Ischemia-modified albumin and total antioxidant status in patients with slow coronary flow: a pilot observational study

Yavaş koroner akımın görüldüğü hastalarda iskeminin değişikliğe uğrattığı albümin ve total antioksidan durum: Gözlemsel bir pilot çalışma

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ABSTRACT

Objective: Slow coronary flow (SCF) is defined as late opacification in the epicardial coronary arteries without significant stenosis. The underlying mechanism of SCF is similar to coronary atherosclerosis. Free radical damage may be responsible for the pathology. In this study, we aimed to investigate ischemia-modified albumin (IMA) levels and differences with regard to total antioxidant status (TAS) between patients with normal coronary arteries and patients with SCF without significant stenosis.

Methods: Thirty patients who were diagnosed with SCF using coronary angiography were included in this cross-sectional observational study (13 male; mean age, 56±10 years). The control group consisted of 30 patients who had normal coronary arteries as shown by coronary angiography (13 male; mean age, 53±11 years). In this study, we assessed serum IMA levels, albumin-adjusted IMA and TAS. The Student t-test was used to compare serum IMA levels and TAS between the two groups. Pearson's correlation test was used to explore the relationship between TAS and serum IMA levels.

Results: Serum IMA levels and albumin-adjusted IMA were similar in both groups (p=0.432, p=0.349). The mean value of TAS was significantly lower in the SCF group compared to control group (p=0.011). The TAS was negatively correlated with the levels of IMA and albumin-adjusted IMA in the SCF group (r=-0.457, p=0.011; r=-0.509, p=0.004).

Conclusion: This study shows that serum IMA levels and albumin-adjusted IMA were similar between the groups, however the mean value of TAS was significantly lower in the SCF group compared to control group and negatively correlated with IMA. These results are important in terms of understanding the pathophysiological basis of SCF. *(Anadolu Kardiyol Derg 2011; 11: 582-7)*

Key words: Antioxidant status, ischemia-modified albumin, slow coronary flow

ÖZET

Amaç: Yavaş koroner akım (YKA) önemli darlık olmaksızın epikardiyal koroner arterlerin geç opasifiye olmasıdır. Yavaş koroner akım oluşumundaki temel mekanizma koroner ateroskleroza benzer ve serbest radikal oluşumu patolojiden sorumlu olabilir. Biz bu çalışmada, normal koroner arterli hastalarla, daralma olmaksızın YKA bulunan hastalar arasında iskemi-modifiye albümin (İMA) seviyeleri ve total antioksidan durum (TAD) açısından farklılık olup olmadığını araştırdık.

Yöntemler: Koroner anjiyografi sırasında YKA bulunan 30 ardışık hasta (13 erkek; ortalama yaş 56±10 yıl) ile normal koroner artere sahip olup YKA olmayan 30 kişi (13 erkek; ortalama yaş 53±11 yıl) kontrol grubu olarak bu gözlemsel enine-kesitli çalışmaya alındı. Bu çalışmada serum İMA seviyeleri, albümine göre düzeltilmiş İMA ve TAD ölçüldü. İki grup arasında serum İMA seviyeleri ve TAD'ı değerlendirmek için Student t-testi kullanıldı. Serum İMA seviyeleri ve TAD arasındaki ilişkiyi açıklamak için Pearson korelasyon testi uygulandı.

Bulgular: Serum İMA seviyeleri ve albümine göre düzeltilmiş İMA her iki grupta benzerdi (p=0.432, p=0.349). Ortalama TAD değeri YKA grubunda kontrol grubuna göre daha düşük bulundu (p=0.011). Yavaş koroner akım hastalarında TAD ile serum İMA seviyeleri ve albümine göre düzeltilmiş İMA arasında negatif ilişki tespit edildi (r=-0.457, p=0.011; r=-0.509, p=0.004).

