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Heart rate variability in major depressive disorder and after antidepressant treatment with agomelatine and paroxetine: Findings from the Taiwan Study of Depression and Anxiety (TAISDA)

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ABSTRACT

Evidence from previous studies suggests that heart rate variability (HRV) is reduced in major depressive disorder (MDD). However, whether this reduction is attributable to the disorder per se or to medication, since antidepressants may also affect HRV, is still debated. There is a dearth of information regarding the effects of agomelatine, a novel antidepressant, on HRV. Here, we investigated whether HRV is reduced in MDD and compared the effects of agomelatine and paroxetine on HRV. We recruited 618 physically healthy unmedicated patients with MDD and 506 healthy volunteers aged 20–65 years. Frequency-domain measures of resting HRV were obtained at the time of enrollment for all participants. For patients with MDD, these measures were obtained again after 6 weeks of either agomelatine or paroxetine monotherapy. Compared with healthy subjects, unmedicated patients with MDD exhibited significantly lower variance (total HRV), low frequency (LF), and high frequency (HF) HRV, and a higher LF/HF ratio. Depression severity independently contributed to decreased HRV and vagal tone. Fifty-six patients completed the open-label trial (n = 29 for agomelatine, n = 27 for paroxetine). Between-group analyses showed a significant group-by-time interaction for LF-HRV and HF-HRV, driven by increases in LF-HRV and HF-HRV only after agomelatine treatment. Within the paroxetine-treated group, there were no significant changes in mean R-R intervals or any HRV indices. We therefore concluded that MDD is associated with reduced HRV, which is inversely related to depression severity. Compared with paroxetine, agomelatine has a more vagotonic effect, suggesting greater cardiovascular safety. Clinicians should consider HRV effects while selecting antidepressants especially for depressed patients who already have decreased cardiac vagal tone.

1. Introduction

Major depressive disorder (MDD) increases the risk for cardiovascular morbidity and mortality (Barth et al., 2004; Nicholson et al., 2006). While the precise mechanisms for this cardiac vulnerability are unknown, a reduction of heart rate variability (HRV) is thought to be one of the important pathophysiological factors (Agelink et al., 2001; Thayer and Lane, 2007). Previous research on HRV and depression has generally been conducted in patients with cardiac conditions. Therefore, factors related to cardiovascular disease (CVD) might have influenced any relationship between depression and HRV. Recent research has focused on patients who have MDD and no CVD in order to avoid overestimation of the association between MDD and HRV (Kemp et al., 2010).

Heart rate variability refers to the complex beat-to-beat variation in heart rate produced by the interplay of sympathetic and parasympathetic (vagal) neural activity at the sinus node of the heart. Lower HRV is an indicator of dysregulated cardiac autonomic function and a predictor of poor health status (Dekker et al., 2000). Short-term power spectral analysis of HRV, standardized since 1996 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), is a reliable and non-invasive tool to probe the autonomic regulation of the heart.

Abbreviations: ANOVA, Analysis of variance; BMI, Body mass index; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; HRV, Heart rate variability; HAM-D, Hamilton Depression Rating Scale; HAM-A, Hamilton Anxiety Rating Scale; HF, High-frequency power; LF, Low-frequency power; MDD, Major depressive disorder; MANOVA, Multivariate analysis of variance; MT_1, MT_1 subtype of mela-toninergic receptors; MT_2, MT_2 subtype of mela-toninergic receptors; SSRIs, Selective serotonin reuptake inhibitors; SADSL, Schedule of Affective Disorder and Schizophrenia-Lifetime; SBP, Systolic blood pressure; TCAs, Tricyclic antidepressants; TAISDA, Taiwan Study of Depression and Anxiety; VLF, Very low-frequency power; 5-HT_{2C}, 5-HT_{2c} subtype of serotonergic receptors.

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Researchers have debated the role of MDD in HRV reduction. Some studies have reported reduced HRV in patients with MDD (Kemp et al., 2010, 2012), while others report no difference in HRV, and conclude that HRV reductions observed in patients with MDD are likely driven by the effects of antidepressant medications (Kemp et al., 2014; Licht et al., 2008; O'Regan et al., 2014). However, most previous HRV studies did not avoid confounding variables affecting autonomic tone such as physical health, psychiatric co-morbidities, and medication use (Kemp et al., 2010). Therefore, in the present study, we enrolled physically healthy, non-comorbid, and unmedicated patients to better examine the relationship between MDD and HRV.

Tricyclic antidepressants (TCAs) are widely known to be able to reduce parasympathetic tone, and therefore HRV (Kemp et al., 2010, 2014; Licht et al., 2008, 2010), due to their anticholinergic and α1-adrenergic properties. However, the literature is inconclusive for other classes of antidepressants. Some researchers have reported that selective serotonin reuptake inhibitors (SSRIs) may decrease HRV (Licht et al., 2010) but have a lower impact on HRV than TCAs (O'Regan et al., 2014), while others have reported that SSRIs had no significant impact on HRV at all (Kemp et al., 2010). Among SSRIs, paroxetine is of particular interest to researchers due to its high antimuscarinic potency (Richelson, 1996). There is, however, limited and inconsistent evidence showing either no HRV effect (Davidson et al., 2005) or a decreasing effect (Lederbogen et al., 2001), of paroxetine in patients with MDD. However, previous studies on paroxetine only used time-domain measures. The lack of data regarding frequency-domain HRV measures in MDD patients before and after the treatment of paroxetine prompted the present investigation.

Agomelatine, a new antidepressant with a novel mechanism of action (Hickie and Rogers, 2011; Kasper et al., 2010), exhibits antidepressant effects by its sleep-promoting and chronobiotic actions. It operates via the melatonin MT_1 and MT_2 receptors present in the suprachiasmatic nucleus as well as by affecting a 5-HT_{2c} receptor blockade (de Bodinat et al., 2010; Demyttenaere, 2011). To date, no study has analyzed changes in the HRV of MDD patients treated with agomelatine.

