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LOW-RENIN HYPERTENSION

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Introduction

Physiology of Arterial Pressure

Renin Release
Renin-Angiotensin-Aldosterone System
Mineralocorticoid Induced Hypertension

Mineralocorticoids in Low-Renin Essential Hypertension Pro & Con

Body Volume Measurements
Escape

Renin and Aldosterone Response to Stimuli

Oral Sodium
Posture and Intravenous Sodium
Circadian Rhythm of Aldosterone
Response to Mineralocorticoid Antagonists
Adrenal Pathology

Differential Diagnosis of Low-Renin Hypertension

Prognosis

Diagnosis of Low-Renin Hypertension

Therapy

[David C. (D.C.) Kem]

LOW-RENIN HYPERTENSION

Introduction

One of the significant medical achievements in the last 20 years has been introduction of effective pharmacological agents to lower blood pressure and documentation that effective control markedly diminishes the incidence of most complications (1,2,3). It is possible that benefits of therapy of essential hypertension relate only to the degree which blood pressure is lowered rather than to use of a specific medication. Nevertheless, there is evidence that maximal decrements in blood pressure are achieved when the pathophysiological basis of hypertension is identified and a rational therapeutic approach is formulated. This is analogous to identifying a bacterial organism for specific therapy rather than using broad spectrum or "shot-gun" therapy.

According to current estimates, the etiology of hypertension can be recognized in less than 10% of cases (4). By far the largest percentage of these 10% are those patients having gross damage to the kidney. Dr. Kaplan has recently reviewed this topic for Grand Rounds.

Since 1954, the syndrome of hypertension, sodium retention, potassium wasting and hypersecretion of aldosterone has been well described. In 1964, low plasma renin activity was demonstrated in these patients and subsequently in those with excessive secretion of other mineralocorticoids. There has therefore developed a concept of mineralocorticoid induced hypertension associated with mild to marked hypokalemia, volume expansion, hyporesponsive PRA, and amenable to either surgery or therapy with agents acting as specific mineralocorticoid antagonists.

Although low-renin was thought to be rather specific for 1° aldosteronism, a number of investigators soon reported low and hyporesponsive renin in 20 to 50% of hypertensive subjects with normokalemia, and normal or low normal urinary aldosterone excretion. (See the recent review by Crane et al (5) for a list of specific references.) Several investigators have marshalled data supporting their contention that a significant number of these patients with low-renin have a subtle form of mineralocorticoid induced hypertension that is amenable to specific therapy.

Todays discussion cannot cover all of these areas in detail, nor will it provide a consensus for others. I hope to provide an overview of recent developments in low-renin hypertension, so that we can develop a rational, simplified, and inexpensive approach to evaluation of the hypertensive patient.

PHYSIOLOGY OF ARTERIAL PRESSURE

Renin Release

Several recent developments in renin physiology should be noted. Reviews by Davis (6) and Vander (7) are recommended. Renin is released from storage granules in myoepithelial cells surrounding the afferent arteriole known as the juxta-glomerular (JG) apparatus. This is probably the site for synthesis and storage of renin and is adjacent to the macula densa, a thickened portion of the distal convoluted tubule of the nephron. These (JG) cells are also richly innervated by the sympathetic nervous system. It has been thought by many that these myoepithelial cells sense a change in pressure and react by releasing renin locally or into the circulation to increase or decrease glomerular filtration by controlling release of Angiotensin I (AI). Other authors have shown that the sodium load either passing by or into the macula densa is important in monitoring total body sodium and volume (8). The sympathetic nervous system also mediates postural induced changes in renin (9). A veritable war has raged over the primacy of each mechanism in the last 10 years.

Davis' group in Missouri have used a unique experimental dog preparation in which the ureter is ligated and the arterial supply to the kidney is occluded for 2 hours (10). The artery is then reopened, producing a perfused but non-filtering kidney. The macula densa is inoperative and functioning JG cells remain. The kidney is denervated and the opposite kidney is removed. By altering arterial flow, pressure, and ionic concentrations of Na^+ and K^+, they have been able to demonstrate a normal response of the JG apparatus to changes in arterial pressure in the absence of the macula densa. Conversly, the macula densa is necessary for a renin response to alterations in sodium and K^+concentration (11). β blockade by propanolol in humans or animals markedly diminishes the rise of renin after changes in posture or sodium intake (12) and exercise (13). Thus, it appears that all three control mechanisms work in concert, the importance of each depending upon the type of stimulus.

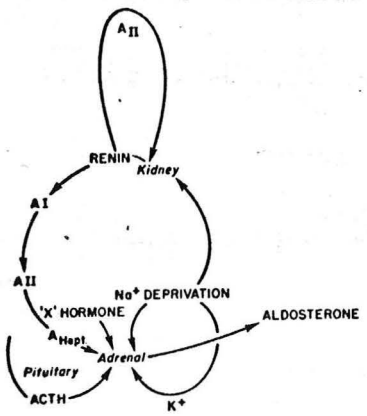


Figure 1. Major stimuli controlling aldosterone production during sodium deprivation.

Renin-Angiotensin-Aldosterone System

Figure 1 illustrates the now familiar role of the renin-angiotensin- aldosterone system in sodium conservation As a result of volume depletion, sodium depletion, change in posture, or a combination of the three, renin is released from the JG cells into the circulation. Jt acts upon an α_2 globulin, renin substrate, releasing the decapeptide Angiotensin I. Angiotensin I (AI) is converted to the vasoconstrictor Angiotensin II (AII) upon circulation through the pulmonary vasculature. While Angiotensin II

has been considered the stimulus for aldosterone production in the adrenal, data presented by Dr. Peach at a recent conference indicates that AII is converted in the circulation or at the adrenal receptor to a 7 amino acid derivative of Angiotensin II, Angiotensin heptapeptide A (hept.) This in turn stimulates aldosterone production and leads to renal sodium conservation. The presence of direct feedback inhibition of AII upon renin release has also been confirmed (14).

Control of renin in hypertension cannot be discussed without consideration of aldosterone, the major salt retaining steroid. There are other potent stimuli for aldosterone. Thus, ACTH (15), K^+ and Na^+ ions (16), and an unknown tropic factor (17) have been implicated in the control of aldosterone concentration. The effective concentrations of renin and aldosterone are determined by both secretion and metabolic clearance (18) rates. This relationship is described by the equation -

$$\text{plasma concentration} = \frac{\text{Secretion Rate}}{\text{Met. Clear. Rate}}$$

. Thus, any factor significantly diminishing or increasing the MCR will affect plasma levels just as do changes in the secretion rate.

Mineralocorticoid Induced Hypertension

How then do changes in renin, Angiotensin, and aldosterone affect systemic arterial pressure?