Sonuç: Bu çalışma göstermiştir ki, serum İMA seviyeleri ve albümine göre düzeltilmiş İMA gruplar arasında benzerken, ortalama TAD değeri YKA grubunda kontrol grubundan daha düşük ve İMA ile negatif olarak ilişkilidir. Bu sonuçlar YKA patofizyolojisini anlamak için önemli bulunmuştur. *(Anadolu Kardiyol Derg 2011; 11: 582-7)*

Anahtar kelimeler: Antioksidan durum, iskemi-modifiye albümin, yavaş koroner akım

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Introduction

Slow coronary flow (SCF) is defined as late opacification in the epicardial coronary arteries without significant stenosis (1, 2). According to selective coronary angiography, SCF appears to have approximately a 1% frequency (3). Several studies have shown that resting microvascular resistance and flow-mediated dilatation are deteriorated in SCF patients (4-6). Potential causes of SCF are small vessel disease, diffuse atherosclerosis, platelet dysfunction, microvascular dysfunction and vasomotor dysfunction (1, 7). Reactive oxygen species (ROS) and oxidative stress may contribute to the pathophysiology of atherosclerotic diseases (8). ROS are regulated in *in vivo* by different antioxidant vitamins and enzymes (9). A decrease in antioxidant activity may lead to increase of ROS activity and thus enhance the risk of atherosclerotic disease (10, 11).

Total antioxidant status (TAS) is an indicator of plasma oxidative system and it may be induced by several factors. TAS levels are elevated in patients with stable coronary artery disease (CAD); moreover, there is a positive and significant correlation between extensity of disease and plasma TAS levels in patients with coronary artery stenosis (12).

Ischemia-modified albumin (IMA) is a biomarker, which is formed as a consequence of modification of albumin by ROS (13). Serum IMA levels are found to be increased in acute coronary syndromes, during percutaneous coronary intervention (PCI), and myocardial ischemia (14-16). IMA is believed to be triggered by a decrease in blood flow. Decreased blood flow may induce ROS and consequently ROS may modify the N-terminal portion of albumin causing an increased formation of IMA (17). These IMA changes in the serum may be used as a marker to predict ischemic injury (13).

There are no published reports on the literature studying IMA and TAS in patients with SCF.

In the present study, we hypothesized that TAS and IMA might be difference between patients with normal coronary arteries and SCF without significant stenosis.

Methods

Study design and population

All participants in this cross-sectional observational study presented to our Cardiology Department of the Faculty of Medicine, Gaziosmanpaşa University with complaints of typical angina or angina-like chest pain and underwent a coronary angiography between 2009 and 2011. None of the subjects with or without SCF had acute coronary syndrome. Complete history, physical and laboratory examinations were obtained from all patients before coronary angiography and risk factors for CAD were recorded. Thirty patients who had angiographically normal coronary arteries with SCF were enrolled in our study as well as 30 controls, similar in age and sex, with angiographically normal coronary arteries and no SCF.

Normal coronary arteries were defined as coronary arteries without any obstructive or nonobstructive lesions in the left anterior descending coronary artery (LAD), left circumflex coronary artery (LCx) and right coronary artery (RCA). Patients with atherosclerotic lesions, coronary ectasia, muscular bridge, myocardial or valvular diseases, left ventricular hypertrophy shown by echocardiography, uncontrolled hypertension and systemic disorders were excluded from the study. We determined the presence of diabetes mellitus by looking for a history of anti-diabetic drug therapy or by a fasting glucose level of >126 mg/dl. Hypertension was diagnosed as blood pressure greater than 140/90 mm Hg or use of antihypertensive therapy. Patients who had been smoking prior to the study were accepted and listed as smokers.

An approval of the study protocol was obtained from the local Ethics Committee and informed consent was obtained from all patients.

