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ORIGINAL ARTICLE

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Autonomic control of the cardiovascular system during sleep in normal subjects

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Abstract The autonomic control of heart rate and blood pressure during sleep is controversial: although it has been reported that vagal activity is more often lower in rapid eye movement sleep (REM) than in other stages of sleep (non-REM, NREM), the opposite has also been described. Initially, it was reported that baroreflex sensitivity (BRS) increases during sleep (REM and NREM), but in later studies, this was only partially confirmed. We therefore studied autonomic control of the cardiovascular (CV) system during sleep in 12 normal adults. The spectral compofnents of the heart rate R-R interval, blood pressure (BP), and BRS were computed at low (LF) and actual breathing frequency (high frequency, HF). Analysis of sleep stage and a cycle-by-cycle stage II analysis were performed. CV variability is affected largely by sleep-stage and sleep-cycle organisation: NREM and the last cycle exhibit the greatest vagal activity and the lowest sympathetic activity. BRS estimation for both the LF and HF bands confirmed previous results obtained by pharmacological and spontaneous slope methods: BRS is greater during sleep than during nocturnal wake periods, and further increased in REM. BRS is frequency dependent: in NREM, the higher value of HF BRS compared to LF BRS favours the HF control of BP variability, whereas higher BRS HF and LF components contribute to the strongest control in REM. BRS variability exhibits no significant pattern during the night. Our results suggest that both sleep-cycle organisation and BRS estimation in the LF and HF bands should be considered in sleep studies of autonomic CV control.

Keywords Spectral analysis · Heart rate · Blood pressure · Baroreflex · Sleep cycles

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Introduction

Spectral analysis of cardiovascular (CV) signals such as the heart rate R-R interval (RR), systolic (SBP) and diastolic (DBP) blood pressure (BP), provides useful indices of short- and long-term changes in neural autonomic control. RR is known to reflect beat-to-beat modulations of the sympathetic and parasympathetic cardiac limbs. The RR high-frequency (HF) component reflects mostly vagal modulation (Malliani et al. 1991, 1998; Pagani et al. 1986), whereas the RR low-frequency (LF) band seems to depend upon both sympathetic and vagal modulations (Eckberg 1997; Hopf et al. 1995; Malliani et al. 1991). The blood pressure LF component is considered as a marker of vascular sympathetic modulation (Pagani et al. 1986, 1988; Van de Borne et al. 1994), whereas the BP HF component reflects the mechanical interaction between respiration and the CV system (Parati et al. 1995).

Baroreflex sensitivity (BRS) is usually defined as the controller gain between SBP and RR. It has been demonstrated that BRS is a band-dependent phenomenon (Mangin et al. 2001; Pitzalis et al. 1998) revealing different autonomic mechanisms responsible for the short- and longer-term control of BP (Parlow et al. 1995; Pitzalis et al. 1998). In day-time studies, BRS has been assessed in the LF band (Hughson et al. 1993; Pagani et al. 1988; Panerai et al. 1995; Robbe et al. 1987; Van de Borne et al. 1994), reflecting the long-term control of SBP by the autonomic nervous system (ANS), and in the HF band (Mangin et al. 2001; Pagani et al. 1988; Pitzalis et al. 1998), reflecting the shorter-term control of the ANS. Therefore, both measurements together give a better insight into autonomic control of the CV system

(Mangin et al. 2001). Until now, there have been no studies of BRS estimation in both frequency bands during the sleep condition.

During the night, sleep follows several cycles, each lasting approximately 90 min, and each comprising light sleep, slow wave sleep (SWS) and rapid eye movement (REM) sleep. The overall influence of sleep on CV control has been analysed, but the results are conflicting (Baharav et al. 1995; Berlad et al. 1993; Negoescu and Csiki 1989; Van de Borne et al. 1994; Vanoli et al. 1995; Vaughn et al. 1995; Veenhof et al. 1997; Zemaityte et al. 1984), whereas the effect of sleep-cycle organisation has not actually been considered. Therefore, the main purpose of this study was to explore the influence of sleep-stage and sleep-cycle organisation on BRS and CV control in two ways: on one hand, sleep-stage influence alone was analysed by averaging the same stage throughout the night; on the other hand, sleep-cycle influence was analysed by exploring the cycle-by-cycle stage II evolution according to the time course of the sleep period.

Methods

Subjects

We studied 12 normal subjects (11 men, 1 woman), aged 25–54 years, with a body mass index of 22–26 kg/m^2, with no sleep complaint and no habitual snoring (as evidenced by their partner). Their physical exams and BP were normal.

