The effect of coronary angioplasty on oxidative and antioxidative status

Koroner anjiyoplastinin oksidatif ve antioksidatif durum üzerine etkileri

Mustafa Gür, M.D.,[1] Ali Yıldız, M.D.,[1] Recep Demirbağ, M.D.,[1] Remzi Yılmaz, M.D.,[1] Altan Koç, M.D.,[2] Ekrem Karakaya, M.D.,[3] Hakim Celik, M.D.,[4] Şahbettin Selek, M.D.,[4] Özcan Erel, M.D.[4]

Departments of [1]Cardiology and [4]Biochemistry, Medicine Faculty of Harran University, Şanlıurfa; [2]Department of Cardiology, Kırşehir State Hospital, Kırşehir; [3]Department of Cardiology, Medicine Faculty of Erciyes University, Kayseri

Objectives: We investigated the alterations in oxidative and antioxidative status during coronary angioplasty and coronary angiography interventions.

Study design: The study included 28 consecutive patients (20 males, 8 females; mean age 58.4 years) who underwent elective percutaneous transluminal coronary angioplasty (PTCA) for a single coronary stenosis. Nineteen patients with normal coronary angiography comprised the control group. Coronary angiography and PTCA were performed according to the standard protocols. Blood samples were taken just before and at 1 to 2 hours after coronary interventions to determine parameters of serum oxidative status including total oxidant status (TOS), lipid hydroperoxide levels, and oxidative stress index (OSI). For antioxidative status, total antioxidant capacity (TAC) and total free sulfhydryl groups were determined.

Results: Before coronary interventions, indicators of oxidative stress (TOS, lipid hydroperoxides, and OSI) were higher ($p<0.001$, $p=0.029$, $p<0.001$, respectively), and TAC ($p=0.032$) and free sulfhydryl levels ($p=0.01$) were lower in the PTCA group. After PTCA, TOS, lipid hydroperoxides, and OSI showed significant increases ($p=0.016$, $p=0.002$, $p=0.003$, respectively), whereas TAC ($p=0.039$) and free sulfhydryl levels ($p=0.03$) were significantly decreased. However, in the control group, none of the parameters changed significantly following angiography ($p>0.05$). In the PTCA group, a significant positive correlation was found between changes in OSI and total inflation time ($r=0.554$, $p=0.002$).

Conclusion: Our findings demonstrate that PTCA is associated with increased oxidative stress through ischemia-reperfusion effect, whose severity is related with total inflation time.

Key words: Angioplasty, transluminal, percutaneous coronary; antioxidants; coronary disease; free radicals; lipid peroxidation; myocardial reperfusion injury; oxidative stress.

Amaç: Koroner anjiyoplasti ve koroner anjiyografi işlemleri sırasında oksidatif ve antioksidatif durum değişikliklerinin araştırılması amaçlandı.

Çalışma planı: Çalışmaya, tek damarda koroner darlık nedeniyle elektif perkütan transluminal koroner anjiyoplasti (PTKA) uygulanan 28 ardışık hasta (20 erkek, 8 kadın; ort. yaş 58.4) alındı. Koroner anjiyografisi normal bulunan 19 hastadan kontrol grubu oluşturuldu. Koroner anjiyografi ve anjiyoplasti işlemleri standart protokole göre yapıldı. İşlemin hemen öncesinde ve sonraki 1-2 saat içinde kan örnekleri alınarak, serumda oksidatif durum için total oksidan durum (TOD), lipid hidroperoksit düzeyleri ve oksidatif stres indeksi (OSİ); antioksidatif durum için ise, total antioksidan kapasite (TAK) ve serbest sülfidril düzeyleri belirlendi.

Bulgular: Girişimler öncesinde, PTKA grubunda oksidatif stres ölçütleri (TOD, lipid hidroperoksit düzeyi, OSİ) kontrol grubuna göre anlamlı derecede yüksek (sırasıyla, $p<0.001$, $p=0.029$, $p<0.001$); antioksidatif durum ölçütleri (TAK, $p=0.032$; serbest sülfidril, $p=0.01$) ise daha düşük bulundu. Koroner anjiyoplasti sonrasında TOD ($p=0.016$), lipid hidroperoksit düzeyi ($p=0.002$) ve OSİ ($p=0.003$) tüm hastalarda anlamlı artış, TAK ($p=0.039$) ve serbest sülfidril ($p=0.03$) anlamlı düşüş gösterdi. Kontrol grubunda ise bu parametrelerin hiçbirinde anjiyografi sonrasında anlamlı değişiklik meydana gelmedi ($p>0.05$). Anjiyoplasti grubunda OSİ'deki değişim ile toplam balon şişirme süresi arasında anlamlı pozitif ilişki saptandı ($r=0.554$, $p=0.002$).

