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Overnight heart rate variability in patients with obstructive sleep apnoea: A time and frequency domain study

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SUMMARY

1. Heightened sympathetic activity plays a role in the cardiovascular sequelae of obstructive sleep apnoea (OSA). Cardiac autonomic function may be assessed non-invasively by studying heart rate variability (HRV). The aim of the present study was to compare overnight HRV between a control group and a group of subjects with severe OSA. The potential confounding effects of age, sex, baseline autonomic status and sleep stage distribution were taken into account.

2. Our prospective Holter study compared overnight (0030 –0530 hours) HRV in 23 controls (apnoea hypopnoea index (AHI) = 5 ± 3 /h) and 23 subjects with severe OSA (AHI = 65 ± 23 /h), matched for age and sex and with a similar percentage of rapid eye movement sleep.

3. The mean normal-to-normal RR interval (NN) was shorter in the OSA compared with control group (903 *vs* 1039 ms, respectively), whereas the other time-domain indices of HRV, as well as the classic frequency-domain indices, were similar. Essentially similar results were obtained hourly and when only subjects with high mean values of the standard deviation of all NN ($\geq$ 90 ms) were evaluated. In the 0.01–0.06 Hz range corresponding to the typical OSA pattern of bradycardia–tachycardia termed cyclic variation of heart rate (CVHR), higher power was documented hourly in OSA, with a significant correlation between overnight power and both AHI and mean oxyhaemoglobin saturation. The percentage of NN > *x* ms different from the previous one (pNN*x* family) had no diagnostic value.

4. The results of the present study suggest that NN may be the best index to quantify the overnight sympathovagal balance in OSA and that a spectral band overlapping the apnoea-related pattern of CVHR slightly improved the characterization of the apnoea-related HRV patterns.

Key words: autonomic nervous system, parasympathetic, spectral analysis, sympathetic.

INTRODUCTION

In patients with obstructive sleep apnoea (OSA), an imbalance cardiac autonomic function with both increased sympathetic drive and reduced cardiac vagal modulation has been documented during the night that continues during the day.[1–4] Heightened sympathetic activity, oxidative stress and inflammation play a role in OSA-induced cardiovascular morbidity and mortality.[3] It is widely acknowledged that heart rate variability (HRV) studied in both the time and frequency domains is a valuable non-invasive method for assessing cardiac autonomic function, and abnormal HRV has been documented during night-time apnoeic episodes and individual sleep stages.[1,3,4] The potential confounding effects of age, sex, disease severity and sleep stage distribution have also been reported.[1,5,6]

The apnoea and subsequent hyperventilation periods are accompanied by various cardiovascular changes, including heart rate variations reflecting the complex interplay between respiration and the cardiac autonomic nervous system. A typical pattern of bradycardia and tachycardia related to the apnoea and the resumption of breathing, termed cyclic variation of heart rate (CVHR), was first described by Guilleminault *et al.*[7]; it has been largely confirmed by others[8–10] and may contribute to increased HRV in OSA patients free of cardiac autonomic dysfunction. The CVHR patterns are characterized by a frequency ranging from approximately 0.01 to 0.06 Hz.[4] This frequency range overlaps the very low-frequency (VLF) and low-frequency (LF) bands, as defined by international guidelines.[11] In attempt to take into account the typical frequency of CVHR, previous studies have tested the slightly modified definitions of spectral bands in OSA evaluation.[9,12,13]

The aim of the present study was to investigate potential differences in overnight HRV between controls and subjects with severe OSA matched for age and sex. Specifically, the following hypotheses were tested: (i) classic time- and frequency-domain indices of HRV[2,11,14] could help improve discrimination between OSA and controls; and (ii) spectral analyses in OSA could be improved by studying a spectral band corresponding to CVHR.

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METHODS

Subjects

The study was conducted in the sleep laboratory of the Antoine-Béclère Hospital (Clamart, France) from January 2009 to September 2011. Patients were eligible for inclusion in the present study if: (i) they had been referred to our sleep laboratory for snoring and/or clinical suspicion of OSA based on witnessed apnoea and daytime hypersomnolence; (ii) they were undergoing a nocturnal polysomnographic (PSG) recording with simultaneous recording of cardiac Holter, as part of our routine protocol[15]; (iii) both PSG and Holter recordings of good technical quality were available; (iv) they were free of periodic leg movements (PLM) on PSG; and (v) they were free of cardiac arrhythmia (including atrial fibrillation and < 1% premature ventricular beats) and free of atrioventricular conduction disorder on Holter recordings. Of the patients eligible for inclusion in the study, only those with an apnoea hypopnoea index (AHI) $\leq$ 10 /h (normal control group) and those who had an AHI > 30 /h (OSA group) were retained for analysis and the two groups were matched for age and sex as closely as possible (n = 46; Table 1).

