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Heart rate variability increases in elderly depressed patients who respond to electroconvulsive therapy

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Abstract

Objectives: To evaluate the parasympathetic modulation in elderly inpatients with major depressive disorder (MDD) before and after electroconvulsive therapy (ECT) using both linear and nonlinear methods of heart rate variability (HRV) analysis. **Method:** A measure of local dimensional complexity (pointwise correlation dimension, PD2), as well as spectral analysis measures (LF, low-frequency range; HF, high-frequency range) were calculated for the heart rate time series of 10 elderly inpatients with MDD (70 ± 7 years) before and after ECT. Hamilton Depression Rating Scale (HAM-D) was evaluated concomitantly. **Results:** Only the responders to ECT ($n = 7$; $\geq 50\%$ reduction in HAM-D) exhibited a significant increase in PD2 ($P = .0035$), which showed a tendency towards a correlation with symptom improvement ($r = .73$, $P = .06$). Spectral analysis measures did not show a significant difference after ECT. **Conclusion:** Elderly patients with MDD, who respond to ECT, might show increased vagal modulation. Since nonlinear HRV measures have been shown to be reduced by aging, similar to cholinergic deficit, they might shed light on the increased risk for cardiac mortality in depression.

Keywords: Autonomic nervous system; Chaos theory; Electroconvulsive therapy; Heart rate variability; Major depression

Introduction

Heart rate variability (HRV), the amount of fluctuations around the mean heart rate, can be used to assess the cardiac autonomic nervous system. Analysis of HRV provides prognostic information in several clinical settings. For example, in survivors of myocardial infarction, decreased HRV was found to be a strong and independent predictor of increased sudden cardiac death [1]. The proposed mechanism is reduced vagal modulation, which lowers the threshold for lethal arrhythmias. HRV is usually assessed using time- and frequency-domain techniques. Time-domain techniques are based on mean and variance of the heartbeat intervals, and frequency-domain techniques, also called, spectral analysis, provides the power spectrum, which can accumulate in at least two frequency ranges: the low- (LF, 0.04–0.15 Hz) and high-frequency ranges (HF, 0.15–0.4 Hz), which are modified by the sympathetic and vagal traffic to the heart, respectively [2,3]. Beside these periodic components, the power spectrum reveals a broad, noise-like variability over a large frequency span [4]. It seems that this irregular variability, which accounts for the largest proportion of HRV, is due to nonlinearity in the control network (hemodynamic, electrophysiological, humoral, and autonomic- and central nervous system-related). The last decade has witnessed an enormous increase in the application of nonlinear methods of analysis, based on the paradigm of deterministic chaos in a wide range of scientific disciplines. Their use 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 us with new ones [5,6]. Recently, several authors have quantified nonlinear measures of HRV to test their feasibility to identify changes in the autonomic nervous system outflow. Positive correlations were found between the LF and HF ranges and nonlinear measures [7]. Interestingly, nonlinear components

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were drastically reduced by vagal blockade in both animal and humans studies [8,9]. In healthy subjects, nonlinear dynamics in heart rate seems 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, diminishes cardiac chaos. This decrease in cardiac complexity is associated with a decrease in the vagal modulation [10,11].

From a "dynamical" point of view, the heart rate time series can be seen as the projection on a line of one trajectory of an unknown discrete deterministic dynamical system in *m*-dimensional space. If the time series are long enough, such a trajectory will converge onto an attractor. A chaotic attractor, also named "strange" attractor, is defined by sensitive dependence on initial conditions for the system's trajectory. If it is a fractal object, it has a noninteger dimension with a complex geometric structure. After reconstruction of the attractor, its geometrical properties can be calculated. For example, the dimension of the attractor can be given by the fractal dimension (obtained by a box-counting algorithm), the information dimension (obtained by computing the information entropy), and the correlation dimension (obtained by the Grassberger–Procaccia algorithm). The amount of chaos and predictability can be quantified by the Lyapunov exponents, which allow the quantification of sensitive dependence on initial conditions, since strange attractors exhibit exponential divergence of nearby trajectories. Another measure of nonlinear dynamics is the information entropy, which quantifies the information uniformity carried by the probability distribution. All these indices assume that the dynamics is the output of a deterministic dynamical system. However, this assumption should not be taken for granted, and tests for nonlinear prediction and comparison tests with surrogate data have been also suggested [12–14].

