Original article

Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes

Christian Guilleminault*, Dalva Poyares, Agostinho Rosa, Yu-Shu Huang

Stanford Sleep Disorders Center, Stanford University, 401 Quarry Road, Suite 3301, Stanford, CA 94305, USA

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Abstract

Background and purpose: We questioned the role of respiratory events in obstructive sleep apnea syndrome (OSAS) and of upper airway resistance syndrome (UARS) on heart rate (HR) during sleep, paying specific attention to the termination of the abnormal breathing events and examining the presence of arousals or termination with only central nervous system (CNS) activation.

Patients and methods: Twenty patients, 10 with UARS and 10 with mild OSAS, were studied. A nocturnal polysomnogram was performed including measurement of respiratory variables and pulse transit time (PTT). According to the presence or absence of a PTT event indicative of autonomic nervous system (ANS) activation, 148 events were extracted after having been randomly chosen in each represented sleep stage, with or without an electroencephalogram (EEG) arousal. RR interval (RRI) in electrocardiogram (ECG) recordings, as well as heart rate variability, was calculated during 60 and 120 s, respectively. Period amplitude analysis (PAA) was applied for RR-interval analysis, and fast Fourier transformation (FFT) was applied to perform HR variability analysis.

Results: Visually scored EEG arousal was significantly associated with an increase in sympathetic index of heart rate, while PTT was associated with a drop in parasympathetic index, after the respiratory events. Patients with mild OSAS presented persistently shorter RRI when compared to patients with UARS. The latter also exhibited a significant decrease in parasympathetic index (High Frequency (HF)) at the termination of a respiratory event.

Conclusion: The HF component was only significantly decreased in patients with UARS, which indicates a predominant involvement of the parasympathetic tone in patients with UARS in comparison to those with OSAS.

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Keywords: Heart rate variability; RR interval; Autonomic nervous system; Parasympathetic tone; Pulse transit time; Obstructive sleep apnea syndrome; Upper airway resistance syndrome

1. Introduction

The cardiovascular system is continuously modulated by the interaction between sympathetic and parasympathetic nerves. The activity of these two arms of the autonomic nervous system (ANS) is modified during normal sleep. The type and degree of the modulation is dependent on state [1–6]. During NREM sleep, compared to quiet supine wakefulness, a decrease in sympathetic activity is observed while parasympathetic activity is increased [5,7–10].

However, these overall ANS changes are modified by short lasting electroencephalogram (EEG) events, such as K-complexes or delta bursts [6,11]. The exact relationship between the observation of EEG discharges and changes in the effectors of the ANS, such as heart rate (HR), blood pressure (BP), and pulse transit time (PTT) is also unknown.

ANS changes have been described more frequently in REM sleep, where the tonic and phasic events have been dissociated [8,12], but this pattern may also be observed during slow wave sleep (SWS) [3]. Sleep disorders may disrupt this complex and state/stage-dependent interaction between parasympathetic and sympathetic tone. The disruption can be related to the intensity of abnormal peripheral stimuli [13,14]. ANS final response varies according to the degree of sensory recruitment triggered...
by any abnormal peripheral event that stimulates peripheral receptors, for instance.

One of the roles of the different subcortical relays in the ascending reticular system during sleep is to filter the ascending stimuli, to maintain sleep continuity, and to provide appropriate reflex response to peripheral challenges [15,16]. If subcortical reflexes cannot resolve the peripheral challenge, in case the intensity of the stimuli is too important, there will be a cortical involvement leading to an EEG arousal that will be the first step toward the possibility of providing an active and sometimes voluntary response to peripheral challenges [17–21]. ANS changes during sleep thus may be seen in association with different degrees of central nervous system (CNS) activation, including EEG arousal [22,11]. Peripheral changes during sleep interfere with ANS regulation, and it has been hypothesized that the disturbances of ANS regulation may increase the morbidity seen with sleep disorders [13,23–30].

