Original Paper

Neuropsychobiology

Neuropsychobiology 2007;55:219–224
DOI: 10.1159/000108381

Received: April 5, 2007
Accepted after revision: July 4, 2007
Published online: September 17, 2007

Depressive Symptoms Are Related to Decreased Low-Frequency Heart Rate Variability in Older Adults with Decompensated Heart Failure

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Key Words
Depression · Heart failure · Autonomic nervous system · Heart rate variability

Abstract
Background/Aims: Depression has been associated with increased mortality among individuals with heart failure, but the mechanism for this association is unsettled. Depression is often found to result in autonomic dysfunction which, if present in heart failure, might help explain worsened outcomes. ***Methods:*** This study was a cross-sectional evaluation of the relationship between depressive symptoms and cardiac autonomic function, as assessed by short-term heart rate variability (HRV) analysis in aged patients with acute/decompensated heart failure of coronary origin (CHF). A 21-item Hamilton Depression score and measures of short-term HRV were obtained in 31 inpatients ≥65 years of age, 24–72 h after admission to the coronary care unit with a diagnosis of CHF. ***Results:*** Clinical depression was present in 22.6% of participants. In the sample as a whole, increasing depressive symptoms were associated with decreased low-frequency HRV. ***Conclusion:*** These results may be important in light of recent indications that decreased low-frequency HRV is a predictor of mortality in patients with heart failure.

Introduction

Depressive symptoms are often accompanied by autonomic nervous system dysfunction in the form of parasympathetic impairment, sympathetic activation, or both [1]. Depression is exceedingly common among patients with heart failure of coronary origin (CHF), which in itself represents a serious public health problem [2]. Whereas the prevalence of depression in the general population is about 5–10%, prevalence rates for patients with CHF range from 11 to 70% [3]. Most importantly, patients with a comorbidity of depression and CHF have a poorer prognosis in terms of hospitalization, functional decline, and death, and the effect of depression seems to be independent of other prognostic factors in this group [3–7]. The physiological mechanisms underlying this depression-

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related worsening of CHF prognosis are unsettled, and to our knowledge, there are no available reports specifically studying samples of older individuals, who are usually underrepresented in clinical trials on the subject [8]. Nevertheless, several potential factors have been proposed to account for this effect of depressive symptoms. For example, patients with depression in general are known to be less compliant with medical treatment [9] and thus more liable to suffer a poor outcome. However, some physiological derangements could be implicated as well [10], including alterations of cardiac autonomic function as assessed by heart rate variability (HRV) analysis. It is known, for example, that elderly patients who suffer from a major depressive disorder have a reduced HRV [11], and we have recently described HRV alterations related to depression in older adults who have just suffered an acute coronary syndrome [12–14]. In fact, CHF and acute coronary syndromes have similar alterations in autonomic function, namely an increase in sympathetic activity and vagal withdrawal, and coronary artery disease is the main cause of CHF [15, 16]. Most importantly, there are recent reports indicating that disturbances of HRV in CHF patients are associated with increased mortality, independent of other well-known prognostic factors [17–19]. In light of these findings linking depression, alterations of cardiac nerve function, and mortality of CHF patients, we sought to evaluate the association between depressive symptoms and abnormalities of the nervous input to the heart in individuals ≥65 years of age admitted to the hospital with decompensated CHF.

