Psychophysiology, 39 (2002), 861–864. Cambridge University Press. Printed in the USA.

DOI: 10.1017/S0048577202010442

BRIEF REPORT

Vagal tone as an indicator of treatment response in major depression

ANDREA S. CHAMBERS AND JOHN J. B. ALLEN
Department of Psychology, University of Arizona, Tucson, Arizona, USA

Abstract

Increased vagal tone has been associated with treatment success using pharmacological agents and cognitive-behavioral treatment in major depression, but not using electroconvulsive therapy. The present study investigated whether increases in vagal tone would be associated with favorable treatment response with nonpharmacological treatment. At baseline and following treatment, 16 subjects were administered the Hamilton Rating Scale for Depression (HRSD) followed by electrocardiographic recording. Those with little change in vagal tone from before to after treatment showed minimal reduction in HRSD score (−4.8); those with larger vagal tone change showed a large decrease in HRSD score (−14.8). Changes in vagal tone are thus related to favorable treatment response in depression, and do not represent anticholinergic pharmacological effects. Future work manipulating vagal tone might prove informative in teasing apart the causal role of vagal tone and depression.

Descriptors: Major depression, Vagus nerve, Heart rate variability, Respiratory sinus arrhythmia, Polyvagal theory, Treatment response

Respiratory sinus arrhythmia (RSA), an autonomic index of vagal influence on the heart, may be related to depression and treatment response among those with depression. The present study sought to clarify the nature of this relationship, unconfounded by pharmacological effects of antidepressant agents on cardiac function, in a nonpharmacological treatment study of major depression.

Heart Rate Variability in Depression

Although heart rate variability (HRV) results from a dynamic relationship between sympathetic and parasympathetic influences, RSA indexes solely the parasympathetic nervous system controlled by the vagus nerve (Porges, 1995). RSA reflects beat-to-beat changes in heart rate coupled to the respiratory cycle, and indexes the extent to which the vagus nerve mediates parasympathetic influence on the heart through a constant neural firing, or tonus (Porges, 1995).

Several studies suggest that patients with depression show decreased HRV and/or RSA compared with controls (Carney et al., 1995; Rechlin, Weis, & Kaschka, 1995; Rechlin, Weis, Spitzer, & Kaschka, 1994; Roose, Glassman, & Dalack, 1989). Not all studies, however, find this pattern (Moser et al., 1998; Rechlin, 1994). The inconsistency may result, in part, from gender differences, with depressed males having decreased RSA and HRV and depressed females increased RSA and HRV compared to their nondepressed counterparts (Thayer, Smith, Rossy, Sollers, & Friedman, 1998). The extent to which gender differences are responsible for inconsistencies in the literature is unclear, however, as Hughes and Stoney (2000) found no gender differences in HRV between depressed and nondepressed participants, but did uncover a gender difference in cardiac reactivity to stressors.

Group differences in RSA could be indicative of either a trait-like characteristic or could vary as a function of clinical state. If indicative of a trait, RSA may tap risk factors and might prove useful for targeting those for prevention. If RSA proves to be a state-related marker of depressive illness, RSA might provide clues concerning mechanisms of depression. Empirical support that RSA is a state marker includes the finding that tricyclic antidepressants (Imipramine, Amitriptyline, Doxepin) decrease RSA over 1 to 3 weeks (Rechlin, 1994; Rechlin et al., 1994; Yeragani et al., 1992), presumably because of anticholinergic effects (Jacobsen, Hauksson, & Vestergaard, 1984). For example, Rechlin (1994) found that RSA decreased after 2 weeks in 16 patients with depression treated

The authors thank Rosa N. Schnyer and Sabrina K. Hitt for their immense assistance with the treatment study, and Stephen W. Porges for providing the MX Edit software. This work was supported, in part, by Grants from the National Institutes of Health (1R21RR09492, 1R01MH56965 and 1R01AT00001) and by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (NARSAD). Portions of the article were presented at the annual meeting of the Society for Psychophysiological Research, October 1999, Granada, Spain.

