Sympathoadrenal Stress Reactivity Is a Predictor of Future Blood Pressure: An 18-Year Follow-Up Study

Arnljot Flaa, Ivar K. Eide, Sverre E. Kjeldsen, Morten Rostrup

Abstract—In the present study we hypothesized that arterial catecholamine concentrations during rest and 2 laboratory stress tests were independent predictors of blood pressure at an 18-year follow-up. At entry, blood pressure, heart rate, and arterial plasma epinephrine and norepinephrine concentrations were measured in 99 healthy men (age: 19.3±0.4 years, mean±SD) at rest, during a mental arithmetic test, and during a cold pressor test. After 18.0±0.9 years of follow-up, resting blood pressure was measured. The norepinephrine and epinephrine concentrations during the mental arithmetic explained 12.7% of the variation of future systolic blood pressure after adjusting for initial resting blood pressure, family history, body mass index, and systolic blood pressure during the stress test in a multiple regression analysis (adjusted $R^2$=0.651; $P<0.001$). To conclude, the present study shows that sympathetic nervous activity during mental arithmetic predicts future blood pressure, indicating a possible causal factor in the development of essential hypertension independent of the initial blood pressure. (Hypertension. 2008;52:336-341.)

Key Words: blood pressure ■ stress reactivity ■ catecholamines ■ cold pressor test ■ epinephrine ■ mental stress ■ norepinephrine

Hypertension and other cardiovascular diseases develop slowly over decades, and although the disease process starts early, clinical manifestations do not usually appear until late middle age. Interestingly, the classical risk factors, like family history, obesity, smoking, diabetes, and hypercholesterolemia, are able to predict only $\approx 50\%$ of future cardiovascular diseases. Thus, much effort has been made to identify other risk factors, and increased reactivity to stress is believed to be one of them.

Although previous prospective studies on reactivity as a predictor of future hypertension have given conflicting results,1 studies with a follow-up of $>5$ years tend to show a strong association between cardiovascular hyperreactivity and future hypertension.2-9 This supports the reactivity hypothesis, which states that exaggerated physical or psychological responses to stress identify subgroups with increased cardiovascular risk.10 However, there are some controversies regarding whether this represents a casual relationship. Intermittent pressure elevations could lead to structural vascular changes, but attempts to produce irreversible, sustained blood pressure elevations purely as a consequence of transient increases of blood pressure in dogs have not been successful.11,12 Another possible link between hyperreactivity and development of hypertension is a direct effect of catecholamines. Sympathetic stimulation is known to be a trophic factor for vascular hypertrophy.13,14 Thus, hyperreactive subjects who have frequent surges of sympathetic activity may develop sustained increased total peripheral resistance and then hypertension.15 Previous reactivity research has almost solely focused on blood pressure and heart rate responses to stress. Norepinephrine during rest has been found to be a significant predictor of hypertension in 2 studies,16,17 and a third study found norepinephrine response to bicycle ergometry together with psychological factors and blood pressure responses to mental arithmetic to be relatively weak predictors of future blood pressure classification.18 However, to our knowledge, there are no follow-up data demonstrating a relationship between catecholamine responses to mental arithmetic or a cold pressor test and future blood pressure.

Mental arithmetic and the cold pressor test have been used extensively in previous reactivity research. They induce different hemodynamic responses, as the mental arithmetic test is a classic example of a $\beta$-adrenergic response with an increased cardiac output, whereas the cold pressor test first and foremost induces an $\alpha$-adrenergic vasoconstriction with an increased total peripheral resistance.19

The present study investigated the predictive role of the sympathoadrenal activity and reactivity in the development of future blood pressure level. We hypothesized that arterial plasma epinephrine and norepinephrine concentrations during

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rest and 2 laboratory stress tests were independent predictors of blood pressure after an 18-year follow-up.

Subjects and Methods
The local ethics committee approved the study, and the procedures followed were in accordance with institutional guidelines. A written and informed consent was obtained from each subject both at the initial examination and at follow-up.

Participants
All 19-year-old men in Norway have to attend a medical examination for the military draft procedure. Blood pressure measurements were undertaken by a trained physician once after 5 minutes sitting by means of a carefully validated automatic auscultatory device (Boso-digital II S, Bosh & Sohn GmbH u Co) or by using a newly calibrated mercury sphygmomanometer. None of the subjects were informed about the blood pressure at this stage. Mean blood pressure was calculated as diastolic blood pressure + pulse pressure/3. A total of 99 subjects were selected from the military draft screening, 30 belonging to the first percentile, 30 to the 50th percentile, and 39 to the 95th to 99th percentile of mean blood pressure distribution. This selection was done to ensure a satisfying blood pressure range, because resting blood pressure is related to sympathetic activity.22 All were white except 1 who was half Asian and half white. They were previously healthy without any history of diabetes, renal disease, increased blood pressure, or other cardiovascular disease, including a normal physical examination, ECG, routine blood tests, and urinalysis. None was on medical treatment or abused drugs or alcohol.

