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REGULAR ARTICLE

Depressive Symptoms are Associated with Heart Rate Variability Independently of Fitness: A Cross-Sectional Study of Patients with Heart Failure

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Abstract

Background Depression is associated with reduced heart rate variability (HRV) in healthy and cardiac samples, which may be accounted for by physical fitness. In a small sample of cardiac patients, activity and fitness levels attenuated the relationship between HRV and depression. In the current study of heart failure (HF) patients, we hypothesized that depressive symptoms and HRV would be inversely related and physical fitness would attenuate this association.

Purpose To determine if previous associations among depressive symptoms, physical fitness, and HRV would replicate in a sample of HF patients.

Methods The sample consisted of HF patients ($N = 125$) aged 68.55 ± 8.92 years, 68.8% male, and 83.2% Caucasian. The study was cross-sectional and a secondary analysis of a nonrandomized clinical trial (Trial Identifier: NCT00871897). Depressive symptoms were evaluated using the Beck Depression Inventory (BDI)-II, fitness with the 2 min step test (2MST), and HRV during a 10 min resting laboratory psychophysiology protocol. The dependent variable in hierarchical linear regressions was the root mean square of successive differences.

Results Controlling for sex, age, β-blocker use, hypertension, and diabetes, higher BDI-II scores significantly predicted lower HRV, β = −.29, $t(92) = -2.79$, $p < .01$. Adding 2MST did not attenuate the relationship in a follow-up regression.

Conclusion Depressive symptoms were associated with lower HRV in HF patients, independent of physical fitness. Given the prevalence of depression and suppressed HRV common among HF patients, interventions addressing depressive symptoms and other predictors of poor outcomes may be warranted.

Keywords Depression • Heart failure • Heart rate variability • Fitness

Introduction

Cardiovascular diseases (CVD) are the leading cause of death in the USA [1], and approximately 6–10% of people over 65 years of age have been diagnosed with heart failure (HF) [2]. Heart rate variability (HRV) is widely used to assess autonomic function in cardiac samples and offers important prognostic information, such as aiding in identification of HF patients who are at risk for sudden death [3]. In HF patients, increased HRV after cardiac resynchronization therapy is thought to be a mechanism in improving survival [4], and those HF patients with improved HRV scores had better outcomes after undergoing treatment [5]. Although heart rate has valuable prognostic significance, HRV indicates the modulation of the autonomic control of the heart and can lend insight into abnormalities in cardiac regulation [6].

Lower HRV is related to depression in both cardiac and healthy samples [7, 8]. Abnormal HRV scores were associated with depression in a review including patients with acute coronary syndromes [9]. In other samples of patients with stable coronary artery disease, those with moderate to severe depression demonstrated significantly reduced HRV when compared to their nondepressed

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counterparts [10], and all time-domain measures of HRV, including root mean square of the successive differences (RMSSD), were lower in patients with major depression [11]. Finally, in a sample of physically healthy, unmedicated patients, RMSSD was significantly reduced in those with major depressive disorder (MDD) versus a control group [7].

Numerous mechanisms that explain the association between HRV and depressive symptoms have been theorized. In healthy samples with MDD, autonomic dysregulation, either deficient parasympathetic modulation or predominant adrenergic activation, has been found [10]. Parasympathetic nervous system activation is thought to be influenced by mood states and to become increasingly dysfunctional during longer-term depression [12]. In patients with MDD, Borrione and colleagues [13] found that decreased HRV was associated with specific depressive symptoms, such as guilt, loss of pleasure in activities, and psychomotor retardation. In a study examining two samples of healthy young adults, the association between depressed mood and low HRV was mediated by habitual dietary patterns and disinhibited eating behaviors, respectively [14]. Additionally, although the association between depression and HRV was once thought to be driven by antidepressant medications [15–17], a recent study has demonstrated the association is exhibited without the effect of antidepressant medication [18].

