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# Evaluation of the Relationship Between Resting Heart Rate and Endocan, Thrombomodulin Levels in Healthy Adults

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## Abstract

**Objectives:** Resting heart rate (RHR) is a physiological parameter that has been reported to be associated with endothelial dysfunction. Endocan and thrombomodulin are mediators released from endothelium, which are determined to increase in blood with endothelial damage. We aimed to investigate the relationship between RHR and these biomarkers.

**Materials and Methods:** Sixty-eight healthy volunteers (28 females; mean age: 44.2±6.3 years) were included in the study. Subjects divided into two groups according to heart rate quartiles: lower two quartiles as group 1 (n=35,) and upper two quartiles as group 2 (n=33). Endocan and thrombomodulin levels in blood of the individuals were measured.

**Results:** Clinical features and laboratory findings were similar in both groups (p>0.05 for all variables). Mean RHRs were 70.9±4.9 in group 1 and 84.8±4.3 in group 2. No statistically significant difference was found in endocan and thrombomodulin levels in both groups (p>0.05 for all variables). No significant correlation was detected between RHR and these molecules.

**Conclusion:** RHR was not associated with endothelium derived biomarkers endocan and thrombomodulin.

**Keywords:** Resting heart rate, endothelial dysfunction, biomarker, endocan, thrombomodulin

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## Introduction

Resting heart rate (RHR) is an indicator of the autonomic nervous system balance and its increase shows that this balance is impaired in favor of sympathetic system. In epidemiological studies, increased heart rate was found to be associated with poor prognosis in cardiovascular diseases (CVD), especially in coronary artery disease (CAD), independent of other known cardiovascular risk factors[1-3]. Although the underlying mechanism is not fully understood, it has been reported in experimental and clinical studies that the increase in RHR accused of endothelial dysfunction with increased sympathetic activity and mechanical stress on the vessel wall which led to atherosclerosis[4-7].

A healthy endothelium is essential in the regulation of vascular tone, platelet adhesion, inflammation, fibrinolysis and vascular proliferation. In doing so, the endothelium secretes a variety of mediators, primarily nitric oxide. Thrombomodulin (sTM) and endocan are two of these released from the endothelium and shown to be associated with endothelial dysfunction[8-11].

Based on the studies showing the relationship between RHR and endothelial dysfunction[6,7], in healthy adults we aimed to investigate the relationship between RHR and endocan, sTM which is thought to play a role in endothelial dysfunction.

## Materials and Methods

A total of 68 healthy volunteers whose age were between 18 and 65 years were consecutively enrolled in the study. All individuals were included in the study after a detailed medical evaluation including clinical history, physical examination, routine laboratory panel, electrocardiography (ECG) and echocardiography. Hypertension, diabetes mellitus, 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 were the exclusion criteria. Twenty-four hours of Holter monitoring with Promedic HECG-12 Holter management system including Ambulatory ECG Systems software running under Microsoft Windows was applied to all cases. All patients were advised to avoid activities that could increase heart rate, such as smoking and drinking coffee during the holter recording. RHR was calculated by the mean of the three lowest heart rates obtained from day time (09:00 a.m.-10:00 p.m.) recordings by two blinded cardiologists. Nighttime heart rate was excluded due to concerns regarding the influence of diurnal variation[12]. Subjects were grouped according to quartiles of RHR as per most previous heart rate studies[13]. Subjects with lower two quartiles heart rate between 60-78 beat/min were included in group 1 and subjects with upper two quartiles heart rate between 79-96 beat/min were included in group 2. Informed consent was obtained from all participants and the study was approved by Harran University Ethics Committee with project number 74059997.0510.01.04/107.

All biochemical and hematologic values were on the day of sample collection following a fasting period of 12 hours. The Abbott Diagnostics C8000i auto-analyzer (Abbott, Wiesbaden, Germany) was used to determine all biochemical panels. Blood samples were collected into plain tubes and serum was separated after centrifugation at 1,500 g for 10 minutes and stored at -80°C for analysis of sTM and endocan. Both serum endocan and sTM levels were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) kit with high sensitivity and specificity for detecting human endocan (Cusabio Bioscience Inc, Wuhan, China). The minimum detectable concentrations of endocan and TM were 0.039 ng/mL and 7.8 pg/mL, respectively. The intra-and inter-assay coefficients of variation were less than 8% and 10%, respectively, for both biomarkers[8,9].

## Statistical Analysis

SPSS for Windows software (ver. 22.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses. A Shapiro-Wilks test was applied to assess the normality of the distributions of continuous variables. For comparison, the independent samples t-test or Mann-Whitney U test

were used where appropriate. The results were presented mean ± standard deviation or median (minimum-maximum). Pearson's correlation analysis was performed for normally distributed variables. P value <0.05 was considered to indicate statistical significance.

