Hypertension | Clinical Studies

Further Evaluation of Saline Infusion for the Diagnosis of Primary Aldosteronism

O. Bryan Holland, Helle Brown, LaVon Kuhnert, Carol Fairchild, Martin Risk, and Celso E. Gomez-Sanchez

SUMMARY Normal subjects, normal-renin hypertensive patients, and low-renin hypertensive patients were evaluated by intravenous saline infusion and with a fludrocortisone acetate (Florinef) protocol to clarify diagnostic criteria for primary aldosteronism that are recommended for the saline infusion protocol. The patients consumed a 200 mEq sodium, 70 mEq potassium diet for 6 days, and on the last 3 days received Florinef 0.5 mg orally twice daily. On Days 3 and 6, urinary aldosterone and tetrahydroaldosterone excretions were determined, and on Days 4 and 7 plasma aldosterone (PA) was determined at 0600 after overnight recumbency and at 0800 after 2 hours of walking. Although the level of normal PA suppression by saline infusion has been commonly defined as 10 ng/dl, a value of 5 ng/dl was originally recommended. In 20 normal subjects and 45 normal-renin hypertensive patients, we found that the PA was almost always suppressed below 5 ng/dl. In 18 of 75 low-renin patients including five with aldosterone-producing adenoma (APA), the PA was never suppressed below 10 ng/dl; thus, these 18 patients had classical primary aldosteronism by generally accepted criteria. The Florinef protocol was performed in eight of these 18 patients and was abnormal in all. An abnormal Florinef protocol was also found in seven of 15 patients studied with PA suppression after saline infusion to between 5 and 10 ng/dl, but in only one of 24 patients studied with PA suppression below 5 ng/dl. Additional studies in the subgroup with abnormal results from the Florinef protocol indicated that none of these patients had evidence of APA, so they had nontumorous primary aldosteronism (NTPA). Thus, failure to suppress PA to less than 10 ng/dl with saline infusion is characteristic of patients with APA. However, the normal level should be lowered to 5 ng/dl when screening is done for NTPA. Additional studies such as Florinef suppression are necessary to gain confidence about the diagnosis of NTPA in those patients with PA suppression of between 5 and 10 ng/dl after saline infusion. (Hypertension 6: 717–723, 1984)

Key Words • aldosterone • adrenal gland • low-renin hypertension • zona glomerulosa hyperplasia

DIAGNOSTIC criteria for primary aldosteronism remain uncertain. Although patients with aldosterone-producing adenoma (APA) have autonomous aldosterone production in response to sodium loading, patients with bilateral zona glomerulosa hyperplasia (ZGHP) retain some feedback suppression of aldosterone production.[1-4] Determination of plasma aldosterone (PA) suppression with intravenous saline infusion has been widely used for the diagnosis of primary aldosteronism.[5-7] Originally, the normal level of PA suppression was stated[5] to be below 5 ng/dl, but later[6] this level was raised to as high as 10 ng/dl. To clarify the diagnostic criteria for mild primary aldosteronism, we undertook the following study which compares the saline infusion protocol with an additional sodium loading protocol.

From the Departments of Internal Medicine, University of Texas Medical Branch, Galveston, Texas; the University of Texas Health Science Center, Dallas; the University of South Florida College of Medicine, Tampa, Florida; and the James A. Haley Veterans Administration Hospital, Tampa, Florida.

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Address for reprints: O. Bryan Holland, M.D., Hypertension — 4.100 OJSH, E72, University of Texas Medical Branch, Galveston, Texas 77550.

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Methods

Patient Population

History, physical examination, blood chemistry analysis with an automated multiple analysis system (SMA-12 or SMA-24), urinalysis, urinary metanephrine, and rapid sequence intravenous pyelogram were done to rule out secondary forms of hypertension other

than possible primary aldosteronism. Patients with low- and normal-renin hypertension were initially identified by determination of plasma renin activity (PRA) during the intravenous furosemide test[8] or after 2 hours of ambulation, which produces about the same degree of renin stimulation.[9] Patients had been off antihypertensive medications for at least 3 weeks prior to these studies. An additional sodium depletion protocol[10] with 6 days of 10 mEq sodium diet was used to confirm the diagnosis in most of the low-renin patients. With this protocol, a decreased PRA response after sodium depletion plus 4 hours of walking was defined as a PRA less than 7.0 ng/ml/hr for white patients and 5.5 ng/ml/hr for black patients. Those subjects who had been classified as outpatients as having low-renin hypertension and who later exhibited a normal PRA in response to the low-sodium diet were reclassified as having normal-renin hypertension.

