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A 48-Hour Holter ECG Study in Migraineurs during Usual Daily Activities

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In order to clarify the condition of cardiac autonomic nervous activity in migraineurs, 48-h Holter electrocardiograms (ECGs) were carried out under free activity on 20 migraineurs during headache free periods and 20 healthy controls. We calculated hourly standard deviation (SD), root mean square successive differences (RMSSD), the proportion fo cycles during which the RR difference is > 50 ms (%RR50), low frequency heart rate fluctuation (LF), high frequency heart rate fluctuation (HF) and LF/HF ratio from heart rate variability, and obtained serial 24 data of these parameters. SD, RMSSD, %RR50 and HF are parasympathetic parameters, and LF/HF is sympathetic. These parameters were fit to cosines curve and analyzed circadian rhythms using the cosinor method. By group mean cosinor analysis, the vectors of the amplitude-acrophases of SD, RMSSD, %RR50, LF, HF and LF/HF significantly differed in the migraineurs from those in the controls. The significant differences of vectors of SD, RMSSD, %RR50 and HF indicate cardiac parasympathetic dysfunction. Midline estimating statistic of rhythms (MESORs) of those parameters did not significantly differ except in LF and LF/HF between both groups. MESORs of LF and LF/HF were significantly decreased in the migraineurs, which indicates cardiac sympathetic hypofunction. We concluded that migraineurs might have cardiac parasympathetic dysfunction and sympathetic hypofunction. By evaluating circadian rhythms using cosinor methods, the parameters of heart rate variability in migraineurs were significantly different from controls. Migraineurs may have some disturbance in their rhythm generator.

Key words: autonomic nervous system; circadian rhythm; headache; parasympathetic nervous system; sympathetic nervous system

Autonomic dysfunction in migraineurs is of broad interest. In a patient with migraine, symptoms of autonomic disturbance can be observed, associated with or without migraine attack, such as blood flow in the cranial artery, Horner's syndrome, etc. However, there is some controversy in the results of various studies on the autonomic nervous system. Abnormalities in the sympathetic nervous system have been fairly well documented in migraineurs during the headache-free phase, such as pupillary sympathetic hypofunction (Fanciullacci, 1979; Herman, 1983; Takeshima et al., 1987a), orthostatic hypotension (Gotoh et al., 1984; Havanka-Kanniainen et al., 1986; Mikamo et al., 1989; Pogacnik et al., 1993), a decrease in overshoot in Valsalva's maneuver (Gotoh et al., 1984; Havanka-Kanniainen et al., 1986), a low level of plasma norepinephrine (Gotoh et al., 1984; Mikamo et al., 1989) and the cold pressor test (Rubin et al., 1985; Takeshima et al. 1989). However, Thomsen and colleagues (1995) recently reported that there was no significant sympathetic dysfunction in migraineurs. On the other hand, dysfunction of the parasympathetic nervous system in migraineurs has not yet been confirmed at all. Some reports showed hyperfunction of parasympathetic activity in

Abbreviations: ABP, ambulatory blood pressure; ECG, electrocardiogram; HF, high frequency heart rate fluctuation; LF, low frequency heart rate fluctuation; MESOR, midline estimating statistic of rhythm; MI, mean interval; RMSSD, root mean square successive differences; RR, between two QRS complexes in ECG; %RR50, the proportion of cycles during which the RR difference is > 50 ms; SD, standard deviation

Table 1. Subjects

		Controls	Migraine group
Number of subjects		20	20
Age	(year)	29.6 ± 10.2*	29.2 ± 12.5*
Sex (male:female)		3:17	4:16
Migraine with aura		–	2
Migraine without aura		–	18
Duration of illness	(year)	–	10.6 ± 11.0* (0.5–35)
Frequency of migraine attack	(times/month)	–	5.0 ± 4.0* (0.2–12)
Duration of migraine attack	(h)	–	17.0 ± 12.7* (2 –72)

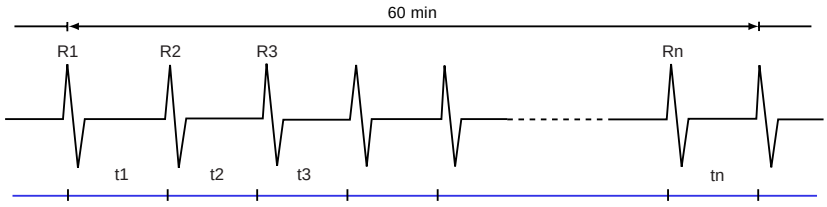
( ), range.
*Mean ± SD.

