Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability

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Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability

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Article abstract—*Objective:* The use of an efficient noninvasive method to investigate the autonomic nervous system and cardiovascular control during sleep. *Background:* Beat-to-beat heart rate variability displays two main components: a low-frequency (LF) one representing sympathetic and parasympathetic influence and a high-frequency (HF) component of parasympathetic origin. Sympathovagal balance can be defined as LF/HF ratio. *Methods/design:* We reviewed normal, standardly staged all-night polysomnograms from 10 healthy children aged 6 to 17 years. Recorded 256-second traces of heart rate and respiration were sampled. Power spectra of instantaneous heart rate and respiration were computed using a fast Fourier transform method. *Results:* The study revealed a decrease in LF during sleep, with minimal values during non-REM slow-wave sleep and elevated levels similar to those of wakefulness during REM. HF increased with sleep onset, reaching maximal values during slow-wave sleep, and behaved as a mirror image of LF. LF/HF ratio displayed changes similar to those in LF. *Conclusion:* The sympathetic predominance that characterizes wakefulness decreases during non-REM sleep, is minimal in slow-wave sleep, and surges toward mean awake levels during REM sleep. The autonomic balance is shifted toward parasympathetic predominance during slow-wave sleep. This noninvasive method used to outline autonomic activity achieves results that are in complete agreement with those obtained with direct invasive tools.

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Spectral analysis of instantaneous heart rate (HR) and blood pressure (BP) fluctuations is a well-established investigation tool of the autonomic nervous system.[1-3] All known mathematical methods for spectral computation reveal two main components of HR and BP variability. Studies[2,3] using pharmacologic and physiologic stimuli have defined these spectral components. The two spectral regions of interest are (1) a low-frequency (LF) component between 0.02 and 0.15 Hz representing vasomotor (0.02 to 0.09 Hz) and baroreceptor activity (0.09 to 0.15 Hz); the LF is under both sympathetic and parasympathetic control[2-4]; and (2) a high-frequency (HF) component around the respiratory frequency (at 0.2 Hz, and higher in small children) under parasympathetic control.[2,3]

Since the neuroautonomic influence at the low end of the spectrum is complex, a useful way to look into the autonomic activity by means of spectral analysis is to define a sympathovagal balance as the LF/HF ratio because it reflects both the reciprocal and the nonreciprocal fluctuations in sympathetic and parasympathetic tonus.[3]

The last few decades have brought great progress in the understanding of sleep and its physiology as well as new and deeper knowledge of the structure and functioning of the central autonomic neural network and its interconnections with the cardiorespiratory physiology and regulation. Theoretical models of sleep[5,6] are based on the description of sleep oscillators in which a network of cholinergic and noradrenergic neurons plays a major role. The main output of the central autonomic network is mediated through preganglionic, sympathetic, and parasympathetic neurons, and both subdivisions of the autonomic nervous system play an important role in the cardiac regulation during sleep.[7] Cardiovascular beta adrenergic blockers[8] also have some central blocking effect; cholinergic agents used as cardiac antiarrhythmic

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drugs[9] may also affect central muscarinic receptors. Thus the same chemical effectors modulate brain sleep oscillators and influence central cardiovascular control. Moreover, cardiovascular and respiratory mechanisms share the same higher cerebral centers.[10]

The objective of our study was to obtain a new insight into the autonomic cardiovascular control during the various sleep states in children, applying power spectrum (PS) analysis of beat-to-beat variability in HR.

Methods. *Subjects.* Ten subjects were chosen following a chart review of children who had undergone all-night polysomnographic studies (PSGs) for suspected obstructive sleep apnea, excessive daytime sleepiness, or as part of workup before pharyngeal flap surgery for cleft palate. Only subjects with normal all-night PSGs and normal Multiple Sleep Latency Test, if indicated, were included in the study.

All PSGs monitored scalp EEG, eye movements, chin and extremity EMG, ECG, nasal and oral airflow, thoracic and abdominal respiratory effort, and transcutaneous oxygen saturation.

