ELSEVIER

Biological Psychology 52 (2000) 53–69

BIOLOGICAL PSYCHOLOGY

www.elsevier.com/locate/biopsycho

Behaviorally-evoked plasma catecholamine response and 24-hour excretion of urinary catecholamines among cardiac and vascular reactors

Jeanne M. McCaffery [a,*], Matthew F. Muldoon [b], Elizabeth A. Bachen [c], J. Richard Jennings [a,d], Stephen B. Manuck [a,d]

[a] *Department of Psychology, University of Pittsburgh, 4015 O'Hara Street, Pittsburgh, PA 15260, USA*
[b] *Department of Clinical Pharmacology, University of Pittsburgh, 200 Cathrop Street, Pittsburgh, PA 15213, USA*
[c] *Department of Psychology, Mills College, 5000 MacArthur Blvd., Oakland, CA 94613, USA*
[d] *Department of Psychiatry, University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213, USA*

Accepted 20 October 1999

Abstract

Individuals differ in the cardiac and vascular processes that underlie blood pressure elevations evoked by environmental stimuli; such differences may reflect variability in sympathoadrenal response. We separated 108 healthy, young-adult males into those with predominant elevations in either cardiac output or peripheral resistance when exposed to psychological challenges. We then asked if they differed on other measures of cardiovascular response, concomitant plasma catecholamine reactions or 24-h urinary excretion of catecholamines. Cardiac reactors, relative to vascular reactors, showed reduced cardiac pre-ejection period, a smaller reduction in stroke volume, and elevated plasma epinephrine response and 24-h urinary epinephrine excretion. Vascular reactors, relative to cardiac reactors, responded to mental stress with more elevated diastolic blood pressure, a rise in peripheral resistance and pulse wave velocity, and a greater reduction in stroke volume. Vascular reactors, however, did not show plasma norepinephrine response or 24-h urinary norepinephrine excretion that was greater than cardiac reactors. The results provide partial support for the hypothesis that variability in sympathoadrenal activity contributes to

* Corresponding author.

PII: S0301-0511(99)00029-0

individual differences in cardiac and vascular reactivity, and extend prior observations by demonstrating covariation of behaviorally-elicited cardiac reactivity with the 24-h excretion of epinephrine.

Keywords: Cardiovascular reactivity; Epinephrine; Norepinephrine; Individual differences

1. Introduction

Individuals differ in the cardiac and vascular processes that underlie blood pressure response to environmental stimuli (Sherwood and Turner, 1995) and may be categorized by the extent to which their pressor responses entail a predominant elevation in cardiac output (cardiac reactors) or peripheral resistance (vascular reactors) (Kasprowicz et al., 1990). Previous research suggests that cardiac and vascular reactors differ in the patterning of their cardiovascular reactions to a variety of mental challenges (Kasprowicz et al., 1990; Sherwood et al., 1990b) and that these differences are reproducible on retesting (Kasprowicz et al., 1990). These data suggest that variability of subject's hemodynamic reactions to behavioral stimuli denote a stable dimension of individual differences.

It is possible that cardiac and vascular reactivity reflect individual differences in sympathoadrenal activation. Plasma concentrations of epinephrine, norepinephrine or both may increase among persons exposed to an acute mental challenge. For example, substantial increases in plasma epinephrine have been observed in response to the Stroop color–word interference test (Forsman and Lindblad, 1983; Muldoon et al., 1992; Light et al., 1994), mental arithmetic (LeBlanc et al., 1979; Kaji et al., 1989; Patterson et al., 1993; Light et al., 1994; Mills et al., 1994), or a combination of both (Arnetz et al., 1985; Manuck et al., 1991). Public speaking, reaction time tasks, video games and cognitive tasks, such as Raven's Progressive Matrices, also provoke plasma epinephrine elevations (Dimsdale and Moss, 1980; Contrada et al., 1982; McCubbin et al., 1983; Eisenhofer et al., 1985; Halbrugge et al., 1988; Tischenkel et al., 1989; Light et al., 1994). Plasma norepinephrine tends to rise at least modestly under these acute mental challenges (Taggart et al., 1973; LeBlanc et al., 1979; Dimsdale and Moss, 1980; Contrada et al., 1982; Forsman and Lindblad, 1983; McCubbin et al., 1983; Lovallo et al., 1986; Halbrugge et al., 1988; Bolm-Audroff et al., 1989; Kaji et al., 1989; Tischenkel et al., 1989; Lovallo et al., 1990; Manuck et al., 1991; Sive and Hattingh, 1991; Light et al., 1994), although no change from baseline has also been reported (Akerstedt et al., 1983; Arnetz et al., 1985; Eisenhofer et al., 1985; Goldstein et al. 1987; Muldoon et al., 1992).

Epinephrine, in turn, activates β_1-adrenergic receptors on the heart, increasing heart rate, decreasing cardiac pre-ejection period and, thereby, acting to raise cardiac output; epinephrine also activates β_2-adrenergic receptors on vascular smooth muscles cells, causing vasodilatation (Shepherd and Vanhoutte, 1979). Thus, a predominant elevation in epinephrine under psychological challenge will likely increase cardiac output, while acting to lower peripheral resistance, causing a hemodynamic response pattern reminiscent of that characterizing cardiac reactors.

Norepinephrine has a high affinity for α-adrenergic receptors, which are located primarily in the resistance vessels and potentiate vasoconstriction, in addition to the β_1 receptors chiefly located on the heart (Shepherd and Vanhoutte, 1979; Piascik et al., 1996). This suggests that elevations in norepinephrine may accompany an elevation in both cardiac output and peripheral resistance. However, the rise in blood pressure resulting from a simultaneous increase in cardiac output and peripheral resistance triggers baroreflex-mediated (vagal) deceleration of heart rate, thereby reducing cardiac output despite the activation of the β_1-receptors (Shepherd and Vanhoutte, 1979). Thus, a preferential increase in norepinephrine during mental challenge would be expected to be associated with elevations in peripheral resistance, accompanied by little or no change in cardiac output — that is, the hemodynamic pattern characterizing vascular reactors.

