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Autonomic cardiovascular control in children with obstructive sleep apnea

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Autonomic cardiorespiratory control changes with sleep-wake states and is influenced by sleep-related breathing disorders. Power spectrum (PS) analysis of instantaneous fluctuations in heart rate (HR) is used to investigate the role of the autonomic nervous system (ANS) in cardiorespiratory control. The two spectral regions of interest are the low frequency component (LF) and high frequency component (HF).

The aim of the present study was to investigate the autonomic cardiorespiratory control in children with obstructive sleep apnea (OSA) syndrome. We studied 10 children with OSA versus 10 normal children. All subjects underwent whole night polysomnography. Spectral analysis of the HR and breathing signals was performed for 256 second long, artifact-free epochs in each sleep-wake state. The LF power was higher in the OSA group compared with control subjects for all states, reflecting enhanced sympathetic activity in OSA subjects. The results indicated sympathetic predominance during REM sleep in all subjects and parasympathetic predominance in slow wave sleep only in controls. The autonomic balance (LF/HF) was significantly higher in OSA patients than in control subjects, at all stages during night sleep, and while awake before sleep onset. An index of overall autonomic balance (ABI) was computed for each subject and correlated well with the measured respiratory disturbance index (RDI).

Key words: autonomic nervous system, cardiovascular control, children, heart rate variability, power spectrum analysis, obstructive sleep apnea.

Sleep disorders in general, and sleep disordered breathing in particular, have significant consequences for daytime function in both adults and children. The cardiovascular consequences of OSA have been well documented in adults [1–3], but its effects have been less investigated in children.

The cardiovascular and respiratory systems are regulated by the autonomic nervous system (ANS) and their function is closely related to the sleep-wake states [4,5]. During non-rapid eye movement (NREM) sleep, there is normally a slight decrease in heart rate (HR) and a concomitant decrease in peripheral vascular resistance, which result in a variable reduction in systolic arterial blood pressure (ABP) [4–6]. During rapid eye movement (REM) sleep, the HR and ABP are characterized by a great variability [7]. This is due to tonic vagal activation and withdrawal of central sympathetic outflow, which alternate with frequent phasic periods of vagal inhibition, bursts of sympathetic activity [8–11], and muscular twitches [9].

Some degree of hypnogenic upper airway narrowing occurs during sleep [12–16]. The tonic activity of the tongue, pharyngeal, and laryngeal musculature that are responsible for upper airway dilation during wakefulness diminishes during NREM sleep and essentially vanishes in REM sleep [4,13–15]. When these physiologic changes are abnormal, and the upper airways become partially or totally occluded, as in OSA syndrome [17], alveolar ventilation and cardiovascular function may be compromised [18–22]. Some of the adverse effects of OSA, especially those involving cardiovascular and respiratory control, are difficult to evaluate.

Beat-to-beat changes in HR are well recognized and result essentially from the autonomic input to the sinoatrial node. Instantaneous HR fluctuations occur in distinct frequency bands [23]. When evaluated in the frequency domain, the HR fluctuations involve two main components [24–26], a low frequency component (LF) that reflects mainly sympathetic and parasympathetic inputs to the sinoatrial node and a high frequency component (HF), around the respiratory frequency, that is almost exclusively under parasympathetic influence. Thus, analysis of heart rate variability (HRV) in the frequency domain gives insight directly into the autonomic control of the cardiac function and, indirectly, into central autonomic activity. It allows us to study the balance between the sympathetic and parasympathetic branches of the ANS in health and disease.

The preexisting knowledge regarding these relationships in pediatric OSA patients is limited. We expected children with OSA to display some pattern of enhanced sympathetic activity, perhaps correlated to their degree of sleep-related breathing disorder. Thus, the purpose of this study was to investigate the autonomic cardiorespiratory control in children with OSA.

