Decreased baroreflex sensitivity in acute schizophrenia

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1Department of Psychiatry and 2Institute of Physiology I, Friedrich-Schiller-University, and 3Department of Medical Engineering, University of Applied Sciences, Jena, Germany; 4Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan; and 5Department of Psychiatry, University of Alberta, Edmonton, Alberta, Canada

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Bär KJ, Boettger MK, Berger S, Baier V, Sauer H, Yeragani VK, Voss A. Decreased baroreflex sensitivity in acute schizophrenia. J Appl Physiol 102: 1051–1056, 2007. First published November 16, 2006; doi:10.1152/japplphysiol.00811.2006.—Decreased vagal activity has been described in acute schizophrenia and might be associated with altered cardiovascular regulation and increased cardiac mortality. The aim of this study was to assess baroreflex sensitivity in the context of psychopathology. Twenty-one acute, psychotic, unmedicated patients with a diagnosis of paranoid schizophrenia were investigated after admission to the hospital. Results were compared with 21 healthy volunteers matched with respect to age and sex. Cardiovascular parameters obtained included measures for heart rate variability, baroreflex sensitivity, as well as cardiac output, left ventricular work index, and total peripheral resistance. All parameters investigated were analyzed using linear and novel nonlinear techniques. Positive and negative symptoms were assessed to estimate the impact of psychopathology on autonomic parameters. Subjects with acute schizophrenia showed reduction of baroreflex sensitivity accompanied by tachycardia and greatly increased left ventricular work index. Nonlinear parameters of baroreflex sensitivity correlated with positive symptoms. For heart rate variability, mainly parameters indicating parasympathetic modulation were decreased. Vascular pathology could be excluded as a confounding factor. These results reflect a dysfunctional cardiovascular regulation in acute schizophrenic patients at rest. The changes are similar to adaptive regulatory processes following stressful mental or physical tasks in healthy subjects. This study suggests that hyperarousal in acute schizophrenia is accompanied by decreased efferent vagal activity, thus increasing the risk for cardiovascular mortality. Future studies are warranted to examine the role of the sympathetic system and possible autonomic differences in hyperarousal induced by anxiety and/or external stressful events.

autonomic function; cardiac mortality; psychosis; vagal tone

LIFE EXPECTANCY IS REDUCED BY ~20% IN SCHIZOPHRENIC PATIENTS COMPARED WITH THE GENERAL POPULATION (17). BESIDES SUICIDE, CARDIOVASCULAR DISEASE HAS BEEN REPORTED TO PLAY AN IMPORTANT ROLE (10, 17, 23). TO DATE, SEVERAL PHYSIOLOGICAL STUDIES ASSESSING THE AUTONOMIC NERVOUS SYSTEM (ANS) IN SCHIZOPHRENIC PATIENTS REPORTED AN INCREASED HEART RATE (5, 28, 37–39). IN PARTICULAR, EFFERENT PARASYMPATHETIC ACTIVITY HAS BEEN SHOWN TO BE DECREASED IN ACUTE (5) AND CHRONIC STAGES (31), POSSIBLY INCREASING THE INCIDENCE OF SERIOUS VENTRICULAR ARRYTHMIAS (30). SUCH INCREASED RISK OF ARRYTHMIAS AND SUDDEN CARDIAC DEATH HAS BEEN REPORTED TO BE ASSOCIATED WITH DECREASED BAROREFLEX SENSITIVITY (BRS) IN OTHER DISEASES (11), INCLUDING MYOCARDIAL INFARCTION (20), HEART FAILURE (26), AND POSSIBLY DIABETES (22). YET BRS HAS NOT BEEN EXAMINED IN SCHIZOPHRENIA TO DATE.

An immediate increase in blood pressure and heart rate is needed at the onset of exertion. Among other simultaneous mechanisms, this is achieved by an inhibition of the decelerating vagal nerve activity, as well as by a stress-related modulation of sympathetic outflow on the heart rate component of baroreflexes [baroreflex vagal bradycardia (BVB)]. Thus arterial baroreflexes, which normally act as powerful, negative feedback loops between heart rate and blood pressure, are inhibited during stressful conditions, including fight-or-flight situations and mental stress (25).

