Diagnosis and Treatment of Primary Hyperaldosteronism

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■ *Objective:* To characterize the clinical and laboratory features of primary aldosteronism and to evaluate which diagnostic tests can discriminate surgically curable forms of this syndrome.

■ *Design:* Retrospective analysis of the following data from 82 patients with primary aldosteronism: blood pressure, serum electrolytes, urinary aldosterone and electrolytes, computed tomographic scans, plasma renin and aldosterone before and during upright posture, atrial natriuretic peptide, and adrenal vein aldosterone and cortisol. Clinical outcomes assessed after treatment included blood pressure, serum electrolytes, and plasma renin activity.

■ *Results:* Drug therapy was discontinued before diagnostic tests were done in 56 of 82 patients (34 with adenomas and 22 with hyperplasia). Compared with patients with hyperplasia, those with adenomas had higher systolic (184 mm Hg and 161 mm Hg, respectively; $P < 0.001$) and diastolic blood pressures (112 mm Hg and 105 mm Hg; $P = 0.03$), lower serum potassium levels (3.0 mmol/L and 3.5 mmol/L; $P < 0.001$), and higher serum CO_2 ($P = 0.001$), atrial natriuretic peptide ($P = 0.008$), and urinary 18-methyl oxygenated cortisol metabolite levels ($P = 0.02$). In patients with adenomas, aldosterone secretion lateralized to one adrenal gland and did not increase during the postural stimulation test; preoperative urinary aldosterone levels were correlated with diastolic pressures ($r = 0.58$; $P = 0.001$). Hypertension was "cured" postoperatively in approximately 35% of patients with adenomas and those with hyperplasia ($P > 0.2$) but was "improved" more frequently in those with adenomas ($P = 0.002$). Cured patients from both groups were younger than those not cured (mean ages, 43 years and 54 years, respectively; $P = 0.002$) and had lower preoperative mean plasma renin activity (0.17 ng/mL per hour and 0.50 ng/mL per hour; $P < 0.001$). All patients with adenomas in whom aldosterone secretion lateralized were either cured or improved.

■ *Conclusion:* Of the 51 patients with primary aldosteronism who had adrenalectomy (43 patients with adenomas and 8 with hyperplasia), those most likely to be cured were younger and had lower plasma renin activity. In patients with adenomas who were cured or improved, aldosterone secretion was more likely to lateralize. Tests that distinguished adenomas from adrenal hyperplasia included the postural stimulation test, urinary excretion rates of 18-oxocortisol and 18-hydroxycortisol, and adrenal vein sampling.

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Primary aldosteronism is characterized by hypertension, hypokalemia, and low plasma renin activity and is most commonly caused by an adrenal adenoma that produces aldosterone. The plasma aldosterone level of affected patients usually fails to increase when renin activity increases during either upright posture or infusion of angiotensin II; thus, aldosterone will be secreted independently from the renin–angiotensin system (1). A less common cause of this syndrome is idiopathic hyperaldosteronism, characterized by nonadenomatous hyperplasia and low plasma renin activity, in which the adrenal gland usually responds to angiotensin II. However, this syndrome has considerable phenotypic heterogeneity, with diagnostic variants differing from the more typical forms by their responsiveness to angiotensin. For example, a subset of adrenal hyperplasia mimics an aldosteronoma because it is associated with angiotensin-independent aldosterone overproduction and can be cured by unilateral adrenalectomy (2). Conversely, some adenomas respond to angiotensin; Tunny and colleagues (3) have correlated the magnitude of this aldosterone response with the proportion of glomerulosa cells present in the tumor. This biochemical diversity is also manifested by characteristic patterns of steroid metabolism. In adenomas, levels of C-18 methyl oxidation metabolites of cortisol (18-oxocortisol and 18-hydroxycortisol) exceed those in idiopathic hyperaldosteronism and were elevated in patients with hyperplasia who were cured by adrenalectomy (4, 5).

The presence of an adrenal adenoma that produces aldosterone is considered the major clinical characteristic distinguishing primary aldosteronism that is curable by surgery. Refinements of imaging techniques have facilitated the detection of subtle adrenal abnormalities early in the clinical course. Coordinated use of these diagnostic approaches should improve the ability to determine which patients are likely to be cured by adrenalectomy. However, several studies have shown that the chances for curing hypertension are less predictable than those for the related biochemical abnormalities. Accordingly, these studies showed that only 50% of patients with adenomas were normotensive 5 years after adrenalectomy and that older patients were more likely to require postoperative antihypertensive medications (6, 7).

The clinical and biochemical diversity of this syndrome has important implications regarding its pathophysiology and responsiveness to therapy. We sought to characterize patients with primary aldosteronism who are followed at The Cardiovascular Center at The New York Hospital–Cornell Medical Center to identify features that would predict favorable responses to treatment and to attempt to understand why adrenalectomy often fails to produce a sustained reduction in blood pressure.

Methods

Patients

A retrospective analysis of the medical records at The Cardiovascular Center of The New York Hospital–Cornell Medical Center indicated that 82 patients with primary aldosteronism were evaluated from 1976 to 1991. This diagnosis was established by the following criteria: 1) hypertension; 2) elevated rates of urinary aldosterone excretion as determined by an established nomogram that relates 24-hour urinary sodium excretion with urinary aldosterone and plasma renin activity (8); 3) low renin activity (in most patients); and 4) hypokalemia that was either spontaneous or diuretic-induced and associated with inappropriate renal potassium loss (>40 mmol/d).

