Adrenergic Responsiveness in Prehypertensive Subjects

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SUMMARY To determine if alterations in adrenergic activity precede hypertension, we evaluated the pressor effect of an α agonist (phenylephrine) and the chronotropic effect of a β agonist (isoproterenol) in prehypertensive young men. The subjects were selected from a 5-year follow-up of individuals in the upper ("high") and lower ("low") deciles of the blood pressure distribution in a high school population. At follow-up, the blood pressure differences between groups were maintained. The baroreflex slopes of the high (n = 13) and low (n = 10) blood pressure groups did not differ. The dose of phenylephrine required to increase systolic blood pressure by 20 mm Hg (PD20) was greater in the high blood pressure group than in the low blood pressure group (250 ± 38 μg vs 167 ± 35 μg, p < 0.05). The dose of isoproterenol required to increase heart rate by 25 beats/min (CDDM) was also greater in the high than in the low blood pressure group (1.9 ± 0.5 μg vs 0.9 ± 0.2 μg, p < 0.05). The increase in plasma renin activity in response to treadmill exercise was less in the high than in the low blood pressure group (1.8 ± 0.6 ng/ml/hr vs 3.4 ± 0.7 ng/ml/hr, p < 0.03). Overall, systolic blood pressure correlated with PD20 (r = 0.52, p < 0.01) and CDDM (r = 0.62, p < 0.001). Plasma norepinephrine correlated with systolic blood pressure (r = 0.44, p < 0.04) and with PD20 (r = 0.63, p < 0.001). We conclude that baroreflex sensitivity is not altered in young men with relatively high blood pressure. Insensitivity to α and β agonists may be related to the positive correlation of systolic blood pressure with plasma norepinephrine concentration.

IN 1973, we obtained standardized measurements of blood pressure in all high school seniors residing in Bourbon County, Kentucky, which has a predominantly white, rural population with a high prevalence of hypertension. Five years later, follow-up measurements were taken in persons in the upper and lower deciles of the original blood pressure distribution, by sex. Follow-up blood pressure measurements were highly correlated with blood pressure measurements recorded 5 years earlier, and blood pressure differences between groups were maintained. Other investigators have demonstrated an association between blood pressure measurements repeated over time in adolescents and young adults. Because of this "tracking" phenomenon and because blood pressure tends to increase with age, these young adults with relatively higher blood pressures are at increased risk for developing hypertension. The association between borderline hypertension and the development of established hypertension is well documented. Identification of adolescents and young adults who maintain relatively high blood pressures over time provides the opportunity to evaluate mechanisms of blood pressure control in the "prehypertensive" state. Alterations in sympathetic nervous system activity have been described in patients with essential hypertension. These alterations include decreased sensitivity of arterial baroreceptors, increased vasoconstrictor responses to infusion of norepinephrine, and decreased endogenous β-receptor sensitivity. Whether these alterations precede the onset of hypertension or are secondary to elevated arterial pressure...
is not clear. Subjects identified as having relatively high blood pressures in our follow-up study of Bourbon County adolescents permitted us to characterize adrenergic responsiveness in prehypertensive subjects.

In the present study, we compared pressor responses to phenylephrine and heart rate responses to isoproterenol in prehypertensive subjects and age-matched controls. Acute increments of arterial pressure with phenylephrine also permitted the comparison of baroreflex responsiveness in these two groups of subjects. Plasma renin activity (PRA) is suppressed in approximately 25% of patients with essential hypertension, but it is unclear whether renin suppression precedes hypertension or is a consequence of elevated arterial pressure. Therefore, we also compared PRA responses to standardized treadmill exercise in subjects selected for isoproterenol and phenylephrine infusions.

Methods

Subjects selected for evaluation of sympathetic nervous system activity were included in a follow-up study of the association of blood pressure levels of young adults with previous measurements obtained during adolescence. Follow-up measurements were obtained in individuals in the upper and lower deciles of the original blood pressure distribution, by sex. Thirteen males (nine white and four black) originally in the upper decile and 10 males (eight white and two black) originally in the lower decile groups were subjects for the present study. The subjects were selected on the basis of availability and willingness to participate. Each subject gave informed consent, and each subject received a stipend of $25. The mean age of the subjects was 22 ± 0.4 years (±SEM).

