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Patterns of cardiorespiratory coordination in young women with recurrent major depressive disorder treated with escitalopram or venlafaxine

Jae Seung Chang [a], Kyooseob Ha [a,b,*], In-Young Yoon [a,b], Cheol Sung Yoo [c], Sang Hoon Yi [c], Ju Young Her [a], Tae Hyon Ha [a], Taesung Park [d]

[a] Bipolar Disorder Translational Research Center & Department of Psychiatry, Seoul National University Bundang Hospital, 166 Gumi-Dong, Bundang-Gu, Seongnam, Gyeonggi 463-707, Republic of Korea
[b] Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine, 101 Daehang-Ro, Jongno-Gu, Seoul 110-744, Republic of Korea
[c] Department of Computer Aided Science, Institute of Basic Science, Inje University, 607 Eobang-Dong, Gimhae, Gyeongnam 621-749, Republic of Korea
[d] Department of Statistics, Seoul National University, 1 Gwanak-Ro, Gwanak-Gu, Seoul 151-742, Republic of Korea

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ABSTRACT

Evidence from previous studies suggests autonomic dysregulation in patients with major depressive disorder (MDD). Antidepressant treatment may also affect central autonomic function. We investigated whether the type of antidepressant might be associated with the pattern of cardiorespiratory coordination in non-depressed women with recurrent MDD. Resting electrocardiograms and respiratory signals were simultaneously recorded from 38 euthymic women with recurrent MDD who were treated with either escitalopram ($n=19$) or venlafaxine ($n=19$) monotherapy and from 38 healthy women. Linear measures of heart rate variability were extracted to assess cardiac autonomic control. Sample entropy (SampEn) was computed to assess the complexity of heart rate and respiratory signals, and cross-SampEn was calculated to measure the nonlinear interaction of both signals. Significant decreases in the cardiovagal tone and cardiorespiratory coupling of women with recurrent MDD receiving venlafaxine, and tendencies toward lower cardiovagal tone and cardiorespiratory coupling in women with recurrent MDD receiving escitalopram were observed when compared with healthy controls. Effect sizes for these differences were large between women receiving venlafaxine and healthy controls. We found a positive association between cardiorespiratory decoupling and venlafaxine dose. Norepinephrine-enhancement, within a therapeutic dose range, seems to be closely associated with decreased vagal tone and reduced nonlinear coupling between heart rate and respiration in euthymic women with recurrent MDD. However, the effects of serotonin enhancement on cardiovagal tone should be considered. Our results suggest that the pharmacodynamic properties of antidepressants may affect autonomic regulation of women with recurrent MDD even in euthymic state.

1. Introduction

Major depressive disorder (MDD) is often considered to be an independent risk factor of mortality in patients with coronary heart disease (CHD) or myocardial infarction (Carney et al., 1995; Kaufmann et al., 1999; Lesperance et al., 2002). Moreover, recent studies have revealed that recurrent MDD and depressive symptoms may increase the risk of cardiovascular events even in physically healthy women (Janssen et al., 2011; Matthews et al., 2010). However, several studies have not found a relationship between pre-existing depression and cardiac mortality (Gehi et al., 2005; Martens and de Jonge, 2009). Although the mechanisms linking MDD to cardiovascular events are not fully understood, previous studies found sympathovagal imbalance in patients with MDD by examining heart rate dynamics, baroreflex sensitivity, and electrogastrography (Koschke et al., 2009; Quick et al., 2010). Because parasympathetic inputs enable biological systems to respond flexibly to environmental changes, sympathetic dominance is physiologically disadvantageous and maladaptive (Cyranowski et al., 2011). Clinical manifestations such as sleep disturbances, dry mouth, and palpitations also support altered autonomic modulation in subjects suffering from MDD. In our recent study, central autonomic dysregulation has been suggested in young women with recurrent MDD (Chang et al., 2012).