Methods

This was a cross-sectional study on the association of depressive symptoms and HRV abnormalities in older individuals with decompensated CHF. Eligible patients had been admitted to the coronary care unit with a clinical diagnosis of acute/decompensated CHF [16], as indicated by the presence of dyspnea of non-traumatic origin, crackling rales, and an S3 sound. Patients had a known history of coronary artery disease, or had suffered a recent (i.e. <12 h evolution upon admission) acute myocardial infarction (MI) or unstable angina (UA) episode. MI was defined as an episode of ischemic chest pain for more than 30 min and less than 24 h, associated with ST segment elevations ≥0.1 mV in at least two leads. All participants with thus defined MI were eventually found to have a level of total serum creatine kinase that was at least twice the upper limit of the normal range, within 48 h of admission. Troponin serum levels were not available in this study. UA was defined as (1) recent onset angina pectoris of prolonged duration (i.e. 15–30 min), (2) onset of angina pectoris while at rest in patients with a history of chronic stable angina or previous MI, or (3) exertion angina whose threshold had diminished recently. In these patients, an electrocardiographic documentation of ST segment depression ≥1 mm, ST segment elevations, T-wave inversion, or a new left bundle branch blocking was required for inclusion. In 29 patients, a bidimensional echocardiogram could be obtained to confirm the presence of left ventricular dysfunction. All tested patients had a depressed systolic left ventricular function as indicated by a left ventricular ejection fraction of less than 50%. Parameters of diastolic dysfunction were not measured in this study. The following were exclusion criteria in the study: (1) a cardiac rhythm other than sinus rhythm or ≥10 abnormal beats per minute (e.g. atrial fibrillation or flutter, atrioventricular block, frequent premature beats, pacemaker), (2) diseases potentially associated to neuropathic or degenerative dysautonomia [20] other than diabetes mellitus, which was present in 6 patients (19%), (3) use of anticholinergic medications in the week prior to the study, or (4) inability to interact with the interviewer due to delirium, dementia, or a device which impeded verbal communication (e.g. tracheal tube). Between July 2, 2004, and December 30, 2005, we recruited 31 consecutive patients (77.8 ± 7.8 years; range 65–95 years), including 16 women (52%), after providing informed consent to participate in this study, as approved by the local bioethics committee. This sample was obtained from an original sample of 98 older patients admitted to the coronary care unit with a diagnosis of CHF (51 women, 53%). Thirty-five patients had a compromised cognition due to dementia or delirium, or wore an endotracheal device, or were on assisted ventilation and thus could not interact with the interviewer, 27 patients were not on sinus rhythm (10 patients had atrial fibrillation, 11 patients had more than 10 ectopic beats per min, and 6 patients had a pacemaker), 1 patient refused consent, 2 patients had Parkinson's disease, and recordings of 2 patients could not be analyzed due to faulty acquisition.

Studies of depressive symptoms and recordings of HRV were obtained within 24–72 h of admission to the coronary care unit, and were performed between 08:00 and 11:00.

The presence of a current major depressive episode as per DSM-IV criteria [21] was established with a semistructured clinical interview which assessed symptoms of depression present for at least 2 weeks. Current symptom severity was measured with a 21-item Hamilton Depression Scale (HAM-D), administered by a psychiatrist or a psychologist blind to the results of the HRV analyses.

HRV analysis was performed as described elsewhere [12, 14, 22]. Briefly, frequency-domain measures of HRV were obtained from samples of 550 sinus beats with the patient in the supine position, 24–72 h after admission to the coronary care unit. Frequency-domain measures resulted from the application of a fast-Fourier transform to the heart rate signal. Bands of interest included high frequency (HF, area under the curve of the power spectrum in the range of 0.15–0.55 Hz), and low frequency (LF, 0.03–0.14 Hz), both expressed as log ms^2 and as percentage of total variability. HF reflects the amplitude of the respiratory sinus arrhythmia, a phenomenon due solely to changes in vagal input to the heart [22, 23]. LF is a measure of fluctuations of heart rate originated in Mayer waves of blood pressure, via the baroreceptor reflex, which depends on both vagal and sympathetic influences on the heart [22, 23].

The relationship between HAM-D score and HRV variables was explored by means of a partial correlation test, controlling for age and dose of β-blocker as covariates. Depressed and nonde-

