Antipsychotic Medication Influences Cardiovascular Coupling in Patients Suffering from Acute Schizophrenia

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Abstract

Schizophrenia (SZO) is one of the most serious mental illnesses in the world associated with the risk for cardiovascular events. The aim of this study was to quantify and characterize how different antipsychotics influence short-term cardiovascular couplings (CVC) in acute SZO. In this study CVC of 42 unmedicated (UNMED), 42 medicated (MED) patients suffering from SZO and 42 age and gender matched healthy subjects (CON) was analyzed applying the High Resolution Joint Symbolic Dynamics. We found decreased CVC in SZO (UNMED, MED) characterized by CVC patterns that were less predominant and more distributed in comparison to CON and mainly dominated by a greater amount of slow increasing, slow decreasing, alternating and fluctuating systolic blood pressure in combination with invariable heart rate responses. The impairment of the cardiovascular system in SZO was much more formed in MED and seems to be due to the anti-cholinergic effects of antipsychotics. Especially, a subgroup of MED treated with clozapine, quetiapine and amisulpride had the strongest influence on CVC than those treaded with olanzapine. These results might contribute to an optimal selection of therapy strategies minimizing cardiovascular pro-arrhythmic effects in SZO and thus to a more individual patient adapted therapy.

1. Introduction

Schizophrenia is one of the most serious mental illnesses in the world. Thereby, those patients are associated with the risk for cardiovascular events (CVE) that has been shown to be considerably higher than in the general population. Besides the well-known impaired cardiac autonomic function and the cardiac risk factors for schizophrenia, increasing concerns have been raised to the antipsychotic treatment that have been associated with significant rates of cardiovascular pro-arrhythmic effects and are known to decrease heart rate variability (HRV) in those patients [1].

The bivariate coupling analysis of heart rate (HR) and systolic blood pressure time series, respectively, might provide further information about the complex system of autonomic regulation in schizophrenia than the univariate approaches can do. Cardiovascular coupling analyses provide useful information about heart rate and blood pressure regulatory processes within the complex interplay of the cardiovascular system [2]. For the characterization of the beat-to-beat changes between HR and systolic blood pressure time series the new High Resolution Joint Symbolic Dynamics (HRJSD) analysis approach was developed [3]. HRJSD seems to be a promising tool to draw conclusions how and in in which way systolic blood pressure and heart rate interact and which CVC patterns are the dominating ones in schizophrenic patients in comparison to that of healthy subjects.

The aim of this study was to investigate the influence of two different atypical antipsychotic drug groups on nonlinear CVC pattern applying HRJSD in acute schizophrenia.

2. Materials and methods

2.1. Patients

In this study, 42 unmedicated (UNMED: 34.9±13.0 years, 18 female), 42 medicated patients (MED: 35.1±12.7 years, 18 female) suffering from acute schizophrenia and 42 age- and gender matched healthy controls (CON, 18 female; 33.7±7.8 years) were enrolled.

Patients did not suffer from any medical or additional psychiatric diseases, and none of them was receiving any interfering medication that might affect cardiac autonomic function, as assessed using a questionnaire and

a careful assessment of patient history. MED received atypical antipsychotics (aripiprazole, clozapine, risperidone, quetiapine, amisulpride, olanzapine) on average 2-3 days after admission to the hospital. MED was subdivided in two subgroups MED1 (n=18, olanzapine) and MED2 (n=15, clozapine, quetiapine, amisulpride) to investigate the effect of specific atypical antipsychotics on the autonomic regulation (the remaining n=9 patients were excluded due to statistical reasons and the inhomogeneity in drugs). Schizophrenia was diagnosed by experienced psychiatrists when symptoms of patients fulfilled DSM-IV criteria as assessed by the Structured Clinical Interview for DSM-IV (SCID) All participants were asked to refrain from drinking coffee, heavy eating or exercising, smoking at least two hours prior to the investigation. This study complied with the Declaration of Helsinki. All participants gave written informed consent to a protocol approved by the Ethics Committee of the University Hospital, Jena.

2.2. Data acquisition and preprocessing

For CVC analysis short-term ECG (1000Hz) and synchronized noninvasive blood pressure (500Hz) were recorded over 30 minutes with the Task Force Monitor®. All measurements were performed under resting conditions (supine position, quiet environment, same time of day and location). Subjects were asked to relax and to breathe normally to avoid hyperventilation. No further instruction for breathing was given. Subjects were asked explicit not to talk during the recording.

From each record time series of heart rate consisting of successive beat-to-beat intervals (BBI) and of systolic blood pressure values (SYS) were automatically extracted. After the extraction these time series were visually inspected and if appropriate edited. These time series were filtered with an adaptive variance estimation algorithm to avoid influences from ectopic beats or artefacts.

