Increased Response to Physical and Mental Stress in Men With Hypertensive Parents

Bengt R. Widgren, John Wikstrand, Göran Berglund, and Ove K. Andersson

Blood pressure and heart rate responses to isometric handgrip exercise were studied at age 31 and after 5 years in young nonhypertensive men with positive family histories of hypertension (n=13) and in those with negative family histories of hypertension (n=13) for two generations to test whether subjects with positive family histories established a pattern of increased blood pressure and heart rate responses during the 5-year follow-up period. At follow-up the response to mental stress (Stroop’s color word test) was also studied. Baseline blood pressure and heart rate at rest did not differ, initially or at follow-up, between the groups. At the initial examination, absolute blood pressure levels were significantly higher during isometric handgrip exercise just before exhaustion in subjects with positive family histories. At follow-up the absolute blood pressure level (p<0.001) and the blood pressure responses (p<0.01–0.001) were found to be significantly increased during handgrip exercise in subjects with positive family histories compared with subjects with negative family histories. In subjects with positive family histories the diastolic blood pressure response was significantly higher (p<0.01) at follow-up than initially and was significantly related (r=0.70, p<0.01) to changes in baseline diastolic blood pressure during the follow-up period. In subjects with negative family histories the systolic blood pressure response was somewhat lower at follow-up than initially. During the mental stress test, the blood pressure response was significantly greater in subjects with positive than with negative family histories. We conclude that nonhypertensive men with positive family histories of hypertension were characterized by increased blood pressure responses under both physical and mental stress compared with subjects with negative family histories. Such increased responsiveness to different stressors could be related to subsequent development of high blood pressure in subjects predisposed to primary hypertension. (Hypertension 1992;20:606–611)

KEY WORDS • family characteristics • stress • hypertension, genetic

Despite varying opinions concerning the etiology of primary hypertension, most investigators agree on the importance of genetic factors.1,2 Page’s mosaic theory3 implies that the hereditary factors underlying primary hypertension consist of a spectrum of variants more or less randomly mixed in the genetic coding of human reproduction. Epidemiological studies have demonstrated that hypertension is also related to genetic and environmental conditions such as body weight and weight gain.4-9 The mechanisms through which the interaction of genetic and environmental factors operate, thus directing the development of increased arterial blood pressure, has yet to be established.

Almost 50 years ago it was proposed that a period of vascular hyperreactivity precedes the development of sustained hypertension.10 Previous studies have shown that the offspring of hypertensive humans differ from those of normotensive persons in that they exhibit enhanced blood pressure responses to laboratory stressors.11-14 This reactivity pattern has also been observed in patients with established hypertension.15 In spontaneously hypertensive rats (SHR), the animal model for primary hypertension, increased sympathetic activity that closely agrees with that of the defense reaction has been found.16,17 During such increased stressor response in SHR, increased sympathetic activity in renal nerves and decreased sodium excretion have also been found.18 It has been suggested that this is mediated by β-adrenergic receptors in the central nervous system.19 In subjects with positive family histories of hypertension, an increased pressor response to various pressor stimuli has recently been found,20,21 and this has also been found in animal models of primary hypertension.18,22

The aim of the present investigation was to study whether subjects with positive family histories of hypertension were characterized by increased blood pressure and heart rate responses to physical and mental stress.

Methods

The present study was approved by the Ethics Committee of the Medical Faculty, University of Göteborg, and informed consent was obtained from the subjects before the investigations. All subjects attended the research laboratory at the Department of Clinical Physiology, Sahlgrenska Hospital. All subjects were instructed to avoid changes in their daily life habits and to avoid heavy exertion during the days before the experimental procedure. On both occasions the subjects were...
investigated between 9 and 11 AM in a soundproof room with a temperature of 22–24°C.

All subjects included in the present study were healthy sons of normotensive or hypertensive fathers who had participated in the Primary Preventive Trial in Göteborg, Sweden, in which a random third \((n=9,996)\) of the male population 47–54 years of age was examined for cardiovascular risk factors.20 All men \((n=686)\) with two consecutive recordings of blood pressure above 175 mm Hg systolic or 115 mm Hg diastolic or being treated for hypertension were referred to the Hypertension Unit. Both parents of 49 of these hypertensive men had been treated for hypertension or stroke before the age of 65 years. These 49 men were asked if they had a son living near Göteborg, and a total of 24 sons with positive family histories of primary hypertension for two generations were contacted and invited to participate. All mothers of the sons with positive family histories of hypertension were also contacted by telephone at the initial examination and asked about current medication. Four mothers of the sons with hypertensive fathers were taking antihypertensive medication. Sixteen subjects \((31±6 \text{ years of age})\) with positive family histories of hypertension were initially examined. Of the remaining eight individuals, one was excluded because of current medication for hypertension, one because of alcoholism, two because they were traveling salesmen, and one because he was in military service and could not participate. Three subjects declined to participate. At follow-up, all 16 subjects with positive family histories were reexamined. However, in the present study three subjects with positive family histories of hypertension dropped out, two because of technical difficulties in the blood pressure measurements during the stress tests and one because he declined to participate in this part of the follow-up.