Measurements

The subjects reported to the sleep laboratory at 8.00 p.m. after a light dinner without alcohol or coffee and were set up for sleep recording, which included placement of four electroencephalogram (EEG) leads (C_1A_2, C_3A_2, C_4A_1, O_2A_1), and preparation for an electro-oculogram, submental and tibial electromyogram (EMG) and electrocardiogram (ECG). Breathing was recorded with the aid of an oronasal thermistor, thoracic and abdominal movement sensors and finger oximetry. BP was recorded continuously by a Finapres 2300 (Ohmeda, Englewood, Colo., USA), which uses a volume-clamped cuff around one finger and provides accurate estimates of BP (Bos et al. 1992; Parati et al. 1989). The cuff was deflated for a period of 5 min in every 20 min to avoid discomfort, and the position of the hand was set at the level of the bed. The subject was monitored continuously by an infrared TV camera.

Data acquisition

ECG and BP data were sampled at 256 Hz, and breathing was sampled at 8 Hz. Data were recorded digitally by a Deltamed system (Paris, France) on an optical disk. Sleep analysis was made visually according to Rechtschaffen and Kales (1968), and scored as stages I (St I), II (St II), III, IV (slow-wave sleep, SWS) and REM sleep. Nocturnal awakenings were defined as awakenings of at least 1 min duration occurring during the sleep period. The signal processing was made by LARY-C, a physiological signal analysis software developed at INRIA (Rocquencourt, France). Rhythm detection software was applied to the raw CV signals: for RR, an adaptive threshold algorithm was applied to the derivative of the ECG. SBP was determined by a modified version of Pan's algorithm (Pan and Tompkins 1985) and DBP was taken as the first minimal diastolic point detected preceding the SBP value. CV and respiratory rhythms were resampled at 2 Hz (Berger et al. 1986).

Period selection

Only segments of 128 s with a visually stationary breathing pattern were selected for fast Fourier transform (FFT) analysis, excluding periods with abrupt changes or breathing abnormalities. This selection probably limited REM analysis to only tonic REM, in which breathing is known be more stable (Aserinsky 1965). In addition, we discarded epochs with noisy signals, periodic deflating of the Finapres device, and body movements.

Spectral evaluations (see Appendix for mathematical equations)

A 256-point FFT was applied to CV and respiratory segments overlapped by half, to obtain CV and respiratory parameters every 64 s. Hamming filtering and smoothing of the power spectral density (SPSD) with a 4-point rectangular moving average were applied to reduce spectral variance. Breathing rate (BR), estimated as the frequency of the maximum in respiratory SPSD, was allowed to centre at the HF component of RR (HF_{RR}) around the peak BR, with a narrow bandwidth of 0.06 Hz to increase coherence between respiratory and CV signals in this band (Saul et al. 1989). The band of LF components of RR (LF_{RR}) was fixed to 0.05–0.13 Hz. The LF and HF components of CV (LF_{CV} and HF_{CV}, respectively) were computed as the area under the SPSD in each band: RR spectral components are expressed in absolute values (LF_{RR}, HF_{RR}), in values normalised to the sum of LF_{RR} and HF_{RR} ($LFnu_{RR}$, $HFnu_{RR}$) and as the LF/HF ratio; The LF and HF components of BP (LF_{BP} and HF_{BP}, respectively) are expressed in mmHg^2/Hz.

Baroreflex sensitivity

In the spectral domain, BRS is defined as the controller gain between SBP and RR and presumes a permanent and linear association between them. A minimal central direct influence of respiration and other external stimuli on RR is assumed, so that RR is related to SBP in a linear way (Pagani et al. 1988). In the first instance, cross-spectral analysis between RR and SBP was performed to assess the coherence function between SBP and RR. The coherence function in (0;1), provides an estimation of the degree of linearity between two signals. Only epochs with coherence values greater than 0.5, validating the hypothesis of linearity, allowed the computation of the averaged gain in the LF ($gLF_{SBP,RR}$; ms/mmHg) and HF bands ($gHF_{SBP,RR}$; ms/mmHg).

Averaged sleep-stage analysis

All periods of a given sleep stage were merged together, independently of sleep cycles, to analyse the between-sleep-stage differences, therefore concealing the time evolution of the different stages during the night. The number of data segments selected within each stage was weighed as a proportion of its duration along the whole night in each subject. Therefore, only 33% of the recording duration was used for analysis (2.5 h on average per subject).

Specific St II analysis throughout the night

St II evolution over the night was followed to analyse between-sleep-cycle differences. The first and last cycles were compared to estimate the time course of CV and respiratory parameters throughout the night. It was only possible to analyse St II in this way because it is the only stage present from the first to the last cycle of sleep (stages III–IV usually occurs predominantly at the beginning of the night, and

REM occurs mostly in the second part of the night). Only seven subjects had at least four or five reliable cycles.

