Research Article (Araştırma Makalesi)

Investigation of the Risk of Sudden Cardiac Death Using Heart Rate Variation in Migraineurs

Migrenli Hastalarda Kalp Hızı Değişkenliği Kullanılarak Ani Kardiyak Ölüm Riskinin Araştırılması

Seyda CEVIK GUNERI[1], Mehmet Celalettin GUNERI[2], Gulay AYDIN[3]

[1] Bossan Hospital, Neurology Clinic, Gaziantep, Türkiye
[2] Bossan Hospital Internal Medicine Clinic, Gaziantep, Türkiye
[3] Darıca Farabi Education and Research Hospital Cardiology Clinic, Kocaeli, Türkiye

Özet

Amaç: Migren sempatik sinir sisteminin disfonksiyonundan kaynaklanan ve çeşitli klinik özelliklerden oluşan epizodik bir sendromdur. Çalışmamızın amacı, migrenli hastalarda ani kardiyak ölüm riskinin ve otonom disfonksiyonun kalp hızı türbülansı (KHT) ve kalp hızı değişkenliği (KHD) ile değerlendirilmesidir.

Gereç ve yöntemler: Bu çalışmaya 18 yaş üstü ve 70 yaş altı Nöroloji kliniği tarafından takipte olan 35 kronik migrenli ve 42 sağlıklı birey olmak üzere 77 kişi dahil edildi. Tüm katılımcıların 24 saatlik holter kaydı yapıldı. Kalp hızı değişkenliği ve kalp hızı türbülansı parametreleri Avrupa Kardiyoloji Derneği çalışmaları kullanılarak hesaplandı.

Bulgular: Tonset ölçümleri bakımından migren ve kontrol grubu arasında anlamlı farklılık bulunmuştur (P=0.004). Diğer değişkenler bakımından istatistiki olarak anlamlı fark bulunmamıştır.

Sonuç: Bulgularımız migrenli hastalarda kalp hızı türbülans parametrelerinden Tonset'in migrenlilerde otonomik fonksiyonla ilişkili olduğunu gösterirken kalp hızı değişkenliği parametrelerinin migrenli hastalarda otonomik disfonksiyonla ilişkili olmadığını göstermiştir.

Anahtar Kelimeler: Migren, kalp hızı değişkenliği, kalp hızı türbülansı

Abstract

Objective: Migraine is an episodic syndrome that results from dysfunction of the sympathetic nervous system and consists of various clinical features. The aim of our study is to evaluate the risk of sudden cardiac death and autonomic dysfunction in patients with migraine by heart rate turbulence (HRT) and heart rate variability (HRV). In addition, it is aimed to inform patients about their cardiovascular risks.

Material and methods: A total of 77 individuals, 35 of whom were chronic migraine sufferers and 42 healthy individuals, who were followed up by the neurology clinic over the age of 18 and under the age of 70, were included in this study. A 24-hour holter recording was made for all participants. Heart rate variability and heart rate turbulence parameters were calculated using European Society of Cardiology studies.

Results: A significant difference was found between the migraine and control groups in terms of Tonset measurements (p=0.004). There was no statistically significant difference in terms of other variables.

Conclusion: Our findings showed that Tonset, one of the heart rate turbulence parameters, was associated with autonomic function in patients with migraine, whereas heart rate variability parameters were not associated with autonomic dysfunction in patients with migraine.

Keywords: Migraine, heart rate variability, heart rate turbulence

Correspondence: Seyda CEVIK GUNERI, Bossan Hospital Neurology Clinic, Gaziantep, Türkiye

Phone: +90 5056295587 **e-mail:** drseydacevik@hotmail.com

ORCID No (respectively): 0000-0002-1756-5062, 0000-0002-2946-5050, 0000-0002-3151-4448

Submission date: 27.04.2024

Acceptance date: 04.09.2024

DOI: 10.17517/ksutfd.1474483

INTRODUCTION

Migraine headaches are generally thought to be associated with arterial vasomotor and autonomic nervous system abnormalities (1). However, it is unclear whether autonomic dysfunction is the result or cause of migraine (2). Like many systems in the body, the heart is controlled by the autonomic nervous system. The heart autonomic nervous system regulates its work through sympathetic and parasympathetic branches that dynamically control beat-to-beat differences.

