Carvedilol and nebivolol improve left ventricular systolic functions in patients with non-ischemic heart failure

Mustafa Karabacak, Abdullah Doğan¹, Şenol Tayyar¹, Mehmet Özaydın¹, Doğan Erdoğan¹
Clinic of Cardiology, Isparta State Hospital; Isparta-Turkey
¹Department of Cardiology, Faculty of Medicine, Süleyman Demirel University; Isparta-Turkey

ABSTRACT

Objective: It is unclear whether carvedilol and nebivolol produce different effects on short-term left ventricle (LV) systolic function in heart failure (HF). These drugs could improve systolic and diastolic functions of the LV. Thus, we aimed to compare their effects on LV systolic functions in patients with non-ischemic HF.

Methods: This study included 61 symptomatic non-ischemic HF patients with low ejection fraction (EF) (EF≤40%) between September 2008 and November 2010. The patients were randomized to carvedilol (n=31, 16 males) or nebivolol (n=30, 19 male). They were evaluated clinically and echocardiographically at baseline and 3 and 6 months after target dose; 42% of patients in the carvedilol group and 47% in the nebivolol group achieved the target dose before randomization. LV systolic functions were evaluated with ventricle diameters, EF, ejection time (ET), isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT), and myocardial performance index (MPI).

Results: At 6 months, carvedilol and nebivolol similarly improved EF (from 33±4% to 36±5%, p<0.01 and from 34±5% to 37±5%, p<0.01, inter-group p=0.30, respectively) and MPI (from 0.71±0.10 to 0.53±0.07, p<0.01 and from 0.69±0.13 to 0.52±0.08, p<0.01, intergroup p=0.45, respectively). LV diameter was reduced by a similar extent in both groups. In each group, IVCT and IVRT were significantly shortened and ET was prolonged, but there was no inter-group difference. Functional capacity improved similarly (from NYHA Class II-III to Class I-0) in both groups, as did heart rate and blood pressure. Reduction of pro-B-type natriuretic peptide levels was also comparable in both groups (p=0.41).

Conclusion: Carvedilol and nebivolol can similarly improve LV systolic functions in non-ischemic HF patients.

Keywords: carvedilol, nebivolol, systolic function, heart failure, myocardial performance index

Introduction

Heart failure (HF) is a complex clinical syndrome with increasing prevalence and high hospitalization and mortality rates despite its therapeutic advances (1). Activation of the sympathetic nervous system is one of the major pathophysiological abnormalities in the HF setting (1, 2). This activation leads to ventricular remodeling and progression of cardiac dysfunction (2). Symptoms and prognosis are usually associated with reduced systolic function of the left ventricle (LV) (3).

Clinical studies have shown that carvedilol and nebivolol reduce mortality and improve event-free survival in HF patients (4-6). Their benefits are largely attributed to improvement in LV ejection fraction (EF), volume, and diameter (7-12). These two agents have favorable properties, such as vasodilatory, antioxidant, and anti-proliferative effects, in addition to other beta-blockers (13, 14).

On the other hand, it is a disputable subject as to which beta-blocker is more effective in HF treatment and whether carvedilol or nebivolol should be a first-choice agent (15). This issue is important for clinicians, since beta-blockers have different properties. Preclinical studies point out a trend toward carvedilol or nebivolol due to their effects on cardiac remodeling and their pleiotropic properties (15, 16).

Up to now, only three studies have compared the effects of carvedilol and nebivolol on LV functions, exercise capacity, and clinical outcomes (10-12). They provided divergent results. However, two of them showed a trend in favor of carvedilol on EF and functional class (10, 11). The last study, with a larger size, reported that carvedilol and nebivolol provided similar effects in
HF patients with low EF at 24 months (12). Thus, we aimed to compare the effects of carvedilol and nebivolol on LV systolic function and pro-B-type natriuretic peptide (proBNP) level in non-ischemic HF patients.