Sonuç: Bulgularımız, PTKA'nın, olasılıkla iskemi reperfüzyon etkisi yoluyla ve toplam balon şişirme süresiyle ilişkili olmak üzere oksidatif streste anlamlı artışa yol açtığını göstermektedir.

Anahtar sözcükler: Anjiyoplasti, transluminal, perkütan koroner; antioksidan; koroner hastalık; serbest radikal; lipid peroksidasyonu; miyokard perfüzyonu hasarı; oksidatif stres.

Received: July 17, 2006 *Accepted:* September 21, 2006

Correspondence: Dr. Mustafa Gür. Harran Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 63100 Şanlıurfa.
Tel: 0414 - 314 11 70 Fax: 0414 - 315 11 81 e-mail: drmugur@yahoo.com

Reactive oxygen species (ROS) are produced in metabolic and physiological processes, and harmful oxidative reactions may occur while removal of these products via enzymatic and nonenzymatic antioxidative mechanisms. Increased oxidative stress has been implicated in more than one hundred disorders.[1] Clinical and experimental studies have shown that oxidative stress and lipid peroxidation are involved in the pathogenesis of atherosclerosis.[2] In addition to traditional risk factors, oxidative stress is regarded as one of the most important contributors of atherosclerosis.[3,4]

Percutaneous transluminal coronary angioplasty (PTCA) is the most routinely used technique for mechanical revascularization of occluded coronary arteries. It represents a clinical model of transient myocardial ischemia-reperfusion. Ischemia followed by reperfusion constitutes a series of events in which the capacity of the antioxidant systems might be overwhelmed by the production of oxygen free radicals.[5,6] Increases in oxidants and decreases in antioxidants may impair the oxidative/antioxidative balance towards the oxidative status.[7] Increased oxidative status may initiate lipid peroxidation in cell membranes, damage membrane proteins, or cause DNA fragmentation, resulting in loss of heart contractile function and severe myocardial cell damage.[8]

Studies investigating oxidative stress during PTCA yielded conflicting results.[9,10] In this study, we investigated the alterations in oxidative and antioxidative status during coronary angioplasty and coronary angiography using oxidative stress parameters including oxidative stress index (OSI) and total oxidant status (TOS).

PATIENTS AND METHODS

Patients. The study included 28 consecutive patients who underwent elective PTCA for a single coronary stenosis in the proximal portion of the left anterior descending coronary artery (n=13), right coronary artery (n=8), and the circumflex artery (n=7). Nineteen patients who had normal coronary angiography comprised the control group.

Exclusion criteria were the presence of a neoplastic disease, heart failure, or a recent major surgical procedure; use of diuretics, antioxidant drugs such as beta-blockers (carvedilol, nebivolol), angiotensin converting enzyme inhibitors (captopril, zofenopril) and statins; smoking, vitamin and alcohol use, concomitant inflammatory diseases such as infections and autoimmune disorders, and liver or kidney disease. Patients with prior myocardial infarction, those with angina episodes in the past 48 hours before admission, and those with valvular heart disease or cardiomyopathy were also excluded. Informed consent was obtained from all subjects after a full explanation of the study. Control subjects were selected among those who did not use any medications, vitamin supplements, antioxidants, or alcohol on a regular basis.

Baseline demographic and clinical characteristics of all the participants were recorded. Body mass index (BMI) was calculated from weight divided by height squared (kg/m^2).

Angiographic study and PTCA procedure. X-ray angiography (Integris HM3000, Philips Medical Systems, Best, the Netherlands) was performed using the standard Judkins technique. Angiograms were obtained for the investigation of clinical manifestations (typical and atypical chest discomfort or an abnormal stress test result) suggesting ischemic heart disease. Angiographic interpretation was made by two expert observers who were unaware of the results of noninvasive tests.

