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The impact of chronic primary insomnia on the heart rate – EEG variability link

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ABSTRACT

Objective: To determine if chronic insomnia alters the relationship between heart rate variability and delta sleep determined at the EEG.
Methods: After one night of accommodation, polysomnography was performed in 14 male patients with chronic primary insomnia matched with 14 healthy men. ECG and EEG recordings allowed the determination of High Frequency (HF) power of RR-interval and delta sleep EEG power across the first three Non Rapid Eye Movement (NREM)–REM cycles. Interaction between normalized HF RR-interval variability and normalized delta sleep EEG power was studied by coherency analysis.
Results: Patients showed increased total number of awakenings, longer sleep latency and wake durations and shorter sleep efficiency and REM duration than controls ($p < .01$). Heart rate variability across first three NREM–REM cycles and sleep stages (NREM, REM and awake) were similar between both groups. In each group, normalized HF variability of RR-interval decreased from NREM to both REM and awake. Patients showed decreased linear relationship between normalized HF RR-interval variability and delta EEG power, expressed by decreased coherence, in comparison to controls ($p < .05$). Gain and phase shift between these signals were similar between both groups.
Conclusions: Interaction between changes in cardiac autonomic activity and delta power is altered in chronic primary insomniac patients, even in the absence of modifications in heart rate variability and cardiovascular diseases.
Significance: This altered interaction could reflect the first step to cardiovascular disorders.

1. Introduction

Insomnia is an independent risk factor for coronary heart disease and myocardial infarction, even in the absence of respiratory pathology such as sleep apnea–hypopnea syndrome (Schwartz et al., 1999). Insomnia can be defined as the difficulty with initiation, maintenance, duration or quality of sleep, and results in impairment of daytime functioning, despite adequate opportunities and circumstances for sleep (Silber, 2005). Chronic insomnia of more than one-month duration has a prevalence of 10–15% (Silber, 2005), and is classified as primary or secondary. The pathogenesis of primary insomnia, which represents 10–15% of chronic insomnia (Becker, 2006), is unknown, while obvious causes are common in the secondary form such as sleep apnea–hypopnea, periodic limb movement syndromes, and chronic pain. Insomnia may predispose an individual to the development of major psychiatric disorders such as depression, anxiety and substance abuse, and it is also associated with other chronic medical disorders such as diabetes, arthritis, and heart disease (Sateia and Nowell, 2004).

Cardiac autonomic activity has been studied by non-invasive techniques in patients suffering from insomnia (Jobert et al., 1995; Bonnet and Arand, 1998) and in healthy subjects who are sleep deprived (Holmes et al., 2002; Zhong et al., 2005). By computation of the RR-intervals (RRI) from the ECG, autonomic indexes of sympathetic and vagal cardiac "activity" can be assessed from spectral analysis of heart rate variability (HRV). The low frequency (LF) of the HRV that occurs between 0.04 and 0.15 Hz reflects the relative sympathetic cardiac activity (Akselrod et al., 1981; Malliani et al., 1994; Pagani et al., 1997) known to increase during REM sleep in healthy men (Zemaityte et al., 1986). The high frequency (HF), which is synchronous with the respiratory frequency, is representative of the relative cardiac vagal predominance (Akselrod et al., 1981; Malliani et al., 1994; Pagani et al., 1997) and is increased during NREM sleep in healthy men (Zemaityte et al., 1986). Moreover, LF is increased and HF is decreased during sleep stages 1

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and 2 in comparison to values during sleep stages 3 and 4 (Ako et al., 2003).

It is unclear how chronic primary insomnia alters the cardiac autonomic control in men. In healthy young subjects deprived of sleep, parasympathetic "activity" was amplified during subsequent recovering sleep (Holmes et al., 2002). In contrast, spectral analysis of HRV revealed increased sympathetic activity and decreased vagal influence during the day in normal controls with acute sleep deprivation (Zhong et al., 2005), and across all sleep stages in patients with insomnia in comparison to healthy controls (Bonnet and Arand, 1998).

It is well-known that sleep architecture is modified in chronic primary insomnia. Insomnia is related to a loss ($\geqslant$15%) of sleep efficiency (the ratio between Total Sleep Time [TST] and Time In Bed [TIB]), and a longer sleep onset latency (>30 min) compared to normal sleep in healthy men. Other sleep parameters such as sleep stage durations may be altered (Merica et al., 1998). Whether this affects cardiac autonomic regulation in the absence of experimental sleep deprivation (Holmes et al., 2002; Zhong et al., 2005) is unknown. Moreover, the impact of chronic primary insomnia on the interaction between autonomic cardiac activity and delta sleep EEG in men (Brandenberger et al., 2001; Ako et al., 2003; Jurysta et al., 2003, 2005) has not yet been established.

