Short-term reproducibility of a mental arithmetic stress test

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SUMMARY

1. To evaluate the short-term reproducibility of heart rate, oscillometrically determined blood pressure, ante-cubital venous plasma catecholamine concentrations and subjective responses to strictly standardized mental arithmetic, we performed two identical tests 1 h apart in 14 young, healthy and normotensive male subjects (age 22–35 years).

2. Heart rate and blood pressure responses to the two stress tests were highly correlated, when expressed both as correlations between levels attained during stress ($r > 0.80$ throughout) and as absolute reactivity measures (all $r > 0.75$). Also, subjective stress responses were highly correlated, when considering both levels during stress and reactivity ($r = 0.97$ and $r = 0.85$, respectively). Stress levels of catecholamines were correlated, but the change scores (reactivity) were unrelated.

3. The measurement error SD for heart rate was 2.6 and 3.0 beats/min for reactivity and stress levels, respectively. The corresponding SD for blood pressure ranged between 2.7 and 4.4 mmHg. Subjective stress experience showed an SD of a similar magnitude. The responses of plasma catecholamine concentrations were subject to considerable variability.

4. It is concluded that haemodynamic and subjective stress responses and stress levels during the mental arithmetic stress test show acceptable reproducibility and high test-retest correlations. However, stress-induced changes in venous plasma catecholamine concentrations show low reproducibility.

Key words: catecholamines, haemodynamic factors, mental stress, mood assessment, test-retest reproducibility.

INTRODUCTION

Much research interest has been devoted to the possible association between enhanced stress reactivity and cardiovascular disorders such as essential hypertension and coronary heart disease [1–6]. Despite this, little is still known about the biological determinants of stress reactivity and the way in which it is influenced by endogenous and exogenous conditions [5, 7, 8]. In part, this may be related to the relative lack of documentation regarding the reproducibility of mental stress test protocols used for reactivity assessment.

Among the protocols that have been employed to evaluate neural and neuroendocrine control of the circulation, the forced mental arithmetic test is probably the most widely used technique for eliciting psychological arousal and cardiovascular activation [4, 9–11]. Mental arithmetic, as a stress test, appears to be easy to perform and standardize, and it is commonly assumed that the response patterns are relatively unaffected by personality idiosyncrasies. The cardiovascular and neuroendocrine responses to mental arithmetic are similar to the so-called defence–alarm reaction, and they include increases in cardiac output, heart rate, blood pressure and muscle blood flow, partly due to an activation of the sympathetic-adrenal system [9, 12].

Although widely used, the reliability of the mental arithmetic protocol as a cardiovascular research tool has not been determined [4, 5]. Previous studies in this field have mainly addressed the issue of the long-term stability of increased stress reactivity as an individual characteristic (see [13–26] for data on this issue), and only a few studies have explicitly dealt with the short-term reproducibility of stress tests [27–30]. Whereas assessment of long-term stability is important for epidemiological studies of stress reactivity as a risk factor for future disease, documentation of short-term reliability is essential for experimental studies (for instance by means of
acute pharmacological interventions) of the mechanisms that modulate stress response patterns.

The present study, which is part of a series of investigations of determinants of stress response patterns, was therefore designed to evaluate the short-term reproducibility of the responses of heart rate, blood pressure, plasma catecholamine concentrations and subjective stress to a strictly standardized mental arithmetic stress test. To determine the reliability of the stress test as such, we performed two identical tests with an hour between them.

MATERIALS AND METHODS

Subjects

Fourteen young normotensive and non-obese male subjects participated in the study. The subjects were recruited among medical and engineering students at the University of Göteborg, and among hospital employees. Their mean age, weight and height were 26.8 years (range 22–35 years), 77.4 kg (67–90 kg) and 186.4 cm (178–195 cm), respectively. All subjects were apparently healthy non-smokers without any medication or history of alcohol abuse or cardiovascular disease.

Informed consent was obtained from each subject before inclusion in the study. The protocol was approved by the Ethics Committee of the University of Göteborg, and the study was performed according to the Declaration of Helsinki.

Experimental design

The stress experiments were performed in the morning or afternoon according to a strictly within-subject standardized procedure [10, 31], i.e. every effort was made to keep all confounding factors that might influence resting levels and stress responses as constant as possible between test I and test II [8]. The participants were instructed to avoid heavy exercise and emotional excitement and to fast for at least 4 h before the experiment. To avoid influences on catecholamine levels and other variables, all subjects were asked to refrain from taking methylxanthine-containing products on the day before the experiment.