Table 1. Patient characteristics and HRV measurements

	Depressed (n = 7)	Nondepressed (n = 24)	Total (n = 31)	Statistic	p
Age, years	74.7 ± 8.6	78.8 ± 7.5	77.8 ± 7.8	t = –1.22	0.234
Women, n (%)	3 (43)	13 (54)	16 (52)	χ^2 = 0.278	0.598
HAM-D score	18.7 ± 2.8	9.3 ± 3.5	11.4 ± 5.2	t = 6.532	<0.001
LVEF, %	42.5 ± 14.2	43.1 ± 10.3	43 ± 10.9	t = –0.124	0.902
Hospitalization due to, n (%)					
UA	2 (29)	10 (42)	12 (39)	χ^2 = 0.556	0.757
AMI	3 (43)	7 (29)	10 (32)		
Other	2 (29)	7 (29)	9 (29)		
Diabetes mellitus type II, n (%)	1 (14)	5 (21)	6 (19)	χ^2 = 0.149	0.700
Atenolol, n (%)	2 (30)	9 (38)	11 (36)	χ^2 = 0.189	0.664
Statins, n (%)	3 (43)	12 (44)	15 (48)	χ^2 = 0.111	0.739
ACE inhibitors, n (%)	5 (71)	22 (92)	27 (87)	χ^2 = 1.975	0.160
Diuretics, n (%)	3 (43)	13 (54)	16 (52)	χ^2 = 0.278	0.598
Ca^{2+} blockers, n (%)	1 (14)	3 (13)	4 (13)	χ^2 = 0.015	0.901
Mean RR interval, ms	821 ± 120	963 ± 183	931 ± 179	t = –1.913	0.066
LF HRV, log ms^2	1.67 ± 0.69	2 ± 0.61	1.92 ± 0.63	t = –1.227	0.230
LF HRV, %	10 ± 4	13 ± 5	13 ± 5	t = –1.507	0.143
HF HRV, log ms^2	2.08 ± 0.44	2.22 ± 0.42	2.19 ± 0.42	t = –0.792	0.435
HF HRV, %	34 ± 19	24 ± 13	26 ± 15	t = 1.575	0.126
Total power, log ms^2	2.68 ± 0.63	2.95 ± 0.63	2.89 ± 0.56	t = –1.126	0.269

ACE = Angiotensin-converting enzyme; AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction.

pressed patients were compared regarding categorical variables by means of a Fisher's exact test, whereas continuous variables were compared with an independent-samples t test, as indicated. Results show mean ± SD of each variable. Significance was assumed at an $\alpha = 0.05$ and all reported results are two tailed.

Results

Table 1 shows the characteristics of the patient sample. Seven patients (22.6%) met the criteria for a current major depressive episode (table 1). In this sample, depressed and nondepressed persons were similar in all aspects of their clinical status, save that depressed individuals had a higher HAM-D score and displayed a tendency to have a higher heart rate (i.e. a shorter average RR interval) which did not attain statistical significance. Causes for decompensation included recent MI (10 patients, 32%), UA (12 patients, 39%) or a cause other than an acute coronary syndrome in individuals with known stable coronary artery disease (9 patients, 29%; table 1). Left ventricular ejection fraction as estimated by echocardiography could be obtained in 29 patients (6 depressed and 23 nondepressed individuals) prior to discharge from the coronary care unit and it averaged 43% (table 1). Treatment at the time of the evaluation is shown in table 1. Apart from medications shown in table 1, all patients were receiving aspirin 250 mg per day and subcutaneous heparin.

Figure 1 shows the series of sinus beats and their associated power spectra in a patient with depression and a HAM-D of 22 and in a patient with a low depressive symptomatology (HAM-D = 7). The larger area under the curve in the LF range (i.e., 0.03 to 0.14 Hz) in the nondepressed patient is noticeable.

When examined in the whole sample, the proportion of spectral density corresponding to LF HRV displayed an inverse relationship with depressive symptoms as assessed by HAM-D (fig. 2). No other HRV measures were associated with depressive symptoms in this sample (not shown).

Discussion

The present study shows that, in a sample of older individuals admitted to the hospital with acute/decompensated CHF, depressive symptoms are associated with decreased LF HRV. The proportion of this variability, which reflects influences of Mayer waves of blood pressure on the heart rate signal via the baroreceptor reflex [22, 23] was lower as a function of increasing score in the 21-item

