Sex Differences in the Endocrine Predictors of Essential Hypertension
Vasopressin Versus Renin

ALLEN W COWLEY, JR, MEREDITH M. SKELTON, AND MANUEL T. VELASQUEZ

SUMMARY The relationships between arterial pressure (BP) and plasma vasopressin levels, plasma renin activity, and other variables were determined in 96 untreated essential hypertensive men (146/100 mm Hg) and women (153/102 mm Hg) whose average age was 44 years, 80 normal men and women (121/79 mm Hg; mean age, 47 ± 2 years), and 40 subjects defined as borderline hypertensive. An analysis of variance indicated significant sex differences in the population. Levels of plasma vasopressin were significantly elevated in hypertensive men, with 26% (high plasma vasopressin hypertensive) exhibiting levels greater than 2 SD of the normal mean, and multivariate regression analysis indicated a significant positive correlation between plasma vasopressin levels and systolic and diastolic blood pressure. Hypertensive men had a larger daily urine volume than normal men. Diastolic pressure and heart rate were significantly elevated in a subgroup of 12 weight-matched and age-matched hypertensive men in the high plasma vasopressin group compared with levels in normal plasma vasopressin hypertensive men. Hypertensive women had lower plasma renin activity than normal women, and multivariate analysis indicated a significant negative correlation between plasma renin activity and systolic and diastolic blood pressure. Other significant abnormalities in both sexes were noted: hypertensive men and women weighed more and excreted more sodium per day, and both had higher heart rates. With a discriminant analysis of 18 variables in male subjects, plasma vasopressin levels, urinary sodium excretion, and heart rate correctly classified 71% of normal and hypertensive subjects. In women, plasma renin activity, urinary sodium excretion, and heart rate correctly classified 77% of normal and hypertensive subjects. Despite the inability to ascertain causal relationships, the ability of the three variables in combination to correctly classify normal and hypertensive subjects indicates that these combined variables are reproducibly altered in persons with essential hypertension. (Hypertension 7 [Suppl I]: I-151-I-160, 1985)

KEY WORDS • sodium intake • sodium excretion • potassium excretion • influence of race • body weight • urine excretion • discriminant analysis • logistic analysis

THE role of arginine vasopressin (AVP) in essential hypertension remains poorly defined. Elevated plasma AVP levels have been observed in many experimental forms of hypertension, including hereditary rat models such as spontaneously hypertensive rats (SHR), stroke prone SHR, and Dahl salt-sensitive rats. Elevated plasma AVP levels also have been found in deoxycorticosterone (DOC)-salt experimental rats, two-kidney, one-clip Goldblatt hypertensive rats, and in rats with partial nephrectomy–salt hypertension. The extent to which AVP influences cardiovascular or renal function, or both, in these forms of hypertension remains to be determined fully.

Plasma AVP in human essential hypertension has not been characterized adequately, and average values ranging from low-normal to markedly elevated have been reported. Increased antidiuretic activity was described in urine of hypertensive subjects 35 years ago, as determined by bioassay. This finding was confirmed more recently by radioimmunoassay. In a study of 104 male subjects, we reported that plasma AVP levels were elevated in nearly 30% of the hypertensive subjects (n = 61), as defined by AVP levels exceeding 2 SD of the normal mean value. Plasma AVP elevations in essential hypertension also have been observed by others. Substantial elevations have been consistently observed in severe and malignant hypertension. A number of investigators, however, have found that plasma AVP levels were not elevated in subjects with mild to moderate essential hypertension.
hypertension. Differences in the populations existed between these studies, including sex, race, and age, and it is uncertain to what extent results have been influenced by these factors.

The present studies were performed on 80 normal, 40 borderline hypertensive, and 96 hypertensive subjects. In contrast to the all male VA population that we evaluated previously, both male and female, black and white subjects were studied. This permitted re-evaluation of our initial observations in female as well as male subjects. Repeated measurements of plasma AVP levels also were obtained for better validation of the observations. In a smaller subset of subjects, the influence of race on the measured variables also was evaluated.

**Methods**

**Subjects**

A total of 216 men and women ranging in age from 18 to 75 years participated in this study. Eighty subjects (40 men and 40 women; mean age, 47 ± 2 years) were normotensive. Of the normal men, 12 were black and 28 white, whereas 10 normotensive women were black and 30 were white. Another 40 subjects were considered borderline hypertensive (22 men and 18 women; mean age, 45 ± 2 years). This subgroup was not categorized according to race. A third group was defined as hypertensive (61 men and 35 women; mean age, 44 ± 1 years). Of the hypertensive men, 31 were white and 30 black, while 26 hypertensive women were black and 9 were white.

