Cardiovascular Reactivity, Coronary Risk Factors, and Sympathetic Activity in Young Men

Morten Rostrup, Arne Westheim, Sverre E. Kjeldsen, Ivar Eide

We have previously demonstrated that awareness of high blood pressure may increase blood pressure, plasma catecholamine levels, and stress responses. In the present study, three groups of 19-year-old men, all unaware of their blood pressure status, were selected from the first (group-1, 62±2 mm Hg, [mean±SEM], n=15), 50th (group-50, 90±4 mm Hg, n=15), and 99th (group-99, 123±5 mm Hg, n=14) percentiles in casual mean blood pressure at a screening. They were studied (blinded examiners) with intra-arterial blood pressure recordings and multiple measurements of arterial plasma epinephrine and norepinephrine during a mental arithmetic challenge and cold pressor test. Despite high mean blood pressure at the screening, group-99 did not differ from group-50 either in intra-arterial mean blood pressure after 30 minutes of supine rest (89±3 versus 86±2 mm Hg) or in serum lipids and resting plasma epinephrine and norepinephrine. However, in group-99 resting plasma epinephrine showed a positive hyperbolic relation to resting diastolic blood pressure (r=.73, P=.004) and a negative hyperbolic relation to the ratio of high-density lipoprotein cholesterol to total cholesterol (r=-.75, P=.002). None of these correlations were present in the two other groups. Furthermore, the three groups differed in heart rate responses (P<.0005) and systolic (P<.0005) and diastolic (P<.05) blood pressure responses to mental arithmetic challenge, group-99 being hyperreactive compared with the other two groups. Plasma epinephrine and norepinephrine responses to mental arithmetic challenge and blood pressure responses to the cold pressor test did not differ. However, changes in mean blood pressure showed a positive hyperbolic relation to plasma epinephrine during mental arithmetic challenge in group-99 (r=.81, P=.0004) but not in the two other groups. These findings support a link between high screening blood pressure, specific hyperreactivity to mental stress, and catecholamine-sensitive coronary risk factors.

(KEY WORDS • blood pressure • cardiovascular hyperreactivity • catecholamines • cold pressor test • epinephrine • hypertension • mental stress • norepinephrine)

The early phase of essential hypertension has been associated with increased baseline sympathetic neurogenic activity1-3 and exaggerated responses to mental stress.4-6 Moreover, in normotensive offspring of hypertensive patients, a similar pattern has been demonstrated7 even though a recent study8 suggested an early permanent blood pressure elevation and the cold pressor test.9,10 Thus, awareness of hypertension may be an important confounding factor in hypertension research. So far, there have not been any extensive pathophysiological studies on subjects deliberately kept unaware of their blood pressure status.

We also found that information about high blood pressure, ie, 2 weeks of worry, was associated with unfavorable changes in some cardiovascular risk factors in subjects belonging to a high percentile in mean screening blood pressure9,11 but not in more normotensive subjects10 despite increased sympathetic activity. This may indicate a specific relation between sympathetic activity and coronary risk factors in subjects belonging to very high screening blood pressure percentiles.

Thus, the present study was undertaken to answer the following two main questions: (1) Are there differences in resting arterial plasma catecholamines, cardiovascular and sympathetic reactivity, and coronary risk factors among young men with high, normal, and low screening blood pressure who are deliberately kept unaware of their blood pressure status? and (2) Is there any association between sympathetic activity and coronary risk factors within these three groups?

In a previous study10 we found considerable anticipatory responses to mental stress and a cold pressor test. Mere announcement of the stress tests may elicit significant cardiovascular and sympathetic responses. Thus, another methodological objective of the present study was to test the hypothesis that such responses were dependent on screening blood pressure.

We examined three groups of 19-year-old men selected from the first, 50th, and 99th percentiles in mean...
blood pressure at a screening, keeping all subjects and examining physicians unaware of the subjects' blood pressure status.

