Resting Heart Rate is Not Associated With Oxidative Stress in Healthy Adults

Sağlıklı Erişkinlerde İstirahat Kalp Hızı Oksidatif Stresle İlişkili Değildir

Sadettin Selçuk Baysal

Şanlıurfa Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Şanlıurfa, Türkiye

ABSTRACT

Introduction: Although the resting heart rate (RHR) and oxidative stress are risk factors for cardiovascular morbidity and mortality, the association between them has not been fully understood. We aimed to investigate the relationship between RHR and oxidative/antioxidative stress markers.

Materials and Method: Study consisted of 56 healthy volunteers (33 males; mean age: 44.1 ± 9.0 years). Subjects divided into two groups according to heart rate quartiles: lower two quartiles as group 1 (n = 29,) and upper two quartiles as group 2 (n = 27). We measured total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI) and ceruloplasmin (CP) levels of subjects.

Results: There was not any significant difference in baseline clinical characteristics and laboratuvary measurements between groups ($p > 0.05$ for all variables). Mean RHRs were 71.3 ± 4.6 in group 1 and 82.4 ± 4.1 in group 2. The TAC, TOS, OSI and CP levels were similar between the two groups ($p > 0.05$ for all variables). We did not detect any significant association between RHR and the oxidative/antioxidative parameters.

Conclusion: RHR was not associated with TOS, TAC, OSI and CP levels in our study.

Keywords: Resting heart rate;oxidative stress;total oxidant status;total antioxidant status;oxidative stress index;

ÖZET

Giriş: Her ne kadar istirahat kalp hızı (İKH) ve oksidatif stress, kardiyovasküler morbidite ve mortalite için risk faktörleri olsa da bunlar arasındaki ilişki tam olarak anlaşılamamıştır. Bu çalışmamızda, İKH ile oksidatif/antioksidatif stres belirteçleri arasındaki ilişkiyi araştırmayı amaçladık.

Hastalar ve Metod: Çalışma 56 sağlıklı gönüllüden (33 erkek; ortalama yaş: 44,1 ± 9,0 yıl) oluşmaktaydı. Gönüllüler kalp hızı çeyrekliklerine göre 2 gruba bölündüler: alt iki çeyreklik grup 1 (n=29) ve üst iki çeyreklik grup 2 (n=27) . Hastaların total oksidan kapasitesi (TOK), total antioksidan kapasitesi (TAK), oksidatif stres indeksi (OSİ) ve serum seruloplasmin düzeylerini ölçük.

Bulgular: Bazal klinik karakteristikler ve laboratuvar ölçümleri açısında iki grup arasında önemli bir fark yoktu (p>0.05 tüm değişkenler için). Ortalama İKH grup 1 de 71,3 ± 4,6 iken grup 2 de 82,4 ± 4,1 idi. TOK, TAK, OSİ ve seruloplazmin düzeyleri her iki grupta benzerdi (p>0,05 tüm değişkenler için). İKH ve oksidatif/antioksidatif stres parametreleri arasında anlamlı bir ilişki saptayamadık.

Sonuç: Çalışmamızda İKH, TOK, TAK, OSİ ve seruloplazmin düzeyleri ile ilişkili bulunmadı.

Anahtar Kelimeler: İstirahat kalp hızı; Oksidatif stress; Total oksidan kapasitesi; Total antioksidan kapasitesi; Oksidatif stres indeksi

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1. INTRODUCTION

Resting heart rate (RHR) is associated with cardiovascular morbidity and mortality, independently of other risk factors, for example age, smoking, hypertension, and diabetes in some clinical studies [1-5]. In human and animal studies it was reported that increased heart rate is associated with atherosclerosis[6-8]. An abnormality of autonomic nervous system such as sympathetic over activity is thought to be the underlying mechanism of this[9, 10]. Experimental and clinical studies suggested the favorable effect of heart rate reduction in progression of atherosclerosis[7, 11, 12].

Oxidative stress is known as dysfunction in balance between reactive oxygen species (ROS) production and antioxidant activity. It was associated with the pathogenesis of many diseases such as coronary artery disease[13-15]. It was demonstrated that lowering heart rate reduces the formation of ROS in rats[16]. But there are limited studies which investigated the relation between heart rate and oxidative stress.