In brief, the general design of the study was as follows. Two identical mental stress tests were performed with an interval of 1 h between them. Each stress test was preceded and followed by 10 min pre- and post-stress baseline periods, respectively. During each stress test, the subjects performed 10 min of forced mental arithmetic. Two experimenters participated in the study (M.P. and S.J.), but each subject always met the same examiner during the first and second stress test.

Procedure

Upon reporting to the laboratory, the subject was placed in a comfortable chair in a semi-recumbent position. A venous cannula (Venflon; Viggo, Helsingborg, Sweden) was inserted percutaneously into an antecubital vein of the dominant arm for blood sampling. A 50 cm polyethylene catheter was connected to the indwelling cannula, and the catheter was led through the wall to an adjacent control room, where all blood samples were drawn. This technique allowed unobtrusive blood sampling, without the subjects knowing exactly when blood samples were being drawn. The intravenous line was kept patent by a slow infusion of saline (150 mmol/l NaCl).

Electrodes for recording of computerized vectorcardiography were fixed to the chest, arms and legs according to a modified Frank system, i.e. leg electrodes were moved to the anterior superior iliac spines. A blood pressure cuff for the non-invasive assessment of blood pressure was applied to the non-dominant arm.

Mental stress

After a 1 h rest period, the experiment commenced with the first 10 min pre-stress baseline period with the subject in the quiet and dimly lit room. After this baseline recording, the experimenter entered the room, which was now fully lit, and gave an approximately 40 s long oral instruction. The subject then performed forced mental arithmetic for 10 min with serial subtractions of 7 from 700, trying to keep pace with a metronome at a rate of approximately 90 beats/min. Since none of the subjects was able to perform calculations at this high rate for more than a brief period of time, the subjects were repeatedly asked to increase the speed by short comments such as ‘Try to go a little faster!’, ‘Follow the metronome!’ etc. The number of correct responses was not recorded, but wrong answers were immediately corrected. Throughout the test, the experimenter vigorously encouraged the subjects to perform at his maximum speed, but assumed an emotionally neutral attitude and the subjects were not harassed. After a positive and reassuring comment, the experimenter reduced the light and left the room. The stress task was then followed by a 10 min post-stress baseline period.

After conclusion of the first part of the experiment, the subjects remained in the same position for 1 h but were allowed to read or listen to the radio. The second stress test was performed in exactly the same way as the first.

Heart rate and blood pressure monitoring

Heart rate was continuously monitored beat-to-beat throughout the experiment by computerized vectorcardiography (MIDA System; Ortivus Medical AB, Täby, Sweden).

Blood pressure was measured using an automatic non-invasive oscillometric blood pressure monitor (Dinamap model 845; Critikon Instruments, Tampa, FL, U.S.A.). A blood pressure recording was initiated every 60 s, and the average duration of each recording was approximately 15 s. The Dinamap has been shown to correlate closely with intra-arterial recordings in a previous study in our
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Laboratory; the correlation coefficients for systolic and diastolic blood pressure were $r = 0.92$ and $r = 0.90$, respectively [32]. There were no significant differences between the reproducibility of blood pressure determined by the Dinamap (systolic blood pressure 2.8 mmHg; diastolic blood pressure 3.4 mmHg) and by the intra-arterial method (systolic blood pressure 2.4 mmHg; diastolic blood pressure 3.7 mmHg). In comparative studies, the Dinamap has been found to give similar systolic and diastolic blood pressure readings to the random-zero sphygmomanometer [33]. Compared with intra-arterial recordings, the Dinamap has been shown to systematically under-estimate systolic blood pressure [34], and in the previous study in our laboratory the oscillometric diastolic blood pressure levels were 5–7 mmHg lower than the intra-arterial measurements [32].

Blood sampling and biochemical analyses

Blood samples for analysis of plasma catecholamine levels were collected before, during and after each stress experiment at the following time points: immediately before stress at the end of the pre-stress baseline, after 10 min of mental arithmetic, and 10 min after cessation of stress at the end of the post-stress baseline period (see Fig. 1). All blood samples were obtained from the indwelling venous cannula. The first 5 ml of blood was always discarded.

