2024 13th Conference of the European Study Group on Cardiovascular Oscillations (ESGCO) | 979-8-3503-9205-0/24/$31.00 ©2024 IEEE | DOI: 10.1109/ESGCO63003.2024.10767058

Assessment of heart rate circadianity alterations in patients with depression using a wearable device

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***Abstract*—The aim of this study is to assess whether the possible loss of circadian rhythm, a modulator of heart rate, is associated with the severity of depression. For that, Cosinor fitting method was applied to heart rate data of 203 patients with major depressive disorder, recorded continuously over 18 months by a wearable device. Results revealed that the amplitude derived from the Cosinor fit is significantly lower in patients with severe depression, implying a loss in circadian rhythmicity when depression is severe.**

***Index Terms*—heart rate, circadian rhythm, Cosinor analysis, depression, wearable device**

I. Introduction

Major depressive disorder (MDD) was considered the third leading cause of global burden of disease in 2008 by the World Health Organization, and is expected to be the first by 2030 [1]. It is related to various physiological alterations, including mood swings and sleep disturbances, often associated with the autonomic nervous system (ANS).

Circadian rhythm is one of the biological rhythms governing our organism, with a periodicity of approximately 24 hours. Its variations have long been known due to their influence on physiological systems, including the cardiovascular system, and its clinical relevance has made it a subject of study in recent years [2]. One way to assess such circadianity in heart rate (HR) is through Cosinor fitting. Wearable devices offer continuous, robust, and inexpensive monitoring of physiological data, including HR. Combining an objective monitoring of the disease with subjective assessments (e.g., Patient Health Questionnaire, PHQ-8 [3]) can help healthcare teams to identify symptoms not easily observed outside clinical settings. This comprehensive approach enables tailored treatment plans to meet the unique needs of each patient.

The starting hypothesis is that depression, especially in its severe form, causes alterations in the ANS and sleep cycle, which will manifest as disruptions of circadianity in heart rate. They can be quantified by Cosinor fitting. The objective of this study is, therefore, to investigate whether MDD severity is associated with alterations in the circadian pattern of HR.

This work has been partially funded by the projects TED2021-131106B-I00, PID2021-126734OB-C21 (Ministerio de Ciencia e Innovacion y Fondo Social Europeo), Spain, BSICoS T39-23R group (Gobierno de Aragón y Fondo Social Europeo). The RADAR-CNS project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115902. Calculations were performed by the ICTS NANBIOSIS (HPC of the University of Zaragoza).

II. Materials

Data has been collected by Centro de Investigación Biomédica en Red de Bioingeniería, Biomateriales y Nanomedicina (Spain), King's College London (United Kingdom), and Amsterdam University Medical Centre (Netherlands), as part of the RADAR-CNS project.

HR data were continuously recorded using wearable devices (Fitbit Charge 2/3) from 203 patients (112 from the United Kingdom, 51 from Spain and 40 from The Netherlands) with major depressive disorder for a period of 18 months. The device uses its own proprietary algorithms to estimate HR from the PPG signal. Access to the raw signal or the algorithms is not provided; only the estimated HR series is available, approximately every 5 seconds (non-uniform sampling rate).

The database includes 114 females and 59 males, with a mean age of 53.24 $\pm$ 15.15 years (minimum 24, maximum 84 years). Simultaneously, they used a mobile application, in which they responded to the PHQ-8 questionnaires every 2 weeks, serving as a reference to assess the severity of depression. A PHQ-8$\geq$10 score is considered indicative of severe depression.

III. Methods

A. Cosinor method

Heart rate presents circadian variations between day and night, with periodic changes every 24 hours. In order to study

circadianity, HR values were averaged every hour and adjusted to a sinusoidal function. Cosinor method is a widely used regression model in the analysis of timeseries data [4]. The single-component model is defined:

$$Y(t) = M + A\cos(2\pi t/\tau + \phi) + e(t), \quad (1)$$

where M is the MESOR (Midline Estimating Statistic of Rhythm, representing the mean of the heart rate adjusted to the rhythm), A is the amplitude of the sine wave (half of the rhythmic variation extent of the heart rate in one cycle), ϕ is the acrophase (the time interval where the highest values of heart rate are expected), τ is the period (duration of one cycle, 24 hours in this case) and e(t) is the error term.

