Heart Rate Variability in Depressed Elderly

Ripu D. Jindal, M.D., **Raymond C. Vasko Jr., Ph.D.**, **J. Richard Jennings, Ph.D.**, **Amy L. Fasiczka, M.A.**, **Michael E. Thase, M.D.**, and **Charles F. Reynolds III, M.D.**
From the Department of Psychiatry, University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA

Abstract

Objective—The present study examines a measure of cardiac autonomic function, the heart rate variability (HRV), in a group of depressed elderly. Cardiac autonomic abnormalities have been implicated as a potential mediator of cardiovascular events and sudden death in depression. Because aging is associated with decreased cardiac vagal activity, it is possible that autonomic abnormalities are even more pronounced in the older depressed patients.

Design—Cross-sectional comparison between those with or without depression. The groups were compared using the Wilcoxon matched-pair sign-rank test.

Setting—Advanced Center for Interventions and Services Research for Late-Life Mood Disorders at University of Pittsburgh Medical Center.

Participants—Fifty-three patients with major depression (mean age: 73.3; SD: 7.4; range: 60–93) and an equal number of age and gender-matched subjects as a comparison group.

Intervention—None.

Measurements—Time domain and frequency domain measures of HRV.

Results—The groups did not differ in any of the time domain or frequency domain measures of HRV. As expected, subjects without depression displayed decreasing cardiac vagal function with aging (Spearman correlation coefficient $r_s = -0.33$, $p = 0.02$). However, there was no significant change in vagal function with age in the depressed ($r = 0.12$, $p = 0.38$). Post-hoc analysis using Fisher's z_r transformation revealed that the relationship between age and cardiac vagal function was significantly different between the groups ($z = 2.32$, $p = 0.02$).

Conclusions—Our findings suggest that age has differential influence on vagal function in individuals with and without depression, a difference with implications for cardiovascular disease risk in depression. Prospective studies of cardiac vagal activity in depressed patients with or without preexisting cardiac disease in different age groups are needed to replicate and extend these findings.

Keywords

Depression; cardiac vagal function; heart rate variability; aging; coronary artery disease

Depression increases risk of cardiovascular morbidity and mortality.[1–3] Though the exact mechanisms are not clear, one hypothesis is that autonomic dysfunction associated with depression increases risk for cardiovascular morbidity.[4–6]

Send correspondence and reprint requests to Ripu D. Jindal, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593. jindalr@upmc.edu.

Heart rate variability (HRV) provides a useful measure of autonomic activity (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[7]) and has found wide application in psychophysiology. Though the clinical significance of the low-frequency (LF) component of HRV remains controversial, the Task Force has supported the use of the high-frequency (HF) component of HRV as a marker of cardiac parasympathetic activity.

Most relevant studies have documented autonomic dysfunction in depression, particularly decreased HRV and reduced cardiac parasympathetic activity.[8–11] In a study by Agelink et al., [8] parasympathetic HRV indices correlated inversely with the severity of depression. An earlier study[12] had shown that an increase in cardiac parasympathetic activity correlated with clinical improvement during successful treatment of depression. In a large multisite study of 804 postmyocardial infarction patients, Carney et al.[4] have demonstrated decreases in several indices of HRV in depressed patients as compared with non-depressed comparison subjects.

Most of the available data describe cardiac autonomic function in young- and middle-aged patients with depression. Although valuable, research in patients at greater risk of heart disease could have more clinical relevance. Because normal aging is associated with reduced HRV, [13–15] it is possible that depression in old age further reduces HRV, potentially posing an increased risk of cardiovascular morbidity and mortality. Moreover, multiple lines of evidence suggest that depression beginning in late life has a different etiopathogenesis from earlier-onset depression.[16–20] Thus, the clinical relevance of cardiac parasympathetic activity in late-life depression needs to be investigated systematically.