Address requests for reprints to: John J.B. Allen or Andrea S. Chambers, Department of Psychology, University of Arizona, PO Box 210068, Tucson, AZ 85721-0068, USA. E-mail: jallen@u.arizona.edu or andreach@u.arizona.edu.

with Amitriptyline or Doxepin, but not over the same period in the 16 patients treated with SSRIs (Fluvoxamine, Paroxetine). When patients are grouped in terms of response versus no response regardless of the type of drug, however, successful treatment is related to increased HRV (Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Khaykin et al., 1998). Further, a recent nonpharmacological treatment study for depression (Carney et al., 2000) found successful treatment with cognitive behavioral therapy increased vagal tone in severely depressed patients with stable coronary heart disease to a level comparable to controls, but did not increase vagal tone in mildly depressed subjects. Complicating the findings, Schultz, Anderson, and van de Borne (1997) discovered that electroconvulsive therapy (ECT) yielded results opposite to those of drug and psychotherapy treatment in a sample of 9 patients. These results may reflect the final severity of the depression. Although all patients improved, Hamilton Depression Rating Scale (HRSD) scores indicated that 5 of the 9 ECT patients still had significant levels of depression (HRSD > 7).

The potential prognostic significance of RSA is further highlighted by findings in patients with coronary heart disease (CHD). Stein et al. (2000) found that CHD patients with low heart rate variability were at a heightened risk of mortality, which increased with increasing severity of depression.

Although HRV and RSA hold promise as markers of depressive illness, extant studies provide mixed findings, and most studies examined patients undergoing pharmacological treatments that could directly impact cardiac function. The present study therefore examined the relationship of RSA and HRV to treatment response using a nonpharmacological and non-ECT treatment (i.e., acupuncture; see Allen et al., 1998) to determine whether increased RSA would be related to treatment response, in a larger sample, unconfounded by drug effects on cardiovascular function.

Methods

Participants

Thirty-eight women aged 18 to 45 with nonchronic major depression (MD) were treated across 8 weeks with acupuncture specifically for depression (for details, see Allen et al., 1998). Participants were diagnosed with MD of less than 2 years' duration according to DSM-IV criteria using the structured clinical interview for the DSM. Exclusion criteria included any other current Axis I or II disorder, history of psychosis or mania, current treatment, endocrine abnormalities, medical disorders or treatment that could cause depression, active suicidal potential, or pregnancy. Due to electrode failure at any one assessment session ($n = 12$ sessions, i.e., 16% of all recorded sessions), study drop-outs ($n = 5$), exclusion of left-handed participants ($n = 3$), exclusion of one participant with a previous head injury, and implementation of the electrocardiographic (EKG) recording after the first participant had completed, 16 women had complete data both before and after treatment. Those with complete data did not differ from those without complete data in terms of age, $F(1,36) = 2.0$, n.s., or initial depressive severity, $F(1,36) = .05$, n.s. Among this final sample, 50% had previously been treated with antidepressant medication, 75% with psychotherapy, and 19% had received no previous treatment.

Procedure

Participants took part in a double-blind randomized controlled trial investigating the efficacy of acupuncture (Allen et al., 1998). Before starting treatment, and again following completion of treatment 8 weeks later, participants were interviewed with a 31-item HRSD modeled after Gelenberg et al. (1990). Reported HRSD scores are based on the standard 24-item version. All patients were interviewed by trained raters blind to treatment condition; an intraclass correlation of .96 was obtained for a sample of 22 interviews comparing the original interviewers' HRSD scores with consensus (original interviewer excluded) HRSD scores. Following the interview, participants sat upright for 8 min while EKG activity was recorded. Ag-AgCl electrodes on the right and left side of the chest provided the EKG that was amplified 5000 times and sampled at 512 Hz.

Interbeat interval (IBI) series for each of eight 60-s recording periods was screened by hand and corrected for artifacts. Log-transformed heart period variance in the high frequency band (0.12–0.4 Hz) was extracted in the time domain using MX Edit software (Delta-Biometrics, Inc., 1988–1993), producing an index of vagal influence of cardiac chronotropy (RSA). Log-transformed total cardiac variance across the entire frequency range was similarly extracted as in index of total HRV. Mean heart rate (HR) was also calculated for each 60-s recording period by transforming each IBI to HR and averaging across all values.

Results

EKG measures were reliable. Internal consistency reliability (Cronbach's alpha) of RSA, treating RSA (i.e., band-limited variance) for each minute as an "item" on an eight-item scale, was .98 before treatment and also .98 following treatment; HRV was .95 before and .97 after treatment; heart rate was .99 before treatment and .99 after treatment. Therefore, in all subsequent analyses, the average value across all eight 60-s recording periods was used.

