

Autonomic cardiac control. III. Psychological stress and cardiac response in autonomic space as revealed by pharmacological blockades

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Abstract

Behavioral contexts can evoke a variety of autonomic modes of response, characterized by reciprocal, coactive, or independent changes in the autonomic divisions. In the present study, we investigated the reactive autonomic control of the heart in response to psychological stressors, using quantitative methods for analyzing single and double autonomic blockades, and through the use of noninvasive indices based on heart period variability and systolic time intervals. Analysis of the effects of pharmacological blockades revealed an overall pattern of increased sympathetic and decreased parasympathetic control of the heart during speech stress, mental arithmetic, and a reaction-time task. Unlike the classical reciprocal sympathetic-parasympathetic response to orthostatic challenge, however, the responses of the autonomic branches to stress were uncorrelated. This reflected notable individual differences in the mode of autonomic response to stress, which had considerable stability across stress tasks. The putative noninvasive indices of sympathetic (preejection period) and parasympathetic (respiratory sinus arrhythmia) control changed in accord with the results of pharmacological blockades. Together, these results emphasize the substantial individual differences in the mode of autonomic response to stress, the advantages of a quantitative approach to analyzing blockade data, and the importance of validity estimates of blockade data.

Descriptors: Autonomic blockades, Autonomic space, Chronotropic response, Heart, Heart period, Parasympathetic, Stress, Sympathetic

Central control of sympathetic and parasympathetic outflows to the heart can be exceedingly flexible (Berntson, Cacioppo, & Quigley, 1991; Koizumi & Kollai, 1992). Orthostatic stress and baroreflex responses entail prominent increases in sympathetic control and reciprocal decreases in parasympathetic control of the heart (for review, see Berntson, Cacioppo, & Quigley, 1993a). Behavioral contexts, however, can evoke a variety of autonomic modes of response, characterized by reciprocal, coactive, or independent changes in the autonomic divisions

(Berntson et al., 1991, 1993a; Berntson, Cacioppo, Quigley, & Fabro, 1994b; Koizumi & Kollai, 1992). This is of relevance not only to basic questions concerning the central links between behavioral states and central autonomic mechanisms but also to health issues. Exaggerated cardiovascular reactivity may represent a risk factor for cardiovascular disease (e.g., Matthews et al., 1986; Turner, 1989). Physiological stressors, however, are known to affect vagal and sympathetic outflows to the heart (e.g., Allen & Crowell, 1989; Grossman, Stemmler, & Meinhardt, 1990; Porges, 1992), and exaggerated cardiac reactivity may arise from distinct modes of autonomic control. Based on noninvasive measures of sympathetic and parasympathetic control of the heart, we recently found sizeable and stable individual differences in the pattern of autonomic response to stress (Cacioppo, Uchino, & Berntson, 1994). This study revealed that exaggerated heart rate responses to stress may arise from various modes of control, ranging from strong parasympathetic withdrawal to reciprocal increases in sympathetic and decreases in parasympathetic control to large increases in sympathetic control (Cacioppo, Uchino, & Berntson, 1994). These distinct

This study was partly supported by Grant M01-RR00034 from the National Center for Research Resources and Grant DBS9211483 from the National Science Foundation.

We thank Gaia Panina for her assistance in screening and monitoring subjects, the nursing staff of the Clinical Research Center for overseeing infusions, and Wendi Gardner, Shannon Reed, Nicole Chaput, Ali Mirzadeh, Lisa Gibson, and Becky Schneider for their assistance in data collection and reduction.

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modes of autonomic control may be of considerable importance, because the health-related significance of a given cardiac response may differ widely based on its autonomic origin. That is, specific patterns of autonomic control may be more closely linked with behavioral states and health outcomes than are simple measures of end organ state.

In view of these considerations, we investigated the reactive autonomic control of the heart in response to psychological stressors, using single and double autonomic blockades, and cardiac indices based on heart period variability and systolic time intervals. Our goals in this research were to (a) confirm the sympathetic and parasympathetic control of the heart under basal sitting conditions; (b) quantify changes in autonomic control of the heart as a function of psychological stress; (c) further evaluate preejection period (PEP) and heart period variance in the respiratory frequency band (HF) as noninvasive indices of phasic change in sympathetic and parasympathetic cardiac control; and (d) explore potential individual differences in the pattern of autonomic control during stress.

Methods

Subjects

Subjects were 10 healthy female undergraduate students (age ($M \pm SEM$): 22.5 ± 0.8 years; height: 164.9 ± 1.8 cm; weight: 59.3 ± 2.1 kg), who completed the studies outlined in the companion paper (Cacioppo, Berntson, et al., 1994). Details as to inclusion criteria can be found in that paper. Because pharmacological blockades may adversely affect a fetus, all subjects were on a prescription birth control agent and were given a pregnancy test prior to the study to insure that none were pregnant. Subjects were scheduled using a forward tracking procedure to participate in the study during the follicular phase of the menstrual cycle.

All subjects were informed of possible side effects of the blocker agents and of their right to withdraw from the study at any time. Each then signed an informed consent document.

Procedure

Subjects were tested on 3 separate days prior to and following infusion of either the saline (control) vehicle or fixed 14-mg doses (≈ 0.24 mg/kg) of metoprolol or 2-mg doses (≈ 0.034 mg/kg) of atropine sulfate. Metoprolol, a β_1 antagonist, served to block sympathetic control of the heart, and atropine sulfate, a muscarinic antagonist, was used to block the parasympathetic control of the heart. The dosages were selected to achieve relatively complete autonomic blockade while minimizing nonselective actions and side effects of the drugs.¹ The order of drug administration was counterbalanced across days and subjects. On the day subjects received metoprolol, they received an additional

2 mg atropine sulfate following the completion of the normal protocol (dual blockade condition).²

Detailed procedures are given in the companion paper (Cacioppo, Berntson, et al., 1994). After task instructions, a 30-min adaptation period, and a 3-min baseline period during which heart period and blood pressure measures were obtained, saline, metoprolol, or atropine sulfate was infused over a 15-min period (using a double-blind procedure). A 3-min postinfusion baseline was then taken, and 3-min recordings were then obtained while the subjects were standing and while they were seated (order of postural testing was counterbalanced across subjects). Basal effects of drug administrations and postural manipulations are reported elsewhere (Cacioppo, Berntson, et al., 1994).

Subjects were then tested in three psychological stress tasks while seated in front of a video monitor. Experimenters were out of view of the subjects but could communicate with them via headphones, which also served to deliver experimental auditory stimuli. Communication was limited to alerting the subjects to the nature of the upcoming task. A 3-min baseline recording preceded each task, a warning tone then sounded 30 s prior to each task, final task instructions were given, and a 3-min stress task commenced while physiological recordings were taken. After each task, an offset tone sounded and a short posttask questionnaire was administered. The remaining two tasks were then administered in the same fashion. Every subject received each of three stress tasks on each test day, with the order of testing counterbalanced across subjects and days.

