Changes in Heart Rate Variability before and after ECT in the Treatment of Resistant Major Depressive Disorder

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ABSTRACT

Background: In this study, we aimed to evaluate the effects of electroconvulsive therapy (ECT) on cardiac autonomic functions (CAF) in patients with major depressive disorder (MDD) using heart rate variability (HRV) analysis.

Method: Fourteen men joined the study. Nine ECTs were administered. Holter monitoring was performed before treatment and at the end of the first, third and sixth weeks of the treatment. The Hamilton Depression Rating Scale (HAM-D) was used to assess symptom severity.

Results: Seven patients responded to ECT. There was a change of 2-hour resting HF, pNN50 and RMSSD scores between week 0 and week 6. This change was not significant after week 1 and week 3. HRV values did not differ when we grouped the patients as responders and non-responders to ECT except the 2-hour resting HF value of responders between week 0 and week 6 and the 24-hour HF value of non-responders between week 1 and week 6. All observed changes showed a decrease in parameters. Overall, the LF/HF ratio did not change significantly in either analysis. HRV values did not correlate with HAM-D scores and no relation was found between treatment response and HRV analysis. After Benferroni-adjustment none of the changes were found statistically significant.

Limitations: The limitations of the study are the small sample size and the absence of healthy controls.

Conclusions: A consistent change in HRV was not observed in response to ECT in patients with MDD. Accepting the HRV as a promising surrogate marker of autonomic activity, ECT does not cause a significant change in nine male treatment resistant MDD patients cardiac autonomic functions.

INTRODUCTION

During electroconvulsive therapy (ECT) there are changes in autonomic nerve system activity, most of which are related to parasympathetic outflow and restricted to several minutes. After parasympathetic stimulation, the sympathetic output increases and may cause a rise in heart rate and blood pressure. This is not only due to electrical stimulation but also to the release of catecholamines from the adrenal gland. Several studies have shown dysrhythmias and transient ST-segment changes. In a study by Huuhka et al. ECT caused increases in bigeminy/trigeminy and supraventricular tachycardia, but did not increase other arrhythmias (1).

The term heart rate variability (HRV) is used to characterize fluctuations in the length of the interbeat intervals that are typical for normal cardiac rhythm and can be used to assess the cardiac autonomic nervous system (2-4). The determinants of HRV are multifactorial and include the autonomic nervous system (ANS), central nervous system functioning, and emotional stressors (5, 6). The HRV

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can be measured as time domain or frequency domain. Standard deviation of normal interbeat (SDNN), standard deviation of means of all NN intervals (the time intervals between consecutive normal beats) measured from successive five minute recording segments over a 24-hour period (SDANN), the square root of the mean of the sum of the squares of differences between all adjacent NN intervals (RMSSD) and the proportion of pairs of adjacent interbeat intervals differing from each other by more than 50 milliseconds divided by the total number of recorded R-R intervals (pNN50) are time domain measures. Frequency domain measures provide an estimate of the frequency of rhythmic oscillations in heart rate. Four main ranges of frequencies are used: High frequency (0.15-0.4 Hz), low frequency (0.04-0.15 Hz), very low frequency (0.003-0.04 Hz) and ultra low frequency (less than 0.003 Hz). Power (variance) of fluctuations within each frequency range is referred to as high frequency power (HF), low frequency power (LF), very low frequency power (VLF) and ultra low frequency power (ULF). HF, RMSSD and pNN50 are strongly influenced by the parasympathetic nervous system. LF might be related to sympathetic or both sympathetic/parasympathetic systems. The LF/HF ratio is a mirror of the sympathovagal balance (2, 6). SDNN and SDANN are also related to both sympathetic and parasympathetic systems.