migraineurs (Gotoh et al., 1984) and others reported hypofunction (Havanka-Kanniainen et al., 1986a; Thomsen et al., 1995), in which short period beat-to-beat variations and spectral analysis in a supine position, standing and during free movement were examined (Appel et al., 1992; Pogacnik et al., 1993). The tone of the sympathetic and parasympathetic autonomic nervous systems is influenced not only by emotional, environmental and physical factors, but also by circadian rhythms. In earlier works, many efforts were made to exclude the diurnal variation of autonomic nervous systems, by fixing the examination hour at a certain time of day. In general, sympathetic activities rise from morning to afternoon and parasympathetic activities rise during night time (Furlan et al., 1990). Depending on the time when the examinations are done, the results of the examinations on the autonomic nervous system may differ and these may be the reason why reported results are contradictory. Recently, we performed a 2-day measurement of ambulatory blood pressure (ABP) in migraineurs and found a decrease in the circadian amplitude of ABP, which suggests sympathetic hypofunction and dysfunction of the central circadian rhythm generator (Takeshima et al., 1997). Measuring serial data and applying rhythm analysis technology for a 2-day period can reveal a subject's state of autonomic function including diurnal variations. Heart rate fluctuations are regulated mainly by the activities of the parasympathetic nervous system. In this study, we evaluated heart rate variability in migraineurs under free daily activity for 2 days, by means of Holter electrocardiogram (ECG) recordings, time domain statistical analysis and spectral analysis of heart rate fluctuations, and cosinor analysis techniques. The aims of this study were: i) to evaluate cardiac parasympathetic tone on the basis of circadian rhythm analysis; and ii) to reveal some specific circadian pattern, if present, of parameters of heart rate variability in migraineurs.

Materials and Methods

Subjects

Twenty subjects who were diagnosed as migraineurs according to the criteria developed by the Headache Classification Committee of the International Headache Society (1988) had Holter ECG recordings (Table 1) performed on them. They were examined during headache-free periods. The mean period between the last attack and the Holter recording was 18.8 ± 19.1 days (mean ± SD, range 1–65 days). During the examinations, they were free from prophylactic medication. Before starting this study, they took anti-migraine drugs only when they had attacks. Two of the migraineurs used a mixture of analgesics 1.0 g (Sedes G, Shionogi, Tokushima, Japan) and metoclopramide 5 mg, 2 days before the examination. The others were free from the abortive use of anti-migraine drugs by at least 7 days prior to testing. The control group consisted of 20 healthy volunteers (Table 1). All participants were neurologically normal, free from respiratory disease and gave their consent after fully understanding the procedure, nature and scope of the study.



$$MI = \frac{\sum_{i=1}^{n} t_i}{n} \text{ (ms)} \qquad RMSSD = \sqrt{\frac{\sum (t_i - t_{i-1})^2}{n-1}} \text{ (ms)}$$

$$SD = \frac{\sqrt{\sum (MI - t_i)^2}}{n} \text{ (ms)} \qquad \%RR50 = \frac{(\text{Number of } (t_i - t_{i-1}) > 50)}{n-1} \text{ (\%)}$$

Fig. 1. Definition of time domain analysis: MI, SD, RMSSD and %RR50. MI, mean interval; n, number of beats in 60 min; SD, standard deviation; RMSSD, root mean square successive differences; %RR50, the proportion of cycles during which the RR difference is > 50 ms; ti, RR interval in ms.

No examinees were admitted to the hospital. All subjects were permitted normal daily activity during the 48-h Holter ECG recordings. They were advised to spend their 48-h period as usual, but were prohibited from hard exercise or the intake of alcohol. They were also required to take note of their activities.

The 48-h Holter recordings

During the examination, the ECGs were recorded continuously using a Space Labs Medical-Holter recorder 90205. Five disposable Ag/Ag-Cl electrodes were located so as to record ECG signals corresponding to the V1 and V5 chest leads. In this way, the 48-h sequential ECGs were recorded. The 2 recorded ECG leads were transferred from the Holter recorder to a Holter ECG analysis system (FT2000A Medical Analysis and Review Station, Space Labs Medical, Inc., Redmond, WA).