Holter monitoring is part of the current monitoring procedures in our sleep laboratory. Our descriptive Holter study was deemed exempt by the Institutional Review Board (CCPPRB de Bicêtre, Le Kremlin Bicêtre, France). All patients provided informed consent prior to participating in the study and their anonymity was preserved.

Polysomnographic and Holter recordings

The one-night PSG (CIDELEC, Sainte Gemmes sur Loire, France) was performed during the patient's hospital stay. It recorded three electroencephalogram channels, two electro-oculogram channels, submental and pretibial electromyograms, airflow with a nasal pressure channel, thoracic and abdominal inductance belts, tracheal sounds, sleeping position and pulse oximetry. Scoring was done visually by a sleep specialist in accordance with the French Clinical Practice guidelines.[16] An apnoea was defined as $\geq$ 90% reduction in airflow lasting $\geq$ 10 s. Apnoeas were defined as obstructive when there was evidence of persistent respiratory effort and as central when there was an absence of any respiratory effort. Hypopnoeas were defined as a reduction in airflow by > 50% of baseline lasting at least 10 s or as a lower reduction in airflow associated with a desaturation $\geq$ 3% and/or an arousal. A 12 channel electrocardiogram (ECG) sampled at 1 kHz was recorded using a commercially available ambulatory ECG Holter monitor (CardioMem CM3000; GETEMED, Teltow, Germany). The reading of PSG was blinded, that is without knowledge of the Holter data.

Table 1 Clinical and polysomnographic characteristics of the control and obstructive sleep apnoea groups

	Control	OSA
n	23	23
Age (years)	45 ± 15	45 ± 8
No. women (%)	9 (39)	8 (35)
BMI (kg/m^2)	25 ± 5	33 ± 6*
AHI (/h)	5 ± 3	65 ± 23*
Mean S_pO_2 (%)	94 ± 2	92 ± 3*
Minimum S_pO_2 (%)	87 ± 4	73 ± 9*
SE (%)	90 ± 9	90 ± 11
TST (min)	384 ± 49	389 ± 84
REM (%)	18 ± 7	16 ± 7

Unless indicated otherwise, data are given as the mean ± SD.

*P < 0.05 compared with the control group (Welch test for normally distributed data; Mann–Whitney U-test for data without normal distribution, preceded by the D'Agostino–Pearson test).

OSA, obstructive sleep apnoea; BMI, body mass index; AHI, apnoea hypopnoea index; S_pO_2, oxyhaemoglobin saturation, as determined by pulse oximetry; SE, sleep efficiency; TST, total sleep time; REM, rapid eye movement sleep.

Analysis of HRV

Only ambulatory ECG of high quality (i.e. free of extrasystoles (< 1%) and free of artefacts) were retained for analysis. The HRV data were available from the Holter analysis software (CardioDay; GETEMED, Teltow, Germany) and were exported as text files (*.txt) for analysis. Given differences in sleeping and awakening times among subjects, data were not available in all subjects before 0030 hours and after 0530 hours. Therefore, time and frequency domain analyses were applied to the 0030–0530 hours period and also over every 1 h period (i.e. 0030–0130, 0130–0230, 0230–0330, 0330–0430 and 0430–0530 hours). The reading of Holter data was blinded, that is without knowledge of the PSG data.

Time domain measures of HRV

Time domain measures of HRV were derived from normal-to-normal intervals (NN), which were recorded directly between adjacent QRS complexes resulting from sinus node depolarization.[11] The mean NN (ms), standard deviation of all NN (SDNN; ms), percentage of NN different from the previous NN (pNN) by > 50 ms (pNN50;%) and root mean square of successive differences of NN (rMSSD; ms) were computed. Mietus *et al.* have suggested that using the pNN thresholds as low as 20 or 10 ms, rather than the standard 50 ms threshold, may allow enhanced discrimination between a variety of normal and pathological conditions, such as ageing and OSA, but this latter point remains to be confirmed.[2,14] Thus, the pNNx statistics (where x varies from 1 to 200 ms with 1 ms increments) were calculated as follows: the absolute values of the differences between consecutive NN were first obtained, then the NN count of particular x values and corresponding pNNx were computed. The pNNx results were smoothed using a five-point moving window average to remove artefactual discontinuities.[14] All calculations were performed using MATLAB (MathWorks, Natick, MA, USA).

