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Heart Rate Variability in Sleep-Related Migraine without Aura

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SCIENTIFIC INVESTIGATIONS

Objectives: This is an observational study aimed to investigate the activity of autonomic nervous system during sleep in patients with sleep-related migraine.

Methods: Eight consecutive migraineurs without aura were enrolled (6 women and 2 men), aged 30 to 62 years (mean 48.1 ± 9.3 years). Inclusion criteria were: high frequency of attacks (> 5 per month) and occurrence of more than 75% of the attacks during sleep causing an awakening. Patients were compared with a control group of 55 healthy subjects (23 men and 32 women, mean age 54.2 ± 13.0 years), and with a further control group of 8 age- and gender-matched healthy controls. Patient and controls underwent polysomnography and heart rate variability analysis.

Results: A significant reduction of the LF/HF ratio during N2 and N3 sleep stages was observed in migraineurs compared with controls. No differences in sleep macrostructure were observed; cyclic alternating pattern (CAP) time and CAP rate were lower in migraineurs than in controls.

Conclusions: These findings indicate a peculiar modification of the autonomic balance during sleep in sleep-related migraine. The reduction of LF/HF ratio in NREM sleep was observed in controls, but it was quantitatively much more evident in migraineurs. Changes in LF/HF could be consequent to an autonomic unbalance which could manifest selectively (or alternatively become more evident) during sleep. These findings, together with the reduction in CAP rate, could be an expression of reduced arousability during sleep in patients with sleep-related migraine. The simultaneous involvement of the autonomic, arousal, and pain systems might suggest involvement of the hypothalamic pathways.

Keywords: Autonomic nervous system, heart rate variability, hypothalamus, cyclic alternating pattern, sleep-related migraine

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Migraine attacks are frequently preceded by premonitory signs and/or associated with symptoms suggesting the involvement of the autonomic nervous system. In particular, symptoms of the prodromic phase[1] (irritability, increased sensitivity to sounds, light, and smells) and symptoms and signs of attacks[2] (nausea, vomiting, cutaneous vasoconstriction or vasodilatation, piloerection, sweating) have an autonomic basis.

Several previous clinical studies investigated a possible dysfunction of the autonomic nervous system in migraineurs, but a large variety of measures have been used to assess autonomic function, and the results are consequently controversial.[3-6] Sympathetic hypofunction,[4,5,7-10] sympathetic instability or hyperfunction,[11,12] and/or parasympathetic dysfunction[4,8,13] have been described or suggested in migraine. Other authors reported mild sympathetic hyperactivity in migraineurs, without evidence for an impairment of the autonomic cardiovascular control.[14] These contradictory results were probably caused by many factors that can bias autonomic function tests: age, weight, gender, test selection, test criteria, conditions of testing, and patient selection. At present, more than 30 years after the first description,[15] the most widely used method for assessing the status of the cardiovascular sympatho-vagal balance is represented by spectral analysis of heart rate variability (HRV),[16,17] which has the advantage of being noninvasive. This analysis, through the quantification of low-frequency oscillatory components (LF) and high-frequency oscillatory components (HF, synchronous with the respiratory rate, marker of vagal modulation) is used to estimate the respective role, and the balance, of the orthosympathetic and the parasympathetic components of the autonomic nervous system.[16,17]

BRIEF SUMMARY

Current Knowledge/Study Rationale: Migraine, as well as sleep, are associated with modifications in the activity of the autonomic nervous system (ANS). The aim of this study was to evaluate the activity of ANS in a population of patients with sleep-related migraine, by means of heart rate variability analysis.

Study Impact: In sleep-related migraine, there is a reduction of LF/HF ratio during N2 and N3 sleep stages, as compared with controls. This reduction occurs in parallel with the decrease of NREM sleep instability measured with cyclic alternating pattern. The results suggest that sleep-related migraine is associated with impairment of EEG and autonomic arousal mechanisms.