Recently, one epidemiologic study that included both middle aged and elderly people (mean age: 62 years for depressed and 68 for the nondepressed) did not detect an association between HRV and depression.[21] The study was comparable in size (N = 873) with that of Carney et al., [4] and the investigators attributed the discrepancy to the fact that they had included medically stable patients with coronary artery disease, whereas Carney et al.[4] had examined postmyocardial infarction patients. Findings of this epidemiologic study[21] thus warrant replication in controlled clinical investigation.

One small clinical study has assessed cardiac parasympathetic activity in late-life depression. [22] In this report, 11 patients (mean age: 70 years; range: 60–84) were studied before and after electroconvulsive therapy. An increase in cardiac parasympathetic activity with successful treatment of depression was noted. However, absent a normal comparison group, it could not be established that the study group actually had diminished cardiac parasympathetic activity before treatment.

We present the results of a study comparing cardiac parasympathetic activity in 53 elderly patients with current major depressive episode and an equal number of age- and sex-matched healthy subjects without depression. We hypothesized that elderly depressed patients would have lower cardiac parasympathetic activity than their nondepressed counterparts, as manifested by time- and frequency-domain measures of HRV.

METHODS

Subjects

Patients participated in a research protocol titled "Use of Sleep Deprivation for Accelerated Recovery from Late-Life Depression."[23] Of the 80 participants enrolled in that study, it was possible to age- and sex-match 53 participants with healthy subjects for comparison. The subjects in the comparison group had been recruited for participation in several studies[24–26] conducted at the Advanced Center for Interventions and Services Research for Late-Life Mood

Disorders at University of Pittsburgh Medical Center (MH071944; C.F. Reynolds III, PI). The matching of cases with comparison subjects was done without knowledge of HRV data. All research protocols were approved by the institutional review board for the ethical treatment of human subjects, and all subjects provided explicit written informed consent.

All participants had a complete physical and neurologic examination, an electrocardiogram (ECG) and routine blood work (including complete blood count, metabolic profile, thyroid function tests, and vitamin B_{12} and folate levels). Thereafter, eligible subjects were further evaluated to determine if they met the inclusion criteria. Patients were offered enrollment in the protocol if they: a) met the criteria of *Diagnostic and Statistical Manual of Mental Disorders —4th edition* for major depressive disorder without psychotic features; b) scored ≥17 on the first 17 items of the Hamilton Rating Scale for Depression;[27] c) had been free of all antidepressant and benzodiazepines for 2 weeks (and fluoxetine for 6 weeks); and d) were clinically and chemically euthyroid, either with or without thyroid replacement therapy. Those meeting criteria for lifetime diagnosis of any psychotic disorder or bipolar disorder as well as those meeting criteria for drug or alcohol abuse in the past 6 months were excluded from participation. A history of seizure disorder, diabetes, baseline apnea–hypopnea index of ≥10, and abnormal ECGs (either rate of less than 50 bpm or conduction disturbance) were also used as exclusion criteria for the study. Subjects were not excluded on the basis of gender or ethnic group status.

Demographic features for the groups are presented in Table 1. Because of the prior matching, the groups were comparable in terms of age and gender. The groups were also comparable in terms of ethnicity. The depressed group had greater scores on the Cumulative Illness Rating Scale for Geriatrics,[23] a measure of coexisting medical burden, with trends toward greater burden of heart disease ($p = 0.07$), and vascular disease in the depressed group ($p = 0.06$).

HRV Indices

All ECG recording and frequency domain analyses were performed according to the standardized practices established by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996). ECG recordings were made in quiet rooms during spontaneous breathing. Because of the well-documented diurnal effects of HRV measures, all recordings were done around the same time of day. HRV measures were recorded in 5-minute segments during wakefulness. The data were recorded in the evening before the participants retired. The ECG was recorded using gold (Au) electrodes, with all electrode impedances verified to be less than 5 kΩ. ECG signals were amplified by using Grass 7P511 amplifiers (Grass Instruments, Inc). The autoregressive analysis of heart period variability was implemented using MATLAB software (The MathWorks Inc, Natick, MA: www.mathworks.com).