Examination at Entry
The protocol at baseline has been described in detail elsewhere,21 and took place between October 1986 and October 1989. Resting heart rate and blood pressure were recorded after 15 minutes in a sitting position with the same equipment as during the initial screening. Height, weight, and waist circumference were measured standing. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. A short teflon catheter (Venflon, 19G, Viggo AB) was introduced under local anesthesia without the subject being able to move. Blood pressure was measured during supine rest and 2 laboratory stress tests were independent predictors of blood pressure after an 18-year follow-up.

Statistics
The data were analyzed using the statistical package SPSS 14.0 for Windows (SPSS Inc). Parametric tests were used for normally distributed data and nonparametric when normality was not achieved by log-normal transformation. The paired samples t-test was used to analyze possible changes in continuous variables from entry to follow-up, whereas the χ² test was used for categorical variables. Associations were assessed using Pearson’s correlation. The subsequent multiple regression analyses of future blood pressure assessed the predictive power of the traditional risk factors of resting blood pressure, family history of hypertension, and body mass index at entry (model 1); the inclusion of blood pressure during the stress tests (model 2); and the inclusion of blood pressure and catecholamine concentrations during the stress tests (model 3). Multicolinearity was tested by examining tolerance and variance inflation factor. Data are presented as means±SDs unless otherwise indicated. Null hypotheses were rejected if 2-tailed P value was <0.05. However, because of multiple analyses, the supplementary univariate correlations were considered statistically significant only if P value was <0.001 according to the Bonferroni correction.

Results
Descriptives
Characteristics of the participants at baseline and follow-up are presented in Table 1. Of the 99 persons included in the entry examination, 80 subjects (81%) were eligible for follow-up. They were on average 19.3 years old (range: 18.2 to 20.8 years) at the first visit and 37.3 years (range: 35.4 to 38.9 years) at re-examination after 18 years. Systolic blood pressure (P=0.003) and diastolic blood pressures (P<0.001) increased significantly, as did body mass index, serum cholesterol, serum triglycerides, and fasting plasma glucose (all P<0.001).

Prediction of Blood Pressure at Follow-Up
Univariate Correlation Analyses
Table 2 shows univariate correlations between cardiovascular and catecholamine variables at entry and resting systolic and
Table 1. Descriptives of the Subjects at Entry and After 18 Years of Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Entry</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>80</td>
<td>19.3±0.4</td>
<td>37.3±0.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>76</td>
<td>126±20</td>
<td>131±16*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>76</td>
<td>70±17</td>
<td>89±10†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>75</td>
<td>66±15</td>
<td>64±12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>80</td>
<td>22.4±3.0</td>
<td>26.7±4.3†</td>
</tr>
<tr>
<td>Total serum cholesterol, mmol/L</td>
<td>79</td>
<td>4.0±0.7</td>
<td>4.9±0.9†</td>
</tr>
<tr>
<td>Serum high-density lipoprotein, mmol/L</td>
<td>78</td>
<td>1.1±0.2</td>
<td>1.2±0.3</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>79</td>
<td>0.8±0.4</td>
<td>1.3±0.9†</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>69</td>
<td>4.2±0.5</td>
<td>5.1±0.8†</td>
</tr>
<tr>
<td>Daily smokers, n (%)</td>
<td>78</td>
<td>28 (36)</td>
<td>20 (26)</td>
</tr>
</tbody>
</table>

Data are presented as means±SDs except for daily smokers. The 5 subjects using blood pressure–lowering medications at follow-up are included in the analyses.

*P<0.01.
†P<0.001.

systolic blood pressure at follow-up after 18 years. Systolic and diastolic blood pressures at follow-up were significantly predicted by systolic and diastolic blood pressures both at rest and during mental arithmetic and cold pressor test at entry 18 years earlier. Furthermore, heart rate during mental arithmetic was a significant predictor. Although not significant because of the strict limits of the Bonferroni correction, the epinephrine and norepinephrine concentrations during the mental arithmetic test were stronger predictors of future systolic blood pressure than the plasma catecholamine levels at rest and during the cold pressor test. The absolute levels during stress (Table 2) tended to be stronger predictors than the responses per se, ie, the Δ values, because none of these variables were significant predictors. The Figure illustrates systolic blood pressure at follow-up according to tertiles of norepinephrine concentration during mental arithmetic at entry.