Migraine has a close relationship with sleep.[18] It is well known that the onset of migraine attacks can occur during sleep; conversely, in some patients, sleep may relieve the symptoms of migraine.[18] On the basis of the time of onset of the attacks, some authors[3,19-21] have defined a "sleep-related migraine," in which the onset of attacks has a close correlation with sleep, that is, more than 75% of the attacks occur during sleep. In the

Table 1—Patient clinical and demographic data

Patient	Age	Gender	Attacks per month	Duration of illness	Comorbidity	Treatment		AHI (events/h)	BMI (kg/m²)
						Prophylaxis	Symptomatic		
1	62	F	8	> 15 years	None	No	Triptans	3.1	23.7
2	47	F	10	10 years	None	No	Indomethacin	2.0	22.1
3	46	F	10	7 years	None	No	Triptans	1.7	19.8
4	49	M	10	6 months	None	No	NSAIDs	0.6	23.2
5	46	F	6	3 years	None	No	Triptans	1.2	22.6
6	48	F	8	1 year	Moebius syndrome	No	Triptans	3.2	20.3
7	30	F	8	5 years	None	No	Triptans	0.5	24.8
8	57	M	8	8 years	None	No	Acetaminophen	2.1	24.2
Mean	48.1		8.5					1.8	22.6
SD	9.3		1.4					1.0	1.8

AHI, apnea-hypopnea index; BMI, body mass index, SD, standard deviation.

International Classification of Sleep disorders (ICSD 2nd edition) sleep-related migraine can be classified among the sleep-related headaches (Appendix A: sleep disorders associated with conditions classifiable elsewhere).[22] Nevertheless, this form of migraine, defined on the basis of relation between sleep and the onset of attacks, is not coded in the International Classification of Headache Disorders - II.[23]

Sleep induces deep modifications in the autonomic output, with a peculiar pattern of circadian and ultradian oscillations.[24-26] In fact, patterns of autonomic activity undergo significant modifications through wake and sleep, through NREM and REM, and in each specific stage of sleep.[25] These findings were confirmed in quantitative EEG and HRV studies during sleep.[27,28] For these reasons, it could be hypothesized that peculiar modifications of autonomic nervous system activity, occurring during sleep, might facilitate the onset of attacks of migraine in predisposed subjects.

The aim of the present study was to investigate the modification in the autonomic activity during sleep stages in a selected group of subjects with a very close relation between migraine attacks and sleep; this condition, in accordance with some previous reports, was called sleep-related migraine.[21] We hypothesized that, in these patients, autonomic modification occurring during sleep stages could predispose to migraine attacks. In order to clinically define sleep-related migraine, we analyzed the sleep diaries and selected patients in whom more than 75% of the migraine attacks occurred during sleep and caused an awakening. Part of this group of patients was the object of a previous study, in which we analyzed the pattern of arousal in sleep-related migraine.[29] Sleep study was performed by means of nocturnal, laboratory-based polysomnography; sympatho-vagal function was evaluated by means of heart rate variability analysis.

METHODS

Patients

We enrolled in the study 8 consecutive patients of both genders (6 women and 2 men), aged between 30 and 62 years (mean 48.1 ± 9.3 years), fulfilling the criteria of the International Classification of Headache disorders 2nd edition[23] for migraine without aura as well as the criteria of the ICSD[22] for sleep-related headache. Patients were recruited from the Headache Center of the Catholic University in Rome over a period of 12 months. All outpatients, after the first evaluation, were asked to fill in a diary of headache episodes for a period of 4 weeks; this constitutes a standard procedure before defining a diagnosis and starting a prophylactic treatment.[23] All the patients underwent a full medical and neurological evaluation, and were asked to complete a migraine diary for 2 weeks before and 2 weeks after the PSG recording.

Inclusion criteria were: (1) high frequency of attacks (≥ 5 per month) and (2) more than 75% of their attacks during sleep, causing an awakening. Episodes in which the patients presented headache on morning awakening but were not directly awakened by the pain were excluded. Other inclusion criteria were: the absence of prophylactic treatment during the study (no patient received drugs of any kind, chronically, in order to prevent the onset of migraine attacks) or in the previous 3 months; absence of pharmacological treatment of any kind in the month prior to the sleep study, with the exception of triptans or non-steroidal anti-inflammatory drugs (NSAIDs) administered for the acute treatment of attacks. Exclusion criteria were heart disease, arrhythmias, or intake of cardiovascular active drugs; diabetes; uncontrolled hypertension; smoking; obesity; chronic respiratory disease; thyroid disease; psychiatric disorders; severe head trauma; and previous history of sleep disorders of any type or of other neurological diseases. The main clinical data concerning the patients' group are summarized in **Table 1**.

Controls

Heart rate variability and polysomnographic data obtained in patients were compared with data recorded in a control group of 55 healthy subjects (23 men and 32 women, mean age 54.2 ± 13.0); this population of healthy volunteers was previously enrolled to act as controls in previous sleep studies. The same exclusion criteria applied to the patients' group were also applied to the controls. Moreover, as requested in the review process, a further comparison was performed between the patients and an age- and gender-matched control group composed of 8 subjects

(6 women and 2 men, mean age 46.7 ± 10.7 years). All patients and controls gave written informed consent to participate. The study was performed in agreement with the Declaration of Helsinki and was approved by Ethics Committee of the Catholic University in Rome.

