SUMMARY

We studied the blood pressure responses to infused norepinephrine in 34 normotensive and 21 unmedicated subjects with essential hypertension. The two groups were similar in age, relative body weight, and urinary electrolyte excretion. Patients were studied on two extremes of dietary salt (200 mEq Na and 10 mEq Na per day). The dose-response curves were highly linear ($p<0.00001$) for both systolic and diastolic blood pressures. There was no evidence for an increased sensitivity to infused norepinephrine among the hypertensive subjects. On the other hand, older subjects had steeper slopes ($p<0.005$). Subjects on a high salt diet had steeper slopes than those on low salt diets ($p<0.0025$); this trend was especially apparent among blacks ($p<0.005$). Black and white hypertensive subjects responded to the high salt diet in opposite fashion: The blacks showed an increased pressor sensitivity ($p<0.05$), whereas the whites demonstrated a nonsignificant decreased pressor sensitivity. These results indicate that age, race, and salt effects must be meticulously controlled in studies of sympathetic nervous system physiology. (Hypertension 10: 564-569, 1987)

KEY WORDS • norepinephrine • sodium • hypertension • race • age • hostility

IN 1948, Goldenberg et al.\(^1\) made the intriguing observation that hypertensive patients seemed unusually sensitive to the blood pressure (BP)-elevating effects of infused norepinephrine (NE). Since then, many investigators have studied the slope of this relationship, comparing hypertensive and normotensive subjects. Since BP is elevated in many essential hypertensive patients because of increased peripheral resistance, many researchers have expected that hypertensive patients would demonstrate an increased vascular sensitivity (or steeper dose-response slopes) to infused NE.\(^2\) Over the years, however, this hypothesized increased sensitivity has not been replicated consistently. Although no one has reported that hypertensive subjects are less sensitive than normotensive subjects to infused NE, the findings are mixed, with some studies reporting increased sensitivity among hypertensive subjects\(^3\)\(^-\)\(^7\) and other studies failing to find such increased sensitivity.\(^8\)\(^-\)\(^17\)

In reviewing these studies, we have been struck by their frequent reliance on small sample size and their failure to control for possibly confounding factors. In some early studies, virtually all hypertensive subjects were grouped together, regardless of subtype, for contrast with normotensive subjects. Other differences in the studies concern the severity of hypertension: Some investigators examined moderately hypertensive subjects, whereas others examined mildly hypertensive subjects. Any of these differences may account for the divergent findings. Finally, a sound, quantitative basis for establishing a dose-response curve is absent in many of the studies. Many studies infused only one or two doses of NE, and from these administrations inferred a linear relationship, despite the fact that the proposed difference in sensitivity could just as well be curvilinear (e.g., apparent principally at low doses of infused NE).

Curiously, many of these studies neglected to examine age effects even though older subjects have decreased clearance of NE from the circulation.\(^18\) Additionally, differences in sodium intake were similarly ignored in many studies, although salt has major actions on sympathetic nervous system activity. For instance, salt depletion shortens the prolonged half-life...
of NE in hypertensive subjects. A number of other factors related to BP might confound studies contrasting normotensive and hypertensive subjects; for example, family history, obesity, and race are clearly related to BP. Two psychosocial factors — depression and hostility — have also been suggested as related to BP. If any of these many factors were unequally represented across hypertensive and normotensive subjects, one would have reason to doubt the validity of attributed slope differences across the diagnostic groups. We have examined this topic anew, trying to take into consideration these various methodological criticisms.

Subjects and Methods

Subjects were recruited from community BP screening or by word of mouth. We studied 34 healthy men and 21 untreated hypertensive men. All subjects (hypertensive and normotensive) were free from any medication for at least 3 weeks before participation in the study. Subjects were classified as normotensive if systolic BP was below 140 mm Hg and diastolic BP was below 90 mm Hg. Hypertensive subjects were defined as having systolic BP above 140 mm Hg or diastolic BP above 90 mm Hg. BPs were taken with a mercury sphygmomanometer after the subject had been seated quietly for at least 5 minutes. Three BP values were obtained, and subjects were classified on the basis of the average of these readings. The subjects returned for a repeat BP screening approximately 1 week later. Subjects were enrolled in the study only if they remained in the same BP group on repeat testing. The mean BPs for the normotensive and hypertensive groups were 120/73 and 144/95 mm Hg, respectively.