Heart rate variability (HRV), which is defined as cyclic changes in sinus rate over time, is considered as a measure of cardiac autonomic tone and an indicator of the cardiorespiratory system, as it provides information about sympathetic-parasympathetic balance (3).

HRV analysis provides very useful information in determining mortality risk and evaluating sinoatrial responses to autonomic stimuli in selected patient populations. The clinical significance of depressed HRV has been demonstrated in two areas; in risk assessment after acute myocardial infarction (AMI) and as an early warning sign in diabetic neuropathy (3).

It is a physiological phenomenon that the intervals of heartbeats constantly change in normal sinus rhythm in healthy individuals. Respiration, thermoregulation and baroreflex mechanisms underlie these periodic fluctuations. Ventricular arrhythmias that can lead to sudden death appear as a combination of 3 factors; arhythmogenic substrate, arhythmogenic trigger and fluctuations in autonomic tone. Coronary angiography, echocardiography, radionuclide ventriculography, and signal-averaged electrocardiography (ECG) are used to identify the arrhythmogenic substrate. Holter monitoring is used to detect arrhythmogenic triggering (ventricular ectopic activity). Autonomic tone is difficult to define. Heart rate variability appears to be very promising in investigating cardiovascular responses to changes in autonomic tone (4). Automation in the heart is intrinsically linked to pacemaker tissues. But speed and rhythm are under the control of the autonomic nervous system. The parasympathetic effect on the heart rate is caused by the secretion of acetylcholine (Ach) through the vagus nerve. Muscarinic Ach receptors respond by increasing potassium (K) transport across the cell membrane. The sympathetic effect on heart rate is mediated by epinephrine and norepinephrine. Membrane phosphorylation, which begins in a cyclic adenosine monophosphate (c-AMP)-dependent manner with beta (β) receptor stimulation, accelerates the slow diastolic depolarization (5).

Vagal indices of HRV increase at night and sympathetic indices increase during the day. This is because both systems have different circadian rhythms. Beside the cardiac sympathetic nerve impulse output rate short-frequency HRV (0.1 Hz) depends on various factors, including, multiple neural reflexes, cardiac adrenergic receptor sensitivity, post-synaptic signal transduction, and electrochemical coupling (5).

Heart Rate Variability is an indirect indicator of cardiac autonomic activity by which the beat-to-beat variability of the R-R interval is measured. HRV measurement is usually made using recordings obtained during Holter monitoring. In order for the recordings to be valid, the factors affecting the heart rate must be constant throughout the recording period. The first step in the measurement is the analysis of the successive R waves measured on the surface electrocardiogram (ECG). After ECG recordings are made, HRV parameters are calculated with the help of statistical methods via a special computer. Since R waves are used, abnormal beats must be cleared from the recording. If more than 85% of the recorded beats are normal R beats, measurement can be made.

Heart rate variability measurement methods are;

- Time Domain Methods
- Frequency Domain Methods. We used time domain methods in our study.

Simple time area variables include the mean normal-to-normal (NN) interval, mean heart rate, and the difference between the longest and shortest NN interval. NN intervals, indexes calculated from the differences between (RMSSD, pNN50) are short-term measurements and show high-frequency variations in heart rate. These are completely independent of diurnal and other effects on heart rate and reflect changes in vagal regulated autonomic tone (6). With these measurements, changes in heart rate secondary to breathing, tilt and valsalva maneuver are evaluated (6). Time-dependent parameters of HRV are shown in **Table 1** (7).