Time domain analysis and spectral analysis

Following the removal of arrhythmia and noise, we carried out, on an hourly basis, time domain statistical analyses which consisted of the RR mean interval (MI), standard deviation (SD), root mean square successive differences (RMSSD) and the proportion of cycles during which the RR difference is > 50 ms (%RR50) (Fig. 1). These parameters reflect mainly parasympathetic nervous system activity. Spectral analysis of heart rate fluctuations was performed as follows. Spectral decomposition was imposed on the heart rate time series by a Fast Fourier transformer. The power spectrum of heart rate fluctuations was calculated with a computer-assisted analysis system, a subtrace every 300 s, which was taken every 60 min from the 48-h ECG signal. The analog signal was sampled by an analog-to-digital converter with a frequency of 128 Hz, and a moving window using a straight line was applied for digital smoothing. The heart rate power spectrum was computed in a frequency band from 0.02–0.40 Hz. Hourly low frequency heart rate fluctuation (LF) (0.02–0.15 Hz), high frequency heart rate fluctuation (HF) (0.15–0.40 Hz) and LF/HF ratio (LF/HF) were calculated. The significance of the circadian rhythm of these parameters was tested using the single and the group-mean cosinor methods (Nelson et al., 1979).

Single and group mean cosinor analyses and comparison of heart rate related variables between groups

Hourly averaged values of MI, SD, RMSSD, %RR50, LF, HF and LF/HF were calculated in each subject. As an example, RMSSD values

for Day 1 from 0900 to 0959, and for Day 2 from 0900 to 0959 were averaged and this value was employed as the RMSSD for 0900. Thus we obtained 24 hourly values of each parameter for each examinee. The significance of the averages of these hourly parameters was examined with the unpaired *t*-test among groups. The significance of the circadian rhythm of these parameters was tested using the single and the group-mean cosinor methods. We applied cosinor analysis to the 24 serial data using BASIC programming language. Following all the single cosinor analyses, we carried out group mean cosinor analyses and statistical comparisons between groups. Details of the cosinor analysis method have been described elsewhere (Takeshima et al., 1997). In brief, we determined a fitted cosinor curve with a 24-h rhythm from measured values. The cosinor curve is represented as $y = M + A \cos(\omega t + \phi)$, where M = midline estimating statistic of rhythm (MESOR), A = amplitude, $\omega = 2\pi/24$, ϕ = acrophase. According to cosinor analysis, the circadian rhythm of any ECG parameter is characterized by MESOR, amplitude and acrophase. The significance of the circadian rhythm was tested by the zero-amplitude test. Single cosinor analysis represents the circadian rhythm of each subject. With χ^2-test, we examined the difference between migraineurs and controls in the number of subjects who had significant circadian rhythms in each parameter. The other side, group mean cosinor analysis represents the circadian rhythm of a group. Inter-group differences of MESORs were tested by the MESOR test (Nelson et al., 1979). Amplitudes and acrophases are given as a vector, so it was necessary to test differences in amplitude and acrophase between groups simultaneously. Inter-group differences in the amplitude-acrophase vector were tested by the amplitude-acrophase test (Nelson et al., 1979). The 5% possibility was regarded as statistically significant throughout the study.

Results

Time domain analysis, i.e., MI, SD, RMSSD and %RR50, and spectral analysis, i.e., LF, HF and LF/HF

MI, SD, RMSSD, %RR50, LF, HF and LF/HF of 48-h data (mean ± SD), were 799 ± 72 ms,

