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Spectral oscillations of RR intervals in sleep apnoea/hypopnoea syndrome patients

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Spectral oscillations of RR intervals in sleep apnoea/hypopnoea syndrome patients. K. Dingli, T. Assimakopoulos, P.K. Wraith, I. Fietze, C. Witt, N.J. Douglas. ©ERS Journals Ltd 2003.

ABSTRACT: A recent study has shown that daytime heart rate variability is reduced in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) patients. In the present study, the hypothesis was that sympathovagal balance around apnoeas/hypopnoeas and nocturnal autonomic activity are altered in OSAHS patients.

Frequency- and time-domain analyses of RR intervals were performed to monitor sympathovagal activity noninvasively. Fourteen untreated OSAHS patients and seven healthy subjects underwent overnight polysomnography.

Low (LF) and total (TF) frequency power increased 2 min around the end of apnoeas/hypopnoeas (LF 229±38 ms^2, TF 345±45 ms^2) compared with undisturbed sleep (LF 106±18 ms^2, TF 203±23 ms^2). The increase in high frequency (HF) power was not significant. LF increase was proportionally higher than the HF increase (normalised LF (LFn) 67±1 units, normalised HF (HFn) 33±1 units) compared with undisturbed sleep (LFn 52±2 units, HFn 48±2 units). RR duration did not change around apnoeas/hypopnoeas (RR 904±28 ms). The LF and TF power increase was greater around arousal-inducing (LF 260±45 ms^2, TF 390±65 ms^2) compared with self-terminating (LF 161±31 ms^2, TF 249±40 ms^2) apnoeas/hypopnoeas; the LF and LFn increases were significant in both groups compared with undisturbed sleep and HF power differences were nonsignificant. RR intervals were longer around self-terminating apnoeas/hypopnoeas (RR 914±29 ms); the differences were not significant compared with undisturbed sleep. RR interval spectral power was not influenced by the event type. RR duration decreased (912±28 ms) and LF, HF and TF power increased (LF 111±16 ms^2, HF 62±6 ms^2, TF 173±21 ms^2) across patients, compared with healthy controls (RR 1138±91 ms, LF 57±3 ms^2, HF 35±3 ms^2, TF 91±6 ms^2). LFn and HFn did not change significantly.

Sympathetic activity increases around apnoeas/hypopnoeas. The recurrent nocturnal fluctuations of sympathovagal balance and the overall increase of nocturnal autonomic activity may be of importance in the development of cardiovascular disease in sleep apnoea patients.

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Heart rate variability (HRV), the variation of RR intervals, can be detected through power spectral analysis of RR intervals. The method has been widely validated in physiological and pathological conditions and used as a noninvasive measure of autonomic cardiac control within and between individuals [1, 2]. This detection is based on the spectral power changes mainly within the low (LF) and high (HF) frequency bands of the RR intervals. The association of efferent cardiac sympathetic nerve traffic with the increase in LF band power has been demonstrated in different conditions [1, 2] and under application of excitatory and inhibitory pharmacological agents. These studies have shown that changes in LF band power reflect sympathetic cardiac activation, whereas HF band power changes reflect parasympathetic, vagal outflow. The RR spectrum of healthy subjects has been compared with their peripheral sympathetic activity, measured invasively from the peroneal nerve [3], the muscle sympathetic nerve activity (MSNA). Although the genesis of the RR interval LF power oscillations is not clear, it has been suggested that these reflect central tonic excitatory sympathetic inputs conditional to brainstem activation [4]. This may explain the dissociation found between RR spectral power, RR duration and MSNA under certain conditions, such as apnoeas or hyperventilation [5], and may reflect the common central control mechanisms of respiratory and cardiac autonomic modulations.

Hypertension [6] and myocardial infarction [7] cause a reduction in HRV, *i.e.* an increase in LF and a decrease in total power. These conditions have been associated with the prevalence of obstructive sleep apnoea/hypopnoea syndrome (OSAHS) [8, 9]. The reduced daytime HRV found in OSAHS patients compared with healthy subjects [10] may be implicated in the development of cardiovascular disorders in these patients.

The present study investigated the nocturnal HRV in OSAHS patients through monitoring of the RR interval spectral oscillations and RR duration. The study hypothesis was that apnoeas/hypopnoeas are associated with sympathovagal changes. HRV characteristics around apnoeas/hypopnoeas

For editorial comments see page 870.

were compared to baseline, nonevent sleep periods across patients. The patients' RR interval spectral oscillations and RR duration were compared with matched normal controls.

Methods

Subjects

The polysomnograms of 14 OSAHS patients, (mean±SD) age 51±9 yrs, body mass index (BMI) 29±2 $kg \cdot m^{-2}$, and seven healthy subjects, age 50±10 yrs, BMI 28±2 $kg \cdot m^{-2}$ were analysed. Diagnosis was based on clinical symptoms and polysomnographic outcomes. The controls were matched for age and BMI. All subjects were otherwise healthy; two patients were on the antihypertensive nifedipine. The study was approved by the Institutional Ethics Committee.

Polysomnography

Polysomnography consisted of electroencephalography (EEG), electro-oculography, submental and tibial electromyography, electrocardiography (ECG), two piezoelectric belts, thermistor, digital microphone and pulse oximeter.

Scoring/definitions

Sleep was scored according to the criteria of RECHTSCHAFFEN and KALES [11]. Apnoeas were defined as cessation of the oronasal airflow lasting $\geqslant$10 s. Hypopnoeas were defined as an airflow reduction of >50% compared with a 10-s peak amplitude during the preceding 2 min, lasting $\geqslant$10 s and associated with either an oxygen desaturation of $\geqslant$3% or an arousal [12]. Arousal scoring was based on the American Sleep Disorders Association (ASDA) definition [13] modified as to the duration threshold, which was set at 1 s. The number of apnoea-hypopnoea-related EEG arousals per hour slept was the Respiratory Arousal Index (RAI). Of all data, 12% were excluded due to artefacts or abnormal R wave morphology.

