Hemodynamic and Endocrine Responsiveness to Mental Arithmetic Task and Mirror Drawing Test in Patients With Essential Hypertension

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To evaluate the reactivity to psychological stress in patients with essential hypertension we investigated hemodynamic and endocrinologic changes during a mental arithmetic task (MAT) and a mirror drawing test (MDT) in 10 hypertensive subjects. Hemodynamic changes were assessed continuously using an ambulatory radionuclide cardiac detector. There were significant increases in systolic blood pressure (ΔSBP: +37.8 ± 11.1 and +41.0 ± 9.4 mm Hg during MAT and MDT, respectively, P < .01) and diastolic blood pressure (ΔDBP: +17.5 ± 3.1 and +21.2 ± 3.9 mm Hg, P < .01) and in heart rate (ΔHR: +17.1 ± 5.3 and +12.5 ± 2.9 beats/min, P < .01) during both tasks in association with an increase in cardiac output (CO). The plasma levels of norepinephrine and epinephrine increased during both the MAT (ΔNE: +0.074 ± 0.022 ng/mL, P < .01; ΔEP: +0.068 ± 0.025 ng/mL, P < .01) and the MDT (ΔNE: +0.067 ± 0.034 ng/mL, P < .01; ΔEP: +0.030 ± 0.011 ng/mL, .05 < P < .1). Although the ΔNE was similar in response to the MAT and MDT, the ΔEP during the MDT tended to be less than half the ΔEP during the MAT (.05 < P < .10). The ΔEP was positively correlated with the ΔDBP and the ΔCO during both tasks and with the ΔSBP and the ΔHR during the MAT. These findings suggest that MAT- and MDT-induced increases in BP were attributable mainly to an increase in CO, possibly as the result of stimulation of the sympathoadrenomedullary system. However, the sympathoadrenomedullary system appeared to be more closely associated with the hemodynamic responses during the MAT than during the MDT.

KEY WORDS: Mental stress test, cardiovascular reactivity, catecholamine.

Stress is thought to contribute to the development and maintenance of hypertension. The incidences of hypertension and left ventricular hypertrophy are higher in men in high stress jobs than in men in less stressful jobs. Individuals with hypertensive risk factors exhibit an exaggerated stress-induced cardiovascular response at a younger age.

The mental arithmetic task (MAT) is the most frequently used mental stress test to evaluate the re-
response to stress in hypertensive subjects. Several studies have demonstrated that hemodynamic reactivity to the MAT is enhanced in hypertensive individuals, as indicated by increases in heart rate (HR), systolic and diastolic blood pressures (SBP and DBP), and cardiac output (CO). However, the results of studies evaluating endocrinologic responses to the MAT in hypertensive subjects have been inconsistent. Increases in the plasma levels of catecholamines during the MAT have been observed in hypertensive subjects in some studies, but not in others. The mirror drawing test (MDT) has also been used to evaluate stress responses. The MAT and MDT have induced similar increases in blood pressure and the plasma levels of catecholamines in healthy subjects in some studies.

Manuck observed two patterns of hemodynamic changes in response to the MAT in normotensive subjects: an increase in CO in association with a decrease in total peripheral resistance (TPR) and a decrease in CO in association with an increase in TPR. The MDT caused a decrease in CO and an increase in TPR. Thus, responses during the MAT and MDT remain controversial. The cardiovascular and sympathoadrenal responses to the MAT and MDT in patients with essential hypertension have not been compared directly.

Hemodynamic parameters change rapidly during stress tasks. Although echocardiography is generally used to assess hemodynamics during mental stress tests, it does not provide continuous monitoring and interpretations of results by different examiners can be inconsistent. Impedance cardiography, which is used to assess hemodynamic aspects of cardiovascular function, is noninvasive and nonobtrusive but has problems in the stroke volume equation. The ambulatory radionuclide cardiac detector has been developed to record measurements of left ventricular function continuously, noninvasively, and consistently. This device has been shown to assess hemodynamic changes reliably and accurately. Previous studies have used the radionuclide cardiac detector to assess cardiovascular responses during the MAT, but data on comprehensive changes in hemodynamic and endocrine parameters in hypertensive patients are limited.

