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Acute and six-month depression-related abnormalities in the sleep-wake rhythm of cardiac autonomic activity in survivors of acute coronary syndromes☆

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ABSTRACT

Objectives: To characterize the influence of changes in depression symptoms severity six months after an acute coronary syndrome (ACS) on the circadian pattern of cardiac autonomic activity, a known independent predictor of adverse outcomes.

Methods: One hundred two patients consecutively admitted to the coronary care unit (CCU) with an ACS were evaluated with a clinical interview (including a psychiatric evaluation for depression), the 21-item Hamilton Depression Scale (HAM-D) for symptom severity and a 24 h recording of heart rate variability (HRV) at admission and six months post-discharge from the CCU. HRV was measured during wake and sleep (23.00 h–07.00 h) with a fast Fourier transform algorithm. We obtained meanRR (mRR), low-frequency HRV (LF) influenced by both sympathetic and parasympathetic activity, high-frequency HRV (HF) determined solely by parasympathetic activity, and LF/HF ratio as a measure of the sympatho-vagal balance onto the heart (LF/HF).

Results: Upon admission to the CCU, major depression was present in 44% of subjects. Depression was associated with shorter mRR (higher heart rate), during sleep ($p < 0.05$). At six months, depression was associated with shorter mRR during wake ($p < 0.05$) and sleep ($p < 0.01$), decreased mRR sleep-wake difference ($p < 0.05$), and lower LF both during wake ($p < 0.05$) and sleep ($p < 0.05$). LF and HF changes were related to HAM-D changes 6 months after the index episode.

Conclusions: Depression influenced circadian rhythm of autonomic activity, most notably upon 6-month follow up. Changes in depressive symptom severity after a 6-month observation period were related to changes in HRV known to adversely affect coronary prognosis.

Introduction

The occurrence of major cardiovascular events, including unstable angina, myocardial infarction, acute aortic dissection, ischemic stroke, cerebral hemorrhage, decompensated heart failure, malignant ventricular arrhythmias, and sudden cardiac death, is not randomly distributed over a 24-h period, but follows a circadian pattern [1–4]peaking in morning hours at around 08:00 h. The outcome of revascularization procedures [5] is also poorer during the night and early morning [6]. There is a second, less significant peak in the occurrence of major cardiovascular events in the evening. Different factors are thought to account for these daily peaks. The circadian rhythm associated with a variety of physiological parameters [7,8] has been proposed to explain the initial daily peak. These parameters include increased blood coagulation, platelet aggregation, and cortisol levels; higher sympathovagal balance; awakening; and onset of diurnal locomotor activity [9–13]. Physiological parameters are more important among elderly and women who suffer an acute coronary syndrome (ACS)

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[14]. The evening peak is associated with younger age, smoking and alcohol use.

Depression is an independent risk factor for the development of coronary artery disease, complications after cardiac revascularization, poorer quality of life after ACSs, and increased mortality [15–17]. The bulk of evidence strongly suggests that previous clinical depression should be considered a major prognostic factor after ACS [18]. Apart from behavioral phenomena associated with depression [19] such as poor compliance with prescribed treatment and lifestyle changes, depression has been regarded to produce abnormalities in autonomic input to the heart (favoring the appearance of ischemia and malignant ventricular arrhythmias), increased thrombus diathesis, platelet aggregation, and systemic immune-inflammatory changes. Those parameters have all been associated with increased incidence of cardiovascular events [20–23].

Depression is in turn associated with disturbances in circadian rhythm [24,25], but to the extent of our knowledge, there has been no investigation as to whether depression adversely affects cardiovascular health via modifications in the circadian rhythmicity of parameters of cardiovascular regulation. Heart rate variability (HRV) analysis has long been used as a noninvasive tool to estimate autonomic input to the cardiovascular system [26], and its alterations have been associated with cardiovascular disease, depression, and as a pathophysiological marker of poor prognosis in both conditions [27].