Percutaneous transluminal coronary angioplasty was performed using the standard procedures. All the patients undergoing PTCA had a single coronary stenosis. Angioplasties were performed in a planned fashion. The choice of the type, length, and diameter of the stent and direct stenting without predilatation were left to the discretion of the operator. A single stent was implanted in all the patients. Angioplasty was considered successful when TIMI III flow was obtained, with a residual stenosis of less than 30%. Radiation exposure time and total inflation time were measured for each patient.

Blood sampling. Two consecutive samples of blood were taken from each patient, just before PTCA and at 1 to 2 hours after PTCA, respectively. Blood samples were also obtained from the control group. Peripheral venous blood samples were taken from the participants in the fasting state. Blood samples were centrifuged at 3000 rpm for 10 min, and serum was separated. The samples were stored at -80 °C until they were analyzed.

Measurement of total oxidant status (TOS). Total oxidant status was measured by a most recently developed automated method whereby hydrophylic and lipophylic oxidants oxidize ferrous ion to ferric ion.[11] The oxidation reaction is enhanced using glycerol and ferric ion produced makes a stable colored

complex with xylenol orange dye. Hydrogen peroxide solution is used as a standard assay procedure. The assay exhibits excellent values of coefficients of variation, being less than 3%.

Measurement of total antioxidant capacity (TAC). Total antioxidant capacity of serum taken before and at 1 to 2 hours after angiography and angioplasty procedures was determined using a novel automated measurement method developed by Erel.[12] In this method, the hydroxyl radical, which is the most potent biological radical, is produced. In this assay, ferrous ion solution in the reagent 1 is mixed with hydrogen peroxide in the reagent 2. The sequential radicals produced by the hydroxyl radical are also potent radicals. In this assay, antioxidative effect of the sample against potent free radical reactions initiated by the hydroxyl radical is measured. The assay has excellent precision values, which are lower than 3%. The results are expressed as mmol Trolox equivalent/l.

Measurement of lipid hydroperoxide. Lipid hydroperoxide level of serum was measured by an automated method using xylenol orange.[13] The method is based on a known principle: oxidation of the Fe (II) to Fe (III) by lipid hydroperoxides under acidic conditions.

Measurement of total free sulfhydryl groups of serum samples. Free sulfhydryl groups of serum samples were assayed according to the method of Ellman as modified by Hu et al.[14] Briefly, 1 ml of buffer containing 0.1 M Tris, 10 mM EDTA, pH 8.2, and 50 µl serum were added to cuvettes, followed by 50 µl 10 mM DTNB in methanol. Blanks were run for each sample as a test without DTNB in the methanol. Following incubation for 15 min at room temperature, sample absorbance was read at 412 nm on a Cecil 3000 spectrophotometer. Sample and reagent blanks were subtracted. The concentration of sulfhydryl groups was calculated using reduced glutathione as free sulfhydryl group standard and the result was expressed as millimolars.

Oxidative stress index. The percent ratio of TOS to TAC gave the oxidative stress index (OSI), an indicator of the degree of oxidative stress.[7,15-17]

Measurements of other biochemical parameters. Plasma triglyceride, total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and fasting glucose were measured by an automated chemistry analyzer (Aeroset, Abbott Diagnostics, IL, USA) using commercial kits (Abbott).

Statistical analysis. The results were presented as mean ± standard deviation or as a percentage. Categorical variables were compared using the chi-square test. Statistical evaluations of differences before and after coronary angiography and PTCA

Table 1. Demographic and clinical characteristics of the participants

	PTCA group (n=28)			Control group (n=19)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			58.4±10.0			56.3±11.8	NS
Gender							
Male	20	71.4		11	57.9		NS
Female	8	28.6		8	42.1		NS
Body mass index (kg/m^2)			27.5±2.4			26.7±2.5	NS
Family history	7	25.0		4	21.1		NS
Hypertension	10	35.7		6	31.6		NS
Diabetes mellitus	6	21.4		4	21.1		NS
Medications							
Aspirin use	27	96.4		16	84.2		NS
Clopidogrel use	27	96.4		–			<0.001
Nitrate use	7	25.0		4	21.1		NS
ACE inhibitor use	8	28.6		4	21.1		NS
Beta-blocker use	23	82.1		13	68. 4		NS
Lipid parameters							
Triglyceride (mg/dl)			166.0±74.9			176.5±87.0	NS
Total cholesterol (mg/dl)			195.1±52.9			181.9±52.6	NS
HDL-cholesterol (mg/dl)			37.8±7.9			35.2±8.9	NS
LDL-cholesterol (mg/dl)			124.0±39.9			111.4±39.5	NS
Total inflation time (sec)			86.1±35.8				
Fluoroscopy exposure time (min)			21.6±4.2			9.7±3.5	<0.001

