Heart Rate Variability in Depressed Patients

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ABSTRACT:
HEART RATE VARIABILITY IN DEPRESSED PATIENTS

Objective: There are conflicting results on the relationship between heart rate variability (HRV) and major depression. There is some research reporting decreased heart rate variability in depressed patients, which may result in increased cardiovascular mortality and morbidity. This study aims to investigate the HRV in a group of physically healthy depressed patients in comparison to healthy subjects. **Method:** Twenty-one depressed subjects were compared to same number of healthy controls on the measures of HRV as measured by Kardiosis DL 700 Digital tree channel recorder Holter monitors. The study group was also assessed with Hamilton anxiety and depression scales. The HRV measures were compared in between the two groups and correlations between levels of anxiety and depression with HRV measures were sought for. **Results:** There was no statistically significant difference between the study and control groups on the measures of HRV. No significant relationship between the levels of anxiety and depression and HRV measures were found. **Conclusions:** In physically healthy depressed adults HRV does not differ from healthy subjects. This means that depression does not pose an additional risk factor for cardiovascular disease in physically healthy adults. This finding gives support to some previous research which did not find any relationship between depression and heart rate variability.

Key Words: depression, heart rate variability, anxiety, coronary artery disease

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INTRODUCTION

Depression is associated with elevated rates of cardiovascular morbidity and mortality. This elevation seems to be due to a significantly increased risk of coronary artery disease and myocardial infarction and, once the ischemic heart disease is established, sudden cardiac death (1). Recent data suggest that the increased rates of cardiovascular disease in patients with depression may be the result of one or more still-unrecognized underlying physiological factors that predispose a patient to both depression and cardiovascular disease (1). Many theories exist about the relationship(s) between depression and coronary heart disease (CHD), ranging from neurobiological theories of stress (encompassing neuronal, hormonal, and immunologic responses) to sociological theories (2). Several prospective studies have found an association between depression and the subsequent development of CHD (3). The relative risk of fatal, as well as nonfatal, CHD ranged from 1.5 to 3.36 in those suffering from depression (1-4). A recent study found that depression increased an individual's chance of experiencing myocardial infarction (MI) 4-fold (3). In patients after MI, depression is associated with increased mortality rate that is similar to that associated with left ventricular dysfunction or a history of previous MI (3). In addition, recent findings suggest that depression is an independent risk factor for progression of heart disease (1-4). Not much is known about how depression might contribute to this increased risk, although factors such as increased platelet aggregation and poor adherence to cardiac treatment regimens have been suggested (2,4). However, altered cardiac autonomic tone remains one of the most plausible explanations (5). Increased sympathetic or decreased parasympathetic nervous system activity predisposes patients with CHD to ventricular tachycardia, ventricular fibrillation, and sudden cardiac death (2,5). Since altered autonomic tone may account for the effect of depression on cardiac mortality, heart rate variability (HRV) analysis has been used widely as a method of assessing the cardiac autonomic modulation (6). Low HRV reflects excessive sympathetic or inadequate parasympathetic tone and is a strong, independent predictor of post-MI mortality (7). Mean 24-hour HRV has been found to

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be lower in depressed than medically similar nondepressed patients with stable CHD, suggesting a possible mechanism linking depression to cardiac mortality (5,7,8).Recent research focuses more on the HRV, a known indicator of increased morbidity and mortality in CHD patients (6). HRV is synonymous with "beat-to-beat variability" and is a measure of cardiac autonomic innervation by the brain. It is proposed that a reduction in parasympathetic innervation allows unopposed stimulation by sympathetic nerves, which may result in arrhythmias and death. This chronic sympathetic stimulation (or loss of vagal stimulation) is also noted in patients with severe neuropathy and in heart transplant recipients as well as major depression (6,7).