In this study we aimed to investigate the relationship between RHR and oxidative/antioxidative stress markers.

2. MATERIALS AND METHODS

2.1 Study design and setting

Fifty six healthy individuals whose age were between 18 and 65 years were enrolled randomly. All subjects underwent a detailed medical evaluation including clinical history, physical examination, routine laboratory panel, electrocardiography (ECG), and echocardiography. 24 hour Holter performed with Promedic HECG-12 Holter management system including Ambulatory ECG Systems software running under Microsoft Windows. All patients were instructed not to exercise, smoke and drink alcohol or coffee during holter recording. Recordings were analyzed by two blinded cardiologists. RHR was determined by the mean of the three lowest heart rates obtained from day time (09:00 - 22:00 h) recordings. Nighttime heart rate was excluded due to concerns regarding the influence of diurnal variation[17]. Subjects were divided into groups according to quartiles of resting heart rate as per most previous heart rate studies. Group 1 consisted of subjects with lower two quartiles heart rate between 60 - 79 beats/ minute and group 2 consisted of subjects with upper two quartiles heart rate between

80 - 94 beats/ minute. The exclusion criteria were as follows: coronary artery disease (CAD), significant valvular heart disease, heart failure (left ventricular ejection fraction < 40%), inflammatory diseases (acute or chronic), smoking, use of any medical drugs which have an impact on heart rate and hepatic, thyroid and renal disorders. Harran University ethics committee approved our study and all of the study population signed the written informed consent.

Complete hematological count, glucose level, lipid profile, liver enzyme level, and creatinine concentration were analyzed in peripheral venous blood samples taken after 12 hours of fasting. All biochemical parameters were determined using the Abbott Diagnostics C8000i auto-analyzer (Abbott, Wiesbaden, Germany). Samples were obtained by centrifugation at 3,000 rpm for 15 minutes and stored at - 80 ºC for analysis of oxidative stress biomarkers, total oxidant status (TOS), total antioxidant capacity (TAC), oxidative stress index (OSI) and ceruloplasmin (CP).

2.2 Measurement of plasma total oxidant status and total antioxidant capacity

The serum TAC and TOS levels were determined with a novel automatic method, developed by Erel[18, 19]. TAC was calculated by measuring the antioxidative power of the sample against the hydroxyl radical initiated reactions. Oxidants, present in the sample oxidize ferrous ion-dianisidine complex to ferric ion which is colored with xylenol orange in the acidic medium to be measured by spectrophotometer to calculate TOS. TAC is expressed as 1 mmol Trolox Equivalent/L where 1 µmol H_2O_2 Equivalent/L is used to state TOS.

2.3 Oxidative stress index

The ratio of TAC to TOS is defined as OSI, expressed as percentage. For the calculation, TAC units were changed to mmol/L, and the OSI value calculated according to the following formula: OSI (arbitrary unit) = TOS (mmol H2O2 equiv./L)/TAC (mmol Trolox equiv /L).

2.4 Ceruloplasmin

The enzyme activity of CP was determined according to Erel's method[19]. Using this assay, ferrous ion is oxidized to ferric ion via CP ferroxidase activity. CP levels are expressed as units per gram protein (U/L).

2.5 Statistical Analysis

All statistical analyses were performed by using SPSS for Windows software (ver. 22.0; SPSS Inc., Chicago, IL, USA). The Shapiro-Wilks test was used to evaluate normality of distributions of continuous variables. The independent samples t-test was used to compare normally distributed continuous variables and, for non-normally distributed continuous variables, the Mann-Whitney U Test was used. Descriptive statistics, and mean and standard deviation values were used for the normally distributed variables. Median and minimum-maximum values were used for non-normally distributed variables. Pearson's correlation coefficients were used for normally distributed variables. A p-value < 0.05 was considered to indicate statistical significance in all analyses.

