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Heart Rate Turbulence Analysis in Healthy Postmenopausal Women

Sağlıklı Postmenopozal Kadınlarda Kalp Hızı Türbülansı Analizi

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ABSTRACT Objective: The aim of the present study was to investigate heart rate turbulence (HRT) parameters in postmenopausal women. **Material and Methods:** A total of 40 postmenopausal women and 43 healthy, regularly menstruating premenopausal women were taken as study and control groups, respectively. All patients had biochemical blood examination, 2-D echocardiography and 24-hour Holter monitorization. HRT parameters, namely turbulence onset (TO) and turbulence slope (TS) were calculated. **Results:** Age, body mass index (BMI), systolic and diastolic pressure, total cholesterol and LDL levels were higher in the postmenopausal group, whereas HDL levels were higher in the premenopausal group ($p<0.05$). TO was significantly higher, TS was significantly lower in postmenopausal women compared to premenopausal women (-2.76±1.34 vs 0.60±1.30 and 3.60±1.54 vs 1.60±1.48, $p=0.000$ for both, respectively). TO was positively correlated, TS negatively correlated with age, BMI, systolic and diastolic blood pressure and LDL cholesterol level. According to multivariate analysis only menopausal status and age had an independent effect on HRT parameters. Receiver operating characteristic analysis showed that the cut-off values of TO and TS for predicting menopausal status were 0.959 and 0.165, respectively (0.835 anti-image). These results showed that TO and TS had diagnostic value for predicting menopausal status. **Conclusion:** Postmenopausal women had blunted HRT response. It is a simple and easily obtainable test and should be implemented in cardiac evaluation in daily practice.

Keywords: Postmenopause; women; heart rate

ÖZET Amaç: Bu çalışma, sağlıklı postmenopozal kadınlarda kalp hızı türbülansı (KHT) analizini incelemek için yapıldı. **Gereç ve Yöntemler:** Çalışmaya, 40 sağlıklı postmenopozal kadın ve 43 düzenli adet gören premenopozal kadın alınmıştır. Tüm bireylere biyokimyasal kan testleri, 2 boyutlu ekokardiyografi ve 24 saatlik Holter monitörizasyonu yapıldı. KHT parametreleri olan türbülans başlangıcı (TB) ve türbülans eğimi (TE) hesaplandı. **Bulgular:** Postmenopozal grupta yaş, beden kitle indeksi (BKİ), sistolik ve diyastolik kan basıncı, total ve LDL kolesterol seviyeleri daha yüksek iken, HDL seviyesi daha düşük bulundu ($p<0,05$). Premenopozal kadınlar ile karşılaştırıldığında, postmenopozal kadınların TB değeri belirgin olarak yüksek, TE değeri ise belirgin olarak düşük idi (sırasıyla -2,76±1,34; 0,60±1,30 ve 3,60±1,54; 1,60±1,48, her ikisi için $p=0,000$). Yaş, BKİ, sistolik ve diyastolik kan basıncı, LDL düzeyi TB ile pozitif, TE ile negatif korelasyon gösterdi. Multivaryant analizine göre sadece menopoz durumu ve yaş, KHT parametreleri üzerinde bağımsız bir etki gösterdi. Alıcı işlem karakteristikleri analizine göre TB ve TE'nin menopozal durumu prediktif değeri sırasıyla 0,959 ve 0,165 idi (0,835 anti-imaj). Bu bulgular TB ve TE'nin menopoz durumunu öngörmede tanısal değeri olduğunu göstermiştir. **Sonuç:** Postmenopozal kadınlarda, KHT cevabı bozulmuştur. Bu test klinikte oldukça kolay olarak uygulanılabilen basit bir testtir ve postmenopozal kadınların kardiyak değerlendirilmesinde düşünülmelidir.