Subjects' ratings on the Beck Depression Inventory and the Buss-Durkee Hostility Scale were obtained before the infusions. A family history was considered positive for hypertension if the subject reported a parent had high BP. Relative obesity was calculated using Metropolitan Life Insurance tables.

Subjects were admitted twice to the Clinical Research Center and randomized to either a high sodium diet (200 mEq/day) for 4 days or a low sodium diet (10 mEq/day) for 5 days. The opposite diet was used during the second admission. Both diets were isocaloric and contained potassium, 100 mEq/day. An interval of approximately 1 week separated the hospitalizations. Four subjects completed only one hospitalization. Twenty-four-hour urine samples were obtained for electrolytes.

The NE infusions were performed in the early afternoon of the final day of each hospitalization. All subjects had been caffeine-free for at least 16 hours before the infusion studies and had been asked to refrain from cigarette smoking for at least 7 hours before the infusion studies.

The subjects were tested in the supine position. A D5W drip (5% dextrose in water) at the rate of 180 ml/hr was administered in the subjects’ nondominant arm, and BPs were taken repeatedly during a half-hour period while the subject became acclimated to the infusion and the repeated BP measurements. At the end of the 30-minute interval, three more BPs were taken, and their average was used as the subject’s baseline BP. After the baseline period, the NE solutions were added to the sustaining infusion. A freshly constituted solution of NE in D5W was infused at the rate of 0.01 μg/kg/min for 10 minutes. Subsequent doses were 0.025, 0.05, and 0.10 μg/kg/min, each given for 10 minutes. The infusion was stopped if systolic BP increased by 30 mm Hg, diastolic BP increased by 25 mm Hg, or if premature ventricular contractions occurred. Throughout the infusion, BP was taken by a mercury sphygmomanometer every minute after the start of each infusion dose and continued until the BP plateaued for 3 successive minutes at that given dose.

The data were initially examined with a repeated-measures analysis of variance (ANOVA) and an orthogonal polynomials decomposition to determine whether the increase of BP with increased amounts of infused NE was linear. The linear term was found to be highly significant (p < 0.00001) for both systolic and diastolic BPs, while the higher order terms were not significant. Moreover, the higher order effects accounted for only a small portion of the total variance. Because of our safety precautions for stopping the NE infusion (see the preceding paragraph), there were some missing data; as a result, we could not rely on a repeated-measures ANOVA as the fundamental tool for analysis. Rather, we used a least-squares analysis for each subject to quantitate the slope of the line relating infused NE and BP. Unpaired t tests were used to contrast the hypertensive and normotensive subjects in terms of the average slope and intercept of such dose-response curves. We examined other variables to ascertain whether they were significantly related to the slope of the dose-response curve. For continuous variables (age, relative obesity, depression, hostility), we calculated Pearson correlation coefficients with slope. For categorical variables (race, family history of hypertension), we employed unpaired t tests to contrast the slopes. Finally, we examined the effect of dietary salt by employing a paired t test.

Results

The hypertensive and normotensive groups did not differ in age or relative obesity. Analysis of 24-hour urine samples obtained the day before the study revealed no significant differences in urinary sodium or potassium excretion (Table 1).

As a result of hospitalization, the BP in both groups fell. Diastolic BP of most of the subjects who were originally classified as hypertensive on two separate occasions decreased below 90 mm Hg after 4 days of hospitalization and rest, but overall BP in this group remained 10/10 mm Hg higher than that of the control group. There were no untoward effects of the NE infusion.

Figure 1 portrays the relationship between infused

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TABLE 1. Characteristics of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n = 34)</th>
<th>Hypertensive (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race (black/white)</td>
<td>19:15</td>
<td>8:13</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>32 ± 6</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>Relative body weight</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>High Na admission electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Na (mEq/24 hr)</td>
<td>217 ± 52</td>
<td>214 ± 87</td>
</tr>
<tr>
<td>Urinary K (mEq/24 hr)</td>
<td>66 ± 17</td>
<td>62 ± 20</td>
</tr>
<tr>
<td>Low Na admission electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Na (mEq/24 hr)</td>
<td>29 ± 25</td>
<td>22 ± 10</td>
</tr>
<tr>
<td>Urinary K (mEq/24 hr)</td>
<td>69 ± 19</td>
<td>57 ± 22</td>
</tr>
</tbody>
</table>

Values, except for race, are means ± SD. There were no significant differences between groups.

