SUMMARY  Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), plasma norepinephrine (NE), and epinephrine (E) levels at rest and in response to orthostatic stress of quiet standing were compared in 19 subjects with borderline hypertension (BH) (SBP-135 mm Hg, DBP-80 mm Hg), nine with significant hypertension (SH) (SBP-150 mm Hg, DBP-95 mm Hg), 14 normotensive siblings (NS) of hypertensives (SBP-113 mm Hg, DBP-64 mm Hg), and 21 age-matched normotensive controls (NC) (SBP-116 mm Hg, DBP-61 mm Hg). Group resting plasma NE levels were significantly higher in BH (454 pg/ml, p < 0.001 pg/ml) and SH (384 pg/ml, p < 0.01 pg/ml) than in NC (281 pg/ml) or NS (309 pg/ml), and more than 2 SD above the NC mean value in 50% of BH, 28% of SH, and 7% of NS. Plasma E levels were similar. On standing, mean arterial pressure (MAP) rose 13.7 mm Hg in NC, 3.9 mm Hg in BH, and 2.8 mm Hg in NS, and fell 7.3 mm Hg in SH. These differences reflect the frequent occurrence of hypotensive responses in study group subjects, which were not observed in NC. The mean rise in plasma NE with standing was blunted in hypertensives, increasing 40% to 50% compared with 95% in NC. In BH and NS, SBP was positively correlated with plasma NE levels at rest and with standing. These observations offer support for the hypothesis that altered adrenergic sympathetic nervous system (SNS) activity is present in a subgroup of young hypertensives and can be a contributing factor to their hypertension. Findings of similar SNS activity in some normotensive siblings suggest that genetic factors might be involved. (Hypertension 4:507–513, 1982)

KEY WORDS • blood pressure • children • norepinephrine • epinephrine • sympathetic nervous system • resting orthostatic stress • genetic

CONSIDERABLE evidence suggests that sympathetic nervous system (SNS) activity may be abnormal in a subgroup of adults with essential hypertension (EH). Plasma norepinephrine (NE) levels are taken as one index of adrenergic activity; circulating plasma catecholamine levels in adults, measured by highly sensitive radioenzymatic techniques, have shown that resting plasma NE levels are elevated in 25% to 30% of adults with EH, especially in younger subjects. This suggests that increased SNS activity is present in this subgroup. Additional evidence in support of this view has been provided by studies in EH subjects correlating hemodynamic changes occurring in response to stress maneuvers known to stimulate increased SNS activity with changes in plasma catecholamines (standing, head-up tilt, isometric and dynamic exercise).

No reports of similar studies in children with EH have been found to compare data obtained by a standardized protocol combining radioenzymatic assays of levels of plasma catecholamines as an index of SNS activity with measurements of blood pressure (BP) and heart rate (HR) at rest and in response to the stress of standing or isometric and dynamic exercise.

Borderline hypertension (BH) or labile hypertension may be present in 9% to 13% of children 12 to 20 years of age, while sustained EH is uncommon (1%). Since BH is considered to be a possible precursor of sustained EH in later life, and hereditary factors have been implicated, it seems important to study children with BH and sustained primary hypertension and com-
päre them to normotensive siblings (NS). This report describes the relationship between BP, HR, and SNS activity, evaluated by measuring plasma NE and epi- nephrine (E) levels, at rest and in response to ortho- static stress in ambulatory children with EH, in their normotensive siblings (NS), and in healthy, age- comparable, normotensive controls (NC).

Methods

Subjects

Asymptomatic ambulatory subjects found to have elevated BP by private physicians or physicians in the Department of Pediatrics of the New York Hospital were recruited into this study. Secondary causes had been excluded by routine urinalysis, blood chemistry profile, cardiologic evaluation, and intravenous rapid sequence pyelograms. To establish normal renin-alderosterone profiles, measurements of 24-hour urinary sodium (Na), potassium (K), and aldosterone excretion, and plasma renin activity (PRA) were performed by Dr. Jean Sealey in the Hypertension Center of Dr. John Laragh at the New York Hospital. When indicated, renal arteriography and renal vein sampling for PRA were done. Siblings 7 to 20 years old were enrolled as volunteers.

Hypertension was classified as "significant" if measurements of SBP or DBP, taken at three separate exams 1 or more weeks apart, were above the 95th percentile values for age and sex, and "borderline" when at least one of three separate measurements for SBP or DBP was above and one below the 90th percentile, age-sex adjusted for standards.