PTCA: Percutaneous transluminal coronary angioplasty; NS: Not significant.

Table 2. Comparison of oxidative stress parameters

	PTCA group (n=28)	Control group (n=19)	*p*
Total oxidant status (μmol H_2O_2 equivalent/l)	17.55±0.76	16.16±0.36	<0.001
Total antioxidant capacity (mmol Trolox equivalent/l)	1.51±0.12	1.59±0.12	0.032
Lipid hydroperoxides (μmol tert-Butyl hydroperoxide/l)	7.28±0.89	6.75±0.69	0.029
Free sulfhydryl	0.40±0.03	0.45±0.06	0.01
Oxidative stress index (arbitrary unit)	1.17±0.02	1.02±0.07	<0.001

were performed using a paired Student's t-test. For continuous variables, differences between the two groups were assessed by an unpaired t-test. Associations between changes in OSI and demographic, clinical, and laboratory indices were assessed by the Pearson's correlation analysis. A *p* value of less than 0.05 was considered statistically significant. Analyses were made using SPSS 11.0 statistical software.

RESULTS

No complications were encountered during coronary angiography and PTCA. Successful reperfusion was obtained in all PTCA procedures.

Clinical characteristics and risk factors of the groups are summarized in Table 1. There were no significant differences between the groups with respect to age, gender, BMI, history of diabetes, hypertension, drug use, family history, and lipid parameters (p>0.05). Apart from clopidogrel use (p<0.001), PTCA and control groups did not differ with regard to medications taken before the study (p>0.05).

Indicators of oxidative stress (TOS, lipid hydroperoxides, and OSI) were higher (p<0.001, p=0.029, p<0.001, respectively), whereas TAC and free sulfhydryl levels were lower in the patient group than controls (p=0.032, p=0.01, respectively; Table 2).

The effect of PTCA on oxidative and antioxidative parameters is demonstrated in Table 3. Indicators of oxidative stress (TOS, lipid hydroperoxides, and OSI) showed significant increases after PTCA (p=0.016, p=0.002, p=0.003, respectively), whereas TAC (p=0.039) and free sulfhydryl levels (p=0.03) were significantly decreased.

The effect of coronary angiography on oxidative and antioxidative parameters in the control group is shown in Table 4. None of the parameters changed significantly following the procedure (p>0.05).

Correlations between OSI and clinical variables are listed in Table 5. A significant positive correlation was found between OSI and total inflation time (r=0.554, p=0.002) in the PTCA group.

DISCUSSION

The main findings of the study concerning the patient group may be highlighted as follows: *(i)* baseline oxidative stress parameters (TOS, lipid hydroperoxides, and OSI) were significantly higher; *(ii)* baseline antioxidant parameters (TAC and free sulfhydryl) were significantly lower; *(iii)* oxidative stress parameters significantly increased after PTCA; *(iv)* antioxidant parameters significantly decreased after PTCA; *(v)* change in OSI was in significant correlation with total inflation time.

There are a number of reports implicating excessive oxidative stress and/or inadequate antioxidant defenses in the pathogenesis of cardiovascular risk and disease.[18-20] Plasma TAC is an accurate index of oxidative stress and denotes total plasma defenses against ROS.[21] In this study, consistent with the literature,[22] we observed increased oxidants and decreased antioxidants in patients with coronary artery disease compared with the control group. It has been suggested that repeated ischemia-reperfusion episodes and/or atherosclerotic process may result in persistent enhancement of ROS generation by locally activated vascular cells.[23,24] Our results obtained in the PTCA group may be related with these mechanisms.

