Published in final edited form as:

J Affect Disord. 2007 November ; 103(1-3): 173–179.

CARDIAC VAGAL CONTROL IN THE SEVERITY AND COURSE OF DEPRESSION: THE IMPORTANCE OF SYMPTOMATIC HETEROGENEITY

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Abstract

Background—Impaired cardiac vagal control (CVC), as indexed by respiratory sinus arrhythmia, has been investigated as a risk factor for major depressive disorder (MDD), but prior findings are mixed with respect to whether impaired CVC predicts greater global depression severity and/or a more severe course of disorder. One possible explanation for mixed findings is that CVC abnormalities in MDD are related more closely to specific depression symptoms than to the syndrome as a whole.

Methods—Depression severity (both global and symptom-specific indices) and electrocardiogram measures of resting CVC were obtained from 151 diagnosed MDD participants at intake, before randomization to a novel treatment for depression (acupuncture), and again after 8 and 16 weeks.

Results—Resting CVC did not predict global indices of depression in cross-sectional or longitudinal analyses. In symptom-specific analyses, resting CVC was positively related to sad mood and crying and inversely related to middle and late-insomnia. Improvement in late insomnia was related to increases in CVC over time.

Limitations—Relationships between CVC and MDD were studied only within the clinical range of severity. Symptom analyses were exploratory and hence did not correct for Type I error.

Conclusions—Resting CVC did not exhibit concurrent or prospective relations with overall depression severity but a few specific symptoms did. Symptomatic heterogeneity across samples may account for mixed findings within the CVC-depression literature.

Keywords

Cardiac vagal control; depression; risk factors; treatment outcome

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1. Introduction

Cardiac vagal control (CVC) is a physiological marker that has been implicated in emotion regulation (e.g., Porges 1995). Because activity in the vagus nerve is an important source of beat-to-beat changes in heart rate, it is possible to assess CVC indirectly by taking electrocardiogram measures of high-frequency variability in cardiac interbeat intervals (Berntson et al. 1997). These high-frequency oscillations in cardiac interbeat interval are related to the respiratory cycle and are thus commonly referred to as respiratory sinus arrhythmia (RSA). Significant evidence supports the idea that low levels of resting CVC, as indexed by RSA, are associated with impaired self-regulation in child and adult populations (Beauchaine, 2001). Low levels of resting CVC have been investigated in cross-sectional and longitudinal studies as risk factors for several adult psychiatric disorders, including Major Depressive Disorder (MDD).

Low CVC has received attention in several domains of MDD research. It has been investigated as a potential psychophysiological marker of impaired emotion regulation and as a predictor of adverse physical health outcomes (e.g., cardiovascular disease) as highlighted in a recent edited compilation on the topic (Chambers and Allen, 2007). Most recently, the vagal pathway has been seen as a potential target for intervention. For example, direct electrical stimulation of brain regions that control the vagus nerve has been investigated as a potential treatment for severe, intractable depression (Rush et al., 2005). In following sections, research specifically focusing on CVC as a predictor of MDD severity and illness course is reviewed.

1.1. CVC and Concurrent MDD severity

Cross-sectional research on MDD suggests that resting CVC exhibits a modest, but inconsistent, relationship with overall depression severity. Depressed individuals are found to have low CVC relative to nondepressed controls in some (Rechlin et al., 1994), but not other (Moser et al., 1998; Gehi et al., 2005) samples. A recent meta-analysis of this literature found a small to medium cross-sectional effect size for an MDD diagnosis ($d = .3$; Rottenberg, 2007). The instability of findings for MDD may be due to several factors, including the heterogeneity of the MDD diagnosis, and the possibility that low CVC is related more closely to individual symptoms of MDD than to the syndrome as a whole. Consistent with this latter possibility, Rottenberg et al. (2002) found that resting CVC was negatively associated with the report of suicidality, positively associated with the report of sadness, but was not associated with overall depression severity. Interestingly, and also consistent with a symptom-based account of the CVC-depression relationship, a study of a non depressed sample revealed a strong negative association between measures of CVC and disturbed sleep (Bonnet and Arnand, 1998), another common symptom of MDD (American Psychological Association, 1994). Despite these preliminary indications of the merit of symptom-based analyses in the context of MDD and CVC, past studies have almost exclusively focused on global MDD severity measures.