Anahtar Kelimeler: Postmenapoz; kadınlar; kalp hızı

Menopause, part of the normal aging process, is characterized by cessation of ovarian activity. A focus of intense research, the postmenopausal period has been linked to cardiovascular disease and osteoporosis.[1,2] Numerous clinical studies have shown autonomic nervous system activity alterations during this period. As high estrogen levels favorably affect cardiac autonomic activity, estrogen deficiency in postmenopause may generate deleterious cardiac effects, including reduced heart rate variability (HRV) and baroreflex sensitivity (BRS).[3-5] Such changes may be caused by elevated cardiac sympathetic activity in combination with reduced vagal influence.[6]

In 1999, heart rate turbulence (HRT) was proposed as a new method for evaluating autonomic activity.[7] The HRT calculation is based on autonomic responses after a ventricular premature complex (VPC). Typically after a VPC, a brief acceleration in

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HR is followed by a gradual deceleration. These two phases are quantified by two parameters: turbulence onset (TO) and turbulence slope (TS). Following a VPC, the systolic blood pressure (BP) drops, leading to a decrease in afferent baroreceptor input that triggers a reflexive vagal activity decline. This relative increase in sympathetic activity causes a rise in HR and BP, which in turn activates the baroreflex arc, dropping the HR. HRT has been proven to have prognostic value in postmyocardial infarction and heart failure patients independent of other risk factors.[8]

Although several studies have shown altered autonomic function as measured by HRV in postmenopausal women, there are no studies investigating the association between menopause and HRT. The aim of the present study was to assess autonomic function in postmenopausal women by measuring HRT parameters.

MATERIAL AND METHODS

The study included 83 consecutive patients (women aged 21-78 years) who presented to our cardiology clinic for checkup visits between November 2019 and February 2020. Diagnosis of menopause was made clinically, which was described as 12 months of amenorrhea. 40 postmenopausal women were taken as study group and 43 regularly menstruating, healthy women were taken as control group. Participants with irregular menstruation (for control group), ischemic heart disease, valvular disease other than mild, hypertension, diabetes mellitus, hyper-hypothyroidism, kidney and/or hepatic disease, current use of any medication conduction-rhythm abnormalities, <5 VPC/24 hr were excluded from the study. The study was approved by Kafkas University Faculty of Medicine Local Ethics Committee (number: 80576354-050-99/226, date 30.10.2019) and each patient gave informed consent before study enrolment.

The body mass index (BMI) of each patient was calculated from self-reported height and weight using following formula: weight (cm)/height^2 (m). Right arm BP was taken after a five-minute rest. Venous blood samples were collected from the antecubital vein after an overnight fast. Two-dimensional echocardiographic examination was performed according to the guidelines of the American Society of Echocardiography.[9] All patients underwent 24-hour ambulatory electrocardiography (ECG) monitoring (Cardio Track Holter Analysis System). In order to evaluate HRT accurately, at least 5 VPCs were needed over long periods. The following formula was used to calculate TO: TO=[Relative risk (RR)1+RR2]-(RR-2+RR-1)/(RR-2+RR-1)x100 where the RR-2, RR-1 and RR1, RR2 are the periods immediately before and after VPC, respectively. TO was expressed as percentage. TS was the steepest slope among all slopes assessed for 5 sinusal beats of the rising portion of the HRT. For each VPC, TO and TS were calculated separately and the mean of the all values was used. Although there is no clear-cut value for HRT, values of TO and TS are expected to be negative and positive, respectively. Calculation of TO and TS following VPC is shown in Figure 1.

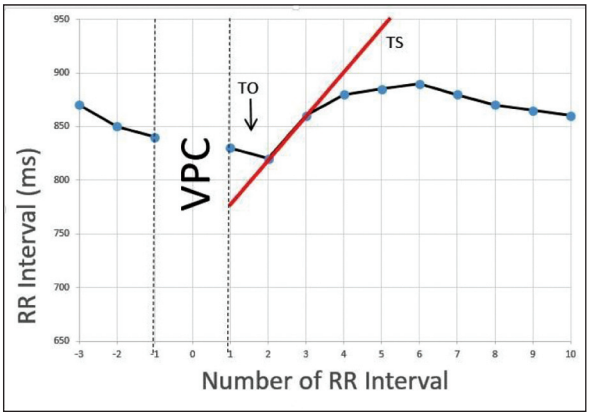

FIGURE 1: Calculation of TO and TS.
TO: Turbulence onset; TS: Turbulence slope;
VPC: Ventricular premature complex; RR: Relative risk.