Study groups included 19 borderline hypertensives (BH), nine significant hypertensives (SH), and 14 of their normotensive siblings (NS) from 10 family units. The normal control (NC) sample consisted of 21 volunteers recruited from students enrolled in neighborhood schools who were healthy, ambulatory, and normotensive, and ranged in age from 13 to 19 years.

The demographic characteristics of these groups are shown in table 1. The age composition of the control sample permits comparison of mean values for specific parameters with study groups. There were more blacks in the control groups than in the other groups, but no effects of race on resting catecholamine levels have been documented in adult studies. 14

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Range</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>NC</td>
<td>21</td>
<td>16.0</td>
<td>13-19</td>
</tr>
<tr>
<td>BH</td>
<td>19</td>
<td>15.5</td>
<td>7-20</td>
</tr>
<tr>
<td>SH</td>
<td>9</td>
<td>13.8</td>
<td>7-17</td>
</tr>
<tr>
<td>NS</td>
<td>14</td>
<td>12.9</td>
<td>7-20</td>
</tr>
</tbody>
</table>

C = Caucasian; B = Black; O = other; NC = normotensive controls; BH = borderline hypertension; SH = significant hypertension; NS = normotensive siblings.

Ponderal mass was also comparable. The mean height ± sd in the groups was 173 ± 8 cm in NC, 159 ± 20 cm in BH, 174 ± 16 cm in SH, and 153 ± 18 cm in NS. Mean weights were 67 ± 13 kg in NC, 57 ± 22 kg in BH, 69 ± 17 kg in SH, and 46 ± 18 kg in NS, with no significant differences found among group mean values. To allow comparison when ponderal mass is known, the mean value for the relative weight index of the groups was calculated. This index was computed as the ratio of the subject's actual weight to ideal weight derived from standard growth charts for the observed height, adjusted for age and sex. The mean group values ± sd for the relative weight index were 1.04 ± 0.17 in NC, 1.10 ± 0.21 in BH, 0.99 ± 0.22 in SH, and 0.87 ± 0.21 in NS. Mean values of study groups did not differ significantly from NC, indicating a similar ponderal mass for all subjects.

Measurement of Blood Pressure

A Narco recording electrosphygmomanometer provided a standardized automated method for recording BP. This instrument makes possible the graphic recording of brachial BP by an automatically inflated cuff with a sound system for detecting Korotkoff sounds. The BP data represent the average of four measurements supine and three standing.

Measurement of Catecholamines

Plasma NE and E levels were measured with the highly sensitive radioenzymatic assay method of Peuler and Johnson. 2 This method uses only a single radioisotope and allows accurate and reproducible measurement of catecholamine concentrations in plasma samples of 50 μl. Blood samples were drawn into cold heparinized centrifuge tubes containing reduced glutathione and EDTA at a pH of 6 or 7. The samples were separated by centrifugation within 1 hour and then stored frozen at −76°C. Assays were repeated after a 1-year period of storage at −76°C, and no significant reduction in catecholamine levels was observed. Interassay variability remained under 12.5% for a series of 10 repeated catecholamine assays. The assay sensitivity was 20 pg/ml of plasma for NE and E.

Experimental Protocol

We used a standard protocol to obtain data for BP, HR, and SNS activity (plasma NE and E levels) in the resting state and in response to 15 minutes of quiet standing, isometric stress, and dynamic exercise (treadmill). (Results of the two latter studies will be reported separately.) All subjects and controls were ambulatory, and all studies were done in the Exercise Laboratory of the Division of Pediatric Cardiology. Written parental consent was obtained on forms approved by the New York Hospital-Cornell Committee on Human Rights in Research.

Subjects were informed about the procedures and asked not to smoke or drink tea or coffee for at least 90 minutes before the test. A no. 19 gauge butterfly needle was inserted into an arm vein and maintained pat-
PLASMA CATECHOLAMINES IN YOUNG HYPERTENSIVES

McCrory et al.

**Table 2. Hemodynamic Findings: Supine and Standing**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No.</th>
<th>Pulse (beats/min)</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>21</td>
<td>66 ± 2</td>
<td>116 ± 2</td>
<td>61 ± 2</td>
</tr>
<tr>
<td>BH</td>
<td>19</td>
<td>73 ± 3</td>
<td>135 ± 4†</td>
<td>80 ± 3†</td>
</tr>
<tr>
<td>SH</td>
<td>9</td>
<td>71 ± 5</td>
<td>150 ± 5‡</td>
<td>95 ± 4‡</td>
</tr>
<tr>
<td>NS</td>
<td>14</td>
<td>75 ± 3*</td>
<td>113 ± 4</td>
<td>64 ± 2</td>
</tr>
</tbody>
</table>

Supine Supine Standing Standing Change Change

- Mean arterial pressure: 68 ± 2
- Heart rate: 66 ± 2
- ECG: 5, 10, 15, and 20 minutes.