Statistical analysis and sleep-stage classification

Non-parametric Wilcoxon tests were applied to the following parameters: mean values ($mean_{RR}$ and $mean_{BP}$), standard deviations (SD_{RR} and SD_{BP}), spectral components, gains, BR. All results are expressed as means (SEM).

Nocturnal wake (nW) was defined as pre- and intra-sleep periods of wakefulness, and were added to St I. as these epochs were usually consecutive and often shorter than 2 min (whereas FFT analysis requires at least 2 min of continuous signal). Thus, we classified four periods of analysis: nW and stage I (nW-St I), stage II (St II), SWS (i.e. stages III and IV) and REM. NREM refers to St II and SWS.

Results

Sleep architecture and events

Sleep stage distribution was within the normal range for the first night of recording in the laboratory (Table 1). Mean sleep efficiency (i.e. total sleep time/time in bed; Table 1) was slightly lower (81%) than usually observed in normal subjects in this age group (90–95%), and this was probably related to the extensive monitoring involved. Breathing pattern during sleep was normal for each subject (apnoea-hypopnoea index below 10/h of sleep) and no significant periodic leg movements were noted during the recording (myoclonus index below 5/h). The video monitoring of the subjects did not show any abnormal movement and snoring was within the normal range.

Comparison of sleep stages

Mean values and spectral components of CV variables

$Mean_{RR}$ and $mean_{BP}$ were not different between sleep stages. SD_{HR} was lower during SWS and SD_{SBP} and SD_{DBP} were lower in all sleep stages compared to nW-St I, and was lowest during SWS (Table 2). For RR spectral components (Table 3), $HFnu_{RR}$ was higher in NREM than in REM and nW-St I, and similar during nW-St I and REM. Conversely, $LFnu_{RR}$ changed in the opposite direction to $HFnu_{RR}$, leading to a LF/HF ratio that was significantly lower during St II and SWS. For BP spectral components, LF_{BP} components were consistently lower in sleep than in nW-St I.

Arterial BRS

$gHF_{SBP,RR}$ was higher in sleep than in nW-St I, revealing a between-wake-sleep difference, whereas $gLF_{BP,RR}$ was higher in REM than in nW-St I and NREM, revealing an additional between-sleep-stage difference (Table 4, Fig. 1).

St II analysis during successive sleep cycles

The time course of CV parameters in a typical subject is shown in Fig. 2. $Mean_{RR}$ and HF_{CV} components increased throughout the night. Changes in BRS varied between subjects, without a general pattern.

Table 1. Sleep architecture. (*nW* Nocturnal wake, S*t* sleep stage, *REM* rapid eye movement sleep, *SWS* slow wave sleep, *AHI* apnoea-hypopnoea index – per hour, *PLM* periodic leg movements index – per hour, *TST* total sleep time)

Parameter	Age (years)	TST (min)	Sleep efficiency[a]	nW (min)	St I (%)[b]	St II (%)[b]	SWS (%)[b]	REM (%)[b]	AHI (per h)	PLM (per h)	Snoring (%TST)
Mean	35.0	344.0	0.81	60.0	37.0 (12)	151.0 (42)	92.0 (27)	57.0 (16)	5.2	3.1	6.2
SEM	2.9	14.5	0.05	16.6	10.6 (4)	18.5 (4)	13.7 (3)	7.4 (1)	2.1	1.2	3.1

[a]Sleep efficiency was calculated as TST/time spent in bed
[b]The length of sleep stage is expressed as a percentage of the total sleep time (%TST)

Table 2. Mean (SEM) and standard deviation (SEM) of cardiorespiratory parameters. (*SBP* Systolic blood pressure, *DBP* diastolic blood pressure, *BR* breathing rate, *RR* R-R interval of the cardiac cycle, *SD* standard deviation)

Variable	Sleep stage			
	nW-St I	St II	SWS	REM
Mean values				
$mean_{RR}$ (ms)	994 (18)	1000 (36)	1011 (40)	1005 (33)
$mean_{SBP}$ (mmHg)	114 (5)	114 (4)	113 (3)	113 (4)
$mean_{DBP}$ (mmHg)	68 (3)	69 (3)	69 (2)	70 (3)
$mean_{BR}$ (Hz)	0.24 (0.008)	0.23 (0.008)	0.24(0.008)	0.23 (0.005)
Standard deviation				
SD_{RR} (ms)	61 (7)	55 (4)	40 (3)‡‡*§	50 (5)
SD_{SBP} (mmHg)	7.37 (0.90)	5.51 (0.33)‡	4.72 (0.28)‡‡§	5.18 (0.41)††
SD_{DBP} (mmHg)	4.95 (0.84)	3.51 (0.31)‡	2.69 (0.19)‡‡§	3.19 (0.25)††

