Published in final edited form as:

Psychosom Med. 2016 May ; 78(4): 481–491. doi:10.1097/PSY.0000000000000296.

THE EFFECT OF HOSTILITY REDUCTION ON AUTONOMIC CONTROL OF THE HEART AND VASCULATURE: A RANDOMIZED CONTROLLED TRIAL

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Abstract

Objective—Hostility is associated with coronary artery disease (CAD). One candidate mechanism may be autonomic nervous system (ANS) dysregulation. In this study, we report the effect of cognitive behavioral treatment (CBT) on ANS regulation.

Methods—Participants were 158 healthy young adults, high in hostility measured by the Cook-Medley (CM) Hostility and Spielberger Trait Anger (TA) scales. Participants were also interviewed using the Interpersonal Hostility Assessment Technique (IHAT). They were randomized to a 12-week CBT program for reducing hostility or a wait-list control group. The outcome measures were pre-ejection period (PEP), low-frequency blood pressure variability (LF-BPV), and high-frequency heart rate variability (HF-HRV) measured at rest and in response to and recovery from cognitive and orthostatic challenge. Linear mixed models were used to examine group $\times$ session and group $\times$ session $\times$ period interactions while controlling for sex and age. Contrasts of differential group and session effects were used to examine reactivity and recovery from challenge.

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Conflicts of Interest

The other authors report no conflicts of interest.

Results—After Bonferroni correction, 2-way and 3-way interactions failed to achieve significance for PEP, LF-BPV or HF-HRV ($p>0.002$) indicating that hostility reduction treatment failed to influence ANS indices.

Conclusion—Reduction in anger and hostility failed to alter ANS activity at rest or in response to or recovery from challenge. These findings raise questions about whether autonomic dysregulation represents a pathophysiological link between hostility and heart disease.

Keywords

Hostility; autonomic nervous system; cognitive behavior therapy; pre-ejection period; low-frequency blood pressure variability; high-frequency heart rate variability; randomized controlled trial

Introduction

Although mechanisms behind the development of cardiovascular disease are increasingly understood, it remains the number one cause of death around the world (1). Coronary artery disease (CAD) accounts for a substantial fraction of these deaths. A recent international case-control study identified not only the well-known risk factors such as smoking, obesity, diabetes and lack of physical activity, but also psychosocial risk factors such as stress and depression (2, 3). Among these psychosocial risk factors, hostility has long been identified as a trait associated with an elevated risk of CAD.

For example, a recent study by Newman et al. showed that the presence of hostility observed during an interview at baseline was associated with a 2-fold increased risk of incident ischemic heart disease over 10 years of follow-up (4). Everson et al. demonstrated that high levels of cynical hostility in middle-aged men representing the general population were associated with more than twice the risk of all-cause mortality, cardiovascular mortality and myocardial infarction (5). However, this risk was significantly reduced when adjusting for behavioral risk factors such as greater alcohol consumption, smoking and higher BMI, thus suggesting that hostile individuals are more prone to those types of behaviors. A recent prospective study by Wong et al. showed that in patients with stable CAD, mortality risk and the risk of secondary cardiovascular events were 50% and 49% greater respectively, in patients with the highest levels of hostility compared to individuals with the lowest levels. This association was no longer significant after adjustment for behavioral factors (smoking and physical activity) (6).

These studies suggest that the link between hostility and CAD may be accounted for by behavioral risk factors. However, many studies demonstrate a relationship between hostility and CAD independent of these factors. For example, even among nonsmokers, evidence of CAD was significantly associated with hostility (7). Among smokers, no such effect was found. In a longitudinal study, patients with both the metabolic syndrome and high levels of hostility were 2 times more likely to develop myocardial infarction in comparison to patients who only had metabolic syndrome, a relationship that remained significant even after adjustment for sociodemographic and behavioral characteristics (8). Finally, a meta-analysis by Miller et al. concluded that hostility was a risk factor for CAD independent of behavioral

risks (9). Several other meta-analyses have also established a link between hostility and CAD (10–12). Overall, the evidence demonstrates that hostility increases risk of coronary events both in relatively healthy people (12, 13) and patients with prior cardiovascular disease (12, 14).

The role of individual factors in the hostility – CAD link is not limited, however, to smoking and physical activity. Hostility also affects a person's response to stress. For example, Brydon et al. (15) showed that patients with a history of acute coronary syndrome (ACS) who in addition scored high in hostility tests display larger and prolonged increases in blood pressure (BP) and heart rate (HR) as well as elevated levels of catecholamines during acute laboratory stress. These findings indicate that hostile individuals with advanced CAD are particularly susceptible to stress-induced increases in sympathetic activity.

