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Short-term heart rate variability in older patients with newly diagnosed depression

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ABSTRACT

Dysfunction of the autonomic nervous system has been considered to be a risk factor for major depressive disorder (MDD) and cardiovascular disease (CVD). The aim of this study was to evaluate short-term heart rate variability (HRV) in elderly patients with newly diagnosed MDD. Thirty MDD patients over 60 years old newly diagnosed by a structured interview were enrolled, free from antidepressants. Socio-demographic data, blood tests, and heart rate variability (HRV) obtained from 5-min ECG were gathered. The MDD group showed significantly lower very low frequency power, low frequency power, high frequency power, and total power in frequency domain. In time domain analysis, the MDD group showed a significantly smaller standard deviation of the NN, root mean square of the differences of the successive NN, and NN50/total number of all NNs. These findings demonstrated a lower HRV in older patients who were newly diagnosed with depression without a history of CVD and antidepressants effect, compared with the control subjects. Low HRV may be an important predictor of both MDD and CVD in elderly. The use of HRV in elderly depressive patients could be a meaningful screening method for risk of CVD.

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1. Introduction

Depression is a common and disabling health problem worldwide. The estimated lifetime prevalence of major depressive disorder (MDD) is 16.2%, and the disease causes remarkable psychosocial impairments (Kupfer et al., 2012). Depression is associated with various medical conditions and is a leading cause of disability, accounting for 40.5% of the years lived with disability worldwide (Whiteford et al., 2013).

Medical illness is a risk factor for depression, and the prevalence of depression increases with increasing illness severity (Li and Rodin, 2011). Co-morbid depression has been associated with 20–40% of cardiovascular disease (CVD) patients (Gonzalez et al., 1996). A meta-analysis of prospective studies reported a dose–response relationship between the severity of depression and the risk of CVD (Ferketich et al., 2000; Rugulies, 2002; Williams et al., 2002).

Depression is associated with many unhealthy behaviors, such as smoking and drinking to excess, which increase the risk of future

CVD. CVD patients who are depressed might have a greater sympathetic response to stress, which may lower the threshold for hypertension and facilitate the progression of the atherosclerotic process (Li and Rodin, 2011). CVD may impair social functioning and has a significant burden of illness, which may increase the risk of developing depression (Alexopoulos et al., 2002).

Although the exact mechanism underlying the association between depression and CVD is not clear, one possible hypothesis is that autonomic dysfunction might be a co-risk factor for both illnesses (Carney et al., 2002; Grippo and Johnson, 2002). Measurement of heart rate variability (HRV) is regarded as a non-invasive and highly sensitive method to evaluate autonomic nervous system (ANS). Low HRV has been associated with the development of CVD and MDD (Carney et al., 2005); furthermore, lower HRV could predict cardiac events in healthy adults and mortality in CVD patients (Vaishnav et al., 1994; Dekker et al., 2000). Many previous studies have revealed that lower HRV was associated with unfavorable health outcomes in depressed patients (Veith et al., 1994; Lehofer et al., 1997; Moser et al., 1998).

There is a significant negative correlation between the severity of depression and HRV (Kemp et al., 2010). A systematic meta-analysis revealed that individuals with more severe depression are likely to have a lower HRV compared with individuals with less severe depression (Kemp et al., 2010). Elderly depressed patients

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have a significant coherent deficit in autonomic tone indicated by lower LF-HRV and total power spectral density compared with non-depressed individuals (Vasudev et al., 2011), which indicate a remarkable deficit in autonomic tone in patients with late-life depression. However, these findings are needed to confirm by other studies because of methodological limitations, such as lack of structured interview for diagnosis and including just frequency domain analysis of HRV test (Vasudev et al., 2011).

Considering the fact that the ANS changes increase with aging, it is difficult to demonstrate that elderly depressed patients display decreased HRV against a background of decreased HRV with aging. It is quite possible that depression in elderly patients further reduces HRV, which potentially results in an increased risk of cardiovascular morbidity and mortality. It is notable, however, that previous reports on these phenomena had several limitations. First, most studies were performed in previously diagnosed depressed patients who were taking anti-depressants. The use of antidepressants may have an effect on the ANS status evaluated by HRV (Licht et al., 2008). Some psychotropic drugs are known to alter cardiac autonomic activity in diverse ways (Glassman et al., 2003). A recent study showed antidepressant effect was significant in lowering HRV in depressive elderly, while depression *per se* did not affect in lowering HRV (O'Regan et al., 2014). Second, studies on the association between HRV and depression have generally been conducted with patients with known CVD. The research results from those subjects can hardly discern the effect of depression on the lowering of HRV from CVD. Last but not least, there were inconsistent results about the association of the lowering of HRV and late-life depression. Vasudev et al. reported that the patients with previous and current late-life depression showed significant changes in HRV compared to controls (Vasudev et al., 2011). However, the other study did not show the differences in the time domain or frequency domain measures of HRV between depressed elderly and normal control (Jindal et al., 2008; O'Regan et al., 2014). The inconsistency among the previous studies could draw from the methodological limitations, such as the use of psychotropics and CVD history of subjects. Therefore, we have performed a study on newly diagnosed and treatment-naïve elderly MDD patients without co-morbid CVD to identify whether elderly depression is associated with the lowering of HRV.

