Heart Vessels (2009) 24:366–370
DOI 10.1007/s00380-008-1129-7

ORIGINAL ARTICLE

**Omer Gedikli · Serkan Ozturk · Hulya Yilmaz
Merih Baykan · Abdulkadir Kiris · Ismet Durmus
Kayhan Karaman · Caner Karahan · Sukru Celik**

Low total antioxidative capacity levels are associated with augmentation index but not pulse-wave velocity

Received: May 27, 2008 / Accepted: November 14, 2008

Abstract It is well known the relationship between oxidative stress and vascular function. However, association between total antioxidative capacity and arterial stiffness was not studied in patients with hypertension (HT). This study investigated whether total antioxidative capacity is associated with arterial stiffness and wave reflections. We studied 46 (age 48.5 ± 10.6 years) never treated patients with HT and age-matched control group of 40 (age 47 ± 8.6 years) normotensive individuals. Total antioxidative capacity level was determined in all subjects. We evaluated arterial stiffness and wave reflections of the study population, using applanation tonometry (SphygmoCor). Carotid–femoral pulse-wave velocity (PWV) was measured as index of aortic stiffness. The heart rate-corrected augmentation index (AIx@75) was estimated as a composite marker of wave reflections and arterial stiffness. Carotid–femoral PWV (10.5 ± 2.2 vs 8.7 ± 1.6, m/s, $P = 0.0001$) and AIx@75 (22.7 ± 9.5 vs 15 ± 11, %, $P = 0.001$) were significantly higher in patients with HT compared with age-matched control subjects. Total antioxidative capacity level (274 ± 70 vs 321 ± 56 μmol/l, $P = 0.001$) was significantly lower in hypertensive patients than controls. In the whole population, total antioxidative capacity level negatively correlated with AIx@75 ($r = –0.24$, $P = 0.02$) in univariable analysis, but not with carotid–femoral PWV ($r = –0.08$, $P = 0.43$). Also, we found that total antioxidative capacity level ($\beta = –0.21$, $P = 0.03$) was an independent determinant of AIx@75 in multivariable analysis. Our results suggest that the decrease in the ability of antioxidant defenses contributes significantly to increased wave reflections.

O. Gedikli (✉) · S. Ozturk · M. Baykan · A. Kiris · K. Karaman · S. Celik
Department of Cardiology, KTU Faculty of Medicine, 61080 Trabzon, Turkey
Tel. +90-462-377-5557; Fax +90-462-328-0752
e-mail: omergedikli@yahoo.com

H. Yilmaz · I. Durmus · C. Karahan
Department of Biochemistry, KTU Faculty of Medicine, Trabzon, Turkey

Key words Hypertension · Total antioxidative capacity · Pulse-wave velocity · Wave reflections

Introduction

Arterial stiffness is an important mechanical property, since it is a potential risk factor for increased cardiovascular events in patients with hypertension (HT) and healthy individuals.[1–4] Arterial stiffness and wave reflections are increasingly used in the clinical assessment of patients with HT.[5] The stiffening of the arteries may be both a cause and a consequence of HT, in which different pathophysiological processes take place. That is, arterial stiffness itself is a complex phenomenon consisting of several distinct processes which include structural elements within the arterial wall, vascular smooth muscle tone, chronic low-grade inflammation, and impaired endothelial function.[6] Carotid–femoral pulse wave velocity (PWV) and the aortic augmentation index (AIx) are the main methods for assessing arterial stiffness.[5]

Hypertension is considered as a state of oxidative stress that can contribute to the development of target organ damage.[7,8] Previous studies have shown that subjects with essential HT have decreased antioxidant capacity and increased levels of reactive oxygen species.[9–11] Under some conditions, increases in oxidants and decreases in antioxidants cannot be prevented, and oxidative/antioxidative balance shifts toward the oxidative stress.[12,13] The measurement of the total antioxidative capacity (TAC) reflects the ability of antioxidant defenses of plasma.[14] An inverse association has been found between antioxidant capacity levels and thoracic aortic intima-media thickness and atherosclerosis.[15] It has been suggest that oxidative stress leads to increased aortic stiffness.[16] However, it is not known whether TAC is related to arterial stiffness and wave reflections. In this study, we investigated whether TAC is an independent variable for the carotid–femoral PWV and AIx in patients with untreated essential HT and in normotensive individuals.