The present study aimed to examine the impact of MDD and antidepressant treatment on HRV. We hypothesized that HRV would be reduced in unmedicated patients with MDD compared with age-, sex-, and education-matched physically healthy controls. Further, we sought to compare the influence of paroxetine and agomelatine on the autonomic regulation of the heart, using power spectral analyses of HRV as the outcome parameter.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board for the Protection of Human Subjects of the Tri-Service General Hospital, a medical teaching hospital of the National Defense Medical Center in Taipei, Taiwan. All of participants were aged between 20 and 65 years, and all provided written informed consent. Subjects participating in the present study came from The Taiwan Study of Depression and Anxiety (TAISDA), an ongoing cohort study conducted to examine the effect of depression and anxiety disorders on HRV as described elsewhere (Chang et al., 2015). After detailed questionnaire screening, a chart review, clinical examination, electrocardiography, and relevant laboratory investigations, the subjects who were pregnant, had cancer, cardiovascular, respiratory, neurological, or endocrinological disorders that affect HRV, or those engaged in regular and strenuous physical training were excluded. Current or past smokers were also excluded. All participants were drug-naïve or had not used psychotropic medications or any medications that have been reported to affect autonomic functioning (e.g., anti-psychotics, anti-cholinergics, anti-depressants, oral contraceptives, anti-convulsants, anxiolytics, cerebral metabolic activators, or cerebral vasodilators) for at least 1 month prior to the beginning of the study.

Fig. 1 is a flow chart showing the progress of participants through the study. Drawn from a pool of 4105 unmedicated patients with a primary diagnosis of MDD evaluated with the Chinese version of the Modified Schedule of Affective Disorders and Schizophrenia-Lifetime (Endicott and Spitzer, 1978), the patient population consisted of 618 individuals meeting the DSM-IV criteria for MDD without any current psychiatric comorbidity or a history of substance dependence. A previous study utilizing this structured diagnostic interview has reported satisfactory inter-rater reliability (Chang et al., 2007). All enrolled patients had a score greater than 16 on the 17-item version of the Hamilton Depression Rating Scale (HAM-D). The control group consisted of 506 physically healthy volunteers with no lifetime history of mental disorders who were recruited from the community as described previously (Chang et al., 2014a,b).

2.2. Control variables

Previous findings have revealed that gender, age, body mass index (BMI), physical activity, and alcohol use are among the factors significantly affecting the autonomic control of heart rate (Antelmi et al., 2004; Chen et al., 2015; Kuo et al., 1999; Rosenwinkel et al., 2001; Wu et al., 2008). These factors were thus selected as control variables. Subjects reported the average frequency of physical exercise per week (A) and hours per session spent in purposeful exercise (B) in the past 6 months. "A" was rated with a five-point scale according to the frequency of exercise involving heavy breathing and sweating as "never", "seldom", "once a week", "twice a week", and "more than twice a week" (Henje Blom et al., 2009). The participants' self-reported weekly habitual physical activity was calculated by the formula: $A \times B$. Alcohol use, assessed with two items of the Alcohol Use Disorder Identification Test questionnaire (Babor et al., 1992), was defined by the average frequency of drinking and the number of drinks consumed on a typical drinking day in the past year. From these items, we derived the average amount of alcoholic drinks per day, with one drink defined as a standard drink, i.e., having the equivalent of 10 g of alcohol (Li et al., 2011).

2.3. Assessment of depression/anxiety severity

All subjects were assessed using self-reported measures of depression and anxiety with the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), respectively. MDD patients were also assessed by attending psychiatrists using clinician-rated scales, i.e., the HAM-D and the Hamilton Anxiety Rating Scale (HAM-A). Both the self-reported inventories and clinician-rated scales provided global indices of depression/anxiety severity.

2.4. Measurements of blood pressure and heart rate variability

Blood pressure (BP) was recorded with a Tensoval duo control Digital Blood Pressure Monitor (HARTMANN AG, Heidenheim, Germany). Systolic BP (SBP) and diastolic BP (DBP) were measured twice from the right arm during supine rest and averaged. The detailed procedures for the analysis of HRV were as reported in our previous studies (Kuo et al., 1999; Liu et al., 2003). Briefly, the subject first sat quietly for 20 min, then a lead I electrocardiogram was recorded for 5 min while they lay quietly in a supine position. To control diurnal changes in cardiac autonomic modulation, all electrocardiogram recordings were performed in a warm and quiet room between 9 and 11 a.m. An HRV analyzer (SSIC, Enjoy Research Inc., Taipei, Taiwan) acquired, stored, and processed the electrocardiography signals. Our computer algorithm then identified each QRS complex and rejected each ventricular premature complex or noise according to its likelihood in a standard QRS template (Liu et al., 2003). Signals were recorded at a sampling rate of 512 Hz, using an 8-bit analog-to-digital converter. Stationary R-R interval values were re-sampled and interpolated at a rate of 7.11 Hz to produce continuity in the time domain. Power spectral analysis was

