2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

The Added Value of Nonlinear Cardiorespiratory Coupling Indices in the Assessment of Depression*

Spyridon Kontaxis[1], Jesus Lazaro[1], Eduardo Gil[1], Pablo Laguna[1], and Raquel Bailón[1]

Abstract— **The present study investigates the differences in autonomic nervous system (ANS) function and stress response between patients with major depressive disorder (MDD) and healthy subjects by measuring changes in ANS biomarkers. ANS-related parameters are derived from various biosignals during a mental stress protocol consisting of a basal, stress, and recovery phase. The feature set consists of ANS biomarkers such as the heart rate (HR) derived from the electrocardiogram, the respiratory rate derived from the respiration signal, vascular parameters obtained from a model-based photoplethysmographic pulse waveform analysis, and cardiorespiratory coupling indices derived from the joint analysis of the heart rate variability (HRV) and respiratory signals. In particular, linear cardiorespiratory interactions are quantified by means of time-frequency coherence, while interactions of quadratic nonlinear nature between HRV and respiration are quantified by means of real wavelet biphase. The intra-subject difference of a feature value between two phases of the protocol, the so-called autonomic reactivity, is considered as a ANS biomarker as well. The performance of ANS biomarkers on discriminating MDD patients is evaluated using a classification pipeline. The results show that the most discriminative ANS biomarkers are related with differences in HR and autonomic reactivity of both vascular and nonlinear cardiorespiratory coupling indices. Differences in autonomic reactivity imply that MDD and healthy subjects differ in their ability to cope with stress. Considering only HR and vascular characteristics a linear support-vector machine classifier yields to accuracy 72.5% and F1-score 73.2%. However, taking into account the nonlinear cardiorespiratory coupling indices, the classification performance improves, yielding to accuracy 77.5% and F1-score 78.0%.**

Clinical relevance— **Changes in the nonlinear properties of the cardiorespiratory system during stress may yield additional information on the assessment of depression.**

I. Introduction

Major depressive disorder (MDD) is the most common mood disorder and the leading cause of disability worldwide [1]. MDD symptoms can range from insomnia, weight loss, or loss of interest to suicidal behavior [2]. Such symptoms can be understood as the consequence of stressful experiences interacting with the genetic predisposition and personality of an individual [3]. It is no coincidence that more than 40% of depressed patients suffer from concurrent anxiety, fact that has been associated with worse outcome [4].

The last decades significant research has been carried out towards the assessment of stress responsiveness in MDD patients [5]. The acute physiological response to stress is initiated by changes in the autonomic nervous system (ANS). These changes are known as autonomic reactivity and they reflect the ability of an individual to cope with stress [6]. Current research points out that depression is related with autonomic dysfunction and reduced autonomic reactivity during challenging situations [7].

Various ANS biomarkers have been explored for assessing autonomic reactivity, with heart rate variability (HRV) indices being the most common ones [8]. Besides HRV, vascular characteristics provide valuable information about the autonomic control of the cardiovascular system. Arterial stiffness measured by photoplethysmographic (PPG) pulse waveform characteristics has been associated with autonomic dysfunction in patients with depression [9]. Recent studies support that respiratory activity can be also altered by emotional states such as sadness and anxiety [10]. However, respiratory information has seldom been taken into account by former HRV approaches in depression.

Joint analysis of respiration and HRV may yield additional information on linear and nonlinear properties of the cardiorespiratory system. Nonlinear coupling between cardiovascular and respiratory systems arises from interactions via feed-forward and feed-back mechanisms, which are influenced by the activity of higher brain regions [11]. Previous studies have reported differences in both linear and nonlinear cardiorespiratory interactions during ANS changes induced by mental stress [12], [13]. Differences in cardiorespiratory coupling function between healthy and MDD subjects might add clinical value to the assessment of depression. In this study, our main interest is to combine ANS biomarkers from various sources to improve the discrimination of patients with depression.

II. Materials

Forty MDD patients and forty healthy control (HC) subjects matched in age, sex, and body mass index were recruited at the Hospital Clínico Lozano Blesa (Zaragoza, Spain) and the Mental Health Unit of the Hospital Sant Joan de Déu (Barcelona, Spain), under clinical studies PI16-0156 and PIC-148-16, respectively. Written informed consent was received from all subjects in accordance with the Declaration of Helsinki. Participants underwent a mental stress protocol which comprises (a) a basal phase $\mathcal{B}$ during which

*This work was supported and by projects RTI2018-097723-B-I00 funded by AEI and FEDER, by Gobierno de Aragón (Reference Group BSICoS T39-20R and project LMP124-18) cofounded by FEDER 2014-2020, and by CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN) through Instituto de Salud Carlos III.

