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Heart rate variability in patients with major depression disorder during a clinical autonomic test

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ABSTRACT

Major depression disorder (MDD) patients express dysfunction autonomic nervous system (ANS) and reduced heart rate variability (HRV). However, previous researches mainly focused on examining resting state without considering a series of stimulation tests of ANS between MDD patients and healthy people. For this purpose, 40 healthy people and 40 MDD patients participated and finished 10 min clinical autonomic test—Ewing test. Parameters of HRV such as time domain, frequency domain, and nonlinear dynamical parameters were calculated. Most of HRV parameters during Ewing test of MDD patients are lower than healthy people, and inversely, the ratio of low frequency to high frequency is higher when standing up. In addition, heart rate of healthy people in deep breathing and Valsalva test states are higher than that in resting state, nonlinear dynamical parameter (RCMSE1) of healthy people in standing up state is higher than that in Valsalva test state. The experimental results suggest that parasympathetic nervous system of MDD patients is influenced by mental state and become dysfunction under long-term depression, it cannot exert normal physiological functions when it is activated. Sympathetic activity increases on MDD patients, and this enhancement is more obvious which expresses higher complexity of HRV time series.

1. Introduction

The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) are the two main branches of the autonomic nervous system (ANS). The SNS prepares the body for stressful or emergency situations, such as fight or flight. The PNS controls body processes during ordinary situations (Roy et al., 2013). In severe cases, ANS dysfunctions are commonly observed characteristics of various psychiatric disorders, including major depression disorder (MDD) (Henry et al., 2010).

Beat-to-beat variability in heart period (heart rate variability, HRV) has been widely investigated as a useful parameter to detect autonomic dysfunctions (Kikuchi et al., 2009; Alessandro et al., 2014). HRV assessment methods have been traditionally classified into time domain, frequency domain, and nonlinear analysis. The standard deviations of normal-to-normal interval (SDNN) can indicate SNS and PNS activities. The root mean square successive difference (RMSSD) and the percentage of normal-to-normal interval of more than 50 ms (PNN50) are highly specific indicators of PNS activity (Kleiger et al., 1991). Frequency domain analyses, such as low frequency (LF) power (0.04–0.15 Hz), is mediated by SNS and PNS, while high frequency power (HF) (0.15–0.40 Hz) is mediated primarily by PNS. The LF-to-HF ratio (LF/HF) is considered to assess the comparative balance of the two ANS branches during a cardiac activity (Henry et al., 2010).

MDD is a common psychiatric disorder. Compared with healthy individuals, MDD patients exhibit abnormal expressions, such as autonomic tone alteration toward a decreased parasympathetic activity, an increased sympathetic activity and an imbalanced ANS, and decreased HRV parameters, including LF, HF, SDNN, RMSSD, and PNN50 (Udupa et al., 2007; Kemp et al., 2010). Although the HRV of MDD patients decreases in a resting state, changes in HRV parameters during a series of ANS stimulation tests for MDD patients have yet to be investigated.

Ewing test, which is a clinical autonomic test for cardiovascular autonomic reactivity, has emerged as a standard tool to examine autonomic functions and simulate stress reaction for MDD assessment without requiring expensive or specific equipment (Ewing and Clarke,

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1982; Dijk, 2003). In the present study, the following measures of Ewing test were used: (1) HRV at rest; (2) HRV during deep breathing; (3) HRV during Valsalva test; and (4) HRV during standing up (Dijk, 2003). Previous research focused on calculating HRV between MDD patients and normal individuals in a resting state. However, the HRV between MDD patients and normal individuals during a series of ANS stimulation tests, such as Ewing test, has been rarely investigated. Therefore, we compared the time domain, frequency domain, and nonlinear HRV parameters of MDD patients and normal individuals during Ewing test, including resting, deep breathing, Valsalva test, and standing up. We also aimed to address the following primary research topics: (1) comparative analysis of HRV in MDD patients at each Ewing test state and (2) relative variation analysis of HRV and cardiac autonomic system of MDD patients under stress reactions between Ewing test sessions.

2. Materials and methods

2.1. Subjects

Patients and controls signed a written informed consent. The sample comprised 40 MDD patients. Of these patients, 25 were females and 15 were males, and their mean age was 35.0 ± 12.4 years (age range = 17–60 years), their mean height was 162.1 ± 7.0 cm, their mean weight was 58.8 ± 8.7 kg, and their mean body mass index (BMI) was 22.4 ± 2.8. These patients satisfied the DSM-IV criteria after they underwent a structured interview at Guangzhou Psychiatric Hospital and showed normal sinus rhythm in their electrocardiography (ECG). None of the subjects reported any history of myocardial infarction, diabetes, arrhythmia, alcohol abuse, head injury, epilepsy, and psychiatric illness other than MDD.

The control group comprised 40 healthy individuals. Of these individuals, 25 were females and 15 were males, and their mean age was 36.1 ± 9.6 years (age range = 22–57 years), their mean height was 164.2 ± 5.6 cm, their mean weight was 60.1 ± 7.7 kg, and their mean BMI was 22.3 ± 2.2. This group consisted of students, teachers, and office employees. None of them had a history of any psychiatric illness. All of them were free of any medication and without abnormal electrocardiogram. Patients and controls were comparable in terms of physical state and fitness.

