The Sympathetic Nervous System and Hypertension in Primary Aldosteronism

EMMANUEL L. BRAVO, ROBERT C. TARAZI, HARRIET P. DUSTAN, AND FETNAT M. FOUAD

SUMMARY To assess the role of the sympathetic nervous system in mineralocorticoid hypertension in humans, results from 24 patients with aldosterone-producing adenoma were compared with those in 27 appropriately matched essential hypertensive subjects and 26 normotensive subjects. Resting plasma catecholamine levels averaged 292 ± 140 (SD) pg/ml in patients with aldosterone-producing adenoma, 305 ± 101 in patients with essential hypertension, and 260 ± 120 in normotensive subjects; none of the differences among the three groups was significant. With head-up tilt (60 degrees for 10 min) plasma catecholamine levels increased similarly in the aldosterone-producing adenoma and essential hypertensive groups (up to 681 ± 111 and 611 ± 57 pg/ml respectively, ns). β-Blockade (propranolol, 10 mg i.v.) in eight aldosterone-producing adenoma patients decreased heart rate (from 78 ± 5 to 68 ± 3 beats/min, p < 0.005) and cardiac output (from 5.5 ± 0.4 to 4.6 ± 0.3 liter/min, p < 0.001), but left mean blood pressure unchanged (127 ± 4 to 127 ± 2 mm Hg). Combined α- and β-blockade with phentolamine and propranolol in five patients with aldosterone-producing adenoma produced no detectable changes in blood pressure. Thus, results from biochemical, functional, and pharmacological studies in humans showed no evidence of enhanced peripheral sympathetic activity in the hypertension of primary aldosteronism. (Hypertension 7: 90–96, 1985)

KEY WORDS • sympathetic nervous system • primary aldosteronism • DOCA-salt rat • catecholamines • essential hypertension

AN important role has been ascribed to the sympathetic nervous system in the development and maintenance of hypertension induced by electrolyte-active steroids. Most of the evidence was derived from studies of the deoxycorticosterone acetate (DOCA)-salt rat model and included (1) increased turnover rate of norepinephrine in the heart,1 (2) increased levels of urinary norepinephrine and its metabolites,2 (3) increased levels of circulating catecholamines, and (4) prevention of DOCA-induced hypertension by intraventricular or intracisternal administration of 6-hydroxydopamine.3 The universal applicability of this evidence has been questioned by finding that in contrast with DOCA-salt rats, dogs made hypertensive with metyrapone had decreased levels of plasma norepinephrine.4

Studies in humans have been relatively few and mostly based on indirect evidence. Biglieri and McIlroy5 contrasted the high plasma renin activity and orthostatic hypertension of renovascular hypertension (secondary aldosteronism) with the suppressed plasma renin activity and tendency to reduced sympathetic reflexes in primary aldosteronism. Even the frequent presence of a hyperkinetic circulation in primary aldosteronism was related more to the associated changes in plasma electrolytes6–7 or to a possible inotropic effect of aldosterone8 than to increased adrenergic drive.

This study was therefore undertaken to assess more directly the relationship between the activity of the sympathetic nervous system and hypertension in 24 patients proved to have solitary aldosterone-producing adenomas at the time of operation. The results provided no support for the concept that increased peripheral sympathetic activity plays an important role in this type of mineralocorticoid hypertension in humans.

Materials and Methods

Patient Population

Twenty-four patients proved to have aldosterone-producing adenoma were studied before undergoing operation. There were 11 men and 13 women ranging in age from 36 to 67 years (mean age, 46.8 ± 8 years).
served for comparison. This group consisted of 13 men and 14 women ranging in age from 33 to 67 years with a mean age of 47.4 ± 10 years. In neither group was there any evidence of cardiac decompensation or of renal dysfunction. All patients are participants in a long-term study of the mechanisms of human hypertension by the Research Division of the Cleveland Clinic Foundation; all were therefore familiar with the various procedures involved and had given their consent to these studies. All studies were approved by the Institutional Review Board for human investigation.