Diagnoses

Adenomas (n = 52) were diagnosed when an adrenal tumor was observed by contrast-enhanced computed tomographic (CT) scan. When possible, this was corroborated by lateralization of adrenal aldosterone secretion by adrenal vein sampling or evidence of functional autonomy, defined by a failure of the plasma aldosterone level to increase when the patient was in upright posture. An adenoma was confirmed surgically in 47 patients. Five patients had radiographic and biochemical features that indicated adenoma, but they refused surgery and were treated medically.

Idiopathic hyperaldosteronism was diagnosed in 22 patients whose CT scans showed unilateral or bilateral adrenal hyperplasia without an adenoma. These patients were treated with antihypertensive medication. Eight additional patients with nonadenomatous hyperplasia had adrenalectomy because their preoperative evaluation suggested an adrenal adenoma; 3 of these 8 patients had adrenal sampling and lateralized aldosterone secretion.

Biochemical Studies

In 56 patients (34 with adenomas and 22 with hyperplasia), medications were withdrawn approximately 2 weeks (for spironolactone, at least 1 month) before hemodynamic, biochemical, and hormonal evaluation. Dietary intake of sodium and potassium was not controlled in most patients during their evaluation. Hormonal profiling was usually done when patients were hypokalemic, although some received potassium supplements. Demographic, blood pressure, and biochemical data from 26 patients (18 with adenomas and 8 with idiopathic aldosteronism) who did not discontinue drug therapy before treatment were excluded from the statistical analysis of pretreatment diagnostic features. Assays for plasma renin activity (9), urinary and plasma aldosterone (10, 11), cortisol (Coat-A-Count Cortisol, Diagnostic Products Corporation, Los Angeles, California; 12), and atrial natriuretic peptide levels (13) have been described previously. In our laboratory, a plasma renin activity of 0.15 ng/mL per hour is at the lower limit of detection.

We recently reported urinary excretion rates of 18-hydroxycortisol and 18-oxocortisol from 42 patients with primary aldosteronism (5). We evaluated the clinical characteristics of a subset of these patients (15 with adenomas and 9 with hyperplasia) and include here the levels of these cortisol metabolites.

A positive postural stimulation test result was defined by an ambulatory plasma aldosterone level that was either lower than the supine baseline level or that was increased less than 30% above that value (14). For this test, plasma samples for aldosterone, renin, and cortisol were obtained from supine patients at 0800 h before they arose from their overnight recumbency, and again after 2 hours of ambulation. We excluded data from analysis if plasma cortisol and aldosterone levels simultaneously increased (for cortisol levels, an increase >30% greater than supine levels) because an increase in cortisol levels after 0800 h indicates a stress adrenocorticotropin hormone response that can also increase aldosterone secretion.

We obtained adrenal vein aldosterone samples using percutaneous catheterization. Adrenal vein catheterization was considered successful when the plasma cortisol level from the adrenal vein was two times higher than the level from the inferior vena cava (15). The mean plasma cortisol level for the adrenal vein was more than 10 times higher than that from the inferior vena cava (256 μg/dL compared with 16 μg/dL [difference, −240 μg/dL; CI of the difference, −320 μg/dL to −160 μg/dL; $P <$ 0.001]). We defined lateralization of adrenal aldosterone secretion as a ratio of adrenal vein [aldosterone/cortisol levels]/inferior vena cava [aldosterone/cortisol levels] greater than 1.0 from the ipsilateral adrenal vein and 1.0 or less from the contralateral adrenal vein (16, 17).

Clinical Outcomes

We considered hypertension to be cured when blood pressure decreased to 140/90 mm Hg or less after adrenalectomy and if postoperative antihypertensive medication was not required, to be improved when systolic pressure decreased by at least 10 mm Hg and diastolic pressure decreased by more than 5 mm Hg after adrenalectomy or medication, or to be not improved when the preceding criteria were not met after treatment.

Statistical Analysis

We used unpaired t-tests to compare baseline blood pressure and hormonal values between groups and used paired t-tests to compare treatment-related changes in these variables within groups. We calculated 95% confidence intervals for the differences in sample means. Chi-square analysis was used to evaluate differences in the numbers of patients in the diagnostic groups for demographic, blood pressure, and laboratory characteristics.

Results

Patient Characteristics

Demographics

Of the 82 patients with primary aldosteronism, 52 had adenomas and 30 had hyperplasia. Patients with adenomas were younger (46 years compared with 54 years [difference, 8 years; CI, 6 years to 10 years]). The sex and race distributions were similar in both groups. The 56 patients (34 with adenomas and 22 with nonadenomatous hyperplasia) who were studied after therapy with antihypertensive medication was discontinued were representative of all 82 patients with primary aldosteronism.

Blood Pressure

Patients with adenomas had higher mean systolic and diastolic blood pressures (Table 1), although moderate to severe hypertension was common in both groups. After medical therapy was discontinued, systolic blood pressure was 175 mm Hg or greater in 66% of patients with adenomas but only in 15% of patients with hyperplasia ($P < 0.001$). Diastolic pressure was 114 mm Hg or greater in 50% of patients with adenomas and in 19% of those with hyperplasia ($P = 0.09$).