Postacquisition analysis

Autonomic activity around the end of apnoeas/hypopnoeas was monitored noninvasively, based on the RR interval analysis [1]. Frequency-domain analysis was performed using the fast Fourier transform (FFT) algorithm. In the time domain, the mean RR interval duration was evaluated.

The end of apnoeas/hypopnoeas was identified as airflow increase/recovery. To assess the fluctuations in RR interval spectral power induced by apnoeas/hypopnoeas, comparisons were conducted between the same frequency bands within 2-min windows centred around the end of apnoeas/hypopnoeas and 2-min periods of undisturbed sleep. To avoid influence on the RR interval power spectrum through adjacent apnoeas/hypopnoeas or arousals, events were selected for the analysis only when the 2-min window was not overlapping with any further respiratory events, arousals or wake epochs (fig. 1). The window was chosen following the recommendations for frequency-domain analysis of RR intervals [1], to maximise detection of power changes related to apnoeas/hypopnoeas and maintain signal stationarity. The 2-min segments are considered as the lower bound for accurate analysis of the

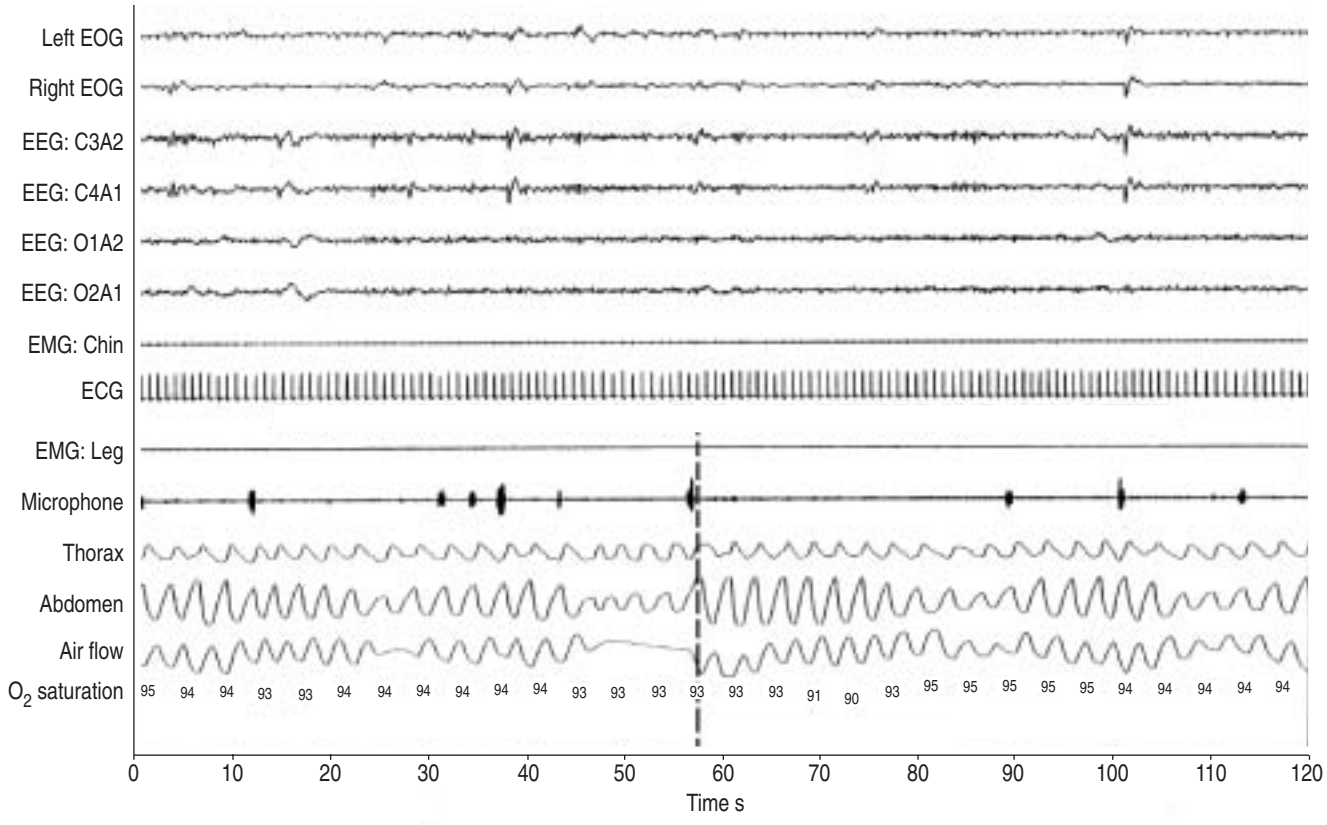

Fig. 1. – Two-minute window (1 min before and 1 min after) around the end of an apnoea (vertical dashed line). The spectral power of RR intervals and their mean duration were calculated during this window and compared with 2-min windows of undisturbed sleep. EOG: electro-oculography; EEG: electroencephalography; ECG: electrocardiography; EMG: electromyography.

0.04–0.40 Hz frequency-band power [1]. A concern was the influence of respiratory oscillations on the RR power spectrum (respiratory sinus arrhythmia) during the 2-min window [14].

Signal processing

HRV parameters were calculated according to the recommendations specified by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [1]. All data were processed with program modules from a custom signal processing framework, written in C language for Unix/Linux operating systems.

Careful editing and visual inspection of the ECG signal, sampled at 100 Hz, helped to eliminate sources of errors arising from missing QRS complexes or spurious RR intervals. The RR interval estimation was obtained by using a "second-order derivative with threshold" method. As this time series (tachogram) is a function of number and not of time, RR interval series were converted to a smoothed heart rate time series through sampling at uniform intervals with 4 Hz (ΔT=0.25s) [15]. To check the stationity of the heart rate series, the mean and SD of all selected heart rate segments within each recording was calculated. The variation of the mean across the segments of the same recording was <1 calculated SD, *i.e.* all the segments selected, fulfilled the stationary requirement.

