ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Predictors of Paroxysmal Atrial Fibrillation: Heart Rate Variability and Heart Rate Turbulence

Paroksismal Atriyal Fibrilasyonun Öngördürücüleri: Kalp Hızı Değişkenliği ve Kalp Hızı Türbülansı

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ABSTRACT

Aim: *Autonomic dysfunction is one of the major contributors to atrial fibrillation (AF) development and recurrence. Predicting AF using autonomic dysfunction parameters such as heart rate variability (HRV) and heart rate turbulence (HRT) in patients with risk factors may influence our daily practice. Thus we compare HRV and HRT measurements derived from 24 hours Holter ECG between paroxysmal AF (PAF) patients and healthy subjects.*

Material and Method: *A total number of 116 patients were included in this case-control study. All patients underwent a 24-h Holter ECG monitoring. HRV (VLF, LF, HF, SDNN, SDANN, ASDNN, rMSSD, pNN50) and HRT parameters [turbulence onset (TO) and turbulence slope (TS)] were analyzed and compared between groups. According to their HRT parameters, all participants were divided into three groups (HRT-0: normal TO, TS; HRT-1; abnormal TO or TS; HRT-2: abnormal TO and TS). A p-value <0.05 was considered significant.*

Results: *All HRV parameters were impaired in patients with PAF (p<0.05 for all parameters). There was a statistically significant difference between groups in TO (PAF 1.23±2.56; control -1.02±1.35; p= <0.001) and TS (PAF 2.59±2.39; control 3.75±1.49; p=0.002) values. In addition, 62% of the PAF patients were in HRT-2 group, on contrary; healthy subjects were predominantly in HRT-0 group (79%).*

Conclusion: *Abnormal HRV and HRT values may reflect an increased risk of PAF. Patients should be closely monitored when both TS and TO are impaired. AF's potential complications may be prevented by early detection and proper treatment using non-invasive, reproducible, easily accessible 24-h ECG Holter monitoring.*

Key words: *autonomic dysfunction; heart rate variability; heart rate turbulence; paroxysmal atrial fibrillation*

ÖZET

Amaç: *Otonomik disfonksiyon, atriyal fibrilasyon (AF) gelişmesine ve tekrarlamasına en büyük sebep olan faktörlerden biridir. Risk faktörleri olan hastalarda kalp hızı değişkenliği (KHD) ve kalp hızı türbülansı (KHT) gibi otonomik disfonksiyon parametrelerini kullanarak AF'yi tahmin etmek günlük pratiğimizi etkileyebilir. Bu çalışmada, paroksismal AF (PAF) hastaları ve sağlıklı denekler arasında 24 saatlik Holter EKG'den elde edilen KHD ve KHT ölçümlerini karşılaştırmayı amaçladık.*

Materyal ve Metot: *Bu vaka-kontrol çalışmasına toplam 116 hasta dahil edildi. Tüm hastalara 24 saatlik Holter EKG monitörizasyonu yapıldı. KHD (VLF, LF, HF, SDNN, SDANN, ASDNN, rMSSD, pNN50) ve KHT parametreleri [türbülans başlangıcı (TO) ve türbülans eğimi (TS)] analiz edildi ve gruplar arasında karşılaştırıldı. Tüm katılımcılar KHT parametrelerine göre üç gruba ayrıldı (KHT-0: normal TO, TS; KHT-1; anormal TO veya TS; KHT-2: anormal TO ve TS).*

Bulgular: *PAF'lı hastalarda tüm KHD parametrelerinin bozulduğu bulundu (tüm parametreler için p<0,05). TO (PAF: 1,23±2,56; kontrol: -1,02±1,35; p= <0,001) ve TS (PAF: 2,59±2,39; kontrol: 3,75±1,49; p=0,002) değerlerinde gruplar arasında istatistiksel olarak anlamlı fark vardı. Ayrıca PAF hastalarının %62'si HRT-2 grubunda iken sağlıklı denekler ağırlıklı olarak HRT-0 grubundaydı (%79).*