There is evidence that cardiac reactivity covaries with concomitant rises in epinephrine (Kaji et al., 1989), and that cardiac reactors exhibit greater elevations in plasma epinephrine in response to mental challenge than do vascular reactors (Light et al., 1994). Changes in plasma epinephrine also correlate positively with heart rate responses to common laboratory challenges, such as mental arithmetic (LeBlanc et al., 1979; Kaji et al., 1989; Mills et al., 1994), the Stroop color–word interference test (Akerstedt et al., 1983; Marsland et al., 1995), and various psychomotor tasks (Eisenhofer et al., 1985), and negatively with change in pre-ejection period on performance of Raven's Progressive Matrices (McCubbin et al., 1983).

Nonetheless, covariation has not been found between behaviorally-evoked changes in plasma norepinephrine and vascular reactivity. In one study, for example, vascular reactors did not differ from cardiac reactors in their norepinephrine responses to a battery of mental challenges, including mental arithmetic, public speaking and a reaction time task (Light et al., 1994), and in a second, vascular reactivity to mental arithmetic also did not correlate significantly with concomitant changes in plasma norepinephrine (Kaji et al., 1989). Thus, although plasma epinephrine responses appear to covary with increased myocardial performance, the expected association between plasma norepinephrine and vascular reactivity has not been found.

Urinary excretion of epinephrine and norepinephrine provide alternative measures of sympathetic activity. Although their origin is unknown (Ziegler, 1989), urinary catecholamine concentrations are responsive to psychological provocation (Frankenhauser and Johasson, 1976; Frankenhauser et al., 1980; Akerstedt et al., 1983; Baum et al., 1985; Arnetz and Fjellner, 1986; Fibiger et al., 1986) and, when assessed over a 24-h period, serve as time-integrated indexes of sympathetic activity that may differ from the punctate measurement of plasma catecholamines. To the extent that cardiac and vascular reactivity reflect generalized patterns of sympathetic response to environmental stimuli, it is possible that these individual differences may also be reflected in 24-h urinary catecholamine excretion.

In summary, the differential affinity of α- and β-adrenergic receptors for epinephrine and norepinephrine suggests that individuals who respond to psychological challenge with predominant elevations in epinephrine will also tend to show elevations in cardiac output, whereas individuals with a predominant norepinephrine response may exhibit increased peripheral resistance. Supporting this hypothesis, several studies have shown that behaviorally-evoked changes in plasma epinephrine correlate positively with concomitant cardiac output and heart rate responses, and negatively with pre-ejection period responses, during mental challenge (LeBlanc et al., 1979; Akerstedt et al., 1983; McCubbin et al., 1983; Eisenhofer et al., 1985; Kaji et al., 1989; Light et al., 1994; Mills et al., 1994; Marsland et al., 1995); however, a similar association between plasma norepinephrine response and vascular reactivity has not been observed (Kaji et al., 1989; Light et al., 1994). The goal of this paper is to re-examine the extent to which cardiac and vascular reactors differ in their cardiovascular and plasma catecholamine responses to psychological stress, in a study of healthy, young adult men. Additionally, we examine whether cardiac and vascular reactors may also be differentiated with respect to their 24-h urinary excretion of catecholamines.

2. Method

2.1. Participants

This report is a re-analysis of data collected as part of the Pitt Family Health Project, a larger study of cardiovascular risk factors, neuropsychological performance, and personality among young adults who differ in their familial history for hypertension (Waldstein et al., 1994; Manuck et al., 1996). A total of 108 male volunteers (ages 18–25) were recruited from the university community. Thirty-five participants had two hypertensive parents (systolic >140 mmHg or diastolic >90 mmHg), 33 participants had one hypertensive and one normotensive parent, 32 participants had two normotensive parents and, for eight participants, parental hypertensive status could not be ascertained. Participants with parents who were deceased, or who had at least one parent with high-normal blood pressure (systolic 135–139 mmHg or diastolic 85–89), coronary heart disease or adopted offspring, were excluded. All participants were also Caucasian, non-obese ($<25\%$ overweight by AHA weight tables), and free of cardiovascular disease, hypertension, diabetes, cancer, kidney disease and any cardiovascular medication. As cardiovascular and neuroendocrine responses did not differ with respect to parental hypertension (Manuck et al., 1996), the sample has been collapsed across family history groups for the purposes of the present analyses.

2.2. Cardiovascular and neuroendocrine measures

Systolic and diastolic blood pressure were monitored oscillometrically with the Dinamap Vital Signs Monitor (Model 8100, Critikon, Tampa, FL), in conjunction

with a blood pressure cuff placed on the non-dominant arm. Heart rate was assessed using a two-lead electrocardiogram, stroke volume and systolic time intervals (pre-ejection period, left-ventricular ejection time) were evaluated by impedance cardiography (Minnesota Impedance Cardiograph, Model A400-B), and the onset of the peripheral pulse wave was estimated by photoplethsysmography from the thumb nail (Jennings and Choi, 1983).

Plasma catecholamine concentrations were derived from blood samples collected through an indwelling catheter inserted in the antecubital vein of the participants non-dominant arm. Blood draws were screened from view by an opaque shield positioned at the upper arm. All samples were collected in EDTA, chilled and centrifuged. Plasma was subsequently extracted and frozen at $-80°$ until analysis with high performance liquid chromatography (HPLC). Inter-assay coefficients of variation for plasma norepinephrine and epinephrine were 10.1 and 10.2%, respectively. Due to technical difficulty in obtaining or maintaining venous access, 29 participants had missing plasma catecholamine data.

Urine was collected for two 24-h periods on non-consecutive days. Participants abstained from prescription medications for 1 week prior to each collection and from all other medications (except acetaminophen and terfenadine) for 24-h. Data from three participants were dropped because collection was either not completed or considered incomplete due to a urinary creatinine concentration less than 800 mg.

Concentrations of urinary catecholamines were also determined by HPLC. Inter-assay coefficients of variation for urinary norepinephrine and epinephrine were 2.2 and 3.7%, respectively. As the mean concentrations of urinary epinephrine and norepinephrine were similar for days 1 and 2 ($t(91)$'s < 1.0, P's > 0.50) and the measures correlated significantly across the two days (epinephrine: $r = 0.58$; norepinephrine: $r = 0.71$), the average of day 1 and day 2 was used in analysis. Urinary catecholamines were also adjusted for urinary creatinine in all analyses.