Study Protocols

The studies to be described were performed during diagnostic maneuvers to confirm or rule out the presence of inappropriate aldosterone production. All studies were conducted in the clinical research wards of the Cleveland Clinic Hospital; the patients ingested the same diet throughout the study. This diet was designed to be isocaloric and to contain 10 mEq Na and 80 mEq K per day. When needed, sodium intake was varied by oral supplementation with sodium chloride tablets. The protocol included three periods: first a daily intake of 110 mEq Na for 3 days, followed by 10 mEq Na for 4 days; then, while the 10 mEq Na diet was continued for 3 more days, normal saline (25 ml/kg) was given daily intravenously over a 4-hour period. The amount of saline infused in any given patient was calculated from the weight recorded after the 3-day equilibration period on the 110 mEq Na diet; it provided an additional sodium intake of at least 250 mEq per day. Appropriate biochemical measurements were obtained at the end of each period of normal, low, and high sodium intake of at least 250 mEq per day. Appropriate biochemical measurements were obtained at the end of each period of normal, low, and high Na intake. Blood for the determination of plasma catecholamines and renin activity was always drawn between 0800 and 0900 hours. Following 30 to 45 minutes of supine rest, the needle having been inserted in an appropriate peripheral vein at least 30 minutes before blood sampling.

To determine the extent to which the sympathetic nervous system might contribute to the maintenance of hypertension in patients with aldosterone-producing adenomas, we undertook the following assessments.

1. Comparison of basal plasma catecholamine values between patients with aldosterone-producing adenomas and patients with essential hypertension. Values obtained during normal dietary sodium intake from 24 patients with aldosterone-producing adenoma and 27 patients with essential hypertension were compared. In addition, these basal plasma catecholamine values were related to the simultaneously determined blood pressure levels; the latter were averaged from at least three supine readings obtained over a 3- to 5-minute period with a standard sphygmomanometer.

2. Response of plasma catecholamines, arterial blood pressure, and heart rate to head-up tilt. The response of 12 patients with aldosterone-producing adenoma was compared with those of 20 patients with essential hypertension. The studies were conducted in the morning, after the 3-day equilibration period on normal sodium intake (110 mEq Na/day). After a 30- to 45-minute rest, supine arterial pressure and heart rate were determined, and blood for plasma catecholamine values was drawn. The patients were then tilted head-up at 60 degrees and the measurements of blood pressure, heart rate, and plasma catecholamines were repeated after 10 minutes in this position.

3. Response of plasma catecholamines to dietary sodium manipulation. The response of 18 patients with aldosterone-producing adenoma was compared with those of 7 patients with essential hypertension. Values used for this assessment were those determined at the end of normal, low, and high dietary sodium intake periods. Blood for plasma catecholamine determinations was drawn as described, after an overnight fast, following 30 to 45 minutes of supine rest, between 0800 and 0900 hours.

4. Hemodynamic responses of patients with aldosterone-producing adenoma to intravenously administered β-adrenergic blocking agent. Seven patients with aldosterone-producing adenoma were subjects of this study. They were fasted overnight and transported by wheelchair to the hemodynamic laboratory. After 45 to 60 minutes of supine rest, arterial blood pressure (direct), heart rate (by electrocardiography), and cardiac output (dye dilution) were determined as previously described in detail. Following this, 10 mg propranolol in 10 ml normal saline was administered intravenously over a 5-minute period. Twenty to thirty minutes later, we obtained the second set of hemodynamic measurements.

5. Cardiovascular responses of patients with aldosterone-producing adenoma to combined α- and β-adrenergic blockade. Five patients with aldosterone-producing adenoma were the subjects of this study. In this test adrenergic influences were blocked by the intravenous administration of 10 mg propranolol followed by a graded intravenous infusion of phenolamine (up to 3 mg/min). Studies were performed in the morning, after 30 to 45 minutes of supine rest. Arterial blood pressure and heart rate were determined at 1-minute intervals throughout the test.

Procedures

Plasma renin activity, plasma catecholamine (norepinephrine and epinephrine) levels, and aldosterone excretion rates were determined by radioassay procedures previously described. Plasma volume was measured with 125I-human serum albumin with use of a 10-minute equilibration period as previously described. Values are expressed as percentage of normal to allow inclusion of values for both men and women. Cardiac output was measured by the dye dilution technique.

