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Reactive heart rate variability in male patients with first-episode major depressive disorder☆

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ABSTRACT

Objective: The association between cardiovascular reactivity and major depressive disorder (MDD) remains unclear. This study aimed to examine this association via reactive heart rate variability (HRV) in a well-diagnosed first-episode MDD group and a control group.
Methods: A total of 160 physically healthy, drug-naive patients presenting with their first-episode MDD and 50 healthy controls were recruited. All participants underwent a 5-min electrocardiography at rest and during a mental arithmetic task. Depression severity was assessed using the Beck Depression Inventory II (BDI).
Results: HRV measures that showed between-group differences at rest did not reached significance during mental stress. In contrast, HRV measures that revealed between-group differences during stress did not reach significance at rest. In response to mental stress, HRV measures did not significantly change in both group. However, LF and HF in response to stress were different between groups. Patients with MDD revealed an increasing trend in HF and a decreasing trend in LF; conversely, healthy controls had a decreasing trend in HF and an increasing trend in LF. BDI scores correlated with changes in heart rate in the control group.
Conclusions: The fundamental change to reactive HRV in patients with first-episode MDD appears qualitative, not quantitative. A distinctly reverse trend in reactive HRV measures were evident between these two groups. Moreover, patients with MDD showed entirely distinct changes in reactive HRV from those in resting HRV. We suggest that in patients with MDD, autonomic system shifts to sympathetic dominance at rest but toward parasympathetic dominance in response to stress.

1. Introduction

Understanding the cardiovagal function in depression is of great significance to public health since a large body of evidence has indicated that depression increases the risk of cardiovascular diseases (CVD) and its related mortality (Frasure-Smith et al., 2009; Van der Kooy et al., 2007). Cardiovascular reactivity (CVR) is the responsiveness of the cardiovascular system to stress, and reactivity is derived as changes from baseline levels not absolute levels during stress. CVR reflects autonomic regulatory capacity, and evidence suggests that CVR predicts the development of preclinical and clinical CVD states (Treiber et al., 2003).

Research on the association between CVR and depression has yield inconsistent results in recent years. A meta-analysis published in 2004, which consisted of 11 relevant studies, suggested depression involving enhanced CVR (Kibler and Ma, 2004); however, the negative association between attenuated CVR and depressive symptoms has been repeatedly observed in non-clinical participants (Schwerdtfeger and Rosenkaimer, 2011), in people with coronary artery disease (York et al., 2007), in large-scale community samples (Carroll et al., 2008; de Rooij et al., 2010; Phillips, 2011), and in patients with major depressive disorder (MDD) (Rottenberg et al., 2007; Salomon et al., 2009, 2013).

Abbreviations: MDD, major depressive disorder; HRV, heart rate variability; CVD, cardiovascular diseases; CVR, cardiovascular reactivity; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; BDI, Beck Depression Inventory II; ECG, electrocardiogram; LF, low frequency; HF, high frequency; TP, total power; VAR, variances of the RR interval; SDNN, the standard deviation of all normal-to-normal interbeat interval; MHR, the mean value of heart rate; MRR, the mean value of the RR interval; SD, standard deviation; SE, standard error; CI, confidence interval.

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Heart rate variability (HRV) is a widely used tool to assess cardiac autonomic activity, and it can reflect the balance between the sympathetic and the parasympathetic regulatory control of heartbeat. HRV has been proposed as a more appropriate measure to examine the association between CVR and depression (Schwerdtfeger and Rosenkaimer, 2011). Although strong evidence from the meta-analysis suggests that depression without CVD is associated with attenuated HRV (Kemp et al., 2010), few studies have investigated HRV in response to stress (also known as reactive HRV or HRV reactivity) in depressed individuals. A study, which enrolled a small sample with non-clinical depression and coronary artery disease, showed that during mental stress, the increases in low-to-high frequency (LF/HF) ratio and heart rate were more pronounced in participants with higher depression scores (Sheffield et al., 1998). Another study with 53 otherwise healthy participants reported greater reduction in high frequency (HF) in the highly depressed mood group (Hughes and Stoney, 2000). The authors suggest that the magnitude of decrease in parasympathetic cardiac control during stress was associated with depressed mood (Hughes and Stoney, 2000). Nevertheless, a recent study including 22 drug-naive, clinical depressed patients produced different results (Shinba, 2013). In this study, patients with clinical depression revealed an increase in reactive HF and decreases in reactive LF/HF ratio and heart rate. Given that during the task performance, reactive HRV for clinical depressed patients were different from those of healthy controls, the authors suggest an altered state of autonomic reactivity in depression (Shinba, 2013).

