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Role of antioxidant property of carvedilol in mild to moderate hypertensive patients: A prospective open-label study

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Abstract:

Objective: Carvedilol is a nonselective third generation β -blocker that does not display the negative effects of traditional β -blockers. Regarding the antioxidant, anti-inflammatory and distinct metabolic properties of carvedilol which are similar to that of high-density lipoprotein (HDL) and paraoxonase 1 (PON1), the present study intends to investigate the effects of carvedilol treatment on malondialdehyde (MDA) and soluble lectin-like ox-low-density lipoprotein (LDL) receptor (sLOX-1) as markers of oxidative stress in association to lipid profiles, apolipoproteins (apo), and PON1 activity in hypertensive patients.

Patients and Methods: This clinical trial study was performed on forty patients with mild to moderate essential hypertension. Subjects were studied before and after 2 months treatment with carvedilol, 25 mg daily. Lipids and lipoproteins were measured using a biochemistry analyzer. PON and arylesterase activity were assayed using paraoxon and phenyl acetate as substrates, respectively. MDA was quantified using a chemical colorimetric assay. ELISA was used to measure sLOX-1.

Results: Our results showed that carvedilol treatment decreased systolic and diastolic blood pressure as much as forty and 16 mmHg, respectively ($P < 0.001$). It also increased HDL, total cholesterol, and serum PON1 activity ($P < 0.05$), but the levels of triglyceride, LDL, apo A-I, and apo B did not significantly change. There was an inverse correlation between serum PON1 activity and serum MDA.

Conclusion: This study confirmed the antihypertensive effect of the drug and its beneficial metabolic effects through augmenting HDL and PON1 activity. We propose that the antioxidant effects of carvedilol can be partially attributed to increased PON-1 activity.

Key words:

Antioxidant, carvedilol, hypertension, lipids, paraoxonase 1

Oxidative stress and dyslipidemia are among the most important independent predictors of cardiovascular mortality in hypertensive patients.^[1] At present, evidence-based guidelines recommend initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive patients.^[2] Based on the Joint National Committee-8 report, there were no good quality RCTs comparing carvedilol to the four recommended classes. Therefore, it is not recommended as the first-line therapy.^[2] Carvedilol is a nonselective third generation β -blocker/ α 1-blocker that does not display the negative effects of traditional β -blockers.

It improves myocardial function and inhibits destructive remodeling in heart failure. Carvedilol decreases blood pressure (BP) by reducing peripheral vascular resistance and vasodilation.^[3] A significant part of favorable effects of carvedilol is provided by its antioxidant, anti-inflammatory, and anti-apoptotic properties.^[4]

Antiatherogenic properties of high-density lipoprotein (HDL) are attributed to the lipid uptake from vessel walls and a broad spectrum of antioxidant and anti-inflammatory functions. These beneficial functions are mediated by proteins and enzymes naturally found in HDL.^[5] Paraoxonase 1 (PON1) is an enzyme exclusively

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found in HDL structure. HDL facilitates PON1 secretion and provides a hydrophobic environment for PON1 binding and activity. PON1 ability in eliminating oxidized species of lipids in the structure of low-density lipoprotein (LDL) and HDL results from its lactonase and phospholipase A2-like activity thereby presents anti-oxidant and anti-inflammatory effects.^[6] The PON1 level in serum inversely correlates with the risk of CAD development and is currently recognized as a biomarker in predicting vascular diseases probability.^[7]

Regarding the antioxidant, anti-inflammatory, and distinct metabolic properties of carvedilol which are similar and overlapping to that of HDL and PON1, the present study intends to investigate the effects of carvedilol treatment on lipids and lipoprotein profiles and PON1 activity in newly diagnosed patients with mild to moderate essential hypertension. Serum apolipoprotein A-I (apoA-I) and apoB levels and the ratio of apoA-I/apoB as a risk marker of cardiovascular diseases were also measured. In addition, malondialdehyde (MDA) and soluble lectin-like ox-LDL receptor (sLOX-1) as markers of oxidative stress were studied with regard to the carvedilol treatment and PON activity. LOX-1 is responsible for the uptake of oxidized LDL to the endothelial cells and launching oxidative stress, proinflammatory, and proapoptotic processes.^[8] LOX-1 is known as a marker of oxidative stress, myocardial infarction, and a risk factor for cardiovascular diseases.^[9]