Statistical Analysis

Student's t test was used to assess statistical significance of differences between groups; however, for analysis of changes within each group, the paired t test was applied. Results are expressed in means ± se.
Results

The clinical and biochemical characteristics of the 24 patients with aldosterone-producing adenoma and the 27 essential hypertensive subjects to whom their responses were compared are shown in Table 1. The two groups were comparable in regard to sex ratio, age, level of arterial blood pressure, heart rate, resting plasma renin activity, and urinary sodium excretion. They differed in the degree of volume expansion, in the concentrations of serum potassium, and in the amounts of 24-hour urinary aldosterone. In neither group was there any evidence of overt renal dysfunction as judged from serum creatinine clearance.

Resting plasma catecholamine levels on normal dietary sodium are shown in Figure 1. Total plasma catecholamine levels averaged 292 ± 140 in patients with aldosterone-producing adenoma and 305 ± 101 pg/ml in essential hypertensive subjects of similar sex and age distribution. These values were not significantly different from each other, nor was either of them significantly different from the normal values obtained in our laboratory (260 ± 120 pg/ml) in 26 age- and sex-matched normal individuals (age range: 26–70 years). Only 1 of 24 patients with aldosterone-producing adenoma had a catecholamine value outside the range of normal values (+2 SD); this particular patient had none of the symptoms suggestive of a hyperkinetic circulation. Neither the systolic nor the diastolic blood pressure levels showed any significant relation with the levels of circulating catecholamines in patients with aldosterone-producing adenoma (Figure 2).

The effect of posture on arterial pressure, heart rate, and circulating catecholamines is shown in Table 2. Basal plasma catecholamine levels did not differ among normal individuals, patients with aldosterone-producing adenoma, and essential hypertensive subjects. Following 10 minutes of 60-degree head-up tilt, plasma catecholamine levels rose by 74.2% to 453 ± 29 (SE) pg/ml (p < 0.001) in normal individuals, by 117.5% to 681 ± 111 pg/ml (p < 0.001) in patients with aldosterone-producing adenoma, and by 74.5% to 611 ± 57 pg/ml (p < 0.01) in essential hypertensive subjects. The relative plasma catecholamine response to tilt was not different in the three groups. In all three groups diastolic pressure increased similarly and heart rate increased slightly but insignificantly.

<table>
<thead>
<tr>
<th>Clinical and biochemical characteristics</th>
<th>Aldosterone-producing adenoma (n = 24)</th>
<th>Essential hypertension (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male ratio</td>
<td>1 2 1</td>
<td>1 1 1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 8 ± 8</td>
<td>47 4 ± 10</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>175 ± 14</td>
<td>174 ± 19</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>111 ± 8</td>
<td>115 ± 8</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>0 83 ± 0 72</td>
<td>1 03 ± 0 75</td>
</tr>
<tr>
<td>Plasma volume (% normal)</td>
<td>107 ± 11*</td>
<td>91 ± 12*</td>
</tr>
<tr>
<td>Serum K (mEq/liter)</td>
<td>2 6 ± 0 2*</td>
<td>4 2 ± 0 4*</td>
</tr>
<tr>
<td>Serum creatinine clearance (mg/dl)</td>
<td>0 7 ± 0 2</td>
<td>0 9 ± 0 2</td>
</tr>
<tr>
<td>Urinary aldosterone excretion (µg/24 hr)</td>
<td>39 ± 9*</td>
<td>11 ± 4*</td>
</tr>
<tr>
<td>Urinary sodium excretion (mEq/24 hr)</td>
<td>103 ± 5</td>
<td>98 ± 4</td>
</tr>
</tbody>
</table>

All values are expressed as means ± 1 SD
*Values are significantly different from each other (p is at least <0.05)
Responses to dietary sodium manipulation are shown in Table 3. Arterial blood pressure and plasma volume fell by significant levels in both hypertensive groups during sodium deprivation. In patients with essential hypertension, plasma catecholamine levels increased during low dietary sodium intake and fell with salt loading, but none of these changes were statistically significant. In patients with aldosterone-producing adenoma, plasma catecholamine values were essentially unchanged by variations in dietary sodium. The lack of change in plasma catecholamines was substantiated by the unaltered values of 24-hour urinary metanephrine and normetanephrines.

