Impact of Disulfide/Thiol Redox Couple on Pulse Wave Velocity in Patients with Normal Coronary Angiography

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ABSTRACT

Introduction: The oxidized thiol/disulfide couple has been investigated and reported as a potential risk factor for cardiovascular diseases. Additionally, an increased pulse wave velocity has been identified as a predictor of cardiovascular events.

Patients and Methods: 262 patients were included in our study. Native and total thiol levels, total disulfide levels, disulfide per total thiol ratios, native thiol per total thiol ratios, and disulfide per native thiol level ratios were calculated.

Results: Patients were divided into Pulse Wave Velocity (PWV) low and PWV high groups. Native and total thiol levels were higher in PWV low group compared to PWV high group ($p< 0.001$ for both). The median disulfide value was higher in PWV high group ($p= 0.002$). Disulfide per native thiol and disulfide per total thiol ratio values were higher in PWV high group ($p< 0.001$). Native thiol per total thiol ratios were higher in the PWV-low group ($p< 0.001$).

Conclusion: The disulfide/native thiol pathway may be an indicator for predicting future atherosclerotic cardiovascular events.

Key Words: Antioxidant; thiol

Koroner Anjiyografisi Normal Olan Hastalarda Disülfit/Tiyol Redoks Çiftinin Nabız Dalgası Hızına Etkisi

ÖZET

Giriş: Oksitlenmiş tiyol/disülfit çifti araştırılmış ve kardiyovasküler hastalıklar ve risk faktörleri için potansiyel tehlike olarak rapor edilmiştir. Artan nabız dalga hızının kardiyovasküler olayların habercisi olduğu gösterilmiştir.

Hastalar ve Yöntem: Çalışmamıza 262 hasta dahil edildi. Doğal ve toplam tiyol seviyeleri, toplam disülfit seviyeleri, toplam tiyol başına disülfür oranları, toplam tiyol başına doğal tiyol oranları ve doğal tiyol başına disülfit seviyeleri oranları hesaplanmıştır.

Bulgular: Hastalar *Pulse Wave Velocity* (PWV) düşük ve PWV yüksek gruplarına ayrıldı. Doğal ve toplam tiyol seviyeleri PWV düşük grubunda PWV yüksek grubuna göre daha yüksekti (her iki veri için $p< 0.001$). Disülfit medyan değeri PWV yüksek grupta daha yüksekti ($p= 0.002$). Doğal tiyol başına disülfit ve toplam tiyol başına disülfit oranı değerleri PWV yüksek grupta daha yüksekti ($p< 0.001$). Doğal tiyol/toplam tiyol oranları PWV alt grubunda daha yüksekti ($p< 0.001$).

Sonuç: Disülfit/doğal tiyol yolu, gelecekteki aterosklerotik kardiyovasküler olayları tahmin etmek için bir prediktör olabilir.

Anahtar Kelimeler: Antioksidan; tiyol

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INTRODUCTION

Thiols, a component of cysteine protein that contribute to thiol/disulfide redox couple, are organic composites within the cytosol and mitochondria[1]. Oxidative stress may cause thiols to oxidize and form disulfide bonds, forming a wide range of products. The oxidized products may also be reduced back to the original thiol groups when oxidative stress is removed from the environment. These reduction/oxidation reactions reach equilibrium and homeostasis is achieved[2]. Oxidation reactions occur when this equilibrium is shifted towards the oxidative side due to oxidative stress caused by excessive amounts of reactive oxygen species (ROS)[3]. Increased oxidation and oxidative stress are known to be involved in the pathogenesis of many diseases including hypertension and other cardiovascular diseases[4]. Thiol groups are known to be highly sensitive to oxidation and the formation of thiol-disulfide bonds[4,5]. Thiol-disulfide proteins are actually known to be protective against oxidative damage by direct reaction with ROS and other free radicals as well as enzymatic and non-enzymatic mechanisms[6]. Therefore, the accumulation of thiol-disulfide compounds can be observed in diseases that are associated with oxidative stress. Fibrogenesis, hypertension, and atherosclerosis are often associated with thiol-disulfide accumulation. The accumulation of the oxidized thiol/disulfide couple has been investigated and has been demonstrated as a sign of increased oxidative stress, indicating its potential as a risk factor for cardiovascular diseases[7].

