Impact of Depression and Antidepressant Treatment on Heart Rate Variability: A Review and Meta-Analysis

Andrew H. Kemp, Daniel S. Quintana, Marcus A. Gray, Kim L. Felmingham, Kerri Brown, and Justine M. Gatt

Background: Depression is associated with an increase in the likelihood of cardiac events; however, studies investigating the relationship between depression and heart rate variability (HRV) have generally focused on patients with cardiovascular disease (CVD). The objective of the current report is to examine with meta-analysis the impact of depression and antidepressant treatment on HRV in depressed patients without CVD.

Methods: Studies comparing 1) HRV in patients with major depressive disorder and healthy control subjects and 2) the HRV of patients with major depressive disorder before and after treatment were considered for meta-analysis.

Results: Meta-analyses were based on 18 articles that met inclusion criteria, comprising a total of 673 depressed participants and 407 healthy comparison participants. Participants with depression had lower HRV (time frequency: Hedges' $g = -.301$, $p < .001$; high frequency: Hedges' $g = -.293$, $p < .001$; nonlinear: Hedges' $g = -1.955$, $p = .05$; Valsalva ratio: Hedges' $g = -.712$, $p < .001$) than healthy control subjects, and depression severity was negatively correlated with HRV ($r = -.354$, $p < .001$). Tricyclic medication decreased HRV, although serotonin reuptake inhibitors, mirtazapine, and nefazodone had no significant impact on HRV despite patient response to treatment.

Conclusions: Depression without CVD is associated with reduced HRV, which decreases with increasing depression severity, most apparent with nonlinear measures of HRV. Critically, a variety of antidepressant treatments do not resolve these decreases despite resolution of symptoms, highlighting that antidepressant medications might not have HRV-mediated cardioprotective effects and the need to identify individuals at risk among patients in remission.

Key Words: Antidepressant, autonomic, depression, heart-rate variability, meta-analysis, review

Depression has a prevalence of between 8% and 12% worldwide (1) and will be the second biggest disease burden by 2020 after cardiovascular disease (CVD) (2). Depression and CVD are themselves related; 20%–40% of CVD patients suffer from depression (3,4), whereas those with depression are at higher risk for myocardial infarction (5), even after controlling for increased body mass index, physical activity, hypertension, and hypercholesterolemia (6–8). The relationship between depression and cardiac mortality is, in part, mediated by reductions in HRV (9–13), and HRV has been identified as providing the best measure for predicting fatal or near-fatal cardiac arrhythmia (14); however, research on HRV and depression has generally been conducted in cardiac patients. Thus, factors concomitant with CVD might be influencing the observed relationship between major depressive disorder (MDD) and HRV. In this report, we examine the impact of depression and antidepressant treatment on HRV with meta-analysis, a quantitative technique that provides a more objective review of the literature, allows for generalizations to be made on a body of literature, and avoids low study power. Importantly, we focus on depressed patients without CVD, to avoid overestimation of the association between depression and HRV.

Heart rate variability indexes beat-to-beat changes in heart rate measured by electrocardiogram (ECG). Variability in heart rate is mediated by the parasympathetic (vagus) nerves, which slow heart rate, and the sympathetic nerves, which accelerate it. Healthy cardiac activity involves a high degree of beat-to-beat variability, which provides a protective effect against myocardial infarction and heart failure (15). High parasympathetic tone helps to maintain heart stability and protect against possible adverse cardiac events (16). Conversely, increased sympathetic tone increases the risk of malignant arrhythmias and sudden cardiac death (17,18). Reductions in HRV, as measured by high-frequency (HF) measures reflecting reductions of parasympathetic activity at respiratory frequencies (19), have been reported in MDD patients in comparison with healthy control subjects (20,21). Consistent with these findings, the LF/HF ratio is higher in MDD patients than in control subjects, suggesting an increase in sympathetic activity and a reciprocal decrease in parasympathetic activity (20) (thus an overall reduction in HRV). Studies on depression have also examined nonlinear measures of HRV (22–24), which provide additional information on time domain and frequency measures that might be important for understanding cardiac health and autonomic function (25,26). Strikingly, one of these studies reported that nonlinear and time-domain HRV measures of the depressed group did not differ from heart-transplant patients, a control group constituting a model of cardiac dysfunction, highlighting considerable autonomic dysfunction in MDD (24). Although a previous meta-analysis recently reported a modest reduction of HRV in depression (27), this study focused only on HF power and the root mean square of successive R-R differences (RMSSD) (a time-domain measure) and collapsed across studies reporting either measure. Although these measures are highly correlated, there is an appreciable contribution of lower frequency (<.15 Hz) in RMSSD estimates, thereby conflating sympathetic and vagal

From the School of Psychology (AHK, DSQ), University of Sydney, Sydney; School of Psychology (KLF), University of New South Wales, New South Wales; Brain Dynamics Centre (KB, JMG), Discipline of Psychological Medicine and Westmead Millennium Institute, University of Sydney and Westmead Hospital, Westmead, Australia; and the Brighton and Sussex Medical School (MAG), University of Sussex, Falmer Campus, Brighton, United Kingdom.

Address reprint requests to Andrew H. Kemp, Ph.D., School of Psychology, Brennan MacCallum Building (A18), The University of Sydney, NSW 2006, Australia. E-mail: andrew.kemp@sydney.edu.au.

Received Nov 4, 2009; accepted Dec 6, 2009.