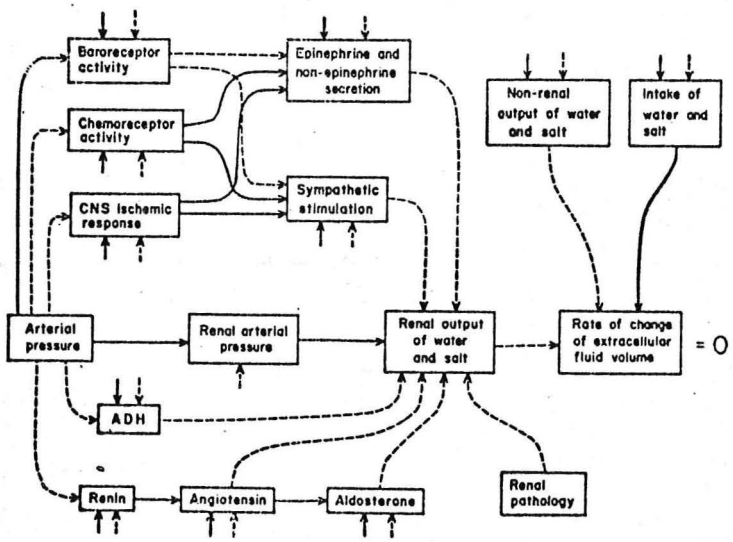
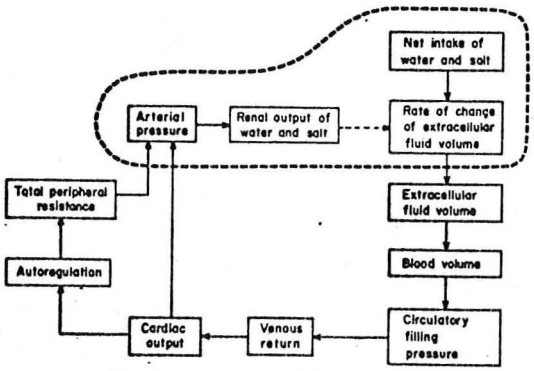


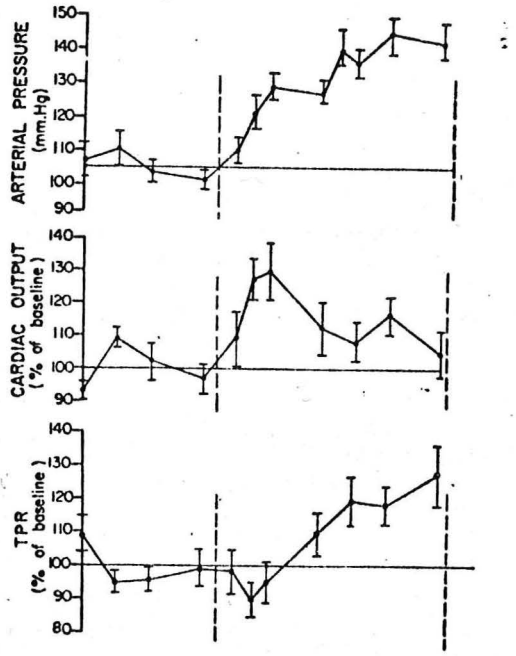
Figure 2 (Ref. 19)

Figure 2 has been taken from a recent review by Guyton (19). Equilibrium of arterial pressure is seen as a function of changes in extracellular fluid volume. The two major determinants of the ECV are intake and loss of salt and water from renal and non-renal routes. The dashed lines represent a negative effect of the Angiotensin-aldosterone system on sodium loss. Following expansion of extracellular volume, the following sequence appears likely: (Figure 3)



The feedback control loop of the renal-body fluid arterial pressure control mechanism. The dashed arrow indicates a negative effect. Those portions of the diagram in the heavy dashed enclosure represent the "determinants" of arterial pressure. Those outside the enclosure represent the dependent variables of the system.

Figure 3 (Ref. 19)



Arterial pressure, cardiac output, and peripheral resistance in six partially nephrectomized dogs infused with 0.9% saline. (Reprinted from Circulation Research.[33])

Figure 4 (Ref. 20)

Increased blood volume and circulatory filling pressure lead to increased cardiac output and a temporary elevation of arterial pressure without renal arterial narrowing. In the normal subject, this decreases proximal and distal tubular reabsorption of sodium, depletes extracellular volume, and returns arterial pressure to normal. If the kidney is unable to excrete the sodium load, equilibrium of intake and output only occur at a higher arterial pressure. Increased peripheral resistance mediated at a regional level (autoregulation) then intervenes to prevent tissue hyperperfusion. Hypertension becomes sustained from increased peripheral resistance with or without an increased cardiac output. Baroreceptors and other regulatory systems in the body then readjust their normal "set" so removal of the original stimulus does not necessarily return blood pressure to normal. This postulated sequence of events has been documented in animal studies (20)(Figure 4) but obviously is more difficult to demonstrate in humans. Nevertheless, it is an attractive formulation that integrates several observations of human hypertension. One critical step in this formulation is missing. It is quite difficult

to provoke hypertension in man and in many animals by giving mineralocorticoids alone. Either renal damage, a very high sodium intake, or pre-existing genetic determinant must also be present (21). In patients without gross renal damage, one must invoke either a subtle abnormality in the renal vasculature induced by long term sodium retention, a congenital or acquired defect at the tubular level. Otherwise, patients with hypermineralocorticoidism compensate for their volume overload by the increased proximal and distal tubular rejection of sodium and sustain only minimal increases in blood pressure.

MINERALOCORTICOIDS IN LOW-RENIN ESSENTIAL HYPERTENSION Pro & Con

The prediction that primary aldosteronism might occur in 20% of hypertensives has not been confirmed (22). Recently, however, several investigators have published data supporting their contention that renin in these hypertensive subjects is suppressed from sodium retention by mildly elevated or abnormally fixed concentrations of aldosterone or other mineralocorticoid. In the following discussion, I shall use primary aldosteronism as a model for such mineralocorticoid-induced hypertension and compare it with normal and low-renin essential hypertension. There are a number of publications in this field with conflicting data. In many cases, these conflicts have not been resolved. These may be due to differences in: 1) methodology, 2) study design, i.e., sodium and potassium intake, posture, time of day, frequency of sampling, etc., 3) patient selection, i.e., using hypertensives from different population subgroups, using inappropriate controls not matched to the hypertensive groups on the basis of race, age or sex and using different criteria for normal and low-renin. These differences between studies often make a direct comparison impossible.

Body Volume Measurements

Plasma volume has been reported as normal or expanded in primary aldosteronism (23,24). Jose et al (25) have reported an expanded ECV and normal plasma volume in low-renin hypertension, while Woods et al (26) found an elevated Na_e in 9 similar patients. These data are in contrast to the decrease in plasma volume seen in long standing normal-renin hypertension (27). While these results are suggestive that volume overload is present in low-renin patients, these papers are based on only a few measurements and considerable error is present with this type of volume estimate.

Escape

Hypertensive patients with primary aldosteronism have an increased rejection of proximal and distal tubular sodium when presented with an acute sodium load (28). This can be duplicated by administering mineralocorticoids to normal subjects. It is of interest therefore, that patients with essential hypertension (29), and particularly those with low-renin hypertension (30) have an exaggerated response to oral or intravenous sodium loads. Although this has been considered evidence for mineralocorticoid excess in low-renin hypertension, these data must be carefully

interpreted: a) increased proximal and distal rejection occurs both in normal and low-renin hypertensives. It is risky to ascribe great significance to the relatively small differences between the low-renin and normal renin hypertensive groups without concurrent knowledge of body volume measurements, b) increased tubular rejection of sodium persisted in one patient with primary aldosteronism and hyperplasia after bilateral adrenalectomy cured the mineralocorticoid hypersecretion; but failed to cure the hypertension. Thus, the increased tubular rejection was due to the hypertension rather than mineralocorticoid (31), c) an increased tubular rejection of sodium does not rule out a primary tubular abnormality as a cause for sodium retention. One can postulate an acquired or congenital defect leading to enhanced sodium reabsorption and volume overload. At an elevated arterial pressure and increased interstitial volume, proximal sodium rejection will occur to maintain equilibrium and the original defect would be obscured, d) patients with low-renin do tend to retain sodium poorly when placed on a low sodium diet and may develop volume deficits leading to mild postural hypotension. Patients with primary aldosteronism however, are noted for their ability to maintain their body volume in spite of marked sodium restriction.