†, ††Significant difference between REM and nW-St I, $P \leq 0.05$ and $P \leq 0.01$, respectively; ‡, ‡‡significant difference between nW-St I and St II or SWS, $P \leq 0.05$ and $P \leq 0.01$, respectively; *significant difference between REM and St II or SWS ($P \leq 0.05$); § significant difference between St II and SWS

Table 3. Spectral components of RR, SBP, DBP. Data are presented as the mean (SEM). (HF_x High-frequency component of x, LF_x low-frequency component of x, $LFnu_{RR}$ LF RR values normalised to the sum of the LF and HF components, $HFnu_{RR}$ HF RR values normalised to the sum of the LF and HF components)

Sleep stage	nW-St I	St II	SWS	REM
LF_{RR}	9.22 (4.08)	7.00 (2.43)	4.64 (1.45)*	8.71 (2.48)
HF_{RR}	2.57 (1.11)	2.89 (1.09)	2.65 (1.06)	2.98 (1.22)
$LFnu_{RR}$[a]	0.76 (0.04)	0.70 (0.04)‡‡**	0.67 (0.06)‡**	0.77 (0.04)
$HFnu_{RR}$[a]	0.23(0.04)	0.30 (0.04)‡‡**	0.32 (0.06)‡*	0.22 (0.04)
LF/HF	8.19 (1.83)	5.92 (1.23)‡‡*	4.84 (1.13)‡**	9.02 (1.65)
LF_{SBP}[b]	0.037 (0.011)	0.019 (0.004)‡	0.022 (0.004)‡	0.023 (0.005)††
LF_{DBP}[b]	0.0180 (0.0057)	0.0074 (0.0015)‡‡	0.0075 (0.0014)‡‡	0.0092 (0.0020)††
HF_{SBP}[b]	0.0035 (0.001)	0.0046 (0.0003)*	0.0030 (0.0011)	0.0026 (0.0008)
HF_{DBP}[b]	0.00094 (0.00028)	0.00078 (0.00026)	0.00056 (0.00018)‡	0.00089 (0.00003)

[a] $HFnu_{RR}$ and $LFnu_{RR}$ are given in normalized units (0–1)
[b] HF_{BP}, and LF_{BP} are given in $mmHg^2/Hz$ †, ††Significant difference between REM and nW-St I, $P \le 0.05$ and $P \le 0.01$, respectively; ‡, ‡‡significant difference between nW-St I and St II or SWS, $P \le 0.05$ and $P \le 0.01$, respectively; *, **significant difference between REM and St II or SWS, $P \le 0.05$ and $P \le 0.01$, respectively

Table 4. Baroreflex sensitivity (BRS) values for RR and SBP. Data are presented as the mean (SEM) in ms/mmHg. (gHF_{SBPRR} High-frequency gain between SBP and RR, $gLF_{SBP,RR}$ low-frequency gain between SBP and RR)

Sleep St	nW-St I	St II	SWS	REM
$gLF_{SBP,RR}$	14.7 (2.42)	15.64 (2.47)*	12.83 (1.40)**	17.7 (2.45)††
$gHF_{SBP,RR}$	20.8 (3.92)	24.3 (3.85)‡	25.5 (4.16)‡	25.9 (3.92)†

†, ††Significant difference between REM and nW-St I, $P \le 0.05$ and $P \le 0.01$, respectively; ‡significant difference between nW-St I and St II or SWS, $P \le 0.05$; *, **significant difference between REM and St II or SWS, $P \le 0.05$, $P \le 0.01$, respectively

Comparison of the first and last sleep cycles

Changes in CV parameters between the first and last sleep cycles are reported in Table 5 for seven subjects. $Mean_{RR}$ and HF_{CV} components increased significantly throughout the night (in particular, HF_{RR} and HF_{BP} approximately doubled), while the LF_{CV} component decreased, showing a between-sleep-cycle difference. Therefore, the LF/HF ratio decreased significantly. There was a very slight decrease in $mean_{BR}$ throughout the night. Contrary to the other CV parameters, $gHF_{BP,RR}$ and $gLF_{BP,RR}$ did not change significantly.