0006-3223/$36.00
doi:10.1016/j.biopsych.2009.12.012

(parasympathetic) influences on HRV (28). Other studies on depression without CVD have reported no differences in HRV, as measured by HF power, (20,29–31), time domain measures (20,29), respiratory sinus arrhythmia (32,33) and log respiratory sinus arrhythmia (32,34). Moreover, a study of (nonclinically) depressed female students reported increases in time and frequency domain HRV measures (35). Some of the contradictory findings reported in the literature might be due, in part, to heterogeneity in relatively small samples, medication confounds, and reporting of different HRV measures.

Antidepressant treatment also impacts on HRV, although a clear picture has yet to emerge (except for tricyclic antidepressants [TCAs]). Critically, a recent study in a large sample of participants with current and remitted MDD (some of whom were receiving a variety of medications and characterized with heart or coronary disease) concluded that, although depression is associated with significantly lower HRV, this association is driven by the effect of antidepressants including, selective serotonin reuptake inhibitors (SSRIs), TCAs, and other antidepressants, rather than depression per se (36). Tricyclic antidepressants (e.g., amitriptyline, imipramine, and nortriptyline) might reduce parasympathetic tone and therefore HRV (37–39), due to anticholinergic and α_1-adrenergic properties (40,41). Other antidepressants with relatively mild anticholinergic properties such as mirtazapine (a tetracyclic) and paroxetine (an SSRI) might also decrease HRV (37,39). However, other lines of research suggest that antidepressant treatment (particularly non-TCA) might provide HRV-mediated cardiac protective effects (23,42) or at least a benign cardiovascular profile (43) (but see [30]). Other treatments, including cognitive behavioral therapy, repetitive transcranial magnetic stimulation (rTMS), ECT, and HRV biofeedback training, might also increase HRV after the resolution of depressive symptoms (44–47). A recent meta-analysis on the impact of antidepressant treatment concluded that TCAs are associated with a large decrease in HRV but that the data for SSRIs were not clear (48). However, this study collapsed across SSRI medications, including paroxetine, which displays six times more antimuscarinic potency than sertraline, the next most potent SSRI (49).

In this study, we examine the impact of depression and its treatment on HRV with meta-analysis. We focus on studies reporting on depressed patients without CVD to avoid overestimating alterations in HRV, given research findings suggesting that both depression and CVD reduce HRV and that depression and CVD are themselves related. In addition, we specifically excluded studies reporting on patients prescribed more than one treatment concurrently to determine the influence of specific medications on HRV. Our meta-analysis also explicitly examined whether there were any differences between different antidepressant treatments with moderator analysis. Our primary research questions were: 1) is HRV reduced in depressed patients, and does HRV decrease with increasing depression severity; and 2) does HRV increase with successful treatment? We were also interested in determining whether different measures of HRV are more sensitive to the impact of MDD and treatment and examined the impact of ECG recording length and treatment type, because these variables might differentially impact on HRV.

Methods and Materials

Search Criteria

Peer-reviewed studies published between 1990 and July 2009 were located in MEDLINE with all relevant combinations of the following keywords: depress*, heart rate variability, vagal, and autonomic nervous system. The beginning date (i.e., 1990) was chosen because this was when the DSM-III-R criteria for depression (introduced in 1987) were in wide use. In addition to these electronic searches, each report's citation list was examined for additional studies. The inclusion criteria were: 1) the comparison of HRV in an unmedicated MDD group as defined by DSM III-R, DSM-IV, or DSM-IV-TR and an age-matched control group without MDD, a pre- and post-treatment comparison of an MDD group, or an unmedicated MDD group with depression severity and HRV measures reported; 2) satisfactory reporting of statistics (i.e., mean, SD, *p*, *t*, *r* or *F* value, and so forth) either in-text or in tables; 3) participants were free from CVD; and 4) the study was written in English.

Procedure

Meta-analyses were conducted to answer the primary research questions. Rather than create a global HRV measure, a number of different meta-analyses were conducted on a variety of different measures, including time domain, LF, HF, the LF/HF ratio, Valsalva ratio, and nonlinear. All HRV measures were collected when participants were at rest or with 24-hour Holter monitor, except for the Valsalva ratio, an output measure from the Valsalva test, which involves participants maintaining a mercury manometer at a given pressure for a period (usually 15 sec) with their breath. The ECG recording length and treatment type were included as moderator variables.

Meta-Analysis Statistics

Meta-analyses were based on a single effect size of a standardized mean. Values were transformed from means and SDs or *r* values to determine a standardized effect size, Hedges' *g*, with the computer software package Comprehensive Meta-analysis (50). Hedges' *g* effect size is a variation of Cohen's *d* that corrects for biases associated with small sample sizes (51) and might be interpreted in the same way as Cohen's *d*—small (.2), medium (.5), and large (.8) (52). The meta-analyses used the random-effects model, which is a more conservative model that assumes that the true effect size could vary from study to study and so offers more generalizable results in comparison with the fixed effects model (51). To measure homogeneity, the *Q* statistic was used to indicate the homogeneity of effect sizes across studies (53). A significant *Q* statistic indicates dissimilar effect sizes across studies, suggesting that methodological or study population differences might be introducing variance in findings across studies. We also calculated the I^2 statistic, which quantifies the percentage of variation across studies due to heterogeneity rather than chance and is less biased by the number of studies included in a meta-analysis (54). Another advantage of the I^2 statistic is that it can be compared across meta-analyses with different sample sizes and types of studies (54)—the higher the I^2 value, the more between-study heterogeneity, with the values of 25%, 50%, and 75% being seen to represent low, moderate, and high heterogeneity, respectively. As with a significant *Q* statistic, high between-study heterogeneity indicates potential methodological or population sample differences. To determine whether there was any publication bias, Egger's regression test (55) was used in lieu of a funnel plot, due to its objectivity. Egger's regression test reveals evidence of publication bias when $p < .05$.

