Heliyon 9 (2023) e20740

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Association and interaction between clinician-rated measures of depression and anxiety with heart rate variability in elderly patients with psychiatric disorders

Joonbeom Kim [a,b], Jae-Jin Kim [a,c], Jeong-Ho Seok [a,c], Eunjoo Kim [a,c], Jin Young Park [a,d], Hesun Erin Kim [a], Jooyoung Oh [a,c,*]

[a] Institute of Behavioral Sciences in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Interdisciplinary Graduate Program in Social Welfare Policy, Yonsei University, Seoul, Republic of Korea
[c] Department of Psychiatry, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[d] Department of Psychiatry, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea

ARTICLE INFO

Keywords:
Heart rate variability
Clinician-rated measures
Elderly patients
Comorbidity
Depression
Anxiety

ABSTRACT

Background: Older adults are vulnerable to comorbid depression and anxiety symptoms; however, these conditions are widely underrecognized and often untreated. Understanding their combined manifestation using objective measurements, such as clinician-rated scales and heart rate variability (HRV), can help refine the diagnosis and select a treatment strategy for geriatric patients.
Methods: This study included patients over 65 years who were mainly diagnosed with either category of depressive or anxiety disorders from the psychiatric outpatient clinic in a university hospital. A total of 114 patients met eligibility with a completed collection of electrocardiograms, the Hamilton Depression Rating Scale (HDRS; clinician-rated depression), and the Hamilton Anxiety Scale (HAS; clinician-rated anxiety) to assess the severity of symptoms. Both main and interaction effects between HDRS and HAS on HRV parameters were examined.
Results: Significant interaction effects between clinician-rated depression and anxiety (HDRS × HAS) on HRV reduction in frequency parameters (i.e., nuLF, nuHF, LF/HF ratio) were found, which consistently indicated autonomic nervous system dysregulation. Findings imply that HRV could reflect synergistic effects of comorbid depressive and anxiety symptoms, perhaps due to the amplification of individual symptoms in geriatric patients.
Conclusions: The results imply that using objective measurements can improve diagnostic accuracy, particularly in geriatric patients with comorbid status, and the normalization of the autonomic nervous system might be a candidate target for prevention and treatment.

1. Introduction

Older adults—people aged 65 years and over in this study—are at risk of developing mental health challenges [1]. One of these most common challenges is depressive and anxiety symptoms. It is estimated that in the U.S. 1.4 %–4.8 % of older adults suffer from severe mental illnesses [1]. Most anxiety and depressive disorders, as "bidirectional risk factor(s) for one another" [2], are predicted

* Corresponding author. Department of Psychiatry, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul, 06273, Republic of Korea.
E-mail address: ojuojuoju@yuhs.ac (J. Oh).

https://doi.org/10.1016/j.heliyon.2023.e20740
Received 1 November 2022; Received in revised form 30 September 2023; Accepted 5 October 2023
Available online 7 October 2023

with similar degrees of strength. As comorbid status can be defined as the presence of more than one disease and the relative risk of developing one in the background of another, the interaction effects on depression and anxiety need to be considered from the perspective of comorbidity [3,4]. Geriatric depression frequently occurs in conjunction with anxiety or comorbid anxiety disorders [5,6], which are associated with greater severity of depression [3] with reported comorbidity of 50%–90 % [7]. Previous studies have shown that the combined manifestation of these symptoms is linked to the need for larger drug doses [2], slower/poorer treatment outcomes [8,9], higher cardiovascular burden [10], and increased mortality [11,12].

However, most mental health conditions are widely under-recognized and often untreated among geriatric populations, perhaps as a result of age-related diagnostic variations. Indeed, age-related changes in physical and neurological functioning can lead to atypical manifestations of psychiatric illness in psychiatric patients of varying ages [5,13]. For example, late-life depression is characterized by atypical variants, which involve emotional complaints (e.g., sadness, feeling of guilt, anhedonia) and more somatic features (e.g., sleep disturbances, loss of appetite and weight, persistent pain) compared to those in younger populations [11]. Additionally, cultural norms may have made them less aware of distressing internal psychological states than younger people, so older adults are less self-disclosing [1,14]. Thus, objective markers and scales used to assess depression and anxiety should be considered to improve the accuracy of evaluation; clinician-rated scales and heart rate variability (HRV) are promising candidates.

Clinician-rated scales would benefit diagnostic accuracy, especially when they are applied to patients with poor mental health literacy. In most clinical settings, psychiatric symptoms are assessed using both clinician ratings and self-report questionnaires. Evidence has shown moderate-to-strong correlations between the two modes, implying the potential measurement interchangeability [15,16]. However, some studies found significant discrepancies between the two modes (e.g., Refs. [15,17]), suggesting that clinician-rated measurements may be preferred because they exclude a participant's personality and/or selection bias. Moreover, results from the meta-analytic study on the compared effect sizes of the two types of measurements have indicated a small but statistically-significant advantage for ratings done by clinicians compared to self-rated symptoms, specific to the targeted group such as older adults [17]. As older adults tend to under-report their depressive symptoms, unique information that is not accessible by self-report can be obtained using a clinician-rated scale [14]. Particularly, considering the higher correlation between clinician-rated depression (the 17-item *Hamilton Rating Scale for Depression, HRSD)* and anxiety (the 14-item *Hamilton Anxiety Scale, HAS*) in more severe groups [16], these measurements may be especially effective for older adults with severe psychiatric symptoms.

HRV can also be used as a mental health indicator of clinical diagnosis [18](Liu et al., 2020), especially that of cardiovascular diseases (CVD). HRV is mediated through the dynamic interplay of parasympathetic and sympathetic (vagus nerve) neuron systems and reflects the capacity for the parasympathetic inhibition of autonomic arousal [12]. Various HRV indices include time and frequency domains with nonlinear measurements [19]. Generally, increased HRV is a relevant marker of a healthy autonomic nervous system (ANS) that reflects greater adaptability to changing environmental demands, whereas decreased HRV is a sign of autonomic inflexibility that can be linked to psychiatric disorders [20]. Evidence suggests that both normal aging and emotional distress are associated with reduced HRV [21,22], so that investigating the clinical relevance of cardiac autonomic changes with late-life psychiatric symptoms is needed. Several meta-analytic studies on the relationships between psychiatric symptoms and HRV have indicated that reduced HRV parameters can frequently be found in patients with an anxiety disorder (AD) [23] and/or major depressive disorder (MDD) [24,25]. This supports the notion that anxiety and/or depressive symptoms may influence ANS regulation with a decreased parasympathetic nervous system [25,26], especially in the elderly population [24,27,28].

