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Am J Physiol Regulatory Integrative Comp Physiol 291:1165-1171, 2006. First published May 4, 2006;
doi:10.1152/ajpregu.00787.2005

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The link between cardiac autonomic activity and sleep delta power is altered in men with sleep apnea-hypopnea syndrome

F. Jurysta,¹ J.-P. Lanquart,¹ P. van de Borne,² P.-F. Migeotte,³
M. Dumont,⁴ J.-P. Degaute,² and P. Linkowski¹

¹Sleep Laboratory, Department of Psychiatry, ²Department of Cardiology and Hypertension Clinic, Erasmus Academic Hospital of Free University of Brussels, and ³Biomedical Physics Laboratory, Free University of Brussels, Brussels; and ⁴Experimental Physics Laboratory, Université de Mons-Hainaut, Mons, Belgium

Submitted 7 November 2005; accepted in final form 29 April 2006

Jurysta, F., J.-P. Lanquart, P. van de Borne, P.-F. Migeotte, M. Dumont, J.-P. Degaute, and P. Linkowski. The link between cardiac autonomic activity and sleep delta power is altered in men with sleep apnea-hypopnea syndrome. *Am J Physiol Regul Integr Comp Physiol* 291: 1165–1171, 2006. First published May 4, 2006; doi:10.1152/jappphysiol.00787.2005.—We hypothesize that sleep apnea-hypopnea alters interaction between cardiac vagal modulation and sleep delta EEG. Sleep apnea-hypopnea syndrome (SAHS) is related to cardiovascular complications in men. SAHS patients show higher sympathetic activity than normal subjects. In healthy men, non-rapid eye movement (NREM) sleep is associated with cardiac vagal influence, whereas rapid eye movement (REM) sleep is linked to cardiac sympathetic activity. Interaction between cardiac autonomic modulation and delta sleep EEG is not altered across a life span nor is the delay between appearances of modifications in both signals. Healthy controls, moderate SAHS, and severe SAHS patients were compared across the first three NREM-REM cycles. Spectral analysis was applied to ECG and EEG signals. High frequency (HF) and low frequency (LF) of heart rate variability (HRV), ratio of LF/HF, and normalized (nu) delta power were obtained. A coherency analysis between HF_{nu} and delta was performed, as well as a correlation analysis between obstructive apnea index (AI) or hypopnea index (HI) and gain, coherence, or phase shift. HRV components were similar between groups. In each group, HF_{nu} was larger during NREM, while LF_{nu} predominated across REM and wake stages. Coherence and gain between HF_{nu} and delta decreased from controls to severe SAHS patients. In SAHS patients, the delay between modifications in HF_{nu} and delta did not differ from zero. AI and HI correlated negatively with coherence, while HI correlated negatively with gain only. Apneas-hypopneas affect the link between cardiac sympathetic and vagal modulation and delta EEG demonstrated by the loss of cardiac autonomic activity fluctuations across shifts in sleep stages. Obstructive apneas and hypopneas alter the interaction between both signals differently.

heart rate variability; delta sleep electroencephalogram; loss of fluctuations; phase shift

SPECTRAL ANALYSIS OF HEART rate variability (HRV) is a noninvasive technique for the assessment of autonomic indexes of cardiac sympathovagal balance (22, 23). From the R-R interval (RRI), which is the time between two successive R-waves of the QRS signal on the electrocardiogram (ECG), two autonomic indexes are calculated: the low frequency (LF) and the high frequency (HF). LF occurs between 0.04 and 0.15 Hz and is a representation of the predominant sympathetic cardiac

activity. HF that is synchronous with the respiratory frequency is defined between 0.15 and 0.4 Hz.

In the last few years, the interaction between autonomic cardiac activity and sleep has been studied in healthy young and elderly men (7, 8, 13, 14). These studies have demonstrated a strong interaction between cardiac sympathetic and vagal activity and delta sleep EEG; this interaction was maintained across the life span (13). This is because non-rapid eye movement (NREM) sleep is accompanied by predominant HF oscillations in RRI and delta wave oscillations in the EEG. The reverse occurs during rapid eye movement (REM) sleep. In middle-aged men, delta power as well as the relative vagal predominance in cardiac autonomic activity decreased across the night, while the gain between the normalized HF (HF_{nu}) of RRI and delta sleep EEG power did not change with aging. This could be explained by a similar relative decrease of both variables with aging (13).

Obstructive sleep apnea syndrome (OSAS) is a common medical condition that occurs in ~5–15% of the population (25) and dramatically affects the quality of the patient's life. OSAS is linked to hypertension, heart failure, myocardial ischemia, myocardial infarction, stroke, and vascular complications (21, 25, 27). However, the effects of sleep apneas on the interaction between cardiac autonomic control and EEG are unknown. Spectral analysis of RRI and blood pressure variability at night indicated an elevation of sympathetic influence on cardiovascular control, while the HF variability did not increase in patients with OSAS (10, 12). Thus OSAS seems to blunt the normal shifts in cardiac vagal and sympathetic predominance during NREM and REM sleep, respectively. Conversely, delta activity was increased during NREM apnea (30).