However, some authors studied the relative sympathetic and vagal cardiac influence in patients suffering from Fatal Familial Insomnia. Insomnia is severe and is not created by experimental conditions. Although this disease is not directly related to the chronic primary insomnia, patients with Fatal Familial Insomnia demonstrate an exaggerated sympathetic activation of the cardiovascular system (Benarroch and Stotz-Potter, 1998; Cortelli et al., 1999), while parasympathetic activity is preserved (Benarroch and Stotz-Potter, 1998).

Moreover, in normal subjects, some cells within the ventrocaudal nucleus of the thalamus show phasic activity related to the cardiac cycle. The authors have suggested that these cells may be involved in the integration of afferent baroreceptor information (Oppenheimer et al., 1998). Thalamic, thalamocortical and cortical neurons are concerned in normal sleep physiology. Their complex interaction, characterized by stimulation or inhibition, provides slow wave sleep or delta rhythm as well as different kinds of arousals (Dang-Vu et al., 2005; Parrino et al., 2006; Steriade, 2006). In chronic insomnia, several authors suggested an elevated basal level of arousal or a failure to down-regulate arousal at night which could imply a hyperarousal state (Bonnet and Arand, 1997; Pigeon and Perlis, 2006). The "activating system" is constituted by neurons located in the midbrain reticular formation projecting to the thalamus and to the cerebral cortex. Sleep is induced by an oscillatory rhythmical activity of thalamic nuclei neurons that show a hyperpolarization of their membranes, while a reduction of polarization induces an abrupt blockade of rhythmical activity with a desynchronization of neuron activity and arousal. Cholinergic and GABAergic neurons as well as adenosine, noradrenalin, serotonin, orexin or hypocretin could be implied in the control of awake and sleep states (Pigeon and Perlis, 2006; Steriade, 2006; Jones, 2008).

The slow rhythms that are observed in polarized thalamic neurons are also observed in the peripheral activity of the sympathetic system, which discloses LF and HF fluctuations in activity. The origins of these oscillations could be attributed to medullary neurons in cardiovascular brainstem structures (Oppenheimer et al., 1998; Massimini et al., 2000; Akerstedt et al., 2002). The interaction between cerebral brainstem structures implied in awake and sleep states and cardiovascular activity was approached with correlation or coherency analysis in healthy controls (Brandenberger et al., 2001; Ako et al., 2003; Jurysta et al., 2003, 2005) and subjects with sleep disorders (Sforza et al., 2007).

Based on the previous findings suggesting that insomnia could be associated with the deregulation of the cardiac vagal and sympathetic balance, we decided to test the hypothesis that the link between autonomic cardiac activity and delta sleep EEG is altered in patients suffering from chronic primary insomnia, in the absence of cardiac or other disease states. This could reflect impairment in sleep and cardiovascular regulation structures, and predispose the individual to future somatic complications.

2. Methods

2.1. Subjects

2.1.1. Patients

Fourteen men, aged 16–63 years (42 ± 12 years) and diagnosed as patients suffering from chronic primary insomnia, were recorded across three successive nights at the Erasmus Sleep Laboratory. To be included, subjects had to complain of sleep disturbance since at least one month, their sleep efficiency had to be lower than 85%. They suffered from no psychiatric, somatic or sleep pathologies, and they consumed no illicit, prescription or OTC (over-the-counter) drugs as confirmed by physical and mental examination and biological analysis. Patients did not drink alcohol, did not smoke and caffeine consumption was restricted (max: 400 mg/day). Sleep medications as benzodiazepines, benzodiazepine-like substances or neuroleptics were stopped at least 14 days prior to the recordings. If subjects suffered from sleep disorders such as a sleep apnea–hypopnea syndrome (defined by an impairment in daytime functioning and a sleep apnea–hypopnea index (AHI) higher than 5 events/hours), a periodic leg movement syndrome (defined by an perturbation of daytime functioning and a periodic leg movement index higher than 5 events/hours), or a parasomnia (abnormal behavior during sleep), they were then excluded from the study. Nevertheless, one patient had an AHI equal to 9 events/hours. Apnea is the complete cessation of breathing for >10 s. Hypopnea refers to a reduction in, but not cessation of, ventilation associated with a larger decrease than 3% in arterial O_2 saturation or an arousal. Apneas and hypopneas are obstructive, central, or mixed (Roux et al., 2000). Subjects did not sleep during the day and were asked to retire around 10:30 p.m. for lights-off time. They awoke spontaneously in the morning. All of our patients meet the criteria of primary chronic insomnia defined in DSM IV (American Psychiatric Association, 1994) and ICSD-R (American Sleep Disorders Association, 2005).