Increased arterial stiffness reflects vascular damage and is a known cardiovascular risk factor[8]. It is considered to be a measure of atherosclerosis severity. Pulse wave velocity (PWV) is an indirect measurement of arterial stiffness and an indicator of subclinical organ damage. Increased pulse wave velocity has been shown to be a predictor of future cardiovascular events[9,10]. In this present study, we aim to investigate a novel oxidative stress marker, thiol/disulfide couple accumulation, and the relationship it may have with PWV in patients with normal coronary arteries shown by coronary angiogram.

PATIENTS and METHODS

Study Population

A total of 262 patients were included in the study, with a mean age of 55.2 ± 11.0 years. The male-to-female ratio was 138 to 125. All patients had undergone coronary angiography within the past six months for various indications, and the results had shown normal coronary arteries. The coronary angiogram was performed diagnostically in response to clinical indications suggestive of ischemic heart disease, such as chest pain, discomfort, and/or abnormal stress test results. The exclusion criteria included the presence of malignancies, other concurrent inflammatory diseases such as infection and autoimmune disorders, diabetes mellitus, familial hypercholesterolemia, major depression, chronic liver and/or renal diseases, recent major surgery, organic CAD, vasospastic angina, heart failure, hypertensive heart disease with left ventricular hypertrophy, severe valvular heart disease, idiopathic hypertrophic or dilated cardiomyopathy. Patients taking antioxidant drugs such as beta-blockers, angiotensin-converting enzyme inhibitors, statins, vitamins, diuretics, and hormone replacement therapy/oral contraceptives were also excluded from the study. Patients who were doing vigorous physical exercise, regular smokers, and alcohol users were also excluded from the study. The study was assessed and approved by the local ethics committee. Written informed consent was obtained from all patients prior to their participation in the study.

Biochemical Parameters

Blood sample collection

Blood samples for biochemical parameters and thiol/disulfide levels were collected from the participants after an overnight fast of eight hours. The samples were obtained from the cubital vein using blood collection tubes. The collected samples were promptly centrifuged for 10 minutes at 3000 rpm to separate the blood serum from other components. The serum was stored at -80 degrees Celsius awaiting analysis. All of the parameters were analyzed from the same serum sample for each patient.

Serum Thiol/Disulfide Homeostasis

Thiol/Disulfide homeostasis tests were conducted using a spectrophotometric assay[11]. A Shimadzu UV-1800 spectrophotometer with a temperature-controlled cuvette holder and a Cobas c501 automated analyzer (Roche) were used for the reduction reaction assay.

The samples were first treated with a reducing agent, sodium borohydride ($NaBH_4$) for a given period to form free functional thiol groups. Any remaining untapped reducing agent $NaBH_4$ residues were consumed and eliminated by adding formaldehyde after the reaction with DTNB [5.5-dithiobis-(2-nitrobenzoic acid)]. This step prevents undesired additional reductions of dynamic disulfide bonds. After these reactions, reduced and native thiol levels were determined spectrophotometrically. Total thiol measurements were obtained using a modified Ellman reagent. The discrepancy between total and native thiol measurements represented the levels of oxidized thiols. Half of this difference corresponded to the amount of dynamic disulfide bonds

present in the samples. Disulfide/total thiol, and native thiol/total thiol ratios were derived from these measurements. Ratios were calculated and recorded as disulfide/native thiol (-S-S)/(-SH), disulfide/total thiol (-S-S-)/(-S-S- + -SH), native thiol/total thiol (-SH)/(-S-S- + -SH).

Echocardiographic examination

All Echocardiographic data were obtained using Vivid-7 (GE Vingmed Sound, Horten, Norway) with a 2.5-3.5 MHz transducer simultaneously with ECG recordings. The echocardiographic examination was conducted by a skilled echocardiographer who was blinded to the patients' clinical and laboratory data. The examination was performed in accordance with the most recent clinical guidelines. The left ventricular ejection fraction (EF) value was calculated using the modified Simpson's technique[12].

