The Renin-Angiotensin-Aldosterone System in Primary and Secondary Hypertension*†

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ABSTRACT

Important advances have been made in understanding the role of the renin-angiotensin-aldosterone system in the pathogenesis and diagnosis of hypertensive disorders. Measurement of plasma renin activity (PRA) and aldosterone is very important in the assessment of secondary hypertension. Hypertensions with increased PRA include renovascular hypertension, some cases of unilateral and bilateral renal parenchymal disease, malignant hypertension, hypertension associated with oral contraceptive agents, and renin-secreting tumors. Hypertension with decreased PRA is observed in four recognized types of primary aldosteronism: adenoma, bilateral hyperplasia, indeterminate aldosteronism, and glucocorticoid-responsive aldosteronism. Other conditions with hypertension and depressed PRA include ACTH and DOC secreting tumors, primary hyperpituitarism, syndromes of 17-hydroxylase and 11-beta-hydroxylase deficiency, Liddle's syndrome, licorice abuse, exogenous administration of mineralocorticoids, and preeclampsia.

Introduction

Renin is a protein with a molecular weight of approximately 40,000, formed and stored in the juxtaglomerular (JG) cells located at the vascular pole of the glomerulus. In response to appropriate stimuli, renin is released into the bloodstream and lymphatic circulation. Renin acts on a plasma globulin, angiotensinogen or renin substrate, to produce an inactive decapetide, angiotensin I.

Neither renin nor angiotensin I have direct physiologic effects. Under the action of angiotensin converting enzyme (ACE), mainly during passage through the lungs, angiotensin I is converted to the
active octapeptide, angiotensin II, the most potent vasoconstrictor substance known to date. Some angiotensin II is further degraded by angiotensinases into the heptapeptide, angiotensin III. Angiotensin II and possibly angiotensin III are believed to be the major physiologic stimuli for aldosterone secretion. However, angiotensin III has a lower pressor potency than angiotensin II. Aldosterone is the major mineralocorticoid hormone which enhances renal tubular sodium reabsorption and volume expansion. Two other factors stimulate aldosterone secretion: adrenocorticotropic hormone (ACTH) and potassium. The ACTH effect on aldosterone secretion is prompt but transient. The aldosterone response to potassium is also prompt and highly sensitive.

Regulation of Renin Release

Renin release is very sensitive to changes in perfusion pressure in the glomerular arteriole. Cells in the arteriolar wall act as baroreceptors, responding to reduction in pressure with release of renin by the JG cells. There is also a sodium sensitive mechanism in the cells of the macula densa. These cells are located in the early distal convoluted tubule and apparently connected by "bridges" to the JG cells. Either sodium or chloride affect renin release. Oddly, there is evidence suggesting that both decreased Na load and increased Na concentration at the macula densa site stimulate renin release. Sympathetic stimulation through the renal nerves also enhances renin release. As the renin-angiotensin cascade is set in motion, angiotensin II is generated, and aldosterone secretion is stimulated. Since this hormone promotes the renal tubular reabsorption of sodium, extracellular volume is expanded. This in turn leads to suppression of renin release: indirect negative feedback. It should be noted also that other negative feedback pathways may come into play. Furthermore, a direct negative feedback mechanism exists between plasma levels of circulating angiotensin II and renin release.

Recently, experimental data have been accumulating in regard to the role of other humoral systems, kallikrein-kinin and prostaglandin, in the mechanism of renin release and blood pressure regulation. Further research is needed to elucidate the precise interaction of these systems and their clinical significance.

The Renin-Angiotensin-Aldosterone System in Hypertensive States

Essential Hypertension

The role of the renin-angiotensin-aldosterone system in essential hypertension is still unsettled. In approximately 55 to 60 percent of patients, plasma renin activity (PRA) is normal, is elevated in 15 percent, and is subnormal in 25 to 30 percent.

The significance of high, low, or normal PRA in essential hypertension remains uncertain. The initial proposal that low renin essential hypertension has a better prognosis than hypertension with normal or high renin has not been confirmed by most observers. It has also been claimed that the classification of essential hypertension based on PRA has important therapeutic implications—namely, that low renin essential hypertension is best managed initially with a diuretic, whereas high renin essential hypertension may best be managed with a beta-adrenergic blocking agent. However, this hypothesis remains controversial. Virtually all patients with essential hypertension are now treated initially with a diuretic agent followed, if necessary, by a beta-adrenergic blocker or other sympatholytic agent, irrespective of their renin levels.