Frequency-domain analysis

For each 2-min segment the power spectral density ($ms^2 \cdot Hz^{-1}$), *i.e.* power (energy) distribution in its constituent frequencies, of the corresponding heart rate time series was computed by applying the WELCH [16] method, after removal of the DC component. This method is based on the averaging of overlapping windowed Fourier transforms (sliding windows). To minimise leakage, a 50% overlapping sliding Hamming window with 128 points was used. The 2-min heart rate series had a length of 480 samples, zero padding was applied to add up to n=512 samples and was divided into seven overlapping frames. The trade-off of spectral resolution and statistical variance is inherent to periodogram approaches. That is, by increasing the length of the Hamming window and thereby improving the spectral resolution, the number of frames to be averaged decreases and hence the statistical variance of the estimate deteriorates. Alternatively, if the number of the frames to be averaged is increased by forming shorter frames, then the spectral resolution deteriorates. The length of the Hamming window and the 2-min analysis window in the present study was a compromise between frequency resolution and signal stationarity. The resolution of isolated peaks was 0.0078 Hz resulting in 0.0156 Hz distinguished adjacent frequency components of unequal amplitude. The FFT frequency bands had a width of 0.03125 Hz.

Power

Power was calculated for the LF and HF bands through Gaussian integration of the corresponding power spectral density function and was expressed in ms^2 (fig. 2). Frequencies below 0.04 Hz were not considered in the analysis, as these require longer data series for an accurate power estimation. LF and HF power were expressed in normalised units (LFn and HFn, respectively) by calculating the percentage of each band power with respect to their sum [1, 2]. Normalised power emphasises the controlled and balanced behaviour of the two branches of the autonomic nervous system, increases sensitivity [1] and correlation with attendant changes in MSNA [3]. The normalisation minimises the effect of the changes in total power on the values of LF and HF components [1].

Time-domain analysis

The mean RR duration of the original tachograms was calculated during the 2-min segments. A decrease in RR duration is a measure of centrally mediated cardiac activation [1, 3].

The influence of cortical arousals and event type on these markers was evaluated. To assess the significance of the changes found in RR duration and spectral power across the OSAHS patients, these were compared with healthy subjects. Comparisons were conducted between the whole night recordings of patients *versus* healthy controls, based on the analysis of nonoverlapping 2-min sliding windows throughout the sleep periods; wake epochs were excluded. A minimum of 1.5 h per subject was analysed. Each subject contributed one data point to the mean of each autonomic marker.

Statistical analysis

Paired t-tests were performed for the within-patients comparisons. Unpaired t-tests assessed differences between patients and healthy controls. Receiver-operating characteristic (ROC) curves [17] evaluated the ability of the autonomic markers to discriminate between apnoeas/hypopnoeas and undisturbed sleep in each patient. To assess the accuracy in reproducing visual scoring, the true-positive (TP), true-negative (TN), false-positive (FP) and false-negative (FN) readings, the sensitivity TP/(TP+FN) and specificity TN/(TN+FP) were calculated for each marker and polysomnogram. The ROC curves were created by stepwise changes of the decision threshold for the normal and pathological state for the investigated parameter. The area under the curve (the minimal value of 0.5 indicates no discrimination, the maximum value of 1.0 indicates perfect discrimination) and its SE were calculated [18]. The area under the curve represents the probability of a randomly selected ECG interval to distinguish apnoeas/hypopnoeas from undisturbed sleep. Using the mean values of the 2-min rolling windows across the 21 subjects, ROC curves were constructed by stepwise changes of the decision threshold to demonstrate the ability of the markers to discriminate between OSAHS patients and healthy subjects. Significance was considered at $p<0.05$. Values are presented as mean±SEM.

Results

The patients′ mean sleep efficiency was 88±2% of sleep period time (SPT). The healthy subjects′ mean sleep efficiency was 92±3% of SPT (table 1). A total of 2,288 apnoeas/hypopnoeas were scored. Across the 14 patients, 87±3% of the apnoeas/hypopnoeas occurred during nonrapid eye movement (NREM) sleep stages 1 and 2, 6±2% during slow-wave sleep (SWS) and 10±2% during rapid eye movement (REM) sleep. In four patients, no apnoeas/hypopnoeas were scored during SWS, in two patients none were scored during REM sleep. Mean apnoea/hypopnoea duration was 25±2 s. Of the scored events, 48% were apnoeas, 52% were hypopnoeas. Mean apnoea/hypopnoea index across patients was 29·h $slept^{-1}$ (range 10–55·h $slept^{-1}$), mean RAI 20·h $slept^{-1}$ (range 7–47·h $slept^{-1}$); 32% of apnoeas/hypopnoeas were terminated by a visually undetectable manner.