Cardiac autonomic involvement in depression in the form of decreased parasympathetic activity and increased sympathetic activity with lower HRV is known even among cardiac-healthy persons (7-9). Since it has been suggested that depression may be associated with decreased parasympathetic activity, it could be expected that treatment of depression with ECT would result in a relative increase in cardiac vagal activity (10). Nevertheless, studies on depression and HRV, mostly performed on psychiatric inpatients, have revealed conflicting results. Several studies reported a reduction of HRV while other studies reported no HRV difference in depressed patients compared to non-depressed controls (11). Some researchers suggest that depressive symptoms are associated with autonomic dysfunction in elderly men. But the rising risk of cardiovascular mortality with the increasing magnitude of depressive symptoms is not explained by its relation to autonomic dysfunction (12). In a review on the effects of ECT and antidepressants in HRV, van Zyl et al. (13) concluded that tricyclic antidepressants (TCAs) are associated with a substantial decrease in HRV and an increase in HR. The effect of selective serotonin reuptake inhibitors (SSRIs) is weaker than that of TCAs, with a small decrease in HR but an increase in one measure of HRV. It was also concluded that no relationship between ECT and HRV had been established in the literature.

Electroconvulsive therapy is an effective treatment of depression, and it is a strong stimulus to the ANS, especially in terms of the effects on the heart. An association between improvement in depression after ECT and changes in HRV has been reported by several groups of researchers. Schultz found a decrease in the HF component of HRV (reflecting decreased vagal activity) following a course of ECT in nine patients diagnosed with major depressive disorder (MDD) (mean age 42.2 years). This was in contrast to the hypothesis that ECT would cause an increase in vagal activity (10). Based on a significant correlation between changes in HRV and an improvement in the Hamilton Rating Scale for Depression (HAM-D) scores, they suggested that these findings might be related to the resolution of depression rather than to the effect of ECT. Agelink reported a significant increase in time domain measures of HRV (mean coefficient of variance and the root mean square of successive differences of R-R intervals) in eight patients (mean age 44.1 years) who favorably responded to ECT (14). Nahshoni found that cardiac vagal modulation increased significantly after ECT treatment in 11 elderly depressed inpatients (mean age 70 ± 7 years) (15, 16). Karpyak et al. reported that standard deviation of interbeat intervals (SDNN, a measure of HRV) increased in subjects who improved with ECT but not in those who became confused and agitated (6). Although these studies showed some changes in HRV after ECT, the results were conflicting.

The effects of ECT on the heart have been evaluated in other studies. Rasmussen et al. found that ECT does not have an effect on heart rate, frequency of ventricular or supraventricular events or in ST segments (17). Solimene studied 47 young adults and 38 individuals older than 50 who underwent ECT. Observed among the younger individuals was an increase in blood pressure and in heart rate, both of which returned to normal within 25 minutes. In the older group, however, the heart rate remained elevated even after one hour. These results show that while ECT may cause an increase in sympathetic activity, it is still a safe procedure for the heart (18).

This study aims to evaluate the effects of ECT on cardiac autonomic functions (CAF) in patients with major depressive disorder (MDD) using HRV analysis. Our hypothesis is that ECT is a safe procedure that does not have an effect on HRV.

SUBJECTS AND METHODS

SUBJECTS

The subjects were recruited from the MDD patients who were hospitalized in the inpatient unit of the Department of Psychiatry at the Gülhane School of Medicine. Fifteen patients were initially selected for the study, but one patient who used a cardio-selective β blocker during the study was left out. The patients completing the study consisted of 14 men aged 30–54 (mean 37.78 ± 6.12 years) with major depressive disorder. The diagnosis of MDD was established according to DSM-IV criteria following the guidelines of the Turkish version of the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P) (19). To be included in the study, the patients had to fit the following criteria: they had to have MDD according to the SCID I; they had to have scores 19 or higher in the HAM-D-17 test; they could not have any physical risks associated with ECT; they had to be between 18 and 60 years of age; they had to join the study willingly and were asked to sign a consent form; they could not have diabetes or any known neurological, cardiac or cardiovascular disease. Patients who had normal findings on physical examination, electrocardiography (ECG) and routine blood tests and had no history, signs or symptoms of cardiovascular or neurologic disorders were included in the study. All patients were taking antidepressant medications other than tricyclics and were subjected to ECT because of non-response to pharmacotherapy. The institutional review board approved the study. After receiving a complete description of the study, written informed consent was obtained from each subject. Patients had at least two adequate trials of antidepressant medications and were considered as treatment resistant to depression. All patients were ECT naïve. The average period of their illness was 0.5–7 years (mean 3,23 ± 2.17years) since their first episodes. The patients were included in the decision making process. Any possible risks and benefits and the number of ECTs were discussed with the patients and mentioned in the informed consent. Non-responders were given the opportunity to have extra sessions of ECT after completing the study. The ECT sessions were planned to stop after the 6th ECT, assuming that there would be signs of response or remission. Since none of the patients showed signs of response or remission by the end of week 2 (6th ECT), all patients received up to 9 ECTs. Since the course length of ECT cannot be predicted, 9-10 treatments are considered to be the response criteria. Kellner et al. found that in 15 patients with major depression who were randomized to receive 3 ECT at 1/wk or 9 ECT at 3/wk, the latter schedule had significantly greater reduction in depression level (20). Janakiramaiah et al. had found that all patients in three times weekly ECT (8.7±1.9) group remitted but only 11 (out of 20) remitted in once weekly group (21). They have used a mean of 8.7 ECTs. Since the number 9 and 10 are the most used frequency in literature and three times weekly usually causes more remission we have scheduled 9 ECTs for this protocol. All patients were hospitalized and then discharged after the 9th ECT. They were reevaluated after week 6.