Coronary Angiography

Coronary angiography was conducted using Siemens Medical Systems or Toshiba Infinix CC-I monoplane equipment. The procedure utilized 6F diagnostic catheters and followed the standard Judkins technique. Trans-femoral access was selected, with either the right or left femoral artery being used. The procedure was performed by two experienced interventional cardiologists who were blinded to the study, and they obtained images in all standard views and interpreted the results.

Measurement of aortic pulse wave velocity

All recordings were acquired using the ARCSolver method and standard oscillometric blood pressure (BP) measurement procedures[13]. Following a 10-minute rest, a properly sized blood pressure cuff was applied to the right arm of each patient. Applanation tonometry of the radial artery and oscillometric pulse wave recordings at the brachial artery were conducted while the patient was in the supine position. Subsequently, a 10-second pulsed wave analysis recording was obtained with the cuff inflated to the diastolic BP level.

The Mobil-O-Graph NG device was used to obtain the aortic blood pressure curves, aortic systolic blood pressures (SBP), aortic diastolic pressures (DBP), and aortic pulse pressures (PP). Within the time domain, a characteristic point of the aortic blood pressure curve, known as the inflection point, was identified. This inflection point signifies the arrival of the reflected wave in the ascending aorta. The aortic pulse wave velocity (PWV) value was automatically calculated using the Mobil-O-Graph NG software package.

Statistical analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, Illinois, USA). Data are expressed as mean value ± SD. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. A simple T-test was used in the analysis of continuous variables. Categorical variables were analyzed using the Chi-square test. The correlations between PWV, laboratory, oxidative, hemodynamic, and echocardiographic variables were assessed using the Pearson correlation test. A multivariate stepwise linear regression analysis was performed to identify the independent association of PWV. All significant ($p< 0.05$) parameters in the bivariate analysis (Age, SBP, DBP, native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol) were selected in the multivariate model. Two-tailed $p< 0.05$ value was considered as statistically significant.

RESULTS

The patients were divided into two subgroups according to their median PWV values. PWV low (mean age 54.2 ± 11.8, n= 129 patients) and PWV high (mean age: 56.3 ± 10.2, n= 133 patients) group. The median PWV value was 7.9 (5.3-12.7). Demographic, and laboratory characteristics, as well as oxidative stress parameters of the patients with PWV low and PWV high groups, are shown in Table 1. The average SBP and DBP values were higher in PWV high group compared with PWV low group ($p= 0.001$ and $p= 0.003$ respectively). Baseline and echocardiographic parameters were not statistically different between the groups ($p> 0.05$ for all mentioned parameters). Triglyceride levels in the PWV high group were higher than in the PWV low group ($p= 0.006$). The other laboratory characteristics were not statistically different between the groups ($p> 0.05$). All oxidative parameters, i.e., native thiol (-SH), total thiol, disulfide, disulfide /native thiol, and native thiol/total thiol were significantly different between groups. Values were higher in PWV low group than in the PWV high group ($p< 0.001$ for both). The median disulfide value was higher in PWV high group than in the PWV low group ($p= 0.002$). The disulfide/native thiol ratio and disulfide/total thiol ratios were higher in PWV high group ($p< 0.001$). Native thiol/total thiol ratio's median values were higher in the PWV low group ($p< 0.001$). Regression analyzes between PWV (m/s) and Total Thiol (μmol/L) ($r=-0.445$, $p< 0.001$) and between PWV (m/s) and Disulphide/Native Thiol ($r= 0.532$, $p< 0.001$) were shown in Figure 1 and Figure 2, respectively.

Bivariate and multivariate relationships of PWV

Pulse wave velocity was significantly associated with age, SBP, DBP, native thiol, total thiol, disulfide, disulfide/native thiol, and disulfide/total thiol (Table 2).