Discussion

Sympathetic and parasympathetic activity

Cardiac autonomic activity

The results of previous sleep studies are conflicting: in some reports it was shown that $mean_{RR}$ was higher and the RR variability lower in NREM than in REM (Negoescu and Csiki 1989; Van de Borne 1994; Zemaityte et al. 1984), but this was not the case in other reports (Baharav et al. 1995; Hornyak et al. 1991; Somers et al. 1993; Vanoli et al. 1995). In some reports, vagal activity was estimated to be higher in NREM than in REM (Baharav et al. 1995; Berlad et al. 1993; Negoescu and Csiki 1989; Van de Borne et al. 1994; Vanoli et al. 1995), but not in others (Vaughn et al. 1995; Veenhof et al. 1997; Zemaityte et al. 1984). Estimated cardiac sympathetic activity was reported to be increased (Baharav et al. 1995; Negoescu et al. 1989; Van

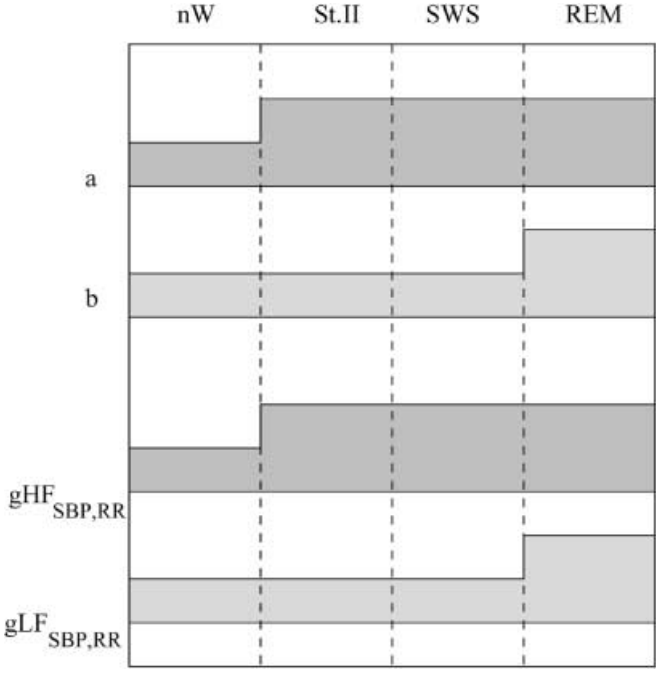

Fig. 1. Comparison between baroreflex sensitivity evolution (arbitrary units) through nocturnal wake (*nW*) and sleep stages (stage II, slow wave sleep and rapid-eye-movement sleep) in three studies. **a**: Smyth's study, using the drug-induced sequence method (Smyth et al. 1969). **b** Data from the study of Van De Borne et al. (1994) study, using a spectral method, in the low-frequency band. **c**: Our study, using a spectral method, in both low (for low frequency gain between systolic blood pressure and R-R interval, $gLF_{SBP,RR}$) and high (for high-frequency gain for a particular systolic blood pressure and R-R interval, $gHF_{SBP,RR}$) frequency bands. (*St II* Stage II sleep, *SWS* slow wave sleep, REM rapid eye movement sleep)

