THIOL-DISULFIDE HOMEOSTASIS AS A MARKER OF OXIDATIVE STRESS IN SOCCER PLAYERS WAS NOT AFFECTED BY HEART RATE VARIABILITY

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ABSTRACT

Objective

The study aims to examine the relationship between thiol-disulfide balance and autonomic nervous system activity in soccer players.

Methods

This study was conducted with 15 male soccer players between the ages of 19-32. ECG measurements were taken from the athletes at rest in the morning after waking up and heart rate variability (HRV) data were analyzed as an indicator of autonomic nervous system activity. Thiol disulfide homeostasis status was determined using a novel automated spectrophotometric analysis method before and after the match. The obtained findings were analyzed by using Pearson correlation and paired t-test.

Results

After the match, an increase was observed in the thiol disulfide (TD) parameters. But there was no statistically significant difference in the TD parameters before and after the match (P>0.05). It was observed that the correlation between age and TD parameters disappeared after the exercise. No overall relationship was observed between HRV parameters and thiol-disulfide parameters (except for MINRR and AVRR parameters). A strong correlation was observed within the time and frequency-dependent HRV parameters

Conclusion

The current study examines the relationship between thiol-disulfide balance and HRV as a marker of oxidative stress for the first time. In addition, it was observed that mild-moderate exercise does not affect oxidative stress in trained athletes and works independently from the autonomic nervous system. It is considered that SDNN and RMSSD can be used as an important marker in the analysis of the parasympathetic system.

Keywords

Thiol-disulfide homeostasis, HRV, Oxidative stress, Football

INTRODUCTION

Thiols are organic compounds containing a sulfhydryl (-SH) group that can react with free radicals to prevent the formation of tissue and cell damage caused by reactive oxygen species (ROS) (Wessendorf and Lu, 2020). Thiol is not only an antioxidant compound; it is a type of organic sulfur species that is characterized by the formation of -SH wastes when it is active. Although thiol is distributed in aerobic life forms, it has many different functions along with its critical role in antioxidant defense (Sen and Packer, 2000). When ROS is produced in an uncontrolled manner, biomolecules such as nucleic acids, proteins and lipids cause oxides and genetic information to change, protein structure to deteriorate, enzyme activity to be blocked and cellular membranes to be damaged. This situation is defined as oxidative stress (Hambrook et al. 2020). Thiol disulfide balance is disturbed under oxidative stress. Dynamic thiol-disulfide homeostasis has a critical role in antioxidation protection, detoxification, signal transduction, regulation of apoptotic enzymatic activity and cellular signaling mechanisms (Bektas, 2020). Oxidative stress occurs as a result of an imbalance between ROS and antioxidant molecules (Ates et al. 2015). As the ROS level increases, the sulfur atom with cysteine oxides the side chain with the redox reaction and disulfide is formed (Cremers and Jacop, 2013). The first level of oxidative damage occurs at the cellular level. Thiol disulfide homeostasis is important for the physiological process to continue in the organism which include apoptosis and stabilization of protein chemical structures (Schafer and Buettner, 2001).

The differences between the functioning of the cardiovascular system and the working tempo of the heart between people who exercise regularly and are sedentary are known. Changes occur in the working functions of the heart in the resting state and exercise state (Kayacan and Yildiz, 2016). Heart rate variability (HRV) is a non-invasive method that evaluates the sympathetic and parasympathetic activity of the heart. The decrease in HRV indicates a decrease in parasympathetic activity and an increase in sympathetic activity (Malik, 1996; Gorman and Sloan, 1996). Although the relationship between ROS and HRV has been examined in different hypotheses in the literature (Chuang et al. 2013; Laumbach et al. 2014), no study was found in relation to exercise or physical activity. In this context, the purpose of this study is to examine the relationship between thiol-disulfide balance, an oxidative stress marker, and HRV, an important indicator of autonomic nervous system activity, in soccer which has an intense training form.