Renal Disease

Baseline creatinine clearance was similar in both groups (1.88 mL/s for the adenoma group and 1.65 mL/s for the hyperplasia group; $P = 0.18$). Only one patient had an elevated serum creatinine level (>141.4 μmol/L [1.6 mg/dL]). However, pathologic levels of proteinuria or microalbuminuria, defined as a daily protein excretion of greater than 0.2 g or an albumin excretion of greater than 0.03 g, were observed in more than 40% of patients in both groups. The most abundant proteinuria (1.5 g every 24 hours) occurred in the patient with adenoma who had the highest plasma renin activity (2.1 ng/mL per hour), although mean plasma renin activity was similar in patients who had elevated urinary protein and albumin ex-

Table 1. Blood Pressure and Laboratory Values before Treatment

Variable	Adenoma Group	Hyperplasia Group	Difference (95% CI)	*P* Value
Systolic blood pressure, *mm Hg*	184	161	−23 (−34 to −12)	<0.001
Diastolic blood pressure, *mm Hg*	112	105	−7 (−13 to −1)	0.03
Urine aldosterone level, *μg/d*	64	27	−37 (−76 to 2)	0.2
Plasma renin activity, *ng/mL per hour*	0.33	0.51	0.18 (−0.08 to 0.44)	>0.2
Serum Na level, *mmol/L*	143	142	−1 (−3 to 1)	>0.2
Serum K level, *mmol/L*	3.0	3.5	0.5 (0.3 to 0.7)	<0.001
Serum CO_2 level, *mmol/L*	32	29	−3 (−5 to −1)	0.001
Atrial natriuretic peptide level, *fmol/mL*	32	13	−19 (−32 to −6)	0.008
Proteinuria, *mg/d*	226	184	−42 (−263 to 179)	>0.2
18-oxocortisol level, *μg/d*	43	14	−29 (−55 to −3)	0.02
18-hydroxycortisol level, *μg/d*	182	70	−112 (−199 to −25)	0.02

cretion. Chronic renal disease was presumably caused by diabetic nephropathy in two patients who had insulin-dependent diabetes with concomitant retinopathy and a history of stroke. However, renal biopsies were not done in any patients.

Incidental radiographic findings indicated simple renal cysts in 13 of 82 patients (7 with adenomas and 6 with hyperplasia; $P > 0.2$). Cysts were asymptomatic, and no patient had more than three cysts in each kidney. Renovascular hypertension had been previously identified in one patient with an adenoma.

Vascular Complications

Six patients (7.3%) had a history of cardiovascular events, including angina and myocardial infarction (five patients with adenomas and one with hyperplasia; $P = 0.2$). Five (6.1%) cerebrovascular events occurred (transient ischemic attack or stroke), two of them in the adenoma group ($P > 0.2$ compared with the hyperplasia group). No morbid events occurred during the relatively brief period when untreated patients were studied.

Biochemical Studies

Laboratory values while patients were not receiving medication are shown in Table 1. Serum potassium levels were lower in the patients with adenomas. Levels less than 2.8 mmol/L were found in 44% of patients with adenomas and in only 9% of those with nonadenomatous hyperplasia ($P = 0.005$). In contrast, potassium levels of 3.5 mmol/L or greater were found in 18% of patients without adenomas and in 6% of those with adenomas ($P = 0.15$). Serum levels of total CO_2 were also higher in the adenoma group.

Urinary aldosterone excretion (Table 1, Figure 1) in the adenoma group was directly related to the pretreatment diastolic ($r = 0.58$; $P = 0.001$) and mean arterial blood pressures ($r = 0.53$; $P = 0.003$; data not shown). In contrast, blood pressure and urine aldosterone excretion in patients without adenomas were not directly related (Figure 1).

Plasma renin activity was low in most patients. A renin value of greater than 1.0 ng/mL per hour was found in only two patients with adenomas and in three with nonadenomatous hyperplasia. However, mean plasma renin activity was lower in more patients in the adenoma group: Seventy-one percent had plasma renin activity of 0.2 ng/mL per hour or less compared with only 41% of patients with adenomas ($P = 0.03$). Regardless of whether an adenoma or hyperplasia was present, the mean preoperative renin value was lower in patients who were cured by adrenalectomy than in those who were not cured (0.17 ng/mL per hour compared with 0.50 ng/mL per hour [difference, 0.33 ng/mL per hour; CI of the difference, 0.14 ng/mL per hour to 0.52 ng/mL per hour; $P < 0.001$]).