**Methods**

**Subjects**

All 19-year-old men in Norway have to attend a medical examination for the military draft procedure. The draft procedure usually takes a whole day and includes a psychological test, a test of physical strength and endurance, and a medical examination. Blood pressure measurements on all 19-year-old men attending in Oslo (n=3861) during 1 year were undertaken once after 5 minutes of sitting by means of an automatic auscultatory device with a hidden printer (Boso-digital II S, Bosh & Sohn GmbH u Co, Jungingen, Germany). Mean blood pressure was calculated as Diastolic Blood Pressure (DBP) + Pulse Pressure/3. Neither physicians nor subjects could read the results of the blood pressure recordings during the medical examination. The subjects were not informed about the results of the blood pressure readings, but it was pretended that they all had normal blood pressure. Therefore, they all got their final military physical fitness score and medical evaluation independent of the blood pressure recording.

We selected a total of 60 subjects from the screening. Twenty subjects belonged to the 99th percentile of mean blood pressure (123±5 mm Hg, group-99, mean±SEM), 20 to the 50th percentile (90±4 mm Hg, group-50), and 20 to the first percentile (62±2 mm Hg, group-1). Six months after the draft procedure, they were all sent a letter asking them to take part in a coronary heart disease prevention program. The three groups were sent identical letters.

On arrival, 5 subjects refused to participate in the invasive part of the study because they were frightened by blood sampling; 1 subject left because of heavy professional burdens. One subject was excluded because of syncope during arterial puncture. Initially, we had decided not to allow a second try if the arterial cannulation was unsuccessful. Thus, another 5 subjects were excluded for technical reasons, leaving 48 to fulfill the entire protocol. Of these, 18 originally belonged to group-99, and 15 each belonged to group-50 and group-1. There were no differences among the three groups with respect to reasons for not participating in the invasive part of the study. All were previously healthy without any history of diabetes, renal disease, elevated blood pressure, or other cardiovascular disease. They had a normal physical examination and medical history.

For practical reasons we used a standard-sized cuff for the screening. In subjects with great upper-arm circumference, this will lead to an overestimation of blood pressure. In 4 subjects belonging to group-99, we found a significant overestimation of the screening blood pressure due to an upper-arm circumference greater than 35 cm. Even though they completed the entire protocol, they were excluded from statistical group comparisons later in the study.

There were no differences in body mass indexes (Table 1).

**Protocol**

The study was approved by the Ethics Committee of Ullevål Hospital, and informed consent was obtained from each subject. All subjects were examined by the same physician and only one subject each day. The physician was unaware of which group the subject belonged to. The examination started at 8 AM after an 8-hour fast and at least 8 hours of abstaining from nicotine and caffeine and 24 hours of abstaining from alcohol. Heart rate, systolic blood pressure (SBP), and DBP were recorded by the same automatic auscultatory device as used at the screening after 15 minutes of sitting.

A short PTFE catheter (Venflon, 19G, Viggo AB, Hälsingborg, Sweden) was introduced into the left brachial artery with subjects under local anesthesia without epinephrine (Xylocain, Astra, Södertälje, Sweden) for blood sampling and intra-arterial pressure monitoring as previously described.

Subjects rested supine for 30 minutes in the presence of the examining physician only. Intra-arterial blood pressure and electrocardiogram were recorded continuously. At the end of this 30-minute period, subjects were told of a mental arithmetic challenge test and asked to mentally subtract the number 13 repetitively for 5 minutes starting with 1079. A metronome making noise at a frequency of 2 Hz was used to distract the subjects. They were informed of any miscalculation. Thereafter, the subjects rested for 30 minutes before a cold pressor test was announced, and the right hand was completely immersed in ice water (0°C) for 1 minute.