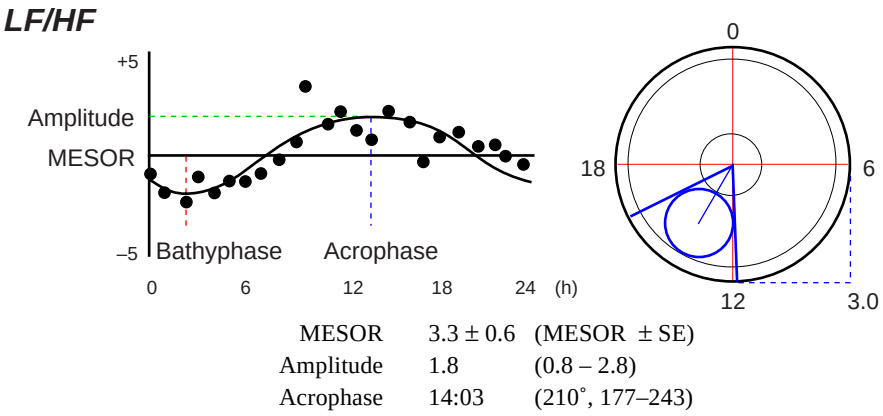


Fig. 2. An example of single cosinor analysis: Single cosinor analysis of LF/HF on a 22-year-old female patient with migraine without aura. **Left:** The base line is MESOR (3.3) and the points of +5 and –5 indicate MESOR ± 5. The hourly sequential data (●) are fitted to the cosinor curve. **Right:** Amplitude and acrophase are shown on the cosinor display by a vector on the coordinates. The outside circle indicates a 24-h period. Zero-amplitude test was performed. In a case where the 95% confidential circle, which is displayed by a small circle, doesn't include a zero-point, the circadian rhythm is regarded as significant. HF, high frequency heart rate fluctuation; LF, low frequency heart rate fluctuation; MESOR, midline estimating statistic of rhythm.

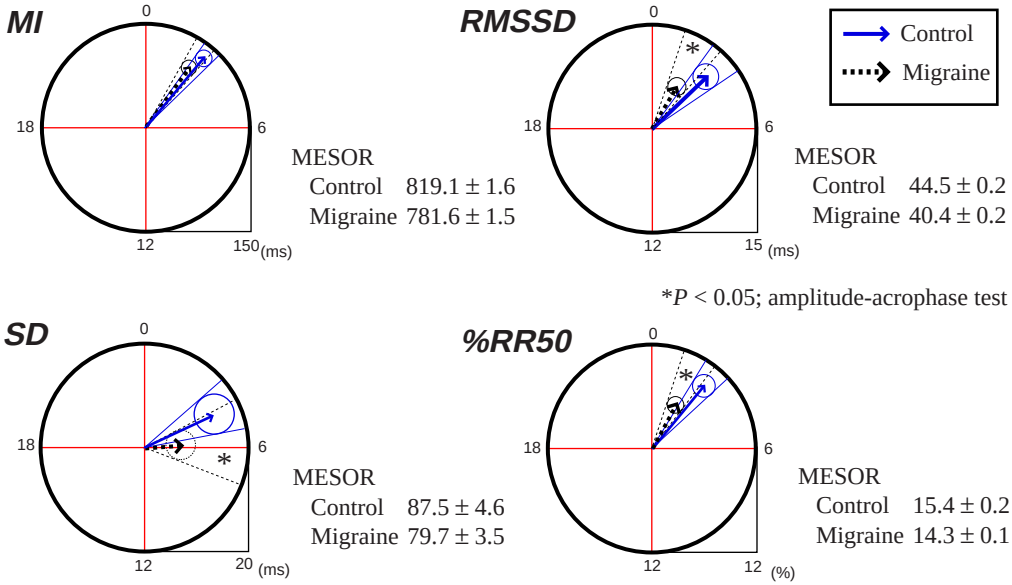


Fig. 3. Group mean cosinor analysis of MI, SD, RMSSD and %RR50. The amplitude-acrophase vector and MESOR of the MI showed no significant difference between groups. Amplitude-acrophase vectors of SD, RMSSD and %RR50 in the migraine group were significantly different from those in controls (amplitude-acrophase test, $P < 0.05$, small circles represent the 95% confidence area). MESORs of these parameters showed no significant difference between groups (MESOR test). MESOR, midline estimating statistic of rhythm; MI, mean interval of heart rate; RMSSD, root mean square successive SD; %RR50, the proportion of cycles during which the RR difference is > 50 ms.

65.8 ± 14.1 ms, 46.0 ± 16.3 ms, 14.2 ± 9.0%, 2141 ± 1073 ms^2, 495 ± 485 ms^2 and 6.02 ± 2.78 in the controls, and 776 ± 80 ms, 61.7 ± 38.4 ms, 43.5 ± 18.3 ms, 15.2 ± 13.2%, 1683 ± 808 ms^2, 582 ± 524 ms^2 and 4.21 ± 2.07 in the migraine group, respectively. Averages of all parameters except for LF/HF were not significantly different between the migraine and the control group. LF/HF in the migraineurs was significantly smaller than that in the controls (unpaired *t*-test, $P < 0.05$).

