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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The effects of carvedilol and nebivolol on oxidative stress status in patients with non-ischaemic heart failure

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Abstract

Background: Carvedilol and nebivolol have favourable properties such as anti-oxidative effects in addition to other beta-blockers. However, which of these drugs is more effective on oxidative stress is unclear.

Aim: To compare the effects carvedilol and nebivolol on oxidative stress status in non-ischaemic heart failure (HF) patients.

Methods: We included 56 symptomatic non-ischaemic HF patients with ejection fraction ≤ 40%. The patients were randomised to carvedilol (n = 29, 18 male) or nebivolol (n = 27, 18 male) groups. They were evaluated clinically and echocardiographically after target dose. We evaluated parameters associated with oxidative stress, such as alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), uric acid, total antioxidant capacity (TAC), total oxidative status (TOS), and oxidative stress index (OSI).

Results: TAC, TOS, GGT, and ALP levels and OSI were comparable in both groups. Uric acid levels were lower in the carvedilol group compared with the nebivolol group (5.8 ± 1.6 vs. 7.0 ± 1.7 mg/dL, p = 0.01). In correlation analysis, uric acid ($p < 0.001$, $r = 0.50$) and TOS level ($p < 0.001$, $r = 0.73$) were positively correlated with OSI.

Conclusions: Carvedilol and nebivolol have similar effects on oxidative stress status in patients with non-ischaemic HF.

Key words: non-ischaemic heart failure, carvedilol, nebivolol, oxidative stress

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INTRODUCTION

Heart failure (HF), a leading cause of morbidity and mortality in industrialised countries, is a complex clinical syndrome with increasing prevalence, and high hospitalisation and mortality rates [1]. Several investigators have emphasised the importance of oxidative stress in the pathogenesis of HF [2, 3]. They have demonstrated that antioxidants prevent the underlying process of left ventricular (LV) hypertrophy, adverse LV remodelling, and chronic HF [4–6].

Oxidative stress is defined as an excess production of reactive oxygen species (ROS) relative to the levels of antioxidants, creating an imbalance between pro-oxidant and antioxidant factors in favour of pro-oxidants, thereby potentiating oxidative damage [7]. In recent decades, clinical and experimental studies have provided substantial evidence that oxidative stress, defined as an excess production of ROS relative to antioxidant defence, is increased in HF [8, 9]. Recently, the oxidative stress index (OSI) has been used as an indicator of oxidative stress and is reflected in the redox balance between oxidation and antioxidation [10, 11].

Clinical studies have shown that carvedilol and nebivolol reduce mortality and improve event-free survival in HF patients [12, 13]. These two agents have favourable properties such as vasodilatory, anti-proliferative, and anti-oxidant effects in addition to other agents [14, 15]. This issue is important for clinicians since beta-blockers differ considerably. Pre-clinical studies conducted on this topic point out a trend toward carvedilol or nebivolol due to their effects on these proper-

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ties [16, 17]. Furthermore, Zepeda et al. [18] have shown that both drugs were effective on oxidative stress with different pathophysiological mechanisms in hypertension patients [18]. Also, they suggested that oxidative stress status was lower with carvedilol compared with nebivolol. Despite the aforementioned data, it is still unclear whether these agents are superior to each other in respect to antioxidant features in HF patients. Thus, we aimed to investigate the effects of carvedilol and nebivolol on oxidative stress in non-ischaemic HF patients.

METHODS

Patients and dose titration of study drugs

This study included 56 consecutive patients with asymptomatic HF (New York Heart Association [NYHA] class I to II) in the cardiology department of our institute between June 2011 and March 2013. Some patients in this study, comprising the effects of both agents on oxidative stress, were common with a study previously published elsewhere [19]. They had undergone coronary angiography, with normal coronary arteries or non-significant stenosis (stenosis < 40%). Fifty-six patients were randomly assigned to receive carvedilol (n = 29, 18 male) or nebivolol (n = 27, 18 male) single-blind and open-label fashion. They had a LV ejection fraction (LVEF) of less than 40% in the preceding three months. Other exclusion criteria were HF with significant coronary stenosis, history of myocardial infarction, moderate or severe valvular heart disease, hypo-hyperthyroidism, hepatic or renal failure (serum creatinine > 2.0 mg/dL), peripheral arterial disease, peripartum cardiomyopathy, severe arrhythmias and hypertension, diabetes mellitus, dyslipidaemia, haematological disorders, history of malignancy, acute or chronic infection, smoking, alcohol use, resting heart rate < 60 bpm, systolic blood pressure < 100 mm Hg, previous intolerance to beta-blocker therapy, history of asthma or use of bronchodilators, rhythm disturbances including second or third degree heart block, sick sinus syndrome, and complete bundle brunch block. After these exclusion criteria, the probable aetiology of our patients may be inflammatory or congenital. The study was conducted according to the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. It was approved by the Institutional Ethics Committee, and informed consent was obtained from each patient.