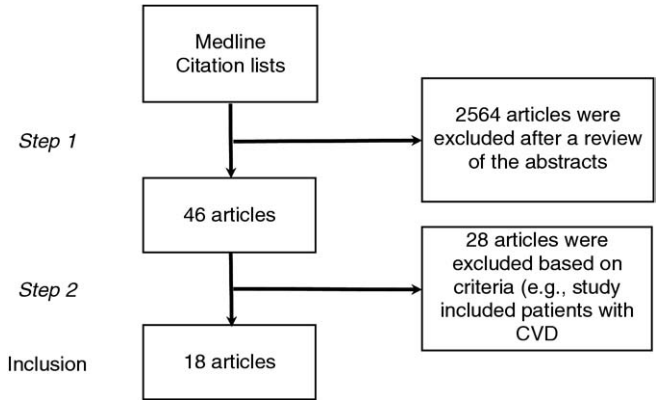

Figure 1. Study inclusion flowchart. CVD, cardiovascular disease.

Results

Included Studies

The electronic search revealed 2564 articles; however, only 46 studies remained after review for inclusion criteria (e.g., studies on CVD patients were removed). Of these remaining studies, 5 had comorbid CVD, 5 were on antidepressant medication, 2 had other potential HRV confounds, 9 had insufficient HRV data, and 7 were subclinical populations; thus, 18 articles remained for meta-analysis (Figure 1, Table 1). Most studies reported on data collected from short-term recordings; however, three studies reported on data collected from long-term recordings.

Impact of Depression on HRV

Depressed patients exhibited reduced time domain (Hedges' $g = -.301$, $p < .001$), HF HRV (Hedges' $g = -.293$, $p < .001$), Valsalva ratio (Hedges' $g = -.712$, $p < .001$), nonlinear HRV (Hedges' $g = -1.955$, $p = .05$), and an increased LF/HF ratio (Hedges' $g = .633$, $p = .005$) but no difference in LF HRV (Table 2). There was also a significant negative correlation between depression severity and HRV (Pearson correlation $= -.364$, $p < .001$) (Table 2). All studies included in meta-analyses contained patients who were either drug naive (e.g., 20,44) or washed-out from previous medication (e.g., 22,29,30,33,38,57) (Table 1). No evidence of publication bias was observed in any of the analyses (Table 2).

Impact of Antidepressant Treatment on HRV

No difference in HRV was observed in the pre- and post-treatment comparison, which collapsed across a variety of treatments, including TCAs (including doxepin, Amitryptiline, and imipramine), SSRIs (including paroxetine, escitalopram, venlafaxine), mirtazapine (a tetracyclic), nefazodone (a serotonin-2A receptor antagonist, and serotonin and noradrenaline reuptake inhibitor), and rTMS (Hedges' $g = .310$, $p = .13$) (Table 3). Because significant heterogeneity was observed between differ-

Table 1. Summary of Studies Included in Meta-Analyses

Study	HRV Measures	Participants with MDD	Healthy Control Subjects	Treatment Type
Depressed vs. Control Subjects				
Agelink *et al.*, 2001 (29)	HF, LF, TD	60	25	
Agelink *et al.*, 2002 (57)	HF, LF, TD	32	64	
Boetteger *et al.*, 2008 (22)	NL	18	18	
Dawood *et al.*, 2007 (30)	HF, LF,	24	15	
Lehofer *et al.*, 1997 (32)	HF	23	23	
Moser *et al.*, 1998 (34)	HF	26	26	
Sayar *et al.*, 2002 (33)	TD	21	21	
Thayer *et al.*, 1998 (35)	HF, LF, TD	15	11	
Udupa *et al.*, 2007 (20)	HF, LF, TD	40	40	
Van der Kooy *et al.*, 2006 (21)	TD	124	136	
Yeragani *et al.*, 2003 (25)	NL	18	28	
Total		401	407	
Depression Severity				
Agelink *et al.*, 2001 (29)	HF	25		
Agelink *et al.*, 2002 (57)	HF,	64		
Watkins *et al.*, 1999 (74)	RSA	56		
Rottenberg *et al.*, 2002 (75)	RSA	55		
Total		200		
Treatment				
Agelink *et al.*, 2001 (29)	TD	25		nefazodone (SNRI)
Davidson *et al.*, 2005 (58)	RSA	48		paroxetine and venlafaxine (SSRIs)
Khaykin *et al.*, 1998 (59)	TD	14		fluoxetine (SSRI) and doxepin (TCA)
Lederbogen *et al.*, 2001 (38)	TD	28		paroxetine (SSRI) and amitriptyline (TCA)
Tulen *et al.*, 1996 (39)	HF	17		Mirtizapine (Nassa) and imipramine (TCA)
Udupa *et al.*, 2007 (44)	HF	54		rTMS and escitalopram (SSRI)
Total		186		

Given our interest in comparison in depressed vs. control subjects, correlations with depression severity, and treatment effects, some studies included in this table have been noted more than once.

HRV, heart rate variability; MDD, major depressive disorder; HF, high frequency; LF, low frequency; TD, time domain (measures include root mean square of successive differences, log root mean square of successive differences, SDs of the averages of N–N intervals in all 5-min segments of the entire recording); NL, nonlinear (measures include relative high frequency of largest Lypomov exponent, minimum embedding dimension of the QT interval; RSA, respiratory sinus arrhythmia; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant; rTMS, repetitive transcranial magnetic stimulation.