2. Methods

2.1. Subjects

We enrolled subjects over 60 years of age who presented at the Health Promotion Center of Asan Medical Center, Seoul, Korea, for a health examination from January to August 2011. The patients visited the Health Promotion Center for regular medical check-ups. All study participants were treatment-naïve and never received treatment for psychiatric illness. All subjects without a past history of a depressive episode received a psychiatric interview by an experienced psychiatrist. Thirty patients who were newly diagnosed with depression using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I/P 2.0) were enrolled through the Health Promotion Center (depression group). All subjects met the criteria of MDD without psychotic features, were free of antidepressants or benzodiazepines during their lifetime, and were in a clinically and medically euthyroid state confirmed by a thyroid function test. We only included patients who had MDD to focus our analyses on a certain degree of depressive symptom severity in patients who sought clinical attention. The severity of depressive symptoms in the MDD subjects was evaluated by the Montgomery-Asberg Depression Rating Scale (MADRS) and had a mean score of 24.6 ± 5.0 . In addition, 30 age- and sex-matched healthy individuals were recruited from a Health Promotion Center as the control group. Subjects who had a previous history of psychiatric illness or CVD were excluded. The controls were examined for depression using the Center for Epidemiological Studies for Depression Scale (CES-D) in the identical time period; an experienced psychiatrist (BSK) confirmed the absence of psychiatric illness in the control group. The institutional review board of the Asan Medical Center Ethics Committee approved this study and waived the requirement for informed consent because the measurements of clinical features and the assessments of the variables included in this study were part of a routine health examination.

2.2. Exclusion criteria

The subjects with known CVD, such as myocardial infarct and arrhythmia, possible dementia assessed by a Mini Mental State Examination score below 24, co-morbid or previous drug or alcohol abuse, head injury, history of epilepsy, and psychiatric illness except MDD in the previous 6 months were excluded from the study. An abnormal electrocardiogram (ECG) (determined by a heart rate < 50 beats per minute (bpm) or by the presence of conduction disturbance) was also used as an exclusion criterion for the study.

2.3. Basic demographic data and biochemical tests

Basic socio-demographic data were obtained and included occupation, level of education, estimated income, marital status, alcohol use, smoking, and regularity of exercise. Blood pressure, body mass index, and blood biochemical test results (e.g., high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol, and glycated hemoglobin (HbA1c)) were obtained for all patients in both groups. Additionally, existing medical illnesses, including diabetes mellitus, hypertension, and metabolic syndrome, and the current use of medications, were investigated.

Lifestyle factors including alcohol, exercise, and smoking were obtained from medical data that were recorded on the basis of the frequency of alcohol consumption (≤ 1 day/week, 2–3 days/week, ≥ 4 days/week) and exercise (no regular exercise, 1–2 day/week, 3–5 days/week, 6–7 days/week) with categorical variables; smoking was categorized as never smoking, past smoking, and current smoking. The diagnosis and treatment history of hypertension and diabetes among the subjects were collected from medical records based on laboratory tests and clinical evaluations. Metabolic parameters including waist circumference, blood pressure, and triglycerides, high-density-lipoprotein cholesterol, and fasting glucose levels were measured before starting treatment. We used the modified the NCEP in Adult Treatment Panel III (Alberti et al., 2009) to define MeS as 3 or more of 5 components in which the cut-off point of waist circumference was modified for Asian according to the recommendation by the International Diabetes Federation (Alberti et al., 2006). According to the modified NCEP in Adult Treatment Panel III definition, MeS is diagnosed by the presence of 3 or more of the following criteria: (1) abdominal obesity—waist circumference Z 90 cm in men and Z 80 cm in women; (2) high blood pressure Z 130/85 mm Hg or use of antihypertensive medication; (3) hypertriglyceridemia Z 150 mg/dL or use of antihyperlipidemic medication (4) low high-density-lipoprotein cholesterol levels, < 40 mg/dL in men and < 50 mg in women; and (5) high fasting glucose, Z 100 mg/dL or use of diabetic medication.

2.4. Measuring HRV

All examinations occurred in the morning, between 8 and 10 AM. The subjects were asked not to drink caffeine or smoke for at least 8 h prior to the examination. The participants were asked to breathe normally with their eyes open and to lie quietly without moving. After approximately 10 min of supine rest, an ECG was recorded for 5 min in the supine position using limb leads according to the QECG-3 model (LXC3203; LAXTHA, Daegu, Korea), and the data were analyzed to obtain the time and frequency domain parameters of HRV using TeleScan software (version 2.0, LAXTHA, Daegu, Korea). The following ECG variables were calculated as indicators of ANS function. In the time domain, the following statistical parameters were calculated: normal-to-normal R-R interval (NN), HRV index (total no. of all NNs/height of the histogram of all NNs), standard deviation of the NN (SDNN), root mean square of the differences of successive NNs (RMSSD), the number of pairs of adjacent NN intervals that differed by > 50 ms in the entire recording (NN50), and the NN50/total number of all NNs (pNN50). In the frequency domain, the power spectrum of the HRV signals was calculated using Fourier transformation, and the power (the area under the curve related to each component) was calculated for the following four components: the total power (TP; variance of NN intervals over the temporal segment), very low frequency power (VLF; < 0.04 Hz), low frequency power (LF; 0.04–0.15 Hz), and high frequency power (HF; 0.15–0.4 Hz). Most HRV measures are predominantly under vagal control, in particular, the short-term measures obtained under laboratory conditions in which participants are typically supine (Martinmaki et al., 2006). Experimental studies have shown that short-term recordings are predictive of CVD (Dekker et al., 2000), are stable (Sinreich et al., 1998), and provide a more accurate picture of physiological changes compared with longer-term recordings (Serrador et al., 1999).

2.5. Statistical analysis

The socio-demographic and clinical variables are reported as the means and standard deviations for the continuous variables and the frequency for the categorical variables. The Fisher's exact test for sex, occupation, and marital status and the Mann-Whitney test for age, education and monthly earnings were used to assess the differences between the depression and control groups. Lifestyle factors,

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