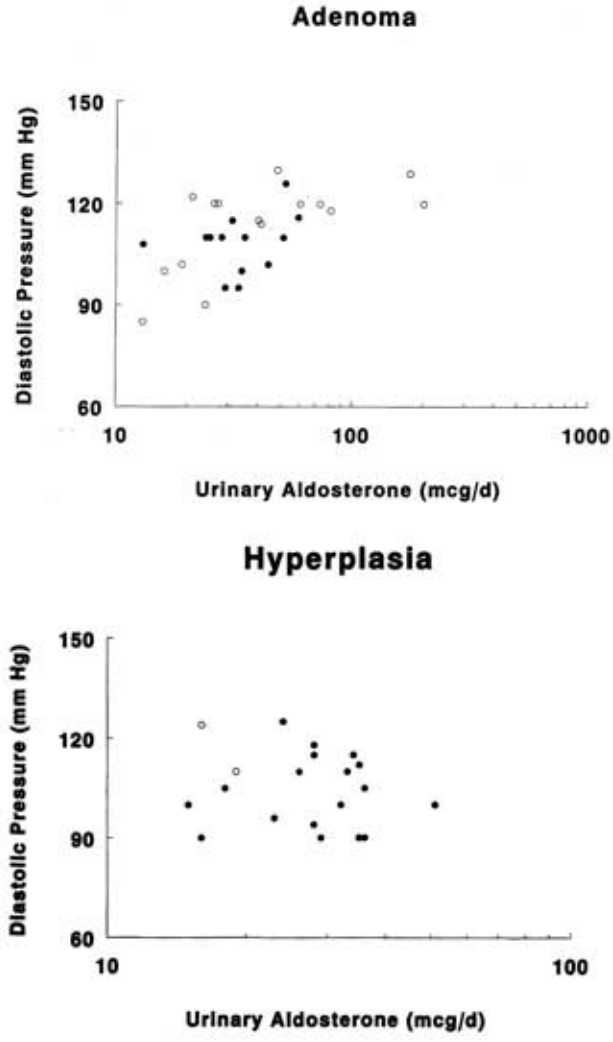

Figure 1. Relation of 24-hour aldosterone excretion to diastolic blood pressure. Top. In patients with an aldosterone-producing adenoma ($r = 0.58$; $P = 0.001$). **Bottom.** In patients with hyperplasia ($r = 0.12$; $P > 0.2$). ● = serum potassium level greater than 3.0 mmol/L; ○ = serum potassium level of 3.0 mmol/L or less.

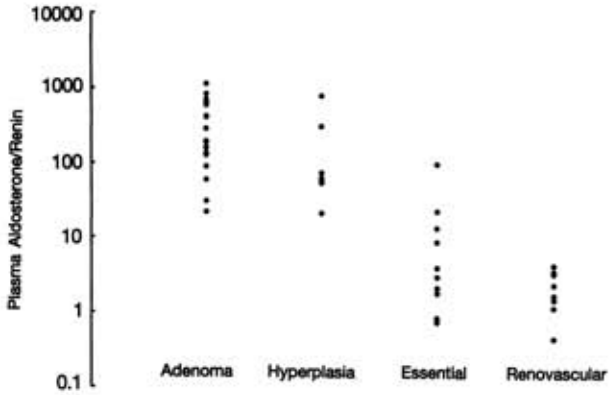

Figure 2. Comparison of the ratio of plasma aldosterone to plasma renin activity for primary aldosteronism (aldosterone-producing adenoma and nonadenomatous adrenal hyperplasia) and renovascular and essential hypertension. A ratio of greater than 50 helped identify patients with primary aldosteronism.

Furthermore, the preoperative mean renin value for the cured group was at the lower limit of detection of our assay.

A ratio of plasma aldosterone to renin activity was quantified in patients with adenomas and hyperplasia (Figure 2). We compared these values with those obtained during routine evaluation of randomly selected outpatients with essential hypertension and renovascular hypertension. We observed a ratio of less than 50 in only 3 patients with primary aldosteronism (2 patients with adenomas and 1 with hyperplasia), whereas we observed a higher ratio in only 2 patients with essential hypertension and in no patients with renovascular hypertension. Consequently, a plasma aldosterone-renin ratio of greater than 50 was more likely to be present in patients with primary aldosteronism than in patients with other common forms of hypertension ($P < 0.001$). However, this ratio did not adequately distinguish adenomas from hyperplasia ($P > 0.2$)

Patients with adenomas had higher rates of excretion of 18-oxocortisol and 18-hydroxycortisol than did patients with hyperplasia. We found an 18-oxocortisol level greater than 15 μg/d in 13 of 15 patients with adenomas (87%) and in only 1 of 9 patients with hyperplasia ($P < 0.001$ compared with patients with adenomas). Furthermore, all patients with adenomas had an 18-hydroxycortisol level greater than 60 μg/d, whereas only one patient with hyperplasia had a level greater than this value ($P < 0.001$ compared with patients with adenomas). This patient was cured by adrenalectomy.

Plasma atrial natriuretic peptide levels were higher in patients with adenomas than in patients with hyperplasia; elevated levels were present in five of eight (62.5%) patients with adenomas. None of the five patients in the hyperplasia group had elevated atrial natriuretic peptide levels ($P = 0.02$ compared with patients with adenomas).

Sixteen of 19 patients (84%) with adenomas had a positive postural stimulation test result. In these patients, plasma renin activity did not increase with upright posture.

In contrast, in 78% of patients with hyperplasia, plasma aldosterone levels increased during upright posture ($P < 0.001$ compared with patients with adenomas), and plasma renin activity also slightly increased (activity during supine posture, 0.29 ng/mL per hour; activity during upright posture, 0.60 ng/mL per hour [difference, 0.31 ng/mL per hour; CI of the difference, 0.01 ng/mL per hour to 0.61 ng/mL per hour; $P = 0.006$]).

Adrenal vein sampling was successful in 31 of the 49 patients (63%) in whom it was attempted. Clinical and laboratory data from 9 of these patients were incomplete and therefore not analyzed further.

Nine of 11 patients (81%) in the adenoma group had criteria for lateralization of aldosterone secretion. The mean aldosterone-cortisol ratio of the ipsilateral adrenal-inferior vena cava was 12.4, and the ratio for the contralateral adrenal gland was 0.3.

In the hyperplasia group, only 4 of 11 patients (36%) ($P = 0.03$ compared with patients with adenomas) met the criteria for lateralization of aldosterone secretion. In those 4 patients, the mean adrenal-inferior vena cava ratio for the dominant adrenal gland ("high adrenal") was 10.8, and the ratio for the contralateral adrenal gland ("low adrenal") was 0.4. These adrenal values were similar to those of patients with adenomas in whom lateralization occurred.

Clinical Outcome

Follow-up data were available for 43 patients with and 25 patients without adenomas for 2 weeks to 15 years. Therapeutic outcomes are shown in Figure 3.