Patients and methods

Subjects

In this study, 46 consecutive newly diagnosed hypertensive individuals (age 48.5 ± 10 years) were enrolled. Forty age- and sex-matched normal subjects (age 47 ± 8.6 years) were also studied. The diagnosis of HT was established according to the Joint National Committee (JNC) seventh report.[17] Two-dimensional echocardiographic examinations were performed on each subject. Subjects with HT had not previously taken any antihypertensive therapy. Patients with hemolytic, hepatic, renal, infectious and inflammatory diseases, diabetes mellitus, heart failure, valvular heart disease, history of coronary artery disease or acute coronary syndromes, pregnancy, and hypertrophic cardiomyopathy were excluded from the study. Written informed consent was obtained from each subject, and the institutional ethics committee approved the study protocol.

Measurement of total antioxidative capacity

A venous blood sample was drawn from each subject into tubes containing ethylenediamine tetra-acetic acid. Immediately after sampling, plasma was separated by centrifugation at 4000×*g* for 10 min and frozen at –80°C. Total antioxidative capacity was measured using an ImAnOx-assay (Immundiagnostik, Bensheim, Germany). This photometric test reflects the sum of all antioxidant components by measuring hydrogen peroxide (H_2O_2) degradation by the plasma antioxidants. Briefly, the determination of the TAC is performed by the reaction of antioxidants in the sample with a defined amount of exogenously provided H_2O_2. The antioxidants in the sample eliminate a certain amount of the provided H_2O_2 and the residual H_2O_2 is determined colorimetrically by an enzymatic reaction, which involves the conversion of tetramethylbenzidine into a colored product. After addition of a stop solution, the samples are measured at 450 nm in a microtiter plate reader. The measurement of the plasma antioxidant capacity was carried out in duplicate for each sample. Total antioxidative capacity activity was expressed as µmol/l. A value less than 280 µmol/l is considered low antioxidant capacity, while a value of 320 µmol/l or higher is considered as high antioxidant capacity according to the provider.

Blood pressure measurement

Brachial artery blood pressure was measured with a mercury sphygmomanometer in an office setting; the first and fifth phases of Korotkoff sounds were used for systolic and diastolic blood pressure. Appropriate cuff sizes were chosen for each subject's arm circumference. In each subject, brachial artery blood pressure was measured in at least three separate days after 15 min of comfortably sitting and the average of the measurements was recorded. According to guidelines from the JNC 7 report, HT was defined as a systolic BP of ≥140 mmHg or diastolic BP of ≥90 mmHg.[17]

Measurement of pulse-wave velocity

Carotid–femoral-PWV was determined with the foot-to-foot method using the SphygmoCor system (AtCor Medical, Sydney, Australia).[5] Consecutive registrations of the carotid and femoral artery pulse waves are electrocardiogram gated and thus, the time shift between the appearance of wave at the first and the second sites can be calculated. The distance between the two sites was measured on the body surface; to determine carotid–femoral PWV in meters/second (m/s). The average of measurements over a period of 8 s (9–10 cardiac cycles) was calculated after the exclusion of extreme values.

Pressure waveform analysis

Assessment of wave reflection characteristics was performed noninvasively using the SphygmoCor system. Radial artery pressure waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, TX, USA). After 20 sequential waveforms had been acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic pressure waveform.[18] AIx and augmentation pressure (AP) were derived from this with the technique of pressure waveform analysis.[5] The merging point of the incident and the reflected wave (the inflection point) was identified on the generated aortic pressure waveform. Augmentation pressure was the maximum systolic pressure minus pressure at the inflection point. The AIx was defined as the AP divided by pulse pressure and expressed as a percentage. Larger values of AIx indicate increased wave reflection from the periphery or earlier return of the reflected wave as a result of increased pulse wave velocity (attributable to increased arterial stiffness). AIx is dependent upon the elastic properties of the entire arterial tree (elastic and muscular arteries). In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 beats/min (AIx@75) was used in accordance with Wilkinson et al.[19]

Only high-quality recordings, defined as an in-device quality index of >80% (derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) and acceptable curves on visual inspection, were included in the analysis. All measurements were performed by the same person (O.G.) with the patient in the supine position in a quiet temperature-controlled room after a brief rest period of at least 5 min.

Statistical analyses

Continuous data are expressed as the mean ± SD. Comparison between two groups was performed using the unpaired

t-test or nonparametric means test (Mann–Whitney *U*-test) for continuous variables, and using the Fisher exact test for categorical variables. Correlations between variables were evaluated by calculation of the Pearson correlation coefficient. Multiple linear regression analysis was used to identify significant determinants of arterial stiffness parameters (AIx@75, Carotid–femoral PWV). For multiple regression, factors showing a value $P < 0.1$ in univariate analysis were selected. A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (Version 10.0, SPSS, Chicago, IL, USA).