The relationship between abnormal respiratory events during sleep and ANS changes is still little explored. We sought to evaluate the effects of sleep-disordered breathing on one indicator of ANS modulation, the heart rate during abnormal respiratory events, paying specific attention to presence/absence of EEG arousals or involvement of subcortical activation. To avoid important co-morbidity, we selected a patient population (a) with low frequency of obstructive sleep apnea (OSA) with minimum SaO2 drops, and (b) with upper airway resistance syndrome (UARS). We questioned (a) whether or not at the end of abnormal breathing events, UARS and mild OSAS patients presented similar changes in heart rate, an index of autonomic activation, (b) whether or not the presence of a visual EEG arousal made a difference on the observed heart rate change, and (c) whether or not we could dissociate the role of the sympathetic and parasympathetic components in the heart-rate response observed with the abnormal breathing events seen in these patients.

2. Methods

2.1. Subjects

Twenty patients, 10 with a low number of OSA events per hour of sleep and 10 with UARS, who fulfilled the inclusion and exclusion criteria described below were recruited from the sleep disorders clinic during a three-month period. All subjects signed an informed consent approved by the Institutional Review Board (IRB).

The inclusion criteria were as follows: men and women ranging in age from 18 to 50 years, clinically suspected of sleep-disordered breathing, without morbid obesity (defined as BMI ≥ 35 kg/m²) with absence of drug or medication intake, absence of other sleep disorders and an Epworth Sleepiness Scale score ≥ 10 [31]. All subjects had a medical and sleep evaluation before entry. UARS was defined as absence of OSA at polysomnography, apnea–hypopnea index (AHI) < 5 events/h, presence of flow limitation at nasal cannula/pressure transducer curve with flow decrease < 30% of normal breath, SaO2 measured by pulse-oximetry always above 92%. Patients with UARS had a respiratory disturbance index (RDI) ≥ 5 events/h, and breathing events were not necessarily associated with a drop in SaO2 of 3% or more and/or an EEG arousal.

The exclusion criteria were based on a review of the nocturnal polygraphic recording. Subjects with AHI > 20 events/h, presence of other sleep disorders such as restless legs or periodic limb movement syndrome, baseline SaO2 ≥ 93%, and episodes of SaO2 drops below 89%, were excluded from the study. Polysomnograms that presented frequent artifacts on EEG, electrocardiogram (ECG) or PTT signals, or with very long awakenings during sleep were also excluded. An individual not involved in the research analysis performed this exclusion. The final sample of 20 patients (Table 1) derived from an initial group of 53 successive recordings. Presence of a SaO2 drop below 89% during the recording was responsible for exclusion of 32 of the 33 subjects who did not meet criteria. This group of subjects has already been reported as they participated in a study on arousal and PTT [32].

2.2. Polygraphic recording

Patients arrived in the sleep clinic by 19:00 h but went to bed at their usual bedtime. A minimum of 7 h of PSG recording was obtained for all patients. The following sleep variables were collected and stored using amplifiers and pre-amplifiers Grass® and a dedicated computerized

Table 1
Subject’s demographic and sleep data (means±SD, N=20)

<table>
<thead>
<tr>
<th></th>
<th>UARS (n=10)</th>
<th>OSAS (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>29.3±5.8</td>
<td>29.6±5.6</td>
</tr>
<tr>
<td>Age</td>
<td>39.7±8.6</td>
<td>46.5±10.0</td>
</tr>
<tr>
<td>TST (min)</td>
<td>340.9±53</td>
<td>321.0±70.0</td>
</tr>
<tr>
<td>Sleep efficiency %</td>
<td>76.4±12.8</td>
<td>76.9±10.3</td>
</tr>
<tr>
<td>AHI</td>
<td>2.7±2.1</td>
<td>15.3±8.1*</td>
</tr>
<tr>
<td>RDI</td>
<td>6.9±1.8</td>
<td>27.3±6.1*</td>
</tr>
<tr>
<td>Mean lowest SaO2</td>
<td>96.9±0.8</td>
<td>95.5±2.4</td>
</tr>
<tr>
<td>Stage 1%</td>
<td>15.1±8.7</td>
<td>15.2±3.7</td>
</tr>
<tr>
<td>Stage 2%</td>
<td>69.0±10.3</td>
<td>63.2±12.1</td>
</tr>
<tr>
<td>SWS %</td>
<td>3.9±8.3</td>
<td>6.5±11.4</td>
</tr>
<tr>
<td>REM sleep %</td>
<td>11.9±5.6</td>
<td>14.0±4.7</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>21.0±31.0</td>
<td>13.0±7.9</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>91.3±29.3</td>
<td>89.6±29.6</td>
</tr>
</tbody>
</table>