Patients with Adenomas

Hypertension was cured by surgery alone (systolic blood pressure, ≤140 mm Hg; diastolic blood pressure, ≤90 mm Hg without postoperative medication) in 34.9% of patients with an adenoma. When we pooled data from the patients with adenomas and hyperplasia who were cured, we found that they were younger (mean ages, 43 years and 54 years, respectively [difference, 11 years; CI of the difference, 4 years to 18 years; $P = 0.002$]) and had lower pretreatment renin activity than those who were not cured (that is, conditions that were improved and those that were not improved). In cured patients, we also observed a correlation between the preoperative urinary aldosterone excretion rate and the relative decrease in diastolic blood pressure after adrenalectomy ($r = 0.59$; $P = 0.03$). All nine patients in whom lateralization of aldosterone secretion occurred were cured or improved by adrenalectomy. One patient in whom lateralization did not occur was also cured by adrenalectomy. Patients with adenoma who were cured or improved were more likely to have lateralization of aldosterone secretion ($P = 0.07$).

Hypertension improved postoperatively in 55.8% of patients in the adenoma group, and blood pressure decreased to 140/90 mm Hg or less in 60% of patients when they received medication after adrenalectomy. Medical treatment without surgery improved blood pressure in two of five patients (40%) ($P > 0.2$ compared with patients with hyperplasia). Thus, hypertension was either cured or improved to an acceptable level in more than 90% of the patients with adenomas.

Hyperplasia

In more than two thirds of all patients with nonadenomatous hyperplasia (17 of 25 patients), hypertension was

Table 2. Blood Pressure and Laboratory Responses to Treatment

Variable	Adenoma Group				Hyperplasia Group			
	Before Treatment*	After Treatment*	Δ (95% CI)	*P* Value	Before Treatment*	After Treatment*	Δ (95% CI)	*P* Value
Systolic blood pressure, *mm Hg*	184	131	−53 (−63 to −43)	<0.001	163	144	−19 (−32 to −6)	0.006
Diastolic blood pressure, *mm Hg*	112	86	−26 (−32 to −20)	<0.001	106	93	−13 (−20 to −6)	<0.001
Plasma renin activity, *ng/mL per hour*	0.39	3.5	3.1 (1.8 to 4.4)	<0.001	0.61	2.8	2.2 (−0.3 to 4.7)	0.07
Serum Na level, *mmol/L*	143	139	−4 (−6 to −2)	0.002	142	140	2 (0 to 2)	0.03
Serum K level, *mmol/L*	3.0	4.5	1.5 (1.3 to 1.7)	<0.001	3.5	4.3	0.8 (0.5 to 1.1)	<0.001
Serum Co_2 level, *mmol/L*	32	27	−5 (−7 to −3)	<0.001	28	28	0 (−1 to 1)	>0.2
Blood urea nitrogen level, *mg/dL*	4.6	6.7	2.1 (0.7 to 3.6)	<0.001	5.4	6.8	1.4 (−0.7 to 0.7)	0.08

*Treatment included medication or surgery.

either cured or improved during treatment. Of the 8 patients who had adrenalectomy, 3 were cured and 1 was improved. Of the 4 patients in whom aldosterone secretion lateralized during adrenal sampling, 3 had surgery and 2 were cured (1 of the latter patients had a negative postural stimulation test result). One patient was not cured even though the criteria for lateralization were present. This patient had insulin-dependent diabetes, did not maximally suppress renin preoperatively, but did not have microalbuminuria or other evidence of diabetic nephropathy. Thirteen of the 17 patients who received medication and did not have surgery improved; 4 did not improve.

In the adenoma and hyperplasia groups, abnormalities of serum electrolytes improved and plasma renin activity increased (Table 2). Renin and serum potassium activity increased with decreases in serum sodium and total CO_2 levels.

Discussion

We sought to characterize patients with primary aldosteronism to determine which clinical and biochemical features identify those most likely to be cured or improved by unilateral adrenalectomy. In our study, 65% of patients had an aldosterone-producing adenoma, and blood pressure was clinically improved in more than 90% of patients with tumors. However, more than half of those patients required postoperative antihypertensive medication. Most patients with adenomas had a positive postural stimulation test result, although this index of "autonomy" from renin-angiotensin stimulation did not predict cure. Aldosterone secretion lateralized more frequently in patients with adenomas, although we also observed this in a small group of patients with hyperplasia. Lateralization was associated with cure or improvement in blood pressure after unilateral adrenalectomy. In general, patients with nonadenomatous adrenal hyperplasia had less severe hypertension and milder biochemical abnormalities and usually received antihypertensive medication. Regardless of their diagnostic subset, patients who were cured surgically were younger and had lower preoperative plasma renin activity. Our results highlight several features that suggest the potential for surgically curable lesions.

In patients with adenomas, the magnitude of hypertension was directly related to the level of aldosterone overproduction. Furthermore, in patients who were cured by adrenalectomy, the preoperative aldosterone level correlated highly with the relative reduction in blood pressure. However, we observed no difference between the mean aldosterone levels in patients who were surgically cured and the levels in those who required postoperative medication, which indicates that other factors contributed to their hypertension.

In our study, hypokalemia was more severe in patients with adenomas than in patients with hyperplasia. Approximately 20% of patients without adenomas had a serum potassium level within the normal range, whereas patients with adenomas rarely had serum potassium levels greater than 3.0 mmol/L. However, we found no apparent relation between urinary aldosterone levels and the magnitude of hypokalemia. This finding probably reflects a relative impairment in aldosterone biosynthesis caused by the total body deficit of potassium. These findings are similar to those reported by Conn (18) and Bravo and colleagues (19). It is unlikely that this phenomenon led us to overlook the diagnosis of primary hyperaldosteronism because at our center, a low renin activity with a serum potassium level in the low to normal range is evaluated further by measuring 24-hour urinary aldosterone excretion. Equivocal aldosterone levels are repeated after potassium repletion.