Saline Infusion Protocol

Usually, we evaluated PA suppression first by saline infusion. A 24-hour urine sample from normal subjects and hypertensive patients was refrigerated during the time of collection on the day before saline infusion. Urinary sodium, potassium, creatinine, aldosterone,[11] and tetrahydroaldosterone[12] values were determined. It has been determined[12] that, when normal subjects consume a usual diet, the normal excretion rates for urinary aldosterone and tetrahydroaldosterone are less than 17 and 60 μg/24 hr, respectively. At 0600 to 0700 on the day of the saline infusion, the patient walked or remained standing as much as possible. Shortly thereafter, the patient came to the General Clinical Research Center where, after 2 hours of walking, blood samples for PRA,[8] PA concentration,[13] and blood chemistry studies (SMA-12 or SMA-24) were collected. The person then remained supine for the next 4 hours during which time 2000 ml of normal saline was infused intravenously. Blood samples for PRA and PA were obtained at 30, 60, 120, and 240 minutes during the infusion. No significant changes have been noted in the sensitivity and precision of the PA radioimmunoassay (RIA)[13] and urinary tetrahydroaldosterone RIA[12] since their original description. The sensitivity is 4 pg for the PA RIA and 6 pg for the tetrahydroaldosterone RIA. Over the last 7 years, the urinary aldosterone assay has had an interassay variation of about 8% and an interassay variation of about 15%, which is about the same as the assays for PA and urinary tetrahydroaldosterone.

Florinef Suppression Protocol

Normal subjects and hypertensive patients who agreed to participate in the additional protocol of aldosterone suppression were admitted to the General Clinical Research Center. They were given a 200 mEq sodium, 70 mEq potassium metabolic diet for 6 days with 3000 ml of fluids per day. On the last 3 days, fludrocortisone acetate (Florinef) was administered by mouth at a dose of 0.5 mg twice daily. Aldosterone, tetrahydroaldosterone, sodium, potassium, and creatinine levels were determined in 24 hour refrigerated urine samples from Days 3 and 6. On those nights, the patients retired to bed at 2230 to 2300 and remained at absolute bed rest from at least 0200 until 0600 the following morning, when blood was drawn. The fasting patient then walked from 0600 to 0800, and blood was again taken for determination of PA, PRA, and plasma cortisol.[14]

All patients gave written informed consent to participate in these studies after explanation of the study in lay language. Study protocols were approved by the Human Research Review Committees of the University of Texas Health Science Center at Dallas and the University of Texas Medical Branch at Galveston. Statistical evaluation was performed with Student's *t* test.[15]

Results

Seventy-five patients with low-renin hypertension and 45 patients with normal-renin hypertension were studied with the saline infusion protocol. Saline infusion suppressed PA to 2.8 ± 1.6 ng/dl (mean ± SD) or to less than 6 ng/dl (mean + 2 SD) in 19 of 20 normal subjects and to less than 5 ng/dl in 18 (Table 1). All but five of the 45 normal-renin patients had a PA suppression below 5 ng/dl with saline infusion, and these five patients had a PA suppression to between 5 and 6 ng/dl. Definite suppression of PA began within the first 30 minutes of saline infusion in all patients except those with an aldosterone-producing adenoma (APA). Normal subjects and normal-renin hypertensive patients also had a definite fall in PRA, whereas low-renin patients had only a slight change in PRA during the first 30 minutes of saline infusion.