Subjects in the control group were recruited from the sons of 50 normotensive randomly selected men (blood pressure below 130 mm Hg systolic, 90 mm Hg diastolic) from the same screening examination.23 These normotensive men had negative family histories of hypertension or stroke. These 50 normotensive men had 26 sons. All mothers of the sons in the control group were also contacted by telephone about their current medication and state of health and whether they were also normotensive according to recent medical investigation. Because the group with positive family histories of hypertension turned out to be heavier than the normotensive control group, slight overweight emerged as an important selection criterion for the group with negative family histories. On this basis, 15 of these 26 men were matched for age and body weight with the men from the group with positive family histories of hypertension. The mothers of those 15 subjects had no hypertension. Thirteen of the 15 subjects with negative family histories of hypertension were reexamined at follow-up, but two were unwilling to participate. Subjects with positive and negative family histories of hypertension who did not participate in the follow-up did not differ in blood pressure response compared with the group mean.

Follow-up blood pressure data\(^a\) and pathophysiological mechanisms in these subjects have previously been reported.20,21

**Blood Pressure, Heart Rate, and Stress Tests**

Baseline blood pressure was measured phonographically\(^b\) after 45 minutes of rest in the supine position and during isometric handgrip exercise, which was performed in the supine position. At follow-up, measurements were also made in a sitting position during the mental stress test. A 12×35-cm standard cuff, automatically inflated and deflated, was used. A microphone (EMT25C, Siemens-Elema, Stockholm, Sweden) was placed over the brachial artery, and signals indicating the Korotkoff sounds were registered on a minograph (Siemens-Elema). Signals indicating cuff pressure were also registered simultaneously on the same minograph. Diastolic blood pressure was recorded when the Korotkoff sounds disappeared (phase V). Mean arterial blood pressure is used in the figures to show changes during isometric exercise and was calculated as one third of the pulse pressure plus the diastolic blood pressure. This method of noninvasive blood pressure measurement has been evaluated during simultaneous intra-arterial blood pressure measurements \((n=32)\) and has been found to be reliable, with a mean±SD difference in systolic blood pressure between the two methods of 0.7±4.68 (confidence interval -2.6 to 1.16) mm Hg \((r=0.95)\) and in diastolic blood pressure of 1.0±3.1 (confidence interval -0.21 to 2.29) mm Hg \((r=0.86)\).

Baseline blood pressure before the stress tests is presented as the mean of three recordings taken at 5-minute intervals during the last 15 minutes before the tests were started. During isometric handgrip exercise, blood pressure was registered at 1 minute, 3 minutes, and just before exhaustion, whereas during the mental stress test blood pressure was registered at 2, 4, 6, 8, 12, 16, and 20 minutes.

Isometric handgrip exercise was performed with the right hand on a strain gauge dynamometer at 30% of the maximum developed force determined before exercise, using an electromechanical device. The mental stress test consisted of exposure to Stroop's color word conflict test in a modified version lasting for 20 minutes.25 The test consists of color words written in incongruent colors, and the subjects are asked to state the color they see and to ignore the written word as well as the color word given by a disturbing voice.

**Statistics**

Mean values, standard deviations (SD), and confidence intervals were calculated using standard methods. Student's \(t\) test was used for comparisons of means between the two groups and regarding changes within the groups. Only two-tailed tests were used, and \(p<0.05\) was regarded as statistically significant. Two-way analysis of variance was used to test the hypothesis of no difference in means between the two groups in repeated measurements. When this analysis yielded significant differences, the \(t\) test was used for comparisons of means between the two groups. The relation between variables was analyzed using linear regression coefficients. All statistics were handled using the STATVIEW \(512+\) package (Abacus Concepts, Inc., Calabasas, Calif.) implemented on an Apple Macintosh personal computer (Cupertino, Calif.).
TABLE 1. Absolute Blood Pressure and Heart Rate Levels During Isometric Handgrip Test at Initial and Follow-Up Examinations in Subjects With Positive and Negative Family Histories of Hypertension

