

Short communication

Heart rate variability and markers of inflammation and coagulation in depressed patients with coronary heart disease

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Abstract

Background: Depression is associated with an increased risk for cardiac morbidity and mortality in patients with coronary heart disease (CHD). Cardiac autonomic nervous system (ANS) dysregulation, proinflammatory processes, and procoagulant processes have been suggested as possible explanations. **Methods:** Heart rate variability (HRV), an indicator of cardiac autonomic regulation, and markers of inflammation [C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α)] and coagulation (fibrinogen) were assessed in 44 depressed patients with CHD. **Results:** Moderate, negative correlations were found between fibrinogen and four

measures of HRV. IL-6 also negatively correlated with one measure of HRV (total power) and was marginally related to two others (very low frequency and low frequency power). Neither CRP nor TNF- α was significantly related to any measure of HRV. **Conclusions:** The finding that fibrinogen and IL-6 are moderately related to HRV suggests a link between these factors in depressed CHD patients. The relationship between ANS function and inflammatory and coagulant processes should be investigated in larger mechanistic studies of depression and cardiac morbidity and mortality.

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Introduction

Depression is an independent risk factor for cardiac morbidity and cardiac and all-cause mortality in patients with coronary heart disease (CHD) [1–4]. At least three biological factors that are thought to play important roles in cardiac morbidity and mortality have been associated with depression: proinflammatory processes, procoagulant processes, and altered cardiac autonomic nervous system (ANS) function [5,6].

Studies of medically healthy depressed psychiatric patients and of depressed CHD patients have found

depression to be associated with higher levels of the inflammatory risk markers interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor- α (TNF- α), and inflammatory-procoagulant markers such as fibrinogen [7–11]. Studies of depressed CHD patients have also reported low heart rate variability (HRV), suggesting inadequate cardiac parasympathetic and/or excessive cardiac sympathetic modulation [12]. These putative mechanisms have generally been described as though they are independent pathways, and no studies have attempted to determine whether or how they are related in depressed patients.

Both inflammatory and coagulant responses can be modulated by ANS activity [13,14], and a cholinergic anti-inflammatory pathway has recently been proposed in which there is vagal efferent inhibition of proinflammatory cytokine release, thereby reducing systemic inflammation

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[14,15] Low HRV, reflecting reduced vagal activity, should therefore be associated with higher levels of both proinflammatory and procoagulant markers. Recent studies have found a relationship between HRV activity and increased markers of inflammation in patients with heart failure [16,17] and acute coronary syndromes [18]. The purpose of this study was to determine whether a similar relationship exists between HRV and inflammatory and coagulant markers in another high-risk group: CHD patients with depression.

Methods

Subjects

One hundred thirty-two patients with documented CHD and without a recent (<3 months) acute coronary syndrome were recruited from cardiology practices at the Barnes-Jewish Hospital at Washington University School of Medicine to participate in a study of sleep disorders and depression. Patients who agreed to participate were scheduled for an eligibility screening. Candidates were excluded if they were found to have severe cognitive impairment, psychiatric conditions other than depression or anxiety, excessive substance or alcohol use, advanced malignancy, diabetic neuropathy, severe pulmonary disease, a diagnosed sleep disorder, valvular heart disease, active congestive heart failure, or an implanted pacemaker. Patients who met the eligibility criteria were scheduled for a two-night stay at the Washington University Sleep Medicine Center. The protocol was approved by the Institutional Review Board of Washington University School of Medicine and has been described in greater detail elsewhere [19]. The collection of blood samples was added to the protocol toward the end of the study, and, as a result, data are available on only 44 cases.

Depression assessment

The Depression Interview and Structured Hamilton (DISH) [20] was administered to diagnose major and minor depression according to the American Psychiatric Association's *DSM-IV* criteria [21] and to measure the severity of depression on an embedded 17-item version of the Hamilton Rating Scale for Depression (HRSD). Twenty patients met the *DSM-IV* criteria for current major depression and 24 met the *DSM-IV* criteria for minor depression.