Subjects were classified as hypertensive if, after 2 weeks without medication, their diastolic pressure exceeded 95 mm Hg on three separate occasions. Subjects with diastolic pressures exceeding 115 mm Hg were excluded from the study and placed on medication regimens. Subjects who demonstrated diastolic pressure greater than 95 mm Hg on only one or two of the three visits were classified as borderline hypertensive.

On entering the study, each subject underwent a thorough evaluation that included a history and physical examination, urinalysis, blood chemistry values, and electrocardiogram (ECG). In addition, secondary forms of hypertension were excluded by intravenous pyelograms and measurements of 24-hour catecholamine or vanillylmandelic acid levels in those patients suspected of having renovascular hypertension, renal disease, or pheochromocytoma. The informed consent was fully understood and properly signed before withdrawal of any of the patients’ existing medications. Exclusions from the study included a history of hypertension, eclampsia or a stroke within 6 months, myocardial infarction within 6 months, heart failure, Raynaud’s disease, bronchial asthma, allergic rhinitis, malignancy (including leukemia), diabetes mellitus, documented evidence of mental depression, regular use of biofeedback relaxation or similar techniques, severe alcohol abuse, and recent history of drug or narcotic abuse. Women who were pregnant, taking oral contraceptives, or breast-feeding were excluded, as were night shift workers, subjects who exhibited a fainting reaction when blood was withdrawn, subjects with anemia, persons with a recent and substantial weight loss or gain, and those who had had a major illness or operation within the previous 6 months. Women were not studied during menstruation.

An additional 80 subjects were screened but excluded from the present study on the basis of the criteria already described.

**Age-Matched and Race-Matched Subgroup**

Of the 216 subjects studied, 32 men were age and race matched (12 normotensive and 20 hypertensive). Eighteen women were also age and race matched (9 normotensive and 9 hypertensive).

**Repeatability of Measurements on Return Visits**

A subset of 63 subjects (17 normotensive, 12 borderline, and 34 hypertensive) were studied on two successive visits, 1 to 2 weeks apart. On the first of these two visits, subjects were instructed to maintain their usual dietary intake, and samples were drawn for plasma AVP measurement. On the day before the second visit for blood withdrawal, a 24-hour urine specimen was collected from which daily sodium, potassium, and creatinine excretions were determined.

**Influence of Low Sodium Diet on Plasma Vasopressin Levels**

The same subset of 63 subjects studied for repeatability also were studied on a third visit to evaluate the influence of restricted sodium intake on plasma AVP levels and arterial pressure. Subjects were asked to follow a 75 mEq/day sodium diet for 1 week before the third visit. Compliance was checked by a 24-hour urine specimen collected before the visit, and from these results, it was determined that only 32 subjects complied with the diet as instructed.

**Statistical Analysis**

Significant differences between subgroups of normotensive and hypertensive men and women were determined using a one-way analysis of variance (ANOVA). A test for least significant differences followed the ANOVA to determine the group differences. When appropriate, subgroups matched for either age, sex, or race were compared using a Student’s t-test.

Pearson correlations were used to measure association between any two variables in subgroups of normal or hypertensive men or women. Those variables that yielded significant associations (p < 0.05) were then analyzed with a modified least-squares regression analysis. This analysis allowed the strength of the relationship to be determined and defined by a line of best fit without making any assumptions about causality.

Because many of the variables were intercorrelated, a discriminant analysis was used to assess how one or more of the independent variables could be used to discriminate between hypertensive and normotensive subjects. With this procedure, a significant (p <
0.05) linear combination of the independent variables was determined. This linear combination of variables was then used to classify individuals as normal or hypertensive.

A logistic model was used to assess which set of the independent variables would be significantly associated with the risk of being hypertensive. From the resulting logistic equation, the probability of having hypertension could be calculated for individuals from an unknown population. All values are reported as means ± SEM.

Collection of Samples

Blood samples for measurement of plasma AVP levels, plasma renin activity (PRA), electrolyte levels (Na and K), and plasma osmolality were collected in the morning, after overnight fasting, between 0800 and 1000 hours. Subjects were seated quietly for at least 30 minutes before blood withdrawal. They were instructed not to smoke or drink beverages containing caffeine in the morning before blood withdrawal.