Methods and patients

Study population

Children, referred to the sleep clinic (Cardinal Glennon Children's Hospital, Saint Louis University Health Sciences Center, between January 1993 and August 1994) for a whole

night polysomnography (PSG) for suspected OSA due to adenoidal/tonsillar hypertrophy, were included in the study. The study population was divided into two groups according to the sleep related breathing disturbance: 1) *the OSA group* included 10 children (ages 3–8 y, mean 5.5; 4 girls and 6 boys) with respiratory disturbance index (RDI) greater than 2; **2)** *the control group* included 10 children (ages 5–14 y, mean 5.5; 6 girls and 4 boys). RDI was defined as the total number of apneas and hypopneas per hour of sleep. Obese children were excluded from the study.

Polysomnography

Using a multiple channel digital polysomnogram machine (Sleep Lab 1000, CNS), all subjects underwent PSG that included continuous monitoring and recording of: 1) scalp EEG (4 derivations: two central C3/A2, C4/A1, and two occipital O3/A2, O4/A1 with C3, C4, O3, and O4 according to the International 10–20 EEG system of electrode placement [27], referred to A1, A2 electrodes placed on the bony surface of the mastoid); 2) electro-oculogram (EOG) (two leads); 3) electromyograph (EMG) (chin and extremity muscle tone); 4) ECG (standard lead II); 5) nasal and oral airflow (by respiratory thermocouple, Rochester Electro-Medical); 6) thoracic and abdominal respiratory effort (strain gauge, RESP-EZ belts, EPM Systems); and 7) oxygen saturation and pulse oximeter waveform (N-200 pulse oximeter, Mallinckrodt, Pleasanton, CA).

The electrodes for EEG, EOG, and EMG were standard gold cup electrodes and were applied to the skin using the collodion technique [28]. All PSGs were manually scored according to the standard criteria of Rechtschaffen and Kales [29]. Apnea was defined as a complete cessation of airflow. Hypopnea was defined as a decrease in the flow signal to less than 50% of the flow level of the preceding breaths. Only respiratory events of 10 seconds or longer were accepted for RDI computation.

Heart rate and respiration data analysis

Traces of ECG, airflow, and chest movement were analyzed from PSG recordings free of artifacts (which accounted for at least 60% of the sleep test time). These traces covered all sleep stages during the night, including periods both with and without respiratory events. The digitized data, involving ECG (sampling rate 200Hz) and breathing (sampling rate 10Hz) information, was simultaneously processed for all consecutive 256 second epochs free of artifacts. The R waves were detected, RR intervals obtained, and instantaneous HR (equally sampled) was computed [24,25,30]. Power spectra of the instantaneous HR and respiration were then computed using the fast Fourier transform (FFT) method and a previously described algorithm [24,25,30].

The analysis included for each subject all of the 256 second long, artifact free epochs retrieved from each of the following states separately: 1) awake (W) before sleep onset at the beginning of the night, 2) non-REM sleep stage I and II (light sleep [LS]), 3) non-REM sleep stage III and IV (slow wave sleep [SWS]); and 4) REM sleep (REM).

We chose two regions of interest in the HR power spectrum (Fig. 1): a slightly extended LF range (0.02–0.15Hz) and a HF range (detected from the inspection of the respiratory spectrum) within the 0.2 to 0.5 Hz range. The energy content of the HR fluctuations was calculated for each spectral component by integration of the corresponding spectral region, which we chose to normalize by mean HR squared [24–26,30]. The results were thus unitless.

For each subject mean values for the energy content for the two regions of interest (LF and HF), the total spectral power (T) for the entire spectral range of interest, LF + HF (0.02–0.5 Hz), and the normalized values LF/T and HF/T were calculated separately for each sleep-wake state: W, LS, SWS, REM.

The autonomic balance, known as the sympathovagal balance and estimated by the ratio LF/HF [31], was also calculated for each epoch. The autonomic balance was averaged over the different sleep stages during the night.