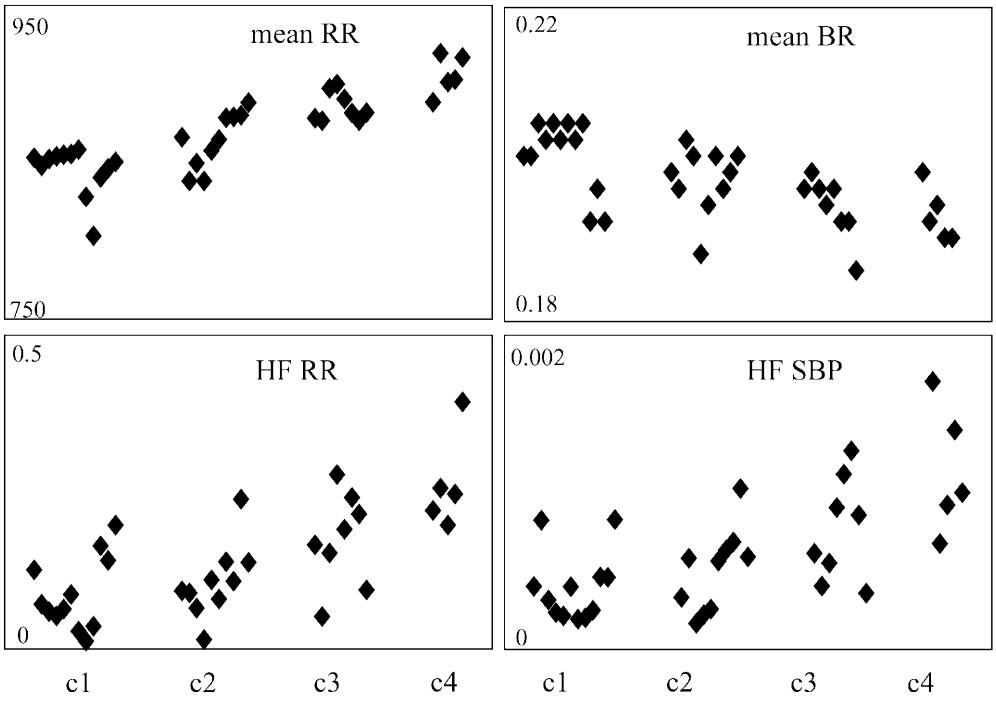

Fig. 2. Cycle-by-cycle evolution (from c1 to c4) of heart period: mean R-R interval of the cardiac cycle (*RR*, ms), breathing rate (*BR*, Hz), high-frequency component of RR and systolic blood pressure (*HF RR*, ms^2/Hz and *HF SBP*, $mmHg^2$/Hz, respectively) in one typical subject during St II. Each data point represents an average value taken over 2 min. Mean RR progressively increased and HF RR and HF SBP rose simultaneously, while mean BR decreased slightly

de Borne et al. 1994; Vanoli et al. 1995; Vaughn et al. 1995), decreased (Berlad et al. 1993; Parmegiani 1994) or equal (Zemaityte et al. 1984) in REM compared to NREM. These differences could be due in part to the use of different variables to estimate cardiac autonomic activity. Indeed, the use of $mean_{RR}$ and absolute spectral values (HF_{RR} and $LF_{RR;}$ Berlad et al. 1993; Vaughn et al. 1995; Veenhof et al. 1997; Zemaityte et al. 1984) or the use of relative values ($HFnu_{RR}$, $LFnu_{RR}$; Baharav et al. 1995; Negoescu et al. 1989; Van de Borne et al. 1994) and the power ratio LF_{RR}/HF_{RR} (Vanoli et al. 1995) do not lead to the same results as those given in Table 2. As far as we are concerned, $mean_{RR}$ better reflects changes in cardiac autonomic tone because it is the net result of opposing sympathetic and parasympathetic tonic activities on the sinus node (Goldberger 1999). Conversely, relative spectral power $LFnu_{RR}$ and $HFnu_{RR,}$ represent autonomic modulation of the heart rate around a given autonomic tone (Porges 1995; Medigue et al. 2001). Together, these parameters provide different information on tone and modulation resulting from sympathovagal interactions (Coumel et al. 1994).

The dissociation between $mean_{RR}$ and RR variability in the sleep-stage analysis is in agreement with the hypothesis of the existence of two independent control mechanisms (Porges 1995; Medigue et al. 2001). The absence of change in $mean_{RR}$ between sleep stages could reflect an absence of change in overall autonomic tone, whereas the higher value of $HFnu_{RR}$ (lower $LFnu_{RR}$) in NREM than in nW-St I and REM suggests a shift in autonomic modulation towards a vagal predominance in NREM sleep. On the contrary, a parallel evolution in $mean_{RR}$ and RR variability was found in the cycle-by-cycle St II analysis. The increase in $mean_{RR}$ and $HFnu_{RR}$ and the decrease in $LFnu_{RR}$ suggest that the autonomic tone and modulation of RR are modified together towards a progressively greater cardiac vagal activity during the night. Therefore, autonomic tone is more sleep-cycle than sleep-stage-organisation dependent, whereas autonomic modulation is influenced by both patterns.

Vascular sympathetic activity

As found previously (Van de Borne et al. 1994), LF_{BP} is similar between NREM and REM, contrary to the sympathetic output to skeletal muscle blood vessels, which is markedly increased during REM at a level similar or even higher than during wakefulness (Somers et al. 1993; Okada et al. 1991; Hornyak et al. 1991). This may be a consequence of the opposing sympathetic drives found in animal studies: a decrease in the

Table 5. Mean variables of St II sleep during the first and last sleep cycles for seven subjects. Data are presented as the mean (SEM)

Variable	First cycle	Last cycle	*P* value
$mean_{BR}$	0.23 (0.008)	0.21 (0.008)	≤ 0.05
$mean_{SBP}$ (mmHg)	128.2 (5.37)	116.3 (5.86)	0.10
$mean_{RR}$ (ms)	979 (47)	1068 (44)	≤ 0.01
HF_{RR} (mmHg)	1.82 (0.76)	3.92(1.54)	≤ 0.01
LF/HF	4.77(1.34)	2.65(1.00)	≤ 0.05
$HFnu_{RR}$	0.300 (0.260)	0.405 (0.239)	0.09
$LFnu_{RR}$	0.700 (0.269)	0.595 (0.239)	0.09
HF_{SBP} ($mmHg^2$/Hz)	0.0027 (0.001)	0.0060 (0.002)	≤ 0.05
HF_{DBP} ($mmHg^2$/Hz)	0.00047 (0.00043)	0.001 (0.001)	≤ 0.05
LF_{SBP} ($mmHg^2$/Hz)	0.021 (0.012)	0.012 (0.002)	≤ 0.05
LF_{DBP} ($mmHg^2$/Hz)	0.006 (0.005)	0.004 (0.003)	≤ 0.01

splanchnic and renal circulation and an increase in the skeletal muscle vessels occurring during REM (Mancia 1993; Parmegiani 1994). Cycle-by-cycle St II analysis shows an overall decrease in sympathetic vascular activity during the night in this stage. Therefore, vascular sympathetic activity is both wake-sleep-transition and sleep-cycle-organisation dependent.

