Hostility, Gender, and Cardiac Autonomic Control

Richard P. Sloan, PhD, Emilia Bagiella, PhD, Peter A. Shapiro, MD, John P. Kuhl, MPhil, Darya Chernikhova, BS, Josh Berg, BS, and Michael M. Myers, PhD

Objective: Although considerable evidence implicates hostility in the development of coronary artery disease (CAD), the pathogenic mechanisms remain poorly understood. We have developed a psychophysiological model that holds that altered autonomic nervous system function links psychological traits with CAD outcomes. In laboratory studies, stressors reduce high-frequency (HF) heart period variability, an index of cardiac vagal modulation. With ambulatory electrocardiographic recording, we demonstrated in a predominantly male sample that hostility was inversely associated with HF power, but only during waking hours. These findings are consistent with the hypothesis that hostile individuals experience multiple stressful interpersonal transactions each day, resulting in overall lower HF power during the day but not at night. **Methods:** To further evaluate this hypothesis, we screened 96 subjects using the Cook-Medley Hostility Scale and selected 15 men and 15 women representing a wide distribution of hostility. These subjects were studied in a laboratory session assessing reactivity to psychological and orthostatic challenges with continuous electrocardiographic, blood pressure, and respiration monitoring. We predicted that for men and women, hostility would be inversely related to reductions in HF power in response to challenge. **Results:** In response to mental stressors, all measures of heart period variability change were inversely related to hostility as predicted. No such relationships were found for responses to tilt. The data suggested a possible effect of gender on these relationships. **Conclusions:** These data add to the growing body of evidence showing that hostility influences vagal modulation of the cardiovascular system and suggest that altered autonomic control is a pathogenic mechanism linking hostility and CAD. **Key words:** hostility, autonomic nervous system, heart period variability, reactivity.

A/D = analog to digital; ANS = autonomic nervous system; BP = blood pressure; CAD = coronary artery disease; ECG = electrocardiographic; HF = high frequency; HPV = heart period variability; HR = heart rate; LF = low frequency; MF = mid frequency; MI = myocardial infarction; rMSSD = root-mean-squared successive difference; SDRR = standard deviation of RR intervals.

INTRODUCTION

The contribution of psychological and psychophysiological characteristics to the development of CAD has been the focus of decades of research, with numerous studies indicating that psychological characteristics such as anxiety, depression, and hostility are associated with increased risk of disease. Although interest in the pathogenic consequences of each of these characteristics has been considerable, evidence may be strongest for hostility. Matthews and Haynes (1) have reported that reanalyses of data from several large studies originally designed to evaluate the impact of the Type A behavior on CAD have shown that hostility predicts the development of CAD. Many more recent studies confirm the relationship between hostility and heart disease. In a case control study of angiographic evidence of CAD, nonsmoking cases had significantly higher hostility scores than control subjects, an association not present among smokers (2). In a prospective study of more than 700 50-year-olds living in Glostrup, Denmark, hostility was associated with increased risk of MI after control for conventional cardiac risk factors, including signs of ischemia at baseline (3). Everson et al. (4) showed that hostility is associated with an increased risk of all-cause mortality and MI but that this risk is mediated primarily by behavioral risk factors. Using the case crossover design, Mittleman et al. (5) demonstrated that episodes of anger trigger MI. In a large community study ($N >$ 12,000), anger proneness predicted CAD outcomes after a median follow-up period of 53 months even after control for standard risk factors (6). A recent meta-analysis of this research area concluded that hostility was an independent predictor of CAD (7).

The pathogenic mechanisms by which hostility confers risk of CAD have not been elucidated completely. Hostility is associated with increased cardiovascular reactivity to challenge (1, 8–14), especially under conditions of interpersonal challenge (15–18). Reactivity has been proposed as a CAD risk factor (19), and considerable empirical support for this hypothesis has been developed (20–23) in both human and animal studies.

From the Behavioral Medicine Program (R.P.S., E.B., J.P.K., D.C., J.B.), Columbia-Presbyterian Medical Center; Department of Psychiatry (R.P.S., E.B., P.A.S., J.P.K.) and Division of Biostatistics, School of Public Health (E.B.), Columbia University; and Departments of Behavioral Medicine (R.P.S., J.P.K.) and Developmental Psychobiology (M.M.M.), New York State Psychiatric Institute, New York, New York.

