Worsening hypoxic load impairs cardiorespiratory coupling

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Abstract—**In obstructive sleep apnea (OSA), the hypoxic load is one of the key factors impairing cardiorespiratory coupling (CRC) but the acute effect of its severity on the degree of CRC has remained unknown. Our data comprised 603 clinical polysomnographies segmented into non-overlapping 5-minute segments (*n* = 36 926). We retrospectively studied the high-frequency (HF, 0.15-0.40 Hz) coupling (HFc) between heart rate variability (HRV) signal determined from electrocardiography and nasal pressure in these 5-minute segments, and compared the HFc in the groups divided by the severity of hypoxic load in the segments. We found that increasing hypoxic load gradually impairs the level of CRC in terms of HFc (decreased from 0.813 to 0.689, *p* < 0.001). Therefore, hypoxic load progressively weakens vagal modulation and could be utilized more thoroughly in conventional OSA diagnostics to better assess OSA-related cardiac stress.**

Keywords— Cardiorespiratory coupling, desaturation severity, heart rate variability, hypoxic load, obstructive sleep apnea

I. Introduction

Hypoxic load due to obstructive sleep apnea (OSA) shifts the sympathovagal balance toward sympathetic overdrive [1]. Additionally, hypoxic load weakens cardiorespiratory coupling (CRC), the biomarker for increased cardiac workload and stable NREM sleep with stable breathing [2], [3]. As nocturnal breathing is disturbed in OSA, respiratory sinus arrhythmia is not a sufficient parameter to describe the degree of CRC in patients with OSA, Therefore, we aimed to study the acute effects of hypoxic load on CRC in terms of cross-spectral coherence between heart rate variability and breathing [4].

II. Methods

We retrospectively analyzed electrocardiography (ECG) and nasal pressure signals of 603 patients (men 53.2%) recorded during clinical polysomnography. We divided the signals into non-overlapping 5-minute segment pairs (*n* = 36 926). We detected and corrected the R peaks with Kubios HRV Premium 3.4.1 (Kuopio, Finland) [5], calculated the power spectral densities of heart rate variability (HRV) and respiratory signals, and determined the spectral coherence between RR intervals and nasal pressure in the high-frequency (0.15-0.40 Hz) band (high-frequency coupling, HFc) in the 5-minute segments. We used Welch's method (eight sections, 50% overlap, Hamming window) when determining the PSDs and the spectral coherence. The segments were pooled into reference group $DesSev_0$ and quartiles $DesSev_{Q1}$-$DesSev_{Q4}$ ($DesSev_0 = 0\% < DesSev_{Q1} \leq 0.301\% < DesSev_{Q2} \leq 0.898\% < DesSev_{Q3} \leq 2.467\% < DesSev_{Q4}$) based on the desaturation severity parameter [6]. HRV (normalized power in the HF band, HF_{NU}; ratio of low-frequency (0.04-0.15 Hz) and HF band powers, LF/HF ratio) and HFc were compared between the DesSev groups. Full details of the methodology are described in our article [7] on which this abstract is based.

III. Results

We observed increasing sympathetic overdrive (decreasing HF_{NU} and increasing LF/HF) and increasing difference between HRV PSD and respiratory peaks in the HF band with more severe hypoxic load (Table 1). In addition, we found a significantly decreasing level of spectral coherence between RR intervals and nasal pressure and a strengthening negative correlation between DesSev parameter values and HFc toward more severe hypoxic load (Fig. 1.).

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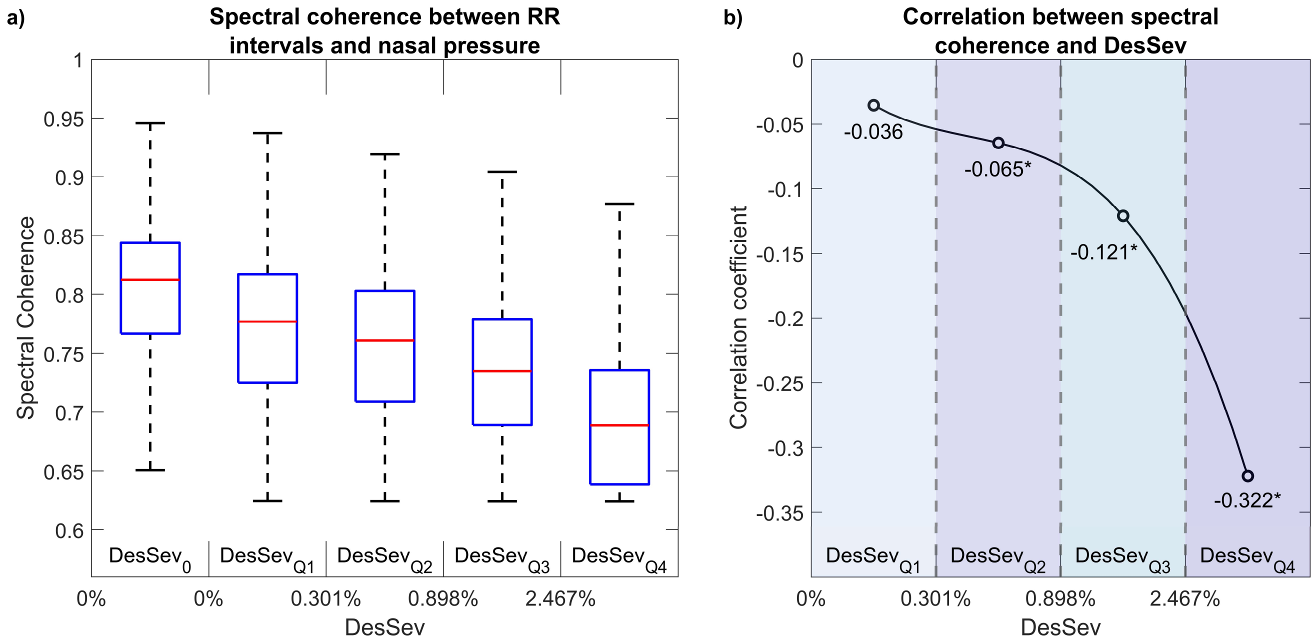