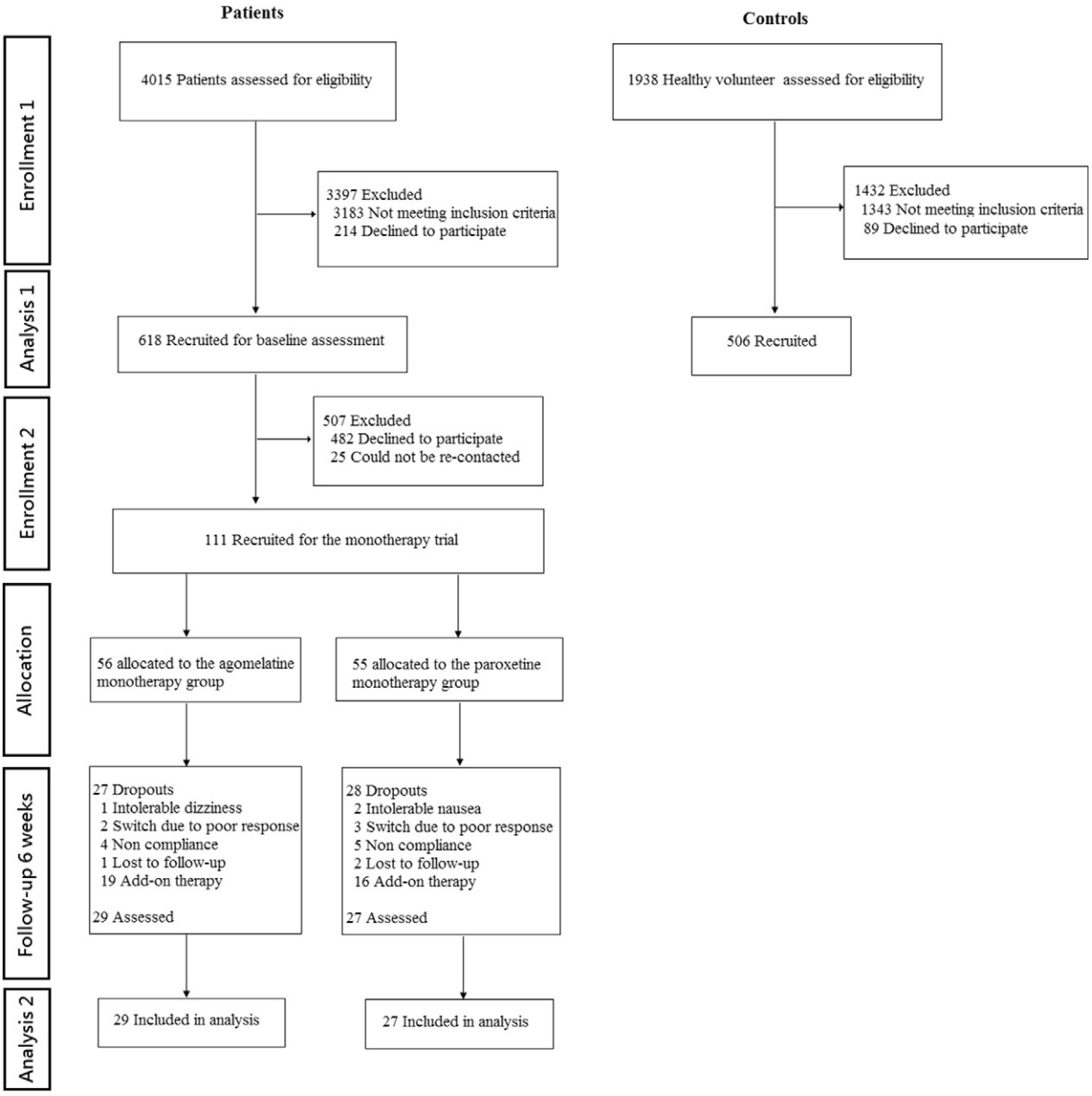

Fig. 1. Flow of participants from screening to completion of the 6-week post-intervention follow-up assessment.

performed using a non-parametric fast Fourier transformation. The direct current component was deleted, and a Hamming window was used to attenuate the leakage effect (Kuo et al., 1999). The power spectrum was subsequently quantified into standard frequency-domain measurements, namely variance (variance of R-R-interval values), very low-frequency power (VLF, 0.003–0.04 Hz), low-frequency power (LF, 0.04–0.15 Hz), high-frequency power (HF, 0.15–0.40 Hz), and the ratio of LF to HF power (LF/HF). All of the measurements were logarithmically transformed to correct for a skewed distribution (Ellis et al., 2008).

Vagal control of HRV is represented by HF, whereas both vagal and sympathetic control of HRV are jointly represented by LF. The LF also reflects baroreflex function during supine rest (Goldstein et al., 2011). The LF/HF ratio could mirror sympatho-vagal balance or sympathetic modulation, with a larger LF/HF ratio indicating a greater predominance of sympathetic activity over cardiac vagal control. The VLF component has been attributed variously to thermoregulatory processes, peripheral vasomotor activity, and the renin–angiotensin system; however, its definite physiological meaning is under debate (Lombardi, 2002).

2.5. Antidepressant treatment

Out of the 618 unmedicated patients with MDD, 111 received open-label treatment with either agomelatine (n = 56) or paroxetine (n = 55) monotherapy (Fig. 1); the drugs were taken once, at night, for a period of 6 weeks in an outpatient setting. Agomelatine was administered in fixed doses (25 mg) and paroxetine as flexible doses (mean ± SD, 20.37 ± 2.97; range, 10–30 mg). Patients who did not remain on monotherapy throughout the treatment period (e.g., switching to another antidepressant or adding benzodiazepines and/or any medications that can potentially affect autonomic functioning) or were lost to follow-up at 6 weeks were not included in the final analysis. We measured BP and HRV in the remaining patients after 6 weeks of monotherapy. Depression and anxiety severities were measured using the HAM-D and HAM-A, respectively, both before and after treatment.