A new overall "autonomic balance sleep index" (ABI) was defined for each subject as the sum of the sympathovagal balance for LS, SWS, and REM. Each was averaged over the corresponding epochs and weighted by the percentage duration of each stage relative to the entire test duration:

$$\mathbf{ABI = (LF/HF)_{LS^*}[\%(LS)] + (LF/HF)SWS_*[\%(SWS)] + (LF/HF)_{REM^*}[\%(REM)]}$$

As a result of our analysis, we obtained two overall indexes for each subject, the generally used RDI and the newly defined ABI. Testing the correlation between RDI and ABI (within the OSA group) is expected to provide important insight into the pathophysiology of OSA in pediatric patients.

Statistical analysis

Friedman's nonparametric test was applied to determine the changes within each study group through the different sleep-wake states. Welch's two tailed t-test was applied to compare results of each specific stage between the two study groups. Results were considered significant for $p < 0.05$.

Results

Sleep architecture did not differ significantly between the groups. *Total test time* (505.88 + 55.23 minutes in control group vs 481.22 + 40.94 minutes in OSA group), *total sleep time* (438.55 + 56.00 min and 415.55 + 43.820 min in OSA, respectively), *sleep maintenance* (calculated as percentage of sleep time after sleep onset was 92.16 + 6.06% in the control group vs 91.92 + 6.44% for the OSA group), *SWS* percentage (23.32 + 9.65 and 27.03 + 6.40, respectively), *NREM stage I and II percentage* (60.25 + 11.31 and 56.86 + 9.26, respectively), *REM percentage* (16.27 + 5.89 and 16.12 + 4.54, respectively), and *arousal index* (10.24 + 5.67 and 13.63 + 5.74, respectively; slightly but not significantly lower in the control group) were similar in both groups. The RDI was 0.47 + 0.69 in the control group and 23.37 + 21.08 in the OSA group.