All PSGs were manually scored according to the standard criteria of Rechtschaffen and Kales.[11]

Traces of ECG, nasal airflow, and chest effort from at least 60% of sleep test time, covering all sleep stages during the night, were recorded on magnetic tape (TEAC R61 tape recorder). The analog signals underwent digitation (using a DT2801/5716A DT board and a PC computer). The digitized data containing ECG and respiratory signal information were simultaneously sampled (300 Hz for ECG signal; 10 Hz for respiration signal) for 300-second-long, artifact-free epochs.

The analyzed time intervals were chosen from (1) awake state at the beginning of the night (AS); (2) non-REM sleep stages I and II—light sleep (LS); (3) non-REM sleep stages III and IV—slow-wave sleep (SWS); and (4) REM sleep (REM).

The RR intervals were detected and the instantaneous HR values were computed using a previously described algorithm.[12] A fast Fourier transform method was then applied on 256-second epochs to obtain the power spectra of breathing and HR instantaneous fluctuations.

We focused on the two regions of interest in the HR spectrum: LF range (0.02 to 0.15 Hz) and HF range (detected for each subject from the inspection of the respiration spectrum; the region 0.2 to 0.5 Hz covered the HF component for all subjects).

The energy content of the PS of HR variability was calculated for each spectral component by integration of the corresponding spectral region after normalization by (mean HR)^2. The power density was thus unitless. An optimal way[4] to analyze the autonomic activity in each frequency range is to divide each spectral component by the total spectral power (0.02 to 2 Hz), thus at least partially accounting for the parasympathetic fluctuations in the LF region.

Mean values for the power density were then calculated separately for the two regions of interest for each sleep-wake stage: AS, LS, SWS, REM. An autonomic balance known as the sympathovagal balance (LF/HF) was calculated for each epoch analyzed, and this variable was then averaged over the different sleep states.

Statistical analysis. We applied ANOVA (nonparametric repeated measures Friedman test) to determine the changes within each group through the different sleep stages. A two-tailed t test was used to compare the mean values of the variables studied during any two sleep stages. Results were considered significant for $p < 0.05$.

Results. The following sleep-wake states were studied: (1) awake at the beginning of the night (AS); (2) non-REM sleep stages I and II (LS); (3) non-REM sleep stages III and IV (SWS); and (4) REM sleep (REM).

Representative power spectra of HR variability during the various stages of the sleep-wake cycle are reproduced in figure 1.

We analyzed mean values of HR, LF component, HF component, and autonomic balance LF/HF during at least 60% of the test time for each subject. Artifact-containing epochs were excluded.

Heart rate. Mean HR decreased significantly with sleep onset and was lower in all sleep stages than the mean value during AS. No significant differences occurred between the various sleep stages. The variability during REM within the same subject was large, with some epochs displaying mean HR and reaching higher values than while awake at the beginning of the test.

PS analysis of HR instantaneous variability. We analyzed the normalized spectral components (ratio between the power density of each spectral component and the total spectral density) as better measures of the autonomic activity than the absolute numbers.[4] We also computed and analyzed the autonomic balance as defined in the introduction/background section.

The power of LF component changed during various sleep stages. The variations during sleep were significant, with a minimal value during SWS as detected by ANOVA ($p = 0.0002$, chi-square approximation). The mean values were significantly (two-tailed t test) lower during SWS than while awake at the beginning of the test ($p < 0.0001$), during sleep stages I and II ($p = 0.0004$), and during REM ($p = 0.0013$).

Values in REM were higher than in sleep stages I and II, although this difference did not reach significance. The variability of the results was great during LS and especially during REM.

The power of HF component. The median values underwent significant changes throughout the night as detected by ANOVA ($p = 0.0023$, chi-square approximation). Maximal mean values were characteristic of SWS, and the difference between this stage and all the other stages was significant. The changes in this component displayed a striking mirror image of LF variations with the different sleep states.