Results

Patient characteristics

Baseline clinical and demographic characteristics of the study population are shown in Table 1. There were no significant differences in age, sex, smoking, heart rate, body mass index, fasting glucose, serum creatinine, and lipid profiles between the groups. As expected, systolic and diastolic blood pressure were higher in patients with HT than in normotensive participants. Total antioxidative capacity (274 ± 70 vs 321 ± 56, µmol/l, $P = 0.001$) levels were significantly lower in patients with HT than control (Table 1). In the whole study population, the plasma TAC level inversely correlated with brachial systolic pressure ($r = –0.3$, $P = 0.004$) and brachial diastolic pressure ($r = –0.37$, $P = 0.0001$).

Pulse wave analysis and velocity

The indices of arterial stiffness and wave reflections of the study population are presented in Table 2. Central aortic systolic, diastolic, and pulse pressure were significantly higher in patients with HT than in control subjects (Table 2). AP, AIx@75, and carotid–femoral PWV were significantly higher in patients with HT than in control subjects (Table 2).

Determinants of arterial stiffness parameters

In bivariate correlation analysis, a significant correlation was found between AIx@75 and age, TAC (Fig. 1), brachial systolic BP, brachial diastolic BP, brachial mean pressure, and brachial pulse pressure (Table 3). Carotid–femoral-PWV was significantly associated with age, glucose, heart rate, brachial systolic BP, brachial diastolic BP, brachial mean pressure, and brachial pulse pressure (Table 3).

Multiple regression analyses were performed for identifying factors that determine the arterial stiffness indices. For AIx@75, significant determinants were TAC ($\beta = –0.21$, $P = 0.03$), age ($\beta = 0.22$, $P = 0.02$), and brachial mean pressure ($\beta = 0.45$, $P = 0.0001$). Brachial systolic BP ($P = 0.17$), brachial diastolic BP ($P = 0.14$), and brachial pulse pressure ($P = 0.7$) were not associated with AIx@75 in multiple regression analyses. Significant determinants of carotid–femoral PWV were brachial mean pressure ($\beta = 0.2$, $P =$

Table 1. Clinical and biochemical characteristics of the study groups

	Control ($n = 40$)	Hypertension ($n = 46$)	P
Age (years)	47 ± 8.6	48.5 ± 10.6	0.45
Male (%)	72	54	0.07
BMI (kg/m^2)	29.1 ± 4.1	29.9 ± 4.7	0.43
Smoking (%)	25	28	0.46
Systolic BP (mmHg)	119 ± 10	160 ± 16	0.0001
Diastolic BP (mmHg)	77 ± 8	94 ± 10	0.0001
Brachial MP (mmHg)	92 ± 9	116 ± 11	0.0001
Brachial PP (mmHg)	42 ± 6	65 ± 15	0.0001
Heart rate (beats/mın)	68 ± 9	71 ± 12	0.18
Total cholesterol (mg/dl)	197 ± 37	211 ± 38	0.08
Triglyceride (mg/dl)	176 ± 92	188 ± 147	0.67
LDL cholesterol (mg/dl)	128 ± 31	147 ± 78	0.13
HDL cholesterol (mg/dl)	47 ± 15	54 ± 17	0.08
Glucose (mg/dl)	95.3 ± 28	93.4 ± 15	0.7
Creatinine (mg/dl)	0.87 ± 0.1	0.85 ± 0.2	0.67
TAC (µmol/l)	321 ± 56	274 ± 70	0.001

BMI, body mass index; BP, blood pressure; MP, mean pressure; PP, pulse pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TAC, total antioxidative capacity

Table 2. Pulse wave analysis and velocity in the study groups

	Normotensive ($n = 40$)	Hypertension ($n = 46$)	P
Central aortic pressure			
Systolic (mmHg)	108 ± 11	141 ± 17	0.0001
Diastolic (mmHg)	78 ± 8	93 ± 10	0.0001
Pulse pressure (mmHg)	30 ± 6	48 ± 14	0.0001
AP (mmHg)	6 ± 4.3	12.5 ± 7.8	0.0001
AIx@75 (%)	15 ± 11	22.7 ± 9.5	0.001
CF-PWV (m/s)	8.7 ± 1.6	10.5 ± 2.2	0.0001

