Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men

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Otzenberger, Hélène, Claude Gronfier, Chantal Simon, Anne Charloux, Jean Ehrhart, François Piquard, and Gabrielle Brandenberger. Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men. *Am. J. Physiol.* 275 (*Heart Circ. Physiol.* 44): H946–H950, 1998.—We have recently demonstrated that the overnight profiles of cardiac interbeat autocorrelation coefficient of R-R intervals (r_{RR}) calculated at 1-min intervals are related to the changes in sleep electroencephalographic (EEG) mean frequency, which reflect depth of sleep. Other quantitative measures of the Poincaré plots, i.e., the standard deviation of normal R-R intervals (SDNN) and the root mean square difference among successive R-R normal intervals (RMSSD), are commonly used to evaluate heart rate variability. The present study was designed to compare the nocturnal profiles of r_{RR}, SDNN, and RMSSD with the R-R spectral power components: high-frequency (HF) power, reflecting parasympathetic activity; low-frequency (LF) power, reflecting a predominance of sympathetic activity with a parasympathetic component; and the LF-to-HF ratio (LF/HF), regarded as an index of sympathovagal balance. r_{RR}, SDNN, RMSSD, and the spectral power components were calculated every 5 min during sleep in 15 healthy subjects. The overnight profiles of r_{RR} and LF/HF showed coordinate variations with highly significant correlation coefficients ($P <$ 0.001 in all subjects). SDNN correlated with LF power ($P <$ 0.001), and RMSSD correlated with HF power ($P < 0.001$). The overnight profiles of r_{RR} and EEG mean frequency were found to be closely related with highly cross-correlated coefficients ($P < 0.001$). SDNN and EEG mean frequency were also highly cross correlated ($P < 0.001$ in all subjects but 1). No systematic relationship was found between RMSSD and EEG mean frequency. In conclusion, r_{RR} appears to be a new tool for evaluating the dynamic beat-to-beat interval behavior and the sympathovagal balance continuously during sleep. This nonlinear method may provide new insight into autonomic disorders.

Poincaré plot; electroencephalographic spectral analysis

A NONLINEAR PROCEDURE, the Poincaré plot, which is a scatter plot of the current R-R interval against the preceding R-R interval, provides a qualitative picture of beat-to-beat interval behavior (11, 17). This procedure has been used to identify abnormalities of cardiac dynamic rhythms in numerous pathological conditions, including sudden infant death syndrome (19), heart failure (11, 28), and obstructive sleep apnea (3). It has been demonstrated that, during sleep, the Poincaré plots have distinctive and characteristic patterns depending on sleep stages, with rapid eye movement (REM) sleep being characterized by wider overall and more regulated variations than those observed during non-rapid eye movement (NREM) sleep (15, 18, 29).

We have recently calculated, at 1-min intervals, the interbeat autocorrelation coefficients of R-R intervals (r_{RR}) derived from Poincaré plots and demonstrated that their overnight profiles are closely related to variations in electroencephalographic (EEG) mean frequency (14), which reflect depth of sleep. Other quantitative measures have been proposed for evaluating heart rate variability (20, 21). In particular, the standard deviation of normal R-R intervals (SDNN), related to the extent of the data projected onto the *x*-axis, and the root-mean-square difference among successive normal R-R intervals (RMSSD), which corresponds to the width of the Poincaré plots, are commonly accepted measures of the Poincaré plots (11). Recently, it has been reported (10) that RMSSD constitutes a measure of parasympathetic activity.

Studies using spectral analysis of R-R intervals have reported (2) that the power spectrum contains both low-frequency (LF, 0.04–0.15 Hz) and high-frequency peaks (HF, 0.15–0.50 Hz). With the use of appropriate autonomic blocking agents and experimental supine-standing strategies, several studies demonstrated that HF power reflects parasympathetic activity, whereas LF power primarily reflects sympathetic activity with a parasympathetic component (2, 7, 16). The LF-to-HF ratio (LF/HF) is commonly regarded as an index of sympathovagal balance (13, 20).

The aim of the present study was to compare the overnight profiles of r_{RR}, SDNN, and RMSSD with the R-R spectral power components, i.e., LF power, HF power, and LF/HF. All of the variables were calculated at 5-min intervals and were studied with regard to the variations in EEG mean frequency. These comparisons were made to clearly establish the relevance of r_{RR} as a tool in exploring the sympathovagal balance continuously during sleep in men.

