Relation between heart rate variability and seizure threshold in electroconvulsive therapy: a pilot study

Aleksey Olekseev¹, Ungvari GS²,³, Gábor Gazdag⁴,⁵,†

ABSTRACT

Objectives: Vegetative dysfunction occurs in a host of medical and psychiatric conditions and is also influenced by their treatment. Heart rate variability (HRV) is an indicator of the heart’s autonomic activity. HRV is also an indicator of treatment outcome in depression. As autonomic activity affects the seizure threshold, it could influence the induction of seizures in electroconvulsive therapy (ECT). This study analyzed the correlation between autonomic nervous system activity measured by HRV and the seizure threshold in the first session of ECT.

Methods: All patients treated with ECT at the Odessa Private Psychiatric Institute between December 2013 and May 2015 meeting study entry criteria formed the study sample. Measures calculated from the analysis of ECGs recorded immediately before the first seizure induction was correlated with the seizure threshold.

Results: Thirty patients were included in the study. Univariate analysis revealed that only age (p=0.023) and the square root of the mean of the sum of the squares of differences (RMSSD) between all adjacent inter-beat (NN) intervals (p=0.007) had significant positive correlations with the initial stimulus intensity.

Conclusion: This is the first report to demonstrate a correlation between the initial stimulus dose of ECT and the RMSSD, a measure of HRV. The RMSSD could be a promising, easily measurable parameter to ascertain initial stimulus intensity in ECT.

Keywords: Heart rate variability, Electroconvulsive therapy, Seizure threshold

Introduction

The seizure threshold is a theoretical construct referring to a certain level of nerve cell activity, above which the excitation of the cells triggers rapidly spreading firing of the neurons. In the healthy brain, nerve cell activation never exceeds the seizure threshold. In the epileptic patient’s brain, there is a local focus with a lower seizure threshold or the nerve cells are generally more excitabile. Thus, nerve cells can start unpredictably firing in synchrony, resulting in a generalized epileptic seizure [1]. Among several other factors, autonomic nervous system activation might also contribute to the elicitation of a seizure. Patients with chronic epilepsy have dysfunctional parasympathetic and sympathetic nervous systems, not only while seizing [2], but also during the interictal period [3,4]. Further confirmation of the role of the autonomic nervous system in the modulation of the seizure threshold comes from vagus nerve stimulation.
LF might be related to sympathetic or both the sympathetic and parasympathetic systems. The LF/HF ratio reflects the sympatho-vagal balance \[12,15\]. SDNN and SDANN are also related to both the sympathetic and parasympathetic systems.

Low HRV, i.e., low power in the HF band, has been found in several conditions, such as major depressive disorder \[16\] and myocardial infarction \[17\]. Significant inverse correlations have been found between HRV and both the severity of depression and the duration of the depressive episode \[18\]. It has been consistently demonstrated that patients with schizophrenia exhibit a diminished capacity to recover from a stress response as a result of deficits in parasympathetic activity. This decreased vagal tone has been found to relate to increased symptom severity in schizophrenia \[19\]. It is assumed that the vagal tone disruption results from anxiety accompanying positive symptoms. Similar parasympathetic dysfunction among non-psychotic relatives of schizophrenia patients has also been found. It is hypothesized that the resulting sympatho-vagal imbalance leads to an overall sympathetic dominance, although sympathetic nervous system activity is not abnormally elevated \[19\].

An increase in HRV is associated with good treatment response to antidepressants, whereas a lack of antidepressant response is associated with a decrease in HRV \[20-22\]. Treatment with tricyclic antidepressants (TCAs; imipramine, doxepin, and amitriptyline) causes a large decrease in most measures of HRV and a large increase in HR \[23,24\]. The effect of selective serotonin-reuptake inhibitors (SSRIs; fluvoxamine, fluoxetine and paroxetine) on HRV is less clear \[24,25\]. Treatment with SSRIs results in a significant decrease in heart rate and a marginally significant increase in SDNN \[26\]. The SSRI-related changes are of much smaller magnitude compared to those associated with TCAs.

Most antipsychotic drugs influence the autonomic nervous system. The use of some antipsychotics (e.g. sertindole) was even temporarily restricted because of concerns about their adverse cardiac effect \[27\]. Antipsychotic drugs affect differently HRV. Olanzapine and amisulpiride increases, thioridazine decreases, while risperidone and haloperidol have no effect on HRV \[28,29\]. A dose-dependent decrease in parasympathetic activity was also documented in
patients with schizophrenia treated with different antipsychotics [30].

There is an association between improvement in depression after ECT and changes in HRV [15,31-33]. A decrease in the HF component of HRV reflecting decreased vagal activity was found following a course of ECT in nine patients diagnosed with major depressive disorder (MDD) [31]. This finding was in contrast to the hypothesis that ECT would cause an increase in vagal activity [31]. Further, cardiac vagal modulation increased significantly after ECT in 11 elderly depressed inpatients [33]. The SDNN increased in patients who improved with ECT, but not in those who became confused and agitated after ECT [15]. Although these studies showed certain changes in HRV following ECT, the results remain conflicting.

This study set out to analyze the correlation between autonomic nervous activity measured by HRV and seizure threshold at the first session of ECT.

Materials and Methods

The study had a retrospective design. As part of the routine administration of ECT, 5-minute resting ECG was registered before induction of anesthesia in the first ECT session. ECG recordings were analyzed with the Kubios HRV free software, version 2.1, released in July 2012 (Department of Applied Physics, University of Eastern Finland, Kuopio, Finland). Seizure threshold was defined as the lowest dose resulting in a minimum of 20 seconds of seizure on the EEG.