2.1.2. Controls

All 14 healthy controls were men aged 16–55 years (41 ± 10 years). This group was matched for age and BMI with the patient group. Healthy men were recorded across four successive nights at the sleep laboratory. They had no current or past history of any substance use, which could potentially affect EEG recordings or cardiac activity. They were free from diseases, as confirmed by physical and mental examinations and biological analysis, and did not suffer from sleep disorders as confirmed by polysomnography, except for one control which had an AHI equal to 9 events/hours. Sleep instructions, alcohol, tobacco and caffeine consumptions were similar to those of the patient group.

2.1.3. Informed consent

All patients and healthy subjects gave written informed consent before participating in this study, in accordance with the local ethics committee of the Erasmus Academic Hospital.

A complete description of the sections 'Recordings, Data Analysis and Coherence Analysis' is presented in a previous paper (Jurysta et al., 2003).

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2.2. Recordings

Subjects were accommodated with conditions for recordings during the first night, while the second night was used to detect sleep pathologies. For the patient group, the recordings of the third night were used for analysis if ECG and EEG recordings were free from artifacts such as insertion of ECG recording in the EEG signal, or from epochs that cannot be visually scored in sleep stages (Rechtschaffen and Kales, 1968). Recordings of all subjects were free from those. For the control group, recordings of either the third or fourth night were used for analysis whichever was free of artifacts. If neither night showed artifacts, one was selected randomly.

The polysomnography of the second night was obtained by a 19-channel digital polygraph (Brainnet, Medatec, Brussels, Belgium). It consisted of two electrooculograms (EOG), three EEGs (Fz-Ax, Cz-Ax, Oz-Ax, where Ax was the linked mastoid reference), one chin electromyogram (EMG), an electrocardiogram, a pulseoximetery (Biox 3740, Ohmeda, Louisville, CO) to detect oxyhemoglobin saturation, thermistors (Infinity, Sleepmate Technologies, Midlothian, VA) to detect oro-nasal airflow and thoracic and abdominal belts with piezoelectric sensors (Resp-EZ, Sleepmate Technologies, Midlothian, VA) to detect respiratory movements. Leg movements were detected with ankle piezo-electric movement strain gauges (Moving images, Sleepmate Technologies).

In order to avoid sleep disturbances, polygraphy used for analysis consisted of only two EOGs, three EEGs, a chin EMG and an ECG. Each signal was filtered through a low-pass anti-aliasing analog filter with a cutoff frequency of 35 Hz and was sampled at 200 Hz to be read and stored in EDF file format (Kemp et al., 1992). The stage determination, the spectrum calculation, as well as the heart rate analysis were carried out on the sampled data. The Endymion program (Endymion, 2008, Sleep Laboratory, Erasme Hospital) was used to score each 20 s epoch visually in agreement with standard criteria (Rechtschaffen and Kales, 1968). Polysomnography was scored by the same certified person.

2.3. Data analysis

Sleep stages were defined in accordance with Rechtschaffen and Kales criterion (Rechtschaffen and Kales, 1968). Each 20 seconds epoch of the Cz-Ax EEG recording was visually scored as stage 1, 2, 3, 4, rapid eye movement (REM) sleep, or awake. Stages 1 to 4 were classified as non-REM (NREM) sleep.

A Fast Fourier Transform (FFT) was applied on each 5 s data window of the EEG Cz-Ax recording. Then, results were averaged every 20 s. From the obtained spectral power band which is generally defined as the total power band, the delta power band was extracted in accordance of the classical limits [0.5–3.0] Hz (Feinberg et al., 2006).

Delta power was expressed in normalized units by calculation of the ratio between the power value in the delta band and the mean power of this specific frequency band (Aeschbach and Borbély, 1993). Mean power was obtained by the ratio of the sum of the delta power values of every 20 s window and the number of these windows across the full night.