METHODS

Subjects. Fifteen healthy male subjects, ages 22 to 30 yr, participated in the experiment. All gave their informed consent, and the local Ethics Committee approved the protocol. The subjects participated in the study after medical examination and screening tests. All had normal sinus rhythm and regular sleep-wake habits, and none was taking medication. The experiments were carried out in a soundproof, air-conditioned sleep room. After spending a habituation night in the laboratory, each subject underwent an experimental night during which sleep and cardiac recording were carried out. Electrodes were applied 2 h before the beginning of the recordings. Lights were switched off at 2300, and the subjects were awakened at 0700.

Sleep analysis. Sleep recordings were performed using two electroencephalographic derivations (C3 vs. A2 and C4 vs.

A1), one chin electromyographic derivation, and one horizontal electrooculographic derivation. An all-night spectral analysis was conducted by converting the EEG signal from analog to digital with a sampling frequency of 128 Hz. Subsequently, spectra were computed every 2 s using a fast Fourier transformation algorithm (9), and a 150-point median filter was used to obtain 5-min power density values. The EEG spectral parameter considered was the mean frequency of the global EEG band (0.5–35 Hz).

Heart rate analysis. The electrocardiogram signal was fed into a generator that produced a pulse at the rising phase of each R wave. The trigger event times were recorded with an accuracy of ±1 ms, and the R-R intervals were calculated on a computer equipped with a data acquisition control board including a timer. Computers and polygraphs were synchronized. Occasional ectopic or missing beats were identified and replaced with interpolative R-R interval data. Each R-R interval was plotted against the previous R-R interval to produce a 5-min Poincaré plot (R-R_{n+1} vs. R-R_n). The interbeat autocorrelation coefficient of R-R intervals (r_{RR}; i.e., Pearson's correlation coefficient between R-R_n and R-R_{n+1}), SDNN, and RMSSD were calculated at 5-min intervals.

Power spectral analyses of each consecutive 5-min recording were performed in a sequential fashion with the use of a fast Fourier transform (based on a nonparametric algorithm using a Hann window) after the ectopic-free data were detrended and resampled. A fixed resampling frequency of 1,024 equally spaced points per 5-min period was used. The powers in the LF band (0.04–0.15 Hz) and in the HF band (0.15–0.50 Hz) were calculated for each 5-min density spectrum by integrating the power spectral density in the respective frequency bands. LF/HF was calculated using the power in each band.

Statistical analysis. To assess the relationships between the overnight profiles of r_{RR}, SDNN, and RMSSD and the R-R spectral power components, Pearson's correlation coefficients were calculated. The temporal links between the overnight profiles of r_{RR}, SDNN, and RMSSD and the profiles of EEG mean frequency were quantified using cross-correlation analysis (Box Jenkins Time Series Analysis, BMDP Statistical Software, Los Angeles, CA). Cross-correlation coefficients were computed for lags −3 to +3, with each lag corresponding to a 5-min interval. For each subject, all data subsequent to sleep onset were evaluated.