Certain associations were found between HRV and psychiatric status; parasympathetic vagal tone may be associated with regulating allostatic systems, emotional control, and global health. It is well understood that both depression and anxiety are highly correlated with decreased HRV; however, detailed studies on the difference in HRV between the two or those on the interaction effects of depression and anxiety on HRV parameters are scarce. Cardiac vagal tone, representing the parasympathetic nervous system in MDD, is driven or exacerbated by co-occurring anxiety [12,29], especially in older geriatric patients [25]. Thus, we postulate a particular association between depression/anxiety and certain HRV parameters. However, studies addressing the psychiatric interaction effects in specific age groups are lacking. Therefore, this study aimed to identify objective psychiatric indicators in geriatric patients with emotional distress using HRV. Specifically, we attempted to find a possible interaction effect of geriatric depression and anxiety on HRV parameters.

2. Materials & methods

2.1. Participants

At the psychiatric outpatient clinic of a university hospital in South Korea (Gangnam Severance Hospital, Seoul), for a routine examination, we retrospectively collected from the electronic medical record (EMR) system the clinical and physiological HRV data of patients with either depression or anxiety symptoms at their first visit. A total of 160 outpatients met the eligibility criteria after the first demographic screening: 1) outpatients at the first psychiatric examination that completed the assessment of HRV, and 2) patients older than 65. Patients with severe medical disease or cognitive disorders that would impede performing HRV procedures and current manic or psychotic symptoms were excluded. Thirteen patients failed to complete all the clinician-rated measurements. Thus, 114 patients aged 65 years or older were finally included. Our study utilized data obtained from the existing clinical process, and informed consent was waived. The study design and protocol were approved by the Institutional Review Board of Yonsei University Gangnam Severance Hospital (3-2022-0009).

2.2. Measures

2.2.1. Clinician-rated depression, anxiety

Depression and anxiety were assessed using the 17-item Hamilton Depression Rating Scale (HDRS) [30] and 14-item Hamilton Anxiety Scale (HAS) [31] respectively, which have been widely used in clinical settings. Both are clinician-administered scales that measure the severity of each symptom with good reliability and validity. The HDRS was developed to assess melancholic and physical symptoms of depression, and both psychic and somatic anxieties were measured. Each item is scored on a scale of 0 (absent) to 4 (severe), with higher scores indicating more severe symptoms.

2.2.2. Heart rate variability

The intervals between consecutive heartbeats (R–R interval) were recorded for 5 min at a sampling frequency of 500 Hz using an SA-3000P arterial testing device (LAXTHA Co., Ltd., and Medicore Co., Ltd., Seoul, South Korea), which provides valid measures with respect to an electrocardiogram (ECG). Participants were placed in a sitting position in a quiet and comfortable room, and electrodes were used on both their wrists and left ankles during the procedure. Trained psychiatrists and clinical psychologists performed data acquisition, and all data were manually inspected to remove noise from the ECG before analysis. Cleaned R–R interval data were imported into MATLAB 2017b (Mathworks, Inc., MA, United States), and time and frequency measures were calculated. The measured time-domain indices were: (1) mean heart rate (HR), (2) standard deviation of R–R intervals (SDNN), (3) the square root of the mean squared differences between successive R–R intervals (RMSSD), and (4) the difference in the percentage of the number of pairs in R–R intervals by more than 50 m/s in the entire recording (pNN50). The frequency-domain indices included: (a) total power (TP; 0–0.5 Hz) of the HRV spectrum, which indicates the overall autonomic activity; (b) a low-frequency (LF; 0.04–0.14 Hz), which consists of a combination of sympathetic and parasympathetic effects; (c) a high-frequency (HF; 0.15–0.50 Hz), which is modulated by the parasympathetic activity of the ANS; and (d) the ratio of low-frequency to high-frequency (LF/HF) ratio, which reflects the sympathovagal interaction [32](Molina et al., 2021). Because some parameters showed non-normality, normalization (e.g., normalized units of LF, HF; nuLF, nuHF) and natural log transformation (e.g., SDNN, RMSSD, TP, LF/HF ratio) were employed.

2.2.3. Demographical and clinical variables, and other covariates

Demographic status included sex (dummy-coded as female = 0, male = 1) and age (65–87 years). Additionally, the other covariates that could affect detailed HRV parameters were controlled: device type, cardioactive medication use, CVD diagnosis, diagnosis of cognitive disorders, BMI, and vital signs, including blood pressure and respiratory rate. Specifically, two different devices were used to measure HRV; thus, we added device type (0 = LAXTHA Co. Ltd. in Daejeon, South Korea, 1 = Medicore Co. Ltd. In Kyounggi, South Korea) as a dummy covariate in the analyses. Additionally, cardioactive medication use was determined by the hospital's EMR system based on the classification of the World Health Organization Anatomical Therapeutic Chemical (ATC) codes [33,34](WHO, 2011; O'Regan et al., 2015). Cardioactive medication was dummy-coded with the following ATC codes: *C02: antihypertensive drugs, C03: diuretic drugs, C04: peripheral vasodilator drugs, C05: vasoprotective drugs, C07: beta-blocking agents, C08: calcium-channel blockers*. Dichotomous variables (1 = yes, 0 = no) for CVD diagnosis were also employed in the analyses. As vital signs, including BMI, blood pressure and respiratory rate, are measured routinely and commonly measured in outpatients patients, we used the values on the day of the HRV measurement.

2.3. Statistical analyses

Descriptive statistics and Pearson correlation analysis were conducted to examine associations between the variables of interest. Multiple linear regression was applied to analyze the main and interaction effects of HRSD and HAS on HRV parameters. Models 1 shows the main effects of primary predictors of the basic confounders, and Models 2 displays the interaction effects of primary predictors of the basic confounders in the time and frequency domains. Furthermore, we utilized the interaction term (HDRS × HAS) to assess comorbid status rather than applying cutoff scores for the following reasons. First, comorbid status tends to be associated with variability in the presentation of original conditions. For example, the combination of depression and anxiety may result in additional symptoms (e.g., overextension) and/or greater severity than in the initial condition [3,4]. Thus, applying interaction effects in comorbid psychopathology can even reflect sub-threshold symptoms that might have been ignored when applying the cutoff scores, which assume that symptoms are only meaningful as indicators of a disorder. 2) Additionally, some limitations of each scale (e.g., HDRS = non-assessment of atypical symptoms of depression; HAS = poor at discriminating comorbid depression status) might be associated with the characteristic features of elderly patients (see Refs. [35,36]). Thus, applying the suggested cutoff scores might be less accurate in identifying geriatric patients because of the low sensitivity and/or specificity concerns. 3) Additionally, the 2 × 2 factorial design by categorizing groups based on cutoff scores could statistically increase the potential risk of information loss and type 1 and/or 2 errors [37,38], using the interaction term would be beneficial in our sample. All statistical analyses were conducted using STATA 16.0.