Analytical Procedures

Plasma AVP levels were determined with a radioimmunoassay procedure developed in our laboratory and described previously. Plasma samples for AVP determination were stored at −35°C for varying times before the acetone precipitation-evaporation extraction procedure. The midrange of the assay averaged 6.5 pg/ml AVP, and the least detectable plasma concentration based on 2 SD from the zero dose response (±6.2%) averaged 0.3 pg/ml. The intraassay coefficient of variation averaged ±4.0%, and the between-assay variability, based on 12 separate standard curves, averaged ±4.4%. The results of 266 individual samples stored for periods ranging from 0 to 120 days indicated no statistically significant correlation or trend between storage time and plasma AVP levels; however, the results of 65 samples reanalyzed after storage for 6 to 12 months showed significant elevations of plasma AVP. In the first analysis, the average sample storage time was 76 days, with an average plasma AVP level of 3.3 ± 0.2 pg/ml. On reanalysis with an average sample storage time of 291 days, plasma AVP levels averaged 9.9 ± 0.6 pg/ml (p < 0.05). Based on these analyses, results of samples stored more than 120 days were not included in the present study. Average sample storage time of reported data was 53 days.

The PRA was determined by the radioimmunoassay methods of Sealey and Laragh. Angiotensin I (ANG I) antibodies were kindly provided by Dr. Jean E. Sealey. Plasma and urine creatinine levels were determined by Autoanalyzer (Technicon, Tarrytown, NY).

Urinary and plasma electrolyte concentrations were determined by flame photometry (Model 443, Instrumentation Laboratory, Lexington, MA). Plasma and urine osmolality were determined in triplicate by using a Wescor Vapor Pressure Osmometer (Wescor, Logan, UT). The coefficient of variation of multiple determinations was 0.4 to 0.8%. Samples were stored in capped polystyrene tubes at 4°C no longer than 10 days before determination.

Results

Plasma Vasopressin Levels

Figure 1 compares the individual plasma AVP levels determined in all three groups of subjects by sex. Plasma AVP levels averaged 3.3 ± 0.2 pg/ml in normotensive men and 3.5 ± 0.2 pg/ml in normotensive women. AVP was elevated significantly (p < 0.05) in hypertensive men (4.4 ± 0.4 pg/ml) compared with levels in normotensive men. As seen by the scattergram of individual data points, plasma AVP levels were within the normal range in the majority of borderline and hypertensive subjects; however, 16 of 61 (26%) of male hypertensive subjects exhibited plasma AVP levels that were greater than 2 SD of the average mean value of normal men (i.e., greater than 5.9 pg/ml). Subjects exceeding this level will be referred to as "high AVP" subjects in the present study. A few male subjects with borderline hypertension also tended to exhibit elevated plasma AVP levels (2 of 20).

In contrast, plasma AVP levels were not elevated significantly in the female hypertensive subjects (4.0 ± 0.4 pg/ml) when compared with levels in female normotensive subjects. Only 3 (8.6%) of the 35 female hypertensive subjects fell into the high AVP category. As with men, a number of borderline hypertensive women (4 of 18) were in the high AVP category, but the average difference when compared with normal women was not statistically significant.

Repeatability of Measurements

A highly significant correlation was obtained between the plasma AVP concentrations of Visit 1 with those obtained 1 to 2 weeks later on Visit 2 in 63
subjects \( r = 0.44, p = 0.001 \) The calculated regression equation was close to the line of identity \( v = 0.9x - 0.05 \). This indicates that plasma AVP tends to remain at a rather constant level in both normal and hypertensive subjects and can be measured repeatedly over time

**Plasma Renin Activity**

Figure 2 compares the individual PRA values determined in the three groups of male and female subjects. The PRA averaged 2.3 ± 0.2 ng of ANG I/ml/hr in normotensive men and 2.7 ± 0.5 ng of ANG I/ml/hr in normotensive women. The PRA of hypertensive men (2.0 ± 0.2 ng of ANG I/ml/hr) did not differ significantly from normal men. In contrast, hypertensive females averaged significantly lower levels of PRA (1.2 ± 0.2 ng of ANG I/ml/hr) than normotensive females. The PRA was elevated in men, but not in women, with borderline hypertension \( p < 0.05 \)