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Positive family history (n=13)</th>
<th>Negative family history (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood pressure (mm Hg)</td>
<td>Blood pressure (mm Hg)</td>
</tr>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td></td>
<td>Heart rate (beats per min)</td>
<td>Heart rate (beats per min)</td>
</tr>
<tr>
<td>Initial examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (prestress)</td>
<td>125±11</td>
<td>122±10</td>
</tr>
<tr>
<td>1 min</td>
<td>145±19</td>
<td>141±11</td>
</tr>
<tr>
<td>3 min</td>
<td>160±14</td>
<td>151±12</td>
</tr>
<tr>
<td>Maximal blood pressure</td>
<td>164±13*</td>
<td>154±12</td>
</tr>
<tr>
<td>Follow-up examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (prestress)</td>
<td>129±19</td>
<td>126±13</td>
</tr>
<tr>
<td>1 min</td>
<td>149±25</td>
<td>137±14</td>
</tr>
<tr>
<td>3 min</td>
<td>161±21†</td>
<td>143±14</td>
</tr>
<tr>
<td>Maximal blood pressure</td>
<td>170±18†</td>
<td>152±18</td>
</tr>
</tbody>
</table>

Values are mean±SD. *p<0.05, †p<0.01, ‡p<0.001 different from negative family history.

Results

Baseline Blood Pressure and Heart Rate

At the initial examination, systolic and diastolic blood pressures and heart rate at supine rest did not differ between subjects with positive family histories of hypertension and control subjects. Heart rate was also similar between the two groups (Table 1).

At follow-up 5 years later, neither systolic nor diastolic blood pressure differed between groups at supine rest (126±14/75±7 versus 126±11/76±11 mm Hg, respectively, for positive versus negative family history groups). Heart rate also did not differ between groups at supine rest (Table 1) or sitting rest (data not shown). Furthermore, there were no significant changes in blood pressure or heart rate within the groups between testing sessions (Table 1).

Blood Pressure and Heart Rate Responses to Handgrip Exercise

Absolute blood pressure levels during isometric handgrip exercise at the initial examination are shown in Table 1. At 30% of maximum developed force, absolute blood pressure levels were significantly higher (p<0.05) just before exhaustion in subjects with positive family histories of hypertension. However, the blood pressure and heart rate responses (i.e., relative changes from baseline level) to isometric handgrip exercise did not differ between groups at the initial examination (Table 2).

At the follow-up examination 5 years later, absolute systolic and diastolic blood pressure levels were significantly higher at 3 minutes (p<0.01, Table 1), as was the maximum blood pressure at 30% of maximum developed force (p<0.001, Figure 2), in subjects with positive family histories of hypertension compared with control subjects. Maximum heart rate was also significantly higher (p<0.01) in subjects with positive family histories during isometric handgrip exercise (Table 1). Moreover, blood pressure and heart rate responses to isometric handgrip exercise at the follow-up examination were significantly greater at 1 minute (p<0.05 and p<0.01, respectively), at 3 minutes (p<0.001 and NS, respectively), and at maximum (p<0.01 and p<0.01, respectively) in subjects with positive family histories than in the control group (Table 2).

In subjects with positive family histories of hypertension, the relative change in diastolic blood pressure to handgrip exercise at follow-up was significantly greater (p<0.01, Table 2) than at the initial examination. Systolic blood pressure and heart rate responses did not differ between examinations in subjects with positive family histories. In control subjects, blood pressure and heart rate responses were somewhat, but not significantly, lower at follow-up than at the initial examination. There was also a significant (r=0.70, p<0.01) relation between changes in baseline diastolic blood pressure level and reactivity (i.e., relative changes in the diastolic blood pressure response, Table 2) to handgrip exercise during the 5-year follow-up in subjects with positive family histories, while in subjects with negative family histories no such relation was found (r=0.18, not significant).