The mechanisms responsible for this hostility-CAD association are far from clear. Candidate mechanisms include increased platelet reactivity (16, 17), inflammation (18, 19), and autonomic dysregulation (20, 21). We previously demonstrated that hostility is inversely related to parasympathetic cardiac control in a study measuring 24-hour heart rate variability (HRV) in young, healthy subjects (20). Decreased parasympathetic control has been shown in high hostile individuals in several studies (22, 23). In addition, anger inhibition has been connected to low vagal tone and slower cardiovascular recovery (24).

Other studies have found a role for the sympathetic nervous system (SNS) in the link between hostility and CAD (21, 25, 26). The possible contribution of the SNS to the hostility-CAD link is consistent with the fact that diseases of the cardiovascular system such as hypertension (27, 28) and heart failure (29, 30) are associated with SNS dysfunction. Sympathetic hyperactivity has also been demonstrated in the time period after myocardial infarction and unstable angina (31, 32). Suarez et al. found that under conditions of harassment, high hostile men had elevated and more prolonged increases in blood pressure, forearm blood flow and vascular resistance, and norepinephrine compared to low hostile men (25). Virtanen et al. reported that hostility was an independent predictor of low frequency blood pressure variability, an index of vascular sympathetic drive (26). Using a model of vestibular stress, Carmona et al. showed that men high in hostility exhibited significantly greater skin conductance responses compared to low hostile men (21).

Thus, the association between hostility and CAD seems relatively solid and one potential pathophysiological mechanism may be autonomic nervous system (ANS) dysregulation. Many studies have demonstrated that cognitive behavior therapy (CBT) can successfully reduce hostility and anger (33–35) and we have previously reported that in a randomized controlled trial of a CBT-based hostility reduction program in high hostile individuals, the intervention reduced hostility and anger (36). However, hostility reduction was not accompanied by an increase in 24-hour cardiac parasympathetic modulation (36). Here, we report on a test of the hypothesis that hostility reduction would favorably alter autonomic nervous system function, both at rest and in response to and recovery from challenge.

METHODS

Study Design

The study was a randomized controlled trial of a CBT treatment for hostility versus a wait-list control, measuring indices of the autonomic nervous system. All subjects provided informed consent. The Institutional Review Board of Columbia University Medical Center approved this study. Data collection began in November 2000 and ended in February 2005. Previously we reported in detail the methods and outcomes from this trial as described above (36). Therefore, below we present a briefer description.

Study participants

The participants were healthy young adults aged 20 to 45 years, high in hostility. They were recruited from the New York City metropolitan area by print and radio advertising. Participants qualified if they scored greater than or equal to one standard deviation above national norms (26) on the 50-point Cook-Medley Hostility scale (37) and on the 30-point trait anger subscale (25) of the Spielberger State-Trait Anger Expression Inventory (STAXI) questionnaire (38). They also completed the Interpersonal Hostility Assessment Technique (IHAT) interview (39). Exclusion criteria consisted of current symptoms of affective disorder, psychosis, substance abuse, current usage of psychoactive medication and any medical condition that affected the ANS or cardiovascular system. A clinician had individual meetings with each eligible participant to assess the appropriateness of CBT for the presenting anger problem. Those who were believed to be in need of immediate treatment, or those for whom the CBT program was regarded as inappropriate, were referred elsewhere for treatment. Participants received free treatment and were paid for testing sessions.

Experimental Protocol Psychophysiology Testing Sessions

Subjects reported to the laboratory early in the morning after having only a light breakfast and abstaining from caffeinated beverages. ECG electrodes were placed on the right shoulder, on the left anterior axillary line at the 10th intercostal space and in the right lower quadrant. Band electrodes for impedance cardiography (ICG) were placed on the upper neck, the root of the neck, on the upper abdomen and at the level of the xiphoid process. A Finapres blood pressure cuff was placed on the middle finger of the non-dominant hand. After instrumentation, the subject rested quietly in the seated position during a 10-min baseline period followed by an instruction period, a 5 min to prepare for a public speech (details below) and a five min period during which the speech was delivered. Participants then were placed in the supine position on a Midland electric tilt table with a computer monitor in their visual field. A numeric keypad for responding was placed in their dominant hand. The subject was allowed to adapt to position during a 6 minute resting period that was followed by a 2 min period of calibration of monitoring devices and a 10 min resting baseline. In fixed order, the 5 min Stroop task and the 5 min mental arithmetic task were then performed, each followed by a 5-min recovery period. After the second recovery period, the tilt table was rotated to the 70° head-up position, and the monitoring devices were recalibrated. Physiological signals were collected for 10 min in the upright position. Except for the speech task, participants were instructed to remain silent throughout the

procedures. The participants were tested prior to randomization and after completion of either treatment or wait list.

Psychological Stressors

Public speaking task—Subjects were instructed to deliver a speech about one out of five controversial topics (e.g., abortion or welfare). They were informed that their performance would be video-recorded for evaluation, and a camera was placed prominently in their view. Five minutes were given for preparation, followed by a 5-min period when they delivered the speech.