[1]Spyridon Kontaxis, Jesus Lazaro, Eduardo Gil, Pablo Laguna, and Raquel Bailón are with BSICoS group at the Aragón Institute of Engineering Research (I3A), IIS Aragón, University of Zaragoza, Zaragoza, Spain, and CIBER-BBN, Madrid, Spain sikontax@unizar.es

the subjects were filling psychometric tests, (b) a stressful phase $\mathcal{S}$ during which the subjects were performing the Trail Making Test, and (c) a recovery phase $\mathcal{R}$ during which the subjects were requested to relax after the execution of the cognitive test. Further details concerning the design of the stress protocol can be found elsewhere [9].

For each participant, three orthogonal ECG leads were recorded at 1000 Hz, a non-dominant hand fingertip PPG signal, and a respiratory signal with belt were recorded at a sampling frequency of 250 Hz . All signals were synchronously recorded using the Medicom system (ABP10 module of Medicom MTD, Ltd, Russia).

III. Methods

1) ANS biomarkers: A HRV signal $x(t)$, sampled at 4 Hz, is generated based on the integral pulse frequency modulation (IPFM) model using the time series of beat occurrence, detected on Y-lead of the ECG [14]. The respiratory signal $y(t)$ is downsampled to 4 Hz. Then, $x(t)$ and $y(t)$ are subjected to bandpass filtering in the interval $[0.04, 0.8]$ Hz.

The coupling between HRV and respiration is partially related with the parasympathetic control of the heart and lungs. The linear cardiorespiratory coupling is assessed using the time-frequency coherence (TFC) [15]:

$$\gamma(t,f) = \frac{|S_{\mathrm{XY}}(t,f)|}{\sqrt{S_{\mathrm{XX}}(t,f)S_{\mathrm{YY}}(t,f)}}, \tag{1}$$

where $S_{\mathrm{XX}}(t,f)$, $S_{\mathrm{YY}}(t,f)$, and $S_{\mathrm{XY}}(t,f)$, are time-varying power spectral densities defined based on the Cohen's class distributions. The time percentage where TFC is above a surrogate data-derived threshold is denoted $\mathcal{T}_\gamma$ [13].

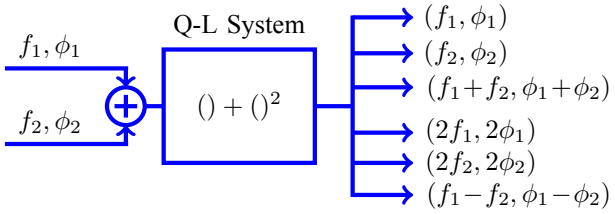

Fig. 1. The products of two oscillations that interact via a Q-L system.

Cardiorespiratory interactions give rise to several types of coupling phenomena characterized either by frequency and/or phase locking between the interacting oscillations [16]. If respiration controls HRV not only through a linear, but also via a nonlinear function, new harmonics with higher-order frequency and phase correlations will appear. A component that arises from the interaction of two oscillations f_1 (ϕ_1) and f_2 (ϕ_2) through a quadratic-linear (Q-L) system (see Fig. 1) is characterized by the same relationship in both frequency and phase. As a result, the phase of the component at the sum of f_1 and f_2 i.e., $f_1 + f_2$, is $\phi_1 + \phi_2$. This phenomenon is known as quadratic phase coupling (QPC) and it can be quantified by means of real wavelet biphase (RWB) [17]:

$$b_\Phi(f_1,f_2,t) = \frac{1}{T'}\int_{t-T'/2}^{t+T'/2} \cos\left(\Phi_{\mathrm{W}}(f_1,f_2,\tau)\right) d\tau, \tag{2}$$

where $\Phi_{\mathrm{W}}(f_1,f_2,t)$ is the instantaneous wavelet biphase:

$$\Phi_{\mathrm{W}}(f_1,f_2,t) = \phi_x(f_1,t) + \phi_y(f_2,t) - \phi_x(f_1+f_2,t), \tag{3}$$

with $\phi_x(f,t)$ and $\phi_y(f,t)$ being the phase of Continuous Wavelet Transform of HRV and respiration, respectively. Assuming that HRV is formed as the output of a Q-L system with input respiratory oscillations among others, high values of RWB imply that $\phi_x(f_1+f_2,t) = \phi_x(f_1,t)+\phi_y(f_2,t)$, which consists in the QPC requirement, i.e., synchronization between the interacting oscillations.