STATISTICAL ANALYSIS

Based on Kretzschmar et al., required sample size for premenopausal was found to be 14 (Effect size= 0.9406593, tcritical= 1.7709334), and postmenopausal found to be 9 patients (Effect size: 1.2380952; tcritical=1.8595480) at 95% sample size power and 0.05 alpha error.[10] Kolmogorov-Smirnov test was used for normality distribution analysis of research parameters. Means and standard deviations were used for description of normally distributed parameters, minimum-maximum and median were used to describe non-normally distributed parameters. In-

TABLE 1: Clinical characteristics of the participants.

	Premenopausal (n=43)	Postmenopausal (n=40)	p value
Age (years)	34.67±6.50	59.35±6.80	<0.001
BMI (kg/m^2)	23.55±3.24	25.49±3.27	0.008
Smoking (n, %)	7 (16.27)	6 (15)	0.442
SBP (mmHg) (minimum-maximum) median	(90-140) 120	(95-141) 130	<0.001
DBP (mmHg) (minimum-maximum) median	(60-86) 75	(62-91) 84	0.007
EF	67.14±2.82	66.23±2.48	0.451
TC (mg/dL) (minimum-maximum) median	(124-274) 173.27	(146-274) 189.65	<0.001
LDL (mg/dL) (minimum-maximum) median	(71-197) 117.38	(99-197) 138.32	<0.001
HDL (mg/dL) (minimum-maximum) median	(26-72) 44.48	(28-55) 38.2	<0.001
TG (mg/dL) (minimum-maximum) median	(92-410) 141.04	(113-425) 160.1	<0.001
Mean HR (beats/minute)	71.25±21.19	77.29±19.87	0.001
VPB (Nr/24 h)	245.58±158.54	584.96±195.74	<0.001
PR interval (msec)	148.54±14.15	150.57±16.14	0.345
QTc (msec)	406±22	417±27	0.067
TO	-2.76±1.34	0.60±1.30	<0.001
TS	3.60±1.54	1.60±1.48	<0.001

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; EF: Ejection fraction; TC: Total cholesterol; LDL: Low-density lipoproteins; HDL: High-density lipoprotein; TG: Triglyceride; HR: Heart rate; VPB: Ventricular premature beat; TO: Turbulence onset; TS: Turbulence slope.

dependent samples t-test was used for normally distributed parameters, Mann-Whitney U test was used for non-normally distributed parameters. Spearman's rho correlation analysis was used for relationship analysis. Receiver operating characteristic (ROC) analysis was used for diagnostic value of TO and TS. SPSS 17.0 for windows was used for analysis at 95% confidence interval.

RESULTS

Age, BMI, systolic and diastolic BP, total cholesterol, and LDL levels were higher in the postmenopausal group, whereas HDL levels were higher in the premenopausal group ($p<0.05$). We did not find any differences with respect to PR and QTc intervals between two groups. Mean HR and number of ventricular premature beats were higher in postmenopausal women. In postmenopausal women compared with premenopausal women, TO was significantly higher (-2.76±1.34 vs 0.60±1.30, p=0.000) and TS was significantly lower (3.60±1.54 vs 1.60±1.48, p=0.000). Clinical, biochemical and HRT characteristics of the groups are given in Table 1. TO values of postmenopausal group showed greater variability than premenopausal women ($p<0.000$) (Figure 2).

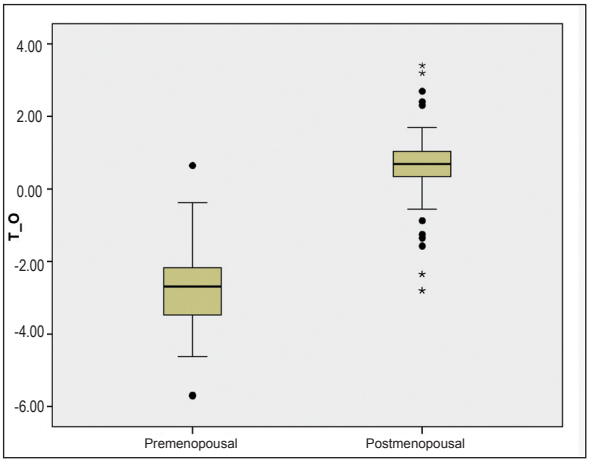

FIGURE 2: TO values of the study groups.
TO: Turbulence onset.