Polysomnography

Patients and controls underwent a full-night, attended, laboratory-based nocturnal video-polysomnography. In order to avoid any influence of acoustic stimuli on sleep,[30] patients and controls slept in a partially soundproof room. Polysomnography were recorded by a Micromed System (Micromed, Mogliano Veneto, Treviso, Italy) 98 digital polygraph. Montages included 8 EEG leads applied to the following locations: Fp1, Fp2, C3, C4, T3, T4, O1, O2; reference electrodes applied to the left (A1) or right (A2) mastoids; 2 electrooculographic electrodes applied to the cantus of each eye, surface elect myography of submental and intercostal muscles, airflow measured by oronasal thermocouple, thoracic and abdominal effort, EKG (V2 modified derivation), and peripheral hemoglobin saturation. Impedances were kept below 5KΩ before starting the recording, and checked again at the end of the recording. Sampling frequency was 256 Hz. A/D conversion was made at 16 bit. Pre-amplifier amplitude range was ± 3,200 μV, and pre-filters were set at 0.15 Hz. Sleep monitoring lasted from 23:00 to 07:00 the next morning. A technician was present for data acquisition, and video monitoring was performed throughout the registration.

Sleep Analysis

Sleep stages were visually classified by an expert physician according to the criteria of American Academy of Sleep Medicine.[31,32] The analysis of sleep-related respiratory events was made visually by an expert scorer, according to the criteria established by the AASM.[31,33] Cyclic alternating pattern analysis was performed according to the standardized criteria.[34]

Heart Rate Variability Analysis

Heart rate variability analysis is the measure of the variations of the interval between consecutive heart beats. It is widely accepted that heart rate variability represents a quantitative marker of autonomic activity.[17,35] The variations in heart rate may be evaluated by time domain methods and frequency domain methods.

The time domain methods are based on the detection of the QRS in a normal EKG and on the determination of normal-to-normal (NN) intervals, which are all the intervals between adjacent QRS sinusal complexes. Time domain variables are: mean heart rate, heart rate standard deviation, the square root of the mean squared differences of successive NN interval (RMSSD), and the number of interval differences of successive NN intervals > 50 ms (NN50).

The frequency domain methods consist in the calculation of the power spectral density analysis of a plot of consecutive NN intervals, called tachogram. This power spectral density can be calculated with nonparametric and parametric methods. The parametric methods, as the autoregressive method used in this study, allow an accurate estimation of power spectral density even on a small number of samples on which the signal is supposed to maintain stationarity. Three major spectral components can be computed: very-low frequency (VLF), low-frequency (LF), and high-frequency (HF). The HF component of the spectrum is widely recognized as a measure of vagal activity, whereas the significance of LF component is more debated, and it seems to reflect at the same time both vagal and sympathetic activity. Overall, the LF/HF ratio may provide a quantitative esteem of the balance of the 2 branches of the ANS (sympatho-vagal balance). For a detailed description of the heart rate variability analysis, see: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[17]

In the present study, HRV analysis was performed during quiet wake before sleep and in the following sleep stages: N2-1C (stage N2, first sleep cycle), N2-LC (stage N2, last sleep cycle), N3, REM. For each sleep and wake stage, we selected a single time interval lasting 5 min during which no stage shift occurred. During these intervals the EKG trace was analyzed. For the analysis, we selected 5-min periods chosen with the following criteria: (1) 5 consecutive min of quiet wakefulness (W) before sleep onset, (2) first 5 consecutive min of stage 2 of NREM sleep in the first sleep cycle (N2-1C), (3) first 5 consecutive min of stage 2 of NREM sleep in the last sleep cycle (N2-CL), (4) first 5 consecutive min of stage 3 of NREM (N3), (5) 5 consecutive min of REM sleep (REM). Stage 1 NREM (N1) was excluded from the analysis because this state is considered, by definition, a stage of transition, and it is very unlikely to observe 5 consecutive min of stable N1 in polysomnographic recordings. We analyzed separately 2 intervals of N2 because this sleep stage may have deep differences when it occurs in proximity of SWS or REM sleep. In particular, it has been described as a progressive decrease in HRV sympathetic indexes during the transition toward SWS, contrasting with high and stable levels during N2 that evolves toward REM.[36] Periods of EKG recording containing awakenings, arousals, extrasystoles, or movement artifacts were excluded from the analysis. We decided to analyze intervals of 5 min because we needed to select consecutive epochs of homogeneous recording for each sleep stage, not interrupted by stage shifts, micro-awakenings, fast-frequency EEG arousals, body movements, extrasystoles, or artifacts. Longer intervals of stable EEG and EKG recordings can hardly be observed, in particular during stages N3 and REM. Moreover, 5 min is the minimal length of EKG recording during which the signal is supposed to be stationary, thus allowing an accurate estimate of the spectral components with the autoregressive method.[17,35]

