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Chronotropic incompetence of the heart is associated with exercise intolerance in patients with schizophrenia

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ABSTRACT

The elevated cardiovascular risk of patients with schizophrenia contributes to a reduced life expectancy of 15–20 years. This study investigated whether cardiac autonomic dysfunction (CADF) in schizophrenia is related to chronotropic incompetence, an established cardiovascular risk marker.

We investigated thirty-two patients suffering from paranoid schizophrenia and thirty-two control subjects matched for age, sex, body mass index and fat free mass. A cardiopulmonary exercise test (CPET) was performed to study heart rate responses to exercise as well as submaximal (ventilatory threshold 1, VT_1) and maximal endurance capacities (peak oxygen consumption, VO_{2peak}; peak power output, P_{peak}). In addition, epinephrine and norepinephrine levels were assessed in a subset of patients. Fitness parameters were significantly reduced in all patients.

Most investigated physiological parameters were significantly different at rest as well as during peak exercise being in line with previously described CADF in schizophrenia. In particular, 14 out of 32 patients were classified as chronotropically incompetent whereas no control subject was below the cut-off value. In addition, a positive correlation of a slope reflecting chronotropic incompetence with peak oxygen uptake ($p < 0.001$) was observed in patients only indicating a close correlation to the lack of physical fitness. The catecholamine increase was reduced in patients after exercise.

This study identified a novel cardiac risk factor in patients with schizophrenia. Moreover, it seems to be associated with reduced physical fitness and indicates targets for exercise intervention studies. Future studies are warranted to elucidate pathophysiological mechanisms of this cardiac condition.

1. Introduction

Ample evidence indicates a life expectancy that is shortened by about 15–20 years in patients with schizophrenia (Bushe et al., 2010; Tiihonen et al., 2009). A point for concern is that this mortality gap between the general population and patients with schizophrenia seems to have increased during the last few decades (Saha et al., 2007). Most importantly, a substantial proportion of this excess mortality is caused by physical illnesses (Brown, 1997; Correll et al., 2017). Cardiovascular disease (mainly coronary heart disease) has been identified as the most common natural cause of death in up to 40–45% of cases (Ringen et al., 2014). The elevated risk of cardiovascular disease is mainly influenced by the high-risk profile including obesity, poor diet, sedentary lifestyle, and smoking behavior. Furthermore, antipsychotic medication is known to additionally influence the risk of sudden cardiac death (Ray et al., 2009).

Beyond the effects accounted for by lifestyle and antipsychotic medications, several lines of evidence indicate a shared underlying pathophysiology between schizophrenia and cardiovascular disease (Ringen et al., 2014). The prevalence of metabolic syndrome is increased in people with schizophrenia and has been defined as a cluster of interconnected factors that directly increase the risk for cardiovascular diseases (Vancampfort et al., 2015a; Vancampfort et al., 2015c). Studies by Vancampfort et al. (2015a, 2015b, 2015c) suggest that severe mental illnesses and the metabolic syndrome share pathophysiological features, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, neuro-inflammation, common genetic links and epigenetic interactions (Vancampfort et al., 2015c). Furthermore, diabetes mellitus is highly predictive of cardiovascular diseases and the prevalence is consistently elevated in patients with schizophrenia when compared to matched controls (Vancampfort et al., 2016). A recent meta-analysis

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suggests that nutrition interventions should be used as standard care in preventing and treating weight gain (Teasdale et al., 2017).

In addition to suggested genetic and metabolic associations, an obvious link lies in the relationship between cardiac autonomic dysfunction (CADF) and the development of cardiovascular diseases, which was previously described for various other conditions (Bauer et al., 2009; Lam et al., 2015; Yperzeele et al., 2015). CADF is clinically characterized by increased resting heart rates and/or elevated blood pressure. This leads to constant strains on the cardiovascular system. Interestingly, increased heart rates at rest are associated with reduced life expectancy in both the general population and in patients with cardiovascular diseases (Jensen et al., 2013). CADF has also been reported in acute and chronic patients with schizophrenia irrespectively of the received treatment (Bär, 2015; Toichi et al., 1999).

For a long time, psychiatrists attributed increased heart rates in patients with schizophrenia to antipsychotic treatment or as a simple reaction to symptoms of the disease. However, this assumption is correct only to a limited extent since profound abnormalities were described in unmedicated or drug-naïve patients and their healthy first-degree relatives (Bär, 2015; Bär et al., 2010; Berger et al., 2010a; Berger et al., 2010b; Castro et al., 2009). Reduced vagal activity might be one crucial mechanism inducing CADF. The physiological consequences of reduced vagal modulation are increased resting heart rates, decreased heart rate variability (HRV) and complexity, reduced baroreceptor sensitivity and reduced vagal thresholds during exercise as an indicator of decreased physical fitness (Bär et al., 2007a; Ostermann et al., 2013). It is important to understand that CADF in patients with schizophrenia does not reflect a simple, short-lasting stress-induced arousal. Moreover, distinct changes occur in heart rate and respiratory regulation and to a far lesser extent in blood pressure regulation (Rachow et al., 2010).