Here we aimed to test the hypothesis that acute psychosis leads to a central inhibition of BRS accompanied by the previously described increased heart rate in schizophrenia. For this purpose, cardiovascular parameters of 21 patients with acute schizophrenia who had not been receiving neuroleptic treatment for at least 8 wk were obtained and compared with age- and sex-matched healthy volunteers. Besides measures of BRS, impedance cardiography (ICG) was employed to allow the estimation of cardiac work and its regulation in the disease. Since heart rate and blood pressure time series are regarded to represent complex system dynamics (35), data were processed employing linear and novel nonlinear models. Epidemiological data and psychopathological scales were obtained and correlated to autonomic parameters, since our laboratory has previously shown that paranoia and disease duration influence autonomic dysfunction in schizophrenia (5).

METHODS

Participants. Twenty-one patients suffering from paranoid schizophrenia and 21 healthy controls matched with respect to age, sex, weight, smoking habits, and education (see Table 1) were included in this study. Control subjects were recruited from hospital staff and medical students. Neither patients nor controls suffered from any medical or additional psychiatric disease, and none of them was receiving any interfering medication that might affect cardiac autonomic function (e.g., cardiac medications or central nervous system active medications), as assessed using a questionnaire and a careful patient history. Furthermore, routine ECG was evaluated “normal” by a cardiologist. Additional routine blood investigations were performed in patients only. Participants were asked to refrain from smoking, heavy eating, or exercising 2 h before the investigation. Diagnosis of paranoid schizophrenia was established by a staff psychiatrist when symptoms of patients who were admitted to our inpatient wards fulfilled DSM-IV criteria (Diagnostic and Statistical Manual of Men-

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Spontaneous sequences of at least three consecutive beats were analyzed. Detailed description has been published previously (3). In brief, the quotient of low-frequency (LF) to high-frequency (HF) (LF/HF) was calculated as a measure of sympathovagal normal beat interval (RMSSD). Furthermore, the numbers of bradycardic and tachycardic baroreflex sequences were computed as an indicator of baroreflex activation.

**Nonlinear joint symbolic dynamics.** To assess heart rate and blood pressure dynamics in a more complex way, an analysis based on joint symbolic dynamics (JSD) was applied (7), which has been described in detail previously (3). Here, the beat-to-beat changes of RR interval and SBP are each coarse grained to two different symbols: increasing values are coded as “1,” whereas decreasing and unchanged values are coded as “0,” respectively. Subsequently, short patterns of symbol sequences (words) are formed, and their distribution properties are analyzed [probability of symmetric baroreflex-related words (JSDsym), probability of diametric non-baroreflex-related words (JSDdiam), etc.]. Based on the considerations mentioned above, words of a three-letter length are feasible for short-term recordings. Consequently, the dynamics between heart rate and blood pressure within three RR intervals (four heartbeats) can be analyzed. The advantage of JSD over the sequence method is that it considers all types of RR interval and SBP beat-to-beat changes, whereas the sequence method considers only two types of patterns. Thus a rough assessment of the overall RR and SBP short-term interactions is obtained.

**ICG.** ICG (18, 32) was used to measure cardiac index (blood volume ejected by the heart per minute) [cardiac output (CO) normalized to the patient’s body surface area], left ventricular work index (LVWI), and total peripheral resistance (TPR). To obtain these measures, a constant sinusoidal alternating current $I_o$ of 400 $\mu$A and 40 mmHg caused an increased BBI of at least 5 ms (bradycardic sequence), whereas an increased systolic blood pressure (SBP) of at least 1 mmHg caused an increased BBI of at least 5 ms (tachycardic sequence). For each sequence, the regression between the three SBP values and three BBI values was calculated, and the slope [tachycardic slope (tslope); bradycardic slope (bslope)] of the regression line was used as an index of BRS. Furthermore, the numbers of bradycardic and tachycardic baroreflex sequences were computed as an indicator of baroreflex activation.

### Data acquisition and preprocessing
Examinations were performed in a quiet room that was kept comfortably warm (22–24°C) between 3 and 6 PM. Subjects were asked to relax, breathe regularly, and move as little as possible. Respiratory rate was obtained for all patients.

The ECG (high resolution, 1,000 Hz) was recorded for 30 min from two separate adhesive monitoring electrodes (CNSystems, Medizintechnik), which were placed on the chest wall to ensure maximal R-wave amplitude. From this, the device automatically extracted the R-wave-to-R-wave (RR) intervals [beat-to-beat interval (BBI)]. Continuous blood pressure was simultaneously recorded noninvasively from the third and fourth finger using the vascular unloading technique (27) and was corrected to absolute values with oscillometric blood pressure measurement by the Task Force Monitor to obtain blood pressure values for every consecutive beat. RR interval and blood pressure time series were afterward filtered and interpolated for ectopic beats and artifacts.