Analysis of the "beat-to-beat oscillation" in the R-R interval (HRV) is generally performed by two methods. **Spectral analysis** provides an assessment of the vagal modulation of the R-R interval. Spectral analysis is most commonly accomplished by fast Fourier transformation to separate R-R intervals into characteristic high (0.15 to 0.40 Hz), low (0.04 to 0.15 Hz), very low (0.0033 to 0.04 Hz), and ultra low (up to 0.0033 Hz) frequency bands. Spectral measures are collected over different time intervals (approximately 2.5 to 15 minutes), depending on the frequency being analyzed. Parasympathetic tone is primarily reflected in the high-frequency (HF) component of spectral analysis. The low-frequency (LF) component is influenced by both the sympathetic and parasympathetic nervous systems. The LF/HF ratio is considered a measure of sympathovagal balance and reflects sympathetic modulations (6). **Nonspectral** or **time domain** parameters involve computing indexes that are not directly related to specific cycle lengths. This method offers a simple means of defining patients with decreased variability in the mean and standard deviations of R-R intervals. Time domain parameters analyzed include mean R-R, the mean coupling interval between all normal beats; SDANN, standard deviation of the averaged normal sinus R-R intervals for all 5-minute segments of the entire recording; SDNN, standard deviation of all normal sinus R-R intervals; SDNN index, mean of the standard deviations of all normal R-R intervals for all 5-minute segments of the entire recording; pNN50, the percentage of adjacent R-R intervals that varied by more than 50 ms; and rMSSD, the root mean square of the difference between the coupling intervals of adjacent R-R intervals. Another time domain measure of HRV is the triangular index, a geometric measure obtained by dividing the total number of all R-R intervals by the height of the histogram of all R-R intervals measured on a discrete scale with bins of 7.8 ms. The height of the histogram equals the total number of intervals found in the modal bin. These 2 analytical techniques are complementary in that they are different mathematical analyses of the same phenomenon. Therefore certain time and frequency domain variables correlate strongly with each other (Table 1) (6).

Tablo 1. Components of HRV

Spectral Component	Time-Domain Correlates	Normal Measures for 24 Hours
HF	rMSSD	<15h
	pNN50	<0.75%
LF	SDDNN index	<30 ms
VLF	SDNN index	<30 ms
ULF	SDNN	<50 ms
	SDANN	<40ms
	HRV index	- - -
HP	SDNN	<50 ms
	HRV index	- - -

VLF indicates very-low frequency: ULF, ultra-low frequency: TP, total power, SDNN index, mean of standart deviation of R-Rs; HRV index, integral of the totail number of normal R-Rs divided by the maximum of the density distribution (an expression of overall 24-hour HRV).

To our notice, no research has been done in Turkish psychiatric settings studying the association between HRV and psychiatric disorders. Our study aims to investigate the hypothesized link between HRV and major depression in a Turkish depressed outpatient sample. This sample is comprised of depressed patients with no known heart problems.

METHODS

Subjects

21 depressed patients and 21 healthy controls were studied.The patients with major depressive disorder were recruited from outpatient Psychiatry Clinics of Karadeniz Technical University, Farabi Hospital.The interviewer had training and prior experience with psychiatric interviewing. The diagnosis of major depression, as defined by the 1994 fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV) was derived from the interview (9). Also depressed patients were assessed with the Hamilton Rating Scales for Depression and Hamilton Anxiety Scales. Patients who could not be clearly characterized as having major depression were excluded from the study. Patients with prior history of CHD were also excluded from the study. Patients with psychotic depression, or any cognitive decline suggestive of a true dementia as assessed with Mini Mental State Examination were also excluded from the study. None of the patients were taking antidepressants or any other drugs that might influence the autonomic system. Healthy controls were subjects with no reported medical or cardiac conditions. Healthy controls had normal ECG recordings prior to being included in the study.

Heart rate variability measurement

Twenty-four hour ambulatory electrocardiographic (ECG) recordings were obtained on an out-patient

Table 2. Comparison of major depressive patients with healthy controls on demographic variables

	Major Depressive Group n: 21	Control Group n: 21	P
Age(years)	38.0±9.1	43.7 ± 8.6	0.044
Gender	18 F, 3 M	14 F, 7 M	NS
Education (years)	6.7 ±4.4	5.3±3.7	NS

F : Female, M: Male, NS : Nonsignificant

Gender was compared according to chi square and for the rest, t test is used

Table 3. Time domain variables of the two groups.

	Major Depressive Group n: 21	Control Group n: 21	p
SDNN (ms)	140.1±27.4	142.6±81.3	>0.05 (NS)
SDNN index (ms)	67.5±15.2	69.3 ±44.4	>0.05
pNN50 (%)	10.8±8.9	13.0± 15.4	>0.05
SDANN (ms)	122±29.1	117±63.5	>0.05
rMSSD (ms)	47.6±32.0	75.5±69.5	>0.05

NS : Nonsignificant, for pNN50 chi square and for the rest t test is used

basis using Kardiosis DL 700 Digital three channel recorder Holter monitors and analyzed with standard holter analysis techniques to accurately label beats and artifact. Patients were excluded if they were not predominantly regular sinus rhythm or if they had sustained atrial arrhythmias such as atrial fibrillation or > 10 % ectopic complexes. In this study time domain variables were studied, namely rMSSD, pNN50, SDNN, SDNN index, and SDANN.