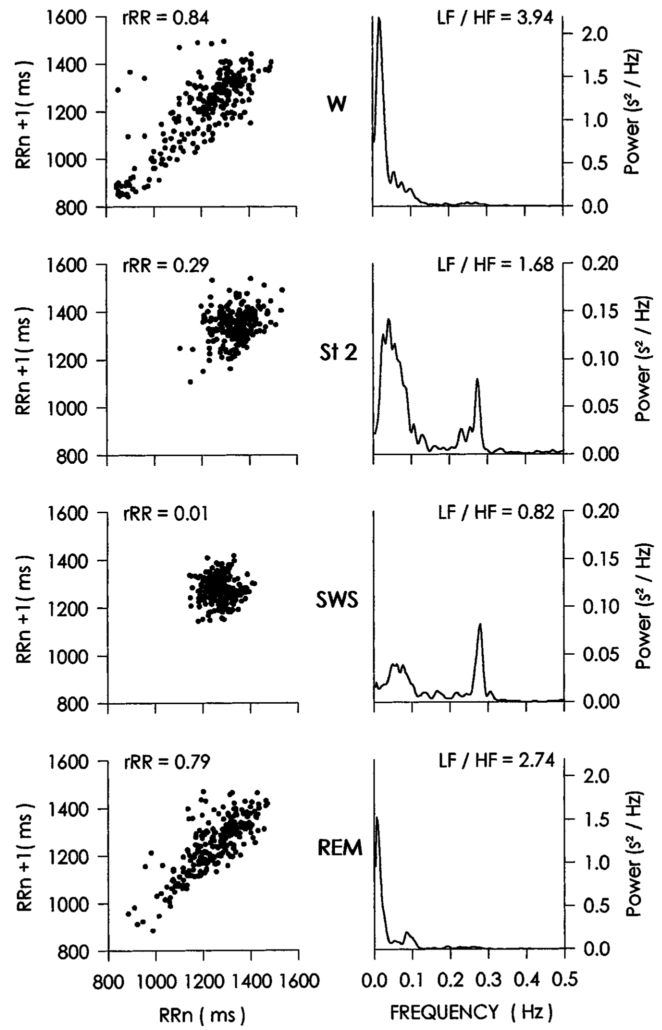

Fig. 1. Examples of 5-min Poincaré plots with regard to power spectra of R-R intervals, according to sleep states: intrasleep awaking (W), *stage 2* (St2), slow-wave sleep (SWS), and rapid eye movement sleep (REM). r_{RR}, Interbeat autocorrelation coefficient of R-R intervals; R-R_n and R-R_{n+1}, successive R-R intervals; LF/HF, ratio of low- to high-frequency power.

RESULTS

Figure 1 shows four examples of 5-min Poincaré plots in one subject with regard to the power spectrum distribution of R-R intervals. Each Poincaré plot showed a distinctive pattern according to the respective sleep stage, a pattern reflected in the distribution of the LF and HF bands. During waking periods, the scattering of points was spread in the bottom left-hand corner of the plot along the diagonal line with a high value of r_{RR}, whereas spectral analyses of R-R intervals yielded a high LF/HF due to the high power of the LF peak (Fig. 1, *top row*). *Stage 2* was characterized by a scattering of the points along the diagonal line with lower r_{RR} values and a lower LF/HF due to a decrease in the power of the LF band and a greater relative power in the HF band (Fig. 1, *2nd row*). Slow-wave sleep was characterized by rounder clusters of points, reflected in a decrease in r_{RR} values, and by a lower power in the LF band and a high relative power in the HF band, yielding a low value of LF/HF (Fig. 1, *3rd row*). During REM sleep, the Poincaré plots were spread along the diagonal line but were situated far from the origin because of higher values of R-R intervals (Fig. 1, *bottom row*). REM sleep was characterized by a high r_{RR} value and a concomitant increase in LF/HF.

The nocturnal individual profiles of r_{RR}, SDNN, and RMSSD were analyzed with regard to the profiles of LF, HF, and LF/HF, respectively. The results are summarized in Table 1. Correlation analysis revealed that the two series, r_{RR} and LF/HF, were positively related in all subjects, with significant correlation coefficients ranging between 0.387 and 0.815 ($P < 0.001$ in all subjects). Figure 2 shows the concomitant overnight profiles of r_{RR} and LF/HF after Z-score transformation in two representative subjects. r_{RR} was also significantly correlated with LF power ($P < 0.001$ in all but 4 subjects). In contrast, SDNN and RMSSD did not show any systematic relationship with LF/HF. SDNN was significantly correlated with LF power, with correlation coefficients ranging between 0.513 and 0.834 ($P < 0.001$ in all

Table 1. *Correlation coefficients between r_{RR}, SDNN, and RMSSD, and power spectrum parameters of R-R intervals during sleep*