MEDICATIONS

Over the course of the study all patients continued to take their antidepressants (either selective serotonin reuptake inhibitor, n=13, or trazadone, n=1) (9 patients sertraline, 2 patients paroxetine, 1 patient fluoxetine, 1 patient escitalopram). Since one inclusion criterion was non-use of tricyclic or tetracylic antidepressants, none of the patients were using those. No other psychotropic medications (neither anxiolytics nor antipsychotics) were allowed during the study period.

ELECTROCONVULSIVE THERAPY

Bilateral ECT was administered three times a week and all patients underwent a total of 9 ECTs. Electrical stimulus was provided by a Mecta Spectrum 5000Q ECT device. The seizure threshold was terminated at the first treatment. Stimuli were given by increasing intensity until a generalized seizure was induced. The anesthetic medications were thiopental (5 mg/kg) and succinylcholine (0.5 mg/kg). All patients were oxygenated by positive pressure ventilation via mask until resumption of spontaneous respiration. Treatments were given three times a week.

HEART RATE RECORDING

Twenty-four-hour Holter monitoring was performed at the following times during the study: one day before ECT started, at the end of the first week; the day after the patient completed his first 3 ECTs, the day after the last ECT, three weeks after the last ECT, which is also the end of the sixth week of the study. Subjects also had a complete rest in bed between 1 and 3 pm during the 24-hour monitoring. In this way it was possible to evaluate the acute and sub-acute effects of ECT on HRV.

CLINICAL MEASURES

The 17-item Hamilton Rating Scale for Depression (HAM-D) was used to assess symptom severity. HAM-D was developed in 1960 by Max Hamilton at the University

of Leeds. The scoring is based on 17 items. Eight items are scored on a 5-point scale ranging from 0 (not present) to 4 (severe). Nine are scored 0 to 2. The sum of the scores from the 17 items are described as following: 0 to 7 (normal), 8 to 13 (mild depression), 14 to 18 (moderate depression), 19 to 22 (severe depression), ≥ 23 (very severe depression). HAM-D is frequently used in clinical practice and has become a standard in trials. Rating scales were obtained before ECT sessions, weekly during ECT sessions and three weeks after the completion of the ECT course. Clinical response to ECT was defined as 50% or more decrease of HAM-D scores from baseline to endpoint of the clinical trial.

STATISTICAL ANALYSIS

Since the data was not normally distributed, Friedman and Wilcoxon signed rank tests were used to analyze the continuous variables. The relationship between the values of HRV and HAM-D scores was evaluated by Spearman correlation coefficients. A "p" value of less than 0.05 was considered significant in all analyses. For adjustment the significance level using Bonferroni's correction we have divided the p values by the number of comparisons.

RESULTS

The mean HAM-D score of patients before treatment was 27.64 ± 4.71 and decreased to 14.64 ± 4.14 after ECT treatment (p<0.01). Of the 14 patients with major depressive disorder, 7 patients responded to ECT. In patients who responded to ECT, the mean HAM-D score decreased from 25.85 ± 3.97 to 11.00 ± 0.81 (p<0.01, Z= -2.14). The mean scores of responders and non-responders are given in the Table 1.