Note that RWB is a function of two frequencies, unlike the power spectrum. The regions in the bifrequency domain where QPC will be assessed are defined based on the respiratory rate $f_r(t)$, which is derived from $y(t)$ as described in [18]. QPC between respiratory sinus arrhythmia (RSA) component of HRV and respiration is identified in the region $\Omega_{\mathrm{R,R}} : \{f_1 \in \Omega_{\mathrm{R}}, f_2 \in \Omega_{\mathrm{R}}\}$, where $\Omega_{\mathrm{R}} = [f_r(t) - 0.05, f_r(t) + 0.05]$ Hz, while QPC between low frequency (LF) components of HRV and respiration is identified in the region $\Omega_{\mathrm{L,R}} : \{f_1 \in \Omega_{\mathrm{L}}, f_2 \in \Omega_{\mathrm{R}}\}$, where $\Omega_{\mathrm{L}} = [0.04, 0.15]$ Hz. The degree of QPC between the interacting frequencies is quantified by,

$$C_{\mathcal{I}}(t) = \max_{f_1,f_2 \in \Omega_{\mathcal{I}}} \{b_\Phi(f_1,f_2,t)\}, \tag{4}$$

where $\mathcal{I} = \{[\mathrm{L,R}], [\mathrm{R,R}]\}$. QPC values that do not exceed a surrogate data-derived threshold are suppressed [17].

Furthermore, the time-varying mean heart rate (HR) signal $d_{\mathrm{HRM}}(t)$ of the IPFM model is also subjected to analysis. Besides the joint analysis of HRV and respiratory signals, a model-based PPG waveform analysis is carried out for deriving ANS biomarkers. The i:th pulse is decomposed into a main wave and two reflected waves as described in [9]. The percentage of amplitude loss in the second reflection $A_{13}(i)$ is subjected to analysis, and it is defined by,

$$A_{13}(i) = \frac{A_1(i) - A_3(i)}{A_1(i)} \cdot 100\%, \tag{5}$$

where $A_1(i)$ and $A_3(i)$ are the amplitudes of the main and the second reflected wave, respectively.

2) Feature selection: For each subject, the temporal mean is used for a feature $\mathcal{F}$ defined on a beat-to-beat or pulse-to-pulse basis, or with time dependence, to assign a unique value $\bar{\mathcal{F}}^{\mathrm{P}}$ at each phase $\mathrm{P} \in \{\mathcal{B}, \mathcal{S}, \mathcal{R}\}$. The feature set consists of various ANS biomarkers including the parameters derived from the ECG ($\bar{d}^{\mathrm{P}}_{\mathrm{HRM}}$) or the respiratory signal ($\bar{f}^{\mathrm{P}}_r$), characteristics associated with the linear ($\mathcal{T}^{\mathrm{P}}_\gamma$) or nonlinear cardiorespiratory interactions ($\bar{C}^{\mathrm{P}}_{\mathcal{I}}$), as well as vascular parameters ($\bar{A}^{\mathrm{P}}_{13}$). The intra-subject difference of a feature from basal to recovery, denoted $\Delta(\mathcal{F})^{\mathcal{B}}_{\mathcal{R}}$, or from stress to recovery, denoted $\Delta(\mathcal{F})^{\mathcal{S}}_{\mathcal{R}}$, which reflect autonomic reactivity, are also considered ANS biomarkers. To avoid the curse of dimensionality, a stepwise linear regression (SLR) approach is employed for reducing the dimension of the feature set [19]. The inclusion or removal of features is carried out considering a statistically significant ($p < 0.01$) improvement of a linear model that contains only an intercept.

3) Classification: The performance of ANS biomarkers on the assessment of depression is evaluated using the following classification scheme. ANS biomarkers are fed into a classification pipeline that reaches a decision on the subject's status (MDD/HC). A leave-one-subject-out (LOSO) scheme is employed to evaluate the discrimination potential of the proposed approach. Each selected feature is normalized to zero-mean and unit variance. Note that the left-out subject is excluded from the calculation of the sample mean and standard deviation. Eventually, the LOSO scheme is completed when all subjects are left out and afterwards evaluated against MDD. A linear support-vector machine classifier (SVC) [20] and a logistic regression classifier (LRC) [21] are examined. Classification performance is evaluated in terms of accuracy (ACC) and F1-score (F1).