According to Spearman's rank coefficient of correlation analysis, TO positively correlated with age, BMI, systolic and diastolic BP, and LDL level; on the other hand, TS negatively correlated with age, BMI, systolic and diastolic BP, and LDL level (Table 2).

Univariate and multivariate analyses were performed to identify the parameters which had an effect on TO and TS. In this analysis, menopausal status (pre-post-) was used as dummy variable. Although all parameters in the equation had significant contribution on

TABLE 2: Spearman's rho correlation analysis results for TO and TS with baseline parameters.

	TO	TS
Age	0.699*	-0.581*
BMI	0.459*	-0.347*
Systolic BP	0.536*	-0.383*
Diastolic BP	0.367*	-0.338*
LDL	0.589*	-0.476*

*p<0.01; TO: Turbulence onset; TS: Turbulence slope; LDL: Low-density lipoproteins; BMI: Body mass index; BP: Blood pressure.

TO in univariate analysis (p<0.01), only menopausal status had significant contribution on TO in multivariate analysis (p<0.05). Similar with TO, all parameters had significant contribution on TS in univariate analysis (p<0.05). However, only age had a significant contribution to TS in multivariate analysis (p<0.01). Univariate and multivariate analyses of the groups are shown in Table 3.

ROC analysis was performed in order to identify cutoff values of TO and TS for predicting menopausal status. The areas under the curve for TO and TS were 0.959 and 0.165, respectively (0.835 anti-image), which showed that TO and TS have predictive value in determining menopausal status (Figure 3).

DISCUSSION

Our study showed that postmenopausal women had a blunted HRT response compared with premenopausal women, which supports the hypothesis that menopause associates with impaired BRS. We found significant associations of TO and TS with age, BMI, systolic and diastolic BP, and LDL level. Multivariate analysis showed that only menopause and age have an independent effect on HRT parameters.

Compared with premenopausal subjects, postmenopausal subjects had significantly higher BMI, systolic and diastolic BP, total cholesterol, LDL, and triglyceride levels; however, the postmenopausal group had lower HDL levels. Considerable evidence indicates that menopause leads to lipid profile deterioration and that menopausal women have increased cardiovascular disease risk.[11,12] Although both of our study groups had normal systolic and diastolic BP, premenopausal women had lower BP than postmenopausal women, suggesting that sex hormone deficiency may contribute to the pathogenesis of hypertension.[13]

The hormonal changes accompanying menopause have significant effects on cardiac autonomic function. Low estrogen levels decrease tonic vagal modulation of the heart in the presence of normal sympathetic activity, leading to a relative increase in sympathetic tonus. The presence of autonomic dysfunction in postmenopausal women has been previously demonstrated using HRV analysis. HRV, which reflects beat-to-beat HR variation, is mainly driven by vagal activity. Loss of vagal activity exposes the heart to unopposed sympathetic activity, resulting in decreased HRV.[3,14]

HRV and HRT are noninvasive tools that provide useful information about autonomic cardiac control. HRV reflects the oscillations in autonomic nervous system activity over time, whereas HRT measures the physiological response of the sinus node to a transient stimulus, probably related to the baroreflex

TABLE 3: Univariate and multivariate analysis results for TO and TS values.

	TO		TS	
	Univariate	Multivariate	Univariate	Multivariate
Age	0.304**	0.058	-0.159**	0.159*
BMI	0.111**	0.004	-0.074**	-0.029
Systolic	0.079**	-0.006	-0.050**	0.002
Diastolic	0.112**	0.004	-0.077**	0.002
LDL	0.055**	0.014	-0.036**	-0.007
Menopausal status (dummy)	3.361**	1.824*	-1.995**	0.989

*p<0.05; **p<0.01; TO: Turbulence onset; TS: Turbulence slope; BMI: Body mass index; LDL: Low-density lipoproteins.