The subjects remained supine for at least 45 minutes before study. Peripheral venous blood was obtained for measurement of plasma catecholamine concentration and PRA, and an i.v. infusion of 5% dextrose in water was begun for injection of vasoactive substances. Peripheral β-receptor sensitivity was evaluated with an isoproterenol bolus dose-response technique described previously. Briefly, the ECG was monitored continuously, and the heart rate was computed electronically using a Beckman 511A polygraph and an R-wave triggered cardiotachometer. When the heart rate was stable, progressively increasing bolus doses of isoproterenol were injected intravenously, beginning with a dose of 0.25 µg. The heart rate was allowed to return to control levels before subsequent doses were given. The maximal change in heart rate in response to each injection of isoproterenol was plotted against the logarithm of the drug dose, and the dose required to increase the resting heart rate by 25 beats/min was interpolated from the resulting graph. This dose was termed the CD25 (chronotropic dose for a 25-beat/min increase). The isoproterenol bolus dose-response method has been established as an accurate and reproducible technique for evaluation of β-adrenoceptor sensitivity.

A 30-minute recovery period was allowed after completion of isoproterenol dosing. To evaluate baroreflex sensitivity, bolus doses of phenylephrine were injected, and blood pressure and heart rate were monitored. After each phenylephrine injection, indirect arterial pressure was measured repeatedly (Beckman indirect blood pressure device) by placing a microphone over the brachial artery. The heart rate was monitored as described previously. Progressively larger doses of phenylephrine were injected, starting with 20 µg, until systolic blood pressure was transiently increased by 30 mm Hg. Blood pressure and heart rate were allowed to return to control levels before each successive injection. For each subject, baroreflex sensitivity was computed as the slope of the line relating the RR interval to the increase of systolic blood pressure in response to phenylephrine. In addition, the increase of systolic blood pressure was plotted against the logarithm of each phenylephrine dose, and the dose of phenylephrine required to increase systolic pressure by 20 mm Hg was interpolated from this graph. This is referred to as PD20 (pressor dose of phenylephrine required to increase systolic blood pressure 20 mm Hg). Dosages of phenylephrine and isoproterenol were not adjusted for body weight; however, body weight was not correlated with PD20 or CD25.

To further evaluate the renin-angiotensin axis, PRA was measured before and immediately after standardized treadmill exercise in these same subjects. Exercise testing using the Balke protocol was not carried out on the day isoproterenol and phenylephrine infusions were given. According to this exercise protocol, subjects walked on a treadmill at 3.5 mph, beginning with a horizontal plane and increasing the elevation by 2 degrees per minute. A 15-minute test was attempted, and reasons for early termination included a heart rate greater than 200 beats/min, appearance of ECG abnormality, or patient fatigue. The mean exercise times in the two groups of subjects did not differ.

Plasma catecholamine concentrations were measured by radioenzymatic assay, and PRA was measured by the radioimmunoassay procedure of Haber et al. To determine whether group differences of plasma catecholamines, PRA, CD25, PD20 and baroreceptor slope were statistically significant, two-group comparisons were made using the t test. Analysis of variance was used for comparisons of three groups. Correlations between variables were determined with Pearson's product-moment correlation coefficient.

Results

At the time of follow-up, the mean systolic and diastolic blood pressures of subjects selected from the upper decile of the original systolic blood pressure distribution were significantly higher than those of subjects selected from the lower decile (table 1). No subject had a diastolic blood pressure greater than 90 mm Hg. Resting heart rates in the two groups did not differ significantly.

Baseline PRA and plasma catecholamine concentrations in the two groups did not differ significantly (table 2). The mean baroreflex slopes of the two
TABLE 1. Blood Pressure and Body Size

<table>
<thead>
<tr>
<th>Blood Pressure group</th>
<th>High (n=13)</th>
<th>Low (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>145 ± 4</td>
<td>120 ± 3*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83 ± 2</td>
<td>74 ± 3†</td>
</tr>
<tr>
<td>Heart rate (systoles/min)</td>
<td>74 ± 3</td>
<td>68 ± 5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.2 ± 6.4</td>
<td>69.1 ± 3.6‡</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.1 ± 3.3</td>
<td>168.7 ± 5.8</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.0001 compared with high BP group.
† p < 0.01 compared with high BP group.
‡ p < 0.05 compared with high BP group.
Abbreviation: BP = blood pressure.

