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Relationship between Sleep Stages and HRV response in Obstructive Sleep Apnea Patients

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Abstract— **Patients suffering from obstructive sleep apnea (OSA) usually present an increased sympathetic activity caused by the intermittent hypoxia effect on autonomic control. This study evaluated the relationship between sleep stages and the apnea duration, frequency, and type, as well as their impact on HRV markers in different groups of disease severity. The hypnogram and R-R interval signals were extracted in 81 OSA patients from night polysomnographic (PSG) recordings. The apnea-hypopnea index (AHI) defined patient classification as mild-moderate (AHI<=30, n=44) or severe (AHI>30, n=37). The normalized power in VLH, LF, and HF bands of RR series were estimated by a time-frequency approach and averaged in 1-min epochs of normal and apnea segments. The autonomic response and the impact of sleep stages were assessed in both segments to compare patient groups. Deeper sleep stages (particularly S2) concentrated the shorter and mild apnea episodes (from 10 to 40 s) compared to light (SWS) and REM sleep. Longer episodes (>50 s) although less frequent, were of similar incidence in all stages. This pattern was more pronounced for the group of severe patients. Moreover, during apnea segments, LF_{nu} was higher (p=0.044) for the severe group, since VLF_{nu} and HF_{nu} presented the greatest changes when compared to normal segments. The non-REM sleep seems to better differentiate OSA patients groups, particularly through VLF_{nu} and HF_{nu} (p<0.001). A significant difference in both sympathetic and vagal modulation between REM and non-REM sleep was only found within the severe group. These results confirm the importance of considering sleep stages for HRV analysis to further assess OSA disease severity, beyond the traditional and clinically limited AHI values.**

Clinical relevance: **Accounting for sleep stages during HRV analysis could better assess disease severity in OSA patients.**

I. INTRODUCTION

Recurrent apnea episodes during sleep can result in a sustained exposure to intermittent hypoxia (IH) in patients with obstructive sleep apnea (OSA). This chronic condition has been associated with some cardiovascular consequences, such as systemic hypertension, myocardial infarction, and stroke among others [1], [2], [3]. The mechanisms linking IH to cardiovascular diseases in OSA patients remain so far unclear. However, some conditions have been associated with this matter including an elevated sympathetic activity of the autonomous nervous system (ANS) [4], oxidative stress [2], inflammation and atherosclerosis [3].

Several studies have reported enhanced sympathetic modulation in OSA patients during both sleep and wakefulness periods [5], [6]. A decreased activity in the muscle sympathetic nerve has also been observed when treated these patients with continuous positive airway pressure (CPAP) [7], [8]. This suggests a causal relationship between OSA and sympathetic tone, which seems to be associated with disease severity. Other factors such as sleep disruption and arousals seem to impact the level of sympathetic activation induced by apnea [11]. Moreover, the occurrence of cortical arousals after obstructive events has been observed to depend on the sleep stage [12]. Therefore, sleep stages appear to influence in different ways the occurrence probability of abnormal respiratory events, affecting their durations and associated desaturation levels [12], [13]. Indeed, studies involving healthy subjects has also confirmed the relationship between sympathetic activation and sleep stages [14], [15]. For these reasons, OSA patients' assessment should consider this information when evaluating its impact on sympathetic modulation and the relationship with severity.

In a previous study, sympathetic modulation was assessed in OSA patients for each sleep stage during the whole night, grouping them according to disease severity [17]. However, the analysis was performed considering the entire PSG recording and with no distinction between normal and apneic segments. In the present study, we have characterized the autonomic response through spectral markers of HRV, assessed in patients with mild-moderate and severe OSA, during normal and abnormal respiratory segments. In addition, the different sleep stages were considered to assess their impact on the occurrence and duration of apneas, besides the level of sympathetic modulation according to OSA severity.

II. MATERIALS AND METHODS

A. Population data

The study population comprises 81 OSA patients, from which conventional polysomnography (Minisomno; Sefam, Nancy, France) was recorded at the University Hospital Germans Trias i Pujol in Badalona, Spain (2008-2009) [16], [17]. The population mean age was 51.4 ±11.0 years old (range: 23-75) while 83.9% (68) were males. These patients were classified according to their AHI (total number of apneas and

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hypopneas per sleep hour) as mild-moderate (n=44) or severe (n=37), by fixing the threshold at AHI=30 . Exclusion criteria included: the presence of upper airway infection and other diseases, actual undergoing treatment for snoring or taking any medication. The clinical protocol was approved by the local hospital ethics committee while all patients provided their informed written consent to participate in the study.