Mann Whitney U-test, ns, non-significant; BMI, body mass index; TST, total sleep time; AHI, apnea–hypopnea index; RDI, respiratory disturbance index; SWS, slow wave sleep; REM, rapid eye movement.
sleep system, with a sampling rate of 128 Hz per second per channel, except for the ECG channel which was 256 Hz. A total of four EEG leads (C3-A2, C4-A1, Fz-A1, O1-A1), two electrooculogram (EOG) channels, two electromyogram (EMG) channels (chin and both legs), and an ECG channel (V2 modified lead).

Respiration was monitored as follows: (a) nasal cannula with the flow measured on a pressure transducer; (b) mouth thermocouple to monitor mouth flow; (c) two channels for chest and abdominal efforts with inductive respiratory plethysmography; (d) esophageal pressure (Pes) using a fluid filled 1.6 mm diameter sensor, placed behind the left atrium before ‘lights out’, calibrated on supine position; (e) oxygen saturation (SaO2) obtained from a Nellcor™ oximeter. PTT signal was recorded using an RM 60 recording unit (Sunrise Medical Instruments) and stored on the computerized polygraphic system with other sleep variables. To obtain PTT values beat by beat, three thoracic ECG electrodes and a modified finger probe to allow detection of pulse shock wave were placed on the subject. The estimated time between the R wave of ECG and the detection of a pulse shock wave at the finger is approximately 200–250 ms [33].

2.2.1. Scoring criteria

All records were scored following the scoring criteria of Rechtshaffen and Kales [34], the American Sleep Disorders Association (ASDA) Scoring task force and the American Academy of Sleep Medicine (AASM) for clinical purposes [35]. EEG arousals were scored using ASDA [36] criteria but also with that reported by Martin et al. [28], including arousals with an EEG frequency shift to fast frequencies greater than 1.5 s, but smaller than 3 s, which were called ‘micro-EEG arousals’.

Two polygraphic signals were selected to define the exact beginning and end of respiratory events: esophageal pressure curve and flow from the nasal cannula; mouth thermocouple and thoraco-abdominal bands were checked again but only to eliminate erroneous attribution. ‘Flow limitation’ was defined as a change in the shape of the nasal flow of at least 5% for two consecutive breaths with simultaneous documented increase in respiratory efforts (Pes), defined as two standard deviations above the mean effort monitored during non-obstructed breathing. When no flow limitation was clearly seen, we defined ‘Pes event’ as a more negative-peak end inspiratory esophageal pressure on three successive breaths (Pes crescendo). It is terminated with an EEG arousal or an abrupt shift of at least 25% of the peak end inspiratory toward less effort (Pes reversal). Thus, the end of an event was defined as cessation of flow limitation and/or Pes reversal. These patterns were visually recognized and could also be analyzed by computer programs performing curve analysis. These events plus those of apnea and hypopneas were called sleep-related respiratory events (SRRE).

Presence of PTT + events was defined as a fall in PTT curve of 15 ms. This is approximately equivalent to a rise in BP of 15 mmHg [32,33].