Frequency domain measures of HRV

The following parameters were computed: LF (0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components, normalized spectral power of LF and HF (LFnu = 100 × LF/(LF + HF); HFnu = 100 × HF/(LF + HF)), the LF/HF ratio and the VLF (0.003–0.04 Hz) component and its relative value (VLF%; calculated as the VLF power divided by the total spectral power rang-

ing from 0.003 to 0.4 Hz). Although still under discussion, it is acknowledged that HF reflects vagal activity under normal circumstances, LF reflects the combined influences of the sympathetic and parasympathetic nervous systems and also captures baroreflex rhythms and that VLF is modulated by a combination of the renin–angiotensin system, the parasympathetic nervous system and the level of activity and movements, with VLF being increased in sleep-disordered breathing.[4,11] From the heart period tachogram, OSA-induced CVHR of 16–100 s have been documented and are thus characterized by a frequency ranging from approximately 0.01 to 0.06 Hz.[4,12] (see Fig. S1 available as Supplementary Material for this paper). Therefore, according to the recommendations of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) task force,[11] these events are currently assigned to either the VLF or LF band, although they share the same apnoea-related pathophysiology. Thus, the spectral component corresponding to the CVHR spectral band (CVHRsb; ranging from 0.01 to 0.06 Hz) was also calculated and analysed. Results are presented as normalized values (CVHRsb% = 100 × CVHRsb/total power).

For data processing, the LF and HF components were computed in 5 min windows according to the recommendations of the ESC and NASPE task force.[11] In each 5 min window, NN were first resampled (1024 data points) using linear interpolation. The segment mean value was subtracted from the time series and a Hanning window was applied to attenuate the leakage effect. Spectrum analysis was performed using the non-parametric fast Fourier transformation (FFT) method. The resulting power spectrum was corrected for attenuation resulting from sampling and application of the Hanning window. Thereafter, the window was shifted ahead by 2.5 min (overlap = 50%) and the analysis was repeated.[5,17] This allowed computation of the LF and HF components each 2.5 min. The same procedure was used to calculate both the VLF and CVHRsb power, except for the length of the window. Indeed, the VLF obtained from short-term recordings is dubious and should be avoided.[11,12] Therefore, 10 min windows were used with a 50% overlap and thus the VLF power values were obtained every 5 min; the same procedure was used for computation of CVHRsb. Spectral calculations were performed using the digital signal processing toolbox of MATLAB (MathWorks).

Statistical analysis

The normal distribution of each variable was first checked by using a D'Agostino–Pearson test. Variables are presented over the 5 h period (0030–0530 hours) as the mean ± SD, median and range. Log-transformed values are also presented when applicable. Comparisons between variables were performed using an unequal variance *t*-test (Welch test) for normally distributed data[18] or a Mann–Whitney *U*-test for non-normally distributed data. Differences in pNN*x* between groups for each *x* value were computed using the unequal variance *t*-test. In addition, differences between groups were assessed every hour throughout the night for all variables in both the time domain (mean NN, SDNN, pNN50, rMSSD) and frequency domain (ln(LF), ln(HF), ln(LF/HF), VLF% and CVHRsb%). The relationship between measured HFnu and the LF/HF ratio was also investigated, as suggested previously.[19,20] Before performing hour-by-hour comparisons, parameters were logarithmically transformed to correct the skewness of the distribution of segment values when applicable. The probability for the differences between groups was calculated every hour using the unequal variance *t*-test given the sufficiently large sample size of the segments under investigation in each group. Correlations were evaluated using Pearson's correlation coefficient (*r*). It may be expected that patients with the most depressed HRV do not exhibit CVHR. Thus, in the overall population, the median value of SDNN was calculated (90 ms) and we also performed a subgroup analysis in patients with SDNN $\geq$ 90 ms. Statistical analyses were performed using MEDCALC software (MedCalc Software, Mariakerke, Belgium) and the Statistics Toolbox of MATLAB (MathWorks). Statistical significance was assumed for two-sided $P < 0.05$.

