Published in final edited form as:
J Psychosom Res. 2007 April ; 62(4): 463–467.

Heart Rate Variability and Markers of Inflammation and Coagulation in Depressed Patients with Coronary Heart Disease

Robert M. Carney, PhD[1], **Kenneth E. Freedland, PhD**[1], **Phyllis K. Stein, PhD**[2], **Gregory E. Miller, PhD**[4], **Brian Steinmeyer, MA**[1], **Michael W. Rich, MD**[2], and **Stephen P. Duntley, MD**[3]

1 *Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA*

2 *Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA*

3 *Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA*

4 *Department of Psychology, University of British Columbia, Vancouver, Canada*

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 (TNF∝)] 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 were 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 autonomic nervous system function and inflammatory and coagulant processes should be investigated in larger mechanistic studies of depression and cardiac morbidity and mortality.

Keywords

Autonomic Nervous System; Coagulation; Depression; Heart Disease; Inflammation

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 have been associated with depression have been suggested as possible mechanisms: altered cardiac autonomic function, proinflammatory processes, and procoagulant processes (5,6).

Requests for reprints should be sent to Robert M. Carney, PhD, Behavioral Medicine Center, 4625 Lindell Blvd., Suite 420, St. Louis, Missouri 63108. Telephone: 314-286-1300. Fax: 314-286-1301. carneyr@bmc.wustl.edu.

These putative mechanisms have generally been described as though they are independent pathways, and few studies have attempted to determine whether or how they are related.

Heart rate variability (HRV) analysis is widely used for studying cardiac autonomic nervous system (ANS) modulation (7). Low HRV reflects inadequate cardiac parasympathetic or excessive cardiac sympathetic modulation (7), and is a strong, independent predictor of mortality in CHD patients (7). Many studies have found lower HRV in depressed compared to nondepressed CHD patients, especially after an acute myocardial infarction (6).

Coronary artery disease is believed to be a chronic inflammatory process involving immune responses to injuries of the vascular endothelium (8,9). There is also evidence that procoagulant processes promote the development of atherosclerosis and thrombotic events (8). Studies of medically healthy depressed psychiatric patients and of depressed CHD patients have generally found depression to be associated with higher levels of the inflammatory risk markers interleukin-6, C-reactive protein, and tumor necrosis factor-alpha, and inflammatory-procoagulant markers such as fibrinogen (10–14).

HRV and markers of inflammation and coagulation have usually not been studied in the same sample of depressed CHD patients. It remains unclear whether or how these putative mechanisms may be related. Both inflammatory and coagulant responses can be modulated by ANS activity (15,16), 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 (16,17). Studies using HRV as an index of vagal modulation have found a relationship between HRV activity and increased markers of inflammation in patients with heart failure (18,19) and acute coronary syndromes (20). The purpose of this study was to examine the relationship between HRV and markers of inflammation and coagulation in a group of depressed patients with stable CHD.

Methods

Subjects

One hundred thirty-two patients with documented CHD 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/alcohol use, patients with 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 (21). The sample for the present substudy consisted of 44 depressed patients who provided data on HRV and inflammatory and coagulant markers. 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) (22) was administered to diagnose major and minor depression according to the American Psychiatric Association’s DSM-IV criteria (23) 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.

Electrocardiograpy and HRV Analyses

Polysomnographic data, including ECG, were obtained from Respironics Alice 3 and Alice 4 digital systems. 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, Wisconsin, USA). HRV spectral analyses were performed by partitioning the heart rate variance into spectral components and quantifying their power according to standard techniques. Details of this analysis are available elsewhere (24). The following indices were calculated: total power (TP)($1.15X10^{-5}$ –0.4hz), very low frequency (VLF) power (0.0033–0.04hz) ; low frequency (LF) power (0.04–0.15hz); and high frequency (HF) power (0.15–0.40hz). 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 (TNF∝)] and a marker of both inflammation and coagulation [fibrinogen] that have been implicated in the development and progression of CHD were measured (8–9,25). Blood samples were drawn through antecubital venipuncture within one hour of awakening on the second night at the Sleep Medicine Center. After the blood had been centrifuged for 25 minutes at 1000 x 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). This assay has a sensitivity of .175 mg/L and intra- and inter-assay coefficients of variation < 10%. IL-6 and TNF∝ were measured using commercially available immunoassay (Linco Research) on a Luminex 100. These assays have a sensitivity of < 3.2 pg/ml and intra- and inter-assay coefficients of variation < 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.