2.6. Statistical analysis

SPSS version 19.0 (SPSS Inc. Chicago, USA) statistical software was used for all analyses. Independent-samples t-tests were conducted to

determine between-group differences in age, gender, BMI, physical activity, and alcohol use. A multivariate analysis of variance (MANOVA) was performed to determine whether there were differences between MDD patients and controls on an interpretable composite of HRV variables across time domain (variance) and frequency domain (VLF, LF, HF, and LF/HF ratio), and to provide a control for multiple comparisons. A significant Pillai's trace effect for group was followed by univariate analyses of variance (ANOVAs) to identify which measures contributed to a significant multivariate effect. A Bonferroni adjustment was used to correct for multiple comparisons. Effect size measures (Cohen's d) for the difference between patients and controls were also determined. Cohen's guidelines (Cohen, 1988, 1992) identify 0.2, 0.5, and 0.8 as small, medium, and large effects, respectively. Eta-squared ($\eta 2$) was reported for ANOVA effects as an indicator of effect size (small = 0.01 medium = 0.06, large = 0.14). Hierarchical regression analysis was used to explore the effect of depression on HRV after adjusting for the control variables. The control variables relating to HRV in univariate analysis ($p < 0.05$) were entered into step 1 of the hierarchical regression analysis, when mean R-R intervals and HRV indices were the dependent variables. Data including R^2, R^2-changes, F, standardization regression coefficient (β), and p value in the regression model were also calculated. In addition, tolerance and variance inflation factors were used to check for multicollinearity. To evaluate the treatment effects of agomelatine versus paroxetine, we performed a two-way repeated measures analysis of variance (ANOVA) with the drug condition as the grouping factor and pre- and post-treatment measures as the repeated measures. Separate ANOVA models were evaluated for each variable. Significant effects were followed up by paired samples t-tests to compare patients separately for each drug condition. Cohen's d effect size statistics were calculated for each pairwise comparison. To handle the dropouts, we used Little's MCAR test to assess whether the data are missing completely at random.

3. Results

3.1. Sample characteristics

3.1.1. Unmedicated patients versus controls

The patients and controls showed no differences in age, gender, BMI, physical activity, or alcohol use (Table 1). As expected, patients differed from controls with respect to measures of depression and anxiety.

3.1.2. Treatment groups

Twenty-seven participants dropped out from the agomelatine group and 28 from the paroxetine group without a final treatment assessment being available. The main reason for the drop-out was adding benzodiazepines to an antidepressant for both groups (Fig. 1). Patients in the study group and drop-out group were statistically comparable with respect to their demographic and major outcome parameters (data not shown but available on request). The Little's MCAR test results (Chi-square = 12.522, DF = 10, Sig. = 0.252) suggested the data of the dropout group are missing completely at random. Thus, we simply excluded these dropouts from the analysis. Fifty-six patients completed the monotherapy trial (n = 29 for agomelatine, n = 27 for paroxetine). Both groups were comparable with regard to their demographic and clinical characteristics at baseline (Table 3). A significant reduction in depression and anxiety measures was noted between the baseline and study endpoint (Table 4). Both measures yielded a significant effect for time, without any evidence of differences between treatments over time.

Table 1
Comparisons of demographic and clinical characteristics between unmedicated patients with major depressive disorder and healthy controls.

Clinical and demographic data	MDD	Healthy controls	Omnibus p-value
Number of participants	618	506	
Female sex (%)	335 (54.20)	275 (54.30)	0.96
Education levels, mean ± SD, years	11.93 ± 3.42	12.03 ± 3.45	0.63
Age, mean ± SD, years	41.37 ± 13.91	42.42 ± 13.72	0.21
BMI, mean ± SD, kg/m^2	23.02 ± 3.87	23.14 ± 3.48	0.62
Weekly regular exercise, hours	1.01 ± 1.86	1.21 ± 2.04	0.09
Alcohol use, drinks/day	0.006 ± 0.022	0.006 ± 0.021	0.77
SBP, mean ± SD, mmHg	118.52 ± 15.13	118.51 ± 13.78	0.99
DBP, mean ± SD, mmHg	74.04 ± 10.47	73.31 ± 7.38	0.19
HAM-D scores, mean ± SD	27.45 ± 9.86	–	
BDI scores, mean ± SD	31.34 ± 12.38	5.67 ± 3.62	<0.001
HAM-A scores, mean ± SD	13.21 ± 5.36	–	
BAI scores, mean ± SD	15.74 ± 5.28	8.10 ± 2.64	<0.001

SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SBP, systolic blood pressure; DBP, diastolic blood pressure; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; HAM-A, Hamilton Anxiety Rating Scale; BAI, Beck Anxiety Inventory.

3.2. Heart rate variability parameters: Unmedicated patients versus controls

The MANOVA comparing the various HRV measures between unmedicated patients and controls showed significant results [$F(6,1117) = 4.49$, $p < 0.001$, $\eta 2 = 0.024$; Fig. 2].

A separate ANOVA was conducted for each dependent variable, with each ANOVA evaluated at an alpha level of 0.0083 (0.05/6). Compared with controls, the unmedicated patients with MDD displayed significant reductions in variance [$F(1,1122) = 8.31$, $p = 0.004$, Cohen's $d = -0.17$],, LF [$F(1,1122) = 10.22$, $p = 0.001$, Cohen's $d = -0.19$], and HF [$F(1,1122) = 20.60$, $p < 0.001$, Cohen's $d = -0.27$] and a significant increase in their LF/HF ratio [$F(1,1122) = 10.98$, $p = 0.001$, Cohen's $d = 0.16$]. However, the groups did not differ on mean R-R intervals [$F(1,1122) = 0.45$, $p = 0.50$, Cohen's $d = -0.04$] or VLF [$F(1,1122) = 3.50$, $p = 0.06$, Cohen's $d = -0.11$].

3.3. Effects of depression severity on resting HRV

For patients with MDD, HAM-D scores correlated with reduced variance, VLF, LF, and HF, independently of covariates (Table 2). Tolerance (range: 0.870–0.998) and variance inflation (range: 1.002–1.149) did not indicate multicollinearity.