RESULTS

Clinical and polysomnographic characteristics

As indicated in Table 1, there were no significant differences between the control and OSA groups in terms of age and sex. Compared with the control group, the OSA group had a higher body mass index (BMI) and lower minimum and mean oxyhaemoglobin saturation, as determined by pulse oximetry (S_pO_2). The control and OSA groups were comparable for sleep efficiency, total sleep time and percentage of rapid eye movement (REM) sleep.

Time-domain HRV indices

Compared with the control group, the OSA group had shorter mean NN over the period 0030–0530 hours, whereas the two groups had similar SDNN, pNN50 and rMSSD values (Table 2). The same findings were observed when data were averaged out every hour through the night (Fig. 1).

The relationship between *x* values and pNN*x* is shown in Fig. 2. In both groups, pNN*x* decreased with *x*. Differences in pNN*x* between the OSA and control groups increased at high values of *x*, although the differences failed to reach statistical significance.

Statistical frequency-domain HRV indices

The distribution of the frequency-domain HRV indices over the period 0030–0530 hours is shown in Fig. 3 (raw and log-transformed data, given the skewed distribution). All these indices were similar in the controls and OSA groups (Table 2). When data were averaged out every hour throughout the night, higher CVHRsb% (normalized units; n.u.) was documented in the OSA group ($P < 0.05$), with no cut-off value between the two groups (Fig. 4). Other spectral indices were essentially similar.

Frequency domain analysis performed over the 0030–0530 hours period in the subgroup with high HRV range (SDNN $\geq$ 90 ms) showed that similar frequency domain HRV indices were seen in the control and OSA groups, regardless of whether the classic definition of spectral bands or the CVHRsb was used (Table 3).

Compared with the non-linear predicted HFnu–LF/HF relationship,[19,20] the HFnu and LF/HF values averaged out over the

Table 2 Heart rate variability indices during sleep hours in the control and obstructive sleep apnoea groups

	Control (n = 23)		OSA (n = 23)	
	Mean ± SD	Median	Mean ± SD	Median
Time domain				
NN (ms)	1039 ± 203	999	903 ± 120*	885
SDNN (ms)	97 ± 43	86	88 ± 24	88
pNN50 (%)	24 ± 25	12	20 ± 18	17
rMSSD (ms)	58 ± 39	41	49 ± 22	41
Frequency domain				
ln (LF)	6.50 ± 1.18	6.12	6.55 ± 0.71	6.53
ln (HF)	5.95 ± 1.43	5.53	5.94 ± 1.02	6.14
ln (LF/HF)	0.55 ± 0.66	0.63	0.60 ± 0.86	0.55
LFnu	61 ± 13	63	62 ± 17	62
HFnu	39 ± 13	37	38 ± 17	38
VLF (%)	50 ± 11	49	53 ± 13	50
CVHRsb (%)	42 ± 10	45	47 ± 13	45

*P < 0.05 compared with the control group (Welch test for normally distributed data; Mann–Whitney U-test for data without normal distribution, preceded by the D'Agostino–Pearson test).

OSA, obstructive sleep apnoea; NN, normal-to-normal intervals; SDNN, standard deviation of all NN intervals; pNN50, percent of NN intervals > 50 ms different from previous; rMSSD, root mean square of successive differences of NN intervals; LF, low frequency (0.04–0.15 Hz); HF, high frequency (0.15–0.4 Hz); VLF, very low frequency (0.003–0.04 Hz); CVHRsb, cyclic variation of heart rate spectral band (0.01–0.06 Hz).

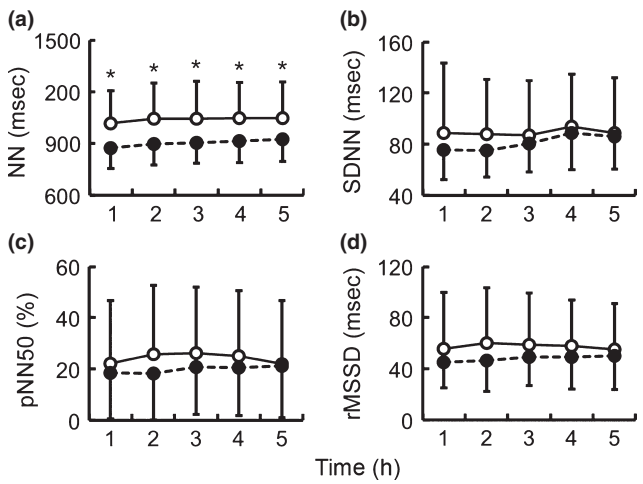

Fig. 1 Time-domain indices of night-time heart rate variability in the control (○) and obstructive sleep apnoea (OSA; ●) groups (n = 23 in each group). Data were averaged out over each hour and one standard deviation is shown. *P < 0.05 compared with the OSA group (unequal variance t-test). NN, mean normal-to-normal heart period; SDNN, standard deviation of NN; pNN50, percentage of NN > 50 ms different from the previous; rMSSD, root mean square of successive differences of NN.

