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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