Table 1. Clinical, laboratory, and oxidative parameters

Variables	PWV_{low} group* (n= 129)	PWV_{high} group* (n= 133)	p
Baseline characters			
Age (years)	54.2 ± 11.8	56.3 ± 10.2	0.130
Gender (male)	64 (49.2%)	62 (45.6%)	0.319
BMI (kg/m^2)	28.9 ± 5.4	28.8 ± 4.4	0.898
Heart rate (b/m)	73.5 ± 10.5	73.3 ± 10.3	0.895
SBP (mmHg)	117.1 ± 7.4	120.4 ± 8.4	**0.001**
DBP (mmHg)	73.2 ± 7.5	75.8 ± 6.4	**0.003**
Laboratory Findings			
Glucose (mg/dL)	90.7 ± 11.0	89.9 ± 15.7	0.657
Hemoglobin (g/dL)	13.5 ± 1.6	13.2 ± 1.5	0.082
WBC ($10^3/\mu L$)	7.2 ± 2.0	7.7 ± 2.3	0.063
TC (mg/dL)	182.1 ± 41.9	190.9 ± 41.1	0.118
Triglyceride (mg/dL)	145.6 ± 75.8	176.1 ± 86.5	**0.006**
HDL (mg/dL)	41.9 ± 12.5	40.0 ± 10.5	0.216
LDL (mg/dL)	121.7 ± 37.8	125.5 ± 35.0	0.448
Creatinine (mg/dL)	0.74 ± 0.2	0.76 ± 0.2	0.693
Oxidative parameters			
Native thiol (µmol/L)	269.2 ± 51.1	217.1 ± 58.8	**<0.001**
Total thiol (µmol/L)	299.6 ± 55.3	251.3 ± 61.6	**<0.001**
Disulphide (µmol/L)	14.7 ± 6.7	17.4 ± 7.4	**0.002**
Disulphide/Native thiol	0.06 ± 0.03	0.09 ± 0.08	**<0.001**
Disulphide/Total thiol	0.05 ± 0.02	0.07 ± 0.04	**<0.001**
Native thiol/Total thiol	0.90 ± 0.04	0.85 ± 0.08	**<0.001**

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WBC: White blood cell, TC: Total cholesterol, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, b/m: Beat/minute, PWV: Pulse wave velocity.
*Subjects were grouped according to their median (min-max) PWV value as ''7.9 (5.3-12.7)"

Table 2. Multivariate linear regression analysis for oxidative parameters

	Pearson correlation		Standardization	
Variables	coefficients	p	B-regression coefficients	p
Age	0.157	**0.011***	-0.007	0.899
SBP (mmHg)	0.161	**0.008***	0.102	0.099
DBP (mmHg)	0.168	**0.006***	0.090	0.141
Native thiol (µmol/L)	-0.511	**<0.001***	-	
Total thiol (µmol/L)	-0.445	**<0.001***	-0.309	**<0.001**
Disulphide (µmol/L)	0.310	**<0.001***	-	
Disulphide/Native thiol	0.532	**<0.001***	0.348	**<0.001**
Disulphide/Total thiol	0.539	**<0.001***	-	
Native thiol/Total thiol	-0.460	**<0.001***	-	

SBP: Systolic blood pressure, DBP: Diastolic blood pressure.
*Variables with a p-value of <0.05 were included in the multivariable regression analysis.

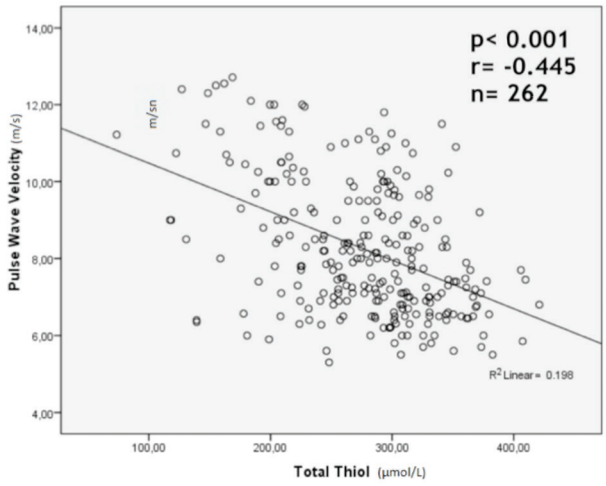

Figure 1. Regression analysis between Pulse wave Velocity (m/s) and Total Thiol (µmol/L).