3.4. Effect of antidepressant treatment on resting HRV

Table 4 presents the pre- and post-treatment changes in HRV, SBP, and DBP. For the two-way ANOVAs, drug effect refers to agomelatine versus paroxetine and treatment effect for pre- versus post-treatment conditions. Two-way ANOVAs showed no significant differences for mean R-R intervals, variance, VLF, LF/HF ratio, SBP, or DBP; however, there were significant interaction effects for LF and HF (Table 4 and Fig. 3). This was due to the significant increases of LF ($t = -2.41$, $df = 28$, $p = 0.023$, Cohen's $d = 0.33$) and HF ($t = -2.62$, $df = 28$, $p = 0.014$, Cohen's $d = 0.27$) only after agomelatine treatment. Within the paroxetine-treated group, there were no significant changes in mean R-R intervals or any HRV indices.

4. Discussion

To the best of our knowledge, this is the largest case–control study to date using frequency-domain methods to analyze HRV in unmedicated patients with MDD but without comorbidities. This is also the first study to examine the effect of agomelatine monotherapy on the resting HRV of these patients.

A major finding of this study is the reduced HRV in the unmedicated patients diagnosed with MDD without CVD as indicated by a variety of measures, an effect associated with a small effect size. Specifically, compared with controls, patients had lower parasympathetic tone, and thus an overall reduction in total HRV. A high degree of HRV aids healthy

Table 2
Hierarchical regression analyses of mean RR intervals and all heart rate variability indices for unmedicated patients with major depressive disorder.

		Mean RR intervals		variance		VLF		LF		HF		LF/HF ratio	
		Standardized regression coefficient and p-value											
		β	p	β	p	β	p	β	p	β	p	β	p
Univariate analyses	Gender	0.07	0.12	0.17	<0.001	0.14	0.001	0.22	<0.001	0.19	<0.001	−0.01	0.72
	Age	−0.02	0.67	−0.45	<0.001	−0.39	<0.001	−0.46	<0.001	−0.43	<0.001	0.06	0.15
	BMI	−0.04	0.38	−0.17	<0.001	−0.14	0.001	−0.17	<0.001	−0.20	<0.001	0.10	0.01
	Physical activity	0.07	0.10	0.02	0.66	0.02	0.57	0.05	0.26	0.06	0.12	−0.07	0.11
	Alcohol use	−0.08	0.06	−0.06	0.12	−0.07	0.10	−0.04	0.30	−0.07	0.09	0.07	0.07
Step 1	Gender	–	–	0.04	0.29	0.02	0.54	0.09	0.01	0.07	0.06	–	–
	Age	–	–	−0.42	<0.001	−0.37	<0.001	−0.41	<0.001	−0.38	<0.001	–	–
	BMI	–	–	−0.10	0.008	−0.07	0.055	−0.09	0.009	−0.13	<0.001	0.10	0.01
	Physical activity	–	–	–	–	–	–	–	–	–	–	–	–
	Alcohol use	–	–	–	–	–	–	–	–	–	–	–	–
	R^2	0%		21.1%		15.6%		22.3%		20.1%		1.0%	
Step 2	Gender	–	–	0.04	0.34	0.02	0.59	0.09	0.02	0.07	0.07	–	–
	Age	–	–	−0.41	<0.001	−0.36	<0.001	−0.41	<0.001	−0.38	<0.001	–	–
	BMI	–	–	−0.10	0.005	−0.08	0.04	−0.10	0.01	−0.14	<0.001	–	–
	Physical activity	–	–	–	–	–	–	–	–	–	–	0.11	0.01
	Alcohol use	–	–	–	–	–	–	–	–	–	–	–	–
	HAM-D	−0.03	0.41	−0.09	0.009	−0.10	0.01	−0.09	0.015	−0.10	0.004	0.06	0.11
	R^2-changes	0.1%		0.9%		0.9%		0.8%		1.1%		0.4%	
	F	0.69		6.91		6.70		5.97		8.30		2.54	
	p value	p = 0.41		p = 0.009		p = 0.01		p = 0.015		p = 0.004		p = 0.11	

VLF, very low-frequency power [ln(ms2)]; LF, low frequency power [ln(ms2)]; HF, high frequency power [ln(ms2)].

cardiac activity and provides a protective effect against myocardial infarction and heart failure (Bigger et al., 1988), whereas decreased parasympathetic tone (Thayer and Lane, 2007) is associated with an increased risk of CVD and mortality. The present study suggests a possible mechanism behind the greater risk of cardiovascular mortality in patients with MDD.

In the present study, LF power is more likely to represent baroreflex function rather than sympathetic activity. In such a situation, the LF/HF ratio only poorly reflects sympathovagal balance, and is more accurately a measure of the relationship between vagal input and other sources of variability (Malliani, 2005). As we did not use a pure measure of sympathetic activity in this study, we cannot say whether sympathetic tone was increased. Additional studies using cardiac noradrenaline spillover, the pre-ejection period, or muscle sympathetic nerve activity, are needed to adequately assess sympathetic tone in patients with MDD. Nevertheless, our results suggest that at least the parasympathetic branch of the autonomic system is influenced by MDD. Consistent with this is our finding that cardiac vagal impairment in patients with MDD remained dependent on depression severity after excluding confounding factors (Table 2). This finding suggests a possible link between depressive symptom burden and elevated cardiovascular risk and lends further support to the neurovisceral integration model (Thayer and Lane, 2000), which proposes that decreased parasympathetic tone may be the final common pathway linking negative affective states and conditions to ill health. In addition, the inverse correlation between parasympathetic tone and depressive symptom expression is not simply an epiphenomenon, but also provides an alternative putative mechanism of action for vagus nerve stimulation in treating patients with chronic or recurrent MDD (George and Aston-Jones, 2010): presumably through correction of the decreased parasympathetic tone.

Our study provides further evidence supporting the argument that the effect of reduced HRV is inherent to depression (Kemp et al., 2010, 2012) and that depression severity is related to HRV (Kemp et al., 2010). In contrast, some researchers have supported the argument that the association between depression and low HRV is actually driven by the effect of antidepressants (Licht et al., 2008; O'Regan et al., 2014). However, research in this area has been hampered by the enrollment of patients with comorbid anxiety disorders, the use of time-domain measures only, and the lack of a structural clinical interview to exclude possible psychiatric confounds. We believe that our study has a number of strengths that reinforce the reliability of our results.

