Psychiatry Research 210 (2013) 710–715

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Association of altered cardiac autonomic function with psychopathology and metabolic profiles in schizophrenia

Ming-Shun Chung [a,1], Albert C. Yang [b,c,d,1], Yu-Chung Lin [a], Chieh-Nan Lin [a], Fang-Rong Chang [a], Shu-hua Shen [a], Wen-Chen Ouyang [a], El-Wui Loh [e], Hsien-Jane Chiu [d,f,*]

[a] Jianan Mental Hospital, Tainan County, Taiwan
[b] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Center for Dynamical Biomarkers and Translational Medicine, National Central University, Chungli, Taiwan
[d] Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[e] Division of Mental Health and Addiction Medicine, Institute of Population Health Sciences. National Health Research Institutes, Miaoli County, Taiwan
[f] Min-Sheng General Hospital, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 10 April 2012
Received in revised form
23 July 2013
Accepted 27 July 2013

Keywords:
Schizophrenia
Autonomic dysregulation
Metabolic syndrome
Heart rate variability
Psychopathology

ABSTRACT

Schizophrenia has been associated with autonomic dysregulation and increased cardiovascular co-morbidity. We hypothesised that autonomic dysregulation in patients with schizophrenia is associated with psychopathology and metabolic profiles. In this study, we aimed to evaluate psychopathology, comprehensive metabolic profiles and cardiac autonomic function using heart-rate variability (HRV) analysis in patients with schizophrenia. A total of 94 patients with schizophrenia and 51 healthy controls were recruited. Each patient underwent a physical examination, laboratory tests and rating scale evaluation, and all subjects underwent a 1-h electrocardiogram monitoring. Analysis of variance was used to compare demographic and HRV variables between control and patient groups. We applied multiple regression analysis with backward selection to examine the association between HRV indices and demographic, metabolic and psychopathology profiles. A decreased HRV was found in patient groups, compared to controls. Reduced vagal-related and complexity domain of HRV indices in patient groups were correlated with increased body mass indices, diastolic pressure, triglycerides, high- and low-density lipoprotein and severity of psychosis mainly in the negative symptom domain. This study provides evidence that altered autonomic function is associated with both psychopathology and metabolic profiles in patients with schizophrenia. These findings may warrant future research in using HRV as objective markers to monitor cardiovascular health and the severity of psychosis in patients with schizophrenia.

1. Introduction

Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes (Lakka et al. 2002; Kohli and Greenland 2006). Although various diagnostic criteria have been proposed (Alberti et al. 2005), the metabolic syndrome is generally defined as a cluster of clinical and laboratory abnormalities including abdominal obesity, insulin resistance, hypertension, low levels of high-density lipoprotein cholesterol and high levels of triglycerides. Many studies have shown that schizophrenia is associated with a high prevalence of the metabolic syndrome (Hert et al. 2009), partly due to the use of second-generation antipsychotics (Lamberti et al. 2006; L'Italien et al. 2007), a less healthy lifestyle (Dixon et al. 2000) and an abnormal glucose metabolism (Ryan et al. 2003).

The association of schizophrenia and the metabolic syndrome as well as cardiovascular co-morbidity may give rise to the importance of evaluating cardiovascular physiology in these patients. Autonomic nervous system (ANS) dysfunction, as evaluated by heart-rate-variability (HRV) analysis, has been implicated in schizophrenia because the limbic system and associated subcortical brain areas are involved in higher-order control of the ANS. Unmedicated patients with schizophrenia have shown lower vagal-related HRV than healthy control subjects (Bar et al. 2005; Mujica-Parodi et al. 2005; Boettger et al. 2006; Bar et al. 2009; Jindal et al. 2009). Other studies have observed a correlation between decreased vagal tone in patients with schizophrenia and increased severity of psychotic symptoms (Toichi et al. 1999; Okada et al. 2003; Fujibayashi et al. 2009; Henry et al. 2010; Kim et al. 2011). Certain antipsychotic drugs have been found to not only increase the risk of the metabolic syndrome but also have adverse effects on ANS functions (Cohen et al. 2001; Lamberti et al.

* Corresponding author at: No. 168, Ching-Kuo Rd, Taoyuan 33044, Taiwan
E-mail address: chiu8@mail2000.com.tw (H.-J. Chiu).
[1] These two authors contributed equally to this work.

0165-1781/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.psychres.2013.07.034

2006). Patients treated with antipsychotic medications, especially clozapine, have shown ANS dysregulation and abnormal cardiac repolarisations (Rechlin et al. 1994; Cohen et al. 2001).