Heart Rate Turbulence (Cycle) originates from the principle of acceleration of sinus rhythm, which occurs as a reflex against hypotension that occurs as a result of the inability to fill the entire ventricle with blood due to the short diastole period during ventricular premature beat in patients in sinus rhythm (sinus rhythm and ventricular premature beat are indispensable rules). HRT is also defined as fluctuations in sinus cycle length after a ventricular premature beat and is an indicator of baroreflex sensitivity (8,9). It has proven clinical importance in demonstrating mortality and sudden cardiac death after myocardial infarction. It is recommended in a few small studies to be used in other heart diseases (10). Under normal conditions, after ventricular premature beat (VPB), the heart accelerates for one or two beats,

Table 1. Time Dependent Parameters of Heart Rate Variability

Variable	Unit	definition
Avarage NN	ms	Mean cycle length between two normal heart beats
SDNN	ms	Difference of all NN intervals throughout the review
SDNN index	ms	Mean of the std. deviations of all NN intervals in 5-minute recordings
SDANN	ms	Std. deviation of mean NN intervals in 5-minute recordings during the study period
RMSSD	ms	In 24-hour recording the squareroot of the sum of the squares of consecutive NN intervals' differences
NN50 Count		Neighborhood Number of the NN intervals separated by more than 50 ms during the entire recording
pNN50	%	NN 50 divided by the total number of all NNs
Triangular Index	ms	All NN intervals divided by the number of NN intervals in the mode length

NN: Normal-normal, ms : milliseconds, mean: avarage, std: standart

Table 2. Normal Values Of Heart Rate Variability (7)

Temporal Measurements	Normal values
SDNN [ms]	141±39
SDANN [ms]	127±35
RMSSD [ms]	27±12

then slows down to 9-10 beats and normalizes before 20 beats. HRT consists of two components; turbulence onset (TO) (Tonset) and turbulent slope (TS) (Tslope). Under normal conditions, a sudden drop in systolic and diastolic blood pressure occurs after VPB. This decrease is followed by an early increase (decreased vagal tone) (TO). This phase of acceleration is followed by an increase in blood pressure and a decrease in blood pressure (TS). These parameters can be calculated through a program over 24-hour ECG Holter recordings, as well as from device memory records of patients with an implantable cardioverter defibrillator and using VPBs created with intracardiac stimulation in the electrophysiology laboratory (11). Although the exact mechanism is not known, the decrease in blood pressure caused by VPB is sensed by the baroreceptors in the aortic and carotid arches and leads to a decrease in vagal activity first and then an increase in sympathetic activity. The pulse pressure, which increases with the beat coming after the compensatory interval, has the opposite effect and causes an increase in vagal activity and a decrease in sympathetic activity. As a result, the heart first accelerates and then slows down (8).

Heart Rate Turbulence Measurement Technique

At least five suitable VPBs are required for HRT measurement. TO is calculated as follows:

$$\frac{(RR_1 + RR_2) - (RR_{-2} + RR_{-1})}{(RR_{-2} + RR_{-1})} X100 = TO$$

In summary, TO represents the percentage of heart acceleration after VPB, with negative values reflecting cardiac acceleration (normal response), positive values reflecting slowing (abnormal response).

TS was defined as "the most positive value from the regression slopes of 5 consecutive RR interval slices within the first 20 sinus RR intervals following VPB", which is an indication of the maximum degree of slowing within 5 beats.

Schmidt *et al.* found the normal values of TO and TS to be <0% and >2.5 ms/RR, respectively. TO≥0 and TS≤2.5 ms/RR are considered abnormal. VPB is performed using ECG-Holter recordings. Not all ventricular premature beats detected by the device are used. Parasites must be removed. Some criteria have been defined that VPBs must meet in order to be used in HRT analysis (8). These criteria are shown in **Table 3**.

MATERIALS AND METHODS

In our study, 45 migraine sufferers and 45 healthy individuals followed by the neurology clinic over the

Table 3. Eligibility Criteria of Ventricular Premature Beats (VPB) For HRT.