The stress tasks included speech stress, mental arithmetic, and a reaction-time task, and the subject was encouraged in all cases to engage in the task as fully as possible. For the speech stressor, the subject was read a short scenario, which differed over test days, around which she was to construct a 3-min speech. She was given 1 min to prepare and several points to cover in her speech. The subject was prompted with further questions if she did not continue speaking for the full 3 min. The three scenarios consisted of (a) confronting a roommate suspected of stealing \$500 from the subject and spending it on a stereo, (b) speaking to a store manager concerning an accusation of theft by a security guard, and (c) speaking to a college dean about being accused by a professor of cheating on an exam. These three scenarios were given in counterbalanced order across subjects, and the subject was instructed to imagine that the scenario was actually happening to her. To enhance engagement in the task, the subject was told that the speech was being audiotaped and would be analyzed and compared with those of others in the study.

In the mental arithmetic task, the subject was given a four-digit number and asked to serially subtract aloud from this number by a one- or two-digit subtrahend. The subject was stopped and corrected if her answer was incorrect, and the four-digit number and subtrahend were changed at 1-min intervals. The subject was instructed to work as quickly and accurately as possible. Different numbers were used for each session.

For the reaction-time task, the subject was shown a four-letter target word on the CRT screen, and immediately below this word was displayed a letter contained within that word. The subject was instructed to press key 1, 2, 3, or 4 on a keypad to

¹Although competitive blockades can never be absolute, the dosages employed are sufficient to block the heart period effects of agonist administrations and autonomic reflexes (see review by Berntson, Cacioppo, & Quigley, 1993b). Metoprolol has a relatively long time course of action (hours), although the duration of action of atropine is considerable shorter. Consequently, there may have been some decline in the effectiveness of atropine over the course of the session. For the phasic analyses of the present study, however, biases related to incomplete blockades appear in the error bias terms of the autonomic estimates. In all cases, interpretations are drawn in light of the ambiguity inherent in autonomic biases.

²The dual blockade was tested at the end of the day in which subjects were infused with metoprolol because the time course of metoprolol is longer than that of atropine.

correspond to the position of the letter in the target word. She was instructed to press the key as quickly and accurately as possible to avoid a noise blast (white noise, 95 dB SPL, 500-ms duration). The subject was informed that the noise blast would occur if she did not respond faster than the average of the subjects completing the task before her. Actually, each subject received eight noise blasts over the 3-min task, irrespective of performance. Target words and letters were randomly drawn from a large pool for each session.

Following completion of stress tasks on the day subjects received metoprolol, an additional infusion of 2 mg atropine sulfate was given to achieve dual autonomic blockade and to permit determination of each individual's intrinsic heart period.

Noninvasive Measures

Based on the results of the companion article (Cacioppo, Berntson, et al., 1994), PEP and high-frequency heart period variance (HF; 0.12–0.40 Hz) were derived as noninvasive indices of sympathetic and parasympathetic chronotropic control. A Minnesota Impedance Cardiograph (Model 304B) was used to measure EKG, basal thoracic impedance (Z_0), and the first derivative of the impedance signal (dZ/dt). Disposable EKG spot electrodes were placed in the tetrapolar configuration (Sherwood, Royal, Hutcheson, & Turner, 1992). The EKG, Z_0 , and dZ/dt signals were digitized at 500 Hz, and interbeat intervals were derived from a custom software package.³ Further details and rationale for the use of spot electrodes can be found in the companion article (Cacioppo et al., 1994). The impedance data were ensemble averaged within 1-min epochs, and each EKG and dZ/dt waveform was verified or edited prior to analyses. The PEP was quantified as the time interval in milliseconds from the onset of the EKG Q-wave to the B-point of the dZ/dt wave.

Interbeat intervals were checked and edited for artifacts using the detection algorithm of Berntson, Quigley, Jang, and Boysen (1990) and were subsequently verified by visual inspection. Heart period (HP) variance in the respiratory frequency band was analyzed for each minute by the methods of Porges and Bohrer (1990) by a PC-based software package (MXedit 2.01, Delta-Biometrics, Bethesda, MD).⁴ The 60-s heart period series was converted to a 500-ms time series and detrended with a 21-pt cubic polynomial filter moved stepwise through the data to remove low-frequency trends. The data were further filtered by a (25 pt) digital band-pass filter to remove variance outside the respiratory frequency band (0.12–0.40 Hz). The natural logarithm of the variance was then calculated on the residual data, within the frequency range associated with respiration (0.12–0.40 Hz).

Respiration was recorded using an EPM Systems strain gauge respirometer placed below the lowest current electrode. The analog signal was quantified at 250 Hz, smoothed by a 10-pt boxcar filter, and verified or edited as necessary. The mean respiratory amplitude and period were calculated for each min-

ute for each subject, and the minute-by-minute means were averaged within each experimental condition to increase reliability.

Systolic and diastolic blood pressure were recorded via the auscultatory method using a Cortronic 7000 blood pressure monitor. Systolic, diastolic, and mean arterial blood pressure readings were averaged over each 3-min recording period. Given our focus on cardiac activity and the similarity in the results for systolic, diastolic, and mean arterial blood pressure, only the results for mean arterial blood pressure (MAP) are reported below.

Blockade Estimates of Autonomic Control

The change in a measure of cardiac activity after blockade of a single autonomic branch reflects the subtractive loss of that branch and provides an index of the normal contribution of the blocked branch (e.g., cardiac vagal control_{estimate} = $HP_{\text{saline}} - HP_{\text{atropine}}$), whereas the residual autonomic control of a cardiac measure after the same blockade provides an index of the functional contribution of the unblocked branch (e.g., cardiac vagal control_{estimate} = $HP_{\text{metoprolol}} - HP_{\text{dual blockade}}$). We have shown that the alternative subtractive and residual estimates, derived from selective autonomic blockades, are inversely corrupted by systematic biases that can arise in blockade studies. These biases tend to be minimized by averaging the subtractive and residual estimates of the contributions of a given autonomic branch. Further, the discrepancy between the subtractive and residual estimates provides a measure of the bias in these estimates (Berntson, Cacioppo, & Quigley, 1994a). In the present study, estimates of the sympathetic (ΔS) and parasympathetic (ΔP) contributions to phasic response and an estimate of the blockade bias ($\Delta \epsilon_{blk}$) were determined according to the methods of Berntson et al. (1994a):