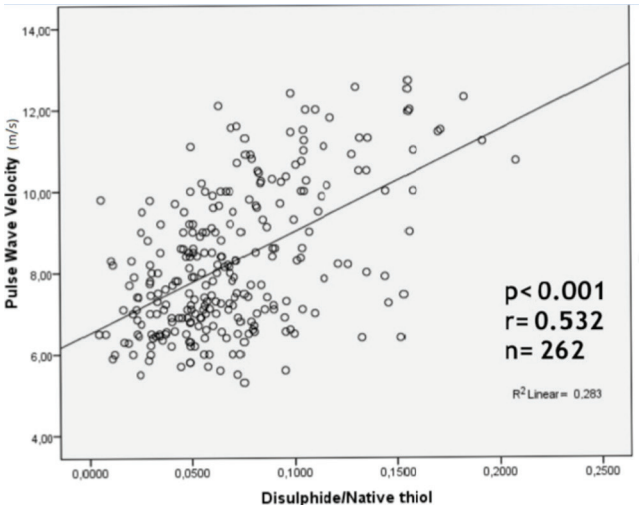

Figure 2. Regression analysis between Pulse Wave Velocity (m/s) and Disulphide/Native Thiol.

DISCUSSION

In the present study, we demonstrated a significant correlation between arterial stiffness assessed by PWV and oxidative stress parameters such as thiol/disulfide redox couple in patients with normal coronary arteries. Our results show that impairment in PWV is associated with an increase in disulfide levels and a decrease in thiol levels which reflects impaired oxidative and anti-oxidation pathways.

Tissue damage and corrupted oxidation mechanisms lead to endothelial dysfunction, apoptosis, and atherosclerosis[14]. Various oxidative-modified agents have been investigated to show oxidative stress and coronary atherosclerosis[15]. Thiol/disulfide redox couple is one of them, and a rapidly growing research area. A decrease in (-SH)/(-S-S-) has been shown to be a predictor of apoptosis, which may lead to accelerated atherosclerosis via macrophages[16-18]. Thiols are organosulfur compounds containing sulfhydryl components. Noxious reactive oxygen species can influence sulfhydryl components along with thiol groups. Thiols can react with one or two electron oxidants, yielding sulfenic acids. Sulfenic acids are bruise products that tend to link with another thiol and formed to oxidized disulfide. This leads to oxidation of thiol molecules and disulfide products are formed. This pathway is reversible, and oxidation can be reversed[1,11]. Loss of equilibrium in reactive oxygen species and abnormal thiol/disulfide ratio is associated with deterioration in intracellular signaling and regulation, and protein function. This in turn leads to accelerated cell death and promotes to atherosclerosis[5,19].

In several experimental laboratory studies, It has been shown that the alterations of the (-S-S)/(-SH) ratio may occur in conjunction with age, diabetes mellitus as well as atherosclerosis, and reported oxidation via chemical agents may lead to increase in apoptosis and vascular aging[16,17]. Oxidative stress, thiol oxidation, and elevated disulfide levels have been shown as critical factors in progress for various diseases such as type 1 diabetes mellitus, cancer, and hypertension[20-22]. All of the aforementioned studies concluded that the thiol/disulfide redox couple may be a fundamental protective guard against oxidative stress and disease progression. Another common finding of these studies was decreased thiol, thiol/disulfide ratio and increased disulfide levels occurred as a result of oxidative damage. A recent study demonstrated an association between the thiol/disulfide ratio and syntax score in patients who had a myocardial infarction[5]. They reported a positive correlation between increased disulfide molecules and coronary artery disease severity. Similarly, decreased median thiol/disulfide ratio was an independent predictor for myocardial infarction in multivariate analysis. In another study, authors examined acute patients with acute myocardial infarction and healthy populations according to their demographical and clinical characteristics. Alongside expected results (troponin, high-density lipoprotein cholesterol), native thiol (-SH), total thiol (-S-S- + -SH), disulfide/native thiol ratio (-S-S-)/(-SH), disulfide/total thiol ratio (-S-S-)/(-S-S- + -SH) levels were significantly different between the groups[23]. Their results support previous reports, and the effect of shifted thiol/disulfide balance on acute cardiovascular events.