We assessed cardiovascular responses to the MAT and the MDT in hypertensive subjects using the radionuclide cardiac detector and investigated the humoral mechanism of cardiovascular reactivity to mental stress.

METHODS

Subjects We studied 10 subjects (3 men and 7 women; mean age, 62.1 ± 2.5 years; range, 49 to 76 years) with mild to moderate hypertension. Casual morning SBP ranged from 140 to 180 mm Hg; DBP ranged from 90 to 100 mm Hg. The results of measurements of the serum levels of electrolytes, creatinine, and aldosterone and plasma renin activity, urinalysis, and an electrocardiographic examination were normal. Thus, there was no evidence of a known cause of hypertension in any of the subjects. Individuals receiving β-blocking agents were excluded from the study because β-blocking agents have been shown to alter reactivity to mental stress tests. Drug therapy was as follows: no antihypertensive drugs (n = 6), diltiazem hydrochloride (n = 1), benidipine hydrochloride (n = 2), and enalapril maleate (n = 1). These antihypertensive agents have not been shown to influence stress reactivity. Because changes in parameters were not significantly different between subjects with and without antihypertensive drugs, we assessed the results in the overall study population.

Test Protocol The study protocol was approved by the Ethics Committee of Tokyo University Branch Hospital, Faculty of Medicine, the University of Tokyo. Written informed consent was obtained from all subjects after the nature and aims of the study were explained.

The experiment was started in the morning. Blood cells were labeled in vivo with 20 mCi 99mTc by the method of Callahan et al. The ambulatory radionuclide cardiac detector (VEST; Capintec Inc., Ramsey, NJ) was positioned on the chest so as to minimize right ventricular and left atrial overlap under the guidance of a gamma camera.

An indwelling catheter was inserted into a cubital vein of the left arm for blood sampling. The cuff of a noninvasive continuous arterial pressure monitor (Finapres; NEC Sanei Co., Tokyo, Japan) was attached to the middle phalanx of the middle finger of the left hand, and the left forearm was placed on an armrest adjusted so that the monitored finger was on the same horizontal plane as the left ventricle.

Measurements were obtained with subjects in the sitting position in an air-conditioned laboratory after a 30-min period of rest. The experiment was started when subjects were relaxed, as confirmed by measurement of HR.

After baseline measurements were obtained, subjects performed the MAT and the MDT in a randomized order. They started the second mental stress task at least 15 min after completing the first task.

Mental Stress Tests Mental Arithmetic Task Subjects were instructed to mentally subtract 17 from 1000 in a serial manner for 3 min as quickly and accurately as possible and to provide the answers verbally.

Mirror Drawing Test The MDT is a laboratory stress task in which subjects trace a metal star shape with an electric probe while watching the progress of the probe in a mirror, which reverses the image. Each time the probe slips off the track, an error is registered on the score counter, and a loud click is heard. Subjects were directed to perform this task for 6 min as quickly and correctly as possible.
Blood Sampling  Blood samples for measurement of epinephrine (EP), norepinephrine (NE), corticotropin (ACTH), and cortisol were collected just before and after each mental stress task.

Hemodynamic Evaluation  Hemodynamic parameters were assessed 5 min before each mental stress task and the average of the 5-min measurements was used as baseline data. Hemodynamic responses were represented by the average of measurements obtained in the last 2 min of the test for the MAT and in the last 5 min of the test for the MDT.

Data Acquisition  The Ambulatory Radionuclide Cardiac Detector  The ambulatory radionuclide cardiac detector is a portable cardiac detector consisting of a nonimaging radionuclide detector, a modified Holter recorder, and a small microprocessor that provides time and electrocardiographic (ECG) gating information. A plastic garment is used to hold the detector in place. The device records ECG and radionuclide data, and the recorder also contains an event marker and a real-time clock. The nuclear data consisted of sequential gamma counts of left ventricular activity obtained 32 times/sec, which were digitized and recorded on tape. The radionuclide and ECG data were averaged at 15- to 30-sec intervals. We determined the ejection fraction (EF), the end-diastolic and end-systolic counts, the relative CO, the peak filling rate (PFR), and the HR over the entire monitoring period. The EF was calculated as follows: left ventricular stroke count (end-diastolic count—end-systolic count) divided by the fixed background count (0.3 × end-diastolic count) because Tamaki et al.29 have suggested that if 70% of the end-diastolic count is used as the baseline count, the EF determined by the radionuclide cardiac detector is correlated with the EF measured by a gamma camera. The baseline end-diastolic volume was defined as 100% and the relative CO was calculated by multiplying the relative stroke volume by the HR.