2.3. Protocol

Participants attended two sessions during which cardiovascular and plasma catecholamine activity was measured at rest and in response to several psychological challenges. Prior to both sessions, subjects fasted overnight and abstained from all medications (except acetaminophen and terfenadine) for 3 days, from caffeine and alcohol for 12 h, and from tobacco products for 3 h.

On day 1, subjects first gave informed consent, as approved by the University of Pittsburgh IRB, after which they were instrumented with the cardiovascular monitors and the venous catheter. After a 30-min, seated rest period, participants were administered a 21-min, PC-based version of the Stroop color–word interference test (Manuck et al., 1991). During the challenge, a target color name, printed in a color other than the color named by the word, was presented on the computer screen, while a computerized voice simultaneously announced a random color name for distraction. Participants were instructed to identify the name of the text color from four response choices presented at the bottom of the screen, while ignoring the

auditory distractor. The task was titrated to each participant's ability by shortening or lengthening the response window, and monetary incentive (up to $20) was provided for good performance.

On day 2, participants again refrained from the excluded substances and were attached to the cardiovascular monitors upon arrival. After a 30-min rest period, participants completed three 6-min tasks, each preceded by a 15-min rest period. The first task, mental arithmetic, required participants to perform several 2–4 digit addition and subtraction problems. Task difficulty was titrated by adjusting the complexity of the problems and monetary incentive (up to $6.00 in total) was provided for good performance. The second challenge, mirror tracing, tests psychomotor abilities as participants are asked to trace the perimeter of a star guided only by its inverted (mirrored) image. Auditory feedback was provided for errors, but no monetary incentive was offered for this task. A reaction time task was also administered but not subjected to analysis, due to equipment failure in data retrieval for scoring.

Electrocardiogram, impedance and pulse wave measures were recorded continuously throughout the laboratory sessions. Blood pressure was assessed at 90 s intervals during the last 6 min of the rest periods and throughout all tasks. Blood samples drawn at baseline and 2, 10 and 18 min into the Stroop task, although only the pre-task baseline and 2 min measurement were used in analysis to maintain consistency of timing across psychological tasks. Blood samples were not collected during the mental arithmetic or mirror tracing tasks.

2.4. Data reduction

Cardiovascular signals were digitized, ensemble-averaged within 30-s segments concurrent with blood pressure readings, and scored as described in Debski et al. (1991). Artifacts were detected by software and visual inspection. Stroke volume was estimated from cardiac-cycle-dependent changes in transthoracic impedance using the Kubicek equation (Kubicek et al., 1966) and cardiac output and total peripheral resistance were subsequently calculated by formula (Sherwood et al., 1990a,b). Pulse wave velocity was defined as the time (ms) from the onset of ventricular ejection, as estimated from the b-point of the impedance waveform, to the onset of the pulse wave signal at the thumb, divided by the estimated distance of pulse propagation. The distance traveled by the pulse from the left ventricle to the thumb was estimated by measuring the distance from the sternum to the middle of the clavicle bone, and from that point to the thumb nail.

Cardiovascular responses were defined by change scores calculated as the arithmetic difference between levels of activity observed during tasks and corresponding pre-task baselines. Stroke volume, cardiac output and peripheral resistance responses were also expressed as percentage change from baseline (Miller and Horvath, 1978). To derive dimensions of individual difference in cardiac and vascular reactivity, percentage change in cardiac output and peripheral resistance during mental arithmetic, mirror tracing and the Stroop task were standardized across the full sample and z-scores averaged over tasks (Kamarck et al., 1992,

1993). In the remainder of the paper, these are referred to as aggregate responses. As with plasma catecholamines, only measurements taken during the first 6 min of the Stroop task were used to allow equivalent time segments from each task.

2.5. Categorizing cardiac, vascular and non reactors

The primary goal of analysis was to contrast persons exhibiting predominantly cardiac and predominantly vascular responsivity with individuals who showed little or no reactivity in either hemodynamic parameter on other measures of cardiovascular response, plasma catecholamine reactions, and 24-h urinary excretion of catecholamines. Due to the strong inverse correlation between change in cardiac output and peripheral resistance observed in this sample, persons 'low' on either dimension are not necessarily 'nonreactive' individuals, in the sense of exhibiting a low response in both cardiac output and peripheral resistance, accompanied by a low or absent pressor response. Thus, correlational analyses alone would not permit the comparison of individuals who exhibit substantial responses to psychological challenge, be it cardiac or vascular, with those marked by an absence of cardiac and vascular reactivity during the task. An alternate, group difference approach would permit the comparison of these three types of reactors (cardiac, vascular and non), but would not permit analysis across the full range of variability in cardiac output and peripheral resistance responses. Accordingly, both group comparison and correlational analyses will be presented as complementary sets of analyses.

Prior to the group analyses, subsets of individuals were selected from the task-averaged distributions of cardiac output and peripheral resistance response as follows: persons exhibiting a positive change in cardiac output greater than one standard deviation above the mean of the sample, and a peripheral resistance response less than the sample mean, were defined as 'cardiac' reactors; those exhibiting peripheral resistance responses greater than one standard deviation above the sample mean and cardiac output responses below the sample mean were labeled 'vascular' reactors (Kasprowicz et al., 1990). As a comparison, participants with combined ranks for change in cardiac output and vascular resistance less than one standard deviation below the mean were designated 'non' reactors. This classification yielded 25 cardiac, 25 vascular and 30 non reactors.

2.6. Data analysis

Analyses of variance (ANOVAs) with one between-subjects factor (reactor group: cardiac, vascular, non) were performed to determine whether the three groups differed on: (1) demographic variables, including age, body mass, alcohol intake and smoking status; (2) baseline cardiovascular states; (3) baseline plasma epinephrine and norepinephrine concentrations; (4) mean cardiovascular responses, as averaged across the three psychological tasks; (5) baseline-adjusted plasma epinephrine and norepinephrine responses to the Stroop task; and (6) mean 24-h urinary catecholamine excretion (expressed in ratio to urinary creatinine). All significant effects were further probed for group mean differences using Tukey's

Honestly Significant Difference Test (Kirk, 1968). In addition, to address the loss of participants through classification, Pearson coefficients were also calculated to express the correlation of cardiac and vascular reactivity (dimensionally across all subjects) with the other response parameters and with 24-h urinary catecholamine excretion.