**Measured Variables**

**Influence of Sex**

A one-way ANOVA was performed on eight subgroups according to sex, race, and blood pressure (normotensive or hypertensive) and examined all measured variables. The results of this analysis indicated that the important differences within the population were attributable to sex and blood pressure but not to race. The analysis was then repeated, grouping subjects according to sex and blood pressure.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal ( (n = 40) )</th>
<th>Hypertensive ( (n = 61) )</th>
<th>Normal ( (n = 40) )</th>
<th>Hypertensive ( (n = 35) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 3</td>
<td>43 ± 2</td>
<td>49 ± 2</td>
<td>45 ± 2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 ± 2</td>
<td>85 ± 2</td>
<td>71 ± 2</td>
<td>82 ± 3</td>
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<td>Systolic pressure (mm Hg)</td>
<td>121 ± 2</td>
<td>146 ± 2</td>
<td>120 ± 3</td>
<td>153 ± 3</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>80 ± 1</td>
<td>100 ± 1</td>
<td>78 ± 1</td>
<td>102 ± 1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 1</td>
<td>73 ± 1</td>
<td>69 ± 1</td>
<td>76 ± 2</td>
</tr>
<tr>
<td>Flow (ml/day)</td>
<td>1370 ± 93</td>
<td>1608 ± 74*</td>
<td>1540 ± 89</td>
<td>1379 ± 90</td>
</tr>
<tr>
<td>( U_{NaV} ) (mEq/day)</td>
<td>150 ± 9</td>
<td>199 ± 15**</td>
<td>117 ± 8</td>
<td>162 ± 13*</td>
</tr>
<tr>
<td>( U_KV ) (mEq/day)</td>
<td>57 ± 3</td>
<td>56 ± 3†</td>
<td>59 ± 5</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>( U_{osm} ) (mosm/kg)</td>
<td>678 ± 39†</td>
<td>664 ± 30†</td>
<td>493 ± 34</td>
<td>565 ± 33</td>
</tr>
<tr>
<td>( U_{Na} ) (mEq/L)</td>
<td>120 ± 8*</td>
<td>129 ± 7</td>
<td>87 ± 7</td>
<td>121 ± 8*</td>
</tr>
<tr>
<td>( P_{Na} ) (mEq/L)</td>
<td>139 ± 0.4</td>
<td>139 ± 0.3</td>
<td>138 ± 0.4</td>
<td>139 ± 0.3</td>
</tr>
<tr>
<td>( P_K ) (mEq/L)</td>
<td>4.62 ± 0.06</td>
<td>4.6 ± 0.06†</td>
<td>4.43 ± 0.06</td>
<td>4.23 ± 0.07*</td>
</tr>
<tr>
<td>( P_{osm} ) (mosm/kg)</td>
<td>286 ± 1†</td>
<td>285 ± 1†</td>
<td>283 ± 1</td>
<td>282 ± 1</td>
</tr>
<tr>
<td>( P_{AVP} ) (pg/ml)</td>
<td>3.2 ± 0.2</td>
<td>4.4 ± 0.4†</td>
<td>3.5 ± 0.2</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td>PRA (ng of ANG I/ml/hr)</td>
<td>2.0 ± 0.2</td>
<td>2.0 ± 0.2</td>
<td>2.7 ± 0.5</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td>( P_{Cr} ) (mg/dl)</td>
<td>1.2 ± 0.03†</td>
<td>1.3 ± 0.04†</td>
<td>0.9 ± 0.02</td>
<td>0.9 ± 0.02</td>
</tr>
<tr>
<td>( C_{Cr} ) (mg/day)</td>
<td>112 ± 5</td>
<td>121 ± 6</td>
<td>96 ± 6</td>
<td>107 ± 6</td>
</tr>
</tbody>
</table>

Values are means ± SEM

\( U_{NaV} = \) urinary sodium excretion, \( U_KV = \) urinary potassium excretion, \( U_{osm} = \) urinary osmolality, \( U_{Na} = \) urinary sodium, \( P_{Na} = \) plasma sodium, \( P_K = \) plasma potassium, \( P_{osm} = \) plasma osmolality, \( P_{AVP} = \) plasma vasopressin, PRA = plasma renin activity, ANG I = angiotensin I, \( P_{Cr} = \) serum creatinine, \( C_{Cr} = \) creatinine clearance