Despite a growing body of clinical research that applies HRV to schizophrenia, studies have not been conducted on the association between cardiac ANS function and the metabolic syndrome in these patients. Therefore, in the present study, we aimed to evaluate psychopathology, comprehensive metabolic profiles and cardiac ANS function using HRV analysis based on 1-h electrocardiogram (ECG) monitoring in patients with schizophrenia. We applied multiple linear regression analysis with backward selection to identify the predictors that contribute to the association between cardiac ANS function and demographic, metabolic and psychopathology profiles.

2. Methods and materials

2.1. Subjects

The study sample consisted of 94 patients with schizophrenia (88.3% male, mean age = 40.8 ± 8.9 years, range = 20–60 years) recruited from the chronic psychiatric ward at Jianan Mental Hospital, Tainan, Taiwan. All subjects provided informed consent before the commencement of the study. The protocol was approved by the institutional review boards of Jianan Mental Hospital. The psychiatric diagnosis of schizophrenia was verified by a psychiatrist using criteria based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Demographic variables including age, age of onset, duration of illness, marital status and smoking were recorded. Each subject underwent an evaluation of history of medical disease and medication use as well as a physical examination and laboratory tests to gather data on body mass index (BMI), blood pressure, waist circumference and lipid profiles. Hypertension was defined as the presence of systolic blood pressure ≧140 mmHg or diastolic blood pressure ≧90 mmHg. Diabetes was defined as fasting glucose ≧126 mg dl^{-1}. The diagnosis of metabolic syndrome was made according to the US National Cholesterol Education Program Adult Treatment Panel III.

Subjects were screened and excluded if they demonstrated (1) the presence of depression, (2) co-morbid substance-related disorders, (3) acute medical illness within 3 months before the study and (4) severe cardiac arrhythmia or frequent ectopic heart beats. Psychopathology and general functioning were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) and Global Assessment of Functioning (GAF) Scale (Jones et al. 1995), respectively. Extrapyramidal side effects (EPSs) were evaluated by the Barnes Akathisia Rating Scale (BARS) (Barnes 1989).

For comparison, 51 healthy control subjects (82.3% male, mean age = 41.1 ± 9.1 years, range = 26–61 years) were recruited from Taipei Veterans General Hospital, Taiwan. Data on healthy subjects were sourced from previous studies of adult HRV in relation to genetic polymorphisms (Yang et al. 2010) and sleep (Yang et al. 2011). These subjects did not have laboratory data but they were screened previously to be free of mental illness, major medical conditions (such as cancer or stroke) and history of metabolic conditions. Healthy subjects matched for age and sex of patient groups with schizophrenia were included in this study.

2.2. Continuous ECG monitoring

Holter recordings (MyECG E3-80 Portable Recorder, Microstar Inc., Taipei, Taiwan) were used to obtain continuous 1-h ECG data. The E3-80 device continuously recorded three channels of ECG signals at a sampling rate of 250 Hz. A previous study has shown that ECG sampled at 250 Hz did not affect the accuracy of QRS detection (Pizzuti et al. 1985). All patients received ECG monitoring at a chronic psychiatric ward. Participants were asked to maintain their typical daily activities and to avoid smoking when undergoing testing. The digitised ECG signals were processed and analysed using open-source HRV algorithms (Goldberger et al. 2000). Briefly, the time series of normal-to-normal intervals was filtered to remove ectopic beats (such as supraventricular or ventricular ectopic beats) and missing or noisy segments by linear interpolation from the surrounding signal. On average, the number of normal sinus heartbeats comprised 97.4 ± 3.7% of the original interbeat interval data. The tachogram was resampled at 4 Hz (http://ecg.mit.edu/dbag/tach-1.htm) to generate a uniformly spaced time series.

2.3. Analysis of HRV

The standard HRV analysis has been well reviewed (Task-Force 1996). The computational algorithms for all HRV indices employed in this study are available publicly at www.physionet.org. Time domain measures of HRV include the mean heart rate and standard deviation of the normal interbeat intervals (SDNN), the root mean square successive difference between adjacent normal interbeat intervals (RMSSD) and the percentage of adjacent intervals that vary by > 50 ms (pNN50) (Mietus et al. 2002). The SDNN assesses the overall variability of interbeat intervals. The RMSSD and pNN50 measure the short-term variation of interbeat intervals, which reflects parasympathetic innervation (Goldberger et al. 2001).