FIGURE 1. Plots of baseline and maximal attained mean arterial blood pressure during handgrip exercise at initial examination in subjects with positive family histories of hypertension (PFH) and subjects with negative family histories of hypertension (NFH). Squares and bars indicate mean±SD. *p<0.05.
TABLE 2. Blood Pressure and Heart Rate Responses to Physical Stress of Initial and Follow-Up Examinations and to Mental Stress at Follow-Up Examination in Subjects With Positive and Negative Family Histories of Hypertension

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Positive family history (n=13)</th>
<th>Negative family history (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood pressure (mm Hg)</td>
<td>Blood pressure (mm Hg)</td>
</tr>
<tr>
<td></td>
<td>Systolic  Diastolic</td>
<td>Systolic  Diastolic</td>
</tr>
<tr>
<td></td>
<td>Heart rate (beats per min)</td>
<td>Heart rate (beats per min)</td>
</tr>
<tr>
<td>Isometric handgrip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>24±15</td>
<td>21±9</td>
</tr>
<tr>
<td>3 min</td>
<td>36±12</td>
<td>31±10</td>
</tr>
<tr>
<td>Maximum response</td>
<td>39±11</td>
<td>35±10</td>
</tr>
<tr>
<td>Follow-up examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 min</td>
<td>20±12*</td>
<td>11±6</td>
</tr>
<tr>
<td>3 min</td>
<td>32±9†</td>
<td>18±10</td>
</tr>
<tr>
<td>Maximum response</td>
<td>41±12‡</td>
<td>27±14</td>
</tr>
<tr>
<td>Mental stress test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 min</td>
<td>22±13*</td>
<td>13±7</td>
</tr>
<tr>
<td>4 min</td>
<td>21±12*</td>
<td>12±7</td>
</tr>
<tr>
<td>6 min</td>
<td>19±5*</td>
<td>10±8</td>
</tr>
<tr>
<td>8 min</td>
<td>16±11</td>
<td>15±5‡</td>
</tr>
<tr>
<td>12 min</td>
<td>15±11</td>
<td>16±5‡</td>
</tr>
<tr>
<td>16 min</td>
<td>14±12</td>
<td>17±7‡</td>
</tr>
<tr>
<td>20 min</td>
<td>5±11</td>
<td>7±8</td>
</tr>
</tbody>
</table>

Values are mean±SD change from baseline.

* p<0.05, † p<0.001, ‡ p<0.01 different from negative family history.

§ p<0.01 different from initial examination.

Blood Pressure and Heart Rate Responses to Mental Stress Test

During the mental stress test, blood pressure and heart rate increased significantly in both groups. The systolic blood pressure response was significantly higher during the first 6 minutes, whereas the diastolic blood pressure response was significantly higher throughout the test, in subjects with positive family histories of hypertension than in control subjects (Table 2). The heart rate response was somewhat higher in subjects with positive family histories but did not differ significantly between groups during the mental stress test (Table 2).

Discussion

Increased blood pressure and heart rate responsiveness (both absolute levels and relative changes from baseline) were observed during isometric handgrip exercise and the mental stress test in subjects with positive family histories of hypertension. This supports the hypothesis of increased central and peripheral cardiovascular responsiveness to different stressors in nonhypertensive subjects predisposed to development of primary hypertension. We also found a significant relation between changes in baseline diastolic blood pressure level and changes in diastolic blood pressure response (i.e., relative change) to handgrip exercise during the 5-year follow-up. This means that those subjects with a positive family history of hypertension whose baseline diastolic blood pressure increased during follow-up also had increased their diastolic blood pressure response to isometric handgrip exercise during the 5-year follow-up.

At the initial examination, the absolute blood pressure level during isometric handgrip exercise at 30% of maximum developed force was increased just before exhaustion in subjects with positive family histories of hypertension compared with control subjects. After the 5 years of follow-up, still without significant differences or changes in baseline blood pressure, the diastolic blood pressure response during isometric handgrip exercise was even more markedly increased in subjects with positive family histories. However, it must be
indicated that the diastolic blood pressure response was somewhat lower in the control group at follow-up than at the initial investigation. A lower response to repeated stress stimuli, such as during handgrip exercise in subjects with negative family histories of hypertension, could be due to habituation to the examination procedure. However, the difference in blood pressure response between the two groups was repeated during the mental stress test.

Cardiovascular responses to stress are often assessed by the application of either physical or emotional stimuli in a laboratory environment. We used both physical and emotional stressors to induce blood pressure and heart rate responses in subjects selected by a procedure suggested by others to study plausible pathophysiological factors in subjects with positive family histories of primary hypertension.

Previously, longitudinal studies have supported the notion that enhanced blood pressure and heart rate responses to mental stress are an important marker of future primary hypertension. In patients with borderline or established primary hypertension, an increased blood pressure and sympathoadrenal response to the color word test has been reported. Such enhanced responsiveness has also been observed in SHR. In SHR, the animal model for primary hypertension, such a cardiovascular pattern also occurs during the development of high blood pressure. In studies by Julius and Esler, convincing evidence has been presented that a hyperkinetic circulatory pattern characterizes early primary hypertension, and follow-up studies in young persons with borderline hypertension also contribute to the hypothesis of an initial defense reaction–like hyperkinetic state, gradually transferred into established primary hypertension.