3. RESULTS

There were 29 patients (17 men, 12 women) in group 1 and 27 subjects in group 2 (16 men, 11 women). The clinical features and laboratory parameters of the study population are presented in Table 1. These groups were similar with respect to age, gender, body mass index (BMI), lipid panel, creatinine, fasting glucose, high sensitive C-reactive protein (hsCRP) and hemoglobin levels. Mean RHRs were 71.3 ±4 .6 in group 1 and 82.4 ± 4.1 in group 2. RHR was normally distributed (Figure 1). Oxidative and antioxidative stress marker levels were shown in Figure 2. We did not find any significant difference in TOS, TAC, OSI and sCP level between groups (p = 0.77; p = 0.69; p = 0.77 and p = 0.54 respectively). When we performed correlation analysis, we did not see any significant correlation between resting heart rate and the oxidative/antioxidative stress biomarkers (Table 2).

4. DISCUSSION

In our study we didn't find any significant relationship between RHR and oxidative/antioxidative stress parameters. Also RHR was not significantly related with age, gender and BMI.

There is strong evidence proving that an increase in RHR leads to an increased risk of cardiovascular morbidity and mortality especially in patients with hypertension, metabolic syndrome and in geriatric population[1, 3, 4, 20, 21]. It was also reported that increased heart rate is associated with atherosclerosis independently of other risk factors[6, 9]. An increased heart rate accumulates the power and frequency of the tensile stress on the arterial wall and prolong the exposure of coronary endothelium to the

systolic low and oscillatory shear stress. These make changes in structure and function of endothelial cells which promotes atherosclerosis[6, 22, 23].

Elevated heart rate could affect the cardiovascular system in different mechanisms. It may increase myocardial oxygen demand and decrease coronary blood flow by reducing diastolic filling time. It may also reflect autonomic nervous system abnormalities such as increased sympathetic tone which could lead to cardiovascular morbidity and mortality in ischemic conditions[6, 8, 10].

Oxidative stress is caused by increased production and insufficient elimination of ROS. Although the underlying exact mechanism has not been fully discovered, oxidative stress is thought to have a significant function in the pathogenesis of many disorders such as cardiovascular diseases, hypertension, Parkinson's disease and Alzhiemer's disease[13-15].

There are limited studies investigated the association between RHR and oxidative stress. In an animal study it was demonstrated that heart rate reduction decreased vascular oxidative stress, improved endothelial function and inhibited the atherosclerotic plaque formation. Underlying mechanism of this finding is that reduced heart rate decreased the superoxide release and lipid peroxidation[16]. But opposing with the previous study in our study we did not found any association between oxidative/antioxidative stress markers and RHR. This could be explained by relatively small sample size of our study.

The main conclusion of this study is that RHR was not significantly associated with oxidative/antioxidative stress parameters (TOS, TAC, OSI and CP).

Limitations

Cross-sectional design, relatively small sample and lack of evaluating heart rate variability are the main limitations of our study. Another limitation of the study is that patients are not questioned for psychiatric disorders, exersice status, dietary and social background variables such as economic and education status which could affect the RHR.

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Author contributions

SSB substantially contributed to the conception and design of the study. SSB substantially contributed to acquisition of data. SSB substantially contributed to the analysis and interpretation of data. SSB drafted the manuscript. SSB critically revised the final manuscript. All authors approved the final version of the manuscript.

Conflict of interest

Authors declare no conflict of interest.

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FIGURES

Figure 1 Histogram of the resting heart rate distribution of the study population.