With regard to cardiac samples, the association between depression and HRV may be partially related to reduced physical activity and physical fitness. In a large prospective study following patients with stable coronary heart disease, the occurrence of cardiac events was higher among those endorsing more depressive symptoms in comparison to those with fewer depressive symptoms; the relationship between cardiac events and depression in patients was largely explained by physical inactivity [19]. Furthermore, in another prospective study following patients who were hospitalized for cardiac-related emergencies, physical inactivity was one of the factors (in addition to patient comorbidity and disability) that accounted for higher rates of mortality among those with MDD [20]. Thus, physical inactivity has demonstrated a strong association with poor outcomes in those with cardiovascular disease. However, the role of physical fitness in the relationship between HRV and depression has not been evaluated in HF patients.

Depressive symptoms and fitness are critically linked, and physical fitness is known to be lower in healthy individuals diagnosed with depression [21]. Cardiorespiratory fitness, and not obesity or higher weight, predicted onset of depressive symptoms in a large, diverse sample [22]. Additionally, maintenance of cardiorespiratory fitness appears to be protective against incidence of depression complaints to physicians [23], and higher cardiorespiratory fitness was associated with a lower risk of incidence of depressive symptoms in a longitudinal study [24]. Thus, fitness is clearly associated with depression and may be mechanistic in the association between depression and HRV, particularly in HF patients. In HF, depression is associated with reduced physical activity [25], which likely leads to reduced physical fitness. Physical fitness may be especially important in HF patients given the severe decompensation of the cardiovascular system. In patients with coronary artery disease, poorer cardiopulmonary fitness was associated with more depressive symptoms [26]. Further, another study demonstrated that improvements in cardiopulmonary fitness during cardiac rehab were associated with a reduction in depressive symptoms [27].

Hughes and colleagues [28] explored the association between depression and physical activity and fitness in a small sample of cardiac rehabilitation patients. Depressed patients were matched with nondepressed controls (22 patients in each group), and both frequency- and time-domain HRV measures were obtained over a 24 hr ambulatory recording period. Depression was significantly associated with HRV measures, and both physical activity and fitness were lower in the depressed patients [28]. HRV indices significantly associated with depression included total frequency power, ultra-low-frequency power, low-frequency power, standard deviation of N-N intervals (SDNN), and standard deviation of the 5 min average of N-N intervals (SDANN) [28]. The association between HRV and depression was attenuated by including physical activity and fitness in the model [28]. Thus, poorer fitness and lower levels of physical activity accounted for altered autonomic function in the sample of depressed cardiac patients. At that time, HF was not an approved indication for cardiac rehabilitation, although some patients in the sample may have had HF comorbid with their qualifying diagnosis (e.g., myocardial infarction). Thus, the application and validity of this association in HF patients needs to be explored.

In sum, depression has been shown to predict mortality in HF [29] and a likely mechanism is reduced HRV. Determining if physical fitness helps account for the association between reduced HRV and depressive symptoms in HF could have important clinical implications. Previous studies have investigated other cardiac samples but not specifically HF patients. The current study sought to examine the association between depressive symptoms and HRV in a sample of HF patients and to extend the findings of Hughes and colleagues [28] and Whooley and colleagues [19]. It was hypothesized that depressive symptoms and HRV would be inversely associated in HF patients and physical fitness would attenuate this association.

Methods

Sample/Setting

This cross-sectional study was a secondary analysis of a large-scale nonrandomized clinical trial investigating cognitive performance in HF older adults. The current study included 125 HF patients and was a secondary analysis of a larger National Institutes of Health (NIH) funded study, for which study design and results are published elsewhere [25]. The Cognitive Benefits of Cardiac Rehabilitation in People with Heart Failure (CHF CaRe) study (Trial Identifier: NCT00871897) was a prospective cohort study of patients with HF. The primary aim of the parent study was to examine the impact of cardiac rehabilitation on cognitive function in HF patients.