2.3. High Resolution Joint Symbolic Dynamics - HRJSD

HRJSD [3] based on a redundancy reduction strategy and the analysis of dynamic processes by means of symbols. The idea of HRJSD is to classify frequent deterministic patterns lasting three beats (symbols). The HRJSD approach enables the classification and characterization of short-term regulatory bivariate coupling patterns that are dominating the interaction generated by the ANS. In this study, we applied the HRJSD to quantify the effects of antipsychotics and their anti-cholinergic effects on nonlinear CVC.

HRJSD works in the way that both time series (BBI and SYS) were transformed into symbol sequences based on their signal amplitudes using a given alphabet A={0,1,2}. Therefore, a bivariate sample vector X of the two time series (BBI, SYS) with x_{BBI} and x_{SYS} is transformed into a bivariate symbol vector S where n are the nth beat-to-beat values of BBI and SYS, respectively (Figure 1, top). Symbol sequences with increasing values were coded as “2”, decreasing values were coded as ‘0’ and unchanging (no variability) values were coded as ‘1’. Afterwards, the symbol vector S was subdivided into short words (bins) w_k of length k=3 leading to 27 different word types for BBI (w_{BBI}) and SYS (w_{SYS}). Then, the word types were sorted into a normalised 27x27 vector matrix W_n ranging from word type $(000,000)^T$ to $(222,222)^T$ (Figure 1, middle). All these single word types $w_{BBI,SYS}$ were afterwards grouped into 8 pattern families wf whereby the probabilities of all single word families’ occurrences $p(wf)$ were normalized to 1. These 8 pattern families (E0, E1, E2, LU1, LD1, LA1, P, V) represent different aspects of autonomic modulation (strong and weak increase/ decrease, no variability, alternations) and were created on a heuristic basis of minimum 20 words per bin. Afterwards, these 8 pattern families for BBI and SYS were sorted into an 8x8 pattern family density matrix Wf resulting in 64 CVC patterns (Figure 1, bottom). For the quantification of these coupling patterns within Wf the normalised joint probabilities of occurrence were estimated. The pattern definition is as follows:

E0, E1 and E2: Words consisting of three equal symbols (no variation of symbols) of type '0', '1' and '2', respectively.

LU1 and LD1: Words consisting of two different symbols with low increasing behaviour (LU1) and low decreasing behaviour (LD1).

LA1: Words consisting of two different alternating symbols of type '0' and '2' with an increasing-decreasing behaviour.

P and V: Words consisting of three different symbols with peak-like behaviour (P) and with valley-like behaviour (V). In addition, 8 pattern families for BBI and SYS were calculated from the matrix Wf as the sum of each (n=8) column *cfSYS* (*cfE0, cfE1, cfE2, cfLU1, cfLD1, cfLA1, cfP, cfV*) and the sum of each (n=8) row *rfBBI* (*rfE0, rfE1, rfE2, rfLU1, rfLD1, rfLA1, rfP, rfV*) and the Shannon entropy (HRJSDshannon) as a measure of the overall complexity of CVC.

2.4. Statistics

The nonparametric Mann-Whitney U-test (IBM SPSS Statistics 21) was performed to evaluate differences between CON and UNMED and CON and MED, MED1 and MED2. Significances were considered for values of $p<0.01$ ($p^*<0.0006$, Bonferroni-Holm adjustment). All results were presented as mean ± std.

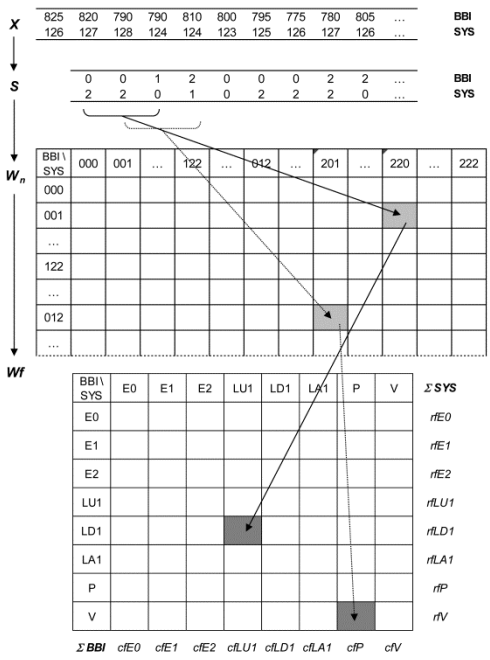

Figure 1. Basic principle of transformation in HRJSD. (Top): Transformation of the bivariate sample vector X into the bivariate symbol vector S (0: decreasing values, 1: equal values 2: increasing values); (Middle): Word distribution density matrix W_n (27x27); (Bottom): Word pattern family distribution density matrix Wf (8x8), rf_{BBI} row sum of specific word family and cf_{SYS} column sum of specific word family.