3. Results

3.1. Sample characteristics

Table 1 presents the characteristics of the study participants. The majority of the sample was female (72.8 %, n = 83) and ranged in

age from 65 to 70 years (46.5 %, n = 53). In the last six months, 47.4 % (n = 54) of the participants had a history of cardio-active medication use and 25.4 % (n = 29) had been diagnosed with CVD. The most prevalent type of DSM-5 diagnosis category was depressive disorders (68.4 %, n = 78), followed by anxiety disorders (59.6 %, n = 68), and neurocognitive disorders (33.3 %, n = 38). Others (5.2 %, n = 6) included psychotic disorders (n = 3) and alcohol dependence (n = 3). All participants showed respiratory rate within the elderly normal range (12-25bpm) [39]. Approximately 50.0 % met the criteria of HDRS, HAS cutoff for moderate-to-severe depression and anxiety symptoms.

3.2. Correlations of the variables of interest

Pearson's correlation analysis (Fig. 1) was conducted among the variables of interest, a few of which showed a significant relationship. The HDRS was positively correlated with HAS ($r = 0.677$. $p < .001$), mean HR ($r = 0.221$, $p < .05$), nuLF ($r = 0.218$, $p < .05$), LF/HF ratio ($r = 0.291$, $p < .01$), and negatively with nuHF ($r = -0.198$, $p < .05$). HAS was associated with the nuLF ($r = 0.281$, $p < .01$), nuHF ($r = -0.271$, $p < .01$), and LF/HF ratio ($r = 0.290$, $p < .01$).

3.3. Model analysis

Table 2 shows associations between primary predictors (HRSD, HAS) and the time and frequency domains after accounting for baseline covariates. Primary predictors in Models 1 did not show a significant association with any HRV parameters. However, the interaction term (HRSD × HAS) was statistically significant in Model 2, except for Mean HR. Specifically, as illustrated in Fig. 2, the interaction term was positively associated with each of nuLF ($t = 2.16$, $p < .05$), LF/HF ratio ($t = 2.03$, $p < .05$) and negatively associated with nuHF ($t = -2.15$, $p < .05$). Gender, age, systolic blood pressure, and diagnosis of neurocognitive disorders were

Table 1
Characteristics of the sample (n = 114).

	Value
Gender, n (%)	
Male	31 (27.2)
Female	83 (72.8)
Age (years), n (%)	
65–70	53 (46.5)
71–75	35 (30.7)
76–80	15 (13.2)
81+	11 (10.6)
Cardioactive medication use[a]*, n (%)*	
No	60 (52.6)
Yes	54 (47.4)
CVD diagnosis[a]*, n (%)*	
No	85 (74.6)
Yes	29 (25.4)
DSM-V diagnosis category[b]*, n (%)*	
Category of depressive disorders	78 (68.4)
Category of anxiety disorders	68 (59.6)
Category of neurocognitive disorders	38 (33.3)
Category of sleep-wake disorders	28 (24.5)
Category of somatic symptom disorders	10 (8.7)
Others	6 (5.2)
BMI, n (%)	
Underweight to normal (≤24.9)	82 (71.9)
Overweight (25.0–29.9)	24 (21.1)
Obese (≥30)	8 (7.0)
Respiratory rate, mean (range)	18.60 (12–22)
Blood pressure, mean (range)	
Systolic	130.57 (94–191)
Diastolic	78.03 (40–102)
HRSD	
Normal to mild (≤16)	57 (50.0)
Moderate (17–23)	41 (35.9)
Severe (≥24)	16 (14.1)
HAS	
Normal to mild (≤17)	55 (49.1)
Moderate (18–24)	34 (30.4)
Severe (≥25)	23 (20.5)

Note.
[a] in the last 6 months; CVD = cardiovascular disease; HRSD=Hamilton Rating Scale for Depression; HAS=Hamilton Anxiety Scale.
[b] Participants could be given more than one diagnosis.

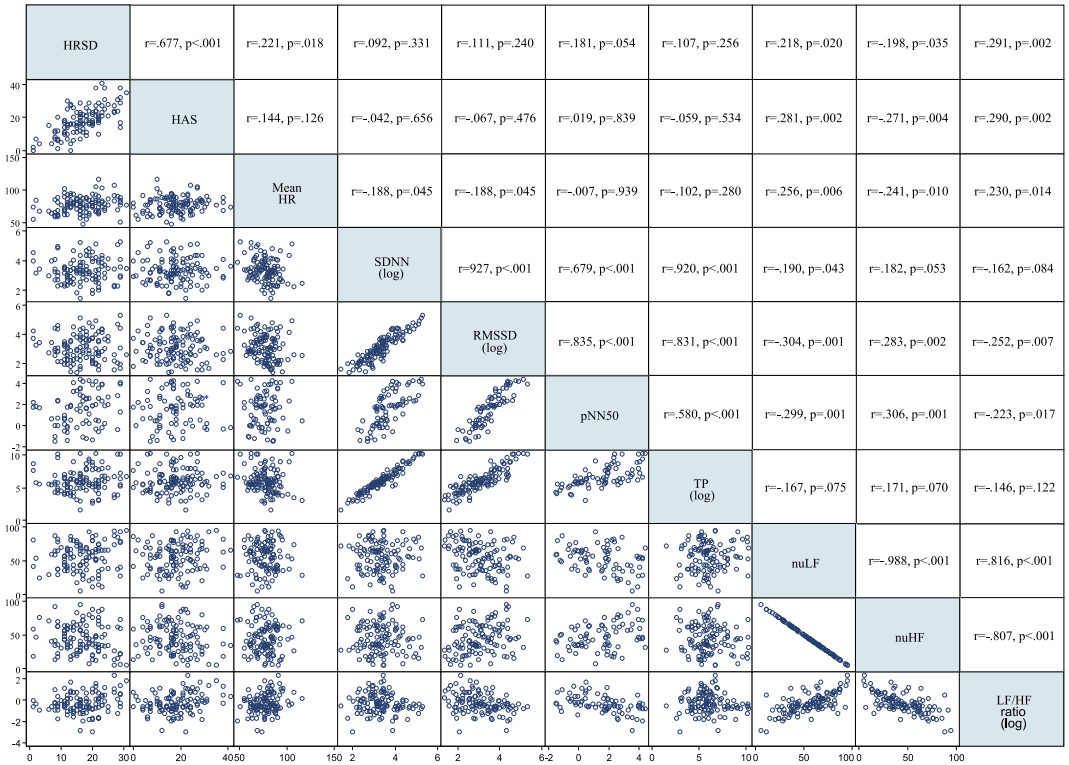

Fig. 1. Correlation matrix for all variables of interest (n = 114).
Note. HDRS=Hamilton Depression Rating Scale; HAS=Hamilton Anxiety Scale; HR = heart rate; SDNN = standard deviation of NN intervals; RMSSD = root mean square of differences of successive RR intervals; pNN50 = proportion of successive RRI > 50 m/s in relation to the total RRI; TP = total power; nuLF = normalized low frequency units; nuHF = normalized high frequency units.

significantly associated with HRV indices among baseline covariates. Females had significantly lower values than males in the time domain index, except for the mean HR. Aging and diagnosis of neurocognitive disorders showed an increasing trend in both time and frequency domains, which may reflect the increased parasympathetic activity. With regard to the potentially significant effects of CVD on HRV, additional analysis was conducted based on a sample excluding CVD diagnosis. In line with results from all samples, interaction effects were significant in LF/HF ratio. More detailed results of the sample without CVD diagnosis are provided in Supplementary Table 1.