Subject	rRR			SDNN			RMSSD			N
	LF	HF	LF/HF	LF	HF	LF/HF	LF	HF	LF/HF	
1	0.609‡	−0.395‡	0.695‡	0.710‡	0.323†	0.214*	0.156	0.950‡	−0.685‡	89
2	0.729‡	0.195	0.734‡	0.806‡	0.673‡	0.432‡	0.558‡	0.928‡	−0.034	94
3	−0.017	−0.497‡	0.683‡	0.825‡	0.863‡	−0.446‡	0.673‡	0.969‡	−0.679‡	89
4	0.703‡	−0.122	0.778‡	0.810‡	0.432‡	0.489‡	0.409‡	0.922‡	−0.227*	95
5	0.403‡	−0.292†	0.649‡	0.707‡	0.462‡	0.330†	0.440‡	0.950‡	−0.334†	88
6	−0.020	−0.588‡	0.504‡	0.513‡	0.557‡	0.212*	0.516‡	0.977‡	−0.564‡	94
7	0.544‡	−0.127	0.524‡	0.687‡	0.495‡	0.203	0.369‡	0.939‡	−0.300†	90
8	0.638‡	−0.051	0.713‡	0.834‡	0.509‡	0.632‡	0.616‡	0.883‡	0.178	94
9	0.672‡	0.251*	0.679‡	0.755‡	0.667‡	0.380‡	0.533‡	0.959‡	0.172	84
10	0.377‡	0.154	0.387‡	0.820‡	0.765‡	−0.190	0.881‡	0.968‡	−0.177	86
11	0.178	−0.231*	0.553‡	0.798‡	0.765‡	0.322†	0.843‡	0.939‡	0.094	92
12	0.544‡	0.189	0.669‡	0.708‡	0.521‡	0.518‡	0.768‡	0.962‡	0.137	88
13	0.075	−0.486‡	0.634‡	0.812‡	0.836‡	−0.208*	0.729‡	0.970‡	−0.417‡	92
14	0.557‡	0.087	0.655‡	0.683‡	0.260*	0.535‡	0.395‡	0.956‡	0.214*	89
15	0.624‡	−0.674‡	0.815‡	0.729‡	−0.157	0.609‡	0.159	0.928‡	−0.468‡	88

Correlation coefficients were calculated on *N* 5-min intervals following sleep onset. Power spectrum parameters of R-R intervals were measured in low-frequency (LF, 0.04–0.15 Hz) as well as in high-frequency (HF, 0.15–0.50 Hz) band. r_{RR}, Interbeat autocorrelation coefficient of R-R intervals; SDNN, standard deviation of normal R-R intervals; RMSSD, root-mean-square difference among successive normal R-R intervals. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

subjects), and with HF power, with correlation coefficients ranging between 0.260 and 0.863 ($P < 0.05$ in all subjects but 1). RMSSD correlated almost perfectly with HF power, with correlation coefficients ranging between 0.883 and 0.977 ($P < 0.001$ in all subjects), and to a lesser extent with LF power, with correlation coefficients ranging between 0.369 and 0.881 ($P < 0.001$ in all subjects but 2).

The nocturnal individual profiles of r_{RR}, SDNN, and RMSSD were analyzed with regard to variations in EEG mean frequency, which reflect depth of sleep (Table 2). As previously described (14), r_{RR} displayed a close temporal relationship with the variations of the EEG mean frequency. The highest significant cross-correlation coefficients ranged between 0.350 and 0.764 ($P < 0.001$ in all subjects) for lags lying at −1 in all subjects but one, indicating that r_{RR} profiles preceded EEG mean frequency profiles by 5 min. SDNN was significantly cross correlated with EEG mean frequency (0.341 to 0.769; $P < 0.001$ in all subjects but 1), whereas no systematic relationship was found between RMSSD and EEG mean frequency. Figure 3 shows the concomitant profiles of r_{RR}, SDNN, and RMSSD with regard to EEG mean frequency after Z-score transformation in one representative subject.

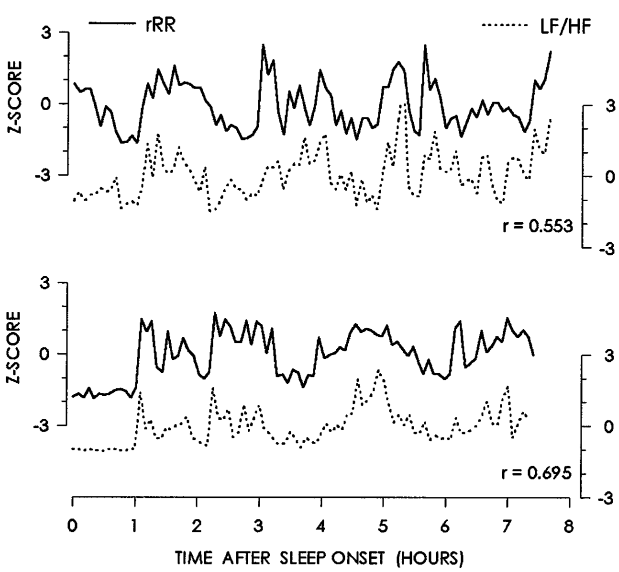

Fig. 2. Overnight profiles of r_{RR} and LF/HF calculated every 5 min in 2 representative subjects. Profiles were transformed into Z scores. Coefficients of correlation (*r*) are given.