Patients and Methods

Subjects

This clinical trial study was performed on forty patients who were first diagnosed with mild to moderate essential hypertension. The sample size was calculated by a statistician based on the standard deviation (SD) of PON-1 in hypertensive patients found in previous studies. Patients underwent physical examination, laboratory tests, electrocardiography, and transthoracic echocardiography examination by an expert cardiologist in Valiaasr Clinic, Ahvaz, Iran. Patients with diabetes mellitus, primary dyslipidemia, cardiovascular, cerebrovascular, hepatic, renal and thyroid diseases, mental and cognitive disorders, and any other chronic diseases and patients receiving any other drug, alcohol consumers, and tobacco smokers were excluded from the study. Eligible patients who were recommended to apply diet modification of restricted salt intake received 10 days run-in after which they underwent ambulatory BP monitoring. All patients having mean systolic BP >130 mmHg and/or mean diastolic BP >85 mmHg after this period were prospectively included into the study. Patients were informed about the study and following obtaining an informed consent, subject's data including age, sex, weight, and body mass index (BMI) were recorded. BP of the subjects was measured on the left arm following 10 min rest in the seated position using a mercury sphygmomanometer. BP was measured three times with a time interval of 5 min for each individual. Patients were treated with 12.5 mg carvedilol twice daily p.o. under the cardiologist supervision. Subjects were referred to our laboratory for blood sampling before carvedilol treatment and following 2-month carvedilol treatment. Serum samples were obtained by centrifugation and maintained in -70°C. This study was approved by the ethics committee and registered at trials registration of Jundishapour University of Medical Sciences with the reference number 4544.

Lipid and Lipoprotein Measurements

Triglyceride (TG), total cholesterol, LDL, HDL, apo A-1, and apo B levels were measured using Pars-azmoon assay kits (Iran) by BT3000 autoanalyzer (Italy).

Enzyme Assays

PON activity was assayed using paraoxon (Sigma-Aldrich, USA) as substrate. About 20 µl of serum samples were mixed with 2 mM paraoxon in 1 ml of 100 mM tris buffer pH: 8 containing 2 mM calcium chloride. The rate of paranitrophenol release was detected by reading the absorbance of the reaction mixtures at 412 nm in 37°C during 1 min. The molar extinction coefficient of 18290 was applied to calculate the enzyme activity as µM/min.

In order to assay arylesterase activity, 10 mM phenyl acetate (Merck, Germany) as substrate in 3 ml of 9 mM tris-HCl pH: 8, containing 0.9 mM CaCl₂ was mixed with 5 µl of sample serums. Phenyl acetate hydrolysis was measured by reading the absorbance at 270 nm during 1 min. The extinction coefficient of 1310 was used to calculate the enzyme activity as µM/min. Shimatzu UV-1650PC spectrophotometer (Japan) was employed for absorbance determinations.

Malondialdehyde Assay

Serum levels of thiobarbituric acid-reactive substances were quantified using a chemical colorimetric assay. In brief, 250 µl of serum was mixed with 1.5 ml phosphoric acid 1% and 500 µl thiobarbituric acid 0.6% (Merck, Germany). Following 1 h incubation in boiling water and cooling the mixture, 2 ml n-butanol was added and vigorously shaken. Butanol phase was decanted after 10 min centrifugation at 3000 rpm. Aqueous phase absorbance at 532 nm was measured and serum MDA concentrations calculated based on the calibration curve of tetramethoxy propane (Merck, Germany) dilutions.

Enzyme-linked Immunosorbent Assay

Soluble LOX-1 levels of serum samples were quantified using a sandwich ELISA kit (Cusabio, China). The assay procedure carried out following the manufacturer instruction. In brief, 100 µl of serum samples and each dilution of calibrator solutions were introduced to the microtiter plate wells and incubated at 37°C for 2 h. After capturing the antigen to the solid phase, 100 µl biotin-conjugated antibody solution was added to the wells and incubated for 1 h. After washing, 100 µl avidin-conjugated HRP solutions were placed in the wells and after 30 min incubation, optical density of the wells was measured at 540 nm. sLOX-1 concentrations as pg/ml were obtained with regard to the calibration curve.