Electrocardiography recording and HRV analyses

Polysomnographic data, including ECG, were recorded using Respironics Alice 3 and Alice 4 digital systems for two consecutive nights. Patients were asked to go to bed between 2200 and 2400 hours, and to remain in their rooms, generally in bed, throughout the recording period. Data

collection was initiated when the patients turned out their light to fall asleep and ended the following morning when they awakened and announced that they had finished sleeping (between 0600 and 0730 hours). The ECG signal quality was checked with a 12-lead ECG prior to recording. The ECG recordings from the second night of the sleep study were scanned at the HRV core laboratory at Washington University School of Medicine, on a Marquette SXP Laser scanner with software version 5.8 (Marquette Electronics, Milwaukee, WI, USA). The following indices were calculated: total power (TP) (1.15×10^{-5} –0.4 Hz), very low frequency (VLF) power (0.0033–0.04 Hz), low frequency (LF) power (0.04–0.15 Hz), and high-frequency (HF) power (0.15–0.40 Hz). HRV spectral analysis was performed on normal-to-normal ((N-N) interbeat intervals. Missing or noisy segments and ectopic beats were replaced by linear interpolation. Spectral power was calculated using fast Fourier transforms. Measurement of TP and VLF power were based on en bloc analysis of the total ECG recording. LF and HF power were measured from 5-min segments in which $\geq 80\%$ of the beats are normal. More details of the HRV analysis are available elsewhere [22]. The HRV distributions were skewed and consequently were natural log transformed (ln).

Inflammatory molecules

Three inflammatory markers (C-reactive protein [CRP], interleukin-6 [IL-6], and tumor necrosis factor- α [TNF- α]) and a marker of both inflammation and coagulation (fibrinogen) that have been implicated in the development and progression of CHD were measured [23–25].

Blood samples were drawn through antecubital venipuncture shortly after awakening the second night at the Sleep Medicine Center, between 0630 and 0730 hours.

Table 1
Demographics, depression, and medical characteristics

Variable (N=44)	Mean \pm S.D. or %
Age, years	59.3 \pm 9.8
Female gender	40.9%
Body mass index	29.7 \pm 5.9
Beck Depression Inventory	20.5 \pm 8.0
Hamilton Rating Scale for Depression	16.1 \pm 5.1
Diabetes	29.6%
History of hypertension	65.9%
History of smoking	65.9%
Hypercholesterolemia	81.8%
History of myocardial infarction	59.1%
History of congestive heart failure	20.5%
Prior angioplasty	59.1%
Prior bypass surgery	38.6%
LVEF <40	11.8%
Ace inhibitor	50.0%
Beta blocker	56.8%
Aspirin	72.7%
Hypolipidemics	77.3%

Table 2
Heart rate variability and inflammatory markers

Variable	Mean±S.D.	Normal range
LnTP (ms ²)	8.4±0.8	9.8±0.5 ^a
LnVLF (ms ²)	7.1±1.1	7.4±0.5
LnLF (ms ²)	6.1±1.3	6.5±0.7
LnHF (ms ²)	5.2±1.2	5.1±0.8
Fibrinogen (mg/dl)	375.3±77.7	150–450 ^b
C-reactive protein (mg/l)	3.9±4.0	1.0–3.0
Interleukin-6 (pg/ml)	12.9±15.7	0.31–5.0
Tumor necrosis factor-α (pg/ml)	8.2±5.8	1.2–15.3

TP, 1.15×10^{-5} –0.4 Hz; VLF power, 0.0033–0.04 Hz; LF power, 0.04–0.15 Hz; and HF power, 0.15–0.40 Hz.

^a Mean HRV for healthy middle-aged subjects [27].

^b Normal range for laboratory.

After the blood had been centrifuged for 25 min at 1000×g, the serum was aspirated, divided into aliquots, and frozen at –70°C. At the end of the study, the samples were thawed and assayed in a single batch. CRP was quantified by a high-sensitivity immunoassay on a BN-100 nephelometer (Dade-Behring, Deerfield, IL, USA). This assay has a sensitivity of 0.175 mg/l and intra- and interassay coefficients of variation of <10%. IL-6 and TNF were measured simultaneously using a commercially available immunoassay (Linco Research, St. Louis, MO, USA) on a Lumindex 100 (Luminex Corp., Austin, TX, USA). These assays have a sensitivity of <3.2 pg/ml and intra- and inter-assay coefficients of variation of <12%.

Results

The demographic and medical characteristics of the participants are presented in Table 1. The majority were male and the average age was 59. None of the patients had experienced a cardiac event within the last 6 months. All were free of acute infectious disease and had a normal complete blood count. ECG was recorded for a mean of 8.0 h (S.D.=0.5), and patients slept, as determined by standard sleep criteria [26], for a mean of 6.4 h (S.D.=0.9; range, 3.6–8.2) during the recording period.