Multiple Regression Analyses

In multiple regression analyses of future systolic blood pressure (Table 3), the established risk factors (resting systolic blood pressure, family history of hypertension, and body mass index) explained 43.0% of the variance (model 1). Adding systolic blood pressure during mental arithmetic increased significantly (P=0.001) the explained variance by 9.4% points to 52.4% (model 2). Moreover, by introducing both the plasma catecholamine concentrations and systolic blood pressure during the mental arithmetic test (model 3), the explained variance increased by 22.1% points compared with model 1, to an overall 65.1%. Although systolic blood pressure and norepinephrine concentration were significant positive predictors in model 3, the epinephrine concentration turned out to be a significant negative predictor of future systolic blood pressure.

Adjusted for the established risk factors, systolic blood pressure during the cold pressor test (β=0.318; P=0.009) was also a significant positive predictor of future systolic blood pressure (adjusted R²=0.478; P<0.001 for the whole model). Plasma catecholamine concentrations during cold pressor test did not contribute any further beyond the stress blood pressure (adjusted R²=0.478 for the whole model).

Compared with systolic blood pressure, prediction of diastolic blood pressure was somewhat weaker for the variables examined. Resting diastolic blood pressure, family
Table 3. Multiple Regression Analyses of Resting Systolic Blood Pressure at Follow-Up After 18 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Covariates</th>
<th>Regression Model</th>
<th>Adjusted R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td>0.430</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Established risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting SBP at entry</td>
<td>0.553</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>0.329</td>
<td></td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BMI at entry</td>
<td>0.075</td>
<td></td>
<td>0.414</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td>0.524</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Established risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting SBP at entry</td>
<td>0.392</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>0.261</td>
<td></td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>BMI at entry</td>
<td>0.068</td>
<td></td>
<td>0.312</td>
<td></td>
</tr>
<tr>
<td>Mental stress test</td>
<td>SBP</td>
<td></td>
<td>0.357</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td>0.651</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Established risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting SBP at entry</td>
<td>0.403</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td>0.349</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>BMI at entry</td>
<td>0.103</td>
<td></td>
<td>0.215</td>
<td></td>
</tr>
<tr>
<td>Mental stress test</td>
<td>SBP</td>
<td></td>
<td>0.441</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>−0.294</td>
<td></td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>0.265</td>
<td></td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; BMI, body mass index.

Discussion

The present study demonstrates that plasma catecholamines during mental arithmetic contribute substantially and significantly to the prediction of future systolic blood pressure in addition to other well-known predictors. Together, in the multiple regression model, epinephrine and norepinephrine levels during mental arithmetic explained 12.7% of the variation of future systolic blood pressure, adjusted for resting blood pressure, family history, body mass index at entry, and systolic blood pressure during stress. In fact, the total regression model explained 65.1% of the variance of systolic blood pressure after 18 years. Furthermore, reactivity parameters to the mental arithmetic test consistently tended to be better predictors than responses to the cold pressor test.

Data indicated that absolute values during both mental arithmetic and the cold pressor test were better predictors of future blood pressure than the responses (Δ values).

Confounding factors were eliminated to a minimum in the present study, compensating for the moderate number of participants. All of the subjects were white men of the same age with no medication and with similar body mass index at entry. As in general in Norway, the population in Oslo is stable, reflecting genetic homogeneity. On the other hand, despite the advantage of a homogenous sample, this also implies a limited generalizability of the present results to other ethnicities, age groups, and women.

Sympathetic activity was assessed indirectly by measuring plasma catecholamines, which, together with microneurography, are preferred tests for analyzing acute effects of stress tests and give similar results.25 Arterial catecholamines are superior to venous catecholamines in separating hypertensive and normotensive groups and better reflect the catecholamine spillover from internal organs, such as the heart and kidney.

The sympathetic nervous system probably plays a key role in the pathogenesis of essential hypertension.26,27 Several cross-sectional studies have found increased activity in the sympathetic nervous system among borderline hypertensive subjects compared with normotensive subjects.28,29 However, the interpretations of cross-sectional study designs are complicated, because the direction of cause and effect may be difficult to assess. The positive relationship in the present long-term follow-up study between mental arithmetic norepinephrine concentration at entry and systolic blood pressure at follow-up suggests that increased sympathetic nervous activity may play a role in the early development of hypertension, although causality cannot be truly established. Possible underlying mechanisms may be sympathetically stimulated arteriolar remodeling increasing the wall:lumen ratio and thereby elevated total peripheral resistance.30 In addition, increased sympathetic activity is known to increase the blood viscosity,31,32 which again affects peripheral resistance.