Methods

Patients and dose titration of study drugs
This study included 68 consecutive patients prospectively with symptomatic moderate or severe non-ischemic HF [New York Heart Association (NYHA) class II to III] who had undergone coronary angiography to define the etiology of HF, with normal coronary arteries or non-significant stenosis (stenosis <40%). However, 7 patients were excluded from the study because of recent atrial fibrillation (n=2), beta-blocker intolerance (n=2), NYHA class IV HF (n=1), and refusal to control echocardiography (n=2). Finally, the remaining 61 patients were randomly assigned to receive carvedilol (n=31) or nebivolol (n=30) in a single-blind and open-label fashion. Other exclusion criteria were heart failure with significant coronary stenosis, history of myocardial infarction, moderate or severe valvular heart disease, resting heart rate <60 beats/min, systolic blood pressure (BP) <100 mm Hg, previous intolerance to beta-blocker therapy, history of asthma or use of bronchodilators, hypo- or hyperthyroidism, hepatic or renal failure (serum creatinine >2.0 mg/dL), rhythm disturbances including second- or third-degree heart block, sick sinus syndrome, atrial fibrillation, and complete bundle branch block.

Some findings of this study on the effects of both agents on diastolic LV function were previously published elsewhere (17). Thus, the patient characteristics and laboratory and echocardiographic findings were similar to those of the previously published study. The study was approved by our institutional ethics committee. All participants gave written informed consent.

In patients who were on beta-blocker therapy before the study, beta-blocker therapy was stopped at least 1 week for drug elimination. Thereafter, carvedilol or nebivolol was randomly started, and they were up-titrated as previously reported elsewhere (17). After the target or maximum tolerable dose, patients were evaluated in the outpatient clinic at the first, third, and sixth months. Complete blood count, biochemical analysis, and echocardiographic measurements were made in patients at baseline and 3 and 6 month after the target dose. Heart rate, BP, and body weight were evaluated at each visit. Also, the functional status of patients was assessed according to NYHA. Other medications were given according to current chronic HF guidelines (1). All patients received angiotensin-converting enzyme inhibitor (ACEI, lisinopril) and diuretics in appropriate dosages. Candesartan, an angiotensin receptor blocker (ARB), was given when ACEI intolerance occurred.

Blood sampling and assays
Blood samples were drawn for hematological and routine biochemical analyses. Biochemical analyses were performed with an Olympus AU-640 (Olympus Diagnostica, Hamburg, Germany). For NT-pro-BNP measurements, a 5-mL blood sample was collected into a plastic tube containing potassium EDTA. Plasma level of NT-proBNP was measured using an electrochemiluminescence immune assay with the Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Echocardiographic evaluation
Echocardiographic examinations were performed by the same investigator (MK), who was blinded to the patients’ data, at baseline and 3 and 6 months. Measurements were acquired at the end of expiration during normal breathing in the left lateral decubitus position. Two-dimensional, M-mode, and Doppler echocardiographic measurements were obtained according to the recommendations of the American Society of Echocardiography (18) with a System 5 echocardiography device (GE Vingmed Ultrasound) with a 2.5 MHz FPA transducer. The mean of 3 cardiac cycles with the ECG record was considered the final measurement. The left atrial size, LV diameter, and wall thickness were measured using M-Mode echocardiography. LV EF was calculated by Simpson’s method.

For transmitral flow, pulsed-wave Doppler sample volume was positioned at the mitral leaflet tips in the apical four-chamber view. Early diastolic peak flow velocity (E) and late diastolic peak flow velocity (A) were measured by transmitral Doppler imaging, and then the mitral E/A ratio was estimated. Isovolumic relaxation time (IVRT) was measured as the interval from the end of LV outflow to the onset of mitral diastolic flow in the apical five-chamber view by recording both flows with pulsed-wave Doppler imaging (18).

As previously defined (19), myocardial performance index (MPI or Tei index) was calculated as the sum of isovolumic times (contraction and relaxation times) divided by the ejection time (ET) of LV outflow. The sum of isovolumic times was obtained by subtracting ET from the interval between the onset and cessation of the mitral inflow Doppler signal in the apical four-chamber view. The ET was measured as the interval between the onset and cessation of the LV outflow signal in the apical five-chamber view with pulsed-wave Doppler imaging. Isovolumic contraction time (IVCT) was estimated by subtracting IVRT from the sum of isovolumic times. The final measurements were considered the mean of three measurements. The intra-observer variabilities were 4.1%, 5.2%, 6.7%, and 3.2% for EF, MPI, IVRT, and ET, respectively.