These studies indicate that RRI variability and EEG variability are likely to undergo distinct changes in patients with OSAS. We, therefore, decided to test the hypothesis that sleep apneas-hypopneas impair the interaction between autonomic cardiac activity and delta sleep EEG and that this impairment is related to the severity of the sleep apnea-hypopnea syndrome (SAHS). Being overweight is closely linked to OSAS and has also distinct effects on cardiac autonomic control (4, 15). We decided to include three groups in our study: control subjects, closely matched with patients with moderate to severe SAHS and with patients with severe SAHS. Body mass index (BMI) was larger in this latter group of patients.

Address for reprint requests and other correspondence: F. Jurysta, Sleep Laboratory, Dept. of Psychiatry, Erasmus Academic Hospital, Free Univ. of Brussels, 1070 Brussels, Belgium (e-mail: fajuryst@ulb.ac.be).

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METHODS

Subjects. Electroencephalogram (EEG) and ECG recordings of each SAHS patient admitted in the sleep laboratory from 1998 to 2004 were screened. Subjects with no artifacts in recordings and showing at least three sleep NREM-REM cycles were selected (13, 14). Moreover, patients with SAHS were recently diagnosed, normotensive, and free of any other known diseases. Patients were matched with normal control subjects for age, gender, sleep parameters, and blood pressure. Sitting blood pressure was measured two times per day with a mercury sphygmomanometer in carefully standardized conditions. A mean systolic blood pressure and a mean diastolic pressure were obtained for each subject.

All subjects were free of any cardiac history; psychiatric pathologies; and drug, alcohol, nicotine, or caffeine abuse or dependence.

Measurements were obtained in three groups of male subjects: normal control subjects ($n = 12$), patients with moderate-to-severe SAHS ($n = 12$), and patients with severe SAHS ($n = 12$).

The apnea-hypopnea index (AHI) was lower than 10 events/h for normal subjects and larger than 30 events/h for the last group, but the BMI was larger in this group than in other groups (Table 1). The moderate-to-severe SAHS group was composed of patients for whom AHI is larger than 20 events/h and lower than 30 events/h, except for five subjects. Their AHI were 32, 35, 38, 45, and 52 events/h, respectively.

Informed, written consent was obtained from all subjects. The study was approved by the local ethics committee of Erasmus Hospital.

Measurements. The polysomnography (PSG) is used to define the sleep architecture using Rechtschaffen and Kales criteria (26), as well as the continuous recording of sleep quality (1). In the first case, five classical sleep stages are defined from an EEG recording. Each period of 20 or 30 s is visually scored as stage 1, 2, 3, 4, or REM sleep. Awake states are also scored, in agreement with the criteria cited above. In the second case, five spectral power bands are obtained by a fast Fourier transformation of EEG recording across the entire night. Each spectral power band is limited by specific limits of frequency. Sleep power bands are associated with specific sleep stages, as well as with delta power band (defined between 0.5 and 3.0 Hz) and slow-wave sleep (stages 3 and 4) (1).

After one night of accommodation, a PSG was recorded on the second night with a 19-channel digital polygraph (Brainnet, Medatec,

Brussels, Belgium). The detailed description of PSG was reported in previous papers (13, 14). Obtained EEG and ECG signals were amplified, filtered, rectified, and integrated to obtain an appropriate voltage, in accordance with stage determination, spectrum calculation, and heart rate analysis (14).

In adults, 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 or hypopneas are obstructive, central, or mixed (27). The most widely used frequency measure of severity is the number of events per hour of sleep. We reported the apnea index (AI) and the AHI. Severity of sleep breathing disorders can be defined using two dimensions: a clinical one (e.g., sleepiness) and a laboratory one, by determining the number of sleep-related breathing events (apneas, hypopneas) per hour of sleep: mild, 5–15 events/h; moderate, 15–30 events/h; severe, >30 events/h (27).

All subjects experienced regular sleep-wake schedules and did not sleep during the day. They went to sleep between 10 PM and midnight and awoke spontaneously.

Data analysis. Sleep stage determination was performed in accordance with the classical criteria defined by Rechtschaffen and Kales (26). Each 20-s epoch of the Cz-Ax EEG recording was visually scored in stage wake, 1, 2, 3, 4, or REM sleep. Stages 1–4 were classified as NREM sleep. Delta EEG power band was obtained by applying a fast Fourier transform on the EEG Cz-Ax signal. Fast Fourier transform was computed on each 5-s data window. The spectral power was averaged over 20-s epochs. The limits of the delta power band are 0.5 Hz for the minimum and 3.0 Hz for the maximum.