Cardiac sympathetic and vagal spectral components were obtained by application of software developed (Jurysta et al., 2003) in accordance with the principles of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). From the ECG recording, QRS complexes were detected and RR-intervals (RRI-time interval between two successive R waves) were identified and used to calculate the RRI time series. Premature ventricular contraction beats and/or ectopic beats were automatically detected in respect to the following criteria: RRI <350 ms or RRI >1500 ms. These "abnormal" values were removed and the RRI time series were linearly interpolated with the surrounding values (<0.03% of all QRS complexes). All detected events and interpolated values were visually inspected. The spectral analysis of the RRI was performed on 120 s windows (Task Force, 1996). Shifting the 120 s windows ahead by 20 s, we obtained a value for the Low Frequency (LF) ([0.04–0.15] Hz), and the High Frequency (HF) ([0.15–0.4] Hz) of the HRV every 20 s. Therefore, values of LF or HF powers and delta EEG power were simultaneous sampled (Jurysta et al., 2003). We then considered the normalized heart rate variabilities, LF_{nu} and HF_{nu}, defined as the ratio of the power value in the specific frequency band (LF or HF of HRV) to the total power value of LF and HF bands. These normalized LF and HF were not defined with reference to the total power of HRV (Pagani et al., 1997). Thus, $LF_{nu} = LF/(LF + HF)$ while $HF_{nu} = HF/(LF + HF)$. The total power value of HRV, which is mentioned as Total Power of HRV (TP), was the sum of the power values of HRV at every frequency less than or equal to .40 Hz, and therefore, included the very low frequency components (frequencies of < .03 Hz). The ratio LF/HF was also calculated to describe the sympatho-vagal cardiac influence (Montano et al., 1994; Pagani et al., 1997). HRV analysis and FFT computation were performed with the software package MATLAB (The Math Works, Inc., USA) and its signal processing toolbox (Matlab 6.1 with Signal Processing Toolbox 5.1).

Sleep characteristics are shown for the whole night and across the first three NREM–REM cycles, while HRV components are only presented for the first three NREM–REM cycles.

2.4. Coherence analysis (Appendix A and Fig 1)

The relationship between cardiac vagal influence and sleep EEG was studied by a coherence analysis across the first three NREM–REM cycles. This analysis establishes a coherence function, a gain function and a phase shift between the occurrence of the modifications in a first signal as HF_{nu}, and in a second signal as normalized delta power. These are calculated at the frequency $f_{NREM-REM}$, which is the main peak in the cross-spectrum between both signals. The $f_{NREM-REM}$ was located below .0011 Hz because this value corresponds to the minimum duration (15 min) to define a new NREM–REM cycle (Rechtschaffen and Kales, 1968).

The coherence function determines the amount of linear coupling between HF_{nu} and delta, while the gain function is the ratio between the amplitudes of both signals. The phase shift is the delay between the appearance of the modifications in a signal, i.e., HF_{nu}, and the appearance of corresponding modifications in a second signal, i.e., delta power. Phase shift was converted into time units as minutes by dividing the angular phase shift by the frequency $f_{NREM-REM}$ (Jurysta et al., 2003).

2.5. Statistics

Results are expressed as means ± standard deviation (SD). When variables showed a normal distribution, a t-test for independent sampling was performed to test differences between both groups (patients vs. controls). When variables did not show a normal distribution, a non-parametric test for independent sampling was performed. Within each group, an analysis of variance for repeated measures was used to compare the characteristics of sleep stages and the spectral components of HRV. A Bonferroni correction was used to determine the significance levels of the pairwise comparisons. A p value <.05 was considered significant. All statistical procedures were computed using SPSS software (SPSS, 11.5.1, SPSS, Inc., Chicago, USA).

To avoid a possible impact of the large spread of ages and the different durations of the first three NREM–REM cycles between groups, we performed therefore a general linear model (GLM) analysis with age and durations of the first three NREM–REM cycles as

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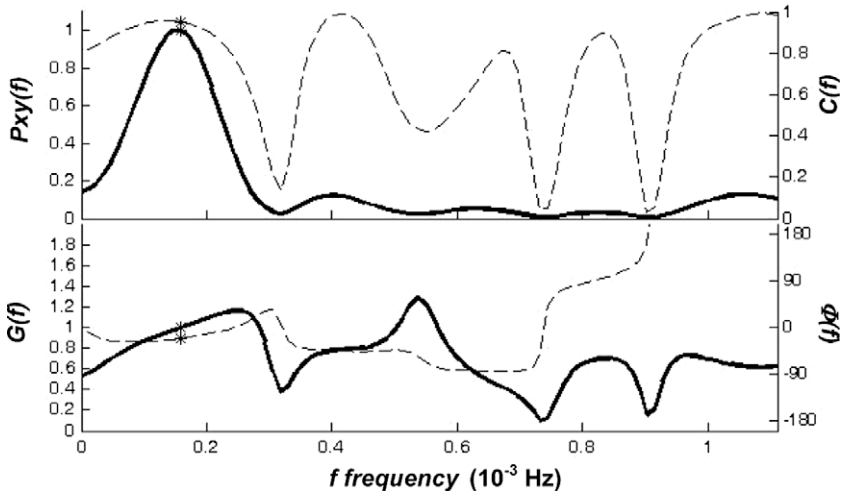