RENIN AND ALDOSTERONE RESPONSE TO STIMULI

Oral Sodium

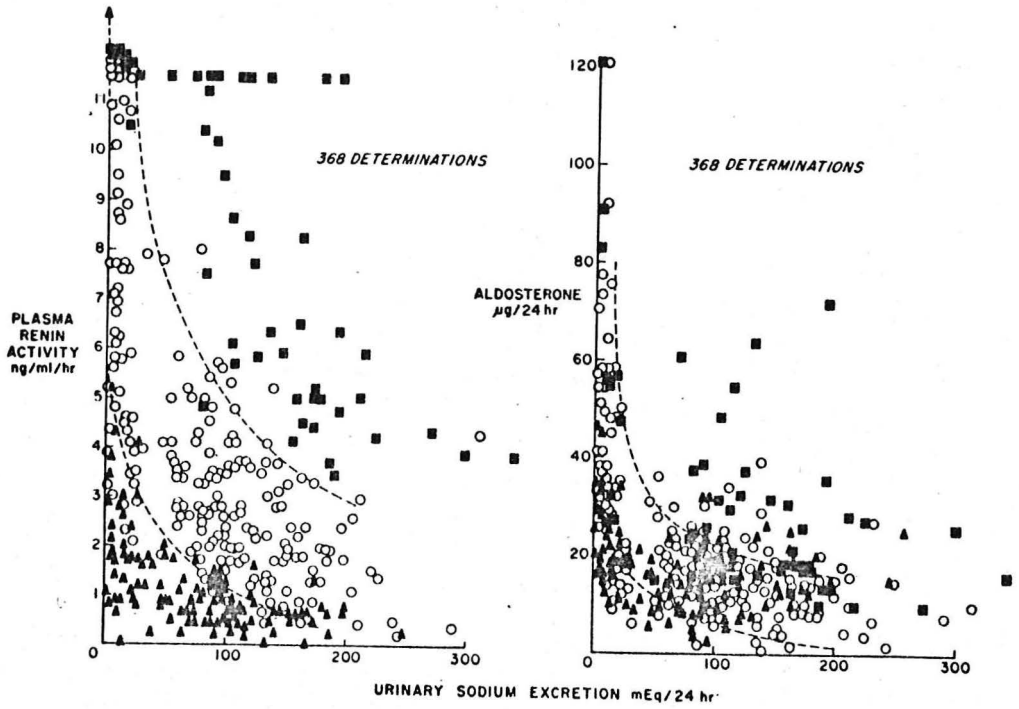


Figure 5 (Ref. 32)

Relation of Noon Plasma Renin Activity and the Corresponding Daily Aldosterone Excretion to the Concurrent Daily Rate of Sodium Excretion in 219 Patients with Essential Hypertension.
Triangles indicate low, open circles normal, and squares high, renin activity.

Laragh and co-workers have examined the PRA response to upright posture and plotted these values (Figure 5) as a function of the 24 hour urinary sodium excretion (32). As sodium excretion decreases, the PRA value increases. Their values for a predominantly young, white control group are seen within the dashed lines. The normal excretion of the 18 glucuronide conjugate of aldosterone formed in the kidney normally ranges from 3 to 18 µg/24 hours on a regular sodium diet. It is compared also to the 24 hour sodium excretion. A low sodium diet is normally associated with an increase in the excretion of aldosterone. Those patients with low PRA < > tend to have lower aldosterone excretion and secretory responses to a low sodium diet than do patients with normal renins. Luetscher (33) has shown that aldosterone secretory rates, excretion, and plasma concentrations fail to suppress normally after administering a high salt diet in subjects with low-renin hypertension.

Posture and Intravenous Sodium

We have examined the effects of posture and rapid intravenous saline loads upon plasma aldosterone in normal subjects and in hypertensive patients (34) (Figure 6).

Plasma aldosterone (PA) after eight hours recumbency (→), after two hours upright (↑), and after four hours recumbency and infusion (→ after infusion). The dotted line indicates the highest value after infusion in groups 1, 2a, and 2b.

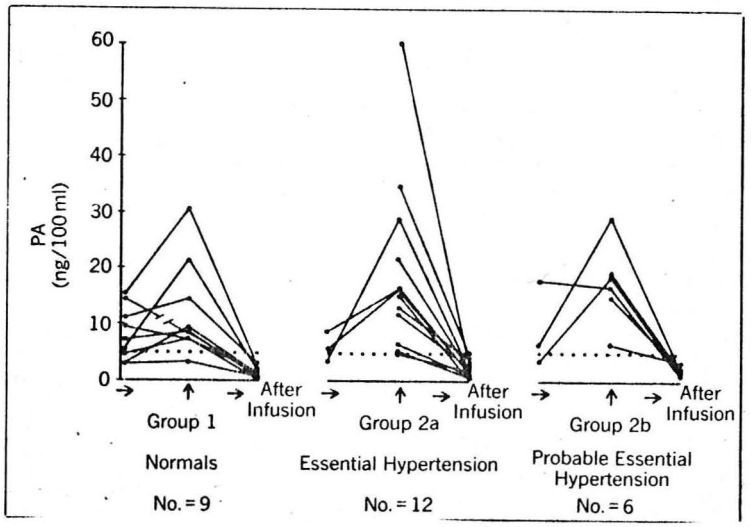


Figure 6 (Ref. 34)

Rapid infusion of saline expands plasma volume and minimizes the possibility that the accelerated renal rejection of sodium in hypertensives might account for the failure of oral salt loading to completely suppress aldosterone. Plasma aldosterone determinations rather than measurement of a

urinary metabolite also provide a better index of hormone activity during the rapidly changing conditions of the study.

The 24 hour urinary excretion of sodium prior to the study did not differ significantly in the 3 groups. Peak PA concentrations 2 hours after upright posture are similar ($p>.10$) in normal subjects (group 1) and patients with normal renin hypertension (group 2). Group 2b had abnormalities on IVP or renogram but responded similarly to those with normal radiographic studies and are hereafter included in the essential hypertension group. PA suppressed equally after saline infusion in the normal subjects and in the normal-renin hypertensive patients.

