituto do Coração do Hospital das Clínicas – FMUSP - São Luiz, MA - São Paulo, SP - Brazil

Objective

To study the effects of metoprolol tartrate therapy in patients with heart failure.

Methods

Fifty patients (36 males) aged 52±14.8 yrs, with functional class II to IV heart failure (HF) and left ventricular ejection fraction (LVFE) < 45%, assessed by radionuclide ventriculography, were evaluated in a retrospective study. Metoprolol tartrate was added to the usual therapy, with a starting dose of 12.5 mg, which was increased weekly to a maximum of 200 mg/day, according to patients' tolerance. Clinical evaluation, electrocardiogram, Doppler echocardiogram, 24-h Holter monitoring and radionuclide ventriculography were carried out in the pre-treatment phase and repeated three and six months after the start of therapy.

Results

At the end of six months, there was functional class (NYHA) improvement with a reduction from 3.04±0.11 to 1.66±0.06($p<0.001$). Ejection fraction increased from 29.84+1.61% to 38.56±1.95% ($p< 0.001$). The left ventricular diastolic diameter showed a reduction from 67.70±1.31 mm to 63.96±1.29 mm ($p<0.001$), and the left ventricular systolic diameter showed a reduction from 54.80±1.67 mm to 48.58±1.38 ($p<0.001$). There was no alteration in noradrenaline levels during the six-month follow-up period ($p>0.05$). Cardiac frequency decreased from 78.84±1.68 to 67.48±1.86 b.p.m. ($p<0.001$).

Conclusion

The adding of metoprolol tartrate to the usual heart failure therapy is followed by an increase of ejection fraction, functional class improvement, and decrease of ventricular diameters and cardiac frequency. These results suggest anti-remodeling effects in patients with HF who utilize metoprolol tartrate in addition to the usual therapy.

Key words

Heart failure, beta-blocker, dilated cardiomyopathy.

Correspondência: José Albuquerque de Figueiredo Neto • Rua Eng. Ruy Ribeiro Mesquita, Ed. Dom Gabriel apto. 402 - 65075-260 – São Luiz, MA - Brazil
E-mail: jafneto@cardiol.br
Received on 07/03/05 • Accepted on 10/17/05

Heart failure (HF) is the usual final outcome of most cardiomyopathies. The socioeconomic cost of the syndrome is high, involving drug therapy, repeated hospital admissions, productivity loss, early retirement, eventual surgery and, occasionally, heart transplant costs[1].

The treatment goal of HF patients includes mortality and morbidity reduction, with the consequent improvement in quality of life by preventing disease evolution.

The attenuation of the sympathetic-adrenergic activation through chronic beta-blocker treatment, whose outcomes are different from those resulting from the acute administration, has led to the alteration of the contraindication paradigm for the utilization of these agents in HF (which represents a great advancement in the syndrome therapeutics). Several studies have documented that beta-blockers reduce the morbidity and mortality of patients with HF[2-5].

The objective of this study was to evaluate the efficacy and tolerance of a selective beta-blocker (ß-1), metoprolol tartrate, in patients with heart failure due to moderate to severe dilated cardiomyopathy, added to the usual therapeutics (digitalis, diuretics, angiotensin-conversion enzyme inhibitors or vasodilators, and nitrates).

Methods

Eighty consecutive patients being followed at the Cardiology Outpatient Clinic of the Hospital Universitário Presidente Dutra – UFMA, were enrolled in the study.

The inclusion criteria were: patients with HF, functional class (FC) II to IV according to the New York Heart Association (NYHA) who had been clinically stable in the previous three months, with sinusal rhythm in the electrocardiogram at rest, left ventricular ejection fraction ≤ 45% at the radionuclide ventriculography, and a thoracic structure that enabled an adequate echocardiographic window for the acquisition of images in order to measure the diameters of the cardiac chambers.

Exclusion criteria were: history of alcohol abuse, AMI in the previous six months, second or third-degree atrioventricular block, systolic arterial pressure < 90 mmHg, cardiac frequency < 60 bpm, and beta-blocker use contraindication.

Eighty patients were recruited for the minimum study of 30 cases, according to the initial design. Twenty-six patients were excluded (ten patients refused to participate in the study, six presented atrial fibrillation or conduction defects at Holter monitoring, eight patients presented an inadequate echocardiographic window, and two patients presented primary valvopathy). All patients received information and explanations regarding the study protocol, and signed a written informed consent form, agreeing to participate in the study. This study was approved by the Review Board of the Hospital Universitário Presidente Dutra-UFMA.

