doi: 10.5505/abantmedj.2013.30592

Abant Medical Journal

Orijinal Makale / *Original Article*

Volume Cilt 2 *Issue* Sayı 3 *Year* Yıl 2013

Carvedilol and Metoprolol in Acute Myocardial Infarction

Early Effect of Oxidized LDL and Paraoxonase-1 Activity

Akut Miyokard İnfarktüsünde Karvedilol ve Metoprolol'ün Okside LDL ve Paraoksonaz-1 Aktivitesine Erken Dönem Etkisi

Sezgin Albayrak[1], Kemal Karaağaç[2], İbrahim Baran[5], Zeynel Abidin Yetgin[3], Hakan Uçar[4], Ali Aydınlar[5]

[1]Ordu Devlet Hastanesi, Kardiyoloji Bölümü, Ordu
[2]Bursa Yüksek İhtisas Hastanesi, Kardiyoloji Bölümü, Bursa
[3]Bolvadin Devlet Hastanesi, Kardiyoloji Bölümü, Afyonkarahisar
[4]Bursa Devlet Hastanesi, Kardiyoloji Bölümü, Bursa
[5]Uludağ Üniversitesi, Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Bursa

Özet

Amaç: Bu çalışmanın amacı akut miyokard infarktüsü (AMİ) geçiren hastalarda dört haftalık karvedilol ve metoprolol tedavisinin okside düşük yoğunluklu lipoprotein (LDL) düzeyi ve paraoksanaz-1 (PON-1) aktivitesi üzerine etkisini araştırmaktır.

Yöntem: Çalışmaya AMİ tanısı konulan 31 hasta ve kontrol grubunu oluşturacak 15 olgu alındı. AMİ grubundan 15 hastaya karvedilol ve 16 hastaya metoprolol tedavisi verilerek çalışma iki guruba randomize edildi. Çalışmanın sonunda başvuru ve kontrol vizitinde alınan ve saklanan kan örneklerinden okside LDL'nin ve PON-1 aktivitesinin başvuru (tedavi öncesi) ve tedavi sonrası 1 aylık sonuçlarına bakıldı.

Bulgular: Hasta grubunda kontrol grubuna kıyasla başlangıç HDL düzeyi ve PON-1 aktivitesi anlamlı derecede düşük olarak saptandı. Okside LDL düzeyi hasta grubunda kontrol grubuna göre daha yüksekti. Hasta grubunda 1 aylık karvedilol (p=0,008) ve metoprolol (p

Sonuç: AMİ geçiren hastalarda diğer çalışmalara paralel olarak, okside LDL' nin arttığı ve HDL-K düzeyi ile PON-1 aktivitesinin azaldığı gösterildi. Antioksidan özellikleri nedeniyle Karvedilol'ün PON-1 aktivitesini arttırmada Metoprolol'e göre daha üstün olması beklenebilir. Fakat bir aylık süre bunu göstermek için yeterli olmayabilir.

Anahtar Kelimeler: Koroner arter hastalığı, okside LDL, paraoksanaz-1

Abstract

Objective: The aim of this study to investigate the effects of Carvedilol and Metoprolol on oxidized low density lipoprotein (oxLDL) and paraoxonase-1 (PON-1) activity in patients with acute myocardial infarction who were treated with these agents for four weeks.

Method: 31 patients with AMI and 15 healhty subjects for control group were contained. 15 patients of AMI group were given Carvedilol treatment and the remained 16 were given Metoprolol treatment and the study was randomized to two groups. At the end of the study oxLDL and PON-1 activity levels were studied from the blood samples taken at admission (pre treatment) and samples taken after one month treatment.

Results: In patient group initial high density lipoprotein (HDL) level and PON-1 activity were found significantly lower but oxLDL level was higher in patient group compared to control group. The oxLDL levels were found to decrease in patient group after Carvedilol(p=0,008) and Metoprolol (p

Conclusion: In paralel to other studies we showed that oxLDL is increased and HDL and PON-1 activity is decreased in patients with AMI. Carvedilol may be expected to be superior to Metoprolol due to its antioxidant effect in increasing PON-1 acitvity. But one month period may not be enough to determine this effect.