Mental arithmetic—Subjects were instructed to as quickly and accurately as possible subtract serially by seven starting with a 4-digit number presented on a monitor. At 1-min intervals, subjects received verbal prompts from the laboratory technician (e.g., “Please subtract faster”). If they made mistakes or lost their place, a new 4-digit starting number was provided.

Stroop color-word task—The computer presented color name words in a color that was either congruent or incongruent with the name. The task was to press a key on the keypad corresponding to the color of the letters, not the color name. The pace was set by the computer so that subjects achieved a 67% correct response rate. Thus, if they performed poorly, the presentation rate slowed and if they performed well, it increased.

Recovery periods—A 5-min recovery period followed each challenge.

CBT Treatment of Hostility

The CBT protocol included 12-weekly sessions of individual therapy and consisted of six categories of methods: 1) psychoeducation; 2) self-monitoring; 3) cognitive therapy; 4) behavioral therapy (including social and communication skills training, and problem-solving training); 5) relaxation and visualization exposure; and 6) in vivo exposure (i.e., contrived exposure to high-risk situations combined with application of cognitive-behavioral skills). Protocol details have been described elsewhere (40).

Measurement of Outcome Variables

Psychological Effects of Treatment—Hostility was measured by self-report (The Cook-Medley and STAXI questionnaires) and by interviews (IHAT) at all data collection sessions. Additionally, patients in the CBT group kept treatment diaries of anger events and completed daily self-ratings of anger levels throughout the 12-week period.

Measurement of Parasympathetic Nervous System Function—Continuous measures of ECG were recorded during the psychophysiology protocol. ECG electrodes were placed on the right shoulder, the left anterior axillary line at the 10th intercostal space, and the right lower quadrant. Analog ECG signals were digitized at 500 Hz by a National Instruments 16 bit A/D conversion board, passed to a microcomputer, and submitted to an R-wave detection routine implemented by custom-written software, resulting in an RR interval

time series. Errors in marking of R-waves were corrected interactively following established procedures (41).

Heart Rate Variability: Mean HR and high (0.15–0.40 Hz (HF)) frequency heart rate variability were computed from 5-min epochs using an interval method for computing Fourier transforms (42). Prior to computing Fourier transforms, the mean of the RR interval series was subtracted from each value in the series, the series was filtered using a Hanning window, and the power (in msec²) over the HF band was summed. Estimates of spectral power were adjusted to account for attenuation produced by the filter (43).

Measurement of Sympathetic Nervous System Function

Pre-Ejection Period: ICG data were collected using the Minnesota 304B system with no gain. The impedance signal (Z0) and the first derivative of pulsatile impedance acquisition (dZ/dt) were digitized at 250 and 500 Hz, respectively, by the NI A/D board and collected by the microcomputer. MindWare software (MindWare Technologies LTD, Gahanna, OH) was used to analyze ECG and ICG signals in 60-second epochs. Pre-ejection period (PEP) was measured as the time interval between the Q wave of the ECG and the B point of the dZ/dt wave. Errors in marking of R waves in the ECG signal and B, Z, and X points in the dZ/dt waveform were corrected by visual inspection.

Low-Frequency Blood Pressure Variability: The beat-to-beat BP waveform was collected using a Finapres noninvasive BP monitor. The analog BP waveform was captured by the NI A/D board and was sampled at 500 samples/s. Systolic and diastolic values for each cardiac cycle were identified using custom-written software resulting in a BP time series. Mean BP and spectral power in the LF (0.04–0.15 Hz) band of the BP power spectrum for both systolic BP and diastolic BP were computed from these time series. Because the servo adjustment of the Finapres monitor was enabled during the last minute of each 300-second period, spectra were calculated on 240-second epochs using the analytic approach described for HRV above.

Computation of Reactivity and Recovery—For each outcome, reactivity to each task was computed as the difference between the mean value during the task and the mean of the preceding baseline. Recovery was computed as the difference between challenge and recovery period. For each 10 min baseline, the two 300-s (for PEP and HF-HRV) or 240 s (for BPV) epochs were averaged to yield a single value. To increase response stability, data from the arithmetic and Stroop tasks were averaged, as were the recovery periods that followed them. The speech task was treated separately because it was delivered in the seated, not the supine, position. To allow for complete equilibration to the upright position, data from the first 5-min epoch after tilt were excluded from analysis. No recovery data were collected after tilt.

Statistical Analysis

Data were analyzed according to intention-to-treat principles, i.e., all subjects randomized to either condition were included in the statistical analysis regardless of whether or not they completed the study. To provide further robust interpretation of ITT results, a supplementary

analysis on all randomized subjects with complete outcome data at both sessions was also performed. Outcomes not following Gaussian distribution were transformed using natural log to satisfy normality assumptions. For comparison of baseline characteristics between CBT and wait list participants, t-tests for continuous measures and Chi-square tests for categorical measures were used. These same analyses were performed for comparisons of dropouts to participants who returned.