Increased RSA from before to after treatment was strongly related to a decrease in depression severity, $r = -.61$, $p < .05$ (see Figure 1). RSA at baseline, however, was neither related to baseline depressive severity, $r = .09$, n.s., nor posttreatment severity, $r = .30$, n.s. Change in heart rate from before to after treatment was also related to change in depression severity, $r = .54$, $p < .05$ (see Figure 2), with greater decreases in heart rate among those with larger decreases in depressive severity. HR at baseline, however, was neither related to baseline depressive severity, $r = .25$, n.s., nor posttreatment severity, $r = -.03$, n.s. Change in HR and change in RSA were highly negatively correlated, as expected, $r = -.89$, $p < .001$.

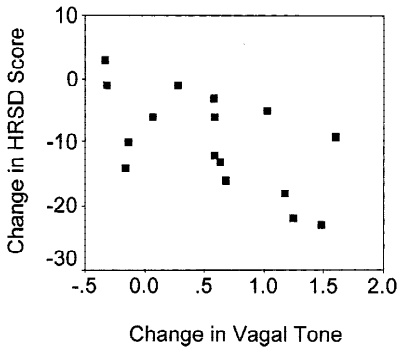

Figure 1. An increase in RSA over 8 weeks was related to a decrease in depression severity as measured by the Hamilton Depression Rating Scale (HRSD), $r = -.0.61$, $p < .05$. For each measure, the change score involved subtracting the pretreatment score from the posttreatment score.

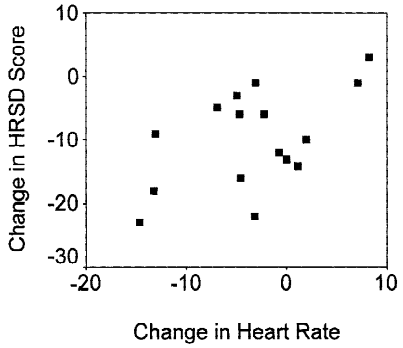

Figure 2. A decrease in heart rate over 8 weeks was related to a decrease in depression severity as measured by the Hamilton Depression Rating Scale (HRSD), $r = .54$, $p < .05$. For each measure, the change score involved subtracting the pretreatment score from the posttreatment score.

A median split on RSA change (median = 0.588) corroborated the correlational finding. Those with little RSA change had a small change in HRSD score (-4.8 ± 5.4; $M \pm SD$) whereas those with larger RSA increases showed a significantly larger drop in HRSD score (-14.8 ± 6.2; $F(1,14) = 11.7$, $p < .01$). These findings were not simply the result of decreased anxiety, as results with HRSD scores comprised only of the depression items (dHRSD) essentially replicated. Those with little RSA change showed a small change in dHRSD score (-4.9 ± 3.4) whereas those with larger RSA increases showed a significantly larger drop in dHRSD score (-12.9 ± 5.8; $F(1,14) = 11.4$, $p < .01$).

Analyses were conducted to assess the extent to which results were specific to vagally mediated cardiac variability. Hierarchical linear regression supported the notion that change in vagally mediated cardiac variability accounted for significant symptom change, even after change in total HRV was accounted for. After entering change in total HRV as a predictor in the first step ($R^2 = .15$, $p = .14$), change in RSA still predicted significant change in depression (semipartial $R^2 = .26$, $p < .05$), with the total model accounting for 41% of the variance in change in depressive severity.

Finally, analyses were conducted to determine the extent to which change in RSA was associated with clinically significant levels of treatment response (cf. Jacobson, Follette, & Revenstorf, 1984). As in Allen et al. (1998), a reduction in HRSD score of greater than 50% was taken as an index of clinically significant response. Treatment responders ($n = 8$) demonstrated significantly greater change in RSA ($.90 \pm .58$) than did nonresponders ($.22 \pm .49$), $F(1,15) = 6.6$, $p < .05$. In terms of the clinical utility of RSA change to discriminate responders from nonresponders (cf. Allen, 2002), a sensitivity of .75 could be obtained with a corresponding specificity of .88, or a slightly higher sensitivity of .88 could be obtained with a specificity of .75. These values correspond to an area under the curve (AUC) from receiver operating characteristic (ROC) curve analysis of .90 (calculated as described by Dorfman & Alf, 1969). The area under the ROC curve provides a simple metric that summarizes the ability of a measure to discriminate groups, with an AUC of 1.0 indicating perfect discrimination, and an AUC of 0.5 indicating no discrimination whatsoever (Mossman & Somoza, 1991). The AUC of 0.90 indicates that change in RSA robustly discriminates treatment responders from nonresponders.