Subjects remained supine for 20 minutes after venipuncture, and BP, HR, and ECG were recorded at 5, 10, 15, and 20 minutes. Following this, blood was drawn from the indwelling needle. The subject then assumed a standing position, and BP, HR, and ECG were recorded at 5, 10, and 15 minutes. A blood sample was obtained at 10 minutes. Heart rate was determined as an average of 5 R-R intervals on ECG recordings.

**Statistical Analysis**

Data were analyzed using an applied statistics package implemented in a 48K Apple II Plus microcomputer. Equivalence of group variances was demonstrated by F-test for hemodynamic data. The group mean differences (± SEM unless otherwise indicated) were then compared by Student’s t test for unpaired observations with pooled variances. The group variances using absolute catecholamine data were not equivalent. The data were, therefore, transformed to the natural logarithm (ln) to minimize differences in variance before employing the F-test for level of significance. Percentage changes in catecholamine levels with standing were compared across groups using the Mann-Whitney nonparametric U test. The p values correspond to a two-tailed test of significance. Correlation coefficients (r) were arrived at by the method of linear regression and their significance was also tested by the Student’s t test.

**Results**

**Observations at Rest**

The HR was higher, but not significantly so, in BH and SH than in NC (table 2). The significantly higher HR value in NS over NC probably reflects the greater number of younger subjects in the NS group (table 1). Systolic and diastolic BP were significantly higher in both hypertensive groups than in NC, while values for NS did not differ from NC.

Resting, supine plasma NE and E levels are given in table 3. We confirmed the finding of others’ that venipuncture itself can elevate plasma catecholamine levels. Values for plasma NE in 19 normotensives and 17 hypertensives at the time of venipuncture were 569 ± 268 and 799 ± 421 (± SD) pg/ml respectively, in contrast to levels of 280 ± 48 and 449 ± 128 pg/ml after 20 minutes rest. These differences were both highly significant (p < 0.001) when compared using paired t tests. Values for plasma E were also higher at venipuncture than after 20 minutes of rest, although the differences were not significant.

The mean value for plasma NE after 20 minutes supine (table 3) in BH (455 ± 37 pg/ml) and SH (384 ± 27 pg/ml) was significantly higher than NC (281 ± 12 pg/ml). The value for NS did not differ significantly from NC. There were no significant differences in plasma E levels between groups.

The pattern of distribution of ln plasma NE values among subjects comprising each of the groups is

**Table 3. Catecholamine Levels Supine and Standing**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>No.</th>
<th>Plasma NE (pg/ml)</th>
<th>% Change</th>
<th>Plasma E (pg/ml)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>21</td>
<td>281 ± 12</td>
<td>547 ± 51</td>
<td>95 ± 19</td>
<td>142 ± 20</td>
</tr>
<tr>
<td>BH</td>
<td>19</td>
<td>455 ± 37‡</td>
<td>637 ± 66</td>
<td>40 ± 11‡</td>
<td>170 ± 26</td>
</tr>
<tr>
<td>SH</td>
<td>9</td>
<td>384 ± 27†</td>
<td>577 ± 48</td>
<td>50 ± 13</td>
<td>119 ± 20</td>
</tr>
<tr>
<td>NS</td>
<td>14</td>
<td>309 ± 25</td>
<td>493 ± 37</td>
<td>60 ± 15</td>
<td>111 ± 14</td>
</tr>
</tbody>
</table>

- *p < 0.05.
- †p < 0.01.
- ‡p < 0.001.

Significance (p) vs NC using log values for plasma catecholamines. NC = normotensive controls; BH = borderline hypertension; SH = significant hypertension; NS = normotensive siblings; NE = norepinephrine.
shown in the histogram (fig. 1). The distribution of NC appeared skewed to the right. The pattern in the other groups showed a broader spread. The vertical line in figure 1 represents 2 SD above the mean value for Ln NE levels in normal controls, thus indicating 50% of BH, 28% of SH, and 7% of NS had values of more than 2 SD above the mean values for the NC group. Regression analysis using Ln NE data suggested a weak linear relationship between supine NE and systolic BP in BH (r = 0.122) and NS (r = 0.234) (fig. 2).