Single cosinor analysis of MI, SD, RMSSD, %RR50, LF, HF and LF/HF

A typical example of single cosinor analysis is illustrated in Fig. 2. Nineteen out of 20 controls and all 20 migraineurs showed significant MI rhythms. The incidence of significant circadian rhythms in SD, RMSSD and %RR50 were 9, 15 and 17/20 in the controls and 10, 14 and 18/20 in the migraineurs, respectively. The incidence of significant circadian rhythms of LF, HF and LF/HF were 10, 13 and 8/20 in the controls and 11, 9 and 11/20 in the migraineurs, respectively. The incidence of significant rhythms of these time domain and spectral parameters showed no significant difference between the migraine group and the controls (χ^2-test).

Group mean cosinor analysis of MI, SD, RMSSD and %RR50

With the group mean cosinor method, significant circadian rhythms were determined in MI, SD, RMSSD and %RR50 in both the migraine group and the controls. In MI, there were no significant differences in the MESOR or the vector of amplitude-acrophase between the 2 groups. The amplitude-acrophase vectors of SD, RMSSD and %RR50 in the migraine group significantly differed from those in the controls (amplitude-acrophase test, $P < 0.05$). There were no significant differences in MESORs of SD, RMSSD and %RR50 between both groups (MESOR test, Fig. 3).

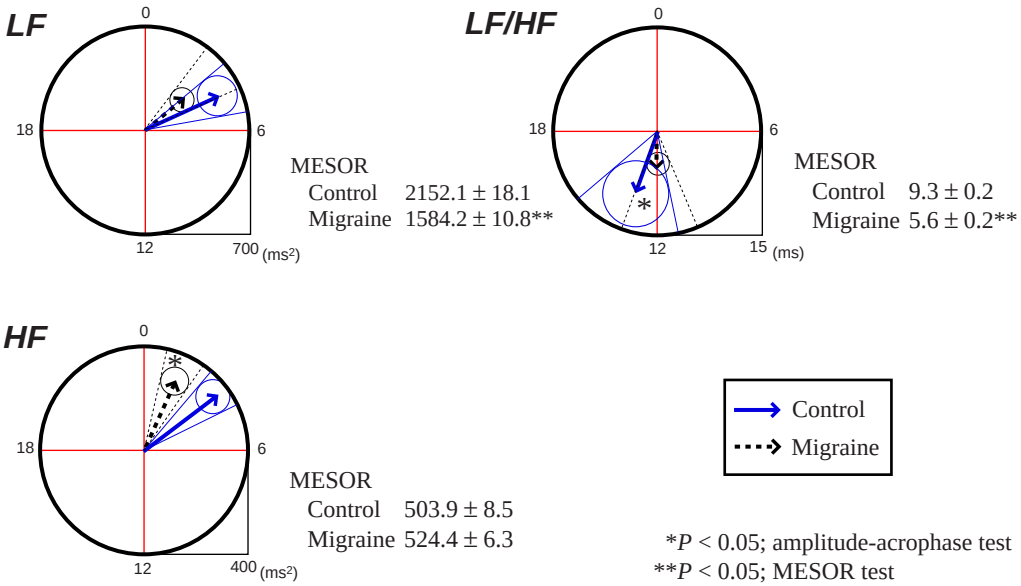


Fig. 4. Group mean cosinor analysis of LF, HF and LF/HF. Amplitude-acrophase vectors of LF, HF and LF/HF in the migraine group were significantly different from those in controls (amplitude-acrophase test, $P < 0.05$, small circles represent the 95% confidence area). There were significant differences in the MESORs of the LF and LF/HF ratio between the migraine group and the controls (MESOR test, $P < 0.05$). These results suggest the dysfunction of the sympathetic nervous system and the possibility of circadian rhythm generators. HF, high frequency heart rate fluctuation; LF, low frequency heart rate fluctuation; MESOR, midline estimating statistic of rhythm.

Group mean cosinor analysis of LF, HF and LF/HF

With the group mean cosinor method, circadian rhythms existed in LF, HF and LF/HF in both the migraine group and the controls. The amplitude-acrophase vectors of LF, HF and LF/HF were significantly different between both groups (amplitude-acrophase test, $P < 0.05$). There were significant differences in the MESORs of LF and LF/HF between the migraine group and the controls (MESOR test, $P < 0.05$, Fig. 4).