In the parent study, HF patients were eligible for inclusion if they were English speaking, between 50 and 85 years old, and had been diagnosed as New York Heart Association (NYHA) class II or III. Exclusion criteria for the parent study included having a history of neurological injury or disorder (e.g., dementia, stroke), a moderate to severe head injury (i.e., losing consciousness for more than 10 min), a history of or current severe mental illness (e.g., schizophrenia, bipolar disorder), a history of drug or alcohol abuse, sleep apnea that has not been treated, or renal failure that necessitated dialysis.

Procedure

The Institutional Review Boards (IRBs) of Kent State University and Summa Health System approved the study protocol. CHF CaRe enrolled patients recruited from the Summa Health System in Akron, Ohio, where research activities were conducted. Both HF patients who were enrolled in a 12 week cardiac rehabilitation program and those who were not participating in a cardiac rehabilitation program attended study visits on three occasions (baseline, Week 12, and Month 12). During study visits, HF patients participated in neuropsychological assessments, blood pressure and heart rate measurements, a walking exercise test, and questionnaires assessing diet, physical activity, and stress levels. Additionally, participants completed questionnaires and returned them via mail at Months 6 and 9. Participants provided informed written consent prior to enrollment.

Measures

Depressive Symptoms

Depressive symptoms were assessed with the Beck Depression Inventory (BDI)-II [30]. Total BDI-II scores range from 0 to 63, with higher scores indicating great depressive symptomology. A score of 0–13 is in the minimal range, 14–19 is mild, 20–28 is moderate, and scores between 29 and 63 are considered severe. The BDI-II demonstrates strong psychometric properties, with good reliability (r = .93 to .96) and internal consistency (r = .54 to .74) in medical patients [31]. Cronbach's α was .92 for BDI-II items in this sample.

Physical Fitness

Physical fitness was assessed via the 2 min step test (2MST), which evaluates aerobic endurance in a limited space and is an effective tool for HF patients [32]. During the 2MST, participants were asked to march in place for 2 min, lifting knees to a target marked on the wall, at the midpoint between the kneecap and crest of the iliac. The total number of times the right knee met the target was counted; the higher the step count, the greater the amount of physical fitness indicated [32]. Normal step count for elderly (aged 60–84) women and men ranges from 60 to 107 and 71 to 115, respectively [32]. In this sample, there was a significant difference between class II HF patients (M = 65.54, SD = 23.82) and class III HF patients (M = 43.13, SD = 26.78) on 2MST scores, $t(104) = 2.536$, $p = .013$, indicating that those with more severe HF had significantly worse aerobic endurance.

Heart Rate Variability

Participants underwent a laboratory protocol in which resting HRV was collected to quantify autonomic nervous system function. A Hutcheson Impedance Cardiograph with a clinical-grade electrocardiogram (ECG; Model HIC-2500, Bio-Impedance Technology, Chapel Hill, NC) was used, and ECG signals were continuously sampled at 500 Hz using three disposable electrodes placed in a lead-II configuration [33]. During the laboratory protocol, participants were continuously monitored for a 10 min resting period while seated in standard room temperature. To ensure optimal placement of electrodes and adaptation to the protocol prior to assessment, a 1 min minimum test recording was obtained.

Generated R-R interval data were imported into Kubios version 2.1 (Biosignal Analysis and Medical Imaging Group, Kupio, Finland) for analysis. A trained research team member manually edited ECG data for electrical interference and artifact. Recordings shorter than 3 min in length were excluded from final analyses, as short epochs can result in estimates of HRV that are not comparable with longer (e.g., 10 min) recordings. The 3 min recording minimum was chosen as the cutoff to preserve as much data as possible for analysis. The interpolation rate was 4 Hz and no trend removal was

used. For the present study, the time-domain component of HRV, RMSSD, generated by Kubios was used in analyses, as it has been shown to be one of the most important HRV measures for HF patients [34] and is suitable for short-term ECG recordings [35]. Additionally, high-frequency (0.15–0.40 Hz), low-frequency (0.04–0.15 Hz), and total power HRV components were generated by Kubios. All HRV variables were highly correlated (r = .82 to .94), and results for each were significant and comparable to the findings for RMSSD. For simplicity, only results regarding RMSSD are reported.