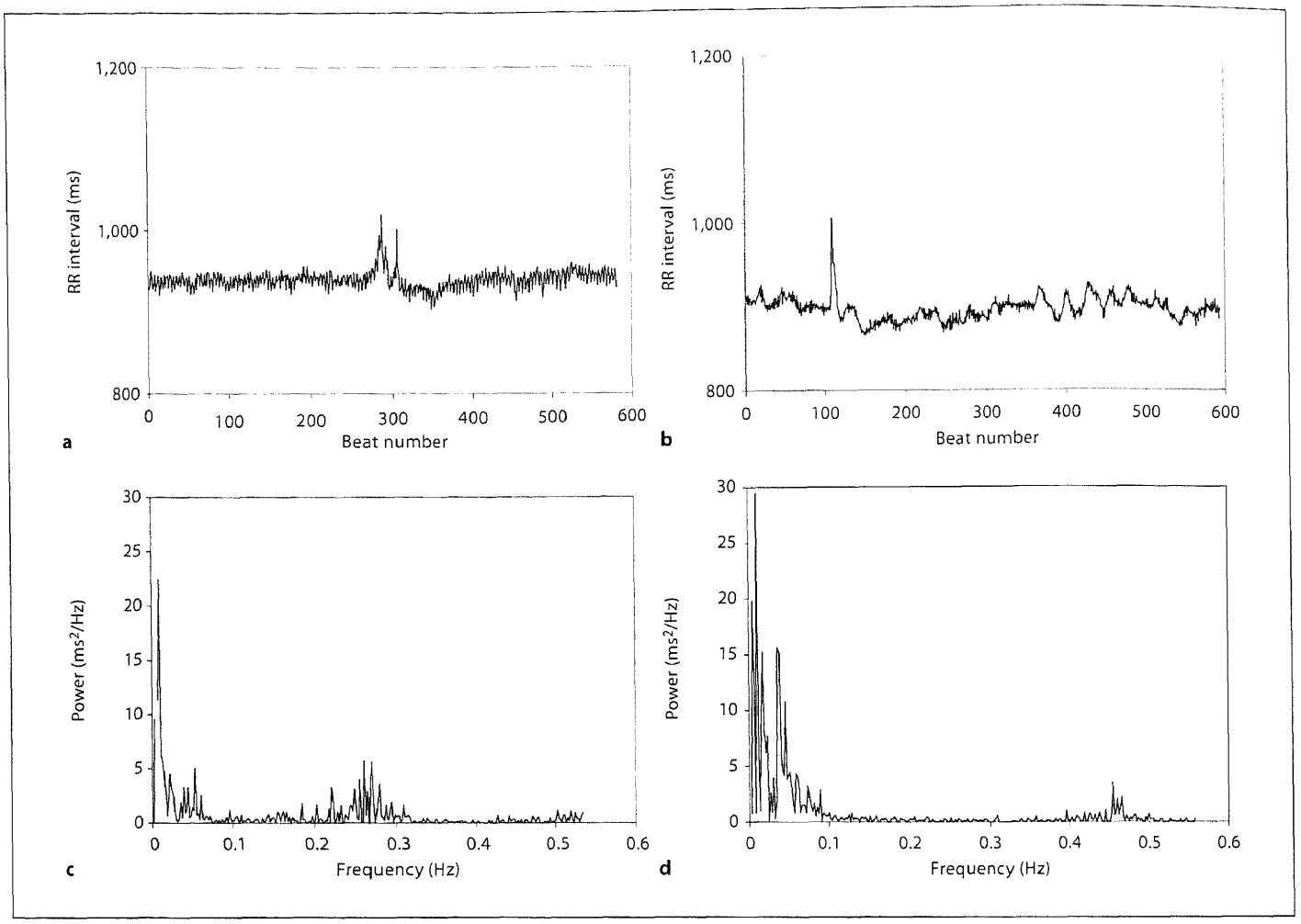

Fig. 1. Tachograms (**a**, **b**) and power spectra (**c**, **d**) of 550-heartbeat epochs in decompensated heart failure patients with high (HAM-D score = 22; **a**, **c**) or low (HAM-D score = 7; **b**, **d**) depressive symptomatology. Both individuals were male and had a left ventricular ejection fraction of 45%. Most noticeable is the decreased HRV in the LF (0.03–0.15 Hz) spectrum in the depressed patient.