Mean HR decreased during sleep in both groups, with

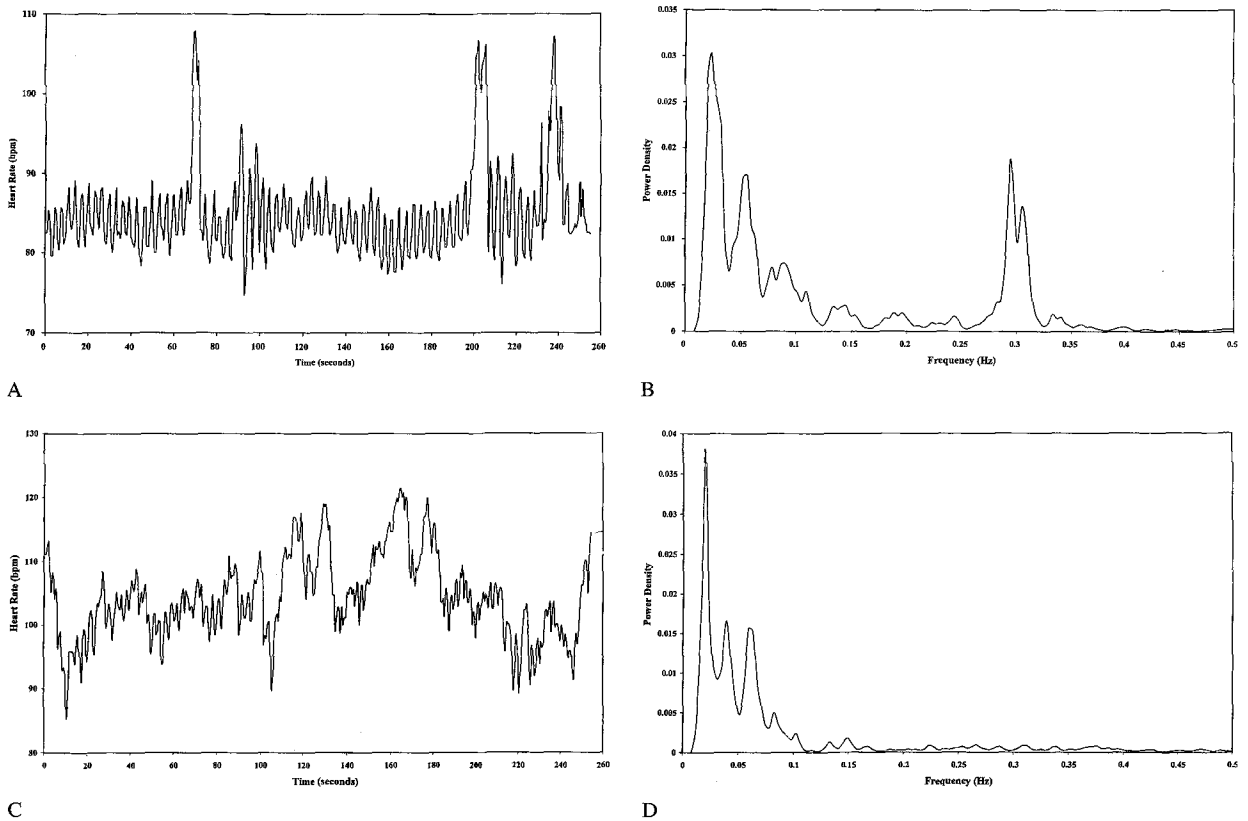

Figure 1. Awake before sleep onset: **(A)** normal control tachogram, **(B)** normal control power spectrum, **(C)** OSA patient tachogram, **(D)** OSA patient power spectrum. Note the disorganized tachogram that fits a spectrum with mainly LF component in the OSA patient, whereas in the normal control one can easily see the HF spectral component. This suggests a less sympathetic autonomic balance in normal subjects.

no significant difference between sleep stages. Examples of HR tachograms and HR power spectra are presented for children in the OSA group and the control group while awake at the beginning of the study (Fig. 1) just before sleep onset and during SWS (Fig. 2). Enhanced variability in the LF range was observed in the OSA subject relative to the normal child.

The tachogram and HR power spectrum during REM sleep in an OSA child (Fig. 3) stresses the overall greater HRV variability during this sleep stage. The differences between the two groups during this specific sleep stage were less obvious on visual inspection; however, they were evident when the quantitative analysis was performed.

Figures 1 to 3 display the differences found between the two groups during each sleep-wake state, as well as those among the different states within the same group. The differences between the spectral components during REM, LS, and SWS were similar during the first and subsequent sleep cycles, thus justifying the averaging of the spectral parameters over the same sleep state across the night. The LF power of the HR fluctuations was high while awake and during REM sleep in both groups and high during SWS only in the OSA group. The LF power was higher in the OSA group compared with controls for all states. HF power was high in SWS and low in REM sleep in each group. No significant difference was found between the groups when this parameter was considered.

The differences between the groups and within each group were more significant when considering the normalized spectral parameters (LF/T, HF/T). For both the patients and the control group, mean LF/T changed significantly along awake state and the various sleep stages (Fig. 4A). Within each group, this variable, which represents a measure of the sympathetic activity [24,25], was high while awake at the beginning of the study, significantly lower during SWS ($p < 0.05$), and high again during REM sleep (significantly higher than during SWS, $p < 0.05$), reaching levels similar to those during wakefulness (before sleep onset). Although LF/T was on the average lower during LS than during both W and REM sleep, this difference was not statistically significant. The trend of the LF and LF/T was similar within each group, yet both of these variables were significantly higher (two-tailed t test, $p < 0.05$, as indicated by * in Fig. 4A) in the OSA group than in the control group, all along the W, SWS, and REM stages.

Epochs containing obstructive apneas were characterized by higher values of LF, LF/T than epochs without respiratory events. Within each group HF/T changed significantly between awake state and the various sleep stages (Fig. 4B), almost as a "mirror image" of the LF/T component: HF/T increased during sleep with the highest values during SWS; it was significantly higher during SWS than during both W and REM ($p < 0.05$). The HF/T was lower in the OSA group compared with the control group, during all sleep-wake states. Yet the difference in HF/T between the two groups was significant (two-tailed t-test, $p < 0.05$ as