Statistics

Two groups were compared to each other in gender and age, for gender comparisons chi square test and for age t test was used. Cardiological measures were compared with t test between the two groups except for the pNN50 which was compared according to chi square. The associations of anxiety and depression levels with the heart rate variables in the patient group was done by using Pearson correlational analysis.

RESULTS

21 major depressive patients and 21 control subjects were studied. The mean age of depressive patients was 38.0±9.1, whereas this was 43.7±8.6 for the healthy comparison group. The difference was statistically significant (t=2.0, p=0.044). There was no statistically significant difference in gender between the two groups as well as in terms of years of education. Table 2. In the patient group mean Hamilton depression scores was 22.2±3.9 and the mean Hamilton anxiety scores was 21.6±4.7.

Time domain parameters were studied. The parameters were as follows: rMSSD, pNN50, SDNN, SDNN index, SDANN. There were no significant differences in any of these parameters between the major depressive and healthy control groups. In the correlational analysis, levels of anxiety and depression were not associated with any of the HRV measures. There was not a statistically significant correlation between anxiety and depression levels and HRV measures. Age was not correlated with HRV measures either (not shown).

DISCUSSION

Our findings contradict with the previous research showing that HRV is decreased in depressed patients (1-5). Attenuated heart rate variability is a well-known risk factor for mortality after myocardial infarction (2). Decreased HRV has been shown to predict subsequent mortality even when it is measured in stable patients 1 year after myocardial infarction and in unselected consecutive patients without any recent cardiac events involving cardiac catheterization (8). Stein et al (10) have shown that heart rates were higher and nearly all indices of HRV were significantly reduced in the moderate-to-severely depressed versus the nondepressed group. Frasure-Smith (2) et al evaluated the effect of depression on 6-month survival in 222 patients after MI. Depression was an independent risk factor for death and a significant predictor of cardiac cause of death. Depressed patients had a 5-fold higher mortality rate rate than nondepressed patients. The authors postulated that decreased HRV in depressed patients may be associated with the occurence of fatal arrhythmias. In a subsequent evaluation of depression and 18-month survival rate in 222 patients after MI, depressive symptoms after an acute MI were significantly associated with cardiac death within the 18-month period (11). Depression may increase the risk of ventricular arrhythmias after

MI because of a decrease in vagal tone and an increase in sympathetic drive (8,11). Why is then we find no difference between depressed subjects and nondepressed ones in terms of HRV? We think that this is related to the sample studied. In almost all studies concerning HRV and depression the samples are composed of patients with coronary heart disease. As is indicated in the methods section, our study group was composed of depressed subjects without a known coronary artery disease. In this group of physically healthy depressed patients depression did not emerge as a predictor of heart rate variability. Rechlin et al (12) in a study using standardized heart rate analysis carried out in unmedicated patients with major depression, melancholic type, panic disorder, reactive depression with suicide attempts during the preceding 24 h and in normal control subjects found no differences in the patients with reactive depression, as compared with the control group. Whereas there was significantly lower values of heart's beat-to-beat intervals and of the high-frequency peak of spectral analysis in the major depressive group, than in the other groups indicating a decreased parasympathetic activity. Balogh et al (13) found that with pharmacological treatment of major depressive disorder there was an increase in heart rate variability. In line with our findings Yeragani et al (14) found no significant difference in any of the heart rate variability measures between depressed patients and normal controls. Again Rechlin (15) compared a total of 32 unmedicated patients with episodes of major depression (DSM-III-R) and 32 normal control subjects matched for age and sex for heart rate variability (R-R variation) while resting and during deep breathing. Compared with the group of healthy subjects, the depressed patients showed no abnormalities before therapy (15). Our finding that there is no alteration in HRV of depressed patients with no heart disease is in accordance with these studies. Our findings are indirectly supported by the correlation analysis showing no association between the levels of anxiety and depression with HRV measures. If depression was to have an impact on these measures we could have expected a significant correlation. To mention several limitations of our study, though there was not any significant relation between age and HRV measures, the slight age difference between the two group may be regarded as a limitation in our study. This study could have provided more knowledge if we would include another group of depressed patients with a coronary heart disease. The sample size could also be increased enabling us more power in our conclusions. Against all these methodological pitfalls, our study sheds further light on this controversial area. Conflicting results have been reported on the relationship between HRV and depression and our study lends support to the view that no association exists between these two, at least in physically healthy adult depressed patients.

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