Discussion

Greater treatment response in depression correlated with increased vagally mediated cardiac variability, using a nonpharmacological intervention. The present study adds to the small literature suggesting treatment response in depression is associated with increased cardiac variability (Balogh et al., 1993; Khaykin et al., 1998), and makes two important advances. First, because the present study did not involve pharmacological treatment, changes in cardiac variability are not due solely to peripheral anticholinergic effects of tricyclic antidepressants. Second, the present study identified specifically that parasympathetically mediated cardiac variability is linked to favorable treatment response.

Inconsistencies in the Literature

Studies involving pharmaceutical agents (Balogh et al., 1993; Khaykin et al., 1998) and psychotherapy (Carney et al., 2000) typically find an increase in RSA with successful treatments whereas the two studies of ECT (Roose et al., 1989; Schultz et al., 1997) find decreases in RSA associated with successful treatment. This discrepancy may reflect the intervention employed. Tricyclic agents have potent anticholinergic properties, which decrease the impact of the cholinergically mediated vagal efferents to the heart (Richardson, Mattio, & Giacobini, 1984). Tricyclic agents may therefore produce an across-the-board decrease in RSA, upon which treatment-related changes in RSA are superimposed. The impact of ECT on cholinergic function, by contrast, is an initial increase followed by an increase in sympathetic activity occurring immediately after the treatment (Gaines & Rees, 1992). Because the present study used an alternative treatment with unknown pharmacological impact, it is possible that the present results are specific to acupuncture-treated patients. On the other hand, the consistency of the present findings with those involving pharmacologic treatments suggests instead that increased vagally mediated cardiac variability is related to treatment response more generally.

The discrepancy in the literature additionally may reflect the small sample sizes (from 3 to 18 per comparison group) that pervade this literature. With small samples, patient characteristics will vary considerably from study to study. Moreover, discrepant findings may reflect variable clinical outcomes across studies, such as Schultz et al.'s (1997) findings where the final HRSD score of 5 of the 9 patients were still in the nonremitted range.

Mechanisms

The mechanisms mediating change in depression and change in vagal tone have yet to be identified, although Polyvagal theory provides one explanation. Porges (1995) purports that the more evolved portion of the vagus nerve serves as a control center for coordinating functions of attention, coordination, emotion, and communication, all of which could underlie manifest symptomatology in MD such as difficulties in concentrating, psychomotor agitation, and retardation and depressed mood. Whether changes in vagal tone cause changes in symptoms is unclear, although recent findings that vagus nerve stimulation has antidepressant effects (Rush et al., 2000) are consistent with this possibility. Alternatively, changes in depressive symptoms may drive changes in vagal tone, by allowing for greater parasympathetic modulation of cardiac function in response to environmental demand. Future work aimed at manipulating RSA might prove informative in delineating the role of vagal tone and depression.

REFERENCES

Allen, J. J. B. (2002). The role of psychophysiology in clinical assessment: ERPs in the evaluation of memory. *Psychophysiology*, *39*, 261–280.

Allen, J. J. B., Schnyer, R. N., & Hitt, S. K. (1998). The efficacy of acupuncture in the treatment of major depression in women. *Psychological Science*, *9*, 397–401.

Balogh, S., Fitzpatrick, D. F., Hendricks, S. E., & Paige, S. R. (1993). Increases in heart rate variability with successful treatment in patients with major depressive disorder. *Psychopharmacology Bulletin*, *29*, 201–206.

Carney, R. M, Freedland, K. E., Stein, P. K., Skala, J. A., Hoffman, P., & Jaffe, A. S. (2000). Change in heart rate variability during treatment for depression in patients with coronary heart disease. *Psychosomatic Medicine*, *62*, 639–647.

Carney, R. M., Saunders, R. D., Freedland, K. E., Stein, P., Rich, M. W., & Jaffe, A. S. (1995). Association of depression with reduced heart rate variability in coronary artery disease. *American Journal of Cardiology*, *76*, 562–564.

Dorfman, D. D., & Alf, E., Jr. (1969). Maximum-likelihood estimation of parameters of signal-detection theory and determination of confidence intervals: Rating-method data. *Journal of Mathematical Psychology*, *6*, 487–496.