B. Signal extraction and processing

The beat-to-beat (RR) interval time series were extracted from the PSG recordings and resampling at 4 Hz before performing the HRV analysis. The hypnogram signals containing the sequence of sleep stages (S1 and S2: deep wave sleep; SWS: slow-wave sleep; and REM: rapid eye movement) was also available. The annotated respiratory events information (onset, duration, end, and type) was used to define normal and abnormal respiratory segments. Each segment, representing a 1-min epoch, was classified as abnormal respiratory segment if at least one respiratory event (either apnea or hypopnea) started or ended within that segment, otherwise, it was classified as normal.

C. Heart rate variability (HRV) analysis

After resampling the RR signals, a bidirectional, 4th order high-pass Butterworth filter at 0.003 Hz was applied to remove low-frequency noise. Subsequently, a non-stationary approach based on the Smoothed Pseudo Wigner-Ville distribution (SPWVD) was used to extract HRV spectral markers. This method incorporates a smoothing kernel to reduce the interferences terms while maintaining a suitable time-frequency resolution. The kernel parameters were set to specific values that allow obtaining temporal and spectral resolutions of 16.7 seconds and 0.033 Hz, respectively [18]. Then, HRV was measured as the total power of SPWVD in the very-low-frequency (VLF: 0.003-0.04 Hz), low-frequency (LF: 0.04-0.15 Hz), and high-frequency (HF: 0.15-0.4 Hz) bands. Finally, these time series accounting for the dynamic fluctuation in sympathetic and parasympathetic influences of the ANS on cardiac rhythm, were normalized referred to the total power, defined here as the sum of the power measured in the three bands $TP(t) = VLF(t) + LF(t) + HF(t)$, leading to the time series $VLF_{nu}(t)$, $LF_{nu}(t)$ and $HF_{nu}(t)$:

$$VLF_{nu}(t) = \frac{VLF(t)}{TP(t)} \tag{1}$$

$$LF_{nu}(t) = \frac{LF(t)}{TP(t)} \tag{2}$$

$$HF_{nu}(t) = \frac{HF(t)}{TP(t)} \tag{3}$$

Once computed the time-series of the spectral markers during the whole night, they were averaged for each 1-min epoch of normal and pathological respiration previously defined, rather than being average for the entire recording.

D. Statistical analysis

Results are expressed in mean ± standard deviation (SD). All markers were compared between mild-moderate and severe patient groups by using either normal segments or only apnea segments. On the other hand, apnea segments were compared for each sleep stage (S1, S2, SWS and REM), in order to characterize their impact on autonomic control in each studied group. Statistical analysis were performed by using the Wilcoxon-Mann-Whitney test to compare severity patient groups, and the Wilcoxon signed-rank test for paired comparison across sleep stages. The level of significance was set to 0.05. Finally, the relationship between sleep stages and the main event features like duration and frequency, were reported for all events mixed, and for each type of event.

III. RESULTS

Table 1 summarizes the main clinical characteristics of the study population for both groups of disease severity, including the body mass index (BMI) and AHI parameter. Figure 1 shows the average number of respiratory events (apneas and hypopneas) starting during each sleep stage, and pooled by different duration ranges for the whole population and both groups of patients.

TABLE I

BASELINE CHARACTERISTICS OF THE STUDY POPULATION GROUPED BY DISEASE SEVERITY.

Clinical marker	**Mild-Moderate (AHI $<$ 30)**	**Severe (AHI $>$ 30)**
Age ($y.o.$)	50.4 ±11.9	52.6 ±9.8
Male sex, N (%)	35 (79.6)	33 (89.2)
BMI (kg/m^2)	27.5 ±3.3	30.8 ±4.6
AHI (h^{-1})	21.6 ±9.7	68.2 ±20.5

As observed, the incidence is higher in deep wave sleep stages (S1 and particularly S2), and decreases significantly in lighter sleep and REM stages. This pattern is also observed when separating hypopnea and apnea events, being more pronounced in the latter (not shown in the figure). Moreover, similar behavior is detected when comparing severe with mild-moderate patients, where S1 and S2 stages concentrate the higher incidence but with a clear dominance of shorter events (10-20 s, 20-30 s, 30-40 s), particularly in the Severe group. Finally, although longer events (>50 s) are present during REM sleep, the incidence is relatively low and quite similar to that of other non-REM stages. This can be the reason for which duration of respiration events in REM sleep are reported to be longer in mean, just because shorter episodes are less common.