During the pre-treatment phase, the patients underwent clinical evaluation, electrocardiogram at rest, 24-hour Holter monitoring, radionuclide ventriculography, echocardiogram, measurement of plasma catecholamines, and routine lab tests.

The addition of metoprolol tartrate was started with a dose of 12.5 mg twice daily and increased weekly, with the objective of reaching a 200-mg/day dose, according to the patients' tolerance. After the maximum desired or tolerated dose had been reached, the patient was reassessed monthly or within a shorter period, according to the clinical necessity. The complementary clinical examinations were repeated after three and six months of medication use.

The patients were being treated with individual maximum-tolerated doses of digitalis, diuretics and angiotensin-conversion enzyme inhibitors. The qualitative variables were represented by absolute (n) and relative frequencies (%). The continuous variables were expressed as means and standard deviations. Differences between the groups were evaluated by analysis of variance with repetition for continuous variables (ANOVA), by Bartlets test for data with normal distribution and Tukey-Kramer test for multiple comparisons, if $p<0.05$. Significance level was set at $p=0.05$ (5%). Descriptive levels (P) lower than this value were considered significant and are represented by an asterisk (*).

Results

Fifty-four patients were followed. Three patients did not tolerate metoprolol use, and a patient died of sudden death in the third month of follow-up; these patients were included in the nonresponder group.

Among the studied patients, 16 (26%) were females and 38 (74%) were males. Age ranged from 18 to 75 years, with a mean of 52.34 yrs; 24 patients (48%) were older than 52 yrs.

As for the etiology of HF, 16 patients (26%) presented ischemic etiology and 38 (74%) non-ischemic etiology; of the latter, 17 presented hypertensive etiology and 21 idiopathic etiology.

Regarding the use of other drugs, 45 (83%) used digitalis, 49 (90%) used diuretics and 48 (88%) used angiotensin-conversion enzyme inhibitors. Follow-up ranged from 6 to 17 months , with a mean of 12 months. The initial dose of metoprolol utilized was 150 mg daily (Tab. 1).

In the studied group, left ventricular ejection fraction (LVEF), assessed by radionuclide ventriculography at the

Table 1 – Patient distribution according to demographic aspects, etiology, time of follow-up and medication dose utilized

Characteristics	
Gender:	
Male	38 (74%)
Female	16 (26%)
Mean age:	52.34 (18-75)
Etiology:	
Ischemic	16 (30%)
Non-ischemic	
Idiopathic	21 (39%)
Hypertensive	17 (31%)
Time of follow-up (months)	12.62 (6-17)
Ejection fraction	12-45 (29%)
FC (NYHA) I/II/III/IV	0/14/20/16
Treatment (%)	
ACE inhibitors (captopril)	88%
Digoxin	83%
Diuretic drugs (furosemide)	90%
Metoprolol (mean)	150 (100 – 200 mg)

start of follow-up, varied from 12 to 45%, with mean ±SD =29.84 ± 1.61%. At least 27 patients (50%) from the sample presented a LVEF mean of 29% or less. After three months of treatment with metoprolol, ejection fraction increased to 34.64±1.92%, and after six months, it increased to 38.5±1.95%. Forty-two patients (77%) presented a significant LVFE increase (p< 0.001). The increase occurred from the third month on, and was maintained until the sixth month of follow-up (Chart 1).

Adequate Doppler echocardiograms were obtained for comparative analysis in 48 (88%) of the patients. In the beginning of the study the left ventricular end-diastolic diameter (LVEDD) varied from 50 to 95 mm, with mean±SD=67.70±1.31 mm. Twenty-eight of these patients (51%) presented a mean of 67 mm or higher. The left ventricular end-systolic diameter (LVESD) varied from 36 to 83 mm, with mean±SD= 54.80±1.61 mm. Twenty-five of these patients (42%) presented a mean of 54 mm or higher.

A significant LVEDD decrease (p<0.001) was observed in 34 patients (62%), as well as a significant LVESD reduction (p<0.001) in 42 patients (77%) at the end of the sixth-month follow-up (Tab. 2).

At the beginning of the follow-up, 14 (25%), 20 (37%) and 16 (29%) of the patients were functional class II, III and IV, respectively.