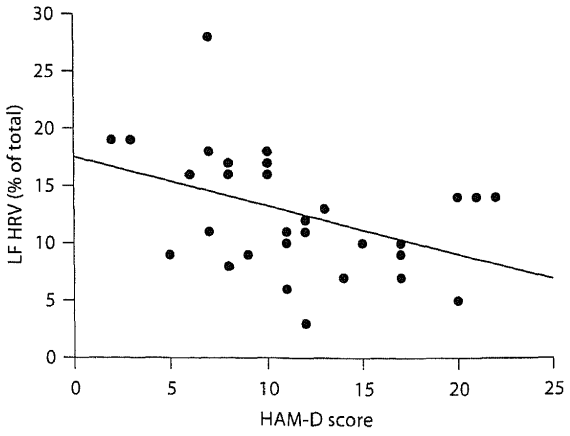

Fig. 2. Relationship between depressive symptoms (as assessed by HAM-D score) and HRV in the LF (0.03–0.15 Hz) spectrum in a sample of 31 older patients with decompensated heart failure ($r = -0.45$; $p = 0.015$).

HAM-D scale. The potential clinical meaning of this finding becomes apparent in light of the recent demonstrations by different groups that, in patients with CHF, decreased LF HRV is an independent predictor of death, when studied on short-term recordings like those used in the present study [18], or in 24-hour epochs [17, 19].

To our knowledge, this is the first observation of an association between LF HRV and depressive symptoms in individuals with CHF. Whereas other biological (e.g. changes in platelet adherence [24] and inflammatory mediators [25]) and behavioral (e.g. medication noncompliance [10]) variables have been proposed to explain the deleterious effects of depression on the course and prognosis of CHF, the present results suggest that depression-related impairment of LF HRV may represent a way in which clinical depression results in increased mortality in older CHF patients.

It may be of interest to consider the possible mechanisms whereby an impairment of LF HRV could result in proclivity to death in patients with depression and CHF. A recent study by Guzzetti et al. [26] has defined the HRV components which are related to different types of death in chronic CHF patients, as assessed in 24-hour Holter recordings. They showed that a reduction of power in the 0.04- to 0.15-Hz band was the only HRV component related to sudden cardiac death, and theirs is the only study to provide insight into how a decreased HRV related to baroreflex activity is associated with mortality in individuals with CHF. Presumably, in CHF patients a decreased LF HRV reflects an impairment of baroreceptor reflex due to overwhelming sympathetic input onto the heart [27], and the latter has long been known to decrease the threshold for malignant ventricular arrhythmias resulting in sudden cardiac death [28]. Our study suggests that depression can be related to a further reduction in LF HRV in older CHF patients, although this conclusion is limited by the small sample size. The observation should be confirmed in further larger studies with enough power to control not only for age and dose of β-blockers, but also for additional potential covariates such as presence of diabetes, smoking status, and gender.

It should be noted that previous data in depressed patients with or without heart diseases suggest that depression is often related to vagal withdrawal as well [12, 29, 30]. However, in our sample we did not observe any inverse relationship between depressive symptoms and vagal activity at the sinus node (as assessed by HF HRV), in contrast to the results of a previous study in older adults with acute coronary syndromes but without heart failure [12]. A possible reason for the lack of association between depressive symptoms and decreased vagal activity in this sample is that the overwhelming sympathetic activation and vagal withdrawal characteristic of CHF are important enough to blunt any depression-related changes in cardiac parasympathetic activity. In addition, cardiac parasympathetic innervation seems to be exquisitely vulnerable to diabetes mellitus [20], a condition present in almost a fifth of the present sample of patients. Other factors that limit the power of the present study to detect vagal activity changes are the short duration of the recordings and the fact that respiratory rate was not paced. Remarkably, HRV indicators of vagal activity have not been shown to have predictive value in CHF in available studies [17–19].

To what extent the impairment of LF HRV in CHF described herein contributes to explain the deleterious effect of depression on cardiovascular prognosis, and how this mechanism is associated to other possible depression-related mechanisms of worsened prognosis such as systemic inflammation and behavior abnormalities, are questions that necessitate further investigation.

Acknowledgements

Funding was provided by the University of Buenos Aires (Biennial Project M084) and FLENI Foundation (S.M.G.). M.N.C. is a medical student research fellow of the University of Buenos Aires. D.E.V. is a fellow from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

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