☐	5 beats before VEA and 15 beats after compensatory pause, there must not be arrthymia, interference or false
☐	RR intervals of sinus beats hould not be shorter than 300 ms or longer than 2000 ms s
☐	There should be no more than 200 ms difference between two consecutive RR intervals
☐	Reference interval with RR intervals (average of the last 5 sinüs intervals before VEA) should not differ by more than 20%
☐	The pre-extrasystolic interval before VEA must be at least 20% shorter than the normal RR interval and the post-extrasystolic interval must be at least 20% longer than the reference interval

VEA: Ventricular Prematüre Beats

age of 18 and under the age of 70 were compared. The diagnosis of migraine was established according to the criteria of the Heada Classification Committee of the International Headache Society. The patients included in the study did not have concomitant heart diseases such as heart valve disease, heart failure and cardiac rhythm disorder, thyroid disorders, did not use diabetic, hypertensive and cardiac medication, had normal blood laboratory values, did not consume alcohol and did not diagnose with any central or peripheral nervous system disease.

A Biomedical Systems Digital Holter Recorder device was installed for ECG Holter. 24-hour recordings were taken. After the data were loaded into the computer, they were read with the Century 3000 program. Artifacts have been removed. Time area measurement parameters of HRV were calculated automatically. Data for HRT were transferred to the "HRT" program and automatic measurements were made.

Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested with the Shaphiro Wilk test. Student's t test was used to compare normally distributed variables in 2 independent groups, and Mann Whitney U test was used to compare non-normally distributed variables in two independent groups. Relationships between categorical variables were tested with the Chi-square test. SPSS 22.0 package program was used in the analysis. $P<0.05$ was considered significant.

RESULTS

In our study, HRV parameters determining cardiac autonomic dysfunction did not show a statistical difference between patients with migraine and the control group. However, Tonset, which is one of the HRT parameters, p value was found <0.05 in patients with migraine and it was statistically significant. Other results are given and commented at the tables, below.

Table 4. General Descriptive Statistics

	N	Min	Max	Mean	Std. Deviation
Age	90	18	69	32,72	11,688
Tonset	49	-10,2320	18,8600	-1,249329	4,5314416
Tslope	49	-3,2000	94,0000	11,879592	14,9803619
SDNN	90	16,0000	210,0000	100,666667	44,9511595
SDANN_index	90	,0000	193,0000	79,188889	47,4384035
SDNN_index	90	16,0000	179,0000	57,755556	23,7705847
RMSSD	90	8,0000	153,0000	36,722222	25,2689034
PNN50	90	,0000	79,0000	10,822222	12,7777702

Table 5. Comparison of HRV And HRT Parameters of Patients With And Without Migraine (Comparison of Categorical Variables)

Present		MIGRAINE		Total	p
		absent			
Tslope	normal	22	21	43	0,233
		51,20%	48,80%	100,00%	
	abnormal	1	5	6	
		16,70%	83,30%	100,00%	
	no response	22	19	41	
		53,70%	46,30%	100,00%	
Tonset	normal	20	11	31	0,004 *
		64,50%	35,50%	100,00%	
	abnormal	3	15	18	
		16,70%	83,30%	100,00%	
	no response	22	19	41	
		53,70%	46,30%	100,00%	
RMSSD	normal	30	24	54	0,197
		55,60%	44,40%	100,00%	
	abnormal	15	21	36	
		41,70%	58,30%	100,00%	
SDANN index2	normal	19	16	35	0,517
		54,30%	45,70%	100,00%	
	abnormal	26	29	55	
		47,30%	52,70%	100,00%	
SDNN	normal	20	18	38	0,67
		52,60%	47,40%	100,00%	
	abnormal	25	27	52	
		48,10%	51,90%	100,00%	

Comment: Significant difference was found between migraine and control groups in terms of tonset measurements (p=0.004). No significant difference was found in terms of other variables.