In the present study baseline blood pressure and heart rate did not differ between the two groups. Furthermore, in a previous report, no signs of difference in the sympathetic nervous system activity measured as 24-hour urinary catecholamine excretion or venous plasma concentrations of norepinephrine and epinephrine have been observed. However, measurements of circulating venous plasma levels of catecholamines have been said to give poor information about the prevailing sympathetic nervous system activity.

The mechanisms involved in the increased blood pressure and heart rate responses in subjects with positive family histories of hypertension are not completely understood. Whether the increases are due to an increase in peripheral resistance, cardiac output, or both has not been clarified in the present study. However, at follow-up the absolute diastolic blood pressure level was significantly higher than at the initial examination, even with the heart rate response somewhat lower than initially. One might speculate if this may indicate increased peripheral vascular resistance in relation to different kinds of stress stimuli in subjects with positive family histories of hypertension, which is further supported by the higher diastolic blood pressure throughout the mental stress test. In previous studies, an enhanced systemic and renal vascular sensitivity to angiotensin II has been reported in subjects with positive family histories of hypertension. However, the cardiovascular response to α-adrenergic receptor agonist stimuli did not differ between subjects with positive family histories of hypertension and control subjects. In the same study, calf and forearm blood flow were found to be similar in normotensive subjects with and without positive family histories of hypertension.

The defense reaction observed in the cardiovascular adjustments to different kinds of stimuli is a composed neurohumoral pattern involving both bulbar and peripheral reflexes as well as changes in cardiovascular hormones. In an interesting study by Koepe and DiBona, increased renal sympathetic nerve activity and decreased sodium excretion owing to a stressful environment related to β-adrenergic receptors in the central nervous system were found in SHR. Interestingly, in a study by Webb et al increased systemic and renal sensitivity to angiotensin was observed in "psychosocial mice," in which hypertension developed under environmental stress.

In a physiological–psychological study, young persons with borderline hypertension revealed significantly higher irritability than normotensive control subjects, which may reflect a mild accentuation of the average level of mental arousal. Other studies have shown that subjects with borderline hypertension had blood pressure responses similar to those of normotensive subjects. Such differences have been demonstrated as an effect of information about blood pressure levels and may also be attributable to different degrees of habituation to the investigative procedures used. In the present study it must be remembered that both groups have been examined several but equally many times and followed up for 5 years and that the baseline blood pressure and heart rate did not differ between subjects with and without positive family histories of hypertension.

One might speculate as to whether a mild defense reaction and slightly increased renal sympathetic nerve activity were involved in previous findings of blunted sodium excretion during saline loading and increased sensitivity to angiotensin II among subjects with positive family histories of hypertension. Previously, sodium intake has been shown to be similar in the two groups. However, this does not exclude the possibility that sodium intake and the sympathetic nervous system are concurrent factors involved in the cardiovascular response to different stress stimuli. An altered renal response that contributes to the differences in cardiovascular reactivity in subjects with positive family histories of hypertension has previously been demonstrated. A psychological, stress-induced sodium and fluid retention has been reported in subjects at high risk for primary hypertension.

In an epidemiological study by Julius et al, hyperreactivity to stress was not found to be a predictor of future hypertension. Another study focusing on the importance of stress and the sympathetic nervous system in the development of hypertension and atherosclerosis has recently been reviewed. One of the most interesting findings in the present study was that the increased response to two different kinds of stress stimuli was present in nonhypertensive subjects with positive family histories of hypertension with apparently similar levels of blood pressure at baseline as in control subjects with negative family histories of hypertension. Another is that subjects with increasing diastolic blood pressure during follow-up also had increased their diastolic blood pressure re-
spontaneous handgrip exercise at follow-up. The present study does not clarify whether this enhanced diastolic blood pressure responsiveness is a marker of future hypertension.

In conclusion, we found that nonhypertensive men with positive family histories of hypertension for two generations were characterized by increased blood pressure and heart rate responsiveness to different stressor stimuli without significant differences in baseline blood pressure. Furthermore, we also found a relation between changes in baseline diastolic blood pressure and changes in the diastolic blood pressure response to handgrip exercise over the 5-year follow-up. Such an increased response to different stress stimuli could be an early marker for subsequent development of primary hypertension.

References
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