To examine the effect of the intervention on PEP, LF-BPV, and HF-HRV outcomes at resting levels (seated and supine baselines) and reactivity to challenge, linear mixed models were fit separately, while adjusting for age and gender. At resting levels, each model examined the prediction of group (CBT versus waitlist), session (baseline and post training), and the effect of CBT by session (group $\times$ session) interaction.

To examine reactivity and recovery to challenge, each model additionally included period within session (baselines, public speaking, arithmetic, and Stroop tasks, tilt, and recovery) as a predictor. Significant 3-way interactions (group $\times$ session $\times$ period) were further examined with contrasts that assess within-group, within-session change between periods, group differences in reactivity within each session, and differential (between groups) change in reactivity across session. A similar modeling procedure was used to assess change in recovery.

To model the correlation among repeated measures, an unstructured covariance matrix was used. This matrix was selected according to the Akaike criterion (44). For all main effects, an alpha level of less than .05 was considered to be statistically significant. Control for multiple comparisons was accomplished by Bonferroni adjustment of alpha levels. All analyses were conducted using mixed modeling software (SAS 9.3 Proc Mixed) to generate restricted maximum likelihood estimates, using all available data.

RESULTS

A total of 158 men ($n=74$) and women ($n=84$) were randomized and tested before training. Demographic, physical and psychological characteristics of the participants are presented in Table 1. At study entry, subjects in the wait-list group and CBT group were well-balanced, except for a trend towards lower diastolic ($t(152) = -1.92, p = .057$) and systolic ($t(152) = -1.71, p = .090$) blood pressure in the wait-list group. The groups did not differ from each other on any other characteristic. Due to data collection failures, technically acceptable data were available for 147, 156, and 157 participants for PEP, LF-BPV, and HF-HRV (including HR) respectively.

The dropout rate for the study was 43% and the rate differed significantly between the groups. In the treatment group, 46 of the 80 participants (58%) were dropouts compared to 22 of the 78 participants (28%) in the wait-list group, $X^2(1, N = 158) = 13.8, p = .002$. The drop-outs did not return for post-CBT testing. On average, dropouts were younger, $t(156) = 1.67, p = .097$ and had higher IHAT-scores, $t(155) = -1.68, p = .094$, though these results were marginally significant. There were no other significant differences between participants

who returned for post-CBT testing and drop outs in terms of demographic, physical and psychological characteristics.

Effect of Treatment on Hostility and Anger

The group $\times$ session interaction for the pooled index (Cook-Medley, Trait Anger and IHAT) was significant ($p < .001$) indicating that reductions in hostility and anger overall were significantly greater in the treatment group compared with the wait-list control. Analyses of the three individual outcomes separately revealed a significant reduction in Trait Anger ($p < .001$), a marginally significant reduction in Cook-Medley hostility ($p = .084$) and no significant reduction in IHAT ($p = .19$). Our previous paper presents these data further (36).

Effect of Treatment on the ANS at Rest

Table 2 presents the results of the resting analyses for HR and HF-HRV. There was no significant group $\times$ session interaction for either HR or HF-HRV during baseline. Thus, there was no effect of the CBT intervention on resting levels of PNS as measured by HF-HRV.

Additionally, table 2 presents the results of the analyses of PEP and LF-BPV at rest. It shows that the predicted group $\times$ session interaction for PEP failed to achieve significance in either the seated or the supine position. Thus, there was no effect of the CBT intervention on resting levels of SNS as measured by PEP. Likewise, there was no significant group $\times$ session interaction for LF-SBPV or LF-DBPV, indicating that there was no effect of treatment on LF-BPV in either physical position. We also tested the effect of the intervention on resting levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP). The results of this analysis also appear in Table 2, which indicates only a marginally significant group $\times$ session interaction for DBP in the seated position, $F(1, 152) = 3.80$, $p = .053$, an effect no longer significant after Bonferroni correction.

Effect of Treatment on ANS Reactivity and Recovery

Table 3 presents the results of the reactivity analysis with the estimated marginal means and standard errors of reactivity to and recovery from the speech and math/stroop tasks. As expected and as depicted in Figure 1, HR increased and HF-HRV decreased in response to both the speech and math/stroop tasks and to tilt, with values returning toward baseline during recovery before and after CBT. However, the group $\times$ session $\times$ period interaction failed to achieve statistical significance for either measure, indicating that CBT treatment failed to alter the PNS response to or recovery from challenge.