*Significantly different from normal of same sex, \( p < 0.05 \)
†Significant differences between sexes (normal versus normal, hypertensive versus hypertensive), \( p < 0.05 \)
subjects compared with volume in normal men. Other significant elevations observed in hypertensive men include daily sodium excretion, heart rate, and body weight ($p < 0.05$). In women, PRA was significantly lower in hypertensive subjects ($p < 0.05$). They also tended to excrete less daily volume, excreted significantly less potassium per day, and had lower plasma potassium levels ($p < 0.05$). Like hypertensive men, hypertensive women excreted more sodium per day, had higher heart rates, and weighed more than normotensive women. Plasma and urine osmolality did not differ between normal and hypertensive groups of either sex.

Relationship Between Plasma Vasopressin Levels

Figure 3 shows that a highly significant positive correlation was obtained in male subjects between plasma AVP levels and both systolic ($r = 0.28; p = 0.005$) and diastolic ($r = 0.26, p = 0.008$) blood pressure. A multiple correlation analysis between plasma AVP and other measured variables in male subjects did not yield biologically meaningful nor statistically significant correlations.

In female subjects, a significant negative correlation was observed between plasma AVP and plasma potassium levels ($r = -0.31, p = 0.009$). Urine osmolality was also significantly correlated with plasma AVP levels ($r = 0.27, p = 0.02$).

Relationship Between Plasma Renin Activity

Figure 4 shows that a highly significant negative correlation was obtained in female subjects between PRA and both systolic ($r = -0.39, p = 0.001$) and diastolic ($r = 0.40, p = 0.001$) pressure. The PRA was also negatively correlated to systolic blood pressure in male subjects ($r = -0.28, p = 0.005$). The multiple correlation analysis yielded a significant positive correlation between PRA and daily potassium excretion in men ($r = 0.29, p = 0.004$) and women ($r = 0.5; p = 0.001$). The women's systolic ($r = 0.37; p = 0.001$) and diastolic ($r = 0.36; p = 0.001$) pressure also correlated significantly with daily potassium excretion.

Relationship Between Daily Sodium Excretion, Plasma Vasopressin Levels, and Plasma Renin Activity

The data summarized in Table 1 were analyzed to evaluate the influence of sodium intake on the relationships between plasma AVP levels and PRA. As seen in Figure 5, no statistically significant differences were observed between sodium intake and plasma AVP concentrations. Plasma AVP levels, however, tended to be elevated in normal male subjects excreting less than 75 mEqNa/day compared with normal men excreting greater amounts of sodium. Plasma AVP concentration was elevated significantly only in male hypertensive subjects within the normal range of urinary sodium excretion (90–175 mEq/day) when compared with that of normotensive subjects. No relationship was observed between urinary sodium excretion and plasma AVP levels in normal or hypertensive women.

Also plotted in Figure 5 is the relationship between urinary sodium excretion and PRA obtained in male
and female subjects. The PRA was significantly and appropriately elevated in hypertensive men and both normal and hypertensive women with urinary sodium excretion of less than 75 mEq/day ($p < 0.05$). There were no other significant differences of PRA observed between normal and hypertensive men at other levels of urinary sodium excretion. In women PRA was significantly lower in hypertensive subjects excreting normal amounts of sodium (90–175 mEq/day; $p < 0.05$).

A subgroup of low renin hypertensive men was compared with a group of 12 age-matched normal renin hypertensive men. Plasma AVP levels (4.6 ± 0.7 pg/ml) of the low renin group (PRA = 0.4 ± 0.05 ng of ANG 1/ml/hr) did not differ significantly from levels in the normal renin group. Too few ($n = 3$) hypertensive women had elevated plasma AVP levels to warrant a similar analysis.

A separate analysis was made of 32 subjects (13 normotensive, 5 men, 8 women, 19 hypertensive, 10 men, 9 women) who complied to the 1-week sodium restriction period (see Methods). Plasma AVP levels were elevated only in the normotensive group, from 3.6 ± 0.4 to 5.9 ± 0.8 pg/ml ($p < 0.05$), although the small group size did not permit a meaningful analysis according to sex.