4. Discussion

The current study aimed to investigate whether clinician-rated scales could potentially indicate comorbid anxiety and depressive symptoms among geriatric patients. As the mental health of the elderly can be characterized by prevalent comorbidity and atypical variants, objective measurements to understand a combined manifestation play a key role in refining the diagnosis and selecting a treatment strategy. However, studies focusing on elderly clinical populations are still lacking. Thus, this study aimed to provide further insight into the relationship between clinician-rated scales and HRV parameters in an elderly clinical population to improve diagnostic accuracy and elucidate the characteristics of ANS function.

In general, previous HRV studies with 5 min of short-term measurement reported that the results are only reliable under the conditions of breath at normal ranges (11–20 bpm) and consistently showed greater LF power, lower HF power, and greater LF/HF ratio with age [19]. However, multiple linear regression analyses revealed that the main effects of both HDRS and HAS were not associated with any HRV parameters. Several HRV meta-analyses have indicated direct HRV reductions in subjects with anxiety [23,40] and depression [24,25]. For example, Ha et al. [41] compared differences between thirty MDD groups over 60 years and control HRV group obtained from short-term using 5-min ECG. The MDD subjects showed significantly lower time and frequency domains. In a 24-h ECG recording study focusing on the impact of depression on HRV in geriatric patients with CAD, Luo et al. [42] reported decreased HRV in depressive patients. This inconsistency may result from individual variability in the normal process of aging, which involves impairments in cognitive functioning, and deterioration of cardiovascular status. A recent meta-analysis focusing on HRV decline in geriatric patients with depression suggests that cardiovascular aging is a more plausible mechanism than pharmacogenetic moderation [24]. In fact, HRV can vary according to age and pathological conditions [43,44], especially in the elderly [45,46].

Our results showed that aging was associated with an increasing trend in the frequency domains. In contrast, the general trend of most HRV parameters confirms a reduced trend associated with increasing age [19]. However, this tendency is mainly observed in

Table 2
Standardized beta coefficients from linear regression models on the association between HDRS, HAS and HRV parameters.

	Main effects (Model 1)								Interaction effects (Model 2)							
	Mean HR		nuLF		nuHF		LF/HF ratio (log)		Mean HR		nuLF		nuHF		LF/HF ratio (log)	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
Primary predictors																
HRSD	1.40	.166	1.33	.188	−1.32	.188	0.33	.744	1.12	.263	−0.93	.353	0.93	.353	−.143	.155
HAS	−0.01	.989	0.09	.932	−0.09	.932	1.72	.088	0.32	.747	−1.87	.064	1.87	.065	−0.98	.328
HDRS × HAS									−0.37	.711	2.16*	.034	−2.15*	.034	2.03*	.045
Baseline covariates																
Gender (0 = female)	2.32*	.023	−0.16	.873	0.16	.874	−1.05	.297	2.30*	.024	−0.12	.905	0.12	.906	−1.02	.309
Age	−0.23	.819	−2.61*	.010	2.61*	.010	−2.74**	.007	−0.19	.852	−2.87**	.005	2.87**	.005	−2.98**	.004
BMI	−1.40	.164	−0.06	.953	0.06	.953	−0.83	.410	−1.44	.153	0.36	.716	−0.36	.717	−0.43	.671
Breath (bpm)	−0.00	.996	−1.37	.172	1.38	.171	−0.94	.348	−0.07	.944	−0.99	.322	1.00	.321	−0.58	.562
Systolic BP	0.38	.703	2.23*	.028	−2.23	.028	1.20	.234	0.35	.725	2.42*	.017	−2.42*	.017	1.36	.178
Diastolic BP	−0.31	.759	−0.78	.438	0.78	.438	−1.29	.201	−0.27	.784	−0.97	.334	0.97	.334	−1.47	.144
Neurocognitive disorders	−0.38	.706	2.66**	.009	−2.66**	.009	2.71**	.008	−0.30	.764	2.26*	.026	−2.26*	.026	2.33*	.022
Device types[a]	0.06	.951	−1.59	.115	1.59	.116	−0.39	.696	0.08	.936	−1.73	.087	1.73	.087	−0.50	.615
Cardioactive medication use	−0.31	.758	−0.38	.701	0.38	.702	0.42	.678	−0.28	.778	0.53	.595	0.53	.596	0.29	.774
CVD diagnosis[b]	−0.99	.328	−0.94	.351	0.94	.352	−1.45	.150	−1.00	.321	−0.88	.380	0.88	.381	−1.41	.163
N	114		114		114		114		114		114		114		114	
F	1.31		2.12*		2.12*		2.66**		1.21		2.38**		2.38**		2.84**	
adj R^2	.031		.106		.106		.149		.023		.137		.137		.174	

*p < .05, **p < .01, ***p < .001.

Note. HR = heart rate; nuLF = normalized low frequency units; nuHF = normalized high frequency units; HRSD=Hamilton Rating Scale for Depression; HAS=Hamilton Anxiety Scale; BP=Blood pressure.

[a] Dummy-coded: 0 = Type 1(LAXTHA Co., Ltd.), 1 = Type 2(Medicore Co., Ltd.).

[b] CVD = cardiovascular disease.