Figure 2 shows the boxplots corresponding to the spectral markers evaluated during normal respiration (top panel) and apnea segments (bottom panel). In the case of normal segments, normalized LF and VLF power were quite similar, but also not significantly different between groups. Only HF power was significantly lower for severe patients (p=0.036), indicating less vagal activity overall. In the case of apnea segments, although only LF_{nu} was significantly different

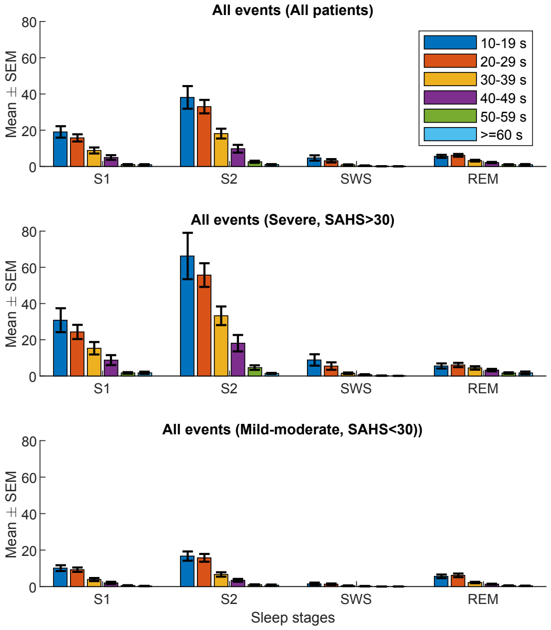

Fig. 1. The average number (Mean ± SEM) of respiratory events (apneas and hypopneas) per sleep stage evaluated for all patients (top), severe patients (middle), and mild-moderate patients (bottom). Colored bars represent duration ranges of the events, pooled in steps of 10 s.

between patient groups (p=0.044), the more remarkable changes were found in VLF_{nu} and HF_{nu} (in the opposite direction) as compared to normal segments. In both severity groups, vagal activity was reduced as HF_{nu} decreased, while VLF_{nu} increased particularly for mild-moderate patients.

Regarding the sleep stage influence, Fig. 3 displays the results obtained for both OSA groups during apneic segments. As it is shown, the group of severe patients presented the more remarkable differences between all non-REM stages and REM sleep for LF_{nu} ($p<0.001$), VLF_{nu} ($p<0.001$) and HF_{nu} ($p<0.002$) markers. Although results for mild-moderate patients seem to have a slightly similar pattern, the differences between stages was not significant: LF_{nu} ($p<0.128$), VLF_{nu} ($p<0.084$) and HF_{nu} ($p<0.217$). Table II summarizes, on the other hand, the sleep-stage analysis for all markers while comparing mild-moderate and severe patients in all stages. Non-REM stages analyzed together presented significant differences values between groups in VLF_{nu} and LF_{nu}, the latter with higher values for more severe patients, indicating high sympathetic modulation in deep and slow-wave sleep. On the contrary, REM sleep did not present any relevant differences in autonomic control among the two groups of OSA severity.

IV. DISCUSSION

The results obtained in this study confirmed somehow previous outcomes from other studies while highlighting some new findings that might result of clinical interest in OSA patients' assessment. From one side, we have confirmed that slow-wave sleep (SWS) remain as the safest stage [13] due to the low incidence of respiratory events in all patients.