The principles of the software for HRV data acquisition and spectral analysis have been described in a previous paper (14). In brief, we have developed an automated algorithm that detects the QRS complexes from the ECG recording and defines the RRI time series. The ectopic beats were removed and corrected by a linear interpolation with surrounding values. Each step was visually controlled. The RRI power spectral analysis was performed on 120-s windows, according to the recommendations of the Task Force (31). Shifting the 120-s windows ahead by 20 s, we obtained a value for the LF and a value for the HF of the HRV every 20 s. The limits of the LF are 0.04 and 0.15 Hz, and those for the HF are 0.15 and 0.4 Hz. Thus we obtained synchronized values for HF, LF, and delta powers.

Delta, LF, and HF powers were expressed in absolute and normalized units. For delta power, the normalized units were obtained by the ratio of the power value in the specific delta frequency band to the full night mean power value in this specific frequency band (2, 6). For LF and HF, the normalized units were obtained by the ratio of the power value in the specific frequency band (LF or HF of HRV) to the total power value of the HRV after subtracting the power of the very LF component (frequencies of <0.03 Hz) (22, 23). Thus normalized LF ($LF_{nu} = LF/(LF + HF)$), while $HF_{nu} = HF/(LF + HF)$.

Sympathovagal cardiac influence is also described by the ratio LF/HF (20, 23). Therefore, we calculated and compared this ratio for the three groups.

As defined in a previous paper, a coherence analysis between HF_{nu} of HRV and normalized delta EEG power was applied to study the relationship between cardiac vagal influence and sleep EEG among our three groups (14). In short, a coherence function was used to determine the amount of linear coupling between HF_{nu} and delta. This measure has the same meaning as the squared correlation coefficient (explained variance) in a linear regression equation and allows a determination of the amount of linear coupling between the oscillations present in different time series. A gain function is the ratio between amplitudes of two signals, i.e., HF_{nu} and delta. The first signal could be considered as the input signal, whereas the second signal could be considered as the output signal across a linear process. The phase shift is the delay between the appearance of modifications in a signal and the appearance of modifications in a second signal. The phase shifts were distributed on a circular scale (from 0 to 360°) and

Table 1. Demographics of normal subjects and patients with sleep apnea-hypopnea syndrome

Variables	Normal Control	Moderate-to-Severe SAHS	Severe SAHS
No. of subjects	12	12	12
Age, yr	43 (6)	44 (4)	44 (6)
Systolic blood pressure, mmHg	11.7 (1.1)	11.7 (1.4)	12.1 (0.7)
Diastolic blood pressure, mmHg	7.4 (0.8)	7.5 (1.4)	7.7 (0.7)
BMI, kg/m ²	25.7 (1.6)	26.5 (1.7)	32.1 (4.2)‡
AHI, events/h	2.8 (3.3)	29.6 (10.8)‡	55.6 (19.0)‡
AI, events/h	1.3 (2.1)	14.8 (10.6)†	30.9 (20.0)‡
Mean SaO ₂ , %	93.6 (1.6)	91.6 (1.4)†	88.9 (4.1)†
Total no. of obstructive apnea	3.3 (6.0)	80.7 (56.4)†	106.3 (66.4)‡
Total no. of central apnea	5.5 (8.6)	6.3 (7.2)	32.3 (28.2)†
Total no. of mixed apnea	0.2 (0.6)	3.3 (6.0)*	57.0 (108.9)‡
Total no. of hypopnea	11.7 (11.2)	82.3 (32.6)‡	160.8 (53.6)‡

Values are means (SD). SAHS, sleep apnea-hypopnea syndrome; BMI, body mass index; AHI, apnea-hypopnea index; AI, apnea index; SaO₂, arterial O₂ saturation. Comparisons were performed with normal control subjects. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

Table 2. Sleep characteristics of normal subjects and patients with sleep apnea-hypopnea syndrome across entire night and across first three NREM-REM cycles

	Normal Control	Moderate-to-Severe SAHS	Severe SAHS
<i>Variables for entire night</i>			
Sleep efficiency, %	88.4 (4.7)	83.1 (8.0)	86.2 (5.6)
TIB, min	477 (51)	449 (44)	451 (53)
TST, min	422 (51)	373 (47)	390 (61)
NREM duration, min	326 (53)	302 (26)	327 (47)
REM duration, min	95 (21)	71 (25)	64 (26)
No. of nocturnal awakenings	45.6 (13.1)	54.6 (25.0)	58.2 (43.8)
No. of sleep changes	231.8 (74.2)	232.1 (66.8)	292.4 (117.3)
<i>Variables for first three NREM-REM cycles</i>			
NREM duration, min	208 (38)	211 (37)	245 (25)*
Light sleep duration, min	186 (34)	199 (32)	231 (34)*
Slow-wave sleep duration, min	22 (16)	12 (12)	15 (17)
REM duration, min	57 (24)	52 (22)	56 (25)
Awake duration, min	14 (8)	29 (16)	26 (20)