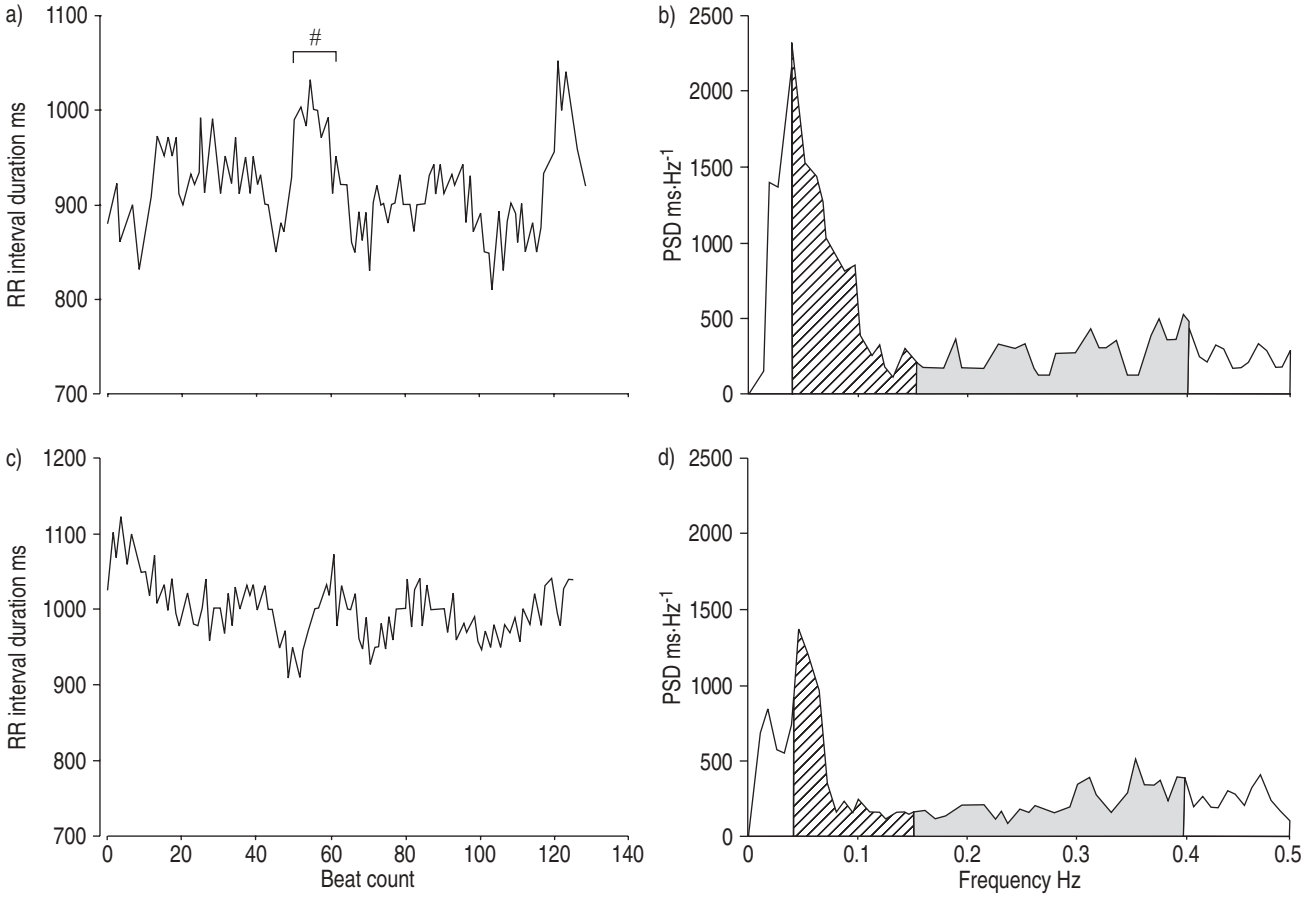

Fig. 2. – a) RR interval time series (tachogram) 2 min around the end of the apnoea on figure 1. The number of RR intervals was 128, their mean duration was 917.46 ms and variance 2175.68 ms^2. #: apnoea. b) Power spectral density (PSD) curve of the same interval, calculated using the nonparametric fast Fourier transform algorithm. Power was calculated for the low frequency band (LF; ▨) between 0.04–0.15 Hz (peak 0.047 Hz), power 82.56 ms^2, and the high frequency band (HF; ▩) between 0.15–0.4 Hz (peak 0.398 Hz), power 60.76 ms^2. c) Interval tachogram of a 2-min period of undisturbed sleep from the same polysomnogram. The number of RR intervals was 126, their mean duration was 1001.2 ms and variance 1481.61 ms^2. d) PSD curve of the same baseline sleep period. LF peak power and peak frequency were 47.09 ms^2 and 0.047 Hz, respectively. HF peak power and peak frequency were 54.97 ms^2 and 0.359 Hz, respectively.

Table 1. – Patient characteristics

	Patients	Healthy controls
TST h	6.4±0.2	4.8±0.5
SPT h	7.2±0.1	5.2±0.3
NREM stages 1 and 2 h	4.0±0.2	3.0±0.3
SWS h	1.4±0.2	1.0±0.2
REM h	1.0±0.1	0.8±0.1
NREM stages 1 and 2 (% of TST)	63±3	62±4
SWS (% of TST)	22±2	21±3
REM (% of TST)	15±1	17±3

Data are presented as mean±SEM. TST: total sleep time; SPT: sleep period time; NREM: nonrapid eye movement; SWS: slow-wave sleep; REM: rapid eye movement.

Across-patient comparison

Of the 2,288 scored apnoeas/hypopnoeas, 214 (mean±SEM 15±2) fulfilled the "nonoverlap" criteria and were selected for analysis. These events were compared with 541 (39±8) nonevent periods (baseline sleep). Across the 14 patients, 77±4% of the apnoeas/hypopnoeas analysed occurred during NREM stages 1 and 2 (12±1), 13±3% during SWS (2±1) and 22±4% (4±1) during REM sleep. In eight patients no apnoeas/hypopnoeas were analysed during SWS, in three patients none were analysed during REM sleep. Mean apnoea/hypopnoea duration was 26±4 s.

LFn increased and HFn power decreased 2 min around event termination compared with undisturbed sleep ($p<0.001$). The increase in absolute LF power ($p=0.002$) was associated with increase in total power ($p=0.01$); no significant increase was found in the absolute HF power ($p=0.3$). Mean RR duration around apnoeas/hypopnoeas did not change compared with undisturbed sleep across patients ($p=0.9$; table 2).