One key interventional approach to impact on CADF is physical exercise. Regular physical exercise also has beneficial effects on several cardio-vascular risk factors (Lavie et al., 2009; Pagels et al., 2012). However, previous studies have shown that people with severe mental illness engage in significantly more sedentary behavior and significantly less physical activity compared to healthy controls (Vancampfort et al., 2017a). In addition, aerobic exercise has been shown to improve cognitive deficits in patients with schizophrenia, mainly global cognition, working memory, and attention (Falkai et al., 2017; Firth et al., 2015; Firth et al., 2017). Therefore, exercise interventions are an interesting non-pharmacological method to improve cognition, physical fitness and other cardiometabolic risk factors in patients with schizophrenia (Firth et al., 2017).

The known CADF profile of patients with schizophrenia might lead to dysregulation during physical strain. It has been shown that patients with severe mental illness such as schizophrenia are less physical fit in comparison to controls (Vancampfort et al., 2017b). We assumed that CADF in patients with schizophrenia leads to the inability to increase heart rate in relation to metabolic demands and leads to reduced physical fitness in these patients. In particular, we hypothesized that chronotropic incompetence (CI) is associated with reduced physical fitness. CI is the term used for the inability of the heart to increase its beating frequency in proportion to an increase in physical activity or higher metabolic demand (Brubaker and Kitzman, 2011). CI is a significant contributor to exercise intolerance and a major independent predictor of risk of major cardiovascular events and of cardiac as well as all-cause death (Brubaker and Kitzman, 2011; Elhendy et al., 2003; Myers et al., 2002; Myers et al., 2007; Savonen et al., 2008). It characterizes risk and prognosis in patients with overt or subclinical cardiovascular diseases (Nishime et al., 2000). Since most studies including patients with schizophrenia had shown reduced physical capacity, we assumed that the occurrence and the degree of chronotropic competence might be related to physical capacity in these patients (Malchow et al., 2013; Ostermann et al., 2013; Scheewe et al., 2013; Vancampfort et al., 2017b). In addition, we analyzed levels of epinephrine and norepinephrine at rest and after the exercise as possible contributing factors in a subgroup of patients.

2. Methods

2.1. Participants

Thirty-two patients suffering from paranoid schizophrenia and thirty-two control subjects matched with respect to age, sex, body mass index, and fat free mass were included in this study. Control subjects were recruited from the local community (n = 26) and medical students (n = 6). All subjects underwent a screening program consisting of a drug screening for legal and illegal substances, an interview, a full clinical examination and hematologic and biochemical profiles to exclude any other psychiatric or somatic disease such as bleeding disorders, history of hypertension, diabetes, or other vascular diseases. Neither patients nor controls suffered from any medical or additional psychiatric disease. Control subjects did not receive any medication that might have influenced the cardiovascular system. Patients taking clozapine or medication influencing heart rate or blood pressure regulation (e.g., beta-blockers) were not included. All patients were inpatients diagnosed with paranoid schizophrenia and on a stable antipsychotic treatment (see Table 1). The diagnosis was established by a staff psychiatrist when patients fulfilled DSM-IV criteria (Diagnostic and statistical manual of mental disorders, 4th edition, published by the American Psychiatric Association) as assessed by the Structured Clinical Interview for DSM-IV (SCID) (First, 1997). Psychotic symptoms were quantified using the positive and negative symptom scale (PANSS) (Kay et al., 1987). The amount of physical activity was assessed by means of the International Physical Activity Questionnaire (IPAQ). This study was carried out in accordance with the Declaration of Helsinki. All subjects were informed about the nature of the procedures one day in advance. All participants gave written informed consent to a protocol approved by the Ethics Committee of the University Hospital, Jena, Germany. Furthermore, the patients were advised that the refusal of participating in the study would not affect future treatment. Every effort was made to ensure that patients were able to give informed consent. Patients were only included after a psychiatrist certified their ability to give full consent to the study protocol.

2.2. Baseline measurements

Body height, mass and body fat were assessed. Skinfold measurements were performed according to published guidelines (ACSM, 2010). A high resolution electrocardiogram (8000 Hz; AMEDTEC ECGpro® CardioPart 12 USB, Aue, Germany) was applied for continuous monitoring of heart rhythm and evaluation of ischemic electrocardiographic changes during exercise and recovery. We controlled for smoking severity by means of carbon monoxide measurements before the test was initiated (CO-Check, Neomed GmbH, Korschenbroich, Germany) (Ostermann et al., 2013).

2.3. Exercise testing protocol of the cardiopulmonary exercise test (CPET)

The cardiac response to exercise and the maximal and submaximal endurance capacities were determined by a bicycle cardiopulmonary exercise test (CPET) carried out with an electronically braked cycle ergometer (Ergometrics 900, Ergoline, Bitz, Germany). After a resting period of 5 min, the incremental bicycle protocol started with the subject pedaling at 15 W for 3 min (pedaling frequency: 70–80 rpm). Thereafter, the power output increased by 15 W for every minute until the subject reached his or her limit of tolerance. Exhaustion levels were determined by measuring maximum lactate levels (La_{Peak}) and by the respiratory exchange ratio (RER) of carbon dioxide (CO_2) output to oxygen (O_2) uptake, which is known to be the most reliable indicator of maximal effort. The subjective effort exerted by participants was further determined using the standardized Rating Perceived Exertion 6-to-20 scale (Borg, 1982). The attainment of $La_{Peak} \geq 6$ mmol/l, $RER_{Peak} \geq 1.10$ and a BORG rating of perceived exertion >18 are regarded as indicators

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