Baroreflex sensitivity

In the time domain, BRS is assessed by spontaneous sequences (sequence-BRS) or drug-induced sequences (drug-BRS) in the same direction as the SBP and RR time series (Bristow et al. 1969; Conway et al. 1983; Hughson et al. 1993; Maestri et al. 1998; Panerai et al. 1995; Parati et al. 1988, 2000; Parlow et al. 1995; Smyth et al. 1969), presuming an adaptive and intermittent mechanism for baroreceptor activation (Panerai et al. 1995). In the spectral domain, BRS is assessed by the RR/BP power ratio in different frequency bands (spectral-BRS; Hughson et al. 1993; Maestri et al. 1998; Mangin et al. 2001; Pagani et al. 1988; Panerai et al. 1995; Parati et al. 2000; Pitzalis et al. 1998; Robbe et al. 1987), presuming a permanent and linear association between BP and RR (Panerai et al. 1995). Smyth et al. (1969) assessed drug-BRS and concluded that BRS is higher in sleep (REM and NREM) than in nW, but in later studies, this was only partially confirmed (Bristow et al. 1969; Conway et al. 1983). More recently, Van de Borne et al. assessed spectral-BRS only in the LF band ($gLF_{SBP,RR}$) and concluded that BRS is higher in REM than in NREM and nW, but found no difference between nW and NREM sleep. Although drug-BRS assessment is an invasive method, it still represents the gold standard (Maestri et al. 1998). The simultaneous determination of $gLF_{SBP,RR}$ and $gHF_{SBP,RR}$ reveals that the results of Smyth et al. (1969) and Van De Borne et al. (1994) are not conflicting, and that the non-invasive spectral analysis gives the same results as obtained by drug application. Indeed, Fig. 1 shows that BRS changes with sleep stages in the LF band ($gLF_{SBP,RR}$) are the same as those assessed by Van De Borne et al. (1994), whereas BRS changes in the HF band ($gHF_{SBP,RR}$) are the same as assessed by Smyth et al. (1969). This could be due to the fact that sequence-BRS enlightens the short RR-SBP sequences in particular, reflecting the short-term control (Hughson et al. 1992; Mangin et al. 2001; Panerai et al. 1995). Thus, the simultaneous assessment of $gLF_{SBP,RR}$ and $gHF_{SBP,RR}$ allows the distinction between the short- and longer-term control in the baroreflex loop.

Sleep-stage organisation affects short- ($gHF_{SBP,RR}$) and longer-term ($gLF_{SBP,RR}$) control differently. BRS increase from wake to sleep is due principally to short-term control, whereas the further BRS increase from NREM to REM is principally due to longer-term control. REM has the greatest values for $gLF_{SBP,RR}$, as found previously (Bristow et al. 1969; Parati et al. 1988; Smyth et al. 1969; Van de Borne et al. 1994), and also for $gHF_{SBP,RR}$. This increased neural feedback could more effectively buffer CV perturbations secondary to bursts of brainstem stimulation during phasic REM, and could also maintain a strong CV control during longer tonic REM periods. REM and nW-St I represent opposite situations: in REM, $gHF_{SBP,RR}$ and $gLF_{SBP,RR}$ are greater, whereas the overall variance in BP and LF_{BP} variability are lower than in nW-St I, showing that in REM sleep, CV control is more involved in buffering CV perturbations. In SWS, a high $gHF_{SBP,RR}$ and a low $gLF_{SBP,RR}$ seem to favour the short-term control, concurs with the fact that CV control in SWS is mainly linked to respiratory influence.

BRS efficiency is a band-dependent phenomenon, as in every sleep stage, $gHF_{BP,RR}$ is greater than $gLF_{BP,RR}$ ($P \leq 0.01$, not shown); this is in agreement with the work of Parati et al. (1988), who observed that sequence-BRS decreased as the time over which baroreceptor modulated the sinus node increased, and concluded that BRS is most effective when engaged briefly.