Characterization of Hypertensive Subjects with High Plasma Vasopressin Levels

A subgroup of 12 normal AVP hypertensive men was age and weight matched with 12 high AVP hypertensive men. This analysis indicated that high AVP hypertensive men had significantly higher diastolic pressures (+6 mm Hg, $p < 0.05$), and heart rates (+6 beats/min; $p < 0.05$). Plasma and urine osmolality did not differ between these two groups. Plasma AVP levels, which averaged 8.1 ± 0.7 pg/ml in the high AVP groups, were therefore inappropriately elevated in these subjects.

Age-, Sex-, and Race-Matched Subgroups of Hypertensive Subjects

No significant race differences were observed following the analysis of variance. This could have been attributed to an imbalanced number of white hypertensive women and black normotensive women. Subgroups of normal and hypertensive subjects were therefore matched according to race, age, and sex. Table 2 summarizes selected variables of interest from this analysis.

Four points of particular interest were observed. First, plasma AVP levels did not differ between blacks and whites except in hypertensive women. Second, PRA was significantly lower in all hypertensive blacks ($p < 0.05$). Third, all black subjects except hypertensive black women (whose values, although not significantly also tended to be lower) excreted significantly less daily urine volume than whites ($p < 0.05$). Fourth, hypertensive blacks excreted significantly less potassium than hypertensive white subjects ($p < 0.05$).

Discriminant and Logistic Analysis

A discriminant analysis was performed to identify those variables other than blood pressure that contributed most to the differences between normal and hypertensive subjects. The results are summarized in Table 2. This analysis, when applied to men, identified urinary sodium excretion, heart rate, and plasma AVP levels as the variables that, in linear combination, could best classify subjects as normal or hypertensive. In contrast, when applied to women, the analysis identified urinary sodium excretion, heart rate, and PRA as the variables that best determined the group classification (see Table 3 for equations). Using these markers, we correctly classified as normal or hypertensive an average of 71% of the 97 men and 77% of the 69 women.

A logistic analysis determined which set of independent variables would best predict the probability of being hypertensive. The three variables were the same as those identified by the discriminant analysis for men and women. Examples of some of these probabilities as related to five levels of heart rates are shown in Table 4.

For example, in men with heart rates of 68 beats/minute, the probability of being hypertensive greatly increased in the presence of high plasma AVP levels and a high urinary sodium excretion. These probabilities were further enhanced in individuals with high heart rates and reached 77% in subjects with heart rates of 74 beats/minute, plasma AVP levels of 5 pg/ml, and urinary sodium excretion of 200 mEq/day (corresponding to the average male hypertensive values in the present study).

Similarly, in women with heart rates of 68 beats/minute, the probability of being hypertensive in-
TABLE 2  Comparisons of Age-, Sex-, and Race-Matched Normal and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 4</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79 ± 3</td>
<td>92 ± 4</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>123 ± 3</td>
<td>148 ± 3</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>81 ± 2</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>P_{AVP} (pg/ml)</td>
<td>3.3 ± 0.5</td>
<td>4.9 ± 0.8</td>
</tr>
<tr>
<td>PRA (ng of ANG I/ml/hr)</td>
<td>2.1 ± 0.4</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>UV24H (ml/day)</td>
<td>1160 ± 69</td>
<td>1313 ± 114</td>
</tr>
<tr>
<td>U_{NaV} (mEq/day)</td>
<td>51 ± 7</td>
<td>45 ± 5</td>
</tr>
<tr>
<td>U_{sm} (mosmol/kg)</td>
<td>709 ± 64</td>
<td>794 ± 44</td>
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</table>

TABLE 3  Discriminant Analysis

<table>
<thead>
<tr>
<th>Sex</th>
<th>Actual group</th>
<th>No of subjects</th>
<th>Predicted group classification</th>
<th>Normal</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Normal</td>
<td>38</td>
<td>79%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>(AVP)</td>
<td>(n = 30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hypertensive</td>
<td>59</td>
<td>36%</td>
<td>64%</td>
<td></td>
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<tr>
<td>(n = 21)</td>
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</tr>
<tr>
<td>Female</td>
<td>Normal</td>
<td>37</td>
<td>76%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>(PRA)</td>
<td>(n = 29)</td>
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<tr>
<td></td>
<td>Hypertensive</td>
<td>32</td>
<td>22%</td>
<td>78%</td>
<td></td>
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<tr>
<td>(n = 7)</td>
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</table>

