Heart Rate Variability in Patients With Major Depression

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This study compared cardiac autonomic modulation in physically healthy patients with major depressive disorder to that in mentally healthy heart transplant recipients and physically and mentally healthy comparison subjects by using a nonlinear measure and a conventional measure of heart rate variability. No significant differences in cardiac autonomic modulation were noted between the depressive group and the transplant recipients, but both of those groups had significantly lower mean values for heart rate variability measures relative to the healthy comparison subjects. The results support the hypothesis that cardiac autonomic imbalance (reduced vagal modulation) to the extent of cardiac neuropathy is present in depression.

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Heart rate variability (HRV), which is the amount of fluctuations from the mean heart rate, provides valuable information in various clinical settings. For example, decreased HRV after myocardial infarction was found to be a strong and independent predictor of increased mortality.[1] HRV is conventionally assessed by using time-domain and frequency-domain techniques, which identify its coupling with a variety of phenomena, including respiration, baroreceptors, autonomic nervous system traffic, body temperature, metabolic rate, hormone levels, and diurnal variations.[2] Time-domain analysis, which is perhaps the simplest to perform, provides measures such as the standard deviation of the normal interbeat intervals (SDRR). Frequency-domain analysis provides the power spectrum and reveals at least two frequency ranges—the low-frequency range (0.04–0.15 Hz) and the high-frequency range (0.15–0.4 Hz)—that are modified by the sympathetic and vagal traffic to the heart. Besides these periodic components, the power spectrum reveals a broad, noise-like variability over a large frequency span.[3] It seems that this irregular variability, which accounts for the largest proportion of HRV, is due to nonlinearity in the control network (related to hemodynamic, electrophysiological, humoral, autonomic nervous system, and central nervous system functions). The last decade has witnessed an enormous increase in the application in a wide range of scientific disciplines of nonlinear methods of analysis based on the paradigm of deterministic chaos. The use of these methods in clinical and basic research in psychiatry is still in its infancy, and it is believed they can complement existing models, as well as provide new models.[4,5] Several authors have quantified nonlinear measures of HRV in order to test their feasibility for identifying changes in cardiac autonomic nervous system outflow. Positive correlations of both the low-frequency and the high-frequency ranges with

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nonlinear measures were found.[6] One such measure is the pointwise correlation dimension (PD2). This measure is based on the presumption that the variability is determined and patterned, whereas the stochastic measures (such as time-domain measures) all assume that the variability is around a stationary mean and is noise. PD2 reconstructs the degrees of freedom (number of independent variables) in the system that generates the time series that is examined, and it does this irrespective of whether the system is stochastic or deterministic or is stationary in time. It is interesting to note that the nonlinear components of HRV have been found to be drastically reduced by cholinergic blockade, but not by adrenergic blockade in both animal and humans studies.[7,8] In healthy subjects, nonlinear dynamics in heart rate seem to represent the normal situation, i.e., a healthy state is characterized by a certain degree of chaos. Thus, it has been proposed that abnormalities in the autonomic nervous system, manifested in various disease states, diminish cardiac chaos. This decrease in cardiac complexity is associated with a decrease in the vagal modulation.[9]

Major depressive disorder is reported to be associated with increased cardiovascular morbidity and mortality, and it is a significant risk factor for increased mortality after myocardial infarction, as well. The earliest observation dates back to 1937, when Malzberg noticed higher cardiovascular mortality rates among institutionalized depressed patients.[10] Subsequent research confirmed Malzberg's original observation.[11,12] More recently, it was demonstrated that depression among patients hospitalized after myocardial infarction is a significant predictor of increased cardiac mortality at 6 months.[13] In a subsequent follow-up of the same cohort, the effect of depression persisted from 6 to 18 months.[14] Furthermore, cardiac patients who were depressed had a significantly heightened long-term risk of mortality even when the follow-up period was extended to 19.4 years.[15]