We hypothesized that depression-induced alterations in cardiac autonomic control are related to autonomic circadian rhythm dysfunction, and that such alterations are more severe at 6-month follow-up, a period which concentrates most ACS-related mortality and other adverse outcomes. To test this hypothesis, we used 24-h recordings of HRV and assessed the presence and severity of major depressive episodes in patients experiencing an ACS, both at the time of the index event and six months later [28,29].

Methods

This was an observational study on the relationship between depressive symptoms and circadian changes in cardiac autonomic activity in survivors of acute coronary syndromes, including unstable angina (UA) and acute myocardial infarction (AMI), both immediately (<72 h) and six months after the index episode.

Patients

One hundred two consecutively admitted patients to the coronary care unit (CCU) of the Hospital Vall d'Hebron, Barcelona, who had a recent (i.e., <24 h) ACS and who were between 40 and 85 years of age were recruited for the study (27 women). The presence of an ACS in the form of UA or AMI was established according to standard criteria, as defined in the next section. Exclusion criteria included a history of neurological disorders with potential autonomic nervous system effects (including idiopathic Parkinson's disease, multiple sclerosis, and diabetes), self-reported history of substance abuse including alcohol abuse, a cardiac rhythm other than sinus rhythm or the presence of a pacemaker, or the presence of congestive heart failure severe enough to decrease the level of consciousness or require a device to assist with ventilation (i.e., tracheal tube, oxygen mask). All patients signed an informed consent form as approved by the local bioethics committee. The study was carried out according to the declaration of Helsinki.

Baseline clinical evaluation

AMI was defined as an episode of ischemic chest pain lasting more than 30 min and less than 24 h, and associated with ST segment elevations >0.1 mV in at least 2 leads. 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 a patient with a history of chronic stable angina pectoris or a previous AMI, or (3) exertion angina whose threshold had recently diminished. Also, electrocardiographic documentation of ST segment depression of at least 1 mm, ST segment elevations for inclusion. Clinical manifestations of heart failure were classified according to the Killip class system [30]. In addition, left ventricular ejection fraction was calculated by bidimensional echocardiography.

The presence of a major depressive episode according to DSM-IV-TR criteria was assessed with the Composite International Diagnostic Interview [31] administered by a consultant psychiatrist and a psychologist (IVP, SLG). Severity of depressive symptoms was measured with a 21-item Hamilton Depression Scale (HAM-D, 32). The clinical interview and administration of the HAM-D were performed 24–72 h after admission to the CCU, between 08:00 h and 10:00 h the same day as HRV recordings. They were not taking antidepressant medication.

6 Month Follow-Up

Patients were contacted over the phone 6 months after their index admission to the CCU, and invited to return to the hospital to repeat the evaluation of their mood status and to obtain a new 24-h electrocardiogram recording. It was assessed with the same semi-structured interview [31] and HAM-D scale [32] administered by a consultant psychiatrist and a psychologist (IVP, SLG). The recording was accomplished by placing the Holter recorder during the clinic visit and returning after 24 h to have the device removed. Clinical evaluation and Holter recorder placing were done between 08:00 h and 10:00 h.

HRV analysis

HRV analysis was performed via 24 h ECG recordings obtained using a Holter device (Mortara Instrument, Inc, Milwaukee, WI). HRV was measured during wake and sleep (11PM-7AM) calculated using a fast Fourier transform algorithm. The mean of sinus RR intervals (mRR) for both wake and sleep was obtained as a reflection of heart rate. Total power spectral density and subcomponents reflecting sympathetic and parasympathetic input to the heart, as defined below, were estimated by application of the fast Fourier transform (FFT) algorithm to the heart rate signal [33]. Total HRV measures the area under the curve of the power spectral density graph, and it represents HRV from all physiological origins. Low-frequency HRV (LF, area under the curve in the 0.03–0.15 Hz range) reflects fluctuations of heart rate originating in Mayer waves of blood pressure, and it therefore represents oscillations originated in the barorreflex arc, depending upon both sympathetic and parasympathetic influences. High-frequency HRV (HF, area under the curve in the 0.15–0.4 Hz range) is a reflection of respiratory sinus arrhythmia, thus measuring only vagal influences on the heart. Finally, we calculated the LF/HF ratio, which indicates the sympatho-vagal balance (LF/HF) onto the sinus node [33].