$$\Delta S = [(HP_{\text{atropine/stress}} - HP_{\text{atropine/bsln}}) + (HP_{\text{saline/stress}} - HP_{\text{metoprolol/stress}})]/2$$

$$\Delta P = [(HP_{\text{metoprolol/stress}} - HP_{\text{metoprolol/bsln}}) + (HP_{\text{saline/stress}} - HP_{\text{atropine/stress}})]/2$$

$$\begin{aligned} \Delta \epsilon_{blk} &= [(HP_{\text{atropine/stress}} - HP_{\text{atropine/bsln}}) \\ &\quad - (HP_{\text{saline/stress}} - HP_{\text{metoprolol/stress}})]/2 \\ &= [(HP_{\text{metoprolol/stress}} - HP_{\text{metoprolol/bsln}}) \\ &\quad - (HP_{\text{saline/stress}} - HP_{\text{atropine/stress}})]/2, \end{aligned}$$

where $HP_{x/y}$ represents the mean heart period value during the drug condition x and the experimental condition y . The ΔS and ΔP values represent the mean of the subtractive and residual estimates, whereas the error bias ($\Delta \epsilon_{blk}$) is specified by the difference between the subtractive and residual estimates.

Results

Basal Effects of Drug Treatments

Within-session effects of drug infusions on dependent measures have been reported previously (Cacioppo, Berntson, et al., 1994). The effects of drug treatments on heart period, heart period variance, MAP, and PEP as reported in our prior study were paralleled by analysis of prestress baseline measures across drug sessions in the present study. Analysis of variance (ANOVA) revealed significant effects of drug treatment on basal heart

³We thank Robert Kelsey and William Guethlein for providing us with copies of their data acquisition and reduction software for impedance cardiography and for their helpful advice.

⁴The respiratory and heart period data from the four subjects showing the most extreme (high and low) respiration rates were also evaluated by spectral (FFT) analysis (after detrending and cosine tapering). In each of these extreme cases, the respiratory peak, and virtually all respiratory power, was within the selected HF band width (0.12–0.40 Hz).

period, with atropine shortening and metoprolol lengthening heart period (mean \pm SEM) heart period after saline = 826 ± 34.4 ms, atropine = 527 ± 3.9 ms, metoprolol = 954 ± 40.3 ms; $F[2,9] = 106.1$, $p < .001$). HF was dramatically reduced by atropine but virtually unchanged by metoprolol (ln HF band variance under saline = 6.46 ± 0.35 , atropine = 1.25 ± 0.36 , metoprolol = 6.65 ± 0.35 ; $F[2,9] = 94.0$, $p < .001$). PEP was increased by metoprolol and to a lesser extent by atropine (PEP under saline = 91.1 ± 1.5 ms, metoprolol = 102.4 ± 1.7 ms, atropine = 100.8 ± 1.3 ms, $F[2,9] = 7.88$, $p < .003$). In contrast, MAP was not altered by drug treatments, nor was respiratory amplitude or period.

Cardiovascular Response to Stress Under Control (Saline) Conditions

Prestress baseline heart period and MAP did not differ across either days or stressors, although significant differences were apparent on both dimensions during the stress period (Figure 1). The primary analyses were by mixed ANOVA according to a 3 Stressors (speech, arithmetic, reaction time) \times 2 Time Blocks (prestress, poststress) \times 3 Orders (day of saline test), with order as a between-subjects variable and stressors and time blocks as within-subjects variables.

All stressors yielded the expected decrease in heart period and increase in MAP (see Figure 1). Analyses of heart period

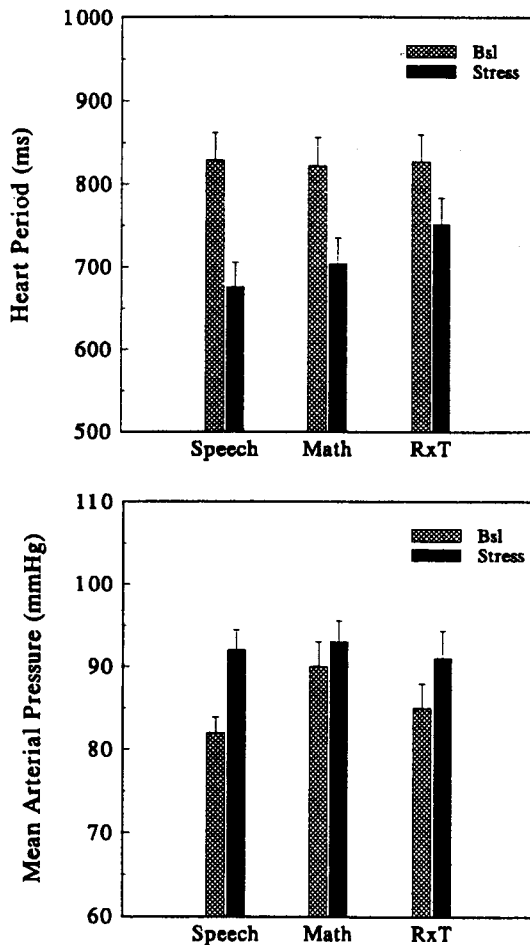


Figure 1. Heart period and mean arterial pressure (mean and SEM) during baseline and stress periods.

revealed a significant main effect of time block, reflecting a stress-induced decrease in heart period ($F[1,7] = 33.19$, $p < .001$). Differences in the magnitude of the heart period response across stressors were revealed by a significant main effect of stressor ($F[2,14] = 12.44$, $p < .001$) and a Stress \times Time Block interaction ($F[2,14] = 6.37$, $p < .01$). Speech stress yielded the largest heart period response, followed by mental arithmetic and reaction time (Figure 1), although post hoc analyses revealed a significant difference only between the speech stressor and reaction-time tasks.

Analysis of variance on MAP yielded a significant main effect of time block (Figure 1), reflecting the stress-induced increase in blood pressure ($F[1,7] = 20.18$, $p < .003$). No other main effect or interaction reached significance.

Origins of the Cardiac Response in Autonomic Space

Each subject was tested in each stress condition over three sessions in which they received intravenous infusions of a sympathetic blocker (metoprolol), a parasympathetic blocker (atropine), or the saline vehicle. These blockade conditions allow the evaluation of the independent contributions of the sympathetic and parasympathetic branches to the autonomic control of the heart (see Berntson et al., 1994a).

Basal autonomic tone.⁵ Results of blockade analyses of basal autonomic control of the heart during the prestress baseline periods are illustrated in Table 1. The s and p columns are the estimates of sympathetic and parasympathetic control, which represent the average of the subtractive and residual model estimates. The error term (ϵ_{blk}) is the difference between the subtractive and residual estimates and provides a metric of potential biases in blockade studies. Validity coefficients (v_b ; see Berntson et al., 1994a) which express the size of autonomic estimates or responses relative to the size of potential biases, reveal that in all cases the autonomic estimates are considerably larger than the validity confidence limits.