Address reprint requests to: Richard P. Sloan, PhD, Columbia University, Box 427, 622 West 168th St., New York, NY 10032. Email: rps7@columbia.edu

Received for publication June 15, 2000; revision received August 10, 2000.

0033-3174/01/6302-0434

We recently developed a psychophysiological model that holds that diminished ANS control is a mechanism linking hostility with CAD (24). Substantial evidence indicates that ANS activity predicts survival after MI. Blunted autonomic control of the heart, as measured noninvasively by analysis of HPV, is associated with lower survival after MI (25–28). Recent evidence from two prospective studies of initially healthy subjects suggests that lower levels of HPV predict the development of CAD (29) and cardiac events (30). Several studies have suggested that hostility is associated with diminished cardiac vagal control (31, 32). In a study using 24-hour continuous ECG monitoring, we demonstrated that in normal subjects under age 40, HF-HPV, an index of cardiac vagal modulation, is inversely related to hostility, but only during daytime hours (33).

In this latter study, we suggested that these findings were consistent with Smith's transactional hypothesis (13): that hostile individuals experience multiple stressful interpersonal transactions each day, resulting in overall lower HF power during the day but not at night. The findings from this study, however, must be qualified because subjects were healthy control subjects matched with cardiac transplant recipients in a study of psychophysiological reactivity after cardiac denervation. Because most transplant recipients are male, only 5 of the 38 subjects in this study were women. Therefore, in the current study we tested the transactional hypothesis in both men and women. Moreover, because some evidence suggests that hostility influences cardiovascular responses to physical stimuli (31, 32), we studied the responses to both psychological and orthostatic challenges. Specifically, we predicted that in response to laboratory challenge, HF power reactivity would be inversely related to hostility in both men and women. We also examined the relationship between hostility and other indices of HPV reactivity.

METHODS

Subjects

Subjects were 15 male and 15 female volunteers. Mean (±SD) age of the subjects was 30.9 ± 6.9 years (range = 22–46 years). All subjects were healthy nonsmokers with no history of cardiac, respiratory, or vascular disease, as measured by self-report during an intake interview. None was taking any medications at the time of the study. This study was approved by the Institutional Review Board of the Columbia-Presbyterian Medical Center, and subjects gave informed consent.

Procedure

Data were collected in two phases. In the first, 96 subjects were screened using a battery of psychological questionnaires including the Cook-Medley Hostility Scale. The mean Ho score for this group was 17.39 ± 8.48 (range = 4–46). From these subjects we selected the five men and five women with the highest scores and the five men and five women with the lowest scores. We then selected the five men and five women closest to the median. These 30 subjects participated in the second phase of the study, which consisted of a laboratory-based psychophysiological study.

On a separate day, subjects arrived at the laboratory having eaten a light breakfast but having abstained from caffeinated beverages that morning. After review of the experimental procedures, subjects then practiced the mental stress tasks. Next, electrodes for ECG monitoring were attached. Stretch bands were placed around the subject's chest and abdomen for measurement of respiration (see below). The subject then was placed in the supine position on a Midland electric tilt table, modified to suspend a computer monitor in the subject's visual field for display of the psychological tasks. A Finapres BP cuff (Ohmeda, Englewood, CO) was placed on the middle finger of the nondominant hand, and a numeric keypad, for responding to the tasks, was secured in a comfortable position relative to the dominant hand. Subjects could not see the keypad but could identify the keys by touch. Subjects then rested quietly for 10 minutes to adapt to the position; this period was followed by a 3-minute period for calibration of respiration and BP monitoring devices, and a 5-minute quiet, resting baseline period. Subjects then performed a mental arithmetic stressor and a Stroop color-word task, each 5 minutes in length and followed by a 5-minute recovery period. Subjects were instructed to remain silent throughout the procedures. After a 5-minute recovery period following the second task, the tilt table was elevated to the 70° head-up position over the course of 1 minute. BP and respiration monitors were recalibrated in the upright position. Subjects remained in the head-up position for 10 minutes unless they developed symptoms of lightheadedness.

