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Tracking the physiological responses in sleep apnea using robust cardiac sympathetic activity estimation

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Abstract—The analysis of heart rate variability (HRV) is essential for assessing autonomic activity in various clinical conditions. However, standard HRV analyses do not effectively capture sympathetic activations during sleep monitoring, particularly those expected in obstructive sleep apnea (OSA). We recently introduced a HRV method based on Poincaré plot analysis, providing time-resolved estimations of the main HRV rhythms, on top of the changes in the baseline interbeat interval duration, using a robust covariance matrix estimation approach based on Ledoit-Wolf approach. Our method yields the Cardiac Sympathetic Index (CSI), which surpasses the capacity of low-frequency HRV for tracking sympathetic activity in standard autonomic elicitation conditions. Here we investigated whether CSI can effectively capture physiological changes in response to OSA events. Our findings demonstrate that our CSI estimator outperforms standard metrics of sympathetic activity, such as low-frequency HRV and mean interbeat interval duration, offering a valuable and cost-effective approach for studying autonomic activity through HRV analysis.

Keywords—obstructive sleep apnea, heart rate variability, cardiac sympathetic activity

I. INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by upper airway collapse, causing breathing interruptions and reduced oxygen levels, which leads to an activation of the sympathetic nervous system [1]. However, standard measures of cardiac sympathetic activity do not successfully detect the physiological responses of OSA events, as compared with blood pressure or sympathetic nerve neurogram [2]. Indeed, the challenges of accurately estimating sympathetic dynamics through heart rate variability (HRV) has been long discussed [3][4]. We recently developed a robust estimator of sympathetic tone called cardiac sympathetic index (CSI) [5]. Our approach separates heart rate and HRV components of cardiac sympathetic activity, building upon a time-resolved estimation of the eigenvalues of the covariance matrices of successive changes in the inter beat intervals, as typically depicted in the Poincaré plot. In this study we show how CSI successfully depicts the physiological response triggered by OSA and compare it to standard heart rate and low-frequency approaches.

II. MATERIALS AND METHODS

A. Dataset description

Twenty-five subjects (21 males and 4 females, aged 50 years on average) were referred to the Sleep Disorders Clinic at St Vincent's University Hospital, Dublin, for the diagnosis of obstructive sleep apnea. Holter ECG was recorded during sleep using a Holter Reynolds Lifecard CF system (Reynolds Medical, UK) with a sampling frequency of 128 Hz.

The OSA events were marked by a specialist, based on breathing patterns. The events inclusion criteria in this study

included: a minimum duration of 20 s and, previous the event onset, there were no other apnea events for at least 60 s. All events that fulfilled the criteria were considered as independent trials. To assess the autonomic adjustments triggered by OSA, the onset of the events was considered 5 s after the one marked by the specialist. Trials were considered in the -10 s to 10 s with respect the onset of the defined event. A total of 63 OSA events fulfilling the above-mentioned criteria were identified among all participants.

All participants signed informed consent to participate in the study as required by the Declaration of Helsinki. For further detail on the experimental procedures, please refer to the original study [6][7].

B. Estimation of cardiac sympathetic activity

The R-peaks from the ECGs were detected automatically [8]. The detected R-peaks were manually corrected for misdetections. Interbeat interval series (IBI) were constructed, based on the R-to-R-peak durations.

The time-resolved estimation of CSI [5] was performed using a sliding time window to quantify the fluctuating properties of the successive changes in IBI, as typically depicted in the Poincaré plot [9]. We quantified two features from Poincaré plot: R and SD_2 , which correspond to the distance to the origin of the formed ellipse, and its long ratio representing the baseline IBI and long-term fluctuations of HRV, respectively. The two metrics were combined as the Cardiac Sympathetic Index (CSI):

$$R(t) = \sqrt{\text{mean}(IBI_{i,\dots,n-1})^2 + \text{mean}(IBI_{i+1,\dots,n})^2} \quad (1)$$

$$SD_2(t) = \sqrt{\lambda_2} \quad (2)$$

$$CSI(t) = SD_2(t) + \tilde{R}(t) \quad (3)$$

where λ_2 is the larger eigenvalue of the covariance matrix of $IBI_{1,\dots,N-1}$ and $IBI_{2,\dots,N}$, and N is the length of the IBI array in the current time window. A robust estimator of the covariance matrix was obtained using a shrinkage covariance estimator based on the Ledoit-Wolf approach for the analytic calculation of the optimal shrinkage intensity [10]. The means were computed using a robust mean algorithm that excludes the 5% of outliers (Matlab *trimmean*). Before CSI computation, $R(t)$ and $SD_2(t)$ means were recentered, based on their computation through the whole recording, and \tilde{R} is the flipped R with respect the mean. The sliding time window used had a length of 15 s, as per previous simulations in humans [11], and a step defined by each heartbeat.