Table 2. Meta-Analysis of HRV in Depression

Meta-Analysis Performed	No. of Data Sets	No. of Depressed Participants	No. of Control Subjects	Comparison of Depressed and Control Participants: Effect Size[b] (95% CI)	SE of Summary Effect Size	Effect Size *p*	Heterogeneity I^2	Heterogeneity *p*	Publication Bias *p*
Time Frequency HRV	8	255	395	−.290 (−.497 to −.084)	.105	.006	.24	.238	.46
LF HRV	9	190	312	−.101 (−.403 to −.202)	.154	.515	.57	.017	.2
HF HRV	14	302	424	−.210 (−.396 to −.024)	.095	.027	.28	.155	.06
LF/HF Ratio	5	111	246	.663 (.200 to 1.126)	.236	.005	.7	.01	.12
Valsalva Ratio	4	99	182	−.671 (−.929 to −.414)	.131	<.001	0	.629	.5
Long-Term HRV[a]	3	43	62	−.462 (−.868 to −.056)	.207	.03	0	.982	.68
Depression Severity	4	200	—	−.131 (−.436 to −.179)	—	<.001	.46	.138	.49

CI, confidence interval; other abbreviations as in Table 1.
[a]Both time and frequency domain measures were used for this analysis due to low sample size.
[b]Hedges' *g*.

ent types of treatment ($Q = 34.746$, $p < .001$), we further investigated the potential source of this between-study heterogeneity. Additional analysis revealed there to be a significant difference between TCAs and all other types of treatment ($Q = 6.446$, $p = .01$), whereby HRV was found to be significantly reduced after treatment with TCAs in comparison with other treatments. We also found a significant reduction in HRV after TCA treatment in comparison with HRV before treatment (Hedges' $g = -1.236$, $p = .008$).

No significant difference in HRV was observed before and after SSRI treatment (Hedges' $g = -.087$, $p = .685$). Furthermore, we found no difference between paroxetine (an SSRI with high anti-muscarinic potency) (49) and other SSRIs (i.e., escitalopram and fluoxetine; $Q = 2.899$, $p = .089$). We also found no difference in HRV before and after paroxetine treatment (Hedges' $g = -.196$, $p = .413$). Additional analysis also revealed no significant differences among nefazodone ($Q = .196$ $p = .658$), mirtizapine ($Q = 1.94$, $p = .164$), rTMS ($Q = 2.544$, $p = .111$) and SSRIs. Interestingly, an increase in HRV was observed after rTMS treatment (Hedges' $g = .618$, $p = .03$), although this finding requires replication, because only one study examined the impact of this treatment on HRV (44). No difference between long- and short-term measures of HRV was observed ($Q_1 = 3.33$, $p = .07$). There was no evidence of publication bias for any of these analyses (Table 2).

It is worth noting that one study (59) reported differences in HRV between participants that responded to treatment and those that did not, such that responders to treatment (as opposed to nonresponders) had increased HRV after treatment with either fluoxetine (an SSRI) or doxepin (a TCA). However, this study was based on a small sample size (i.e., 10 patients displayed a therapeutic response to doxepin, $n = 7$, or fluoxetine, $n = 3$). All other studies (except for Agelink *et al.* [29]) reported >50% reduction of depressive symptoms after treatment, highlighting that regardless of successful treatment HRV was not altered at the posttreatment assessment.

Discussion

Systematic meta-analysis revealed that depression is associated with reduced HRV and that individuals with more severe depression are likely to have lower HRV than those with less severe depression. Furthermore, antidepressant treatment did not resolve reductions in HRV, despite reduction in depressive symptoms, suggesting that affective illness might have residual effects on neurophysiological systems, as proposed previously (46,60). The finding that antidepressant treatment does not resolve decreases in HRV calls into question the degree to which antidepressant treatment is able to provide HRV-mediated cardioprotective effects (48,61). That is, although SSRIs might have other cardioprotective effects such as dampening of platelet aggregability (56), our results suggest that SSRI treatment does not increase (or decrease) HRV, thereby conferring no HRV-mediated protective effects against cardiac arrhythmias. Instead, HRV results support the proposal that SSRI medication is associated with benign cardiac effects (43). We also found that tricyclic medication significantly reduces HRV after treatment in comparison with other antidepressant treatments. These findings highlight the importance of assessing HRV in currently and previously

Table 3. Meta-Analysis of HRV in Depression Treatment

Meta-Analysis Performed	No. of Data Sets	No. of Depressed Participants	Comparison of Depressed and Control Participants: Effect Size (95% CI)	SE of Summay Effect Size	Effect Size *p*	Heterogeneity I^2	Heterogeneity *p*	Publication Bias *p*
HRV in Overall Treatment[a]	11	186	.310 (−.712 to .091)	.205	.13	72%	>.001	.07
HRV in SSRI Treatment	5	92	−.087 (−.506 to .332)	.214	.685	51%	.088	.38
HRV in TCA Treatment	3	32	−1.236 (−2.146 to .326)	.464	.008	65%	.06	.28

Abbreviations as in Tables 1 and 2.
[a]Overall treatment includes SSRI ($n = 5$), TCA ($n = 3$) Mirtazapine ($n = 1$), Nefazodone ($n = 1$), and rTMS ($n = 1$).

depressed patients, given the higher risk for cardiac complications in these individuals and the possibility that treatment does not resolve these complications. Findings also reinforce prior reports urging caution in the prescription of TCAs in patients with cardiovascular dysfunction (62). We now discuss our findings in light of theories that highlight the link between the autonomic nervous system and depression and antidepressant action.