Under basal sitting conditions (left columns of Table 1), there exists a significant degree of tonic parasympathetic control of heart period (323 ± 32.1 ms; $t[9] = 10.1$, $p < .001$) and a lesser but still significant degree of sympathetic control (-91 ± 13.1 ms; $t[9] = 6.8$, $p < .001$). These results are consistent with those of previous studies (see Berntson et al., 1993a) and with those of our prior report on these same subjects under postural variations (Cacioppo, Berntson, et al., 1994).

In a series of previous papers (Berntson et al., 1991, 1993a, 1994b), we have developed a three-dimensional representation of autonomic control of cardiac chronotropy. Figure 2 (left) illustrates this autonomic space model. The sympathetic and parasympathetic axes represent the dynamic ranges of control of the sympathetic and parasympathetic divisions, and the overlying chronotropic surface depicts the heart period associated with given levels of sympathetic and parasympathetic control. The independent estimates of sympathetic and parasympathetic

⁵The blockers employed (atropine and metoprolol) afford an analysis of only muscarinic cholinergic (parasympathetic) and β_1 adrenergic (sympathetic) control. This analysis is applicable to the autonomic control of the heart because the autonomic branches act on these receptor populations at the sinoatrial node. In contrast, vascular control is primarily related to other receptor classes (e.g. α and β_2 adrenergic), and hence the blockers used are not optimal for analyses of autonomic contributions to blood pressure.

Table 1. Mean Autonomic Estimates of Heart Period Derived from Blockade Analyses

| Stress | Baseline | | | | Stress | | | | Reactivity | | | |
|---------------|---------------|------------------------|------------------------|------------------|---------------|-------------------------|------------------------|------------------|----------------|------------------------|-------------------------|------------------|
| | ϕ | s | p | ϵ_{blk} | ϕ | s | p | ϵ_{blk} | ϕ | s | p | ϵ_{blk} |
| Speech | 829 (32.8) | -94 (12.5) [.78] | 329 (31.8) [.93] | ± 26 | 676 (30.3) | -125 (18.3) [.80] | 207 (23.5) [.87] | ± 31 | -153 (24.1) | -31 (13.1) [.84] | -122 (19.5) [.96] | ± 5 |
| Arithmetic | 822 (34.3) | -95 (15.2) [.67] | 323 (33.5) [.86] | ± 50 | 704 (30.6) | -124 (17.7) [.78] | 234 (27.0) [.87] | ± 35 | -118 (23.5) | -29 (7.8) [.64] | -89 (21.8) [.85] | ± 16 |
| Reaction time | 828 (32.5) | -84 (16.8) [.70] | 318 (32.7) [.90] | ± 36 | 752 (32.2) | -105 (21.6) [.76] | 263 (32.5) [.89] | ± 33 | -76 (22.1) | -21 (12.1) [.88] | -55 (24.0) [.95] | ± 3 |
| Mean | 826 | -91 | 323 | ± 37 | 711 | -111 | 235 | ± 33 | -116 | -27 | -89 | ± 8 |

Note: The SEM is given in parentheses and the coefficient of validity, v_b , is given in brackets; $v_b = |\text{effect size}| / (|\text{effect size}| + |\text{error bias}|)$ (Cacioppo, Berntson, et al., 1994). When $v_b < 0.5$, the error bias equals or exceeds the magnitude of the experimental effect, and the contrast should not be considered valid. Mean autonomic nervous system estimates (s , p) that fall within the associated SEM and/or within ϵ_{blk} should not be considered meaningful.

basal tone derived in the present study permit a graphical depiction of the basal locus of autonomic control on the chronotropic surface. These estimates are illustrated in Figure 2, together with estimates of basal autonomic tone under different postural conditions, as derived in our previous report (Cacioppo, Berntson, et al., 1994). There is a high degree of consistency in the estimates of basal autonomic control. In general, there appears to be about three times as much parasympathetic (≈ 320 ms) as sympathetic (≈ 90 ms) control under basal sitting conditions, as expressed in milliseconds of heart period. Because of the much wider dynamic range of parasympathetic control (Berntson et al., 1993a), however, this result translates into a relative basal locus that lies in the lower one third of the dynamic range of parasympathetic control and the middle one third of the sympathetic division.

Reactive responses. Stressors yielded an appreciable shift in the basal locus in autonomic space (Figure 2, Table 1). Analyses of variance revealed a significant increase in sympathetic control and a significant decrease in parasympathetic control during the stressors. Separate ANOVAs were run on the estimates of autonomic control, according to a 3 Stressor (speech, arithmetic, reaction time) \times 2 Time Block (baseline vs. stress) repeated measures design. Analysis of variance revealed a significant main effect of time block on the sympathetic estimate, reflecting the increase in sympathetic control during the stress conditions ($F[1,9] = 10.52, p < .01$). This sympathetic response did not significantly differ among the stressors, as indicated by the lack of a main effect of or interaction with the stress variable.

Analysis of variance on the parasympathetic estimate also revealed a significant main effect of time block, reflecting the decrease in parasympathetic control during the stress periods ($F[1,9] = 20.93, p < .001$). A Stress \times Time Block interaction, however, revealed significant differences in the parasympathetic effects of the stressors. Speech yielded the largest parasympathetic withdrawal, followed by mental arithmetic, and then reaction time. Post hoc analyses revealed a significant difference between the speech and reaction-time tasks.

The general pattern of results is illustrated by the solid arrow on the autonomic surface of Figure 2. For comparison, results

of postural manipulations (sitting to standing, open arrow) are also illustrated, as derived in a previous report for these same subjects from a separate experimental condition (postural manipulations; Cacioppo, Berntson, et al., 1994). The relative translations along the sympathetic and parasympathetic axes are more clearly depicted in the expanded insert of Figure 2, which shows the response vectors along the sympathetic and parasympathetic axes of the chronotropic surface. All stressors yielded a reciprocal pattern of sympathetic activation and parasympathetic withdrawal, although appreciable task differences existed in the length of the response vectors.

Individual response stereotypy in autonomic space. In a previous report on tonic autonomic control in the present subjects, the orthostatic change from sitting to standing was found to induce an overall reciprocal pattern of sympathetic activation and parasympathetic withdrawal (see Figure 2). This reciprocal pattern of autonomic response was consistent from individual to individual, as indicated by a negative correlation ($r = -.71, p < .02$) between the activities of the autonomic branches as revealed by autonomic blockades. In contrast to postural manipulations, however, we previously reported sizeable and temporally stable individual differences in the relative contributions of the autonomic branches (the mode of autonomic control) to a speech stressor, through the use of noninvasive indices of sympathetic (PEP) and parasympathetic (HF) control of the heart (Cacioppo, Uchino, & Berntson, 1994). Consistent with this latter finding and in contrast to the effects of postural manipulations, further analyses indicate considerable individual differences in the mode of autonomic control during stress.