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groups were identical. However, the PD₂₀ was significantly greater in the group of subjects with higher blood pressures (p < 0.05). Similarly, the CD₂₅ was also greater in subjects selected for higher blood pressure (p < 0.05).

PRA increased (p < 0.01) in both groups of subjects in response to treadmill exercise (table 3). The values before and after exercise did not differ significantly between the two groups. However, in the subjects with higher blood pressures, the increase in PRA in response to exercise was significantly less (p < 0.05) than that in subjects with lower blood pressures.

In the two groups of subjects selected on the basis of blood pressure measurements obtained 5 years previously, there was some overlap of current blood pressures. Therefore, subjects were reclassified on the basis of follow-up blood pressure measurements into “high” (upper quartile), “low” (lower quartile) and “middle” (remaining 50%) groups (table 4). Systolic blood pressures differed significantly between the groups (p < 0.0001). Plasma norepinephrine concentration of subjects in the high blood pressure group was greater than that of subjects in the low blood pressure group (p < 0.05). The baroreflex slopes in the three groups were similar. However, the PD₂₀ was greater (p < 0.01) in the high blood pressure group than in the middle and the low blood pressure groups (fig. 1). The CD₂₅ was also greater (p < 0.05) in the high blood pressure group in the other two groups (fig. 2).

Overall, the preinfusion systolic blood pressure correlated positively (p < 0.01) with PD₂₀ (table 5), with CD₂₅ (p < 0.001) and with plasma norepinephrine concentration (p < 0.04). Plasma norepinephrine also correlated (p < 0.001) with the PD₂₀. Plasma norepinephrine concentration and body weight did not correlate.

**Discussion**

Several methods have been used to study reflex control of the circulation (phenylephrine, Valsalva maneuver, application of negative pressure to the lower torso, variable pressure neck chamber technique). Most observers agree that the baroreflex is reset to a higher level and has diminished gain with both age and increased arterial pressure.⁰¹-⁰³ Using the same phenylephrine bolus technique as that in the present study,⁰⁴ we found that the baroreflex slope was not as steep (p < 0.001) in an older group of patients (n = 23) with established essential hypertension (3.8 ± 0.7 msec/mm Hg) as that in the young adults in this report (12.4 ± 1.4 msec/mm Hg). Secondary resetting of the baroreflex has been convincingly demonstrated in both the experimental animal and in patients with

TABLE 2. Plasma Renin Activity and Indexes of Sympathetic Nervous System Activity

<table>
<thead>
<tr>
<th>Blood pressure group</th>
<th>High (n=13)</th>
<th>Low (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE (pg/ml)</td>
<td>223 ± 27</td>
<td>178 ± 23</td>
</tr>
<tr>
<td>E (pg/ml)</td>
<td>73 ± 20</td>
<td>38 ± 5</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.9 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Baroreflex slope (msec/mm Hg)</td>
<td>12.4 ± 1.6</td>
<td>12.4 ± 2.4</td>
</tr>
<tr>
<td>CD₂₅ (µg)</td>
<td>1.9 ± 0.5</td>
<td>0.9 ± 0.2*</td>
</tr>
<tr>
<td>PD₂₀ (µg)</td>
<td>250 ± 38</td>
<td>167 ± 35*</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 compared with high blood pressure group.
Abbreviations: NE = norepinephrine; E = epinephrine; PRA = plasma renin activity; CD₂₅ = chronotropic dose (isoproterenol) required to increase heart rate 25 beats/min; PD₂₀ = pressor dose (phenylephrine) required to increase systolic blood pressure 20 mm Hg.