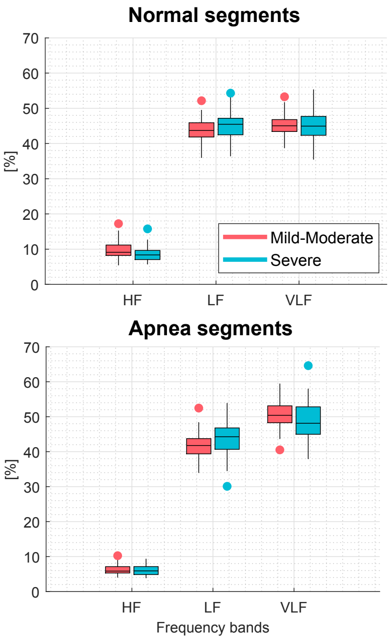

Fig. 2. Average normalized power of the VLF, LF and HF bands, obtained for mild-moderate and severe patients in normal and apnea segments.

TABLE II

Average HRV espectral measures for non-REM and REM sleep (mean ± standard deviation) in mild-moderate and severe OSA patients. *p-value<0.05. test.

Index	**Mild-moderate (AHI<30)**	**Severe (AHI>30)**	*p*-value
VLF_{nu} (%)			
Non-REM	49.9 ± 5.7	47.7 ± 7.2	0.001
REM	52.4 ± 5.4	54.9 ± 6.1	0.089
LF_{nu} (%)			
Non-REM	41.9 ± 5.1	44.1 ± 5.9	<0. 001
REM	40.2 ± 4.4	38.5 ± 5.4	0. 188
HF_{nu} (%)			
Non-REM	6.7 ± 2.8	6.8 ± 3.7	0.941
REM	6.2 ± 2.5	5.2 ± 1.5	0.127

On the other side, although for REM sleep it has been reported more frequent obstructive events [19], [20], and with longer duration [21], our results showed that shorter events are significantly less frequent compared to S1 and S2 stages, and this fact would become the average event duration to be large. Indeed, longer events are quite similar in number among all sleep stages except for SWS (as shown in Fig. 1).

Another relevant fact is that OSA severity might be reflected through different patterns in HRV markers, when these are analyzed during normal and pathological respiration. Therefore, evaluating both periods during night PSG recordings might provide additional useful insights for OSA patients' assessment. Moreover, apart from assessing just LF and HF bands during HRV analysis, the VLF band has demonstrated to capture relevant differences between normal and apnea segments, suggesting the need to be included. This is supported by the results from experimental OSA model in rats [22], and from clinical studies in OSA patients [23].

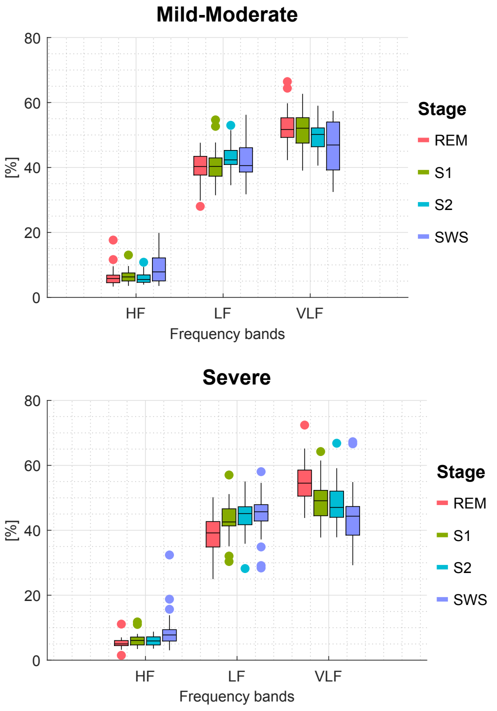

Fig. 3. Sleep-stage analysis and normalized HRV markers comparison for mild-moderate (left) and severe (right) patients during apneic epochs. REM: Rapid eyes movement; S1 and S2: deep sleep wave; SWS: slow sleep wave.

Finally, the autonomic modulation during REM and non-REM stages seems to be clearly differentiated in more severe patients during apnea segments. Besides, only non-REM sleep stages were useful to distinguish mild-moderate from severe patients, especially when assessing sympathetic modulation measures, in line with results reported in [17]. Our findings complement somehow those of [24] and [25] reported for free-apnea epochs, and between mild, moderate and NonOSA patients, respectively, only using REM and S2 stages. All the above let us conclude the relevant role of sleep stages when assessing disease severity in OSA patients, beyond the clinical apnea-hypopnea index (AHI).

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