Statistical Analysis

Data have been shown as a mean ± SD ($n = 40$). Paired *t*-test with $\alpha = 0.05$ (two-tailed) and $\beta = 0.2$ was used to analyze the differences before and after carvedilol treatment. In order to evaluate the correlation between the variables, Pearson's correlation analysis was performed and *P* values were defined. Differences with a $P \leq 0.05$ were considered significant. Results were analyzed using IBM SPSS 22 software.

Results

The study was conducted on forty patients with essential hypertension with initial systolic BP of 167 ± 11.1 mmHg.

Subjects consisted of 24 men and 16 women with the mean age of 44.5 ± 10.6 years, mean weight of 81.5 ± 14.3 Kg, and mean BMI values of 28.4 ± 5 .

Carvedilol Effects on Blood Pressure

As shown in Table 1, following 2 months treatment with 12.5 mg carvedilol twice daily, BP showed a significant decrease in comparison to the initial values. Systolic and diastolic BPs were decreased from 167 ± 11 and 91 ± 6 mmHg to 127 ± 10 and 75 ± 5 mmHg, respectively ($P < 0.001$). The effect of carvedilol on systolic BP found to be more evident than diastolic BP.

Carvedilol Effects on Lipid Profiles

Serum levels of TG, cholesterol, LDL, and HDL were measured using a biochemistry analyzer before and after 2 months carvedilol treatment. Mean values of total cholesterol showed 12 mg/dl increase following treatment which was statistically significant in paired *t*-test analysis ($P < 0.05$). TG levels were slightly increased from 157.9 ± 68.9 to 163.6 ± 103.0 mg/dl in response to the intervention. The increase was not considered significant ($P = 0.063$). LDL levels also did not show a significant change following treatment. Mean LDL concentration was 6 mg/dl higher at the end of drug therapy ($P = 0.179$). Our results showed that 25 mg carvedilol daily for 2 months increased the HDL level to 54.3 ± 16.4 mg/dl which was found to be statistically significant ($P < 0.05$).

Apolipoproteins Analysis

Apo A-I and B were measured using immunoturbidimetry method and results have been presented as mg/dl. Following carvedilol treatment, apo concentrations raised from 121.6 ± 11 to 124.3 ± 15.2 and from 84.9 ± 15.2 to 88.1 ± 12.8 , for apo A-I and apo B, respectively. However, the increases were not statistically significant ($P = 0.077$ for apo A-I and $P = 0.09$ for

apo B). Apo A-I/apoB ratio was also remained unchanged in response to the treatment ($P = 0.162$).

Carvedilol Effects on Enzymes

PON and arylesterase activity assays were performed on serum samples before and after the intervention. As shown in Table 1, mean PON1 activity found to be 109 ± 32.4 U/L initially that significantly increased to 127.1 ± 33.8 U/L at the end of study ($P < 0.001$). Similarly, arylesterase activity increased from 59.5 ± 8.3 to 64.4 ± 10.3 U/L ($P < 0.01$).

Carvedilol Effects on Oxidative Markers

For MDA assay, calibration curve was obtained using tetramethoxy propane dilutions. Serum MDA quantification based on this calibration curve showed that carvedilol treatment significantly decreased MDA level from 2.15 ± 1 to 1.4 ± 0.7 μ M ($P < 0.001$) [Table 1]. Serum sLOX-1 was quantified using a commercial ELISA kit, and the results were presented as pg/ml. In contrast to the MDA changes, carvedilol therapy increased sLOX-1 levels from 866 ± 624 to 1051 ± 794 . Although the increase was not found to be statistically significant ($P = 0.085$).

Paraoxonase 1 Activity Inversely Correlates with Malondialdehyde Levels

Pearson's correlation analysis between values of serum PON1 activity and MDA concentrations in the patients studied showed that PON1 activity inversely correlates with MDA levels ($r = -0.256$, $P < 0.05$) [Figure 1] but a significant correlation was not found for arylesterase activity and MDA levels ($P = 0.377$). Neither of the enzymes established a significant correlation with serum sLOX-1 concentrations [Table 2].