Statistical analysis

Demographic data of patients with and without DSM-IV-TR depression upon admission were compared using independent-samples *t* tests for continuous variables or chi square (X^2) tests for categorical variables. The same statistical analyses were performed at six-month follow-up for the HAM-D score, Killip class and medications. The occurrence of drop-outs in the analysis was not handled with any specific method. Thus, for the comparison analyses between follow-up and admission we considered only those cases that participated at both assessments points.

At admission we used an independent samples *t* test to study the changes in HRV variables between depressive and non-depressive patients. Additionally, we performed a paired *t* test to compare HRV changes during sleep and wake period within those groups. At six-months follow-up we performed the same analysis between and within groups.

Subsequently, four groups were defined according to mood status upon admission and at six months, namely those who remained syndromally depressed since CCU admission, those becoming depressed after six months, those who remained non-depressed throughout, and finally patients who recovered from depression. Then, we performed a repeated measures general linear model. We included as independent variables: group (to evaluate the effect of mood sta-

tus), time of evaluation (to evaluate the effect of the progression of cardiovascular disease on changes of autonomic variables) and HAM-D progression (to investigate the influence of depressive symptoms on HRV parameters). Pearson correlation coefficients between severity of depressive symptoms (via HAM-D) and HRV variables were calculated to investigate their association.

SPSS v18 was used for all analyses. Results were considered significant at $p < 0.05$, with two-tailed tests of significance.

Results

Sample characteristics and HRV variables at index episode

One hundred two patients were evaluated. Table 1 shows the characteristics of enrolled patients. Patients with depression represented 44.1% of the sample. Women were overrepresented in the depression group, accounting for 26.5% of the total sample, but 37.8% of those with depression (Table 1). Individuals without depression were more likely to exhibit clinical symptoms of congestive heart failure, as indicated by a Killip class of B or greater; in the sample as a whole, however, left ventricular function as estimated by bidimensional echocardiography was similar in both groups (Table 1). Use of various treatments such as β-blockers, angiotensin converting enzyme (ACE) inhibitors, statins and calcium-channel blockers were also similar in both groups (Table 1).

Table 2 shows HRV measures during wake and sleep upon admission to the CCU. Not surprisingly both patients with and without depression presented significant differences in mRR between sleep and wake, showing shorter mRR, that is, higher heart rate, during wake as indicated the paired *t* test (Table 2). Patients without depression displayed higher absolute and relative HF-HRV during sleep, and lower sympathovagal balance during wake (Table 2). Such differences were not present in patients with depression.

When we compared the two groups using independent samples *t* test we observed that depressed patients had a higher heart rate during sleep (Table 2).

Sample characteristics and HRV variables at 6-month follow up

Six month data were obtained in 73 patients (71.6% of baseline sample), of whom 34.2% fulfilled criteria for a major depression diagnosis. Women represented 28.8% of the total sample, and again, they were overrepresented, 52%, among those with depression. Five patients (6.8%) had been readmitted for AMI or UA.

Table 1
Demographic characteristics at the Acute Coronary Episode.

	No depression (n = 57)	Depression (n = 45)	Statistic	*p*
Age (years)	63.8 ± 10.4	63.7 ± 12.0	$t = 0.027$	.98
Female, n (%)	10 (17.5)	17 (37.8)	$X^2 = 5.29$	.021
Type of ACS, n (%)				
Unstable angina	12 (21.1)	10 (22.2)	$X^2 = 0.02$	.88
Myocardial infarction	45 (78.9)	35 (77.8)		
Medication, n (%)				
β-blockers	28 (49.1)	25 (55.6)	$X^2 = 0.42$	.54
Calcium channel blockers	1 (1.8)	2 (4.4)	$X^2 = 0.64$	.57
Statins	24 (42.1)	20 (44.4)	$X^2 = 0.56$	.83
ACE Inhibitors	12 (21.1)	10 (22.2)	$X^2 = 0.02$	>.99
Killip Class A, n (%)	50 (87.7)	44 (97.8)	$X^2 = 7.069$	.029
Ejection	52.3 ± 10.4	51.2 ± 9.3	$t = 0.54$	.59

Table 2
HRV at the index episode.