From the ECG recordings, measures calculated were a) mean interbeat interval (mean duration of the interbeat interval between *R*-wave spikes; and b) the root mean square successive difference (RMSSD; the root mean square of the difference between successive *R*-R intervals in milliseconds), an index of vagally mediated HRV.[28] The autoregressive algorithm used for data analyses has been validated in previous studies by different research groups.[29,30] The frequency bands extracted from the power spectrum were HF power (0.15–0.40 Hz) and LF power (0.04–0.15 Hz). These indices are measured in units of power ($msec^2$).

Statistical Analysis

Demographic variables were compared using group t tests or χ^2 tests for contingency tables. Because of the distribution of HRV data, Wilcoxon matched-pairs signed rank test and Spearman rank correlation were used. Analyses were performed with alpha set at 0.05.

RESULTS

Because of prior matching, the groups were comparable in terms of age and gender. The groups were also comparable in terms of ethnicity. The depressed group expectedly scored higher on the Hamilton depression scale (Ham-D17), but also had lesser scores on the Folstein Mini-Mental Status Exam and greater scores on the Cumulative Illness Rating Scale for Geriatrics, [31] a measure of coexisting medical burden.

HRV Measures

The two groups did not differ in terms of RMSSD, HF, very low-frequency power, LF power, LF or HF ratio, total power or normalized HF power. Even male and female subgroups when compared separately did not differ statistically.

Correlations Between Age and HRV

Because the physiologic significance of LF HRV is controversial (Task Force Report[11]), we decided to focus on HF measures for the correlational analyses between age and HRV. We used Spearman rank correlation analyses to examine the relationship between age and HF power for patients and comparison subjects separately. As expected, increasing age was associated with decreased HF power in the comparison group ($r_s = -0.33$, p <0.02). However, the depressed group did not show an association between age and HF power ($r_s = 0.12$, p = 0.38). A Fisher's z_r transformation of the two correlation coefficients revealed that the relationship between age and HF significantly was different between the two groups (z = 2.32, p = 0.02). Excluding data from one outlier did not alter the relationship.

DISCUSSION

Although our study of elderly subjects did not detect any difference in HRV measures between the depressed and the nondepressed during wakefulness, there was an interesting (and unanticipated) interaction between age and diagnostic group. Specifically, we found the expected decrease in HRV with increasing age among the nondepressed group; however, no such association was observed in the depressed group. Inspection of regression lines, in fact, suggests that between-group differences might be evident before age 60, but not thereafter. The correlation between age and decreased HRV in the comparison subjects was only modest ($r_s = -0.33$, p <0.02). This was not surprising since continued decline in HRV may leave the elderly with very little (HRV) to lose.

As stated earlier, two large studies, i.e., Carney et al.[4] and Gehi et al.[21] have yielded conflicting results for the 24-hour HRV in depression. Gehi et al.[21] attributed their failure to replicate the finding of decreased HRV in depression to the stable nature of coronary artery disease of participants. Our results suggest that older age of the participants in the study by Gehi et al. [21] (62 years[11] N = 195 versus 57.1[12.3], N = 380, t = 4.64, p <0.0001) may also have contributed to their failure to replicate the findings of Carney et al.[4]

Because the group with depression showed evidence of greater overall medical burden, with trends toward greater burden of heart disease and vascular disease, which can be expected to decrease cardiac vagal activity, the differential in medical burden is unlikely to have contributed to our inability to find lesser cardiac vagal activity in the depressed group.