The overall magnitude of heart period response varied across both tasks and subjects. The tasks differed considerably in the magnitude of the evoked heart period response, which ranged from -76 ± 10 ms (reaction time [rt]) to -153 ± 24 ms (speech stress). Moreover, individual subjects displayed wide differences in the magnitude of response independent of stressor (ranging from a mean over tasks of 5 ± 30 ms to -195 ± 57 ms). These individual differences in heart period response were not random but were consistent from task to task. Subjects with large responses on one task tended to respond with large responses

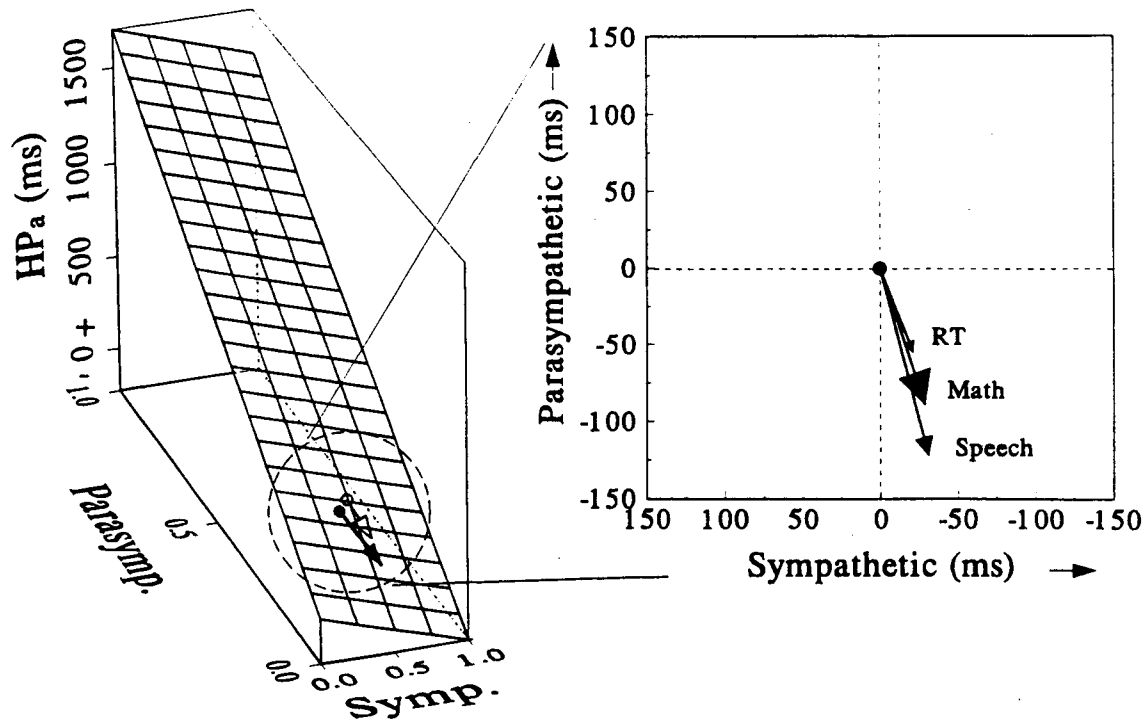


Figure 2. Cardiac responses to stress as depicted in autonomic space. Left: Autonomic space and its associated effector surface for the human. The sympathetic and parasympathetic axes are expressed in proportional units of activation (0-1). The length of the axes are scaled relative to the dynamic ranges of the autonomic divisions (see Berntson et al., 1993b), so that a given displacement along either of the axes represents an equivalent millisecond change in heart period. The z-axis (HP_a) represents the autonomic contribution to heart period as a change from the intrinsic period in the absence of autonomic control (dual blockade). The effector surface overlying the autonomic axes represents the chronotropic state of the heart for all loci within autonomic space (see Berntson et al., 1993b). The solid arrow on the effector surface depicts the mean response vector across the effector surface. Baseline locus is indicated by the solid dot, and the maximal response (to the speech stressor) is indicated by the solid arrowhead. For comparison, the open arrow indicates the response vector, for these same subjects, to a change in posture from sitting to standing (see Cacioppo, Berntson, et al., 1994). Right: The relevant segment of the autonomic plane is expanded in the insert. For illustration, the axes units of the inserts are expressed in millisecond change in heart period from baseline. The expanded inserts depict the cardiac response as movements along the two autonomic axes, expressed in milliseconds of heart period as defined by the equations in the Methods. The large dot at the center (0,0) of the insert is the basal starting point, and the arrow vectors extending from this basal point depict the overall autonomic responses to the speech stressor, mental arithmetic, and the reaction-time task. The width of the arrowheads illustrate the size of the bias estimate (ϵ_{blk}), corresponding to the confidence range of the autonomic blockade analyses. The overall pattern of the autonomic response to each stressor is characterized by sympathetic activation and reciprocal parasympathetic withdrawal. The primary distinction between the stressors is in the magnitude of the response.

on other tasks (mean intertask correlation between heart period responses, $r = .66$; speech-math, $r = .72$, $p < .02$; math-rt, $r = .73$, $p < .02$; rt-speech, $r = .52$, n.s.).

As illustrated in Figure 2, the mean values across subjects entailed a reciprocal pattern of sympathetic activation and parasympathetic withdrawal in response to the stressors. Although the overall means suggest a reciprocal pattern of control during stress, in striking contrast to effects of postural manipulations in these same subjects, there was no correlation between the sympathetic and parasympathetic responses of individuals ($r = +0.09$, n.s.). That is, considerable individual differences were apparent in the mode of autonomic control in response to stress (the relative contributions of the autonomic branches). This finding suggests that individual differences in autonomic response cannot be characterized as a simple magnitude vector along a single reciprocal dimension of increased sympathetic and decreased parasympathetic control. Indeed, individual differences in the relative contributions of the sympathetic and para-

sympathetic divisions to the heart period response were large and stable across tasks (mean intertask correlation, $r = .76$; stress-math, $r = .86$, $p < .01$; math-rt, $r = .75$, $p < .01$; math-speech, $r = .68$, $p < .02$).