study period were shifted to right in both the control and OSA groups (Fig. 5). In some cases, there were marked differences between predicted and observed values (e.g. theoretically, HFnu = 20% corresponds to LF/HF = 4, whereas the LF/HF ratio in one subject in the control group was 6.7 and one subject in the OSA group had an LF/HF ratio of 12; Fig. 5).

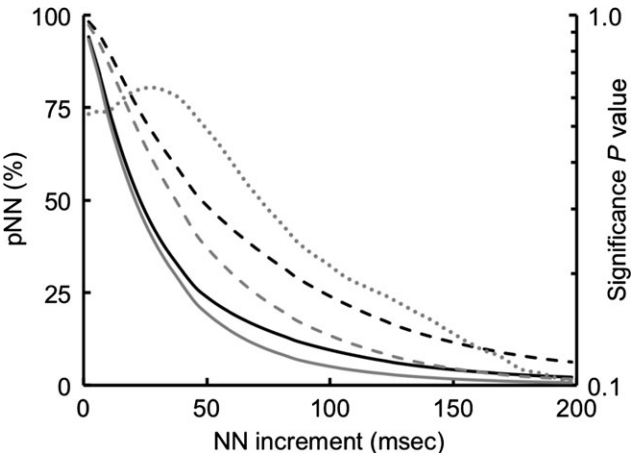

Fig. 2 Percentage of normal-to-normal RR intervals (NN) > x ms different from the previous one (pNNx) family, with x increasing from 0 to 200 ms. The mean pNN is given as a function of x (NN increment in ms) in controls (solid black line) and obstructive sleep apnoea (OSA; solid grey line). In addition, mean + 1 SD values are shown for the control (dashed black line) and OSA (dashed grey line) groups. The significance of differences between the control and OSA groups (P values), as determined by unequal variance t-tests, is also shown (dotted grey line). Note that the lowest P value was documented at high x values, although the P value remained > 0.05 at the highest x value.

Relationship between HRV indices and PSG results

In the overall study group (n = 46), there was a negative correlation between AHI and NN (r = –0.40; P < 0.05) and a positive correlation between AHI and CVHRsb% (r = 0.38; P < 0.05). There was no correlation between AHI and all other time- and frequency-domain indices of HRV. The CVHRsb% was negatively correlated with the mean S_pO_2 (r = –0.42; P < 0.05).

DISCUSSION

In an attempt to highlight differences in overnight HRV between normal healthy individuals and patients with severe OSA, the present prospective study compared results from 23 controls (AHI = 5 ± 3 /h) and 23 subjects with severe OSA (AHI = 65 ± 23 /h) matched for age and sex with similar percentage REM sleep. The main results were as follows: (i) mean NN was shorted in the OSA compared with the control group, whereas the classic time- and frequency-domain indices of HRV were similar between the two groups; (ii) by using a definition of spectral band that takes into account the apnoea-related patterns of cyclic variation of heart rate, (i.e. CVHRsb), higher power was documented in OSA each hour and there was also a significant but mild correlation between overnight mean CVHRsb% and AHI and mean S_pO_2; and (iii) the previously suggested usefulness of the pNNx family[14] was not confirmed in OSA. Our study suggests that NN may be the best index quantifying the overnight sympathovagal balance in OSA and that a definition of CVHR spectral band slightly improved the characterization of the apnoea-related HRV patterns.

The autonomic nervous system (sympathetic and parasympathetic systems) exerts combined effects on the sino-atrial node and thus modulates heart rate on a beat-to-beat basis. In the present study, the mean NN in OSA was shorter than in controls,