In our laboratory, the correlation between PRA, blood volume and other hemodynamic functions was examined in
# TABLE I

Plasma Renin Activity and Hemodynamic Data in Patients with Low, Normal or High Renin Essential Hypertension

<table>
<thead>
<tr>
<th>Patients</th>
<th>Low (ng/ml/hr)</th>
<th>Normal (ng/ml/hr)</th>
<th>High (ng/ml/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>0.54 ± 0.35</td>
<td>0.64 ± 0.40*</td>
<td>7.05 ± 5.30**</td>
</tr>
<tr>
<td>Standing</td>
<td>1.13 ± 0.59</td>
<td>1.80 ± 0.82**</td>
<td>9.60 ± 7.07**</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>114.25 ± 9.41</td>
<td>109.91 ± 7.02</td>
<td>114.0 ± 18.38</td>
</tr>
<tr>
<td>Total blood volume (ml/cm)</td>
<td>30.78 ± 5.85</td>
<td>28.79 ± 3.06</td>
<td>33.85 ± 2.47</td>
</tr>
<tr>
<td>Plasma volume (ml/cm)</td>
<td>17.96 ± 3.85</td>
<td>16.24 ± 1.82</td>
<td>20.15 ± 4.88</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.44 ± 1.56</td>
<td>5.41 ± 1.76</td>
<td>7.97 ± 3.30</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>78.00 ± 24.30</td>
<td>79.45 ± 15.42</td>
<td>97.30 ± 48.51</td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
<td>18.33 ± 6.95</td>
<td>17.11 ± 4.44</td>
<td>13.94 ± 5.61</td>
</tr>
</tbody>
</table>

*p < 0.05  **p < 0.005

Studies were done in patients with essential hypertension who had not been treated before the studies. Most of them were black and hypertension was mild to moderate. Plasma renin activity (PRA) was measured by the method of Sealy and Laragh (Cardiovasc. Med. 2:1079-1092, 1977).

21 untreated patients with mild to moderate essential hypertension on unrestricted sodium intake. Eight patients (38.1 percent) had low PRA, 11 (54.8 percent) normal, and two (7.1 percent) high PRA. The hemodynamic data are presented in table I. Plasma volume was not expanded in the group with low renin hypertension, and there were no significant differences in mean blood pressure, cardiac output, stroke volume, and total peripheral resistance between groups.

Diuretic therapy alone decreased diastolic blood pressure to 90 mm Hg or less in about two thirds of these patients, regardless of pretreatment PRA levels. These observations are consistent with published data. As to beta blockade, our own experience as well as that by others has shown that propranolol alone significantly reduces blood pressure in 52 to 57.6 percent of the cases. Thus, determination of PRA for instituting treatment of essential hypertension is of limited practical consequence.

Race, age and sex are important in interpreting renin values. Low PRA is more frequently found in black than in white patients. Both PRA and aldosterone levels decrease with advancing age, and they are lower in older women than in men of comparable age.

The mechanism and significance of renin suppression in essential hypertension remains unclear. The hypothesis that overproduction of an undefined mineralocorticoid is responsible has not been documented. Renin suppression may be attributable to extracellular fluid expansion but definitive evidence concerning this point is lacking. It is clear, however, that patients with low renin essential hypertension show greater natriuresis and weight loss than normal renin hypertensives when placed on restricted sodium intake or treated with diuretic agents.

Low renin essential hypertension is probably not a distinct entity, since there is no evidence of a bimodal distribution of PRA in essential hypertension. The low PRA levels may simply represent the lower end of a continuum of values.

Since several factors can influence renin and aldosterone, careful attention must be paid to the conditions under which blood and urine samples are obtained. Factors such as sex, age, race, sodium and potassium intake, body posture, and time of day are important. In women of reproductive age, the date of the last menstrual cycle must be known. Oral contraceptives elevate PRA and the effect may last as long as three months. A
number of drugs influence PRA (table II). They should be withdrawn if possible.

Some investigators have recommended that PRA and aldosterone be correlated with 24-hour sodium excretion. Others use stimulating maneuvers such as assumption of upright posture or exercise, with or without sodium depletion. Others prefer to collect samples with the patient supine in the morning, after at least three days of normal sodium and potassium intake. It is our practice to choose the conditions of collection according to the purpose of the measurement. If one is looking for a low renin state, such as primary hyperaldosteronism, it is preferable to collect the sample under maximal stimulation, with a diuretic and upright posture or under salt restriction. Conversely, if one is looking for a high renin state, such as renovascular hypertension, collection of unstimulated renin seems preferable.