Keywords: Coronary Artery Disease, oxidized LDL, paraoxonase-1

Introduction

Oxidized low density lipoprotein (oxLDL) rather that LDL has an important role in atherosclerosis pathogenesis and lesion formation (1). Oxidized LDL occurs after a series of chemical reactions after LDL passes to vessel wall. After its formation it causes beginning or fastening a series of events realaed to atherosclerosis (2,3). Paroxanase-1 (PON-1) is an esterase of which structure is a calcium dependent glycoprotein. Studies have showed that Paroxonase-1 (PON-1) has antioxidant effects due to csytein aminoacid in its structure and has an important role in protecting LDL from oxidation and moreover it has the property of hydrolising lipid peroxides and thus it reduces accumulation of hydroperoxides in HDL and LDL (4,5). Besides it is reported that oxidized LDL inactivates PON-1 via the interaction between sulfidryl group of PON-1 and oxidized lipids (6).

In this study we aimed to compare the oxidized LDL levels and PON-1 activities of patients with AMI to those of healhty subjects and investigate

İletişim Bilgisi / Correspondence
Uzm. Dr. Kemal Karaağaç, 152 Evler Mahallesi, Prof Tezok Caddesi, No: 2 Yıldırım, Bursa
E-mail: drkaraagac2001@gmail.com **Tel:** +90 224 360 50 50

Geliş tarihi / *Received*: 07.02.2013 **Kabul tarihi / Accepted:** 03.04.2013 **Çıkar Çatışması / Conflict of Interest:** Yok / None

effects of carvedilol and metoprolol treatment on oxidized LDL levels and PON-1 activity.

Patients and Methods

31 patients admitted to coronary care unit with AMI as the patient group and 15 healhty subjects as control group were included in the study. The presence of at least two of the following criteria were accepted as AMI: İschemic chest pain longer 30 minutes, the presence of spesific ECG changes related to myocardial infarction and the significant increase in plasma CK, CK-MB levels. After the admission to coronary care unit the history of patients were taken in detail and their examinations were made. Then venous blood samples were taken for routine biochemical tests, complete blood counting and paroxonase (PON-1) level determination. 15 patients with AMI were given carvedilol and the remained 16 patients were administered metoprolol treatment and patients were randomized to two groups. At the end of the forth week of trestment patients were evaluated. The exclusion criteria were as follows: age >80, chronic disease like renal or hepatic failure, malignant disease, conditions causing contraindication for beta blokers (heart blocks, end stage heart or lung failure etc. and patients taking beta blockers for the last 48 hours. The study was approved by hospital Ethics Committee and patients gave their written informed consent.

Blood Sampling and Laboratory Parameters:

Glucose, AST, ALT and CBC of patients admitted to hospital was studied. Lipid parameters were studied within the first 24 hours of myocardial infarction after 10-12 hours of fasting. In addition blood samples of 5 cc were taken and centrifugated at 1500 cycles for 5 minutes and they were stored at -20°C for the future evaluations. The control visits were made 4 weeks after the initiation of therapies. Examinations, biochemical tests (glucose, AST, ALT, urea, creatinine, fasting lipid profiles) were made again for control visit. Once again blood samples of 5 cc were taken and centrifugated in the same procedure and stored at -20°C for future evaluations.

Oxidized LDL measurement:

The measurements were made by ELISA method. The oxLDL measured from the samples taken before the treatment was defined as the oxLDL before treatment and the value measured from the samples taken after the treatment was defined as the oxLDL after the treatment. The results were expressed as ng/ml.

The measurement of paraoxonase (PON) activity:

Base line PON activity was measured by spectrophotometric method in the absence of sodium chloride. The hydrolisis velocity of paraoxon (diethyl-p-nitrophenylphosphate) was estimated from the coefficient (17000/mol/l/cm) of molar absorption of p-nitrophenol at Ph 8, 371 degrees and 412 nanometers (7). The serum PON activity was expressed as unit/L (U/L). The PON-1 aciti-vity measurements at admission and at the end of forth week were defined as PON-1 activity before treatment and PON-1 activity after treatment respectively and PON-1 activities were recorded as unit/L.