The correlation of decreased HRV with increased mortality rates after myocardial infarction led to the hypothesis of cardiac autonomic imbalance in major depression. Specifically, it was thought that major depression might be associated with decreased parasympathetic and increased sympathetic modulations, which lower the threshold for lethal arrhythmias.[16,17] Early time-domain analyses were equivocal.[16,18] However, Balogh et al.[19] correlated changes in short-term time-domain measures of HRV with clinical response to major depression treatment. Later, studies that incorporated frequency-domain techniques gave conflicting results because of the autonomic side effects of antidepressant medication,[18,20] or because of failure to correlate HRV measures with clinical improvement,[21] although decreased cardiac vagal modulation was found in patients with major depression.[22] The effect of the various classes of antidepressants on HRV depends on their receptor target profile. Traditionally, the tricyclic antidepressants are well known for their anticholinergic activity, which reduces HRV. The selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine) are not entirely devoid of anticholinergic side effects. However, most of the studies, including those comparing SSRIs to tricyclics, have not associated reduced HRV with SSRIs. Some studies have even showed increased vagal modulation in patients treated with SSRIs.[19–22]

Thus, different methodological designs and lack of standardized criteria of HRV measurement have made firm conclusions impossible. Schultz et al.[23] reported on a relative decrease in cardiac vagal activity in depressed patients after electroconvulsive therapy. However, Nahshoni et al.,[24] using a larger battery of frequency-domain measures, found that vagal modulation increases after successful treatment of major depression with electroconvulsive therapy.

The aim of the present study was to test the hypothesis of cardiac autonomic imbalance in patients with major depression by comparing their HRV measures (a conventional time-domain measure and a nonlinear measure) with those of both heart transplant recipients and healthy comparison subjects. We hypothesized that the HRV measures of the major depression patients would be higher than those of the heart transplant recipients (who have denervated hearts) but lower than those of the healthy comparison subjects. Such a finding would indicate the extent of cardiac autonomic dysregulation associated with major depression.

METHOD

Subjects

Ten inpatients (mean age = 58.2 years, SD = 8.8; four women, six men) who met the DSM-IV criteria for major depressive disorder, recurrent episode, assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P),[25] were recruited. Inclusion criteria were normal findings on physical examination, ECG, and routine blood tests on admission and no history, signs, or symptoms of cardiovascular, pulmonary, or endocrine diseases. All had at least two prior major depressive episodes and had been taking SSRIs for at least 1 year

before the current admission (four were treated with 20–30 mg/day of paroxetine, four with 250–300 mg/day of fluvoxamine, and two with 40 mg/day of fluoxetine). The patients undergoing treatment with SSRIs served as the study group, despite the possible small effect of SSRIs on HRV, in order to ascertain the presence of well-diagnosed and well-characterized DSM-IV major depressive disorder. Ten nonhospitalized patients who had had orthotopic heart transplantation a mean of 21.5 months (SD = 10.8) earlier were also recruited (mean age = 51.4, SD = 10.4 years, three women, seven men). None of the heart transplant recipients had a mental disorder, as confirmed by a psychiatric interview according to the guidelines of the SCID-P.[25] All heart transplant subjects were taking a standard drug immunosuppression protocol only (4–6 mg/kg per day of cyclosporine and 0.2 mg/kg per day of prednisone) and had good physical performance. None of the heart transplant recipients had a history of sinus node dysfunction after the cardiac transplantation. The heart transplant recipients had undergone routine serial surveillance right ventricular endomyocardial biopsies, and no allograft rejection, a factor known to affect the HRV measures,[26] was detected. Ten physically healthy volunteers (mean age = 55.9, SD = 5.6; four women, six men) served as comparison subjects. None of the comparison subjects had a mental disorder, as confirmed by a psychiatric interview according to the guidelines of the SCID-P.[25] The age distribution was similar in the three groups ($F = 1.65$, $df = 2, 27$, $p = 0.21$). None of the subjects was taking sedatives or anxiolytics, and none abused alcohol, tobacco, or drugs.

Study Design

ECG recordings during spontaneous breathing were obtained for all subjects in the same quiet room after the subject had 10 minutes of adjustment in the supine position. The recordings were made between 10:00 a.m. and 12:00 noon to obviate diurnal influences. One unfiltered ECG limb lead was digitized on-line with 16-bit signal resolution at 1000 Hz by using a computerized system (Hipec analyzer HA-200, Aerotel Computerized Systems, Ramat Gan, Israel). A well-tested algorithm that uses a template and a threshold was chosen by the operator before recording to localize the fiducial point of every heartbeat in real time. A series of 2,000 normal interbeat intervals was extracted in each recording session and stored for off-line analysis.

