Published in final edited form as:

Biol Psychol. 2007 April ; 75(1): 32–36.

Sex Differences in Cardiac Vagal Control in a Depressed Sample: Implications for Differential Cardiovascular Mortality

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Abstract

Previous studies suggest depression is a risk factor for all cause mortality, with depressed men at greater risk than depressed women. Diminished cardiac vagal control (CVC) in depressed patients has also been found to increase risk of cardiac mortality. Previous research found that depressed women have higher CVC than depressed men suggesting CVC might be related to the discrepancy in mortality rates between depressed men and women. This finding, however, was in the context of a study with several methodological weaknesses. The current study sought to replicate the sex difference in CVC in a sample of 137 medically healthy and clinically diagnosed depressed patients. Main effects of sex and age significantly predicted CVC such that depressed women had greater CVC and CVC decreased with age in the cross-sectional sample. The results suggest greater CVC in depressed women might confer cardioprotective functions, which may partially explain the sex difference in mortality rates in the depressed population.

Keywords

major depression; sex differences; heart period variability

Sex Differences, Cardiac Vagal Control, and Depression

Sex differences in the relationship between cardiac vagal control (CVC) and depression have been previously reported by one study (Thayer et al., 1998). Depressed males were found to have lower CVC while depressed females had higher CVC. This possible sex difference is important considering the differential impact depression has on the mortality rate between depressed men and women (Cujpers & Smit, 2002). A recent meta-analysis of 25 studies, which included a total of 106,628 subjects, spanning in age from 16 to over 85 years, examined risk of mortality in depressed men and women (Cujpers & Smit, 2002). Initial analyses of relative risk revealed overlapping 95% confidence intervals for men and women, however, in a multivariate regression controlling for methodological differences in the studies included in the analyses, the relative risk of mortality was higher in depressed men than in depressed women, particularly men 40 years or older. Related to this last finding, although depressed men and women have the same risk for cardiovascular problems, depressed men are more likely

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This research was supported, in part, by a grant from the National Institutes of Health (R01 AT00001).

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to die of cardiovascular disease than women (Penninx et al., 1999). The risk for cardiac mortality is increased in those with a diagnosis of current or past major depression or evidence of depressive symptoms even in healthy cohorts who exhibited no clinical evidence of coronary heart disease when depression was initially assessed (Barefoot, et al, 1996; Ferketich et al, 2000; Ford et al, 1998; Hippiusley-Cox et al, 1998; Pratt et al, 1996; Sesso et al, 1998). CVC is one of several proposed mechanisms to explain the increased mortality rate in the depressed population (Carney et al., 2005; Rozanski et al., 1999; Tsuji et al., 1996). CVC reflects the 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 (see Berntson et al., 1997 for a review). Studies suggest greater levels of CVC have cardioprotective functions (Ahern et al., 2001; Katona & Jih, 1975). If depressed women indeed have greater CVC than depressed men, as the Thayer et al study (1998) suggests, the cardioprotective benefits conferred to the women might partially explain their reduced risk of mortality (Thayer et al., 2003).

Thayer et al's study (1998) was suggestive of a sex difference but their sample had a number of methodological limitations. They examined a young age group (mean age 20.37 years old), had small comparison group sizes (5 to 8 participants per group; the power to detect a small effect $<.11$), and did not clinically diagnose depression, relying instead on a split of high and low scores on the Beck Depression Inventory. Although there are numerous reports comparing resting levels of RSA between depressed and non-depressed samples (Austen & Wilson, 2001; Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Carney, Freedland, Stein, Skala, Hoffman, & Jaffe, 2000; Carney, Saunders, Freedland, Stein, Rich, & Jaffe, 1995; Gehi, Mangano, & Pipkin, 1995; Guinjoan, de Guevara, Correa, Schauffele, Nicola-Siri, Fahrer, Ortiz-Fragola, Martinex-Martinez, & Cardinali, 2004; Khaykin, Dorian, Baker, Shapiro, Sandor, et al, 1998; Moser, Lehofer, Hoehn-Saric, McLeod, Hildebrandt, Steinbrenner et al, 1998; Rechlin, Weis, & Kaschka, 1995; Rechlin, Weis, Spitzer, & Kaschka, 1994; Schultz, Anderson, and van de Borne, 1997; Stein, Carney, Freedland, Skala, Jaffe, Kleiger, et al, 2000; Yerandgi, Pohl, Balon, Ramesh, Glitz, et al, 1992), only one other study besides Thayer et al (1998) has actually reported examining sex differences in CVC. These studies typically do not have enough power to compare differences in CVC between sexes in the small samples of depressed and non-depressed participants. The one exception to this is Carney et al (2001) who found no sex differences within their depressed and non-depressed sample, however, the participants had all previously suffered from a myocardial infarction.