First, since anxiety (Friedman and Thayer, 1998) and substance use disorders (Chen et al., 2015; Henry et al., 2012) are comorbidities often found in patients with MDD and can profoundly influence HRV measures (Chalmers et al., 2014; Quintana et al., 2013), both patients and controls were evaluated with a structured diagnostic interview to rule out any psychiatric co-morbidities and psychiatric disorders, respectively. Second, all participants underwent relevant laboratory investigations in addition to their physical health self-report. Our recent studies have emphasized this objective procedure for excluding subjects with physical co-morbidities, since subjects might underestimate their biological risk factors (e.g., elevated glucose and atherogenic lipid profile) for cardiac autonomic dysregulation when these factors are self-reported (Chang et al., 2014a,b). Finally, none of the study subjects was a current or past smoker. Smoking clearly depresses HRV (Stein et al., 1996) and is an important factor in any study evaluating the effect of MDD on HRV, because a substantial proportion of patients with MDD smoke (Lasser et al., 2000). Collectively, our sample was well suited for studying HRV, as the effects of potential confounding factors were minimized.

Consistent with an earlier report (Rechlin, 1994), our results clearly showed that paroxetine (mean dose = 20.37 ± 2.97 mg/d) did not produce any significant change in HRV measures in patients with MDD. It is notable that another previous study (Lederbogen et al., 2001) reported

Table 3
Characteristics of patients with major depressive disorder treated with different antidepressants.

Clinical and demographic data	Agomelatine (n = 29)	Paroxetine (n = 27)	Omnibus p-value
Female sex (%)	18 (62.10)	15 (55.60)	0.79
Education levels, mean ± SD, years	13.21 ± 2.97	13.19 ± 3.50	0.98
Age, mean ± SD, years	38.72 ± 3.49	39.11 ± 14.56	0.92
BMI, mean ± SD, kg/m^2	22.34 ± 3.48	23.36 ± 3.39	0.27
Weekly regular exercise, hours	0.74 ± 2.01	0.52 ± 1.87	0.67
Alcohol use, drinks/day	0.02 ± 0.09	0.03 ± 0.10	0.73
Baseline HAM-A scores, mean ± SD	10.34 ± 4.52	8.15 ± 4.24	0.07
Baseline HAM-D scores, mean ± SD	19.28 ± 3.82	19.63 ± 3.24	0.71

SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale.

Table 4
Comparison of heart rate variability (HRV) parameters, blood pressure, and clinical parameters during treatment and drug influence differences.

Variables	Agomelatin (n = 29)		Paroxetine (n = 27)		Statistics		
	Pre	Post	Pre	Post	Treatment	Drug	Treatment * drug
Mean RR intervals	788.83 ± 126.47	802.72 ± 123.54	864.48 ± 258.93	809.37 ± 224.25	$F_{1,54} = 0.41$ $p = 0.52$	$F_{1,54} = 1.08$ $p = 0.30$	$F_{1,54} = 1.15$ $p = 0.29$
Total HRV (variance)	7.27 ± 1.31	7.48 ± 1.20	7.08 ± 0.95	6.88 ± 1.39	$F_{1,54} = 0.003$ $p = 0.95$	$F_{1,54} = 2.05$ $p = 0.16$	$F_{1,54} = 1.44$ $p = 0.24$
VLF	6.35 ± 1.31	6.52 ± 1.03	6.12 ± 0.84	5.99 ± 1.16	$F_{1,54} = 0.02$ $p = 0.90$	$F_{1,54} = 2.43$ $p = 0.12$	$F_{1,54} = 0.80$ $p = 0.38$
LF	5.59 ± 1.57	6.05 ± 1.22[a]	5.43 ± 1.19	5.19 ± 1.55	$F_{1,54} = 0.46$ $p = 0.50$	$F_{1,54} = 2.36$ $p = 0.13$	$F_{1,54} = 4.45$ **$p = 0.04$**
HF	4.90 ± 1.27	5.26 ± 1.36[a]	4.77 ± 1.39	4.51 ± 1.43	$F_{1,54} = 0.13$ $p = 0.72$	$F_{1,54} = 1.69$ $p = 0.20$	$F_{1,54} = 5.40$ **$p = 0.024$**
LF/HF ratio	1.76 ± 0.62	1.79 ± 0.62	1.66 ± 0.56	1.76 ± 0.76	$F_{1,54} = 0.32$ $p = 0.58$	$F_{1,54} = 0.28$ $p = 0.60$	$F_{1,54} = 0.11$ $p = 0.74$
SBP	115.14 ± 17.51	114.41 ± 13.37	110.90 ± 13.97	113.81 ± 10.55	$F_{1,54} = 0.84$ $p = 0.37$	$F_{1,54} = 0.16$ $p = 0.69$	$F_{1,54} = 0.48$ $p = 0.49$
DBP	74.34 ± 12.92	73.52 ± 8.51	72.30 ± 9.81	71.85 ± 8.52	$F_{1,54} = 1.65$ $p = 0.20$	$F_{1,54} = 0.28$ $p = 0.60$	$F_{1,54} = 1.22$ $p = 0.73$
HAM-A	10.34 ± 4.52	5.62 ± 2.04[c]	8.15 ± 4.24	5.52 ± 2.38[c]	$F_{1,54} = 38.09$ $p < 0.001$	$F_{1,54} = 2.60$ $p = 0.11$	$F_{1,54} = 3.09$ $p = 0.08$
HAM-D	19.28 ± 3.82	8.24 ± 3.78[c]	19.63 ± 3.24	10.59 ± 4.92[c]	$F_{1,54} = 204.16$ $p < 0.001$	$F_{1,54} = 2.87$ $p = 0.10$	$F_{1,54} = 2.02$ $p = 0.16$