**Secondary Hypertension**

Plasma renin activity is increased above normal levels in certain forms of secondary hypertension, whereas it is decreased in other types (table III).

**CONDITIONS ASSOCIATED WITH INCREASED PLASMA RENIN ACTIVITY**

**Renovascular Hypertension.** The incidence of renovascular hypertension has been reported to range between one and five percent. In general, stenosis of the renal artery is likely to cause hypertension when the diameter of the lumen is reduced about 50 percent, corresponding to a reduction in the cross section area of approximately 80 percent. Plasma renin activity in peripheral blood is found elevated in about 60 percent of cases of renal artery stenosis with hypertension. This finding, however, does not assure the diagnosis of renovascular hypertension; it only increases its probability. The diagnostic sensitivity of peripheral PRA may be increased by administration of saralasin or of a converting enzyme inhibitor. A marked increase in PRA immediately after such administration makes clinically significant renovascular hypertension more probable, but it still does not confirm the diagnosis. Also, the demonstration of anatomical stenosis by arteriography does not necessarily establish its functional significance. Assessment of functional significance requires demonstration of enhanced renin release by the contralateral kidney. Sampling of blood from both renal veins and inferior vena
cava below renal veins or from a peripheral vein is required for this purpose. This is commonly referred to as the "split renal renin test." Many studies concerning the usefulness of this test have been published. There is general agreement that the test is positive if PRA in the venous blood from the ischemic kidney is at least 1.5 times greater than that from the contralateral kidney, and the latter is equal or lower than PRA in the inferior vena cava. Since about 20 percent of patients with essential hypertension have been found to have a split renal renin ratio above 1.5, it has been proposed that a ratio of at least 2.0 be used for the diagnosis of renovascular hypertension. This higher ratio would reduce the incidence of false positive results but would increase that of false negative. The controversy arising from this issue is still unsettled.

Marks et al have found that a renal vein renin ratio greater than 2.0 could predict a surgical success (cure/improvement) rate of approximately 90 percent. However, in patients operated upon despite lower ratios, the cure/improvement rate was also high: 57 to 83 percent. Various maneuvers which stimulate renin release have been proposed in an attempt to improve the sensitivity of the test, but the results have been conflicting.

Our own experience with stimulating maneuvers includes 16 patients with hypertension and unilateral renal artery stenosis (RAS), all of whom had surgery, and 19 cases of essential hypertension. All patients studied were off antihypertensive medications for at least one week, on ad libitum sodium intake and supine. Timed intravenous pyelography and selective renal arteriography were performed in all. Then, following overnight fasting, venous blood was sampled from both renal veins and from the inferior vena cava before and 30 min after intravenous furosemide, 1 mg per kg, or isoproterenol infusion, 1 to 4 μg per kg per min. Among the patients with essential hypertension (control), renal vein PRA ratio was less than 1.5 in 18 (95 percent) and did not change after stimulation. As to the patients with RAS, the results were correlated with the outcome of surgery at one year or more. Among 12 patients cured or improved by surgery, PRA ratio was greater than 1.5 before and, after stimulation in six patients, increased from below to above 1.5 with stimulation in three, and remained below 1.5 in the other three cases. In the group of patients unimproved by surgery, PRA ratio did not change with stimulation and remained above 1.5 in two and below 1.5 in the other two cases. Thus, although stimulating maneuvers for widening the PRA ratio permit more sharply the separation of patients with RAS from essential hypertensives, their value is less obvious for predicting the response to corrective surgery for RAS.

The recent advent of specific inhibitors of angiotensin converting enzyme and of angiotensin II antagonists may help identify cases with renin dependent hypertension. It has been reported that administration of either agent accentuates the difference in PRA between the ischemic and non-ischemic kidney. In addition, both drugs lower blood pressure in the presence of renin dependent hypertension.

