Plasma Norepinephrine and Age as Determinants of Systemic Hemodynamics in Men with Established Essential Hypertension

JOSEPH L. IZZO, JR., ROBERT J. SMITH, PATRICIA S. LARRABEE, AND MICHAEL C. KALLAY

SUMMARY Two primary predictor variables, age and supine plasma norepinephrine, were studied with respect to their influences on supine hemodynamic variables in 52 white men with essential hypertension who were 23 to 67 years of age and had been off active therapy for at least 4 weeks. Plasma norepinephrine was related to age (r = 0.39, p < 0.01), correlated closely with mean arterial pressure (MAP; r = 0.54, p < 0.0002) and systemic vascular resistance (r = 0.49, p < 0.0005), and was related inversely to cardiac output (r = −0.26, p < 0.06) and stroke volume (r = −0.31, p < 0.05). Age correlated weakly with MAP (r = 0.31, p < 0.05) and more strongly with systemic vascular resistance (r = 0.46, p < 0.005) but was negatively related to cardiac output (r = −0.41, p < 0.005) and heart rate (r = −0.33, p < 0.05). Weight did not correlate with any of the hemodynamic variables. Partial regression techniques yielded significant residual correlations between age-adjusted plasma norepinephrine and MAP (r = 0.42, p < 0.005) or systemic vascular resistance (r = 0.38, p < 0.005). Residual correlations with cardiac output (r = −0.34, p < 0.05), heart rate (r = −0.36, p < 0.02), and systemic vascular resistance (r = 0.33, p < 0.05) remained after adjusting age for the corresponding plasma norepinephrine values. These correlations demonstrate the independent effects of sympathetic nervous activity and the aging process on the systemic vasoconstriction and decreased cardiac function observed in essential hypertension. (Hypertension 9: 415–419, 1987)

KEY WORDS • hypertension • norepinephrine • age • hemodynamics

In industrialized societies, there is a well-known association between age and blood pressure.1,2 This phenomenon has been further analyzed to reveal age-related increases in systemic vascular resistance (SVR) and decreases in cardiac output (CO) in essential hypertension.3–7 Advancing age is also associated with increasing plasma norepinephrine (NE) concentration,5,8,9 a relationship that could confound any study of either variable with respect to systemic hemodynamics.

The role of the sympathetic nervous system and the utility of plasma catecholamine measurements in essential hypertension have been the subjects of intensive investigation and controversy. In general, most studies have demonstrated marginal increases in plasma NE when essential hypertensive subjects were compared with normotensive controls.10–18 Some investigators have correlated plasma NE or its metabolites directly with blood pressure,3,10,14,19,20 while others have suggested that appropriate age control eliminates the difference in plasma NE between hypertensive patients and normal controls.5,9,21,22 Less clear are the relationships of plasma NE and systemic hemodynamic changes.

The purpose of the present study was to further elucidate the interactions of age and plasma NE as predictors of the hemodynamics of established essential hypertension.

Subjects and Methods

Fifty-two ambulatory white men with essential hypertension, off antihypertensive medications for at least 4 weeks, fasted overnight and refrained from caffeine or tobacco intake for at least 16 hours before the study. Each subject had sitting diastolic blood pres-
sures of 95 to 110 mm Hg in the outpatient clinic on three separate occasions, including the morning of study. After body weight was obtained, a heparin lock was inserted into an antecubital vein. Subjects were then studied between 0900 and 1200, both supine and upright, with the order of the two positions randomized. After at least 15 minutes of equilibrium in the supine or upright positions, duplicate CO measurements were obtained.

CO was measured by acetylene-helium rebreathing with continuous gas analysis by mass spectroscopy. This method has been shown to agree closely \( r = 0.9 \) with invasive determinations using green dye and is accurate in subjects with forced expiratory volumes as low as 30% of predicted normal. Heart rates during rebreathing were measured by 30-second electrocardiographic tracings. Blood pressures were determined by a single observer with a standard cuff immediately before and after each CO measurement, with the four determinations meaned. Mean arterial pressure (MAP) was calculated as diastolic plus \( \frac{1}{3} \) pulse pressure. SVR was calculated from MAP and CO. In each position, venous blood for catecholamines was obtained from the heparin lock after the CO determinations. Plasma catecholamines were determined by a radioenzymatic technique that has been validated against high performance liquid chromatography with electrochemical detection \( r = 0.99 \).

Variables were first compared by Pearson linear regression techniques. Data were further analyzed by partial regression techniques, where the interaction of three variables was studied by adjusting for one variable and observing the effects of the absence of this variable on the interaction of the other two. In addition, multiple stepwise linear regression values were calculated for the interactions of predictor and dependent variables. Significance was accepted at the 5% level for simple and partial regression values. Data are presented as means ± SD.