Mild cognitive impairment in one group may have been the result of depression. However, in a recent study, cognitive depressive symptoms were not associated with low HRV, but somatic depressive symptoms were.[32] Extrapolation may suggest that our results were not influenced by the mild cognitive impairment due to depression. A second possible threat to validity could be that our sample size (N = 53) did not give us enough power to detect difference between

the groups. However, even smaller studies have detected decreased HRV in younger patients with depression.[12,33] The generalizability of our data are also limited by the lack of information regarding history of smoking, head injury, physical activity, and eating choices of the subjects. However, since patients with depression can be expected to be the ones more likely to smoke than those without depression, it is unlikely that smoking contributed to our failure to detect differences in the groups. Finally, interpretation of HRV is not without its own caveats.[34]

Despite these limitations, our work underscores the need for future studies of HRV in elderly depressed patients. The association of depression with greater nonsuicide related mortality rates, usually attributed to cardiovascular factors, may be explained in part by decreased HRV. Wulsin et al.[35] have reviewed studies of depression and heart disease, and concluded that though these studies overwhelmingly show an association between depression and increased mortality rates, the majority are poorly controlled and do not account adequately for physical illness, smoking, alcohol, and suicide. Our results indicate that stratification of data by age in the studies of heart disease in depression may lead to more conclusive results.

Acknowledgments

References

1. Anda R, Williamson D, Jones D, et al. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. Epidemiology 1993;4:285–294. [PubMed: 8347738]

2. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. JAMA 1993;270:1819–1825. [PubMed: 8411525]

3. Luukinen H, Laippala P, Huikuri HV. Depressive symptoms and the risk of sudden cardiac death among the elderly. Eur Heart J 2003;24:2021–2026. [PubMed: 14613738]

4. Carney RM, Blumenthal JA, Stein PK, et al. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001;104:2024–2028. [PubMed: 11673340]

5. Carney RM, Freedland KE, Miller GE, et al. 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. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. Neurosci Biobehav Rev 2002;26:941–962. [PubMed: 12667498]

7. Inoue T, Domae M, Yamada K, et al. Effects of the novel antipsychotic agent 7-(4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2(1H)-quinolinone (OPC-14597) on prolactin release from the rat anterior pituitary gland. J Pharmacol Exp Ther 1996;277:137–143. [PubMed: 8613910]

8. Agelink MW, Majewski T, Wurthmann C, et al. Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. J Affect Disord 2001;62:187–198. [PubMed: 11223106]

9. Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. J Clin Psychiatry 1990;51(suppl):4–9. [PubMed: 2195012]discussion 10–11

10. Guinjoan SM, Bernabo JL, Cardinali DP. Cardiovascular tests of autonomic function and sympathetic skin responses in patients with major depression. J Neurol Neurosurg Psychiatry 1995;59:299–302. [PubMed: 7673960]

11. Tulen JH, Bruijn JA, de Man KJ, et al. Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine (Org 3770). J Clin Psychopharmacol 1996;16:135–145. [PubMed: 8690829]

12. Balogh S, Fitzpatrick DF, Hendricks SE, et al. Increases in heart rate variability with successful treatment in patients with major depressive disorder. Psychopharmacol Bull 1993;29:201–206. [PubMed: 8290666]

13. Yeragani VK, Sobolewski E, Kay J, et al. Effect of age on long-term heart rate variability. Cardiovasc Res 1997;35:35–42. [PubMed: 9302345]

14. Jennings JR, Mack ME. Does aging differentially reduce heart rate variability related to respiration? Exp Aging Res 1984;10:19–23. [PubMed: 6734682]

15. Agelink MW, Malessa R, Baumann B, et al. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 2001;11:99–108. [PubMed: 11570610]

16. Nobler MS, Pelton GH, Sackeim HA. Cerebral blood flow and metabolism in late-life depression and dementia. J Geriatr Psychiatry Neurol 1999;12:118–127. [PubMed: 10593700]

17. Alexopoulos GS, Meyers BS, Young RC, et al. 'Vascular depression' hypothesis. Arch Gen Psychiatry 1997;54:915–922. [PubMed: 9337771]

18. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry 1997;154:497–501. [PubMed: 9090336]

19. Krishnan KR, Hays JC, Tupler LA, et al. Clinical and phenomenological comparisons of late-onset and early-onset depression. Am J Psychiatry 1995;152:785–788. [PubMed: 7726320]