	No depression (n = 57)	Depression (n = 45)	Total (n = 102)
meanRR (ms)			
Wake	900 ± 121	850 ± 140	878 ± 132
Sleep (11PM to 7AM)	960 ± 131	905 ± 146[§]	936 ± 140
Sleep-Wake difference	60 ± 52[***]	54 ± 46[***]	57 ± 49
Total power HRV (ln)			
Wake	3 ± 0.4	2.9 ± 0.4	2.9 ± .042
Sleep (11PM to 7AM)	2.9 ± 0.5	2.8 ± 0.5	2.9 ± 0.49
Sleep-Wake difference	−0.04 ± 0.04	−0.1 ± 0.3[*]	−0.07 ± 0.34
LF (ln ms^2)			
Wake	2.1 ± 0.54	2 ± 0.54	2.1 ± 0.54
Sleep (11PM to 7AM)	2.1 ± 0.55	1.9 ± 0.65	2 ± 0.59
Sleep-Wake difference	−0.04 ± 0.4	−0.1 ± 0.36	−0.06 ± 0.38
HF (ln ms^2)			
Wake	1.9 ± 0.55	2 ± 0.60	1.99 ± 0.57
Sleep (11PM to 7AM)	2.1 ± 0.51	2 ± 0.62	2.06 ± 0.56
Sleep-Wake difference	.13 ± 0.38[*]	−0.01 ± 0.34	0.07 ± 0.37
LF/HF			
Wake	2.4 ± 2.2	1.7 ± 1.5	2.1 ± 1.9
Sleep (11PM to 7AM)	1.6 ± 1.5	1.3 ± 0.96	1.5 ± 1.3
Sleep-Wake difference	−0.80 ± 1.7[**]	−0.41 ± 1.6	−0.63 ± 1.6

All values are expressed as mean ± SD. [***]p < .001; [**]p < .010; [*]p < .050 between sleep and wake (paired *t* test); [§]p < .050 between patients with and without depression (independent samples *t* test).

Four groups were defined according to mood status upon admission and at 6 months, namely those who remained syndromally depressed since CCU admission, those becoming depressed after six months, those who remained non-depressed throughout, and finally patients who recovered from depression. Thus 21.9% were depressed at baseline and at follow-up; 12.3% were non-depressed at baseline but developed depression in this observation period; 39.9% without depression at baseline and at follow-up and 26% recovered from depression at baseline. Clinical symptoms of congestive heart failure were similar in patients with and without depression at 6 months. Treatments with β-blockers, angiotensin converting enzyme inhibitors, statins, and calcium-channel blockers were similar in both groups. None of the patients received any psychopharmacological treatments in the 6 months observation period (data not shown).

HRV measures during wake and sleep phases are shown in Table 3. At six months, paired *t* test showed that again both depressed and non-depressed patients displayed lower meanRR, that is shorter HR, during sleep compared with wake. On the other hand, independent sample *t* test indicated that depression was associated with lower RRm during wake and sleep, as well as lower mRR sleep-wake difference compared with non-depressed patients (Table 3). Moreover, depressed patients showed a lower total power-HRV and lower LF-HRV during both wake and sleep compared with non-depressed subjects (Table 3).

Influence of depressive symptoms on HRV variables

General linear model showed significant differences in wake and sleep LF (lnLF; $p = 0.003$) and wake-HF (lnHF; $p = 0.009$) between admission and six-months follow-up (data not shown). Taking HAM-D progression as a co-variable, we observed a significant difference in wake LF ($p = 0.021$) wake HF ($p = 0.044$) between admission and follow up (data not shown).

An inverse correlation between changes in depressive symptoms and circadian autonomic variables was observed when we performed Pear-

Table 3
HRV at six months.