Artifact rejection was performed visually. Dedicated software (Rembrandt SleepView-Medcare) calculated the RR intervals (tachogram). Another software program was used for automatic evaluation of heart rate variability parameters (HRV Analysis Software, Biomedical Signal analysis Group, Dept of Applied Physics, University of Kuopio, Finland).[37]

HRV analysis was performed both in the time domain and in the frequency domain. In the time domain, the parameters calculated were: RMSSD and NN50; geometric measures: the NN triangular index, determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals (i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization), SD1 (standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of

the Poincaré plot), and SD2 (standard deviation of the long term RR interval variability major axis of the Poincaré plot).

In the frequency domain, HRV was analyzed using the autoregressive model (AR, model 16). The frequency bands considered were low frequency (LF, 0.04-0.15 Hz) and high frequency (HF: 0.15-0.4 Hz). The physiological explanation of the very low-frequency component (VLF, 0-0.04 Hz) is poorly defined; moreover, the very low-frequency assessed from short-term recordings is a dubious measure; for this reason the very low-frequency component was excluded from the analysis. The frequency domain parameters analyzed were therefore: the power of the LF and HF bands expressed in absolute values, normalized units, and the LF/HF ratio.

Statistical Analysis

Statistical comparisons were performed between migraineurs and controls (n = 55), as well as between migraineurs and the restricted group of matched controls (n = 8). Since HRV parameters show a skewed distribution in the general population,[38] a nonparametric Mann-Whitney U-test was used for comparison. The same test was used to compare sleep parameters between migraineurs and controls. The comparisons for categorical variables were performed by means of Fisher exact test. In case of multiples comparison, in order to avoid family-wise type I errors, a formal Bonferroni correction was applied to each family of comparisons, by dividing the limit of significance by the number of comparisons (for HRV parameters, 5 comparisons were made, in the conditions Wake, N2-1C, N2-LC, N3, REM; therefore the threshold level for significance was p = 0.05/5 = 0.01). Statistics were performed using the SYSTAT 12 software, version 12.02.00 for Windows (SYSTAT Software).

RESULTS

The diaries of migraine attacks collected by the patients in the weeks before and after the sleep study showed that all patients had ≥ 5 migraine attacks during this interval (**Table 1**). No patient presented migraine attacks in the 48 h before or after the sleep study. Migraineurs and controls did not differ for age (migraineurs = 48.1 ± 9.3, controls = 54.2 ± 13.0; U-test: 284.5, p = 0.183), gender (χ^2 = 0.572, p = 0.364) and body mass index (BMI migraineurs = 22.6 ± 1.8 kg/m^2; controls = 22.6 ± 1.8 m/kg^2, p = 0.465; matched controls = 20.9 ± 2.6 kg/m^2; p = 0.753). No patient presented polysomnographic evidence of sleep disordered breathing (AHI migraineurs = 1.8 ± 1.0 events/h; AHI controls = 2.4 ± 1.3 events/h; AHI matched controls = 2.1 ± 0.8 events/h).

Sleep Structure

All patients had a normal night's sleep; no patient had a migraine attack in the night of the sleep study. Patients and controls did not show snoring or other sleep-related breathing abnormalities. On average, the patients included in this study slept for 428.4 ± 43.4 min; their sleep efficiency index (total sleep time/time in bed) was 92.9% ± 3.0%; the number of awakenings > 1 min was 5.4 ± 4.0. No significant differences in sleep parameters and sleep stage composition was observed between patients and controls; only a trend towards decrease in N1 percentage was observed in patients (migraineurs = 5.5% ± 1.6%, controls = 10.8% ± 8.3%; U-test: 325, p = 0.030). As compared to controls (n = 55), migraineurs showed lower cyclic alternating pattern (CAP) rate (migraineurs = 22.8% ± 2.5%, controls = 30.1% ± 6.5%; U-test: 414, p < 0.001) and CAP time (migraineurs = 78.8 ± 8.0 min, controls = 118.3 ± 36.9 min; U-test: 354, p = 0.006). No significant differences were observed in the indexes of EEG arousals (number of arousals per hour of sleep, per hour of NREM, and per hour of REM). Mean values ± standard deviation of sleep macrostructure and microstructure parameters in patients and controls, and results of the statistical comparison, are reported in **Table 2**. When compared with the matched controls (n = 8), migraineurs showed no significant differences in macrostructural parameters, but they showed lower CAP rate (migraineurs = 22.8% ± 2.5%, matched controls = 47.01 ± 11.2%; U-test: 8.0, p = 0.004).