AP, augmentation pressure; AIx@75, heart rate-corrected augmentation index; CF-PWV, carotid–femoral pulse-wave velocity

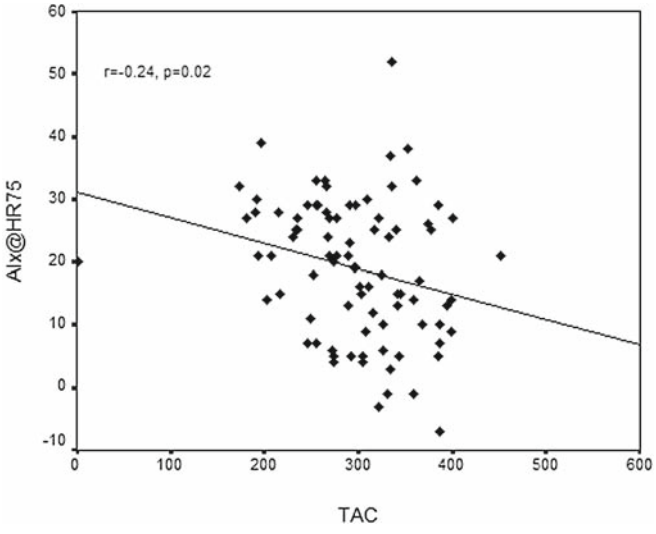

Fig. 1. Univariable associations of heart rate-corrected augmentation index (*AIx@75*, %) and total antioxidative capacity (*TAC*, µmol/l) in the whole population

Table 3. Correlations between arterial stiffness parameters and other variables

Variables	AIx@75		Carotid–femoral PWV	
	r	*P*	*r*	*P*
Age	0.37	0.0001	0.36	0.001
BMI	0.03	0.7	–0.11	0.3
Glucose	0.09	0.4	0.25	0.01
Creatinine	–0.11	0.28	0.15	0.15
Total cholesterol	0.2	0.06	0.12	0.25
Triglyceride	–0.05	0.6	–0.14	0.18
LDL cholesterol	0.13	0.22	0.07	0.47
HDL cholesterol	–0.03	0.74	0.17	0.1
TAC	–0.24	0.02	–0.08	0.43
Heart rate	0.16	0.12	0.24	0.02
Brachial SBP	0.42	0.0001	0.49	0.0001
Brachial DBP	0.36	0.001	0.28	0.008
Brachial MP	0.51	0.0001	0.46	0.0001
Brachial PP	0.36	0.06	0.52	0.0001

AIx@75, heart rate-corrected augmentation index; PWV, pulse-wave velocity; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TAC, total antioxidative capacity; SBP, systolic blood pressure; DBP, diastolic blood pressure; MP, mean pressure; PP, pulse pressure

0.03), age ($\beta = 0.21$, $P = 0.02$) and heart rate ($\beta = 0.24$, $P = 0.006$). Glucose ($P = 0.12$), brachial systolic BP ($P = 0.4$), brachial diastolic BP ($P = 0.5$), and brachial pulse pressure ($P = 0.13$) were not associated with carotid–femoral-PWV in multiple regression analyses.

Discussion

In the present study, we investigated the relationship between TAC and arterial stiffness in patients with newly diagnosed HT. We found that TAC level was an independent determinant of AIx@75 as a composite marker of wave reflections and arterial stiffness. In contrast, TAC level was not associated with carotid–femoral-PWV as indices of elastic-type, aortic stiffness.

Previous studies have demonstrated decreased levels of TAC in patients with HT.[9,10] Our results confirm previous observations showing a negative association between TAC and blood pressure.[20] Compared with normotensive individuals, carotid–femoral PWV and AIx@75 were higher in our hypertensive subjects, indicating a deterioration in arterial stiffness and wave reflections. In this study TAC and brachial mean pressure were significantly associated with AIx@75. However, TAC was not related to carotid–femoral PWV. AIx@75 is primarily determined by the magnitude and timing of reflected pressure waves which depends on the tone of the resistance arteries.[21] Carotid–femoral PWV is a measure of elastic-type large artery stiffness which depends on the structural remodeling of large elastic arteries.[5] It is probable that decreased antioxidative capacity may impact on the peripheral arteries more than the aorta. Also, previous studies showed that aortic stiffness and wave reflection indices do not always change in parallel.[22,23]