	No depression (n = 38)	Depression (n = 25)	Total (n = 68)
meanRR (ms)			
Wake	948 ± 125	874 ± 151[§]	919 ± 139
Sleep (11PM to 7AM)	1060 ± 119	929 ± 170[§§]	1008 ± 154
Sleep-Wake difference	112 ± 87[**]	54 ± 94[*§]	89 ± 93
Total power HRV (ln)			
Wake	3.4 ± 0.27	3.2 ± 0.41[§]	3.3 ± 0.34
Sleep (11PM to 7AM)	3.4 ± 0.34	3.2 ± 0.47[§]	3.3 ± 0.41
Sleep-Wake difference	0.004 ± 0.37	−0.03 ± 0.34	−0.01 ± 0.35
LF (ln ms^2)			
Wake	2.7 ± 0.46	2.3 ± 0.6[§]	2.5 ± 0.53
Sleep (11PM to 7AM)	2.7 ± 0.38	2.4 ± 0.75[§]	2.6 ± 0.55
Sleep-Wake difference	0.12 ± 0.49	0.09 ± 0.41	0.11 ± 0.46
HF (ln ms^2)			
Wake	2.5 ± 0.47	2.2 ± 0.53	2.4 ± 0.51
Sleep (11PM to 7AM)	2.5 ± 0.46	2.3 ± 0.64	2.4 ± 0.54
Sleep-Wake difference	0.02 ± 0.5	0.05 ± 0.46	0.03 ± 0.48
LF/HF			
Wake	3.1 ± 9.1	1.7 ± 0.98	3.1 ± 7.2
Sleep (11PM to 7AM)	2.3 ± 1.77	1.8 ± 1.2	2.1 ± 1.6
Sleep-Wake difference	−1.7 ± 9.7	0.13 ± 1.4	−1 ± 7.7

All values are expressed as mean ± SD. [**]p < .001; [*]p < .010, between sleep and wake (paired *t* test); [§§]p < .010; [§]p < .050 between patients with and without depression (independent samples *t* test).

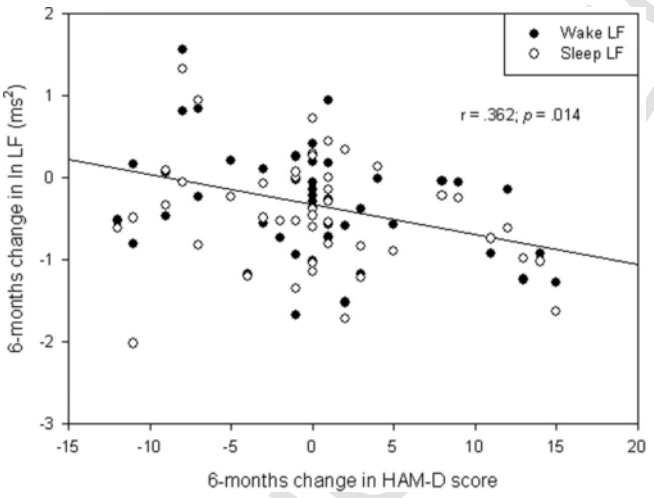

Fig. 1. Inverse correlation between ln-LF during wake and sleep and progression of depressive symptoms over 6 months (r = 0.362, p = 0.014 for wake ln-LF). LF: Low-Frequency; HAM-D: Hamilton Depression score.

Discussion

The main findings of this study are that in survivors of ACS 1) depression is associated with an higher heart rate during sleep and smaller amplitude of sleep-wake differences in HF-HRV and sympathovagal balance acutely, and 2) higher HR and decreased Total HRV and LF-HRV throughout the sleep-wake cycle six months after the index episode, and 3) progression of depressive symptoms in such period is associated with decreased LF and HF-HRV. To our knowledge, this is the first study exploring the relationship between changes of depression assessed with a standardized depression symptom severity scale and changes in the diurnal variation of cardiac autonomic activity over a 6-month period.