3. Results

3.1. Unmedicated schizophrenic patients vs. healthy subjects

HRJSD revealed 6 significant (n=2, p*<0.0006) different cardiovascular coupling patterns (CVCP) between CON and UNMED. One significant (p<0.01) heart rate families pattern (BBI-E1) showed also univariate changes in UNMED in comparison to CON. Thereby, CVCP were mainly formed by the systolic blood pressure family LU1 (50%) and 50% by the families E1, LA1 and P; heart rate patterns families were dominated by E1 (67%) and 33% by LD1 and V, respectively. Furthermore, we found that 83% (n=5) of these CVCP and the heart rate pattern (BBI-E1) were significantly increased in UNMED in comparison to CON. Furthermore, significant increased HRJSDshannon was found in UNMED in comparison to CON.

3.2. Medicated schizophrenic patients vs. healthy subjects

HRJSD revealed 12 significant (n=6, p*<0.0006) different CVCP between CON and MED. Two significant heart rate families pattern (BBI-E1, BBI-P) showed also univariate changes in MED in comparison to CON. Here, the systolic blood pressure patterns were mainly formed by the families LU1, LD1 and P (58%) and 42% by the families E0, E1, E2, LA1 and V; heart rate patterns were dominated by E1 (67%) and 33% by LU1, LD1, E0 and V, respectively. Furthermore, we found that 75% (n=9) of these CVCP and the heart rate pattern (BBI-E1, BBI-P) were significantly increased in MED in comparison to CON. The same patterns (SYS-LU1/BBI-LD1, SYS-LD1/BBI-LU1, SYS-P/BBI-E0) which were decreased in UNMED were also deceased for MED in comparison to CON.

Comparing MED1 (olanzapine) with CON HRJSD revealed 8 significant (n=1, p*<0.0006) different CVCP and one significant univariate heart rate pattern family (BBI-E1). These 8 significant indices also belong to the 14 indices differentiating MED from CON.

Comparing MED2 (clozapine, quetiapine, amisulpride) with CON HRJSD revealed 11 significant (n=7, p*<0.0006) different CVCP and three significant univariate heart rate pattern families (BBI-E1, BBI-P, BBI-V). Eleven of these significant indices also belong to the 14 indices differentiating MED from CON. Interferingly, these indices in MED2 which fulfilling the Bonferroni-Holm adjustment (p*<0.0006) were the same indices comparing CON vs. MED.

4. Discussion

We could demonstrate significantly altered distributed CVCP in patients with acute schizophrenia especially for medicated patients applying HRJSD. UMED and MED revealed a higher number of CVCP that were less predominant and more distributed in comparison to CON that can be defined as a decreased cardiovascular coupling in schizophrenia.

The altered CVC in schizophrenia was mainly characterized by greater amount of low increased, low decreased, alternating and fluctuating patterns (LU1, LD1, LA1, P, V) of SYS and invariable heart rate responses (E1). These results might support previous findings that SZO are characterized by a lack of “fine-tuning” of baroreflex modulation expressed by the impairment of the baroreflex control feedback loop and reduced efferent vagal activity. This behavior was independent from medication (UNMED) but was much more formed in MED and seems to be due to the anti-cholinergic effects of antipsychotics. Due to that, MED2 contributed to the differentiating between CON and MED, it seems to be that clozapine, quetiapine, amisulpride reveal the strongest anticholinergic side effects of cholinergic or adrenergic receptors on ANS modulation than olanzapine. MED2 exhibit a stronger influence on CVC and ANS modulation than MED1. The

ANS of SZO treated with MED2 is more impaired. Thus, we hypothesis that at least a part the drugs of this group are probably more associated with cardiovascular pro-arrhythmic effects and therefore, are possibly leading to increased cardiac mortality rates in those patients. It is known that clozapine increases mean heart rate and reduces HRV by a reduction of vagal control whereas the effect of olanzapine on ANS is still under debate since some studies reported a decrease of vagal control and others an increase [1, 3]. Thus, antipsychotic medications may further increase the risk of CVE as some antipsychotics may cause prolongation of the QT-interval, produce serious ventricular arrhythmias, increase heart rate and predispose to sudden cardiac death. However, due to the complex interaction of various risk factors for sudden death, schizophrenic patients need a comprehensive follow-up of their physical health. In further studies, enrolling a higher number of subjects the different antipsychotics and their contribution to the increased cardiac mortality rates should be investigate.