Noninvasive Continuous Arterial Pressure Monitor  SBP, DBP, and mean arterial pressure (MAP) were transduced according to Penaz’s volume clamp method using a noninvasive continuous arterial blood pressure monitor (Finapres)30,31 and the data were recorded onto a personal computer (PC9801, NEC, Tokyo, Japan).

Hormone Assays  Plasma levels of EP and NE were analyzed by high-performance liquid chromatography (HPLC)32 coupled to an electrochemical detector. The interassay coefficients of variance (CV) were 6.0% for NE and 7.0% for EP. The lower limit of detection was 0.01 ng/mL for both NE and EP. The plasma level of ACTH was determined by an immunoradiometric assay (IRMA)33 with a lower limit of detection of 5 pg/mL. The intraassay CV was 5.0%, and the interassay CV was <6.0%. The plasma level of free cortisol was also analyzed by a radioimmunoassay (RIA)34 with a lower limit of detection of 0.23 µg/dL, an intraassay CV of 5.0%, and an interassay CV of 9.0%.

Statistical Analyses  Data are expressed as the mean ± SEM. Analyses were performed with the Statistical Analysis System on a personal computer. Analysis of variance according to the cross-over method was conducted on hemodynamic and endocrinologic parameters. This entailed a 2 (Order) × 2 (Task) × 2 (Period) design. The relations between intraindividual changes in parameters induced by each test and between changes in same parameters induced by both tests were evaluated by determining Pearson’s correlation coefficients. A P < .05 was considered significant.

RESULTS

There was no significant effect of two task orders.

Mental Arithmetic Task  Heart rate, SBP, DBP, the relative CO, and PFR increased significantly during the MAT (Table 1). There were no significant changes in the EF, end-diastolic volume (EDV), or systemic vascular resistance (SVR). Plasma levels of NE, EP, and ACTH showed significant increases (Table 2).

The change in the plasma level of EP was positively correlated with changes in HR, SBP, DBP (Figure 1) and the relative CO (r = 0.791, P < .01).

The change in SBP was significantly correlated with the changes in EF (r = 0.765, P < .01), relative CO (r = 0.866, P < .01), and SVR (r = −0.726, P < .05). The change in SBP was not significantly correlated with the change in EDV.

Mirror Drawing Test  The MDT was associated with significant increases in HR, SBP, DBP, and the relative CO (Table 1). There were no significant changes in the EF, EDV, or PFR. The plasma level of NE increased significantly, but the plasma levels of EP, ACTH, and cortisol did not change significantly (Table 2).

The change in the plasma level of EP was not significantly correlated with changes in SBP and HR but was positively correlated with changes in DBP (Figure 1) and the relative CO (r = 0.662, P < .05).

The change in SBP was significantly correlated with the change in relative CO (r = 0.694, P < .05). The change in SBP was not significantly correlated with the changes in EF, EDV, and SVR.

Comparison of MAT and MDT  The MAT- and the MDT-induced changes in HR, SBP, DBP, PFR, the relative CO, and the plasma levels of NE and EP were correlated positively (Table 3). The MAT tended to produce greater increases in the plasma level of EP than the MDT (.05 < P < .10) (Table 2).

DISCUSSION

In the present study, both the MAT and the MDT caused similar cardiovascular responses. The increase in arterial pressure was mediated mainly by
TABLE 1. EFFECT OF MENTAL ARITHMETIC TASK AND MIRROR DRAWING TEST ON HEMODYNAMIC PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>Mental Arithmetic Task</th>
<th>Mirror Drawing Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64.0</td>
<td>81.1</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>148.4</td>
<td>186.2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>77.0</td>
<td>94.5</td>
</tr>
<tr>
<td>Mean</td>
<td>98.4</td>
<td>123.4</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>57.0</td>
<td>57.2</td>
</tr>
<tr>
<td>Cardiac output (/EDV)</td>
<td>36.0</td>
<td>46.3</td>
</tr>
<tr>
<td>EDV (%)</td>
<td>97.5</td>
<td>96.7</td>
</tr>
<tr>
<td>Peak filling rate (EDV/s)</td>
<td>1.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg × EDV)</td>
<td>2.9</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*P < .01 stress v rest.
†Differences of cardiac output, EDV, peak filling rate, and systemic vascular resistance are percent increases.