HRV: Time Domain Analysis

The most relevant difference observed in time domain concerned mean heart rate. In the migraineurs group, when compared with control group, there was a higher mean heart rate during wake (migraineurs = 69.6 ± 3.0, controls = 59.0 ± 3.3 beats/min; U-test: 7.0, p = 0.006), stage N2-1C (migraineurs = 69.3 ± 2.6, controls = 49.0 ± 2.1 beats/min; U-test: 39.0, p < 0.001), and stage N2-LC (migraineurs = 63.5 ± 7.2, controls = 53.5 ± 10.3 beats/min; U-test: 37.0, p = 0.003). Notably, no differences were observed in N3 and in REM sleep. The results of the HRV analysis in the time domain in migraineurs and control groups, with results of U-test and levels of significance, are reported in **Table 3**. Similar results were observed in the comparison between migraineurs and the matched control group (n = 8) (**Table 4**).

HRV: Frequency Domain Analysis

No significant differences in the measured parameters (LF, HF, LF/HF) were observed between migraineurs and controls in wake. In sleep stage N2, in the migraineurs group there was a statistically significant reduction of LF/HF ratio as compared to control group (migraineurs = 0.09 ± 0.01; controls = 1.49 ± 2.26; U test: 42.5, p < 0.001); this occurred without significant modifications of the HF and LF spectral powers. The same result was observed in deep slow wave sleep N3 (migraineurs = 0.09 ± 0.02; controls = 0.78 ± 1.01; U test: 64, p = 0.001). No significant differences were observed, between the 2 groups in REM sleep. Detailed results of the statistical comparison between migraineurs and controls are shown in **Table 3**; a plot of the LF/HF values in each sleep stage is shown in **Figure 1**. Similar results were observed in the comparison between migraineurs and the matched control group (n = 8) (**Table 4**).

DISCUSSION

The main result of this study is the reduction of LF/HF ratio during N2 and N3 sleep stages in migraineurs when compared with controls. As concerns sleep structure, no significant differences between migraineurs and controls were observed in sleep macrostructure; migraineurs had a lower degree of NREM sleep instability measured by CAP time and CAP rate. These latter findings have been described and discussed in a previous paper.[19]

Table 2—Results of the PSG study in migraineurs, controls, and matched controls, and results of statistical comparison

	Migraineurs (n = 8)		Controls (n = 55)		Mann-Whitney		Matched Controls (n = 8)		Mann-Whitney	
PSG Parameters	**Mean**	**SD**	**Mean**	**SD**	**U-test**	**p**	**Mean**	**SD**	**U-test**	**p**
Macrostructure										
Sleep onset latency, min	32.3	24.7	31.3	23.7	205.5	0.765	37.3	29.1	32.0	1.000
Total sleep time, min	428.4	43.4	391.8	53.3	130.0	0.063	419.8	52.8	34.0	0.834
Sleep period time, min	457.6	41.3	443.4	39.8	195.0	0.606	454.1	37.9	32.0	1.000
Sleep efficiency index, %	92.9	3.0	92.0	5.3	215.0	0.918	91.3	5.3	41.0	0.345
Sleep stages, %										
REM	19.3	5.8	17.3	7.8	187.0	0.496	21.0	6.4	26.0	0.529
N1	5.5	1.6	10.8	8.3	325.0	0.030	10.9	8.0	14.0	0.059
N2	42.7	7.3	39.5	11.3	183.0	0.445	36.1	15.0	41.0	0.345
N3	25.2	7.5	20.7	10.5	148.0	0.137	24.2	14.8	38.0	0.529
Wake	7.1	3.0	33.1	46.5	282.0	0.201	21.7	43.5	36.0	0.674
Wake parameters										
WASO, min	33.2	13.4	54.2	40.6	294.5	0.124	40.3	28.0	26.0	0.529
Awakenings > 1 min	5.4	4.0	5.5	3.5	235.0	0.748	6.0	4.1	29.5	0.791
Microstructure										
Arousal index, n	10.2	2.6	11.5	2.2	286.5	0.167	14.4	6.1	19.0	0.172
Arousal Index NREM, n	10.6	2.7	10.9	1.8	306.0	0.074	14.7	6.7	17.0	0.115
Arousal Index REM, n	6.4	2.4	11.6	5.3	251.0	0.521	13.0	4.8	26.0	0.528
CAP time, min	78.8	8	118.3	36.9	354.0	0.006*	156.5	36.8	16.0	0.093
CAP rate, %	22.8	2.5	30.1	6.5	414.0	< 0.001*	47.0	11.2	8.0	0.004*

*Statistically significant differences. WASO, wake after sleep onset; CAP, cyclic alternating pattern; SD, standard deviation.