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 fibrinogen concentration was associated with low HRV. Patients with higher IL-6 had lower LnTP, and tended to have lower LnVLF, and LnLF. Levels of CRP and TNF were unrelated to any measure of HRV.

Discussion

Moderate, negative correlations were found between fibrinogen and all four HRV indices. Il-6 also negatively correlated with LnTP and was marginally related to both LnLF and LnVLF. Neither CRP nor TNF-α were 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 were similar to those reported in a larger study of patients with unstable angina (20), suggesting that the present study may have lacked adequate statistical power. 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 a cofactor in platelet aggregation (26–27).

LnTP, which correlated with fibrinogen and Il-6, and LnLF, which correlated with fibrinogen and marginally with Il-6, reflect both parasympathetic and sympathetic modulation, as well as other sources of variations in heart rhythm (7). LnHF, which was associated with fibrinogen in this study, reflects parasympathetic modulation of heart rate (7). LnVLF power also reflects parasympathetic modulation of heart rate(28), and was correlated with fibrinogen, and marginally correlated with 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 (16,17), but the possibility that elevated sympathetic activity also plays a role cannot be 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, and that HRV continued to be associated with markers of inflammation after adjusting for relevant covariates. (20) This suggests that the relationship between HRV and markers of inflammation generalizes across risk factors, medical treatment regimens, and medical history.

The purpose of this study was to determine whether there is a relationship between HRV and markers of inflammation and coagulation in depressed patients with stable CHD. The finding that fibrinogen and Il-6 are moderately related to HRV suggests a link between these factors in depressed CHD patients. 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 be designed to further elucidate their relationship to each other and to depression, and to determine how they may contribute to an increased risk for cardiac morbidity and mortality.

Acknowledgements

This research was supported by Grant No. R01 HL65356 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, the Lewis and Jean Sachs Charitable Lead Trust, and the National Alliance for Research on Schizophrenia and Depression (GEM).

References

1. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. Am J Psychiat 1998;155:4–111. [PubMed: 9433332]
2. Carney RM, Freedland KE. Depression, mortality and medical morbidity, in patients with coronary heart disease. Biol Psychiat 2003;54:241–247. [PubMed: 12893100]
3. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. Psychosom Med 2004;66:802–813. [PubMed: 15564343]
4. Van Melle JP, de Jonge P, Spijkerman TA, Tijssen JG, Ormel J, van Veldhuisen DJ, van den Brink RHS, van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: A meta-analysis. Psychosom Med 2004;66:814–822. [PubMed: 15564344]
5. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: A review of potential mechanisms. J Psychosom Res 2002;53:897–902. [PubMed: 12377300]