Three patients responded to treatment at the end of week 3 (after ECT 9), and by the end of week 6, three more responded. One of the first three responders had a relapse, but then four additional patients responded. When we analyzed 14 subjects together (Table 2), the HF scores decreased significantly at the end of the treatment compared to the pre-treatment scores (baseline 239. 41 ± 128. 47; end of study 178. 57 ± 112. 11; Z= -2.14, p=0.033). The change in HF scores is seen during the 24-hour recording that occurred between week 0 and week 6. The change of HF is also significant between week 0 and week 6 in the two-hour resting scores (baseline 223.29 ± 100.69; end of study 137.29 ± 75.43; Z= -2.42, p=0.016).

There is a similar decrease seen in the pNN50 and RMSSD scores. But the changes are significant only in the 2-hour resting scores between week 0 and week 6 (baseline 9.14 ± 7.05; end of study 5.38 ± 4.23; Z= -2.14, p=0.032; baseline 29.86 ± 7.94; end of study 24.50 ± 6.56; Z= -2.36, p=0.018 respectively). All parameters show a decrease, which actually shows a decrease in parasympathetic tonus. But the change was not significant after the first 3 ECT procedures in week 1 and after the 9 ECT procedures at the end of week 3. Pre- and post-treatment HRV values did not differ when we grouped the patients

Table 1. *Changes in Mean HAM-D Scores of All Patients*

	Before Treatment	Week 1 After 3 ECT	Week 3 After 9 ECT	Week 6 End of Treatment	Statistic
Responders	25,86 ± 3,98	23,57 ± 4,79	16,00 ± 4,69	11,00 ± 0,82	Z= -2.371 p= 0.018[a]
Non- responders	29,43 ± 5,00	27,14 ± 4,85	21,00 ± 5,32	18,29 ± 2,36	Z= -2.371 p= 0.018[a]

[a]Difference between week 0 and week 6.

Table 2. *Changes in Mean HRV Scores of All Patients*

	Before Treatment	Week 1 After 3 ECT	Week 3 After 9 ECT	Week 6 End of Treatment	Statistic
pNN50	9.93 ± 7.42	12.07 ± 6.80	8.92 ± 6.47	7.30 ± 6.18	NS
RMSSD	30.21 ± 9.48	33.36 ± 8.24	29.29 ± 8.12	27.29 ± 7.13	NS
LF	1091.54±1331±02	765.57±382.84	708.86±313.31	718.21±352.54	NS
HF	239.41±128.47	256.71±134.42	201.00±118.79	178.57±112.11	Z= -2.14 p= 0.033[a]
LF/HF	3.42±1.20	3.17±1.09	3.94±1.72	4.43±1.88	NS

[a]Difference between week 0 and week 6. NS: Not significant

Table 3. *Changes in Mean HRV Scores of Responders and Non-Responders to Treatment*

		Before Treatment	Week 1 After 3 ECT	Week 3 After 9 ECT	Week 6 End of Treatment	Statistic
pNN50	Responders	11.00±7.33	13.00±8.00	11.67±7.45	9.86±7.06	NS
	Non-responders	8.86±7.93	11.14±5.84	6.57±4.86	4.33±3.50	NS
RMSSD	Responders	31.71±9.18	34.57±9.59	32.00±9.07	30.29±7.57	NS
	Non-responders	28.71±10.26	32.14±7.20	26.57±6.58	24.29±5.65	NS
LF	Responders	1438.37±1815.61	697.57±228.91	776.86±212.02	818.86±304.28	NS
	Non-responders	744.71±511.29	833.57±504.34	640.86±396.15	617.57±391.23	NS
HF	Responders	233.24±102.82	215.57±82.69	201.29±99.99	200.86±127.97	NS
	Non-responders	245.57±158.43	297.86±168.40	200.71±143.44	156.29±98.48	Z= -2.37 P=0.018[a]
LF/HF	Responders	3.49±1.16	3.54±1.40	4.58±2.10	4.78±1.73	NS
	Non-responders	3.34±1.33	2.80±0.54	3.30±1.02	4.07±2.08	NS

