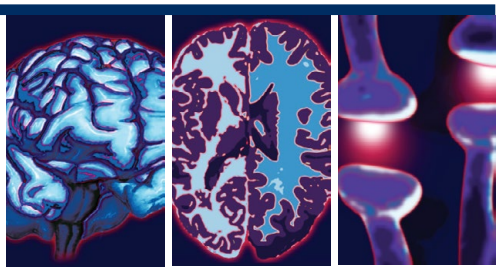

Relation between heart rate variability and seizure threshold in electroconvulsive therapy: a pilot study

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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 excitable. 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

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(VNS). Increasing the parasympathetic tone of the vagus nerve significantly increases the seizure threshold in animal models [5,6]. This method is also used as an antiepileptic treatment modality in human neurology [7-9].

Dynamic changes in cardiac autonomic nervous activity caused by electroconvulsive therapy (ECT) have been well described [10,11]. ECT first produces sinus bradycardia through electrical stimulation of the nucleus of the vagus nerve via the parasympathetic nervous system [10]. The initial parasympathetic response is immediately followed by sympathetic discharges, leading to a considerable rise in blood pressure (BP) and heart rate (HR). This sympathetic excitatory response continues until the seizure ends, when the parasympathetic nervous system is reactivated. Finally, BP and HR return to their baseline levels [11].

Heart rate variability (HRV) is an indicator of the autonomic activity on the heart. HRV can be measured with standard electrocardiography (ECG) devices and appropriate software by registering successive beat-to-beat heart activity to assess the instantaneous heart rate [12]. HRV is particularly useful for examining autonomic nervous system activity because it can evaluate sympathetic and parasympathetic activity separately. Several measurements can be estimated through HRV analysis. Time-domain and frequency-domain measures are used most commonly. Besides HR, the following time-domain variables are evaluated: (1) the inter-beat interval (NN); (2) the standard deviation of normal inter-beat (SDNN); (3) the standard deviation of the means of all NN intervals (SDANN; the time intervals between consecutive normal beats measured from successive 5-minute recording segments over a 24-hour period); (4) the square root of the mean of the sum of the squares of differences between all adjacent NN intervals (RMSSD); and (5) the proportion of pairs of adjacent inter-beat intervals differing from each other by more than 50 milliseconds divided by the total number of recorded R-R intervals (pNN50) [13]. Frequency-domain measures are presented as the power (variance) of fluctuations distributed within different ranges (bands) of the frequency spectrum [14]. Traditionally, high-frequency (HF) and low-frequency (LF) values are differentiated and their ratio calculated.

HF, RMSSD and pNN50 are strongly influenced by the parasympathetic nervous system, while 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

as the mean and standard deviation. The association between seizure threshold and HRV measures were calculated. Univariate analysis of variance was used to explore the association between variables. Stimulus intensity was the dependent variable, with age, sex, and diagnosis and HRV measures as the independent variables. HRV values in patients with schizophrenia and affective disorders were compared using t-tests.

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).

Discussion

Setting the proper stimulus intensity at the first ECT session is a challenging task, as the seizure threshold varies 6-7-fold between patients [36]. There are various methods available to guide clinicians in defining the initial stimulus intensity [37], but none of them can ensure adequate seizure following the first stimulation. For this reason, variables correlating with the seizure threshold might be useful in set the proper stimulus intensity in the first ECT session.

To the best of our knowledge, this was the first study to investigate the influence of autonomic nervous system activity on seizure threshold in ECT. The main finding is that the RMSSD is the only HRV measure that shows a significant correlation with the initial seizure threshold. This result confirms earlier findings in epilepsy research that increased parasympathetic tone, reflected by higher RMSSD values, has an anticonvulsant effect manifested in higher initial seizure threshold parameters [38].

Both depressive and schizophrenia spectrum disorders are associated with changes in HRV [16,19]. Comparison of the two major diagnostic groups in this study revealed no significant differences in terms of HRV measures, although the patients differed significantly in age and treatment with psychotropic drugs.