Values are means (SD). Comparisons were performed with normal control subjects. TIB, time in bed; TST, total sleep time; NREM, non-rapid eye movements; REM, rapid eye movements. * $P < 0.01$.

were converted in time units to minutes by dividing the angular phase shift by the frequency $f_{\text{NREM-REM}}$. The frequency $f_{\text{NREM-REM}}$ is the main peak in the cross-spectrum between both signals HF_{nu} and δ . The $f_{\text{NREM-REM}}$ was located below 1.1×10^{-3} Hz, because this value corresponds to the minimum duration (15 min) to define a NREM-REM cycle. Indeed, 15 min is the minimum amount of time between two successive REM epochs to define a new NREM-REM cycle (26).

Coherence, gain, and phase shift between HF_{nu} and δ were calculated at the $f_{\text{NREM-REM}}$.

Statistical analysis. Results were expressed as means (SD). When variables showed a normal distribution, a one-way ANOVA was performed, followed by a *t*-test to allow for pairwise testing for

significant differences between groups. When variables were not normally distributed, a nonparametric test for independent samples was performed, followed by a Mann-Whitney *U* test. Bivariate correlations were estimated with Pearson or Spearman coefficients, as appropriate. A value of $P < 0.05$ two-tailed was considered significant.

RESULTS

Descriptive results. Mean AHI was 3 (3) events/h for the 12 control subjects, 30 (11) events/h for the 12 patients with moderate-to-severe SAHS, and 56 (19) events/h for the 12 patients with severe SAHS ($P < 0.001$). The BMI was similar between both of the first two groups [25.7 (1.6) vs. 26.5 (1.7) kg/m^2] and was increased in the third group [32.1 (4.2) kg/m^2] ($P < 0.001$).

Other sleep measurements (AI, total number of obstructive, central, mixed apnea, or hypopnea, mean saturation in oxygen across the night) are reported in Table 1.

Sleep parameters. Classical whole-night sleep parameters, such as sleep efficiency, time in bed, total sleep time, NREM and REM durations, number of nocturnal awakenings, or sleep changes, were similar in the three groups. During the first three NREM-REM cycles, patients with severe SAHS showed a longer mean duration of NREM sleep than other groups ($P = 0.016$). In patients with severe SAHS, mean duration of light sleep (i.e., stage 1 + stage 2) was higher than that of both of the other groups ($P < 0.004$). The mean duration of slow-wave sleep (i.e., stage 3 + stage 4) was similar in all groups. Mean durations of REM sleep and wake were equivalent in the three groups. Values are shown in Table 2.

HRV. Although AHI grew from the normal control subjects to patients with severe SAHS (Table 1), total frequency of HRV of RRI as well as LF and HF variabilities of the RRI were comparable in the three groups. In patients with severe SAHS

Table 3. Characteristics of heart rate variability of RR interval in normal subjects and patients with sleep apnea-hypopnea syndrome across first three NREM-REM cycles

	Normal Control	Moderate-to-Severe SAHS	Severe SAHS
<i>Heart rate variabilities of RRI</i>			
TF, ms^2	2,945.38 (2,003.55)	3,056.27 (1,897.29)	3,360.21 (2,178.15)
LF, ms^2	1,121.59 (606.26)	1,156.65 (848.03)	1,127.52 (720.26)
HF, ms^2	392.10 (331.74)	478.62 (367.54)	552.70 (622.95)
LF-to-HF ratio	3.89 (2.25)	3.19 (2.74)	2.78 (1.59)
LF_{nu}	75.86 (9.78)	68.76 (14.10)	69.19 (11.83)
HF_{nu}	24.14 (9.78)	31.24 (14.10)	30.81 (11.83)
<i>Heart rate variabilities of RRI across sleep stages</i>			
NREM RRI, s	1.02 (0.15)	0.93 (0.11)	0.95 (0.09)
REM RRI, s	0.98 (0.13)†	0.92 (0.13)	0.94 (0.12)
Awake RRI, s	0.98 (0.13)†	0.89 (0.10)†	0.88 (0.07)‡
NREM LF-to-HF ratio	4.15 (2.22)	3.18 (2.69)	4.07 (2.04)
REM LF-to-HF ratio	6.44 (2.96)†	4.65 (3.15)‡	5.04 (2.56)
Awake LF-to-HF ratio	6.25 (2.82)†	4.82 (2.85)*	5.83 (2.95)†
NREM LF_{nu}	65.59 (11.29)	60.61 (11.39)	66.23 (13.74)
REM LF_{nu}	77.64 (9.84)‡	70.90 (11.09)‡	71.27 (12.23)
Awake LF_{nu}	75.63 (8.63)‡	70.05 (11.28)‡	74.18 (11.51)†
NREM HF_{nu}	34.41 (11.29)	39.39 (11.38)	33.77 (13.74)
REM HF_{nu}	22.36 (9.84)‡	29.10 (11.09)‡	28.73 (12.23)
Awake HF_{nu}	24.37 (8.63)‡	29.95 (11.28)‡	25.82 (11.51)†

Values are means (SD). Comparisons were performed with normal control subjects. TF, total frequency; LF, low frequency; HF, high frequency; LF_{nu} , normalized LF; HF_{nu} , normalized HF. For comparisons of heart rate variability of RR interval across sleep stages, * $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ vs. NREM sleep.