ROC curves, based on the LFn and HFn power values, demonstrated that these spectral power markers of autonomic activity can discriminate well between apnoeas/hypopnoeas and undisturbed sleep, with the areas under the curves being between 0.74–1.00 ($p<0.03$) across patients and SE between 0.0001–0.09 (table 3). The ROC curves are identical for both measures of autonomic activity, as their calculation is based on the percentage of each band power with respect to their sum:

$$LFn = \frac{LF \times 100}{LF + HF} \quad (1)$$

$$HFn = \frac{HF \times 100}{LF + HF} \quad (2)$$

High SE values reflect outlying differences between apnoea/hypopnoea values and baseline sleep in some patients. The

Table 2. – Frequency- and time-domain analyses around apnoeas/hypopnoeas and baseline sleep

	Respiratory events	Baseline sleep	p-value
LFn	67±1	52±2	<0.001
HFn	33±1	48±2	<0.001
LF ms^2	229±38	106±18	0.002
HF ms^2	116±17	97±7	0.3
TF ms^2	345±45	203±23	0.01
RR duration ms	904±28	904±33	0.9

Data are presented as mean±SEM unless otherwise stated. The normalised low (LFn) and high (HFn) frequency power, absolute low (LF), high (HF) and total (TF) power and RR duration across the 14 patients during 2-min periods centred around the end of apnoeas/hypopnoeas and during undisturbed baseline sleep. Differences between apnoea-/hypopnoea-related changes and baseline sleep were evaluated using a paired t-test. Each patient contributed are data point to each mean.

Table 3. – Area under the receiver-operating characteristic curve for the normalised low (LFn) and high (HFn) frequency power in each patient

Patient	LFn/HFn	Respiratory events# n	Baseline sleep# n
1	0.97 (0.02)***	14	86
2	0.97 (0.03)***	10	7
3	1.00 (0.001)***	17	10
4	0.96 (0.03)***	15	36
5	0.78 (0.05)¶	24	49
6	0.93 (0.04)***	9	19
7	0.91 (0.03)***	11	105
8	0.74 (0.06)+	7	36
9	0.95 (0.03)***	15	60
10	0.74 (0.09)§	10	19
11	0.96 (0.03)***	14	28
12	0.91 (0.05)***	34	28
13	0.81 (0.07)***	18	9
14	0.81 (0.07)***	16	49
Mean	0.88 (0.04)	15	39
Range	0.74–1.00	7–34	7–105

Data are presented as mean (SE) unless otherwise stated. #: the number of 2-min periods around respiratory events and during undisturbed, baseline sleep used for each curve, is indicated in the last two columns. Patients 6 and 12 were on the antihypertensive, nifedipine. The areas under the curves are identical for both measures of autonomic activity, as their calculation is based on the percentage of each band power with respect to their sum: LFn=LF×100/(LF+HF) and HFn=HF×100/(LF+HF). ***: p<0.001; ¶: p=0.002; +: p=0.003; §: p=0.02.

small number of samples used in some curves, may contribute to the SE increase.

Cortical arousals, apnoeas versus *hypopnoeas*

Of the 214 apnoeas/hypopnoeas analysed across the 14 patients, 154 (11±1), *i.e.* 72%, were terminated by visible cortical arousals, and 60 (4±1), *i.e.* 28%, were nonarousal-inducing apnoeas/hypopnoeas. LF, TF and LFn power were higher (p<0.05), RR duration and HFn power lower (p<0.05) around arousal-inducing compared with self-terminating apnoeas/hypopnoeas (table 4). In both groups, LF and LFn power increased (p<0.02) and HFn decreased (p<0.001) compared with baseline sleep. The increase in TF power was significant around arousal-inducing (p=0.01), not around self-terminating apnoeas/hypopnoeas (p=0.1); HF power did not differ significantly from baseline sleep in the two groups (p>0.1; table 5).

Of the events, 139, *i.e.* 65%, were hypopnoeas (10±1) and 75 (5±1), *i.e.* 35%, were apnoeas. No significant differences were found between apnoeas and hypopnoeas in any of the autonomic markers (p>0.6; table 4). The LF, TF, LFn and HFn power differed significantly around apnoeas and around hypopnoeas compared with baseline sleep (p<0.04; table 5).

Patients versus *healthy subjects*

Based on the 2-min analysis throughout the sleep periods, all absolute power values were higher among patients (p<0.03). No significant differences were found in LFn and HFn across patients compared with healthy controls (p=0.5; table 6). Mean RR duration dropped across patients (p=0.04; fig. 3a). To assess the likelihood of the measured parameters to distinguish patients from a healthy population, ROC curves were constructed based on the outcomes of time- and frequency-domain analysis. Each subject contributed one data point to each curve. The area under the RR duration curve was 0.88 (SE 0.08, p=0.006; fig. 3b). The area under the absolute LF and HF power curves was the same, 0.91 (SE 0.06, p=0.002), which indicates similar LF:HF ratios between patients and healthy controls. The area under the TF power curve was 0.93 (SE 0.06, p=0.002) across the 21 subjects (fig. 3c).

Discussion

The novel finding of this study is the increase in LF power around apnoeas/hypopnoeas, irrespective of arousal visibility

Table 4. – Frequency- and time-domain measures of autonomic activity around arousal-inducing and self-terminating events and apnoeas/hypopnoeas

	Apnoeas+hypopnoeas+ arousal	Apnoeas+hypopnoeas+ no arousal	p-value	Apnoeas	Hypopnoeas	p-value
LFn	69±1	64±2	0.04	67±1	68±2	0.8
HFn	31±1	36±2	0.04	33±1	32±2	0.8
LF ms^2	260±45	161±31	0.01	228±42	222±39	0.8
HF ms^2	129±22	88±10	0.08	116±21	110±19	0.8
TF ms^2	390±65	249±40	0.02	344±62	332±56	0.8
RR duration ms	903±28	914±29	0.03	909±28	905±33	0.7

Data are presented as mean±SEM unless otherwise stated. LFn: normalised low frequency power; HFn: normalised high frequency power; LF: low frequency power; HF: high frequency power; TF: total frequency power. Evaluation of the influence of arousals and event type on the RR interval power spectrum and RR duration. Paired t-tests showed that the increase in LFn, LF and TF was higher around arousal-inducing compared with self-terminating apnoeas/hypopnoeas. RR duration dropped around arousal-inducing apnoeas/hypopnoeas. No differences were found between apnoeas and hypopnoeas. Each patient contributed one data point to each mean.