METHODS

15 male soccer players between the ages of 19-32 who continue their active sports life in soccer participated in the study. Physical characteristics of athletes (age, height, weight, BMI) are presented in Table 1. Prior to the study, an approval was obtained from the Clinical Research Ethics Committee with the decision number 2017/453. The training match was implemented within the normal soccer game rules for 90 minutes. Maximum and minimum heart rate (HR) values of the athletes were determined. In the calculation of training load, the Karvonen aerobic zone was determined ((220-age) - resting heart rate) x 0.8) + resting heart rate = maximum heart rate in the aerobic zone). As preparation before starting the training match, the athletes did a 10-minute warm-up run and continued to warm up for another 5-minute with a game without a target in a 10x10 meter area, and lastly, practiced passes in groups of three which was followed by opening and stretching movements.

Biochemical analyses

While the athletes were at rest before training, 5 cc of blood was taken from the venous vein of the forearm by expert nurses in the sports facilities. After the training, 5 cc of blood was taken in the same way. After the samples were taken into yellow capped gel tubes, they were transferred to the

biochemistry laboratory in accordance with the cold chain. The tubes were gently inverted 5-6 times to ensure that the samples in the tubes were in good contact with the silica particles. Then, they were left for 30 minutes and centrifuged (refrigerated, 4000 rpm for 10 minutes). The obtained sera were stored at -800C in capped Eppendorf (Isolab centrifuge tubes 2.0 ml, flat cap-without skirt) tubes until the analysis day.

24 hours before the analysis, the samples were transferred to the Samsun Medical Faculty Biochemistry Laboratory in the cold chain (dry ice system). The received samples were re-centrifuged and total thiol and native thiol test parameters were analyzed using Rel Assay Diagnostics brand kits. During the analysis, a fully automated Beckman Coulter brand AU 680 (Beckman Coulter, chemistry analyzer AU 680, serial number: 2016024580, Mishima K.K, made in Japan) autoanalyzer was used. DTNB (5,5'-dithiobis-2-nitrobenzoic acid) was calculated by using the disulfide level (serum total thiol - serum native thiol) / 2 formula. Blood thiol-disulfide homeostasis was analyzed with the automatic measurement method developed by Erel and Neselioglu (Erel and Neseliooglu, 2014). Total thiol (-SH + -S-S-) and native thiol (-SH) mixtures were measured by Ellmann's method and arranged according to the Ellmann scale. Native thiol content was deducted from the total thiol content. Half of the difference provided the proportion of dynamic disulfide (-S-S-) bonds. Additionally, (–S – S–) × 100 / (- SH), (–S – S–) × 100 / (–SH + –S – S–), and –SH × 100 / (–SH + - S – S–) ratios were calculated using these parameters.

HRV analysis

Subjects came to the laboratory after being asked to avoid strenuous activity on the day before testing and to delay their daily exercise until after the test session. Subjects were laid on the mat in the laboratory and electrocardiogram (ECG) electrodes were placed. The subjects were instructed to close their eyes in the supine position for 10 minutes, relax and breathe at their own pace. Subjects controlled their respiratory frequency during data readings because the HRV component is affected by the breathing pattern.

All measurements were carried out by using TLC 5000 four channels ECG (China). Standard extremity derivations were used, and ECG parameters were set at 50 mm/sec and 10 mm/mV. ECGs were recorded for 5 min in sportswomen at resting (12:00-2:00 PM). A sampling rate of 1000 Hz was chosen and recordings were transferred to a PC via a USB interface. The epochs gained from the V5 lead were saved in a computer for further analysis. All R-R intervals were edited by visual inspection to exclude all the undesirable or ectopic beats. They were deleted with the post extra systolic beat and replaced automatically with interpolated adjacent R-R interval values.

Measured time and frequency-dependent parameters were as follows: heart rate (HR bpm), average normal-to-normal R-R intervals (AVNN/ms), the standard deviation of all R–R intervals (SDNN/ms), square root of the mean squared differences between normal adjacent R–R intervals (rMSSD/ms), percentage of consecutive R–R intervals that deviate from one another by more than 50 ms (pNN50 %).