The patients were usually newly diagnosed with HF. In patients who were on beta-blocker therapy before the study, beta-blocker therapy was stopped for at least one week for drug elimination (≈ 36%). Thereafter, carvedilol was started at 3.125 mg twice daily and then up-titrated to 6.25, 12.5, and 25 mg (target dose) twice daily at 3- to 5-day intervals if the previous dose was tolerated. Similarly, nebivolol was given at 1.25 mg once a day and then up-titrated to 2.5, 5, and 10 mg (target dose) once a day if the previous dose was tolerated. When the up-titrated dose was not tolerated, the previous tolerable dose was considered as the maximum tolerable dose for each agent. The patient's tolerance was evaluated with the following criteria: resting heart rate > 55 bpm, systolic blood pressure ≥ 100 mm Hg, no drop in systolic blood pressure < 30 mm Hg in standing position, and no new symptoms of dizziness or dyspnoea. After the target or maximum tolerable dose, patients were evaluated in the out-patient clinic. Complete blood count, biochemical analysis, and echocardiographic measurements were made in patients after the target dose. Heart rate, blood pressure, and body weight were evaluated. Other medications were prescribed according to current chronic HF guidelines. All patients received angiotensin-converting enzyme inhibitor (ACE-I, lisinopiril) and diuretics in appropriate doses. Candesartan angiotensin receptor blockers (ARB) were given when ACE-I intolerance occurred.

Blood sampling and assays

Blood samples were drawn from an antecubital vein by careful vein puncture at 08.00 to 10.00 a.m. after a fasting period of 12 h. Routine biochemical parameters were determined by standard methods. Haematological indices were measured within 30 min of collecting the blood samples in tubes containing dipotassium EDTA. Biochemical analyses were performed using an autoanalyser Olympus AU-640 (Olympus Diagnostica, Hamburg, Germany). An automatic blood counter (Beckman-CoulterCo, Miami, Florida, USA) was used for whole blood counts.

For total antioxidant capacity (TAC)/total oxidative status (TOS) measurements, a 5 mL blood sample was collected into a plastic tube containing potassium EDTA. TAC and TOS were examined in every patient and control group. Blood samples (4 mL) were obtained following overnight fasting. The serum was separated from the cells by centrifugation for 10 min, and then stored at –80°C until biochemical examination. TAC and TOS levels were measured using commercially available kits (RelAssay, Turkey). The level of TAC was measured using an automated method, which is based on the bleaching of the characteristic colour of a more stable 2.2'-azino-bis [3-ethylbenzothiazoline-6-sulfonic acid (ABTS)] radical cation by antioxidants. The results were expressed as mmol Trolox Eq/L. The level of TOS was measured by a method in which oxidants present in the sample oxidise the ferrous-ion-o-dianisidine complex to ferric ion. The oxidation reaction is enhanced by glycerol molecules abundantly present in the action medium. The ferric ion produces a coloured complex with xylenol orange in an acidic medium. The colour intensity, which was measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide and the results were expressed in terms of micromolar hydrogen peroxide equivalent per litre (μmol H_2O_2 Eq/L) [20].

Determination of OSI. The ratio of TOS to TAC was accepted as the OSI. For calculation, the resulting unit of TAC

was converted to mmol/L, and the OSI value was calculated according to the following formula: OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/l)/TAC (mmol Trolox Eq/l) [11].

Echocardiographic evaluation

Echocardiographic examinations were performed by the same investigator (MK), who was blinded to the patients' data. Measurements were acquired at 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 [21] with a Vivid 3 Echocardiography Machine (GE Vingmed Ultrasound) with a 2.5 MHz FPA transducer. The mean of three cardiac cycles with electrocardiography record was considered as the final measurement. The left atrial size, LV volumes, and wall thickness were measured by using M-mode echocardiography. LVEF was calculated by Simpson's method.

Statistical analyses

All analyses were performed with commercially available statistical program (SPSS Version 13.0, SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± standard deviation and categorical ones as a percentage (%). To compare continuous variables, the Student t test or Mann-Whitney U test were used as appropriate. Categorical variables were compared using the χ^2 test. Spearman correlation coefficients were calculated to evaluate relationships between variables. A two-tailed p value < 0.05 was considered statistically significant.