**Unilateral Renal Parenchymal Disease.** PRA is usually normal or even low in patients with unilateral renal disease. Our observations and those of others show that in most of these patients, PRA does not change significantly with either isoproterenol or furosemide administration. Rarely, the diseased kidney may release excessive amounts of renin causing hypertension. Unilateral nephrectomy in such patients does not usually result in cure or improvement of hypertension unless, of course, it can be proven that their hypertension was renin dependent. If unilateral RAS co-exists with unilateral or bilateral parenchymal renal disease, assessment of
the renal pressor system is carried out in
the manner outlined.

**Bilateral Renal Parenchymal Disease.** In patients with chronic renal failure on maintenance dialysis, two major mechanisms contribute to hypertension: volume and renin. In nearly 90 percent of cases, hypertension is volume dependent and will be controllable by dialysis alone or in combination with modest doses of antihypertension agents. In these patients, PRA and angiotensin II are normal or slightly increased before dialysis and change little or not at all with volume depletion. In about 10 percent of patients, removal of sodium and water by dialysis does not lower blood pressure adequately. PRA and angiotensin II, already elevated before dialysis, may increase further afterwards.8 As time progresses, hypertension may worsen and become uncontrollable. This form of renin dependent hypertension is more frequently found in patients with nephrosclerosis or with primary glomerular disease. Bilateral nephrectomy is occasionally necessary to control hypertension in these patients. The indication for this procedure, however, is increasingly rare with the availability of more powerful hypertensive agents, such as minoxidil and converting enzyme inhibitors.

**Malignant Hypertension.** Malignant hypertension occurs in about two percent of the hypertensive population. It is more common in patients with renovascular hypertension or pre-existing renal disease, especially glomerulonephritis. In most cases, PRA is extremely elevated, although it may be normal in some.16 The exact sequence of events leading to malignant hypertension and high PRA is unknown. It is currently believed that as severe nephrosclerosis and renal ischemia come about, the renin producing cells release large amounts of renin into the systemic circulation with greater generation of angiotensin II. This in turn results in further cortical ischemia and more renin release. Activation of angiotensin II formation also enhances secretion of aldosterone. The resultant sodium and water retention is another additional predisposing factor for hypertension and vascular injury. Vigorous treatment, permitting healing of hypertension-induced vascular disease, may interrupt this vicious cycle.

**Contraceptive Hypertension.** Most women taking contraceptive agents exhibit a slight, though distinct, increase in mean blood pressure of ± 5 mm Hg. Long term follow-up observations have shown that approximately five percent of these women eventually develop sustained hypertension. The mechanism of contraceptive hypertension is probably attributable to the estrogen component of the pill, which promotes an increase in renin substrate and enhanced generation of angiotensin.9 Consequently, the production of aldosterone is also increased.

In general, PRA is increased one to two-fold above normal, though decreased PRA ascribed to the sodium retaining property of estrogen has been reported.25,28 Regardless of PRA levels, there usually is an increase in circulating angiotensin II. In contrast to natural progesterone, the progestational component of contraceptive pills has a mineralocorticoid effect which causes sodium retention and volume expansion, thus compounding the hypertensive effect. It has been suggested that an increase in sympathetic activity may also play a role in the pathogenesis of contraceptive hypertension.24 The alterations in the renin-angiotensin-aldosterone system return to normal in one to six months after discontinuation of the contraceptive.

**Renin Secreting Tumors.** Two rare tumors, renal hemangiopericytoma or juxtaglomerular cell tumor and nephroblastoma or Wilms's tumor, are associated with hypertension, increased PRA, angiotensin II, and aldosterone. Both tumors have been found to contain large amounts of renin. Although uncommon, renin secreting tumors should be suspected in
children, adolescents and young adults with unexplained hypertension and high PRA. The diagnosis of hemangiopericytoma is difficult because the lesion may be too small to be visualized by renal angiography. Cannulation of both renal veins for measurement of PRA is overall important for the diagnosis. In some cases, it has proved valuable to collect blood from branches of the renal veins as well. Further, increased PRA in the peripheral blood may be unaffected by sodium loading or deoxycorticosterone acetate (DOCA) administration.\textsuperscript{31} Removal of the Wilms's tumor, if resectable, or of the kidney containing the hemangiopericytoma will cure the hypertension.