The following frequency-domain metrics were obtained: total spectral power (TP, ≤ 0.4 Hz), very low (VLF, < 0.04 Hz), low (LF, 0.04–0.15 Hz), high frequency (HF, 0.15–0.4 Hz), and the ratio of LF to HF (LF/HF %). The experimental design is shown schematically in Figure 1.

Statistics

The literature study on the subject was examined, and the test power (Pass 2008) was calculated as 12 people when the significance level of 0.90 was taken as 0.05 as a result of the analysis. It was organized from 15 people to increase testing power and reduce possible errors. SPSS (IBM USA ver.20) software was used for statistical analysis in the study.

Normally distributed data were analyzed with paired t test and Pearson correlation. Alpha value was accepted as <0.05.

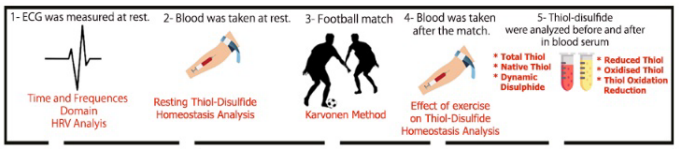

Fig 1. The procedures performed in the study (HRV measurement, blood sampling and biochemical analysis).

RESULTS

Descriptive statistical findings of the athletes are presented in Table 1. After the match, an increase was observed in the NT, TT, DDS and OT parameters (Table 2). However, there was no statistically significant difference in the Thiol Disulfide (TD) parameters before and after the match (P> 0.05; Table 2, Fig. 1). It was observed that the correlation between age and TD parameters disappeared after the exercise. No overall relationship was observed between HRV parameters and thiol-disulfide parameters (except for MINRR and AVRR parameters; Table 3). A strong correlation was observed within the time and frequency-dependent HRV parameters (Table 4, P <0.05, P <0.01).

Table 1. Descriptive statistical findings of physical properties and HRV parameters

Parameters	Min	Max	Mean	SEM
Age/Years	19	32	24	3,664
Height/cm	170	187	177,266	4,682
Weight/kg	66	93	76,266	7,777
MAXRR (ms)	1065	2000	1387,666	284,867
MINRR (ms)	460	1120	817	164,813
AVRR (ms)	947,7	1351,5	1090,173	137,159
SDNN (ms)	32,4	134	75,766	26,223
RMSSD (ms)	35,4	162,4	82,686	34,45
PNN50 (%)	10,7	61,1	40,753	14,522
ULF (Hz)	3,5	488,3	137	148,619
VLF (Hz)	37,1	1610,1	766,02	492,761
LF (Hz)	40,1	4404,7	997,793	1049,094
HF (Hz)	56	3900,2	748,786	959,74

Descriptive statistical findings of age, height, weight and HRV parameters (time and frequency dependent) of the soccers are given in Table 1.

Table 2. The statistical findings of pre (1)-post (2)-match TD parameters

Parameters	Mean Difference	Std. Dev.	SEM	P
NT	-4,266	41,948	10,83	0,7
TT	-16,466	166,815	43,071	0,708
DDS	-24,4	252,808	65,274	0,714
RT	,133	,743	,191	0,499
OT	-,133	1,457	,376	0,728
TOR	,066	,883	,228	0,774

NT: Native thiol, TT: Total thiol, DDS: Dynamic disulfide RD: Reduced thiol, OT: Oxide thiol, TOR: Thiol oxide ratio

Parameters indicating thiol-disulfide balance are compared according to the findings before and after training match in Table 2. No statistically significant difference was found in the findings (p> 0.05).