Arterial blood for catecholamine assay was collected into polypropylene syringes after 30 minutes of supine rest, during announcement of the two stress tests, during tests, and during recovery periods; a total of 21 samples were collected from each subject. Blood samples were immediately mixed with glutathione and EGTA, placed on ice, and centrifuged at 4°C; the plasmas were frozen at −70°C until catecholamine measurements within a few weeks.

**Table 1. Heart Rate, Systolic and Diastolic Blood Pressure, Body Mass Index, and Serum Lipids in Study Groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-1 (n=15)</th>
<th>Group-50 (n=15)</th>
<th>Group-99 (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening heart rate, bpm</td>
<td>70±13</td>
<td>61±11</td>
<td>70±18</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68±16</td>
<td>67±20</td>
<td>71±17</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>114±2</td>
<td>128±3*</td>
<td>131±5†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>58±1</td>
<td>66±2‡</td>
<td>66±2†</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>20.9±1.7</td>
<td>22.7±3.2</td>
<td>22.0±2.9</td>
</tr>
<tr>
<td>Serum HDL cholesterol/total cholesterol ratio</td>
<td>0.29±0.01</td>
<td>0.27±0.02</td>
<td>0.31±0.02</td>
</tr>
<tr>
<td>Triglycerides, nmol/L</td>
<td>0.75±0.06</td>
<td>0.91±0.14</td>
<td>0.71±0.08</td>
</tr>
</tbody>
</table>

bpm indicates beats per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HDL, high-density lipoprotein. Except for screening heart rate, measurements are after 30 minutes of supine rest in the laboratory. Values are mean±SEM. *P<.025, ‡P<.01, †P<.005, compared with group-1.
A technician entered the room shortly after announcement of the mental stress test and the coinciding blood sampling. She helped with blood sampling during the mental stress test, and left the room thereafter. In all other parts of the study, subject and physician were left alone.

**Assays**

Plasma catecholamines were measured by a radioenzymatic technique according to Peuler and Johnson as previously reported. On all samples, the assay was performed by the same blinded technician. Serum lipids were analyzed as previously reported.

**Statistics**

Data were analyzed using the SPSS-PC+ statistical package (SPSS-PC+ Inc, Chicago, Ill). A total of seven baseline variables (SBP, DBP, heart rate, plasma epinephrine and norepinephrine, the ratio of high-density lipoprotein [HDL] cholesterol to total cholesterol, and triglycerides) were compared among the three groups by running seven univariate analyses of variance (ANOVAs). Subsequent Student's *t* tests were run for the three comparisons among the means for the three groups, adjusting the critical value for each variable separately using Tukey's method. Plasma epinephrine was not normally distributed according to the Kolmogorov-Smirnov test. By reciprocal (1/X) transformation, a high degree of normality was obtained.

The changes in mean blood pressure from screening and the responses to the stress tests were analyzed primarily by repeated-measures ANOVA. Within each group a treatment effect (ie, changes of the variables over time) was assessed by considering the whole period comprising baseline, the stress test, and recovery. The two stress tests were analyzed separately. A group×treatment interaction effect and a main group effect were tested. Huynh-Feldt's probability value corrections for correlated values across time were used. The corrected degrees of freedom are presented in parentheses with the F ratios for the tests considering the three groups simultaneously. In the subsequent pairwise group comparisons, only probability values are given.

As a supplementary analysis we also compared peak values and maximal change from baseline, both absolute and in percent, among the groups using ANOVA and then subsequent Student's *t* tests as above. Associations between plasma epinephrine and coronary risk factors within each group were analyzed by Pearson's correlation coefficient (*r*) and linear regression using transformed variables when appropriate. A 95% confidence interval (CI) is given for all correlation coefficients. The slopes of the regression lines in group-99 were compared with those of the two other groups using the double dummy technique.

A secondary objective of the present study was to assess the effects of announcement of a forthcoming stress test. Repeated-measures ANOVA was applied in this analysis.