TABLE 2. Variables Associated with Slope (Systolic BP)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive (n = 34)</th>
<th>Hypertensive (n = 21)</th>
<th>Total (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>r = 0.297</td>
<td>r = -0.017</td>
<td>r = 0.407†</td>
</tr>
<tr>
<td>Relative obesity</td>
<td>r = 0.100</td>
<td>r = 0.212</td>
<td>r = 0.206</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>r = 0.36</td>
<td>r = 0.96</td>
<td>r = 0.15</td>
</tr>
<tr>
<td>Beck depression score</td>
<td>r = 0.025</td>
<td>r = 0.075</td>
<td>r = 0.231</td>
</tr>
<tr>
<td>Buss-Durkee total hostility score</td>
<td>r = -0.154</td>
<td>r = -0.226</td>
<td>r = -0.022</td>
</tr>
<tr>
<td>Black vs white race</td>
<td>t = +0.01</td>
<td>t = +0.60</td>
<td>t = +2.51‡</td>
</tr>
<tr>
<td>High Na vs low Na diet</td>
<td>t = 3.47‡</td>
<td>t = 2.23*</td>
<td>t = 1.39</td>
</tr>
</tbody>
</table>

Subjects were studied during high salt (200 mEq/day) and low salt (10 mEq/day) diets.

*p < 0.05, †p < 0.005, ‡p < 0.025, §p < 0.0025. For r values, p indicates the strength of association; for t values, p indicates the degree of difference between subgroups in terms of slope.

Discussion

This research was undertaken to clarify the relationship between infused NE and resulting BP. This technique does not measure only α-adrenergic receptor sensitivity, because the pressor response to NE is modulated by a reflex bradycardia that is mediated by the vagus.23 By assessing the change in heart rate per millimeter-of-mercury increase in BP over the range of the dose-response curve, we obtained an index of baroreceptor activity. This activity was not significantly different in subgroups by race or diagnosis on either diet (by one-way ANOVA). As a result, we doubt that vagal activity differences in our subgroups could be obscuring our index of α-adrenergic receptor sensitivity.

NE and BP for the normotensive and hypertensive subjects. Despite the relative normalization of BP in the hypertensive group, there was still a significant difference (p < 0.001) in the overall BP (or intercept) between the hypertensive and the normotensive groups (t = 3.90 systolic; t = 4.24 diastolic). However, the amount of that difference was consistent at all dose increments. In other words, the slopes of the relationship were not different for the hypertensive and normotensive groups (t = 1.29 systolic; t = 0.37 diastolic).

We examined whether other variables would influence the slope of the dose-response curve (Table 2). Relative obesity, family history of hypertension, depression, and hostility were unrelated to slope. On the high salt diet, older subjects had a greater BP response to infused NE (p < 0.005; Figure 2). Race and diet powerfully affected slope (Figure 3). The slope was steeper on the high salt diet than on the low salt diet for all the subjects and for the normotensive group (p < 0.0025). This salt effect was not observed among the hypertensive group because the hypertensive blacks and hypertensive whites responded in opposite fashion. The blacks had steeper slopes on the high salt diet (p < 0.05), whereas the whites had a nonsignificant decrease in slope in response to the high salt diet.
An additional issue concerns the variable rate of clearance and half-life of plasma NE across individual subjects. A dose-response calculation employing blood levels, as opposed to infused doses, would allow a more accurate estimation of receptor sensitivity and would eliminate the confusing factor of different rates of NE clearance in different subjects. We did draw a baseline plasma NE level before beginning the infusion and observed no significant overall correlation between resting NE and slope for systolic or diastolic BP on either diet. Future studies will examine NE levels at each step of the NE infusion. Predictably, NE levels increased in response to the low salt diet; however, the degree of increase was unrelated to the change in slope of the dose-response curve ($r = 0.005$ for systolic slope, $r = 0.195$ for diastolic slope).