Table 5. – p-Values of paired comparisons across the 14 patients

	Apnoeas+hypopnoeas+arousal	Apnoeas+hypopneas+no arousal	Apnoeas	Hypopnoeas
LFn	<0.001	<0.001	<0.001	<0.001
HFn	<0.001	<0.001	<0.001	<0.001
LF ms^2	0.002	0.01	0.005	0.005
HF ms^2	0.2	0.4	0.3	0.5
TF ms^2	0.01	0.1	0.03	0.03
RR duration ms	0.8	0.2	0.6	0.8

Paired comparisons between 2-min periods of undisturbed sleep and arousal-inducing apnoeas/hypopnoeas, between undisturbed sleep and self-terminating apnoeas/hypopnoeas, between undisturbed sleep and apnoea, between undisturbed sleep and hypopnoeas for all autonomic markers.

Table 6. – Frequency- and time-domain measures of autonomic activity in obstructive sleep apnoea/hypopnoea syndrome (OSAHS) patients and healthy subjects during nonoverlapping 2-min sliding windows throughout the sleep periods

	OSAHS patients	Healthy subjects	p-value
LFn	66±1	67±1	0.5
HFn	34±1	33±1	0.5
LF ms^2	111±16	57±3	0.02
HF ms^2	62±6	35±3	0.005
TF ms^2	173±21	91±6	0.01
RR duration ms	912±28	1138±91	0.04

Data are presented as mean±SEM unless otherwise stated. LFn: normalised low frequency power; HFn: normalised high frequency power; TF: total frequency power; LF: low frequency power; HF: high frequency power. Differences between the two groups were assessed using an unpaired t-test.

or type of respiratory event. The RR interval analysis throughout the sleep periods, based on 2-min rolling windows, showed a drop in RR duration and an increase in LF, HF and total power across OSAHS patients compared with age- and BMI-matched healthy subjects.

The present study was carefully designed to maintain analysis requirements while enabling detection of autonomic activity changes during apnoeas/hypopnoeas and after their termination. To ensure accurate outcomes, only 9% of the scored events were analysed, namely those that were not adjacent to further events, arousals or wake epochs within a 1-min radius from their termination. The outcomes of frequency-domain analysis demonstrate a significant increase in sympathetic activity during and after apnoeas/hypopnoeas compared with periods of undisturbed sleep. This difference could not be demonstrated in the time-domain analysis of the same segments, as the segments analysed included both the bradycardia during the events and the tachycardia following their end, resulting in an overall unchanged mean RR duration around the events compared with undisturbed sleep. These findings demonstrate the superiority of frequency-domain analysis in the detection of autonomic activity changes induced by apnoeas/hypopnoeas.

RR duration is influenced by the baroreflex loop, reflects phasic sympathetic activity and interacts with power oscillations during apnoea or hyperventilation [5]. The increase in LFn power demonstrates central tonic sympathetic activation [5, 19]. This is associated with an increase in respiratory effort due to the inspiratory attempts against the occluded/narrowed airways and the gradual elevation of negative intrathoracic pressure towards the end of apnoeas/hypopnoeas. The haemodynamic consequences are the increased venous return to the right ventricle accompanied by the increased myocardial transmural pressure and a negative chronotrope attitude during the respiratory abnormalities. During the postapnoeic/post-hypopnoeic recovery period the intrathoracic pressure decreases towards zero resulting in a decreasing transmural myocardial