Discussion

This clinical trial study was conducted on patients with early stages of hypertension without concomitant diseases such as diabetes mellitus, dyslipidemia, or evident coronary heart disease. Therefore, the patients were managed with carvedilol monotherapy, and the observed results could be attributed

Table 1: Comparisons of variables before and after carvedilol treatment

Variable	Before treatment	After treatment	P
Blood pressure (mmHg)			
Systolic	167±11	127±10	0.0*
Diastolic	91±6	75±5	0.0*
Lipid profiles (mg/dL)			
Total cholesterol	186.4±42.8	198.4±41.6	0.028*
TG	157.9±68.9	163.6±103.0	0.063
LDL-C	106.3±37.7	112.0±32.9	0.179
HDL-C	50.9±12.3	54.3±16.4	0.03*
Apolipoproteins A-I	121.6±11.0	124.3±15.2	0.077
Apolipoproteins B	84.9±15.2	88.1±12.8	0.09
Apolipoproteins A-I/B ratio	1.48±0.3	1.44±0.3	0.162
Enzymes activity (U/L)			
PON1	109.4±32.4	127.1±33.8	0.0*
ARE	59.5±8.3	64.4±10.3	0.006*
Oxidative markers			
MDA (μ M)	2.15±1.0	1.4±0.7	0.001*
sLOX-1 (pg/ml)	866.8±624.0	1051.2±794.0	0.085

*Significant change ($P < 0.05$) based on paired-samples *t*-test. TG=Triglycerides, LDL-C=Low-density lipoprotein cholesterol, HDL-C=High-density lipoprotein cholesterol, PON1=Paraoxonase 1, MDA=Malondialdehyde, sLOX-1=Soluble lectin-like ox-LDL receptor 1, ARE=Arylesterase

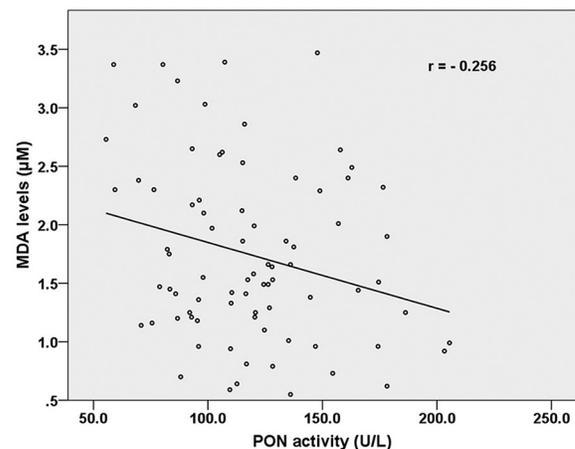


Figure 1: Scatter plot of Pearson's correlation between values of serum paraoxonase 1 activities and malondialdehyde concentrations in hypertensive patients treated with carvedilol. The correlation was found to be statistically significant ($P < 0.05$)

Table 2: Coefficients of correlation between high-density lipoprotein enzymes activities and markers of oxidative stress

	MDA(P)	sLOX-1(P)
PON1	-0.256* (0.035)	-0.11 (0.33)
ARE	-0.02 (0.86)	0.157 (0.165)

*A significant correlation ($P < 0.05$) based on Pearson's correlation analysis. PON1=Paraoxonase 1, MDA=Malondialdehyde, sLOX-1=Soluble lectin-like ox-LDL receptor 1, LDL=Low-density lipoprotein, ARE=Arylesterase