Fig. 1. Values of the cross-spectrum P*xy*(*f*), the coherence *C*(*f*), the gain *G*(*f*) and the phase shift $\varphi(f)$ in degrees (deg) between the normalized High Frequency of RRI variability and the normalized delta EEG power band for a control subject. On the upper panel, P*xy*(*f*) and *C*(*f*) are represented by the bold and the dashed line, respectively. On the lower panel, *G*(*f*) is represented by the bold line while $\varphi(f)$ is represented by the dashed line. The $f_{NREM-REM}$ frequency representing the frequency of the maximum of the cross-spectrum between both signals is marked by an asterisk (*).

covariables. The results did not differ from those obtained by the statistical methodology defined above and presented in the next section.

3. Results

3.1. Demographic and sleep results

Each group (healthy controls and patients with primary chronic insomnia) included 14 age- and sex-matched subjects. Groups did not differ with respect to body mass index, apnea–hypopnea index, apnea index or periodic leg movement indexes (Table 1, upper panel).

As expected, in subjects with insomnia, sleep efficiency was decreased while time in bed and sleep latency were longer in comparison to normal healthy controls (Table 1, middle panel). NREM sleep duration as well as mean duration of each sleep stage (1–4) were similar in both groups. Patients with chronic insomnia showed a larger mean duration of awake stage and smaller mean duration of REM sleep compared to normal controls.

Mean duration of the first three NREM–REM cycles was longer in subjects suffering from chronic insomnia than in control subjects (Table 1, lower panel). Across the first three NREM–REM cycles, NREM and awake durations as well as mean duration of stage 2 were longer in the group of patients compared to the group of control subjects, while REM duration was longer in this latter group. Stage 3 and stage 4 durations did not differ between subjects with chronic insomnia and normal healthy men.

3.2. Heart rate variabilities

None of the HRV parameters differed between groups, normal controls and subjects with insomnia, across all three first cycles combining NREM and REM sleep (Table 2, upper panel).

In each sleep stage of the first three NREM–REM cycles, comparisons of heart rate variabilities of the RRI did not either show differences between controls and patients (Table 2, lower panel).

In healthy men, RRI was similar across sleep stages while LF/HF and LF_{nu} were decreased in NREM sleep compared to REM sleep and awake stage. HF_{nu} evolved in mirror of LF_{nu}. In patients with chronic insomnia, RRI decreased from NREM sleep to awake stage, and, as it was observed in control subjects, LF/HF and LF_{nu} increased from NREM sleep to both REM and awake stages. HF_{nu} decreased in parallel to the increase in LF_{nu} (Table 2, lower panel).

3.3. Coherency analysis (Table 3)

The maximum peak frequency of the cross-spectrum, $f_{NREM-REM}$, and the gain between HF_{nu} and delta power were similar in both groups. The coherence between both signals was larger in control subjects compared to subjects with insomnia. Phase shift, expressed in either degree or minutes, was equivalent between healthy men and patients. In the latter, phase shift between HF_{nu} and delta power was more variable and did not differ from zero.

4. Discussion

In this paper, we demonstrated that (1) patients suffering from chronic primary insomnia showed a decreased amount of linear coupling between a marker of cardiac vagal activity and delta sleep EEG power in comparison to normal control subjects and (2) the delay between modifications in markers of the cardiac vagal activity and those in the delta EEG power band is more variable in subjects with chronic primary insomnia (SD/mean = 2.33) than in healthy control men (SD/mean = .89).

In our study, the group of subjects suffering from chronic primary insomnia showed more difficulties to initiate and maintain sleep with lower sleep efficiency than healthy control subjects. Sleep stages 1–4 durations were similar between both groups, but REM sleep duration in subjects with insomnia was shorter than REM sleep duration in controls. Sleep characteristics of our patients suffering from primary chronic insomnia are in agreement with sleep characteristics previously reported (Merica et al., 1998).

The subjects with primary chronic insomnia did not suffer from specific insomnia at the first or end part of the night. The distribution of increased awake was continuous during the whole night, from sleep onset to waking up. None of our patients showed a hyperactivity of the cardiovascular autonomic activity, evidenced by an accelerated heart rhythm, as has been reported in patients suffering from insomnia (Bonnet and Arand, 1997, 1998; Pigeon and Perlis, 2006). Our study could suggest that insomnia is induced by an impairment of sleep mechanisms more than a hyperarousal state induced by a high level of relative sympathetic activity (Bonnet and Arand, 1997, 1998).

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Table 1
Demographic (upper panel) and sleep characteristics of patients suffering from chronic primary insomnia and normal healthy subjects across the entire night (middle panel) and across the first three NREM–REM sleep cycles (lower panel).