Sonuç: *Anormal KHD ve KHT değerleri, artan PAF riskini yansıtabilir. Hem TS hem de TO bozuk olan hastalar yakından izlenmelidir. AF'nin olası komplikasyonları, invaziv olmayan, tekrarlanabilir, kolay erişilebilir 24 saatlik EKG Holter monitörizasyonu kullanılarak erken teşhis ve uygun tedavi ile önlenebilir.*

Anahtar kelimeler: *otonomik disfonksiyon; kalp hızı değişkenliği; kalp hızı türbülansı; paroksismal atriyal fibrilasyon*

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Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with an increased risk of heart failure, stroke, and all-cause mortality. Although there are variously responsible for the initiation and maintenance of AF[1], autonomic dysfunction is an important contributor in this setting. Although paroxysmal atrial fibrillation (PAF) is a common clinical form of AF, clinical course and absence of symptoms frequently can delay the time of diagnosis. The onset of PAF episodes may show circadian variation. It is more prevalent in the morning, suggesting autonomic involvement[2].

Heart rate turbulence (HRT) and heart rate variability (HRV) are easily detectable and reliable measurements derived from 24-h electrocardiogram (ECG) monitoring. These parameters can provide information about the sympathetic system (SS) and parasympathetic system (PSS) influence on the cardiovascular system. Decreasing the dominance of the PSS and increasing the dominance of the SS in the heart causes impairment in HRV and HRT parameters. Impaired values are associated with poor prognosis in patients with acute myocardial infarction, heart failure, and diseases[3–5]. It has been shown that some HRV and HRT parameters are impaired in chronic AF[6,7].

Previously the importance of different HRV parameters was evaluated in AF patients[8]. However, the role of HRV and HRT parameters was never addressed in PAF patients without structural heart disease. This study investigated the relationship between all HRV and HRT parameters and the development and recurrence of AF in patients with PAF.

Materials and Methods

Study Population

This is a case-control study conducted between March 2017 and February 2019. A total of 116 patients were included in this study. The study population was divided into two groups. Group 1 consists of the patients with newly or previously diagnosed PAF with 12-lead ECG. Group 2 consisted of age and sex-matched patients admitted to our outpatient clinic with palpitation providing an adequate number of ventricular premature beats (VPBs) for HRT measurement. Patients with structural heart disease, moderate-severe valve disease, known significant coronary artery disease, stroke, inflammatory disease, malignancies, chronic kidney disease (GFR <60 ml/min), endocrine disorders (hyper/hypothyroidism), left ventricular systolic dysfunction (EF <50%), sustained arrhythmias and sleep apnea; were excluded from the study. Informed consent form signed by all participants. The study was approved by the local ethical committee (approval no: 28.09.2015/12).

HRV and HRT Analysis

All subjects underwent 24-h Holter ECG monitoring (GE medical systems technologies, version 8.0.3, Milwaukee, USA). All recordings were analyzed by the Holter software and then reviewed manually. All VPBs were scanned and those detected as artifacts were deleted. In at least 70% of Holter recordings, the patients were in sinus rhythm, and ectopic beats were <10%. At least five VPBs were taken into account to avoid any misinterpretation. The software Holter program measured HRV and HRT parameters.

Two measurements (time domain and frequency domain) for HRV signals were analyzed to appraise the ANS function. The measurements and abbreviations are given in Table 1.

Two phases of HRT were quantified numerically as turbulence onset (TO) and turbulence slope (TS)[9]. Definitions and properties of TO and TS are given in Table 1. The patients were divided into three groups as follows;

i) patients with normal HRT (HRT-0),

ii) patients with abnormal TO or TS (HRT-1),

iii) patients with abnormal TO and TS (HRT-2).