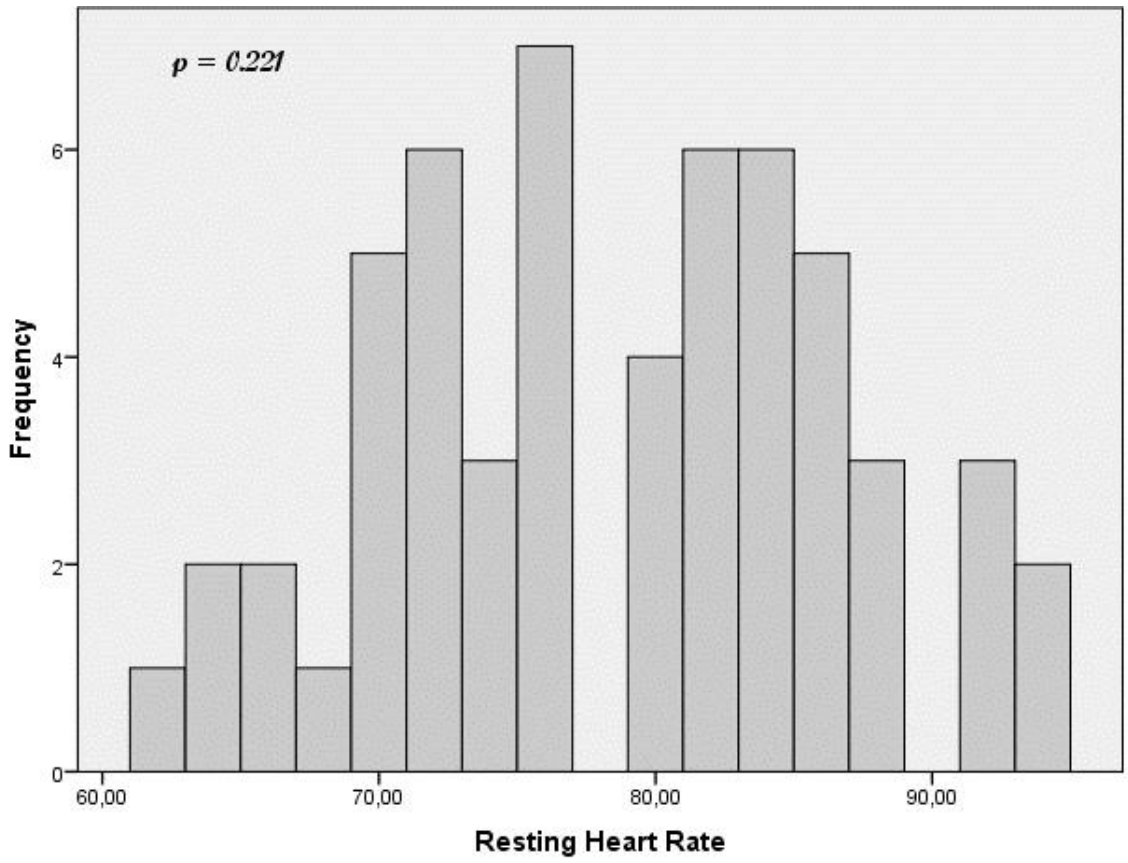

Figure 2 Oxidative/antioxidative (A: total oxidant status, B: total antioxidant status, C: oxidative stress index, D: ceruloplasmin)concentration of study population grouped by heart rate quartiles.