Differences in ANS biomarkers between MDD patients and HC subjects are also assessed using the area under the curve (AUC) of the receiver operating characteristic curve, which measures the degree of separability between groups.

IV. Results

The most discriminative ANS biomarkers, which were selected using the SLR method, are related with HR and autonomic reactivity of both vascular and nonlinear cardiorespiratory coupling indices. On the contrary, indices associated with the linear cardiorespiratory coupling and respiratory rate were not chosen. The classification results are summarized in Table I. In particular, SVC offers the best performance, compared to LRC, when all selected features are combined, yielding ACC = 77.5% and F1 = 78.0%. It should be noted that the classification performance of SVC deteriorates of about 5% (in ACC and F1) when nonlinear cardiorespiratory coupling indices are excluded from the feature set. This implies that the nonlinear properties of the cardiorespiratory system may yield additional information on MDD classification. The AUC values of all ANS biomarkers are summarized in Table II. Results show that changes in ANS function quantified by autonomic reactivity indices are associated with larger AUC values. Functional boxplots of ANS biomarkers are shown in Fig. 2.

TABLE I
CLASSIFICATION RESULTS

	Features				Metrics	
	$\bar{d}^{\mathcal{R}}_{\text{HRM}}$	$\Delta\left(\bar{A}_{13}\right)^{\mathcal{S}}_{\mathcal{R}}$	$\Delta\left(\bar{C}_{\text{R,R}}\right)^{\mathcal{B}}_{\mathcal{R}}$	$\Delta\left(\bar{C}_{\text{L,R}}\right)^{\mathcal{S}}_{\mathcal{R}}$	ACC (%)	F1 (%)
SVC	X	X	X	X	77.5	78.0
SVC	X	X			72.5	73.2
LRC	X	X	X	X	76.2	76.5
LRC	X	X			73.7	74.1

TABLE II
AUC VALUES OF ANS BIOMARKERS

	$\mathcal{B}$	$\mathcal{S}$	$\mathcal{R}$	$\Delta()^{\mathcal{B}}_{\mathcal{R}}$	$\Delta()^{\mathcal{S}}_{\mathcal{R}}$
$\bar{d}_{\text{HRM}}$	0.69	0.62	0.72	0.56	0.70
$\bar{A}_{13}$	0.63	0.69	0.72	0.72	0.77
$\bar{f}_r$	0.54	0.52	0.63	0.70	0.66
$\bar{C}_{\text{R,R}}$	0.65	0.71	0.61	0.71	0.76
$\bar{C}_{\text{L,R}}$	0.51	0.62	0.51	0.51	0.62
$\mathcal{T}_\gamma$	0.53	0.50	0.51	0.51	0.54

V. Discussion

The present study investigates the discrimination potential of ANS biomarkers in depression. ANS-related parameters are derived from various biosignals during a mental stress protocol. The response to stress is also evaluated by means of autonomic reactivity.

Results show that MDD patients, compared to HC subjects, exhibit higher HR values (Fig. 2(a)) and larger percentages of amplitude loss in reflected waves (Fig. 2(b)), both yielding AUC=0.72 during $\mathcal{R}$ (Table II). This implies that depression is associated with increased sympathetic activity and ANS dysfunction. Similar findings have been also reported in previous studies [7]. Differences between groups are also observed for the respiratory rate (Table II), mainly during the recovery phase $\mathcal{R}$ (AUC=0.63). Lower respiratory rate (Fig. 2(c)) in HC compared to MDD group at the post-task relaxation period indicates that patients with depression recover at a less extent after stress exposure. In [22], it was suggested that respiration focused training might be an important tool assisting the treatment of depression.

Regarding cardiorespiratory coupling function during ANS changes induced by the cognitive task, nonlinear indices that reflect QPC between HRV and respiration ($\bar{C}_{\text{R,R}}$, $\bar{C}_{\text{L,R}}$) show larger AUC values (Table II) compared to linear cardiorespiratory coupling quantified by means of TFC ($\mathcal{T}_\gamma$). In particular, during $\mathcal{S}$, HC subjects show an increased synchronization between respiration and RSA component of HRV (Fig. 2(d)) and a reduced synchronization between respiration and LF component of HRV (Fig. 2(e)). These results suggest that healthy individuals reacted more to the stressful stimuli, while, in MDD group, small changes are observed. Reduced ability to cope with stress in MDD patients may be enhanced due to ANS dysfunction. Blunted autonomic reactivity in MDD patients has been also reported in previous works [7], [8], [13].