These findings add to previous data about autonomic abnormalities in depressed patients by our group and others [34-36]. These

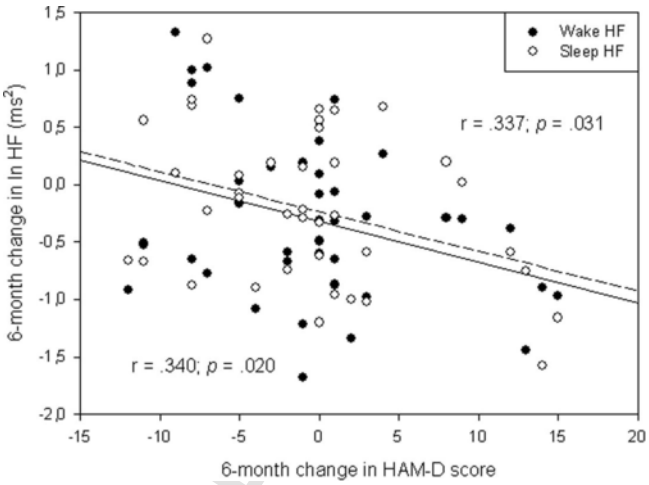

Fig. 2. Inverse correlation between both ln-HF wake and sleep, and progression of depressive symptoms over 6 months (r = 0337, p = 0.031 for wake, and r = 0.340, p = 0.020 for sleep ln-HF). HF: High-Frequency; HAM-D: Hamilton Depression score.

creased sympathetic activity, or both. However, most of them refer to short-time autonomic analysis. Carney et al. showed an abnormal very low frequency (VLF-HRV) in 24 h ECG recordings, but they evaluated 24 h data without discriminating diurnal phases [16,21]. Indeed, Andruskevicius [37] showed an improvement of LF after antidepressant treatment during 24 h recordings, but again not ascertaining day-night differences. In contrast, our results refer instead to an association between depression and circadian rhythmicity of autonomic activity, both acutely and six months after an ACS.

Our finding of higher HR during sleep in depressive patients at admission could be a consequence of increased sympathetic activity, reduced parasympathetic activity, or the combination of the two. Our method could not discriminate the relative contribution of each factor. Nevertheless, we observed smaller sleep-wake differences in both HF and sympathovagal balance associated with clinical depression indicating a possible parasympathetic deficit. This could signal a lack of circadian flexibility and a "rigid" autonomic control in depressive patients, as observed in samples of coronary disease patients with poor prognosis. It should be noted that mortality after an ACS is greatest in early morning hours; plausibly, a higher heart rate may ultimately reflect an abnormal sympathovagal balance favoring the appearance of adverse events in clinical samples like the one studied herein.

At six months we found that depression was associated with a difference of total HRV between as non-depressed patients. However, patients with depression presented a decreased HRV possibly at the expense of a decrement in LF throughout the sleep-wake cycle as indicated when we compare depressed versus non-depressed patients. LF depends on both sympathetic and parasympathetic system activity, as both systems contribute to barorreflex regulation. Whatever its origin, our finding could be important in light of previous data implicating LF as a variable independently associated with mortality [38]. In fact, we previously observed an association between increased depressive symptoms and decreased LF immediately after acute/decompensated cardiac heart failure of coronary origin [36]; LF impairment is a possible mechanism whereby depression results in increased mortality in older CHF patients [36]. Therefore, poor barorreflex control could be an explanation for flattening of the diurnal variation in autonomic control observed acutely, although this impairment would be less intense than that observed at six months, when symptoms of depression turned more severe.

On the other hand, at six months we observed that progression of depressive symptoms was associated to decreased LF during the day and decreased HF throughout sleep-wake cycle. This is in accordance with a previous study in which we found an inverse correlation between depressive symptoms and total-HRV, LF and HF-HRV at six months from CCU admission in ACS patients with short recordings of HRV [34]. As noted above, LF is an independent risk factor for mortality. Additionally, decreased vagal activity has been described

in depressed patients without cardiac issues and is largely associated with myocardial ischemia and ventricular fibrillation [39,40] leading to poor prognosis including mortality.