There was a significant functional class improvement (NYHA) with metoprolol tartrate use after a six-month follow-up (p<0.001)

Fifteen patients presented improvement from functional class IV to II, and one patient improved to functional class I.

Of the 20 patients initially classified as functional class III, 17 improved to functional class II and 3 to functional class I.

Of the patients who were initially classified as functional class II, 12 improved to functional class I and 2 patients showed no alteration (Chart 2).

Sodium and creatinine levels remained unaltered throughout the six-month follow-up (p> 0.05) of metoprolol use.

Noradrenaline levels at the beginning of follow-up varied from 77.2 to 1,493.2 pg/mL, with mean ± SD= 758.26 ± 62.11 pg/mL. Noradrenaline levels decreased at the end of the third month of follow-up (p<0.001), returning to pre-treatment levels at the end of the six months of follow-up. This increase was significant only between the third and the sixth months of follow-up (p<0.01), but it was non-significant between the beginning and the sixth month of follow-up (p>0.05) (Chart 3).

The patients studied presented mean cardiac frequency (CF) of 78.84±1.67 bpm at the beginning of the follow-up. A significant CF reduction was observed on the sixth month with metoprolol use. FC reduction was observed from the third month on and persisted until the sixth month of follow-up (Table 3). This decrease was observed in 30 (55%) of the patients (p<0.0001).

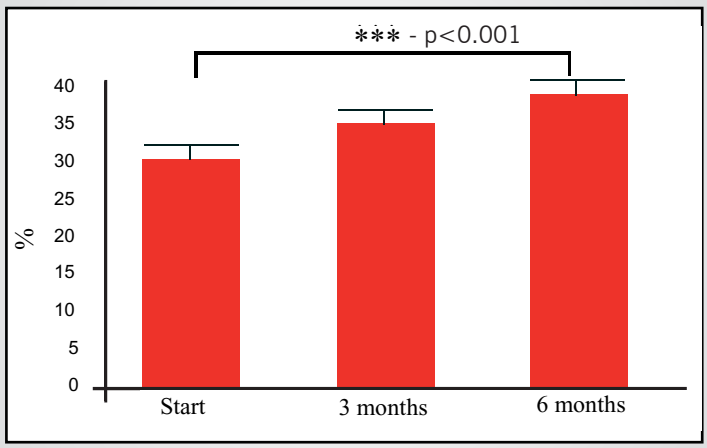

Chart 1 *– Evaluation of the ejection fraction during a six-month follow-up of metoprolol use.*

Table 2 – Evaluation of left ventricular diameters at the Doppler echocardiogram during the six-month follow-up

Echocardiography parameters	Start	Three months	Six months	p
LVEDD (mm)	67.70 ± 1.31	65.52 ± 1.26	63.96 ± 1.29	0.001
LVESD (mm)	54.80 ± 1.67	50.50 ± 1.48	48. 58 ± 1.38	0.001

LVEDD - left ventricular–end diastolic diameter; LVESD - left ventricular-end systolic diameter.

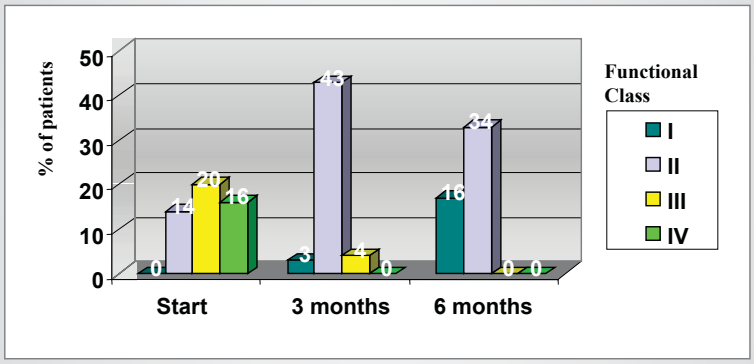

Chart 2 *– Patient distribution according to functional class (NYHA) during a six-month follow-up of metoprolol use.*