Statistical Analyse

Statistical analyses were made with SPSS 13.0 package programme (SPSS Inc, Chicago, Illinois). The Standard deviations were given with mean values as variability measures. For continual variables when comparing two groups Mann Whitney U test and independent sample T test were used for comparison. Matched sample T test and Wilcoxon test were used for dependent group comparisons. Pearson's chi-square test, Fischer's exact chi-square test and Yates chi-square test were used to compare cathegoric variables. p value $p<0.05$ was accepted as significant for all tests.

Results

20 patients (%64,5) of 31 patients in patient group were men and remained 11 were women (%35,5) whereas in control group there were 8 men (%53,3) and 7 women (%46,7). There was no significant difference between two groups about total cholesterol, LDL and triglycerid levels. HDL cholesterol ($p<0,002$) and oxLDL ($p<0,001$) values of patients were higher at admission whereas their mean values for PON-1 activity ($p<0,001$) were lower significantly in comparison to control group (Table 1).

Table 1. The demographic characteristics of patient and control groups

	Patient (n=31)	Control (n=15)	p value
Age	65±11	56±10	NS
Gender			
Female	11 (% 35,5)	7 (% 46,7)	
Male	20 (% 64,5)	8 (% 53,3)	
Smoke n(%)	11 (%35,5)	1 (% 6,7)	NS
HT n(%)	20 (% 64,5)	8 (% 53,3)	NS
DM n(%)	6 (% 19,4)	1 (% 6,7)	NS
HL n(%)	11 (% 35,5)	7 (% 46,7)	NS
TotalCholesterol (mg/dL)	203±59	194±35	NS
Trigliseride (mg/dL)	134±60	139±53	NS
HDL (mg/dL)	36±9	44±8	**0.002**
LDL (mg/dL)	130±32	131±41	NS
Oxidized LDL(ng/mL)	275±23	175±24	**< 0.001**
PON-1 (U/L)	115±13	220±32	**< 0.001**

DM: Diabetes mellitus, HL: Hyperlipidemia, HT: Hypertention PON:Paraoxsonase, HDL: High-density lipoprotein, LDL:Low-density lipoprotein, NS:Non significant, Data are presented as means ± SD

In AMI patients there was not difference between Carvedilol and Metoprolol groups about oxLDL and PON-1 activities (Table 2).

Table 2. The mean initial oxLDL and PON activity values in Metoprolol and Carvedilol groups

	Metaprolol (n=16)	Carvedilol (n=15)	p
Pre treatment Oxidized LDL (ng/ml)	272±26	278±20	NS
Pre treatment PON-1 (U/L)	112±13	117±15	NS

LDL: Low-density lipoprotein, PON:Paraoxsonase, ***NS***:Non significant, Data are presented as means ± SD

At the end of the treatment with Metoptolol or Carvedilol for four weeks we found that oxLDL of Metoprolol group was reduced from 272±26 ng/mL to 264±22 ng/mL (p<0,001) and that of Carvedilol group was reduced from 278±20 to 270±21 (p=0,008) after the treatment. On the other hand we found that PON-1 activity increased from 112±13 U/L to 120±11 U/L in Metoprolol group and from 117±15 U/L to 132±34 U/L in Carvedilol group after the treatment. The p values were 0.01 and 0.002 respectively (Figure 1) (Table 3).