Major depressive disorder (MDD) is accepted as significant risk factor for increased mortality in patients after myocardial infarction, as well as for increased cardiovascular morbidity and mortality without documented cardiac illness [15,16]. The first definitive evidence, which supports the notion of higher cardiovascular mortality rates in depression, dates back to the observation made by Malzberg in 1937 [17]. He found that the death rate in the depressed group was six to seven times greater than that of the general population. Subsequent studies [18,19] confirmed Malzberg's original observation. Since decreased HRV correlates significantly with increased mortality after myocardial infarction, it was hypothesized that MDD might also be associated with decreased HRV, i.e., decreased vagal modulation and increased sympathetic modulation [20,21]. Attempts to unravel the autonomic nervous system's modulation in MDD using the traditional HRV measures have made firm conclusions impossible, partly due to different methodological designs. Early time-domain analysis proved unfruitful in this area [20,21], and later studies incorporating frequency-domain analysis were confounded by the anticholinergic side effects of tricyclic antidepressants [22] or failed to correlate HRV measures to clinical improvement [20], although decreased vagal modulation was found in patients with major depression [23–25]. Thus, different methodological designs and lack of standardized criteria for HRV measurement have made firm conclusions impossible [3]. In a recent study, using spectral analysis, Schultz et al. [26] reported on a relative decrease in vagal activity after electroconvulsive therapy (ECT) in nine depressed patients and of a positive correlation between improvement of depressive symptoms and the decrement in vagal activity. They suggested that treatment of depression with ECT might be associated with decreased vagal activity and concluded that it might be related to the resolution of depression and not the ECT per se. A recent study reported on increased plasma norepinephrine in MDD, which might predispose the patients to sustained ventricular arrhythmias and as a consequence, to a high risk for sudden death, thus emphasizing a different aspect of autonomic neurohumoral dysregulation [27].

The abovementioned studies were conducted on younger depressed cohorts. The elderly depressed population is unique in the sense that physical illness (cardiovascular, cerebrovascular, cancer, etc.) and social factors may be posed as major determinants for increased mortality rates [28]. However, Murphy et al. [29], who followed elderly depressed patients over 4 years, found that increased mortality rates are not due to poor physical health alone or to a single social factor. Since HRV decreases with normal aging [30–32] and MDD confers risk for sudden death, the elderly population might be particularly vulnerable. Thus, the mechanism of cardiac autonomic modulation in elderly patients with MDD, via analysis of HRV, is of more than pure academic interest.

In the present study, we hypothesized that clinical improvement of depression in elderly patients, achieved by ECT, might be associated with an increase in vagal modulation, which will be reflected in both linear and nonlinear analysis of HRV. To this end, the present preliminary study was designed to analyze the changes in the cardiac autonomic nervous system modulation using spectral analysis and a nonlinear measure (pointwise correlation dimension, or PD2) [33], which describes the system's complexity (i.e., the number of degrees of freedom) in 10 physically healthy elderly inpatients with recurrent MDD, before and after ECT. The main advantage in using the PD2 algorithm is its ability to analyze nonstationary signals, requiring a relatively small data set compared with the classic Grassberger–Procaccia determination of the correlation dimension.

Method

Subjects

The study population included seven women and three men aged 60–84 years (mean 70 ± 7 years) with major

depression, recurrent episode. All were interviewed by a senior psychiatrist (D.A.). The diagnosis of MDD was established according to DSM-IV criteria, following the guidelines of the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P 2.0) [34]. Inclusion criteria were normal findings on physical examination, electrocardiography (ECG), routine blood tests on admission, and no history, signs, or symptoms of cardiovascular, pulmonary, neurological, or endocrine diseases. All patients had had at least two prior major depressive episodes and were maintained on nontricyclic antidepressants before admission. The patients were subjected to ECT because of nonresponse to pharmacotherapy. The study was approved by the Institutional Review Board of Geha Hospital. All patients provided written informed consent after receiving a complete description of the study.