## Results

Demographic, clinical and laboratory data of the study sample were given in Table 1. A total of 68 individuals with mean age 44.2±6.3 years were enrolled in this study. Group 1 consisted of 35 patients (21 men) with mean age 44.9±7.1 years and group 2 consisted of 33 subjects (19 men) with mean age 43.3±7.7. With respect to age, gender, body mass index (BMI), lipid panel, creatinine, fasting glucose, high-sensitive C-reactive protein (hsCRP) and hemoglobin levels there were not any significant difference between groups. Normally distributed RHR values of the study population are shown in Figure 1. Mean RHR values were 70.9±4.9 in group 1 and 84.8±4.3 in group 2.

**Table 1.** Baseline demographic, clinical and laboratory characteristics of the study population

| | Group 1 (n=35) | Group 2 (n=33) | P value |
|---|---|---|---|
| RHR (beats/min) | 70.9±4.9 | 84.8±4.3 | < 0.001 |
| Age, years | 44.9±7.1 | 43.3±7.7 | 0.24 |
| SBP (mmHg) | 121±7 | 122±6 | 0.67 |
| DBP (mmHg) | 78±5 | 79±4 | 0.76 |
| Female, n (%) | 14 (40) | 14 (42) | 0.79 |
| BMI, kg/m² | 25.9±2.8 | 25.3±1.7 | 0.56 |
| Total cholesterol, mg/dL | 185(133-270) | 190 (84-256) | 0.52 |
| LDL, mg/dL | 104±29 | 109±21 | 0.66 |
| HDL, mg/dL | 35.4±6.2 | 34.7±7.3 | 0.75 |
| Triglyceride,mg/dL | 195 (85-317) | 181 (75-303) | 0.69 |
| Fasting glucose, mg/dL | 87 (72-105) | 89 (79-103) | 0.84 |
| Creatinine, mg/dL | 0.77±0.12 | 0.80±0.17 | 0.35 |
| Hemoglobin, g/dL | 15.5 (13.1-16.8) | 15.2 (13.4-17) | 0.74 |
| hsCRP, mg/dL | 0.46±0.21 | 0.44±0.23 | 0.56 |

*RHR: Resting heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure BMI: Body mass index, HDL: High-density lipoprotein, hsCRP: high sensitive C-reactive protein, LDL: Low-density lipoprotein, n: Number of the patients*
*Values are expressed as mean ± standard deviation*

There was not any significant difference in endocan and sTM concentration between groups as shown in Figure 2 (p=0.23 and p=0.81 respectively). In correlation analysis, no significant association was found between RHR and endocan, sTM (Table 2).

## Discussion

RHR is a simple non-invasive physiological parameter of autonomic dysfunction which was reported to be a strong predictor of adverse cardiovascular events and all-cause mortality both in healthy individuals and population with CVD in epidemiologic studies[1-3,14]. In some studies, although heart rate was suggested to be associated with CVD independent of other known risk factors, others claimed that this relationship was dependent to confounding risk factors[3,15,16]. Moreover, RHR has been found to be associated with sudden cardiac death and cardiovascular risk factors such as diabetes, hypertension, dyslipidemia and obesity[17-19].

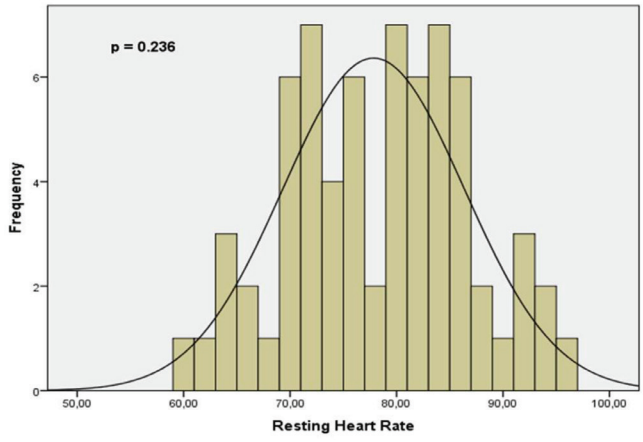


**Figure 1.** Histogram of the resting heart rate distribution of the study population

**Table 2.** Correlation between resting heart rate and other parameters

| | Coefficient* | p |
|---|---|---|
| Age | -0.245 | 0.33 |
| BMI | 0.354 | 0.24 |
| Thrombomodulin | 0.261 | 0.19 |
| Endocan | 0.378 | 0.21 |
| hsCRP | -0.215 | 0.42 |

*BMI: Body mass index, hsCRP: High sensitive C-reactive protein*
**From Pearson's correlation analysis*