RESULTS

Baseline demographic and clinical features were comparable in both groups (Table 1). Mean age, gender, heart rate, blood pressure, body mass index, and waist circumference were comparable in each group. In addition, concomitant medications did not differ in both groups (Table 1). Laboratory tests and echocardiographic variables were also comparable in both groups (Table 2). However, posterior wall thickness was slightly higher in the nebivolol group compared with the carvedilol group (11.2 ± 0.9 vs. 11.6 ± 0.7, respectively, p = 0.07). LVEF was similar in both groups (29.6 ± 4.8 vs. 30.7 ± 5.0, respectively, p = 0.20). The target dose of study drugs was reached in 62% and 66% of patients in the carvedilol and nebivolol groups, respectively, (p = 0.55). Eight patients received ARB (candesartan) due to intolerance to ACE-I (four patients in both groups).

Table 3 shows temporal changes associated with oxidative stress in the carvedilol and nebivolol groups. TAC, TOS, GGT, and ALP levels were comparable in both groups. Similarly, there was no significant difference in OSI between the groups (2.53 [0.45–10.2] vs. 2.13 [0.76–5.38], respectively, p = 0.82; Fig. 1). However, the uric acid level was significantly lower in the carvedilol group (5.8 ± 1.6 vs. 7.0 ± 1.7 mg/dL, p = 0.01).

Table 1. Demographic, clinical characteristics and concomitant medications of the carvedilol and nebivolol groups

	Carvedilol group (n = 29)	Nebivolol group (n = 27)	P
Mean age [year]	60 ± 9	63 ± 11	0.20
Male/female	18/11	18/9	0.72
Current smoker [%]	5 (17%)	5 (18%)	0.90
Hypertension [%]	8 (27%)	6 (22%)	0.64
Diabetes mellitus [%]	6 (21%)	3 (11%)	0.33
Hyperlipidaemia [%]	10 (34%)	5 (19%)	0.18
Body mass index [kg/m^2]	28 ± 6	29 ± 6	0.48
Waist circumference [cm]	94 ± 13	99 ± 13	0.14
Systolic BP [mm Hg]	127 ± 17	135 ± 17	0.27
Diastolic BP [mm Hg]	84 ± 13	85 ± 12	0.93
Heart rate [bpm]	74 ± 8	71 ± 8	0.18
Medications:			
ACE inhibitor	22 (76%)	18 (62%)	0.45
ARB	6 (20%)	6 (22%)	0.89
Spironolactone	27 (93%)	23 (85%)	0.34
Thiazide	24 (82%)	17 (63%)	0.19
Furosemide	20 (69%)	13 (48%)	0,22
Statins	8 (27%)	11 (40%)	0.30
Digoxin	7 (24%)	3 (11%)	0.90
Corolan	8 (27%)	3 (11%)	0.12
Nitrate	10 (34%)	7 (26%)	0.57

ACE — angiotensin converting enzyme; ARB — angiotensin-1 receptor blockers, BP — blood pressure

In correlation analysis, uric acid ($p < 0.001$, $r = 0.50$), TSH ($p = 0.008$, $r = 0.36$), RDW ($p = 0.01$, $r = 0.35$), and TOS level ($p < 0.001$, $r = 0.73$) were positively correlated with OSI. However, TAC level was negatively correlated with OSI ($p < 0.001$, $r = 0.51$).

DISCUSSION

Heart failure is a complex clinical syndrome with increasing prevalence, and high hospitalisation and mortality rates but poor diagnostic and treatment options. Beta-blockers are the mainstay therapy for HF patients [1]. They improve symptoms and clinical outcomes such as death and hospitalisation [1, 12, 13]. However, it is a subject of debate whether all beta-blockers accepted for HF are similarly effective for HF treatment, because carvedilol and nebivolol have additional favourable properties [16, 17].

Carvedilol, from the same class, blocks not only beta1- and beta2-adrenoreceptors, but also alfa1 receptor, producing an additional vasodilatory effect. Furthermore, it has anti-apoptotic, anti-proliferative, anti-endotelin, and antioxidant

Table 2. Laboratory and echocardiography characteristics of the carvedilol and nebivolol groups