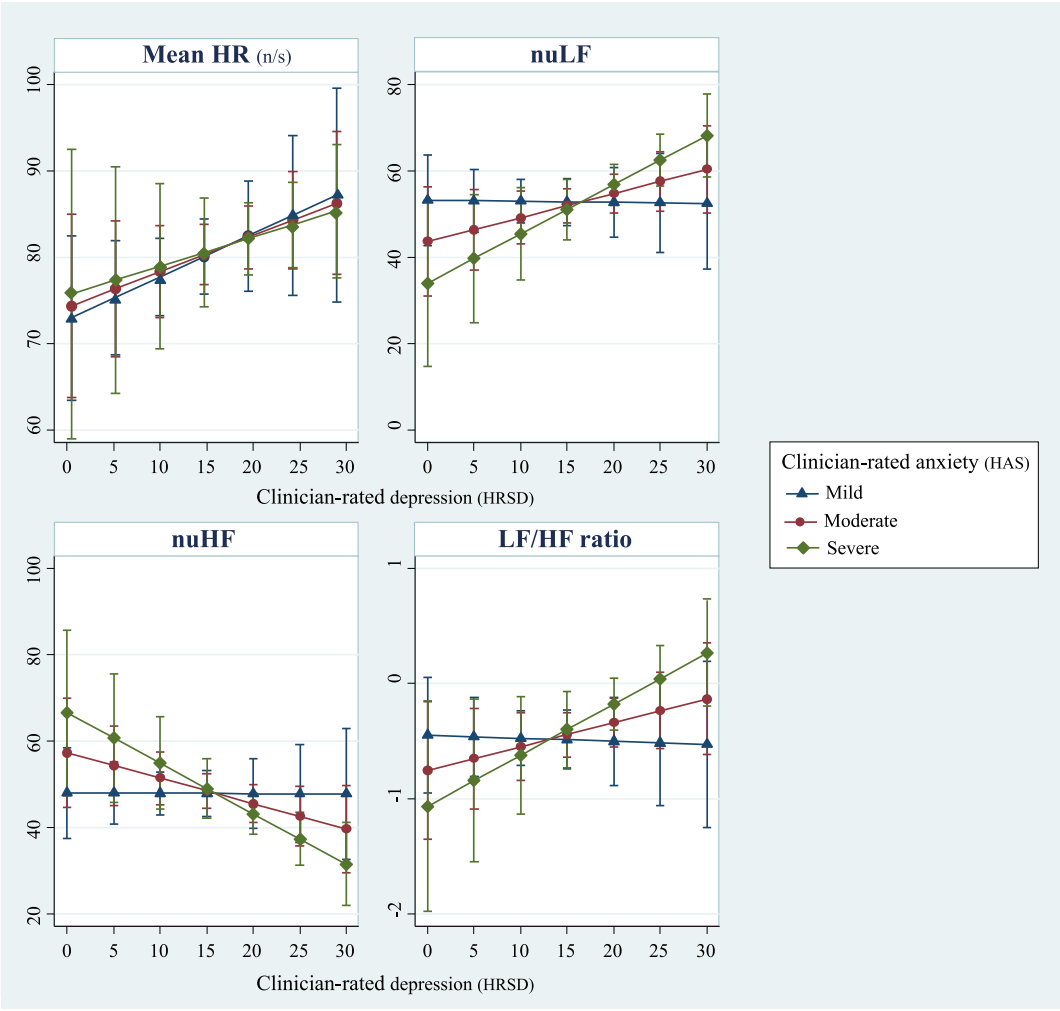

Fig. 2. Interaction effects between clinician-rated depression and anxiety on HRV parameters.

younger and/or healthy subjects [24], whereas inconsistent evidence has been reported in older adults due to great individual variability [21,43,45,46]. This can be attributable to the fact that "aging is the main factor that impacts cardiac autonomic control; therefore, knowledge of the HRV patterns in the elderly may display unexpected findings" [47]. Geovanini et al. [47] investigated the differences in HRV measures by age and showed that, although most HRV parameters decreased as age increased in general, nonlinear relationships were found; HF showed an increasing tendency, and RMSSD and pNN50 showed a reversal increase over 60 years of age. Recent biological psychiatric evidence showed that both ANS and sinoatrial node (SAN) dysfunctions determine decreased HRV, which is highly prevalent in aging [48,49]. Considering SAN and ANS contribute mainly to long- and short-term HRV [49], the current results might mainly correspond to the ANS contribution to short-term variability. Furthermore, Stein et al. [45] found that age-related values for HF declined in 70–74 years compared to 65–69 years; however, no further decline over 75 years was observed. These nonlinear relationships could indicate that a U-shaped pattern in the parasympathetic indices may be related to age-related autonomic dysfunction, as aging is closely associated with cardiac autonomic control. In summary, as age-related autonomic dysfunction can elicit HRV changes, the interpretation of aging effects on HRV, especially in subjects over 65 years of age, needs to be considered with caution. Additionally, our results add to the evidence that depression and anxiety in clinical geriatric populations may have physiological distinctions from those in the younger and/or general populations.

Notably, we found significant interaction effects between depression and anxiety on HRV reduction in frequency parameters, indicating ANS dysregulation via parasympathetic activity. Our novel findings imply that HRV domains with 5-min ECG monitoring reflect synergistic effects of depressive and anxiety symptoms, perhaps as a result of the amplification of individual symptoms in geriatric patients. Even though short records are suitable for outpatients due to their clinical utility, a long-term HRV analysis (24-h) better represents the response to environmental stimuli [19]. As both methods are not interchangeable but complementary, a decrease in the parasympathetic modulations can be explained by comorbid depression and anxiety of elderly outpatients [43]. Also, Thayer et al. [50] reported the association between neurocognitive impairments and lower HRV (especially for HF), which was in line with the

previous findings while significant comorbid effects of depression and anxiety were maintained. Considering that the neurocognitive impairments and psychiatric symptoms in older adults are closely intertwined [51], both reported bidirectional causality of the associations, which, in turn, contributed to autonomic inflexibility.

Broad evidence, based on Massimo Pagani's groups, presented an HRV model [52,53] that supports three core statements: (1) the power of the HF component can be taken as an index of cardiac parasympathetic tone; (2) the LF component is a marker of cardiac sympathetic outflow, and (3) the LF/HF ratio is an index of sympathetic cardiac control and autonomic balance [40,53,54]. Thus, anxiety or depression status in older adults is associated with impaired ANS down-regulation via parasympathetic activity, indexed by lower HF, higher LF and LF/HF ratios. It could be explained that a reduced parasympathetic activity might be a trait index for increased vulnerability to psychiatric disorders [20,55]. This view of HRV as a universal vulnerability marker is supported by evidence that HRV reduction is also a risk factor contributing to the severity of psychiatric disorders, such as anxiety, mood, and psychotic disorders [21, 22]. On this basis, higher psychophysiological interactive effects can be predicted in patients with comorbid symptoms. Multiple disorder pairs may result in additional symptoms and/or greater severity than the non-comorbid initial condition [3]. Thus, HRV might be a transdiagnostic biomarker of the psychopathological vulnerability of comorbid symptoms but not a specific biomarker of a single diagnosis [20,54]. Another potential explanation is based on the cumulative effect (i.e., combining the psychophysiological impact of the two disorders). Previous research [12,29] has shown that HRV reductions in MDD are associated with decreased cardiac vagal control (CVC), mainly owing to comorbid anxiety status. Kemp et al. [12] explained that comorbid patients characterized by worry and hypervigilance may have more difficulty disengaging from threat detection, which may lead to chronic withdrawal of parasympathetic nervous system activity, overactivation of sympathetic nervous system activity, and long-term reductions in HRV, subsequently increasing the risk for CVD [12]. Moreover, SAN receptors which are the pacemaker of the heart showed age-related deterioration [47, 56], elderly patients with psychiatric disorders showed greater CVD risk with ANS dysregulations [42,41]. Thus, even though few studies investigated the association between psychiatric disorders and SAN alterations, it can be assumed that geriatric patients coupled with comorbid depression and anxiety may have deteriorated SAN receptors significantly, resulting in a lower HRV. In summary, HRV might be considered a reflection of the synergistic effects between anxiety and depression, which the interaction may further amplify.