Of 1008 plasma catecholamine samples, 31 were lost because of practical problems. This did not influence the results of the statistical analysis. In the present study a large number of statistical tests were performed, and we did not perform any severe adjustment for multiple comparisons. Therefore, the conclusions must be considered with caution, and further confirmatory investigations testing specific hypotheses will have to be performed. This is especially true for probability values larger than .001.

Data are presented as mean±SEM. The null hypothesis was always tested against a two-sided alternative.

**Results**

**Baseline**

Mean blood pressures at screening, after 15 minutes of sitting, and after 30 minutes of supine rest in our laboratory are given in Fig 1. Mean blood pressure changed over time within each group (*P<.0001* for all groups), and the changes differed among the three groups (group×time interaction effect, *F*[4,80]=58.61, *P<.0001).

SBP and DBP were the only variables that differed among the three groups at baseline (ANOVA, *P=.003* for both pressures). Group-1 had significantly lower SBP and DBP compared with the other two groups, which did not differ (Table 1). There were no differences in heart rate, plasma catecholamines, or serum lipids.

**Correlations Between Coronary Risk Factors and Plasma Epinephrine at Baseline**

In group-99, baseline DBP varied with arterial plasma epinephrine in a hyperbolic fashion (*r*=-.73, *P=.004, after transformation; 95% CI, 0.33 to 0.91; Fig 2), as did the ratio of HDL cholesterol to total cholesterol (*r*=-.75, *P=.002; 95% CI, −0.92 to −0.36; Fig 3). Such correlations were not found in the two other groups (group-50: *r*=-.18; 95% CI, −0.63 to 0.37; *P=.40* and *r*=.01; 95% CI, −0.51 to 0.52; *P=.98*; group-1: *r*=-.01; 95% CI, −0.52 to 0.52 and *r*=.00; 95% CI, −0.51 to 0.51; *P=.98*). The slopes of the regression lines for group-99 were significantly different from the slopes of the two other groups (DBP: *P<.005*; HDL-total cholesterol ratio: *P<.01*).
FIG 2. Plot shows that resting diastolic blood pressure varied with resting arterial plasma epinephrine (E) in a hyperbolic fashion with a best fit for the equation $y = 79.6 - 1.94/E$ (calculated curved line in top panel). Transforming the independent variable (E) into reciprocal scale (see Reference 14) changes the relation from hyperbolic to linear (bottom panel) ($y = 79.6 + 1.94x'$, where $x' = -1/E$; $r = .73$, $P = .004$). No such association was present in the two other groups.

Responses to the Mental Stress Test

Changes during mental stress (ie, treatment effect) were significant ($P < .0001$) within each group for the variables measured (Fig 4). The three groups differed in their cardiovascular responses to mental stress; ie, the group $\times$ treatment interaction effect was significant for SBP ($F[11, 64, 221.23] = 3.28$, $P < .0005$, corrected degrees of freedom), DBP ($F[13, 60, 258.35] = 1.76$, $P < .05$), and heart rate ($F[10, 24, 194.5] = 6.51$, $P < .0005$). Plasma catecholamine responses did not differ, and there was no main group effect on plasma catecholamines.

Cardiovascular responses to mental stress in group-99 were larger compared with the two other groups (group $\times$ treatment interaction effect, Fig 4) for heart rate (group-99 versus group-50 and group-1, respectively, $P = .01$, $P < .0001$), SBP ($P < .005$, $P < .0001$), and DBP ($P < .025$, $P < .02$). There were no differences in the cardiovascular responses to mental stress between group-50 and group-1, but group-1 had significantly lower SBP ($P < .0005$) and DBP ($P < .001$) (main group effect) compared with group-50.

Table 2 shows peak values for all variables and changes from baseline to peak in millimeters of mercury and percent. Blood pressure and heart rate changes were larger in group-99 compared with the other two groups, which responded similarly.