Gaines, G. Y. & Rees, D. I. (1992). Anesthetic considerations for electroconvulsive therapy. *South Medical Journal*, *85*, 469–482.

Gelenberg, A. J., Wojcik, J. D., Falk, W. E., Baldessarini, R. J., Zeisel, S. H., Schoenfeld, D., & Mok, G. S. (1990). Tyrosine for depression: A double-blind trial. *Journal of Affective Disorders*, *19*, 98–103.

Hughes, J. W., & Stoney, C. M. (2000). Depressed mood is related to high-frequency heart-rate variability during stressors. *Psychosomatic Medicine*, *62*, 769–803.

Jacobson, N. S., Follette, W. C., & Revenstorf, D. (1984). Psychotherapy outcome research: Methods for reporting variability and evaluating clinical significance. *Behavior Therapy*, *15*, 336–352.

Jakobsen, J., Hauksson, P., & Vestergaard, P. (1984). Heart rate variation in patients treated with antidepressants. An index of anti-cholinergic effects? *Psychopharmacology*, *84*, 544–548.

Khaykin, Y., Dorian, P., Baker, B., Shapiro, C., Sandor, P., Mironov, D., Irvine, J., & Newman, O. (1998). Autonomic correlates of antidepressant treatment using heart-rate variability analysis. *Canadian Journal of Psychiatry*, *43*, 183–186.

Moser, M., Lehofer, M., Hoehn-Saric, R., McLeod, D. R., Hildebrandt, G., Steinbrenner, B., Voica, M., Liebmann, P., & Zapotoczky, H. G. (1998). Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *Journal of Affective Disorders*, *48*, 115–124.

Mossman, D., & Somoza, E. (1991). ROC curves, test accuracy, and the description of diagnostic tests. *Journal of Neuropsychiatry & Clinical Neurosciences*, *3*, 330–333.

Porges, S. W. (1995). Orienting in a defensive world: Mammalian modifications of our evolutionary heritage. A polyvagal theory. *Psychophysiology*, *32*, 301–318.

Rechlin, T. (1994). The effect of amitriptyline, doxepin, fluvoxamine, and paroxetine treatment on heart rate variability. *Journal of Clinical Psychopharmacology*, *14*, 392–395.

Rechlin, T., Weis, M., & Kaschka, W. P. (1995). Is diurnal variation of mood associated with parasympathetic activity? *Journal of Affective Disorders*, *34*, 249–255.

Rechlin, T., Weis, M., Spitzer, A., & Kaschka, W. P. (1994). Are affective disorders associated with alterations of heart rate variability? *Journal of Affective Disorders*, *32*, 271–275.

Richardson, J. S., Mattio, T. G., & Giacobini, E. (1984). Amitriptyline and imipramine inhibit the release of acetylcholine from parasympathetic nerve terminals in the rat iris. *Canadian Journal of Physiology & Pharmacology*, *62*, 857–859.

Roose, S. P., Glassman, A. H., & Dalack, G. W. (1989). Depression, heart disease, and tricyclic antidepressants. *Journal of Clinical Psychiatry*, *50* (Suppl.), 12–16.

Rush, A. J., George, M. S., Sackeim, H. A., Marangell, L. B., Husain, M. M., Giller, C., Nahas, Z., Haines, S., Simpson, R. K., Jr., & Goodman, R. (2000). Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study [see comments]. *Biological Psychiatry*, *47*, 276–286.

Schultz, S. K., Anderson, E. A., & van de Borne, P. (1997). Heart rate variability before and after treatment with electroconvulsive therapy. *Journal of Affective Disorders*, *44*, 13–20.

Stein, P. K., Carney, R. M., Freedland, K. E., Skala, J. A., Jaffe, A. S., Kleiger, R. E., & Rottman, J. N. (2000). Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *Journal of Psychosomatic Research*, *48*, 493–500.

Thayer, J. F., Smith, M., Rossy, L. A., Sollers, J. J., & Friedman, B. H. (1998). Heart period variability and depressive symptoms: Gender differences. *Biological Psychiatry*, *44*, 304–306.

Yeragani, V. K., Pohl, R., Balon, R., Ramesh, C., Glitz, D., Weinberg, P., & Merlos, B. (1992). Effect of imipramine treatment on heart rate variability measures. *Neuropsychobiology*, *26*, 27–32.

(Received April 1, 2001; Accepted December 23, 2001)