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Primary aldosteronism: new approaches to diagnosis and management

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- Primary aldosteronism remains a diagnostic challenge. Certain immunoassay techniques, simplified diagnostic testing, and the introduction of sensitive imaging techniques have facilitated the diagnosis, but obstacles that remain include a lack of optimal screening methods, low sensitivity and specificity of current diagnostic tests, and a growing number of etiological subgroups. A rational approach to the diagnosis of primary aldosteronism is described, as is the differentiation of the surgically correctable lesion (adenoma) from the other etiological subgroups.

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P RIMARY aldosteronism remains a diagnostic challenge. The availability of sensitive and specific immunoassay techniques, the development of simplified diagnostic testing, and the introduction of sensitive imaging techniques have enhanced the clinician's ability to make the diagnosis with greater certainty.

Nevertheless, there are still uncertainties about optimal screening methods, the sensitivity and specificity of the various diagnostic tests, the diagnostic process, diagnostic criteria, and differentiation of the growing number of etiological subgroups.

This review deals primarily with the clinical recognition and diagnosis of primary aldosteronism and the differentiation of lesions that are surgically correctable (adenomas) from the other etiological subgroups. Emphasis will be placed on a rational approach to diagnosis. Because of space limitations, this review will omit a lengthy discussion of alternative diagnostic approaches.

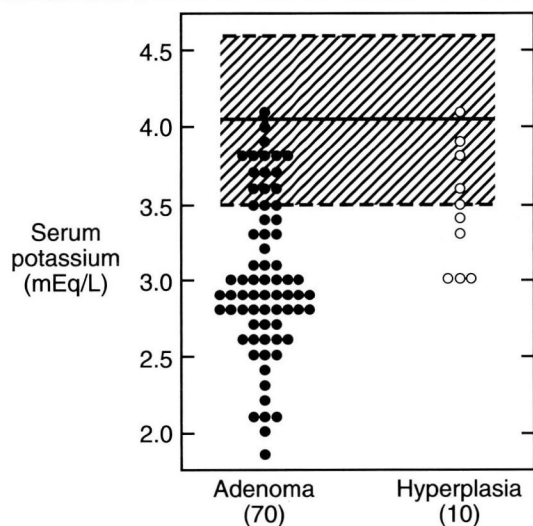


FIGURE 1. Basal serum potassium values with normal dietary sodium. Each point represents the mean of at least three determinations. The cross-hatched area represents 95% confidence limits (3.5 to 4.6 mEq/L) of values obtained from 60 healthy subjects. Twenty-two patients (36%), 17 with adenoma and 5 with hyperplasia, had fasting serum potassium values of 3.5 mEq/L or greater. Serum potassium values below 3.0 mEq/L were usually associated with adenoma. (From Bravo EL. Primary aldosteronism. In: Libertino and Novick, editors. *Urol Clin North Am*. Philadelphia: WB Saunders, 1989; 16(3):481–486. Reprinted with permission.)

DIAGNOSIS

Clinical recognition

The common presenting complaints in primary aldosteronism are not distinctive and include: (a) headaches, usually bitemporal and nagging and unrelated to the height of arterial blood pressure; (b) weakness of proximal muscle groups; (c) polyuria and nocturia; and (d) tachycardia, with or without palpitations. Some patients have signs and symptoms indicative of a hyperkinetic circulatory state.

Any of the following hypertensive patients deserve strong consideration for additional studies to determine the presence of primary aldosteronism: (a) patients who develop spontaneous hypokalemia (serum potassium concentration < 3.5 mEq/L); (b) patients who develop moderately severe hypokalemia (serum potassium concentration < 3.0 mEq/L) or who have difficulty maintaining normal potassium values despite concomitant use of oral potassium supplements or potassium-sparing agents

