Original Article

Comparing the Effects of Clozapine with Non-clozapine on Heart Rate Variability in Patients with Schizophrenia

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Objectives: With portable wireless heart rate detector, we intended in this study to investigate autonomic nervous activities with heart rate variability analysis during different daily activities in patients with schizophrenia treated with clozapine and non-clozapine antipsychotic drugs. Methods: We enrolled 30 male inpatients with schizophrenia (9 with clozapine treatment, 21 with non-clozapine antipsychotic treatment) participated. They received a 24-hr electrocardiogram recordings during 24 hours daily-life activities as usual and 3-minute step-test exercise. Their records were manually divided into five periods of activities, namely, daytime, nap, sleep, exercise, and after exercise. Results: Compared to those with non-clozapine antipsychotics, the patients with clozapine were found to be significantly associated with increased heart rates and elevated low frequency/high-frequency ratio during all five daily activities (all p < 0.001). Clozapine group was also demonstrated significantly decreased high frequency band power only in after-exercise state (p < 0.01). The significant difference in resting heart rate recovery ratios between two groups was found (p < 0.01) especially at the third and fourth minutes after exercise (all p < 0.01). Conclusion: In line with existing studies, the results confirmed changes in autonomic nervous activity in patients treated with clozapine, with marked difference at all day activities and heart rate recovery after exercise. These changes are primarily due to drug-related elevation in sympathetic activity and inhibition in vagal tone, independent of age, depression and severity of symptoms. The data also suggested a possible risk of cardiovascular adversity in the clozapine treatment among patients with chronic schizophrenia especially after exercises.

Key words: clozapine, schizophrenia, vagal tone, heart rate recovery after exercise


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Introduction

The results of a current meta-analysis study suggest that some antipsychotic medications, especially clozapine, have adverse impacts on autonomic nervous system [1], and sudden cardiac death [2]. Patients with schizophrenia on clozapine show higher heart rate, lower heart rate variability in lower high-frequency and higher low-frequency components compared to those on other antipsychotic drugs, e.g., haloperidol or olanzapine, or matched controls subjects [3]. Still being unknown are the rôles of parasympathetic activity (vagal tone) mainly due to the muscarinic M1-receptor effect of clozapine [4], and/or sympathetic activity, mainly due to its high affinity for dopamine receptors [5] or alpha 1-adrenergic receptors in vivo [6], in different activity states, e.g., during and/or after exercise.

The prognostic value of the rate of decline in heart rate after exercise has been considered as a result of dynamic sympatho-vagal balance [7]. The rise in heart rate during exercise indicates the combined effects of parasympathetic inactivation and sympathetic activation [8], and the fall in heart rate immediately after exercise implies the reactivation of the parasympathetic nervous system (vagal tone) [9]. Thus, increased vagal activity is associated with reduced risk of death [10]. A series of experimental and clinical studies has demonstrated a strong association between reduced vagal activity and increased sudden and non-sudden cardiovascular mortality, especially among chronic cardiovascular failure patients [16]. Especially, during the ischemia tests, as well as exercise, vagal stimulation reduces the heart rate and increases diastolic perfusion time and then may improve collateral coronary flow distribution [17].

In this study, we intended to clarify how clozapine affects autonomous nervous systems in different daily activities and which activity shows the highest risk of cardiovascular adversity.

Methods

Study subjects

We recruited 30 all-male inpatients (aged 23 to 65 years) with schizophrenia in this study. Nine of them were currently with clozapine treatment for at least three months (the clozapine group), the rest (n = 21, the non-clozapine group) with non-clozapine antipsychotic treatment – risperidone (n = 13), olanzapine (n = 7) and haloperidol (n = 3), and multiple antipsychotic drugs (n = 2, i.e. risperidone and olanzapine). To eliminate confounding effects on cardiovascular of medications other than antipsychotics, we had stopped anticholinergic and antipsychotics adjuvants for two days before experiment with clinic permission.

The study protocol was approved by the institutional review board of Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No.: 2-102-05-091) with the need to obtain written consents from participating subjects.

Study parameters and procedures

We recorded patients’ activity data with the time schedule on the psychiatry ward. We determined five daily-life states in five minutes epochs. Upon visual inspection of the ECG signal, no subjects showed any evidence of abnormal cardiac functioning or activity.