In our study, few patients, mostly those with hyperplasia, had plasma renin activity greater than 1.0 ng/mL per hour. More than 90% of patients with adenomas had plasma renin activity less than 1.0 ng/mL per hour, more than half of whom had renin activities that were maximally suppressed. The finding that the mean renin level before treatment was lower in patients who were subsequently cured by adrenalectomy suggests that a failure to suppress renin secretion may be a useful indicator for estimating which patients will require postoperative medication. Bravo and colleagues (19) reported that plasma renin activity was not suppressed (range, 1.0 to 5.0 ng/mL per hour) in 20% of patients with adenomas and in 60% of patients with hyperplasia. It is unclear from that study whether the relatively high renin values represented a residual effect of discontinued medication therapy (that is, diuretics). Surgical outcomes in that study were not re-

ported, and, therefore, a potential relation between the failure of renin to suppress and the likelihood of surgical cure could not be evaluated.

A positive postural stimulation test result reportedly identifies forms of primary aldosteronism in which hypertension is cured by adrenalectomy (14). In our study, this test had a high sensitivity (84%) and specificity (78%) for identifying an adenoma, a value similar to that reported by Fontes and coworkers (14). The predictive accuracy of this test for identifying surgically curable hypertension could not be determined with certainty because most patients with hyperplasia did not have an adrenalectomy. However, the accuracy was relatively low because approximately 50% of patients with adenomas had a positive postural stimulation test result but required postoperative antihypertensive medication.

The elevated ratio of plasma aldosterone to plasma renin activity is another indicator of autonomous aldosterone secretion that has been proposed as a screening test for primary aldosteronism (20, 21). We more frequently observed a ratio greater than 50 in patients with primary aldosteronism than we did in patients with either essential hypertension or renovascular disease (Figure 2). However, there was considerable overlap between the hyperplasia and adenoma groups, so this is therefore not a useful index for differentiating these diagnostic subsets. Furthermore, this ratio did not predict surgical cure.

Ulick and Chan (4) reported that urinary levels of the C18-oxygenated metabolites of cortisol, 18-hydroxycortisol and 18-oxocortisol, are increased in primary aldosteronism caused by adenomas. This steroid pattern appears to reflect the loss of normal functional zonation of the adrenal gland. These "hybrid steroids" are formed when cortisol, a fasciculata zone product, is accepted as a substrate by 18-hydroxylase ($P450_{C18}$), which is normally exclusively found in the glomerulosa zone. In a large series of patients, some of whom we describe here, urinary excretions of oxocortisol greater than 15 μg/d and hydroxycortisol greater than 60 μg/d distinguished adenomas from hyperplasia with a high sensitivity (5). Two of the patients with adenomas who had levels in the hyperplasia range also had a negative postural stimulation test result. Their blood pressures were improved but not cured by surgery. These findings accord with those in a previous report by Gordon and colleagues (22), in which patients with adenomas in whom aldosterone production is increased during upright posture or infusion of exogenous angiotensin II were found to have low levels of these cortisol metabolites. Taken together, these findings show the limitations of the noninvasive tests that are commonly used to evaluate and predict surgical cure in patients with primary aldosteronism.

Patients who are most likely to have their blood pressure cured or improved by adrenalectomy can be identified prospectively with adrenal vein sampling when aldosterone secretion lateralizes (16, 17, 23, 24). We observed ipsilateral hypersecretion and contralateral suppression of aldosterone in the adenoma group. We detected a similar pattern in patients with adrenal hyperplasia in whom an adenoma was not identified. These results indicate that adrenal sampling identifies patients with primary aldosteronism who respond favorably to adrenalectomy, even when an adrenal tumor is not apparent radiographically or