	Subjects with chronic primary Insomnia	Normal controls	*P*-value
Demographic variables			
Number of subjects	14	14	
Age (years)	42 ± 12	41 ± 10	.794
BMI (kg/m^2)	26±5	24 ± 3	.122
AHI (events/hours)	3 ± 2	3 ± 3	.534
AI (events/hours)	1 ± 1	1 ± 2	.822
PLMI for right leg (events/hours)	.04 ± .05	.03 ± .05	.427
PLMI for left leg (events/hours)	.03 ± .06	.02 ± .03	.306
Simultaneous PLMI for left and right legs (events/hours)	0	.01 ± .02	.352
Variables for the entire night			
Sleep efficiency (%)	74 ± 9	90 ± 3***	*<.001*
TIB (min)	508 ± 66	456 ± 51*	*.029*
SPT (min)	461 ± 61	440 ± 58	.368
TST (min)	372 ± 54	410 ± 54	.074
Sleep latency (min)	24 ± 17	10 ± 5**	*.006*
Total number of awakenings	60 ± 27	39 ± 14*	*.017*
NREM duration (min)	301 ± 46	312 ± 51	.545
Stage 1 duration (min)	34 ± 22	28 ± 15	.378
Stage 2 duration (min)	243 ± 51	254 ± 56	.601
Stage 3 duration (min)	19 ± 20	20 ± 14	.794
Stage 4 duration (min)	5 ± 15	10 ± 20	.429
REM duration (min)	71 ± 16	98 ± 18***	*<.001*
Wake duration (min)	89 ± 42	30 ± 15***	*<.001*
NREM duration (%)	65.5 ± 7.4	70.8 ± 5.6	.056
REM duration (%)	15.5 ± 3.1	22.4 ± 4.4***	*<.001*
Wake duration (%)	19 ± 8.3	6.8 ± 3.2***	*<.001*
Variables for the first three NREM–REM cycles			
Mean duration (min)	326 ± 42	273 ± 39**	*.002*
NREM duration (min)	228 ± 37	197 ± 27*	*.018*
Stage 1 duration (min)	20 ± 16	12 ± 6	.111
Stage 2 duration (min)	186 ± 44	157 ± 29*	*.049*
Stage 3 duration (min)	18 ± 19	18 ± 13	.933
Stage 4 duration (min)	5 ± 15	10 ± 20	.440
REM duration (min)	47 ± 15	63 ± 21*	*.030*
Wake duration (min)	50 ± 30	12 ± 7***	*<.001*

Comparisons were performed with normal control subjects, with Bonferroni correction. Values are means ± SD. BMI: body mass index; AHI: apnea–hypopnea index (during TST); AI: apnea index (during TST); PLMI: periodic leg movement index (during TST); TIB: time in bed; SPT: sleep period time; TST: total sleep time; NREM: non-rapid eye movement sleep; REM: rapid eye movement sleep. NREM, REM and wake durations are expressed in minutes (min) or in percentages (%). Percentages are obtained by the ratio between the variable and SPT.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 2
Characteristics of heart rate variabilities of RR-intervals in patients suffering from chronic primary insomnia and normal healthy subjects across the first three NREM–REM sleep cycles.

	Subjects with chronic primary insomnia	Normal controls	*P*-value
Heart rate variabilities of RRI across the first three NREM–REM cycles			
RRI (s)	.94 ± .10	1.01 ± .14	.155
TP (ms^2)	13839 ± 14094	19057 ± 12259	.306
HF (ms^2)	4285 ± 7774	2859 ± 2362	.517
LF (ms^2)	4403 ± 3920	6446 ± 4056	.187
HF_{nu}	36.61 ± 17.77	36.60 ± 13.78	.999
LF_{nu}	63.39 ± 17.77	63,40 ± 13.78	.999
LF/HF	3.37 ± 1.98	3.2 ± 2.00	.876
Heart rate variabilities of RRI across sleep stages of the first three NREM–REM cycles			
NREM RRI	.93 ± .10	.97 ± .18	.451
REM RRI	.92 ± .08	.98 ± .13	.147
Awake RRI	.89 ± .09†††	.96 ± .13	.138
NREM HF_{nu}	38.38 ± 16.77	36.56 ± 11.45	.741
REM HF_{nu}	27.44 ± 17.19†††	29.0 ± 12.95†††	.788
Awake HF_{nu}	28.24 ± 14.04††	27.62 ± 10.05†††	.894
NREM LF_{nu}	59.71 ± 19.77	58.83 ± 15.22	.896
REM LF_{nu}	72.56 ± 17.19†††	71.0 ± 12.95†††	.788
Awake LF_{nu}	71.76 ± 14.04†††	72.38 ± 10.05†††	.894
NREM LF/HF	3.47 ± 2.27	3.21 ± 2.20	.757
REM LF/HF	6.27 ± 5.32†	5.01 ± 3.49†	.467
Awake LF/HF	5.83 ± 3.54††	5.07 ± 2.76†††	.537