1.2. CVC and Prospective MDD Severity

Longitudinal studies of CVC as an etiological factor in MDD have evaluated the hypothesis that low resting CVC among depressed individuals will predict a more pernicious course of the disorder, as indexed by a failure either to recover from MDD, or failure to demonstrate symptomatic improvement. Support for the hypothesis that low resting CVC predicts a worse course of depression has been mixed, with reports of positive (Balogh et al. 1993; Carney et al., 2000; Chambers and Allen, 2002), null (Khaykin et al., 1998), and paradoxical Schultz et al 1997; Rottenberg et al. 2002) findings.

Notably, studies of CVC and depression have often suffered from methodological limitations such as small sample sizes, samples with varied pharmacotherapy regimens, and the inclusion of psychiatric and medical comorbidity, all of which might obscure the concurrent and prospective relationship between resting CVC and depression. Indeed, medical conditions may confound the measurement of CVC because the comorbid disease itself or its treatment may impact cardiovascular functioning, making the CVC metric invalid. Additionally, prospective studies have rarely examined CVC outside the context of pharmacotherapy, which itself is likely to confound the measurement of resting CVC (Rottenberg, 2007). Two exceptions included: Chambers and Allen (2002), who found that increases in resting CVC among 16 depressed patients undergoing an 8 week trial of acupuncture therapy were associated with decreases in depression severity; Carney et al. (2000), who found CVC increased to levels comparable to controls in a sample of severely depressed patients with stable coronary heart disease treated with cognitive behavioral therapy, but not in the mildly depressed patients.

The present study of CVC and depression remedies the limitations of many previous investigations. Levels of resting CVC and depression were assessed in a large sample of unmedicated, medically stable, physically healthy patients with MDD who were free of psychiatric comorbidity. Resting CVC and depression were both measured at intake before treatment and at multiple time points after randomization. Primary analyses examined the relationship between CVC and global depression severity. Secondary exploratory analyses examined the CVC-depression relationship using select individual symptom severity measures.

2. Method

2.1 Participant Selection

The parent study to this investigation examined the efficacy of acupuncture as a treatment for depression (Allen et al., in press). From among 2965 potential participants who responded to newspaper advertisements, 151 (104 women, 47 men) met initial study entry criteria and were enrolled. Inclusion criteria were: age 18–65; met DSM-IV diagnostic criteria for current Major Depression, assessed by the Structured Clinical Interview for DSM-IV (First et al. 1994); and ≥ 14 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1967). Patients were excluded if any of the following were present: 1) dysthymia or chronic (> 2 years) major depression; 2) seasonal pattern; 3) any current Axis I diagnosis besides Major Depressive Disorder, or any Cluster B Axis II disorder; 4) history of psychosis or mania; 5) substance abuse or dependence within the past 4 months; 6) any current treatment for depression; 7) endocrine abnormalities; 8) history of CNS lesions; 9) any medical disorder or treatment that could cause depression; 10) active suicidal potential necessitating immediate treatment, or suicide attempt within the past year; 11) pregnancy; or 12) any serious medical condition (participants completed a medical exam, thyroid test, drug test, and pregnancy test). After complete description of the study to the participants, written informed consent was obtained. Patients began treatment or waitlist for the first eight-week phase of the study, following which all patients received treatment.

2.2. Missing Data and Attrition

Fifteen of the 151 participants did not have usable physiological data: four had heart murmurs, six enrolled in the parent trial prior to introduction of the ECG recording protocol, two were not recorded due to time limitations, two more were not recorded due to time limitations and then subsequently dropped out of the study, and equipment failed for one individual. Thus, the final sample with valid data at intake includes 136 participants (94 females) between the ages 19 and 62 ($M = 40.9$). The mean ($\pm$ SD) HRSD score for all participants was 22.3 (± 4.6). Ethnicity included 79.8% Caucasian, 10.1% Other/mixed, 8.5% Latino, 1.6% Asian, 0%

African American, and 0% Native American. Participants with useable baseline data did not differ from those with incomplete data in terms of age ($F[1,149]=1.79$, $p=ns$) or initial depression severity based on the 17-item Hamilton Rating Scale for Depression (HRSD), $F[1,149]=.05$, ns . Mean ($\pm$ SD) intake HRSD for those with useable baseline data = 22.25 ($\pm$ 4.66); incomplete data = 22.53 ($\pm$ 4.58). Finally, sample size is further reduced for the prospective analyses examining CVC in later weeks, due to: equipment failure (6), time constraints (1), space constraints (3), and drop outs at various phases during the treatment phase (38). Those with and without data in prospective analyses were comparable in age, $F[1,149]=.663$, ns and in intake HRSD scores, $F[1, 149]=1.96$, ns , (HRSD mean ($\pm$ SD) complete data = 22.14 ($\pm$ 4.13); incomplete data = 22.48 ($\pm$ 5.30).