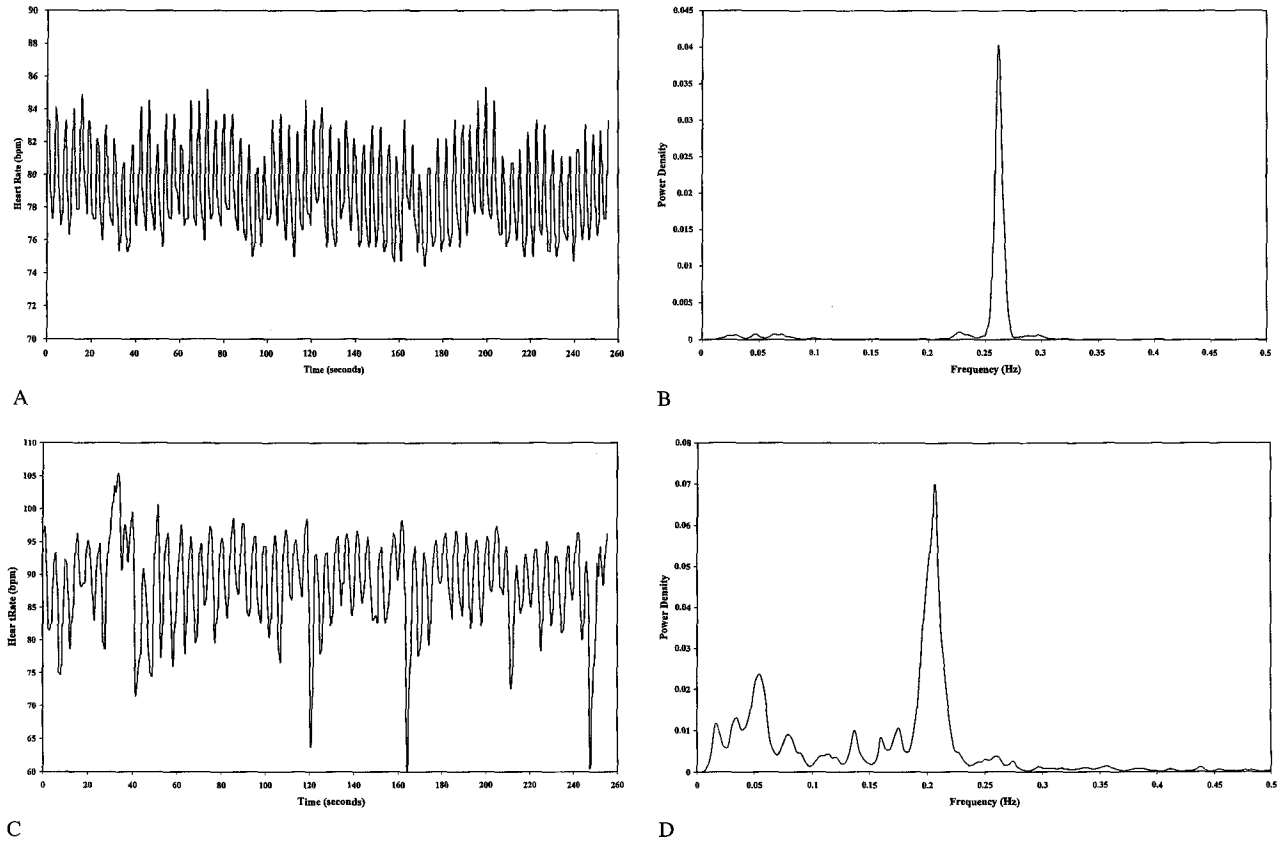

Figure 2. Slow wave sleep: **(A)** normal control tachogram, **(B)** normal control power spectrum, **(C)** OSA patient tachogram, **(D)** OSA patient power spectrum. Note the lack of lesser HR variability in the normal subject, which results in a power spectrum with only a HF component, which points towards parasympathetic predominance in this case. The patient displays a significant LF contribution to the power spectrum.

indicated by * in Fig 4B) during the awake state and REM sleep only.