3. Results

3.1. Demographic variables and baseline cardiovascular and neuroendocrine measures

Group comparisons for demographic variables and baseline cardiovascular and neuroendocrine measures are presented in Table 1. Cardiac, vascular and non reactors were similar in age, body mass index, alcohol intake per week (F's $(2,77) < 0.63$, P's > 0.10) and smoking status (Kruskall–Wallis $H(2) = 1.25$, $P > 0.10$). Moreover, these groups did not differ on the baseline cardiovascular (F's $(2,71) < 2.04$, P's > 0.10) or neuroendocrine variables (F's $(2,57) < 0.72$, P's > 0.10).

3.2. Behaviorally-evoked cardiovascular responses

3.2.1. Group comparisons

To document differences in cardiovascular response patterns among cardiac, vascular and non reactors, the group means for changes in systolic and diastolic blood pressure, heart rate, pre-ejection period, cardiac output, peripheral resistance

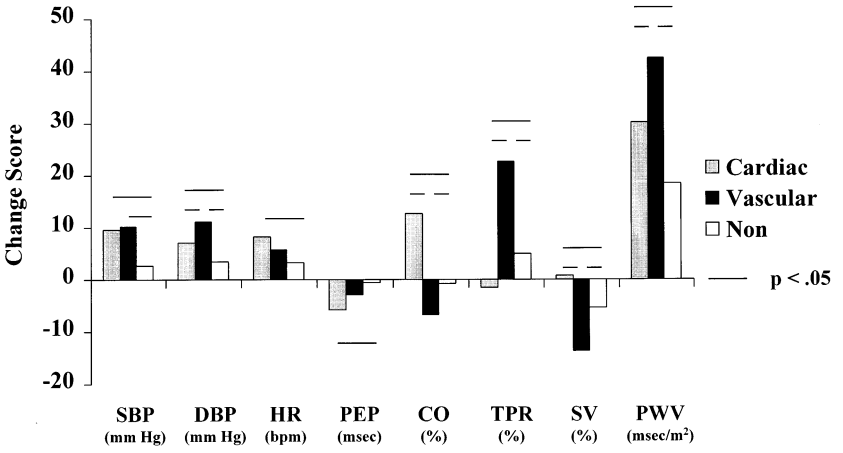

Fig. 1. Differences among cardiac, vascular and non reactors in cardiovascular reactivity to psychological challenge. Lines above bar graphs denote significant differences between groups at the ends of each line.

Table 1
Demographic and baseline differences among cardiac, vascular and non reactors

	Cardiac		Vascular		Nonreactor		*F* test	*P* value
	Mean	SD	Mean	SD	Mean	SD		
Demographic variables								
Age (years)	20.56	1.50	20.48	1.78	20.23	1.46	$F(2,77) = 0.33$	ns
Body mass index (kg/m^2)	23.69	2.96	24.60	3.22	23.84	2.92	$F(2,77) = 0.63$	ns
Current smoker (%)[a]	17		13		24		$H(2) = 1.25$	ns
Alcohol (drinks/week)	8.14	10.17	7.49	9.64	5.77	6.22	$F(2,77) = 0.55$	ns
V_{O_2} (ml/kg per min)	37.35	4.61	36.68	6.97	37.47	3.99	$F(2,77) = 0.18$	ns
Cardiovascular baselines								
SBP (mmHg)	120.61	7.65	122.80	7.36	120.51	8.57	$F(2,71) = 0.52$	ns
DBP (mmHg)	62.80	6.31	66.58	6.73	65.28	6.72	$F(2,71) = 2.04$	ns
HR (bpm)	66.65	6.66	68.40	9.05	67.52	8.03	$F(2,71) = 0.25$	ns
PEP (ms)	109.96	10.66	111.37	12.38	114.97	10.75	$F(2,71) = 1.32$	ns
CO (l/min per m^2)	3.09	0.59	2.93	0.64	3.13	0.62	$F(2,71) = 0.68$	ns
TPR (dynes/cm^5 per s)	1130.51	266.39	1195.10	293.60	1135.83	239.43	$F(2,71) = 0.44$	ns
SV (ml/beat per m^2)	47.35	11.91	43.76	10.89	46.64	8.45	$F(2,71) = 0.80$	ns
PWV (ms/m^2)	543.29	43.20	549.14	51.09	525.82	46.90	$F(2,71) = 1.67$	ns
Plasma catecholamine baselines								
Epinephrine (pg/ml)	39.85	20.82	34.52	12.67	34.58	13.53	$F(2,57) = 0.72$	ns
Norepinephrine (pg/ml)	199.95	69.23	198.85	73.31	209.70	129.72	$F(2,57) = 0.08$	ns

[a] Kruskal–Wallis non-parametric test used.

Table 2
Correlations between the aggregated distributions of blood pressure (SBP, DBP), cardiac output (CO) and peripheral resistance (TPR) reactivity to psychological stress (bold $P<0.05$)

	Aggregate			
	CO	TPR	SBP	DBP
Aggregate				
Systolic blood pressure (mmHg)	0.12	**0.31**		**0.69**
Diastolic blood pressure (mmHg)	−0.20	**0.60**	**0.69**	
Heart rate (bpm)	**0.39**	−0.16	**0.29**	0.12
Pre-ejection period (ms)	**−0.42**	0.11	**−0.52**	**−0.29**
Cardiac output (l/min per m^2)		**−0.84**	0.12	−0.19
Total peripheral resistance (dynes/cm^5 per s)	**−0.84**		**0.31**	**0.60**
Stroke volume (ml/m^2)	**0.56**	**−0.59**	−0.06	−0.16
Pulse wave velocity (ms)	−0.01	**0.30**	**0.50**	**0.44**

and stroke volume, across the three tasks, are depicted in Fig. 1. As expected, significant group main effects were found for each of the cardiovascular parameters recorded in this study (F's $(2,71) = 5.25–78.95$, P's $= 0.007–0.0001$).