Previous studies have presented strong evidence proving the association between increased RHR and many stages of atherosclerosis, such as endothelial dysfunction, CAD severity, and even plaque rupture[5,6]. An increase in RHR increases the frequency and strength of the mechanical load applied to the arterial wall. Relatively shortening of the duration of diastole as a result of the increase in heart rate causes increase in the time spent in systole which prolong the exposure of arterial endothelium to the systolic low and oscillatory shear stress. Furthermore, increase in frequency of periodically change in arterial geometry due to high heart rate promotes the power of tensile and shear stress on the vascular wall. All these changes induce structural changes in vascular endothelium which promotes vascular stiffening and then atherosclerosis[5].

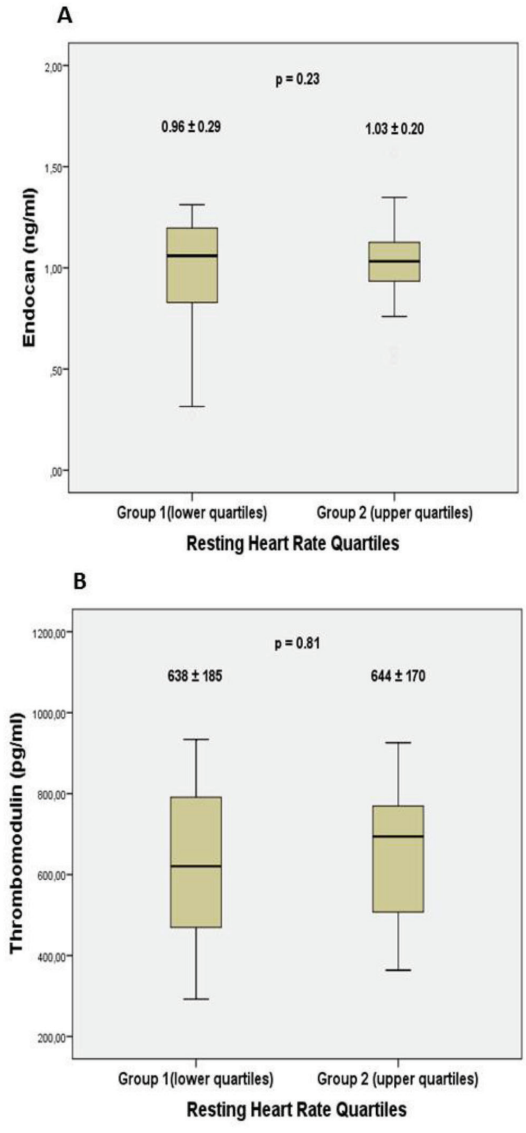


**Figure 2.** (A) Endocan, (B) thrombomodulin levels of the study population grouped by heart rate quartiles

In a study conducted in a multiethnic population with 6484 participants, RHR was associated with increased arterial stiffness, which is an indicator of endothelial dysfunction[20]. Moreover, both in animal studies and in human studies, the beneficial effects of decreased heart rate on endothelial function have been demonstrated[4,6,7]. Endocan and TM are two molecules released from endothelium that have been shown to be associated with endothelial dysfunction in previous studies[8-11]. In our study, we tried to evaluate the relationship between RHR and endothelial function by investigating whether there is a relationship between these endothelium derived molecule levels and RHR in healthy participants. Our study groups were homogeneous according to their demographic, clinical and laboratory characteristics. In our work, we did not detect any difference in both sTM and endocan levels in patients grouped due to their heart rates (Figure 2). Unlike previous studies mentioned, we did not find any relationship between RHR and these biomarkers which are thought to have role in endothelial dysfunction. We also did not detect any relationship between RHR and age, gender and BMI. Although previous studies have shown a positive correlation between the hsCRP concentration[13,21]. which is an indicator of inflammation, and RHR, we did not find any relationship in our study.

Observational design and relatively small sample may be the reasons of our study's inability to detect significant correlations. Single time measurement of biomarkers could not clearly reflect the long-term state of subjects. We did not also measure nitric oxide level, which is considered to be the primary biomarker in demonstrating endothelial functions. Lack of evaluating heart rate variability, psychiatric disorders and social background

variables such as economic and education status are the other limitations of our study.

Our study results presented that RHR was not associated neither with endothelium derived biomarkers sTM and endocan nor with age, gender and BMI. Further large prospective studies with large sample size are required to its clinical utility.

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### Ethics

**Ethics Committee Approval:** This study was approved by Harran University Ethics Committee with project number 74059997.0510.01.04/107.

**Informed Consent:** Informed consent was obtained from all participants.

**Peer-review:** Externally peer-reviewed.

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