Table 2 presents the means and standard deviations of all of the HRV measures and blood markers. The correlations between the four HRV indices and the markers of inflammation and coagulation are presented in Table 3. The sample sizes vary slightly across these correlations due to missing

blood test data. Higher concentrations of fibrinogen and IL-6 were associated with lower HRV. Levels of CRP and TNF were unrelated to any measure of HRV.

In order to determine whether actual time spent asleep was related to the primary variables, the number of hours of sleep was correlated with the indices of HRV, inflammation, and coagulation. The correlations ranged from 0.00 to 0.29 (all *P*'s >.05).

Discussion

Three of the four HRV indices tended to be lower than those reported for a medically well, middle-aged population [27], and all of the inflammatory markers as well as fibrinogen were in the high normal or abnormal range, as would be expected in patients with CHD and depression [1,2]. Moderate, negative correlations were found between fibrinogen and all four HRV indices. IL-6 also negatively correlated with LnTP, LnLF, and LnVLF. Neither CRP nor TNF-α was significantly related to any measure of HRV in this sample of depressed CHD patients. However, the magnitude of the correlations between the HRV measures and CRP was just below that reported in a larger study of patients with unstable angina [18], suggesting that the present study may have lacked adequate statistical power to detect a significant effect. Fibrinogen, an index of both inflammation and coagulation, was more strongly related to HRV than any other marker. Like CRP, fibrinogen is an inflammation-sensitive protein which is comparable to CRP as a risk factor for CHD [25], but it is also involved in the clotting cascade as a major determinant of blood viscosity and as a cofactor in platelet aggregation [28,29].

LnTP, which correlated with fibrinogen and IL-6, and LnLF, which correlated with fibrinogen and IL-6, reflect both parasympathetic and sympathetic modulation, as well as other sources of variations in heart rhythm [12]. LnHF, which was associated with fibrinogen in this study, reflects parasympathetic modulation of heart rate [12]. LnVLF power also primarily reflects parasympathetic modulation of heart rate [30] and was correlated with fibrinogen and IL-6. Thus, the associations between the HRV measures and inflammatory markers may be attributable to deficits in parasympathetic modulation of immunity and coagulation, as has been proposed [14,15], but the possibility that elevated sympathetic activity also plays a role cannot be

Table 3
Correlations between nighttime HRV and inflammatory and coagulant markers

	Fibrinogen		IL-6		CRP		TNF-α	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
LnTP	–0.50	0.002	–0.40	0.02	–0.12	0.49	–0.04	0.84
LnVLF	–0.55	0.0005	–0.37	0.04	–0.15	0.40	–0.12	0.53
LnLF	–0.54	0.0007	–0.38	0.03	–0.17	0.32	–0.04	0.83
LnHF	–0.35	0.04	–0.26	0.15	–0.11	0.54	–0.15	0.41

ruled out. Furthermore, because this study has only established a cross-sectional relationship, it is possible that increased inflammatory and coagulant activity may be acting in some way to lower HRV.

Because of the small sample size, subgroup analyses (e.g., diabetes, older age, use of beta blockers) were not performed. However, a previous study of patients with unstable angina found little variation in the relationship between HRV and inflammation among these subgroups. HRV continued to be associated with markers of inflammation after adjusting for relevant covariates [18]. This suggests that the relationship between HRV and markers of inflammation generalizes across risk factors, medical treatment regimens, and medical history.

We only analyzed nighttime HRV and morning levels of the inflammatory markers. Future studies should measure HRV and the inflammatory markers over the course of 24 h to determine whether there is a consistent circadian pattern to these relationships. Furthermore, this study did not include a nondepressed group of patients with CHD, or a group of medically well-depressed patients, and thus it cannot be concluded that depression is responsible for the relationships that were observed. In fact, it is unlikely that depression per se is responsible for them, as similar relationships between these risk markers have been reported in studies of other high-risk patients [17,18]. The present study was only intended to show that these risk markers are also related in depressed patients.

The actual time spent asleep during HRV measurement varied across subjects, but it was not significantly related to either HRV or to the inflammatory markers, perhaps because patients generally remained inactive and in bed during the night, regardless of whether or not they were asleep. However, a modest relationship between the duration of sleep and the risk markers cannot be ruled out due to the relatively low statistical power of the study.

Although the procoagulant and inflammatory markers, HRV, and depression were carefully assessed in this group of patients with documented CHD, the sample consisted of only 44 cases. Thus, replication of these findings in a larger sample is needed. Future studies of the putative mechanisms underlying the relationship of depression to medical outcome should further elucidate their relationship to each other and to depression, and determine how this relationship may contribute to an increased risk for cardiac morbidity and mortality.

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