The calculation % of Baseline = $\frac{\text{PA post infusion}}{\text{PA 2 hour upright}} \times 100\%$ plotted as a function of the post infusion plasma aldosterone concentration (Figure 7) provides a convenient graph for discriminant analysis. The control subjects and patients with normal-renin hypertension suppress equally. Subjects with high upright PA values due to a low salt diet or to renovascular hypertension tend to run along the lower border while those on a high sodium diet and with relatively low 2-hour upright PA values will occasionally have less suppression after saline infusion. We have subsequently compared the effect of saline loading and recumbency on a larger number of hypertensive subjects divided into low and normal-renin groups. (Figure 8). Patients with primary aldosteronism and either documented adrenal adenoma or hyperplasia fail to suppress normally. Several patients with overt hypokalemia have not had a pathological diagnosis by surgery or venography and are listed simply as low-renin hypertensives. I am confident that patients with values greater than 10 ng/100 ml do in fact have hyperaldosteronism from either an adenoma or hyperplasia. Of particular interest are those patients with low-renin hypertension who do not have hypokalemia and have generally normal or low-urinary aldosterone.

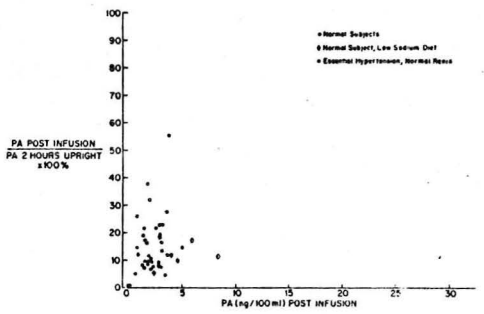


Figure 7. The % of baseline is plotted as a function of PA after infusion.

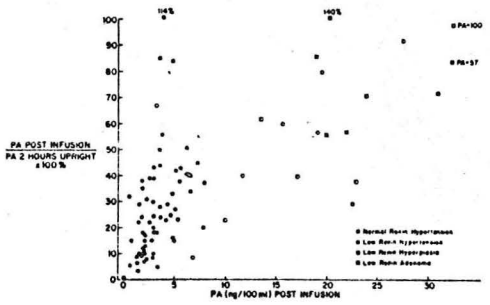


Figure 8. The % of baseline is plotted as a function of PA after infusion in patients with normal and low-renin hypertension.

TABLE I

	PA ng/100 ml 2 hour upright Mean ± SEM		PA ng/100 ml 4 hour recumbent + saline Mean SEM	
Normotensive	15 ± 2.4	NS	2.1 ± 0.3	NS
Hypertensive normal-renin	18 ± 1.8	NS	3.0 ± 0.3	(<0.05)
Hypertensive low-renin	16 ± 3.5	NS	3.7 ± 0.4	NS

The mean post infusion PA for the low-renin group is 3.7 ng/100 ml, not significantly different from the normal-renin hypertensives. This value is significantly higher than the 2.1 ng/100 ml for the normotensive subjects ($p<.05$). Harris et al have reported no difference in the post infusion PA value between a group of 16 patients with low-renin and 13 patients with normal-renin hypertension (35). Figure 9 compares the response of both PA and PRA in our normal and low-renin hypertensive subjects to saline infusion and recumbency. These subjects were divided on the basis of a PRA response to 2 hours of upright posture greater or less than p.7 ng/ml·h^{-1}. Some patients in the low-renin group have less suppression of PRA and PA. Whether this is significant or is due to the relatively low 2 hour upright values which approach an irreducible minimum is not yet known. No consistent difference in the relationship of PRA and PA is apparent between the normal and low-renin groups. It is interesting to speculate on the nature of the stimulus for PA in those subjects with low PRA.

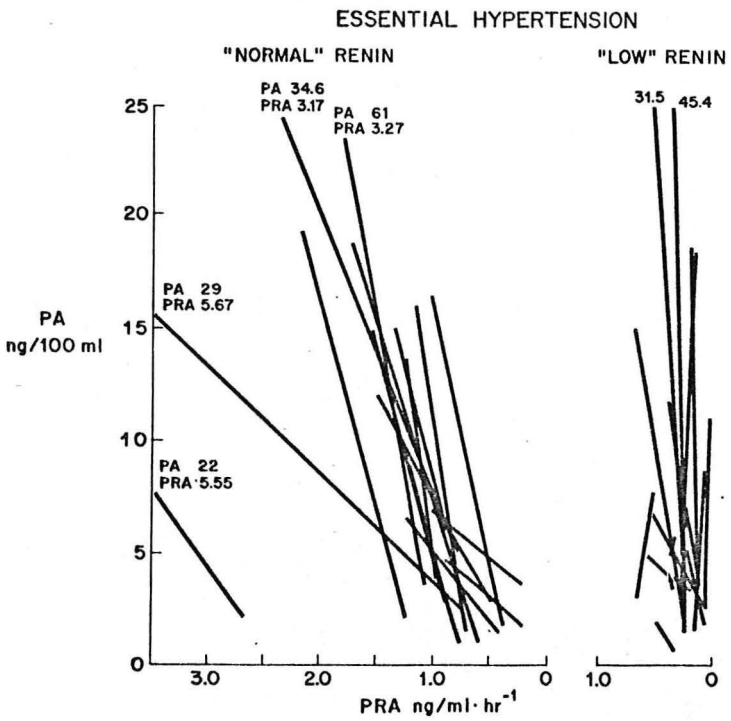


Figure 9. PA is plotted as a function of PRA during upright posture and after saline infusion in hypertensive patients with normal (>0.7 ng/ml·hr^{-1}) and low PRA.

and high upright PA concentrations. Since decreased aldosterone excretion (36) and secretory rates have been reported in patients with low-renin (37), it was surprising to find that PA concentrations in these patients were normal (14,33).

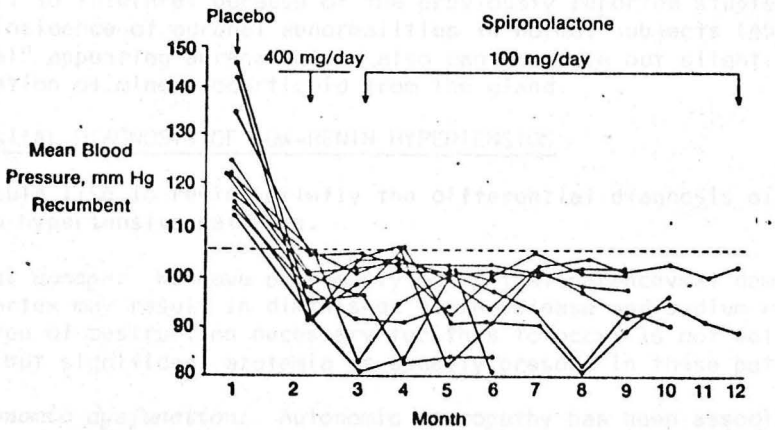
These data fit with the observation of Nowacynski et al (38) that hypertensive subjects have a decreased aldosterone metabolic clearance rate. The decreased secretory rate of aldosterone may represent normal compensation for the decreased hepatic aldosterone clearance rate to maintain normal plasma aldosterone concentrations. Several unanswered questions remain. The low MCR was found in all of their hypertensive patients. These patients were not identified as to renin responsiveness and it therefore seems likely that a majority of these patients had normal-renin. Normal secretory and excretory rates of aldosterone have been reported by most investigators in hypertensive patients with normal-renin. In these patients, one would expect elevated plasma aldosterone concentrations if the MCR were indeed low. This decrease in hepatic aldosterone clearance has not yet been confirmed (39).