Table 3. Correlation findings between thiol-disulfide parameters of athletes and age, height, body weight and HRV

Parameters		Age	Height	Weight	MAXRR	MINRR	AVRR	SDNN	RMSSD	PNN50	ULF	VLF	LF	HF
NT1 (µmol/L)	r	-0,410	0,402	-0,422	0,019	0,002	0,176	0,143	-0,036	0,151	-0,032	-0,020	0,022	-0,109
	P	0,129	0,137	0,117	0,946	0,994	0,531	0,610	0,899	0,592	0,910	0,944	0,938	0,699
TT1 (µmol/L)	r	-,516	0,413	-0,350	-0,076	-0,092	0,099	0,110	-0,060	0,158	-0,046	-0,051	0,005	-0,132
	P	**0,049**	0,127	0,201	0,789	0,745	0,725	0,698	0,831	0,574	0,871	0,856	0,987	0,638
DDS1 (%)	r	-,539	0,410	-0,326	-0,100	-0,116	0,077	0,099	-0,066	0,158	-0,049	-0,059	0,000	-0,137
	P	**0,038**	0,129	0,235	0,723	0,681	0,784	0,725	0,815	0,574	0,862	0,834	1,000	0,626
RT1 (%)	r	,551	-0,290	-0,051	0,303	0,408	0,221	-0,028	0,007	-0,297	-0,027	0,105	0,085	0,139
	P	**0,033**	0,294	0,857	0,272	0,132	0,429	0,922	0,981	0,283	0,923	0,710	0,764	0,621
OT1 (%)	r	-,542	0,211	0,015	-0,306	-0,380	-0,174	-0,035	-0,107	0,056	-0,026	-0,076	-0,051	-0,122
	P	**0,037**	0,450	0,959	0,268	0,162	0,535	0,902	0,704	0,842	0,926	0,787	0,857	0,664
TOR1 (%)	r	,566	-0,256	0,070	0,398	0,189	0,082	0,141	0,156	0,018	0,267	0,209	0,050	0,142
	P	**0,028**	0,356	0,804	0,141	0,501	0,772	0,616	0,579	0,949	0,336	0,455	0,858	0,614
NT2	r	0,062	-0,074	-0,480	0,181	,587	,608	-0,021	-0,113	-0,193	-0,061	0,041	-0,008	-0,089
	P	0,825	0,792	0,070	0,520	**0,022**	**0,016**	0,942	0,689	0,492	0,830	0,885	0,977	0,754
TT2	r	-0,055	-0,018	-0,477	0,180	,535	,572	0,023	-0,126	-0,214	0,012	0,101	0,037	-0,076
	P	0,846	0,950	0,072	0,521	**0,040**	**0,026**	0,935	0,656	0,444	0,966	0,721	0,897	0,787
DDS2	r	-0,096	0,003	-0,471	0,178	0,511	,553	0,038	-0,129	-0,219	0,038	0,121	0,052	-0,071
	P	0,733	0,992	0,076	0,527	0,051	**0,032**	0,892	0,648	0,433	0,894	0,668	0,853	0,802
RT2	r	,555	-0,352	-0,081	-0,133	0,194	0,155	-0,278	-0,074	-0,006	-0,274	-0,256	-0,275	-0,147
	P	**0,032**	0,198	0,773	0,636	0,489	0,581	0,316	0,793	0,982	0,323	0,358	0,322	0,601
OT2	r	-,555	0,243	-0,102	-0,087	-0,255	-0,203	0,152	-0,134	-0,149	0,359	0,267	0,162	0,001
	P	**0,032**	0,382	0,717	0,758	0,359	0,467	0,589	0,633	0,596	0,189	0,337	0,565	0,998
TOR2	r	0,488	-0,224	-0,077	0,205	0,221	0,237	0,032	0,292	0,239	-0,203	-0,065	-0,042	0,163
	P	0,065	0,422	0,784	0,464	0,429	0,395	0,910	0,291	0,391	0,469	0,817	0,882	0,562

It was observed that the correlations between age and thiol-disulfide parameters at rest decreased after the match in Table 3. It was observed that oxidative stress parameters did not have a significant relationship with time and frequency-dependent HRV findings. At the end of the match, it was observed that min r-r and AVRR parameters had a positive correlation with oxidation parameters.

