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Orjinal Article

R-R interval variation in migraine patients

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Abstract. The aim of this study was to evaluate possible cardiovascular autonomic dysfunction in migraine patients with the R-R interval variation (RRIV) measurement, which is an easy and reliable method for the evaluation of parasympathetic function. We studied 71 migraine patients in headache- free intervals (mean age: 31.6±8.9, range 13-57 years; 52 females and 19 males), all without any known heart disease, and 51 age-matched healthy subjects (mean age: 28.8±9.1, range 13-52 years; 25 females and 26 males). RRIVs at rest (R%) and during deep breathing (D%) were studied in all the subjects. The difference between D% and R% (D-R) and the ratio of D% to R% (D/ R) was also determined.The mean values of RRIV in migraine patients at rest [mean RRIV in patients, 15.98±6.30% vs controls, 18.92±5.82% ($p < 0.05$)] and during deep breathing [mean RRIV in patients, 28.72±9.95% vs controls, 34.57±11.50% ($p < 0.05$)] and D-R [mean in patients, 12.74±7.90% vs controls, 15.64±8.20% ($p < 0.05$)] were significantly lower compared with the controls, but D/R [mean in patients, 1.90±0.58% vs controls, 1.86±0.42% ($p > 0.05$)] was not significant. Patients with migraine have hypofunction in the parasympathetic nervous system during routine daily activity in the headache-free period.

Key words: Migraine, autonomic dysfunction, R-R interval variation, parasympathetic nervous system

1. Introduction

The pathophysiology of migraine is still not sufficiently known. Autonomic nervous system (ANS) involvement has been stressed in the pathophysiology of migraine. Some symptoms observed during the migraine attack indicate an unstability of the ANS. Likewise; autonomic symptoms such as nausea, vomiting, diarrhea, flushing due to vasodilatation, piloerection and diaphoresis are common. Havanka-Kanniainen (1) proposed that both sympathetic and parasympathetic dysfunctions have played important roles in the patophysiology of migraine. Sacks (2) has suggested that parasympathetic activity is increased during, and sympathetic activity is increased before and after a migraine attack. In the cases of migraine, ANS functions have been investigated for years. The study results are contradictory.

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Some (3-4) have reported normal ANS functions whereas the others (5-8) did report dysfunctions of the sympathetic nervous system (SNS) or both (9-12) sympathetic and parasympathetic nervous systems (PSN).

R-R interval variation RRIV, a measure of the heart rate variability is a simple and reliable test used for the evaluation of PSN autonomic functions of the heart (13-15). In this study, RRIV test was used to evaluate the cardiac parasympathetic autonomic status of migraine cases in periods free of headache.

2. Materials and methods

2.1.Migraine patients

For this study, 71 migraine patients (52 females and 19 males) confirming the diagnostic criteria (16) proposed by the International Headache Society, and admitted to the Neurology Department in Ataturk University, Faculty of Medicine between October 2002 and December 2003 have been chosen. Their ages ranged between 13-57 years old and the mean age was 31.6±8.9 years. Detailed neurological and physical examinations of all cases have been performed. Cases with known neurological or

systemic diseases affecting the nervous or the cardiovascular systems directly or indirectly, such as diabetes mellitus, uremia, heart failure and cardiac arrhythmias have been excluded from the study. None of the cases were on medications affecting the cardiovascular functions.

Table 1

Mean R-R interval variation values for the patient and control groups

	Control group	Migraine group	P
R% (X±SD)	15.98±6.30	18.92±5.82	< 0.05
D% (X±SD)	28.72±9.95	34.57±11.50	< 0.05
D-R (X±SD)	12.74±7.90	15.64±8.20	< 0.05
D/R (X±SD)	1.90±0.58	1.86±0.42	> 0.05

R%: rest, D%: RRIVs at during deep breathing, D-R: The difference between D% and R%, D/ R: the ratio of D% to R%

Table 2

Correlation coefficients of R-R interval variations with age for the control and patient groups

	Control group		Migraine group	
	Correlatin coefficient	P	Correlation coefficient	P
R%	-0.283	< 0.045	-0.593	<0.001
D%	-0.309	< 0.027	-0.534	<0.001
D-R	-0.096	0.504	-0.245	0.040
D/R	0.075	0.603	0.126	0.294

R%: rest, D%: RRIVs at during deep breathing, D-R: The difference between D% and R%, D/ R: the ratio of D% to R%

2.2.Controls

The control group consisted of 51 healthy subjects (25 females and 26 males) lacking a history of any systemic or neurological disease, or the presence of any autonomic symptom. Their age distribution was similar to that of the patient group (mean age was 28.8±9.1 and the ages ranged between 13-52 years). The members of neither group have used medications able to influence the autonomic test, during the study or the previous 24-hours.