Spectral HRV measures (Task-Force 1996) were calculated using a fast Fourier transform with Welch window and include high-frequency (HF) power (0.15–0.40 Hz), low-frequency (LF) power (0.04–0.15 Hz) and very-low-frequency (VLF) power (0.003–0.04 Hz). LF power is suggested to be modulated by both sympathetic and parasympathetic activities, whereas HF power is primarily modulated by parasympathetic activity (Katona and Jih 1975; Pomeranz et al. 1985). The LF/HF ratio was computed as a measure of the sympathovagal balance towards sympathetic activity (Malliani et al. 1994; Task-Force 1996). The physiological mechanism underlying VLF power is disputed but has been suggested to be partially mediated by the renin–angiotensin–aldosterone system (Akselrod et al. 1981; Task-Force 1996; Taylor et al. 1998).

Physiologic complexity was quantified by two well-validated entropic measures: approximate entropy (ApEn) (Pincus 1991) and multiscale entropy (MSE) (Costa et al. 2002). ApEn measures entropy at a single timescale, whereas MSE is based on the sample entropy (Richman and Moorman 2000) derived from multiple timescales. Physiologic complexity measures the degree of 'unpredictability' in the output of organ system function (Goldberger et al. 2002b). A conventional entropy measure such as ApEn increases with the degree of irregularity, reaching its maximum in completely random systems. However, this approach could yield ambiguous results in which a high degree of entropy is observed not only in healthy conditions, but also in pathological states, such as heart-rate rhythm in atrial fibrillation (Costa et al. 2003). Therefore, MSE has been proposed based on sample entropy (Richman and Moorman 2000) by measuring entropy over multiple timescales inherent in a time series (Costa et al. 2002). MSE has been applied to heart-rate time series (Norris et al. 2008a; Norris et al. 2008b; Yang et al. 2011) and various neurophysiologic signals (Escudero et al. 2006; Mizuno et al. 2010; Takahashi et al. 2010; Protzner et al. 2011).

The emergence of physiologic complexity is thought to reflect the body's ability to adapt to stress, which declines with ageing and illness (Ivanov et al. 1999; Goldberger et al. 2002a). Alterations in physiologic complexity have been suggested to indicate underlying autonomic dysregulation, which is known to be associated with increased co-morbidity and poor outcomes of cardiovascular diseases (Goldberger et al. 2002a; Goldberger et al. 2002b). In the present study, ApEn was calculated using $m = 2$ and $r = 0.2$ (Vikman et al. 1999) and MSE was calculated using $m = 2$ and $r = 0.15$ (Costa et al. 2002). The sum of sample entropy over all scale factors from 1 to 20 was computed for each subject and used as a representative MSE measure in subsequent analyses.

2.4. Statistical analysis

Data are expressed as mean ± standard deviation (S.D.). The spectral HRV indices were log-transformed to produce normalised distributions. Chi-squared tests were used to compare categorical variables. Analysis of variance or Student's *t*-test was used to compare between-group differences in demographic, clinical and HRV measures and to assess the difference of these variables between patients with and without metabolic syndrome. Because the metabolic syndrome was not a clear-cut phenotype and confounding effects existed between HRV indices and other clinical variables, we comprehensively examined the association of HRV indices with all available data collected in the study, including demographic, clinical and laboratory profiles. We applied multiple linear regression analysis with backward selection, using each HRV measure as a dependent variable and available clinical psychopathology assessment and laboratory data as predictors. Multicollinearity was checked by the variance inflation factor (VIF) for all dependent variables and a VIF value of ≥ 10 was considered an indication of significant collinearity. The R^2 of the regression model and partial correlations between HRV indices and each predictor were reported. To test the reliability of HRV data, we conducted a split-half analysis on 1-h interbeat interval time series. We split the time series into first, second, third and fourth 15-min segments and calculated averaged HRV values from the first and third as well as the second and fourth segments. We then tested the correlation coefficient between averaged HRV values from split parts of data. Statistical Package for the Social Sciences (SPSS, version 15.0, Chicago, IL, USA) software was used for the statistical analyses. A P value of < 0.05 (two-tailed) was required for all statistical comparisons.

3. Results

Demographic and clinical data are presented in Table 1. Of the 94 patients, 30 patients fulfilled the criteria for metabolic syndrome. Compared to controls, patients with schizophrenia had a higher rate of single and smoking status. Patients with and