HRJSD analyses revealed detailed information about short-term nonlinear CVCs and cardiovascular physiological regulatory mechanisms (patterns) of autonomic function in patients with acute schizophrenia. The HRJSD results might contribute to an optimal selection of therapy strategies in schizophrenia and thus to a more individual patient adapted therapy. Prospective studies: might figure out how different antipsychotics influence autonomic regulation (cardiovascular) in those patients and might therefore help to plan optimal treatment (selection of antipsychotics and their dosages) strategies.

Table 1. Significant HRJSD indices from cardiovascular coupling analysis between CON vs. UNMED, CON vs. MED, MED1, MED2. (*p<0.01, **p<0.0006).

index	CON vs. UNMED	CON vs. MED	CON vs. MED1	CON vs. MED2	CON mean ± std	UNMED mean ± std	MED mean ± std	MED1 mean ± std	MED2 mean ± std
SYS-E0/BBI-E1	n.s.	*	n.s.	*	0.00 ± 0.02	0.03 ± 0.08	0.1 ± 0.3	0.1 ± 0.2	0.2 ± 0.4
SYS-E1/BBI-E1	*	**	**	**	0.1 ± 0.2	0.5 ± 1.0	1.1 ± 2.7	1.3 ± 3.5	0.9 ± 1.9
SYS-E1/BBI-P	n.s.	n.s.	*	n.s.	0.8 ± 0.8	1.2 ± 1.4	1.3 ± 1.1	1.3 ± 1.1	0.8 ± 0.9
SYS-E2/BBI-E1	n.s.	**	*	*	0.01 ± 0.03	0.03 ± 0.1	0.1 ± 0.3	0.1 ± 0.4	0.2 ± 0.4
SYS-LU1/BBI-E1	*	**	*	**	0.1 ± 0.4	0.8 ± 1.6	1.8 ± 3.6	1.2 ± 2.5	3.0 ± 5.1
SYS-LU1/BBI-LD1	**	*	*	n.s.	6.7 ± 1.8	5.5 ± 1.6	5.4 ± 2.0	5.4 ± 2.3	5.5 ± 2.0
SYS-LU1/BBI-V	*	*	n.s.	*	1.3 ± 0.6	1.9 ± 1.0	1.8 ± 0.9	1.8 ± 1.1	1.8 ± 0.6
SYS-LD1/BBI-E1	n.s.	**	*	**	0.1 ± 0.3	0.7 ± 1.4	1.8 ± 3.6	1.3 ± 2.8	2.7 ± 5.0
SYS-LD1/BBI-LU1	n.s.	*	n.s.	n.s.	6.9 ± 3.0	5.8 ± 2.3	5.2 ± 2.0	5.4 ± 2.0	5.4 ± 1.8
SYS-LA1/BBI-E1	*	*	n.s.	*	0.01 ± 0.03	0.1 ± 0.1	0.1 ± 0.5	0.02 ± 0.04	0.4 ± 0.7
SYS-P/BBI-E0	n.s.	*	*	n.s.	0.5 ± 0.4	0.5 ± 0.6	0.4 ± 0.6	0.4 ± 0.8	0.4 ± 0.4
SYS-P/BBI-E1	**	**	*	**	0.04 ± 0.13	0.2 ± 0.4	0.5 ± 1.1	0.2 ± 0.2	1.0 ± 1.7
SYS-V/BBI-E1	n.s.	**	n.s.	**	0.1 ± 0.2	0.2 ± 0.4	0.6 ± 1.1	0.3 ± 0.4	1.1 ± 1.7
SYS-V/BBI-LD1	n.s.	n.s.	n.s.	*	1.9 ± 1.3	2.3 ± 1.2	2.1 ± 1.2	1.8 ± 1.1	2.9 ± 1.0
SYS-V/BBI-V	n.s.	n.s.	n.s.	**	0.8 ± 0.5	1.0 ± 0.8	1.1 ± 0.8	0.9 ± 0.7	1.6 ± 0.8
SYS-E2	n.s.	n.s.	n.s.	*	4.7 ± 3.9	3.8 ± 2.6	3.9 ± 2.5	4.7 ± 2.4	2.4 ± 1.6
BBI-E1	*	**	*	**	0.4 ± 1.1	2.5 ± 4.8	6.2 ± 11.9	4.5 ± 9.8	9.4 ± 15.9
BBI-P	n.s.	*	n.s.	*	6.4 ± 2.0	7.7 ± 3.3	8.2 ± 3.4	7.8 ± 3.5	8.9 ± 3.7
BBI-V	n.s.	n.s.	n.s.	*	6.7 ± 2.3	8.1 ± 3.1	8.3 ± 3.5	7.5 ± 3.3	9.4 ± 3.0
HRJSDShannon	*	n.s.	n.s.	n.s.	3.2 ± 0.2	3.3 ± 0.2	3.2 ± 0.2	3.2 ± 0.2	3.2 ± 0.2

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