Statistical Analysis

SPSS (version 23.0) statistical program was used for data analysis. Kolmogorov-Smirnov test was used for the distribution pattern of numerical data. Standard deviation was used for normal distribution data, and the interquartile range was used for non-normal distribution. Categorical data were presented as percentages. The student t-test was used for comparisons between groups regarding the means of the numerical variables, and the Mann–Whitney U test was used to compare medians. Categorical data were compared using the Pearson Chi-square test. P-values <0.05 were considered statistically significant.

Table 1. *Abbreviations, definitions and features of HRV and HRT parameters*

HRV parameters	
Time domain	
SDNN	The standard deviation of normal-to-normal (NN) intervals
SDANN	The standard deviation of the average NN interval, calculated over 5-min periods
ASDNN	Average standard deviation of the averages of all normal-to-normal R-R intervals in all 5-min segments of the entire recording
rMSSD	Root mean square successive differences that reflect short-term oscillations
pNN50	The percentage of normal-to-normal intervals more than 50 ms
Frequency domain	
VLF	Very low frequency (0.003–0.04 Hz)
LF	Low frequency (0.04–0.15 Hz)
HF	High frequency (0.15–0.4 Hz)
LF/HF ratio	Low frequency/high frequency ratio
HRT parameters	
TO	Turbulence onset. Percentage change RR intervals after VPBs compare to pre-VPB period. TO represents the initial acceleration of heart rate following VPB.
TS	Turbulence slope. Maximum positive regression slope obtained over any 5 consecutive sinus RR intervals within the first 15 sinus RR intervals following the VPB. TS represents the late deceleration of heart rate after VPB. TO ≤% 0 (negative TO) and TS >2.5 ms/RR (positive TS) were accepted as normal values.

VPB: ventricular premature beats.

Results

The baseline demographic features were similar, as shown in Table 2. The mean age was 59.5±10.8 (52.9±7.3 vs. 51.0±9.8 in groups 1 and 2, respectively). 44% of the total study population were male (51 male, 65 female). The median time to diagnosis in the PAF group was 66.6 (33.3–84.0) months. 8 patients in the control group and 28 patients in the PAF group received b-blockers. There were no patients in the control group using anticoagulant (either vitamin K antagonist or direct oral anticoagulant (DOAC)); on the contrary, 24 patients were under anticoagulant therapy (10 patients vs. 14 patients, warfarin and DOAC, respectively) in PAF group (Table 2). The baseline ECGs of all patients were in sinus rhythm.

There were no significant differences in the groups' minimum, median, and maximum heart rates. HRV parameters (HF, LF, VLF, ASDNN, rMSSD, SDANN, SDNN, pNN50) were all lower ($p<0.05$ for all parameters), and LF/HF ratio was increased in PAF patients compared with controls ($p=0.003$). VPBs counts were also similar (26.50 (11.75–65.00) in group 1; 32.50 (14.00–74.00) in group 2, $p=0.86$). There was a statistically significant difference between groups in TO (PAF 1.23±2.56; control -1.02±1.35;

Table 2. *Baseline clinical and laboratory parameters*

	PAF (N=58)	Control (N=58)	P
Age, (years)	59.8±10.8	59.2±10.9	0.73
Gender male, n (%)	25 (43)	26 (45)	0.85
BMI, (kg/m2)	25.9±3.6	25.9±3.9	0.97
Hypertension, n (%)	24 (43)	28 (48)	0.58
Diabetes, n (%)	18 (31)	21 (36)	0.55
Smoking, n (%)	21 (36)	24 (41)	0.57
EF%	60.8±3.6	61.3±4.0	0.55
Left atrial diameter (cm)	32.8±3.8	31.9±3.4	0.21
Creatine, mg/dL	0.81±0.18	0.79±0.16	0.62
Sodium, mmol/L	138.5±3.2	137.8±3.5	0.30
Potassium, mmol/L	4.19±0.45	4.26±0.32	0.34
WBC ($x10^3$/ml)	7.53±2.18	7.80±2.4	0.55
Hemoglobin, g/dL	12.1±2.3	11.8±1.7	0.54
AF duration (months)	66.6 (33.3–84.0)	N/A	N/A
Medications, n (%)			
Beta-blocker	28 (48)	8 (14)	<0.001
Diltiazem	9 (16)	0 (0)	0.003
ACEI or ARB	16 (28)	21 (36)	0.32
Warfarin	10 (17)	0 (0)	0.001
DOAC	14 (24)	0 (0)	<0.001
OAD/Insulin	15 (26)	21 (36)	0.23