2.3. Assessment of CVC

Resting electrocardiographic (ECG) recording occurred at each monthly assessment prior to the HRSD interview. Participants sat quietly in a lounge chair for 5 minutes during which ECG was recorded. Electrodes were placed on the right and left arm (Einthoven's Triangle Lead I) just below the elbow with a ground electrode placed below the wrist on the right arm.

Interbeat interval (IBI) series were derived from the ECG series and were hand corrected for artifacts. In this study CVC was indexed by measuring respiratory sinus arrhythmia (RSA), the rhythmic oscillation in heart period accompanying breathing. Heart period variability in the high frequency band (.12-.4 Hz) was extracted using CMET software (Allen, 2002; available at www.psychofizz.org). CMET uses an optimal finite impulse response digital filter, converts the IBI series to a time-series sampled at 10 Hz, filters the series using a 241-point optimal finite impulse response filter with half-amplitude frequencies of .12 and .40 Hz, and then takes the natural log of the variance of the filtered waveform as the estimate of RSA. The measure of RSA derived using CMET has been shown to correlate $> .99$ (Allen, 2002) with the RSA measure derived from Porges' MXEdit program (Delta-Biometrics, Inc, 1988–1993).

2.4. Assessment of Overall Depression Severity and Individual Depression Symptoms

At intake and at 4-week intervals thereafter, patients were interviewed by trained raters masked to treatment condition using 17-item HRSD. An intraclass correlation of .97 was obtained for a sample of 30 interviews comparing the original interviewers' HRSD scores with those of other interviewers (original interviewer excluded). The intake, 8 week, and 16 week HRSD scores are used in primary analyses below. The Beck Depression Inventory (Beck et al., 1961), a self report measure, was administered at the same time points as the HRSD. Both the HRSD and the BDI provide global indices of depression severity. To avoid multiple testing of the same hypothesis only the analysis of the relationship between CVC and global depression severity was based on only one measure of depression severity, the HRSD. (The results were unchanged whether interviewer or self-reported measures of depression severity were used as an outcome.) In contrast, at the specific symptom level the HRSD and the BDI each contains items not included by the other, thus allowing examination of the union of the specific symptoms covered. For example, the HRSD allows differentiation of sleep difficulty by time of night whereas the BDI has only one item to assess sleep difficulty. Therefore, both HRSD and BDI items were considered for inclusion in the analyses of the relationship of CVC to selected symptoms.

To facilitate secondary analyses, several MDD symptoms were selected on the basis of prior literature showing associations with CVC. Symptoms selected included sadness (Rottenberg et al, 2002), suicidality (Rottenberg et al., 2002; Crowell et al., 2005), crying (Rottenberg et al., 2003), and disturbed sleep (Bonnet and Armand, 1998). Sadness and crying were assessed with the Beck Depression Inventory (items 1 and 10, respectively). The Hamilton Rating scale was used to assess suicide (item 3) and insomnia symptoms (early insomnia, middle insomnia,

late insomnia, items 4–6, respectively). Sleep diary data was also used in the symptom specific analyses because diaries, which were collected in the parent study, provide a prospective and quantified measure of sleep. Participants had completed sleep diaries for 7 continuous days after intake and for 7 days after each subsequent assessment. Diaries were completed each morning at waking, with respondents indicating (a) when they retired (b) when they turned lights out (c) when they fell asleep (d) when they had planned to wake up (e) when they actually woke up (f) the degree to which they felt rested (g) estimated sleep quality (h) the number of nighttime awakenings, (i) the total amount of time awake during these awakenings and (j) duration of daytime naps in the prior day. To derive standard insomnia metrics from sleep diaries, early insomnia (c–b), middle insomnia (i), and late insomnia (d–e) were examined for relationships with CVT.

3. Results

3.1. Resting CVC and Global MDD Severity

Primary analyses examined the relationship between resting CVC and global depression severity measured concurrently and prospectively. As displayed in Table 1, intake resting CVC was not associated with interview-rated global depression scores at intake.

