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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

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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) [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, T wave inversion or new bundle branch blocking were prerequisites 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

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