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Characterization of Changes in HRV Metrics During Sleep Apnea Episodes in Pediatric Patients

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Abstract— **Previous studies, through heart rate variability (HRV) analysis, revealed an increased sympathetic dominance during sleep in patients suffering from obstructive sleep apnea (OSA). However, a separate analysis comparing episodes of apnea and normal breathing during sleep has not been performed, to characterize whether the increased sympathetic dominance is just due to the instantaneous autonomic response to each apnea or there is a sustained sympathetic activation. The HRV metrics evaluated are the temporal and frequency HRV indices, along with new spectral bands, recently identified as specific for pediatric patients diagnosed with OSA. Nonparametric paired statistical test exhibits clear significant differences in HRV, comparing for each patient values in apnea events and normal breathing during sleep and such findings are applicable for all HRV metrics except RMSSD and HF band power, whose significance during apnea events is questionable. While all previous studies analyzed HRV either for the overnight recordings or after removing the apnea events, results obtained in this work highlight the need to perform the analysis separately, both in apnea events and in normal breathing.**

I. Introduction

When pediatric obstructive sleep apnea (OSA) is persistent, OSA-induced physiologic alterations derive into major cardiovascular comorbidities. Previous studies, using polysomnography (PSG), revealed altered autonomic nervous system (ANS) during sleep in patients suffering from moderate to severe OSA when compared with healthy controls [1]. In this context, non-invasive ANS monitoring, through heart rate variability (HRV) analysis, was used to quantify the increased sympathetic dominance in OSA patients.

The physiological response to apnea ends with an acute increase in sympathetic activity that may trigger or is triggered by an arousal [1]. However, all previous studies aiming to characterize the ANS activity in OSA patients, did not compare or separate the analysis between apnea events and normal breathing during sleep. In other words, the increased sympathetic dominance observed in OSA patients is biased by the so characteristic and strong sympathetic activation taking place just in response to the episodes of apnea [2]. This masks the behavior of any ANS index, and results might not be reflecting the basal state of the ANS [1].

The objective of this work is to characterize HRV metrics in pediatric patients suffering from OSA symptoms, between measurements obtained in apnea events, with acute sympathetic activity, or in normal breathing during sleep. This aims to help interpret the HRV physiological indices, in order to assess whether the increased sympathetic dominance is just due to an instantaneous autonomic response to each apnea or there is a sustained sympathetic activation.

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II. Materials and Methods

A. Sleep Data

The Childhood Adenotonsillectomy Trial (CHAT) was a prospective randomized trial designed to evaluate the efficacy of different OSA treatments [3]. Our study included 311 children with OSA symptoms, between 5-10 years old. The pediatric patients were recruited for a baseline nocturnal PSG at the clinical laboratory before the OSA treatment. The apnea–hypopnea index (AHI) was used to establish the OSA severity [3], between mild-, moderate- and severe-OSA.

B. HRV analysis guided by respiration

To derive indices related to the joint analysis of HRV and respiration, the instantaneous respiratory rate, $F_r(n)$, has been estimated using the thoracic and abdominal respiratory signals [4]. The heartbeats are detected on the electrocardiogram and the integral pulse frequency modulation (IPFM) model is used to estimate the HRV signal [5], sampled at 4 Hz. After ectopic correction, the normal-to-normal interval (NN) is used to compute mean Heart Rate (mHR), standard deviation of the NN intervals (SDNN), and root mean-square of successive NN differences (RMSSD).

The frequency metrics of HRV are the power in the Low Frequency (LF) band: Ω_{LF} = [0.04, 0.15] Hz; and the power in the Very Low Frequency (VLF) band: Ω_{VLF} = [0.0033, 0.04] Hz. The high frequency (HF) band is redefined to be time-varying and centered at the respiratory rate: $\Omega_{HF}(n)$= $F_r(n)$±0.15 Hz [2], with the lower bound limited to 0.15 Hz. In addition, previous studies identified new specific HRV spectral bands for pediatric OSA stratification [6], being: Ω_{B1} = [0.001, 0.005] Hz, Ω_{B2} = [0.028, 0.074] Hz and $\Omega_{BR}(n)$ = $F_r(n)$±0.04 Hz. All frequency parameters are calculated using a time-frequency distribution belonging to the Cohen's class [7]. Therefore, for each HRV frequency band, the power is monitored continuously for the overnight recordings at the resampling frequency, 4 Hz.