### Table 1. Clinical and demographic data of participants

<table>
<thead>
<tr>
<th>Participants, no.</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, no.</td>
<td>21/19</td>
<td>21/18</td>
</tr>
<tr>
<td>Age, yr</td>
<td>31.5 ± 2.3</td>
<td>32.1 ± 2.6</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.80 ± 0.918</td>
<td>24.54 ± 0.972</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Education</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary, no.</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Secondary, no.</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Smoker/nonsmoker, no.</td>
<td>7/14</td>
<td>8/13</td>
</tr>
<tr>
<td>≤5 cigarettes/day, no.</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5–10 cigarettes/day, no.</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10 cigarettes/day, no.</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>First episode of psychosis, no.</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of illness, yr</th>
<th>Controls</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset in male/female, yr</td>
<td>21.00 ± 1.3/31.00 ± 3.734</td>
<td></td>
</tr>
<tr>
<td>SAPS</td>
<td>41.90 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>SANS</td>
<td>35.95 ± 4.6</td>
<td></td>
</tr>
</tbody>
</table>

SAPS, scale for the assessment of positive symptoms; SANS, scale for the assessment of negative symptoms. Despite the number of smokers assigned to the different subgroups, there were no significant differences between patients and controls.

### Table 2. Heart rate variability and baroreflex sensitivity parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Patients With Schizophrenia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>65 (61–68)</td>
<td>83 (73–90)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>HRV</td>
<td>51 (39–70)</td>
<td>24 (18–45)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>1.3 (0.8–2.6)</td>
<td>2.3 (1.4–4.4)</td>
<td>0.035</td>
</tr>
<tr>
<td>LF/HF</td>
<td>120 (114–128)</td>
<td>135 (122–146)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>74 (71–80)</td>
<td>84 (78–96)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>22.4 (17.0–26.1)</td>
<td>11.2 (7.7–14.3)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>tslope, ms/mmHg</td>
<td>18.4 (16.3–25.9)</td>
<td>13.8 (8.0–18.7)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>bslope, ms/mmHg</td>
<td>47 (21–67)</td>
<td>67 (22–87)</td>
<td>0.39</td>
</tr>
<tr>
<td>tcount, no.</td>
<td>31 (14–72)</td>
<td>46 (19–87)</td>
<td>0.3</td>
</tr>
<tr>
<td>bcount, no.</td>
<td>0.42 (0.38–0.48)</td>
<td>0.26 (0.18–0.36)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>JSDsym</td>
<td>0.01 (0.01–0.02)</td>
<td>0.04 (0.02–0.08)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>JSDdiam</td>
<td>3.0 (2.1–3.7)</td>
<td>3.9 (3.4–4.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>CI, l/min⁻¹×m⁻²</td>
<td>3.6 (2.5–3.9)</td>
<td>4.9 (4.5–6.2)</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>TPR, mmHg×min⁻¹</td>
<td>1.309 (928–1,628)</td>
<td>1.178 (967–1,496)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range). HRV, heart rate variability; RMSSD, square root of the mean squared differences of successive NN intervals (normal-to-normal beat interval); LF/HF, low frequency/high frequency ratio; BP, blood pressure; BRS, baroreflex sensitivity; tslope, tachycardic slope; bslope, bradycardic slope; tcount, number of tachycardic sequences; bcount, number of bradycardic sequences; JSD, joint symbolic dynamics; JSDsym, JSD for symmetric baroreflex-related words; JSDdiam, JSD for diametric non-baroreflex-related words; ICG, impedance cardiogram; CI, cardiac index; LVWI, left ventricular work index; TPR, total peripheral resistance.
kHz is passed through the chest between an (outer) electrode placed around the neck and another (outer) electrode placed around the lower thorax aperture. The resulting voltage \( u(t) \) is acquired by two further (inner) electrodes placed between the admitting electrodes. This allows the calculation of the electrical bioimpedance \( Z(t) \). The detected voltage \( u(t) \) is proportional to the thorax impedance \( [Z(t) = u(t) \times I_o] \), which allows the determination of CO.

The impedance signal, the ECG, and the beat-to-beat blood pressure were sampled with 1,000 Hz per channel. These data were used to calculate all hemodynamic parameters online. Stroke volume was calculated according to Kubieck et al. (18). TPR was calculated according to Ohm’s law; \( \text{TPR} = \text{MABP/CO} \) (where MABP is mean arterial blood pressure).