[a]Difference between week1 and week 6. NS: Not significant

as responders and non-responders to ECT except the resting 2-hour HF value of responders between week 0 and week 6 (baseline 206.86 ± 95.43; end of study 122.86 ± 34.29; Z= -2.03, p=0.043) and the 24 hours HF value of non-responders between week 1 and week 6 (baseline 297.86 ± 168.40; end of study 156.29 ± 98.48; Z= -2.37, p=0.018) (Table 3). Again, there was a decrease of parasympathetic tonus. There were no significant changes in other time domain measures. Overall the LF/HF ratio did not change significantly in either analysis.

HRV values did not correlate with HAM-D scores and no relation was found between treatment response and HRV analysis (p>0. 05).

DISCUSSION

The results of this study revealed that in nine male treatment resistant MDD patients, ECT had no major and consistent impact on HRV parameters that were used as surrogate markers of CAF.

Some studies reported variable changes in HRV after ECT (6, 10, 14, 15), but none of them used 24-hour ECG monitoring, which is important because circadian rhythms may influence HRV. We used 24-hour Holter monitoring in order to avoid circadian rhythm bias and repeated the HRV recordings one week after the initial ECT, immediately after ECT sessions and three weeks after sessions ended to evaluate both acute and sub acute effects of ECT on HRV. Although we have analyzed the HRV three weeks after the last ECT we cannot interpret that these changes are related to the delayed effects of ECT. We also used a resting period between 1 and 3 pm in every recording. This gave us the chance to compare full resting HRV changes. As pointed out by Karpyak et al. (6), in some studies there were specific restrictions applied on patients' activities, such as on breathing and talking (10, 14, 15). Such restrictions may affect HRV measures and were avoided in this study.

The findings reveal only a few HRV changes. One is the difference of HF during resting between pre-treatment and the end of study measures. First of all, these changes were seen in both resting and 24-hour recordings at the end of week 6. But they were not seen after the 3 ECTs at end of week 1 and after 9 ECTs at the end of week 3. The last ECT was at the end of week 3 and the last Holter monitoring at the end of week 6. So the Holter monitoring changes at the end of week 6 cannot be interpreted as an immediate effect of ECT. We know that response rates to ECT are very high, but relapse after discontinuation is also high. A possible cause could be that patients who responded to ECT were likely candidates for relapse, and the first signal of this could be the decreasing parasympathetic tonus. But neither the HAM-D nor the clinical interview showed any indication of relapsing. We cannot explain this finding as Schultz et al. did (10). They suggested that such a finding might be related to the resolution of depression, or the treatment of depression with ECT may be associated with cardiac vagal withdrawal. But in our study there was no correlation between HAM-D scores and changes of parasympathetic tonus markers (HF, RMSSD, pNN50). The mechanism of action is not clear.

When we analyzed all subjects (responders and non-responders) together, there was a decrease in parasympa-

thetic tonus too. This was seen in both 24-hour recording and resting recordings of HF, resting recordings of pNN50 and RMSSD. But the change was only significant between pre-treatment and end of week 6. There were no changes observed during week 1 and week 3 compared to pre-treatment values. It may be suggested that the effect of ECT was not directly responsible for those changes, or, as suggested by Schultz et al. (10), at least in some patients there might have been a vagal withdrawal, which was observed late (in week 6) in this study.

Grouping subjects as responders and non-responders did not show changes related to the theoretical point that cardiac autonomic involvement in depression should decrease parasympathetic activity, which increases after treatment. The change in pre- and post-treatment HRV values is only seen in the resting 2-hour HF value of responders between week 0 and week 6 and the 24-hour HF value of non-responders between week 1 and week 6 that does not show an increase in parasympathetic activity. Here again the changes did not occur immediately after ECT.