Impact of Depression on HRV

Findings supported the hypothesis that depression without CVD is associated with reductions in HRV. Patients were observed to display reduced HF HRV (indicating reduced parasympathetic activity) and reduced time domain HRV in comparison with healthy control subjects, consistent with research highlighting a strong correlation between RMSSD and HF HRV ($r = .85$) (19). However, these findings were associated with relatively small effect sizes (52), consistent with conclusions made in a recent meta-analysis (27). Interestingly, reductions in the predictability and complexity of heart rate (as determined by nonlinear HRV measures) were associated with a particularly large effect size (52), highlighting the utility of such measures. Although a limitation of the nonlinear meta-analysis was the small number of studies used for analysis (i.e., only three studies reporting nonlinear measures were included; $n = 42$), these measures might be more reliable than time domain or frequency domain measures (63). These findings are complemented by a significant negative association between depression severity and HRV such that the more severe the depression, the lower the HRV. Research suggests that somatic symptoms of MDD (i.e., sleeping difficulties, changes in appetite, fatigue) tend to be associated with greater reductions in HRV to a greater extent than cognitive symptoms of depression (i.e., anhedonia, poor concentration, feelings of worthlessness, suicidal ideation) (64). It is possible, therefore, that these somatic symptoms, commonly observed in patients with more severe depression, contributed to the observed significant relationship between severity and HRV.

Heart rate variability reflects a measure of an individual's capacity for parasympathetic inhibition of autonomic arousal in emotional expression and regulation (65). Connections between the vagus and other cranial nerves control peripheral structures involved in behavioral expression of emotion, such as emotion facial expressions, and these connections allow for the coordination of the autonomic nervous system and social behavior (66,67). Depression is associated with somatomotor deficits (e.g., lack of facial expressiveness) and reduced social engagement, which might be mediated by reduced HRV. A network of brain regions (known as the central autonomic network)—including the orbitofrontal and medial prefrontal cortices and central nucleus of the amygdala—that project to the hypothalamic and brainstem autonomic nuclei, where sympathetic and parasympathetic efferents to the heart originate (68), control appetitive (approach) and aversive (withdrawal) behaviors by regulation of visceromotor, neuroendocrine, and behavioral responses. Depression might relate to reductions in vagally mediated cardiovascular control and disinhibition of sympathoexcitatory influences that are mediated by deficits in the central autonomic network, leading to reduced flexibility in responding to environmental demands and appropriate responsiveness (68). Underlying autonomic dysregulation (hypersympathetic/hypovagal state) is one of the putative core mechanisms of depression related to abnormality of the hypothalamo-pituitary-adrenal axis and hyperproduction of cortisol. These abnormalities lead to cardiovascular somatic symptoms of depression such as tachycardia, blood pressure lability, and tendencies toward hypertension, which place severely depressed individuals at higher risk for CVD and higher associated mortality.

Impact of Antidepressant Treatment on HRV

Findings highlight that antidepressant treatment (except for tricyclic medication) has minimal impact on HRV, despite reduction in symptom severity, at least in the short term. Our meta-analyses revealed significant heterogeneity among different treatment studies, and further investigation revealed a significant reduction in HRV in response to treatment with TCAs relative to all other treatments. A reduction in HRV associated with TCA treatment is consistent with known anticholinergic and α_1-adrenergic properties of this class of medication (40,41). Because reductions in HRV are a strong predictor of sudden cardiac death (14), our results lend support to prior studies that indicate TCAs pose a risk to the cardiovascular system. Our results further suggest that, regardless of the mechanism by which different antidepressant treatments might impact on HRV, most treatments (with the exception of TCAs) have a benign effect on HRV. Several neurotransmitters are implicated in the control of heart rate, including serotonin, dopamine, and acetylcholine (69). It was interesting to observe, considering the antimuscarinic (i.e., anticholinergic) potency of paroxetine in comparison with other SSRIs (49), no difference in HRV in patients administered paroxetine compared with other SSRIs. Although the normalization of platelet function after paroxetine treatment (70) might outweigh any potential antimuscarinic effects on the autonomic nervous system, consistent with research suggesting an overall safer cardiovascular profile of paroxetine in comparison with TCAs (71), it is notable that higher doses of paroxetine (e.g., 40 mg) influence HRV in much the same way as TCAs (38).

A recently published study concluded that the association between depression and HRV is driven by the effect of antidepressants rather than depression per se (36). This prior study (36) was particularly impressive, given the large sample size from which conclusions were drawn ($n = 2373$) and the attempt to control for lifestyle factors including smoking, use of alcohol, high body mass index, and low physical activity, comorbid anxiety, and psychoactive medication. Although results from the current study highlight that HRV is clearly reduced in unmedicated patients with MDD relative to control subjects, the results from this prior study further highlight that antidepressants might contribute to reductions in HRV. However, our findings highlight that antidepressant treatment (other than TCAs), in the short-term, neither increases nor decreases HRV. Regardless, SSRI antidepressants might still reduce medical morbidity and mortality due to other factors, such as the dampening of platelet aggregability (56). For instance, 6 weeks of sertraline treatment in MDD patients has been found to normalize platelet function (72).