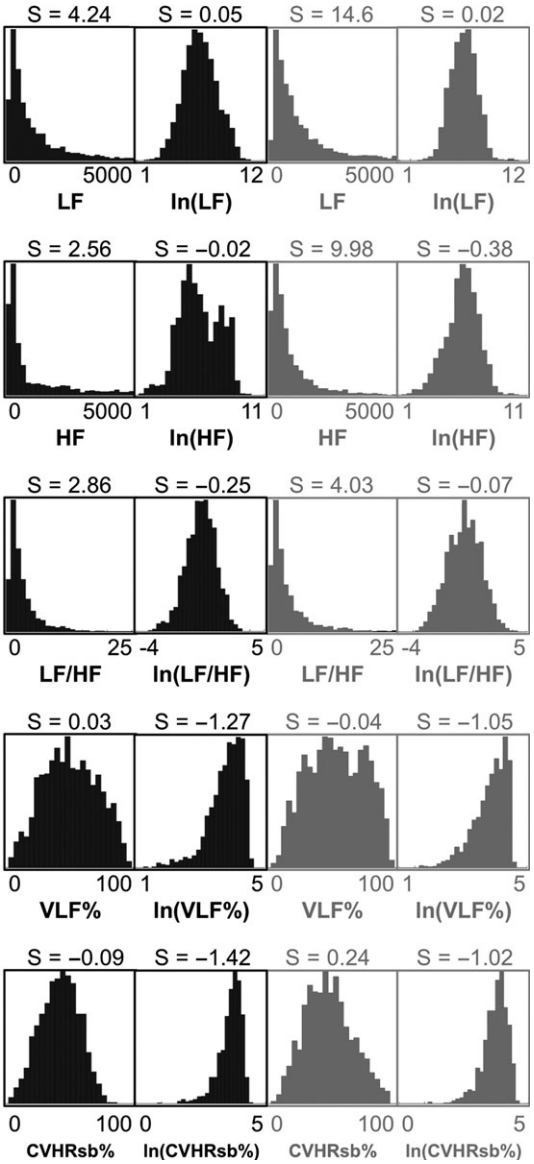

Fig. 3 Histograms and corresponding skewness (S) of the frequency-domain indices of heart rate variability in control (left black panels) and obstructive sleep apnoea (OSA; right grey panels) groups. LF, low frequency; HF, high frequency; VLF, very low frequency; CVHRsb, cyclic variation of heart rate spectral band.

whereas the time-domain indices of HRV were similar. As noted previously by Coumel *et al.*, heart rate 'is probably the best index of ANS balance and occasionally the easiest to measure'[17] and our results may thus confirm increased sympathetic drive and proportionally reduced cardiac vagal modulation in OSA.[1,3,6,7] It is also possible that the time spent in arousals for the OSA events contributes to the decreased NN compared with that in the control group.[10] As expected, our OSA patients presented with relative obesity as opposed to lean patients and this may explain, at least in part, our findings because obese patients often present with increased heart rate.[21] As far as the sympathetic/parasympathetic balance is concerned, the respective role of the ventrolateral medulla nucleus versus the nucleus ambiguus in mediating such differences in heart rate at the central level deserves further investigation in OSA.

During the night, there were no significant between-groups differences in LF/HF. This result was unexpected given that the LF/HF ratio is currently used to estimate the sympathetic–parasympathetic balance. In an attempt to explain the apparent discrepant results between mean NN and the LF/HF ratio, the following points must be considered: (i) the ability of the LF/HF ratio to reflect the sympathetic–parasympathetic balance has been challenged recently[22–25]; (ii) whether the LF/HF ratio during sleep has been documented in the presence of apnoea or not,[5,26,27] the results often show a lack of consistency and are highly affected by the database chosen[26,27]; (iii) inconsistencies have been noted depending on whether the LF/HF ratio is reported as an aggregated arithmetic mean or from individual samples. Burr has suggested that such inconsistency may relate to the modest non-linearity of the relationship between the variables.[19] In fact, the markedly positively skewed distribution of LF/HF ratio should be highlighted. In the present study, the mean LF/HF ratio values were shifted to the right compared with the theoretical individual measures. Hence, the arithmetic mean is not appropriate and the skewness should be eliminated by log transformation, as also suggested in the recent analysis by Nunan *et al.*[27] Despite this transformation, the two groups still displayed similar ln(LF/HF).