Heart rate variability (HRV) data were derived from the 24-hr ECG detector signal. The beat-to-beat hear rate intervals (i.e., R-R intervals) were calculated using computer software. After excluding outliers which exceed the three stan-
standard variances from mean of the state they belonged, the HRV signal for each state was subjected to overall spectral analysis (periodogram method) yielding very low-frequency (VLF), low-frequency (LF), and high-frequency (HF) band powers.

The VLF band power was defined as the power (ms²) in the VLF frequency band (0.01-0.05 Hz), the LF band power the power (ms²) in the LF frequency band (0.05 - 0.15 Hz), and the HF band power the power (ms²) in the HF frequency band (0.15 - 0.5 Hz). The LF/HF ratio was calculated simply dividing the LF band power by the HF band power.

We calculated the heart rate recovery rate by subtracting the heart rate (per minute) immediately after 5-minute aerobic step exercise (HR₀) from the heart rate at the first minute (HR₁), second minute (HR₂), third minute (HR₃), fourth minute (HR₄), and fifth minute (HR₅) after exercise. And the heart rate recovery equals each recovery rate by the heart rate at HR₀.

**Statistical analyses**

In this study, we used a 2 × 5 mixed factor repeated measures design, with each subject serving as his own control for the dependent measures in other daily activity states to minimize inter-subject variability. The independent variables were medications (clozapine verses non-clozapine antipsychotic drug) and three well-known confounders: age, body-mass index (BMI), and depression (measured using Hamilton Depression Score; HAMD_T). Dependent variables in this study included the VLF, LF, HF band power and LF/HF ratio measured during five daily-life states (daytime, nap, sleep, exercise, and after exercise).

For statistical analysis, repeated-measures analysis of variance (repeated-measures ANOVA) was computed using alpha (α) set at 0.05. We used independent-sample t-test to compare confounding factors and HRV parameters between the clozapine and the non-clozapine groups. But pairwise multiple comparison for five states’ HRV parameters between two groups were alpha-adjusted using Bonferroni method set at 0.01. In analyzing the heart rate recovery after exercise, we used the same methods (repeated measures ANOVA, pairwise post hoc and independent sample t-test with Bonferroni adjustment) to compare of their differences. All results are presented as mean ± standard error of the mean (SEM).

We used Statistical Package for Social Science version 20 (SPSS Inc., Chicago, Illinois, USA). The differences between groups were considered significant if p-values were smaller than 0.05.

**Results**

In this study, we collected 9 patients in the clozapine group, and 21 patients in the non-clozapine antipsychotic group. Table 1 lists study patients’ demographic data and clinic symptoms at baseline (N = 30).

Figures 1, 2, and 3 depict heart rate difference, power of high frequency band, and LF to HF ratio, respectively, across states of five daily activities in patients with chronic schizophrenia administered with clozapine and non-clozapine antipsychotic drugs. Figure 4 presents heart rate recovery after exercise in patients with clozapine and non-clozapine antipsychotic treatment. Figure 4 shows heart rate recovery ratio after exercise in patients with clozapine and non-clozapine antipsychotic treatment.
Patients with schizophrenia on clozapine show higher heart rate compared with patients on other antipsychotic drugs, e.g., haloperidol or olanzapine [3]. In this study (Figure 1), we found significantly differences existed in patients’ 24-hour and five different activity states, namely, day-time, sleep, nap, exercise and after-exercise ($p < 0.05$). This finding confirms the adverse effect of clozapine on autonomic nervous system [1]. But the effect of clozapine on lower high-frequency (HF) component of HRV was only found in the state of after-exercise in this study (Figure 2). And against our expecting, no difference on effect on the heart rate variability (total power) and low-frequency (LF) components which is expected to be higher [3]. On the other hand, the significant higher low-high frequency ratio (LF/HF ratio) indicates a significant higher sympathetic activity because that clozapine has high affinity for dopamine receptors [5]. In contrast, this study revealed that the impact of clozapine on parasympathetic activation (vagal tone) was found only in the state of after-exercise. To our best knowledge, it is a novel finding.

Regarding to the changes in heart rate after exercise which mainly due to the vagal tone [9], the significant retard prognostic value of the rate

Table 1. Demographic and clinic symptoms at the baseline of study patients (N = 30).