The interval between screening and psychophysiologic testing was 17.7 ± 3.9 months.

Psychological Stressors

Mental arithmetic. In this task subjects were presented with a four-digit number on the computer monitor and were instructed to subtract serially by 7 starting with this number, which disappeared after the first answer was entered. At 1-minute intervals, subjects received verbal prompts (eg, "please subtract faster"). This task was not paced by the computer, but subjects were instructed to subtract as quickly and as accurately as possible.

Stroop color-word task. In this version of the Stroop task, the computer presented color names (blue, green, yellow, and red) in colors that were either congruent or incongruent with the names. The subject's task was to press the key on the keypad that corresponded to the color of the letters. The task was paced by the computer, and an incorrect response or failure to respond rapidly enough resulted in a message indicating "incorrect" on the screen.

Physiological Stressor

The orthostatic challenge was response to passive tilt. After the tilt table was elevated to 70° head-up over the course of 1 minute, subjects remained in this upright position while the respiration and BP monitors were recalibrated. This recalibration required approximately 2 minutes. After calibration was completed, data collection was resumed for a 10-minute period. Because we were interested in the steady-state response to the upright position and not the immediate cardiovascular response to the positional change, data from the final 5 minutes of this 10-minute period were submitted to analysis. Evidence suggests that after 2 minutes in the upright position, there

is a substantial contribution of the sympathetic nervous system to the cardiovascular response (34).

Acquisition and Processing of ECG Signals

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. Analog ECG signals were digitized at 500 Hz by a National Instruments A/D board and passed to a Toshiba microcomputer. The ECG waveform was submitted to a specially written R-wave detection routine, resulting in an RR interval series. Errors in the marking of R waves were corrected interactively.

Acquisition of BP and Respiration Signals

BP was measured by an Ohmeda Finapres 2300 monitor with the servo self-adjustment disabled except for the last minute of each period. The analog pressure waveform was digitized at 500 Hz and collected by the microcomputer. Systolic and diastolic pressures were identified on the pressure waveform by a specially written program. Errors in marking systole and diastole were corrected interactively.

Respiration was monitored by inductive plethysmography using the Respitrace system (Ambulatory Monitoring, Inc., Ardsley, NY). Analog signals from chest and abdomen bands were digitized at 20 Hz.

Heart Period Variability

Mean HR and the following indices of HPV were computed: the standard deviation of the RR interval series (SDRR), the root-mean-squared successive difference (rMSSD), and spectral power in the LF (0.02–0.07 Hz), MF (0.07–0.15 Hz), and HF (0.15–0.50 Hz) bands. Spectra were calculated separately for HF power and rMSSD on 60-second epochs and for LF and MF power on 240-second epochs using an interval method for computing Fourier transforms similar to that described by deBoer et al. (35). Before computing Fourier transforms, the mean of the RR interval series was subtracted from each value in the series. The residual series was then filtered using a Hanning window (36), and the power (ie, variance, in milliseconds; Ref. 3) over the LF, MF, and HF bands was summed. Estimates of spectral power were adjusted to account for attenuation produced by this filter (36).

Respiration

Chest and abdominal respiration signals were submitted to a specially written respiration scoring program that produced minute-by-minute means of respiratory rate.

Data Reduction and Analysis

Because the servo self-adjustment of the Finapres was enabled during the final minute of each 5-minute recording period, only data from the first 4 minutes of each period were analyzed. For HF power, a mean value for each period was computed from the four 60-second estimates. For LF and MF power, a single value was produced from the spectral analysis of the 240-second epoch.

Data from the first 5 minutes of the tilt period were excluded from analysis to permit full equilibration to the upright position. Therefore, data from minutes 6 to 10 of tilt were selected for analysis.

Following the recommendation of Kamarck et al. (37), data from the two psychological stressors were aggregated to increase response stability. Specifically, reactivity to the tasks was computed as a change score, the difference between the mean from each of the stressors and the value during the initial baseline period.

For each period, mean HR, HPV, and respiratory frequency were presented. For purposes of statistical analysis, HPV data were log transformed to correct for skewness.

HF power was analyzed before and after correction for respiratory rate. This correction was accomplished by regressing HF power on respiratory rate across all measurement periods for each subject and then analyzing the residuals.