One potential explanation for the finding that antidepressant medications (except for TCAs) do not impact on HRV is that no studies in the meta-analysis examined nonlinear HRV measures before and after treatment in depressed patients without CVD. Research on CVD patients (with MDD) suggests that 6 weeks of treatment with paroxetine increases nonlinear heart rate complexity (i.e., increases HRV) (37). Furthermore, our finding that nonlinear measures were associated with the strongest effect size for the comparison between depressed patients and control subjects highlights that nonlinear measures might be a useful tool for future research on the impact of antidepressant treatment on HRV. Although recordings of HRV were taken after a period during which it was expected that patients would respond, the

time after treatment was shorter than that for other studies (73). For example, results from the SADHART study (Sertraline Anti-Depressant Heart Attack Randomized Trial) reporting on the impact of 16 weeks of SSRI (sertraline) treatment on HRV in depressed patients with CVD found an increase in HRV as measured by ultra-low frequency power (73). However, these findings were due primarily to decreased HRV in the patient group receiving placebo rather than increased HRV in patients treated with sertraline, in part, supporting our findings in patients without CVD that HRV does not change after administration of antidepressant treatment. Regardless, future studies should confirm the impact of treatment with a longer post-treatment period in patients without CVD with nonlinear measures of HRV in particular.

Concluding Comments and Implications

In summary, this study provides an important clarification on the impact of depression on HRV—the best measure for predicting fatal or near-fatal cardiac arrhythmia—in patients without CVD. Although recently published findings (36) reported that the association between depression and reduced HRV is driven by the effect of antidepressants, our study, in contrast, highlights that HRV is clearly reduced in unmedicated patients with MDD (relative to control subjects) and that antidepressant treatment (other than TCA's) neither increases nor decreases HRV. We conclude that depression without CVD reduces HRV and that a variety of antidepressants do not reverse the observed reductions, emphasizing the need for health care providers to be mindful of the impact depression might have on the cardiovascular system. Because clinical improvement does not guarantee normalization of the hypersympathetic state, it is especially important to identify individuals at risk among a cohort of clinically remitted patients.

Although a potential limitation of this study was a lack of studies reporting on long-term HRV measures in depressed patients without CVD, shorter recordings provide a more controlled and standardized assessment of cardiac function, which might give a purer view of physiological changes (48). This study has a number of advantages, including use of a standardized methodology to determine the impact of depression and its treatment on HRV, employment of a meta-analytic approach (with random-effects analyses) allowing for generalizations to be made on a body of literature that has reported inconsistent findings, examination of a range of HRV measures to determine whether certain measures (e.g., nonlinear HRV measures) provide increased sensitivity of change in HRV, comparison of studies that examined the impact of different antidepressants, application of strict inclusion and exclusion criteria, and assessment for publication bias. Future studies should consider differences in HRV in responders and nonresponders across a range of antidepressant treatments, allowing for the impact of symptom resolution on HRV to be better clarified. Future studies would also benefit from using nonlinear measures, because this metric offers information over and above time domain and frequency domain metrics and seems to be more sensitive to alterations in HRV.

This research was supported by a National Health and Medical Research Council (NHMRC) Project Grant (464863) and a GlaxoSmithKline, Australia, Postgraduate Support Grant (2007-2008). The author AHK is supported by an NHMRC Career Development Award (571101), and KLF is supported by an NHMRC Australian Clinical Research Fellowship (358676). The author JMG is supported by an Australian Research Council (ARC) Postdoctoral Industry Fellowship (LP0883621). Sponsors played no role in analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors AHK and DSQ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Finally, we would like to acknowledge the helpful feedback provided by many anonymous reviewers of earlier drafts of this manuscript.

The authors report no biomedical financial interests or potential conflicts of interest.

1. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl RV, De Graaf R, Vollebergh W, *et al.* (2003): The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) surveys. *Int J Methods Psychiatr Res* 12:3–21.
2. Murray CJ, Lopez AD (1997): Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet* 349:1498–1504.
3. Carney RM, Rich MW, Tevelde A, Saini J, Clark K, Jaffe AS (1987): Major depressive disorder in coronary artery disease. *Am J Cardiol* 60:1273–1275.
4. Gonzalez MB, Snyderman TB, Colket JT, Arias RM, Jiang JW, O'Connor CM, *et al.* (1996): Depression in patients with coronary artery disease. *Depression* 4:57–62.
5. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW (1996): Depression, psychotropic medication, and risk of myocardial infarction. Prospective data from the Baltimore ECA follow-up. *Circulation* 94:3123–3129.
6. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, *et al.* (1996): Depression and long-term mortality risk in patients with coronary artery disease. *Am J Cardiol* 78:613–617.
7. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, *et al.* (2001): Depression and cardiac mortality: Results from a community-based longitudinal study. *Arch Gen Psychiatry* 58:221–227.
8. Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A, *et al.* (1993): Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of US adults. *Epidemiology* 4:285–294.
9. Grippo AJ, Johnson AK (2002): Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev* 26: 941–962.
10. Sheffield D, Krittayaphong R, Cascio WE, Light KC, Golden RN, Finkel JB, *et al.* (1998): Heart rate variability at rest and during mental stress in patients with coronary artery disease: Differences in patients with high and low depression scores. *Int J Behav Med* 5:31–47.
11. Cameron O (1996): Depression increases post-mi mortality: How? *Psychosom Med* 58:111–112.
12. Thayer JF, Lane RD (2007): The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psych* 74:224–242.
13. Carney R, Blumenthal J, Freedland K, Stein P, Howells W, Berkman L, *et al.* (2005): Low heart rate variability and the effect of depression on post-myocardial infarction mortality. *Arch Intern Med* 165:1486–1491.
14. Huikuri H, Raatikainen M, Moerch-Joergensen R, Hartikainen J, Virtanen V, Boland J, *et al.* (2009): Prediction of fatal or near-fatal cardiac arrhythmia events in patients with depressed left ventricular function after an acute myocardial infarction. *Eur Heart J* 30:689.
15. Bigger JT, Kleiger RE, Fleiss JL, Rolnitzky LM, Steinman RC, Miller JP (1988): Components of heart rate variability measured during healing of acute myocardial infarction. *Am J Cardiol* 61:208–215.
16. Hughes JW, Stoney CM (2000): Depressed mood is related to high-frequency heart rate variability during stressors. *Psychosom Med* 62: 796–803.
17. Verrier RL, Lown B (1982): Experimental studies of psychophysiological factors in sudden cardiac death. *Acta Med Scand Suppl* 660:57–68.
18. La Rovere M, Pinna G, Maestri R, Mortara A, Capomolla S, Febo O, *et al.* (2003): Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 107:565.
19. Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, *et al.* (1997): Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology* 34:623–648.
20. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Lavekar GS, Raju TR, *et al.* (2007): Alteration of cardiac autonomic functions in patients with major depression: A study using heart rate variability measures. *J Affect Disord* 100:137–141.