Normal results with the Florinef protocol were established by study of 21 age-matched normal subjects. This included a subgroup of 12 of the 20 normal subjects that participated in the saline infusion protocol. At the end of the baseline phase of the Florinef protocol in these normal subjects, 0600 supine PA was less than 13 ng/dl (mean + 2 SD), and PA after 2 hours of ambulation was less than 32 ng/dl. Normal urinary aldosterone excretion was less than 17 μg/24 hr, and normal urinary tetrahydroaldosterone excretion was less than 60 μg/24 hr. Normal PA suppression (mean + 2 SD) at the end of this protocol was found to be less than 6 ng/dl for 0600 PA and less than 11 ng/dl for 0800 PA after 2 hours of ambulation; the 24-hour urinary aldosterone was less than 6 μg and the 24-hour urinary tetrahydroaldosterone less than 32 μg, respectively. The Florinef protocol was considered to have produced abnormal results if it failed to suppress normally supine or ambulatory PA, urinary aldosterone, and urinary tetrahydroaldosterone, or if all three of these determinations were elevated in the baseline phase. When these criteria were used, no normal subjects or normal-renin patients had abnormal testing with the Florinef protocol.

Eighteen low-renin patients had primary aldosteronism by generally accepted criteria,[6] since they had hypokalemia and failure to suppress PA to less than 10

TABLE 1. *Suppression of Plasma Aldosterone and Plasma Renin Activity (PRA) with Saline Infusion in Normal Subjects and Hypertensive Patients*

Subjects	No.	Age (yrs)	Plasma potassium (mEq/liter)	Minutes of saline infusion 0	30	60	120	240
Normal	20	39±3	4.2±0.1					
PA (ng/dl)				15.5±2.3	8.8±1.1	6.2±0.8	4.1±0.5	2.8±0.4
PRA (ng/ml/hr)				2.8±0.6	1.6±0.4	1.2±0.3	0.8±0.2	0.4±0.1
Low-renin hypertension	57	49±1	3.8±0.1					
PA (ng/dl)				16.0±1.5	10.3±1.0	7.4±0.6	5.9±0.6	4.4±0 4
PRA (ng/ml/hr)				0.4±0.1	0.3±0.1	0.2±0.1	0.2±0.1	0.1±0.1
Normal-renin hypertension	45	46±2	4 1±0.1					
PA (ng/dl)				20.2±2.5	11.4±1.5	8.5±1.0	5.4±0.6	3.1±0.3
PRA (ng/ml/hr)				2.3±0.4	2.1±0.6	1.3±0.2	0.9±0.1	0.6±0.1
Classical primary aldosteronism								
Hyperplasia	13	47±4	2.9±0.1					
PA (ng/dl)				45.7±4.7	31.8±10.3	17.9±2.8	18.2±3.9	22.8±3.6
PRA (ng/ml/hr)				0.4±0.1	0.2±0.1	0.2±0.1	0.2±0.1	0.2±0.1
Adenoma	5	38±5	2.9±0.1					
PA (ng/dl)				49.2±16.5	34.7±10.8	31.3±10.4	34.9±8 3	34.2±6.6
PRA (ng/ml/hr)				0.4±0.1	0.2±0.1	0.1±0.1	0.1±0.1	0.1±0.1

Data are expressed as means ± SE. PA = plasma aldosterone; PRA = plasma renin activity.

ng/dl after saline infusion (Table 1). The Florinef protocol produced abnormal results in all eight of these patients in whom it was performed. Thirty-nine of the remaining 57 low-renin patients with PA suppression after saline infusion to less than 10 ng/dl underwent the Florinef suppression protocol. This group included 15 of 20 patients with PA suppression to 5 to 10 ng/dl with saline infusion and 24 of 37 patients with PA suppression to less than 5 ng/dl. Seven of the 15 patients with PA suppression to between 5 and 10 ng/dl had abnormal results from the Florinef protocol (Table 2).

In contrast, only one of 24 patients with PA suppression to less than 5 ng/dl had an abnormal Florinef protocol. This latter patient had elevated excretion levels of PA, urinary aldosterone, and urinary tetrahydroaldosterone in the baseline phase of the Florinef protocol (Table 2, Patient 8). Thus, no patients with an abnormal Florinef protocol would have been missed if urinary aldosterone and tetrahydroaldosterone and plasma potassium had been evaluated at the time of saline infusion and if the normal level of PA suppression was determined as less than 5 ng/dl. All of these eight patients with abnormal results from the Florinef protocol had elevated 0600 supine PA at the end of the baseline phase of the Florinef protocol, whereas only three had elevated ambulatory PA, three had elevated urinary aldosterone excretion, and six had elevated urinary tetrahydroaldosterone excretion at that time.