**Arterial Pressure and Heart Rate Changes With Standing**

The HR increased in all subjects but only in SH was the increase significantly greater than in NC (table 2). Systolic BP rose in NC (5 ± 2 mm Hg) and fell slightly but significantly in BH (−1 ± 2 mm Hg) and NS (−2 ± 2 mm Hg). In SH the BP fell (−11 ± 2 mm Hg), and this differed significantly from the change in NC. The difference between resting and standing SBP was significant in NC (p < 0.001) and SH (p < 0.01) by paired r test. With standing, DBP rose in NC, BH, and NS but fell in SH. The greatest increase was in NC, where the difference between resting and standing DBP was highly significant (p < 0.001). The change from baseline DBP was significantly less in BH, SH, and NS than NC (table 2). These differences in BP between NC and study groups are shown in figure 3, reflecting the effect of variability of BP response with standing among individuals in BH, SH, and NS groups.

We selected mean arterial pressure (MAP) (calculated as the DBP plus one-third of the pulse pressure) for this comparison since it reflects the sum of the effects of change in both SBP and DBP on the circulation. The mean values for standing MAP in the groups (X in fig. 3) were +13.7 ± 1.7 mm Hg in NC, +3.9 ± 2.3 mm Hg in BH, −7.3 ± 3.1 mm Hg in SH, and +2.8 ± 2.0 mm Hg in NS. On standing, MAP was maintained or elevated above baseline level in all NC, but the response differed among the study subjects. Some had a rise (pressor response) but seven of 19 BH, six of nine SH, and six of 14 NS failed to maintain a MAP greater than baseline level on standing (hypotensive response) and the most pronounced fall was in SH. One SH subject developed hypotensive syncope after 8 minutes of quiet standing, terminating the observation. Her normotensive sister also developed hypotensive
syncope after 12 minutes of standing. One of the normal controls complained of transient light-headedness, as did several of the borderline hypertensives, but none fainted.

Catecholamine Changes with Standing (OS)

Plasma NE levels increased with standing. The rise was quantitatively less in the hypertensive groups than in NC. The change above resting level was 95% in NC, in contrast to an increase of 40% in BH and 50% in SH; the change in BH differed significantly from NC ($p < 0.01$).

A positive linear relationship was found (fig. 2) between In NE levels and SBP during standing in BH ($r = 0.305, p = 0.06$) and NS ($r = 0.390, p < 0.05$). A positive linear relationship was evident when change in In NE with standing was related to change in SBP in BH ($r = 0.447, p < 0.001$) and NS ($r = 0.436, p < 0.05$). No such relationships were found with similar comparisons in NC or SH.

The reproducibility of the lying and standing hemodynamic and catecholamine mean values has been evaluated using 12 hypertensives (7 BH and 5 SH) in a second study 9 to 15 months after the initial test. The values for HR, SBP, DBP, plasma NE and E lying and standing, and change with standing, did not differ significantly (paired $t$ test), indicating that the hypertensives group mean responses were reproducible.

Discussion

There are no data reporting values for resting or standing NE and E levels in normotensive children of comparable age to compare with our results. The mean value of $281 \pm 12$ pg/ml in our normal controls for resting plasma NE level is similar to that reported by Hofman et al.,$^{15}$ namely, $281 \pm 20$ pg/ml for a sample of normal 13- to 23-year-old teenagers selected from an open population, even though their environmental setting and methods of blood sampling were not comparable. They obtained blood samples by venipuncture after normal subjects had reclined for 30 minutes. They reported plasma NE levels in 18 subjects with elevated BP (140/90 mm Hg, or higher) to be significantly higher ($351 \pm 26$ pg/ml) than in 18 age-matched normotensive controls ($248 \pm 29$ pg/ml, $p < 0.01$) from the same population sample. The mean value for plasma NE extrapolated from the data of Lake et al. to match our age group gives a somewhat lower figure, approximating 230–240 pg/ml.

Since our protocol required an indwelling needle and ECG monitoring, we cannot consider our values necessarily to be representative of the basal resting state in other circumstances. Anxiety is known to be a potent stimulus for release of NE and E. It is possible that our protocol created a greater emotional stress than that associated with other studies. Since our situational environment was identical for all subjects, we have assumed that environmentally induced anxiety was comparable in all subjects. We thus feel that our control data permit comparison with data of study groups within the limits of this standardized protocol.