Statistical Analyses

Paired *t* tests were used to measure reactivity to psychological and orthostatic challenge. We used Pearson correlation coefficients to test the linear relationship between hostility and measures of cardiac autonomic control. Separate analyses were conducted for each autonomic measure and for the psychological and orthostatic stressors.

RESULTS

Reactivity to Challenge

As expected, mental and orthostatic challenge produced substantial reactivity in measures of autonomic control. These data are presented in Table 1.

Mental challenge produced significant increases in HR and decreases in all measures of HPV with the exception of SDRR for both men and women. Respiratory rate increased significantly for both men and women. Although we did not correct for multiple comparisons, the consistency of these findings suggests that psychological challenge has a substantial impact on cardiovascular autonomic control.

Responses to tilt were less consistent. Although HR increased for both men and women, there was no change in SDRR, MF power, or respiratory rate. HF power and rMSSD fell for both men and women, and LF power increased only for men. Control for respiratory rate did not alter any of these findings.

Effect of Hostility

The mean Cook-Medley score for men was 17.1 (SD = 10.6, range = 4–40). For women, it was 17.3 (SD = 7.2, range = 9–28). Table 2 presents the Pearson correlation coefficients between hostility and psychophysiological indices. During the baseline period, there was little relationship between hostility and HPV: Only LF power ($r = 0.38$, $p < .05$) and HF power after correction for respiratory rate ($r = 0.36$, $p < .10$) were significant or marginally significant.

Unlike data from the baseline period, all measures of HPV responses to the psychological challenges were inversely related to hostility. For all HPV indices ex-

TABLE 1. Heart Rate, Heart Period Variability, and Respiratory Rate During Baseline and Challenge for Men and Women

	Men (N = 15)			Women (N = 15)		
	Baseline	Psychological Challenge	Tilt	Baseline	Psychological Challenge	Tilt
HR (beats/min)	59.7 ± 5.3	68.9 ± 2.7**	72.6 ± 6.5***	67.9 ± 10.2	75.4 ± 10.8***	78.9 ± 10.8*
SDRR (ln ms)	4.12 ± 0.43	4.04 ± 0.48	4.24 ± 0.29	4.05 ± 0.31	3.96 ± 0.32	4.00 ± 0.38
rMSSD (ln ms)	3.91 ± 0.65	3.71 ± 0.54***	3.46 ± 0.39**	3.86 ± 0.46	3.56 ± 0.50**	3.30 ± 0.48**
LF-HPV (ln ms^2)	6.38 ± 0.76	5.85 ± 0.88*	7.39 ± 0.57***	6.32 ± 0.64	5.44 ± 0.79***	6.76 ± 1.24
MF-HPV (ln ms^2)	6.40 ± 1.21	5.89 ± 1.24*	6.84 ± 0.78	6.20 ± 1.03	5.40 ± 1.02*	6.10 ± 1.06
HF-HPV (ln ms^2)	6.90 ± 1.33	6.31 ± 1.14***	5.78 ± 0.88**	6.87 ± 0.88	6.15 ± 1.01***	5.78 ± 1.05**
Respiratory rate (breaths/min)	14.1 ± 2.0	18.5 ± 2.9***	14.3 ± 2.2	14.7 ± 2.0	18.5 ± 3.0***	15.9 ± 2.3

[a] Significantly different from baseline value: * $p < .05$; ** $p < .01$; *** $p < .001$.

TABLE 2. Correlations Between Cook-Medley Hostility Score and HR and HPV

	Baseline	Change Score/ Psychological Task	Change Score/ Tilt
HR	−0.16	0.12	−0.08
LF-HPV	0.38*	−0.49**	−0.29
MF-HPV	0.16	−0.31†	−0.29
HF-HPV	0.02	−0.33†	−0.02
HF-HPV[a]	0.36†	−0.40*	−0.19
rMSSD	0.03	−0.38*	−0.09
rMSSD[a]	0.39*	−0.39*	−0.09
SDRR	0.13	−0.55**	−0.14
Respiratory rate	0.12	0.24	−0.04

[a] After correction for respiratory rate as described in Methods.
† $p < .10$; * $p < .05$; ** $p < .01$.