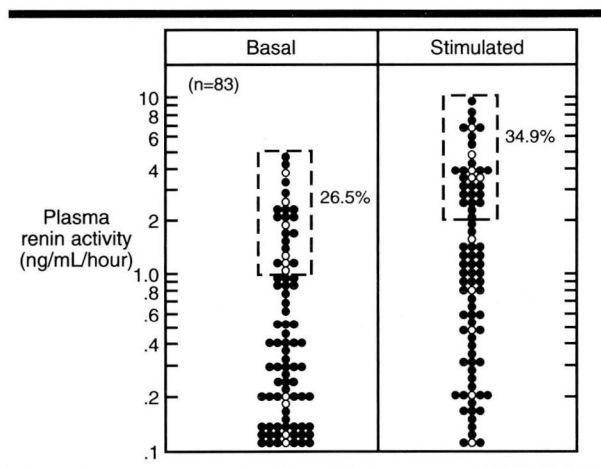


FIGURE 2. Basal and stimulated plasma renin activity in patients with primary aldosteronism. Basal activity was measured after an overnight fast and then at 30 minutes supine in the morning following 3 to 5 days of normal dietary sodium. Stimulated activity was measured under similar conditions after 4 days of sodium deprivation. Black dots represent patients with adenoma ($n = 73$) and circles represent those with hyperplasia ($n = 10$). About 26% of patients had normal-to-high plasma renin activity in the basal state and about 35% had values of at least 2.0 ng/mL after sodium deprivation. Based on the stimulated activity, 42% of patients had false-negative tests. Using a value of 2.0 ng/mL or less after 4 days of sodium deprivation as the reference value, the test has a sensitivity of 64% and a specificity of 83%. (From Bravo EL. Primary aldosteronism. In: Libertino and Novick, editors. *Urol Clin North Am*. Philadelphia: WB Saunders, 1989; 16(3):481–486. Reprinted with permission.)

during conventional doses of diuretics; and (c) patients with refractory hypertension with no evidence of a secondary cause.

Screening for the presence of primary aldosteronism

Serum potassium concentration. Hypokalemia, whether spontaneous or provoked, provides an important clue to the presence of primary aldosteronism (Figure 1). However, a substantial number of patients do not present with hypokalemia: the serum potassium concentration is normal in 7% to 38% of reported cases.^{1,2} In addition, 10% to 12% of patients with proven tumors may not have hypokalemia during short-term salt loading.¹ It is worth emphasizing that conventional diuretic therapy usually produces moderately severe hypokalemia (ie, serum potassium concentration ≤ 3.0 mEq/L) in this “normokalemic” group.

Plasma renin activity. Suppressed plasma renin activity (< 1.0 ng/mL/hour) that fails to rise above 2.0 ng/mL/hour after salt and water depletion and upright posture has been used as a screening test to exclude primary aldosteronism (Figure 2). However, a substantial number (about 35%) of patients have values that rise more than 2.0 ng/mL/hour when appropriately stimulated.¹ In addition, about 40% of subjects with essential hypertension have suppressed plasma renin activity, and 15% to 20% of these patients have values below 2.0 ng/mL/hour under conditions of stimulation. Therefore, the large number of false-positive and false-negative results make plasma renin activity determinations of limited use in screening patients for the presence of primary aldosteronism.¹

Confirming the diagnosis

Confirmation of the diagnosis of primary aldosteronism requires the demonstration of aldosterone values that are higher than in normal subjects or patients with essential hypertension and that fail to suppress normally in response to the administration of salt. In rare cases, aldosterone values are normal during normal dietary sodium but remain unaltered with high sodium intake.

Often, the diagnosis can be established with relative ease. For example, in the hypertensive patient receiving no treatment who demonstrates significant hypokalemia (serum potassium < 3.0 mEq/L) with inappropriate kaliuresis (24-hour urinary potassium > 30 mEq), plasma renin activity below 1.0 ng/mL, and elevated plasma or urinary aldosterone values, the diagnosis is incontrovertible. Often, however, the diagnosis is not obvious because of equivocal values; in such cases, multiple measurements during salt loading are needed.

The intravenous infusion of 2000 mL of physiologic saline over 4 hours has been advocated as a quick and simple test to assess suppressibility of aldosterone production. Suppression of plasma aldosterone values to less than 10 ng/dL is considered a normal response. In one series of 51 patients with surgically proven primary aldosteronism, the sensitivity of the test was reported as 100%.^{2,3} However, some studies report a false-positive rate as high as 20%.⁴ One drawback of the test is the inherent variability of plasma levels of aldosterone. Another is the expected decrement of aldosterone production over the time taken to infuse the saline.