DISCUSSION

This study demonstrates that r_{RR}, derived from the Poincaré plots, is a new tool that can be used to

Table 2. *Highest significant cross-correlation coefficients between EEG mean frequency and r_{RR}, SDNN, and RMSSD during sleep*

Subject	EEG/r_{RR}		EEG/SDNN		EEG/RMSSD	
	r	Lag	*r*	Lag	*r*	Lag
1	0.728‡	−1	0.492‡	−1	−0.279†	0
2	0.524‡	−1	0.532‡	−1	0.388‡	−1
3	0.351‡	−1	0.348‡	−1	0.233*	0
4	0.589‡	−1	0.618‡	−1	0.372‡	−1
5	0.542‡	−1	0.454‡	−1	−0.114	−1
6	0.350‡	−1	0.542‡	−1	0.121	−1
7	0.440‡	−1	0.442‡	−1	0.216*	−1
8	0.540‡	−1	0.546‡	−1	0.330†	−1
9	0.764‡	−1	0.769‡	−1	0.576‡	−1
10	0.667‡	−1	0.461‡	−1	0.253*	−1
11	0.350‡	−1	0.173	−1	0.147	0
12	0.650‡	−1	0.538‡	−1	0.284†	−1
13	0.465‡	−1	0.540‡	−1	0.266†	−1
14	0.569‡	0	0.341‡	0	−0.267*	0
15	0.751‡	−1	0.592‡	−1	−0.462‡	0

Cross-correlation coefficients (*r*) were calculated for lags −3 to +3, with each lag corresponding to a 5-min interval. For negative lags, cardiac changes precede changes in electroencephalographic (EEG) activity. * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

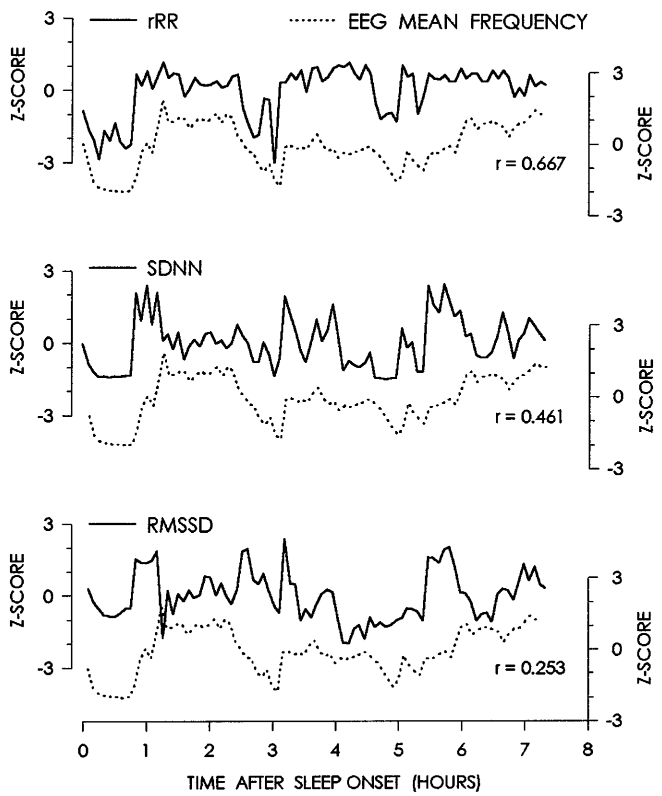

Fig. 3. Overnight profiles of r_{RR}, standard deviation of normal R-R intervals (SDNN), and root-mean-square difference among successive normal R-R intervals (RMSSD) with regard to EEG mean frequency in 1 representative subject. Profiles were transformed into Z scores. Highest respective r values are given.

evaluate the sympathovagal balance continuously during sleep. We established that the 5-min overnight profiles of r_{RR} are closely correlated with the profiles of LF/HF, which quantifies the sympathovagal balance. The decreases in r_{RR} reflect the predominant vagal influence, which coincides with sleep deepening, whereas the increases in r_{RR} reflect a sympathetic dominance and coincide with sleep lightening.