These individual differences in autonomic response are illustrated in Figure 3, which depicts the individual response vectors within autonomic space. The arrows represent the mean responses of the 10 individual subjects averaged across tasks. The horizontal (sympathetic) and vertical (parasympathetic) error bars at each arrowhead illustrate the standard error range for the responses across the three separate stressors.⁶ Although the error bars of closely adjacent response vectors overlapped

⁶ Because the tasks differed in the overall magnitude of the reactive response, data were normalized across tasks to the mean task response to eliminate task-specific contributions to the within-subjects variance in response across tasks.

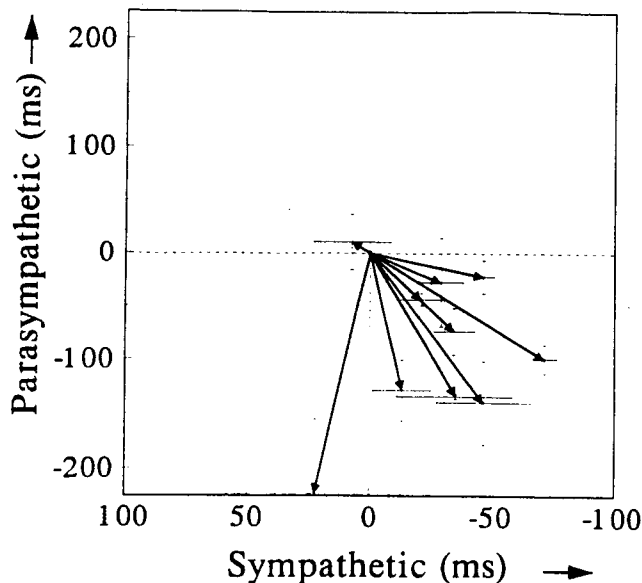


Figure 3. Cardiac responses of individual subjects, as depicted in autonomic space. The arrows represent individual autonomic responses (from baseline) along the sympathetic and parasympathetic axes, expressed in milliseconds of heart period as derived from the equations in the Methods. Each arrow vector represents the mean response across all three tasks of a given subject. The horizontal and vertical error bars at each arrowhead depict the standard errors of the sympathetic and parasympathetic responses, respectively, across the three tasks for that subject. Although the overall responses depicted in Figure 2 were largely reciprocal, the present figure illustrates considerable, and relatively stable, individual differences in the amplitude and direction of the response vectors.

considerably, sizeable individual differences existed in the mode and the magnitude of autonomic response.

Noninvasive Indices of Autonomic Control

Because it is generally not feasible and frequently undesirable to employ pharmacological blockades in human psychophysiological studies, noninvasive indices of autonomic control are important. In an earlier report on postural manipulations, we evaluated a wide range of potential noninvasive estimates of sympathetic and parasympathetic control (Cacioppo, Berntson, et al., 1994). The metrics that showed the greatest promise were PEP (for sympathetic control) and respiratory sinus arrhythmia (RSA) (for parasympathetic control). We here further evaluate these measures as indices of phasic autonomic response.

HF and parasympathetic control of the heart. The magnitude of RSA has been suggested as a noninvasive index of parasympathetic control of the heart (for reviews, see Berntson et al., 1993b; Porges & Bohrer, 1990). Consistent with this suggestion, baseline HF was virtually eliminated by parasympathetic blockade with atropine (ln HF variance after saline = 6.59 ± 0.34 , after atropine = 1.25 ± 0.38 ; $F[1,8] = 121.11$, $p < .001$) but was unaltered by sympathetic blockade with metoprolol (baseline HF after metoprolol = 6.78 ± 0.34 ; n.s. relative to saline). When submitted to formal blockade analysis as outlined above, these data reveal a predominant parasympathetic contribution to basal

HF (ln HF variance attributable to parasympathetic control = 5.2 ± 0.20) compared with a negligible sympathetic contribution (-0.36 ± 0.12 , which is smaller than the validity range of the blockade estimates; $\epsilon_{blk} = 0.58$; $v_b = .38$).

Effects of stress manipulations on the sympathetic and parasympathetic contributions to HF (s_{HF} , p_{HF}) were evaluated by repeated measures ANOVAs (3 Stress \times 2 Time Block). Analysis of the p_{HF} revealed a significant main effect of time, reflecting a stress-induced decrease in the parasympathetic contribution to HF (mean HF during prestress baseline = 5.2 ± 0.20 ; during stress = 4.7 ± 0.22 ; $F[1,8] = 5.0$, $p = .05$). In contrast, the sympathetic contribution to HF was negligible, and the ANOVA revealed no significant differences under stress.

The above analyses were based on the parasympathetic and sympathetic contributions to HF, as derived from blockade analysis. In the absence of pharmacological blockades, however, the specific parasympathetic contribution to HF would not be available. The utility of HF as a noninvasive metric therefore relates to its ability to index parasympathetic control of the heart in the unblocked condition. HF estimates on saline control days (Figure 4, left panel) reveal the expected stress-induced decrease in the amplitude of HF variance. In accord with the general individual stability of autonomic responses across stressors, as defined pharmacologically, HF responses across tasks were significantly correlated (mean intertask correlation, $r = .64$; range = .48–.92).

HF data, however, may be confounded by potential stress-induced alterations in respiratory period and/or amplitude, which are known to effect the magnitude of HF (Grossman, Karemaker, & Wieling, 1991; Grossman & Kollai, 1993). Although minimal, the stress manipulations of the present study yielded significant alterations in both respiratory period and amplitude. Analysis of respiratory amplitude revealed a significant main effect of time, reflecting a stress-induced decrease in respiratory amplitude (mean respiratory amplitude [in arbitrary units] during prestress baselines = 6.36 ± 0.09 , during stress = 6.10 ± 0.10 ; $F[1,8] = 6.78$, $p < .03$). In addition, a significant Stress \times Time interaction emerged for respiratory period ($F[2,16] = 6.21$, $p < .01$). Post hoc analyses revealed a significant stress-induced decrease in respiratory period during the reaction-time task (mean during prestress baseline = 3.90 ± 0.32 s, reaction time = 3.03 ± 0.25 s), with no changes apparent for other stressors (mean baseline period for mental arithmetic = 3.65 ± 0.26 s, during stress = 3.36 ± 0.17 s; mean baseline period for speech = 3.70 ± 0.31 s, for speech stress = 3.73 ± 0.22 s).

To normalize for potential respiratory influences, we submitted the data to a hierarchical regression in which the HF contributions of respiratory period and amplitude were extracted, with residuals analyzed by ANOVAs. This approach is highly conservative in that any consistent effect of the stress on respiratory parameters would be extracted from the stress effects. Nevertheless, the normalized HF data continue to indicate a significant stress effect (Figure 4, right panel). Analyses of these data continue to reveal an overall effect of stress on the amplitude of HF variance (mean value for prestress baseline = 6.6 ± 0.19 , for stress periods = 6.1 ± 0.18 ; $F[1,8] = 4.54$, $p < .03$, one tail).