Results are expressed as: mean ± SD or median (IQR) or frequency (%). PAF: paroxysmal atrial fibrillation, EF: Ejection fraction, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, DOAC: direct oral anticoagulants, OAD: oral anti-diabetic drug.

p<0.001) and TS (PAF 2.59±2.39; control 3.75±1.49; p=0.002) values (Table 3). 79% of the control group and 10% of the PAF group were in HRT-0; on the contrary, 2% of the control group and 62% of the PAF group were in HRT-2, which were both statistically significant (p<0.001) (Table 4). The remaining 28% of PAF patients and 19% of control patients were in the HRT-1 group.

Discussion

In this study, we evaluated the characteristics of HRV and HRT parameters that are affected by the SS and PSS of the heart in patients with PAF. All HRV parameters were decreased, and the LF/HF ratio was increased in PAF patients. In addition, patients with PAF were predominantly in the HRT-2 group, whereas AF-free patients were predominantly in the HRT-0 group.

Several electrophysiological mechanisms were defined in the development of AF. The initiation of AF is related to atrial premature beats (APBs) originating from pulmonary veins[10]. Autonomic dysfunction such as SS predominance may increase the likelihood of APB occurrence and shortening of APB coupling interval resulting in more frequent AF episodes[11]. Several studies demonstrate the relationship between autonomic nervous system (ANS) dysfunction and AF onset. ANS precipitates AF through enhanced automaticity, triggered activity, and facilitating reentrant substrate[12].

Paroxysmal AF has a better prognosis with lesser thromboembolic events, but; identifying patients with a high risk of AF development in the follow-up is important because paroxysmal AF may degenerate into permanent AF[13–15]. Conventional risk factors such as heart failure, diabetes mellitus, left atrial dilatation, age, and risk scores (CHA_2DS_2-VASc) are the most common predictors of AF in our daily practice; the most reliable risk factor for AF is AF itself[16]. It is also known that the exact incidence of atrial fibrillation is underestimated because most of the episodes are asymptomatic[17,18]. Therefore novel clinical indicators of the development and progression of AF are essential. Predicting these patients and modifying their therapy according to recent guidelines may improve long-term outcomes in these patients.

HRV parameters provide reliable information about the cardiac PSS/SS balance. VLF is related to SS, and reduced VLF is associated with various arrhythmias[19]. LF reflects both SS/PSS tonus, whereas HF reflects the predominant vagal tonus. Increased LF/HF ratio indicates it pronounced cardiac SS activity[20]. SDNN was shown to be an indicator of proper cardiac PSS function. Besides, some previous studies demonstrated that SDNN is the best HRV parameter to assess cardiovascular autonomic innervation[19]. RMSSD and pNN50 are also related to PSS predominance and are associated with sudden cardiac death when impaired[21]. Increased PSS and decreased SS influence on the heart are responsible for AF development. In the light of these data, studies investigating the relationship between AF and HRV have been conducted. Low HRV recordings from 2 minutes of ECG recording were related to an