Large AUC values for most of autonomic reactivity indices (Table II) suggest that stress response can be used to assess depression. ANS biomarkers, including HR, and autonomic reactivity indices of both vascular and nonlinear cardiorespiratory coupling indices, show a high diagnostic performance (Table I) for classifying subjects as having MDD or not. A reduction in the discriminative power of ANS biomarkers when the nonlinear interactions between HRV and respiration are not taken into account implies that nonlinear properties of the cardiorespiratory system may yield additional information on the assessment of depression. Previous studies involving MDD patients showed that entropy measures of cardiorespiratory coupling can be also used to assess depression [23].

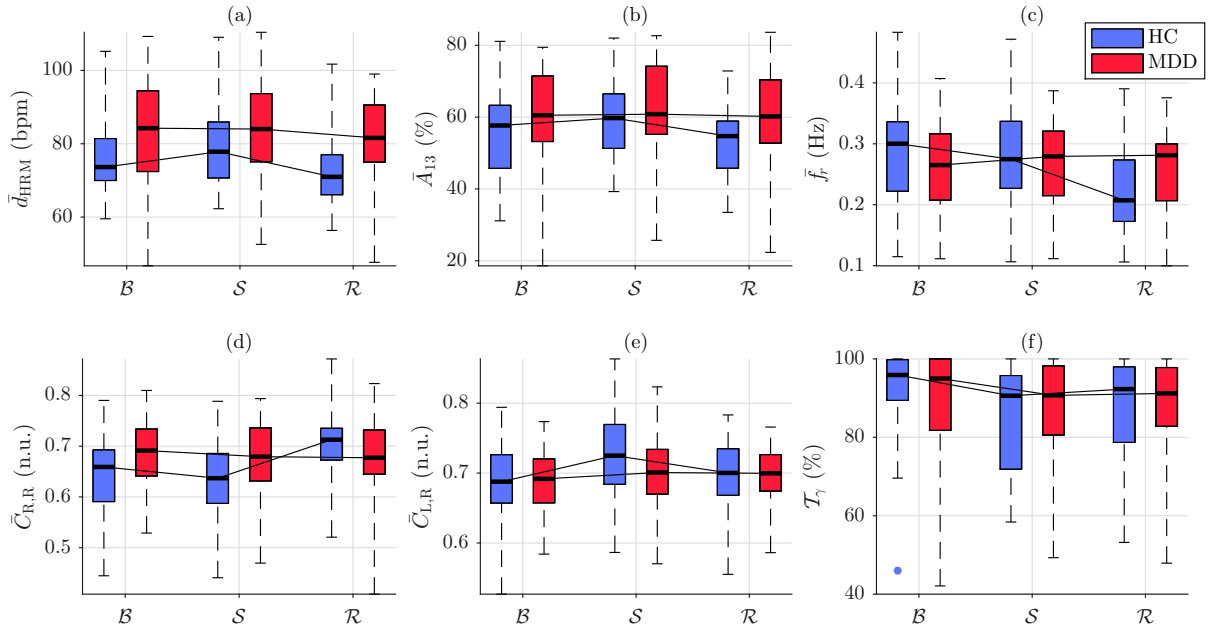

Fig. 2. Functional boxplots of ANS biomarkers. (a) Heart rate, (b) percentage of amplitude loss in the second reflection, (c) respiratory rate, (d) QPC degree between RSA component of HRV and respiration, (e) QPC degree between LF component of HRV and respiration, and (f) time percentage of linear cardiorespiratory coupling.

VI. Conclusions

Differences in ANS function and stress response between MDD and healthy individuals can add a clinical value to the assessment of depression. The discrimination potential of ANS biomarkers in depression is higher when nonlinear interactions between respiration and HRV are taken into consideration, suggesting that nonlinear properties of cardiorespiratory coupling function may add complementary information on MDD classification.

Acknowledgment

The computation was performed by the ICTS "NANBIOSIS", more specifically by the High Performance Computing Unit of the CIBER in Bioengineering, Biomaterials & Nanomedicine (CIBER-BBN) at the University of Zaragoza.