TABLE 3. Correlations Between Cook-Medley Score and Reactivity to Psychological Tasks by Gender

	Men	Women
HR	0.27	0.07
LF	−0.21	−0.71**
MF	−0.28	−0.33
HF	−0.42	−0.30
HF[a]	−0.75**	−0.23
rMSSD	−0.59*	−0.34
rMSSD[a]	−0.70**	−0.26
SD	−0.37	−0.67**

[a] After correction for respiratory rate as described in Methods.
* $p < .05$; ** $p < .01$.

cept MF power ($p < .10$) and HF power before correction for respiratory rate ($p < .10$), these negative correlations were significant at the .05 level or lower. Thus, higher hostility scores were associated with greater reductions in HPV in response to psychological challenge. Hostility was unrelated to HPV responses to tilt. As with the analyses of reactivity presented above, although we did not correct for multiple comparisons, the consistency of the Pearson coefficients suggests that hostility is inversely related to reactivity to psychological challenge.

Effect of Gender

There was a wide distribution of hostility scores for both men (mean ± SD = 17.3 ± 7.2) and women (17.1 ± 10.6). Table 3 presents the gender-specific correlation coefficients between hostility and reactivity to psychological challenge.

These data suggest a possible effect of gender. Specifically, gender seems to have a frequency-dependent effect on the inverse relationship between HPV reactivity to psychological challenge and hostility. For men this inverse relationship was seen for higher frequency (HF power and rMSSD) responses to challenge. For women it was seen only in responsiveness of lower frequency (LF power) or global indices (SD) of HPV.

To further explore this possible effect of gender, we conducted a regression analysis with gender, hostility, and their interaction as predictive variables for HF power reactivity. Although the interaction term failed to reach significance ($p = .25$), this may be attributable to insufficient statistical power.

DISCUSSION

The findings of this study support the hypothesis that HF power reactivity to psychological challenge is inversely related to hostility. Other measures of HPV responses to psychological challenge also were inversely related to hostility. There was no effect of hostility on the HPV responses to orthostatic tilt. Separate Pearson correlations for men and women suggested the possibility of a gender-specific frequency dependence of HPV reactivity to psychological challenge. However, a specific test of this interaction failed to reach statistical significance, possibly due to insuf-

ficient statistical power. Generally, however, the effect of hostility on the fall in HPV in response to psychological challenge was seen for both men and women.

Although HPV reactivity was inversely related to hostility, there was no significant relationship between resting levels of HPV and hostility. These findings are broadly consistent with our previous data (33). In that study we found an inverse relationship between hostility and HF power during 24-hour continuous ECG monitoring only during the daytime, an effect we suggested was consistent with Smith's (13) transactional hypothesis. This hypothesis holds that hostile individuals engage in multiple stressful transactions throughout the day. Because laboratory studies repeatedly have shown that stressors lead to reductions in HF power, the cumulative effect of such multiple transactions is to reduce HF power during continuous ECG monitoring. However, because these stressful transactions occur only during waking hours, no relationship between hostility and HF power would be seen at night. Other evidence also supports this hypothesis (38).

There is substantial evidence that HF-HPV represents a noninvasive index of cardiac vagal modulation (39-41). The physiological significance of lower frequency oscillations is less well established. However, recent studies by Taylor et al. (42) and Grasso et al. (43) suggest that lower as well as higher frequency HPV reflects parasympathetic influences. Earlier studies also reflect the contribution of vagal effects on LF- as well as HF-HPV (40, 41). Thus, our data are broadly consistent with the original hypothesis: Hostility is inversely related to cardiac parasympathetic responses to psychological challenge.

In this study hostility did not modulate the HPV responses to a physical challenge, passive orthostatic tilt. Other studies, however, suggest that hostility affects parasympathetic responses to physiological challenge. Muranaka et al. (32) showed that a vagomimetic cold facial stimulus led to enhanced vagal responsiveness, as measured by greater HR slowing, in Type B men. Similarly, Fukudo et al. (31) found diminished vagal responsiveness to a β-adrenergic challenge, isoproterenol infusion, in Type A compared with Type B men. These inconsistencies in vagal responses to physical stimuli are likely to result from methodological differences. Cold facial stimuli simultaneously activate vagal and α-adrenergic reflexes. Fukudo et al. measured T-wave attenuation rather than HPV as the index of vagal responsiveness. These differences in stimuli and indices of vagal activity may account for the inconsistency of these findings.