The present study thus attempted to replicate the Thayer et al. study using a large medically healthy and clinically depressed sample spanning a wide range in age. Age was also examined, as several studies (e.g. Antelmi et al., 2004) have found CVC to decrease with age in nonclinical samples, with a trend within a depressed sample (Moser et al., 1998).

The current study also sought to test whether other factors might mediate the relationship between sex and CVC. The Penn State Worry Questionnaire (Meyer et al., 1990) was included to assess the magnitude of worrying since CVC is lower in populations of patients with Panic Disorder (Yeragani et al., 1991) and Generalized Anxiety Disorder (Thayer et al., 1996). The Medical Outcome Study 36 (Ware & Sherbourne, 1992) is a commonly used measure in which the participant indicates the extent of impairment of activity in 8 health domains. Because CVC is purported to be an indicator of homeostatic functioning (Porges, 1995), its relationship to general health perceptions was investigated. The Rumination Scale (Nolen-Hoeksema et al., 1993; Nolen-Hoeksema et al., 1994) assesses the degree to which one ruminates or distracts oneself both cognitively and behaviorally. Women have been found to ruminate more often than men, a finding which has been proposed to explain the greater incidence of major depression in women (Nolen-Hoeksema, 2001).

Methods

Participants

One hundred fifty one participants with Major Depressive Disorder were recruited through newspaper advertisements and practitioner referrals, as part of a larger clinical treatment trial (see Allen, Chambers, & Towers, in press). Eligibility was determined by Master- or Ph.D.-level clinicians, based on a total score of at least 14 on the 17-item Hamilton Rating Scale for Depression (Hamilton, 1967; HRSD), and by meeting criteria for Major Depressive Disorder (American Psychiatric Association, 1994) based on Structured Clinical Interview for the DSM-IV (First et al. 1994). Inter-rater reliability for SCID and HRSD measures, calculated on a random sample of interviews for the trained raters from this and other contemporaneous studies, yielded an intraclass correlation of .90 for SCID diagnoses, and .96 for HRSD scores. Potential participants were excluded if any of the following were present: 1) dysthymia or chronic (> 2 years) major depression; 2) any other current Axis I diagnosis; 3) history of psychosis or mania; 4) substance abuse or dependence within the past 4 months; 5) any current treatment for depression, including antidepressant medications, or any medical illness; 6) endocrine abnormalities (e.g. diabetes); 7) history of CNS lesions or any medical disorder (i.e. hypothyroidism, previous stroke, diabetes, epilepsy, HIV, previous myocardial infarction, Parkinson's Disease) or treatment that could cause depression; 8) Major uncontrolled medical conditions (e.g. high blood pressure); 9) Axis II Cluster B personality disorders as assessed by the SCID-II (First et al. 1997); 10) active suicidal potential necessitating immediate treatment; or 11) pregnancy. Participants were not taking concomitant medications that might impact heart rate.

Fourteen of these 151 patients did not have complete or usable physiological data: four were excluded for the presence of heart murmurs because heart murmurs represent a non-vagal influence that impacts the measurement of respiratory sinus arrhythmia, three did not have data recorded due to time limitations, one could not be recorded due to equipment failure, and six enrolled in the treatment trial prior to initiation of the physiological recording protocol. Complete data thus included 137 patients (95 women) aged 20 to 61 (mean = 40.7). Ethnicity included 78.1% Caucasian, 9.5% Latino, 1.5% Asian, and 11% Other/mixed. Participants with complete data did not differ from those without data in terms of age ($F[1,149]=2.23, p=ns$) or initial depression severity based on the HRSD, ($F[1,149]=.00, p=ns$) or Beck Depression Inventory (Beck et al. 1961; $F[1,149]=.11, p=ns$). Participants' mean ($\pm$ s.d.) HRSD score was 22.7 ($\pm$ 4.6.) and mean BDI score was 28.5 ($\pm$ 7.2).