HF is proved as one of the most parasympathetic-specific markers [40,54], suggesting that HF is a peripheral index of psychopathology that is partly heritable and partly socialized and is associated with global impairment and cognitive dysfunction [54]. However, the physiological meaning of both LF and LF/HF ratio is somewhat controversial, and some recent studies have suggested counter-evidence against traditional views; LF may be determined by the parasympathetic activity [53] or modulation of cardiac autonomic outflows by baroreflexes [57]. The interpretation LF/HF ratio cannot accurately quantify cardiac sympathovagal balance either in health or disease owing to its association with HR (lower at slower HR and higher at faster HR), and mathematical considerations between LF and HF (ref. [58]). Although the relevant mechanisms are not entirely understood, inconsistency in the literature might have been due to the heterogeneity of the study sample., i.e. the age, sex, diagnosis, and specifically the comorbidity status. Thus, recent evidence-based interpretations may be disturbed by 1) dysfunction of the cardiac ANS, especially in the context of the elderly population, and 2) single disorders such as depression, which are etiologically heterogeneous, especially in geriatric patients [5,13]. This adds to the evidence that depression in geriatric patients may have physiological distinctions from depression in younger and/or general populations and that comorbid status might be a candidate target for future research on the prevention, diagnosis, and treatment of psychological conditions in geriatric patients.

Several limitations of the present study warrant further discussion. First, all participants in this study, with relatively small sample size, were diagnosed with more than one psychiatric disorder based on the DSM-5 criteria. Thus, although the findings of this study cannot be generalized to the entire elderly population, they can be used as a basis for further physiological studies on geriatric depression and anxiety on HRV parameters. Second, based on the existing study design of CVD diagnosis and cardioactive medication use (e.g., Refs. [34,59]), we included participants regardless of both conditions in the last six months and controlled for these in the model analysis. While controlling for these variables addresses statistical confounding, the interaction effects between HRSD and HAS in the present results may further need to be conducted in samples without these exogenous effects. Third, the potential effects of the use of antidepressants on HRV parameters should be considered in the results [12,34,60]. A previous longitudinal NESDA study (Netherlands Study of Depression and Anxiety, N = 6994) by Hu et al. [60], investigating HRV in depression and anxiety disorders, suggested that current depression/anxiety status is not directly associated with cardiac autonomic dysregulation, but with the use of antidepressants. As the HRV records of the current sample were obtained in the first outpatient visit, most of the antidepressants' effects might be excluded in this study design. However, prescription records are not completely shared between the community clinic and the university hospital; some patients may have already been prescribed the medications in community-based clinics before visiting the university hospital. Forth, although a 5-min measurement of HRV in a controlled environment can be methodologically adequate [61], HRV variation may be influenced based on the time of the day. As ECG data of the sample had been performed their usual day time, methodological limitations should be considered when interpreting the results. Fifth, due to the limited sample size, we did not apply Bonferroni correction in the p-level setting and applied the usual significance level. However, we calculated appropriate sample size applying a medium effect size ($f2 = 0.15$) and robust power (=0.95) of 13-predictor variable equation for linear multiple regression using G*Power 3.1. As a results, required sample size are at least 107, ensures that the sample size and power of the study are appropriate that the results are valid. However, future analyses with more samples and p-value correction will be necessary.

5. Conclusion

The present study examined the interaction effects of clinician-rated depression and anxiety on HRV in geriatric clinical samples.

The interaction term between depression and anxiety showed significant reductions in the frequency-domain parameters of HRV, which consistently indicated dysregulation of the autonomic nervous system in patients with comorbid depression and anxiety. The results imply that objective measures can improve diagnostic accuracy, particularly in geriatric patients with comorbid status, and normalization of the autonomic nervous system might be a candidate target for prevention and treatment.

Funding statement

This work was supported by the Industrial Technology Innovation Program (No. 20012603, Development of Emotional Cognitive and Sympathetic AI Service Technology for Remote (Non-face-to-face) Learning and Industrial Sites) funded By the Ministry of Trade, Industry & Energy (MOTIE, Korea).

Date availability statement

The authors do not have permission to share data.

CRediT authorship contribution statement

Joonbeom Kim: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Jae-Jin Kim:** Data curation, Resources, Supervision, Validation, Writing – review & editing. **Jeong-Ho Seok:** Resources, Supervision, Validation, Writing – review & editing. **Eunjoo Kim:** Data curation, Resources, Supervision, Validation, Writing – review & editing. **Jin Young Park:** Data curation, Resources, Supervision, Validation, Writing – review & editing. **Hesun Erin Kim:** Data curation, Formal analysis, Investigation, Validation, Writing – review & editing. **Jooyoung Oh:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Jooyoung Oh reports article publishing charges was provided by Korea Ministry of Trade Industry and Energy.

Acknowledgements

We thank all of the geriatric participants and Yonsei Gangnam Severance Oju Lab team that made this study possible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20740.