Guilleminault *et al.*[7] first described a typical pattern of bradycardia and tachycardia in relation to the apnoea and the resumption of breathing termed CVHR and this has been largely confirmed by others.[8–10] The CVHR patterns are characterized by a 0.01–0.06 Hz frequency range overlapping the VLF and LF bands.[4,11] To overcome this problem, previous studies have tested the usefulness of slightly modified definitions of spectral bands.[9,12,13] For example, Drinnan *et al.* defined an apnoea-related spectral band ranging from 0.01 to 0.05 cycles/beat,[13] whereas Babaeizadeh *et al.* defined their band from 0.0117 to 0.0633 Hz,[12] and both obtained a good automated apnoea score for both training and evaluation parts using the PHYSIONET[28] sleep apnoea database. In the present study, we added a CVHR spectral band integrated from 0.01 to 0.06 Hz to the classic definition of spectral bands.[11] Our study highlighted significant differences in CVHRsb between the OSA and control groups when data were computed hourly overnight. Significant but mild correlations were also found between the overnight CVHRsb% and PSG parameters. However, the overnight CVHRsb power did not allow discrimination between the OSA and control groups, even after having excluded patients with the most depressed HRV. One possible explanation for this may be that a single AHI value cannot simply relate to the complex, instantaneous respiratory patterns of OSA patients. A minute-by-minute apnoea classification may be needed for precise analysis,[9,29] which was beyond the scope of the present study. The potential interest of our CVHRsb definition deserves further investigation.

Another result of the present study related to the so-called pNN*x* family analysis. Indeed, Mietus *et al.* have suggested that pNN*x* allows enhanced discrimination between a variety of normal and pathological conditions, such as ageing[14] and OSA.[2] This was not confirmed in the present study. Moreover, despite the lack of statistical significance, differences between the control and OSA groups appeared more marked at higher values of *x*. This is also at variance with previous reports showing the highest discriminative power of pNN20.[2,14] The reasons for such different findings remain to be explained. One possibility may be

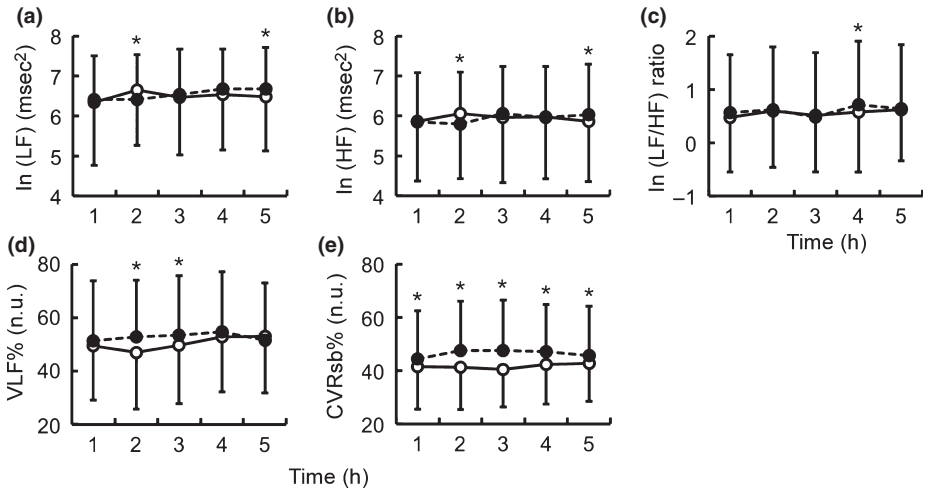

Fig. 4 Frequency-domain indices of night-time heart rate variability in the control (○) and obstructive sleep apnoea (OSA; ●) groups (n = 23 in each group). Data were averaged out over each hour and one standard deviation is shown. *P < 0.05 compared with the control group (unequal variance t-test). LF, low frequency; HF, high frequency; VLF, very low frequency; CVHRsb, cyclic variation of heart rate spectral band; n.u., normalized units.

Table 3 Frequency domain analysis during sleep hours in the standard deviation of all normal-to-normal intervals (SDNN) ≥ 90 ms subgroups in the control and obstructive sleep apnoea groups

	Control (n = 10)		OSA (n = 11)	
	Mean ± SD	Median	Mean ± SD	Median
ln (LF)	7.52 ± 0.88	7.26	6.92 ± 0.52	7.00
ln (HF)	7.09 ± 1.25	7.46	6.22 ± 1.17	6.47
ln (LF/HF)	0.43 ± 0.80	0.37	0.70 ± 0.89	0.79
LFnu	59 ± 16	58	64 ± 17	67
HFnu	41 ± 16	42	36 ± 17	33
VLF (%)	46 ± 14	42	52 ± 15	51
CVHRsb (%)	37 ± 12	36	44 ± 14	42

There were no significant differences in any parameters between the two groups (Welch test for normally distributed data; Mann–Whitney U-test for data without normal distribution, preceded by the D'Agostino–Pearson test).