The explanation of the difference in vagal responses to psychological and orthostatic challenge in the current study is unclear but may be due to the physiological differences between these two types of stressors. Tilt is recognized as a profound sympathetic stressor: To compensate for pooling of blood in the lower limbs and the consequent fall in BP produced by the change from the supine to the upright position, baroreflex-mediated increases in sympathetic drive to the blood vessels and heart and withdrawal of cardiac parasympathetic tone are produced to maintain BP. The response to psychological challenge is less dramatic. Psychological stressors do not cause BP to fall; therefore, no baroreflex-mediated autonomic alterations are required. Thus, these particular psychological stressors may be more purely parasympathetic in nature, in contrast to the mixed parasympathetic and sympathetic nature of the orthostatic response.

Alternatively, the effect of hostility on mental but not orthostatic challenge may be due to the involvement of higher centers linked to personality characteristics. In a pilot study, we presented data suggesting that psychological stressors are associated with reduced blood flow to the prefrontal cortex and that this effect is greater in high-hostile than in low-hostile subjects (44).

Potential Limitations

Analyses suggested the possibility of gender-related differences in the correlations between hostility and HF power reactivity to psychological challenge, with a significant inverse relationship found for men and a nonsignificant inverse relationship found for women. Two possible explanations for these different correlation coefficients exist. One is that there is a true difference between men and women, but because of the small sample size there was insufficient statistical power to detect it. The second is that there is no difference between men and women in the relationship between hostility and HF power reactivity and that the apparent difference in the correlation coefficients is due to the narrower range of hostility scores in the women. Further studies are required to distinguish between these two alternatives.

Another potential limitation is the length of the interval between hostility assessment and psychophysiological testing: nearly 18 months. It is conceivable that because of this long interval, the assessed relationships between hostility and reactivity are actually underestimated because of instability in measurement of hostility. However, Barefoot et al. (45) have shown that measurement of hostility by the Cook-Medley scale is reliable over intervals as long as 4 years. Therefore, we believe that the interval between

hostility assessment and psychophysiology testing does not invalidate these findings.

A third limitation of our study is the methodology used for the orthostatic challenge. In response to abrupt changes postural change (eg, standing or rapid tilting), HR increases immediately and then falls before reaching a new level of sustained increase. These immediate responses to positional change are known to be mediated by changes in cardiac vagal activity (46). Although these acute responses may be of interest, our study used a relatively slow tilting procedure and allowed subjects to equilibrate to the 70° upright position before data were analyzed. We allowed this equilibration for two reasons. First, our interest was in measuring and comparing changes in steady-state autonomic controls from baseline to those levels required to adjust to the sustained changes in position or cognitive activity. Evidence suggests that after 2 minutes in the upright position, in contrast to the immediate response to positional change, HR is regulated by both the parasympathetic and sympathetic systems (40). Second, the methodological restrictions of Fourier-based spectral analysis require that the data be relatively stable. The time course of the acute HR changes described above violate this assumption and would lead to erroneous interpretation of changes, especially at low frequencies.

CONCLUSIONS

These data indicate that the psychological trait of hostility is inversely related to cardiac autonomic responses to psychological but not orthostatic challenges in the laboratory and that gender does not moderate these effects. They support our previous finding that hostility is inversely related to daytime levels of HF power in younger subjects. Moreover, the findings are broadly consistent with the view that hostile individuals experience multiple stressful transactions throughout waking hours and that each of these transactions drives down cardiac vagal modulation in proportion to the degree of hostility. Cumulatively this results in lower daytime levels of cardiac parasympathetic activity for high-hostile subjects. Although this conclusion applies to both men and women, the data provide a suggestion of a gender-specific frequency dependence of reactivity to psychological challenge.