	Carvedilol (n = 29)	Nebivolol (n = 27)	P
Glucose	123 ± 41	111 ± 28	0.23
Creatinine [mg/dL]	1.11 (0.8–3.4)	1.07 (0.4–1.8)	0.20
Sodium [mg/L]	139 ± 3	138 ± 2	0.17
Potassium [mg/L]	4.7 ± 0.4	4.7 ± 0.5	0.86
Aspartate transaminase [U/L]	23 ± 6	21 ± 9	0.51
Alanine transaminase [U/L]	22 ± 13	21 ± 12	0.94
TSH	1.2 (0.01–5.1)	1.7 (0.01–6.26)	0.53
RDW [$10^6/\mu L$]	16 ± 2.1	15 ± 1.4	0.20
Haemoglobin [g/dL]	13 ± 1.8	15 ± 4.2	0.12
Platelet [$10^3/mm^3$]	215 ± 50	215 ± 52	0.98
Total cholesterol [mg/dL]	163 ± 53	169 ± 42	0.65
LDL-C [mg/dL]	107 ± 34	101 ± 40	0.54
Triglycerides [mg/dL]	169 ± 94	159 ± 86	0.68
HDL-C [mg/dL]	35 ± 7	37 ± 7	0.31
LVEDV [cm^3]	203 (137–491)	185 (102–388)	0.33
LVESV [cm^3]	142 (90–381)	129 (66–289)	0.26
Septal thickness [mm]	12.2 ± 1.4	12.5 ± 1.4	0.52
Posterior wall thickness [mm]	11.2 ± 0.9	11.6 ± 0.7	0.07
LVEF [%]	29.6 ± 4.8	30.7 ± 5.0	0.20
LA diameter [mm]	41 ± 1.3	43 ± 4.5	0.78

HDL-C — high density lipoprotein cholesterol; LA — left atrium; LDL-C — low density lipoprotein cholesterol; LVEDV — left ventricular end-diastolic volume; LVESV — left ventricular end-systolic volume; LVEF — left ventricular ejection fraction; RDW — red blood cell distribution TSH — thyroid stimulating hormone

Table 3. Comparison of parameters associated with oxidative stress in the carvedilol and nebivolol groups

	Carvedilol (n = 29)	Nebivolol (n = 27)	P
TOS [$\mu mol\ H_2O_2$ Eq/L]	2.64 (0.62–9.20)	2.45 (1.06–4.40)	0.88
TAC [mmol Trolox Eq/L]	1.25 (0.39–2.71)	1.23 (0.65–1.88)	0.92
Oxidative stress index [AU]	2.53 (0.45–10.2)	2.13 (0.76–5.38)	0.82
Uric acid [mg/dL]	5.8 ± 1.6	7.0 ± 1.7	0.01
Alkaline phosphatase [U/L]	77 ± 37	68 ± 20	0.60
Gamma-glutamyl transferase [U/L]	31 (11–106)	33 (8–88)	0.58

TAC — total antioxidant capacity; TOS — total oxidative status

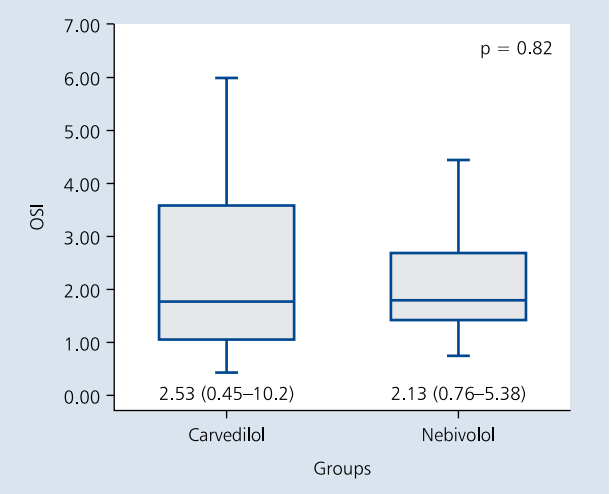

Figure 1. The change of oxidative stress index (OSI) value between carvedilol and nebivolol groups. OSI value was comparable in both the groups

properties [14]. A placebo-controlled study demonstrated that, long-term therapy with carvedilol was effective on oxidative stress status [14]. The multiple lines of evidence for the antioxidant activities of carvedilol have been summarised in several prior reviews [22, 23]. In vitro and in vivo, carvedilol prevented lipid peroxidation in myocardial cell membranes initiated by generated oxygen radicals. Therefore, it protected endothelial cells from oxygen radical-mediated injury and it also prevented depletion of endogenous antioxidants [24]. Carvedilol and atenolol were evaluated by lipid peroxidation in hypertensive patients. Carvedilol treatment was associated with a 30% decrease in the oxidative stress markers, not shared by atenolol [25]. Arumanayagam et al. [26] compared antioxidant effects of carvedilol and metoprolol. Similarly to our study, the TAC level was comparable between two groups at the end of 12 weeks. Other parameters associated with oxidative stress were significantly lower with carvedilol treatment. In the present study, the TOS level was higher in the carvedilol group than in the nebivolol group, but it was not significant. In addition, uric acid levels were significantly lower in the carvedilol group. This result might be associated with the suppressive effects of carvedilol on oxidative stress mechanisms unlike nebivolol [27].