C. Effects of apnea on HRV

Apnea segments are considered from 5 seconds before the apnea onset to 15 seconds after its end, this is including the tachycardia recovery compensation pattern following an episode of apnea [2]. As mentioned, the frequency power of

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each HRV band is obtained continuously at 4 Hz, for the whole overnight recordings. After that, the power signals are separated in normal breathing during sleep and episodes of apnea. For each patient, the median value of each HRV metric is obtained, averaged both in the apnea events and after excluding them. After that, for each patient, a paired Wilcoxon signed-rank test is applied to assess the differences between values obtained in the apnea events vs. values obtained in the overnight recordings after excluding the apnea events.

III. RESULTS & DISCUSSION

For each patient, and each metric, the median value is obtained. The average values are shown in Tab. I, separately: in the episodes of apnea and at normal breathing during sleep, after removing the apnea events. In addition, for illustrative purposes, the average values in both cases are depicted separately by severity group, for mild, moderate and severe OSA patients. The *p-value* of the paired statistical analysis is also displayed, comparing, for each patient, the median values in episodes of apnea vs. values in normal breathing.

TABLE I.
AVERAGED MEDIAN VALUES FOR HRV METRICS, CALCULATED SEPARATELY IN NORMAL BREATHING AND IN APNEA EPISODES

	normal breathing			apnea segments			N=311
	mi	mo	se	mi	mo	se	*p-value*
mHR[1]	87	90	92	89	90	92	*≪0,01**
SDNN[2]	104	108	90	102	96	97	*≪0,001**
RMSSD[2]	76	77	58	60	56	60	*0,15*
$P(\Omega_{VLF})$[3]	3,9	4,0	4,2	11,9	11,1	11,4	*≪0,001**
$P(\Omega_{LF})$[3]	8,2	7,4	7,8	33,6	34,3	36,2	*≪0,001**
$P(\Omega_{HF})$[3]	13,9	11,8	12,9	10,6	10,3	13,0	*0,29*
$P(\Omega_{B1})$[3]	0,4	0,4	0,5	1,1	1,0	1,0	*≪0,001**
$P(\Omega_{B2})$[3]	3,4	3,4	3,6	13,3	12,6	13,3	*≪0,001**
$P(\Omega_{BR})$[3]	1,5	1,2	1,4	1,3	1,2	1,8	*≪0,01**

[1]*[b.p.m]*; [2]*[ms]*; [3]*[s/Hz]*.
mi: mild-, mo: moderate-, se: severe-OSA patients.

As expected, clear significant differences are observed for all metrics, except for the RMSSD and $P(\Omega_{HF})$ parameters. The so clear differences are something expected, but this was not reported in any previous study. With these results we can state the importance of separately deriving indices at the apnea events and at normal breathing during sleep. Contrary to what has been done so far, a different and particular physiological interpretation must be made in these two situations, to avoid bias in the interpretation. Both apnea events and normal breathing during sleep contain information of the ANS, but the situations are totally different: in the first, patients are under severe stress and in the other, they are totally relaxed, respectively.

Some clear differences are visible in the averaged values comparing apnea vs. no-apnea results. The $P(\Omega_{B2})$ band is strongly related to the apnea presence, and changes in this band were specifically attributable to OSA resolution mediators [6]. The sudden significant increase in the $P(\Omega_{B2})$, $P(\Omega_{VLF})$ and $P(\Omega_{LF})$ bands during apnea may be explained by the characteristic tachycardia-bradycardia pattern during the apnea, which matches the frequency of these bands.

The fact that $P(\Omega_{HF})$, and the RMSSD related to it, did not result in significant differences, is worth mentioning. First, the use of the modified HF band, instead of the classic one, is specifically encouraged by the increased F_r observed in children, higher than 24 rpm, i.e., 0.4 Hz. However, this band showed no differences between apnea events and normal breathing during sleep periods. The interpretation of these indices during apneas is questionable: in the case of $P(\Omega_{HF})$, there are two issues. The first is methodological, which is what and how to estimate the respiratory rate during episodes of apnea. The second is physiological, as with RMSSD, since these parameters are related to respiration and parasympathetic activity, contrary to what occurs in apnea.

While all previous studies analyzed HRV either for the overnight recordings or after removing apnea events, results obtained in this work highlight the need to perform the analysis separately for a complete interpretation of HRV indices, both in apnea events and in normal breathing. Furthermore, it is possible that sleep stages will also need to be separated to evaluate their contributions and effects on autonomic dysregulation in pediatric OSA [8].

IV. CONCLUSION

This work exhibited the important differences that exist in the HRV metrics, considering the separate analysis in episodes of apnea, with strong sympathetic activity, and normal breathing during sleep. In fact, this work evidenced that the interpretation of the power in the HF band and the RMSSD parameters is not adequate during apnea events.

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