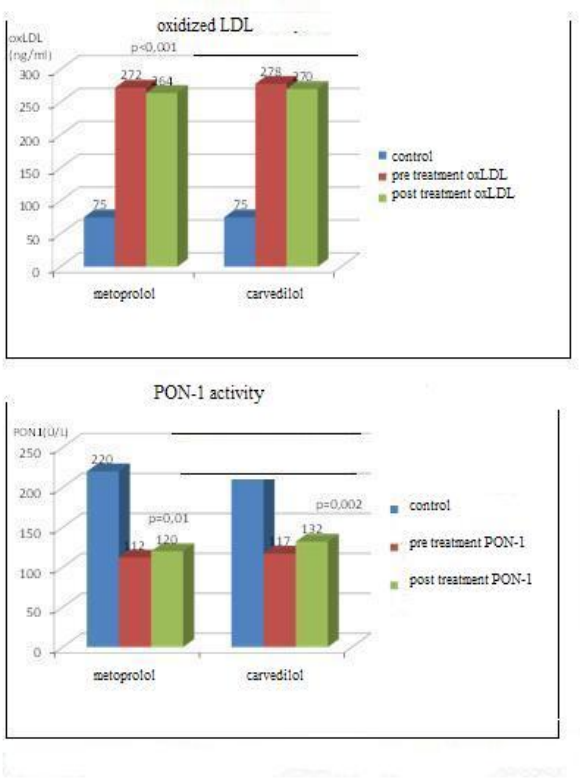

Figure 1. The mean pre treatment and post treatment oxidized LDL and PON activity

When Metoprolol and Carvedilol were compared about their effects on oxLDL and PON-1 acitivity in percentage Metoprolol and Carvedilol was not found to be superior to each other, they were found to have similar effects (figure 2)(Table 4).

Table 3. The oxidized LDL and PON-1 activity levels after treatment in Metoprolol and Carvedilol groups

	OxidizedLDL PreTreatmeant	OxidizedLDL PostTreatmeant	p	PON-1 PreTre-atmeant	PON-1 PostT-reatment	p
Metoprolol	272±26	264± 22	**<0.001**	112± 13	120± 11	**0.01**
Carvedilol	278±20	270± 21	**0.008**	117± 15	132± 34	**0.002**

NS:Non significant, Data are presented as means ± SD, PON:Paraoxsonase

Table 4. The percent changes of oxidized LDL and PON-1 activity in Metoprolol and Carvedilol groups.

	Metaprolol(n=16)	Carvedilol(n=15)	p
Oxidized LDL percent changes (%)	-0,3±0,02	-0,3±0,04	NS
PON-1 percent changes (%)	0,07±0,09	0,12±0,23	NS

LDL: Low-density lipoprotein, PON:Paraoxsonase, NS:Non significant, Data are presented as means ± SD