Discussion

In most earlier studies, the time domain statistical analysis and power spectral analysis of heart rate variability were examined in a condition of rest, supine position for a short period, and the examinations were performed at a certain time of day to exclude the influence of circadian variations. We carried out 48-h Holter ECG recordings under free activity in order to obtain data during normal daily activity including circadian rhythms. Two-day recording and an hourly averaging method over a 2-day period can minimize the influence of environmental, physical and emotional incidental factors and enable an effective analysis of autonomic nervous functions during normal daily activity (Takeshima et al., 1997). Other advantages of this method are: i) the procedures are non-invasive; ii) examination of circadian variations in combination with cosinor analysis or other rhythm analysis technologies is possible; and iii) comparison of groups utilizing group-mean cosinor analysis can be performed.

The time domain analysis parameters, i.e., SD, RMSSD and %RR50, are thought to reflect the activities of the parasympathetic nervous system. LF (0.02–0.15 Hz), which is one type

of spectral analysis parameter, is mediated by both sympathetic and parasympathetic contributions. Below 0.04 Hz relates to sympathetic and parasympathetic function, and near 0.10 Hz reflects sympathetic activity of the vasomotor reflex. HF is mediated by parasympathetic nervous control and is related to respiratory sinus arrhythmia (Akselrod et al., 1981 and 1985; Pomeranz et al., 1985). Therefore, the LF/HF ratio reportedly represents sympathetic nervous control. These parameters of spectral analysis vary with respiratory frequency or posture. On standing with eupnea, the LF component increases, which shows a relation to sympathetic nervous activity, while the HF component decreases in the same conditions, relating to parasympathetic nervous activity (Pomeranz et al., 1985; Zigelman et al., 1994). In the present study, we did not record respiration, so we can not tell how much influence it may have on sympathetic function, and still more on LF and HF. All of the subjects were free from any heart or respiratory disease, so we think respiration may not have had muc effect on the data of either group.

In this study, only 2 patients had migraine with aura. We also analyzed data excluding migraine patients with aura (data not shown); the overall results were essentially identical to the presented data. Within 3 days before the examinations, 3 migraineurs each had an attack. One patient, who had an attack 24 h before the Holter ECG recording, did not take any medication. Regarding the possibility that migraine pain by itself might influence their autonomic function, we performed the recordings during a headache free period and long enough after the last attack, so that these influences were minimal even if they existed.

Using the rhythm analysis technique, we found significant differences of time domain and spectral analysis parameters of heart rate fluctuation during normal daily activity between migraineurs and controls. The vectors of amplitude-acrophases of SD, RMSSD, %RR50, LF, HF and LF/HF in the migraineurs were significantly different from those in the controls. There were no significant differences in the MESORs of these parameters except for LF and LF/HF between the migraine group and controls. The significant differences of vectors of amplitude-acrophases for SD, RMSSD, %RR50 and HF indicate parasympathetic dysfunction in migraineurs during headache free periods. The MESORs of LF and LF/HF in migraineurs were smaller, which suggests hypofunction of the sympathetic nervous system.

As for the coordinates, the time of acrophases in SD, RMSSD and %RR50 seemed almost similar between both groups, while the length of vectors of the migraine group were shorter than those of controls (Fig. 3). The decrease in amplitudes might contribute mainly to significant differences in the amplitude-acrophase test. The decrease in heart rate variability in migraineurs may be due to hypofunction of the parasympathetic nervous system.

In the case of a certain degree of disorder in the effector organs, not only the amplitude but also the MESOR should decrease (Takemiya, 1994). The decreased MESOR of LF/HF suggests that sympathetic hypofunction might be associated with a disorder at the level of the effector organs. While only amplitudes of SD, RMSSD and %RR50 were decreased, the oscillator of circadian rhythms may form weak rhythms in parasympathetic parameters.

In mammals, the circadian rhythm of the autonomic systems including heart rate fluctuations, blood pressure, body temperature and hormonal regulations are generated at the suprachiasmatic nuclei, which have a rich innervation of serotonergic neurons (Moore et al., 1978; Malmgren, 1990). Serotonergic abnormalities in migraineurs are well documented (Sicuteri et al., 1961; Curran et al., 1965; Takeshima et al., 1987b). Recently, serotonin agonists have successfully been applied to the treatment of migraine. Dysfunction of serotonergic systems may cause the change of the circadian rhythm of heart rate fluctuations in migraineurs.

Considering the presented data, we concluded that migraineurs might have both cardiac parasympathetic and sympathetic hypofunction and might have some disorder in the rhythm generator. Also, the cosinor method seems like a very useful tool in evaluating cardiac autonomic dysfunction in migraineurs.

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