Circadian Rhythm of Aldosterone

We have demonstrated a circadian rhythm of PA in patients with I° aldosteronism. PA values in these patients are generally but not always higher for a given sodium intake than in normal subjects.

Grim et al (40) have similarly investigated patients with low-renin and "normal" aldosterone excretion. They reported a low but definite circadian rhythm of PA. They concluded that concentrations of PA are inappropriately high in these patients when compared to the circulating PRA. They also demonstrated a small but significant increase in PA after 40 to 48 hours of their study suggesting mild but chronic hypersecretion of aldosterone.

Response to Mineralocorticoid Antagonists



—Serial mean blood pressure values of 11 patients treated consistently with spironolactone in doses in 100 mg daily.

Figure 10 (Ref. 42)

Several investigators have described a significant improvement of blood pressure in low-renin hypertensive patients after therapy with high doses of spironolactone. (5,41,42,43,44). This medication (aldactone) acts primarily by blocking the distal tubular sodium retaining action of aldosterone. By itself, it is a poor diuretic. Therefore, the impressive results with this medication in patients with low-renin (Figure 10) have heightened interest in the possible role of mineralocorticoids in this type of hypertension. Two recent papers (42,43) have demonstrated that spironolactone is more effective in lowering blood pressure in low-renin than in normal-renin hypertension. On the other hand, Laragh's group (44) have reported spironolactone to be only moderately effective in low-renin hypertension and have shown comparable blood pressure responses in patients with normal-renin. The discrepancy between these studies is not yet resolved. The dosage of spironolactone employed in Vaughan's study (mean dosage = 190 mg/d) was significantly lower than that initially used in the other studies, but not different from the lower dosage usually sufficient thereafter to control blood pressure. Patient selection in the study by Vaughan was based on renin responsiveness after upright posture, while the other studies used either diuretics or a low sodium diet as a stimulus for renin production. Woods et al (26) administered an adrenal inhibitor with no inherent diuretic activity, aminoglutethamide, to patients with low-renin hypertension and demonstrated a significant effect on blood pressure while no effect was observed in patients with normal renin hypertension.

Adrenal Pathology

Surgery has been performed on a number of patients with low-renin hypertension with conflicting results. Gunnells et al (36) examined 7 such patients and found most to have adrenal lesions [hyperplasia or adenomas] similar to those found in 1° aldosteronism. Grim reported similar findings in 3 additional patients (40). Crane et al (5) however, found 7 patients with low-renin hypertension who had normal adrenals at surgery and an additional 19 patients with low-renin hypertension had normal adrenal venograms. This type of pathological study is difficult to interpret because of the previously reported studies revealing a high incidence of adrenal abnormalities in normal subjects (45,46). A "normal" appearing adrenal gland also can not rule out slight increases in secretion of mineralocorticoid from the gland.

DIFFERENTIAL DIAGNOSIS OF LOW-RENIN HYPERTENSION

I would like to review briefly the differential diagnosis of low-renin in hypertensive patients.

1. *Renal damage:* We have previously noted that parenchymal damage to renal cortex may result in diminished renin release and sodium retention. The degree of destruction necessary for this to occur is not well documented, but significant azotemia is usually present in these patients.

2. *Autonomic dysfunction:* Autonomic neuropathy has been associated

with very low-renin and aldosterone concentrations (47). While some of these patients may have hypertension, it is generally very mild and associated with significant postural hypertension. Diabetes mellitus may occur in these patients and be responsible for the autonomic dysfunction.

3. *Medications:* ∝ methyl dopa (aldomet) (48) has been shown to lower PRA, presumably by acting as a false transmittor in the adrenergic innervation of the kidney. We have already mentioned that propanolol blunts the β adrenergic induced rises in renin. Other medications increase PRA by affecting either sodium balance (thiazides and aldactone) or renin substrate (estrogens)(49) and might elevate low renin values into the normal range. Licorice ingestion or administration of florinef will cause sodium retention and suppress renin.

4. *Recovery phase of malignant hypertension:*

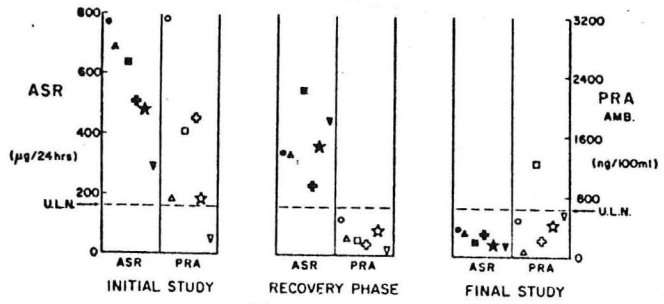


Figure 11 (Ref. 50)

Dissociation of aldosterone from renin during the recovery phase in treated malignant hypertension. Each symbol represents a different patient. AMB. = sample drawn after three hours of ambulatory activity.

McAllister et al (50) have studied 22 patients with malignant hypertension who were subsequently controlled with medications (Figure 11). A significant number of these patients developed low-renin and maintained mildly elevated aldosterone secretory rates simulating 1° aldosteronism during the recovery phase. Aldosterone and PRA eventually returned to normal in some of the patients. The cause for this dissociation of renin and aldosterone is still not known.

5. *Congenital and acquired adrenal hyperplasia:* The adrenal may secrete abnormal quantities of mineralocorticoids (51) other than aldosterone and produce hypokalemia, hypertension, and suppressed PRA. Congenital adrenal hyperplasia resulting from defects in hydroxylation at the 11, 17 or 18 positions are also associated with increased secretion of other mineralocorticoids (52). Elevated 18-OH DOC has been reported in some patients with low-renin and labile hypertension (53,54). This compound has only 1/50th of the mineralocorticoid activity of aldosterone and therefore hypersecretion appears to be significant in only a few subjects.

6. *Cushings syndrome* (37) and ectopic ACTH production (51) from a neoplasm can produce volume overload and suppressed PRA.

7. *Errors in interpretation:* The most frequent source of "low-renin" is incorrect interpretation of data due to improper patient preparation and lack of adequate control subjects. The incidence of low PRA in blacks has been estimated to be 30 to 60%, much higher than in white hypertensives (55,56). We became concerned at the apparent high incidence of low-renin in black patients seen in the Parkland Hypertension Clinic. One possible explanation for this was our using control subjects different in race and age from those patients seen in the clinic. In reviewing the literature, it became apparent that black hypertensive subjects have been compared to control groups which were predominantly white and young. For this reason, we have recently studied a large number of control subjects matched for race, age and sex (57). We have used two different stimuli in an attempt to assess which might be most satisfactory for outpatient use. One is the response of PRA 30 minutes after 40 mg of intravenous furosemide and upright posture. The second stimuli was 2 hours of upright posture. Each test was preceeded by discontinuing medications 2 weeks prior to testing, and the patients were encouraged to add salt to their diet. The patients collected a 24 hour urine for Na^+, K^+ and creatinine prior to testing to estimate sodium intake (Figure 12). As seen in figure 13, the mean and range of PRA in black normotensive controls is significantly lower than that of white normals. Normotensive blacks have values of renin so low as to make it impossible to use a range or standard deviation as criteria for suppression. When the PRA response to 2 hours of upright posture is plotted as a function of urinary sodium excretion (figures 14 & 15) it is clear that blacks have a lower distribution of PRA, and both groups would need to be placed on sodium restriction in order to adequately separate them from the lower limits of the control subjects. A low sodium diet may not be successful in separating the two groups as we have preliminary evidence that low-renin normotensives also have an impaired PRA response to this stimulus and again

	Normotensive		*Hypertensive*	
	White	Black	White	Black
Age	35±2	36±2	48±5	49±3
Sex M:F	15:15	12:12	11:6	6:19
	24 Hour Urinary Excretion			
Na^+	140±10	124±8	167±33	147±19
	NS		NS	
K^+	55±4	36±3	58±5	45±8
	<.001		NS	
Creat.	1.4±0.1	1.3±0.1	1.5±0.2	1.5±0.3
	NS		NS	

Figure 12. Some characteristics of normotensive and hypertensive white and black subjects.