Results

Mean supine blood pressure in the outpatient clinic on the day of study (mean of 2 determinations per subject) was 153 ± 20/99 ± 7 mm Hg. Subsequent data obtained in the hemodynamic laboratory for the 52 subjects formed a representative cross-section of patients with mild to moderate essential hypertension with respect to age (48 ± 12 years), weight (89 ± 14 kg), supine blood pressure (144 ± 22/93 ± 10 mm Hg), MAP (110 ± 13 mm Hg), CO (6.5 ± 1.2 L/min), stroke volume (86 ± 16 ml), heart rate (76 ± 12 beats/min), and SVR (1420 ± 390 dyn·sec·cm⁻⁵).

Figure 1 demonstrates the simple linear relationships of age with MAP, SVR, CO, and plasma NE. Age was related more closely to systolic \( r = 0.39 \) than to diastolic \( r = 0.17 \) blood pressure. Figure 2 shows the parallel correlations of plasma NE with MAP, CO, and SVR. Plasma NE was related closely to both systolic \( r = 0.49 \) and diastolic \( r = 0.52 \) blood pressure. Table 1 summarizes the linear regression equations for age and plasma NE as predictors of the hemodynamic variables. No relationships were found between age and weight \( r = -0.10 \) or between plasma NE and weight \( r = -0.01 \). In addition, weight did not relate to MAP \( r = -0.06 \), CO \( r = 0.09 \), SVR \( r = -0.11 \), heart rate \( r = 0.15 \), or stroke volume \( r = 0.02 \).

Age and plasma NE exhibited a linear relationship \( r = 0.39 \) that exerted a potential confounding effect on subsequent correlations with the hemodynamic variables studied. We therefore employed partial linear regressions to assess the interactions of age and plasma NE in predicting the five hemodynamic variables (MAP, CO, SVR, heart rate, and stroke volume). Table 2 demonstrates the simple Pearson correlation coefficients relating age and plasma NE to the hemodynamic variables. This table also demonstrates the correlations that remain when age and plasma NE are mutually adjusted by partial regression techniques for the confounding influence of the other variable.

Stepwise multiple linear regression was also used to corroborate the partial regression techniques in investi-
gating the interactions of age, plasma NE, and weight as predictors of the five hemodynamic variables. The multiple correlation coefficients were not meaningfully greater than the simple primary hemodynamic correlation coefficients obtained with either age or plasma NE alone.

Discussion

It has long been suggested that the sympathetic nervous system, which occupies a pivotal position among the interacting cardiovascular regulatory mechanisms, must play some role in the development or maintenance of elevated arterial pressure.38-41 The present study supports this concept and helps define a component of sympathetic nervous system activity that contributes to blood pressure regulation. Statistical elimination of the influence of age on systemic hemodynamics revealed a strong residual correlation between plasma NE and SVR in established essential hypertension. Similar relationships between plasma NE and SVR were also seen.

Aging and sympathetic nervous system effects on cardiovascular function are both direct and indirect. Table 1. Regression Equations for Age and Plasma Norepinephrine as Hemodynamic Predictor Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Age-adjusted</th>
<th>PNE-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>680 + 1.6 (PNE)</td>
<td>680 + 15 (age)</td>
<td>680 + 15 (PNE)</td>
</tr>
<tr>
<td>CO</td>
<td>100 + 0.01 (PNE)</td>
<td>96 - 0.21 (age)</td>
<td>96 - 0.21 (PNE)</td>
</tr>
<tr>
<td>SV</td>
<td>100 + 0.01 (PNE)</td>
<td>96 - 0.21 (age)</td>
<td>96 - 0.21 (PNE)</td>
</tr>
<tr>
<td>HR</td>
<td>85 - 0.04 (PNE)</td>
<td>93 - 0.34 (age)</td>
<td>93 - 0.34 (PNE)</td>
</tr>
<tr>
<td>SVR</td>
<td>860 + 1.6 (PNE)</td>
<td>680 + 15 (age)</td>
<td>680 + 15 (PNE)</td>
</tr>
</tbody>
</table>

Linear regression equations of age and plasma norepinephrine (PNE) with dependent hemodynamic variables (y), including MAP, cardiac output (CO), stroke volume (SV), heart rate (HR), and systemic vascular resistance (SVR); m and b are slopes and intercepts for each independent variable, and subscripts define variable relationships (a = age-related, p = PNE-related).