Table 3—Results of the HRV analysis in migraineurs and controls, and results of the statistical comparison

	Migraineurs (n = 8)					Controls (n = 55)					Mann-Whitney U-test (p)				
Time Domain	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**
Mean HR, bpm	69.6	69.3	63.5	68.1	68.8	59.0	49.0	53.5	56.9	67.4	0.006*	< 0.001*	0.003*	0.173	0.853
SD, bpm	3.0	2.6	3.0	2.2	3.6	3.3	2.1	2.5	2.4	3.6	0.665	0.201	0.591	0.836	0.918
RMSSD, ms	24.6	28.6	37.9	29.6	29.1	28.9	27.2	36.8	32.9	34.7	0.256	0.869	0.901	0.563	0.283
NN50, count	21.8	30.4	52.1	43.0	33.1	48.9	52.6	79.4	71.9	59.1	0.107	0.403	0.476	0.501	0.353
NNTI	0.1	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.1	0.445	0.433	0.092	0.025	0.951
SD1, ms	17.6	20.2	26.9	21.0	20.6	20.5	19.3	26.1	23.3	24.6	0.304	0.869	0.901	0.563	0.283
SD2, ms	47.9	43.3	57.4	35.7	62.5	55.1	39.5	52.1	40.4	71.4	0.483	0.665	0.885	0.496	0.680
Frequency Domain	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**
Abs. Power LF, ms^2	69.8	156.2	149.0	93.0	105.4	130.1	138.5	132.6	115.6	105.4	0.099	0.984	0.757	0.901	0.180
Abs. Power HF, ms^2	60.8	128.2	198.7	208.8	133.3	140.8	170.1	179.1	101.5	133.3	0.099	0.536	0.757	0.695	0.231
LF, n.u.	47.7	49.8	45.0	39.2	48.7	41.5	33.3	36.6	30.2	55.7	0.457	0.035	0.248	0.154	0.757
HF, n.u.	33.7	36.3	46.0	52.5	31.8	35.2	32.4	42.6	52.3	42.8	0.084	0.665	0.421	0.885	0.563
LF/HF	2.4	0.1	1.1	0.1	4.2	2.9	1.5	1.3	0.8	3.0	0.464	< 0.001*	0.549	0.001*	0.877

*Statistically significant differences. HR, heart rate; SD, standard deviation; RMSSD, root mean square of the differences between consecutive RR intervals; NN50, number of consecutive RR intervals differing by more than 50 ms; NNTI, NN triangular index (determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals [i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization]); SD1, standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of the Poincaré plot; SD2, standard deviation of the long-term RR interval variability major axis of the Poincaré plot; Abs. Power, absolute power; LF, low frequency; HF, high frequency. N2-1C, sleep stage N2, first cycle; N2-LC, sleep stage N2, last cycle; bpm, beats per minute; n.u., normalized units.