REFERENCES

1. Matthews KA, Haynes SG. Type A behavior pattern and coronary disease risk: update and critical evaluation. Am J Epidemiol 1986;123:923–60.
2. Barefoot JC, Patterson JC, Haney TL, Cayton TG, Hickman JR, Williams RB. Hostility in asymptomatic men with angiographically confirmed coronary artery disease. Am J Cardiol 1994;74: 439–43.
3. Barefoot JC, Larsen S, Von der Lieth L, Schroll M. Hostility, incidence of acute myocardial infarction, and mortality in a sample of older Danish men and women. Am J Epidemiol 1995; 142:477–84.
4. Everson SA, Kauhanen J, Kaplan GA, Goldberg DE, Julkunen J, Tuomilehto J, Salonen JT. Hostility and increased risk of mortality and acute myocardial infarction: the mediating role of behavioral risk factors. Am J Epidemiol 1997;146:142–52.
5. Mittleman MA, Maclure M, Sherwood JB, Mulry RP, Tofler GH, Jacobs SC, Friedman R, Benson H, Muller JE. Triggering of acute myocardial infarction onset by episodes of anger. Circulation 1995;92:1720–5.
6. Williams JE, Paton CC, Siegler IC, Eigenbrodt ML, Nieto FJ, Tyroler HA. Anger proneness predicts coronary heart disease risk. Circulation 2000;101:2034–9.
7. Miller TQ, Smith TW, Turner CW, Guijarro ML, Hallet AJ. A meta-analytic review of research on hostility and physical health. Psychol Bull 1996;119:322–48.
8. Booth-Kewley S, Friedman HS. Psychological predictors of heart disease: a quantitative review. Psychol Bull 1987;101:343–62.
9. Dembroski TM, MacDougall JM. Behavioral and psychophysiological perspectives on coronary-prone behavior. In: Dembroski TM, Schmidt TH, Blumchen G, editors. Biobehavioral bases of coronary heart disease. Basel: Karger; 1983. p. 106–29.
10. Glass D, Krakoff L, Contrada R, Hilton WF, Kehoe K, Mannucci EG, Collins C, Snow B, Elting E. Effect of harassment and competition upon cardiovascular and plasma catecholamine response in type A and type B individuals. Psychophysiology 1980;17:453–63.
11. Glass DC, Contrada RJ. Type A behavior and catecholamines: a critical review. In: Lake CR, Ziegler MG, editors. Norepinephrine: clinical aspects. Baltimore: Williams & Wilkins; 1983. p. 346–67.
12. Matthews K. Psychological perspectives on the type A behavior pattern. Psychol Bull 1982;91:293–323.
13. Smith TW. Hostility and health: current status of a psychosomatic hypothesis. Health Psychol 1992;11:139–50.
14. Williams RB, Lane JD, Kuhn LM, Melosh W, White AD, Schanberg SM. Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. Science 1982;218: 483–5.
15. Gallo LC, Smith TW, Kircher JC. Cardiovascular and electrodermal responses to support and provocation: interpersonal methods in the study of psychophysiological reactivity. Psychophysiology 2000;37:289–301.
16. Guyll M, Contrada RJ. Trait hostility and ambulatory cardiovascular activity: responses to social interaction. Health Psychol 1998;17:30–9.
17. Smith TW, Gallo LC. Hostility and cardiovascular reactivity during marital interaction. Psychosom Med 1999;61:436–45.
18. Suls J, Wan CK. The relationship between trait hostility and cardiovascular reactivity: a quantitative review and analysis. Psychophysiology 1993;30:615–26.
19. Krantz DS, Manuck SB. Acute psychophysiologic reactivity and risk of cardiovascular disease: a review and methodologic critique. Psychol Bull 1984;96:435–64.
20. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen RS, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle aged Finnish men: findings from the Kuopio Ischemic Heart Disease Study. Circulation 1997;96: 3842–8.
21. Kaplan JR, Manuck SB, Adams MR, Williams JK, Register TC, Clarkson TB. Plaque changes and arterial enlargement in athero-