Table 4. The results of the correlation of HRV parameters within their

Parameters		MAXRR	MINRR	AVRR	SDNN	RMSSD	PNN50	ULF	VLF	LF	HF
MINRR	r	,033	1								
	P	,908									
AVRR	r	,297	,577*	1							
	P	,283	**,024**								
SDNN	r	,727**	-,332	,192	1						
	P	**,002**	,226	,493							
RMSSD	r	,710**	-,354	,071	,855**	1					
	P	**,003**	,196	,802	**,000**						
PNN50	r	,214	-,355	,050	,529*	,723**	1				
	P	,443	,194	,859	**,042**	**,002**					
ULF	r	,109	-,350	-,015	,423	,112	,097	1			
	P	,699	,201	,957	,116	,691	,732				
VLF	r	,549*	-,245	,261	,868**	,574*	,270	,739**	1		
	P	**,034**	,378	,347	**,000**	**,025**	,330	**,002**			
LF	r	,735**	-,125	,055	,827**	,747**	,218	,047	,626*	1	
	P	**,002**	,658	,847	**,000**	**,001**	,434	,867	**,013**		
HF	r	,751**	-,321	-,114	,818**	,869**	,349	,122	,604*	,916**	1
	P	**,001**	,244	,687	**,000**	**,000**	**,203**	,665	**,017**	**,000**	

The correlations within the heart rate variability time and frequency-dependent parameters are shown in Table 4. It was determined that time and frequency-dependent HRV parameters have correlations within themselves. In addition, it was observed that the parameters of MAXRR, SDNN, RMSSD, VLF, LF, HF are the parameters that best describe the variability of heart rate.

DISCUSSION

In the current study, the relationship between thiol-disulfide balance and autonomic nervous system activity in soccer was evaluated together for the first time using a new method. The findings obtained are discussed under separate headings.

Thiol disulfide balance was not affected by the exercise protocol

In the present study, it was determined that the mild/moderate exercise protocol increased the level of disulfide, which is an oxidative stress marker, but did not significantly affect it.

Although there are many studies on oxidative stress parameters in the context of exercise intensity/time, discussions on this subject continue (Yazar et al. 2019). Oxidative stress reflects the imbalance between the production of reactive oxygen species and the detoxification of reactive intermediates or the restoration of damage with an appropriate antioxidant defense (Pingitore, 2015). As a general principle, exercise can be very beneficial for health; however, it can also create dangerous compounds. The effect of exercise on redox balance is extremely complex depending on age, gender, exercise level, exercise intensity, and duration (Yazar et al. 2019).

There are different findings in the literature on exercise in terms of increasing or decreasing oxidative stress (OS). In some studies, exercise did not have a significant effect on the OS level. For example, Schneider et al. (2005) stated in their study that they did not find a significant difference in lipid peroxidation and total antioxidant capacity in both trained and untrained subjects before and after a moderate exercise (Schneider et al. 2005). Aldred and Rohalu (2011) found that a moderate exercise program did not increase oxidative stress in older adults (Aldred and Rohalu, 2011). Similar findings were obtained in our study. In the determination of these findings, the intensity of exercise is considered to be the main reason because Ravi Kiran et al. (2004) found that the intensity of exercise had a significant effect on OS parameters in rats which were exposed to 20 and 40 minutes of swimming exercise daily for 4 weeks at mild, moderate and high intensity (Ravi et al. 2004). Similarly, Düzova et al. (2007) studied the effects of medium and high-level treadmill running exercise on muscle and erythrocyte oxidant/antioxidant system in rats. Rats were divided into three groups as control, moderate-intensity exercise (30 min) and high-intensity exercise (60 min) (19). The treadmill runs were implemented by changing the incline of the treadmill for 30 minutes and 60 minutes a day for 13 weeks. As a result, it was found that moderate exercise was more effective on antioxidant activity, however; high level of training regulated the balance between oxidant/antioxidant systems better in animals. In the literature, it has been found that high-intensity exercise increases oxidative stress both acutely and chronically (Kayacan et al. 2022; Pal, 2018; Beck, 2018). In the current study, a mild/moderate training protocol was applied. The disulfide value, which is an important indicator of oxidation, was not found to be significant in this context, which is compatible with the findings in the presented study and the literature. Researchers reported that people who exercise regularly adapt to the physical activity program and are more resistant to oxidative damage (Huertas, 2017; Kayacan et al. 2018). Therefore, regular exercise increases chronic resistance to OS. This situation is thought to be effective in the findings determined in the current study.