Correlations Between Responses to Mental Stress and Plasma Epinephrine

In group-99, changes in mean blood pressure after 5 minutes of mental stress varied with arterial plasma epinephrine at the end of the stress test in a hyperbolic fashion ($r = .81$, $P = .0004$, 95% CI, 0.49 to 0.94; Fig 5). In the two other groups no such correlations occurred.
Responses to Announcement of the Stress Tests

Changes during the cold pressor test (ie, treatment effect) were significant within each group for heart rate (P<.001), SBP (P<.001), DBP (P<.001), plasma epinephrine (P=.005), and plasma norepinephrine (P<.05) (Fig 4). Heart rate responses differed among the three groups (group x treatment interaction effect, F{10.44,198.42}=2.33, P<.01), whereas there were no differences in blood pressure or plasma catecholamine responses. However, there was an overall difference among the three groups (main group effect) in SBP (F{2,37}=6.36, P=.004) and DBP (F{2,37}=5.40, P=.009). Group-50 and group-99 did not differ in blood pressure (Fig 4), whereas both SBP and DBP were lower in group-1 compared with the other two groups (main group effect: group-1 versus group-99 and group-50, respectively, SBP: P=.006, P=.002; DBP: P=.004, P=.01).

Table 2 shows peak values for all variables and changes from baseline to peak. There were no differences in the responses to the cold pressor test among the three groups.

Blood pressures during the mental stress test and the cold pressor test and baseline and screening blood pressures were all intercorrelated. Multiple regression analysis showed that mean blood pressure during mental stress (r=.77; 95% CI, 0.61 to 0.87; P<.001, N=44) and not baseline blood pressure (r=.52; 95% CI, 0.26 to 0.71; P<.001, N=44) correlated best with screening blood pressure.

Responses to Announcement of the Stress Tests

The SBP and DBP of all three groups responded to announcement of the mental stress test compared with baseline (SBP and DBP, respectively, group-1: P=.001, P=.003; group-50: P<.001, P<.001; group-99: P<.001, P<.001; Fig 4). The response in DBP was larger in group-99 compared with the other two groups (main group effect: group-1 versus group-99 and group-50, respectively, SBP: P=.006, P=.002; DBP: P=.004, P=.01).

Within all groups heart rate increased during announcement (P<.001 for all groups, Fig 4). Plasma epinephrine and norepinephrine levels increased significantly from baseline during announcement of the mental stress in both group-50 (epinephrine: P=.003; norepinephrine: P=.005) and group-99 (epinephrine: P=.006; norepinephrine: P<.001). There were no significant changes in group-1. There were no differences in heart rate and epinephrine and norepinephrine responses among the three groups.

In group-99 SBP and DBP (P<.001), heart rate (P=.002), and plasma epinephrine (P=.002) increased during announcement of the cold pressor test. In group-50 only heart rate (P<.001) and in group-1 only SBP (P<.01) and DBP (P<.01) increased significantly.

Heart rate responses to announcement of the cold pressor test were lower in group-1 than the two other groups (group x treatment interaction effect, F{2,38}=3.34, P=.046).

Discussion

In the present study we found that 19-year-old men with high screening blood pressure were characterized by normal supine resting intra-arterial blood pressure in our laboratory and cardiovascular hyperreactivity to mental stress but not to a cold pressor test. Subjects with low screening blood pressure were characterized by normal cardiovascular responses to mental stress and lower resting blood pressure compared with a group with normal screening blood pressure. Blood pressure at a screening may only partly reflect true baseline blood pressure. Cardiovascular reactivity to mental stress is also reflected, especially in subjects with high screening blood pressure.

The present study also suggests new associations between coronary risk factors, cardiovascular hyperreactivity to mental stress, and sympathetic activity. Resting DBP and the ratio of HDL cholesterol to total cholesterol were closely related to plasma epinephrine in hyperreactive subjects only, as was the blood pressure reactivity to mental stress.