References

[1] SAMHSA, Older Adults Living with Serious Mental Illness: the State of the Behavioral Health Workforce, 2018. Retrieved from, https://store.samhsa.gov/product/Older-Adults-Living-with-Serious-Mental-Illness-The-State-of-the-Behavioral-Health-Workforce/PEP19-OLDERADULTS-SMI.
[2] N.C. Jacobson, M.G. Newman, Anxiety and depression as bidirectional risk factors for one another: a meta-analysis of longitudinal studies, Psychol. Bull. 143 (11) (2017) 1155.
[3] J.W. Keeley, M.S. Chmielewski, R.M. Bagby, Interaction effects in comorbid psychopathology, Compr. Psychiatr. 60 (2015) 35–39.
[4] J. Keeley, R.K. Blashfield, Clinicians' conceptualizations of comorbid cases: a test of additive versus nonadditive models, J. Clin. Psychol. 66 (10) (2010) 1121–1130.
[5] D.V. Jeste, D.G. Blazer, M. First, Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients, Biol. Psychiatr. 58 (4) (2005) 265–271.
[6] E.J. Lenze, B.H. Mulsant, M.K. Shear, H.C. Schulberg, M.A. Dew, A.E. Begley, C.F. Reynolds III, Comorbid anxiety disorders in depressed elderly patients, Am. J. Psychiatr. 157 (5) (2000) 722–728.
[7] I. Skoog, Psychiatric disorders in the elderly, Can. J. Psychiatr. 56 (7) (2011) 387–397.
[8] A.G. Galyamina, I.L. Kovalenko, D.A. Smagin, N.N. Kudryavtseva, Interaction of depression and anxiety in the development of mixed anxiety/depression disorder. Experimental studies of the mechanisms of comorbidity, Neurosci. Behav. Physiol. 47 (2017) 699–713.
[9] E.J. Lenze, B.H. Mulsant, M.A. Dew, M.K. Shear, P. Houck, B.G. Pollock, C.F. Reynolds III, Good treatment outcomes in late-life depression with comorbid anxiety, J. Affect. Disord. 77 (3) (2003) 247–254.
[10] C. Andreescu, S. Lee, Anxiety disorders in the elderly, Anxiety Disorders (2020) 561–576.
[11] V. Morichi, G. Dell'Aquila, F. Trotta, A. Belluigi, F. Lattanzio, A. Cherubini, Diagnosing and treating depression in older and oldest old, Curr. Pharmaceut. Des. 21 (13) (2015) 1690–1698.
[12] A.H. Kemp, D.S. Quintana, K.L. Felmingham, S. Matthews, H.F. Jelinek, Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk, PLoS One 7 (2) (2012), e30777.
[13] T.R. Skinner, I.A. Scott, J.H. Martin, Diagnostic errors in older patients: a systematic review of incidence and potential causes in seven prevalent diseases, Int. J. Gen. Med. 9 (2016) 137.