Values were means ± SD. *P* values (4th column) relates to comparisons performed with normal control subjects, with Bonferroni correction. For comparisons of HRV of RRI across sleep stages in each group. RRI: RR intervals; TP: total power; HF: high frequency, LF: low frequency; nu: normalized units.
† $p < .05$ vs. NREM sleep.
†† $p < .01$ vs. NREM sleep.
††† $p < .001$ vs. NREM sleep.

Table 3
Coherence analysis between HF_{nu} and delta in patients suffering from chronic primary insomnia and normal healthy subjects across the first three NREM–REM cycles.

Variables	Subjects with chronic primary insomnia	Normal controls	*P*-value
$f_{NREM-REM}$ ($\times 10^{-4}$ Hz)	1.69 ± .41	1.86 ± .57	.384
Coherence	.74 ± .27*	.91 ± .06	*.034*
Gain	4.63 ± 3.67	4.34 ± 1.50	.785
Phase Shift (deg)	17.52 ± 56.92	33.43 ± 23.05	.341
Phase Shift (min)	6 ± 14	9 ± 8	.497

Values were mean ± SD.
* $p < .05$ vs. normal control subjects.

The cardiovascular autonomic modulation has been well studied during sleep in healthy subjects (Jurysta et al., 2003, 2005; Brandenberger et al., 2005), in apneic subjects (Vanninen et al., 1996; Dingli et al., 2003), and in patients with cardiac pathologies (Vanoli et al., 1995; Yamazaki et al., 2005). In normal control subjects, the cardiac vagal influence predominates across NREM sleep, while REM sleep and awake are dominated by the sympathetic component of the cardiac autonomic influence (Vanoli et al., 1995; Jurysta et al., 2005). In subjects with insomnia, only a few studies have measured the respective influence of cardiac autonomic components during sleep (Jobert et al., 1995; Bonnet and Arand, 1998). To approximate the impact of chronic insomnia on the cardiac autonomic balance, normal control subjects have also been deprived of sleep in some past studies (Holmes et al., 2002; Sforza et al., 2004; Zhong et al., 2005). Several limits are related to this methodology such as the use of stimulations to maintain the awake state, the absence of chronic impact of sleep deprivation, and a rebound in slow wave sleep in the subsequent recovery sleep. Nevertheless, some studies have shown a predominance of cardiac sympathetic activity in patients with insomnia (Bonnet and Arand, 1998) or with sleep deprivation (Zhong et al., 2005), while others have not demonstrated these results (Holmes et al., 2002; Sforza et al., 2004). In our study, the normal control subjects disclosed the expected predominance in cardiac vagal influence during NREM sleep in comparison to REM sleep and awake. Inversely, the relative cardiac sympathetic activity was greater during REM sleep and awake. Patients suffering from chronic insomnia showed similar results to normal controls and demonstrated that their cardiac autonomic influence was not altered across the night. The lack of changes in RRI during awakenings in the control subjects can be explained by their very short duration (46 ± 5 s). This contrasts with the longer duration of awakenings for the patients with chronic primary insomnia (104 ± 92 s) which were accompanied by a shortened RRI.

Different authors studied the interaction between cardiac autonomic activity and EEG delta sleep by linear processes (Brandenberger et al., 2001; Ako et al., 2003; Jurysta et al., 2003, 2005). The link between cardiac vagal influence and delta sleep EEG re-

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mains unchanged across the lifespan for middle-aged men (Jurysta et al., 2005) and the occurrence of modifications in HF_{nu} precedes those of delta (Brandenberger et al., 2001; Jurysta et al., 2003, 2005). In this present study, we showed that in patients with chronic primary insomnia the linear relationship between the cardiac vagal influence and delta EEG is decreased in comparison to normal control subjects. This could be possibly related to the alteration in sleep architecture in patients. However, despite this reduction in the linear relationship, the gain between the amplitudes of the modifications in the HF_{nu} band and in the delta power band was unchanged in patients with chronic insomnia. This last conclusion could be expected given that the HRV parameters and mean duration of slow wave sleep did not differ between the two groups.