Abbreviations: ANOVA, analysis of variance; ApEn, approximate entropy; BMI, body mass index; CHD, coronary heart disease; MDD, major depressive disorder; DSM-IV, diagnostic and statistical manual of mental disorders, fourth edition; ECG, electrocardiogram; HDRS, Hamilton depression rating scale; HF, high-frequency component of the heart rate power spectrum; HRV, heart rate variability; LF, low-frequency component of the heart rate power spectrum; MANOVA, multivariate analysis of variance; M.I.N.I, mini-international neuropsychiatric interview for DSM-IV; NN, normal-to-normal; RMSSD, mean squared differences of successive NN intervals; RR, beat-to-beat interval; SampEn, sample entropy; SDNN, standard deviation of all RR intervals; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; YMRS, Young mania rating scale.

* Corresponding author. Tel.: +82 31 787 7431; fax: +82 31 787 4058.
E-mail address: kyooha@snu.ac.kr (K. Ha).

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Antidepressant use may be a confounding factor associated with decreased cardiovagal modulation (Licht et al., 2010). In particular, the potent anticholinergic property of tricyclic antidepressants (TCAs) is often associated with decreased vagal activity and increased cardiovascular risk (Bär et al., 2010b; Yeragani et al., 2000). On the contrary, some authors found a beneficial influence of serotonin-selective reuptake inhibitors (SSRIs) on the recurrence of CHD in depressed patients with CHD (Pizzi et al., 2011). In a recent study comparing the effects of TCA and SSRI treatment on vagal modulation in subjects with MDD, decreased nonlinear HRV measures and reduced cardiorespiratory coupling were observed after nortriptyline treatment, whereas no significant changes were detected in subjects treated with escitalopram (Bär et al., 2010b). A recent meta-analysis showed that although TCAs and SSRIs have similar antidepressant effects, their influences on cardiac autonomic measures are substantially different (Kemp et al., 2010). While serotonin and norepinephrine reuptake inhibitors (SNRIs) including venlafaxine and duloxetine are currently recognized as effective options in the management of MDD (Ye et al., 2011), the effects of norepinephrine-enhancing SNRI treatment on cardiac autonomic modulation remain unclear (Davidson et al., 2005; Emul et al., 2009). Thus, additional evidence is required to elucidate the relationship between MDD, types of antidepressants, and autonomic regulation.

In addition to heart rate variability (HRV) parameters, nonlinear measures of the coordination between heart rate and respiration have been recently introduced as useful indices of vagal output from central autonomic network in subjects with a broad range of psychiatric disorders (Bär et al., 2010b; Berger et al., 2010; Peupelmann et al., 2009). Indices of HRV are considered physiologic markers of cardiac autonomic regulation and diminished HRV indicates an increased risk for CHD and myocardial infarction (Ehrenthal et al., 2010; Kop et al., 2010; Licht et al., 2010). On the other hand, cardiorespiratory coupling indicates a coupling between heart rate and respiration (Bär et al., 2010b) and reflects the strength of the association between the two systems under the control of the central autonomic network (Dick and Morris, 2004). Resting cardiorespiratory coupling is largely associated with vagal tone of central autonomic modulation (Bär et al., 2008; Peupelmann et al., 2009).

In the current study, we hypothesized that the pharmacodynamic properties of antidepressants would be associated with the differential pattern of autonomic regulation in euthymic MDD patients treated with various antidepressants. We investigated HRV indices and cardiorespiratory coupling in young women with recurrent MDD who were given either escitalopram or venlafaxine monotherapy compared with healthy matched controls. Furthermore, we hypothesized that venlafaxine treatment might be associated with greater decreases in vagal tone and nonlinear cardiorespiratory coupling compared with escitalopram treatment. In addition, we explored the dose-dependent effects of antidepressants on autonomic modulation in MDD.