Table 6. Relationship Between Heart Rate Variability Parameters And Migraine

GROUP STATISTICS					
	MIGRAINE	N	Mean	Std. Deviation	P
SDNN_index	absent	45	56,11111	2,603072	0,515
	present	45	59,4	4,301092	
SDANN_index	absent	45	82,02222	7,026824	0,574
	present	45	76,35556	7,170306	
SDNN	absent	45	102,6444	6,522855	0,679
	present	45	98,68889	6,935403	

Comment: There was no significant difference between heart rate variability parameters and migraine

Table 7. Relationship Between Patients with Migraine and Age

	MIGRAINE	N	MEAN	Std. Deviation	P
AGE	present	45	34,24	11,983	0,192
	absent	45	31,20	11,313	

Comment: There was no significant difference in age between patients with and without migraine (p=0.192).

DISCUSSION

Autonomic dysfunction symptoms are common both during and among migraine attacks in patients with migraine (12). Many studies evaluating the autonomic balance of migraineurs have produced conflicting results regarding the extent of sympathetic and parasympathetic dysfunction. Most studies show sympathetic disorder with lesser degree of parasympathetic disorder (12). Parasympathetic activity continues to be less affected by sympathetic activity in the interictal period. HRV studies have shown stronger parasympathetic impairment than autonomic cardiovascular reflex test studies (13).

A decrease in HRV is an indicator of increased sympathetic tone and decreased vagal tone, and is associated with an increase in fatal ventricular arrhythmias (14). It has been stated in previous studies that HRV can be used to predict arrhythmic events after myocardial infarction. It has been reported in observational studies that it can also be used in non-ischemic dilated cardiomyopathies (15). Fauchier et al. found a weak to moderate correlation between SDNN and left ventricular functions in 93 patients with dilated cardiomyopathy. In multivariate analyzes, these investigators stated that SDNN is an independent risk factor for cardiac death or heart transplant (16). In the study investigating the relationship of HRV with occupational health, it was found that HRV values decreased when sympathetic activity increased; it has also been observed that HRV values increase in cases where parasympathetic activity increases (17). In assessments using HRV frequency domain measurements, cardiac autonomic function was observed to begin to decline between the ages of 60 and 70, and became evident above the age of 75 (18). Contrary to these studies, Pogacnik et al. and Mikamo et al. found no impairment in cardiac autonomic function in patients with migraine using HRV (19,20).

In our study, however, no significant difference was found between the migraine patients and the control group in terms of age and HRV parameters, and no autonomic dysfunction was found. Thus, it was thought that HRV values in terms of cardiac autonomic disorder were not a predictor of autonomic dysfunction in patients with migraine and were not suitable for evaluation in terms of sudden cardiac death.

HRT was first reported by Schmidt et al. defined as a predictor for mortality after acute myocardial infarction (8). Abnormal HRT values were found in heart failure and it was observed that hemodynamic changes, sympathetic system activation, impaired baroregulatory mechanisms, and abnormal HRT values were closely related (8).

In a study investigating HRT in migraine patients, it was reported that no difference was found between the patients with migraine and the control group in the TO and TS data (21).

In our study, while TS values, one of the HRT parameters, were found to be normal, significant deterioration was found in TO values.

Since the TO and TS values, which are among some of the patients' HRT parameters we included in our study, were not found in the holter records, the HRT parameters were determined in a limited number. Therefore, the results presented in the study should be evaluated in the light of these limitations. It was thought that if our study was conducted with larger sample groups, it could provide more meaningful results.

As a result, no statistically significant difference was detected between the patients with migraine and the control group, whose heart rate variability was evaluated. TO, which is the heart rate turbulence parameter, was found to differ significantly in patients with migraine compared to the control group. In the light of these data, it was concluded that the relationship between migraine and sudden cardiac death could not be determined using heart rate variability, but TO, which is a heart rate turbulence parameter, may be a predictor for cardiac problems due to autonomic deterioration in patients with migraine. On the other hand, due to the limitations mentioned above, it was thought that more meaningful results could be obtained by conducting comprehensive cardiac autonomic function studies.

Ethic Approval and Informed Consent: The study complied with the principles of the international Declaration of Helsinki, and ethical approval was obtained from Cumhuriyet University Clinical Research Ethics Committee (Date: 22.02.2011; protocol no:45). An informed consent form was taken from the participants.