20. Krishnan KR, Taylor WD, McQuoid DR, et al. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol Psychiatry 2004;55:390–397. [PubMed: 14960292]

21. Gehi A, Mangano D, Pipkin S, et al. Depression and heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. Arch Gen Psychiatry 2005;62:661–666. [PubMed: 15939843]

22. Nahshoni E, Aizenberg D, Sigler M, et al. Heart rate variability in elderly patients before and after electroconvulsive therapy. Am J Geriatr Psychiatry 2001;9:255–260. [PubMed: 11481133]

23. Reynolds CF III, Smith GS, Dew MA, et al. Accelerating symptom-reduction in late-life depression: a double-blind, randomized, placebo-controlled trial of sleep deprivation. Am J Geriatr Psychiatry 2005;13:353–358. [PubMed: 15879583]

24. Hoch CC, Dew MA, Reynolds CF III, et al. A longitudinal study of laboratory- and diary-based sleep measures in healthy "old old" and "young old" volunteers. Sleep 1994;17:489–496. [PubMed: 7809561]

25. Monk TH, Buysse DJ, Reynolds CF III, et al. Circadian temperature rhythms of older people. Exp Gerontol 1995;30:455–474. [PubMed: 8557094]

26. Monk TH, Buysse DJ, Carrier J, et al. Effects of afternoon "siesta" naps on sleep, alertness, performance, and circadian rhythms in the elderly. Sleep 2001;24:680–687. [PubMed: 11560181]

27. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62. [PubMed: 14399272]

28. Hayano J, Sakakibara Y, Yamada A, et al. Accuracy of assessment of cardiac vagal tone by heart rate variability in normal subjects. Am J Cardiol 1991;67:199–204. [PubMed: 1987723]

29. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–193. [PubMed: 2874900]

30. Thayer JF, Peasley C, Muth ER. Estimation of respiratory frequency from autoregressive spectral analysis of heart period. Biomed Sci Instrum 1996;32:93–99. [PubMed: 8672696]

31. Conwell Y, Forbes NT, Cox C, et al. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. J Am Geriatr Soc 1993;41:38–41. [PubMed: 8418120]

32. de Jonge P, Mangano D, Whooley MA. Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: findings from the Heart and Soul Study. Psychosom Med 2007;69:735–739. [PubMed: 17942844]

33. Stein PK, Carney RM, Freedland KE, et al. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. J Psychosom Res 2000;48:493–500. [PubMed: 10880671]

34. Berntson GG, Bigger JT Jr, Eckberg DL, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34:623–648. [PubMed: 9401419]

35. Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med 1999;61:6–17. [PubMed: 10024062]

TABLE 1

Demographic and Clinical Characteristics

| | Controls (n = 53), Mean SD | Depressed (n = 53), Mean SD | Test | |
			t or χ^2	p
Age (years)	74.1 (7.4)	73.3 (7.4)	t = 0.7[a]	0.52
Gender (men/women)	16/37	16/37	χ^2 = 0.0[b]	1.00
Race (white/other)	39/12	45/8	χ^2 = 1.2[b]	0.28
Hamilton 17-item total[c]	2.0 (2.1)	20.3 (3.1)	t = −34.7[a]	0.0001
Folstein Mini-Mental Exam[d]	29.2 (1.0)	28.3 (2.2)	t = 2.5[a]	0.01
Cumulative Illness Rating Scale[e]	7.3 (3.5)	9.1 (4.0)	t = 32.3[a]	0.02
Age of first episode of depression		55.3 (21.0)		
Median	—	62.0	—	—
Depressive subtype (single/recurrent)	—	26/27	—	—
Number of previous episodes of depression		0.5 (0.6)		
Median	—	1.0	—	—
Duration of current episode (weeks)		120.5 (169.3)		
Median	—	52.0	—	—

[a] t test for independent groups.

[b] Chi-square for contingency tables.

[c] N reduced to 46 in the control group.

[d] N reduced to 44 in the control group.

[e] N reduced to 46 in the control group and 52 in the depressed group.