Hemodynamic responses to acute β-adrenergic blockade were assessed in nine patients with aldosterone-producing adenoma (Table 4). Intravenous propranolol (10 mg over 5 min) reduced heart rate (from 78 ± 5 beats/min to 68 ± 3, p < 0.005) and cardiac output (from 5499 ± 391 to 4589 ± 331 liter/min, p < 0.001). Arterial blood pressure remained unchanged (from 126 ± 4 to 127 ± 4 mm Hg) because of a compensatory rise in total peripheral resistance (from 45 ± 3 to 54 ± 4 mm Hg). These responses were not unlike those exhibited by essential hypertensive subjects.

Cardiovascular responses to combined α- and β-adrenergic blockade were assessed in five patients with aldosterone-producing adenoma. Basal mean arterial pressure averaged 142 ± 7 mm Hg; plasma catecholamine levels were 205 ± 27 pg/ml, and plasma renin activity was 0.9 ± 0.4 ng/ml/hour. Following the combined blockade, mean arterial pressure fell by only −10 ± 6 mm Hg, and reached a final steady state value of 135 ± 9 mm Hg, which was not statistically different from control levels. Typical responses in a single patient are shown in Figure 3.
The present findings are consistent with results of other studies that suggest that mineralocorticoid-induced hypertension in humans need not be associated with enhanced sympathetic nervous activity. The pressor response to tyramine (which is mediated by the liberation of norepinephrine from sympathetic nerve endings) has been shown to be diminished in patients with primary aldosteronism. Circulatory reflexes have been reported as either normal or impaired in these patients. Similarly, a fall in plasma norepinephrine was reported by Philipp and co-workers in normal individuals treated with fludrocortisone. Finally, patients with autonomic insufficiency have been shown to develop recumbent hypertension during treatment with fludrocortisone and salt. Taken together, these studies suggest that in humans, mineralocorticoid hypertension is not associated with increased sympathetic activity, but rather, a tendency to some decrease in that activity. Moreover, they indicate that an intact sympathetic nervous system is not crucial for its pathogenesis.

Whether peripheral sympathetic activity is reduced in experimental mineralocorticoid hypertension is less clear. DOCA-salt hypertensive rats showed increases in plasma concentrations of norepinephrine. Prior destruction of central catecholaminergic nerve cells with centrally administered 6-hydroxydopamine prevented the increase in both plasma norepinephrine concentration and arterial blood pressure in this model. Abdominal sympathetic nerve firing produced by hypothalamic stimulation was enhanced in rats with established DOCA-salt hypertension. All these results have been taken as evidence for the hypothesis that a centrally mediated increase in sympathetic activity is important in the development and maintenance of experimental mineralocorticoid hypertension. Other studies, however, reached different conclusions.

Some reports have even suggested that the sympathetic nervous system is depressed in experimental mineralocorticoid hypertension and that increased sympathetic nerve activity is not essential for its initiation and maintenance. Crab and co-workers found that the norepinephrine content of the vasculature of DOCA-salt hypertensive rats is lower than normal. Rascher and co-workers reported that hypertension without associated increases in circulating catecholamines developed in intact, unstressed Wistar rats treated with high doses of DOCA and kept on a standard salt diet. In dogs with deoxycorticosterone (DOC) hypertension, plasma norepinephrine levels were reduced during both the development and maintenance phases of hypertension; moreover, the rise in blood pressure could not be prevented by agents that suppress catecholamine release by either a central or a peripheral mechanism.

It has been postulated that even if the sympathetic nervous system were not overactive, it may still contribute to the hypertension that results from excess mineralocorticoid levels. Enhanced sensitivity of vas-
cular smooth muscle to vasoconstrictor substances during administration of electrolyte-active steroids has been demonstrated in a number of studies. Schmid and co-workers\(^9\) showed that constriction of resistance and capacitance vessels in response to norepinephrine is potentiated by treatment with 9α-fluorohydrocortisone. Enhanced pressor responsiveness to norepinephrine has been demonstrated in fludrocortisone-treated patients with autonomic insufficiency.\(^15\) Berecek and Bohr\(^20\) found a distinct lowering of threshold doses for both angiotensin II and norepinephrine during the early stages of the development of hypertension in the DOCA hypertensive pig. Rascher and associates\(^18\) reported similar findings in DOCA-treated Wistar rats kept on a standard salt intake. It has recently been suggested that DOCA also may indirectly affect vascular reactivity in the rat by releasing vasopressin,\(^21-23\) but no data are available in humans.