**Exclusion of vascular pathology as a confounding factor.** Pulse-wave velocity (PWV) between both brachial and ankle arteries was measured using a sphygmomanometer and a sphygmograph device (Vascular Screening System, VaSera VS-1000; Fukuda Denshi, Tokyo, Japan). A cuff for measuring blood pressure with a pressure sensor (tonometric procedure) was attached around both upper arms and ankles. Mechanocardiograms were simultaneously recorded with limb-lead ECGs and phonocardiograms. The difference in pulse transit time between the right brachial artery and the ankle artery was determined. The PWV was calculated using the vascular distance from the heart to the lower leg, which was estimated from body height using a regression formula (19).

The ankle-brachial index (ABI) was calculated automatically by dividing the ankle pressure by the brachial pressure (24). From the indexes obtained, the lower for the two legs was used. The ABI value was obtained in a single measurement.

Overall, both PWV and ABI did not significantly differ between groups (data not shown), thus indicating no difference with regard to vascular pathology.

**Statistical analyses.** Wilcoxon rank-sum test was used to calculate the significance probability that the parameters of controls are identical with those of the patients. Furthermore, the correlations between variability parameters and clinical measures were computed. Significance was assumed when \( P < 0.003 \), according to Bonferroni correction, since we assessed 14 parameters.

**RESULTS**

Medians of all results are depicted in Table 2.

**HRV.** The analysis revealed a significantly increased heart rate in schizophrenic patients \( (P < 0.003) \) compared with matched controls. The RMSSD, indicating parasympathetic activity, was significantly reduced in the patient group \( (P < 0.003) \). The frequency band parameter LF/HF ratio \( (P < 0.035) \) was not significantly different (see Table 2).

**BRS.** The tslope as an index of BRS was significantly reduced in schizophrenic patients \( (P < 0.003, \text{Fig. 1A}) \). Similarly, the bslope was reduced in schizophrenic patients \( (P < 0.003, \text{see Table 2}) \). However, baroreflex activity was similar for the tachycardic and bradycardic baroreflex sequences, revealing a similar number of events being analyzed in both groups (Table 2).

**Fig. 1.** Baroreflex sensitivity and impedance cardiography data presented as box plots. Tachycardic slopes (tslope; A), indicating baroreflex sensitivity, and nonlinear joint symbolic dynamics (JSDsym; B), indicating complexity of heart rate and blood pressure dynamics, were significantly increased in schizophrenic patients. Left ventricular work index (LVWI), as obtained using impedance cardiography, was significantly increased in the patient group (C). Boxes indicate data between the 25th and 75th percentile, with the horizontal bar reflecting the median ( ■ = mean; ○ = 1st and 99th percentile; – = minimum and maximum of data) ***\( P < 0.001 \).
Here, we present evidence for severely disturbed autonomic function in acute schizophrenia as obtained from the assessment of BRS, which showed to be significantly decreased in patients with schizophrenia. As illustrated in Fig. 2, which displays baroreflex regulations in one representative patient and one control subject, the slope indicating BRS is not only shifted to increased blood pressure values and decreased BBIs (increased heart rate) but also shows to be more flat. Thus the fine-tuning of blood pressure and heart rate is severely impared in acute psychotic patients. This assumption is further supported by the significantly altered distribution of baroreflex-related and non-baroreflex-related words (JSDsym and JSDdiam, respectively), representing a novel method for BRS investigation applying a nonlinear analysis. Complex dynamics arise, since heart rate and blood pressure are regulated via numerous neural and hormonal feedback mechanisms, including various types of baro-, volume-, and chemoreceptors located in the heart, great arteries and veins, lungs, and brain. The application of complex measures such as JSDsym or JSDdiam is, therefore, mandatory (34). The number of baroreflex sequences that were obtained during the analysis was similar in both groups, suggesting that the peripheral gain was not disturbed in our patients and that central mechanisms may be responsible for the baroreflex dysfunction.

It is intriguing to speculate that these changes of autonomic function induced by the pathophysiology of schizophrenia might reflect the inhibition of BVB, which has likewise been demonstrated as an adaptational process after stressful mental load in healthy volunteers (25). For instance, BRS has been shown to be decreased during specific cognitive demands, such as basic arithmetic operations (29) or physical activity (25). Thus this might imply that the previously described decrease of efferent vagal activity in acute schizophrenia is actually caused by a process that allows the organism to adjust to demanding environmental strains under physiological conditions. Furthermore, our findings presented here might explain the correlation with paranoia that we have found previously (5) and that could be corroborated here. We, therefore, assume that paranoia and cognitive load might provoke similar basic autonomic changes, namely inhibition of BVB, thus inducing tachycardia, hypertension, and reduced BRS. Therefore, the previously described lack of activation in the medial prefrontal cortex in schizophrenia might affect the inhibitory control over amygdala-autonomic function (12), which can subsequently lead to an exacerbation of arousal responses (36) and, therefore, to a central inhibition of BRS.