With the aim of relating Cosinor parameters to the results from the PHQ-8 tests, a Cosinor fit synchronized with these depression questionnaires is performed. Using the registration date of each PHQ-8 as a reference, the Cosinor method is applied to the HR data series from 2 weeks preceding it. Thus, each value of PHQ-8 is associated with the Cosinor parameters describing the circadian variation of HR. Only Cosinor fit results with a p-value$<$0.05 are considered.

For a patient to be included in the analysis, they are required to have at least 12 PHQ-8 values with simultaneous Cosinor fit within a period equal to or less than 1 year.

A common occurrence in HR acquired by wearable devices is data loss and the presence of artifacts. A robustness study was conducted to ensure a reliable number of samples in order to guarantee goodness-of-fit.

B. Statistical analysis

We investigate whether there are significant differences in the circadian variation (in terms of MESOR, amplitude, and acrophase) of HR between patients with severe and non-severe depression levels, defined according to the baseline PHQ-8 values. For this, the Mann-Whitney U test has been used, and the significance level set to p-value $<$ 0.05.

IV. Results and Discussion

From the subset of 203 patients used in the analysis, only 108 patients passed the restriction criteria based on HR and PHQ-8 data quality. Since the number of patients with severe depression is smaller (n=52), to balance the data, the same number of non-severe patients was randomly selected. Several repetitions are carried out to ensure greater statistical robustness of the result.

Fig.1 illustrates an example of a Cosinor fit for the 2 weeks preceding the baseline PHQ-8 value in a patient with non-severe depression, and another with severe depression. It can be observed that, in the case of severe depression, the amplitude of the oscillation is lower.

Fig.2 shows boxplots with the distribution of cosinor amplitude, A, values for each group of patients. In the case of severe depression, this amplitude is significantly lower, indicating a reduced day-night oscillation of heart rate when depression is severe. Higher MESOR values are also observed in the severe depression group, suggesting higher average HR, but these differences do not reach statistical significance.

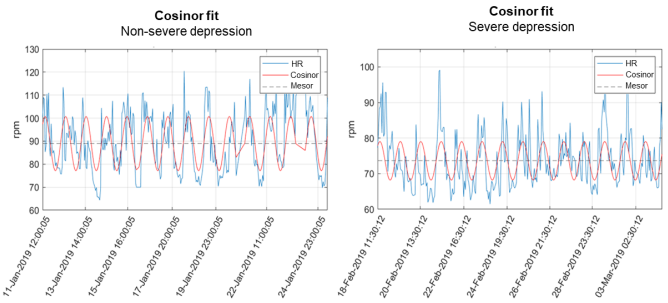

Fig. 1. Cosinor fit synchronized with PHQ-8, 2-week time window. Non-severe depression, A=11.82 bpm. Severe depression, A=5.43 bpm.

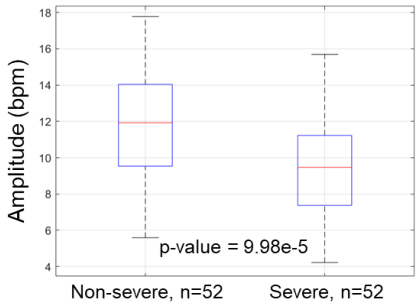

Fig. 2. Amplitude distribution obtained from Cosinor fit in 1-day time intervals, averaging 2 weeks, for patients with severe depression (PHQ-8$\geq$10) and non-severe depression (PHQ-8$<$10).

V. Conclusions

This study has evaluated the effect of circadian modulation on HR in patients with different degrees of depression. The results showed a loss of circadianity in heart rate, induced by the severity of depression: those patients whose questionnaires determined a state of severe depression have a Cosinor fit with significantly lower amplitude. Studying the alteration of circadian rhythm in heart rate creates new possibilities. As pointed out by [5], most research in mood disorders (such as MDD) has focused on emotions, paying less attention to sleep cycles and circadian disruptions, despite being common indicators of the disease.

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