Demographic, Medical, and Psychosocial Variables

Self-reported demographic and clinical variables examined in this sample included: sex (0 = female, 1 = male), age (years), ethnicity (Caucasian = 1, Hispanic/Latino = 2, Asian American = 3, African American = 4, Native American/Alaskan Eskimo = 5, Mixed = 6), education (years completed), β-blocker use, hypertension (0 = not present, 1 = present), and diabetes mellitus (0 = not present, 1 = present). Severity of HF was determined by inquiring about participants' current limitations and symptoms, and responses were used to categorize HF severity as NYHA class I, II, III, or IV [36].

Statistical Analysis

Descriptive statistics (e.g., means, standard deviations, frequencies) were generated for sample characteristics. Before testing study hypotheses, data were inspected for violations of hierarchical multiple regression assumptions (e.g., distributional normality, homogenous error variance). RMSSD was log-transformed to ensure data were normally distributed (skewness <3 and kurtosis <10); no additional violations of assumptions were evident. Two hierarchical multiple regressions were performed to examine the relationships between depressive symptoms, physical fitness, and HRV (RMSSD) in HF patients. Missing data were handled using listwise deletion based on missing HRV data, as most missing data were due to problematic ECG recordings in this sample. The parent study included 226 participants; after HF patients with missing HRV data were excluded, the total sample size was 125. The statistical significance criterion was set at $p < .05$.

In both regression analyses, demographic and medical covariates were controlled for in the first block entered. In the first regression analysis, Block 1 comprised demographic and medical variables, including sex, age, β-blocker use, hypertension, and diabetes. Block 2 included BDI-II scores to assess the incremental predictive validity of depressive symptoms. In the second regression analysis, Block 1 included the same demographic and medical variables. In Block 2, 2MST scores were entered, and Block 3 included BDI-II scores. Log-transformed RMSSD scores were used as the dependent variable for both regression analyses. All analyses were conducted using IBM SPSS version 24.

Results

The sample consisted of 125 HF patients. The sample was predominately male (68.8%) and Caucasian (83.2%). Most participants had NYHA class II HF (88.9%), and approximately 26% of patients had some type of implantable cardiac device (see Table 1). No patients in this sample had diastolic dysfunction. Average depressive symptoms on the BDI-II were 8.14 (SD = 8.12), and the mean for RMSSD scores was 36.93 (SD = 55.47). Four percent of the sample identified experiencing severe depressive symptoms (BDI-II scores of 29–63) and 5.6% reported experiencing moderate depressive symptoms (BDI-II scores of 20–28). Regarding 2MST scores, 55.3% of men and 55.6% of women demonstrated physical fitness scores below their respective normal ranges. Additional demographic and medical characteristics are presented in Table 1. Cardiac medications used by this sample can be found in Table 2. Small correlations emerged between RMSSD and age (r = .20, $p < .05$) and RMSSD and BDI-II scores (r = −.18, $p < .05$). A small, negative association between 2MST and BDI-II scores was also significant (r = −.20, $p < .05$). Correlations between all primary variables are presented in Table 3.

Two hierarchical multiple linear regressions were conducted to examine the relationship among BDI-II scores, 2MST scores, and RMSSD. In the first regression, Block 1 contained demographic and medical control variables (sex, age, β-blocker use, hypertension, and diabetes) and did not significantly predict RMSSD. In Block 2, adding BDI-II scores improved model fit, $\Delta F(7,92) = 7.54$, $\Delta R^2 = .06$, $p < .01$. Controlling for sex, age, β-blocker use, hypertension, and diabetes, higher BDI-II scores significantly predicted lower RMSSD, β = −.26, $p < .01$ (see Table 4).

2MST was added to the model to assess the incremental predictive value of depressive symptoms after controlling for demographic and medical control variables, as well as 2MST scores. Controlling for 2MST, BDI-II remained a significant predictor of RMSSD, β = −.29, $p < .01$. No relationship emerged between 2MST scores and RMSSD, $p > .05$ (see Table 5).