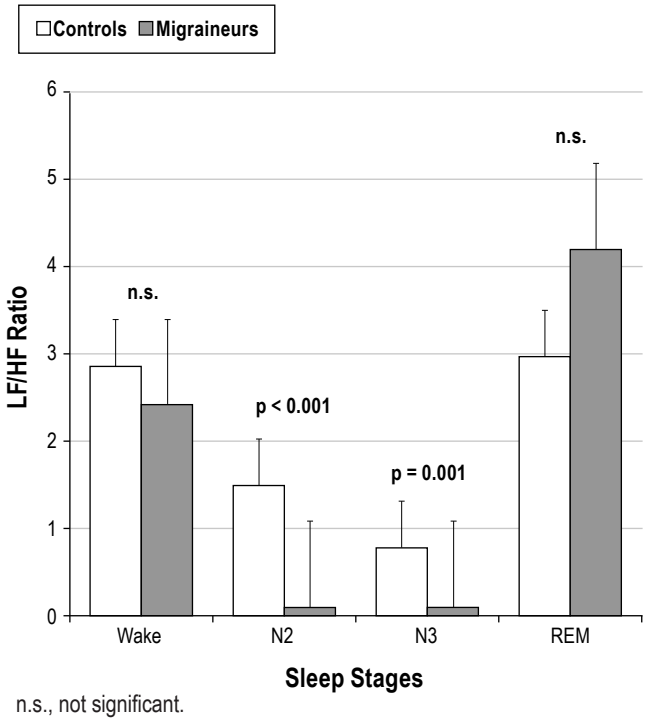
General agreement exists on the functional meaning of spectral component of heart rate variability; nevertheless some matters of debate still exist. The HF component is universally considered as a marker of parasympathetic activity; whereas some doubt exist of the functional meaning of the LF component, which could be an expression of sympathetic tone or a mixture of sympathetic and parasympathetic activation.[17,35] Most authors agree that the LF/HF ratio provides an esteem of the sympatho-vagal balance and its oscillations[17,24,35]; although this point of view has been critically reviewed and questioned by Eckberg.[39] More recently, Burr demonstrated that LF and HF, expressed in normalized units, are predictable from each other, and that there is only one degree of freedom inherent in these two measures.[40] With these limitations, we used the LF/HF ratio as an indicator of fluctuations of the sympatho-vagal balance during sleep.[40]

Table 4—Results of the HRV analysis in migraineurs and matched controls and results of the statistical comparison

	Patients (n = 8)					Matched Controls (n = 8)					Mann-Whitney U-test (p)				
Time Domain	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**
Mean HR, bpm	69.6	69.3	63.5	68.1	68.8	54.2	46.4	65.7	69.3	56.0	0.006*	0.001*	0.036	0.753	0.916
SD, bpm	3.0	2.6	3.0	2.2	3.6	3.5	1.9	2.7	3.3	2.7	0.248	0.208	0.753	0.345	0.529
RMSSD, ms	24.6	28.6	37.9	29.6	29.1	35.4	28.9	35.3	29.0	34.9	0.036	0.834	0.753	0.462	0.600
NN50, count	21.8	30.4	52.1	43.0	33.1	76.9	52.5	58.0	43.1	72.3	0.008*	0.345	0.875	0.563	0.674
NNTI	0.06	0.05	0.1	0.04	0.06	0.1	0.0	131.5	0.1	0.1	0.172	0.792	0.400	0.012	0.462
SD1, ms	17.6	20.2	26.9	21.0	20.6	25.1	20.5	25.0	20.5	24.7	0.036	0.834	0.753	0.462	0.600
SD2, ms	47.9	43.3	57.4	35.7	62.5	67.6	39.1	46.7	62.6	54.9	0.074	0.834	0.834	0.172	1.000
Frequency Domain	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**	**W**	**N2-1C**	**N2-LC**	**N3**	**REM**
Abs. Power LF, ms^2	69.8	156.2	149.0	93.0	105.4	301.3	260.3	165.9	276.6	289.4	0.074	0.462	0.916	0.248	0.074
Abs. Power HF, ms^2	60.8	128.2	198.7	208.8	133.3	216.6	164.3	172.5	103.3	262.0	0.012	0.462	0.834	0.834	0.753
LF, n.u.	47.7	49.8	45.0	39.2	48.7	42.7	35.3	43.4	70.2	41.3	0.529	0.248	1.000	0.753	0.248
HF, n.u.	33.7	36.3	46.0	52.5	31.8	40.7	31.9	46.8	22.6	51.9	0.529	0.916	0.600	0.529	0.674
LF/HF	2.41	0.09	1.1	0.09	4.20	3.8	2.6	1.9	4.8	1.1	0.172	0.001*	0.916	0.001*	0.462

*Statistically significant differences. HR, heart rate; SD, standard deviation; RMSSD, root mean square of the differences between consecutive RR intervals; NN50, number of consecutive RR intervals differing by more than 50 ms; NNTI, NN triangular index (determined from the histogram of RR intervals, in which NN stands for normal-to-normal intervals [i.e., intervals between consecutive QRS complexes resulting from sinus node depolarization]); SD1, standard deviation of the instantaneous beat-to-beat RR interval variability, minor axis of the Poincaré plot; SD2, standard deviation of the long-term RR interval variability major axis of the Poincaré plot; Abs. Power, absolute power; LF, low frequency; HF, high frequency; N2-1C, sleep stage N2, first cycle; N2-LC, sleep stage N2, last cycle; bpm, beats per minute; n.u., normalized units

Figure 1—Plot of the mean values of LF/HF ratio in migraineurs and controls



n.s., not significant.