Sympathovagal balance (figure 2) changed significantly with the sleep stages (ANOVA of log LF/HF: $p = 0.0004$, chi-square approximation). The changes in this variable were parallel to the changes in the LF component, with minimal values during SWS. The mean values during this stage were significantly lower than during AS and LS

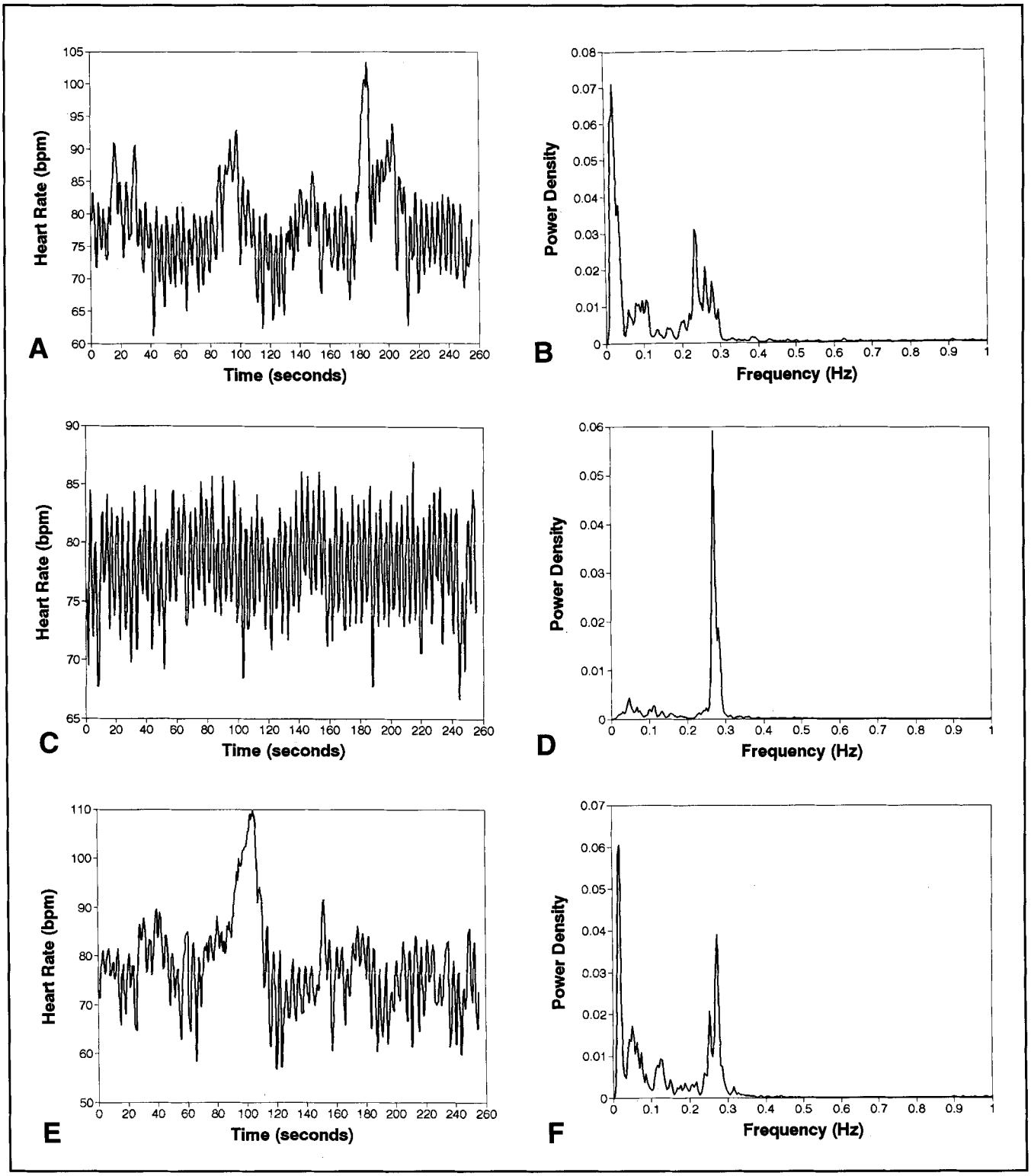

Figure 1. Representative graphs of heart rate as function of time (tachograms) and power spectra taken from 256-second epochs during different sleep stages: (A) tachogram while awake at the beginning of the night; (B) power spectrum for the epoch in panel A; (C) tachogram during slow-wave sleep; (D) power spectrum for the epoch in panel C; (E) tachogram during REM sleep; (F) power spectrum for the epoch in panel E.

(two-tailed t test, $p = 0.0013$) or REM ($p = 0.0008$). Values in REM were higher than values in LS, yet the difference did not reach significance due to the variability within this stage.

Discussion. Our results show, as in previous studies,[7] that the mean HR decreased during sleep, but it does not display significant variation of its mean values in different sleep stages in normal children.