TABLE 2. *Plasma Aldosterone and Urinary Aldosterone and Tetrahydroaldosterone Results in Patients with Plasma Aldosterone Suppression to Less Than 10 ng/dl With Saline Infusion But With an Abnormal Florinef Protocol*

	Saline infusion		200 mEq sodium diet				200 mEq sodium diet and Florinef			
	Plasma		Plasma aldosterone		Urinary		Plasma aldosterone		Urinary	
Patient no.	K (mEq/liter)	Aldo (ng/dl)	Supine (ng/dl)	Ambulatory (ng/dl)	Aldo (μg/24 hr)	THAldo (μg/24 hr)	Supine (ng/dl)	Walking (ng/dl)	Aldo (μg/24 hr)	THAldo (μg/24 hr)
1	3.5	6.8	14.4	14.3	7.4	105	13.1	13.0	6.0	34
2	2.7	8.2	15.8	18.9	8.7	135	14.4	22.0	10.3	82
3	3.5	8.0	34.3	60.0	20.0	129	11.7	30.1	9.2	82
4	3.7	8.3	19.2	55.4	16.2	56	15.0	24.3	16.2	52
5	4.1	7.9	28.4	41.1	11.2	27	5.6	23.6	7.5	48
6	3.6	9.3	15.4	19.4	15.8	79	7.1	13.8	11.0	81
7	3.5	7.3	13.0	20.7	17.8	78	9.1	14.3	9.1	64
8	3.6	1.8	14.9	27.0	17.1	69	3.4	10.2	5.3	69

Aldo = aldosterone; THAldo = tetrahydroaldosterone.

TABLE 3. *Changes in Urinary Aldosterone, Tetrahydroaldosterone, and Sodium, Body Weight, and Plasma Potassium with Sodium Loading*

			200 mEq sodium diet					200 mEq sodium diet and Florinef				
Subjects	No.	Age (yrs)	Aldo (μg/24 hr)	THAldo (μg/24 hr)	Sodium (mEq/24 hr)	Weight (kg)	Plasma K^+ (mEq/liter)	Aldo (μg/24 hr)	THAldo (μg/24 hr)	Sodium (mEq/24 hr)	Weight (kg)	Plasma K^+ (mEq/liter)
Normal	21	48 ±2	7.1 ±0.9	25.2 ±2.8	167 ±6	71 2 ±3.4	4.2 ±0.1	3.0 ±0.4	15.8 ±1.8	98 ±9	72.4 ±3.3	3.7 ±0.1
Low-renin												
Abnormal Aldo suppression	8	48 ±4	14.3 ±1.6	84.7 ±12.9	177 ±18	93.5 ±7.5	3.5 ±0.2	9.3 ±1.2	64.1 ±6.4	161 ±9	92.9 ±7.6	3.2 ±0.1
Normal Aldo suppression	31	51 ±2	6.9 ±0.7	34.8 ±2.6	164 ±9	70.3 ±2.3	4.0 ±0.1	3.7 ±0.5	23.5 ±2.0	136 ±7	70.6 ±2.3	3.5 ±0.1
Normal-renin	27	48 ±2	6.9 ±0.7	30.4 ±2.7	175 ±10	76.1 ±2.9	4.1 ±0.1	2.8 ±0.3	15.4 ±1.6	125 ±8	76.7 ±2.9	3.6 ±0.1
Classical primary aldosteronism												
Hyperplasia	5	49 ±7	23.4 ±6.6	109 ±30	172 ±38	99.2 ±5.1	3.4 ±0.2	14.7 ±6.4	85 ±14	135 ±3	98.6 ±5.1	2.8 ±0.1
Adenoma	3	34 ±5	31.4 ±14	153 ±49	179 ±8	57.6 ±2.0	3.0 ±0.4	22.9 ±5.8	183 ±88	183 ±28	57.2 ±2.3	2.5 ±0.2

Data are expressed as means ± SE. Aldo = aldosterone; THAldo = tetrahydroaldosterone; PA = plasma aldosterone.