The significance rendered in bold represents a significant treatment x drug interaction effect ($p < 0.05$). VLF, very low-frequency power [ln(ms2)]; LF, low frequency power [ln(ms2)]; HF, high frequency power [ln(ms2)]; SBP, systolic blood pressure; DBP, diastolic blood pressure; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale. Significance indicates change from predrug condition in a paired *t* test (two-tailed). [a] $p < 0.05$; [b] $p < 0.01$; [c] $p < 0.001$.

that paroxetine at higher doses (up to 40 mg/d) led to a further decline of HRV in patients with MDD and suggested that paroxetine at 40 mg/d may influence HRV in a manner similar to TCAs. These higher-dose effects, however, have failed to be replicated (Davidson et al., 2005). In fact, previous animal (Johnson, 1989; Thomas et al., 1987) and human (Hunter and Wilson, 1995) studies have revealed that compared with TCA, paroxetine has weak affinity for muscarinic receptors. In addition, paroxetine has been shown to have no significant effects on the pupillary light reflex (Bitsios et al., 1999). All these studies support the lack of significant antimuscarinic effects of paroxetine (Owens et al., 1997). On the other hand, it is also possible that the positive effects of serotonin on HRV neutralize the negative effects of paroxetine's anticholinergic properties on HRV because serotonin has a direct central effect on HRV (Shields, 1993) and cardiac vagal control (Jordan, 2005). In summation though, a recent meta-analysis concluded that paroxetine had no significant impact on HRV in patients with MDD (Kemp et al., 2010).

The present study demonstrates that agomelatine has a favorable effect on HRV compared with paroxetine, which is in agreement with a recent review suggesting that agomelatine is superior to SSRIs with respect to cardiovascular safety (Mago et al., 2014). As both antidepressant treatments have a similar effect on depression severity, the difference in effect on HRV are probably attributable to the pharmacodynamic properties of antidepressants rather than on any differing improvement in depression. In fact, the significant increases in parasympathetic tone in our agomelatine group were expected considering the unique mode of action of agomelatine: synergy between

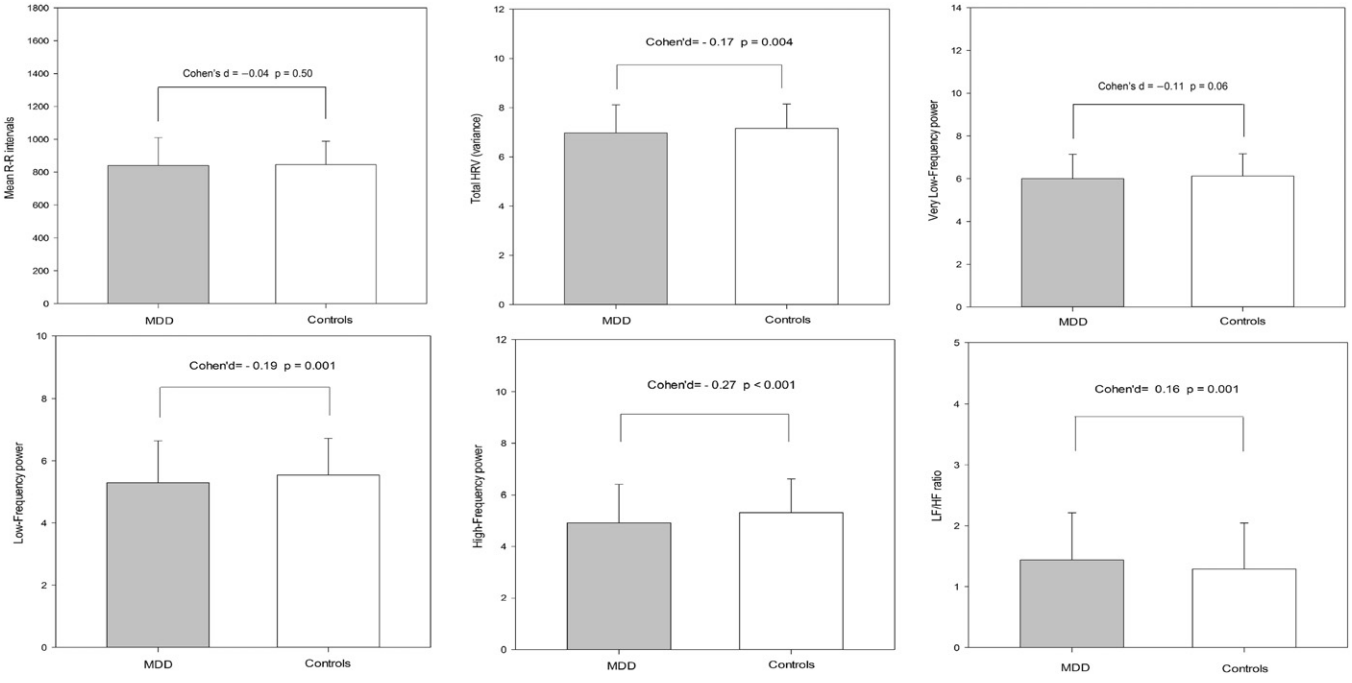

Fig. 2. Mean R-R intervals and all measures of HRV in unmedicated patients with major depressive disorder (MDD) relative to controls. Error bars indicate the standard deviation.