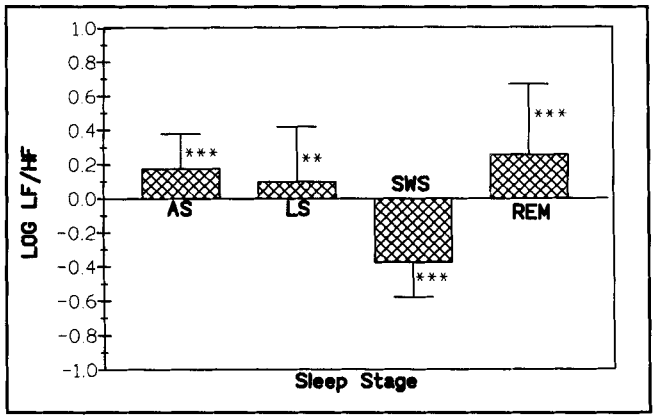

*Figure 2. Autonomic balance during sleep. The balance points towards HF during SWS, with significant differences between this stage and AS, LS, REM. AS—awake at the beginning of the night; LS—light sleep; SWS—slow-wave sleep. ** for p < 0.001, *** for p < 0.0001 on two-tailed t test. The error bars show standard deviation.*

Therefore, as expected, mean HR is not a sufficiently sensitive indicator of the complex regulatory and physiologic changes during sleep.

The LF component decreased during sleep with minimal values in SWS, whereas the HF component displayed a reciprocal trend with increased values during sleep, reaching a maximum at the time of the LF nadir in SWS. At each epoch studied, the variations in LF and HF were reciprocal. This suggests that the increases in LF represent mainly surges in sympathetic activity and the decrease in LF expresses a declining sympathetic activity. Our results indicate a clear decrease in sympathetic activity during sleep, with lowest values being reached during SWS. During REM, an increase in the overall sympathetic activity occurred toward almost the level of AS. The parasympathetic activity, expressed by the HF, increased during sleep as expected. The maximal parasympathetic activity was reached during SWS.

The above conclusions are further enhanced by the values of LF/HF reflecting autonomic balance that indicates a sympathetic predominance during REM and a parasympathetic predominance during SWS.

Our results corroborate previous studies[13-15] in which direct microneurographic studies of skeletal muscle sympathetic nerve activity showed similar changes in sympathetic activity during the different sleep stages. A great variability in muscle sympathetic nerve activity occurs during REM in connection with phasic changes.[13-15] Our study also uncovered a great variability in the same subject during this sleep stage (sometimes reaching values higher than the AS ones, most probably as an expression of the phasic REM). Yet the mean values were consistently high, suggesting that the sympathetic activity during REM sleep is similar to the awake levels. However, the nature of the sympathetic activity during REM is different from that while awake due to tonic suppression alternating with phasic bursts of activity.[16,17] The high sympathetic activity levels during LS in our study might be due to the sympathetic bursts associated with K-complexes,[13-15] because our results deal with values obtained over 256-second epochs and not with the short time intervals characteristic for K-complexes or electrophysiologic arousals.

The estimation of parasympathetic activity during sleep as previously described[7] is also in complete agreement with our results. Direct studies of parasympathetic nerve activity in humans are difficult to perform. The information supplied noninvasively by the HF component of the HR PS is a valuable and accurate quantitative measure of the parasympathetic activity, at least at the level of the sinus node.

The approach used in this study is a noninvasive method and can allow continuous monitoring of the autonomic cardiorespiratory control throughout the night sleep. Additional information can be gained by noninvasive monitoring of arterial BP and skin blood flow, which can be analyzed as we analyzed the HR variability (to obtain more information on the autonomic activity during sleep). This information might be more accurate than data obtained by invasive methods that may cause changes in autonomic nervous functioning due to the apprehension they cause.

A limitation of the methods we used to obtain the PS is the need to quantify sympathetic activity over periods of at least 256 seconds, thus implicitly losing information on rapid changes of the autonomic activity within the studied epoch. New methods[18,19] of time-dependent spectral computation can avoid information loss.

The analysis of the instantaneous variability in HR (or BP, skin blood flow) may offer a simple method of on-line monitoring of autonomic activity during normal sleep as well as during pathologic sleep.

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