Creatinine clearance averaged 95.0 ± 10.9 ml/min (mean ± SE) in normal-renin hypertensives; it was somewhat higher (105.6 ± 6.7 ml/min) in the subgroup of eight low-renin patients with abnormal results from the Florinef protocol than in the subgroup with normal aldosterone suppression (86.0 ± 5.2 ml/min). This points to the possibility that subtle renal dysfunction with sodium retention may have led to the low-renin state in many of these latter patients.

In comparison to hypertensive patients, normal subjects had a greater weight gain by the end of the Florinef protocol, but they still had not come as close to restoring 24-hour urinary sodium to the baseline level and thus to achieving mineralocorticoid escape (Table 3). Plasma potassium was lower in patients with classical primary aldosteronism and in the subgroup of eight low-renin patients with abnormal Florinef results than in normal subjects. Furthermore, plasma potassium fell to a lower level in these two groups compared to normal subjects with Florinef administration (Table 3).

Plasma cortisol remained essentially unchanged or fell slightly from 0600 (supine) to 0800 (ambulation) in normal subjects and in all hypertensive subgroups (Table 4). Plasma cortisol levels at 0600 were slightly higher in patients with classical primary aldosteronism due to bilateral ZGHP than in normal subjects, although this difference was significant ($p < 0.05$) only at the end of the Florinef protocol (Table 4). These differences probably reflect the small sample size of

TABLE 4. *Changes in Plasma Renin Activity (PRA), Cortisol, and Plasma Aldosterone (PA) with Sodium Loading*

	200 mEq sodium diet						200 mEq sodium diet and Florinef					
	PRA (ng/ml/hr)		Aldosterone (ng/dl)		Cortisol (μg/dl)		PRA (ng/ml/hr)		Aldosterone (ng/dl)		Cortisol (μg/dl)	
Subjects	Supine	Walking	Supine	Walking	Supine	Walking	Supine	Walking	Supine	Walking	Supine	Walking
Normal	0.8 ±0.2	3.3 ±0.6	6.1 ±0.7	14.3 ±2.3	10.3 ±0.8	10.2 ±0.5	0.1 ±0.1	0.4 ±0.1	2.8 ±0.3	4.5 ±0.9	8.2 ±0.8	9.7 ±0.6
Low-renin												
Abnormal Aldo suppression	0.2 ±0.1	0.3 ±0.1	18.7 ±2.5	31.8 ±5.6	12.8 ±1.4	12.3 ±1.8	0.1 ±0.1	0.2 ±0.1	9.5 ±1.4	17.7 ±2.5	12.7 ±3.2	11.4 ±2.2
Normal Aldo suppression	0.2 ±0.02	0.4 ±0.1	10.2 ±0.8	18.6 ±1.5	10.7 ±0.7	10.9 ±0 7	0.1 ±0.1	0.2 ±0.1	4.2 ±0.5	9.3 ±1.2	9.0 ±0.6	9.7 ±0.6
Normal-renin	0.7 ±0.1	2.0 ±0.3	8.5 ±0.7	21.4 ±2.5	9.6 ±0.6	10.2 ±0 8	0.2 ±0.1	0.5 ±0.1	3.3 ±0.5	8.0 ±1.6	9.0 ±0.6	9.4 ±0.6
Classical primary aldosteronism												
Hyperplasia	0.1 ±0	0.1 ±0.1	30.6 ±6.6	54 ±11	12.2 ±3.7	8.4 ±1.2	0.1 ±0	0.1 ±0.1	24 ±5 8	37 ±8.8	14.7 ±3.1	8.8 ±0.5
Adenoma	0.1 ±0	0.1 ±0	72 ±15	70 ±18	10.6 ±2.4	9.7 ±2.0	0.1 ±0	0.1 ±0	76 ±34	69 ±11	8.8 ±3.7	6.9 ±0.7

Data are expressed as means ± SE.

the ZGHP group (five patients). During the 2 hours of ambulation in the baseline phase of the Florinef protocol, there was an increase in PA in normal subjects, normal-renin hypertensive patients, and low-renin hypertensive patients, except for two of three patients with APA who showed a fall in PA during this time (Table 4). All but one of the eight low-renin patients with abnormal Florinef suppression increased PA with ambulation (Table 2, Patient 1).