Post-hoc analyses showed systolic blood pressure elevations to be comparable for cardiac and vascular reactors and, in each of these groups, significantly greater than the responses of non-reactors (P's < 0.0001). Despite their similarity in systolic responsivity, cardiac and vascular reactors could be differentiated on other response parameters. Predictably, cardiac reactors responded with larger increases in cardiac output than vascular reactors (P's < 0.0001); the latter group actually showed a small decline in cardiac output, relative to baseline. Pre-ejection period also tended to be attenuated among cardiac reactors, relative to vascular reactors (Post-hoc t-test, $P < 0.05$). Conversely, vascular reactors exhibited heightened peripheral resistance and reduced stroke volume, by comparison with cardiac reactors, who showed little or no change on either measure during the tasks (P's < 0.0001). Changes in diastolic blood pressure and pulse wave velocity were also larger in vascular reactors than among cardiac-reactive subjects (P's < 0.05).

As with systolic blood pressure, non reactors showed significantly smaller changes in diastolic blood pressure and pulse wave velocity than both cardiac and vascular reactors (P's < 0.05). Heart rate and pre-ejection period responses were also attenuated among non-reactors, compared to the other groups, but in both instances the non reactors only differed significantly from cardiac reactive participants (P's < 0.005). Finally, the cardiac output, peripheral resistance and stroke volume responses of non reactors were intermediate between cardiac and vascular reactors, with non reactors differing significantly from both cardiac and vascular reactors on all three response measures (P's < 0.005).

3.2.2. Correlations

Next, we evaluated the extent to which individual differences in cardiac and vascular reactivity correlated with other measures of cardiovascular response (Table

2). Larger elevations in cardiac output were associated with increased heart rate and stroke volume, and shortened pre-ejection period (P's < 0.0001). In contrast, peripheral resistance responses correlated positively with changes in systolic blood pressure, diastolic blood pressure and pulse wave velocity, and negatively with change in stroke volume (P's < 0.003). It is important to note that the aggregated distributions of cardiac and vascular reactivity were themselves highly negatively correlated ($P < 0.0001$), reflecting more than 60% common variance. No other significant correlations were observed (P's > 0.10).

3.3. Plasma catecholamine responses and 24-h urinary catecholamine excretion

Significant group main effects were found for plasma epinephrine responses to the Stroop task ($F(2,53) = 5.22$, $P < 0.009$)[1] and 24-h urinary epinephrine excretion ($F(2,75) = 7.17$, $P = 0.002$, see also Fig. 2). Post-hoc analyses indicated that cardiac reactors responded with heightened plasma epinephrine during mental challenge, and excreted more epinephrine over a 24-h period, relative to both vascular and non reactors (P's < 0.05). No other significant effects were observed (P's > 0.10).

Across all participants, cardiac reactivity correlated significantly with the change in plasma epinephrine concentration during the Stroop task ($r = 0.29$, $P = 0.01$) and

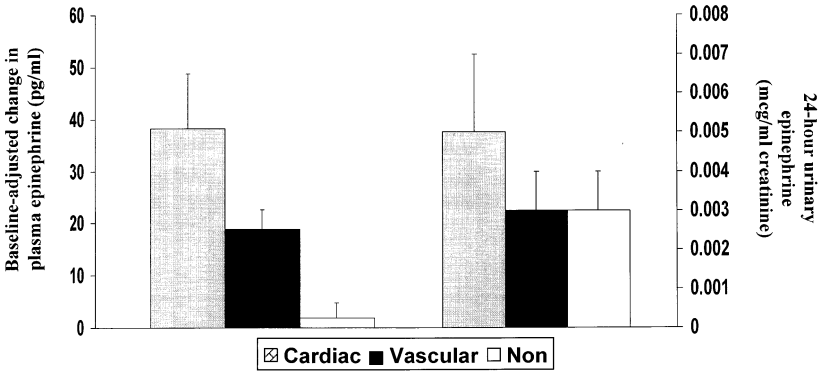

Fig. 2. Change in plasma epinephrine in response to the Stroop task and 24-h concentrations of urinary epinephrine among cardiac, vascular and non reactors. Brackets denote standard errors.

[1] Mixed-design ANOVAs with one between-subjects factor (reactor group) and one within-subjects factor (min 2, 10, 18 of the Stroop task) were also performed on baseline-adjusted changes in plasma epinephrine and norepinephrine to determine whether cardiac, vascular and non reactors differed in their catecholamine responses throughout the Stroop task. The results were similar to the analyses of the first period alone. A significant group main effect was found for changes in epinephrine across the three measurements ($F(2,53) = 3.57$, $P < 0.04$). Post-hoc analyses indicated that cardiac reactors exhibited greater epinephrine responses than both vascular reactors and non reactors, although they differed significantly from non reactors alone ($P < 0.03$). The group $\times$ time interaction was also significant ($F(4,108) = 4.50$, $P < 0.003$) and indicated that the difference in epinephrine response between cardiac, vascular and non reactors occurred primarily at the first measurement. No significant group main effect was observed in analyses of plasma norepinephrine.

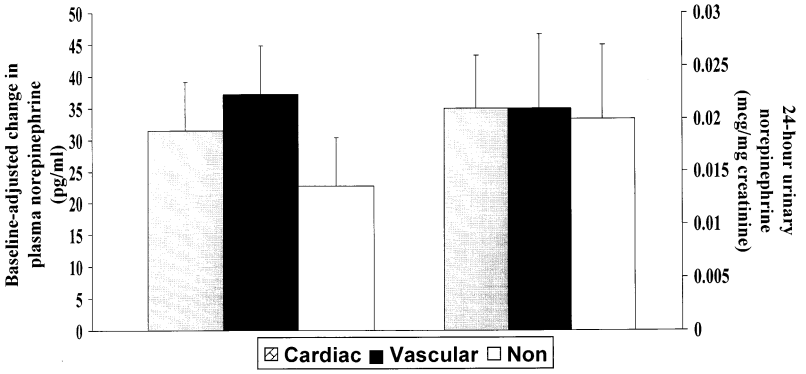

Fig. 3. Change in plasma norepinephrine in response to the Stroop task and 24-h concentrations of urinary norepinephrine among cardiac, vascular and non reactors. Brackets denote standard errors.

with 24-h urinary epinephrine excretion ($r = 0.29$, $P < 0.03$). No other significant correlations were observed (P's > 0.10).