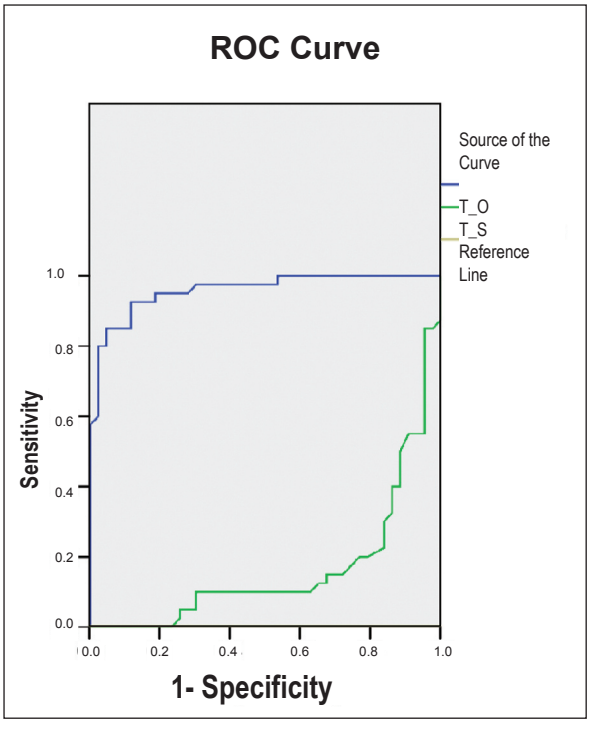

FIGURE 3: ROC analysis for diagnostic value for TO and TS. ROC: Receiver operating characteristic; TO: Turbulence onset; TS: Turbulence slope.

arc.[15] HRT correlates with BRS and HRV time domain parameters and has prognostic value for certain diseases, as it becomes abnormal in ischemic heart disease, congestive heart failure, polycystic ovary syndrome, and metabolic syndrome.[16-20] HRT, HRV, and BRS are complementary methods, though their values may not move in the same direction in the same disease. Ortak et al. demonstrated that postmyocardial infarction patients had altered HRV indices but no change in HRT parameters.[21] Previous studies reported abnormal autonomic activity in postmenopausal women using HRV parameters; we aimed to investigate such activity using HRT parameters.

Our results showed that age, BMI, systolic and diastolic BP, and LDL level significantly correlated with a blunted HRT response. Postmenopausal women are older, and age-related decline in cardiac vagal influence and baroreflexes have been reported.[22] Our study demonstrated that age independently predicted abnormal HRT in healthy postmenopausal women, a finding consistent with some research that associated increased age with impaired BRS.[23] Similarly, high BP and obesity have been correlated with blunted HRT parameters.[24,25] Although studies other than ours have not correlated plasma lipid levels with HRT parameters, an association between decreased HRV and hyperlipidemia, which may be partially reversible with statin treatment, has been documented.[26,27] Research is needed to elucidate the relationship between increased serum lipid levels and HRT parameters.

We found that menopausal status independently predicted an impaired HRT response. To the best of our knowledge, ours is the first study to establish this relationship. Specifically, menopause independently affected TO but not TS. The pathophysiology behind this association is not clear, but our outcome suggests that menopause primarily decreases baroreceptor stimulation.

The hormonal and metabolic changes in postmenopausal women accelerate atherosclerosis, increasing the risk of cardiovascular mortality and morbidity.[28] Atherosclerosis-related ischemic heart disease may cause cardiovascular death associated with arrhythmia. A noninvasive method for analyzing cardiac autonomic activity, HRT may help predict the risk of cardiovascular death associated with arrhythmia.[17] HRV and HRT measure different aspects of autonomic system activity and may be used together for diagnosis and prognosis in postmenopausal women.

CONCLUSION

A simple and easily obtainable test, HRT should be implemented in cardiac evaluation in daily practice. The HRT response may be blunted in healthy postmenopausal women, reflecting a diminished baroreflex response. Studies are needed to clarify the relationship between HRT and other parameters.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cennet Yıldız;* ***Design:*** *Cennet Yıldız, Ahmet Karakurt;* ***Control/Supervision:*** *Cennet Yıldız, Ahmet Karakurt;* ***Data Collection and/or Processing:*** *Cennet Yıldız, Ahmet Karakurt;* ***Analysis and/or Interpretation:*** *Cennet Yıldız, Ahmet Karakurt;* ***Literature Review:*** *Cennet Yıldız;* ***Writing the Article:*** *Cennet Yıldız;* ***Critical Review:*** *Cennet Yıldız, Ahmet Karakurt;* ***References and Fundings:*** *Cennet Yıldız;* ***Materials:*** *Cennet Yıldız, Ahmet Karakurt.*

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