21. van der Kooy KG, van Hout HP, van Marwijk HW, de Haan M, Stehouwer CD, Beekman AT (2006): Differences in heart rate variability between depressed and non-depressed elderly. *Int J Geriatr Psychiatry* 21:147.
22. Boettger S, Hoyer D, Falkenhahn K, Kaatz M, Yeragani VK, Bar K (2008): Nonlinear broad band dynamics are less complex in major depression. *Bipolar Disord* 10:276–284.
23. Yeragani VK, Rao KA, Smitha MR, Pohl RB, Balon R, Srinivasan K (2002): Diminished chaos of heart rate time series in patients with major depression. *Biol Psychiatry* 51:733–744.
24. Nahshoni E, Aravot D, Aizenberg D, Sigler M, Zalsman G, Strasberg B, *et al.* (2004): Heart rate variability in patients with major depression. *Psychosomatics* 45:129–134.
25. Yeragani V, Radhakrishna Rao K (2003): Nonlinear measures of QT interval series: Novel indices of cardiac repolarization lability: MEDqthr and LLEqthr. *Psychiatry Res* 117:177–190.
26. Rajendra AU, Paul JK, Kannathal N, Lim C, Suri J (2006): Heart rate variability: A review. *Med Biol Eng Comput* 44:1031–1051.
27. Rottenberg J (2007): Cardiac vagal control in depression: A critical analysis. *Biol Psychol* 74:200–211.
28. Berntson G, Lozano D, Chen Y (2005): Filter properties of root mean square successive difference (RMSSD) for heart rate. *Psychophysiology* 42:246–252.
29. Agelink MW, Majewski T, Wurthmann C, Postert T, Linka T, Rotterdam S, *et al.* (2001): Autonomic neurocardiac function in patients with major depression and effects of antidepressive treatment with nefazodone. *J Affect Disord* 62:187–198.
30. Dawood T, Lambert EA, Barton DA, Laude D, Elghozi JL, Esler MD, *et al.* (2007): Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk. *Hypertens Res* 30:285–293.
31. Volkers AC, Tulen JH, van den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L (2003): Motor activity and autonomic cardiac functioning in major depressive disorder. *J Affect Disord* 76:23–30.
32. Lehofer M, Moser M, Hoehn-Saric R, McLeod D, Liebmann P, Drnovsek B, *et al.* (1997): Major depression and cardiac autonomic control. *Biol Psychiatry* 42:914–919.
33. Sayar K, Gülec H, Gökçe M, Ak I (2002): Heart rate variability in depressed patients. *Bulletin Clin Psychopharmacol.* 12:130–133.
34. Moser M, Lehofer M, Hoehn-Saric R, McLeod DR, Hildebrandt G, Steinbrenner B, *et al.* (1998): Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J Affect Disord* 48:115–124.
35. Thayer JF, Smith M, Rossy LA, Sollers JJ, Friedman BH (1998): Heart period variability and depressive symptoms: gender differences. *Biol Psychiatry* 44:304–306.
36. Licht CMM, de Geus EJC, Zitman FG, Hoogendijk WJG, van Dyck R, Penninx BWJH (2008): Association between major depressive disorder and heart rate variability in the Netherlands study of depression and anxiety (NESDA). *Arch Gen Psychiatry* 65:1358–1367.
37. Yeragani V, Pesce V, Jayaraman A, Roose S (2002): Major depression with ischemic heart disease effects of paroxetine and nortriptyline on long-term heart rate variability measures. *Biol Psychiatry* 52:418–429.
38. Lederbogen F, Gernoth C, Weber B, Colla M, Kniest A, Heuser I, *et al.* (2001): Antidepressive treatment with amitriptyline and paroxetine: Comparable effects on heart rate variability. *J Clin Psychopharmacol* 21:238–239.
39. Tulen JHM, Bruijn JA, de Man KJ, Pepplinkhuizen L, van den Meiracker AH, 't Man VAJ (1996): Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine (orig 3770). *J Clin Psychopharmacol* 16:135.
40. Richelson E (1982): Pharmacology of antidepressants in use in the United States. *J Clin Psychiatry* 43:4.
41. Jakobsen J, Hauksson P, Vestergaard P (1984): Heart rate variation in patients treated with antidepressants. An index of anticholinergic effects? *Psychopharmacology* 84:544–548.
42. Balogh S, Fitzpatrick D, Hendricks S, Paige S (1993): Increases in heart rate variability with successful treatment in patients with major depressive disorder. *Psychopharmacol Bull* 29:201.
43. Sala M, Lazzaretti M, De Vidovich G, Caverzasi E, Barale F, d'Allio G, *et al.* (2009): Electrophysiological changes of cardiac function during antidepressant treatment. *Ther Adv Cardiovasc Dis* 3:29.
44. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Raju TR, Gangadhar BN (2007): Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. *J Affect Disord* 104:231–236.
45. Karavidas MK, Lehrer PM, Vaschillo E, Vaschillo B, Marin H, Buyske S, *et al.* (2007): Preliminary results of an open label study of heart rate variability biofeedback for the treatment of major depression. *Appl Psychophysiol Biofeedback* 32:19–30.