Similarly, for the SNS indices, while there was the expected significant effect of period ($F(6, 144) = 181.7$, $p < .0001$), with PEP shortening in response to psychological challenge and lengthening during recovery (as seen in Figure 2), the absence of a significant group $\times$ session $\times$ period effect indicates that exposure to hostility reducing treatment did not alter the response to or recovery from challenge differently from a waitlist control group. For BP and LF-BPV, as expected, there also was a significant effect of period (SBP: $F(6, 153) = 79.6$, $p < .0001$; DBP: $F(6, 153) = 139.9$, $p < .0001$; LF-SBPV: $F(6, 153) = 127.9$, $p < .0001$; LF-DBPV: $F(6, 153) = 125.8$, $p < .0001$). A significant group $\times$ session $\times$ period interaction was

found in SBP ($F(6, 153) = 3.30, p = .004$), however, after Bonferroni adjustment this result no longer achieved statistical significance, indicating that like PEP, neither the BP or LF-BPV response to nor recovery from challenge was altered by treatment (see Figure 2).

Supplementary analysis

A secondary analysis replacing treatment group with change in hostility scores was also performed to examine whether reductions in hostility and anger irrespective of treatment group assignment would alter autonomic activity. A total of 21 models were examined testing the hostility change $\times$ session $\times$ period interaction, with only one surviving Bonferroni adjustment (change in Cook Medley Score predicting DBP, $F(6, 79) = 4.85, p = .0003$). However contrasts of differential change in reactivity and recovery across sessions were not significant (pre-CBT – post-CBT difference: reactivity to speech, $0.240, t(79) = 0.17, p = .16$; reactivity to math/stroop, $0.028, t(79) = 0.4, p = .69$; recovery from speech, $0.091, t(79) = 0.85, p = .40$; recovery from math/stroop, $0.037, t(79) = 0.56, p = .58$), suggesting no relationship between hostility reduction and reactivity or recovery to challenge in any of the autonomic nervous system indices.

Supplementary analyses restricted to those subjects who completed both pre- and post-CBT sessions showed similar results to the ITT analysis. At resting periods, DBP in the seated position was significantly predicted by group $\times$ session, $F(1, 84) = 5.39, p = .023$, and for reactivity, the three-way interaction predicting SBP was significant, $F(6, 84) = 2.32, p = .04$. Change in hostility did not predict outcomes, although the original result of Cook Medley predicting DBP became marginally significant, $F(6, 76) = 2.08, p = .066$. However, none of these results remained significant after Bonferroni adjustment.

DISCUSSION

It is well established that psychological factors such as hostility, anger and depression are linked to the development of heart disease (11, 12). Evidence also suggests that these factors are associated with ANS dysregulation, and that ANS dysregulation is associated with CAD (30, 45). Therefore, it is plausible that the ANS could be a mechanistic link between these psychological traits and CAD (46) and it is equally plausible that intervening to reduce hostility would reduce ANS dysregulation.

To our knowledge, no definitive intervention trials have been conducted but one closely related study has appeared. The impact of hostility reduction combined with treatment of other elements of the Type A Behavior Pattern (TABP) on recurrent coronary events in post-myocardial infarction patients has been assessed. Friedman et al. (47) reported significant reductions in outcomes in patients in whom the TABP was reduced. However, this finding was based on a secondary analysis of the data rather than the strictest intention to treat analysis. Also, the intervention targeted elements of the TABP beyond hostility. Nonetheless, it remains suggestive, especially because it assessed true clinical endpoints.

Here, we report the results of a hostility-reducing CBT intervention on healthy but high hostile participants using surrogate endpoints of cardiac and vascular indices of autonomic nervous system function. Our findings, along with other reports from this RCT, are not

consistent with a role for the ANS in the hostility-CAD association. We report that although the CBT treatment program succeeded in reducing indices of anger and hostility, treatment had no impact on myocardial and vascular indices of autonomic nervous system control at rest and in response to or recovery from psychological and orthostatic challenge. These findings complement our finding that hostility reduction in this trial also failed to alter 24-hour measures of cardiac parasympathetic control (36). Together, they suggest that while hostility and anger are recognized risk factors for the development of CAD in healthy individuals and of exacerbation of existing CAD in patients, the ANS may not be a pathophysiological link between this psychological characteristic and heart disease.

Although the evidence linking hostility to heart disease is persuasive, the association of hostility to ANS dysregulation may not be as strong. We reported significant inverse relationships between levels of HRV and hostility in healthy subjects but these studies were small and in one, the relationship was seen only in younger subjects (20, 22).

There are several reasons, however, why our negative findings may not rule out a pathophysiologic role for the ANS. The failure to support our hypothesis might have been because our psychophysiological challenges were not stressful enough. According to the transactional model that guides this research, interpersonal stress is the strongest trigger for sympathetic activity, but non-social stressors such as mental arithmetic may not be sufficiently stressful to provoke a clinically significant reaction/response (48). A real-life stressor such as public speaking has been shown to be more stressful and to be capable of triggering higher blood pressure reactivity (49). The speech task however, was the most interpersonal task and also the task that triggered the highest blood pressure elevations. However, even responses to and recovery from this more provocative challenge were not altered by treatment.