CSI values were averaged for the conditions pre- vs post-OSA events, in an interval of 10 seconds, and compared to those markers obtained from mean IBI and low-frequency

HRV (LF), as computed with a smoothed pseudo-Wigner-Ville distribution [12].

C. Statistical analysis

To evaluate the performance of the markers in discerning the conditions pre and post OSA, we used a non-parametric signed-rank test for paired samples. Time series were z-score normalized per trial. The group-wise descriptive measures are expressed as medians and median absolute deviations (MAD).

III. RESULTS

We examined sympathetic dynamics in individuals undergoing OSA. Cardiac sympathetic activity (CSI) was computed using our proposed methodological approach based on Poincaré plot. In Table I are presented the statistical comparisons of the pre and post OSA, where CSI successfully distinguish the two conditions. Additionally, comparisons in standard markers mean low frequency (LF) and IBI confirm the robustness of the CSI in describing sympathetic dynamics. Fig. 1 illustrates that following the onset of an OSA event, the CSI begins to increase, reaching a peak after approximately 10 seconds, which is sustained for another 5-10 seconds. These findings demonstrate that CSI can precisely distinguish the period before the OSA event from the period afterward.

TABLE I. SIGNED-RANK TEST ON HEART RATE VARIABILITY MARKERS COMPARING PRE VS POST APNEA EPISODES

Marker	Median (MAD) pre vs post apnea	p-value ^a	Z-value
CSI	-0.389(0.393) vs 0.396(0.399)	0.0027	-2.9986
LF	-0.229(0.669) vs 0.233(0.681)	0.0857	-1.7184
IBI	0.136(0.239) vs -0.138(0.243)	0.0148	2.4372

^a Significance based on Bonferroni correction defined at $p < 0.0167$.

IV. DISCUSSION

We studied the physiological response associated to OSA events through our method for the precise and time-resolved estimation of cardiac sympathetic activity. Our method can accurately capture the typical alterations in sympathetic activity observed in OSA events [2].

Our approach is grounded on Poincaré plot, which effectively captures the beat-to-beat alterations in heart rate and long-term fluctuations in HRV without relying on the observation of specific frequencies [5]. Our proposal focuses on delivering a time-resolved estimation method, enabling a comprehensive exploration of the dynamic shifts in autonomic regulations. This study demonstrates the efficacy of CSI for estimating sympathetic activity, specifically in accurately tracking the sympathetic response to OSA, surpassing the capabilities of previous standard estimators based on heart rate and LF-HRV.

While this study contributes valuable insights, it is limited by the absence of direct registry of sympathetic nerve activity, though existing literature supports the anticipated correlation between sympathetic activity and OSA [1][2]. Another limitation is the defined minimum trial duration, set at 20 s, as a balance between the rhythms up to 25 s duration that can be found in LF-HRV, and the 15 s time window used for the model.

Despite its current offline nature, advancements in real-time estimation of cardiac sympathetic activity hold promise

for expanding applications in sleep medicine. The implications of this research can be noted from numerous perspectives, as the cost-effectiveness of this approach opens avenues for widespread autonomic monitoring of sleep. By offering a robust means of estimating cardiac sympathetic activity, this line of research could enhance our understanding of sleep physiology and its disorders.

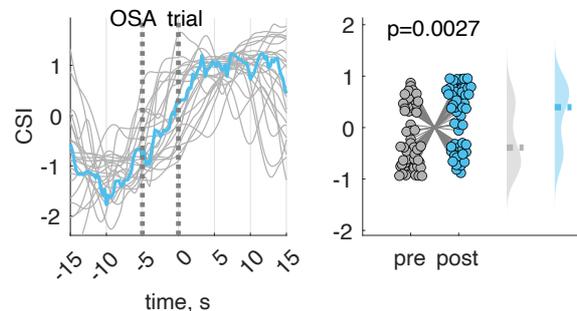


Fig. 1. Cardiac sympathetic index (CSI) under obstructive sleep apnea (OSA). CSI values were used to quantify the autonomic changes triggered instants (5 s) after OSA events. Thick blue signal indicates the group median and light gray ones individual trials (one third for visualization purposes). Time series were z-score normalized per trial before averaging. The right panel displays the distribution of the average pre and post-OSA within a 10 s latency. All amplitude units are arbitrary units.

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