Table 3. The effect of percutaneous transluminal coronary angioplasty on oxidative and antioxidative parameters

	Before PTCA	After PTCA	*p*
Total oxidant status (μmol H_2O_2 equivalent/l)	17.55±0.76	17.86±1.00	0.016
Total antioxidant capacity (mmol Trolox equivalent/l)	1.51±0.12	1.45±0.08	0.039
Lipid hydroperoxides (μmol tert-Butyl hydroperoxide/l)	7.28±0.89	9.22±2.73	0.002
Free sulfhydryl	0.40±0.03	0.38±0.02	0.03
Oxidative stress index (arbitrary unit)	1.17±0.02	1.23±0.11	0.003

Table 4. The effect of coronary angiography on oxidative and antioxidative parameters in the control group

	Before angiography	After angiography
Total oxidant status (μmol H_2O_2 equivalent/l)	16.16±0.36	16.36±0.32
Total antioxidant capacity (mmol Trolox equivalent/l)	1.59±0.12	1.57±0.14
Lipid hydroperoxides (μmol tert-Butyl hydroperoxide/l)	6.75±0.69	6.76±0.70
Free sulfhydryl	0.45±0.06	0.44±0.05
Oxidative stress index (arbitrary unit)	1.02±0.07	1.04±0.10

Ischemia-reperfusion injury may occur as damage to the myocardium following blood restoration after a critical period of coronary occlusion.[25] Percutaneous transluminal coronary angioplasty represents a clinical model of transient, brief myocardial ischemia-reperfusion. Lipid peroxidation of membrane polyunsatured fatty acids by ROS is considered a major mechanism of ischemia-reperfusion injury.[26] Complete or partial restoration of oxygenated blood flow during reperfusion leads to a sudden massive increase in oxygen concentration, impairing the balance in favor of antioxidative processes. Excess oxygen leads to the production of ROS, which may initiate lipid peroxidation in cell membranes, damage membrane proteins, or cause DNA fragmentation. These processes may result in a decrease in heart contractile function and lead to severe myocardial cell damage.[8]

Direct evidence for increased cardiac oxidative stress has been demonstrated after PTCA.[27] However, the presence of cardiac oxidative stress in patients undergoing transient episodes of myocardial ischemia such as that in PTCA is controversial.[9,10] Our results demonstrated marked increases in oxidative stress parameters (TOS, lipid hydroperoxides, and OSI) and decreases in antioxidant defenses (TAC and free sulfhydryl). Previous studies showed no[9] or mild[10] oxidative stress after transient episodes of ischemia-reperfusion, probably because of inadequate sensitivity. Our results were similar to those reported by Buffon et al.[28] and Rigattieri et al.,[27] who demonstrated increases in conjugated dienes and lipid hydroperoxides and a decrease in TAC after PTCA. However, these authors did not examine OSI and TOS as indicators of oxidative stress, and free sulfhydryl as an antioxidant. Recently, oxidative stress index has often been used as an indicator of oxidative stress.[7,15-17] In addition, we used TOS which is a novel method in determining oxidant status.[11]

Table 5. Bivariate correlation analyses between OSI and clinical variables following percutaneous transluminal coronary angioplasty

	r	*p*
Hypertension	0.58	NS
Systolic blood pressure	0.172	NS
Diastolic blood pressure	0.210	NS
Total cholesterol	0.144	NS
LDL-cholesterol	0.161	NS
HDL-cholesterol	-0.120	NS
Triglyceride	0.143	NS
Diabetes mellitus	0.009	NS
Aspirin use	-0.200	NS
Clopidogrel use	-0.151	NS
Nitrate use	-0.313	NS
ACE inhibitor use	0.063	NS
Beta-blocker use	-0.353	NS
Body mass index	0.224	NS
Age	0.368	0.054
Total inflation time	0.554	0.002
Fluoroscopy exposure time	-0.009	NS

NS: Not significant.

Based on our results, increased oxidants and decreased antioxidants, together with a higher OSI may imply oxidative injury to vascular cells and myocytes.

We found that change in OSI was significantly correlated with total inflation time. Buffon et al.[28] showed that longer balloon inflation time might be associated with higher ischemia-reperfusion injury. The simultaneous reduction in TAC and increases in TOS, lipid hydroperoxides, and OSI further support reperfusion-mediated oxidative stress.