On average, patients became less depressed over the sixteen weeks of the study. Mean depression severity decreased from intake to week 8, (Mean HRSD change=7.3, $F[1,115] = 132.2$, $p < .001$), with those receiving acupuncture demonstrating larger decreases in HRSD than those in the waitlist (group by time interaction $F[2, 115] = 8.6$, $p < .001$). The decrease from week 8 to week 16, when all participants received acupuncture, was also significant ($M = 5.6$, $F[1,95] = 33.7$, $p < .001$). Controlling for treatment group, however, did not affect any of the reported correlations for any of the analyses involving post-treatment assessments. As displayed in Table 1, intake resting CVC did not predict interview-rated global depression scores at 8 or at 16 weeks. Moreover, following Chambers and Allen (2002), we computed the correlations between changes in CVC (from 0 to 8 weeks and from 8 to 16 weeks) and the concurrent changes in depression over the same periods of time. These correlations were not significant (displayed in Table 1). In fact, neither these correlations nor the correlations between CVC and global depression severity scores exceeded $r = .13$ for any time point (intake, 8, 16 weeks). To examine change across all weeks and to take advantage of the full data set, without losing cases due to missing data, slopes for change in CVC and slopes for change in depression were derived for individual participants through individual linear regressions, but the correlations between these slopes were also not significant ($r = -0.04$, $p = .71$).

3.2. Resting CVC and Specific MDD Symptoms

Secondary analyses examined the relationship between resting CVC and MDD symptom severity measures that indexed sadness, crying, suicidality, and insomnia (early, middle, and late).

At intake, resting CVC was positively associated with the symptoms of sadness, $r = .17$, $p < .05$, and crying, $r = .17$, $p = .05$, but not the symptom of suicidality, $p > .15$. Interviewer indices of middle and late insomnia were both inversely related to resting CVC (middle: HRSD item 5, $r = .18$, $p < .05$; late: HRSD item 6, $r = .17$, $p < .05$), while early insomnia was not related to resting CVC (HRSD item 4, $r = .04$, $p > .15$). Interestingly, daily diary measures of late insomnia (early morning awakening) were also inversely associated with CVC ($r = -.29$, $p < .01$), whereas diary based measures of early and middle insomnia were unrelated to resting CVC.

Further exploratory analyses of depression course were conducted to examine whether the changes in the symptomatic correlates of CVC were concurrently associated with changes in

CVC over time. To answer this question, slopes for individual participants were derived for each item through individual linear regressions, where each symptom was the dependent variable and RSA at each time (linear) was the independent variable. Four of five analyses found nonsignificant relationships between symptom change and change in CVC: sadness (BDI# 1), crying (BDI# 10), middle insomnia (HRSD# 5), and late insomnia (HRSD# 6), all $r_s < .089$, all $p_s > .15$. However, reductions in late insomnia (sleep diary) were related to increases in CVC, $r = -.22$, $p < .05$.

4. Discussion

The present study examined the relationship between resting CVC and depression in a large unmedicated sample of patients with MDD. The primary goal was to investigate whether resting CVC is a psychophysiological marker of global depression severity. Resting CVC was not associated with concurrent depression severity at intake or at subsequent points, nor was change in CVC prospectively associated with change in the severity of depression. Although null findings are generally difficult to interpret, the large sample size, and the consistency of the null findings across three separate time points increase confidence in the conclusion that in absence of comorbidity or concurrent pharmacotherapy, depression severity is not associated with low levels of resting CVC. These results do not address potential differences in CVC between patients with MDD and nondepressed controls, as the entire sample was depressed, but within the broad range of depression (HRSD range 14–36), it would appear there is no robust relationship between CVC and overall severity. In the context of mixed results on the association between CVC and depression severity (e.g., Chambers and Allen, 2002; Rottenberg et al., 2002), the current report supports an overall conclusion that studies with large unmedicated non-comorbid samples are unlikely to find that resting CVC is a strong autonomic correlate of global indices of depression severity.