TABLE 3. Response of Plasma Renin Activity (ng/ml/hr) to Treadmill Exercise

<table>
<thead>
<tr>
<th>Blood pressure group</th>
<th>Pre-exercise</th>
<th>Post-exercise</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>High BP</td>
<td>1.5 ± 0.3</td>
<td>3.3 ± 0.7*</td>
<td>1.8 ± 0.6†</td>
</tr>
<tr>
<td>Low BP</td>
<td>1.0 ± 0.3</td>
<td>4.4 ± 0.8*</td>
<td>3.4 ± 0.7</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.01 vs preexercise.
† p < 0.05 vs low BP group.
Abbreviation: BP = blood pressure.

TABLE 4. Plasma Catecholamine Concentrations and Baroreceptor Slope in Subjects Classified on the Basis of Current Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Blood pressure group</th>
<th>High</th>
<th>Middle</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>158 ± 3</td>
<td>132 ± 2†</td>
<td>115 ± 3†</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td>257 ± 35*</td>
<td>201 ± 27</td>
<td>153 ± 35</td>
</tr>
<tr>
<td>E (pg/ml)</td>
<td>63 ± 24</td>
<td>67 ± 17</td>
<td>36 ± 24</td>
</tr>
<tr>
<td>Baroreflex slope (msec/mm Hg)</td>
<td>13.0 ± 2.9</td>
<td>12.1 ± 2.0</td>
<td>12.3 ± 2.6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 vs low blood pressure group.
† p < 0.0001 vs other two groups.
Abbreviations: SBP = systolic blood pressure; NE = norepinephrine; E = epinephrine.
renovascular hypertension.\textsuperscript{18, 22} However, several observations suggest that diminished baroreflex responsiveness may contribute to the development of hypertension. Although production of sustained hypertension by peripheral baroreceptor denervation is inconsistent,\textsuperscript{23} hypertension has been produced in the rat and the dog by bilateral electrical lesions in the nucleus tractus solitarius,\textsuperscript{24, 31} the site at which baroreceptor afferents terminate.\textsuperscript{26} Sleight\textsuperscript{19} recently described the appearance of hypertension in a patient after surgical denervation of the carotid sinuses. Resetting and reduced sensitivity of baroreceptors are associated with reduced arterial wall distensibility.\textsuperscript{27} Such alterations may also occur in the absence of vascular changes.\textsuperscript{28, 29}

At lower levels of arterial pressure, brief increases or decreases of carotid distending pressures do not affect heart rate.\textsuperscript{30} Our demonstration that heart rate responses to baroreceptor manipulation are not altered in prehypertensive subjects indicates that differences in baroreflex sensitivity are also not detectable in normotensive subjects with relatively high and relatively low blood pressures and do not precede the onset of overt hypertension. In contrast to our findings in prehypertensive subjects, Takeshita et al.\textsuperscript{32} reported decreased baroreceptor sensitivity in young adults (mean age 19 years) referred for evaluation of hypertension with systolic blood pressures greater than 150 mm Hg or diastolic blood pressures greater than 90 mm Hg on at least three occasions. Julius et al.\textsuperscript{33} found normal responses in borderline hypertensive patients whose blood pressures were lower than those of the patients reported by Takeshita et al.\textsuperscript{32} Eckberg\textsuperscript{34} reported that a gradation of baroreflex responsiveness exists among young adults classified as having borderline hypertension. Overall reflex sensitivity was normal; however, sensitivity was subnormal in the subgroup of patients with more severe borderline hypertension. Resetting of baroreceptor activity also occurs in the early stages of hypertension in the spontaneously hypertensive rat; however, resetting does not occur when these rats are made normotensive from 6 weeks of age.\textsuperscript{4} This suggests that resetting is in some way caused by elevated arterial pressure. Nevertheless, despite normal baroreflex sensitivity to acute increments of blood pressure in young adults with relatively high blood pressures, this reflex is reset to a higher level of arterial pressure.