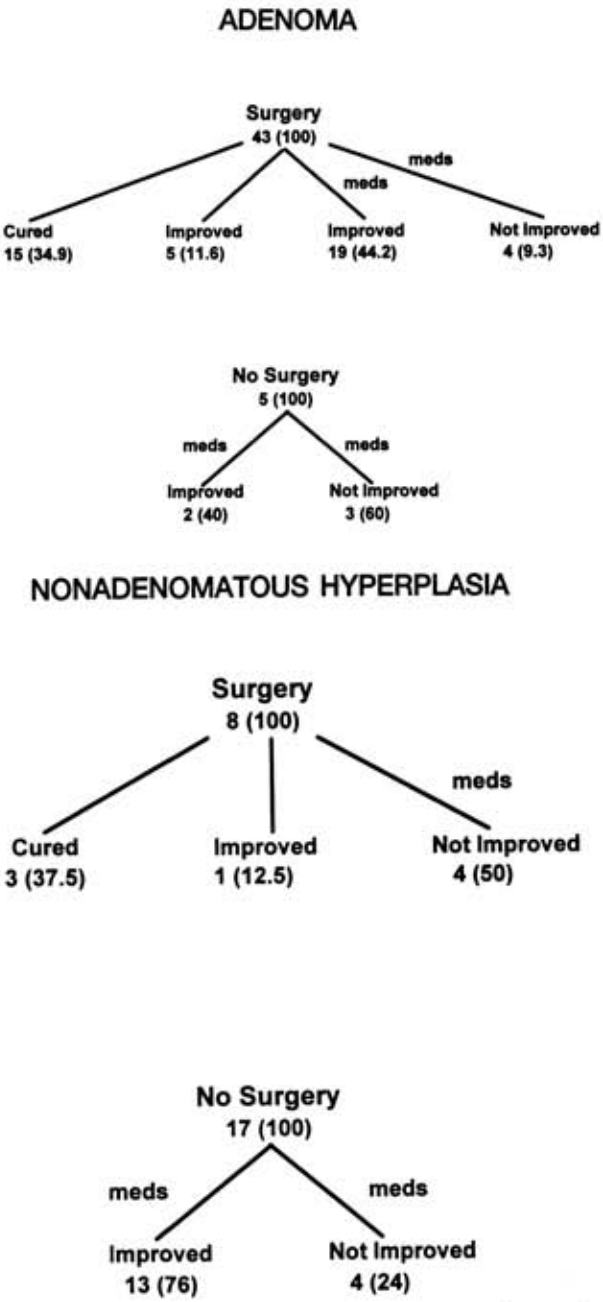

Figure 3. Therapeutic outcomes for primary aldosteronism caused by adenoma (*top*) and nonadenomatous hyperplasia (*bottom*). Values in parentheses represent the percentage of the treatment group.

when other noninvasive studies do not suggest autonomous aldosterone secretion. In our study, adrenocorticotropin hormone was not infused during adrenal vein sampling. However, simultaneous infusion of adrenocorticotropin hormone does enhance adrenal steroid production, thereby avoiding sampling artifacts associated with episodic secretion that can lead to ambiguous results regarding lateralization (24).

Primary aldosteronism is characterized by intravascular volume expansion as determined by the increased extracellular sodium content and high levels of plasma atrial natriuretic peptide (25–28). In our study, the mean atrial natriuretic peptide level was high in the adenoma group,

although some patients had normal values. By contrast, none of the patients with hyperplasia had high levels. Thus, an elevated level suggests an adenoma, but a normal value does not exclude its presence. Although atrial natriuretic peptide levels were not measured after treatment, the blood urea nitrogen level increased (Table 2) without an associated increase in the creatinine level (not shown), consistent with reduced intravascular volume.

Microalbuminuria and increased urinary protein excretion were present in approximately 40% of the study patients regardless of their diagnostic group. This exceeds the prevalence reported in earlier studies in patients with primary aldosteronism (29) and essential hypertension (30). Although the serum creatinine levels and creatinine clearances were normal in these patients, abnormal levels of protein excretion indicate that incipient renal disease is common in this syndrome. Renal cysts were also present in 16% of our study patients, a proportion similar to that seen in normal persons. In contrast, renal medullary cysts were recently reported in 44% of patients with primary hyperaldosteronism and in 62% of those with an aldosterone-producing adenoma (31). However, a subsequent report did not confirm that association (32). Furthermore, there was no relation between the likelihood of surgical cure and either abnormal protein excretion or the presence of renal cysts.

Diagnostic Strategy

The results of diagnostic screening of patients with this syndrome are often ambiguous, especially when the serum potassium level is within the normal range. Relatively simple tests that can improve the diagnostic accuracy include the following: 1) a 24-hour urinary aldosterone excretion rate of 38.9 nmol/d (14 μg/d) or greater, after sodium loading for at least 3 days (urinary sodium content >250 mmol/d [19]); 2) a ratio of plasma aldosterone to renin activity of greater than 50; and 3) the failure to increase plasma renin activity after sodium restriction and furosemide-induced diuresis (24). The sensitivity and specificity of each of these diagnostic maneuvers can be adversely influenced by concurrent use of antihypertensive medications. For example, β-adrenoceptor antagonists markedly decrease plasma renin activity in essential hypertension and may alter the interpretation of these test results (33). Hypokalemia caused by thiazide diuretics may be difficult to distinguish from primary aldosteronism, particularly when aldosterone biosynthesis is attenuated by potassium depletion. Angiotensin-converting enzyme inhibitors and calcium channel antagonists reportedly reduce aldosterone biosynthesis and improve hypokalemia in some patients with primary aldosteronism (15, 34). Therefore, therapy with antihypertensive medications should be discontinued for at least 2 weeks before diagnostic evaluation takes place and potassium supplements are provided to hypokalemic patients.

The diagnostic algorithm in Figure 4 can be useful for directing treatment when biochemical screening tests indicate primary aldosteronism. If a solitary unilateral adrenal mass is identified unequivocally on a CT scan of the adrenal gland in a patient with biochemical criteria for primary aldosteronism, surgery is indicated. Adrenal vein sampling is not essential, although lateralization of aldosterone secretion confirms the diagnosis. Adrenalectomy should be preceded by several weeks of adequate control of hypertension and correction of hypokalemia and other metabolic abnormalities.

In the patient with biochemical criteria for primary aldosteronism whose CT scan of the adrenal gland is normal or indicates hyperplasia, additional evaluation is required because a subgroup will be cured by unilateral adrenalectomy. Additional diagnostic tests that suggest the potential for surgical cure include a positive postural stimulation test result, elevated levels of plasma 18-hydroxycorticosterone and urinary 18-methyl oxygenated cortisol metabolites, and lateralization of aldosterone secretion. If the patient has bilateral aldosterone secretion, a negative postural stimulation test result, and low levels of cortisol metabolites, then adrenalectomy is not indicated. If secretion is bilateral or sampling is unsuccessful, and the ancillary diagnostic tests described above indicate autonomous aldosterone production, the patient should be treated medically and re-evaluated in 6 to 12 months. Re-evaluation should include adrenal vein sampling.