There are only a few other prospective studies assessing the predictive power of sympathetic activity on the development of hypertension. Bohm et al16 found a higher resting norepinephrine concentration at rest in subjects who became hypertensive compared with those who remained normotensive or borderline hypertensive during a 7-year follow-up. In another study, mental stress-induced blood pressure responses, together with plasma norepinephrine responses to bicycle ergometry and psychological factors, were found to be relatively weak predictors of future blood pressure classification after 2.5 years.18 Finally, Masuo et al17 demonstrated that resting norepinephrine concentration was a predictor of increases in mean blood pressure during a 5-year follow-up in Japanese subjects. In contrast to these studies mainly focusing on resting norepinephrine and with relatively short follow-up periods, our study was composed of a life span including an early age when a hyperkinetic circulation may predominate and a follow-up at a time when hemodynamic changes may have occurred, involving reduced cardiac output and increased total peripheral resistance.33
Although resting norepinephrine predicted blood pressure in these previous studies, we found no such significant associations during rest. In fact, there was a tendency in the univariate analyses that blood pressure, heart rate, and catecholamines during the stress tests (especially mental arithmetic) were better predictors than the variables recorded after 30 minutes of rest. This supports earlier findings showing that casual office and ambulatory blood pressure not measured in a resting position are stronger predictors than the recommended standardized office measurements after several minutes of rest. Laboratory stress responses have been found to correspond with reactivity to challenges of daily life during ambulatory blood pressure monitoring. Thus, in the present context, it seems that measurements performed during situations involving elements of stress may be more useful as predictors of future blood pressure than resting measurements.

One possible mechanism explaining the actual relationship between stress reactivity and development of hypertension could be the direct effect of frequent increases in blood pressure on the vasculature. However, transient blood pressure elevations are not capable of developing sustained blood pressure elevations, per se, in animal models, although care should be taken to extrapolate these findings to humans. Our data indicate that activity in the sympathetic nervous system may have implications for later development of hypertension independent of blood pressure. One may speculate whether test-retest reproducibility of stress reactivity is sufficient enough to give the present findings prognostic value. Because stability has been found to increase when the number of measurements during stress tests increase, we performed 3 measurements during mental arithmetic and 2 during the cold pressor test and then calculated the mean during each test. There are, however, as yet no data available on the reproducibility on catecholamine reactivity.

We found in our 18-year-old subjects that responses to mental arithmetic, which are predominantly \( \beta \)-mediated, may be better predictors than responses to the cold pressor test. This finding may support the assumption that subjects prone to develop hypertension are characterized by a hyperkinetic circulation at a young age. Using the cold pressor test in longitudinal hypertension studies may be suboptimal in young subjects, because it elicits an \( \alpha \)-adrenergic vascular response more than and a \( \beta \)-adrenergically mediated myocardial response. On the other hand, one may speculate whether the duration of the cold pressor test was too short compared with the 5-minute mental arithmetic. However, the peak response usually occurs within 30 seconds, and the cold pressor test lasted for 1 minute in accordance with Hines and Brown, who introduced the test. Furthermore, both stress tests induce significant increases in blood pressure, heart rate, and catecholamines, indicating a satisfactory duration.

Although plasma epinephrine during mental arithmetic was a near significant positive predictor of later blood pressure in univariate analysis, it became a negative predictor in the multiple regression analysis when initial blood pressure was introduced. The statistical tests did not indicate multicollinearity, which could be one explanation of this finding. A possible explanation could be that subjects with a high epinephrine level during mental arithmetic also had a larger stress component in their initial resting blood pressure, thus reducing the degree of further increase at follow-up.

Systolic and diastolic blood pressure increased significantly during the follow-up, and diastolic blood pressure increased more than systolic, which is in accordance with the Framingham study. The reduced SDs of blood pressures at follow-up probably represent regression to the mean, because the subjects originally were selected from the first, 50th, and 95th to 99th percentiles of the mean blood pressure distribution, thus securing a maximal dispersion of blood pressure at entry. One may question the weak relationship between sympathetic activity and future diastolic blood pressure. A possible explanation could be an insufficient sample size. Nevertheless, the apparent rise of diastolic blood pressure with age may have to do with other mechanisms not necessarily associated with sympathetic activity, such as increasing blood volume or total peripheral resistance.

To conclude, the present study shows that sympathetic nervous activity during mental arithmetic is an independent predictor of future blood pressure, suggesting a possible role in the development of essential hypertension.

**Perspectives**

In the present study, there was a clear tendency that blood pressure, heart rate, and catecholamine concentrations measured during stress were better predictors of future blood pressure than resting levels. In fact, by adding stress-induced systolic blood pressure and catecholamine concentrations, the explained variance of future systolic blood pressure increased by 22.1% points compared with traditional risk factors, with the whole model explaining 65.1% of the variance. Although stress testing may not be feasible in daily clinical practice, blood pressures measured in not fully relaxed individuals, eg, before the recommended 5 minutes of rest in the office, may actually provide important predictive information regarding the risk of future hypertension.

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**Disclosures**

None.

**References**

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