In the control subjects included in this present study, the time course of the LF/HF along sleep stages was consistent with a well-known circadian and ultradian rhythm[24-26,36,41]: the LF/HF values decreased progressively from wake to N2 and N3, and increased again in REM (**Figure 1**). This pattern of sympathetic-nerve activity has been demonstrated in living humans during sleep by means of a direct, microneurographic recording of sympathetic fibers.[25] The pattern of autonomic oscillations observed in the migraineurs was similar, but it was characterized by a much deeper reduction of LF/HF in NREM sleep; no difference between N2 and N3; and a greater, though not significant, rise in REM.

The functional meaning of these autonomic modifications during sleep in subjects with sleep-related migraine is not defined. It has been reported that during headache-free periods, migraineurs have a reduction in sympathetic function compared to controls, and that migraine is a disorder characterized by chronic sympathetic dysfunction.[42] Seen in this view, sleep-related migraine could be a peculiar condition in which the sympathetic impairment occurs selectively during sleep, hypothetically due to modifications of central nervous system arousability.[19]

Migraine attacks during sleep could be facilitated by this autonomic imbalance, and in particular by the relative prevalence of parasympathetic activity in NREM. In this case, most of the attacks should be emergent from NREM sleep stages. Alternatively, the trigger could be rapid shift from parasympathetic to sympathetic predominance which occurs at the NREM-to-REM transition. In this case, attacks should be more frequent in proximity to REM. Literature data suggest that migraine attacks can occur both in deep NREM sleep stages and in REM.[43,44] No attacks were recorded in our patients.

Whatever the mechanism, these data are in accordance with our previous observation, concerning a group of patients who largely overlapped with this present sample.[19] In that study we observed that migraineurs, compared to controls, had a significant reduction of NREM sleep instability (measured with cyclic alternating pattern) without modifications of the fast-frequency EEG arousals.[19] It is known that CAP reflects a different arousal mechanism than that measured by fast-frequency EEG arousal.[45] Essentially, slow-frequency microarousal (CAP phases type A1) and fast-frequency microarousal (fast EEG arousal and CAP phases types A2 and A3) represent state-specific

arousal responses, differently distributed along the NREM/REM cycles.[45] Moreover, they differ in the power of autonomic effect which is associated: hierarchically, an increasing magnitude of vegetative activation is observed from the weaker slow-frequency microarousals (coupled with mild autonomic activation) to the stronger fast-frequency microarousal (coupled with a vigorous autonomic activation).[45] Our sleep-related migraine patients seem to differ from controls essentially in the amount of slow-frequency microarousal, and this in accordance with the reduced amount of autonomic activation during NREM sleep. Taken together, these data suggest that a close correlation exists between the activity of arousal systems during sleep and the activity of the autonomic nervous system; and that in sleep-related migraine, a peculiar modification of both these systems can be observed.

It could be speculated that the hypothalamus might play a crucial role in the pathogenesis of sleep-related migraine. First, hypothalamus has a major role in regulation of autonomic activity. Second, neuroimaging studies have demonstrated that hypothalamic dysfunction may cause migraine attacks.[46] Finally, the hypothalamus is a part of the arousal system.[47] Experimental evidence indicates that regulation of autonomic functions and nociceptive processing are closely coupled in the hypothalamus and by means of the orexinergic transmission.[48,49] Thus, the orexinergic system in the posterior hypothalamus is modulated by the biological clock and the cortex, and is involved in the modulation of dural nociceptive transmission.[49] Moreover, it is well known that the posterior hypothalamus, as well as the orexinergic pathways, are involved in the regulation of wake, sleep, and arousal.[47] Therefore, we are proposing that a hypothalamic dysfunction, probably involving the orexinergic system, is responsible for the link between the pain of primary neurovascular headaches,[50] the autonomic dysfunction, and the reduced arousability.

In conclusion, in the present study we observed concurrent modifications of NREM sleep instability (CAP) and autonomic modulation during sleep in patients with sleep-related migraine. This is in accordance with a bulk of observations which consider the hypothalamus, where arousal-related and autonomic relays are located, a crucial structure in the pathogenesis of migraine attacks. This is analogous to what happens in another primary, autonomic, closely sleep-related headache, namely cluster headache. Nevertheless, in order to define a causal relationship between these phenomena and to clarify the pathogenesis of migraine attack during sleep, further studies are necessary, and in particular neurophysiological recordings performed in the course of migraine attacks emerging from sleep.

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DISCLOSURE STATEMENT

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