2. Methods

2.1. Subjects

Thirty eight women with recurrent MDD receiving escitalopram ($n=19$) or venlafaxine ($n=19$) and 38 healthy controls matched for sex, age, and body mass index (BMI) were included in this study. Table 1 depicts the demographic and clinical characteristics of the three groups. The patients were recruited from the Mood Disorders Clinic at Seoul National University Bundang Hospital, Seongnam, Republic of Korea. The patients had been in the remission state for at least 8 weeks prior to study participation, as confirmed by a score of 7 or less on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and a score of 6 or less on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Given the symptomatic overlap between recurrent MDD and bipolar disorders (Smith et al., 2011), the YMRS was used to assess the potential manic or hypomanic symptoms. All of the patients received either venlafaxine or escitalopram monotherapy without changes in their daily dose during this remission period, indicating a plateau of clinical response to their antidepressant treatment. A clinical interview using the Mini-International Neuropsychiatric Interview for DSM-IV (M.I.N.I.) (Sheehan et al., 1998) and a comprehensive review of all available clinical data confirmed the psychiatric diagnoses. Complete medical or psychiatric histories of the patients were available through paper charts and electronic medical recording systems. We defined recurrent MDD as follows: 1) the occurrence of at least two episodes of DSM-IV major depression with interepisode intervals of at least two months and 2) the occurrence of at least one major depressive episode after the age of 18 years (Levinson et al., 2003). Using these criteria, we recruited non-reactive patients, implicating a high level of biological predisposition to depression. To decrease diagnostic heterogeneity and sources of confounders, we excluded patients with comorbid Axis I diagnoses from the study using the M.I.N.I. and medical records. We recruited a community-based control group using advertisements. Controls did not meet the DSM-IV criteria for any Axis I disorders. None of the participants had a prior history of cardiovascular events. Neither patients nor controls suffered from any medical (e.g., diabetes or hypertension) or neurological (e.g., epilepsy or stroke) conditions. Fourteen patients treated with escitalopram and 18 controls have participated in our previous study on the interaction between electroencephalogram and ECG, but we used the different set of ECG data for the current study (Chang et al., 2012). The institutional review board approved the study protocol, and we obtained written informed consent from each participant. All of the procedures used in this study were based on the Good Clinical Practices guidelines and were in accordance with the most recent version of the Declaration of Helsinki.

Table 1
Comparisons of demographic and clinical characteristics between the control and major depressive disorder groups.

	Control ($n=38$)	Patients		p value
		Escitalopram ($n=19$)	Venlafaxine ($n=19$)	
Age, mean (SD), year	35.63 (7.51)	37.11 (7.47)	34.89 (8.83)	0.673[a]
Age at illness onset, mean (SD), year		32.63 (8.22)	30.05 (6.93)	0.303[b]
BMI, mean (SD), kg/m^2	21.39 (2.84)	21.91 (2.67)	21.63 (2.42)	0.789[a]
Education				
≤12 years	6	4	8	
≥13 years	32	15	11	
Occupation, yes/no	30/8	10/9	13/6	
Number of episodes, mean (SD)		3.32 (0.75)	3.21 (0.92)	0.701[b]
Antidepressant dose, mean (SD), mg/d		9.73 (4.24)	78.95 (32.82)	
Total HDRS score, mean (SD)	0.76 (1.38)	2.32 (1.49)	3.26 (3.21)	<0.001[a]
Total YMRS score, Mean (SD)	0.03 (0.16)	0.26 (0.56)	0.63 (1.30)	0.013[a]

Note. BMI, body mass index; HDRS, Hamilton depression rating scale; MDD, major depressive disorder; SD, standard deviation; YMRS, Young mania rating scale.
[a] p values were computed from a one-way analysis of variance (ANOVA).
[b] p values were computed from an independent t-test.

2.2. Study procedures

We simultaneously recorded the high-resolution (1000 Hz) electrocardiograms (ECGs) and the respiratory signals of the participants using a Synamps 2 amplifier (Compumedics, Melbourne, Australia)