Second, for at least one index, LF-BPV, the underlying physiology is unclear. The literature supporting LF-BPV as an index of vascular sympathetic control is controversial, with evidence both supporting this theory (50–53) and other evidence suggesting it is merely a resonance phenomenon (54–56). However, there is considerable evidence supporting the PEP as a sensitive index of β -adrenergic influence on the heart (57–62) and little question about HF-HRV as an index of cardiac parasympathetic modulation. In other words, even if LF-BPV is a somewhat questionable SNS-index, PEP and HF-HRV are much more reliable autonomic indices.

Limitations

This randomized controlled trial began with a large number of participants but the dropout rate was substantial and significantly higher in the treatment group than in the wait list group. However, the dropouts did not differ significantly from those who remained in the trial and therefore, it is unlikely that the outcome was affected significantly.

A further limitation could be the modest reduction in hostility after treatment. Hostility scores were significantly reduced according to STAXI and the pooled index but not for Cook-Medley and IHAT scores. One could therefore argue that greater hostility reduction might have led to alterations of the ANS. However, the secondary analysis presented above

shows that greater reductions in hostility scores do not correspond to larger reductions in sympathetic activity or increases in parasympathetic activity. Nevertheless, it is possible that even the subjects with the greatest reductions in hostility did not have a big enough change to affect ANS activity.

As indicated above, it is possible that the tasks were not stressful enough. The transactional model suggests that interpersonal environmental factors are the most provocative challenges. Laboratory math and color word challenges are not at all interpersonal and may therefore not be sufficiently stressful. During the speech task, the participants were told that their performance and ability to argue in a controversial matter would be assessed, thus involving more of an interpersonal stressor than the math and Stroop tests. Correspondingly, the speech task elicited the greatest blood pressure response. Nonetheless, hostility reduction had no impact on ANS responses to the speech task. Brondolo et al. have shown that BP responses to real-world interpersonal conflictual situations during ambulatory monitoring are greatest in participants with greater levels of hostility (63, 64). Therefore, the effect of treatment may be seen only in real world interactions. Although we had a significant SBP reaction during speech task (seen in Table 3), it did not survive Bonferroni adjustment.

These limitations notwithstanding, this study had several strengths. First, it was a randomized controlled trial that followed intention-to-treat principles. Second, participants were selected to be healthy but with levels of hostility and anger greater than one standard deviation above national norms on two well established scales. Third, the CBT-based hostility reduction treatment has been well validated in the literature and significantly reduced hostility and anger. Fourth, we used a standard laboratory psychophysiology challenge protocol and at least two widely accepted measures of SNS and PNS function.

CONCLUSIONS

We previously reported that although CBT reduced hostility and anger in healthy young adults, there was no effect on 24-hour levels of parasympathetic regulation of the heart. Here we once again report that the intervention failed to influence parasympathetic regulation as well as two indices of sympathetic nervous system function at rest and in response to and recovery from cognitive and orthostatic challenge. Our results do not support the ANS as a pathophysiologic mechanism linking hostility and heart disease.

Acknowledgments

Source of Funding

This study was supported by Grant R01 HL63872 from the National Heart, Lung, and Blood Institute (R.P. Sloan), Grant K02 MH01491 from the National Institute of Mental Health (R.P. Sloan), and by the Nathaniel Wharton Fund.

Glossary

CAD	coronary artery disease
ACS	acute coronary syndrome

BP	blood pressure
HR	heart rate
HF-HRV	high frequency heart rate variability
SNS	sympathetic nervous system
ANS	autonomic nervous system
CBT	cognitive behavior therapy
STAXI	State-Trait Anger Expression Inventory
IHAT	Interpersonal Hostility Assessment Technique
ICG	impedance cardiography
PEP	pre-ejection period
LF	low frequency
LF-BPV	low-frequency blood pressure variability
SBPV	systolic blood pressure variability
DBPV	diastolic blood pressure variability
SBP	systolic blood pressure
DBP	diastolic blood pressure
PNS	parasympathetic nervous system

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Figure 1.

Levels of heart rate (HR) and high frequency heart rate variability (HF-HRV) between treatment and wait-list control group before training (pre-CBT) and after training (post-CBT). Data are shown as least-square means. Error bars represent standard errors. B1 = baseline (seated), S1 = Public Speaking Task, R1 = Recovery 1, B2 = baseline (supine), AS = average of Math and Stroop task, R23 = average of Recovery periods after math and Stroop task, T1 = tilt (upright).

Figure 2.

Levels of blood pressure, pre-ejection period (PEP), and low frequency systolic (LFSBPV) and diastolic (LF-DBPV) blood pressure variability between treatment and wait-list control group before training (pre-CBT) and after training (post-CBT). Data are shown as leastsquare means. Error bars represent standard errors. PEP = pre-ejection period; LF-SBPV = low frequency systolic blood pressure variability; LF-DBPV = low frequency diastolic blood pressure variability; B1 = baseline (seated), S1 = Public Speaking Task, R1 =

Recovery 1, B2 = baseline (supine), AS = average of Math and Stroop task, R23 = average of Recovery periods after math and Stroop task, T1 = tilt (upright).