An Analysis of Variance indicated that there were no differences between men and women in terms of depression severity (HRSD: $F[1,135]=1.77, p=ns$; BDI: $F[1,135] = 2.80, p=ns$), number of previous episodes ($F[1,134]=.11, p=ns$), length of current episode ($F[1,135]=.08, p=ns$), age ($F[1,135]=0.34, p=ns$), frequency of exercise ($F[1,134]=.006, p=ns$), or frequency of cigarette smoking ($F[1,134]=0.34, p=ns$).

Experimental Procedures

After providing written informed consent, resting electrocardiographic (ECG) activity was recorded for five minutes before the screening interview using electrodes placed on the left and right forearm in a Lead I Einthoven Triangle configuration. Signals were sampled at 512 HZ.

During a subsequent visit, patients completed the following questionnaires: Penn State Worry Questionnaire (PSWQ), Medical Outcome Study 36 (MOS-36) and the Rumination Scale.

All procedures were approved by the Human Subjects Protection Program at the University of Arizona.

Data Reduction

Interbeat interval (IBI) series were derived from the ECG and were hand corrected for artifacts and ectopic beats by analysts blind to participant sex. Heart period variability in the high frequency band (.12-.4 Hz) was extracted using CMet software (Allen, 2002). CMet converts the IBI series to a time-series sampled at 10 Hz, filters the series using a 241-point optimal finite impulse response filter (from FWTGEN V3.8; Cook & Miller, 1992) 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 Respiratory Sinus Arrhythmia (RSA), a measure of CVC. Values of RSA from CMet correlate almost perfectly ($r=.992$) with those from Porges' MXEdit program and also with natural log spectral power ($r=.986$) and with natural log spectral amplitude ($r=.984$; Allen et al., in press).

RSA is the preferred metric for CVC but in order to compare the results to the findings of Thayer et al. (1998) we also extracted the mean of the absolute value of the difference between consecutive IBIs (MSD) as well as the proportion of absolute differences between consecutive IBIs that are greater than 50 ms (PNN50; Ewing et al., 1981; Von Neumann et al. 1941). MSD and PPN50 are also putative indices of cardiac vagal tone.

Results

Statistical Analyses

MSD, and PNN50 were moderately skewed and were Log_{10} transformed based on the recommendations of Tabachnick and Fidell (2001). A general linear model was constructed with the physiological indices predicted by sex, age, and their interaction.

Sex, Age, and Interaction Effects

Main effects for sex and age were found on several measures. In terms of sex effects (Table 1 and Figure 1), depressed women had significantly higher RSA and MSD, than did depressed men ($F's[1,135]>4.5$, $p's < .04$). Due to the unequal sample sizes of men and women, a t-test with equal variances not assumed was conducted and the sex difference remained significant for RSA ($t[70]=2.11$, $p<.05$) and nearly significant for MSD ($t[75]=2.02$, $p=.052$). In terms of age effects, RSA decreased significantly as a function of age ($F=[1,135] = 1.7$, $p = .03$; $R^2=.07$). There were no significant sex by age interactions for any of the heart rate metrics.

Mediators of Sex Differences

Mediation models were designed to test whether the sex differences in cardiac variability (significant only for RSA and MSD) could be accounted for by sex differences in other relevant variables. Evidence to support a possible mediation (Baron & Kenny, 1986) of the sex difference in cardiac variability requires the following separate regressions: (1) the predictor (sex) predicts the mediator, (2) the predictor (sex) predicts the criterion (cardiac variability), and (3) the mediator predicts the criterion when both predictor (sex) and mediator are entered as predictors of the criterion (cardiac variability). Proposed mediators of the sex difference in cardiac variability included depression severity (as measured by the 17-item Hamilton Rating Scale for Depression), worry, ruminative thoughts and behaviors, and health status.

The first regression of sex predicting the mediator revealed that depression severity, ruminative thoughts, and general health perceptions, did not differ by sex. Although this first regression found sex differences with scores on the PSWQ ($F[1,113]= 7.71$, $p<.01$; $R^2=.06$), and

Ruminative Behaviors ($F[1,130]=4.85, p<.05; R^2=.04$), neither of these potential mediators were significantly related to RSA or MSD (all r 's $< .15$) in the third regression, thus ruling out the possibility that they mediated the observed sex differences in RSA or MSD. Missing data from one or another questionnaire account for differing degrees of freedom for these mediational analyses.