Fig. 1. **a)** High-frequency (0.15-0.40 Hz) spectral coherence between RR intervals and nasal pressure in the groups pooled based on the hypoxic laod (DesSev) in the 5-min segments. Red lines present the median spectral coherences and blue boxes their interquartile ranges. Whiskers correspond to approximately ±2.7 standard deviation and 99% data coverage. Each severity group $DesSev_{Q1-4}$ differed statistically significantly from the reference group $DesSev_0$ and each other ($p < 0.001$). **b)** The correlation between spectral coherence and DesSev parameter values within the severity groups.
* = a statistically significant ($p < 0.001$) correlation coefficient.

TABLE I. HEART RATE VARIABILITY AND RESPIRATORY CHARACTERISTICS

	HF_{NU}	**LF/HF**	**ΔHF peak [Hz]**
$DesSev_0$	0.49 (0.31-0.67)	1.05 (0.49-2.20)	0.001 (-0.003-0.006)
$DesSev_{Q1}$	**0.42 (0.26-0.61)**	**1.37 (0.65-2.80)**	**0.002 (-0.003-0.013)**
$DesSev_{Q2}$	**0.43 (0.27-0.62)**	**1.34 (0.63-2.67)**	**0.003 (-0.003-0.021)**
$DesSev_{Q3}$	**0.41 (0.26-0.58)**	**1.45 (0.73-2.92)**	**0.006 (-0.003-0.042)***
$DesSev_{Q4}$	**0.36(0.22-0.53)***	**1.81 (0.88-3.51)***	**0.039 (0-0.097)***

The values are presented as the median with the interquartile range. The statistical significance of differences between DesSev groups was assessed with the Wilcoxon signed-rank test. *Abbreviations: $DesSev_0$ = Reference group with desaturation severity of 0% during the 5-min segment, $DesSev_{Q1-4}$ = Severity groups pooled based on the desaturation severity during the 5-min segment, HF_{NU} = Normalized power in the high-frequency band (0.15–0.40 Hz), LF/HF = Ratio of the powers in the low-frequency (0.04–0.15 Hz) and HF bands, ΔHF Peak = Difference between the respiratory and HRV peak frequencies in the HF band.*
The bolded values denote the statistically significant ($p < 0.001$) difference compared to the corresponding reference group.
* = statistically significant difference ($p < 0.001$) compared to all other DesSev-groups.

IV. CONCLUSIONS

This study demonstrated that worsening hypoxic load gradually increases sympathetic overdrive and vagal withdrawal, and impairs CRC. These physiological consequences increase the cardiac workload and are known risk factors for several cardiovascular diseases and even sudden cardiac death [8], [9]. OSA patients could thus benefit from a more thorough assessment of the disease severity as hypoxic load, HRV, and CRC could be utilized to complement the conventional OSA diagnostics when assessing OSA-related cardiac stress.

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REFERENCES

[1] S. Hietakoste *et al.*, “OSA-related respiratory events and desaturation severity are associated with the cardiac response,” *ERJ Open Res*, vol. 8, pp. 00121–02022, 2022.
[2] A. Ben-Tal, S. S. Shamailov, and J. F. R. Paton, “Evaluating the physiological significance of respiratory sinus arrhythmia: Looking beyond ventilation-perfusion efficiency,” *Journal of Physiology*, vol. 590, no. 8, pp. 1989–2008, 2012.
[3] R. J. Thomas, C. Wood, and M. T. Bianchi, “Cardiopulmonary coupling spectrogram as an ambulatory clinical biomarker of sleep stability and quality in health, sleep apnea, and insomnia,” *Sleep*, vol. 41, no. 2, pp. 1–11, 2018.
[4] M. Orini, R. Bailon, L. T. Mainardi, P. Laguna, and P. Flandrin, “Characterization of dynamic interactions between cardiovascular signals by time-frequency coherence,” *IEEE Trans Biomed Eng*, vol. 59, no. 3, pp. 663–673, Mar. 2012.
[5] M. P. Tarvainen, J. P. Niskanen, J. A. Lipponen, P. O. Ranta-aho, and P. A. Karjalainen, “Kubios HRV - Heart rate variability analysis software,” *Comput Methods Programs Biomed*, vol. 113, no. 1, pp. 210–220, 2014.
[6] A. Kulkas, P. Tiihonen, P. Julkunen, E. Mervaala, and J. Töyräs, “Novel parameters indicate significant differences in severity of obstructive sleep apnea with patients having similar apnea-hypopnea index,” *Med Biol Eng Comput*, vol. 51, no. 6, pp. 697–708, 2013.
[7] S. Hietakoste *et al.*, “Acute cardiorespiratory coupling impairment in worsening sleep apnea-related intermittent hypoxemia,” *IEEE Trans Biomed Eng*, vol. 71, no. 1, pp. 326–333, 2024.
[8] F. Yasuma and J. Hayano, “Respiratory Sinus Arrhythmia: Why Does the Heartbeat Synchronize with Respiratory Rhythm?,” *Chest*, vol. 125, no. 2, pp. 683–690, 2004.
[9] H. Gilat, S. Vinker, I. Buda, E. Soudry, M. Shani, and G. Bachar, “Obstructive sleep apnea and cardiovascular comorbidities: A large epidemiologic study,” *Medicine (Baltimore)*, vol. 93, no. 9, p. e45, 2014.