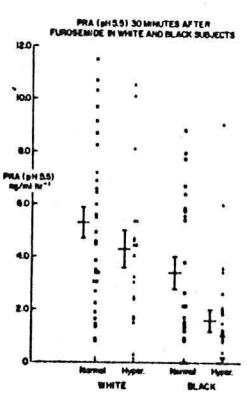
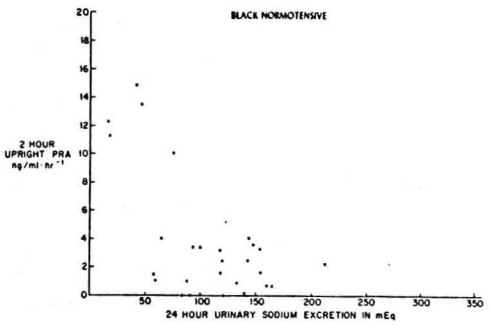
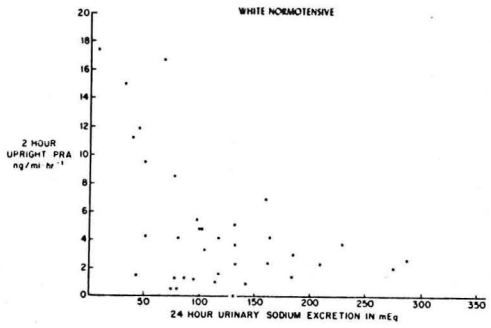


Figure 13. PRA (pH 5.5) 30 minutes after IV Furosemide in white and black subjects line and bars = mean ± SEM





Figures 14 & 15. PRA (pH 5.5) is plotted as a function of 24 hr. urinary sodium excretion.

will have values overlapping with the hypertensive patients. It is apparent that if PRA in black hypertensives is compared to that in white normotensives, the incidence of low-renin will be much higher than when comparing them with black normotensives. The question must be asked as to whether the mechanism producing low-renin in normotensive black subjects the same as that in hypertensive blacks:

PROGNOSIS

I should like to turn briefly to the possibility of using PRA to establish prognosis for hypertensive patients. Most investigators agree that very high PRA's are found in patients with malignant hypertension and they have a poorer prognosis than patients with essential hypertension or normal PRA. Brunner et al (58) recently presented data suggesting that low-renin exerts a protective effect against strokes and myocardial infarctions. They divided their patients into 3 groups (high, normal and low) on the basis of renin responsiveness to 4 hours of upright posture and an unrestricted diet (Figure 16). They evaluated each patient retrospectively and prospectively for complications such as strokes or myocardial infarctions. Those patients with the lowest PRA had no significant complications. Although not stated

Renin Activity	Patients with Left Ventricular Enlargement	Patients with Strokes or Heart Attacks*		
		Total	Strokes	Heart Attacks
Low	12 (20%)	0	0	0
Normal	18 (15%)	14 (11%)	8 (6%)	6 (5%)
High	8 (22%)	5 (14%)	4 (11%)	2 (6%)
Totals	38 (17%)	19 (9%)	12 (5%)	8 (4%)

*One patient in group with high renin activity had both stroke & heart attack.

Figure 16. Cardiovascular complications in hypertensive patients divided on the basis of upright PRA.

explicitly in the paper, an obvious question arises as to the importance of treating such patients.

The relatively benign course of some patients with low-renin and primary aldosteronism has been previously noted(59). Nevertheless, it has been our personal experience as well as others (60) to have seen several such patients with significant complications. There are a large number of such complications in the black hypertensive population where "low" PRA is common. We have therefore measured the renin-response to furosemide in black hypertensives with a history of a stroke or myocardial infarction 3 or more months previously. If low-renin should exert a protective effect against such complications, we would expect to find fewer low-renin hypertensives in this group and therefore a higher mean PRA value than in non-complicated black hypertensives. As seen in figure 17, this is not so. The distribution of PRA in the group with complications is identical to that of the black hypertensives, lower than the black normotensives, and both white groups. We have extended this study to include diabetic hypertensives with strokes and found a similar distribution with low PRA values.

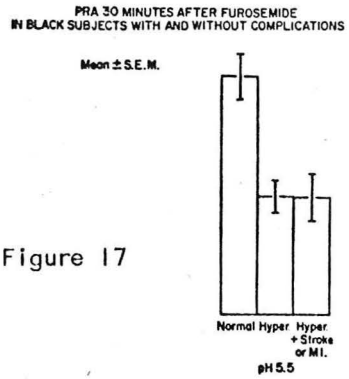


Figure 17

Our study is retrospective and relatively small. Nevertheless, it fails to substantiate the benign nature of hypertension in patients with low-renin and raises considerable question in our minds about using low PRA as an indication of a favorable prognosis. We feel that low-renin hypertensive patients should be actively treated to lower their blood pressure.

DIAGNOSIS

We have tried to formulate a simple and direct approach to evaluating patients for abnormalities in renin production. For the new patient off of medication we have used the response of PRA 30 minutes after intravenous administration of 40 mg of furosemide and upright posture. As you recall from figure 13, this test appears most effective in white patients. The frequency of "low-renin" occurring in the black normotensive subjects after either upright posture or after furosemide makes us skeptical about transferring data from white patients to black hypertensives. It is possible that more aggressive furosemide therapy (42) or a low sodium diet (43) in the black patients prior to obtaining the PRA might separate potential responders and non-responders to aldactone therapy.

I have included our protocol and data sheet in the appendix. These data are derived from incubation of plasma at pH 5.5 in order to maximally generate A-I for radioimmunoassay. Most laboratories using commercial kits incubate the plasma at pH 7.4 rather than 5.5 and therefore report lower values. I cannot over-emphasize the importance of having each laboratory determine their own normal values. There is no standardization for such assays and even slight modifications in each laboratory produce different results for the same plasma. To illustrate this, we recently sent 4 plasma pools to 2 other laboratories where renin research is actively pursued and each has published their laboratory technique.

TABLE 2

Spec.	Our Lab pH 5.5	Lab X pH 5.5	Lab Y pH 5.5
#. 1	0.42 $ng/ml \cdot hr^{-1}$	<0.16 $ng/ml \cdot hr^{-1}$	0.46 $ng/ml \cdot hr^{-1}$
# 2	2.1 ± 0.1	1.2	4.56
# 3	4.3 ± 0.3 0.85 (pH 7.4)	2.06	6.02
# 4	5.6 ± 0.5	4.2	5.96

It is impossible to say whose values are "correct" - but it is apparent that values vary by as much as 4 fold.