There appeared to be no pattern to the evolution in BRS throughout the night in $gHF_{SBP,RR}$ or $gLF_{SBP,RR}$, which is consistent with the results of Parati et al. (1988). This suggests that BRS is not clearly influenced by sleep-cycle organisation and that other mechanisms must be predominant in CV autonomic control throughout the night. Therefore, the HF_{CV} increase and the LF_{CV} decrease observed during the night might be related to a reduced low-pass characteristic of the vascular system, possibly due to a decrease in total peripheral resistance, one of the mechanisms responsible for the fall in blood pressure observed during sleep (Bristow et al. 1969). The different time evolution of BRS between subjects might be due to different resetting mechanisms of the cardiac baroreflex, as illustrated previously (Bristow et al. 1969; Smyth et al. 1969).

Conclusion

During sleep, autonomic control of the CV system depends upon both sleep-stage and sleep-cycle organisation. CV variability is affected largely by sleep-stage organisation: the greatest vagal modulation is combined with the lowest vascular sympathetic activity in NREM. Throughout the night, vagal tone increases and the vascular sympathetic activity decreases from the first to the last sleep cycle in St II. BRS estimation in both the LF and HF bands allowed us to confirm results obtained previously using drugs and non-invasive methods: BRS is greater in sleep than in nW, and is further increased in NREM. In sleep-stage organisation, BRS exhibits a band-dependent behaviour: in NREM, the high $gHF_{SBP,RR}$ value combined with the low $gLF_{SBP,RR}$ value favours short-term control, whereas in REM, both BRS components are high, contributing together to the strongest control in this state, which could more effectively buffer CV perturbations secondary to bursts of

brainstem stimulation during phasic REM. Sleep-cycle organisation does not clearly affect BRS, as BRS exhibits no significant pattern through the night, suggesting that other CV control mechanisms are predominant. Our results suggest that both sleep-cycle organisation and BRS estimation in both the LF and HF bands should be taken into account in analyses of CV autonomic control during sleep.

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Appendix

Complex spectrum, smoothed power spectral density, energy and smoothed cross-spectral density are given by Eqs. 1, 2, 3 and 4, respectively:

$$X(k\Delta f) = \sum_{i=0}^{N-1} x_i w_i e^{-j2\pi k\Delta f i t_0} \tag{1}$$

$$\bar{D}_{xx}(k\Delta f) = \frac{1}{M+1} \times \frac{1}{t} \sum_{k=-\frac{M}{2}}^{\frac{M}{2}} |X(k\Delta f)|^2 \tag{2}$$

$$x*F = \sum\nolimits_{k\Delta f \in *F} \bar{D}_{xx}(k\Delta f) \tag{3}$$

$$\bar{D}_{xy}(k\Delta f) = \frac{1}{t(M+1)} \sum_{k=-\frac{M}{2}}^{\frac{M}{2}} X*(k\Delta f) Y(k\Delta f) \tag{4}$$

where the frequency band $*F$ can be either high frequency (HF) or low frequency (LF), $t_0 = 0.5$ s is the time step of the resampled data series, w_i stands for ith value of 256-Hamming window, $t = Nt_0 = 128$ s is the analysing-period, the $k\Delta f = 1/t = 0.008$ Hz is the kth discrete frequency value (or spectral frequency resolution), M defines the smoothing frequency bandwidth.

The coherence function, coherence values, transfer function and baroreflex sensitivity were calculated using Eqs. 5, 6, 7 and 8, respectively:

$$\gamma^2_{xy}(k\Delta f) = \frac{\left|\bar{D}_{xy}(k\Delta f)\right|^2}{\bar{D}_{xx}(k\Delta f)\bar{D}_{yy}(k\Delta f)} \tag{5}$$

$$\mathrm{coh}_{*F} = \frac{1}{L_{*F}} \sum k\Delta f \in *F \gamma^2_{xy}(k\Delta f) \tag{6}$$

$$\left|H_{xy}(k\Delta f)\right| = \frac{\left|\bar{D}_{xy}(k\Delta f)\right|}{\bar{D}_{xx}(k\Delta f)} \tag{7}$$

$$g*F = \frac{1}{L_{*F}} \sum k\Delta f \in *F \left|\bar{H}_{xy}(k\Delta f)\right| \tag{8}$$

where x can be SBP or DBP, and y the RR signal, $£_{*F}$ stands for HF or LF bandwidth.

Finally, the dispersion index was calculated as:

$$\mathrm{DI} = \frac{\sum\limits_{k\Delta f \in \mathrm{RW}} (k\Delta f - i\Delta f)^2 \bar{D}_{\mathrm{resp}}(k\Delta f)}{\sum\limits_{k\Delta f \in \mathrm{RW}} (k\Delta f - i\Delta f)^2 \bar{D}_{\mathrm{resp}}(i\Delta f)} \tag{9}$$

where $\mathrm{BR} = i\Delta f$ is the frequency corresponding to the maximum of respiratory spectra in the analysis window fixed to 0.08–0.40 Hz.

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