Previous studies have demonstrated increased sympathetic activity in young hypertensive subjects. However, in the present study we found no differences in baseline plasma catecholamine levels among the three groups. Because we eliminated the effects of awareness of hypertension, this finding was not unexpected.

Moreover, blood pressure of the original hypertensive group normalized at the second examination, leaving smaller differences in baseline blood pressure among the groups. The normalization may partly be a regression to the mean phenomenon and partly be due to the fact that we kept the subjects with high screening blood pressure uninfomed. We have previously shown that informing such subjects about their possible hypertension may increase blood pressure at a second examination.

The statistical power to detect differences in plasma catecholamines and blood pressure was limited because of the relatively small study groups, even though use of a large screening base of subjects for inclusion in the study and careful standardization and arterial sampling may substantially compensate for small numbers.

Mental Stress and Cardiovascular Hyperreactivity

The three groups were actually exposed to four different stress situations. The original screening was probably by itself stressful (first stress situation), including both physical and psychological testing throughout an entire day and a final evaluation of physical and psychological fitness. Our selection of subjects was based on the blood pressure percentiles of this screening. Thus, we selected subjects based partly on blood pressure responses to this examination, ie, to a kind of mental stress. True baseline blood pressure was probably not measured at the screening. Interestingly, the three groups did not differ in heart rate despite rather large differences in blood pressure. The second stress situation was the start of the medical examination in our laboratory. After 15 minutes of sitting the three groups still differed in mean blood pressure but not in heart rate. Subjects belonging to group-99 showed an increased relaxation response, and after 30 minutes of supine rest their blood pressures were normal, indicat-
**TABLE 2. Responses to Mental Arithmetic Challenge and Cold Pressor Test**