Table 3

Correlation coefficients of R-R interval variations with the durations of headache for patient groups

	Migraine group Correlation coefficient	p
%R	-0.173	0.149
%D	-0.209	0.081
D-R	-0.065	0.589
D/R	0.03	0.978

2.3. Heart rate variability in the time domain

RRIV is used for the evaluation of PSN functions. During both rest and deep breathing, an abnormality of RRIV indicates PSN dysfunctions. For the migraineurs, records have been taken during pain-free periods. The electrophysiologic examination was performed with the subject supine and relaxed, at room temperature (24-26^{0}C C) and body temperature over 31^{0}C. A Medelec Teca Premerie Plus vE05 electromyography device has been used for all recordings. The recordings were performed according to the method described by Shahani *et al*. (15) RRIV recordings were performed via a couple of ring electrodes placed over index fingers, the one on the left as the active one. A circular surface ground electrode was placed over the wrist. For the RRIV recordings, electromyography device setting adjustments were made as 20-50 Hz for filter, 0.5 mV / div. for sensitivity, and 0.2 sec/div. for period of analysis. The first QRS interval is a triggering potential, whereas the time-related alterations of the second QRS complex reflect the alterations in R-R interval. During rest, 20 QRS complexes have been recorded repeated 5 times each. Afterwards, another 20 QRS complexes were recorded, repeated this time twice each, following a deep inspiration of 6-8 times per minute. The range between 20 of the R-R interval pairs was assigned as (a), and the mean of R-R intervals was assigned as (b). RRIV mean percentage (%) ratio of the QRS complexes gathered in each recording was calculated via RRIV=a/bX100 formula. The mean of five recordings during rest was assigned as %R and the mean of two recordings during deep inspiration was assigned

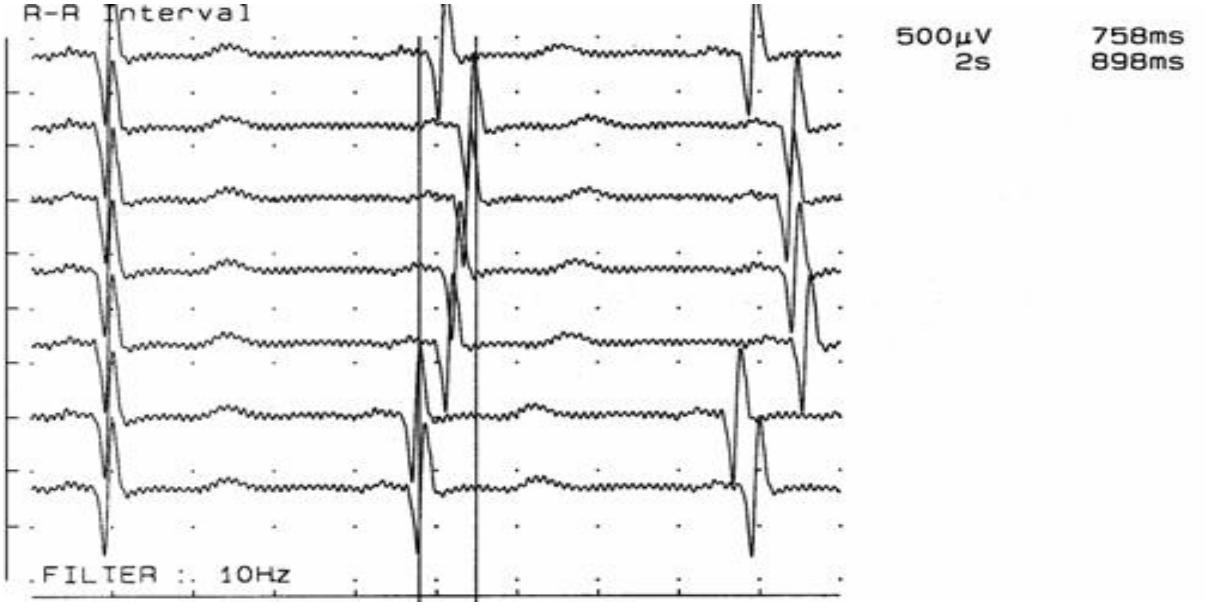

Figure 1. RRIV recording at rest in migraine patients.