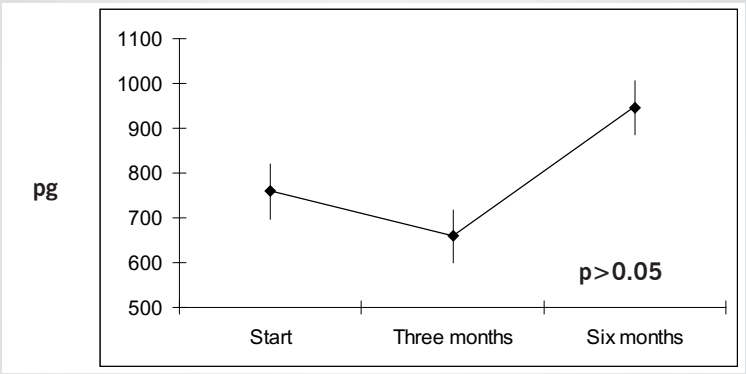

Chart 3 *– Distribution of the noradrenaline levels during a six-month follow-up.*

Table 3 - Cardiac frequency assessment during a six-month follow-up

Time	Start	Three months	Six months	p
Cardiac frequency (bpm)	78.84 ± 1.67	68.68 ± 2.06	67.48 ± 1.86	<0.0001

Discussion

Several studies have demonstrated that beta-blockers reduce morbidity and mortality in patients with HF[2-5]. The mechanisms through which beta-blockers produce beneficial effects in patients with HF are not accurately known. Among the several proposed mechanisms are: decrease of plasma and tissue noradrenaline levels through reduction in sympathetic activity; increase of noradrenaline clearance and blocking of the toxic catecholamine effects on myocytes with apoptosis and cell death reduction; restoration of decreased beta-receptor density due to chronic adrenergic activation, allowing the myocardium to respond to the stimulation of endogenous catecholamines, resulting in a symptomatic improvement and better tolerance to exercises, considerable increase in stimulatory G-protein levels (Gs), with higher adenylyl cyclase activity, higher energy production and more efficiency of contractile units; reduction of rennin secretion levels through the sympathetic blocking, mimicking the action of angiotensin-converting enzyme inhibitors and preventing the escape of angiotensin II suppression by the angiotensin-converting enzyme inhibitors; barorreflex function improvement, decreased aortic impedance (post-load) and circulatory efficiency improvement; heart failure decrease, with lower oxygen consumption by the myocardium, improved diastolic function, increased coronary flow and decreased ischemia, ventricular arrhythmias and sudden death.

Metoprolol is a selective, lipophilic blocker, with no intrinsic sympaticomimetic activity. Among the beta-blockers, metoprolol was the first one to be used and the most studied in patients with HF. Several non-controlled studies were carried out before the first randomized study with beta-blocker in patients with HF was published by Anderson et al[6].

In patients with HF, metoprolol improves cardiac function, left ventricular remodeling, exercise capacity

and decreases HF symptoms[7,8].

The study by Engelmeier et al[8] showed that patients receiving metoprolol improved their exercise capacity in 3 METS and NYHA functional class. However, the small sample size (9 patients in the metoprolol group and 16 in the placebo group) and other design problems made its results difficult to interpret and were little convincing. Cucchini et al[9] studied metoprolol action in 20 patients with idiopathic dilated cardiomyopathy, who were followed for a six-month period. Patients in the metoprolol group presented functional class improvement, left ventricular ejection fraction increase from 34±12% to 44±11%($p<0.001$); end systolic volume as well as capillary pressure were reduced. These results were not observed in the placebo group.

The MDC study[10] was the first broad study carried out with metoprolol. Three hundred and eighty-three patients with idiopathic dilated cardiomyopathy were enrolled; 94% of them were functional class II or III (NYHA). The primary aim of this study was a combined objective (mortality and transplant necessity). There was a 34% reduction of transplant necessity ($p<0.058$); however, there was no alteration regarding mortality. The follow-up showed a significant functional improvement of functional class in the metoprolol group, and the number of patients who needed hospitalization was smaller in the metoprolol group compared to the placebo group, although this number was non-significant.

The beneficial hemodynamic effects of metoprolol tartrate in patients with non-ischemic dilated cardiomyopathy were evaluated by Eichhorn et al[11]: 24 patients underwent catheterism before and after three months of metoprolol therapy ($n=15$) or placebo ($n=9$), in addition to the usual therapy. In the metoprolol group, there was an increase of the left ventricular ejection fraction with no increase of myocardial oxygen consumption, suggesting myocardial efficiency improvement.