2.2.2. Data analysis

Visual scoring of all above-mentioned EEG and respiratory events were performed by two researchers blind to patient condition. This process also included identification of all other sleep phenomena such as body or leg movements. At the end of this process, all EEG arousals including microarousals of 1.5–3 s duration or autonomic activation not related to abnormal respiratory pattern, were excluded.

A total of 1,168 respiratory events were identified for all patients. The events were then divided in four subcategories of association of events as follows:

<table>
<thead>
<tr>
<th>Event type 1</th>
<th>Event type 2</th>
<th>Event type 3</th>
<th>Event type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1: PTT + event and EEG arousal (greater than 1.5 s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2: PTT + event and NO EEG arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3: NO PTT + events and NO EEG arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4: NO PTT + event and EEG arousal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The unequal numbers of events classified as 1–4 had to be taken into account for comparison purpose (Table 2). Type 4 had only 37 events classified for all recordings. Thus, the number of events selected for analysis in each of the other bins had to be matched. A grouping by event type and sleep stage was performed for each patient prior to randomization. There was at least one event per bin per patient, and each sleep stage was represented for each event. A total of 148 events were submitted to the following analysis.

2.2.3. RR interval analysis

Period amplitude analysis (PAA) on zero crossings intervals was applied in an ECG pre-processed signal using a moving average filter. A double sequence of negative–positive peaks associated with a level thresholding is able to obtain the ‘R’ peaks, even when they are disturbed by low frequency artifacts. The temporal difference between two peaks of ‘R’ wave provides the RR interval (RRI), which is also known as interbeat interval, and is inversely proportional to heart rate. PAA was performed on 148 PTT events from 60 s of ECG. The termination of the respiratory event was placed at the mid-point of the 60 s of the selected ECG recordings. The segment was then divided

Table 2

<table>
<thead>
<tr>
<th>Event type 1</th>
<th>Event type 2</th>
<th>Event type 3</th>
<th>Event type 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>24</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage 2</td>
<td>594</td>
<td>137</td>
<td>52</td>
</tr>
<tr>
<td>SWS</td>
<td>12</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>REM sleep</td>
<td>226</td>
<td>41</td>
<td>16</td>
</tr>
<tr>
<td>N total%</td>
<td>856, 73.3%</td>
<td>204, 17.4%</td>
<td>71, 6.1%</td>
</tr>
</tbody>
</table>

Total n = 1,168; SWS, slow wave sleep.
in 15 non-overlapped 4-s windows, leaving the termination of the respiratory event in window 8 as a marker.

2.2.4. Heart rate variability analysis

Fast Fourier transformation (FFT) was applied to stable sequences of RRI within a spectrum of 0–1 Hz of heart rate. The heart rate variability has been usually analyzed in two main bands: (a) the low frequency band (LF), 0.1–0.15 Hz, which corresponds to 20-s variation and refers to a cumulative variation of sympathetic and parasympathetic components (sometimes also considered from 0.05 to 0.15 Hz); (b) the high frequency band (HF), 0.15–0.25 Hz, corresponding to fast variations, faster than five seconds containing almost exclusively the parasympathetic component of heart rate. Thus, the ratio between LF/HF allows us to obtain the sympathetic component. It has also been shown that this sympathetic index correlates to heart rate changes [37].

The FFT were performed in 120 s surrounding the respiratory event. The termination of the respiratory event was placed at the mid point of the 120 s of the selected ECG recordings. Thus, the comparisons were made between the 60 s before and 60 s after the termination of the respiratory event.

3. Statistics

The Mann Whitney U-test was used to compare demographic data. Two-way analysis of variance (ANOVA) was applied considering the following two major effects: (a) RR interval and (b) UARS×OSA, presence/absence of PTT deflection (PTT×NO PTT), and presence/absence of a visual EEG arousal (EEG×NO EEG). The level of significance was set at $P \leq 0.01$, after correction for multiple comparisons.

A similar two-way ANOVA design was also performed to analyze both effects, sympathetic and parasympathetic components of heart rate variability.