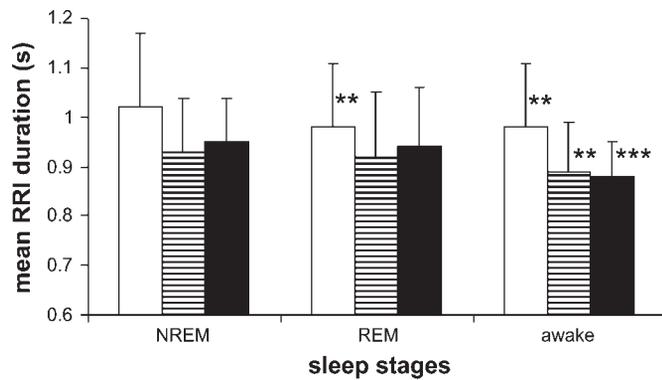


Fig. 1. Mean duration of RR intervals (RRI) in normal subjects and patients with sleep apnea-hypopnea syndrome (SAHS) across sleep stages. Comparisons were performed with non-rapid eye movement (NREM) sleep. Values are means (SD). ** $P < 0.01$, *** $P < 0.001$. RRI are expressed in seconds. REM, rapid eye movement. Open bars, normal control subjects; striped bars, subjects with moderate-to-severe SAHS; solid bars, subjects with severe SAHS.

and with moderate-to-severe SAHS, values for LF-to-HF ratio of RR variability, and LF_{nu} and HF_{nu} components of RR were not different from those observed in the control subjects. During NREM sleep, REM sleep, and awake periods, the RRI was similar in the three groups. LF-to-HF ratio of RR variability as well as LF_{nu} and HF_{nu} components of HRV were equivalent in normal, healthy controls and in patients with moderate-to-severe SAHS or severe SAHS.

HRV parameters across sleep stages as well as the results reported above are shown in Table 3.

The shift from NREM to REM sleep and to the awake state in the controls reduced RRI, increased the LF component, reduced the HF component, and increased the LF/HF component (Figs. 1–3). Similar changes were seen for the patients with moderate-to-severe SAHS, except for the reduction in RRI during REM sleep, which disappeared (Figs. 1–3). In patients with severe SAHS, only reductions in RRI and HF variability and increases in LF variability and in the LF/HF persisted during changes from NREM sleep to wake, while all modifications in RRI and RRI variability between NREM and REM sleep stages disappeared (Figs. 1–3). The only comparison that differed across groups for RRI and RRI variability was the reduction in HF variability between NREM and REM sleep, which was lowest in the patients with severe OSAS (12.05 (6.63) in normal control subjects vs. 5.04 (8.50) in severe SAHS, $P < 0.05$).

The $f_{NREM-REM}$ of the main peak in the cross-spectrum between HF_{nu} and delta power was similar in all groups.

Fig. 2. Normalized low frequency (LF_{nu}) and normalized high frequency (HF_{nu}) of heart rate variability (HRV) in normal subjects and patients with SAHS across sleep stages. Values are means (SD). Comparisons were performed with NREM sleep. ** $P < 0.01$, *** $P < 0.001$. Open bars, normal control subjects; striped bars, subjects with moderate-to-severe SAHS; solid bars, subjects with severe SAHS.

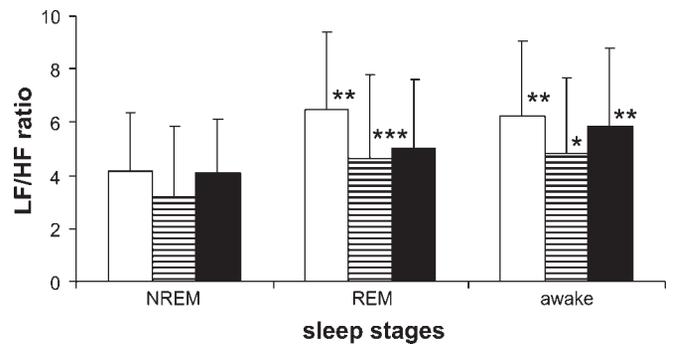
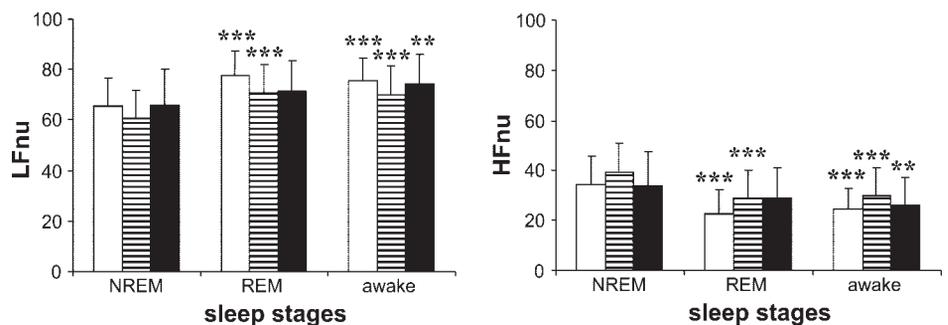