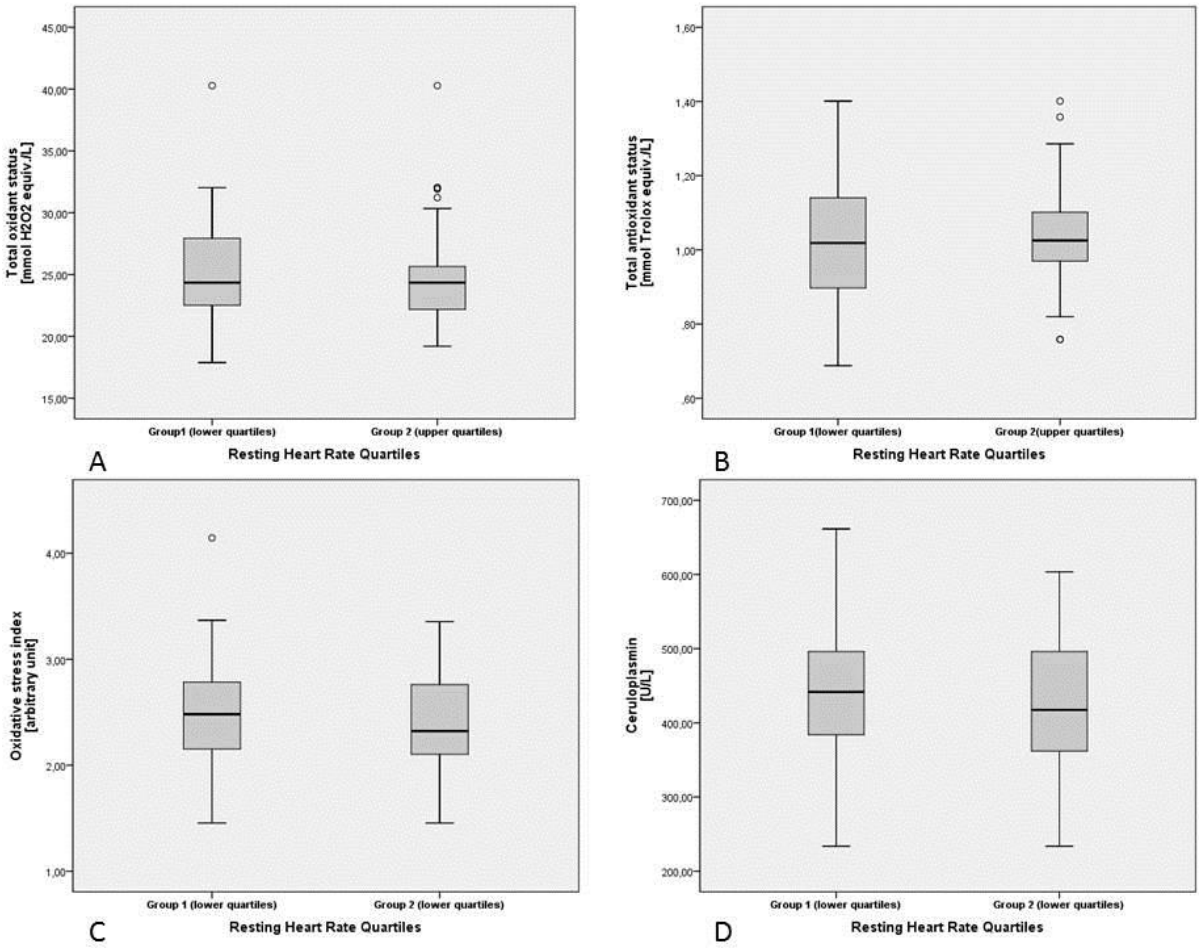

Table 1: Baseline clinical and laboratory features of the study population.

	Group 1 (n = 29)	**Group 2 (n = 27)**	**P value**
Resting heart rate (beats/min)	71.3 ± 4.6	82.4 ± 4.1	< 0.001
Age, years	44.4 ± 9.4	43 ± 8.7	0.11
Female, n (%)	12 (41)	11 (40)	0.71
BMI, kg/m²	26.3 ± 2.0	25.6 ± 1.4	0.12
Total cholesterol, mg/dl	196 (165-252)	190 (92-290)	0.42
LDL, mg/dl	100 (76-139)	104 (69-156)	0.77
HDL, mg/dl	39.2 ± 5.7	39.2 ± 8.4	0.99
Triglyceride,mg/dl	156 (58-351)	169 (96-480)	0.72
Fasting glucose, mg/dl	88 (72-100)	91 (75-103)	0.27
Creatinine, mg/dl	0.78 (0.70-0.95)	0.80 (0.65-1.0)	0.30
Hemoglobin, g/dl	15.2 (13.6-17)	15.1 (13.6-17)	0.70
hscrp, mg/dl	0.48 ± 0.24	0.43 ± 0.20	0.40

BMI: body mass index, HDL: high-density lipoprotein, hscrp: high sensitive C-reactive protein, LDL: low-density lipoprotein.

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Table 2: Correlation between resting heart rate and other variables.

	Coefficient*	**p**
Age	- 0.153	0.26
BMI	-0.213	0.11
Total oxidant status	- 0.030	0.82
Total antioxidant status	0.068	0.61
Oxidative stress index	- 0.108	0.42
Ceruloplasmin	- 0.078	0.56
hsCRP	- 0.254	0.46

* From Pearson's correlation analysis.

hsCRP: high sensitive C-reactive protein