For analysis of plasma catecholamine levels, 11 ml of blood was drawn into pre-chilled tubes containing 220 µl of glutathione–EDTA (60 mg/ml and 90 mg/ml, respectively) and immediately placed on ice. The samples were centrifuged within 2 min of collection at 2000 $g$ (4°C) for 5 min. Plasma aliquots were stored at −70°C until assay. The catecholamines were isolated from plasma by adsorption on to alumina. Plasma adrenaline and noradrenaline were separated by reversed-phase h.p.l.c. and were quantified by a highly sensitive electrochemical detector (Waters 641; Millipore Ltd, Griesenheim, Germany). All samples from each subject were analysed in the same assay-run. Dihydroxybenzylamine was used as internal standard to compensate for incomplete recovery, and the analytical procedure followed that described by Weicker et al. [35]. This method has previously been validated against assessments by radioenzymic assay [35, 36]. In our laboratory, the intra-assay variation coefficients for basal and stress levels are 2.5% and 3.3% for noradrenaline and 8.6% and 8.1% for adrenaline, respectively. The mean recovery rate is 62%. The detection limit is estimated to be 0.011 nmol/l for noradrenaline and 0.013 nmol/l for adrenaline in aqueous solutions, and ranges between 0.05 and 0.10 nmol/l plasma when defined as the concentration equivalent to five times the baseline noise.

Assessment of subjective arousal

The degree of subjective arousal and stress experience was assessed by four bipolar analogue scales from the ASPECT scale [37]. The following dimensions were used: hedonic tone, activity, relaxation and subjective stress experience. The assessments were performed immediately after each blood sample had been collected.

Data reduction

Haemodynamic data from the stress experiment were reduced by dividing baseline and stress periods into 2.5 min epochs, and by computing mean values for heart rate, blood pressure and diastolic blood pressure for each period. Since the duration of the initial oral instruction varied slightly among the subjects and the two experiments, the start of the calculations was not fully synchronized with the blood pressure measurements. Consequently, the number of blood pressure recordings varied between 2 and 3 per 2.5 min period. Data from the subjective assessments and catecholamine analyses were not reduced.

Reactivity was defined for each stress experiment as the difference between the mean level during the 10 min stress period and the corresponding mean from the 10 min pre-stress baseline period. Similarly, recovery was
defined as the difference between the stress and post-stress level. Adaptation of the heart rate and blood pressure variables during stress was defined for each individual and stress experiment as the slope (k value) of the four data points during the mental arithmetic test.

Statistical analysis

Standard statistical methods were used. Differences between the two tests were evaluated by one- and two-way analyses of variance for repeated measures with subject as random factor. For all repeated measures analyses, degrees of freedom were corrected according to the conservative Greenhouse & Geisser procedure for possible violation of the assumption of sphericity [38]. In addition, the significance of the stress-induced changes in response to each test and the possible difference between the two tests were analysed by Student’s t-test for paired comparisons. In all instances two-tailed tests were used, and the test was considered significant at \( P<0.05 \). The relations between levels and changes during the two experimental sessions were evaluated by Pearson’s product–moment correlation coefficients and Spearman’s rank correlation coefficients [39].

The test–retest reproducibility of stress levels and reactivity was expressed as the sd of the two measurements according to the formula [39]:

\[
\text{SD} = \sqrt{\frac{\Sigma (X_1 - X_2)^2}{2n}}
\]

where \( X_1 \) is the individual mean of the first observation, \( X_2 \) is the individual mean of the second, and \( n \) is the number of paired observations.

Table 1. Correlations expressed as univariate correlation coefficients between levels and stress-induced changes (reactivity) in haemodynamics, subjective arousal and plasma catecholamines during the two stress tests

| Abbreviation: BP, blood pressure. Statistical significance: \( ^aP<0.05 \), \( ^bP<0.01 \), \( ^cP<0.001 \), \( ^dP<0.0001 \). |