Oxidation has been implicated in the development of atheroma and restenosis after PTCA.[29] In-stent restenosis arises primarily from neointimal hyperplasia. Kawamoto et al.[30] suggested that C-reactive protein deposition and oxidative stress might be involved more significantly in neointimal development after stent implantation. Hinagata et al.[31] showed that lectin-like oxidized LDL receptor-1 (LOX-1) expressed in smooth muscle cells was associated with intimal hyperplasia in a rat model of balloon injury. They concluded that manipulation of LOX-1 activity might be a novel potential therapeutic target to prevent restenosis after angioplasty.

Molyneux et al.[32] reported that endothelial cell swelling correlated with the degree of oxidative stress and that antioxidant vitamins reduced membrane damage by preventing lipid peroxidation. They found that combined antioxidant treatment with ascorbic acid and a hydrophilic analog of alpha-tocopherol (Trolox) improved both the stress ratio and capillary measurements to control values. Kaminnyi et al.[33] showed that low daily dose of antioxidant probucol decreased the incidence and severity of restenosis after PTCA.

Study limitations. The patients continued to take medications (beta-blockers, aspirin, and angiotensin converting enzyme inhibitors) after participation in the study, which might have influenced oxidative stress markers. However, baseline medications were not different between the two groups, and patients receiving antioxidant beta-blocking agents (carvedilol, nebivolol), antioxidant angiotensin converting enzyme inhibitors (captopril, zofenopril), and statins were not included into the study. Furthermore, baseline medications were included in correlation analyses, which showed no significant association between these drugs and change in OSI.

Our results provide further evidence for increased oxidative stress associated with PTCA, similar to that of ischemia-reperfusion injury mechanism, and suggest that oxidative stress may be a common event following brief episodes of myocardial ischemia.

REFERENCES

1. Halliwell B, Gutteridge JM, editors. Free radicals, other reactive species and disease. In: Free radicals in biology and medicine. 3rd ed. Oxford: Oxford University Press; 1999. p. 617-24.
2. Young IS, McEneny J. Lipoprotein oxidation and atherosclerosis. Biochem Soc Trans 2001;29(Pt 2):358-62.
3. Norman A, Cochran ST, Sayre JW. Meta-analysis of increases in micronuclei in peripheral blood lymphocytes after angiography or excretory urography. Radiat Res 2001;155:740-3.
4. Casalone R, Granata P, Minelli E, Portentoso P, Giudici A, Righi R, et al. Cytogenetic analysis reveals clonal proliferation of smooth muscle cells in atherosclerotic plaques. Hum Genet 1991;87:139-43.
5. Frei B. Reactive oxygen species and antioxidant vitamins: mechanisms of action. Am J Med 1994;97:5S-13S.
6. Cross CE, Halliwell B, Borish ET, Pryor WA, Ames BN, Saul RL, et al. Oxygen radicals and human disease. Ann Intern Med 1987;107:526-45.
7. Kosecik M, Erel O, Sevinc E, Selek S. Increased oxidative stress in children exposed to passive smoking. Int J Cardiol 2005;100:61-4.
8. Chen LY, Nichols WW, Hendricks J, Mehta JL. Myocardial neutrophil infiltration, lipid peroxidation, and antioxidant activity after coronary artery thrombosis and thrombolysis. Am Heart J 1995;129: 211-8.
9. Blann A, Midgley H, Burrows G, Maxwell S, Utting S, Davies M, et al. Free radicals, antioxidants, and endothelial cell damage after percutaneous transluminal coronary angioplasty. Coron Artery Dis 1993;4:905-10.
10. Roberts MJ, Young IS, Trouton TG, Trimble ER, Khan MM, Webb SW, et al. Transient release of lipid peroxides after coronary artery balloon angioplasty. Lancet 1990;336:143-5.
11. Erel O. A new automated colorimetric method for measuring total oxidant status. Clin Biochem 2005; 38:1103-11.
12. Erel O. A novel automated method to measure total antioxidant response against potent free radical reactions. Clin Biochem 2004;37:112-9.
13. Arab K, Steghens JP. Plasma lipid hydroperoxides measurement by an automated xylenol orange method. Anal Biochem 2004;325:158-63.
14. Hu ML, Louie S, Cross CE, Motchnik P, Halliwell B. Antioxidant protection against hypochlorous acid in human plasma. J Lab Clin Med 1993;121:257-62.
15. Demirbag R, Yilmaz R, Erel O, Gultekin U, Asci D, Elbasan Z. The relationship between potency of oxidative stress and severity of dilated cardiomyopathy. Can J Cardiol 2005;21:851-5.
16. Harma M, Harma M, Erel O. Measurement of the total antioxidant response in preeclampsia with a novel automated method. Eur J Obstet Gynecol Reprod Biol 2005;118:47-51.
17. Aycicek A, Erel O, Kocyigit A. Increased oxidative stress in infants exposed to passive smoking. Eur J Pediatr 2005;164:775-8.
18. Martinet W, Knaapen MW, De Meyer GR, Herman AG, Kockx MM. Elevated levels of oxidative DNA damage and DNA repair enzymes in human atherosclerotic plaques. Circulation 2002;106:927-32.
19. Andreassi MG. Coronary atherosclerosis and somatic mutations: an overview of the contributive factors for oxidative DNA damage. Mutat Res 2003;543:67-86.
20. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med 1999;340:115-26.
21. Rice-Evans C, Miller NJ. Total antioxidant status in plasma and body fluids. Methods Enzymol 1994;234: 279-93.
22. Azarsiz E, Kayikcioglu M, Payzin S, Yildirim Sozmen E. PON1 activities and oxidative markers of LDL in patients with angiographically proven coronary artery disease. Int J Cardiol 2003;91:43-51.
23. Stringer MD, Gorog PG, Freeman A, Kakkar VV. Lipid peroxides and atherosclerosis. BMJ 1989;298:281-4.
24. Kovacs IB, Jahangiri M, Rees GM, Gorog P. Elevated