Fig. 3. Ratio between low frequency and high frequency of HRV (LF/HF ratio) in normal subjects and patients with SAHS across sleep stages. Values are means (SD). Comparisons were performed with NREM sleep. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. Open bars, normal control subjects; striped bars, subjects with moderate-to-severe SAHS; solid bars, subjects with severe SAHS.

Normal control subjects showed larger values for the coherence between HF_{nu} and delta EEG band than those observed in patients with moderate-to-severe SAHS ($P = 0.035$) and in patients with severe SAHS ($P = 0.014$). Despite the fact that values of the gain between HF_{nu} and delta EEG power increased from patients with severe SAHS to patients with moderate-to-severe SAHS to normal control subjects, only the difference between normal control subjects and patients with severe SAHS was significant ($P = 0.002$). Although phase shift between HF_{nu} and delta was not different in the three groups ($P = 0.877$), it did not differ from zero in patients with moderate-to-severe SAHS or with patients having severe SAHS. Values are shown in Table 4.

Coherence and gain between HF_{nu} and delta correlated negatively with AHI ($r = -0.51$, $P = 0.001$ and $r = -0.44$, $P = 0.005$, respectively). Moreover, coherence between HF_{nu} and delta correlated negatively with obstructive AI ($r = -0.46$, $P = 0.007$) and also negatively with hypopnea ($r = -0.39$, $P = 0.01$). Gain correlated negatively with hypopnea ($r = -0.44$, $P = 0.005$) (Figs. 4–6).

DISCUSSION

The original findings reported in this study are that 1) apneas-hypopneas affect the link between the cardiac sympathetic and vagal modulation and delta EEG power band; 2) the coherence between cardiac vagal predominance and delta sleep EEG correlates negatively with obstructive AHI; and 3) the gain between both signals is negatively linked to hypopnea index only.

Table 4. Coherence analysis between HF_{nu} and delta for normal subjects and patients with SAHS across first three NREM-REM cycles

Variables	Normal Control	Moderate-to-Severe SAHS	Severe SAHS
$f_{NREM-REM}$ ($\times 10^{-4}$ Hz)	1.82 (0.45)	1.45 (0.49)	1.60 (0.63)
Coherence	0.91 (0.09)	0.77 (0.19)*	0.70 (0.24)†
Gain	4.74 (1.96)	3.52 (2.24)	2.22 (1.50)‡
Phase shift, °	-28 (15)	-30 (50)	-39 (78)
Phase shift, min	-7 (5)	-9 (16)	-12 (28)

Values are means (SD). $f_{NREM-REM}$, NREM-REM cycle frequency. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$ vs. normal control subjects.

Since 2003, nasal pressure and oronasal thermal sensors appear better for detecting respiratory events than one of them alone in apneic subjects with AHI < 50 events/h. If AHI is >50 events/h, nasal pressure associated with oronasal thermal sensor, nasal pressure alone, and oronasal thermistors alone have similar ability to detect respiratory events (32). In our study, we cannot exclude that AHI was slightly underestimated for subjects with moderate-to-severe SAHS. Despite this limitation, the difference between AHI observed in subjects with moderate-to-severe SAHS and AHI of subjects with severe SAHS is high enough (26 events/h) to validate our conclusions.

As previously reported (12, 13), we confirm that heart rate decreases from REM sleep and wake to NREM sleep. This decrease is associated with an increase in cardiac vagal modulation. Moreover, we report that, during the shift from NREM sleep to REM sleep, fluctuations in cardiac autonomic activity are attenuated when patients with severe SAHS are compared