Although baroreflex sensitivity was normal, other indexes of sympathetic nervous system activity were altered in these young adult males with relatively high blood pressures. Plasma norepinephrine concentration was elevated and the subjects were relatively resistant to both the pressor effect of phenylephrine and to the chronotrope effect of isoproterenol. Groups of subjects selected from the upper and lower deciles of the original blood pressure distribution included a relatively small number of blacks. We did not observe racial differences in blood pressure\textsuperscript{1} or in indexes of sympathetic nervous system activity and responsiveness. Plasma norepinephrine concentrations are inversely correlated with large variations of sodium intake.\textsuperscript{34–36} However, Nicholls et al.\textsuperscript{37} reported that supine plasma norepinephrine concentrations in healthy men are higher on a very high sodium diet (180–300 mEq/day) than on an intermediate sodium diet (105–180 mEq/day). Although sodium intake was not estimated in the current study, we previously

### Table 5. Correlations of Systolic Blood Pressure with Indexes of Sympathetic Nervous System Activity

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP vs PD\textsubscript{20}</td>
<td>0.52</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>SBP vs CD\textsubscript{25}</td>
<td>0.62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP vs NE</td>
<td>0.44</td>
<td>&lt; 0.04</td>
</tr>
<tr>
<td>PD\textsubscript{20} vs NE</td>
<td>0.63</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: SBP = systolic blood pressure. See table 2 for other abbreviations.
reported that sodium excretion in a single timed overnight urine collection did not differ in subjects in the upper and lower deciles of our original blood pressure distribution. Consequently, although we cannot confidently exclude small differences of sodium intake in these two groups of subjects, if a difference did exist, it is unlikely to be of sufficient magnitude to account for group differences of plasma norepinephrine concentrations.

Although the results of plasma catecholamine measurements and urine catecholamine excretion rates are variable in patients with essential hypertension, most reports indicate increased levels in at least some patients. Hoffman et al. reported that resting plasma norepinephrine concentrations are increased in teenagers and young adults with mild hypertension. In contrast to our demonstration of decreased pressor responsiveness to phenoxyphenyl in young adults with relatively high blood pressures, patients with established hypertension have an increased pressor sensitivity to both norepinephrine and angiotensin. In both clinical and experimental hypertension, vascular reactivity (measured in terms of both pressure and flow) increased in several different vascular beds. Our results suggest that increased α-adrenergic sensitivity is not present in prehypertensive subjects.

Decreased responsiveness to the chronotropic effect of isoproterenol has been observed in patients with established hypertension, in young adult males with borderline hypertension and in several experimental models of hypertension. In the spontaneously hypertensive rat, decreased chronotropic responsiveness to isoproterenol and decreased concentrations of myocardial β receptors have been reported, even before the appearance of hypertension.

Responsiveness to the chronotropic effect of isoproterenol decreases with age. Dillon et al. reported an age-related decrease in the production of cAMP by lymphocytes in response to isoproterenol. A sustained increase in endogenous catecholamines or ingestion of β-adrenergic agonists is also associated with a decrease in the number of adrenoreceptors and responsiveness. In the present study, both the CD28 and the PD28 were correlated with plasma norepinephrine concentration, raising the possibility that greater receptor occupancy by circulating catecholamines or down-regulation of adrenoceptors contributes to the decreased sensitivities to both isoproterenol and phenylephrine.

Beta adrenoceptors, possibly β1 receptors, stimulate renin secretion by catecholamines. We previously demonstrated a correlation between plasma norepinephrine and PRA responses to exercise and suggested that the renin response to exercise is mediated by the sympathetic nervous system. In the present study, the increment of PRA in response to treadmill exercise was less in subjects with higher blood pressures. Similar to the decreased responsiveness of the heart rate to infusion of isoproterenol, the diminished renin response to exercise may also reflect relative β-adrenoceptor insensitivity to endogenous catecholamines.

In conclusion, the baroreflex slope was not altered in prehypertensive young adults with relatively high blood pressures sustained over 5 years. However, plasma norepinephrine concentration increased, and sensitivities to the chronotropic effect of isoproterenol and to the pressor effect of phenylephrine decreased in these subjects. The increment of PRA in response to standardized exercise was also decreased. Identification of prehypertensive subjects may provide a unique opportunity to study mechanisms in the pathogenesis of hypertension.

Acknowledgment

The authors are grateful to Mary Neill, R.N., and Susan Koenig, R.N., for their assistance and to Dr. Russell McAllister, Jr. for his critical review of the manuscript.

References


Adrenergic responsiveness in prehypertensive subjects.
T A Kotchen, G P Guthrie, Jr, H McKean and J M Kotchen

Circulation. 1982;65:285-290
doi: 10.1161/01.CIR.65.2.285
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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