<table>
<thead>
<tr>
<th></th>
<th>Group-1</th>
<th>Group-50</th>
<th>Group-99</th>
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<tr>
<td><strong>Mental arithmetic challenge</strong></td>
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<tr>
<td>Systolic blood pressure</td>
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<tr>
<td>Peak, mm Hg</td>
<td>137±3</td>
<td>154±3*</td>
<td>169±4†</td>
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<td>Change from baseline, mm Hg</td>
<td>23±2</td>
<td>26±2</td>
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<td>75±2</td>
<td>84±2</td>
<td>90±4§</td>
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<tr>
<td>Change from baseline, mm Hg</td>
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<td>18±1</td>
<td>25±1</td>
</tr>
<tr>
<td>Change from baseline, %</td>
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<td>27±2</td>
<td>39±4</td>
</tr>
<tr>
<td>Heart rate</td>
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<tr>
<td>Peak, bpm</td>
<td>75±3</td>
<td>86±5#</td>
<td>104±4‡§</td>
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<td>Change from baseline, bpm</td>
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<td>39±4§</td>
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<tr>
<td>Change from baseline, %</td>
<td>28±4</td>
<td>41±6#</td>
<td>62±7‡§</td>
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<td>Arterial plasma epinephrine</td>
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<tr>
<td>Peak, nmol/L</td>
<td>0.62±0.13</td>
<td>0.97±0.22</td>
<td>1.17±0.15</td>
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<td>Change from baseline, nmol/L**</td>
<td>0.31</td>
<td>0.56</td>
<td>0.72</td>
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<tr>
<td>Change from baseline, %**</td>
<td>(0.14,0.80)</td>
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<td>(0.49,1.24)</td>
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<td>Arterial plasma norepinephrine</td>
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<td>Peak, nmol/L</td>
<td>1.06±0.09</td>
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<td>Change from baseline, nmol/L</td>
<td>0.47±0.07</td>
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<td>Change from baseline, %</td>
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<td>220±59</td>
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<td><strong>Cold pressor test</strong></td>
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<td>Systolic blood pressure</td>
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<td>Peak, mm Hg</td>
<td>146±4</td>
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<td>Change from recovery, mm Hg</td>
<td>33±3</td>
<td>32±3</td>
<td>34±4</td>
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<td>Change from recovery, %</td>
<td>29±2</td>
<td>25±2</td>
<td>27±3</td>
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<tr>
<td>Diastolic blood pressure</td>
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<td></td>
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<tr>
<td>Peak, mm Hg</td>
<td>84±2</td>
<td>90±2</td>
<td>90±3</td>
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<tr>
<td>Change from recovery, mm Hg</td>
<td>24±2</td>
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<td>Change from recovery, %</td>
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</tr>
<tr>
<td>Heart rate</td>
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<td>Peak, bpm</td>
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<td>Change from recovery, bpm</td>
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<tr>
<td>Change from recovery, %</td>
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<td>Arterial plasma epinephrine</td>
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<tr>
<td>Peak, nmol/L</td>
<td>0.49±0.07</td>
<td>0.75±0.13</td>
<td>0.65±0.07</td>
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<tr>
<td>Change from recovery, nmol/L**</td>
<td>0.28</td>
<td>0.44</td>
<td>0.42</td>
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<tr>
<td>Change from recovery, %**</td>
<td>(0.19,0.38)</td>
<td>(0.27,0.73)</td>
<td>(0.30,0.58)</td>
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<tr>
<td>Arterial plasma norepinephrine</td>
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</tr>
<tr>
<td>Peak, nmol/L</td>
<td>1.23±0.24</td>
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<td>Change from recovery, nmol/L</td>
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<td>0.34±0.14</td>
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<tr>
<td>Change from recovery, %</td>
<td>56±11</td>
<td>52±16</td>
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</tbody>
</table>
The cold pressor test is thought to elicit a generalized increase in peripheral sympathetic nerve activity, including activation of peripheral sympathetic nerves to skeletal muscle. A recent study by Victor et al demonstrated a rather specific effect of the cold pressor test on sympathetic outflow to the heart and skeletal muscles. The heart rate responses to the cold pressor test appeared earlier than the pressure responses. We have previously found that the heart rate responses to the cold pressor test may depend on psychological stimuli, eg, awareness of hypertension. Thus, in subjects belonging to the 98th percentile of the same screening as in the present study, subjects aware of their hypertension showed a greater increase in heart rate during the cold pressor test than an unaware control group. Furthermore, the increase in heart rate appeared during the announcement of the test, and there was no further increase during the test, indicating that heart rate responses to the cold pressor test may be more related to psychological than physical stimuli, as further confirmed by the present study. We found that the main increase in heart rate in group-99 and group-50 appeared during the announcement and not during the test itself.

On the other hand, the mental arithmetic challenge induces a defense reaction characterized by a differentiated sympathetic pattern. The sympathetic discharge increases to the heart, thereby increasing cardiac output and inducing vasodilation in renal and visceral vascular beds while causing vasodilation in skeletal muscles. Moreover, during the mental stress test there is a substantial release of epinephrine, especially during the first minute, as demonstrated in the present study. This finding and the close relation between plasma epinephrine and blood pressure responses to mental stress in the hyperreactive group suggest that increased sensitivity to arterial plasma epinephrine may play a role in the hyperreactivity. However, as discussed by Freyschuss et al, infusion studies of epinephrine show that much higher plasma concentrations were necessary for similar cardiovascular responses as seen during mental stress. Infusion studies are not readily comparable to the mental stress test. Epinephrine may have important effects by facilitating norepinephrine release through stimulation of presynaptic β-receptors. Such effects may depend on increased noradrenergic activity before, as during mental stress, but not during infusion of epinephrine in resting subjects. Thus, increased sensitivity to plasma epinephrine may play a key role in cardiovascular hyperreactivity selectively to mental stress.

As suggested by Matsukawa et al, skeletal muscle vasodilatation may be impaired during mental stress in the cardiovascular hyperreactive group. Alternatively, a baroreceptor reflex dysfunction may occur. However, the lack of cardiovascular hyperreactivity to the cold pressor test in the present study does not support this latter assumption.