Drug treatment

Over the course of the study, all patients were on the same nontricyclic medication (either selective serotonin reuptake inhibitor, $n = 6$, or mianserin, $n = 4$). No anxiolytics or sedatives were administered throughout the entire study period.

Electroconvulsive therapy

The anesthetic medications were methohexital sodium (1.0 mg/dg) and succinylcholine (0.5 mg/kg), which were adjusted based on the response after the first ECT treatment. The electrical dose was titrated to seizure threshold during the first treatment [35]. Seizure presence and duration were confirmed by both clinical observation and electroencephalography recordings. ECT was administered with a constant current, brief bidirectional square-wave device (Thymatron DGx, Somatics, Lake Bluff, Illinois). Right or left unilateral (d'Elia placement) ECT was used in all patients except one, who received bilateral (frontotemporal) ECT. Sessions were scheduled twice weekly for a maximum of 12, if needed.

Heart rate recording

ECG recording was performed before onset of the ECT course and again on its completion. To avoid the confounding effects of anesthetic agents on the HRV measures, the second recording was done 48 h after the last ECT. The recordings were made in the same quiet room during spontaneous quiet breathing following 10 min of adjustment in the supine position between 10:00 and 12:00 a.m. (to avoid circadian rhythm bias). One unfiltered ECG limb lead (LII) was digitized on-line with 16-bit signal resolution at 1000 Hz using a computerized system (Hipec analyzer HA-200/Aerotel Computerized Systems, Ramat Gan, Israel). A well-tested algorithm that employs a template and a threshold was chosen by the operator before recording to localize the fiducial point of every heartbeat (QRS complex) in real time. A series of 2000 interbeat intervals (RR intervals) was extracted in each recording session and stored for off-line analysis.

Heart rate variability measures

All recordings and frequency-domain analysis were performed according to the recent standards published by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology Task Force [3].

Frequency domain

The nonparametric method employed in our study is based on the fast Fourier transform (FFT) algorithm and a Hanning spectral window. The following frequency bands were extracted from the power spectrum: LF (0.04–0.15 Hz) and HF bands (0.15–0.4 Hz). These indices are measured in units of power (m s^2).

Pointwise correlation dimension algorithm

The PD2 estimates of heart beat intervals (RR) were calculated following the algorithm developed by Skinner et al. [33], as follows: state space was constructed through the method of time delays: RRi=[RR(tiτ), . . ., 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, its local correlation integral $C(r)$ 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 $\geq .98$). This was done for successive m values, looking 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 whole 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 justified using the mean PD2 values of each series as the best estimate of the correlation dimension. The detailed implementation of PD2, including appropriate figures, was presented previously [36].

Clinical rating

The 17-item Hamilton Depression Rating Scale (HAM-D) was used to assess symptom severity [37]. The rating scales were obtained on the day of the first ECG recording (pre-ECT) and within 3 days after completion of the ECT course.

A short-term clinical response to ECT was defined as 50% or greater reduction from the baseline depression scores.

Statistical analysis

Two-tailed paired t test or Mann–Whitney test were performed as appropriate. Correlations between changes in PD2 measures and changes in HAM-D scores were performed by Pearson's test. A P value $<.05$ was considered significant. All values are presented as mean ± S.D.