Fisher et al[7] studied 50 patient with HF associated to coronary artery disease. After a six-month period, metoprolol promoted a decrease in the number of hospital admissions, improvement of functional class, exercise capacity and increase of ejection fraction. The RESOLVD[12] study included 426 patients with HF due to multiple causes. The study utilized a 3x2 factorial design with a two-stage randomization. At stage I, patients were randomized to receive candesartan, enalapril or a combination. At stage II, the patients were randomized to receive 200 mg/day of metoprolol or placebo. Metoprolol did not affect the results of the six-minute walk test, functional class (NYHA) and quality of life. However, there was a significant improvement in left ventricular function, with reduction of left ventricular end-diastolic and end-systolic volumes and increase of the left ventricular ejection fraction in the metoprolol group when compared to the placebo group.

In spite of the evidence pointing to the beneficial effects of metoprolol use in patients with HF, the MERITI-HF study was the one that definitely demonstrated the unquestionable resulting decrease in mortality in patients with HF[5]. The primary objective of this study was to evaluate the effect of metoprolol on mortality and a combined objective of total mortality and all reasons for hospital admission, with secondary objectives of hospitalization, symptoms, functional class (NYHA) and quality of life. The study was planned to last two years, being interrupted prematurely after one year due to a precocious reduction in mortality. Three thousand, three hundred and ninety-one patients in HF, with functional class II to IV (NYHA) and left ventricular ejection fraction < 40% were studied. Patients were randomized to receive metoprolol or placebo, with a goal of 200 mg/day of metoprolol. The galenic formulation of metoprolol utilized in this study - slow-release metoprolol succinate - was different from the one used in previous studies, such as MDC[10], which utilized metoprolol tartrate. The first one ensures a constant plasma concentration with a 24-hour administration interval. The release velocity does not depend on physiological factors such as pH or peristalsis. Due to the lack of plasma concentration peaks, the clinical selectivity to beta-1 receptors is increased, when compared to the conventional formulations of selective beta-blockers.

These studies have demonstrated that metoprolol use improves functional class, left ventricular function, and prognosis regarding mortality and necessity of hospitalization, regardless of the HF etiology. Nonetheless, it is not possible to state that the efficacy differences observed in these studies are due to the difference between the formulations utilized (tartrate or succinate), as there have been no studies that directly compared these two formulations.

The COMET[13] study was a multicentric, randomized and double-blind study designed to directly compare the effects of carvedilol and metoprolol therapies on survival and morbidity of individuals with systolic HF and LVEF ≤ 35%. Its main hypothesis was an increased benefit of carvedilol use when compared to metoprolol tartrate in such patients, as carvedilol is a non-selective beta-blocker (BB), with varied potentially favorable actions, such as α-receptor inhibition, higher anti-ischemic effect, apoptosis inhibition and antioxidant action[14].

The results of COMET[13] showed that carvedilol therapy significantly reduced (17% decrease) the death risk due to all the causes related to metoprolol, with an absolute decrease of 5.7% in 5-year mortality rate. Annual mortality was 10% for the metoprolol group and 8.3% for the carvedilol group. Although the combined analysis of outcome (total mortality or hospital admission due to any cause) numerically favored carvedilol, no statistically significant differences were observed between the two groups.

Therefore, some considerations must be made in face of the reported superiority of carvedilol when compared to metoprolol tartrate in the COMET study[13]: initially, the annual mortality rate reported for the metoprolol group in this study (10%) seems high, when compared to those reported in recent clinical trials that evaluated the effect of BB in HF morbi-mortality. The MERIT-HF[5] study, which tested metoprolol succinate versus placebo, showed that mortality in the BB group was 7.2%. The CIBIS II[4] study, comparing bisoprolol and placebo, showed an annual death rate in the bisoprolol group of 8.8%. These rates seem closer to the annual mortality rate described for the carvedilol group in the COMET[13] study itself (8.3%). Additionally, it was observed that the mean daily dose of metoprolol (85 mg) achieved in the COMET[13] study was lower than the ones utilized in previous clinical trials[5,10].

The Metoprolol Dilated Cardiomyopathy (MDC)[10] study utilized a "real" mean dose of metoprolol tartrate of 108 mg/day (target dose: 100-150 md/day), resulting in a mean cardiac frequency (CF) reduction of 15 bpm, quite better compared to the CF reduction observed in the COMET[13] study (11.7 bpm).