Funding: This work has not received any funding.

Declaration of Competing Interest: None.

Author Contribution Statement: The authors declarate they equally contributed to the manuscript.

REFERENCES

1. Laffitte C, Even C, Henry-Lebras F,et.al. Migraine and angina pectoris by coronary artery spasm. Headache 1996;36:332–4.
2. Yakinci C, Mungen B, Er H,et.al. Autonomic nervous system func- tion in childhood migraine. Pediatr Int 1999;41:529–33.
3. Kayıkçıoğlu M, Payzın S. Kalp hızı değişkenliği Türk Kardiyoloji Derneği Arş. 2001;29:238-45
4. Pieper SJ, Hammill SC. Heart rate variability:tecnique and investigational applications in cardiovascular medicine. Mayo Clin Proc 1995;70:955-64
5. Schwartz PJ, Zipes DP. Autonomic modulation of cardiac arrhymias. In:Zipes DP, Jalife I, eds. Cardiac Elektrophisology. From cell to Bedside. Philadelphia:W. B. Saunders, 2000;300-14
6. Kleiger RE, Stein PK, Bosner MS,et.al. Time domain measurements of heart rate variability Cardiol Clin 1992;10:487-498
7. Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. Heart rate variability:standarts of measurement, physiological interpretation, and clinical use. Circulation 1996;93:10431065
8. Schmidt G, Malik M, Barthel P,et.al. Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 1999;353:1390–1396.
9. Lin LY, Lai LP, Lin JL, et.al. Tight mechanism correlation between heart rate turbulence and baroreflex sensitivity: sequential autonomic blockade analysis. J Cardiovasc Electrophysiol 2002;13:427–431.
10. Mari A. Watanabe, MD, Heart Rate Turbulence: a Review,PhDIndian Pacing and Electrophysiology Journal 2003;3(1):10-22
11. Francis J, Watanabe MA, Schmidt G. Heart rate turbulence: A new predictor for sudden cardiac death. Ann Noninv Electrocardiol 2005;10:102–109.
12. Miglis, M. G. Migraine and Autonomic Dysfunction: Which Is the Horse and Which Is the Jockey? Current Pain and Headache Reports 2018;22(3).
13. Mosek A, Novak V, Opfer-Gehrking TL,et.al. Autonomic dysfunctionin migraineurs. Headache J Head Face Pain [Internet]. 1999 [cited 2017 Nov 8];39(2):108–17
14. Kleiger RE, Stein PK, Bigger JT. Heart rate variability: Measurement and clinical utility. Ann Noninvasive Electrocardiol 2005;10:88–101.
15. Zipes DP, Camm AJ, Borggrefe M et al. ACC/AHA/ESC 2006 guidelines management of patients with ventricular arrhytmias and the prevention of sudden cardiac death Europen Heart J, 2006;27:2099-2140
16. Fauchier L, Babuty D, Cosnay P,et.al. Heart rate variability in idiopathic dilate cardomyopathy: characteristics and prognostic value. J Am Coll Cardiol,1997;30:1009-1014
17. Togo F., Takahashı, M. Heart Rate Variability in Occupational Health —A Systematic Review. Industrial Health, 2009;47(6):589–602.
18. Stein, P. K., Barzilay, J. I., Chaves, P. H. M., et.al.(2008). Heart rate variability and its changes over 5 years in older adults. Age and Ageing, 2008;38(2):212–218.
19. Pogacnik T, Sega S, Pecnik B,et.al. Autonomic function testing in patients with migraine. Headache 1993;33:545–50.
20. Mikamo K, Takeshima T, Takahashi K. Cardiovascular sympathetic hypofunction muscle contraction headache and migraine. Headache 1989;29:86–9.
21. Avşar, A., Yaman, M., Kilit, C.,et.al. A Heart Rate Turbulence Study to Assess Cardiac Autonomic Function in Migraineurs Turbulence Česká a Slovenská neurologie a neurochirurgie 2007;70(2):174-177