The Poincaré plot is a dynamic, noninvasive method that reveals the complexity of beat-to-beat behavior of heart rate variability (10, 17, 29). Analysis of heart rate variability with the use of spectral analysis methods assumes stationarity of data within the sample, an assumption that is often violated by sudden changes in heart rate, resulting in a power spectrum that is difficult to interpret. These techniques therefore require a filtering of the data that have been corrupted by abrupt changes in cardiac rhythm. In contrast, the Poincaré plots and the r_{RR} make use of unfiltered data and therefore are simpler tools for studying several aspects of dynamic heart rate variability. Previous studies have shown differing patterns of Poincaré plots for subjects during sleep, depending on sleep stages, with REM sleep associated with larger but more regulated interbeat variations than those observed during NREM sleep (15, 18, 29). However, it would be misleading to describe the sleep EEG as a series of discrete stages, because doing so tends to obscure the fact that sleep is a continuous oscillatory process. Therefore, the spectral analysis of the sleep EEG is a more useful tool for obtaining a quantitative and detailed analysis of the sleep processes (1). By computing r_{RR} with to regard to the overnight profiles of EEG mean frequency, we recently described (14), and the present study confirms, that heart rate variability and EEG activity are closely linked in normal men, with the variations in r_{RR} preceding variations in EEG mean frequency by ~5 min. The fact that changes in heart rate variability precede variations in EEG activity has been previously described (6, 23), and this behavior could possibly be attributed to changes in central nervous system activity.

Heart rate variability is determined by complex interactions between sympathetic and parasympathetic influences that have been previously quantified by spectral power analysis with two main frequency components, an HF and an LF component (2, 20, 21). In previous studies, REM sleep has been reported to be characterized by a high LF/HF, revealing increased sympathetic activity, and NREM sleep by a predominance of parasympathetic activity, revealed by a decrease in LF/HF (4, 22, 25, 26). In the present study, the continuous evaluation of r_{RR} with regard to LF/HF provides evidence that the two variables are highly related throughout the night. Because the profiles of r_{RR} were also cross correlated with EEG mean frequency, r_{RR} can be regarded as a tool in evaluating the sympathovagal balance continuously during sleep in humans.

However, one should take into account that HF power is affected not only by vagal tone. HF power is also sensitive to changes in respiratory frequency or tidal volume. Because the breathing parameters are not constant during sleep [tidal volume diminishes during NREM sleep and respiration frequency is more regular during NREM than during REM sleep (12)], part of HF power as well as part of LF power of heart rate variability may be attributed to ventilation changes (8). Ventilation changes have their own effect on vagal tone, but it has been reported (5) that heart rate variations induced by ventilation changes can occur independently of vagal influences.

The study of commonly accepted measures of heart rate variability, i.e., SDNN and RMSSD, revealed that SDNN was highly correlated with LF power, which mainly reflects sympathetic activity with a low parasympathetic component, whereas RMSSD was highly correlated with HF power. This latter result corroborates recent results from Kamen et al. (10), who used a head-up tilt test and appropriate drugs, i.e., scopolamine and atropine, and demonstrated that RMSSD correlated almost perfectly with HF power. In the present study, RMSSD also correlated with LF power, which means that either RMSSD reflects the parasympathetic component of the LF band or RMSSD during sleep is not a pure measure of parasympathetic activity. RMSSD did not show any systematic relationship with EEG mean frequency, whereas both r_{RR} and SDNN were significantly cross correlated with EEG mean frequency. However, r_{RR} reveals a dynamic interbeat behavior not readily perceived from standard deviation information.

Taken together, these results suggest that r_{RR} represents a new tool for evaluating the beat-to-beat interval behavior and the autonomic control of heart rate variability continuously during sleep. This simple and easily implemented method may be useful for diagnosis of syndromes characterized by specific sleep-dependent changes in heart rate variability, such as sleep apnea (3), congestive heart failure (27), myocardial infarction (25), and sudden infant death syndrome (19). The relevance of this method during waking states compared with other measures of heart rate variability (21, 24) remains to be evaluated.

We thank Daniel Joly and Michèle Simeoni for technical assistance. We are indebted to Formation et Recherche en Neurosciences Appliquées á la Psychiatrie (FORENAP, Rouffach, France) for providing software for data acquisition and spectral analysis of sleep EEG.

The experiments were performed at the Laboratoire de Physiologie et de Psychologie Environnementales, Centre National de la Recherche Scientifique, France, directed by A. Muzet.

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Received 5 November 1997; accepted in final form 7 May 1998.

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