Heart Rate Variability Measures

The PD2 estimates of heart beat intervals (RR) were calculated according to the algorithm developed by Skinner et al.,[27] as follows: state space was constructed through the method of time delays, i.e., $RRi = [RR(ti), \ldots, RR(ti + (m-1)\tau]$, for successive embedding dimensions from $m = 1$ to $m = 16$, where $\tau = 1$ was taken as the most reasonable choice for delay (since longer lags may induce undue loss of spatial correlation between points). Starting with the initial point in the series, the local correlation integral C(r) of the point was calculated, i.e., all vector differences (r) relative to this point were calculated and rank-ordered from the smallest to the largest. Plotting C(r) as a function of r on a log-log scale results in a sigmoid-shaped curve. The slope over the largest linear range was then measured (with a regression coefficient ≥ 0.98). This was done for successive m values to look for a plateau beyond a certain m. This plateau was considered as the PD2 estimate, and its value was calculated with a weighted average technique (each value in the plateau region was weighted by the variance of its underlying slope calculation). Then, the algorithm was stepped to the next point in the series, and the whole procedure was repeated until the entire file was exhausted. Because each point in the series had a new coordinate that could be of any value, the PD2 values were independent of each other, and this independence justified the use of the mean PD2 values of each series as the best estimate of the correlation dimension. The advantage of the PD2 algorithm is that it requires fewer data points compared with the classic Grassberger-Procaccia determination of the correlation dimension.[28] In addition, it offers an added feature in that it can extract "dimensional complexity" from nonstationary signals.[29] (For background and a fuller description of the algorithm, see Nahshoni et al.[30]) The time-domain measures mean of the normal RR intervals (in msec) and the standard deviation of the entire recording (SDRR, in msec) were obtained for each of the data points.

Statistical Analysis

Analysis of variance, followed by Student-Newman-Keuls post hoc tests, was used for between-group comparisons. Statistical significance was accepted at the $p < 0.05$ level. All values are expressed as means and standard deviations.

RESULTS

The electrophysiological results are presented in Table 1. The mean interbeat interval for the major depression and heart transplant groups were similar and significantly lower than that of the comparison group (major depression group: mean = 712.1 msec, SD = 74.0; heart transplant group: mean = 783.5 msec, SD = 107.4; comparison group: mean = 854.9 msec, SD = 107.6) ($F = 5.35$, $df = 2, 27$, $p < 0.02$). Both the major depression group and the heart transplant group had similar mean PD2 values, which were significantly lower than that of the comparison group (major depression group: mean = 2.09, SD = 0.29; heart transplant group: mean = 2.19, SD = 0.72; comparison group: mean = 3.21, SD = 0.23) ($F = 17.58$, $df = 2, 27$, $p < 0.0001$). The same was true for SDRR (major depression group: mean = 21.2 msec, SD = 7.9; heart transplant group: mean = 27.5 msec, SD = 16.3, comparison group: mean = 41.3 msec, SD = 14.5) ($F = 5.89$, $df = 2, 27$, $p < 0.008$).

DISCUSSION

The aim of our study was to examine the hypothesis of cardiac autonomic imbalance in patients with major depression by comparing their HRV measures (a nonlinear measure [PD2] and a conventional time-domain measure [SDRR]) with those of heart transplant recipients and healthy comparison subjects. We found that the mean interbeat intervals, PD2 and SDRR, were comparable in the major depression and heart transplant groups and significantly lower in those groups than in the healthy comparison subjects. To our knowledge, the present study is the first attempt to study cardiac autonomic dysfunction in depression by incorporating a comparison group of mentally healthy heart transplant recipients, in addition to mentally and physically healthy comparison subjects. Indeed, heart transplant patients constitute the paradigm of the denervated heart. Hence, we believe that this group can serve as a model for comparison and assessment of cardiac autonomic dysfunction. We hypothesized that HRV measures for the major depression group would show intermediate values between those of the heart transplant recipients and those of the comparison subjects. As expected, we found PD2 and SDRR to be higher for the healthy comparison subjects than for either the depressed patients or the heart transplant recipients. But, to our surprise, our results showed that the major depression patients were indistinguishable from heart transplant recipients with respect to both measures of HRV analysis.