No correlation was detected between HRV and Thiol disulfide parameters

In this study, it was determined that there are many correlations between age and pre-training TD parameter. However, no relationship was found between TD and HRV parameters. In fact, animal experiments indicate that reactive oxygen species (ROS) and HRV are associated with

other cardiovascular diseases in the pathogenesis of cardiovascular diseases. Oxidative stress is a condition in which the levels of reactive oxygen species in the body increase or in other words, are caused by an oxidant-antioxidant imbalance (Kayacan et al. 2022). It has been reported to play a role in the pathogenesis of many cardiovascular diseases including hypertension (Pavithran et al. 2008). ROS also plays a role in increasing central and peripheral sympathetic activity by decreasing nitric oxide production (Campese et al. 2004). There is no study examining the relationship between the oxidant/antioxidant capacity and HRV in athlete groups in the literature. Studies in this context are observed to examine the relationships between ROS levels resulting from air pollution and HRV (Chuang et al. 2013; Laumbach et al. 2014; Chahine et al. 2007). However, studies provide more evidence of decreased HRV presence and changes in oxidant-antioxidant status in newly diagnosed hypertensives (Nandeesha et al 2007; Sathiyapriya et al. 2007). Oxidative stress parameters are known to cause changes in the structure of the heart by activating myocardial growth, reshaping the matrix, and also damage the vascular endothelium (Takimoto and Kass, 2007). Low HRV has been associated with arrhythmias and the risk of arrhythmic death (Pavithran et al. 2008). Thus, the combination of a low HRV and a high oxidative stress reveals the relationship between these two mechanisms. It is thought that the exercise protocol and the athlete profile may have an effect on the findings obtained in the presented study as studies show that athletes are different from sedentary people in terms of OS and that people who exercise regularly adapt to the physical activity program over time and are more resistant to oxidative damage (Huertas, 2017; Kayacan et al. 2017). In other words, regular exercise increases chronic resistance to OS. Niess et al. (1996) had participants run to exhaustion to investigate the effects of progressive intensity of treadmill exercise on oxidative stress and DNA damage in athletes and sedentary men (Niess, 1996). As a result, they found that training adaptation can reduce the effects of DNA damage and free radicals. Similarly, it has been shown that professional runners' resting HR is generally less than 50 beats ‘min-1’, and that lower resting HR occurs after exposure to aerobic training in sedentary individuals (Boutcher and Stein, 1995). Thus, HRV works differently in sedentary and athletes.

SDNN and RMSSD were the parameters that best described heart rate variability

When the correlations among HRV findings were examined, it was observed that the correlations of SDNN and RMSSD parameters with both time and frequency-dependent parameters were high. When the literature is examined, it was found that these parameters have correlations with different HRV measurement techniques (Windham et al. 2012; DeGiorgio et al. 2010). HRV measurements can be measured by linear or non-linear methods. However, regardless of the method used for measurement, the obtained findings must have a correlation within themselves because heart rate variability is the traditional method of analyzing the overall magnitude of the average R-R interval fluctuations at some predetermined frequencies by time and frequency domain methods (Huikuri et al. 2003). Therefore, the data obtained are calculated according to the R-R interval reference range. However, some HRV parameters can have strong correlations with other parameters. According to the data we obtained, SDNN and RMSSD had a higher correlation with time and frequency-dependent parameters which overlaps with the findings in the literature.

In this study, the relationship between thiol-disulfide balance, which is a new oxidative stress marker, and heart rate variability, which is accepted as an indicator of the autonomic nervous system, was analyzed for the first time. Not keeping the exercise protocol completely under control constitutes an important limitation of the study. It would be beneficial to analyze oxidative stress and the autonomic

nervous system together in studies to be carried out in different athlete populations and exercise protocols.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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