Primary analyses were also tested in a moderation framework and results largely replicated regression analyses. Physical fitness (2MST) was examined as a moderator of the relation between BDI-II and HRV. BDI-II and 2MST were centered and entered in the

Table 1. Demographic and clinical characteristics of sample ($N = 125$)

	$M \pm SD$ or N (%)
Age (years)[a]	68.55 ± 8.92
Male	86 (68.8%)
Caucasian	104 (83.2%)
Education (years)[a]	13.53 ± 2.61
Married[a]	84 (67.7%)
Diabetes (no = 0; yes = 1)[a]	46 (37.1%)
Hypertension (no = 0; yes = 1)[a]	83 (66.9%)
Heart attack (no = 0; yes = 1)[a]	70 (56.5%)
Bypass valve replacement surgery (no = 0; yes = 1)[a]	42 (33.9%)
High cholesterol (no = 0; yes = 1)[a]	82 (66.1%)
Thyroid problems (no = 0; yes = 1)[a]	30 (24.2%)
Ejection fraction[b]	42.19 ± 14.48
Device[c]	
Pacemaker	13 (10.7%)
ICD	11 (9.0%)
Combination	8 (6.6%)
New York Heart Association class[b]	
Class I	0 (0%)
Class II	104 (88.9%)
Class III	12 (10.3%)
Class IV	1 (0.9%)
RMSSD	36.93 ± 55.47
Low-frequency HRV	614.58 ± 1846.16
High-frequency HRV	1139.17 ± 4455.46
2MST[d]	63.04 ± 24.92
Depressive symptoms (BDI-II)[e]	8.14 ± 8.12

Means and standard deviations are presented for continuous variables. Sample size and percentages are presented for categorical variables. RMSSD, low-frequency HRV, and high-frequency HRV represent raw values in milliseconds.

BDI Beck Depression Inventory; *HRV* heart rate variability; *ICD* implantable cardioverter defibrillator; *RMSSD* root mean square of successive differences; *SD* standard deviation.

[a]*n* of 124.

[b]*n* of 117.

[c]*n* of 122.

[d]*n* of 113.

[e]*n* of 123.

second step of the regression analysis (covariates entered in first step). Prior to entering the interaction term, only BDI-II was a significant, unique predictor of HRV [$\beta = -.29$, $t(92) = -2.79$, $p = .007$]. In the third step, the interaction term did not explain significant variance. Thus, 2MST was not a significant predictor of the relation between the BDI-II and HRV; results support the assertion that physical fitness does not attenuate the association between depressive symptoms and HRV.

Table 2. Cardiac medication use of sample ($N = 108$)

	N (%)
ACE inhibitors	63 (58.3%)
ARBs	12 (11.1%)
Aspirin	77 (71.3%)
Beta blockers	74 (68.5%)
Calcium channel blockers	10 (9.3%)
Diuretics	56 (51.9%)
Inotropes	7 (6.5%)
Nitrates	6 (5.6%)
Plavix	44 (40.7%)
Statins	47 (43.5%)

ACE angiotensin converting enzyme; *ARBs* angiotensin II receptor antagonists.

Table 3. Bivariate correlations between primary variables and demographic, medical, and psychosocial variables

Variable	1	2	3	4	5	6
1. Sex	–					
2. Age	.15	–				
3. Hypertension	−.14	.06	–			
4. Diabetes	−.06	−.15	.25**	–		
5. BDI-II	−.20*	−.20*	.10	.01	–	
6. 2MST	.17	−.14	−.19*	−.17	−.20*	–
7. RMSSD	−.09	.20*	.02	−.22*	−.18*	.00

2MST 2 min step test; *BDI* Beck Depression Inventory; *RMSSD* root mean square of successive differences.

*p-value <.05; **p-value <.01.

Discussion

In this sample of HF patients, depressive symptoms and HRV were negatively associated. In contrast to findings in other samples of cardiac patients, physical fitness did not attenuate the association between HRV and depressive symptoms. Thus, results in this sample of HF patients do not corroborate previous findings [19, 28].