Previous research examining cardiac autonomic imbalance in depression and its relation to the etiopathology of cardiac morbidity and mortality has been based almost exclusively on the orthodox methods of HRV analysis (time-domain and frequency-domain techniques). Because of the differences in methodological designs in previous studies, including differences in data acquisition techniques, the lack of consensus regarding the standards for HRV analysis before 1996, the use of cross-sectional versus longitudinal studies, and emphasis on examination of the autonomic nervous system side affects of antidepressants, the issue of cardiac autonomic imbalance in depression has not yet been settled.[16,18,20–22,24] However, new methods of nonlinear analysis of physiological function are being developed, and it is intriguing and clinically relevant to try to implement these methods to examine this issue.

The present study had several limitations that are worth noting. First, the size of the study group was relatively small. However, it was dictated by the small number of heart transplant recipients available at the time of the study. Second, the study was cross-sectional. In general, cross-sectional studies are inherently limiting in assessment of variable responses between subjects, especially in the analysis of time-dependent events. However, in our

TABLE 1. Electrophysiological Data on Heart Rate Variability in Patients With Major Depression, Heart Transplant Recipients, and Healthy Comparison Subjects

	Major Depression Patients (N = 10) (Group A)		Heart Transplant Recipients (N = 10) (Group B)		Healthy Comparison Subjects (N = 10) (Group C)		Analysis of Variance		
Heart Rate Variability Parameter	Mean	SD	Mean	SD	Mean	SD	F (df = 2, 27)	p	Student-Newman-Keuls Post Hoc Test
Interbeat interval (RR) (msec)	712.1	74.0	783.5	107.4	854.9	107.6	5.35	<0.02	A = B<C
Standard deviation of RR (msec)	21.23	7.94	27.51	16.33	41.34	14.53	5.89	<0.008	A = B<C
Pointwise correlation dimension	2.09	0.29	2.19	0.72	3.21	0.23	17.58	<0.0001	A = B<C

study design, the heart transplant recipients provided a comparison group that can serve as a gold standard for cardiac autonomic denervation. This presumption, we hope, might compensate for the aforementioned limitations. Still, larger comparison groups are needed. Third, the heart transplant recipients were taking standard immunosuppressant drugs, and, to our knowledge, the influence of these drugs on the cardiac autonomic nervous system is still unknown. Thus, we could not control for the influence of these drugs on HRV measures. Furthermore, clinical research has demonstrated that reinnervation of the transplanted human heart and allograft rejection are associated with changes in HRV measures.[26,31,32] However, allograft rejection in the study subjects was ruled out by serial right ventricular endomyocardial biopsies. As for reinnervation, most clinical studies have demonstrated that HRV measures of heart transplant recipients are significantly lower than those of healthy comparison subjects and that reinnervation is a long-term process that exceeds the length of posttransplantation period of the patients included in the present study.[33] As for the choice of HRV measures, we did not use spectral analysis, since data obtained from heart transplant recipients by using this method are contradictory. For example, clinical studies have demonstrated both the presence and the absence of prominent frequency spectral peaks in the HRV time series in heart transplant recipients.[34,35] These discrepancies can be attributed to the dynamic process of allograft assimilation within the recipient, as well as to the methodological limitations in extracting pertinent information from power spectrum analysis, particularly when the dominant spectral reserves are grossly attenuated. However, although studies using nonlinear methods of analysis in heart transplant recipients have recently been accumulating, we felt that incorporation of a traditional time-domain measure would be appropriate for the sake of comparison with previous clinical studies. Fourth, the depressed patients, despite being well diagnosed and characterized, were taking SSRIs, which could influence cardiac autonomic activity to some extent. However, the patients were taking SSRIs that are presumed to have minimal effects on the autonomic nervous system. Paroxetine, which has some anticholinergic activity, might affect HRV measures. However, since recent studies have demonstrated that therapeutic doses of SSRIs (including paroxetine) given to depressed patients do not alter HRV measures, the effects of these drugs on the measured cardiac autonomic activity should be minimal.[21,36–40]

Despite these limitations, the present preliminary study clearly demonstrates that depression is associated with cardiac autonomic imbalance of an extent that is almost comparable to that of a denervated heart. Further large-scale and follow-up studies are needed to clarify and substantiate the complex dynamics of cardiac autonomic imbalance in mood disorders and its clinical significance.

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