These studies point out that the net blood pressure effect of adrenergic stimulation is the composite result of both sympathetically and vascular responsiveness. In fact, an inverse relationship has been reported between vascular sensitivity to norepinephrine and indexes of sympathetic activity,\(^24\) possibly because reduced occupancy of norepinephrine receptors can lead to vascular hyperresponsiveness to adrenergic stimuli. Enhanced responsiveness to norepinephrine is a well-known feature of autonomic insufficiency.\(^15\) Our results do not address the question of vascular reactivity in primary aldosteronism, they simply point out the absence of any evidence for sympathetic nerve stimulation.

It could be argued that the measurement of circulating catecholamine levels is not an accurate index of sympathetic nervous activity,\(^25\) although this does not necessarily mean that plasma levels cannot give some qualitative indication of that activity. Indeed, more recent studies have shown that venous plasma norepinephrine levels can provide a useful estimation of average sympathetic outflow.\(^26\) Furthermore, it has been amply demonstrated that under postural stresses, plasma norepinephrine levels do reflect the acute sympathetic responses at the time of blood sampling.\(^27\) In the present study orthostatic responses of plasma catecholamine levels, arterial blood pressure, and heart rate were similar in patients with primary aldosteronism and essential hypertension.

Species differences could account for the differences in results between DOCA-salt hypertensive rats and mineralocorticoid-induced hypertension in dogs and humans. The chronicity of hypertension in primary aldosteronism is another factor that should be considered; however, we have followed dogs with DOCA-induced hypertension over several months during both development and maintenance phases and have observed persistent decreases rather than increases in circulating catecholamine levels.\(^4\) Whatever the reason for the differences between earlier results in rats and our observations in humans, it is important to point out that increased sympathetic activity is not the only hypothesis advanced to explain mineralocorticoid hypertension. Much stronger arguments have been advanced for different mechanisms that suggest increased vascular responses to normal stimuli.

There is now considerable evidence that induction of hypertension in animals with DOCA is related to altered membrane properties of vascular smooth muscle that could account entirely for the increased peripheral vascular resistance and consequent rise in blood pressure. This evidence has accrued largely from the work of Jones and Hart,\(^28\) Friedman and Friedman,\(^29\) and Berecek and Bohr.\(^20\) Their results suggest that altered membrane permeability leads to abnormal cation turnover that enhances vasoconstruction; the structural changes (increased wall-lumen ratio) that follow, further augment vascular reactivity responses to even normal stimuli, thus potentiating and maintaining the hypertensive process.\(^3\)

Another attractive possibility was advanced by the demonstration of a circulating "Na pump inhibitor" in experimental "volume-overload hypertension" as well as in some patients with essential hypertension.\(^30-33\) The consequent increase in intracellular sodium leads to increased intracellular calcium,\(^33\) which in turn could explain the increased vascular tone and even some of the cardiac hyperkinetic features of primary aldosteronism.\(^7\) In a larger context, these links may eventually provide an explanation for the well-documented relationship between sodium and hypertension.

**Conclusion**

There is no doubt that disturbances in either vascular receptors, arteriolar structure, or cellular electrolyte balance can modulate the effectiveness of normal adrenergic factors; all these are common in hypertension and form part of its multifactorial nature.\(^26\) Our data are related, however, only to the evidence for or against the presence of increased peripheral sympathetic activity in aldosterone-producing adenoma and not to the net effect of adrenergic stimuli on an altered vasculature. We have found neither biochemical, functional, nor pharmacological evidence in support of increased sympathetic nervous activity in patients with primary aldosteronism. These results coupled with the demonstrated sensitivity of these patients to salt and water depletion suggest that mineralocorticoid hypertension in humans could be explained by the combined effect of sodium overload and peripheral membrane alteration without the need to invoke abnormal increases in sympathetic nervous activity.

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