plasma lipid hydroperoxides in patients with coronary artery disease. Am Heart J 1997;134:572-6.
25. Goldhaber JI, Weiss JN. Oxygen free radicals and cardiac reperfusion abnormalities. Hypertension 1992;20: 118-27.
26. Zweier JL, Flaherty JT, Weisfeldt ML. Direct measurement of free radical generation following reperfusion of ischemic myocardium. Proc Natl Acad Sci U S A 1987;84:1404-7.
27. Rigattieri S, Buffon A, Ramazzotti V, Mordente A, Crea F, Maseri A, et al. Oxidative stress in ischemia-reperfusion injury: assessment by three independent biochemical markers. Ital Heart J 2000;1:68-72.
28. Buffon A, Santini SA, Ramazzotti V, Rigattieri S, Liuzzo G, Biasucci LM, et al. Large, sustained cardiac lipid peroxidation and reduced antioxidant capacity in the coronary circulation after brief episodes of myocardial ischemia. J Am Coll Cardiol 2000;35:633-9.
29. Azevedo LC, Pedro MA, Souza LC, de Souza HP, Janiszewski M, da Luz PL, et al. Oxidative stress as a signaling mechanism of the vascular response to injury: the redox hypothesis of restenosis. Cardiovasc Res 2000;47:436-45.
30. Kawamoto R, Yamashita A, Nishihira K, Furukoji E, Hatakeyama K, Ishikawa T, et al. Different inflammatory response and oxidative stress in neointimal hyperplasia after balloon angioplasty and stent implantation in cholesterol-fed rabbits. Pathol Res Pract 2006;202:447-56.
31. Hinagata J, Kakutani M, Fujii T, Naruko T, Inoue N, Fujita Y, et al. Oxidized LDL receptor LOX-1 is involved in neointimal hyperplasia after balloon arterial injury in a rat model. Cardiovasc Res 2006;69: 263-71.
32. Molyneux CA, Glyn MC, Ward BJ. Oxidative stress and cardiac microvascular structure in ischemia and reperfusion: the protective effect of antioxidant vitamins. Microvasc Res 2002;64:265-77.
33. Kaminnyi AI, Lankin VZ, Samko AN, Sozykin AL, Provatorov SI, Konovalova GG, et al. Low daily dose of antioxidant probucol decreases incidence and severity of restenosis after transluminal coronary balloon angioplasty. Bull Exp Biol Med 2005;139:183-5.