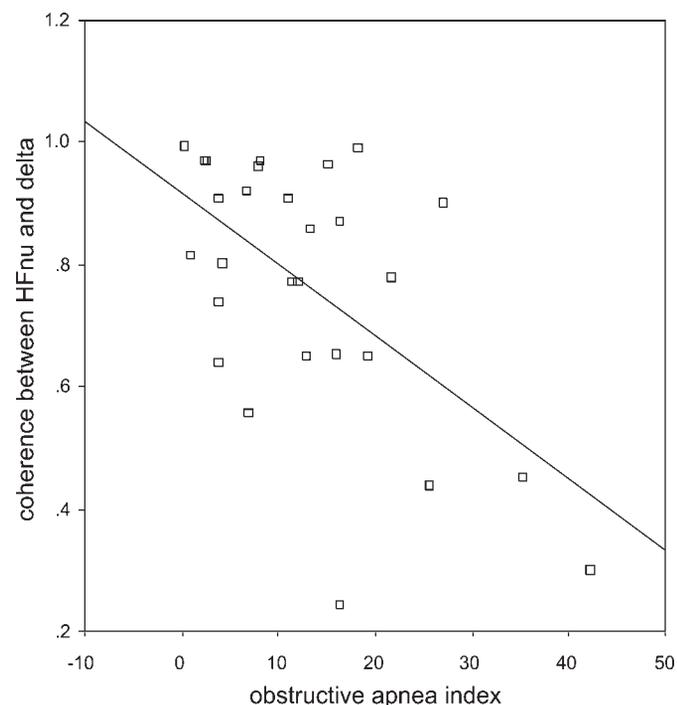


Fig. 4. Correlation between coherence between HF_{nu} of RRI and normalized delta power and obstructive apnea index across the first three NREM-REM cycles. Coherence between HF_{nu} of RRI and normalized delta power correlated negatively with obstructive apnea index ($r = -0.460$; $P = 0.007$; $r^2 = 0.32$).

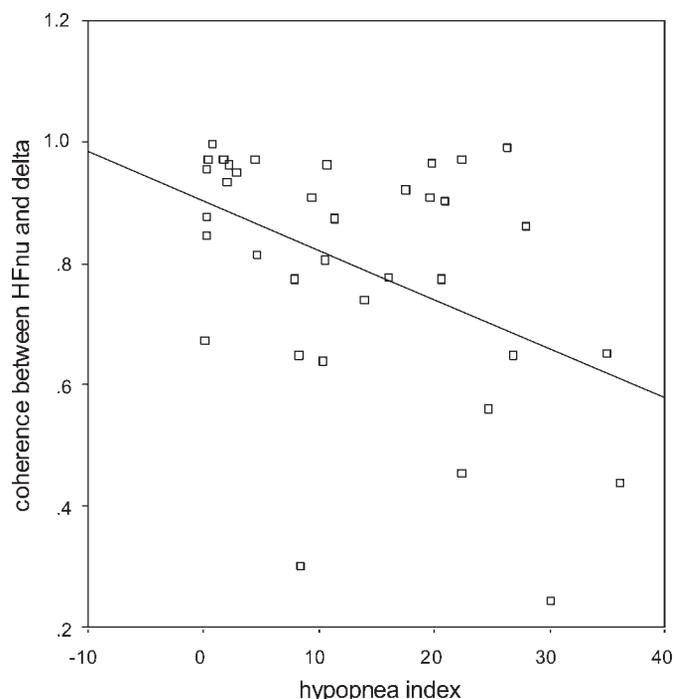


Fig. 5. Correlation between coherence between HF_{nu} of RRI and normalized delta power and hypopnea index across the first three NREM-REM cycles. Coherence between HF_{nu} of RRI and normalized delta power correlated negatively with hypopnea index ($r = -0.388$; $P = 0.010$; $r^2 = 0.19$).

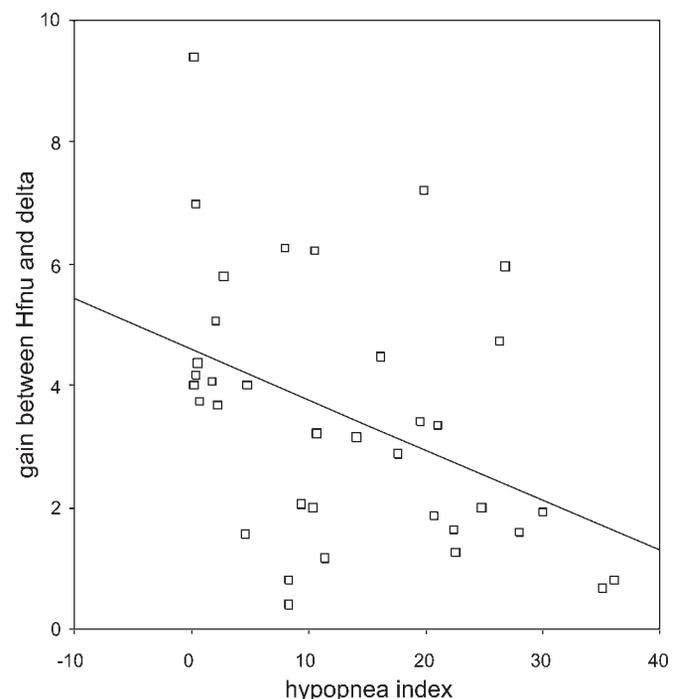


Fig. 6. Correlation between gain between HF_{nu} of RRI and normalized delta power and hypopnea index across the first three NREM-REM cycles. Gain between HF_{nu} of RRI and normalized delta power correlated negatively with hypopnea index ($r = -0.441$; $P = 0.005$; $r^2 = 0.18$).