4. Discussion

The results of this study indicate that persons who exhibit a predominance of cardiac output or peripheral resistance on exposure to common laboratory stressors differ in a corresponding manner on other indices of cardiovascular response, as well as in plasma epinephrine responses and in the 24-h urinary excretion of epinephrine. Specifically, cardiac reactors showed hemodynamic reactions consistent with heightened myocardial responsivity, including elevated cardiac output, reduced pre-ejection period, and a smaller reduction in stroke volume during task exposure, relative to vascular reactors. Both the rise in plasma epinephrine concentration and 24-h urinary epinephrine excretion were also greater among cardiac reactors than among vascular reactors and non reactors. In comparison to cardiac reactors, vascular reactors responded to mental stress with more elevated diastolic blood pressure, a rise in peripheral resistance and pulse wave velocity, and a greater reduction in stroke volume. However, the prediction that vascular reactors might show a more pronounced elevation in plasma norepinephrine concentration, compared to cardiac reactors and non reactors, was not supported in these data (Fig. 3).

Correlations corroborated the results of group analyses. Relative cardiac reactivity, across all subjects, covaried positively with heart rate and stroke volume, negatively with cardiac pre-ejection period, and positively with plasma epinephrine response to the Stroop test and with the 24-h urinary excretion of epinephrine. On the other hand, vascular reactivity correlated positively with changes in systolic and diastolic blood pressure and pulse wave velocity, and negatively with changes in stroke volume, but did not correlate significantly with any of the catecholamine

measurements. Finally, although change in cardiac output and peripheral resistance showed a strong inverse correlation ($r = -0.84$), their differential covariation with other response parameters, particularly those that were measured independently of cardiac output and total peripheral resistance (pre-ejection period, pulse wave velocity and the catecholamine measurements), provide evidence for the discriminant validity of cardiac and vascular reactivity.

These results offer partial support for the hypothesis that variability in sympathoadrenal activity contributes to individual differences in cardiac and vascular reactivity. Because epinephrine preferentially activates β_1- and β_2-adrenergic receptors, promoting enhanced myocardial performance and vasodilatation, respectively, it was predicted that a predominant epinephrine release in response to psychological challenge would coincide with the hemodynamic pattern observed among cardiac reactors. In this regard, the results of this study are consistent with several previous reports demonstrating an association between elevated plasma epinephrine concentration and enhanced myocardial performance (e.g. McCubbin et al., 1983; Eisenhofer et al., 1985; Kaji et al., 1989; Light et al., 1994). Moreover, we extend earlier findings by demonstrating a significant relationship between cardiac reactivity, as observed in a laboratory setting, and urinary excretion of epinephrine in the naturalistic environment.

However, it was also predicted that greater elevations in plasma norepinephrine would be associated with enhanced vascular reactivity, due to the high affinity of norepinephrine for α-adrenergic receptors, which reside principally in peripheral vasculature and mediate vasoconstriction. Instead, our findings are consistent with previous reports showing a lack of significant correlation between vascular reactivity and plasma norepinephrine responses (Kaji et al., 1989; Light et al., 1994).

Because norepinephrine shows high affinity for α-adrenergic receptors (and ought, therefore, to promote vasoconstriction) and exogenous infusion of norepinephrine raises peripheral resistance (Shepherd and Vanhoutte, 1979), the lack of correlation between behaviorally-evoked elevations in norepinephrine and vascular reactivity is somewhat surprising. Several methodological considerations may account for this discrepancy. First, cardiovascular effects of norepinephrine are achieved primarily by its release as a neurotransmitter (Ziegler, 1989) and resulting 'spillover' into the circulation, as reflected in the plasma concentration, may not accurately index sympathetic release. Second, plasma catecholamines are typically sampled from the antecubital vein. It has been estimated that 45% of the norepinephrine concentration in antecubital venous plasma is derived from local, forearm release, and may not be representative of sympathetic activity in other areas (Hjemdahl et al., 1984). Venous norepinephrine levels also do not appear to reflect the increase in arterial norepinephrine seen in response to mental challenges, further suggesting that venous norepinephrine concentrations may be a poor indicator of central sympathetic activity (Hjemdahl et al., 1984). In contrast, plasma epinephrine is considered a good index of sympathoadrenal activation in response to psychological challenge (Ziegler, 1989). Epinephrine is released from the adrenal medulla directly into the circulation and acts as a hormone. Moreover, plasma epinephrine levels tend to be low at rest and show a marked change is response to

several mental stressors (Shepherd and Vanhoutte, 1979). These increases in plasma epinephrine are often sufficient to provoke physiological effects, such as altering heart rate or glucose metabolism (Ziegler, 1989).

Finally, it should also be noted that cardiac and vascular reactivity are likely to reflect individual differences in α- and β-adrenoreceptor density and sensitivity, in addition to catecholamine release. Previous research indicates that relative elevations in heart rate induced by isoproterenol (a β-adrenergic agonist) are associated positively with heart rate response to mental arithmetic (Mills et al., 1994) and a visual-spatial task and video game (Eisenhofer et al., 1985); blood pressure responses to exogenous norepinephrine also predict with behaviorally-evoked blood pressure change (Mills et al., 1994). Lastly, β-adrenoreceptor density and sensitivity, as measured in lymphocytes, predict heart rate and blood pressure responses to mental arithmetic (Mills et al., 1990; Marsland et al., 1995).