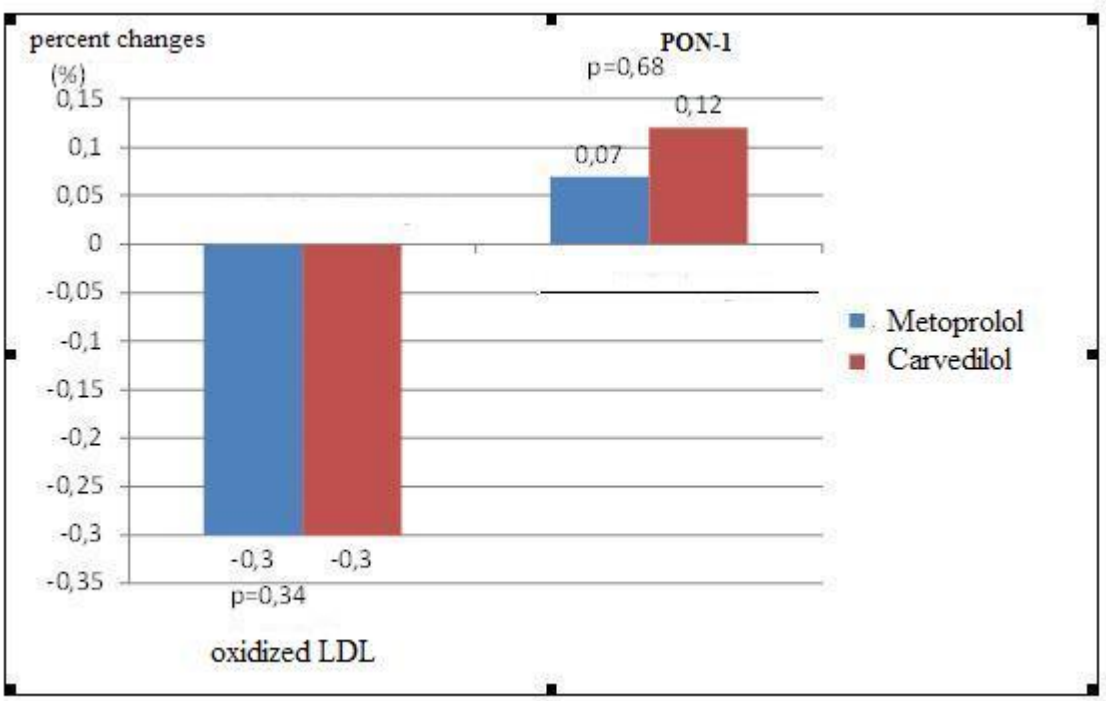

Figure 2. The percent changes of oxidized LDL and PON-1 activity

Discussion

Beta blockers applied in early hours of AMI aim at reducing the size of the myocardial infarction and the frequency of the disturbance of the heart rhythm (8). This effect of blockers is achieved by reducing the myocardial oxigen consumption and reducing the ischemia. Comparing the effects of beta blockers, it has been experimentally shown that Carvedilol is significantly more efficient in reducing the size of the infarction compared to Propranolol and Celiprolol (9). With its strong antioxydation effect Carvedilol neutralizes the activity of free oxygen radicals and prevents reperfusion damages of the myocardium.

In our study we investigated the early term effects of beta blocker treatment on oxLDL and PON-1 activity in patients with AMI. Human

PON-1 enzyme is thougth to have antioxidant effects (10). PON-1 plays important role in protecting LDL from oxidizing (11). It is thought to have catalyzer effect on HDL for protecting LDL from oxidizing (12). Not only PON-1 prevents oxidation of LDL but also it prevents oxidation of HDL (13). OxLDL is a marker of coronary artey disease and oxidative stres and this relation has been shown by a lot of investigators (14,15). Holvet et al (16) compared oxLDL levels in patients with stable coronary artery disease and patients with acute coronary seyndrome, they found that higher oxidized levels in patients with stable angina pectoris, unstable angina pectoris and AMI compared to control group. In our study we found higher oxLDL levels in patients with AMI compared to healthy subjects consistent with other studies. The higher oxLDL levels but similar LDL level in patient group compared to control group may be due to increased oxidation, impaired antioxidant defence and the disequilibrium between these two factors (17,18).

Serdar et al (19) in their study investigated the relation between oxidant and antioxidant parameters and acute coronary syndromes and its severity. They found antioxidant parameters lower and oxidant parameters significantly higher in coronary artery disease group compared to control group. Moreover they found that this relation was directly correlated to acute coronary syndrome severity. Similarly we found higher levels of oxLDL and lower levels of PON-1 activity in patients with AMI in our study. PON-1 is thought to have catalyzer effect on HDL in protecting LDL from oxidation (20). Besides PON-1 makes HDL itself more resistant to oxidation (21,22).

In conclusion we found that beta blocker treatment reduces oxLDL levels and increases PON-1 activity in early term in patients with AMI in our study. We also found that Metoprolol and Carvedilol were not superior to each other when they were compared although they both have positive effects on PON-1 activity. Carvedilol may be expected to be superior to Metoprolol in increasing PON-1 activity due to its antioxidant effects. But one month period may not be enough to show this effect.

REFERNCES

1.Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 1993; 362(6423):801-9

2.Carmena R, Ascaso JF, Camejo G, Varela G, Hurt-Camejo E, Ordovas JM, et al. Effect of olive and sunflower oils on low density lipoprotein level, composition, size, oxidation and interaction with arterial proteoglycans. Atherosclerosis. 1996;125(2):243-55.

3.Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med 2005; 353(1):46-57

4.Mackness MI, Arrol S, Durrington PN. Paraoxonase prevents accumulation of lipoperoxides in low-density lipoprotein. FEBS Lett 1991;286(1-2): 152–4.