Previous studies have found a relationship between oxidative stress and arterial stiffness. Tsuji et al. found that plasma malondialdehyde level negatively correlated with arterial elasticity in rats.[24] This study suggested that oxidative stress was important as a mechanism of impaired wall distensibility. Noma et al. demonstrated that the concentration of serum malondialdehyde-modified low-density lipoprotein, an index of oxidative stress, was significantly correlated with aortic stiffness.[16] It has been suggested that vascular smooth muscle cells might be regulated by oxidative stress.[25] A previous study showed that change of smooth muscle cell contractile components may alter arterial stiffness.[6] Some experimental studies suggested the importance of pressure changes on the arterial wall in the development of lipoprotein oxidation.[26,27] It is likely that the increase in mechanical forces on the arterial wall may increase influx of low-density lipoprotein and cause oxidative stress. There is increasing evidence that reactive oxygen species such as superoxide, hydrogen peroxide, and hydroxyl radicals may play a role in the development of organ damage associated with hypertension.[7,8] Antioxidant mechanisms are important in protecting the molecules, cells, or tissues against the threat of oxidative damage. A decreased TAC level may contribute to impaired arterial function.

Previous studies suggest that the impairment of oxidant/antioxidant balance is associated with the reduction of plasma nitric oxide availability.[28,29] Importantly, reduced endothelial nitric oxide availability not only impairs endothelium-dependent vasodilation, but also leads to vascular smooth muscle cell hypertrophy.[30] Thus, the decrease nitric oxide availability may be responsible for the increase in peripheral resistance and wave reflections.

The overall balance between the pro-oxidant forces and antioxidant defenses would be important information to have on the antioxidant capacity of organisms. Total antioxidative capacity, defined as the ability of serum to quench free radical production, consists of multicompartmental protection against molecular damage of the cell structure. Decreased antioxidant activity has been shown to be associated with cardiovascular risk factors.[31,32] Also, TAC is closely associated with cardiovascular disease.[33,34] Demirbag et al. showed that TAC is an independent determinant of thoracic aortic intima-media thickness and thoracic aortic atherosclerosis.[15] These findings support that a low level of TAC may play a role in alteration of vascular function.

The present study has some limitations. The small number of patients is a potential limitation. Furthermore, arterial stiffness itself is a result of structural and functional changes of large arteries, which include structural elements within the arterial wall and vascular smooth muscle tone. In our study, markers of several processes were not evaluated. The relationship between oxidative/antioxidative balance and arterial stiffness should be confirmed with new larger scale studies.

In conclusion, the level of TAC is independently associated with wave reflections. This finding suggests that the decrease in the ability of antioxidant defense contributes significantly to the development of arterial damage.

Acknowledgment This study was supported by the Karadeniz Technical University Fund.