As for the MERIT-HF[5] study, the largest metoprolol trial in HF, the drug tested was slow-release metoprolol succinate, at a "real" mean dose of 159 mg in a single administration, which is equivalent to 106 mg/day of metoprolol tartrate, the formulation utilized in the COMET[13] and MDC[10] studies. With this dose, the authors of MERIT-HF[5] reported a mean reduction of 14 bpm in HF at rest, also higher to the one reported in the COMET[13] study. Regarding carvedilol, on the other hand, the decrease of 13.3 bpm in HF at rest after 4 months of treatment was achieved with a "real" mean daily dose of 41.8 mg[13], which is similar to the results of the US carvedilol study [3](45 mg/day dose and decrease of 13 bpm at HF), which was the basis for the definition of the target-dose of carvedilol for the COMET[13] study.

The extent to which these differences in metoprolol doses utilized or even the formulation chosen (metoprolol succinate was not available yet when the COMET[13] study was initiated) have influenced the results in favor of carvedilol cannot be assured.

Our results demonstrate that the addition of metoprolol tartrate to the usual therapy in patients with HF promote cardiac frequency reduction, increase of the left ventricular ejection fraction, decrease of the ventricular diameters and functional class improvement, with no alteration of plasma noradrenaline and sodium levels.

Regarding the functional class (NYHA), 28% of the patients were class II, 40% were class III and 32% were class IV. There was a significant improvement in functional class, with six patients presenting no symptomatic improvement.

The distribution of patients according to the functional class was concordant with the literature for classes II and III. Regarding functional class IV, the number of patients found was higher than that observed in other literature studies. This fact is probably due to the difficult access to specialized cardiology services in our country, which causes patients to present at advanced HF stages.

There was left ventricular function improvement with a significant increase of the ejection fraction at the radionuclide ventriculography with the addition of metoprolol tartrate to the usual therapy in patients with HF, which is in agreement with literature[15]. This LVEF increase with the use of beta-blockers has been higher than the ones observed with other therapeutic interventions in HF.

This improvement is frequently, but not uniformly associated with the decrease in left ventricular-end systolic and diastolic diameters[16]. In our study, we observed a significant decrease in both ventricular diameters at the end of the six-month follow-up. This favorable effect was achieved earlier, at the end of the third month, and was maintained until the end of the sixth month.

In this study, plasma noradrenaline levels were observed, with basal values of 758.60±6211 pg. These are elevated values, which predict an adverse evolution. Several studies[17,18] have demonstrated the prognostic value of plasma noradrenaline concentrations. The study by Cohn et al[17] showed values between 400 and 800 ng/ml, which were related to high mortality. It is important to point out that the prognostic significance of noradrenaline depends on the population studied, being higher in those populations of patients that have reached advanced disease stages[18].

In this series, the patients with functional class IV (NYHA) presented the highest plasma noradrenaline levels. In addition, noradrenaline levels showed to be associated to other HF severity indexes, such as ejection fraction and left ventricular-end systolic and diastolic diameters.

A non-significant decrease of noradrenaline levels was observed between the start of follow-up and the end of the third month, which returned to pre-treatment levels at the end of the sixth month. These results are similar to those obtained by Satostasi et al[19], Gilbert et al[20] and Tjeerdsma et al[21], who utilized metoprolol in patients with HF for a period of six months, with no resulting significant alterations in noradrenaline levels. As beta-blockers interfere with the action of an endogenous neuroendocrine system at cellular level, the hormonal benefits of these drugs may not be evident through the measurement of circulating catecholamines. Serum catecholamine levels may remain unaltered or decrease during beta-blocker use[22].

An approximate 15% CF reduction was observed at the end of the sixth month of follow-up, and this reduction had been observed earlier, at the end of the third month of follow-up of metoprolol tartrate use. This fact demonstrates the evident beta-adrenergic blocking effect. These results are in accordance with other studies in literature, which have demonstrated CF decrease in patients receiving beta-blocker therapy[4,5].

This study presents some limitations, the main one being the absence of a control group. However, the fact that metoprolol tartrate therapy results in symptom improvement, decrease of ventricular diameters and ejection fraction increase is concordant with the outcomes demonstrated in previous placebo-controlled studies.