**Hypertension Associated with Decreased Plasma Renin Activity**

**Hyperaldosteronism.** Primary hyperaldosteronism is characterized by excessive production of aldosterone, hypervolemia, hypertension, and hyporeninemia. Its incidence is less than 0.5 percent in an unselected hypertensive population. The severity of hypertension varies and malignant hypertension is uncommon. Hypokalemia (plasma potassium less than 3.5 mEq per L) is almost invariably present, and urinary potassium excretion is usually more than 30 mEq per day.\textsuperscript{27} Sodium loading further decreases plasma potassium while increasing its urinary excretion. The diagnosis requires demonstration of autonomous hyperaldosteronism associated with hyporeninemia. Baseline plasma/urinary aldosterone is increased and does not decrease with saline loading or administration of DOCA. Plasma renin activity is low and does not respond to measures which stimulate renin release, such as volume depletion or erect posture.

Primary hyperaldosteronism has been subclassified into four types: adrenal cortical adenoma, adrenal cortical hyperplasia, indeterminate hyperaldosteronism, and glucocorticoid-responsive hyperaldosteronism.\textsuperscript{4} The vast majority of cases fall into one of the first two categories. Adenoma is the only type which is often unilateral and in which hypertension successfully responds to surgical excision. The differentiation between adenoma and cortical hyperplasia may be difficult. Plasma aldosterone tends to increase in the upright position in patients with hyperplasia, while it remains unchanged or even falls in cases with adenoma.\textsuperscript{2} Other diagnostic procedures, such as adrenal isotopic scan, adrenal venography, and measurement of aldosterone in the adrenal veins, have technical limitations. They have been utilized to differentiate adenoma from hyperplasia with varying degrees of success. Glucocorticoid responsive hyperaldosteronism is extremely rare, occurring primarily in children or young adults and is due to a deficiency of either 11-beta-hydroxylase or 17-a-hydroxylase. Administration of dexamethasone reverses all manifestations of this type of hyperaldosteronism.\textsuperscript{30} Indeterminate hyperaldosteronism is suppressible by administration of DOCA.\textsuperscript{3} With DOCA, aldosterone secretion declines more than 50 percent and falls into the normal range. Such suppression, however, does not occur in cases with adenoma and is unusual in hyperplasia. It has been speculated that indeterminate hyperaldosteronism may be an early presentation of adenoma or hyperplasia. The treatment of choice for hyperplasia is spironolactone, 200 to 400 mg per day,\textsuperscript{2} while surgery is indicated in cases with adenoma.

**Other Mineralocorticoids.** Plasma renin activity is suppressed in certain hypertensive syndromes characterized by overproduction of mineralocorticoids other than aldosterone.\textsuperscript{20} Excessive production of deoxycorticosterone (DOC) may be seen in patients with ectopic adrenocorticotropic hormone (ACTH) secreting tumors, DOC secreting tumors,
primary hyperpituitarism, and in patients with 17-hydroxylase deficiency or 11-beta-hydroxylase deficiency. The underlying defect in the latter two disorders is the inability of the adrenal cortex to secrete cortisol. As a result, ACTH secretion is increased and DOC secretion is in turn stimulated. In general, aldosterone is normal or reduced, whereas PRA may be normal, low, or elevated. Hypertension is a common, although not universal, finding in these patients with an incidence of about 87 percent.  

Liddle's Syndrome. This is a very rare familial disorder characterized by subnormal PRA, decreased aldosterone secretion, hypertension, hypokalemia and renal potassium wasting. The cause and mechanism of these abnormalities are still unknown.

Loricice Abuse and Exogenous Mineralocorticoid Administration. Loricice contains glycyrrhizic acid which has a mineralocorticoid-like action. If ingested in large amounts and for sufficiently long time, loricice may cause chronic sodium retention, volume expansion and hypertension with suppression of the renin-angiotensin-aldosterone axis. Plasma aldosterone will be markedly low along with renin and angiotensin. Carbenoxolone also contains glycyrrhizic acid and may induce a similar syndrome. These syndromes resolve a few days after discontinuation of the responsible agents.

Preeclampsia. In normal pregnancy, PRA and plasma angiotensin and aldosterone are increased, whereas the pressor responsiveness to exogenous angiotensin is decreased. Paradoxically, in preeclampsia PRA, angiotensin II and aldosterone are decreased and the pressor responsiveness to exogenous angiotensin is enhanced. The mechanism by which the renin-angiotensin-aldosterone axis is suppressed in preeclampsia remains unclear. Reduced prostaglandin E in plasma and placenta have been described in preeclampsia, and it has been speculated that the increased sensitivity to angiotensin may reflect a decrease in prostaglandin activity.

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References