It is noteworthy that an association between cardiac reactivity and the urinary excretion of epinephrine was observed in this study. Although urinary epinephrine levels are responsive to psychological stress and single measurements appear to correlate with concomitant changes in plasma epinephrine in response to acute challenge (Akerstedt et al., 1983), numerous other factors also affect urinary epinephrine excretion. For example, posture, exercise, eating, smoking and caffeine consumption each may increase urinary epinephrine concentration (Ziegler, 1989). Given the variety of these behaviors and the frequency with which they may be encountered in daily life, it might seem surprising that any one variable would predict urinary epinephrine excretion over significant intervals of time and in natural environments. Nonetheless, the results of this study indicate that individuals who respond to psychological challenge with a predominant increase in cardiac output exhibit heightened excretion of urinary epinephrine over 24 h. Notably, plasma epinephrine responses to the Stroop task also showed a small, but significant, correlation with the 24-h urinary epinephrine excretion ($r = 0.27$, $P < 0.05$).

Finally, a few limitations of this study should be noted. First, as the Pitt Family Health Project was comprised exclusively of white males, it remains to be determined whether the associations observed here would be found among women or in ethnically-diverse samples. In addition, as the measurement of plasma catecholamine responses was limited to the Stroop task, we were not able to aggregate catecholamine responsivity across tasks. As previous work suggests that aggregated reactivity indexes are more reliable than individual measures (Kamarck et al., 1992, 1993), it is conceivable that behaviorally-evoked plasma catecholamine responses are actually more strongly associated with measures of cardiovascular response and 24-h urinary catecholamines than observed in this study.

In summary, this study replicates and extends previous investigations characterizing individual differences in cardiac and vascular reactivity by demonstrating that cardiac, vascular and non reactors may be differentiated on other measures of cardiovascular response, plasma epinephrine responses to psychological challenge, and 24-h urinary epinephrine excretion. These results provide further discriminant validity for cardiac and vascular reactivity and suggest that different sympathoadrenal mechanisms may underlie cardiovascular responses in these groups.

Acknowledgements

Preparation of this article was supported in part by grant NHLBI 40962 and 07560.

References

Akerstedt, T., Gillberg, M., Hjemdahl, P., Sigurdson, K., Gustavsson, I., Daleskog, M, Pollare, T., 1983. Comparison of urinary and plasma catecholamine responses to mental stress. Acta Physiol. Scand. 117, 19–26.

Arnetz, B.B., Fjellner, B., 1986. Psychological predictors of neuroendocrine responses to mental stress. J. Psychosom. Res. 30, 297–305.

Arnetz, B.B., Fjellner, B., Eneroth, P., Kallner, A., 1985. Stress and psoriasis: psychoendocrine and metabolic reactions in psoriatic patients during standardized stressor exposure. Psychosom. Med. 47, 528–541.

Baum, A.S., Lundberg, U., Grunberg, N.E., Singer, J.E., Gatchel, R.J., 1985. Urinary catecholamines in behavioral research stress. In: Lake, C.R., Ziegler, M.G. (Eds.), The Catecholamines in Psychiatric and Neurologic Disorders. Butterworths, Woburn, pp. 55–72.

Bolm-Audroff, U., Schwammle, J., Ehlenz, K., Kaffarnik, 1989. Plasma level of catecholamines and lipids when speaking before an audience. Work Stress 3, 249–253.

Contrada, R.J., Glass, D.C., Krakoff, L.R., Krantz, D.S., Kehoe, K., Isecke, W., Collins, C., Eltin, E., 1982. Effects of control over aversive stimulation and type A behavior on cardiovascular and plasma catecholamine responses. Psychophysiology 19, 408–419.

Debski, T.T., Kamarck, T.W., Jennings, J.R., Young, L.W., Eddy, M.J., Zhang, Y., 1991. A computerized battery for the assessment of cardiovascular reactivity. Int. J. Biomed. Comput. 27, 277–289.

Dimsdale, J.E., Moss, J., 1980. Plasma catecholamines in stress and exercise. J. Am. Med. Assoc. 243, 340–342.

Eisenhofer, G., Lambie, D.G., Johnson, R.H., 1985. β-adrenoceptor responsiveness and plasma catecholamines as determinants of cardiovascular reactivity to mental stress. Clin. Sci. 69, 483–492.

Fibiger, W., Evans, O., Singer, G., 1986. Hormonal responses to a graded mental workload. Eur. J. Appl. Physiol. 55, 339–343.

Forsman, L., Lindblad, L.E., 1983. Effect of mental stress on baroreceptor-mediated changes in blood pressure and heart rate and on plasma catecholamines and subjective responses in healthy men and women. Psychosom. Med. 45, 435–445.

Frankenhauser, N., Johasson, G., 1976. Task demand as reflected in catecholamine excretion and heart rate. J. Hum. Stress 2, 15–23.

Frankenhauser, N., Lundberg, U., Forsman, L., 1980. Dissociation between sympathetic-adrenal and pituitary-adrenal responses to an achievement situation characterized by high controllability: comparison of type A and type B males and females. Biol. Psychol. 10, 79–91.

Goldstein, D.S., Eisenhofer, G., Sax, F.L., Keiser, H.R., Kopin, I.J., 1987. Plasma norepinephrine pharmacokinetics during mental challenge. Psychosom. Med. 49, 591–605.

Halbrugge, T., Gerhardt, T., Ludwig, J., Heidbreder, E., Graefe, K., 1988. Assay of catecholamines and dihydroxyphenylethyleneglycol in human plasma and its application in orthostasis and mental stress. Life Sci. 43, 19–26.

Hjemdahl, P., Freyschuss, U., Juhlin-Dannfelt, A., Linde, B., 1984. Differentiated sympathetic activation during mental stress evoked by the Stroop test. Acta Physiol. Scand. 527 Suppl., 25–29.

Jennings, J.R., Choi, S., 1983. An arterial to peripheral pulse wave velocity measure. Psychophysiology 20, 410–418.

Kaji, V., Ariyoshi, K., Tsuda, Y., Kanaya, S., Fujino, T., Kuwabara, H., 1989. Quantitative correlation between cardiovascular and plasma epinephrine response to mental stress. Eur. J. Appl. Physiol. 59, 221–226.

Kamarck, T.W., Jennings, J.R., Debski, T.T., Glickman-Weiss, E., Johnson, P.S., Eddy, M.J., Manuck, S.B., 1992. Reliable measures of behaviorally-evoked cardiovascular reactivity from a PC-based test battery: results from student and community samples. Psychophysiology 29, 17–28.