2.2. Study protocol

Ewing test was divided into four basic sessions: (1) subjects sat and maintained spontaneous breathing for 4 min of resting state; (2) patients inhaled and held their breath for 5 s and then exhaled and held their breath for another 5 s for a total of 1 min of deep breathing state, which was repeated six times; (3) subjects performed a breathing–holding cycle for 15 s and then exhaled and relaxed for 15 s for a total of 1 min and 30 s of Valsalva test state, which was repeated thrice; and (4) subjects stood up and spontaneously breathed for 2 min of standing up state. In each state, the participants were allotted 30 s of relaxation and adjustment between each state. The whole Ewing test continued for 10 min.

2.3. Data recording

ECG signals in the whole Ewing test were recorded. ECG was recorded in the supine position by using three-limb ECG leads (ECG-B; SAYES, Shenzhen, China) through Red DotTM Ag/AgCl disposable electrodes placed in accordance with a sample rate of 500 Hz. The peak of the R wave of ECG was extracted to obtain HRV signals. The HRV signals were then analyzed to obtain the time domain, frequency domain, and nonlinear parameters. The time domain parameters were as follows: mean value of RR interval (MEAN), SDNN, RMSSD, and PNN50. The frequency domain parameters were calculated after the HRV signals were re-sampled at 4 Hz and Fourier transformation was performed: LF power of 0.04–0.15 Hz, HF power of 0.15–0.40 Hz, and LF-to-HF ratio (LF/HF).

Nonlinear analysis has been performed to characterize cardiac functions, such as Poincaré plots and sample entropy (Henry et al., 2010; Kemp et al., 2010). In Poincaré plots, SD1 is the long axis of the ellipse of RR interval and SD2 is the short axis of the ellipse of RR interval (Brennan et al., 2010). Nonlinear dynamical analyses, such as approximate entropy (ApEn), sample entropy (SampEn), multi-scale entropy (MSE), and composite multi-scale entropy (CMSE), are effective algorithms to measure the complexity of time series. ApEn strongly depends on data length and lacks relative consistency in some cases (Choi et al., 2011). SampEn is not always associated with complexity. MSE is an effective method to determine complexity, but it may inaccurately estimate entropy and induce undefined entropy because the coarse-graining procedure reduces the length of the time series considerably at large scales. CMSE can improve the accuracy of MSE, but it does not resolve undefined entropy. Wu introduced a nonlinear dynamical analysis about refined composite multi-scale entropy (RCMSE) to improve CMSE (Wu et al., 2014; Azami and Escudero, 2016). RCMSE can increase the accuracy of entropy estimation and reduce the probability of inducing undefined entropy. In this study, three nonlinear parameters of RCMSE: RCMSE1, RCMSE2, and RCMSE3 are obtained from nonlinear dynamical analysis (Wu et al., 2014; Azami and Escudero, 2016). The other nonlinear parameters and time domain and frequency domain parameters of HRV can be calculated with KUBIOS HRV software (version 2.1, released by Biosignal Analytics and Medical Imaging Group).

2.4. Statistical analysis

The HRV parameters of MDD patients and healthy individuals (Table 1) were individually calculated in each session (resting state, deep breathing state, Valsalva test state, and standing up state). The HRV parameters were statistically analyzed from two aspects: Statistic I, for each parameter, differences between MDD patients and healthy individuals were compared through ANOVA and nonparametric statistics (Mann–Whitney test). Statistic II, the variations of two sessions were analyzed by comparing two sessions of Ewing test with nonparametric test (Wilcoxon test) for two related samples. Data were statistically analyzed in SPSS, and statistical significance was defined as $p < 0.05$. Values were presented as mean and standard deviation.

3. Results

In this study, 40 MDD patients and 40 healthy individuals were enrolled. Their HRV data during Ewing test are shown in Table 1. Comparing the HRV parameters of the MDD patients with those of the healthy individuals as statistic I, we observed that some parameters significantly differed. In the resting state, the RCMSE3 ($p = 0.033$), LF ($p = 0.012$), and LF/HF ($p = 0.044$) of MDD patients were lower than those of the control group. In the deep breathing state, the MEAN ($p = 0.005$), SDNN ($p = 0.001$), RMSSD ($p = 0.028$), SD1 ($p = 0.029$), SD2 ($p = 0.001$), and LF ($p = 0.012$) of the MDD patients were lower than those of the control group. In the Valsalva test state, the SDNN ($p = 0.000$), RMSSD ($p = 0.019$), SD1 ($p = 0.019$), SD2 ($p = 0.000$), and LF ($p = 0.012$) of the MDD patients were lower than those of the control group. In the standing up state, the SDNN ($p = 0.032$), RMSSD ($p = 0.000$), PNN50 ($p = 0.004$), SD1 ($p = 0.000$), SD2 ($p = 0.043$), RCMSE1 ($p = 0.001$), RCMSE2 ($p = 0.032$), LF ($p = 0.012$), and HF ($p = 0.000$) of the MDD patients were lower than those of the control group. The LF/HF ($p = 0.050$) of the MDD patients was higher than that of the control group. These findings indicated that the HRV parameters of the MDD patients were lower than those of the control group.

Comparing the two sessions of Ewing test as statistic II, we found significant changes ($p < 0.05$) between the control group and the MDD