In the author's experience, the single best test for

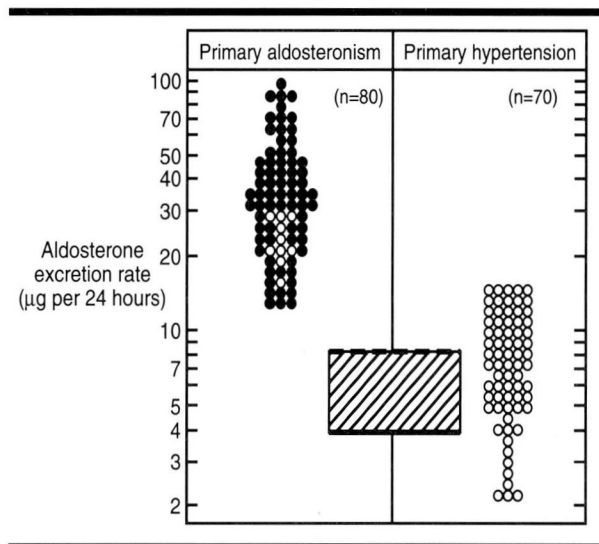


FIGURE 3. Aldosterone excretion rate after 3 days of high sodium intake. For patients with primary aldosteronism, black dots represent adenoma ($n = 70$) and open circles represent hyperplasia ($n = 10$). The cross-hatched area represents the mean (4.0 $\mu\text{g}/24$ hours) + 2 standard deviations (8.0 $\mu\text{g}/24$ hours) of values obtained from 47 healthy subjects. No patient with primary aldosteronism had a value within the 95% normal range. Ten patients (14%) with primary hypertension had values that fell within the range obtained in patients with primary aldosteronism. Using a reference value of greater than 14 $\mu\text{g}/24$ hours after a high sodium intake for 3 days, the sensitivity and specificity of the test are 96% and 93%, respectively. (From Bravo EL, Tarazi RC, Dustan HP, et al. The changing clinical spectrum of primary aldosteronism. *Am J Med* 1983; 74:641–651. Reprinted with permission.)

identifying patients with primary aldosteronism is the measurement of 24-hour urinary aldosterone during salt loading.¹ A rate greater than 14.0 $\mu\text{g}/24$ hours following 3 days of salt loading (25 mL/kg of physiologic saline over 4 hours for 3 days) distinguishes most patients with primary aldosteronism from those with essential hypertension; only 7% of patients with primary aldosteronism have values that fall within the range for essential hypertension (Figure 3). By contrast, a substantial number (about 39%) of patients with primary aldosteronism have plasma aldosterone values that fall within the range for essential hypertension (Figure 4).

Sensitivity and specificity of tests

Figure 5 shows the sensitivity and specificity of four laboratory tests commonly used to screen for primary aldosteronism. The single best test to iden-

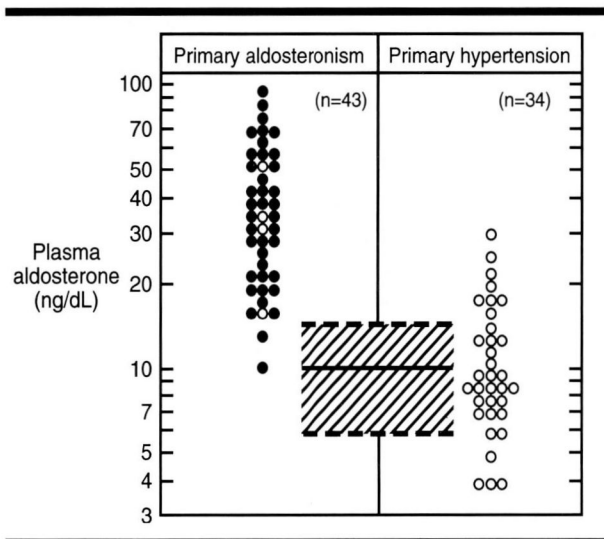


FIGURE 4. Plasma aldosterone concentration after 3 days of high sodium intake. Patient identification same as in Figure 3. The cross-hatched area represents the 95% confidence limits of values (5.3 to 13.7 ng/dL) obtained from 47 healthy subjects. Seventeen patients (39%) with primary aldosteronism had values that fell within the range obtained in patients with primary hypertension. This gave a false-negative rate of 39.5%. Using a reference value of greater than 22 ng/dL after high sodium intake for 3 days, the sensitivity and specificity of the test are 72% and 91%, respectively. (From Bravo EL, Tarazi RC, Dustan HP, et al. The changing clinical spectrum of primary aldosteronism. *Am J Med* 1983; 74:641–651. Reprinted with permission.)

tify patients with primary aldosteronism is the measurement of the aldosterone excretion rate after 3 days of salt loading. An aldosterone excretion rate exceeding 14.0 μg in 24 hours provides the highest sensitivity and specificity in identifying patients with primary aldosteronism. Suppressed plasma renin activity is the least sensitive and specific.