<table>
<thead>
<tr>
<th>Group</th>
<th>Clozapine (n = 9)</th>
<th>Non-clozapine (n = 21)</th>
<th>Statistics ($t$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.70 ± 1.90</td>
<td>51.72 ± 2.40</td>
<td>-1.29</td>
</tr>
<tr>
<td>Baseline condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26.97 ± 1.26</td>
<td>24.51 ± 0.71</td>
<td>1.82</td>
</tr>
<tr>
<td>BP (Systolic)</td>
<td>111.33 ± 5.18</td>
<td>115.52 ± 3.76</td>
<td>-0.63</td>
</tr>
<tr>
<td>BP (Diastolic)</td>
<td>71.44 ± 3.09</td>
<td>71.90 ± 2.17</td>
<td>-0.12</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>93.11 ± 4.43</td>
<td>80.52 ± 3.09</td>
<td>2.27*</td>
</tr>
<tr>
<td>Serum level of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>147.89 ± 7.21</td>
<td>142.95 ± 5.82</td>
<td>0.49</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>142.67 ± 12.56</td>
<td>106.05 ± 10.87</td>
<td>1.97</td>
</tr>
<tr>
<td>HDL</td>
<td>35.00 ± 3.27</td>
<td>36.40 ± 1.73</td>
<td>-0.42</td>
</tr>
<tr>
<td>LDL</td>
<td>100.22 ± 6.93</td>
<td>89.90 ± 5.38</td>
<td>1.11</td>
</tr>
<tr>
<td>Hgb</td>
<td>14.51 ± 0.52</td>
<td>14.25 ± 0.24</td>
<td>0.53</td>
</tr>
<tr>
<td>Psychiatry manifesta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS_P</td>
<td>10.11 ± 0.70</td>
<td>13.29 ± 1.25</td>
<td>-1.61</td>
</tr>
<tr>
<td>PANSS_N</td>
<td>13.33 ± 1.29</td>
<td>16.52 ± 1.32</td>
<td>-1.45</td>
</tr>
<tr>
<td>HAMD_T</td>
<td>3.00 ± 0.62</td>
<td>5.62 ± 0.53</td>
<td>-2.89**</td>
</tr>
<tr>
<td>CGI_S</td>
<td>3.22 ± 0.28</td>
<td>4.29 ± 0.14</td>
<td>-3.80**</td>
</tr>
<tr>
<td>CGI_I</td>
<td>2.78 ± 0.15</td>
<td>2.48 ± 0.13</td>
<td>1.35</td>
</tr>
</tbody>
</table>

*p < 0.05; **p < 0.01.

BMI, Body mass index; HDL, High-density lipoprotein; LDL, low-density lipoprotein; Hgb, Hemoglobin; PANSS_P, Positive and Negative Symptom Scale, positive part; PANSS_N, Positive and Negative Symptom Scale, negative part; HAMD_T, Hamilton depression rating scale, total score; CGI_S, Clinical global Impression- Severity scale; CGI_I, Clinical global impression-Improvement scale.
Figure 1. Heart rate difference across states of five daily activities in patients with chronic schizophrenia administrated with clozapine and non-clozapine antipsychotic drugs. Significantly different in within-subject effect (states), repeated measures ANOVA ($F = 11.82, p < 0.001$).
Significantly different in between-subject effect (clozapine) after controlling effects of age, HAMD and CGI_S ($F = 18.07, p < 0.001$).
§ Significantly different from other states in all five states ($p < 0.05$).
† Significantly higher, the clozapine vs. the non-clozapine group ($p < 0.01$).

Figure 2. Power of high frequency (HF) band across states of five daily activities in patients with clozapine and non-clozapine antipsychotic treatment.
Significantly different in within-subject effect (states), repeated measures ANOVA ($F = 7.42, p < 0.001$).
Significantly different in between-subject effect (clozapine) after controlling effects of age, HAMD and CGI_S ($F = 10.17, p < 0.01$).
† Significantly higher, the clozapine group vs. the non-clozapine group ($p < 0.05$).
of decline in heart rate in clozapine group can be considered a reconfirmed evidence. It is fairly well believed that the high frequency (HF) indicates a measurement of parasympathetic activity, or vagal tone [14]. Perini and Veicsteinas in 2003 compared the HRV differences at rest and during exercise, and they have found a tendency of slightly increasing HF power above resting values [18]. In this study, the similar results can be only observed among non-clozapine groups (Figure 2). Another study showed that, in normal volunteers, heart rate recovery after exercise were markedly prolonged by atropine administration. More over the heart rate decay for the first 30 seconds was found almost independent of the exercise intensity and sympathetic blockade. On the other hand, that after 120 seconds is affected by sympathetic nerve activity and exercise work load [9]. In this regard, our results reconfirmed the highest parasympathetic activity, HF power, in non-clozapine chronic schizophrenia patients immediately after exercise. However that discrepancy was not so salient in clozapine group may mainly reflex the inhibition of parasympathetic system (Figure 2). Given that the increased vagal activity is associated with a reduced in the risk of death [10]. The significant after exercise reducing vagal tone among patients treated with clozapine implies an increased risk of sudden death, especially after exercise.