Coronary angiography

Coronary angiography was performed using Judkin's techniques. Coronary arteries were visualized in left and right oblique planes with cranial and caudal angles at a speed of 30 frames per second. An injection of 5-8 mL of contrast medium was given manually at each position. Coronary blood flow was quantified by two independent observers who were blinded to the clinical data. Coronary flow rates of all subjects were documented by thrombolysis in myocardial infarction (TIMI) frame count (TFC). The TFC for each coronary artery was determined according to a distal marking point specific for the coronary artery of interest (18). Diagnosis of SCF was established as previously described (19).

Biochemical measurements

Blood samples were drawn from an antecubital vein before coronary angiography after a 12-h overnight fast. Serum samples were immediately frozen and stored at -80°C for IMA and TAS assays.

Ischemia-modified albumin assay

IMA was measured by a colorimetric assay developed by Bar-Or et al. (20) based on measurement of unbound cobalt after incubation with patient serum. Increased amounts of IMA results in less cobalt binding and more residual unbound cobalt available for complex with a chromogen [dithiothreitol (DTT)], which can be measured photometrically. The procedure was as follows: Fifty µL of 0.1% cobalt chloride (Merck KGaA, Darmstadt, Germany) was added to 200 µL of serum, gently mixed, and waited 10 min for adequate cobalt-albumin binding. Fifty microliters of DTT (Merck KGaA, Darmstadt, Germany), at a concentration of 1.5 mg/ml, was added as a colorizing agent and the reaction was stopped 2 min later by adding 1.0 mL of 0.9% NaCl. The colored product was measured using a spectrophotometer at 470 nm (Shimadzu, UV1601, Japan) and compared to a serum-cobalt blank without DTT and reported in absorbance units

(ABSU). Albumin-adjusted IMA was calculated according to the following formula=(Individual serum albumin concentration/ median albumin concentration of the population)×IMA value (21).

Total antioxidant status assay

Serum TAS levels were measured by Erel's method (22) which is based on the bleaching of the characteristic color of a more stable 2.2'-azino-bis (3-ethylbenz-thiazoline-6-sulfonic acid) (ABTS) radical cation by antioxidants (Rel Assay Diagnostics, Mega Tıp, Gaziantep, Turkey). Serum TAS levels were measured on the SYNCHRON LX System (Beckman Coulter, Fullerton, CA, U.S.A). The results were expressed in mmol Trolox equiv/L.

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 15 (SPSS, Chicago, IL, USA). Chi-square test was used to compare the categorical variables between groups. Categorical variables are presented as counts and percentages. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. The unpaired Student t or Mann-Whitney U tests were used to compare continuous variables between the two groups. Continuous variables are presented as mean (standard deviation [SD]) or as median (interquartile range [IQR]). Pearson's correlation coefficient test was used to explore the relationship between TAS and serum IMA levels. A p value of less than 0.05 was considered as statistically significant.

Results

There were no differences between patients with and without SCF with respect to gender (13 male vs 13 male, p=1) and age (56±10 years vs 53±11 years, p=0.200). The risk factors for CAD were similar between the groups (Table 1). In the SCF group, TFC in LAD, LCx and RCA was significantly higher than the normal coronary artery group.

Serum IMA levels and albumin-adjusted IMA were similar in both groups (p=0.432 and p=0.349, Table 2). The mean value of TAS was significantly lower in the SCF group compared to a control group (p=0.011, Table 2).

The TAS was negatively correlated with the levels of IMA and albumin-adjusted IMA in SCF group (r=-0.457, p=0.011; r=-0.509, p=0.004, Fig. 1).

Discussion

We demonstrated that serum IMA levels and albumin-adjusted IMA were similar between the groups, however the mean value of TAS was significantly lower in the SCF group compared to control group and negatively correlated with IMA and albumin-adjusted IMA.