In each group, the sympathovagal balance, LF/HF, (Fig. 5) was high while awake (before sleep onset) and during REM sleep, and was relatively low during SWS ($p < 0.01$). The sympathovagal balance was higher in the OSA group relative to the control one while awake at the beginning of the study (Welch's two tailed t-test, $p = 0.005$), in NREM sleep stage I and II ($p = 0.14$, not significant), in SWS ($p = 0.035$), and during REM sleep ($p = 0.018$). This parameter of autonomic balance pointed toward sympathetic predominance during REM compared with other sleep states, in all subjects. The LF/HF ratio was smaller than unity during SWS in control subjects only, indicating a strong parasympathetic predominance at that sleep state.

The newly defined "autonomic balance index" (ABI) (computed according to equation 1, for each subject in the OSA group) and the subject's respiratory disturbance index RDI (Fig. 6) were clearly correlated (Spearman rank correlation: $r = 0.8182$, two tailed t-test: $p = 0.0058$; with exclusion of the outlier, the correlation was: $r = 0.8333$ and $p = 0.0083$).

Discussion

The autonomic changes during normal and disturbed sleep in humans are difficult to investigate, since invasive methods cause both sleep disturbances and unwanted perturbations of the ANS functioning. Noninvasive estimate of ANS functioning during sleep [32] can be achieved by analysis of HRV, as extracted from the ECG signal (usually monitored during standard sleep studies).

In the present study, the analysis of HRV in the frequency domain was performed by means of the fast Fourier transform method so that the spectral results dealt with time intervals of 256 seconds each. Any information on brief and transient events during sleep, such as apneas, arousals, and movements, is thus not uncovered by this analysis. When considering the data for each subject, we averaged over all epochs belonging to the same sleep stage, thus reducing even more the insight into possible brief transients. In this study, we indeed focused on steady state information, specific for the various sleep stages, in order to compare the ANS functioning in children with OSA and normal children. The fact that the HF/T is lower while awake (before sleep onset) and during REM sleep in OSA patients as compared with control subjects, whereas the LF/T is higher, implies that the increase in the sympathetic activity in children with OSA is not artifactual.

The results of this study confirm previous results concerning the autonomic activity during sleep in normal adults [7–10] and children [32] and in adults [33,34] with OSA. Aljadeff *et al.* [35] found that the R-R intervals behave differently in children suffering from OSA than in children with primary snoring. In the present study, children with

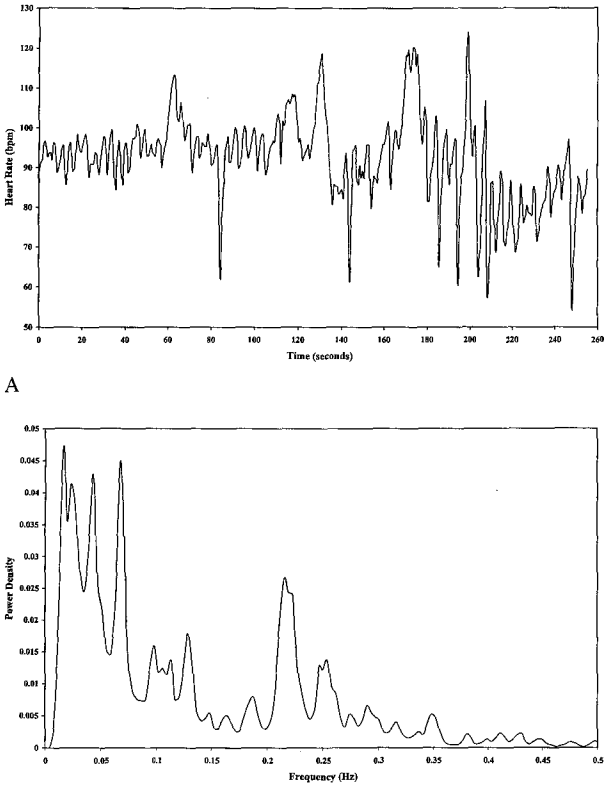

Figure 3. REM Sleep: **(A)** OSA patient tachogram, **(B)** OSA patient power spectrum. Note the greater variability in the tachogram as well as the fact that the power spectrum displays a large LF component. Normal subjects present with very similar power spectra; however, their LF and LF/HF ratio are significantly different as illustrated in figures 4A and 5.