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Table 1Demographic, Physical and Psychological Characteristics (Mean $\pm$ SD) of Subjects at Study Entry

	Active Treatment (n=80)	Wait-List Control (n=78)	p-value
Age (yr)	30.64 $\pm$ 6.70	30.91 $\pm$ 6.77	.80
Female	52.50%	53.85%	.87
Weight (lb)	157.70 $\pm$ 33.74	152.90 $\pm$ 32.86	.38
Height (in)	67.77 $\pm$ 4.17	67.58 $\pm$ 3.95	.77
BMI (kg/m ²)	23.96 $\pm$ 3.70	23.45 $\pm$ 3.69	.39
Heart Rate (bpm)	70.21 $\pm$ 9.12	70.80 $\pm$ 8.89	.69
HF-HRV (ln bpm ²)	6.54 $\pm$ 1.13	6.39 $\pm$ 1.16	.40
LF-SBPV (ln mmHg ²)	16.01 $\pm$ 13.71	17.29 $\pm$ 13.39	.56
LF-DBPV (ln mmHg ²)	6.80 $\pm$ 4.38	7.40 $\pm$ 4.79	.42
PEP (msec)	102.20 $\pm$ 9.61	103.60 $\pm$ 10.70	.42
Seated SBP (mmHg)	126.50 $\pm$ 14.71	122.50 $\pm$ 14.58	.090
Seated DBP (mmHg)	73.17 $\pm$ 10.14	70.08 $\pm$ 9.83	.057
IHAT	2.12 $\pm$ 1.93	2.29 $\pm$ 1.96	.57
Cook Medley	32.71 $\pm$ 5.78	32.72 $\pm$ 5.37	1.0
Trait Anger	30.80 $\pm$ 4.66	30.69 $\pm$ 3.85	.87

SD = standard deviation, BMI = body mass index, HF = high frequency, HRV = heart rate variability, LF = low frequency, SBPV = systolic blood pressure variability, DBPV = diastolic blood pressure variability, PEP = pre-ejection period, SBP = systolic blood pressure, DBP = diastolic blood pressure, IHAT = Interpersonal Hostility Assessment Technique.

Table 2
Association between treatment condition with resting levels of physiological measures.

Effect	HR		HF HRV		PEP		SBP		DBP		LF SBPV		LF DBPV	
	SEAT	SUP	SEAT	SUP	SEAT	SUP	SEAT	SUP	SEAT	SUP	SEAT	SUP	SEAT	SUP
Intercept	69.81 (4.11)	64.17 (3.71)	7.80 (0.44)	8.27 (0.48)	96.52 (3.47)	92.89 (3.26)	120.84 (4.33)	120.01 (5.17)	68.03 (3.15)	65.33 (3.11)	2.57 (0.34)	2.13 (0.34)	2.08 (0.31)	1.70 (0.28)
Age	0.05 (0.11)	0.07 (0.10)	-0.06*** (0.01)	-0.06*** (0.01)	0.27* (0.10)	0.10 (0.09)	0.19 (0.12)	0.15 (0.14)	0.17 [^] (0.09)	0.14 (0.09)	0.004 (0.01)	0.008 (0.01)	-0.007 (0.009)	-0.004 (0.008)
Female (ref: Male)	1.22 (1.42)	2.26 [^] (1.33)	0.49** (0.16)	0.21 (0.17)	-4.16*** (1.51)	-4.08*** (1.42)	-9.48*** (1.84)	-5.19*** (1.96)	-7.03*** (1.20)	-3.68*** (1.17)	-0.44*** (0.12)	-0.56*** (0.12)	-0.27*** (0.10)	-0.30*** (0.11)
Group (ref: Wait-list)	-0.45 (1.80)	0.14 (1.87)	0.08 (0.21)	0.09 (0.23)	-0.98 (2.20)	0.61 (2.01)	-0.13 (2.86)	-2.68 (3.01)	-1.02 (1.72)	-1.47 (1.59)	0.05 (0.19)	-0.08 (0.18)	0.05 (0.15)	-0.02 (0.15)
Session (ref: post-CBT)	-1.12 (1.20)	-0.71 (1.16)	0.09 (0.14)	0.11 (0.12)	0.67 (1.88)	0.35 (1.57)	0.94 (1.92)	1.88 (2.07)	0.66 (1.21)	0.49 (1.17)	0.09 (0.13)	0.03 (0.11)	0.06 (0.11)	0.09 (0.09)
Group*Session	-0.10 (1.63)	-1.20 (1.73)	0.07 (0.18)	0.06 (0.20)	-0.07 (2.34)	-1.39 (2.16)	4.04 (3.25)	3.10 (3.24)	4.04 [^] (2.07)	1.60 (1.88)	-0.13 (0.19)	0.02 (0.19)	-0.12 (0.15)	-0.04 (0.15)

Data present parameter estimates and standard errors from linear mixed model analyses.