Results

The number of ECT sessions ranged from 6 to 12 (10.5 ± 2.2). A significant decrease was noted after ECT in scores in the HAM-D, from 24.6 ± 4.5 to 12.1 ± 7.3 ($t=4.63$, $df=9$, $P=.0003$). There was no significant change in PD2 (2.35 ± 0.60 vs. 2.68 ± 0.41; $t=1.36$, $df=9$, $P=.21$) and the LF and HF bands (548 ± 629 vs. 313 ± 213: $t=0.74$, $df=9$, $P=.48$; 264 ± 326 vs. 397 ± 441: $t=1.19$, $df=9$, $P=.26$, respectively), following the ECT course. The HF power showed a significant correlation with PD2 values ($r=.75$, $P=.02$, $n=10$).

No correlation was found between HAM-D scores and PD2 values for the total cohort of depressed patients, including both responders and nonresponders (Fig. 1). However, when the cohort was divided by response to ECT (≥50% improvement in HAM-D), a significant post-ECT increase was noted for PD2 for the responders ($n=7$) as compared to the nonresponders (from 2.09 ± 0.37 to 2.82 ± 0.41; $t=4.65$, $df=6$, $P=.0035$). Regression analysis between the magnitude of improvement in depressive symptoms (change in HAM-D scores) and the magnitude of change in PD2 showed a tendency towards a significant correlation ($r=.73$, $n=7$, $P=.06$).

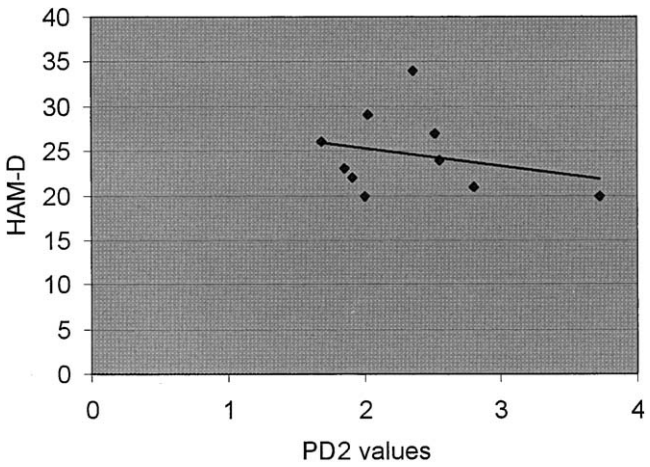

Fig. 1. A regression plot between HAM-D scores and PD2 values in the total depressed cohort ($n=10$).

No significant differences in the response to ECT were observed in either HAM-D or PD2 changes between males and females ($U=2.0$, $P=.07$; $U=6.0$, $P=.38$, respectively). In SSRI-treated patients no significant correlation was found between the daily dose of SSRI and the changes in PD2 values following ECT ($r=.26$, $n=6$, $P=.62$). Moreover, there was no significant difference in the changes in PD2 values following ECT between SSRI- and non-SSRI-treated patients (0.31 ± 1.02 vs. 0.37 ± 0.31, $U=11$, $P=.91$, respectively).

Discussion

The relationships between cardiac autonomic modulation, as expressed by HRV measures, and major depression may be crucial in elderly patients in whom MDD could aggravate their already age-related reduced autonomic modulation [30–32], exposing them to the risk of sudden cardiac death. Previous studies of HRV in depression have not clarified the relationship between depression and cardiac autonomic modulation, owing mainly to the different methodological designs employed and inclusion of young depressed patients [20–27].

In this preliminary prospective study, 10 elderly patients with MDD were assessed for the severity of depressive symptoms and HRV before and after ECT. The study was designed to exclude any organic cause that might interfere with modulation of the autonomic nervous system. Each patient served as his/her own control, thus avoiding the necessity to include control groups, i.e., a cross-sectional study, which might be the source of variation in the results reported for HRV in previous depression studies. A quantitative nonlinear analysis measure (PD2) [33] was added to traditional spectral measures of HRV. This was motivated by interesting findings of Osaka et al. [38], who used cholinergic and adrenergic blockade and found a positive correlation between the vagal modulation and the correlation dimension. Moreover, recently, Zwiener et al. [8] confirmed that the nonlinear components of HRV are drastically reduced by cholinergic blockade and not by beta-adrenergic blockade. Thus, PD2 was chosen as a measure of HRV on the assumption that it may express properties not captured by the orthodox methods of HRV analysis. Hence, it can provide additional information about the cardiac autonomic modulation, especially the vagal modulation. Indeed, we found a significant positive correlation between PD2 values and the HF band, which is known to be influenced mainly by the vagal arm of the autonomic nervous system. Although the response rate to ECT in our study seems to be low (70%), compared to the higher effective response rates reported in the literature (80–90%), our results are still consistent with recent reports on response rates to ECT in medication-resistant depression [39,40], especially elderly patients.