References

[1] W. H. Organization *et al.*, "Depression and other common mental disorders: global health estimates," World Health Organization, Tech. Rep., 2017.

[2] A. P. Association *et al.*, *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub, 2013.

[3] E. S. Friedman *et al.*, *Handbook of depression*, 2014.

[4] R. Gaspersz *et al.*, "Patients with anxious depression: overview of prevalence, pathophysiology and impact on course and treatment outcome," *Curr. Opin. Psychiatry*, vol. 31, no. 1, pp. 17–25, 2018.

[5] C. E. Angermann and G. Ertl, "Depression, anxiety, and cognitive impairment," *Curr. Heart Fail. Rep.*, vol. 15, no. 6, pp. 398–410, 2018.

[6] D. Carroll *et al.*, "The behavioural, cognitive, and neural corollaries of blunted cardiovascular and cortisol reactions to acute psychological stress," *Neurosci. Biobehav. Rev.*, vol. 77, pp. 74–86, 2017.

[7] C. Schiweck *et al.*, "Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. a systematic review," *Psychol. Med.*, vol. 49, no. 2, pp. 200–211, 2019.

[8] J. L. Hamilton and L. B. Alloy, "Atypical reactivity of heart rate variability to stress and depression across development: Systematic review of the literature and directions for future research," *Clin. Psychol. Rev.*, vol. 50, pp. 67–79, 2016.

[9] S. Kontaxis *et al.*, "Photoplethysmographic waveform analysis for autonomic reactivity assessment in depression," *IEEE. Trans. Biomed. Eng.*, 2020.

[10] B. Bordoni, F. Marelli, and G. Bordoni, "A review of analgesic and emotive breathing: a multidisciplinary approach," *J. Multidiscip. Healthc.*, vol. 9, p. 97, 2016.

[11] S. Schulz *et al.*, "Cardiovascular and cardiorespiratory coupling analyses: a review," *Philos. Trans. R. Soc. A*, vol. 371, no. 1997, p. 20120191, 2013.

[12] S. Kontaxis *et al.*, "Heart rate variability analysis guided by respiration in major depressive disorder," in *2018 Comput. Cardiol. (CinC)*, vol. 45. IEEE, 2018, pp. 1–4.

[13] S. Kontaxis *et al.*, "Blunted autonomic reactivity to mental stress in depression quantified by nonlinear cardiorespiratory coupling indices," in *2020 Comput. Cardiol. (CinC)*, vol. 47. IEEE, 2020, pp. 1–4.

[14] R. Bailón *et al.*, "The integral pulse frequency modulation model with time-varying threshold: application to heart rate variability analysis during exercise stress testing," *IEEE. Trans. Biomed. Eng.*, vol. 58, no. 3, pp. 642–652, 2010.

[15] M. Orini *et al.*, "Characterization of dynamic interactions between cardiovascular signals by time-frequency coherence," *IEEE. Trans. Biomed. Eng.*, vol. 59, no. 3, pp. 663–673, 2011.

[16] M. Elstad *et al.*, "Cardiorespiratory interactions in humans and animals: rhythms for life," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 315, no. 1, pp. H6–H17, 2018.

[17] S. Kontaxis *et al.*, "Assessment of quadratic nonlinear cardiorespiratory couplings during tilt-table test by means of real wavelet biphase," *IEEE. Trans. Biomed. Eng.*, vol. 66, no. 1, pp. 187–198, 2018.

[18] S. Kontaxis *et al.*, "ECG-derived respiratory rate in atrial fibrillation," *IEEE. Trans. Biomed. Eng.*, vol. 67, no. 3, pp. 905–914, 2019.

[19] R. A. Armstrong and A. C. Hilton, *Statistical analysis in microbiology*. Wiley-Blackwell Pub, 2011.

[20] L. Wang, *Support vector machines: theory and applications*. Springer, 2005, vol. 177.

[21] D. Collett, *Modelling binary data*. CRC press, 2002.

[22] V. Zamoscik *et al.*, "Modulation of respiration pattern variability and its relation to anxiety symptoms in remitted recurrent depression," *Heliyon*, vol. 6, no. 7, p. e04261, 2020.

[23] L. Zhao *et al.*, "Cardiorespiratory coupling analysis based on entropy and cross-entropy in distinguishing different depression stages," *Front. Physiol.*, vol. 10, p. 359, 2019.