SEAT = seated position, SUP = supine position, HR = heart rate, HF = high frequency, HRV = heart rate variability, PEP = pre-ejection period, SBP = systolic blood pressure, DBP = diastolic blood pressure, LF = low frequency, SBPV = systolic blood pressure variability, DBPV = diastolic blood pressure variability, ref = reference group. All intercepts were significant at $p < 0.0001$.

[^]
p < .10

*
p < .05

**
p < .01

p < .001

Table 3

Physiological reactivity and recovery from speech and math/Stroop task: Comparison between hostility intervention versus wait list control.

Outcome	Group	Reactivity to Speech		Reactivity to Math/Stroop		Recovery from Speech		Recovery from Math/Stroop		F-value ^a
		pre-CBT	post-CBT	pre-CBT	post-CBT	pre-CBT	post-CBT	pre-CBT	post-CBT	
HR	treatment	12.20 (1.10)	10.85 (1.05)	4.96 (0.56)	4.96 (0.66)	11.09 (0.90)	8.81 (0.98)	5.05 (0.54)	4.51 (0.63)	1.73
	wait-list	14.12 (1.12)	9.51 (0.92)	6.30 (0.57)	4.99 (0.57)	12.54 (0.92)	7.65 (0.84)	6.04 (0.55)	4.53 (0.56)	
HF HRV	treatment	-0.47 (0.11)	-0.51 (0.15)	-0.63 (0.08)	-0.67 (0.11)	-0.28 (0.10)	-0.21 (0.14)	-0.63 (0.09)	-0.71 (0.11)	0.26
	wait-list	-0.61 (0.11)	-0.54 (0.13)	-0.69 (0.08)	-0.69 (0.09)	-0.38 (0.10)	-0.21 (0.12)	-0.69 (0.09)	-0.71 (0.09)	
PEP	treatment	-4.74 (1.03)	-2.45 (1.04)	-3.32 (0.46)	-2.75 (0.64)	-4.45 (0.79)	-3.26 (0.99)	-2.59 (0.41)	-3.49 (0.55)	1.68
	wait-list	-6.75 (1.02)	-2.61 (0.82)	-3.89 (0.46)	-2.61 (0.45)	-5.07 (0.78)	-2.32 (0.75)	-3.30 (0.41)	-2.53 (0.38)	
SBP	treatment	22.75 (1.75)	22.74 (2.13)	7.13 (1.29)	7.15 (1.51)	13.07 (1.51)	12.98 (1.67)	3.09 (1.01)	2.05 (1.29)	3.30 [*]
	wait-list	29.11 (1.78)	18.12 (1.81)	8.35 (1.30)	5.30 (1.18)	15.63 (1.54)	10.80 (1.40)	4.69 (1.02)	0.07 (1.08)	
DBP	treatment	16.03 (1.00)	15.50 (1.14)	5.09 (0.64)	3.70 (0.70)	10.62 (0.88)	8.92 (0.88)	3.15 (0.51)	1.66 (0.65)	0.94
	wait-list	16.83 (1.01)	13.13 (0.97)	5.06 (0.65)	2.82 (0.56)	10.05 (0.90)	7.61 (0.76)	2.98 (0.52)	0.72 (0.54)	
LF SBPV	treatment	0.45 (0.10)	0.36 (0.15)	-0.50 (0.09)	-0.55 (0.16)	0.50 (0.10)	0.25 (0.15)	-0.48 (0.08)	-0.79 (0.12)	0.64
	wait-list	0.37 (0.10)	0.36 (0.12)	-0.55 (0.09)	-0.73 (0.12)	0.55 (0.10)	0.48 (0.12)	-0.60 (0.09)	-0.71 (0.09)	
LF DBPV	treatment	0.53 (0.08)	0.37 (0.13)	-0.36 (0.08)	-0.40 (0.12)	0.50 (0.08)	0.16 (0.13)	-0.43 (0.07)	-0.61 (0.10)	0.73
	wait-list	0.45 (0.08)	0.37 (0.10)	-0.37 (0.08)	-0.58 (0.10)	0.47 (0.08)	0.41 (0.11)	-0.45 (0.07)	-0.65 (0.08)	

Data reflect estimated marginal means and standard errors of reactivity and recovery from the challenge tasks from linear mixed model analyses.

^aF-value of group by session by treatment interaction. HR = heart rate, HF = high frequency, HRV = heart rate variability, PEP = pre-ejection period, SBP = systolic blood pressure, DBP = diastolic blood pressure, LF = low frequency, SBPV = systolic blood pressure variability, DBPV = diastolic blood pressure variability.

[^]p<.10

* p<.05

** p<.001