sclerotic monkeys after manipulation of diet and social environment. Arterioscler Thromb 1993;13:254–63.
22. Manuck SB, Kaplan JR, Clarkson TB. Behaviorally induced heart rate reactivity and atherosclerosis in cynomolgus monkeys. Psychosom Med 1987;49:95–108.
23. Williams PD, Puddey IB, Martin NG, Beilin LJ. Genetic and environmental covariance of serum cholesterol and blood pressure in female twins. Atherosclerosis 1993;100:19–31.
24. Sloan RP, Shapiro PA, Bagiella E, Myers MM, Gorman JM. Cardiac autonomic control buffers blood pressure variability responses to challenge: a psychophysiological model of coronary artery disease. Psychosom Med 1999;61:58–68.
25. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. The ability of several short-term measures of RR variability to predict mortality after myocardial infarction. Circulation 1993;88:927–34.
26. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. J Am Coll Cardiol 1993;21:729–36.
27. Bigger JTJ, Fleiss JL, Rolnitzky LM, Steinman RC. Stability over time of heart period variability in patients with previous myocardial infarction and ventricular arrhythmias. Am J Cardiol 1992;69:718–23.
28. Kleiger RE, Miller JP, Bigger JT, Moss AJ, the Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987;59:256–62.
29. Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, Rautaharju P, Heiss G. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. Am J Epidemiol 1997;145:696–706.
30. Tsuji H, Larson MG, Venditti FJ, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events: the Framingham Heart Study. Circulation 1996; 94:2850–5.
31. Fukudo S, Lane JD, Anderson NB, Kuhn CM, Schanberg SM, McCown N, Muranaka M, Suzuki J, Williams RB. Accentuated vagal antagonism of β-adrenergic effects on ventricular repolarization: evidence of weaker antagonism in hostile type A men. Circulation 1992;85:2045–53.
32. Muranaka M, Lane JD, Suzrez EC, Anderson NB, Suzuki J, Williams RB. Stimulus-specific patterns of cardiovascular reactivity in type A and B subjects: evidence for enhanced vagal reactivity in type B. Psychophysiology 1988;25:330–8.
33. Sloan RP, Shapiro PA, Bigger JT, Bagiella E, Steinman RC, Gorman JM. Cardiac autonomic control and hostility in healthy subjects. Am J Cardiol 1994;74:298–300.
34. Marin Neto JA, Gallo L Jr, Manco JC, Rassi A, Amorim DS. Mechanism of tachycardia on standing: studies in normal individuals and in Chagas' heart patients. Cardiovasc Res 1980;14: 541–50.
35. deBoer RW, Karemaker JM, Strackee J. Comparing spectra of a series of point events, particularly for heart rate variability spectra. IEEE Trans Biomed Eng 1984;31:384–7.
36. Harris FJ. On the use of Windows for harmonic analysis with the discrete Fourier transform. Proc IEEE 1978;66:51–83.
37. Kamarck TW, Jennings JR, Debski TT, Glickman-Weiss E, Johnson PS, Eddy JJ, Manuck SB. Reliable measures of behaviorally-evoked cardiovascular reactivity from a PC-based test battery: results from student and community samples. Psychophysiology 1992;29:17–28.
38. Powch IG, Houston BK. Hostility, anger-in, and cardiovascular reactivity in white women. Health Psychol 1996;15:200–8.
39. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell'Orto S, Piccaluga E, Turiel M, Baselli G, Cerutti S, Malliani A. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–93.
40. Pomeranz B, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248:H151–3.
41. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;30:H1231–45.
42. Taylor JA, Carr DL, Myers CW, Eckberg DL. Mechanisms underlying very-low-frequency RR-interval oscillations in humans. Circulation 1998;98:547–55.
43. Grasso R, Schena F, Gulli G, Cevese A. Does low-frequency variability of heart period reflect a specific parasympathetic mechanism? J Auton Nerv Syst 1997;63:30–8.
44. Shapiro PA, Sloan RP, Bagiella E, Kuhl JP, Anjilvel S, Mann JJ. Cerebral activation, hostility, and cardiovascular control during mental stress. J Psychosom Res 2000;48:485-91.
45. Barefoot JC, Dahlstrom WG, Williams RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. Psychosom Med 1983;45:59–63.
46. Ewing DJ, Hume L, Campbell IW, Murray A, Neilson JMM, Clarke BF. Autonomic mechanisms in the initial heart rate response to standing. J Appl Physiol 1980;49:809–14.