TABLE 4  Logistic Analysis

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>AVP</td>
<td>U_{NaV} %</td>
<td>PRA</td>
</tr>
<tr>
<td>No</td>
<td>Prob</td>
<td>No</td>
</tr>
<tr>
<td>0</td>
<td>40</td>
<td>10.7</td>
</tr>
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<td>64</td>
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<td>120</td>
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<td>150</td>
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<td>80</td>
<td>5</td>
<td>120</td>
</tr>
<tr>
<td>100</td>
<td>200</td>
<td>93.3</td>
</tr>
<tr>
<td>150</td>
<td>280</td>
<td>99.5</td>
</tr>
</tbody>
</table>

Values are means ± sem

P_{AVP} = plasma vasopressin, PRA = plasma renin activity, ANG I = angiotensin I, UV24H = 24-hour urine excretion, U_{sm} = urinary sodium excretion, U_{NaV} = urinary sodium excretion

*Significantly different from black subjects in same pressure group. p < 0.05

Discussion

The role of AVP in human hypertension remains a controversial subject due to conflicting results from a number of laboratories. Some of these studies have found that subjects with benign essential hypertension exhibit elevated levels of plasma AVP, while others have found no significant differences from normotensive subjects. The results of the present study provide a plausible explanation for some of these ambiguities. Specifically, we found that high AVP essential hypertension is confined almost exclusively to male hypertensive subjects. Statistical analysis of our data indicated that sex was the only distinguishing characteristic whereby a significant subgroup could be identified in the hypertensive subjects. It should be noted that the previous study in which we...
reported elevated plasma AVP levels with hypertension was carried out on an all male VA population, whereas the present study included normotensive and hypertensive subjects of both sexes.

Characteristics of Male Hypertensive Subjects

We found that 26% of men with mild to moderate hypertension exhibited inappropriately elevated levels of plasma AVP. High levels of AVP were defined conservatively by plasma levels that exceeded the normal mean by 2 SD. A highly significant correlation between plasma AVP levels and systolic and diastolic blood pressure was obtained in the male population. The proportion of high AVP hypertensive men found in the present study conforms with results of our previous study (VA Cooperative Study No. 127) in Jackson, Mississippi, in which nearly 30% of hypertensive male subjects exhibited high plasma AVP levels.

It appears that a major reason for the conflicting results of previously reported studies can be attributed to the failure to discriminate on the basis of sex. The exception to this was the study by Preibisz et al. who, even with small numbers of patients, found that plasma AVP levels were significantly elevated in male (n = 11) compared with female (n = 9) subjects with established hypertension. In the present study there was no indication that plasma AVP levels in men were influenced by race, which agrees with results of our previous study. A nearly equal number of black and white hypertensive male subjects were studied (30 versus 31), and a subgroup of 20 of these matched for age, sex, and race was selectively analyzed (see Table 2). No significant differences were observed between black and white subjects in either analysis.

The present results were validated by the observation that plasma AVP levels of normotensive as well as hypertensive subjects remained relatively constant when determined on repeat visits at least 1 to 2 weeks apart. The closeness of the regression equation of Visit 1 versus Visit 2 to the line of identity indicated that plasma AVP levels were appropriately high levels of AVP, as there were only eight men older than 50 years of age with high daily sodium excretion (average 250 mEq/day) exhibited in hypertensive male or female subjects. We were unable to confirm our previous observation that male hypertensive subjects older than 50 years of age with high daily sodium excretion (average 250 mEq/day) exhibited inappropriately high levels of AVP, as there were only eight men older than 50 found to be excreting sodium in excess of 175 mEq/day.

Low sodium excretion in our study was associated with high PRA in all groups, as described by Laragh. Hypertensive subjects excreted significantly greater amounts of sodium than normal subjects, which indicates a higher sodium intake. It is unlikely that this was the stimulus for elevated AVP levels in hypertensive men since in the present study plasma AVP levels were not related to daily sodium excretion in normal, hypertensive male or female subjects. We were unable to confirm our previous observation that male hypertensive subjects older than 50 years of age with high daily sodium excretion (average 250 mEq/day) exhibited inappropriately high levels of AVP, as there were only eight men older than 50 found to be excreting sodium in excess of 175 mEq/day.