Physical activity is a multidimensional construct that involves numerous kinds of behavior and varies on a day-to-day basis, making it difficult to reliably measure [37]. Fitness, which is construed as a capacity measure and was used in this study, can be assessed with more reliability and accuracy [37]. Indeed, cardiorespiratory fitness and physical activity levels are considered independent risk factors for cardiovascular diseases [38]. For example, greater cardiorespiratory fitness is associated with fewer CVD risk markers [39] and lower incidence of hypertension [40], and healthy individuals with greater cardiorespiratory fitness have exhibited lowered risk for CVD [41].

Table 4. Association of depressive symptoms (BDI-II) with RMSSD in heart failure patients

	B (*SE b*)	*t*	β
Block 1			
Sex	−0.33 (0.21)	−1.57	−.15
Age	0.02 (0.01)	1.97	.19
B-blocker	0.40 (0.21)	1.95	.19
Hypertension	0.04 (0.20)	0.17	.02
Diabetes	−0.34 (0.20)	−1.71	−.17
R^2	0.10		
F	2.29		
Block 2			
BDI-II	−0.03 (0.01)**	−2.75	−.26
ΔR^2	0.06**		
F for ΔR^2	7.54**		

Sex: male = 1, female = 2; β-blocker use: no = 0, yes = 1; hypertension: no = 0, yes =1; diabetes: no = 0, yes = 1.

BDI Beck Depression Inventory; *RMSSD* = root mean square of successive differences.

**p-value <.01.

Table 5. Association of physical fitness (2MST) and depressive symptoms (BDI-II) with RMSSD in heart failure patients

	B (SE *b*)	*t*	β
Block 1			
Sex	−0.26 (0.21)	−1.21	−.13
Age	0.02 (0.01)	1.87	.19
B-blocker	0.29 (0.21)	1.39	.14
Hypertension	0.08 (0.20)	0.38	.04
Diabetes	−0.30 (0.20)	−1.51	−.15
R^2	0.08		
F	1.66		
Block 2			
2MST	0.00 (0.00)	−0.22	−.02
ΔR^2	0.00		
F for ΔR^2	0.05		
Block 3			
BDI-II	−0.03 (0.01)**	−2.79	−.29
ΔR^2	0.07**		
F for ΔR^2	7.76**		

Sex: male = 1, female = 2; β-blocker use: no = 0, yes = 1; hypertension: no = 0, yes =1; diabetes: no = 0, yes = 1.

2MST 2 min step test; *BDI* Beck Depression Inventory; *RMSSD* root mean square of successive differences.

**p-value <.01.

Whooley and colleagues [19] used a measure of physical activity, which may partially explain discrepant findings. Alternatively, Hughes and colleagues [28] included physical fitness and demonstrated attenuation of the association between HRV and depression in a cardiac sample. However, that study examined cardiac rehabilitation patients, which included post-myocardial infarction and post-cardiac event patients but not necessarily HF patients. Thus, the different findings regarding physical fitness may be specific to the inclusion of HF patients in this sample. Additionally, results of the current study may be limited due to range restriction in variability of HRV scores, as suppressed HRV in HF is common. Therefore, findings may be distorted and should therefore be interpreted with caution. Furthermore, no distinction between cognitive and somatic symptoms was made during analyses in this sample, which could be problematic as patients with somatic complaints specific to a medical condition can be confused with depressive symptoms [42]. Thus, some depressive symptoms reported by HF patients may be attributable to symptoms caused by HF. Additionally, in this sample, only a small proportion of patients reported clinically significant depressive disorders. Further, although the BDI-II has demonstrated validity and reliability [31], results may have varied if a different measure of depression or clinician diagnosis were used instead.