The underlying mechanism of late opacification in the epicardial coronary arteries without stenosis observed in SCF is not entirely known. Nevertheless, the histopathological characteristics are similar to coronary atherosclerosis and microvascular dysfunction and free radical damage may be responsible for the pathology (1, 7, 23). Previous studies reported significantly increased intima- media thickness (IMT) of the carotid artery which is known as a marker of subclinical atherosclerosis in patients with SCF (24, 25). Furthermore, positive scintigraphic findings, which indicate myocardial ischemia occurred in a majority of patients with SCF in another study (26). Atherosclerosis is a complex syndrome resulting from several factors (27). Oxidative damage disturbs normal function of the arterial wall and is believed to play a significant role in atherosclerosis (28). Antioxidants may suppress atherogenesis and develop vascular

Table 1. Demographic and clinical characteristics of the study groups

Variables	SCF group (n=30)	Control group (n=30)	p*
Age, years	56±10	53±11	0.200
Sex, male/female	13/17	13/17	1
Systolic blood pressure, mmHg	122±19	127±21	0.370
Diastolic blood pressure, mmHg	80 (70 to 90)	80 (70 to 83)	0.758
Diabetes mellitus, n (%)	4 (13)	8 (26)	0.197
Hypertension, n (%)	16 (53)	15 (50)	0.796
Family history, n (%)	7 (23)	5 (17)	0.519
Smoking, n (%)	3 (10)	6 (20)	0.274
Fasting serum glucose, mg/dL	95 (86 to 112)	103 (96 to 119)	0.371
Total cholesterol, mg/dL	195±42	204±38	0.383
HDL-cholesterol, mg/dL	46±12	44±11	0.406
LDL-cholesterol, mg/dL	118±32	132±25	0.095
Triglycerides, mg/dL	110 (93 to 148)	168 (103 to 222)	0.075
Medications, n (%)			
ACEI/ARB	14 (46)	9 (30)	0.184
Beta blockers	9 (30)	6 (20)	0.371
Calcium antagonists	3 (10)	3 (10)	1
Nitrates	4 (13)	1 (3)	0.161
Statin	10 (33)	7 (17)	0.136
TIMI frame counts, frames			
LAD	54 (41 to 69)	34 (32 to 36)	<0.001
LCX	29 (23 to 37)	21 (21 to 23)	<0.001
RCA	28 (25 to 36)	20 (19 to 22)	<0.001

Data are presented as mean±standard deviation and median (interquartile, Q1 to Q3) values

*Chi-square, unpaired Student t and Mann-Whitney U tests

ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin II receptor blocker, HDL - high density lipoprotein, LAD - left anterior descending coronary artery; LCX - left circumflex coronary artery, LDL - low density lipoprotein, NS - not significant, RCA - right coronary artery, SCF - slow coronary flow, TIMI - thrombolysis in myocardial infarction

Table 2. The study parameters in SCF and control groups

Variables	SCF group (n=30)	Control group (n=30)	p*
TAS, mmol Trolox equivalents/L	2.77±0.19	2.98±0.40	0.011
IMA, ABSU	0.354±0.082	0.373±0.093	0.432
Albumin, g/dL	4.32±0.34	4.39±0.41	0.475
Albumin-adjusted IMA, ABSU	0.348±0.086	0.0370±0.089	0.349

Values are presented as mean±standard deviation
*unpaired Student t-test
ABSU - absorbance unit, IMA - ischemia modified albumin, SCF - slow coronary flow, TAS - total antioxidant status