Low sodium excretion in our study was associated with high PRA in all groups, as described by Laragh. In our studies no relationship was apparent between sodium excretion and plasma AVP levels. In men and women excreting less than 75 mEq/day, there was no apparent relationship between PRA and plasma AVP levels. In those subjects instructed to maintain a low sodium diet for 1 week, however, a significant elevation of plasma AVP was observed, but only in the normotensive subjects. These results suggest that a relatively prolonged and consistent low sodium intake may be required to raise plasma AVP levels and that this relationship is in some way blunted in hypertensive subjects.

It should be noted that plasma AVP levels were no different in low renin hypertensive subjects than in
normal renin hypertensive subjects, an issue on which there have been conflicting results reported. Ando et al. observed that plasma AVP levels were significantly lower in low renin essential hypertension, while Skjoto et al. found plasma AVP levels nearly three times higher in low renin hypertension. Unfortunately, neither of these studies considered the influence of sex on the measured variables.

**Discriminant and Logistic Analysis**

The discriminant and logistic statistical analyses performed with the present data revealed some important markers that, in combination, are good predictors of hypertension and specific for sex of the individual. These analyses suggest that elevated levels of AVP, urinary sodium excretion, and heart rate, may be important in the hypertensive process in men. Similarly, PRA, urinary sodium excretion, and heart rate appear to be intimately involved in the hypertensive process in women. The logistic analysis illustrates the increasing statistical probability of being hypertensive with alterations of these three variables. These analyses in no way imply cause and effect relationships, however, nor do they enable one to predict whether hypertension will develop in an individual. It is possible that the observed values of heart rate, AVP, and PRA could all be consequences of other important primary alterations that have led to the hypertensive state, such as impaired renal excretory ability, altered body fluid volumes status, and alterations of autonomic nervous system function.

It would not be unreasonable to speculate that both heart rate and elevated AVP levels in male subjects could reflect an upward shift in the set point of neural controllers of AVP and autonomic activity. In such a situation, hypertension could be aggravated by increased sodium intake. Alternatively, elevated plasma AVP levels in hypertensive men could reflect a tendency toward extracellular fluid volume contraction, perhaps related to reduced renal tubular reabsorption, as suggested by the elevated urine volumes. This could lead to increased drinking and AVP secretion. The tendency toward low PRA and normal levels of plasma AVP in hypertensive women could reflect a greater tendency toward fluid retention.

Despite the inability to ascertain causal relationships in these analyses, the fact that levels of AVP, urinary sodium excretion, and heart rate, in combination, correctly classified 71% of normal and hypertensive male subjects, and that PRA, urinary sodium excretion, and heart rate successfully classified 77% of normal and hypertensive female subjects, indicates that these combined variables are reproducibly altered in essential hypertension.

**Role of Vasopressin in Pathogenesis of Hypertension**

The role of AVP in essential hypertension remains to be determined. The elevated plasma AVP levels, which ranged from 6 to 16 pg/ml in hypertensive men, were similar to those that have been shown to lower cardiac output and cause vasoconstriction in unanesthetized dogs. These vasoconstrictor actions do not, however, result in acute elevations of arterial pressure in normal conscious states because of strong reflex buffering mechanisms. It has not been possible to produce hypertension in normal dogs with prolonged administration of vasopressin (AVP), even though baroreflex adaptation would be expected to unmask the acute buffering actions of the autonomic reflexes.

Arginine vasopressin could participate in the hypertensive process in many ways that remain to be explored. For example, the elevations of plasma AVP levels seen in essential hypertension would be capable of influencing body fluid volume and electrolyte status. They also may be capable of influencing tissue perfusion in various regions such as the skeletal muscle, skin, and various splanchic regions, as shown in dogs. It is also possible that hereditary defects in AVP secretion and in central neural vasopressinergic pathways could alter autonomic activity and other functions. The pathogenic role of AVP in essential hypertension may be better clarified with future applications of selective antagonists of the renal, vascular, and central nervous system actions of AVP.

**Acknowledgments**

The authors gratefully acknowledge the many important contributions made by Ms Ruth Schertenbach in the daily management of the studies and the reduction of the data. The assistance of Mr. Jerry Anderson in the design and conduct of statistical analysis of these studies is also appreciated. Finally, we thank Ms Deborah Schoenhorn for her careful analytical work, Ms. Therese Gauthier for her excellent secretarial and editorial assistance with the manuscript, and Ms. Eileen Graybar for her clinical assistance.

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Hypertension. 1985;7:I151
doi: 10.1161/01.HYP.7.3_Pt_2.I151

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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