Statistical analyses
All analyses were performed with a commercially available statistical program (SPSS Version 13.0, SPSS Inc., Chicago, IL, USA). All data were tested for normal distribution with the Kolmogorov-Smirnov test. For data showing an abnormal distribution, median and interquartile ranges were displayed. Continuous variables were presented as mean±standard deviation, and categorical ones were presented as percentage (%). The two study groups were compared using student t-test or Mann-Whitney U and chi-square or Fisher exact test as appropriate. In each group, follow-up comparisons (baseline and 6

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months) were performed using paired t-test and Wilcoxon rank tests as appropriate. A two-tailed p value of <0.05 was considered statistically significant.

Results

Baseline demographic and clinical features, except for use of aspirin, were comparable in both groups (Table 1). Laboratory tests and initial echocardiographic variables were also comparable in both groups (Table 2). Target dose of the study drugs was reached in 42% and 47% of patients in the carvedilol and nebivolol groups, respectively (p=0.85).

Table 3 shows the temporal changes in clinical and echocardiographic variables in the carvedilol and nebivolol groups at 3 and 6 months. Heart rate, blood pressure, and body weight were significantly reduced in each group at 3 and 6 months. However, there were no differences in inter-groups at any point (Table 3). Similarly, functional class significantly improved in each group (p<0.01), but there was no difference in inter-groups. In addition, concomitant medications did not differ in either group. Four patients received ARB (candesartan) due to intolerance to ACEI (2 patients in both groups).

The LV systolic and diastolic diameters were significantly reduced in each group (each p<0.01, Table 3). Accordingly, EF was significantly elevated in each group at 6 months but was comparable in both groups, though it was slightly higher in the nebivolol than carvedilol group at 3 months (from 33±4.2 to 33±5% and 36±5%, from 34±4.9% to 36±5% and 37±5%, respectively) (Table 3, Fig. 1a).

Carvedilol and nebivolol significantly shortened IVCT and IVRT but prolonged ET. However, there was no difference with regard to these variables in both groups. Similarly, both agents significantly reduced MPI in each group (from 0.71±0.10 to 0.53±0.07 and from 0.69±0.13 to 0.52±0.08, each p<0.01, respectively) but was comparable in both groups (Fig. 1b).

During the 6 months, median NT-proBNP levels were significantly reduced with carvedilol and nebivolol therapy (p<0.001, Table 4). Obesity was defined as body mass index ≥30 kg/m².

ACE - angiotensin-converting enzyme; ARB - angiotensin-1 receptor blocker; BP - blood pressure; NT-proBNP - n-terminal pro-B-type natriuretic peptide; NYHA - New York Heart Association

Table 4. Demographic, clinical, and laboratory characteristics of the therapy groups

|                        | Carvedilol group, n=31 | Nebivolol group, n=30 | P     |
|------------------------|------------------------|-----------------------|-------|
| Mean age, year         | 61±11                  | 60±14                 | 0.73  |
| Male/Female            | 16/15                  | 19/11                 | 0.36  |
| Body weight, kg        | 78±18                  | 75±12                 | 0.48  |
| NYHA class, II/III     | 52%/48%                | 60%/40%               | 0.61  |
| Smoking                | 8 (26%)                | 11 (37%)              | 0.42  |
| Hypertension           | 15 (45%)               | 15 (48%)              | 0.90  |
| Diabetes mellitus      | 5 (16%)                | 5 (17%)               | 0.99  |
| Hyperlipidemia         | 7 (22%)                | 10 (33%)              | 0.40  |
| Obesity                | 11 (35%)               | 8 (26%)               | 0.46  |
| Systolic BP, mm Hg     | 143±17                 | 141±13                | 0.57  |
| Diastolic BP, mm Hg    | 91±15                  | 90±10                 | 0.60  |
| Heart rate, bpm        | 81±9                   | 82±9                  | 0.72  |

Figure 1. Temporal changes in ejection fraction and myocardial performance index (MPI) of the left ventricle after carvedilol and nebivolol treatment. There was no significant difference in ejection fraction (A) and MPI (B) between the two groups at the follow-up. However, ejection fraction was slightly higher in the nebivolol group at 3 months
Drugs were well tolerated.

Table 3). However, the reductions did not differ in either therapy group at 3 and 6 months.

Discussion

At the 6-month follow-up, carvedilol and nebivolol produced a similar improvement in functional capacity and LV functions, including EF, MPI, isovolumic times, and ET, in patients with non-ischemic HF in the present study. Also, mitral E/A ratio and LV and LA diameters were similarly reduced with both agents.