PWV is a diagnostic marker of arterial stiffness, and it has been used to stratify risk for subclinical organ damage[10]. Basic mechanisms of arterial stiffness and increased PWV are the ultimate results of inappropriate architectural components of arterial vessels. The process of arterial stiffness, characterized

by increased intraluminal pressure, reduced elastin quality, increased collagen accumulation, vascular muscle thickening, and excessive fibrogenesis, can be triggered by factors such as advancing age, hypertension, and external stimuli. These factors contribute to the unfavorable manifestations of arterial stiffness. These changes occur as PWV increases[24,25]. Recently, PWV has been shown to be a decisive parameter as an independent predictor of future cardiovascular events in patients with acute myocardial infarction[9]. Blacher et al. concluded that PWV is more specific as an independent predictor of cardiovascular events compared to conventional cardiovascular risk factors[26]. In another study, patients with no prior cardiovascular events or symptoms were studied for six years via measuring PWV; the authors reported that patients who did have a cardiovascular event in this period had higher PWV compared to the event-free group[27]. Pulse wave velocity has a positive correlation with oxidative stress markers in patients without cardiovascular disorders[28]. Since increased PWV may be observed even in patients without cardiovascular events, dissemination of arterial stiffness should be evaluated in high-risk populations[25]. Patel et al. observed positive correlations between oxidized thiols and arterial stiffness markers in healthy subjects. Oxidized thiols such as cystine had an independent correlation with PWV in univariate and multivariate models[29]. Despite these findings, Sharmen et al. reported applying a thiol component called alpha-lipoic acid in healthy subjects, neither oral nor intravenous forms, did not influence PWV and oxidative stress parameters[30].

In our study, PWV values had a positive correlation with disulfide, disulfide/native thiol ratio, and disulfide/total thiol ratio. Pulse wave velocities had a negative correlation with native thiol and native thiol/total thiol ratio. Besides a known prognostic indicator in acute coronary heart syndromes, oxidative thiol, and increased disulfide may show oxidative stress and elevated inflammation in patients without coronary artery disease. Based on our findings, we recommend conducting further investigations in populations with a high suspicion of coronary artery disease before disease progression occurs. If necessary, primary treatment should be initiated based on these investigations.

The absence of a follow-up period is one of the limitations of our study. Another limitation is the relatively small sample size of our population. Moreover, although the patients had similar dietary and exercise habits, there was a lack of precise follow-up regarding these parameters. Lastly, it should be noted that the diagnosis of a normal coronary angiogram may be subjective since intravascular ultrasound (IVUS) was not utilized in the evaluation of patients.

CONCLUSION

Increased oxidative stress via the disulfide/native thiol (-S-S-)/(-SH) pathway may be an indicator for predicting future atherosclerotic cardiovascular events. To enhance our understanding of the mechanisms underlying vascular aging, it is crucial to conduct additional studies that assess changes in oxidative stress, thiol-disulfide accumulation, and their impact on arterial stiffness.

Ethics Committee Approval: The approval for this study was obtained from Adana Numune Training and Research Hospital Non-invasive Clinical Research Ethics Committee (Decision no: 79, Date: 24.12.2014).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - SA; Analysis/Interpretation - MG, HÇ; Data Collection - SA, HH, ÖE; Writing - SA, HH; Critical Revision - HH, MG; Final Approval - All of authors; Statistical Analysis -MG; Overall Responsibility - SA.

Conflict of Interest: The authors have no conflicts of interest to declare.

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