Treatment Strategies

The cornerstone of antihypertensive therapy in primary aldosteronism is spironolactone, a competitive antagonist of the aldosterone receptor. The efficacy of this drug relates to the reduction in plasma volume in disorders associated with aldosterone excess. Although a favorable blood pressure response to spironolactone has been asso-

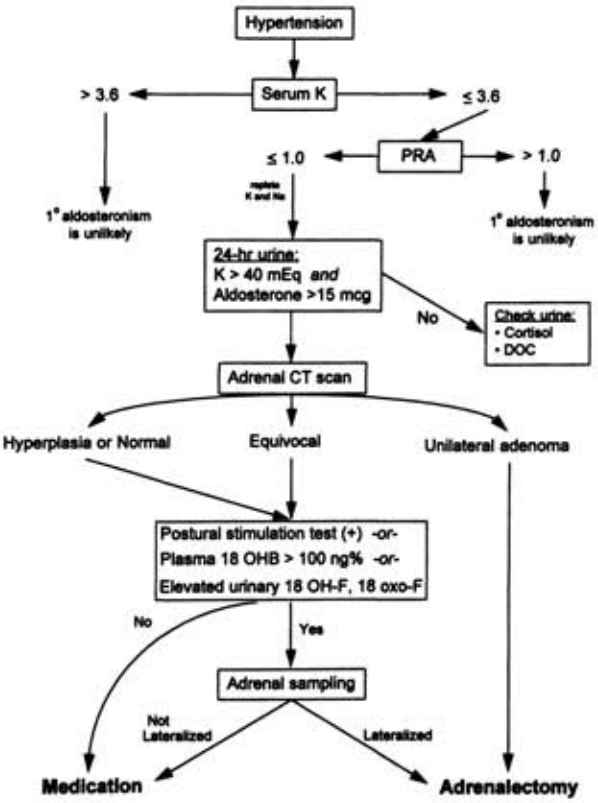

Figure 4. Algorithim for evaluating and treating patients with primary aldosteronism. 18-OHB = 18-hydroxycorticosterone; 18-OH-F = 18-hydroxycortisol; 18-oxo-F = 18-oxocortisol; CT = computed tomography; DOC = deoxycorticosterone; PRA = plasma renin activity.

ciated with improved chances of surgical cure, it does not reliably predict outcome (35). Amiloride can also effectively lower blood pressure and correct hypokalemia in patients with gynecomastia or other side effects associated with spironolactone. The dihydropyridine calcium channel antagonists can acutely decrease aldosterone secretion and blood pressure in patients with this syndrome (34). However, studies of longer duration have failed to show these beneficial effects when nifedipine was used as monotherapy (36, 37). Angiotensin-converting enzyme inhibitors have been used to successfully treat some patients with hyperplasia in whom aldosterone production is not completely autonomous from angiotensin II stimulation (15). A role for α-adrenergic receptor antagonists has not been clearly defined—in a previous study, phentolamine did not acutely reduce blood pressure (38). However, long-term treatment with prazosin is effective in treating low-renin essential hypertension (39), suggesting that α-adrenergic receptor antagonists may have an ancillary role in treating primary aldosteronism.

Summary

Establishing the diagnosis of primary aldosteronism is important because hypertension and metabolic disturbances are potentially curable in patients with adenomas and nonadenomatous hyperplasia by unilateral adrenalectomy. Furthermore, the hypertension is often severe and can be difficult to control with only antihypertensive medication. However, the diagnosis may be obscured because the complete clinical and biochemical expression of mineralocorticoid hypertension may not be present, particularly in patients with nonadenomatous hyperplasia who have serum potassium levels within the normal range. The diagnosis is supported by a low plasma renin activity, elevated 24-hour urinary aldosterone level and ratio of plasma aldosterone to renin activity, a positive postural stimulation test result, and elevated urinary excretion of 18-oxocortisol and 18-hydroxycortisol and high levels of plasma 18-hydroxycorticosterone. Adrenal vein sampling has an important role in the diagnostic evaluation of primary aldosteronism because lateralization of aldosterone secretion can indicate the presence of a curable lesion regardless of the radiographic findings (40).

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Jerome W. Conn, MACP

24 September 1907–11 June 1994

Primary Aldosteronism

His original description of primary aldosteronism identifying the clinical picture, the pathologic physiology and the effect of treatment will doubtless remain a medical classic. In this a sound basis was established for the relation of excessive secretion of aldosterone to cardiac, renal and liver diseases.

> Citation for award of the John Phillips Memorial Medal, American College of Physicians, 46th Annual Session, 25 March 1965, Chicago, Illinois

It is believed that these studies delineate a new clinical syndrome which is designated temporarily as primary aldosteronism. In its fully developed state it is characterized by the presence in the urine of excessive amounts of a sodium-retaining corticoid, by severe hypokalemia, hypernatremia, alkalosis, and a renal tubular defect in the reabsorption of water.... The clinical picture consists of intermittent tetany, paresthesia, periodic severe muscular weakness and "paralyses," polyuria and polydipsia, hypertension, and no edema.... From a therapeutic point of view and in the light of present knowledge, these data indicate that total adrenalectomy followed by substitute therapy should abolish the entire metabolic abnormality. The patient is now in the hospital in preparation for this procedure. We hope to report other studies, as well as the results of adrenalectomy, at a later date.

Jerome W. Conn
Presidential address ... Part II. Primary Aldosteronism, a New Clinical Syndrome
J Lab Clin Med. 1955;45:3-17.

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