Discussion

Classical primary aldosteronism with definite hypokalemia and elevated urinary aldosterone excretion is generally considered to occur in less than 1% of hypertensive patients.[16] However, these estimates have been derived with diagnostic criteria that have led to a predominance of patients with APA instead of ZGHP. Aldosterone secretion in patients with APA appears to be relatively autonomous in response to sodium loading since adrenocorticotrophic hormone (ACTH) commonly regulates acute changes.[17] In contrast, patients with ZGHP have intact, though abnormal, feedback regulation of aldosterone secretion in response to sodium loading.[1-4] Although part of this feedback is mediated by changes in circulating angiotensin II, there is evidence that other sodium-sensing mechanisms are important.[18] As a consequence of this intact feedback regulation, these patients tend to have decreased aldosterone secretion as they become progressively sodium loaded, so random aldosterone determinations based on the usual normal ranges may not identify these patients correctly. In our study, a steady-state increase in total body sodium during the Florinef protocol was suggested by the lack of weight gain and earlier achievement of mineralocorticoid escape in patients with primary aldosteronism in comparison to normal subjects and normal-renin hypertensives. Patients with NTPA were also noted to have a rapid fall in PA levels with saline infusion. Thus, sensitive diagnostic methodology for ZGHP should provide for quantification of aldosterone after sodium loading. Until diagnostic methodology for ZGHP is clarified, it will be difficult to evaluate the postulate that low-renin "essential" hypertension is a subtle form of primary aldosteronism.[19]

Determination of PA concentration during the saline infusion test is utilized widely for the diagnosis of primary aldosteronism.[5-7] However, the normal level of suppression has been reported to be from 5 ng/dl[5] to 10 ng/dl.[6] Undoubtedly, some of this ambiguity about the normal level of suppression results from slight differences in PA RIA techniques. As noted by previous investigators,[6, 7] we found that patients with APA invariably failed to suppress PA to less than 10 ng/dl with saline infusion. However, the appropriate level of suppression to use for the diagnosis of ZGHP is less clear. Unlike the case with APA, surgical correction of the disease cannot be used to confirm the diagnosis. Thus, definition of abnormal PA suppression must be derived through the study of the response of normal subjects and patients with normal-renin essential hypertension. We would presume that the Florinef suppression protocol would be more accurate for the diagnosis of ZGHP than the saline infusion protocol since it provides more complete evaluation of both basal aldosterone production and its response to sodium loading through three determinations (PA, urinary aldosterone, urinary tetrahydroaldosterone) instead of just PA determination alone with the saline infusion protocol. All low-renin patients who failed to suppress PA below 10 ng/dl with saline infusion also had abnormal Florinef suppression.

However, we noted a certain lack of correlation of the results from saline infusion and Florinef suppression in those patients with PA suppression below 10 ng/dl with saline infusion. Seven of 15 low-renin patients with PA suppression with saline infusion to between 5 and 10 ng/dl had abnormal Florinef suppression. In contrast, only one of 24 patients with PA suppression with saline infusion to less than 5 ng/dl had abnormal Florinef suppression. Thus, when normal PA suppression with the saline infusion protocol was set at 10 ng/dl, some patients with primary aldosteronism appeared to be missed.

Those seven patients who after saline infusion had PA suppression to between 5 and 10 ng/dl and who also had an abnormal Florinef suppression provided excellent evidence for primary aldosteronism. In the baseline phase of the Florinef protocol, five of these patients had elevated urinary aldosterone or tetrahydroaldosterone excretion, and all had elevated 0600 supine PA levels (Table 2). Thus, the normal level of PA suppression with saline infusion would need to be set at 5 ng/dl to avoid an appreciable rate of false-negative testing for primary aldosteronism. However, when normal suppression was set at this level, we noted that eight of 15 patients had a normal Florinef protocol. Therefore, additional testing appears indicated in those patients with PA suppression to between 5 and 10 ng/dl with saline infusion, to obtain better evidence for a diagnosis of primary aldosteronism.