5.Mackness MI, Mackness B, Durrington PN, Connelly PW, HegeleRA. Paraoxonase: biochemistry, genetics and relationship to plasmalipoproteins. Curr Opin Lipidol 1996;7(2): 69–76.

6.Aviram M, Rosenblat M, Billecke S, Erogul J, Sorenson R, Bisgaier CL, et al. Human serum paraoxonase is inactivated by oxidized low density lipoprotein and preserved by antioxidants. Free Radic Biol Med 1999;26(7-8): 892–904.

7.Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/ arylesterase polymorphism. Am J Hum Genet 1983; 35(6): 1126-38.

8.Yusuf S, Sleight P, Rosi PRF, Ramsdale D, Peto R, Furze L, et al. Reduction in infarct size, arrhythmias, chest pain, and morbidity by early intravenous beta-blockade in suspected acute myocardial infarction. Circulation 1983; 67 (6 Pt 2): I32-41.

9.Feuerstein GZ, Hamburger SA, Smith EF, Bril A, Ruffolo RR, Myocardial protection with Carvedilol. J Cardiovasc Pharmacol 1992; 19:S138-41.

10.McElveen J, Mackness MI, Colley CM, Peard T, Warner S, Walker CH. Distribution of paraoxon hydrolytic activity in the serum of patients after myocardial infarction. Clin Chem1986; 32(4): 671-3.

11.Ombres D, Pannitteri G, Montali A, Candeloro A, Seccareccia F, Campagna F, et al. The Gln-Argl92 polymorphism of human paraoxonase gene ıs not associated with coronary artery disease in Italian patients. Arterioscler Thromb Vasc Biol 1998;18(10):1611-6.

12.Aviram M, Hardak E, Vaya J, Mahmood S, Milo S, Hoffman A, et al. Human serum paraoxonases (PON1) Q and R selectively decrease lipid peroxides in human coronary and carotid atherosclerotic lesions. Circulation 2000; 101(21): 2510-7.

13.Aviram M, Rosenblat M, Bisgair CL, Newton RS, Primo-Parmo SL, La Du BN Paraoxonase inhibits high density lipoprotein (HDL) oxidation and preserves its functions: a possible peroxidative role for paraoxonase. J Clin Invest 1998; 101(8): 1581-90.

14.Watson AD, Berliner JA, Hama SY, La Du BN, Faull KF, Fogelman AM, et al. Protective effect of high density

lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. J Clin Invest 1995;96(6):2882–91.
15.Ehara S, Ueda M, Naruko T, Haze K, Itoh A, Otsuka M, et al. Elevated levels of oxidized low density lipoprotein show a positive relationship with the severity of acute coronary syndromes. Circulation 2001;103(15):1955–60.
16.Holvet P, Vanhaecke J, Janssens S, Van de Werf F, Collen D. Oxidized LDL and Malondialdehyde-Modified LDL in Patients With Acute Coronary Syndromes and Stable Coronary Artery Disease. Circulation 1998;9(15)8:1487-1494.
17.Halliwell B, Gutteridge JM, Cross CE, Free radicals,antioxidants, and human disease: where are we now? J Lab Clin Med 1992:119(6):598-620.
18.Devasagayam TP, Tilac JC, Boloor KK Sane KS, Ghaskadbi SS, Lele RD. Free radicals and antioxidants in human health: curent status and future prospects. J Assoc Phisicians India 2004;52: 794-804.
19.Serdar Z, Serdar Z, Altın A, Albayrak S. et al. The relation between oxidant and antioxidant parameters and severity of acute coronary syndromes. Acta Cardiol 2007; 62(4):373-80.
20.Jialal I, Vega G, Grundy S. Physiological levels of ascorbate inhibit the oxidative modification of LDL. Atherosclerosis 1990;82(3):185–91.
21.Aviram M, Rosenblat M, Bisgair CL, Newton RS, Primo-Parmo SL, La Du BN Paraoxonase inhibits high density lipoprotein (HDL) oxidation and preserves its functions: a possible peroxidative role for paraoxonase. J Clin Invest 1998; 101(8): 1581-90.
22.Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. J Am Med Assoc 1986;256(20):2835–8.