Although no firm conclusion as to what constitutes low-renin in blacks can be made at the present time, one can use this technique to screen for elevated renins associated with accelerated or renovascular hypertension. If a low PRA is obtained, the patient can then be placed on a 200 mEq + Na diet for 5 days and plasma K^+ determined to screen for overt primary aldosteronism. This screening method has worked well in 3 studies where 95% or more of patients with biochemically documented hyper -aldosteronism developed hypokalemia after such a diet (5,61,62). Normal ranges for plasma and serum K^+ must be available to correctly interpret these data. Using plasma and autoanalyzer, the lower limits for normal in the Parkland lab are 3.0 mEq/L and for medical students 3.2 mEq/L. (63). If electrolytes are performed separately, values below 3.4,or a drop of greater than 0.5 mEq/L after salt loading should be considered suspicious. Since hemolysis may markedly affect the K^+ concentration, 2 or more specimens may be obtained on suspicious cases. If hypokalemia occurs and low-renin has been documented, the patient most likely has hypermineralocorticoidism. This can be confirmed by performing the saline infusion study discussed earlier in this presentation and given in detail in the appendix. An alternative method is to collect a 24 hour urine after sodium loading and administration of large doses of Florinef 1.2 mg/d for 3 days (64). This suppresses aldosterone excretion below 5 µg/24 hrs.

in normal subjects. Both plasma and urine aldosterone assays are available in some commercial labs. We can perform a limited number of assays on patients likely to have 1° aldosteronism on the basis of documented low PRA and hypokalemia off of medications.

These tests can be easily performed on outpatients. We feel it is essential that patients be off of diuretics and aldomet, and preferably all other medications for at least 2 weeks prior to testing. The effects of estrogen containing medications on PRA my persist for six months. Hypokalemia is extremely common with thiazide administration and often not improved with K^+ supplements. We have seen mild hypokalemia persisting for several weeks after stopping thiazides and administering KCL. These patients have not had evidence for hyperaldosteronism and eventually replete their potassium stores. This inability to retain K^+ may be due to renal tubular damage induced by hypokalemia or from 2° aldosteronism due to long-term sodium depletion. This persistent depletion of body potassium might lower aldosterone concentrations (64) and increase renin (65) but does not appear to interfere with normal PA suppression. We routinely test patients after being off of medications for two weeks. While all should be concerned with the effect of withdrawing medications, it has been our experience that patients without a history of accelerated or malignant hypertension rarely develop trouble within a two week period off of medications.

THERAPY

"Specific therapy" of low-renin hypertension was first suggested by Woods et al (26) who used aminoglutethimide to inhibit adrenal steroid production. This is experimental and difficult therapy which cannot be recommended except as a research tool. High dose spironolactone therapy has improved or cured approximately 80% of the patients. The lesser response in the studies by Laragh and Adlin may be attributable to their using doses of 200 mg/d rather than 400/d. Variable results are reported when the lower dosage is employed. Spark et al (41) reported very little improvement using 100-200 mg/d while Carey et al (42) reported a significant number were improved with the lower dosage (Figure 10) and only a few patients required the larger dosage. Vaughan et al (44) reported a similar blood pressure response to spironolactone therapy in patients with normal-renin. They suggested that it works primarily as a diuretic in both groups.

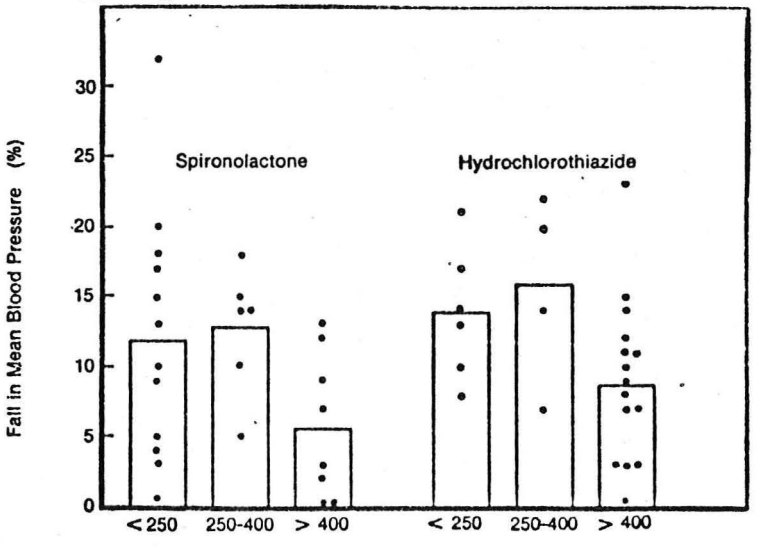
The high dosage of spironolactone necessary to control blood pressure in some patients has been associated with a significant incidence of GI intolerance, gyecomastia and occasional impotence in the male, and menstrual abnormalities in the female. One study reported some type of side effect in approximately 50% of patients (5)(Table 3) while others have an incidence of approximately 10% (42,43). The effect of long term therapy at this dosage level in humans is not completely known. These side effects and the cost of the medication have placed a premium on minimizing dosage.

TABLE 3

Side effects of spironolactone administration

	Hyporesponsive PRA (Group II)	*Normal PRA (Group III)*	*Elevated PRA (Group IV)*
Total number of patients	43	24	13
Generalized weakness			
Mild	17	0	2
Moderate	8	1	1
Severe	3	0	2
Mental cloudiness, nervousness or depression	4	1	1
Paresthesias	3	0	0
Muscle cramps	2	1	1
Headaches	2	0	0
Nausea			
Mild	4	0	0
Severe	10	0	2
Vomiting	5	0	0
Maculopapular skin rash	5	4	1
Dizziness with postural hypotension			
Mild	2	0	0
Severe	6	1	0
Chest pain (anginal type)	2	1	0
Hyponatremia (below 130)	1	0	1
Hyperkalemia (above 5.4)	4	1	2
% of patients without side effects	42%	67%	46%

It has been demonstrated that these patients (42,43) as well as those with primary aldosteronism will have marked improvement with intensive diuretic therapy (Figure 18). This can usually be managed in the



-Percent fall in mean blood pressure in response to treatment with spironolactone and hydrochlorothiazide in patients with varying levels of plasma renin activity.

Figure 18 (Ref. 43)

normokalemic low-renin patients by administering 50 mg of hydrochlorothiazide twice a day and adding spironolactone or triamterene to maintain body potassium. Because of its anti-mineralocorticoid effect, spironolactone would be my first choice of the latter two drugs. Larger doses of spironolactone are necessary for 1° aldosteronism because hypokalemia is exacerbated by increased distal tubular Na^+ when using a thiazide. Nevertheless, careful manipulation of this combination of drugs should provide satisfactory blood pressure control in most low-renin patients, without the need for autonomic blocking drugs that are associated with side effects such as postural hypertension and drowsiness. If the therapy is not adequate, greater volume depletion should be attempted prior to using more potent drugs.