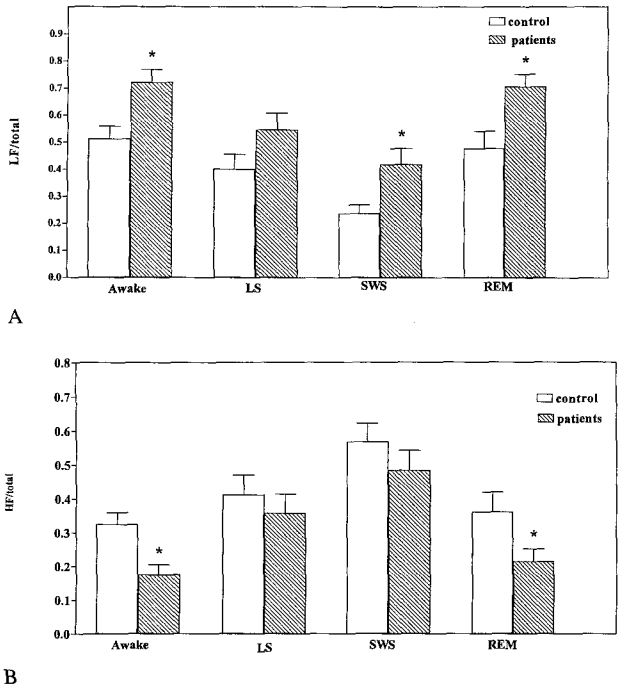

Figure 4. **(A)** The normalized low frequency power density (LF/total power) and **(B)** the normalized high frequency power density (HF/ Total Power) in normal children as compared with children with OSA during the different sleep-wake states: 1) Awake before sleep onset at the beginning of the night, 2) non-REM sleep stage I and II (light sleep [LS]), 3) non-REM sleep stage III an IV (slow wave sleep [SWS]), and 4) REM sleep (REM). The bars represent averaging of the sleep wake states across the whole night (two-tailed t-test, $p < 0.05$, specified by *).

OSA had a higher level of sympathetic activity throughout the night sleep and, strikingly, also while awake at the beginning of the study. The high sympathetic activity before sleep onset in children with OSA represents an entirely new finding. It reflects the enhanced sympathetic activity in children with OSA. This augmented sympathetic activity is partly responsible for the consequence of sleep-related breathing disorder on the cardiovascular system.

We found that, with the deepening of NREM sleep, the sympathetic activity decreases gradually both in children with OSA and in the control group. An overall increase in sympathetic activity reaching levels similar to those of wakefulness occurs in both groups during REM sleep.

While autonomic changes during sleep may represent the immediate result of respiratory events, the enhanced sympathetic activity before sleep onset, in the OSA group, is somewhat surprising. This finding might be related to a basic change in the level of sympathetic activity established due to the chronic sleep-related breathing disorder. The sympathetic activity was higher in the OSA patient group, during all sleep-wake states. The finding of enhanced sympathetic activity, in children with OSA syndrome, raises the question of cause-effect relationship. It is reasonable to assume that OSA causes a sustained increase in sympathetic activity as a result of the sleep-related breathing disorder and fragmented sleep. Indeed, it has been shown that effective treatment of OSA in adult patients may reverse some of the adverse effects of the syndrome [36–38]. Nevertheless, the reverse hypothesis might also be considered: perhaps increased sympathetic activity represents a genetic, predisposing factor for OSA. Such a possibility might explain the well known co-morbidity, observed in adults with OSA syndrome, which consists of hypertension, obesity, and sleep-related breathing disorder as well as the clustering of OSA in families [39]. Our observations in children may provide further support for the hypothesis that increased sympathetic activity has a predisposing role for OSA and hypertension.