Table 2. Interactions of Plasma Norepinephrine and Age as Hemodynamic Correlates in Essential Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Age-adjusted</th>
<th>PNE-adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>0.54*</td>
<td>0.42†</td>
<td>0.31†</td>
</tr>
<tr>
<td>CO</td>
<td>-0.26</td>
<td>-0.14</td>
<td>-0.41†</td>
</tr>
<tr>
<td>HR</td>
<td>0.01</td>
<td>0.16</td>
<td>-0.33†</td>
</tr>
<tr>
<td>SV</td>
<td>-0.31†</td>
<td>-0.28‡</td>
<td>-0.15</td>
</tr>
<tr>
<td>SVR</td>
<td>0.49*</td>
<td>0.38†</td>
<td>0.46†</td>
</tr>
</tbody>
</table>

Values shown are simple Pearson correlation coefficients (unadjusted) and correlation coefficients adjusted by partial regression techniques for the confounding effects of other predictor variables. The strongest relationships, plasma norepinephrine (PNE) versus MAP and systemic vascular resistance (SVR), were independent of any age-related effects, whereas the marginal correlation between age and MAP disappeared when age was adjusted for PNE. Inverse relationships between age and either cardiac output (CO) or heart rate (HR) were independent of PNE-related effects, whereas age-independent marginal effects of PNE on stroke volume (SVR) were also seen.

Age and increased sympathetic nervous system activity independently contribute to decreased cardiac function through their effects on SVR and afterload. A more direct age-dependent reduction in CO also occurs, perhaps further contributing in reflex fashion to adaptive vasoconstriction in the hypertension of older persons. These observations help explain the therapeutic effects seen with antihypertensive drugs, including reduced effectiveness of β-adrenergic blockers34,35 and increased effectiveness of vasodilators36,37 in elderly hypertensive patients.

In our studies, increases in plasma NE related to aging (r = 0.39) were used to statistically adjust for the effects of aging on the relationship between plasma NE and systemic hemodynamics. Variations in this age-plasma NE relationship could potentially influence the conclusions of our study. For example, many investigators have reported a subset of younger hypertensive patients who have high plasma NE and increased CO.12-14,18 We made no attempt to exclude young patients with high catecholamines, but we did not clearly identify this specific subgroup in our studies. If we had

Figure 2. Relationship of plasma norepinephrine (NE) to hemodynamic variables. Abbreviations as in Figure 1.
included such a subgroup, we would have simultaneously improved the negative correlation between plasma NE and CO and diminished the correlation between plasma NE and SVR. However, the relative magnitude of the age adjustment for plasma NE would also have been diminished, so that the age-adjusted relationship of plasma NE with MAP and SVR probably would have been preserved.

Various other factors including sex have confounded prior analyses of plasma NE and blood pressure. Chobanian et al. 17 conducted a large cross-sectional study relating several predictor variables to blood pressure and found plasma NE-blood pressure correlations in male but not female subjects. In general, studies that have failed to find correlations between plasma NE and blood pressure have included both male and female subjects. 8,21,22 The importance of this sex dichotomy is not yet clear, but the possibility is raised that neurogenic vasoconstriction is modified by hormones such as estrogens. Factors such as race may also play a role in the interpretation of interindvidual differences in plasma NE; our choice of white men probably helped reduce biological variation. Finally, we did not find a relationship between weight and blood pressure despite observations to the contrary. 23 Had we studied a comparative normotensive population or found more subjects at the extremes of weight, a separate component of weight might have emerged.

Failure of some investigators to find a correlation between blood pressure and plasma NE 21,22 may be related to the lack of each of the variables. We limited blood pressure variability by employing the mean of four determinations in well-characterized subjects. In addition, we did not use the values obtained in the outpatient clinic but rather monitored blood pressure at the time of the hemodynamic studies. We have found a consistent 9 ± 1/6 ± 1 mm Hg drop in blood pressure in the hemodynamic laboratory compared with the outpatient clinic that is not due to observer variability. The explanation for this systematic variation is not known, but the data argue that stress factors are higher in the clinic than in the laboratory. In the present studies, we obtained plasma NE values just after the rebreathing exercises, with subjects resting quietly in the supine position. It is possible that the rebreathing exercises slightly stimulated the plasma NE concentrations, but plasma NE drawn before the rebreathing exercise did not vary more than 10% from samples obtained immediately after rebreathing in the few subjects tested (n = 6). Rebreathing does not significantly increase CO using our protocol. 24

The pathophysiology of age-related decreases in CO may be complex, 25 but the implications are relatively obvious. Extrapolation of the regression equations for age and CO to the seventh and eighth decades reveals CO values in the range of patients with congestive heart failure. Cohn et al. 40 have elegantly demonstrated that plasma NE is the best predictor of mortality and morbidity in patients with congestive heart failure. Other investigators have shown that plasma NE correlates with the NYHA functional class of heart failure. 41 Thus, high plasma NE may actually be another cardiovascular risk factor, marking persons at risk to acquire low output states and congestive cardiomyopathy. Increases in catecholamines in low output states may be an adaptive response that attempts to maximize endogenous inotropic and chronotropic effects. However, this catecholamine-inotropic response is unable to compensate fully for the vasoconstrictive effects of age and increased sympathetic nervous activity.

Acknowledgments

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