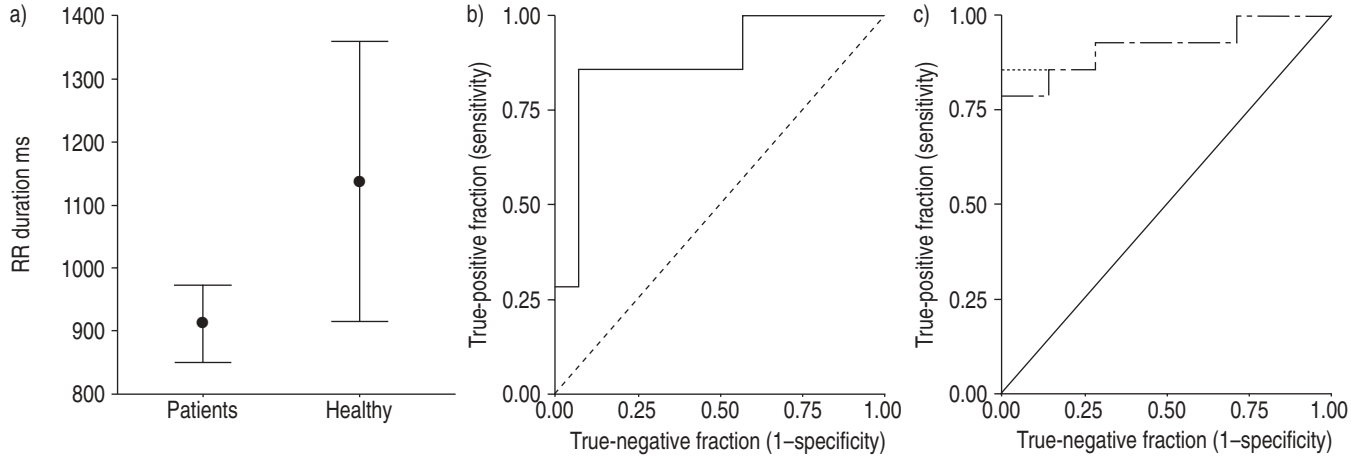

Fig. 3. – a) Mean values and 95% confidence intervals of the RR duration in patients (n=14) and healthy controls (n=7). These values were used to construct the receiver-operating characteristic (ROC) curve in b). b) ROC curve based on the mean RR duration during 2-min sleep-related rolling windows across the 14 patients and seven healthy controls, *i.e.* the curve consists of 21 points. The area under the curve is 0.88 (SE 0.08, p=0.006). Mean RR duration during this time window can differentiate well between obstructive sleep apnoea/hypopnoea syndrome (OSAHS) patients and healthy controls. c) ROC curves of RR interval absolute low (LF) and high (HF) frequency power values (- - -) yielded an area of 0.91 (SE 0.06, p=0.002), total (TF=LF+HF) power (·····) yielded an area of 0.93 (SE 0.05, p=0.002) across the 21 subjects. All three absolute power values differentiated well between OSAHS patients and healthy controls. Solid indicates reference.

pressure with a positive ino- and chronotrope effect. This abnormal breathing pattern is associated with increase in sympathetic activity, demonstrated through the increase in RR interval LF power around apnoeas/hypopnoeas and the postapnoeic increase in heart rate and blood pressure [20].

The present study shows that the LF power increase around apnoeas/hypopnoeas is irrespective of event type or arousal induction. This is in accordance with previous observations of postapnoeic increase in heart rate and blood pressure in the absence of arousals [21]. The present study found that the LF power increase is greater around arousal-inducing apnoeas/hypopnoeas. This was associated with an increase in total power and drop in RR duration. Changes in HF power, although nonsignificant, may have resulted from the apnoea-/hypopnoea- and arousal-related respiratory oscillations. When compared with baseline sleep, sympathetic activity was higher around both the arousal-inducing and self-terminating apnoeas/hypopnoeas.

The present outcomes were not validated against MSNA or blood pressure, as their monitoring would disrupt sleep, influence autonomic activity and would not necessarily reflect central tonic sympathetic traffic on the sinus node [5, 19]. Some modelling studies suggest that the influence of apnoeas/hypopnoeas on peripheral MSNA may be different to the centrally mediated sympathetic activity. Compared with baseline breathing, MSNA increased during and decreased directly after apnoeas, parallel to the central sympathetically mediated [19] increase in blood pressure and heart rate in healthy awake subjects during 20-s periods [22]. Another modelling study on healthy subjects demonstrated dissociated activity patterns between central and peripheral sympathetic activity during voluntary apnoeas and hyperventilation compared with quiet, paced breathing [5]. WATANABE *et al.* [23] studied OSAHS patients during sleep and detected an increase in MSNA, a decrease in blood pressure during apnoeas and a further increase in MSNA and in blood pressure in the immediate postapnoeic period. The finding of an increase in LF power around apnoeas/hypopnoeas compared with quiet sleep, is in agreement with the outcomes of KEYL *et al.* [24], which were based on 20-min windows.

The present study found a sleep-related reduction in RR duration and an increase in LF, HF and TF power in OSAHS patients compared with age- and BMI-matched controls. The drop in RR duration may represent sympathetic activation. This is in agreement with previous assessments of sympathetic activity using different markers, such as blood pressure and MSNA before and after treatment in OSAHS and compared with healthy controls [25]. Daytime HRV in OSAHS patients is reduced compared with healthy subjects [10]. A causative link may be speculated between nocturnal and diurnal changes in autonomic activity that results in disturbed circadian sympathovagal balance in these patients. This is in accordance with the findings of GROTE *et al.* [26] who demonstrated reduced vascular response to α-β_2-receptor stimulation in OSAHS patients compared with controls, a result of down-regulation of peripheral vascular receptors linked to chronic circadian hyperstimulation.

In the frequency-domain analysis, the present study found an overall increase in total, LF and HF power across patients; the nocturnal increase in HRV was associated with an increase in sympathetic and parasympathetic activity. None of the two branches of autonomic activity dominated across patients compared with healthy controls. This may be due to the 2-min window used for the analysis, allowing the breathing pattern of OSAHS patients to influence the RR interval power spectrum. BROWN *et al.* [14] demonstrated a strong influence of respiratory rate and tidal volume on the RR interval HF power but not on the RR duration, under experimentally controlled conditions in wake healthy subjects with stable cardiac sympathetic outflow. According to these findings, the presently detected increase in HF power across patients may be the result of the periodically abnormal breathing pattern during the analysis windows. This is supported by the parallel significant drop in RR duration found across patients compared with healthy controls, reflecting the overall increase in sympathetic activity, the detection of which in the frequency-domain analysis is affected by the breathing pattern. The importance of this factor would have been evaluated through elimination of the respiratory oscillations from the RR tachogram, but this was not performed during the present study. Had shorter analysis windows been used to minimise the influence of the breathing pattern on the RR interval power spectrum, these would not have been based on the standards for power spectral analysis [1] and would have required validation against objective markers of autonomic activity, such as MSNA.

Potential limitations of the study include definitions, the number of apnoeas/hypopnoeas analysed and the number of subjects studied. The hypopnoea definition presently used, fulfils the ASDA recommendations [11]. The inclusion of arousals in the definition may lead to a greater association with arousals compared with other definitions, *i.e.* based on thoracoabdominal movement or nasal pressure alone. To avoid influence on the RR interval power spectrum through adjacent apnoeas/hypopnoeas, arousals or wake epochs, only 9% of all the scored apnoeas/hypopnoeas were analysed. The distribution of the events analysed was representative of the total events scored, their distribution across the sleep states, the proportion of arousal-inducing events and also the event type. Therefore, the RR power changes around the apnoeas/hypopnoeas analysed are representative of the apnoeas/hypopnoeas scored across the night. Based on the areas under the ROC curves, the differences between apnoeas/hypopnoeas and undisturbed sleep are consistent across the 14 mild-to-severe OSAHS patients. The patients were randomly selected based on their symptoms and polysomnographic findings, typical of the syndrome. The outcomes are therefore likely to be robust and represent clinically important differences.