Discussion

The present study confirms a provocative finding from an earlier small scale study of psychometrically defined subjects (Thayer et al, 1998). The current study included unmedicated and carefully diagnosed clinically depressed patients who are medically healthy. The results indicated that CVC was greater in depressed women than in depressed men. Both depression and low CVC are risk factors for cardiovascular disease and mortality (Cujpers & Smit, 2002; Thayer & Lane, in press). In a recent review, Thayer and Lane (in press) provide a synthesis of the involvement of the autonomic nervous system in various disease states and mortality by proposing a model of neurovisceral integration that links the neural control of CVC with the prefrontal cortex and highlights the importance of inhibitory processes on health outcomes, also noting sex differences in vagal function and its neural control (Ahern et al., 2001, Thayer & Lane, in press). In terms of mechanisms, high CVC may protect individuals from future disease or mortality through one or more mechanisms, including reduced catecholamine release from sympathetic nerve endings, a reduction in cardiac work and oxygen demand, and inhibition of the immune system's inflammatory response (Masi et al., in press).

Whether the current results mirror a sex difference in the healthy population or whether the direction of the sex difference switches in a depressed population is unclear. Previous studies examining sex differences in healthy populations report mixed findings (Bonnemeier et al, 2003; Elsenbruch et al, 1999; Evans et al, 2001; Huikuri et al, 1996; Rossy & Thayer, 1998; Ryan et al, 1994; Umetani et al, 1998; Yamasaki et al, 1996) possibly due to small group size, and a failure to control for confounds that might affect CVC (e.g. smoking, drinking, estrogen replacement therapy). In either case the psychological and health variables explored as mediators in this study failed to explain the sex difference in CVC within the depressed sample. Alternatively, Thayer, Rossy, Ruiz-Padial, and Johnsen (2003) suggest that high CVC in depressed women might reflect an attempt by women to overcompensate in their emotion regulatory strategies.

The sex difference was apparent with two of the three measures including the measure which a priori has the greatest validity as a measure of CVC (i.e. RSA). Despite high correlations amongst the measures (r 's = .75–.95), PNN50 did not significantly differ between men and women. One explanation lies in the criticism of PNN50 by Grossman, Karemaker, and Wieling (1991), who contend that PNN50 is not a pure measure of CVC and, instead, also reflects sympathetic activity. An analysis of the gain function of PNN50 in part supports this possibility, in that frequencies below the respiratory band may influence the metric but also frequencies within the respiratory band are attenuated, suggesting PNN50 may also be a less sensitive measure of CVC (Allen et al., in press).

There are a few limitations to this study to consider. This study did not control for respiration rate or tidal volume when deriving the measures of CVC (see for example, Taylor, Conrad, Wilhelm, Neri, DeLorenzo, et al, 2006). On the other hand, recent evidence suggests that most laboratory tasks, including the recording of resting measures of CVC are not likely to be confounded by respiration variables (Denver et al., in press; Houtveen et al., 2002). The 5-minute recordings of heart rate were assessed in a laboratory setting. Future research can explore the extent to which the present findings may generalize across other settings and tasks,

including the possibility of Holter monitoring to assess whether sex differences are seen in everyday situations.

Acknowledgements

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

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Acronyms

CVC

cardiac vagal control

Figure 1. Clinically depressed Females have greater Respiratory Sinus Arrhythmia than males. The bold line in the middle of the box designates the median value.

Table 1
Mean ($\pm$ s.d.) Heart Period Variability Assessed by Various Metrics for Men and Women

	Female	Male	Effect Size (<i>d</i>)
CVC Measure			
RSA *	5.69 ($\pm$ 1.14)	5.19 ($\pm$ 1.28)	.43
Log_{10} (PPN50)	.77 ($\pm$.56)	.64 ($\pm$.54)	.23
Log_{10} (MSD) *	1.31 ($\pm$.26)	1.22 ($\pm$.27)	.33

* Note: indicates $p < .05$. CVC = Vagally Mediated Heart Period Variability; RSA = Respiratory sinus arrhythmia (natural log of the variance in respiratory band of .12–.40 Hz); PPN50 = proportion of absolute differences of consecutive interbeat interval that differ by more than 50 ms; MSD = Mean absolute successive difference in IBI.