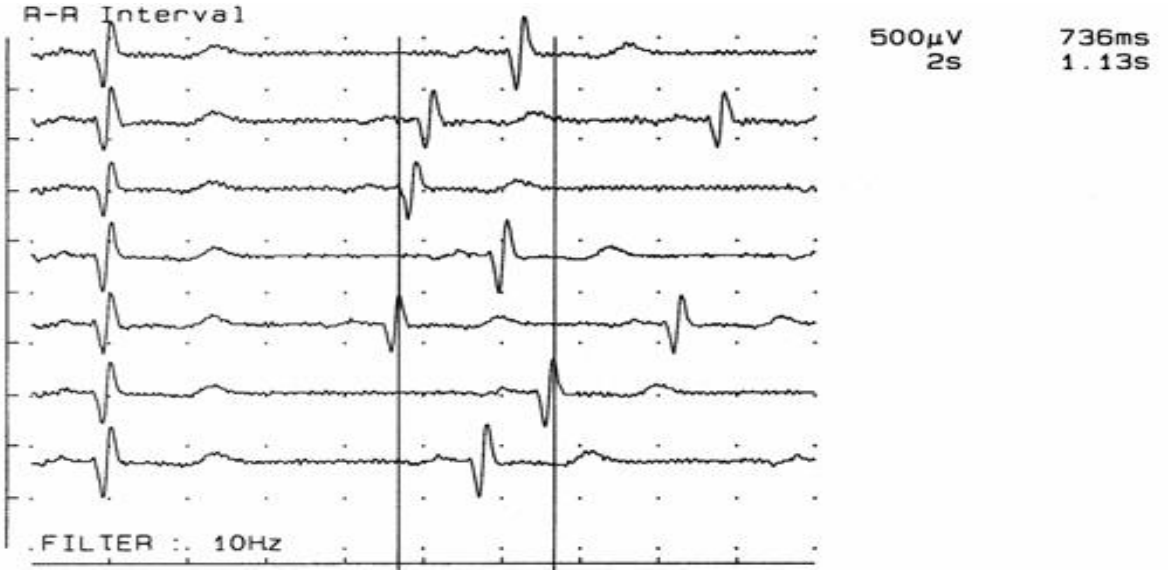

Figure 2. Physiological increase in R-R interval variability is observed during deep breathing.

as %D. At the same time, the difference between %D and %R (D- R) and the ratio of %D to %R (D/R) was also calculated.

2.4.Statistical Analyses

SPSS for Windows version 10.0 for the statistical analysis was used. Student's *t*-test was used for the comparisons of continuous data of the groups. The relations of duration of headache and age with RRIV parameters were estimated with Pearson's coefficient correlation. The results less than or equal to 0.05 have been considered as statistically significant.

3. Results

This study consisted of 52 females and 19 males. There was no statistically significant difference regarding the ages (p = 0.072). Of the migraine cases, 24 (33.8%) were with aura, whereas 47 (66.2%) were without. The mean age

of the onset of headache in the migraine group was 21.42±8.67, and the mean duration of headache was 9.90±8.15 years.

The mean percentage ratios for RRIV in the migraine cases and the healthy controls are displayed in table 1. There were statistically significant differences of the migraine and the control groups, regarding the RRIV values during resting (%R), and deep breathing (%D) and the D-R values ($p < 0.05$), but not the D/R ratios ($p > 0.05$). There was a negative correlation of %R, %D and D- R with age in the migraineurs. However, in the control group, while %R and %D were negatively correlated with age, there was no such correlation for D-R and D/R. The correlation coefficients of RRIV with age are displayed in table 2. The correlation coefficients of the durations of headache with RRIV are displayed in table 3, and no significant correlation was observed between those parameters.

4. Discussion

The suggestion for the investigation of ANS functions in headache patients is primarily based on clinical observations. Different symptoms of migraine attacks; nausea, vomiting, diarrhea, pallor, flushing, piloerections and diaphoresis; are explained with the unstabilities of ANS. Therefore, many studies have focused on determining the ANS functions in migraineurs. Some of the previous studies (3, 4) have reported normal ANS functions, whereas others have reported dysfunctions of SNS (5-8) or both SNS and PNS (9-12). These contradictory results of the ANS function studies might result from the use of various methods for ANS function determinations.