Our study highlights that the analysis of the link between oscillations in HRV and EEG activity provides information beyond that which is in the analysis obtained from each parameter. Moreover, while HF oscillations preceded those of delta in the controls, this time delay became less predictable in men suffering from chronic primary insomnia. Thus, not only the linear coupling of the link between changes in HRV and EEG, but also the delay between the oscillations was modified in patients with insomnia.

Synchronization of neural discharges in two different brain sites is associated with an increased coherence and an decreased phase coherence as demonstrated by the measurement of neuronal activity in two different brain regions during the transition from interictal to ictal states (Li et al., 2007). A decreased coherence can be understood as a desynchronization of both neural population activities and a relative independency in their activity. In our study, the decreased coherence between relative vagal cardiac activity and delta sleep observed in patients with insomnia in comparison to normal controls could suggest a loss of control between brainstem structures implied in cardiovascular and sleep controls. We would carefully propose the hypothesis that even in the absence of cardiovascular modifications in patients suffering from chronic primary insomnia, the alterations of the linear coupling between relative cardiac vagal influence and delta could be associated with physiological mechanisms preventing impairment in cardiovascular activity related to chronic insomnia. This hypothesis should be further tested by nonlinear methods as Synchronization Likelihood (Stam et al., 2002) or Detrended Fluctuation Analysis (Perkiömäki et al., 2005).

Limitations of our study would be the large spread of ages of the subjects and the different durations of the first three NREM–REM cycles between groups. GLM analysis demonstrated the same results as with ANOVA. It is explained by the fact that the patients were paired with control subjects for age and that slow wave sleep durations of the first three NREM–REM cycles were similar between both groups.

Cardiac diseases and insomnia have been studied for a long time (Schwartz et al., 1999). In the last few decades, discovery and successful treatment of the sleep apnea–hypopnea syndrome has significantly decreased cardiac complications and sudden death (Doherty et al., 2005, Shivalkar et al., 2006). However, a high association between insomnia and coronary heart disease (CHD) persists even in the absence of sleep apneas or hypopneas (Elwood et al., 2006; Schwartz et al., 1999). Furthermore, effects of insomnia, in the absence of respiratory diseases, are independent of classical CHD risk factors such as age, systolic blood pressure, cholesterol, diabetes, smoking and body mass index (Schwartz et al., 1999). These authors have concluded that sleep disturbances, associated with vital exhaustion, induced or were induced by early onset of autonomic dysfunction (Schwartz et al., 1999). The altered link between cardiac autonomic influence and delta sleep in men with chronic insomnia could be a first step towards this derangement.

In conclusion, we report the new finding that, even in the absence of modifications in heart rate variability, the link between changes in cardiac autonomic activity and delta power is altered in patients suffering from chronic primary insomnia.

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Appendix A

The cross-spectrum **Pxy(f)** examines the linear relationship between two stationary time series (x and *y*) in the *f* frequency domain. In our analysis, the normalized High Frequency of RRI variability and the normalized delta EEG power band correspond, respectively, to the x and *y* time series. To maintain a compromise between the requirement of the stationarity of time series and the increase in the frequency resolution of the power spectra, we limited our investigation to the first three NREM–REM cycles.

The output signal *y* corresponds to the linear filtered version of the input signal x. This linear filter is represented by the transfer function **H(f)** (1). From the transfer function *H*(*f*), we obtained the gain **G(f)** (2) and phase shift **φ(f)** (3) that characterizes the relationship between both linear signals *x* and y.

The reliability of the linearity of the transfer function *H*(*f*) is estimated by the coherency **C(f)** (4). Thus, C(*f*) measures the amount of the linearity of the relationship between both time series, *x* and *y* signals. Then, *C*(*f*) = 0 indicates a total linear independence of both signals while C(*f*) = 1 indicates that the 2 processes *x* and *y* (at frequency *f*) are entirely linearly related.

In the frequency domain defined by the duration of the first three NREM–REM cycles, our analysis was performed at the frequency of the maximum of the cross-spectrum between normalized HF and delta power bands, $\mathbf{f_{NREM-REM}}$.

(1) H(*f*) = *Pxy*(*f*)/*Pxx*(f) where *Pxx*(*f*) is the autospectrum of the time series x, and allow to minimize the mean squared error resulting from this linear description.

(2) *G*(*f*) = |*H*(*f*)| and (3) φ(*f*) = tan − 1 (HI(*f*)/*HR*(*f*)) where |H(*f*)|, HI(*f*) and HR(*f*) denote the modulus, the imaginary and real part of H(*f*), respectively.

(4) *C*(*f*) = |*Pxy*(*f*)|^2/Pxx(*f*) *Pyy*(*f*) where *Pyy*(*f*) is the autospectrum of the time series *y*.

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