The methodological differences, clinical heterogeneity of subjects, and differences in medication use may have led to the inconsistent findings. Moreover, the sample size in prior studies was relatively small, probably skewing the results. The aim of the study was to explore the association between CVR and MDD by analyzing reactive HRV. We carefully enrolled only drug-naive, CVD-free, male participants diagnosed with their first episode of MDD. The study design could provide a better window into CVR in the early stage of MDD. We also examined whether changes in reactive HRV were different from changes in resting HRV and how depression severity was associated with changes in reactive HRV.

2. Methods

2.1. Participants

Participants were recruited from the inpatient division of Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, a psychiatric teaching hospital in Taiwan. Written informed consent was obtained in accordance with the National Health and Medical Research Council guidelines. All subjects were fully informed regarding the aims and details of the study and were free to withdraw their consent at any time.

Between 2009 and 2012, a total of 160 individuals with a first episode of MDD were judged eligible. To avoid the potential confounders, such as age, gender, ethnicity, use of psychotropics, and CVD (Liao et al., 1995), individuals were required to be unrelated Han Chinese males, between the ages of 20 and 40 years, drug-naive, and in good health. The diagnosis of MDD—meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria—was made by two certified psychiatrists by diagnostic interview. The severity of depression was assessed with the Chinese version of the Beck Depression Inventory II (BDI) (Beck et al., 1961).

Individuals were excluded from the study for any of the following reasons: systolic blood pressure exceeding 180 mmHg or diastolic blood pressure exceeding 110 mmHg; histories of or concurrent medical illnesses such as heart disease, diabetes, CVD, liver or renal disease, endocrinopathies, neurological disorders, or cancer; meeting the DSM-IV criteria for substance-related disorders, psychotic disorders, or bipolar disorder; use of any drugs or over-the-counter preparations; and being shift workers.

A series of examinations were performed, including a complete physical examination, a routine biochemical panel, a complete blood count, a urine test, a stool study, a chest X-ray, and an electrocardiogram (ECG). Height (cm) and weight (kg) of each participant were measured by a standard balance beam scale, and body mass index (BMI) was calculated. The medical charts were systematically reviewed in order to confirm that all participants met the above operational criteria.

The control group consisted of 50 healthy, never-depressed volunteers matched for sex, age, smoking status, and time of day of ECG recordings. Controls also signed an informed consent form, were interviewed, and completed a BDI rating. Two certified psychiatrists confirmed that none of the healthy controls had a history of any psychiatric illness or were taking any medications. The Institutional Review Board for the Protection of Human Subjects at the Tri-Service General Hospital, a medical teaching hospital within the National Defense Medical Center in Taiwan, approved the protocol.

2.2. HRV recording procedures

Detailed procedures for HRV analysis have been previously reported and are only briefly summarized here (Kuo et al., 1999). Prior to the measurements, participant were instructed to refrain from alcohol and caffeine consumption for 24 h and from smoking, exercising, and heavy eating for at least 8 h. All participants had a usual breakfast on the study day to ensure standardization of ECG recordings. After the participants had rested for 15 m in a quiet, air-conditioned room, the ECG for the analysis of beat-to-beat HRV was recorded under standardized conditions. They were asked to relax, breath naturally, and move as little as possible. Experimental procedures were performed between 08.30 h and 11.30 h in a fixed order of rest followed by an arithmetic task. The mental arithmetic task consisted of a serial subtraction by 7, beginning with the number 2193. During the arithmetic task, participants were prompted to perform faster because they were going "slowly," and this feedback was for all participants. Mental arithmetic tasks have been recognized as active, self-relevant stressors (Schwerdtfeger and Rosenkaimer, 2011).

A 288-s signal sequence of the telemetrically transmitted lead I ECG was recorded. The raw ECG signals were amplified with a gain of 1000 and band-pass filtered (0.68–16 Hz). Signals were then recorded with an 8-bit analog-to-digital converter with a sampling rate of 256 Hz. The digitized ECG signals were analyzed online and simultaneously stored on removable hard disks for offline verification. Signal acquisition and data storage and processing were performed via a general-purpose personal computer. Our computer algorithm identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template. Stationary RR values were re-sampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain.

Frequency-domain analysis was performed by a nonparametric method of fast Fourier transformation. The direct current component was deleted, and a Hamming window was used to attenuate the leakage effect. For each time segment (288-second; 2048 data points), our algorithm estimated the power spectrum density based on the Fourier transformation. The resulting power spectrum was corrected for attenuation resulting from the sampling and the Hamming window. The power spectrum was subsequently quantified into standard frequency-domain measurements including low frequency (LF) (0.04–0.15 Hz), HF (0.15–0.40 Hz), and total power (TP). The time-domain parameters were the standard deviation of all normal-to-normal interbeat interval (SDNN) and the variance of RR interval (VAR). Both parameters were measured in milliseconds (ms). Although mean value of HR (MHR) and mean value of RR interval (MRR) during the 5 min did not belong to HRV components, these two measure were also calculated under both conditions. The spectral components