Wilcoxon ranked pairs test was applied to compare sympathetic and parasympathetic heart rate components’ dependent variables, before and after the respiratory events, during NREM and REM sleep. The level of significance in this case was set at $P < 0.05$.

4. Results

4.1. General

Subjects’ demographic and sleep data are presented in Table 1. There were no differences between the two groups of subjects, with the exception of the AHI, which was obviously greater for the mild OSA group (Mann Whitney U-test).
4.3. Heart rate variability: sympathetic and parasympathetic components

(a) High frequency (HF) (the parasympathetic component). The following results are presented on Table 3.

<table>
<thead>
<tr>
<th>Sleep stages</th>
<th>HF before</th>
<th>HF after</th>
</tr>
</thead>
<tbody>
<tr>
<td>UARS NREM (50)</td>
<td>26.4±18.2</td>
<td>20.5±10.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>OSAS NREM (50)</td>
<td>21.6±12.8</td>
<td>22.9±15.6</td>
</tr>
<tr>
<td>UARS REM (24)</td>
<td>13.8±8.9</td>
<td>17.4±12.5</td>
</tr>
<tr>
<td>OSAS REM (24)</td>
<td>16.7±9.2</td>
<td>15.7±9.6</td>
</tr>
<tr>
<td>PTT NREM (50)</td>
<td>25.0±14.5</td>
<td>18.1±11.0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>NO PTT NREM (50)</td>
<td>23.2±16.3</td>
<td>23.9±14.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PTT REM (24)</td>
<td>16.3±9.7</td>
<td>15.1±13.2</td>
</tr>
<tr>
<td>NO PTT REM (24)</td>
<td>14.6±8.8</td>
<td>17.5±9.8</td>
</tr>
<tr>
<td>EEG NREM (50)</td>
<td>23.1±16.8</td>
<td>19.7±11.9</td>
</tr>
<tr>
<td>NO EEG NREM (50)</td>
<td>24.5±14.7</td>
<td>23.6±14.8</td>
</tr>
<tr>
<td>EEG REM (24)</td>
<td>14.4±9.3</td>
<td>22.3±12.2</td>
</tr>
<tr>
<td>NO EEG REM (24)</td>
<td>15.7±9.1</td>
<td>13.5±9.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Differences between before and after periods in each respiratory event.
<sup>b</sup> Differences between PTT and NO PTT condition.

(b) Low frequency/high frequency ratio (LF/HF) (the sympathetic component). The following results are presented on Table 4.

The LF/HF component was significantly increased after respiratory events during NREM sleep (P<0.001) but not during REM sleep.

4.4. Summary of results

(a) Significant increase in heart rate was found in window 9, just after an abnormal respiratory event. Mild OSA subjects presented a persistently shorter RR interval when compared to UARS patients, i.e. OSAS subjects exhibited a consistent pattern of increased heart rate (Fig. 1).

(b) There was no association between RR interval and PTT event. However, when an EEG arousal was visually detected, there was a significantly increased heart rate after a respiratory event (Fig. 2).

(c) The analysis of heart rate variability showed consistent changes after respiratory events during NREM sleep. NREM sleep was associated with a significant increase in LF/HF in both clinical conditions and a decrease in HF components in UARS subjects in response to abnormal breathing.
effort. No significant changes could be detected during REM sleep.

d) PTT was associated with a significant drop in the HF component of heart rate after an abnormal breathing event.

e) In OSAS as well as in UARS patients, a presence of PTT+ event or EEG arousal did not lead to a significant change in the LF/HF ratio, i.e., sympathetic component, during either NREM or REM sleep.

5. Discussion

5.1. Non-significant results in REM sleep

We have already presented data obtained on the same group of subjects using PTT and indicating that the finding reaches significance during NREM sleep only [32]. The non-significant finding during REM may be related to (a) the presence of muscle atonia that limits the amount of inspiratory effort and thus the degree of the negative inspiratory pressure that can be generated (and the secondary degree of ANS change that can be induced), (b) the fact that ANS balance is different compared to NREM sleep and at times not very different from short awakening, with the resultant stimulation of the ANS afferents lower during REM sleep compared to NREM sleep in these non-morbidly obese patients and (c) possibly to the limited number of subjects in the analysis.