to the carvedilol treatment. Our results showed that 12.5 mg carvedilol twice daily for 2 months decreased systolic and diastolic BP as much as 40 and 16 mmHg, respectively. The effect of carvedilol on systolic pressure was much more considerable than diastolic pressure. This is in accordance with hemodynamic properties of the drug.^[10] In the present study, carvedilol treatment for 2 months in hypertensive patients, resulted in significant increase in HDL-C, and total cholesterol but the levels of TG, LDL-C, and apos A and B did not significantly change. TG, LDL, HDL, and PON1 changes in our study are similar to the results of previous reports which compared carvedilol with traditional β -blockers and other antihypertensive agents.^[11-13] Our results confirmed the favorable metabolic effects of carvedilol and its effect on lowering BP. The favorable hemodynamic and metabolic properties of carvedilol are due to its pharmacology in part. Carvedilol is a nonselective β -blocker/ α 1-blocker. Blockade of α 1 receptors relaxes the peripheral vessels and facilitate the uptake of glucose and lipids to the skeletal muscles. It also affects lipoprotein lipase bioavailability and TG metabolism. Blockade of α 1 adrenergic receptors in liver modulates glycogenolysis and gluconeogenesis and diminishes TG efflux and cholesterol synthesis which enhances LDL binding to its hepatic receptors.^[14,15] We found that HDL was significantly increased in response to the treatment, but the level of apo A-I did not show a significant change. This suggests that the content and function of HDL particles were changed rather than their number. Increased PON-1 activity also confirmed the enhanced HDL function. It has been shown that the environmental conditions of PON-1 such as HDL lipid composition, the presence of other proteins and enzymes, and oxidative status affect its activity.^[6] An alternative mechanism in PON1 upregulation could be enhanced hepatic expression in response to carvedilol. The effects of multiple nutritional and pharmacologic factors such as lifestyle modification, alcohol, diet, polyphenolic phytochemicals, antioxidant agents, and various drugs have been studied on HDL-associated PON-1 activity.^[16] Further studies are required to determine carvedilol effect on hepatic PON1 expression and increased serum PON1 activity. Our results are in agreement with a previous study that showed the treatment of AMI patients with carvedilol and metoprolol for 1 month caused a significant increase in serum PON1 activity in both groups.^[17] Our results showed the increased ratio of serum PON1 activity to serum apo A-I level. This suggests that the changes in PON-1 level occurred independent of HDL particles quantity. HDL plays antioxidant roles, removes oxidized lipids from cell membrane and lipoprotein particles, decrease oxidative stress, and inhibits pro-inflammatory responses in which PON-1 plays a substantial role.^[5,6] We showed that there was an inverse correlation between serum PON1 activity and serum MDA following carvedilol treatment and the antioxidant

properties of carvedilol can be partially mediated through PON1 upregulation. The shear stress upon vessel walls due to hypertension as a major risk factor of cardiovascular diseases causes vascular inflammation and oxidative stress.^[18] Carvedilol as an α 1/ β adrenoceptor antagonist decreases the BP and the shear stress upon vessel walls, leading to down-regulation of renin-angiotensin system, NADPH oxidase, and superoxide production.^[19] Thus, carvedilol presents direct and indirect antioxidant and anti-inflammatory effects. In the present study, 25 mg carvedilol for 2 months did not produce a significant change in serum level of sLOX-1. Considering the antioxidant properties of carvedilol, it was expected that the drug could affect this marker. Although the serum level of soluble LOX-1 did not significantly change following carvedilol treatment in our study, it cannot be generalized to tissue expression of the receptor. In the present study, patients with mild to moderate hypertension were selected who were managed with medium doses of 12.5 mg carvedilol, twice daily. In many of previous studies, antioxidant and anti-inflammatory effects of carvedilol were achieved with a high dose of the drug (50 mg a day).^[13,20,21] Furthermore, previous studies were different to our study in terms of studied population, disease condition, administered drugs, and duration of intervention.^[12,20,22] In addition, sLOX-1 is considered as a marker of advanced stages of cardiovascular diseases with atherosclerotic lesions and myocardial infarction.^[23] It seems that its expression and release are not significantly developed in mild to moderate hypertension. Considering the normal homeostasis and disposition of lipids and lipoproteins, a 2 months study could demonstrate the metabolic outcomes of the treatment. Longer periods may indicate long-term changes, but the variability of results increases due to changes in patient's condition, diet, prescribed medications, and lack of compliance. The results of this study cannot be generalized to the cases of severe and resistant hypertension and disease states with extensive metabolic complications such as diabetes mellitus and metabolic syndrome.

Conclusion

The results of the current study confirmed the effectiveness of the drug as monotherapy in managing patients with mild to moderate hypertension. Carvedilol, in contrast to the conventional β -blockers, lacks the negative side effects on lipid profile and provided beneficial metabolic effects through augmenting HDL and PON-1 activity. Increased PON-1 activity was in association with decreased serum MDA level. We propose that the antioxidant effects of carvedilol can be partially attributed to increased PON-1 activity.

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Conflicts of Interest

There are no conflicts of interest.

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