It should also be noted that occasional patients with primary aldosteronism may have PA suppression below 5 ng/dl. This has been reported by others,[7] and we found one such patient. Our patient had elevated PA and urinary aldosterone and tetrahydroaldosterone in the baseline phase of the Florinef protocol, but had normal suppression of all three of these values with Florinef. Thus, determination of urinary aldosterone and/or tetrahydroaldosterone on the day before saline infusion is desirable to provide greater sensitivity in screening for primary aldosteronism.

A more difficult question concerns those patients with abnormal suppression of PA, urinary aldosterone, or urinary tetrahydroaldosterone at the end of the Florinef protocol but with normal urinary aldosterone and tetrahydroaldosterone excretion in the baseline phase. Abnormalities in aldosterone suppression during sodium loading have been noted previously in a significant percentage of hypertensive patients,[20-22] but the percentage of these patients who might have had subtle primary aldosteronism was not determined. We identi-

fied seven patients who failed to suppress two of the three aldosterone determinations but who had normal basal urinary aldosterone and tetrahydroaldosterone excretion. Six of these seven patients had borderline abnormal or elevated PA levels in the baseline phase of the Florinef protocol. Thus, many of these patients may have exceedingly mild primary aldosteronism. Plasma potassium determinations were also somewhat suggestive that these patients had subtle primary aldosteronism in that most of these patients had borderline hypokalemia. In addition, some of these patients demonstrated an enhanced aldosterone response to ACTH,[23] which is generally a characteristic of patients with classical primary aldosteronism but not of patients with low-renin hypertension.[17] But, although there are some suggestions that these patients with abnormal suppression of one or more aldosterone determinations with Florinef have primary aldosteronism, we cannot rule out the possibility that an abnormality in suppression may not reflect enhanced aldosterone secretion. Thus, additional studies of the aldosterone secretory rate and 24-hour integrated PA will be needed to clarify this question.

All of our five patients with APA failed to suppress PA below 10 ng/dl with saline infusion and had marked abnormalities in aldosterone suppression with the Florinef protocol. None of the patients with PA suppression below 10 ng/dl and abnormal Florinef suppression appeared to have APA. This was established by additional studies in these patients incuding adrenal venography, bilateral adrenal vein sampling with PA determination, adrenal scanning during dexamethasone suppression with NP-59,[24] and adrenal CT scanning. Thus, these patients had presumed NTPA. Most of these patients had been documented in previous reports to have bilateral ZGHP. However, we did not perform adrenal biopsy to confirm the diagnosis since this is no longer clinically indicated. We cannot rule out the possibility that some of these patients had small unilateral or bilateral APA.

Other protocols of sodium loading for the diagnosis of primary aldosteronism have included the use of a high sodium diet by itself[3, 20–22] or the administration of exogenous mineralocorticoids such as deoxycorticosterone[1, 2, 7] or fludrodhydrocortisone.[25–28] A regular sodium diet was utilized in all but two[7, 28] of these latter protocols involving mineralocorticoid administration. Although all of these sodium loading studies have proved useful for the diagnosis of primary aldosteronism, the small number of their normal subjects and their way of determining aldosterone suppression to establish the normal response have been considerably more limited than in our study. These factors would tend to decrease the confidence with which a diagnosis of primary aldosteronism could be made.

In one study,[28] determination of PA changes with ambulation after sodium loading with Florinef was said to provide totally accurate differentiation of APA from ZGHP. Although we performed ambulation at a slightly different time (0600–0800 vs 0800–1200), we noted that one of our three patients with APA evaluated with the Florinef protocol had a clear increase in PA with ambulation in both the basal and Florinef phases. Thus, the differentiation of APA from NTPA should be based on several methods.

The saline infusion protocol with 24-hour urinary aldosterone and tetrahydroaldosterone done, if possible, on the day before would appear better suited than the Florinef protocol for initial evaluation of patients with possible primary aldosteronism. Patients with APA should only rarely have a PA suppression below 10 ng/dl with saline infusion. In contrast, patients with NTPA may frequently have a PA suppression of 5 ng/dl. In those patients with PA suppression between 5 and 10 ng/dl, additional studies should be done to provide better evidence for a diagnosis of primary aldosteronism.

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