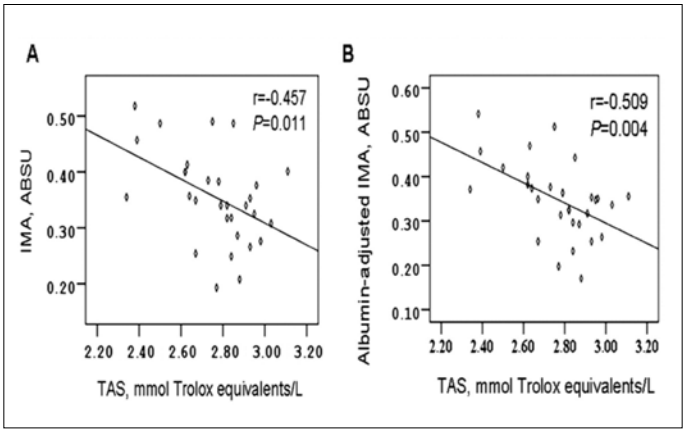

Figure 1. The relationship between TAS with serum IMA levels (A) and albumin-adjusted IMA (B) in patients with SCF
IMA - ischemia-modified albumin, SCF - slow coronary flow, TAS - total antioxidant status

function by several mechanisms (29).

Oxidative status is described as a balance between the development and inactivation of ROS. Any increase in the rate of ROS development, or decrease in their inactivation, may disrupt this balance, resulting in oxidative damage (30). Previous studies showed decreased levels of TAS in patients with CAD. A significant relation between plasma TAS levels and extent of CAD has been determined (12). Nevertheless, human (31) and animal (32) studies have shown decreased levels of TAS in cases with acute myocardial infarction. Enli et al. (23) reported elevated parameters of oxidative stress in patients with SCF compared to control group.

Overproduction of ROS may produce a chemical modification of serum albumin, resulting in an increased IMA. Thus, IMA is likely to serve as an effective oxidative stress biomarker. Serum IMA levels have a close relationship with oxidative balance. An inadequate antioxidant supply may lead to increased levels of IMA (17, 33). Subsequently, elevated IMA levels may contribute to development and progression of atherosclerotic plaque (34). Nevertheless, recent studies demonstrated that post-exercise IMA levels may be used to determine ischemia during exercise not only in acute coronary syndromes, but also in patients with stable coronary artery disease (CAD) (35). Use of IMA as a biomarker may contribute in improving the accuracy of a cardiovascular stress test (35). Kazanis et al. (13) found higher IMA levels in stable CADs compared to healthy controls and TAS was lower in the CAD group. Besides the role of serum IMA levels in atherosclerotic heart disease (36, 37), this marker may be beneficial in determining of diagnosis and mortality in such circumstances as acute mesenteric ischemia, cerebrovascular accidents, end-stage renal disease, cardiopulmonary resuscitation, and pulmonary embolism (33, 38-41). Although serum IMA levels were similar between SCF and control groups, we found a negative correlation between serum IMA levels and TAS in patients with SCF. The possible explanation of similar IMA levels in both SCF group and control subjects might be due to the lower count of TFC in our patients compared to the other studies (42, 43). In our present study, patients with SCF have a mean TFC of 54, 29, and 28 for LAD, LCx and RCA, respectively. However, Demirkol et al. (42) showed that SCF patients with exercise perfusion SPECT detected reversible perfusion defect have a mean TFC of 85, 57 and 53 for LAD, LCx and RCA, respectively. Pilz et al. (44) showed that patients with subendocardial ischemia detected via cardiac magnetic resonance (CMR) have prolonged coronary blood flow. In addition, subendocardial perfusion deficit as seen by CMR highly correlates with slowed coronary artery flow as determined by TFC.

Study limitations

The major limitation of our study is to detect sample size in different groups without doing power analysis. However, this study should be considered as a pilot study. Second, hypertension, hyperlipidemia and CAD risk factors, such as smoking may affect on the oxidative stress and IMA (45). Unfortunately, in the present study, we did not evaluate the effect of these factors and this is an important limitation. However, because of the equal presentation of these factors in both groups, the value of the study was not fully compromised and further studies ought to be conducted.

Conclusion

The present study is novel in that it investigates serum IMA levels and TAS in patients with SCF. Serum IMA levels were similar between SCF and control groups and TAS was lower than controls. A negative correlation between serum IMA levels and TAS was observed in patients with SCF. These results improve the understanding of the pathophysiology of SCF.

Conflict of interest: None declared.

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