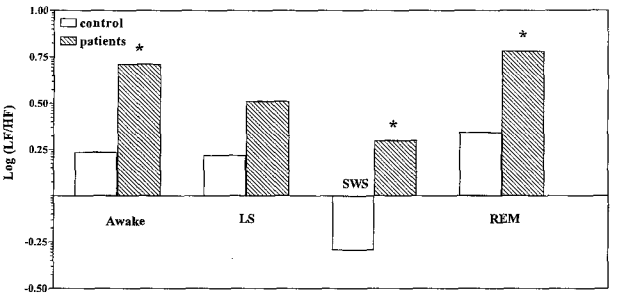

Figure 5. The autonomic balance (represented as log LF/HF) in normal children compared with children with OSA during the different sleep-wake states: 1) Awake before sleep onset at the beginning of the night, 2) non-REM sleep stages I and II (light sleep, [LS]), 3) non-REM sleep stage III and IV (slow wave sleep [SWS]), and 4) REM sleep (**REM**). The bars represent averaging during the different sleep-wake states across the whole night (* for $p < 0.05$, two-tailed t-test).

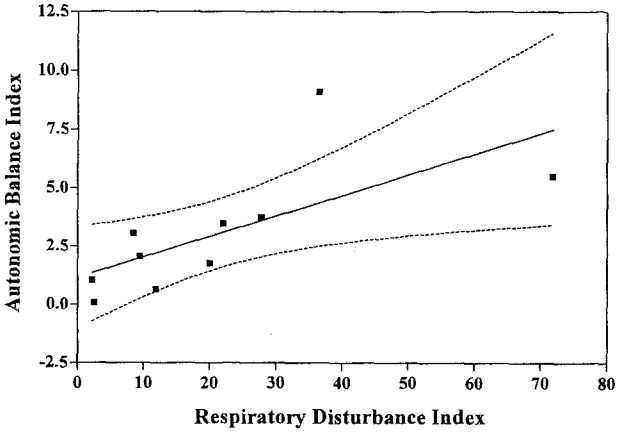

Figure 6. The autonomic balance index (ABI)(defined and calculated as described in the equation in the "methods and patients" section) as function of the respiratory disturbance index (RDI). Note that the higher the RDI, the higher the ABI, indicating a good correlation between the level of sleep-related breathing disorder and the sympathovagal balance throughout the night (Spearman rank correlation: r = 0.8182).

The parasympathetic activity was lower in sleep apnea patients as compared to normal children during all the sleep stages. However, this difference reached significance only during SWS. During this sleep stage control subjects displayed a marked parasympathetic predominance (LF/HF < 1) while patients with OSA continued to display sympathetic predominance (LF/HF > 1). This may be associated with the observation that sleep is not restorative in pediatric patients with sleep-related breathing disorders, even when there is no significant sleep fragmentation on PSG.

The correlation we found between the RDI and the ABI suggests a strong connection (perhaps of cause and effect) between the degree of sympathetic activity and the level of respiratory compromise during sleep. Moreover, the newly defined ABI might become an indicator of the degree of respiratory compromise during sleep.The analysis of HR variability is a noninvasive bedside technique and can be easily performed in order to provide additional evaluation of children with OSA. It can be applied as a screening tool for suspected sleep apnea, testing whether the autonomic balance remains predominantly sympathetic throughout the night. Spectral analysis of HR variability might also be used for follow up in pediatric patients after treatment, either surgical or with nasal continuous positive airway pressure.

Transient changes in autonomic activity can be studied by the use of time-frequency analysis [40], especially designed to uncover brief or transient changes in the frequency content of a time-dependent signal. Preliminary results dealing with isolated apneic events suggest that an increase in sympathetic activity starts before the apneic event itself, thus providing additional information on the pathophysiology of OSA.

Instead of the tedious, complicated studies [10,11] used to diagnose the impact of OSA on a pediatric patient, the analysis of beat-to-beat fluctuations in HR provides the relevant information in a noninvasive, elegant way. The method may be used for both clinical diagnosis and treatment follow up, as well as for basic physiologic investigations.

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