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<thead>
<tr>
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<th>Levels</th>
<th>Changes</th>
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<td></td>
<td>Pre-stress baseline</td>
<td>Stress</td>
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<tr>
<td>Haemodynamics</td>
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<tr>
<td>Heart rate</td>
<td>+0.88^c</td>
<td>+0.80^c</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>+0.95^d</td>
<td>+0.88^d</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>+0.94^d</td>
<td>+0.88^d</td>
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<tr>
<td>Subjective arousal</td>
<td></td>
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<tr>
<td>Perceived stress</td>
<td>+0.57^a</td>
<td>+0.97^d</td>
</tr>
<tr>
<td>Relaxation</td>
<td>+0.85^c</td>
<td>+0.43</td>
</tr>
<tr>
<td>Activation</td>
<td>+0.76^b</td>
<td>+0.91^d</td>
</tr>
<tr>
<td>Hedonic tone</td>
<td>+0.92^d</td>
<td>+0.32</td>
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<tr>
<td>Plasma catecholamines</td>
<td></td>
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<tr>
<td>Noradrenaline concn.</td>
<td>+0.88^c</td>
<td>+0.86^c</td>
</tr>
<tr>
<td>Adrenaline concn.</td>
<td>+0.87^c</td>
<td>+0.75^b</td>
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RESULTS

Pre-stress resting heart rate, subjective stress experience and plasma catecholamine concentrations were similar before the two stress experiments. Systolic blood pressure was slightly, but significantly higher before the second test [test I 118.5 versus test II 120.7 mmHg; \( t(13)=2.6, P=0.02 \)]. Also, diastolic blood pressure was somewhat higher before the second test [64.2 versus 65.9 mmHg; \( t(13)=1.9, P=0.08 \)]. As shown in Table 1, the pre-stress heart rate, blood pressure and plasma catecholamine concentrations before the two stress tests were closely correlated \((r_r> +0.86\) throughout). For levels of subjective assessments before the two tests, the correlation coefficients ranged from \( r=+0.57 \) to \( r=+0.92 \).

Mental arithmetic induced significant changes in heart rate on both occasions [Table 2, Figs. 1 and 2; \( F_{fs}(11,143)=39.9, P<0.0001 \)]. Significant changes in systolic and diastolic blood pressure were also elicited by stress \([F_{fs}(11,143)=7.5, P<0.0002 \]). Also, ratings of subjective stress experience increased significantly in response to both stress tests \([F_{fs}(2,26)=38.4, P<0.0001 \]. The degree of subjective relaxation decreased significantly on both occasions \([F_{fs}(2,26)=22.2, P<0.0002 \]. The plasma noradrenaline concentration increased significantly in response to both tests \([r(13)=2.6, P=0.02 \) and \( r(12)=3.5, P=0.004 \), respectively]. The plasma adrenaline concentration did not change significantly in response to the first stress test, but increased significantly on the second occasion \([r(12)=2.6, P=0.03 \).

Two-way analysis of variance revealed no significant condition effects of the two tests for any of the haemodynamic variables or subjective ratings, but a significant test \( \times \) period interaction was observed for diastolic blood
Table 2. Levels attained during stress and absolute reactivity of haemodynamics, subjective arousal and plasma catecholamines in response to the two stress tests
Values are means ± SEM. Abbreviations: BP, blood pressure; NS, not significant. Statistical significance (t-test) of change from pre-stress baseline: \(^a\)P < 0.05, \(^b\)P < 0.01, \(^c\)P < 0.001.

<table>
<thead>
<tr>
<th>Haemodynamics</th>
<th>Levels attained during stress</th>
<th>Reactivity</th>
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<tbody>
<tr>
<td></td>
<td>Stress test I</td>
<td>Stress test II</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.3 ± 1.9</td>
<td>72.1 ± 1.6</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>129.0 ± 3.2</td>
<td>126.9 ± 1.3</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>75.6 ± 2.4</td>
<td>74.7 ± 2.1</td>
</tr>
<tr>
<td>Subjective arousal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived stress</td>
<td>60.1 ± 5.5</td>
<td>58.4 ± 5.5</td>
</tr>
<tr>
<td>Relaxation</td>
<td>37.1 ± 5.5</td>
<td>43.1 ± 6.2</td>
</tr>
<tr>
<td>Activation</td>
<td>62.9 ± 5.7</td>
<td>63.4 ± 6.3</td>
</tr>
<tr>
<td>Hedonic tone</td>
<td>61.5 ± 5.9</td>
<td>62.5 ± 5.9</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td></td>
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</tr>
<tr>
<td>Noradrenaline conc. (nmol/l)</td>
<td>2.68 ± 0.19</td>
<td>2.81 ± 0.29</td>
</tr>
<tr>
<td>Adrenaline conc. (nmol/l)</td>
<td>0.37 ± 0.04</td>
<td>0.32 ± 0.05</td>
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</table>
The variability of heart rate and blood pressure was low (Table 2). The measurement error SD for heart rate were 2.6 and 3.0 beats/min for reactivity and stress levels, respectively. The corresponding measurement error SD for blood pressure ranged between 2.7 and 4.4 mmHg. Variability was greater for the subjective assessments, except for the subjective stress experience, which showed a measurement error SD of the same magnitude as the heart rate and blood pressure changes (when related to the mean response to the test for each variable). Plasma catecholamine concentrations were subject to considerable variability, especially the reactivity measures.