46. Carney RM, Freedland KE, Stein PK, Skala JA, Hoffman P, Jaffe AS (2000): Change in heart rate and heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosom Med* 62:639–647.
47. Nahshoni E, Aizenberg D, Sigler M, Zalsman G, Strasberg B, Imbar S, Weizman A (2001): Heart rate variability in elderly patients before and after electroconvulsive therapy. *Am J Geriatr Psychiatry* 9:255–260.
48. van Zyl L, Hasegawa T, Nagata K (2008): Effects of antidepressant treatment on heart rate variability in major depression: A quantitative review. *Biospsychosoc Med* 2:12.
49. Richelson E (1996): Synaptic effects of antidepressants. *J Clin Psychopharmacol* 16:1–7.
50. Borenstien M, Hedges LV, Higgins J, Rothstein H (2000): *Comprehensive Meta-Analysis*. Englewood, New Jersey: Biostat.
51. Hedges LV, Olkin I (1985): *Statistical Methods for Meta-Analysis*. Orlando: Academic Press.
52. Cohen J (1988): Set correlation and contingency tables. *Appl Psych Meas* 12:425.
53. Shaddish WR, Haddock CK (1994): Combining estimates of effect size. In: Cooper H, Hedges LV, editors. *The Handbook of Research Synthesis*. New York, NY: Russel Sage Foundation, 261–285.
54. Higgins JP, Thompson SG, Deeks JJ, Altman DG, Higgins JPT, Thompson SG, *et al.* (2003): Measuring inconsistency in meta-analyses. *BMJ* 327: 557–560.
55. Egger M, Smith GD (1998): Bias in location and selection of studies. *BMJ* 316:61–66.
56. Bruce E, Musselman D (2005): Depression, alterations in platelet function, and ischemic heart disease. *Psychosom Med* 67:34–36.
57. Agelink MW, Boz C, Ullrich H, Andrich J (2002): Relationship between major depression and heart rate variability. Clinical consequences and implications for antidepressive treatment. *Psychiatry Res* 113:139–149.
58. Davidson J, Watkins L, Owens M, Krulewicz S, Connor K, Carpenter D, *et al.* (2005): Effects of paroxetine and venlafaxine XR on heart rate variability in depression. *J Clin Psychopharmacol* 25:480–484.
59. Khaykin Y, Dorian P, Baker B, Shapiro C, Sandor P, Mironov D, *et al.* (1998): Autonomic correlates of antidepressant treatment using heart-rate variability analysis. *Can J Psychiatry* 43:183–186.
60. Post RM (1992): Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry* 149:999–1010.
61. Sauer WH, Berlin JA, Kimmel SE (2001): Selective serotonin reuptake inhibitors and myocardial infarction. *Circulation* 104:1894–1898.
62. Rechlin T, Claus D, Weis M (1994): Heart rate analysis in 24 patients treated with 150 mg amitriptyline per day. *Psychopharmacology* 116: 110–114.
63. Maestri R, Pinna G, Porta A, Balocchi R, Sassi R, Signorini M, *et al.* (2007): Assessing nonlinear properties of heart rate variability from short-term recordings: Are these measurements reliable? *Physiol Meas* 28:1067–1077.
64. de Jonge P, Mangano D, Whooley M (2007): Differential association of cognitive and somatic depressive symptoms with heart rate variability in patients with stable coronary heart disease: Findings from the heart and soul study. *Psychosom Med* 69:735–739.
65. Appelhans B, Luecken L (2006): Heart rate variability as an index of regulated emotional responding. *Review Gen Psych* 10:229–240.
66. Porges S (2003): The Polyvagal theory: Phylogenetic contributions to social behavior. *Physiol Behav* 79:503–513.
67. Porges S (2007): The polyvagal perspective. *Biol Psych* 74:116–143.
68. Thayer J, Siegle G (2002): Neurovisceral integration in cardiac and emotional regulation. *IEEE Eng Med Biol Mag* 21:24–29.
69. Shields R Jr (1993): Functional anatomy of the autonomic nervous system. *J Clin Neurophysiol* 10:2.
70. Musselman D, Marzec U, Manatunga A, Penna S, Reemsnyder A, Knight B, *et al.* (2000): Platelet reactivity in depressed patients treated with paroxetine: Preliminary findings. *Arch Gen Psychiatry* 57:875–882.
71. Roose S, Laghrissi-Thode F, Kennedy J, Nelson J, Bigger J, JT, Pollock B, *et al.* (1998): Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. *JAMA* 279:287–291.

72. Markovitz J, Shuster J, Chitwood W, May R, Tolbert L (2000): Platelet activation in depression and effects of sertraline treatment: An open-label study. *Am J Psychiatry* 157:1006–1008.
73. Glassman A, Bigger J, Gaffney M, Van Zyl L (2007): Heart rate variability in acute coronary syndrome patients with major depression: Influence of sertraline and mood improvement. *Arch Gen Psychiatry* 64:1025.
74. Watkins LL, Grossman P, Krishnan R, Blumenthal JA (1999): Anxiety reduces baroreflex cardiac control in older adults with major depression. *Psychosom Med* 61:334–340.
75. Rottenberg J, Wilhelm FH, Gross JJ, Gotlib IH (2002): Respiratory sinus arrhythmia as a predictor of outcome in major depressive disorder. *J Affect Disord* 71:265–272.