**DISCUSSION**

JSD of BRS. To assess the complexity of baroreflex dynamics, we applied JSD, considering all types of RR interval and SBP beat-to-beat changes. Both JSDsym \((P < 0.003, \text{Fig. 1B})\) and JSDdiam \((P < 0.003)\) differed significantly between patients and controls, indicating decreased BRS in acute schizophrenia.

Parameters of ICG. ICG analysis was applied to allow the estimation of actual cardiac work. ICG parameters showed a trend for the CO normalized to the body surface (cardiac index, \(P < 0.009, \text{Table 2}\)), being higher in schizophrenic patients. A significant difference was observed for the LVWI \((P < 0.003, \text{Fig. 1C})\). No difference was observed for the TPR (Table 2).

Correlation of autonomic measures with paranoia and duration of disease. According to our hypothesis, we correlated the paranoia subscore of the scale for the assessment of positive symptoms with parameters of BRS (tslope, bslope, JSDsym, JSDdiam) and found a significant correlation for JSDsym \((r = -0.611; P = 0.003)\) and for JSDdiam \((r = 0.502; P = 0.02)\).

To control for previous results (5), we correlated disease duration with significant parameters of HRV (RMSSD), and we were able to show a significant negative correlation with the duration of the disease for RMSSD \((r = -0.573; P < 0.007)\).
However, this excessive arousal, seen especially in paranoid patients, as included in this study, limits the applicability of our findings to recovered patients. In the acute stage, BRS is altered, possibly due to a functional breakdown of the autonomic-amgydala-prefrontal system (33, 36), and this effect might be absent in later stages. Figure 3 depicts some cortical areas that are involved in the excessive arousal and functional autonomic consequences. We cannot certainly conclude which of the autonomic branches, i.e., the sympathetic or the parasympathetic nervous system, is mainly responsible for the decrease in BRS. Yet HRV data from this and our laboratory’s previous study (5) indicate a more pronounced reduction in parasympathetic than an increase in sympathetic parameters. In addition, we have recently shown vagal information flow and other parasympathetic parameters to be decreased in acute patients with schizophrenia in 24-h recordings, therefore reducing the acute fear or discomfort induced by an acute, short-term investigation (9). Furthermore, we have not observed changes in blood pressure variability (4) in these patients. Future studies are warranted in which BRS should be examined in remitted as well as unmedicated patients to answer the question of whether autonomic dysfunction is state or trait related. Furthermore, it is important to study whether autonomic changes in patients with schizophrenia differ significantly from autonomic changes due to arousal caused by fear or anxiety. Most importantly, the sympathetic system needs to be assessed in greater detail in patients with schizophrenia, and studies are needed to compare autonomic changes due to different arousal states to elucidate the specificity of changes in different disease states.

Another area of uncertainty is the influence of disease-independent factors on HRV, such as physical fitness, which might differ significantly across subjects and is rather difficult to control for (15). Furthermore, previous studies showed that increased cardiovascular mortality in patients with schizophrenia may be related to an unhealthy lifestyle, consisting of obesity, caffeine intake, and smoking (10). Of these, cigarette smoking especially has been shown to significantly alter HRV parameters (6). In this study, we tried to control for smoking behavior by including smokers in our control population. However, the number of cigarettes consumed was smaller in the controls, which may have somewhat influenced our results.

The presented data also point to another important issue in schizophrenia research. It is likely that increased SBP and diastolic blood pressure values, as well as the pathological LVWI, substantially contribute to the previously described increased cardiovascular morbidity and mortality in schizophrenia (16). The decreased parasympathetic tone in acute psychosis exposes the heart to unopposed sympathetic stimulation, thus reducing BRS. Future prospective studies should, therefore, address the question of whether dysregulation of BRS persists after acute psychosis and how this might contribute to the reported increase of cardiac mortality in schizophrenia (2).

In conclusion, the reduction of BRS in acute schizophrenia seems to be similar to the adaptational response of the ANS to mental and physical tasks in healthy volunteers. Thus, in addition to other known risk factors in patients with schizophrenia, such as enhanced smoking behavior, higher rates of metabolic syndrome, obesity, less access to medical care, and lack of compliance to medication (14, 17), this assumed permanent stress response with hyperarousal, decreased BRS, tachycardia, and increased blood pressure might play a significant role in cardiovascular morbidity and mortality in patients with schizophrenia.

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