The small sample size is a significant limitation of our study. Another limitation might stem from the co-administration of antidepressants during the ECT treatment. However, the patients were maintained on antidepressants that are presumed to have minimal effects on the autonomic nervous system. Paroxetine, which has anticholinergic activity, might affect HRV measures. However, since recent research has demonstrated that therapeutic doses of SSRIs (including paroxetine) given to depressed patients did not change HRV measures [41,42], we are less concerned with the effects of these drugs on the measured cardiac autonomic activity. Furthermore, in an effort to minimize the effects of antidepressants on the HRV, the medications and doses were not changed before or during the ECT course.

PD2 showed an increase in HRV after successful ECT ($\geq 50\%$ reduction in HAM-D), i.e., only in responders ($n = 7$) and a tendency towards correlation with improvement in symptomatology. Thus, our results of an increase in PD2 after successful ECT point to a possible pre-ECT decreased vagal activity. Since the parasympathetic system has a modulating effect on sympathetic function [43], our electrophysiological finding gains further support from a recent study demonstrating increased plasma norepinephrine levels in MDD patients [27]. Such putative increased cardiac sympathetic activity is associated with a high risk for cardiac arrhythmias. Therefore, an ECT-induced increase in vagal activity might counteract relative sympathetic overactivity and thus decrease the risk for cardiac morbidity.

Implementation of nonlinear techniques for heart rate time series in patients with MDD was pioneered only recently in the study of Yeragani et al. [44]. The authors compared the Lyapunov exponents and the degree of nonlinearity between young MDD patients and normal controls. Their study suggests that MDD is associated with reduced vagal activity and a relative increase in sympathetic function. Despite the differences between their study and the present one (cross-sectional design, age range, drug treatment, and a different nonlinear analysis), their results conform with the results found in our study.

Recently, Schultz et al. [26] reported on a decrease in vagal modulation after ECT in nine depressed patients. They found, contrary to our findings, that the decrease in vagal modulation correlated with clinical improvement. However, their study differs from our study in population characteristics (young vs. elderly depressed patients), as well as in the method of analysis (spectral analysis vs. a nonlinear approach). Linear methods, like spectral analysis, are appropriate for stable linear systems, i.e., those which are characterized by a few peaks in the power spectrum. However, the heartbeat's time series often reveal broadband spectra instead of pronounced peaks, indicating that their dynamics stem from multivariate sources. PD2 reconstructs the degrees of freedom (number of independent variables) in the system that generates the time series examined, and does this irrespective of whether the system is stochastic or deterministic or is stationary in time. Furthermore, it is based on the presumption that the variability is determined and patterned and might be proposed as superior to the conventional power spectrum or other stochastic measures in detecting subtle changes in the cardiac autonomic nervous system [12–14].

In conclusion, the approach used in this study of a nonlinear method to quantify the vagal arm of the cardiac autonomic nervous system, suggests that vagal modulation might be reduced in elderly patients with MDD. PD2 showed a significant increase after a successful ECT course and a tendency towards correlation with symptom improvement. Thus, novel applications, such as dimensional analysis, might provide additional information on the cardiac autonomic modulation in mood disorders. The present data warrant longitudinal studies with a larger drug-free sample of elderly depressed patients to clarify the predictive value of nonlinear measures of HRV for response of MDD patients to antidepressive treatment strategies, as well as for cardiovascular complications associated with depression.

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