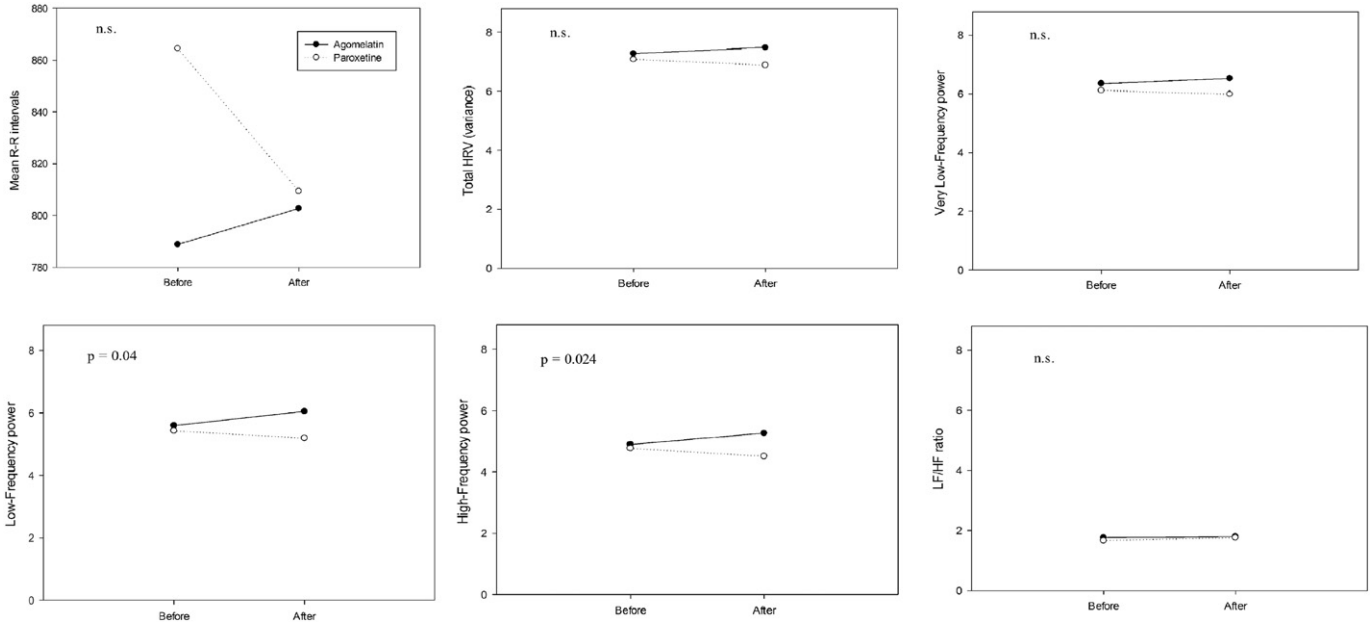

Fig. 3. Modulation of time and frequency domain heart rate variability (HRV) measures before and after different antidepressants. P values refer to interaction effects as measured by repeated measures analysis of variance. Abbreviation: n.s., not significant.

melatonergic and 5-HT_{2c} receptors. As suggested by a recent review, activation of melatonergic receptors modulates the tone of the autonomic nervous system (Pechanova et al., 2014). Specifically, acute administration of melatonin increased cardiac vagal tone (Nishiyama et al., 2001) and attenuated sympathetic tone (Yildiz et al., 2006), while chronic administration was associated with an inhibition of sympathetic activity (Girouard et al., 2003) and improvement of baroreflex functioning (Girouard et al., 2004). On the other hand, activation of serotonergic 5-HT_{2c} receptors in the nucleus tractus solitarius neurons inhibit vagal outflow to the heart (Jordan, 2005) and this inhibitory action can be prevented by a selective 5-HT_{2c} receptor antagonist (Sevoz-Couche et al., 2000). It should, however, be stressed that repeated activation of MT_1/MT_2 receptors by melatonin has been reported to alter the timing of the endogenous circadian rhythms of HRV and thereby phase-advanced HRV indices (Vandewalle et al., 2007). This factor may interfere with the comparison between short-term HRV before and after agomelatine treatment. Thus, the beneficial effects of agomelatine on cardiac autonomic regulation reported herein should be considered preliminary and confirmed in future large-scale studies.

The present study has several significant limitations. First, the selection of patients without psychiatric comorbidity may limit the generalizability of our findings to clinical samples in certain settings, where comorbidity is generally the rule rather than the exception. Second, the present study employed a prospective design to appropriately examine the intra-individual changes in HRV before and after antidepressant treatment. However, because subjects were not randomized into a specific antidepressant group, other clinical factors might have influenced the clinical response to a given antidepressant. Third, the clinical implications of antidepressant-associated changes in autonomic regulation should be interpreted cautiously. These changes might reflect a therapeutic process associated with clinical improvements in both autonomic dysregulation and depressive symptoms (Kemp et al., 2010; Pizzi et al., 2011). Finally, our study exhibits a higher dropout rate compared to other relevant clinical trials (Guaiana et al., 2013). This high attrition rate can limit the interpretation of our results and is mainly due to restricting treatment to monotherapy without allowing benzodiazepines as add-on treatment for anxiety and insomnia. Although evidence indicated patients receiving the combination of an antidepressant and benzodiazepine for MDD were less likely to discontinue treatment than those receiving antidepressant monotherapy (Furukawa et al., 2001), comedication could lead to outcome measure bias because benzodiazepines per se may have significant influence on HRV (Agelink et al., 2002). Strategies to improve satisfaction with treatment could help to reduce attrition in the future studies.

5. Conclusions

Limitations notwithstanding, the results of the current study indicate that unmedicated, physically healthy patients with MDD have reduced HRV. Importantly, each case should be treated on its own merit, and when possible, a 5-minute HRV analysis, which is only a minimal burden on the patient, should be performed before and after antidepressant treatment. Our 6 weeks of observation showed that agomelatine, but not paroxetine, might increase cardiac vagal tone. We propose that agomelatine has a more vagotonic effect, suggesting greater cardiovascular safety than paroxetine. Agomelatine may therefore be a better choice of pharmacological treatment for patients who have MDD and already have decreased cardiac vagal tone, in order to potentially decrease their risk for CVDs.

Statement of interest

The authors have no conflicting interests to declare.

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