Patients

The medical files of all patients treated at the Odessa Private Psychiatric Institute (OPPI) and referred for ECT between December 2013 and May 2015 were assessed for inclusion in the study. Patients on beta-blockers, benzodiazepines or GABA-ergic medications were excluded. Relevant somatic co-morbidities, such as history of myocardial infarct or thyroid dysfunction, were also exclusion criteria. Two-channel resting ECG was routinely recorded for 5 minutes before sleep induction. Patients without pre-treatment ECG recordings were also excluded. Patients receiving a course of ECT more than once during the study period entered the analysis only once, at their first treatment. The indication for ECT was affective disorder in 16 cases (15 with depression, 1 with mania) and schizophrenia in 14 cases. Diagnoses were established according to ICD-10 criteria by the treating psychiatrists.

Approval of the study protocol from the Research Ethics Committee of the hospital was not sought because retrospective chart reviews where patients’ personal data are not mentioned do not require approval according to Ukrainian law. Written informed consent was obtained from the patients or from their next-of-kin if the patient lacked the capacity to consent.

Administration of ECT

ECT was administered three times a week, early mornings Monday, Wednesday and Friday. Bitemporal electrode position was used in all sessions. Electrical stimuli were delivered by a Niviqure VR square-wave device (Niviqure Meditech Pvt. Ltd, Bangalore, India) that in standard mode provides a stimulus of 0.8 A, with a pulse width of 1.0 ms and a frequency of 60 PPS. The intensity of the stimulus can be adjusted with the duration of the stimulation between 0.4 and 3.6 sec. Initial stimulus dose was calibrated according to the half-age method [34]. In case of no seizure, or a seizure shorter than 20 seconds, patients were re-challenged with a 50% higher stimulus dose. Seizures were monitored with EEG and visual observation using the ‘cuff method’ [35].

Pre-treatment anesthesia

No premedication was used in this facility. Anesthesia was induced by a fixed dose of 200 mg of thiopental with an additional 50 mg if necessary but never exceeding 300 mg. For muscle relaxation, 0.5 mg/kg succinylcholine was administered. Ventilation was assisted using a face mask with 6-8 l/min oxygen. The oxygen saturation and CO2 were monitored with a pulsoxymeter and gas analyzer (Datex Ohmeda 5250 RGM).

Concomitant psychotropic medications

Twenty-six patients were taking psychotropic drugs, 24 of whom were on antipsychotics: 11 patients were on haloperidol (dose range: 2.5-10 mg), 10 on quetiapine (dose range: 50-400 mg), 8 on olanzapine (dose range: 5-10 mg), 2 on aripiprazole (dose: 15 mg) and 1 each on clozapine (dose: 200 mg) and risperidone (dose: 2 mg). Nine patients were receiving antidepressants: 8 venlafaxine (dose range: 75-300 mg) and 1 escitalopram (dose: 5 mg).

Statistical analysis

Statistical analyses were performed with SPSS, Version 20.0. Demographic data are reported
Results

During the study period altogether 1,147 patients were treated in the OPPI of whom 73 (6.4%) received a course of ECT. Forty-three patients were excluded for the following reasons: 4 were taking gabapentin with propranolol and gidazepam, a locally manufactured benzodiazepine; 3 were prescribed pregabalin and propranolol, 3 propanolol, and 1 each pregabaline and bisoprolol. Four and two patients needed intravenous metoprolol and esmolol respectively for tachycardia of >120 beats/min. at baseline. Further 16 patients were taking benzodiazepines. In 7 cases no analyzable ECG was recorded. Two patients were excluded because of hyperthyreosis. Eventually 30 patients were included the statistical analysis.

The mean age of the sample was 33.6 ± 13.1 years; there were 14 (47%) female patients. The mean stimulus intensity required to elicit a seizure was 77.20 ± 32.09 mC. Descriptive results in the time domain were as follows: NN (ms): 693.5 ± 148.4; SDNN (ms): 36.2 ± 18.7; HR (1/min): 90.3 ± 18.1; SDHR (1/min): 4.7 ± 1.9; RMSSD: 24.82 ± 21.67. In the frequency domain LF/HF ratio was 2.86 ± 2.43.

Univariate analysis revealed that age (F=6.159; p=0.023) and RMSSD (F=9.179; p=0.007) had significant positive correlations with initial stimulus intensity. Comparison of the HRV values between affective and schizophrenia spectrum disorders showed no significant difference, even though patients with schizophrenia were significantly younger than their affective disorder counterparts (28.29 ± 7.21 vs. 38.25 ± 15.21, p=0.036). The schizophrenia group tended to have higher LF/HF ratios compared to the affective group (2.12 ± 1.24 vs. 3.70 ± 3.15; p=0.074).

Limitations of the study

The main limitations of the study are its retrospective design and the relatively small sample size. Further, the sample included a mixed clinical population referred for ECT with different indications. Although comparison of the diagnostic groups revealed no significant difference in HRV measures, in a larger sample the difference in the LF/HF ratio may reach a statistically significant level. Antidepressant and antipsychotic medications also have a proven effect on HRV parameters. Nine patients in this study were taking antidepressants and 24 different antipsychotics, which may have compromised the results. A further limitation was the lack of systematic seizure titration at the first ECT session. As the “half-age” method was used to set the initial stimulus dose, some patients might have had a lower seizure threshold using systematic seizure titration. A final limitation was the fixed dose of the initial anesthetic drug, which might also have affected the initial seizure threshold.

Conclusion

This study demonstrated a correlation between
initial stimulation dose in ECT and one HRV measure, the RMSSD. The RMSSD is a promising, easily measurable parameter for ascertaining the initial stimulus intensity in ECT. Further research with more sophisticated methodology is warranted.

Conflicts of Interest and Source of Funding
None declared.

References


31. None declared.