Table 3. *24-h Holter ECG findings of study population*

	PAF (N=58)	Control (N=58)	P
Minimum HR (beat/min)	52.9±7.3	51.0±9.8	0.23
Average HR (beat/min)	77.9±7.7	76.1±7.7	0.21
Maximum HR (beat/min)	144.1±15.6	140.3±17.9	0.24
Total QRS	106784.6±15319.6	103735.9±14174.9	0.27
VLF	26.7±8.7	33.9±10.4	<0.001
LF	23.5±10.4	30.2±20.5	0.03
HF	13.1±5.7	18.9±8.4	<0.001
LF/HF ratio	1.8±0.5	1.5±0.5	0.003
SDNN	133.9±37.0	152.3±53.7	0.034
SDANN	117.6±27.7	134.4±46.3	0.013
ASDNN	55.0±15.8	66.5±32.8	0.017
rMSSD	33.7±10.2	39.5±12.5	0.008
pNN50	13.6±10.6	17.8±9.2	0.023
Tonset	1.23±2.56	-1.02±1.35	<0.001
Tslope	2.59±2.39	3.75±1.49	0.002
PVBs	26.50 (11.75–65.00)	32.50 (14.00–74.00)	0.86

Results are expressed as: mean ± SD or median (IQR) or frequency (%). PAF: paroxysmal atrial fibrillation; VPBs: premature ventricular beats, HR: heart rate, To: turbulence onset, Ts: turbulence slope.

Table 4. *HRT status of PAF and controls*

	PAF (N=58)	Control (N=58)	P
HRT-0, n (%)	6 (10)	46 (79)	<0.001
HRT-1, n (%)	16 (28)	11 (19)	0.27
HRT-2, n (%)	36 (62)	1 (2)	<0.001

Results are expressed as: frequency (%). PAF: paroxysmal atrial fibrilation, HRT: Heart rate turbulence.

increased risk of sudden cardiac death and incidence of AF in population-based studies[22,23]. The interaction between abnormal HRV values and prognostic implications also demonstrated an increased risk of AF incidence among patients with relevant risk factors[24]. Relevant studies showed a significant association between HRV and AF recurrence after index episode[25,26].

HRT is associated with HRV parameters, which are also derived from 24 hours Holter recordings. Moreover, HRT, which is thought to represent the PSS predominance better, was a stronger predictor of cardiovascular prognosis than HRV. Previously published studies have described the role of HRT in predicting sudden cardiac death, ventricular arrhythmia after myocardial infarction, and heart failure[5,27]. HRT defines the fluctuations of normal sinus rhythm after and VPBs due to baroreceptor reflex mechanism and represents noninvasive cardiac autonomic functions (28). Combining different screening modalities in high-risk patients (such as HRV and HRT analysis) may improve our understanding of the precise contribution of ANS to AF pathophysiology. In the future, these parameters may be used as a therapeutic target.

Our study showed that PAF patients have abnormal HRV and HRT compared to control subjects which reflects the possible role of ANS on PAF development. Normal values of HRV parameters and HRT-0 may be used as an exclusion parameters. In addition, HRT-2 may serve as a strong predictor of PAF development. HRT-1 did not differ between groups, and the utility of one abnormal HRT parameter is questionable compared to HRT-0 and HRT-2. Close monitoring of subgroups of patients with abnormal HRT, especially HRT-2, may be feasible. This study evaluated all HRV and HRT parameters in patients with PAF, which were not included in previous similar studies. The major limitation of our study is the limited number of patients. Although atrial HRT measurements are not routinely used in clinical trials, especially considering that APCs play an important role in AF development, measuring atrial HRT may contribute to our study. Several factors that affect the HRV and HRT, such as medical therapy (b-blockers, RAAS blockers, anti-arrhythmic drugs), may intervene with our results. PAF group was more likely under AV nodal blocking agents, which may influence our results. Additionally, we can not rule out the presence of PAF, which may influence our results.

In conclusion, our study showed that PAF patients have abnormal HRV and HRT compared to control subjects which reflects the possible role of ANS on PAF development. Patients at risk of AF may be distinguished by using this technique. Close monitoring of subgroups of patients with abnormal HRT, especially HRT-2, may be feasible. Besides, proper precautions may reduce the rate of cardiovascular complications. Future prospective studies are needed to confirm our results and their impact on long-term prognosis.

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Conception and design of the study or analysis and interpretation of data, or both (MC, BS, HMO);

Manuscript drafting or critical revision for important intellectual content (MC, BS, HMO);

Final approval of the manuscript submitted (MC, HMO).

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