Conclusion

The use of metoprolol tartrate in patients with dilated cardiomyopathy was followed by functional class (NYHA) improvement, left ventricular ejection fraction increase, left ventricular-end systolic and diastolic diameter decrease and HF reduction. There was no alteration in serum noradrenaline levels.

As there is no evidence in literature showing mortality reduction in patients with HF, metoprolol tartrate must be used concomitantly with one of the three beta-blockers approved for HF (carvedilol, bisoprolol or metoprolol succinate) until further studies have better established the potential differences in the clinical effects of beta-blockers in HF.

Potencial Conflict of Interest

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

References

1. II Diretrizes da Sociedade Brasileira de Cardiologia para o Diagnóstico e Tratamento da Insuficiência Cardíaca. Arq Bras Cardiol. 2002;79 (Supl 4):1-30.
2. Packer M, Collucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial.Circulation. 1996;94:2793-9.
3. Packer M, Bristow MR, Cohn JN, et al.The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med. 1996;334:1349-55.
4. THE CIBIS-II investigators and committees.The Cardiac Insufficiency Bisoprolol Study II (CIBIS- II): a randomized trial. Lancet. 1999;353:9-13.
5. MERIT-HF Study Group. Effect of metropolol CR/XL in chonic heart failure: Metropolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001-7.
6. Anderson JL, Lutz JR, Gilbert EM, et al. A randomised trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. Am J Cardiol. 1985;55: 471-75.
7. Fisher ML, Gottlieb SS, Plotnick GD, et al. Beneficial effects of metoprolol in heart failure associated with coronary artery disease: A randomized trial. J Am Coll Cardiol. 1994;23:943.
8. Engelmeier RS, O'connel JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized placebo-controlled trial. Circulation. 1985;72:536-546.
9. Cucchini F, Compostella L, Papalia D, De Domenico R, Iavernaro A, Zeppelini R. Trattamento cronico della cardiomiopatia dilatativa con betablocanti. G Ital Cardiol. 1988; 18:835±842.
10. Waagstein F, Bristow MR, Swedberg K, et al. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Lancet. 1993;342:1441-6.
11. Eichhorn EJ, Heesch CM, Barnet JH, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy:a randomized,doublé-blind,placebo-controled study. J Am Coll Cardiol. 1994;24:1310-20.
12. The RESOLVD investigators. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy. Circulation. 2000;101:378±384.
13. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol andmetoprolol on clinical outcomes in patientswith chronic heart failure in the CarvedilolOr Metoprolol European Trial (COMET): randomized controlled trial. Lancet. 2003;362: 7-13.
14. Yue TL, Cheng HY, Lysko PG, et al.Carvedilol, a new vasodilator and betaadrenoceptor antagonist, is an antioxidantand free radical scavenger. Pharmacol ExpTher. 1992; 263(1): 92-8.
15. Waagstein F,Caidahl K,Wallentin I, et al: Long- term ß-blockade in dilated cardiomyopathy.Circulation. 1989;80:551-63.
16. Austrália-New Zealand Heart Failure Research Collaborative Group: Effects of carvedilol,a vasodilatador-ß-blocker,in patients with congestive heart failure due to ischemic heart disease.Circulation. 1995;92:212-8.
17. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patientes with chronic congestive heart failure. N Engl J Med. 1984;31:819-22.
18. Thomas JA, Marks BH. Plasma norepinephrine in congestive heart failure. Am J Cardiol. 1978;41:233-43.
19. Satostasi G, Fraccarollo D, Dorigo P, et al. Early reduction in plasma norepinephrine during beta-blocking therapy with metoprolol in chronic heart failure. J Card Failure. 1998;4(3):177-84(Abstract).
20. Gilbert EM, Abraham WT, Olsen S, et al. Comparative hemodynamic, left venticular functional, and antiadrenergic effects of chronic treatment with metoprolol versus carvedilol in the failing heart. Circulation. 1996;11:2817-25 (Abstract).
21. Tjeerdsma G, Szabo BM, Van Wijk LM, et al. Autonomic dysfunction in patients with mild heart failure and coronary artery disease and the effects of add-on betablockade. Eur J Heart Failure. 2001;3(1):33-9.
22. Nemanich JW,Veith RC,Abrass IB,Stratton JR. Effects of metoprolol on rest and exercise cardiac function and plasma catecholamines in chronic congestive heart failure secondary to ischemic or idiopathic cardiomyopathy. Am J Cardiol .1990;66:843-8.