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

1. Amzica F. Neurophysiology of Epilepsy. In: Shorvon S, Guerrini R, Cook M, Lhatoo S (eds.): Oxford Textbook of Epilepsy and Epileptic Seizures. Oxford University Press, Oxford, London (2012).
2. Eggleston KS, Olin BD, Fisher RS. Ictal tachycardia: The head–heart connection. *Seizure* 23(7), 496-505 (2014).
3. Ansakorpi H, Korpelainen JT, Suominen K, *et al.* Interictal cardiovascular autonomic responses in patients with temporal lobe epilepsy. *Epilepsia* 41(1), 42-47 (2000).
4. Harnod T, Yang CC, Hsin YL, *et al.* Heart rate variability in children with refractory generalized epilepsy. *Seizure* 17(4), 297-301 (2008).
5. De Herdt V, De Waele J, Raedt R, *et al.* Modulation of seizure threshold by vagus nerve stimulation in an animal model for motor seizures. *Acta. Neurol. Scand* 121(4), 271-276 (2010).
6. Alexander GM, McNamara JO. Vagus nerve stimulation elevates seizure threshold in the kindling model. *Epilepsia* 53(11), 2043-2052 (2012).
7. Erőss L, Entz L, Fabó D. Invasive neuromodulation in the treatment of drug-resistant epilepsies. Orv. Hetil 156(52), 2103-2109 (2015).
8. Krishna V, Sammartino F, King NK, *et al.* Neuromodulation for Epilepsy. *Neurosurg. Clin. N. Am* 27(1), 123-131 (2016).
9. Panebianco M, Zavanone C, Dupont S, *et al.* Vagus nerve stimulation therapy in partial epilepsy: a review. *Acta. Neurol. Belg* (1):CD002896 (2016).
10. Beyer JL, Weiner RD, Glenn MD. Seizure monitoring: the cardiovascular response. Electroconvulsive therapy. A programmed text. 2nd ed. Washington DC: American Psychiatric Pres, USA 111-117 (1998).
11. Suzuki Y, Miyajima M, Ohta K, *et al.* A Triphasic Change of Cardiac Autonomic Nervous System During Electroconvulsive Therapy. *J ECT* 31(3), 186-91 (2015).
12. ESC. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart. J* 17(3), 354-381 (1996).
13. Stein PK, Bosner MS, Kleiger RE, *et al.* Heart Rate Variability: A measure of cardiac autonomic tone. *Am. Heart. J* 127(), 1376-1381 (1993).
14. Karemaker JM. Autonomic integration: the physiological basis of cardiovascular variability. *J. Physiol* 517(Pt 2), 316 (1999).
15. Karpyak VM, Rasmussen KG, Hammill SC, *et al.* Changes in heart rate variability in response to treatment with electroconvulsive therapy. *J ECT* 20(2), 81-88 (2004).
16. Kemp AH, Quintana DS, Gray MA, *et al.* Impact of depression and antidepressant treatment on heart rate variability: a review and meta-analysis. *Biol. Psychiatry* 67(11), 1067-1074 (2010).
17. Buccelletti E, Gilardi E, Scaini E, *et al.* Heart rate variability and myocardial infarction: systematic literature review and metanalysis. *Eur. Rev. Med. Pharmacol. Sci* 13(4), 299-307 (2009).
18. Carney RM, Blumenthal JA, Stein PK, *et al.* Depression, heart rate variability, and acute myocardial infarction. *Circulation* 104(17), 2024-2028 (2001).
19. Montaquila JM, Trachik BJ, Bedwell JS. Heart rate variability and vagal tone in schizophrenia: A review. *J. Psychiatr. Res* 69(1), 57-66 (2015).
20. Khaykin Y, Dorian P, Baker B, *et al.* Autonomic correlates of antidepressant treatment using heart-rate variability analysis. *Can. J. Psychiatry* 43(2), 183-186 (1998).
21. Agelink MW, Majewski T, Wurthmann C, *et al.* Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. *J. Affect. Disord* 62(3), 187-198 (2001).
22. McFarlane A, Kamath MV, Fallen EL, *et al.* Effect of sertraline on the recovery rate of cardiac autonomic function in depressed patients after acute myocardial infarction. *Am Heart J* 142(4), 617-623 (2001).
23. Rechlin T. The effect of amitriptyline, doxepin, fluvoxamine, and paroxetine treatment on heart rate variability. *J. Clin. Psychopharmacol* 14(6), 392-395 (1994).
24. Volkers AC, Tulen JH, van den Broek WW, *et al.* Effects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder. *Pharmacopsychiatry* 37(1), 18-25 (2004).
25. Straneva-Meuse PA, Light KC, Allen MT, *et al.* Bupropion and paroxetine differentially influence cardiovascular and neuroendocrine responses to stress in depressed patients. *J. Affect. Disord* 79(1-3), 51-61 (2004).
26. Van Zyl LT, Hasegawa T, Nagata K. Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. *Biopsychosoc. Med* 2(1), 12 (2008).
27. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics : differential risk and clinical implications. *CNS. Drugs* 21(11), 911-36 (2007).
28. Silke B, Campbell C, King DJ. The potential cardiotoxicity of antipsychotic drugs as assessed by heart rate variability. *J. Psychopharmacol* 16(4), 355-60 (2002).
29. Wang YC, Yang CC, Bai YM, *et al.* Heart rate variability in schizophrenic patients switched from typical antipsychotic agents to amisulpride and olanzapine. 3-month follow-up. *Neuropsychobiology* 57(4), 200-205 (2008).
30. Iwamoto Y, Kawanishi C, Kishida I, *et al.* Dose-dependent effect of antipsychotic drugs on autonomic nervous system activity in schizophrenia. *BMC. Psychiatry* 12(1), 199 (2012).
31. Schultz SK, Anderson EA, van de Borne P. Heart rate variability before and after treatment with electroconvulsive therapy. *J. Affect. Disord* 44(1), 13-20 (1997).
32. Agelink MW, Lemmer W, Malessa R, *et al.* Improvement of neurocardial vagal dysfunction after successful antidepressive treatment with electroconvulsive therapy (ECT). *Eur Psychiatry* 13(4), 259s (1998).
33. Nahshoni E, Aizenberg D, Sigler M, *et al.* Heart rate variability increases in elderly depressed patients who respond to electroconvulsive therapy. *J. Psychosom. Res* 56(1), 89-94 (2004).
34. Petrides G, Fink M. The "half-age" stimulation strategy for ECT dosing. Convuls Ther 12(3), 138-146 (1996).
35. Fink M, Johnson L. Monitoring the duration of electroconvulsive therapy seizures: "cuff" and EEG methods compared. *Arch. Gen. Psychiat* 39(10), 1189-1191 (1982).
36. Sackeim HA, Decina P, Prohovnik I, *et al.* Seizure threshold in electroconvulsive therapy: Effects of sex, age, electrode placement, and number of treatments. Arch Gen Psychiat 44(4), 355-360 (1987).
37. Gazdag G, Tolna J, Iványi Z. Az optimális stimulus-intenzitás beállításának stratégiái elektrokonvulzív kezelés során [Strategies for optimizing stimulus dosage during electroconvulsive therapy.] *Psychiatr. Hung* 22(3), 185-190 (2007).
38. Ben-Menachem E. Vagus-nerve stimulation for the treatment of epilepsy. *Lancet. Neurol* 1(8), 477-482 (2002).