**Study limitations**

The readers are warned again over-interpreting the study data because this study has four major limitations:
The study are mainly focusing on restrictive sample size and mixed non-clozapine antipsychotic drugs using in control group. The former hindered the further conclusion about whether it is relatively more savable before and during exercise among the chronic schizophrenia patients with long-term clozapine use than after exercise. The later lead us reconsider where it is schizophrenia itself accompanied by a loss of vagal efferent activity, probably due to disturbed cortical–subcortical circuits modulating the autonomic nervous system [11]. With this study limitation in mind, we suggest that further studies with larger sample-size and with drug-naïve schizophrenia counterparts are warranted. Although some studies revealed a sympathetic blocking or reducing effects of clozapine [15], some authors claimed that clozapine may activate sympathetic activity, mainly due to its high affinity for dopamine receptors [5] and α1-adrenergic receptors in vivo [6]. Our results seem preferable to the latter because all LF/HF ratios were higher in the clozapine group (Figure 3).

Another limitation of this study is the accuracy of visual-inspection in dividing 24-hr activity into five states manually according to subjects’ activity and RR values. It is especially harder in the distinguish from daily activity and nap due to subjects’ half-sleep state during their prolonged awaking time on bed. That might be the reason for the undistinguished manifestations

![Figure 4. Heart rate recovery ratio after exercise in patients with clozapine and non-clozapine antipsychotics treatment.](image)

- Significantly different in the first minute after exercise ($p < 0.05$)
- Significantly different in the second minute after exercise ($p < 0.05$).
- Significantly different, clozapine vs. non-clozapine group ($p < 0.01$).
- Nonsignificantly different in within-subject effect (minutes after exercise) using repeated measures ANOVA ($F = 0.575$).
- Significantly different in between-subject effect of clozapine ($F = 8.36, p = 0.01$).
- Nonsignificantly different) in HAMD after controlling effects of age, CGI-F ($F = 0.01$).
- Nonsignificantly different in interaction of minutes after exercise ($F = 0.67$).
during non-REM dominant nap periods in autonomic nerve systems, especially vagal tone (Figure 2). For the same reason, the salient high LF/HF ratio during nap times (Figure 3) might also partially reflect the problems in activity recognition from others. But it still needs to rule out the possible fadedness of parasympathetic effects of clozapine that administrated last night because that clozapine averagely has a half-life effect about 14 hours. Therefore, further studies with more accurate dividing technology and serum levels are warranted.

- This study has the all-man samples. The characteristic of the subjects prevent us from interpreting the study data for female population.
- Depression has been considered having effect on HRV parameters [12], even the antidepressants [13]. In this study, non-clozapine group had higher depression (mean HAMD_T score) implying greater autonomic dysfunction, as reflected by decreased HRV. Although we have controlled the effect of depression in ANOVA analyses, we still suggest that further investigations to explore interaction of effects of schizophrenia-depression and clozapine-antidepressant. In order to eliminate confounding effects on cardiovascular of medications other than antipsychotics, we had, with clinic permission, hold anticholinergic adjuvants for one non-clozapine patient for two days prior to experiment. In the same way, we also hold 2-day antidepressant administration for one clozapine patient and one non-clozapine patient (all selective serotonin reuptake inhibitors). However, to our best knowledge, it is still lacking about the proper length of reducing or stopping them for cleaning out their cardiovascular effects. Thus, further studies with larger sample size counting on confounding effects of non-antipsychotics cardiovascular effects are needed.

**Study summary**

Even with above-noted four limitations, the study results confirmed the changes in autonomic activity in patients treated with clozapine, with marked difference at all day activities and the heart rate recovery after exercise. These changes were primarily due to drug-related alternations in vagal tone, independent of age, the presence of depression, and severity of symptoms. Since the increased vagal activity is associated with a reduced risk of cardiac sudden death [10]. Based on study data, we also suggest a possible risk of cardiovascular adversity in treating patients with chronic schizophrenia with clozapine especially after exercises.

**Acknowledgements**

This work was supported by a grant from Beitou Branch, Tri-service General Hospital, Taiwan (TSGH-BT_103-4). The authors declare no potential conflicts of interest in writing this report.

**References**

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