RRIV is a simple and reliable electrophysiologic test for the determination of cardiac PSN functions (13-15). In some neurologic diseases such as migraine (17), Huntington's disease (18), multiple sclerosis (19) and Parkinson's disease (20), it has been shown to be valuable in the determination of ANS involvement. Normally, the alterations of heart rate in healthy individuals during resting are induced by respiration, and these alterations are more prominent in children. The neural control of RRIV by respiration is partially related to a parasympathetic reflex, and is primarily via the vagal innervations of the heart. An intact vagal innervation and a normal brainstem functioning are important factors for normal beat-to-beat alterations. Expansion of the lungs during inspiration stimulates the pulmonary stretch reflexes of the trachea and the bronchioles. These stimuli are transmitted to the cardio inhibitory center, and as a result, the efferent vagal tonus is increased, and the heart rate decreases (21, 22). In all age groups, deep respiration increases RRIV, though at different grades. It is well recognized that, increasing age results in a reduction of the beat-to-beat alterations due to a decreased vagal tonus (23, 14, 15). As the neural control of RRIV is related to a PSN reflex integrated at the medullary level, disorders of this area can be responsible of the abnormal RRIV.

In our study, the RRIV, %R, D%, and D-R values of the migraine patients were significantly lower than those of the controls (table 1). These findings bring up the presence of a PSN hypoactivity in migraineurs. In the migraineurs and controls, there was a negative correlation of %R and %D with age (table 2). These findings are consistent with the previous studies, which have revealed a strong negative correlation of heart rate response with age appearing as a progressive decrease during both normal and deep breathing. Though the %R, %D and D-R values of the migraineurs during periods free of attacks were significantly lower than those of the controls, the presence of a negative correlation of %R, %D and D-R with age may indicate that the parasympathetic involvement is rather mild. However, this condition can also result from the heterogeneity of the age distributions in both patient and control groups. Besides, the lack of correlation of the disease duration with the RRIV values might be because the time period was relatively short, or that the migraine cases were not classified according to the disability of disease. Shechter *et al.,* (11) in their population-based case-control study evaluating the ANS functions in migraine have suggested that, the cases with disabling migraine attacks might be tending to have ANS dysfunctions. Apel *et al.* (24) have used a spectral analysis of heart rate fluctuations via 24-hours Holter ECG monitoring to determine the autonomic control of the heart in migraine cases, and reported spectral analysis findings indicating sympathetic hyperfunction and parasympathetic hypofunction. Thus, they concluded that there is an imbalance between SNS and PSN in migraineurs. Again, Tabata *et al.* (25) have detected PNS hypofunctioning in the cosinor analyses of heart rate variability in migraine cases during headache-free periods of their routine daily activities. Thomsen *et al.* (26) have reported mild parasympathetic hypofunctioning in migraine cases both with and without aura, using transcranial doppler imaging and cardiovascular tests to evaluate cardiovascular responses, and have suggested a

mild parasympathetic hypofunctioning, with the sympathetic functions preserved, in migraine cases both with and without aura.

The mechanism of migraine indicates an unstable trigeminovascular reflex with a defect in the pain control pathways. This defect allows an excessive discharge of a part of the trigeminal nerve and the thalamic connections responding to the excessive afferent input, or the cortico- bulbar drive. The result is the interaction of the brainstem and the cranial blood vessels, and the afferent impulses resulting from the throbbing headaches. The brainstem mechanisms can be triggered by the cerebral cortex as a response to emotion and stress; by the thalami as a response to excessive afferent stimuli (such as glare, noise, odors, etc.); or by the hypothalamus as a response to the "internal clocks" or alterations of the internal environment. Mood changes thirst and hunger, somnolence and libido are the hypothalamic dysfunction- related warning signs of a developing migraine attack (27). It can be suggested that, factors such as stress, hormone levels and nutrients can affect the brain via alterations of hypothalamic and subsequently brainstem activities of decreased cortical threshold (28). The role of hypothalamus as a centre of initiation and regulation of autonomic activity is generally accepted (29). As a result of the mechanisms pointed out above, it is likely that a hypothalamic dysfunction is the source of both the ANS dysfunction and the migraine headaches. Determination of the reasons of hypothalamic dysfunction in migraineurs will clarify these cases.

In conclusion, our study has revealed that, the migraine patients have mild parasympathetic dysfunction during the headache-free periods of their routine daily activities.

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