The order of the two tests was fixed; ie, the mental arithmetic challenge always preceded the cold pressor test. We cannot rule out possible effects of this sequence in the present study, even though we allowed for 30 minutes of supine rest between the two tests. However, we recently presented new data on different groups belonging to similar percentiles in which the order of
the two tests was reversed.31 We still found cardiovascular hyperreactivity to mental stress only, and normal responses to the cold pressor test.

Even though the reported correlations within the 99th percentile seem strong and are independent of extreme plasma epinephrine values, one should be cautious not to derive generalizable conclusions from these findings because of relatively small numbers. The close relation between plasma epinephrine and blood pressure responses during mental stress in the hyperreactive group may suggest an altered sensitivity or an atypical response pattern to plasma epinephrine.

The negative relation between plasma epinephrine and the ratio of HDL cholesterol to total cholesterol may be due to a catecholamine-dependent inactivation of lipoprotein lipase, possibly through a vascular α-adrenergic mechanism.32

It is still uncertain whether cardiovascular hyperreactivity by itself is a risk factor for cardiovascular disease. A recent study by Alderman et al12 suggested that blood pressure reactivity predicts myocardial infarction among treated hypertensive subjects. The reactivity was measured as the difference between pretreatment DBP taken by a nurse and physician, ie, a variation on mental stress.

Raviogli et al16 recently demonstrated that offspring of hypertensive subjects did not reveal any increased reactivity to laboratory stressors but rather a 24-hour blood pressure elevation and higher prolonged resting blood pressure. As such, their study seems to refute the cardiovascular reactivity hypothesis. However, it is possible that the offspring were more apprehensive throughout the study because of their and their parents' knowledge of hypertension and its consequences. Such apprehension may be specifically important in young subjects living with their parents during 24-hour blood pressure recording. This increased alertness may by itself be responsible for the blood pressure elevation reported in their study and also for lack of a further exaggerated increase in blood pressure during the mental stress tests. In addition, performing four different stress tests separated by 5 minutes only may increase the variance substantially, thus reducing the statistical test power.

Thus, the present association between coronary risk factors and plasma catecholamines in cardiovascular hyperreactive subjects may suggest an alternative hypothesis linking cardiovascular hyperreactivity to future hypertension and coronary disease. Because there were no differences in peak or baseline catecholamines, cardiovascular hyperreactivity to mental stress may be a marker of an underlying increased sensitivity to plasma epinephrine, not only comprising blood pressure but serum lipids as well. One might speculate whether such subjects are also more prone to white coat hypertension. If so, our finding may illustrate a possible mechanism linking white coat hypertension to lipid abnormalities.34

Methodological Considerations

The present study confirms our previous finding10 of considerable announcement responses to stress tests. The mere information of a stress test may elicit significant sympathetic and cardiovascular responses. These responses seem to vary according to selection of subjects. Therefore, caution must be advocated in interpretation of differences in baseline values between groups in studies in which the subjects have been informed about forthcoming stress tests before baseline registrations.

Conclusion

Young men with high screening blood pressure are characterized by normal blood pressure after 30 minutes of supine rest and by an increased cardiovascular reactivity to mental stress but not to a cold pressor test. The hyperreactivity may be related to increased sensitivity to epinephrine. Furthermore, subjects with high screening blood pressure reveal a consistent relation between important cardiovascular risk factors such as resting DBP, the ratio of HDL cholesterol to total cholesterol, and plasma epinephrine. We do not know whether these hyperreactive subjects will develop hypertension or cardiovascular disease. If, however, the subjects do have such a generally increased sensitivity to catecholamines, more prolonged mental stress might evoke adverse responses comprising both blood pressure and serum lipids, thus predisposing them to both hypertension and coronary heart disease.

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