The finding that resting NE in 50% of the BH and 28% of the SH were higher (i.e. $> 2$ sd) than those of age-matched normotensive controls suggests that increased SNS activity could be present (to the extent that plasma NE levels reflect levels of SNS activity) in a subgroup of young BHs. It appears to be more prevalent in BH than in young adults with EH. The broader spread of resting NE levels found in NS than NC suggests that the former may represent a heterogenous population with respect to adrenergic SNS activity and that increased SNS activity could be under genetic control.

A direct relationship between resting NE levels and BP has not been demonstrated to exist in normotensive adult subjects. Vlachakis and Mendlowitz$^3$ found a significant positive correlation between both systolic and diastolic BP and plasma NE in hypertensives at rest, as did Louis et al.,$^3$ while others have failed to show this.$^{17, 18}$ Watson et al.$^4$ reported that plasma NE levels increased progressively with increasing levels of physical activity in hypertensive subjects and that there was a linear relationship between plasma NE levels and systolic BP. Their observations support the hypothesis that plasma NE reflects short-term changes in sympathetic activity.
The findings that SBP and plasma NE levels were positively correlated in these young borderline hypertensives at rest and with standing, suggests that the level of SNS activity could be affecting their BP. Hofman et al.\textsuperscript{15} also reported finding plasma NE levels positively correlated with SBP. A similar positive correlation between plasma NE levels and SBP in NS suggests that this relationship may not be dependent on the presence of hypertension.

Our finding that normal children have a pressor response to standing differs from most reports of BP responses of normal adults to standing, where no significant changes in BP have been noted.\textsuperscript{1,19} Vlachakis and Mendlovitz\textsuperscript{5} have reported an elevation in DBP (+9.7 mm Hg) in normal adults after 10 minutes of the upright position. This is of special interest because their protocol was similar to ours, BP being measured serially during the period of standing. They also found an elevation in both SBP (+4.5 mm Hg) and DBP (+14 mm Hg) in hypertensive adults.

Voors et al.\textsuperscript{20} have reported findings similar to ours in normal children 7 to 15 years old subjected to a standardized stress of quiet standing. Their subjects (272 children: 134 whites, 138 blacks) were a random sample of children in a total community matched for age, sex, and race. BP and HR were measured serially for 3 minutes of quiet standing. They found the mean response to be an increase in SBP of +6.4 ± 1.4 mm Hg, DBP of +13.0 ± 1.4 mm Hg, and MAP +15.7 ± 2.2 mm Hg, values closely similar to findings in our normal controls.

Assumption of the upright posture causes an abrupt decrease in the venous return of blood to the heart. The compensatory mechanisms involved in normal maintenance of standing BP include activation of a baroreceptor reflex that increases peripheral vascular resistance (both venous and arterial), limits the decrease in cardiac output, and modifies renal function.\textsuperscript{21} Postural activation of this reflex in normal subjects results in a sharp increase in plasma NE with an approximate doubling of NE levels.\textsuperscript{1} Since a prompt increase in NE levels was observed in all subjects, there does not appear to be a defect in this arc as has been described in patients with autonomic failure and marked postural hypotension, where no significant increase in plasma NE occurred with standing.\textsuperscript{22}

Although none of the hypertensive children had an exaggerated pressor response to standing, a number exhibited a hypertensive response to standing and a blunted rise in NE. We have demonstrated that the response to standing of our hypertensive groups showed reproducibility. If changes in plasma NE reflect the degree of stimulation of SNS activity, these quantitative differences could account in part for the variability in pressor response observed in hypertensives since NE is a potent peripheral vasoconstrictor. This also suggests that SNS activity differs in a subgroup of the hypertensives from that in normotensive controls.

Although the major contribution to increased plasma NE with acute stress is release secondary to increased neural stimulation, other factors influence plasma concentration including the rate of neural re-uptake, metabolic degradation, and renal excretion. Esler et al.\textsuperscript{23} recently reported presumptive evidence of defective neuronal uptake of NE in some patients with EH who also had higher plasma NE concentrations than EH subjects with normal neuronal uptake of NE. Without data concerning these factors, we can only speculate about the level of sympathetic activity based solely on the resting levels of NE and the magnitude of changes with stress.

Our observations do offer support for the hypothesis that increased SNS activity is a contributing factor to hypertension in a subgroup of young subjects with EH. Preliminary findings suggest that a subgroup of normotensive siblings of young hypertensives appear to have biochemical and hemodynamic evidence of altered SNS activity at rest and with orthostasis similar to some hypertensives. These findings, if confirmed by further study, have the potential to provide a means of identifying individuals among genetically predisposed normotensive children in the prehypertensive state who might be at increased risk for later development of sustained essential hypertension.

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