Kamarck, T.W., Jennings, J.R., Manuck, S.B., 1993. Psychometric applications in the assessment of cardiovascular reactivity. Homeostasis Health Dis. 34, 229–243.

Kasprowicz, A.L., Manuck, S.B., Malkoff, S.B., Krantz, D., 1990. Individual differences in behaviorally-evoked cardiovascular response: temporal stability and hemodynamic patterning. Psychophysiology 27, 605–619.

Kirk, R.E., 1968. Experimental Design: Procedures for the Behavioral Sciences. Brooks, Belmont.

Kubicek, W.G., Karnegis, J.N., Patterson, R.P., Witsoe, D.A., Mattson, R.H., 1966. Development and evaluation of an impedance cardiograph system. Aerospace Med. 37, 1208–1212.

LeBlanc, J., Cote, J., Jobin, M., Labrie, A., 1979. Plasma catecholamines and cardiovascular responses to cold and mental activity. J. Appl. Physiol. 47, 1207–1211.

Light, K.C., Turner, J.R., Hinderliter, A.L., Girdler, S.S., Sherwood, A., 1994. Comparison of cardiac versus vascular reactors and ethnic groups in plasma epinephrine and norepinephrine responses to stress. Int. J. Behav. Med. 1, 229–246.

Lovallo, W.R., Pincomb, G.A., Brackett, D.J., Wilson, M.F., 1990. Heart rate reactivity as a predictor of neuroendocrine responses to aversive and appetitive challenges. Psychosom. Med. 48, 125–133.

Lovallo, W.R., Pincomb, G.A., Edwards, G.L., Brackett, D.J., Wilson, M.F., 1986. Work pressure and the type A behavior pattern exam stress in male medical students. Psychosom. Med. 48, 125–133.

Manuck, S.B., Cohen, S., Rabin, B.S., Muldoon, M.F., Bachen, E.A., 1991. Individual differences in cellular immune response to stress. Psychol. Sci. 2, 111–115.

Manuck, S.B., Polefrone, J.M., Terrell, D.F., Muldoon, M.F., Kasprowicz, A.L., Waldstein, S.R., Jennings, J.R., Malkoff, S.B., Marsland, A., Graham, R.E., 1996. Absence of enhanced sympathoadrenal activity and behaviorally-evoked cardiovascular reactivity among offspring of hypertensives. Am. J. Hypertens. 9, 248–255.

Marsland, A.L., Manuck, S.B., Wood, P., Rabin, B.S., Muldoon, M.F., Cohen, S., 1995. β_2-adrenergic receptor density and cardiovascular response to mental stress. Physiol. Behav. 57, 1163–1167.

McCubbin, J.A., Richardson, J.E., Langer, A.W., Kizer, J.S., Obrist, P.A., 1983. Sympathetic neuronal function and left ventricular performance during behavioral stress in humans: the relationship between plasma catecholamines and systolic time intervals. Psychophysiology 20, 102–110.

Miller, J.C., Horvath, S.M., 1978. Impedance cardiography. Psychophysiology 15, 80–91.

Mills, P.J., Dimsdale, J.E., Neleson, R.A., Jasiewicz, J., Ziegler, M.G., Kennedy, B., 1994. Patterns of adrenergic receptors and adrenergic agonists underlying cardiovascular responses to a psychological challenge. Psychosom. Med. 56, 70–76.

Mills, P.J., Dimsdale, J.E., Ziegler, M.G., Berry, C.C., Bain, R.D., 1990. Beta-adrenergic receptors predict heart rate reactivity to a psychosocial stressor. Psychosom. Med. 52, 621–623.

Muldoon, M.F., Bachen, E.A., Manuck, S.B., Waldstein, S.R., Bricher, P.L., Bennett, J.A., 1992. Acute cholesterol responses to mental stress and change in posture. Arch. Intern. Med. 152, 775–780.

Patterson, S.M., Gottdiener, J.S., Hecht, G., Vargot, S., Krantz, D.S., 1993. Effects of acute mental stress on serum lipids: mediating effects of plasma volume. Psychosom. Med. 55, 525–532.

Piascik, M.T., Soltis, E.E., Piascik, M.M., Macmillan, L.B., 1996. adrenoreceptors and vascular regulation: molecular, pharmacological and clinical correlates. Pharmacol. Ther. 72, 215–241.

Shepherd, J.T., Vanhoutte, P.M., 1979. The Human Cardiovascular System. Raven Press, New York.

Sherwood, A., Allen, M.T., Fahrenberg, J., Kelsey, R.M., Lovallo, W.R., van Dooren, L.J.P., 1990a. Methodological guidelines for impedance cardiography. Psychophysiology 27, 1–23.

Sherwood, A., Dolan, C.A., Light, K.C., 1990b. Hemodynamics of blood pressure responses during active and passive coping. Psychophysiology 27, 656–668.

Sherwood, A., Turner, J.R., 1995. Hemodynamic responses during psychological stress: implications for studying disease processes. Int. J. Behav. Med. 2, 193–218.

Sive, W.J., Hattingh, J., 1991. The measurement of psychophysiological reactions of pilots to a stressor in a flight simulator. Aviation Space Environ. Med. 62, 831–836.

Taggart, P., Carruthers, M., Somerville, W., 1973. Electrocardiogram, plasma catecholamines and lipids, and their modification by oxyprenolol when speaking before an audience. Lancet 341–346.

Tischenkel, N.J., Saab, P.G., Schneiderman, N., Nelesen, R.A., DeCarlo Pasin, R., Goldstein, D.A., Spitzer, S.B., Woo-Ming, R., Weidler, D.J., 1989. Cardiovascular and neurohormonal responses to behavioral challenge as a function of race and sex. Health Psychol. 8, 503–524.

Waldstein, S.R., Ryan, C.M., Polefrone, J.M., Manuck, S.B., 1994. Neuropsychological performance of young men who vary in familial risk for hypertension. Psychosom. Med. 56, 449–456.

Ziegler, M.G., 1989. Catecholamine measurement in behavioral research. In: Schneiderman, N., Weiss, S.M., Kaufman, P.G. (Eds.), Handbook of Research Methods in Cardiovascular Behavioral Medicine. Plenum, New York, pp. 167–183.