References

1. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 37:1236–1241
2. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P, Laurent S (2002) Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients. Hypertension; 39:10–15
3. Hansen TW, Staessen J, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J (2006) Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. Circulation 113:664–670
4. Nemes A, Forster T, Csanady M (2007) Simultaneous echocardiographic evaluation of coronary flow velocity reserve and aortic distensibility indices in hypertension. Heart Vessels 22:73–78
5. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H (2006) Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 27:2588–2605
6. Laurent S, Boutouyrie P (2007) Recent advances in arterial stiffness and wave reflection in human hypertension. Hypertension 49:1202–1206
7. Romero JC, Reckelhoff JF (1999) Role of angiotensin and oxidative stress in essential hypertension. Hypertension 34:943–949
8. Raij L (1998) Nitric oxide in hypertension: relationship with renal injury and left ventricular hypertrophy. Hypertension 31:189–193
9. Russo C, Olivieri O, Girelli D, Faccini G, Zenari ML, Lombardi S, Corrocher R (1998) Anti-oxidant status and lipid peroxidation in patients with essential hypertension. J Hypertens 16:1267–1271
10. Goch A, Lewkowicz P, Tchorzewski H, Goch JH (2004) Serum total antioxidative capacity in patients with essential hypertension. Pol Merkur Lekarski. 17:564–566
11. Lacy F, O'Connor DT, Schmid-Schonbein GW (1998) Plasma hydrogen peroxide production in hypertensive and normotensive subjects at genetic risk of hypertension. J Hypertens 16:291–303
12. Young IS, Woodside JV (2001) Antioxidants in health and disease. J Clin Pathol 54:176–186
13. Kaul N, Siveski-Iliskovic N, Hill M, Slezak J, Singal PK (1993) Free radicals and the heart. J Pharmacol Toxicol Methods 30:55–67
14. Ghiselli A, Serafini M, Natella F, Scaccini C (2000) Total antioxidant capacity as a tool to assess redox status: critical review and experimental data. Free Radic Biol Med 29:1106–1114
15. Demirbag R, Yilmaz R, Kunt AS, Gur M, Ulucay A, Unlu D (2006) Relationship between plasma total antioxidant capacity and thoracic aortic intima-media thickness. Echocardiography 23:183–188
16. Noma K, Goto C, Nishioka K, Jitsuiki D, Umemura T, Ueda K, Kimura M, Nakagawa K, Oshima T, Chayama K, Yoshizumi M, Liao JK, Higashi Y (2007) Roles of rho-associated kinase and oxidative stress in the pathogenesis of aortic stiffness. J Am Coll Cardiol 49:698–705
17. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ (2003) National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 289:2560–2572
18. Pauca AL, O'Rourke MF, Kon ND (2001) Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. Hypertension 38:932–937
19. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ (2000) The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol 525:263–270
20. Chrysohoou C, Panagiotakos DB, Pitsavos C, Skoumas J, Economou M, Papadimitriou L, Stefanadis C (2007) The association between pre-hypertension status and oxidative stress markers related to atherosclerotic disease: The ATTICA study. Atherosclerosis 192:169–176
21. Nichols WW, MF O'Rourke (1998) McDonald's blood flow in arteries: theoretical, experimental and clinical principles. Arnold, London, 170–222
22. Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, Toutouza M, Stefanadis C (2005) Acute systemic inflammation increases arterial stiffness and decreases wave reflection in healthy individuals. Circulation 112:2193–2200
23. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ (2001) Vasoactive drugs influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension 37:1429–1433
24. Tsuji T, Mizushige K, Noma T, Murakami K, Miyatake A, Kohno M (2002) Improvement of aortic wall distensibility and reduction of oxidative stress by pioglitazone in pre-diabetic stage of Otsuka Long-Evans Tokushima fatty rats. Cardiovasc Drugs Ther 16: 429–434
25. Itoh S, Umemoto S, Hiromoto M, Toma Y, Tomochika Y, Aoyagi S, Tanaka M, Fujii T, Matsuzaki M (2002) Importance of NAD(P)H Oxidase–Mediated oxidative stress and contractile type smooth muscle myosin heavy chain SM2 at the early stage of atherosclerosis. Circulation 105:2288–2295
26. Meyer G, Merval R, Tedgui A (1996) Effects of pressure-induced stretch and convection on low-density lipoprotein and albumin uptake in the rabbit aortic wall. Circ Res 79:532–540
27. Inoue N, Kawashima S, Hirata KI, Rikitake Y, Takeshita S, Yamochi W, Akita H, Yokoyama M (1998) Stretch force on vascular smooth muscle cells enhances oxidation of LDL via superoxide production. Am J Physiol 274:1928–1932
28. Di Massimo C, Lo Presti R, Corbacelli C, Pompei A, Scarpelli P, De Amicis D, Caimi G, Tozzi Ciancarelli MG (2006) Impairment of plasma nitric oxide availability in senescent healthy individuals: apparent involvement of extracellular superoxide dismutase activity. Clin Hemorheol Microcirc 35:231–237
29. Di Massimo C, Scarpelli P, Di Lorenzo N, Caimi G, di Orio F, Ciancarelli MG (2006) Impaired plasma nitric oxide availability and extracellular superoxide dismutase activity in healthy humans with advancing age. Life Sci 9;78:1163–1167
30. Landmesser U, Drexler H (2007) Endothelial function and hypertension. Curr Opin Cardiol 22:316–320
31. Harangi M, Remenyik E, Seres I, Varga Z, Katona E, Paragh G (2002) Determination of DNA damage induced by oxidative stress in hyperlipidemic patients. Mutat Res 513:17–25
32. Negishi H, Ikeda K, Kuga S, Noguchi T, Kanda T, Njelekela M, Liu L, Miki T, Nara Y, Sato T, Mashalla Y, Mtabaji J, Yamori Y (2001) The relation of oxidative DNA damage to hypertension and other cardiovascular risk factors in Tanzania. J Hypertens 19:529–533
33. Demirbag R, Yilmaz R, Kocyigit A (2005) Relationship between DNA damage, total antioxidant capacity and coronary artery disease. Mutat Res 570:197–203
34. Demirbag R, Yilmaz R, Gur M, Kocyigit A, Celik H, Guzel S, Selek S (2005) Lymphocyte DNA damage in patients with acute coronary syndrome and its relationship with severity of acute coronary syndrome. Mutat Res 578:298–307