I would like to conclude by saying that: 1) there are currently data for and against the possibility that patients with low hypertension have mineralocorticoid excess, 2) further evaluation of this group of patients is necessary in order to define whether renin is suppressed by long-term volume overload or primarily suppressed by an intrinsic renal abnormality, 3) it is likely that there are several different causes for what we now call low-renin hypertension, 4) low-renin must be defined in the black subject before conclusions reached in studies of predominantly white groups can be applied to the black population, 5) renin samples should be obtained under carefully specified conditions and compared with their appropriate control populations in order for the data to be of value, 6) it is too early to reach any conclusion concerning a more favorable prognosis for patients with low-renin hypertension. We strongly feel that therapy should be made available to those patients as it is to others, 7) therapy should primarily be directed to volume depletion with control of hypokalemia by a combination of medications active at the loop of Henley and distal tubule. The addition of autonomic blocking agents such as α methydopa, reserpine & guanethidine can then be reserved for those refractory to volume depletion alone.

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PROTOCOL

Recumbency-saline Infusion Suppression Test
(Arch. Int. Med. 128:380, Sept. 1971)

Preparation of patient

The patient should be eating a diet unrestricted in sodium. All estrogen containing medications are discontinued one month or longer prior to the test. Spironolactone (aldactone A or aldactazide) and other diuretics should not be taken in the preceeding week and preferably for two weeks prior to the study.

Day prior to test

1) A twenty four hour urinary collection is started at 8:00 A.M. in the morning in order to determine sodium, potassium, and creatinine excretion.
2) The patient retires before 11:00 P.M. at night and remains recumbent throughout the night.

Day of test

1) The patient arises at 6:00 A.M. and remains upright until 8:00 A.M. The patient may walk or stand, and it is permissible to lean on something for support if necessary. If the patient is physically unable to stand or lean on support for this period, sitting with the legs dependent is a less desirable alternative.
2) The patient should not have breakfast since CHO ingestion might influence the plasma aldosterone concentration. Some water is permissible but coffee or tea should not be ingested.
3) If the test is being performed on an outpatient, the subject should stand 30 minutes after arriving at the laboratory before beginning the study.
4) The patient should finish collecting the twenty four hour urine specimen at 8:00 A.M.
5) At 8:00 A.M., upright specimens are obtained:
   a) The patient may sit or the specimen is drawn immediately after lying down.
   b) (Plasma aldosterone, K^+ and Na^+): 12 ml in heparinized vacutainer (one large tube or two small ones).
   c) (Plasma renin activity): 4 ml in a powdered EDTA tube.

   The EDTA tube should be placed immediately in ice, separated under refrigerated conditions and stored frozen. There is less information available about care of the PA specimen. We find it most convenient to process it as we do the specimen for renin.
6) The patient then is recumbent for 4 hours and two liters of isotonic saline are given intravenously at 500 ml per hour during this time. The post infusion specimens are obtained for plasma aldosterone at the end of this infusion. Although they are of less diagnostic importance, we have collected a specimen for plasma renin activity at this time also to confirm expansion of the extra cellular volume and suppression of PRA.
7) The subject may need to void during the study. This should be accomplished with a urinal or bedpan while the patient remains recumbent.
8) In research oriented patients, we have collected the 4 hour urinary excretion for TV, Na^+, K^+ and creatinine.

This infusion should not be performed in patients with congestive heart failure or malignant hypertension. No ill effects of the infusions have been observed. The blood pressure might be taken occasionally prior to and during the infusion, but no substantial changes have been observed in over 60 studies.

DATA SHEET - PLASMA RENIN ACTIVITY (PRA)

Date of Study_____

Patient's Name
Hospital #
Physician Ordering Study

Age:
Sex: M F
Race: Black Chicano White

Dx. Circle Type Suspected: Essential 1° Aldosteronism Renovascular

Circle Current Medications & Date Stopped:
- Diuretics
- Estrogens (Premarin, etc.)
- Oral Contraceptives (BCP)
- Aldomet
- Ismelin

Circle Dietary Sodium Prior To Study: Regular No Added Salt Low

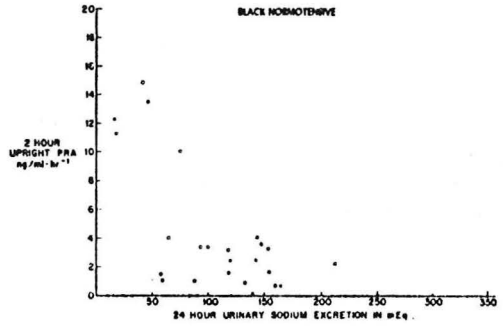
24 Hr. Urine Prior To Study: _____mEq/L _____mEq/L _____mg/100 ml _____ ml
(Send urine specimen to lab with renin samples.)

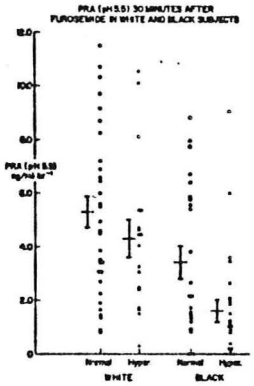
Circle Conditions For Study:

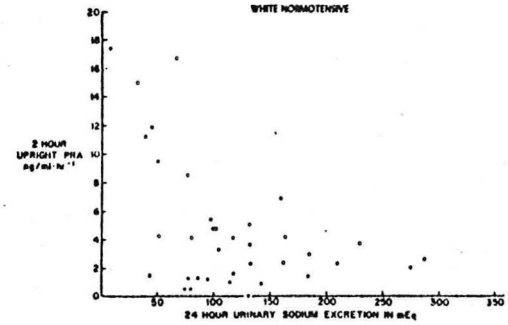
30 Min. Post Lasix
PRA Baseline_____ng/ml.hr-1
30 min $\bar{p}$ 40 mg Lasix_____ng/ml.hr-1

2 Hr Upright
_____ng/ml.hr-1

Renal Vein
L Basal_____ng/ml.hr-1
L $\bar{p}$ _____mg/ml.hr-1
R Basal_____ng/ml.hr-1
R $\bar{p}$ _____ng/ml.hr-1
IVC Basal_____ng/ml.hr-1
IVC $\bar{p}$ _____ng/ml.hr-1







Intepretation:

Signature_____

Date of Study _____

Data Sheet PA - Recumbency Saline Infusion Test
(Ref. Arch. Int. Med. 128:380, Sept. 1971)

Pts Name Hospital #
Age Wt Ht Sex: M F Race _____
Diagnosis (Circle)
Normal Other _____
Hypertension - Type suspected: Essential Primary Aldosteronism Renovascula
Current medications and date stopped:
Diuretics - thiazides Estrogens
Spironolactone (aldactone)
Hx of hypokalemia? on or off thiazides
Current or representative electrolytes Na^+ Cl
K^+ HCO_3
Urinalysis Protein or casts?
IVP results if available
Renogram results if available

	24 hr urine	4 hr urine during inf. (optional)
TV	ml/24 hr	ml/4 hr
Na	meq/24 hr	meq/4 hr
K	meq/24 hr	meq/4 hr
Creatinine	mgm/24 hr	mgm/4 hr

	PA	PRA	K^+	Na^+
2 hr upright	_____	_____	_____	_____
4 hr recumbent plus saline	_____	_____	_____	_____

$$\% \text{ of Baseline} = \frac{\text{4 hr recumbent PA}}{\text{2 hr upright PA}} \times 100\%$$