A second goal in this study was to follow intriguing preliminary indications that resting CVC levels might be related to a few specific MDD symptoms. Although the analyses were explicitly exploratory in nature, and hence did not correct alpha for multiple comparisons, relationships were observed between resting CVC and symptom measures of sadness, crying, and poor sleep, results that replicated prior findings (Miller and Wood, 1997; Rottenberg et al., 2003; Bonnet and Arnand, 1998). The previous finding of an association with CVC and suicidality (Crowell et al., 2005) did not replicate, however. Because individual symptoms were both negatively (disturbed sleep) and positively (sadness and crying) correlated with resting CVC, these data raise the possibility that inconsistency in the results of prior studies of depression may relate to the clustering of different depression symptom profiles in different patient samples. For example, based on these data, one might predict that MDD samples with significant insomnia would be more likely to exhibit an inverse relationship between CVC and depression severity than would MDD samples characterized by marked sadness and crying behavior.

Because persistent sad mood is a cardinal symptom and a defining emotional feature of MDD, the significant positive association between RSA and reports of acute sadness is particularly intriguing and warrants replication. A positive association between sadness and RSA is consonant with theory that highlights the importance of the vagal pathway in emotion expression and social bonding (Porges, 1995). The association of greater sadness and crying with higher levels of resting CVC in MDD is also consistent with empirical findings both in within-subject experimental research demonstrating that CVC increases with self-reported sad mood state (Miller and Wood, 1997) and with crying behavior more specifically (Rottenberg et al., 2003).

4.1. Future Research Directions

In light of these findings, two future directions are identified for extending understanding of the CVC-depression relation. First, these findings demonstrate the importance of making fine-grained reliable measurement of specific symptoms of depression. Indeed, results for poor sleep suggest that even within “a single symptom”, there may be variation in the relationship to CVC based on the type of poor sleep experienced. The most consistent association between CVC and poor sleep in this sample emerged in relation to late-insomnia. Whereas late insomnia, measured with the HRSD and the sleep diary, was inversely related to CVC, neither measure of early insomnia was related to CVC. Such convergence when using multiple measures of the same symptoms increases confidence in findings. In contrast, the relationship between CVC and the two measures of middle insomnia were inconsistent, rendering those results relatively equivocal. It is possible that the inconsistency stemmed from measurement artifact. A larger error in the diary as compared with an interview measure of middle insomnia might have arisen in this study because without sufficient training in completion of sleep diaries, people often include the time lying in bed awake in the morning before their planned rise time as part of their response to the diary item measuring time awake after sleep onset. This is less likely to occur in response to the clinical HRSD interview, during which interviewer typically make a clear distinction between the middle and the end of the night.

The second direction for future research is to test whether or not the results from this study are specific to the way CVC was measured in this study. Specifically, this study, like most previously published studies, used resting CVC as an autonomic correlate of depression. Although this study found no relationship between resting CVC and globally measured depression, the results might differ when the measurement of CVC is done in the context of environmentally challenging conditions (cf. Coan et al., 2006). Because CVC is a dynamic system, and CVC dynamism is theoretically meaningful (Porges 1995; 1997), it will be important to assess the extent to which short-term fluctuations in CVC (e.g., vagal withdrawal as elicited by laboratory stressors) are indicative of concurrent or future depression. Indeed, there are preliminary indications that fluctuations in CVC may predict the course of depression in patient samples (Rottenberg et al., 2005). Therefore, the use of laboratory challenge paradigms to examine the predictive power of CVC fluctuations in depression is strongly warranted.

Acknowledgments

The authors wish to thank Rosa N. Schnyer, Sabrina Hitt, Sandra Gallagher, Keo Taitano, Maritza Martinez, and Kristin Ertter for their assistance in carrying out this study.

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Table 1
Relationships between RSA and global depression symptom severity at 0, 8, and 16 weeks

	W0 HRSD	W8 HRSD	W16 HRSD	Δ W0-W8 HRSD	Δ W8-W16 HRSD
W0 RSA	-.08	-.05	.09	-.01	.13
W8 RSA	-.03	.01	.05	.03	.06
W16 RSA	-.00	.04	.05	.05	.01
Δ W0-W8 RSA	.06	.09	.03	.06	-.04
Δ W8-W16 RSA	.11	.05	-.01	-.02	-.04

Note: W0=Intake (week 0), prior to randomization; W8=at end of 8 weeks; W16=at end of 16 weeks HRSD=Hamilton Rating Scale for Depression (17-item version); RSA=respiratory sinus arrhythmia, defined as the natural log of the variance in the .12-.40 Hz band of the interbeat interval series.