Based on the present findings, the authors speculate that sympathetic enhancement is induced by apnoeas/hypopnoeas during sleep. This reflects the functional overlap of cerebral morphological substrates in the regulation of sleep and autonomic cardiorespiratory function [4]. The hypothesis is supported by ZINKOVSKA and KIRBY [27] who prevented the increase of central sympathetically mediated vascular resistance [19] in response to airway obstructions, by blocking the autonomic responses to apnoeas through propranolol injection into porcine cerebral ventricles. Further evidence was provided during the observation of patients with autonomic nervous system dysfunction and coexisting sleep apnoea; a "decoupling" of heart rate from the respiratory cycle was noted [28]. The present study found increased nocturnal sympathetic activity around apnoeas/hypopnoeas probably linked to increased central tonic efferent traffic in otherwise healthy obstructive sleep apnoea/hypopnoea syndrome patients. This suggests an overall increased nocturnal sinus node activity in response to neural modulatory inputs. This is supported by the nocturnal reduction in RR duration across obstructive sleep apnoea/hypopnoea syndrome patients. The nocturnal sympathovagal fluctuations may contribute to the previously demonstrated changes in daytime autonomic activity [10]. These observations may be of causative and prognostic importance for the development of cardiovascular disease in untreated obstructive sleep apnoea/hypopnoea syndrome patients.

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References

1. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; 93: 1043–1065.
2. Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; 84: 482–492.
3. Pagani M, Montano N, Porta A, *et al.* Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 1997; 95: 1441–1448.
4. Guzzetti S, Cogliati C, Broggi C, *et al.* Influences of neural mechanisms on heart period and arterial pressure variabilities in tetraplegic patients. *Am J Physiol* 1994; 266: 1112–1120.
5. van de Borne P, Montano N, Narkiewicz K, *et al.* Importance of ventilation in modulating interaction between sympathetic drive and cardiovascular variability. *Am J Physiol Heart Circ Physiol* 2001; 280: H722–H729.
6. Singh JP, Larson MG, Tsuji H, Evans JC, O′Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Study. *Hypertension* 1998; 32: 293–297.
7. Valoni E, Adamson P, Piann GD. A comparison of healthy subjects with patients after myocardial infarction. *Circulation* 1995; 91: 1918–1922.
8. Young T, Pepperd P, Palta M, *et al.* Population-based study of sleep-disordered breathing as a risk factor for hypertension. *Arch Intern Med* 1997; 157: 1746–1752.
9. Hung J, Whitford EG, Parsons RE, Hillman DR. Association of sleep apnoea with myocardial infarction in men. *Lancet* 1990; 336: 261–264.
10. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. *Circulation* 1998; 98: 1071–1077.
11. Rechtschaffen A, Kales A. A Manual of Standardised Terminology: Techniques and Scoring Systems for Sleep Stages of Human Subjects. Publication No. 204. Washington, National Institutes for Health, 1968.
12. American Academy of Sleep Medicine Task Force Report. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep* 1999; 22: 667–689.
13. American Sleep Disorders Association Task Force Report. EEG arousals: scoring rules and examples. *Sleep* 1992; 15: 173–184.
14. Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. *J Appl Physiol* 1993; 75: 2310–2317.
15. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng* 1986; 33: 900–904.
16. Welch PD. The use of fast Fourier transformation for the estimation of power spectra: a method based on time averaging over short modified periodograms. *IEEE Trans Audio Electroacoust* 1967; 15: 70–73.
17. Zweig MH, Campbell G. ROC plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993; 39: 561–577.
18. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver-operating characteristic (ROC) curve. *Radiology* 1982; 143: 29–36.
19. Katragadda S, Xie A, Puleo D, Skatrud JB, Morgan BJ. Neural mechanism of the pressor response to obstructive and nonobstructive apnea. *J Appl Physiol* 1997; 83: 2048–2054.
20. Schneider H, Schaub CD, Andreoni KA, *et al.* Systemic and pulmonary hemodynamic responses to normal and obstructed breathing during sleep. *J Appl Physiol* 1997; 83: 1671–1680.
21. Lorenzi-Filho G, Dajani HR, Leung RS, Floras JS, Bradley TD. Entrainment of blood pressure and heart rate oscillations by periodic breathing. *Am J Respir Crit Care Med* 1999; 159: 1147–1154.
22. Morgan B, Denahan T, Ebert TJ. Neurocirculatory consequences of negative intrathoracic pressure *vs.* asphyxia during voluntary apnea. *J Appl Physiol* 1993; 74: 2969–2975.
23. Watanabe T, Mano T, Iwase S, *et al.* Enhanced muscle sympathetic nerve activity during sleep apnea in the elderly. *J Auton Nerv Syst* 1992; 37: 223–226.
24. Keyl C, Lemberger P, Pfeifer M, Hochmuth K, Geisler P. Heart rate variability in patients with daytime sleepiness suspected of having sleep apnea syndrome: a receiver-operating characteristic analysis. *Clin Sci* 1997; 92: 335–343.
25. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995; 96: 1897–1904.
26. Grote L, Kraiczi H, Hedner J. Reduced alpha- and beta(2)-adrenergic vascular response in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2000; 162: 1480–1487.
27. Zinkovska S, Kirby DA. Intracerebroventricular propranolol prevented vascular resistance increases on arousal from sleep apnea. *J Appl Physiol* 1997; 82: 1637–1643.
28. Guilleminault C, Briskin JG, Greenfield MS, Silvestri R. The impact of autonomic nervous system dysfunction on breathing during sleep. *Sleep* 1981; 4: 263–278.