PEP and the sympathetic control of the heart. Preejection period frequently has been employed as a noninvasive index of sympathetic control of the heart (e.g. Allen, Obrist, Sherwood,

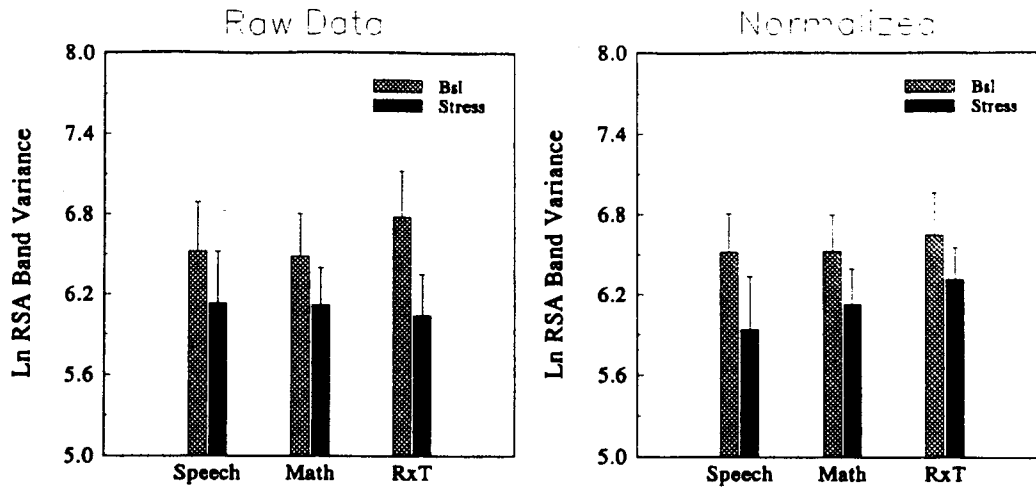


Figure 4. Effects of stressors on respiratory sinus arrhythmia (HF), expressed in the natural log of the respiratory band variance. Left: Uncorrected HF values during baseline (prestress) and stress periods. Right: Corresponding HF values after normalization for respiratory amplitude and period.

& Crowell, 1987; Cacioppo, Uchino, & Berntson, 1994; Light & Obrist, 1983). Consistent with this suggestion and with the stress-induced increase in sympathetic control defined by blockade analyses of heart period, PEP on saline days was significantly decreased by stress. Analysis of variance on PEP according to 3 Stressor (speech, arithmetic, reaction time) \times 2 Time Blocks (baseline vs. stress) revealed a significant effect of time block ($F[1,9] = 15.69, p < .003$). This result reflected the significant decrease in PEP during the stress periods. Although no significant interaction emerged across stressors in the PEP response (as was also the case for blockade analysis), Figure 5 reveals that PEP responses across stressors were graded in accord with the magnitude of sympathetic response as defined by blockades (see Table 1, right columns). Moreover, as with pharmacologically defined responses, PEP responses across tasks were significantly correlated (mean intertask correlation, $r = .59$, range = $-.42$ – $.69$).

Also consistent with PEP as a noninvasive index of sympathetic control of the heart is the finding that β -adrenergic blockade led to a significant increase in PEP and a virtual loss of

the PEP response to stress. Under saline conditions, the mean prestress PEP baseline was $91.1 (\pm 2.5)$ ms, and this decreased to $80.0 (\pm 3.3)$ ms during the stress periods ($F[1,9] = 15.69, p < .01$). After metoprolol, the corresponding baseline value increased to $102.4 (\pm 2.8)$ ms, and the stress-induced decrease was no longer significant (99.5 ± 2.8 ms, n.s.).

Discussion

Autonomic blockade analyses revealed that speech stress, mental arithmetic, and a reaction-time task yielded an overall pattern of increased sympathetic and decreased parasympathetic control of the heart. The overall group responses to stress were similar to the response to orthostatic stress (sitting to standing) as reported previously for these same subjects (Cacioppo, Berntson, et al., 1994). Whereas the response to orthostatic stress was characterized by a significant negative within-subjects correlation between the activities of the sympathetic and parasympathetic branches ($r = -.70$), the correlation between responses of the autonomic branches to psychological stressors employed here were nonsignificant and of opposite sign ($r = +.09$). This result was attributable to notable individual differences in the mode of autonomic control to stress, characterized by various combinations of sympathetic and parasympathetic contributions to the stress response. These individual differences in the mode of autonomic response were consistent across stress tasks and appeared to reflect relatively stable response dispositions. This constitutes the first demonstration of individual response stability at the level of the modes of autonomic control.

Behavioral contexts evoke diverse modes of autonomic response, including sympathetic and parasympathetic coactivation (Berntson et al., 1991, 1993a, 1994b). Autonomic coactivation, for example, was apparent in the responses of rats to an orienting stimulus (Quigley & Berntson, 1990) and in the responses of human subjects to a conditioned stimulus in an aversive conditioning paradigm (Obrist, Wood, & Perez-Reyes, 1965; see also Berntson et al., 1993a). Despite the consistent individual differences in the mode of autonomic control under stress, individual response vectors in the present study were

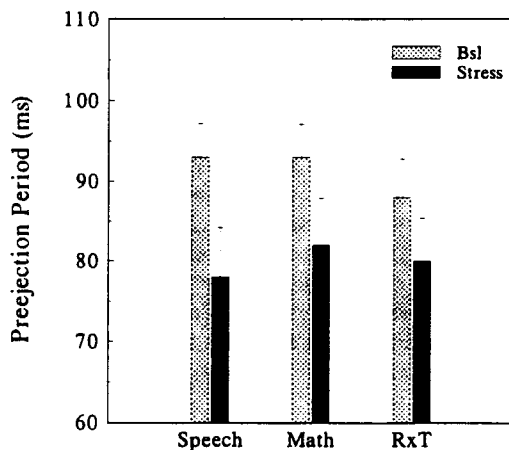


Figure 5. Preejection period (PEP) during baseline (prestress) and stress periods.

largely limited to the reciprocal quadrant (Figure 3), reflecting various combinations of sympathetic activation and parasympathetic withdrawal. The relative similarity in the direction of autonomic response across stressors in the present study may have been due in part to the general similarity in the nature of the stress tasks employed. All stressors were administered in a disquieting hospital setting with intravenous infusions, all stressors required active responses, and all entailed (implicitly or explicitly) performance evaluation of the college student subjects. Thus, a reciprocal mode may not be a uniform pattern of response to all stressors. Autonomic coactivation was reported in the aversive conditioning study of Obrist et al. (1965), and passive coping contexts may yield predominantly uncoupled sympathetic responses (Allen & Crowell, 1989; Allen et al., 1987; Quigley & Berntson, 1990), although this may not invariably be the case (Allen & Crowell, 1990). These results suggest that different stressors may foster a wide range of autonomic modes of response. This is an important area for investigation, because the mode of autonomic response may relate more closely to specific experimental contexts or behavioral states than does the pattern of end-organ response.