6. Carney RM, Freedland KE, Rich MW, Jaffe AS. Depression as a risk factor for cardiac events in established coronary heart disease: A review of possible mechanisms. Ann Behav Med 1995;17:142–149.
7. Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology. Circulation 1996;93:1043–1065. [PubMed: 8598068]
8. Berliner A, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: Basic mechanisms. Circulation 1995;91:2488–2496. [PubMed: 7729036]
9. Ross R. Atherosclerosis - An inflammatory disease. NEJM 1999;340:115–126. [PubMed: 9887164]
10. Maes M, Meltzer HY, Bosmans E, Bergmans R, Vandoolaeghe E, Ranjan R, Desnyder R. Increased plasma concentrations of interleukin-6, soluble interleukin–6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disorders 1995;34:301–309. [PubMed: 8550956]
11. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9:853–858. [PubMed: 9367546]
12. Dentino AN, Pieper CF, Rao KMK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. J Am Geriatrics Soc 1999;47:6–11.
13. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. Am J Cardiol 2003;90:1279–1283. [PubMed: 12480034]
14. Von Kanel R, Mills PJ, Fainman C, Dimsdale JE. Effects of psychological stress and psychiatric disorders on blood coagulation and fibrinolysis: A biobehavioral pathway to coronary artery disease? Psychosom Med 2001;63:531–544. [PubMed: 11485106]
15. März P, Cheng JG, Gadient RA, Patterson PH, Stoyan T, Otten U, Rose-John S. Sympathetic neurons can produce and respond to interleukin 6. Proc Natl Acad Sci USA 1998;95:3251–3256. [PubMed: 9501249]
16. Tracey KJ. The inflammatory reflex. Nature 2002;420:853–859. [PubMed: 12490958]
17. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun 2005;19:493–499. [PubMed: 15922555]
18. Aronson D, Mittleman MA, Burger AJ. Interleukin-6 levels are inversely correlated with heart rate variability in patients with decompensated heart failure. J Cardiovasc Electrophysiol 2001;12:294–300. [PubMed: 11291801]
19. Malave HA, Taylor AA, Nattama J, Deswal A, Mann DL. Circulating levels of tumor necrosis factor correlate with indexes of depressed heart rate variability: a study in patients with mild-to-moderate heart failure. Chest 2003;123:716–724. [PubMed: 12628868]
20. Lanza GA, Sgueglia GA, Cianflone D, Rebuzzi AG, Angeloni G, Sestito A, Infusino F, Crea F, Maseri A. for the SPAI (Stratificazione Prognostica dell' Angina Instabile) Investigators. Relation of heart rate variability to serum levels of C-reactive protein in patients with unstable angina pectoris. Am J Cardiol 2006;97:1702–1706. [PubMed: 16765117]
21. Carney RM, Howells WB, Freedland KE, Duntley SP, Stein PK, Rich MW, Miller GE. Depression and obstructive sleep apnea in patients with coronary heart disease. Psychosom Med 2006;68:443–448. [PubMed: 16738077]
22. Freedland KE, Skala JA, Carney RM, Raczynski JM, Taylor CB, Mendes de Leon CF, Ironson G, Youngblood ME, Krishnan KRR, Veith RC. for the ENRICHD Investigators. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. Psychosom Med 2002;64:897–905. [PubMed: 12461195]
23. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington DC: 1994.
24. Rottman JN, Steinman RC, Albrecht P. Efficient estimation of the heart period power spectrum suitable for physiologic or pharmacologic studies. Am J Cardiol 1990;66:1522–1524. [PubMed: 2252008]
25. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease. JAMA 1998;279:1477–1482. [PubMed: 9600484]

26. Sinzinger, H.; Pirich, C. Platelet function and fibrinogen. In: Ernst, E.; Koenig, W.; Lowe, GDO.; Meade, TW., editors. Fibrinogen: A “New” Cardiovascular Risk Factor. Vienna, Austria: Blackwell-MZV; 1992. p. 46-50.

27. Thompson, WD.; Stirk, CM.; Smith, EB. Fibrin degradation products as the pathological growth stimulus to atherosclerotic plaque formation. In: Ernst, E.; Koenig, W.; Lowe, GDO.; Meade, TW., editors. Fibrinogen: A “New” Cardiovascular Risk Factor. Vienna, Austria: Blackwell-MZV; 1992. p. 35-40.

28. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low- frequency RR-interval oscillations in humans. Circulation 1998;98:547–55. [PubMed: 9714112]

Table 1

Demographics, Depression, and Medical Characteristics

Variable	MEAN ± SD OR PERCENT
Age, years	59.3 ± 9.8
Gender, female	40.9%
Body Mass Index	29.7 ± 5.9
Beck Depression Inventory	20.5 ± 8.0
Hamilton Rating Scale	16.1 ± 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 Inhibitors	50.0%
Beta Blockers	56.8%
Aspirin	72.7%
Hypolipidemics	77.3%

Table 2

Heart Rate Variability and Inflammatory Markers

VARIABLE	MEAN ± SD
N Log Total Power	8.4 ± 0.8
N Log Very Low Frequency Power	7.1 ± 1.1
N Log Low Frequency Power	6.1 ± 1.3
N Log High Frequency Power	5.2 ± 1.2
Fibrinogen	375.3 ± 77.7
C-Reactive Protein, mg/L	3.9 ± 4.0
Interleukin-6, pg/ml	19.2 ± 35.7
Tumor Necrosis Factor-α, pg/ml	8.2 ± 5.8

Table 3

Correlations Between HRV and Inflammatory and Coagulant Markers

	Fibrinogen		IL-6		CRP		TNF-α	
	r	p	r	p	r	p	r	p
LnTP	−0.50	0.002	−0.38	0.03	−0.12	0.49	−0.04	0.84
LnVLF	−0.55	0.0005	−0.32	0.07	−0.15	0.40	−0.12	0.53
LnLF	−0.54	0.0007	−0.32	0.07	−0.17	0.32	−0.04	0.83
LnHF	−0.35	0.04	−0.19	0.31	−0.11	0.54	−0.15	0.41