In HF, chronic alterations of the autonomic nervous system may obscure associations between HRV and health markers typically found in healthy populations. For example, physical training improved spectral HRV in diabetics without cardiovascular neuropathy and with mild neuropathy [43]. However, in those with severe cardiovascular neuropathy, the physical activity intervention did not demonstrate any benefit [43]. Further, vagally mediated heart rate recovery in patients with chronic HF is blunted after exercise in comparison to healthy individuals [44], which is likely due to changes in autonomic function caused by HF. In HF, compensatory countermeasures, such as increased sympathetic nervous system activity, are chronically activated to maintain cardiac function [45]. After chronic overactivation of these systems, functionality becomes impaired and the typical association found between HRV and physical activity or physical fitness is likely obscured.

Numerous mechanisms between CVD and depression have been proposed. In a review by Joynt, Whellan, and O'Connor [46], factors such as noncompliance with medical regimens, clustering of risk factors (e.g., smoking, obesity), inflammation, stress, and decreased HRV have all been implicated in the association between CVD and depression. Additionally, although antidepressant medication has been hypothesized as mediating the effect, only tricyclic medication significantly impacted HRV in a meta-analysis [47]. Although depression has largely been considered an independent risk factor for CVD and mortality [48], little research has elucidated the

direction of associations. In a large longitudinal cohort study, Jandackova, Britton, Malik, and Steptoe [18] concluded that in those without depressive symptoms, lower heart rate and HRV predicted future incident depressive symptoms. Additional research replicating and better clarifying the direction of the association between HRV and depressive symptoms is needed.

Findings in this sample of HF patients are novel and contradictory to those found in other cardiac samples. No studies to date have examined the impact of physical fitness on the association between depressive symptoms and HRV in HF patients. Given the high prevalence of depression and suppressed HRV characteristics of HF, interventions addressing these predictors of poor outcomes may be warranted. As clinically significant depression is estimated to occur in 21.6% of HF patients [49], depression may be a potential target for treatment to enhance autonomic function. Additionally, depressive symptoms predict higher rates of cardiac events and mortality [50] and short-term declines in health status [51] in HF patients.

Limitations regarding this study are notable. As previously mentioned, compromised autonomic nervous systems of HF patients may provide less reliable HRV measures. Interestingly, HRV was not negatively correlated with age in this sample, which is uncharacteristic of the variable [52] and raises concerns about the validity of the measure. Further, respiration was not controlled for and can impact short-term recordings of HRV [53], which were used in this sample. Listwise deletion was used to exclude those with missing HRV data, which limits interpretability of findings to only those patients from which adequate ECG recordings can be obtained. Next, physical fitness scores were restricted in range, with approximately half of the sample demonstrating impaired or poor fitness, which could be problematic in analyses. Other factors may also have affected physical fitness, such as medication use, implantable medical devices, or differences in ejection fraction among patients. Additionally, this study used cross-sectional data which limits conclusions about causality. Our sample was primarily Caucasian, comprised HF patients, and included a relatively small sample of clinical cardiac patients; thus, findings may not generalize to different populations. Future studies should consider potential mechanisms and confounds such as nutritional habits.

Consistent with the literature on depression and autonomic function in cardiac samples, HRV was negatively associated with depressive symptoms in this sample of HF patients. However, this association was not attenuated when including physical fitness in a regression model. In HF patients, compromised autonomic function may obscure important associations with HRV. However, it is important to consider intervention implications with HF patients. During the course of interventions that target secondary prevention, such as exercise-based cardiac rehabilitation, devoting greater attention to screening and, if necessary, treatment of depression may be both psychologically and physiologically more beneficial to HF patients.

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Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards Authors Fawn A. Walter, Emily Gathright, Joseph D. Redle, John Gunstad, and Joel W. Hughes declare that they have no conflict of interest.

Author contributions FAW conceived of and designed analysis, interpreted data, drafted and revised for intellectual content, final approval of version to be published. EG provided statistical consultation and contributed to revisions. JR investigator and contributed to design of parent study; reviewed article for content. JG investigator and contributed to design of parent study, reviewed article for content. JWH primary investigator of parent study, substantially contributed to conception and design of study, revised it critically for intellectual content.

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