Nebivolol, a third-generation beta-blocker, shown to have antioxidant properties in addition to enhancing vascular nitric oxide (NO) generation, was investigated for its potential beneficial effect in elderly patients with HF [28]. A study in rabbits demonstrated that nebivolol, unlike other beta-blockers, improves endothelial function, reduces vascular superoxide production via prevention of endothelial NO syntase uncoupling, reduces vascular macrophage infiltration, and inhibits nicotinamide adenine dinucleotide phosphate-oxidase dependent superoxide production in neutrophils isolated from hyperlipidaemic rabbits [29].

Until this time, there has been no study that has compared the effects of carvedilol and nebivolol on oxidative stress status in non-ischaemic HF patients with low LVEF. Saeidnia and Abdollahi [30] suggested that carvedilol and nebivolol are the principle medicines in prevention or treatments of some oxidative stress-related diseases, and are mainly involved in different oxidative pathways of the human body. Zepeda et al. [18] conducted a study to evaluate the effect of carvedilol and nebivolol on the oxidative stress parameters and endothelial function in hypertension. Only after administration of carvedilol, patients showed lower systemic oxidative stress levels, compared with nebivolol treatment [18]. Moreover, they showed that this effect of carvedilol and nebivolol treatment arises with different mechanisms. Carvedilol could mediate these effects by enhancing the antioxidant capacity, while nebivolol mediated via increasing NO concentration [18]. In the present study, we did not observe any superiority of either beta-blocker in respect to their antioxidant activity.

Limitations of the study

There are several limitations of this study. Firstly, our study population was small because we used strict exclusion criteria. Accordingly, this limited the statistical power of the study. Finally, our findings reflect the situation only in patients with non-ischaemic HF. It may be possible that carvedilol and nebivolol have different effects on LV function in ischaemic HF patients.

CONCLUSIONS

Our findings suggest that carvedilol and nebivolol have similar effects on oxidative stress status in patients with non-ischaemic HF.

Conflict of interest: *none declared*

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Wpływ karwedilolu i nebiwololu na stan stresu oksydacyjnego u pacjentów z nie-niedokrwienną niewydolnością serca

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Streszczenie

Wstęp: Karwedilol i nebiwolol oprócz działań wspólnych dla grupy leków beta-adrenolitycznych mają dodatkowo korzystne właściwości antyoksydacyjne. Jednak nie ustalono, który z tych leków działa skuteczniej na stan stresu oksydacyjnego.

Cel: Badanie przeprowadzono w celu porównania wpływu karwedilolu i nebiwololu na stres oksydacyjny u chorych z nie-niedokrwienną niewydolnością serca (HF).

Metody: Do badania włączono 56 chorych z nie-niedokrwienną HF, u których frakcja wyrzutowa wynosiła ≤ 40%. Pacjentów przydzielono losowo do grupy leczonej karwedilolem (n = 29, 18 mężczyzn) lub nebiwololem (n = 27, 18 mężczyzn). Po zastosowaniu docelowej dawki chorych poddano badaniu klinicznemu i echokardiograficznemu. Oceniono parametry związane ze stresem oksydacyjnym, takie jak stężenie fosfatazy zasadowej (ALP), gamma glutamylotransferazy (GGT) i kwasu moczowego, całkowita pojemność antyoksydacyjna (TAC), całkowity stan oksydacyjny (TOS) i wskaźnik stresu oksydacyjnego (OSI).

Wyniki: Wartości TAC, TOS, GGT, ALP i OSI były podobne w obu grupach. Stężenie kwasu moczowego było niższe wśród pacjentów przyjmujących karwedilol niż u osób stosujących nebiwolol (5,8 ± 1,6 *vs.* 7,0 ± 1,7 mg/dl, p = 0,01). W analizie korelacji wykazano dodatnią korelację stężeń kwasu moczowego (p < 0,001; r = 0,50) i TOS (p < 0,001; r = 0,73) z OSI.

Wnioski: Karwedilol i nebiwolol podobnie wpływają na stan stresu oksydacyjnego u chorych z nie-niedokrwienną HF.

Słowa kluczowe: nie-niedokrwienna niewydolność serca, karwedilol, nebiwolol, stres oksydacyjny

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