TABLE 2. EFFECT OF MAT AND MDT ON ENDOCRINOLOGIC PARAMETERS

<table>
<thead>
<tr>
<th></th>
<th>Mental Arithmetic Task</th>
<th>Mirror Drawing Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Stress</td>
</tr>
<tr>
<td>Norepinephrine (ng/mL)</td>
<td>0.31</td>
<td>0.39</td>
</tr>
<tr>
<td>Epinephrine (ng/mL)</td>
<td>0.03</td>
<td>0.09</td>
</tr>
<tr>
<td>ACTH (pg/mL)</td>
<td>35.8</td>
<td>54.6</td>
</tr>
<tr>
<td>Cortisol (µg/dL)</td>
<td>13.4</td>
<td>14.1</td>
</tr>
</tbody>
</table>

*P < .01 stress v rest.

ACTH, corticotropin.

an increase in CO in response to both stress tasks. These results provide support for previous results obtained by echocardiography, an arterial catheter, and impedance cardiography in hypertensive subjects. A few studies have evaluated the responses to mental stress tests using the radionuclide cardiac detector. Kiess et al showed that mental stress increased BP accompanied by an increase in CO in normotensive subjects, and Young et al demonstrated that the MAT caused increases in BP and EF in normotensive and hypertensive subjects as a whole; however, they did not show stress reactivity in hypertensive subjects. In the present study the radionuclide cardiac detector showed that CO increased in association with pressor responses to mental stress in hypertensive subjects.

The plasma level of EP is thought to play an important role in the development and maintenance of hypertension. Plasma level of EP is increased in older subjects with essential hypertension independently of the plasma level of NE; the plasma level of NE is elevated only in younger hypertensive subjects. The MAT caused an increase in the plasma level of EP in the present study, which is consistent with the results of some studies although Spence et al did not observe a significant change in the plasma level of EP. The discrepancy among results may be attributable to differences in subject characteristics:
FIGURE 1. Correlation between the increases (Δ) in heart rate and systolic and diastolic blood pressure and increases in plasma epinephrine (Δ epinephrine) in mental arithmetic task (MAT) and in mirror drawing test (MDT).

| TABLE 3. CORRELATIONS BETWEEN MENTAL ARITHMETIC TASK AND MIRROR DRAWING TEST |
|---------------------------------|---------|
|                                  | r       |
| ΔHeart rate                      | 0.798*  |
| ΔSystolic blood pressure         | 0.796*  |
| ΔDiastolic blood pressure        | 0.793*  |
| ΔEjection fraction               | 0.502   |
| ΔCardiac output                  | 0.706†  |
| ΔPeak filling rate               | 0.859*  |
| ΔEnd-diastolic volume            | 0.329   |
| ΔSystemic vascular resistance    | 0.365   |
| ΔNorepinephrine                 | 0.733†  |
| ΔEpinephrine                     | 0.677†  |
| ΔACTH                            | −0.160  |
| ΔCortisol                        | −0.348  |

Δ, changes in; ACTH, corticotropin.

* P < .01; † P < .05.
of the adrenosympathetic nervous system during the MAT than during the MDT. The MDT may influence hemodynamic responses by a nonepinephrine-related mechanism, such as the peripheral sympathetic nervous system. Although there was no significant difference between the MAT- and the MDT-induced increases in the plasma level of NE, the present findings suggest that the sympathetic nervous system may not mediate the response to these tests to the same extent; plasma NE levels are complex to interpret because they represent spillover from the sympathetic cleft and because local effects of the sympathetic nervous system may differ among organs. More accurate methods of assessing sympathetic tone may resolve this question.

In conclusion, the radionuclide cardiac detector showed that both the MAT and the MDT increased BP in association with an increase in CO in hypertensive subjects. Our findings suggest that the sympathoadrenomedullary system may respond differently to the MAT and the MDT in these individuals.

REFERENCES