A general linear model confirmed that depressive symptom progression influenced autonomic changes during the sleep-wake cycle six months after an ACS. Whereas observation after 6 months permitted us to find a relationship between course of depression and autonomic variables, we were not able, given the sample size, to establish any relationship with mortality. However, depression influenced changes in cardiac autonomic activity known to be prognostically unfavorable in a variety of other cardiovascular patient samples.

An important limitation of this study is that cardiac autonomic activity changes is just one of a variety of possible mechanisms explaining the epidemiological link between depression and adverse cardiovascular outcomes. None of such mechanisms was evaluated in this study, namely, changes in platelet aggregation, poor compliance with medical treatment and systemic inflammation [41-43].

Of note, we observed that in the present sample women were overrepresented among depressed patients, not only at the index episode (as observed by other authors, 44), but also after six months. Incident depression in women with cardiovascular disease is known to be about twice as high as that in men, as is the case for depression in the general population [45,46]. In fact, in unselected samples of patients with depression, long known depression-related changes in autonomic activity (e.g., 47) display significant gender differences [48]. Since abnormal systemic inflammation has been proposed in women as a potential mechanism explaining the deleterious effect of depression on cardiovascular outcomes, the present results suggest depression-related abnormalities in the cardiac autonomic activity deserve consideration for further, controlled exploration in this group.

Moreover, analysis in the subgroups of depressed patients upon admission and at follow-up could not be performed. These two groups were small, inhomogeneous and not fully comparable. It is worth remarking, as was previously mentioned, that we were not able to establish any relationship between depression and mortality because of the sample size. Therefore, it restricts the scope of our results. Additionally, we are aware that the standard statistical significance level is not able to exclude type I errors. However, the objective of the study is to find promising areas that might be followed up in later studies. In this situation, correcting for multiplicity may result in too many type II errors and prematurely close off potentially fruitful areas of research. Therefore any positive results should be seen as possible hypothesis generators, more than as definitive findings [49].

On the other hand, patients were on treatment with cardiac medication such as β-blockers, angiotensin converting enzyme (ACE) inhibitors, statins and calcium-channel blockers, which could influence our results. However use of medication was similar in both groups. Furthermore, it is important to note the absence of antidepressants in patients who presented depressive symptoms, which was probably related to an inadequate recognition of depression on a medical context, as previously reported in other samples (see 50 for a review on this topic).

In sum, depression-related alteration of circadian cardiac autonomic control should be considered a candidate to explain higher mortality related to depression in survivors of ACS.

Conflicts of interest

Nemeroff C.B. declares: Research/Grants:National Institutes of Health (NIH); Consulting (*last three years*):Xhale, Takeda, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., Lundbeck, Prismic Pharmaceuticals, Bracket (Clintara), Total Pain Solutions (TPS), Gerson Lehrman Group (GLG) Healthcare & Biomedical Council, Fortress Biotech, Sunovion Pharmaceuticals Inc., Sumitomo Dainippon Pharma, Janssen Research & Development, LLC, Magstim, Inc.; Stockholder:Xhale, Celgene, Seattle Genetics, Abbvie, OPKO Health, Inc., Bracket Intermediate Holding Corp., Network Life Sciences Inc.; Scientific Advisory Boards:American Foundation for Suicide Prevention (AFSP), Brain and Behavior Research Foundation (BBRF) (*formerly named National Alliance for Research on Schizophrenia and Depression* [*NARSAD*]), Xhale, Anxiety Disorders Association of America (ADAA), Skyland Trail, Bracket (Clintara), RiverMend Health LLC, Laureate Institute for Brain Research, Inc.; Board of Directors:AFSP, Gratitude America, ADAA; Income sources or equity of $10,000 or more:American Psychiatric Publishing, Xhale, Bracket (Clintara), CME Outfitters, Takeda; Patents:Method and devices for transdermal delivery of lithium (*US 6,375,990B1*)Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (*US 7,148,027B2*); Speakers Bureau: None.

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