Because the application of pharmacological blockades to analysis of the modes of autonomic control is generally not feasible, the availability of noninvasive indices of sympathetic and parasympathetic control would substantially facilitate studies on the relationship between autonomic control and behavioral states and processes. In this regard, RSA (HF) and PEP are among the more frequently employed noninvasive indices of autonomic control of the heart.

Respiratory sinus arrhythmia has long been proposed as a noninvasive index of vagal control of the heart (Berger, Saul, & Cohen, 1989; Berntson et al., 1993b; Porges & Bohrer, 1990). Respiratory sinus arrhythmia is a rhythmical fluctuation in heart period, associated with phasic activity of a central respiratory generator and phasic pulmonary gating of excitatory influences to central autonomic neurons. Although the sinoatrial node of the heart is innervated by both sympathetic and parasympathetic fibers and respiratory rhythms are apparent in the activities of both autonomic divisions, the frequency response of the sympathetic cardiac effectors largely precludes the manifestation of sympathetic respiratory rhythms in heart period fluctuations (Berger et al., 1989; Berntson et al., 1993b). In contrast, the higher frequency response of parasympathetic effector synapses permits these innervations to pass respiratory rhythms (Berger et al., 1989; Berntson et al., 1993b). In accord, HF variance in the respiratory frequency band was virtually eliminated by parasympathetic blockade and was largely unaffected by sympathetic blockade. Also consistent with HF as an index of vagal control of the heart was the finding that HF was attenuated by stress-induced decreases in parasympathetic control of the heart. Unfortunately, the blockade approach is not optimal for evaluation of the potential individual correspondence between HF and vagal control of the heart. This is because HF (or any other noninvasive index of autonomic control) can only be properly evaluated during nondrug (saline) conditions, whereas rigorous pharmacological analyses require multiple drug conditions (saline, sympathetic blockade, and parasympathetic blockade).

In a recent study, Grossman and Kollai (1993) evaluated HF against a criterion measure of vagal control derived from the change in heart period after vagal blockade with atropine. These authors report that although HF was correlated with parasympathetic control, unblocked heart period was even more highly

correlated with the criterion measure. Their data further indicate that at moderate inspiratory amplitudes, inhibition of vagal control of the heart may not be complete. Consequently, these authors suggested that RSA may reflect only a component of tonic vagal control. Although these interpretations are reasonable, the use of a single autonomic blockade condition to estimate vagal control does not permit evaluation of potential biases in blockade data (Berntson et al., 1994a), which could degrade the potential correlation of RSA and vagal tone. Moreover, although heart period was highly correlated with the pharmacological criterion index of vagal control in the Grossman and Kollai (1993) study, the utility of heart period as a vagal index is probably limited. Subjects in the Grossman and Kollai (1993) study were relatively homogenous and were tested under constrained conditions. With a more heterogeneous group and/or under conditions of varied sympathetic arousal, the correspondence between heart period and vagal control would likely be severely degraded. Nevertheless, although the present data support the utility of RSA as an index of changes in vagal control of the heart, if potential respiratory alterations are accounted for, its utility at indexing absolute levels has yet to be completely resolved.

Preejection period, as derived from systolic time intervals, has been employed as a noninvasive index of sympathetic control of the heart (e.g., Allen et al., 1987; Cacioppo, Uchino, & Berntson, 1994; Light & Obrist, 1983). Interpretation of systolic time intervals has been thought to be less ambiguous with respect to their autonomic origins because the myocardium is innervated primarily, although not entirely, by the sympathetic nervous system (Randall, Randall, & Ardell, 1991). Of the systolic time intervals, PEP has received the most attention in psychophysiology (e.g., Allen et al., 1987; Cacioppo, Uchino, & Berntson, 1994; Light & Obrist, 1983). The PEP decreases following infusion of sympathetic agonists and shows strong correlations with noninvasive indices of contractility (Ahmed, Levinson, Schwartz, & Ettinger, 1972; Walsh, Crawford, & O'Rourke, 1982) and circulating norepinephrine (Cousineau, LaPointe, & de Champlain, 1978). Further, abbreviations in PEP accompany the increases in heart rate resulting from adrenergic cardiostimulation but not heart rate increases resulting from vagal blockade or atrial pacing (Harris, Schoenfeld, & Weissler, 1967).

The present results are in general accord with PEP as a noninvasive index of sympathetic control of the heart. The pattern of changes in PEP across stress tasks paralleled the pattern of sympathetic response as defined pharmacologically. As detailed above for HF, however, blockade studies are not optimal for evaluation of the utility of PEP as an index of sympathetic control at the level of the individual subject. Moreover, a caveat in the application of PEP emerges from the literature and is related to the fact that PEP can be altered by changes in ventricular preload or afterload, independent of alterations in sympathetic control (Lewis, Leighton, Forester, & Weissler, 1974). Lewis, Rittgers, Forester, and Boudoulas (1977) summarized evidence showing that the PEP is inversely related to preload (ventricular filling) and directly related to afterload (aortic diastolic pressure). This relationship was apparent in our previous report, where PEP changes were correlated with sympathetic control within but not between postures (Cacioppo, Berntson, et al., 1994). The present results are also consistent with the use of PEP as a noninvasive measure of sympathetic control of the heart, if indirect effects related to preload or afterload are controlled or accounted for.

In summary, the present results clarify the mode of autonomic control of the heart across several common laboratory stressors. Moreover, these results emphasize the substantial individual differences in the mode of autonomic response to stress and the general stability of this mode of response for a given individual across stressors. Although the study of individual differences was limited by the small sample size, the results are in accord with those of a larger study of individual differences in PEP and RSA responses to stress (Cacioppo, Uchino, & Berntson, 1994), suggesting considerable generality of the present findings. The present results also emphasize the impor-

ance of a quantitative approach to analyzing blockade data and the importance of validity estimates of blockade data. The combined use of blockades of both autonomic divisions permits the evaluation of potential biases introduced by the pharmacological antagonists. When appropriately applied and interpreted, pharmacological blockades can offer important criterion indices of autonomic control of the heart. These indices, together with further development and validation of noninvasive metrics of sympathetic and parasympathetic control, offer powerful tools for the refined specification of the pattern of cardiac response in behavioral contexts.

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(RECEIVED September 27, 1993; ACCEPTED March 25, 1994)