Beta-blockers are the mainstay therapy for HF patients (1). They attenuate the activation of the sympathetic nervous system in the development of HF, prevent ventricular remodeling, and improve cardiac function (7-12, 16). As a result, they improve symptoms and clinical outcomes, such as death and hospitalization (1, 4-6, 10-12). However, it is a subject of debate whether all beta-blockers accepted for HF are similarly effective for HF patients with reduced EF. However, it is uncertain whether the two agents have similar effects on LV function and clinical outcomes (10-12).

Up to now, three studies have compared the effects of carvedilol and nebivolol on LV function and clinical outcomes in HF patients with low EF (10-12). Their results are different. Two of them showed a trend in favor of carvedilol, although there was no clear difference between the two agents (10, 11). However, a larger-sized study (n=160) recently reported that carvedilol and nebivolol similarly improve LV systolic function, exercise capacity, and survival in hypertensive HF patients at the 24-month follow-up (12). In our study, functional capacity, LV dimensions, and EF were also similarly improved with carvedilol and nebivolol after a 6-month therapy. Furthermore, MPI was also reduced to a similar extent in both therapy groups. But, in our study, we evaluated only non-ischemic HF patients, and only 45%-48% of them showed a trend in favor of carvedilol, although there are no differences between the two agents. However, the results in the study of Patrianakos et al. (10) showed that carvedilol-treated patients had higher EF than nebivolol-treated ones after 12-month treatment, unlike our findings. The reason for this can be the use of a lower dose (5 mg) as the target dose for nebivolol (10 mg in our study), with a slightly lower initial EF in the nebivolol group. Similarly, Lombardo et al. (11) showed a similar elevation in EF in carvedilol- and nebivolol-treated patients with ischemic or non-ischemic HF, though they used a target dose of 5 mg for nebivolol, whereas we and Marazzi et al. (12) used a target dose of 10 mg for nebivolol, as recommended in HF treatment.
The Tei index or MPI is a reliable marker reflecting both LV systolic and diastolic function. It is less dependent on heart rate, loading states, and LV geometry, compared with EF (19). The MPI can increase with severity of HF, and its high value has been reported to be associated with mortality and the need for heart transplantation in patients with severe systolic dysfunction (EF <30%) (22). Palloshi et al. (23) reported that compared with EF, MPI was improved earlier in HF patients on carvedilol therapy and was more sensitive to the improvement in LV function.

In our study, carvedilol or nebivolol therapy significantly reduced MPI (from 0.71±0.10 to 0.53±0.07, p<0.01 and from 0.69±0.13 to 0.52±0.08, p<0.01, respectively) at 6 months, but both agents produced a similar improvement at 3 and 6 months. To our knowledge, there is no study investigating the comparative effects of carvedilol and nebivolol on MPI in HF patients. However, it has been reported that MPI is significantly reduced in HF patients with carvedilol treatment (23, 24).

Based on the improvement in LV function, beta-blocker therapy is likely to lower NT-proBNP levels in HF patients over time, but previous results are divergent (11, 25-28). This might be due to small sample size, variable follow-up times, and differences between study populations. Both carvedilol and nebivolol therapy reduced NT-proBNP levels similarly in our study at 3 and 6 months, but there was no difference in both therapy groups, whereas, Lombardo et al. (11) reported no reduction in NT-proBNP levels in carvedilol and nebivolol groups at the 6-month follow-up.

Parallel to the echocardiographic and neurohormonal improvement, we observed that both drugs significantly improved functional capacity, blood pressure, and heart rate to a similar extent at 3 and 6 months. These findings are concordant with results from previous studies (4-8, 10-12).

Study limitations

There are several limitations to this study. Firstly, our study population is small, since we used strict exclusion criteria. Accordingly, it limits the statistical power of the study. Secondly, we did not perform exercise or 6-minute walk test for the evaluation of functional capacity. However, functional capacity according to NYHA classification has been commonly used for HF patients. Also, we did not use a scoring system to determine the life quality. Finally, our findings reflect the situation in only patients with non-ischemic HF. It may be possible that carvedilol and nebivolol might have different effects on LV function in ischemic HF patients.

Conclusion

Our findings suggest that carvedilol and nebivolol have similar beneficial effects on LV systolic function, MPI, and functional capacity in patients with non-ischemic HF. In addition, each drug is well tolerated.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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