The individual heart rate and blood pressure responses to the two stress tests were closely correlated, both when expressed as correlations between levels attained during stress and as correlations between reactivity measures (Table 1 and Fig. 3). Correlation coefficients for heart rate and blood pressure levels attained during stress were equal to or above r = 0.80 throughout, and the corresponding reactivity (change) values were all above r = 0.75. Similar correlations emerged when the reactivity measures were expressed as rank correlation coefficients: r = 0.71, r = 0.75 and r = 0.92 for changes in heart rate, systolic blood pressure and diastolic blood pressure, respectively.

Also, assessments of subjective stress experience were highly correlated, when considering both levels during stress and reactivity (r = 0.97 and r = 0.85, respectively). Plasma catecholamine levels during stress were highly correlated, but the change scores (reactivity and recovery) were poorly correlated or unrelated.

Adaptation of the heart rate response during stress, defined as the slope of the decrease in the heart rate during stress, showed a close correlation (r = +0.92) between the two occasions. The heart rate decreased by 0.26 and 0.27 (beats/min) min⁻¹ during test I and test II, respectively. The adaptation coefficients of systolic and diastolic blood pressure during the two stress experiments were unrelated.

With regard to the relations between the various response measures, the heart rate and blood pressure variables were moderately well to closely correlated (Table 3). The subjective stress response showed a weak and insignificant correlation to heart rate reactivity, but was unrelated to the blood pressure response to stress. No systematic correlations were observed between the stress-induced changes in plasma catecholamine concentrations and any of the other response measures.

**DISCUSSION**

The variability of responses to stress tests is dependent both on methodological errors and biological fluctuations [24]. For purposes of analysis, three major sources of variability may be recognized: (1) variability of the methods used for response monitoring (i.e. blood pressure measurements, catecholamine assays, etc.), (2) variability of responses to the stress test as such (including variations in performance as well as changes in biological response patterns from one test to another), and (3) long-term intra-individual biological fluctuations in stress reactivity. The present study was designed to evaluate the combined contributions of the first two sources of variation.

Our results show that levels of stress activation in response to the standardized mental arithmetic stress test were highly reproducible with regard to activation levels attained during stress for heart rate, blood pressure and subjective stress ratings. The coefficients of variation for these measures ranged between 3.1 and 6.2%, and there were no significant differences between levels of activation attained during the two tests for any of the response variables. Furthermore, activation levels during the two tests were closely correlated (rs ≥ +0.75) for seven out of nine response measures.

However, in view of the lower amplitude of the change scores, the variability was considerably larger for the reactivity measures. This was not unexpected, since change scores by necessity involve the combined variations of several measurement errors and consequently are usually associated with substantially greater coefficients of variations. This phenomenon is not confined to mental stress tests, but is characteristic also of experimental physical and pharmacological tests of neural circulatory control, as shown by Parati et al. [27]. However, while this variability limits predictability of individual stress responses, it should be recognized that on the group level the test may still be useful provided...
that (1) there are no large systematic differences when repeating the tests (i.e. little response adaptation), and (2) individual differences in reactivity are reproduced when the test is repeated (i.e. inter-individual stability of response amplitudes). Since both criteria were satisfied to a reasonable degree for haemodynamic and subjective stress responses to the mental arithmetic test, this test may also represent a useful tool for investigation of stress reactivity and recovery.