5.2. ANS response in UARS and OSAS patients

The present results indicate that UARS patients and those with mild OSAS do not present the same type of ANS response when challenged by an abnormal breathing event. The presence of a visual EEG arousal leads to an acceleration of heart rate with any type of sleep-disordered breathing (OSAS or UARS). The descending influences from the cortex consistently increase heart rate. Interestingly, presence or absence of PTT+ signal did not influence the change in heart rate.

However, independent of the sleep state and number or group distribution of patients, our patients present a consistently faster heart rate with OSAS even if the breathing events are only associated with modest SaO2 drops. Complete or partial occlusion of the upper airway lasting at least 10 s associated with some degree, even if mild, of SaO2 drop, and a visually scored EEG arousal, have more impact on heart rate acceleration than any other abnormal breathing efforts. In addition, isolated increased inspiratory effort associated or not with flow limitation at the nose leads to much less increase in heart rate at the time strain is removed.

The analysis of the HF (parasympathetic component) and LF/HF ratio (sympathetic component) during NREM sleep shows changes related to the type of SRRE and to the presence or absence of a visually scored EEG arousal. SRRE lead to an increase in LF/HF ratio, more pronounced for apneas and hypopneas than for other types of SRRE events, such as those seen in UARS. However, the presence of increased inspiratory effort with or without flow limitation and without an important SaO2 drop, lead to a decrease in the HF component (parasympathetic tone) at termination; this change in vagal tone plays a role in the observed heart rate acceleration in UARS.

The heart rate acceleration during NREM sleep is mostly related to an increase in sympathetic tone (or its LF/HF index), but a significant drop in parasympathetic tone (or its HF index) is present in UARS subjects and is associated with PTT positive event, while OSAS patients fail to show significant change in this index. However, the sympathetic index is consistently increased after the end of the breathing events in both groups of subjects. Furthermore, OSAS subjects always have higher heart rate compared to those with UARS (Figs. 1 and 2).

Either OSAS patients have a continuous resetting of their sympathetic tone, or heart-rate modulation is more related to parasympathetic activity in UARS patients. Even when airway is reopened in OSAS patients, they have less leeway to decrease their parasympathetic tone, which is due to the need to continuously balance the sympathetic tone resetting, probably caused by hypoxemia and apneas during sleep. UARS patients present evidence of dominant parasympathetic tone [38], and in the absence of hypoxemia, the lifting of the parasympathetic modulation at the end of the resistive breathing is an important component in changes in heart rate and plays a more important role than sympathetic stimulation. These two phenomena are occurring during sleep-disordered breathing but prominence of one type is dependant of the type of sleep-disordered breathing monitored. The importance of the role of the vagal tone, dominant in UARS patients [38], is well shown in the literature. Normal subjects demonstrate a fall in mean arterial pressure of more than 10 mmHg during inspiratory strain with a drop in blood pressure, followed by a rise above baseline on release of the strain, that is related to increase in parasympathetic stimulation [14,39–41]; and resistive breathing without hypoxemia during wakefulness causes a fall in arterial pressure, associated with a decline in muscle sympathetic nerve activity (MSNA), allowing the parasympathetic tone to be the main regulator [42,43].

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References

[16] Lambertz M, Langhorst P. Simultaneous changes of rhythmic organization in brainstem neurons, respiration, cardiovascular system and EEG between 0.05 and 0.5 Hz. J Autonom Nerv Syst 1998;68: 58–77.
[46] Lambertz M, Langhorst P. Simultaneous changes of rhythmic organization in brainstem neurons, respiration, cardiovascular system and EEG between 0.05 and 0.5 Hz. J Autonom Nerv Syst 1998;68: 58–77.