[14] J.M. Lyness, C. Cox, J. Curry, Y. Conwell, D.A. King, E.D. Caine, Older age and the underreporting of depressive symptoms, J. Am. Geriatr. Soc. 43 (3) (1995) 216–221.
[15] A.J. Rush, T.J. Carmody, H.M. Ibrahim, M.H. Trivedi, M.M. Biggs, K. Shores-Wilson, T.M. Kashner, Comparison of self-report and clinician ratings on two inventories of depressive symptomatology, Psychiatr. Serv. 57 (6) (2006) 829–837.
[16] R. Uher, R.H. Perlis, A. Placentino, M.Z. Dernovšek, N. Henigsberg, O. Mors, A. Farmer, Self-report and clinician-rated measures of depression severity: can one replace the other? Depress. Anxiety 29 (12) (2012) 1043–1049.
[17] P. Cuijpers, J. Li, S.G. Hofmann, G. Andersson, Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis, Clin. Psychol. Rev. 30 (6) (2010) 768–778.
[18] I. Liu, S. Ni, K. Peng, Happiness at your fingertips: assessing mental health with smartphone photoplethysmogram-based heart rate variability analysis, Telemedicine and e-Health 26 (12) (2020) 1483–1491.
[19] F. Shaffer, J.P. Ginsberg, An overview of heart rate variability metrics and norms, Front. Public Health (2017) 258.
[20] S. Neyer, M. Witthöft, M. Cropley, M. Pawelzik, R.G. Lugo, S. Sütterlin, Reduction of depressive symptoms during inpatient treatment is not associated with changes in heart rate variability, PLoS One 16 (3) (2021), e0248686.
[21] B.S. Tegegne, T. Man, A.M. van Roon, H. Riese, H. Snieder, Determinants of heart rate variability in the general population: the Lifelines Cohort Study, Heart Rhythm 15 (10) (2018) 1552–1558.
[22] M. Reardon, M. Malik, Changes in heart rate variability with age, Pacing Clin. Electrophysiol. 19 (11) (1996) 1863–1866.
[23] J.A. Chalmers, D.S. Quintana, M.J. Abbott, A.H. Kemp, Anxiety disorders are associated with reduced heart rate variability: a meta-analysis, Front. Psychiatr. 5 (2014) 80.
[24] L. Brown, C. Karmakar, R. Gray, R. Jindal, T. Lim, C. Bryant, Heart rate variability alterations in late life depression: a meta-analysis, J. Affect. Disord. 235 (2018) 456–466.
[25] C. Koch, M. Wilhelm, S. Salzmann, W. Rief, F. Euteneuer, A meta-analysis of heart rate variability in major depression, Psychol. Med. 49 (12) (2019) 1948–1957.
[26] E. Patron, S.M. Benvenuti, G. Favretto, C. Valfrè, C. Bonfà, R. Gasparotto, D. Palomba, Association between depression and heart rate variability in patients after cardiac surgery: a pilot study, J. Psychosom. Res. 73 (1) (2012) 42–46.
[27] P. Spinhoven, D.C. Van der Veen, R.O. Voshaar, H.C. Comijs, Worry and cognitive control predict course trajectories of anxiety in older adults with late-life depression, Eur. Psychiatr. 44 (2017) 134–140.
[28] R.D. Jindal, R.C. Vasko Jr., J.R. Jennings, A.L. Fasiczka, M.E. Thase, C.F. Reynolds III, Heart rate variability in depressed elderly, Am. J. Geriatr. Psychiatr. 16 (11) (2008) 861–866.
[29] H.A. Chang, C.C. Chang, N.S. Tzeng, T.B. Kuo, R.B. Lu, S.Y. Huang, Generalized anxiety disorder, comorbid major depression and heart rate variability: a case-control study in Taiwan, Psychiatry investigation 10 (4) (2013) 326–335.
[30] M. Hamilton, A rating scale for depression, Journal of neurology, neurosurgery, and psychiatry 23 (1) (1960) 56–62.
[31] M. Hamilton, The assessment of anxiety states by rating, Br. J. Med. Psychol. 32 (1959) 50–55.
[32] G.E. Molina, C.J. da Cruz, K.E. Fontana, E.M. Soares, L.G.G. Porto, L.F. Junqueira Jr., Post-exercise heart rate recovery and its speed are associated with cardiac autonomic responsiveness following orthostatic stress test in men, Scand. Cardiovasc. J. 55 (4) (2021) 220–226.
[33] WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment 2012, 2011. Oslo.
[34] C. O'Regan, R.A. Kenny, H. Cronin, C. Finucane, P.M. Kearney, Antidepressants strongly influence the relationship between depression and heart rate variability: findings from the Irish Longitudinal Study on Ageing (TILDA), Psychol. Med. 45 (3) (2015) 623–636.
[35] N. Koerner, M.M. Antony, M.J. Dugas, Limitations of the Hamilton Anxiety Rating Scale as a primary outcome measure in randomized, controlled trials of treatments for generalized anxiety disorder, Am. J. Psychiatr. 167 (1) (2010) 103–104.
[36] D. Carrozzino, C. Patierno, G.A. Fava, J. Guidi, The Hamilton rating scales for depression: a critical review of clinimetric properties of different versions, Psychother. Psychosom. 89 (3) (2020) 133–150.
[37] Y.S. Seo, Testing mediator and moderator effects in counseling psychology research: conceptual distinction and statistical considerations, The Korean Journal of Counseling and Psychotherapy 22 (4) (2010) 114–1168.
[38] C.A. Mason, S. Tu, A.M. Cauce, Assessing moderator variables: two computer simulation studes, Educ. Psychol. Meas. 56 (1) (1996) 45–62.
[39] A. Rodríguez-Molinero, L. Narvaiza, J. Ruiz, C. Gálvez-Barrón, Normal respiratory rate and peripheral blood oxygen saturation in the elderly population, J. Am. Geriatr. Soc. 61 (12) (2013) 2238–2240.
[40] Y.C. Cheng, M.I. Su, C.W. Liu, Y.C. Huang, W.L. Huang, Heart rate variability in patients with anxiety disorders: a systematic review and meta-analysis, Psychiatr. Clin. Neurosci. 77 (6) (2022) 292–302.
[41] J.H. Ha, S. Park, D. Yoon, B. Kim, Short-term heart rate variability in older patients with newly diagnosed depression, Psychiatr. Res. 226 (2–3) (2015) 484–488.
[42] Y. Luo, S. Zhang, R. Zheng, L. Xu, J. Wu, Effects of depression on heart rate variability in elderly patients with stable coronary artery disease, J. Evid. Base Med. 11 (4) (2018) 242–245.
[43] L. Garavaglia, D. Gulich, M.M. Defeo, J. Thomas Mailland, I.M. Irurzun, The effect of age on the heart rate variability of healthy subjects, PLoS One 16 (10) (2021), e0255894.
[44] T. Shinba, N. Kariya, Y. Matsui, N. Ozawa, Y. Matsuda, K.I. Yamamoto, Decrease in heart rate variability response to task is related to anxiety and depressiveness in normal subjects, Psychiatr. Clin. Neurosci. 62 (5) (2008) 603–609.
[45] P.K. Stein, J.I. Barzilay, P.H. Chaves, P.P. Domitrovich, J.S. Gottdiener, Heart rate variability and its changes over 5 years in older adults, Age Ageing 38 (2) (2009) 212–218.
[46] M.A. Almeida-Santos, J.A. Barreto-Filho, J.L.M. Oliveira, F.P. Reis, C.C. da Cunha Oliveira, A.C.S. Sousa, Aging, heart rate variability and patterns of autonomic regulation of the heart, Arch. Gerontol. Geriatr. 63 (2016) 1–8.
[47] G.R. Geovanini, E.R. Vasques, R. de Oliveira Alvim, J.G. Mill, R.V. Andreão, B.K. Vasques, J.E. Krieger, Age and sex differences in heart rate variability and vagal specific patterns-baependi heart study, Global Heart 15 (1) (2020) 71, 71.
[48] Y. Yaniv, I. Ahmet, K. Tsutsui, J. Behar, J.M. Moen, Y. Okamoto, E.G. Lakatta, Deterioration of autonomic neuronal receptor signaling and mechanisms intrinsic to heart pacemaker cells contribute to age-associated alterations in heart rate variability in vivo, Aging Cell 15 (4) (2016) 716–724.
[49] A.A. Rosenberg, I. Weiser-Bitoun, G.E. Billman, Y. Yaniv, Signatures of the autonomic nervous system and the heart's pacemaker cells in canine electrocardiograms and their applications to humans, Sci. Rep. 10 (1) (2020) 9971.
[50] J.F. Thayer, A.L. Hansen, E. Saus-Rose, B.H. Johnsen, Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health, Ann. Behav. Med. 37 (2) (2009) 141–153.
[51] M. Polyakova, N. Sonnabend, C. Sander, R. Mergl, M.L. Schroeter, J. Schroeder, P. Schönknecht, Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review, J. Affect. Disord. 152 (2014) 28–38.
[52] A. Malliani, M. Pagani, F. Lombardi, S. Cerutti, Cardiovascular neural regulation explored in the frequency domain, Circulation 84 (2) (1991) 482–492.
[53] G.A. Reyes del Paso, W. Langewitz, L.J. Mulder, A. Van Roon, S. Duschek, The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: a review with emphasis on a reanalysis of previous studies, Psychophysiology 50 (5) (2013) 477–487.
[54] T.P. Beauchaine, J.F. Thayer, Heart rate variability as a transdiagnostic biomarker of psychopathology, Int. J. Psychophysiol. 98 (2) (2015) 338–350.
[55] A.R. Brunoni, A.H. Kemp, E.M. Dantas, A.C. Goulart, M.A. Nunes, P.S. Boggio, I.M. Benseñor, Heart rate variability is a trait marker of major depressive disorder: evidence from the sertraline vs. electric current therapy to treat depression clinical study, Int. J. Neuropsychopharmacol. 16 (9) (2013) 1937–1949.
[56] S.A. Jones, M.R. Boyett, M.K. Lancaster, Declining into failure: the age-dependent loss of the L-type calcium channel within the sinoatrial node, Circulation 115 (10) (2007) 1183–1190.
[57] D.S. Goldstein, O. Bentho, M.Y. Park, Y. Sharabi, Low-frequency power of heart rate variability is not a measure of cardiac sympathetic tone but may be a measure of modulation of cardiac autonomic outflows by baroreflexes, Exp. Physiol. 96 (12) (2011) 1255–1261.
[58] G.E. Billman, The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance, Front. Physiol. 4 (2013) 26.

[59] K. Kircanski, L.M. Williams, I.H. Gotlib, Heart rate variability as a biomarker of anxious depression response to antidepressant medication, Depress. Anxiety 36 (1) (2019) 63–71.
[60] M.X. Hu, Y. Milaneschi, F. Lamers, I.M. Nolte, H. Snieder, C.V. Dolan, E.J. de Geus, The association of depression and anxiety with cardiac autonomic activity: the role of confounding effects of antidepressants, Depress. Anxiety 36 (12) (2019) 1163–1172.
[61] U. Nussinovitch, K.P. Elishkevitz, K. Katz, M. Nussinovitch, S. Segev, B. Volovitz, N. Nussinovitch, Reliability of ultra-short ECG indices for heart rate variability, Ann. Noninvasive Electrocardiol. 16 (2) (2011) 117–122.