Catecholamine responses were, on the other hand, small and subject to large intra- and inter-individual variability. This may, at least in part, be due to the fact that venous sampling is not ideal for assessment of plasma catecholamine concentrations, since there is a variable extraction of noradrenaline and adrenaline over the peripheral tissues [40-43]. Also, since noradrenaline is a locally released transmitter and sympathetic nerve activity does not change uniformly in response to stress, its antecubital venous plasma concentration is not an index of stress-induced changes in the venous plasma adrenaline concentration at least partly mimic changes in arterial plasma [29]. Also, since arterial blood pressure attained during two 5 min mental arithmetic tests repeated within 2 h. However, the reactivity scores were somewhat lower in their study (range r = +0.56 to r = +0.81 for heart rate and blood pressure). In a study in which the mental arithmetic test was repeated within 1 week in normotensive and hypertensive subjects, Lenders et al. [28] reported correlation coefficients that were only marginally lower for heart rate and blood pressure measurements than those that we observed in the present study.

These observations are compatible with the view that the mental arithmetic protocol, when strictly standardized, has a rather good methodological reproducibility, but that stress reactivity as an intra-individual characteristic is subject to long-term biological variability. In fact, our findings indicate that the reliability of the mental arithmetic test hitherto may have been under-estimated. This appears to be especially true of the reactivity (change) scores.

In some previous studies, an adaptation phenomenon has been observed when the same mental stress test was used twice [45-47]. In our study, there was no attenuation of the magnitude of the response of heart rate or subjective stress arousal, but the blood pressure response was slightly lower in the second test. However, a closer look at the blood pressure recording revealed that this was caused by a higher pre-stress level on the second occasion and not by a lower stress activation (Fig. 1). In fact, the difference between levels attained during stress was less than 1 mmHg for both systolic and diastolic blood pressure (Table 2). Thus the 'adaptation' phenomenon may in part be related to changes in resting baseline levels and not only to changes in stress reactivity as such.

An interesting observation in the present study was that the heart rate adaptation during stress (i.e. the gradual decrease in activation during the arithmetic task) appears to be a highly reproducible phenomenon. While many previous studies of cardiovascular responses to

<table>
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<tr>
<th>Test I</th>
<th>Test II</th>
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<tr>
<td>(\Delta HR)</td>
<td>+0.64^A</td>
</tr>
<tr>
<td>(\Delta SBP)</td>
<td>+0.75^b</td>
</tr>
<tr>
<td>(\Delta DBP)</td>
<td>+0.89^c</td>
</tr>
<tr>
<td>(\Delta Stress)</td>
<td>+0.07</td>
</tr>
<tr>
<td>(\Delta NA)</td>
<td>+0.17</td>
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<tr>
<td>(\Delta Adr)</td>
<td>+0.46</td>
</tr>
<tr>
<td></td>
<td>+0.58^e</td>
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<td></td>
<td>+0.01</td>
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<td>+0.34</td>
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Table 3. Correlations expressed as univariate correlation coefficients between stress response measures expressed as the change (\(\Delta\)) from pre-stress baseline (absolute reactivity)

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Stress, perceived stress; NA, plasma noradrenaline concentration; Adr, plasma adrenaline concentration. Statistical significance: ^P<0.05, ^P<0.01, ^P<0.001, ^P<0.0001.
stress have focused on increased reactivity, possible detrimen
tal effects of a reduced adaptation capacity during 
exposure to enduring (or repeated) environmental stress 
stimuli have received little attention. Since the average 
‘haemodynamic load’ on the circulation is probably more 
important for development of hypertensive and athero-
sclerotic cardiovascular lesions than brief pressor 
episodes a reduced capacity to adapt to recurring stress 
would lead to more prolonged cardiovascular activations.

Hence, if it can be confirmed that heart rate adaptation 
during stress is a stable individual characteristic, this 
would pave the way for systematic elucidation of mechan-
isms that influence heart rate adaptation and of whether 
the capacity for adaptation is different in various patient 
populations.

In conclusion, heart rate, blood pressure and subjective 
stress responses and stress levels during the mental 
arthmetic stress test show acceptable reproducibility and 
close test–retest correlations. Thus when strictly standard-
ized, the mental arithmetic stress protocol is a 
potentially useful research tool for the elucidation of fac-
tors that modulate cardiovascular and subjective stress 
reactivity, i.e. determinants of biological variability of 
stress reactivity and response patterns. However, the low 
reproducibility of the stress-induced catecholamine 
responses indicates that it is practically impossible to 
draw any conclusions regarding changes in sympa-
thetic-adrenal activity from variations in the response of venous 
plasma catecholamine levels.

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