Despite these caveats, we believe these data lead to...
an important and clear conclusion. There is a disagreement in the literature about the relationship between infused NE and the resulting BP in normotensive and hypertensive subjects. Our data argue against a difference in sensitivity across the two groups. It is possible that subjects with moderate to severe hypertension could be more sensitive than normotensive subjects, but in comparing values for normotensive subjects with those for mildly hypertensive subjects, there was no difference in slope. Our methodology was designed explicitly to control for factors that might influence the dose-response relationship. When we examined such factors, we found that they could have marked effects on slope, thus possibly confounding the relationship between diagnosis and slope.

There is some evidence that older subjects have a reduced clearance of NE from the circulation. In addition, there is some evidence that the pressor response increases with age; however, not all groups have observed such an effect. Even across our modest age span (19–48 years), we found that older subjects on the high salt diet had steeper slopes relating BP to infused NE. If previous studies did not meticulously control for dietary salt and age differences, their comparisons of hypertensive and normotensive subjects would thus be of diminished value.

Since weight loss is associated with a decrease in adrenergic activity, it is possible that obese hypertensive persons have a steeper slope; however, Boehringer et al. found no difference in NE sensitivity among obese patients. In our study as well, relative obesity was not related to slope. However, our obesity range was quite circumscribed (91–151% of ideal body weight).

We could not reconfirm the observation by Bianchetti et al. that a family history of hypertension was related to slope. We relied on unverified self-report of family history; thus, these data are subject to question.

There is a growing psychiatric literature about possible sympathetic dysregulation in depressed patients. In addition, depression has long been known to increase BP. Our tool for depression was a self-reported demoralization measure that is related to but not identical to a formal psychiatric diagnosis of depression. We found no association between slope and the Beck Depression Inventory. If there is a slope effect, it may be evident only in clinically depressed patients. Abnormalities in regulation of hostility have been related to hypertension, but they were unrelated to slope in this study. Taken together, these two findings suggest that no confounding of diagnosis and slope occurred because of these psychosocial factors.

We know of no study that has explicitly compared black and white dose-response curves. As race was rarely discussed in previous studies, no information was available about possible differences in the racial composition of the hypertensive or control groups. In our study we found a significant difference across the races. On the high salt diet, black hypertensive subjects had steeper slopes than white hypertensive subjects (p < 0.025); there was no racial difference for the normotensive subjects.

We reconfirmed the observation by Rankin et al. of a steeper dose-response curve on high salt diets. Rankin et al. contrasted sodium diets of 800 and 10 mEq/day; as our work demonstrates, the salt sensitization is apparent even at a dietary sodium intake of 200 mEq/day (p < 0.0025). In addition, we again found a race effect: In general, blacks were particularly sensitive to salt loading (p < 0.005); whereas whites had a nonsignificant response to salt loading. However, in the diagnostic subgroups, the pattern of sensitization was exactly opposite. There was salt sensitization among the normotensive whites and hypertensive blacks (see Figure 3). Using diet as a within-subject measure and race and diagnosis as between-subjects measures, we employed a repeated-measures ANOVA to examine the role of salt, race, and diagnosis. The analysis revealed a significant three-way interaction among salt, race, and diagnosis (p < 0.02). These racial and salt response differences are new observations. However, they must be tempered by the small sample size in the subgroups.

A final observation relates to our method of data analysis. We used each subject’s total data to generate a dose-response curve rather than rely on only one or two points. At the doses infused, this relationship was highly linear, suggesting that elaborate data transformations are not necessary.

At first glance, our findings may seem primarily negative in nature. We are yet another research group that has failed to replicate observation of an increased sensitivity to NE infusions among hypertensive subjects. However, the reasons for such confusion are now clearer. Age, dietary salt intake, and race all impinge rather clearly on the sensitivity of the dose-response curve. Few reported studies controlled for one of these factors, let alone three. Our findings point to the importance of meticulous care in controlling for these factors in studies of sympathetic nervous system physiology. These data also suggest a basic difference between black and white subjects’ pressor sensitivity in the face of increased dietary salt.

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