OSA, obstructive sleep apnoea; NN, normal-to-normal intervals; SDNN, standard deviation of all NN intervals; pNN50, percent of NN intervals > 50 ms different from previous; rMSSD, root mean square of successive differences of NN intervals; LF, low frequency (0.04–0.15 Hz); HF, high frequency (0.15–0.4 Hz); VLF, very low frequency (0.003–0.04 Hz); CVHRsb, cyclic variation of heart rate spectral band (0.01–0.06 Hz).

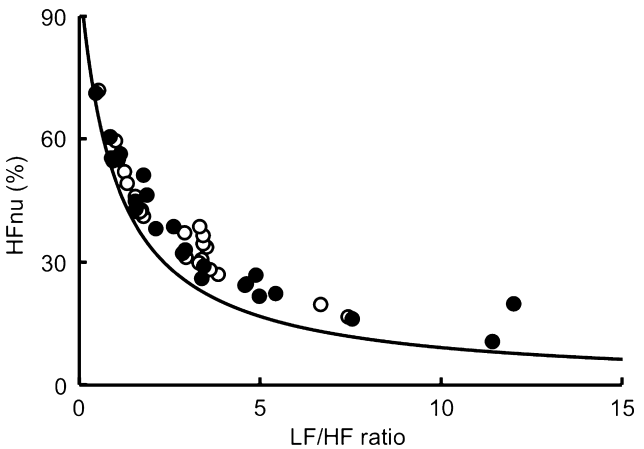

Fig. 5 Relationship between the high frequency spectral power (HF) in normalized units (HFnu) and the low frequency/high frequency (LF/HF) ratio. The solid line indicates the theoretical non-linear relationship between HFnu and LF/HF (individual measurement over one segment). In both control (○) and obstructive sleep apnoea (OSA; ●) individuals, the HFnu and LF/HF values were averaged out over the overall study period and the aggregate arithmetic means obtained were shifted to the right.

related to the duration of the analysis and the daytime versus night-time period under investigation.

The strength of the present study was that patients were matched for age and sex. The HRV is highly sensitive to age and younger subjects present typically higher values for HRV.[11,27] Furthermore, middle-aged women and men have different dominant regulation of heart rate: parasympathetic in women but sympathetic in men.[5] Heart rate and HRV progressively increase during REM sleep (consistent with increased sympathetic control) and both decrease during non-REM sleep (consistent with increased vagal control).[4] In the present study, the differences in mean NN observed between groups were not explained by differences in the percentage of REM sleep because the control and OSA groups exhibited similar percentage REM. Finally the OSA group was homogeneous because all patients suffered from severe OSA.

Of the study limitations, a formal calculation to find the number of patients needed for comparison was impossible given no prior knowledge about precision for HRV frequency-domain measurements and the skewness of their distribution. Thus, we cannot exclude the possibility that increasing the number of subjects would have resulted in increased discriminative power of HRV indices in OSA. Sleep stages have not been taken into consideration because our primary aim was to improve OSA screening based on Holter-derived HRV indices only. Data were averaged out over 5 h (overnight) and each hour and, thus, the results strictly apply to the hourly averaged influences of the autonomic nervous system on heart rate. Burst changes in the

sympathovagal balance occurring at the onset and end of apnoeic episodes have been reported in OSA,[4,6] but the present study was not designed to quantify them. In addition, it was not our aim to compare overnight HRV with values documented when subjects were awake. Only patients with severe OSA were studied and we did not study patients suffering from mild OSA because the aim of the present preliminary study was to highlight differences in HRV between controls and the most severe forms of OSA recruited in our sleep laboratory. It was not possible to match controls and OSA patients for BMI, but it must be noted that studies of the relationship between BMI and HRV have reported conflicting results.[30] Finally, although FFT is widely used to quantify HRV in OSA, the underrated problem of the stationarity condition should be kept in mind.[4,11]

In conclusion, compared with age- and sex-matched controls with similar percentage REM sleep, patients suffering from severe OSA exhibited a shorter mean NN overnight, whereas the other time-domain indices of HRV (including the pNN*x* family), as well as the classic frequency-domain indices, were similar. By using the CVHRsb (0.01–0.06 Hz), higher power was documented hourly in OSA, with mild correlation between overnight power and increased AHI and decreased mean S_pO_2. The present findings could be used in the future to confirm that a modified definition of spectral band may improve the screening of apnoea-related HRV patterns in OSA.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Cyclic variation of heart rate in obstructive sleep apnoea patients.

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