with normal control subjects. We also report that modifications in RRI and the absolute spectral components of HRV are less sensitive than normalized spectral components to quantify changes in the respective influence of cardiac vagal and sympathetic activity induced by apneas (22). This suggests that frequency domain indexes of HRV are more sensitive to fluctuations in cardiac autonomic influence than time domain indexes of HRV (22).

An increase in the severity of the sleep AHI was not associated with a rise in the makers of cardiac sympathetic or vagal modulation across the sleep stages. This suggests that neither of the two branches of autonomic activity predominates in patients compared with healthy controls (10). Apneas are associated with a relative increase in sympathetic influence (33, 34), but our apneic subjects do not show larger values of sympathetic variability nor larger values of cardiac vagal fluctuation than normal controls. However, SAHS blunts changes in cardiac autonomic control during the shift from NREM to REM sleep compared with the controls. We hypothesize that mechanisms implied in the normal changes in cardiac vagal and sympathetic predominance during sleep in control subjects are not operative in patients with SAHS (16, 18). Sleep apnea induces sudden surges in sympathetic (29) and cardiac vagal activity (28). This mechanism likely suppresses the normal shifts in cardiac sympathetic and vagal predominance during sleep. Other mechanisms, such as a reduction in baroreflex sensitivity (5, 24) and suppression of changes in baroreflex sensitivity during sleep stages in patients with SAHS, may also play a role (24).

BMI was matched for normal control subjects and for patients with moderate-to-severe SAHS. Our patients with severe SAHS differ from both groups by a higher BMI. Obesity is a well-known risk factor for SAHS (9, 19). To date, the influences of obesity and apnea on the relative influence of vagal and sympathetic activity are controversial. There is evidence that peripheral sympathetic activation occurs independently of obstructive sleep apnea in obesity (11). However, Antelmi et al. (3) found no correlation between autonomic cardiac indexes of HRV and BMI. As we did not study obese subjects free of sleep apneas, we cannot disentangle the effect of apneas-hypopneas and obesity in our findings.

In our study, sleep analysis revealed that whole-night sleep stage durations did not differ between groups, but patients with severe SAHS showed longer NREM sleep durations than normal subjects across the first three NREM-REM cycles. Indeed, patients with severe SAHS showed longer durations of light sleep than normal subjects, while durations of slow-wave sleep were similar in both groups. However, three patients with severe SAHS experienced short durations of slow-wave sleep (≤ 1 min). In patients with severe SAHS, decreased coherence and gain between the autonomic cardiac fluctuations and delta sleep EEG may be mainly due to a loss of changes in HRV during shifts in sleep stages rather than in EEG variability.

Vagal oscillations in heart rate precede delta EEG modifications in young and middle-aged subjects (13, 14). Our investigation reveals that the delay between the appearance of modifications in cardiac vagal influence and modifications in delta sleep EEG disappears in patients suffering from a SAHS. The exact mechanism responsible for this remains, however, unclear.

In our study, obstructive apneas and hypopneas exerted differential effects on the link between cardiac autonomic regulation and delta EEG. As reported by Kohler and Sconhler (17), these results further support the hypothesis that apneas and hypopneas are two different entities that can occur in the same patient. Both obstructive apneas and hypopneas alter the linear relationship between the autonomic cardiac activity and delta sleep, while only hypopneas modify the strength of this interaction. Moreover, the negative correlation observed between cardiac vagal predominance and delta sleep EEG is overall implied by a large sleep AI (≥ 30 apneic events/h).

Abnormalities in the link between autonomic cardiac control and delta power band could be the first step before the occurrence of overt abnormalities in cardiovascular variability and cardiovascular disease in patients with SAHS.

In conclusion, we demonstrate that the interaction between cardiac autonomic control and delta sleep EEG is altered in patients with SAHS. This alteration is related to the severity of the disease and is evident even in the absence of hypertension, cardiovascular or psychotropic medications, or other disease states.

ACKNOWLEDGMENTS

We thank Bernard Jacques for technical assistance and Chantal Kempeneers for pertinent commentaries, as well as all of the other members of the sleep laboratory for active participation.

GRANTS

Research reported in this paper was supported by the Erasmus Foundation, the Belgian National Fund for Scientific Research, the Foundation for Cardiac Surgery, the Marc Hurard Foundation, Pfizer, and Astra Zeneca (Belgium). M. Dumont is a Research Associate of the National Fund for Scientific Research (Belgium).

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