When we compare results with similar studies, Karpyak et al. (6) reported SDNN increase in patients which acutely responded to ECT. The increase has continued in subjects with sustained response but not in subjects who relapsed. Nahshoni et al. (15) reported that cardiac vagal modulation increased after ECT and was associated with symptom improvement. Different from these findings Schultz et al. (10) found cardiac vagal withdrawal (decreased parasympathetic activity) after treatment of depression with ECT. They concluded that this could be found in some patients. Comparing all studies with our study there were different approaches used in data analysis. Karypak et al. used SDNN, Nahshoni et al. LF/HF proportion and Shultz et al. respiratory sinus arrhythmia and RR interval. Rasmussen et al. (17), although methodologically very different, used heart rate, frequency of ventricular or supraventricular events or in ST and found no change in these parameters before and after ECT. Since the discrepancy between results might be related to different parameters we have used a broader number of parameters including time domain variables SDNN, SDANN, RMSSD, and pNN50, and the frequency domain variables HF and LF. We did not find major and consistent changes in all HRV parameters which we have used in our study. Overall we can conclude that ECT does not have direct effects on HRV in 9 male treatment resistant MDD patients since the mirror of sympathovagal balance (LF/HF) did not change.

One of the important findings that Karpyak et al. addressed was that the SDNN was significantly lower at baseline in the group of subjects that relapse within three weeks after ECT compared with the group with sustained response. We have found that the SDNN, SDANN, RMSSD, pNN50, LF, HF and LF/HF are not different at baseline when we compare groups as responders or non-responders.

Since the data were not normally distributed nonparametric tests were used. Bonferroni correction is necessary in order to correct for multiple testing in the same data set. We divided the p values by the number of comparisons. Since there were four tests being compared we divided p value (0.05/4=0,125). After Bonferroni's correction found no significant difference in any parameters that were compared. This supports our hypothesis that ECT does not have an effect on HRV.

In taking a closer look at the results, we found that none of our subjects had a clinical response after the 6th ECT at the end of week 2. Only subject 4 had a decrease of HAM-D from 22 to 12 at that point. Three other subjects, 1, 3 and 6, had a decrease more than 25% at end of week 2 (26%, 31%, and 28% respectively). All other 10 subjects had a decrease in HAM-D of less than 25% at end of week 2. Subjects 2, 4 and 6 had a decrease of more than 50% at the end of week 3 (9th ECT). The changes of SDNN of those three subjects are 59-59, 65-52 and 52-61; so one did not change, one increased and one decreased slightly. These results may be compared with those of responders of whom four had a decrease (58-50, 49-36, 71-58, 60-48), three had an increase (43-50, 49-58, 34-40), and four had a slight change (58-61, 41-42, 71-69, 59-62). Therefore SDNN cannot predict an early response relation. When we compare RMSSD, pNN50, LF and HF changes in these early responders, changes are similarly in different directions. When we compare responders and non-responders at end of week 6 we cannot find a specific type of change as described by Karypak et al. (6). For example, SDNN decreased in four responders and increased in three. It increased in one of non-responders and decreased in six non-responders. This suggests that the changes of different parameters cannot be used as possible predictors of response.

One limitation of this study is the fact that the patients were taking psychotropic medications. Studies on the effects of psychotropic medications on HRV revealed that TCAs were associated with a decline in most measures of HRV and a significant increase in HR in studies with short recording intervals. No significant changes were found for longer recording times (13). Treatment effects with SSRIs were more variable. Short recording studies revealed a significant decrease in HR and an increase

in one HRV measure. In two 24-hour recording studies no significant changes were observed (13). In this study, patients were mostly treated with SSRIs (13 of 14 patients; one patient taking trazadone), and they all continued to take their medications throughout the study.

Another limitation of the study is that we did not compare depressive patients who are not treated with ECT or subjects who are healthy.

In conclusion a consistent change was not observed in HRV in response to ECT in patients with MDD. This result was true for both responders and non-responders to ECT as reflected in the HAM-D scores. Accepting the HRV as a promising surrogate marker of autonomic activity, we may speculate that ECT does not cause an immediate significant change in cardiac autonomic functions. There was also no change three weeks after the last ECT, but to evaluate the delayed effects of ECT we need reevaluation of HRV after longer periods. However, the sample size in this study is too small to make a definite conclusion and further research with larger sample sizes is necessary to clarify the relationship between ECT and HRV.

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