Adenoma: biochemical clues

Severe spontaneous hypokalemia (≤ 3.0 mEq/L), increased plasma 18-hydroxycorticosterone values (above 100 ng/dL), and an anomalous postural decrease in plasma aldosterone concentration, when present, provide the best indicators of the presence of an aldosterone-producing adenoma.⁴ In addition, adenomas are largely unresponsive to changes in sodium balance and appear to be exquisitely sensitive to adrenocorticotrophic hormone (ACTH), unlike hyperplasias, which are more sensitive to angiotensin II infusions.⁵ A plasma 18-hydroxycorticosterone value less than 100 ng/dL, a postural

increase in plasma aldosterone, or both are findings usually associated with hyperplasia; however, in themselves, they do not completely rule out the presence of an adenoma.¹

Diagnostic approach

In view of the absence of hypokalemia in a large number of patients and the number of false-positive and false-negative results with plasma renin activity measurements, we recommend that patients suspected of having primary aldosteronism should have as the initial screening test the determination of urinary aldosterone levels obtained during prolonged salt loading (Figure 6). This evaluation can be accomplished readily in the outpatient setting by simply adding 10 to 12 g of sodium chloride to the patient's daily intake and determining the serum potassium concentration and 24-hour urinary sodium. A 24-hour urinary sodium of at least 250 mEq would give some assurance that the patient has had adequate salt repletion. Priority of evaluation should be given to patients with a history of spontaneous hypokalemia, marked sensitivity to potassium-wasting diuretic agents, or refractory hypertension. Patients who demonstrate nonsuppressible aldosterone production (ie, an aldosterone excretion rate greater than 14.0 $\mu\text{g}/24$ hours) when the urinary sodium value is at least 250 mEq/24 hours should undergo additional studies to rule out primary aldosteronism. The presence of hypokalemia or suppressed plasma renin activity provides corroborative evidence, but their absence does not preclude the diagnosis.

Localization procedures

Preoperative localization of an adenoma simplifies the surgical procedure and significantly reduces mortality. Confirmation of the presence and ultimate location of an adenoma has been accomplished by computed tomographic (CT) scan of the adrenal glands, scintigraphy with radiolabeled iodocholesterol, adrenal venography, and measurement of the aldosterone concentration in adrenal venous effluent.

Adrenal CT scan. Because of its noninvasive nature, the adrenal CT scan should be considered the initial step in localization. All adenomas 1.5 cm in diameter or larger can be accurately located with CT scanning. However, only 60% of nodules measuring 1.0 to 1.4 cm in diameter are detected by CT, and nodules smaller than 1.0 cm in diameter are

very difficult (if not impossible) to demonstrate. The overall sensitivity of localizing adenomas by high-resolution CT scanning exceeds 90%.⁶⁻⁸

Scintigraphy with radiolabeled iodocholesterol. Adrenal imaging with iodocholesterol (¹³¹I-6-beta-iodomethyl-19-norcholesterol, NP-59) provides a noninvasive means of differentiating patients with an aldosterone-producing adenoma from those with idiopathic hyperaldosteronism and also for identifying the site of an adenoma when present.⁹ It accurately localizes an aldosterone-producing adenoma in more than 90% of patients. Because NP-59 accumulates rapidly in the adrenals, it permits scintigraphy within 5 days of administration. Patients with an adenoma concentrate radioactivity at the site of the tumor, whereas patients with idiopathic hyperaldosteronism usually show diffuse uptake or bilaterally reduced activity. Some patients in the latter group may show asymmetrical uptake, but dexamethasone will suppress uptake bilaterally in these cases and will also enhance the early difference in uptake between the two sides in patients with adenoma.¹⁰ A small adenoma that is less than 1.0 cm in diameter may be missed, and aldosterone-producing carcinomas show little or no radioactivity. Imaging with NP-59 may supplant adrenal vein catheterization for diagnosis and localization in primary aldosteronism. However, some false-negative results have been observed.¹¹

Adrenal vein sampling for plasma aldosterone concentration. Adrenal venous aldosterone levels should be measured when the results of the adrenal CT scan and scintigraphy are ambiguous. Bilateral adrenal venous sampling for the measurement of the aldosterone concentration is still the most accurate test for localizing aldosterone-producing tumors. However, the procedure is invasive, technically demand-

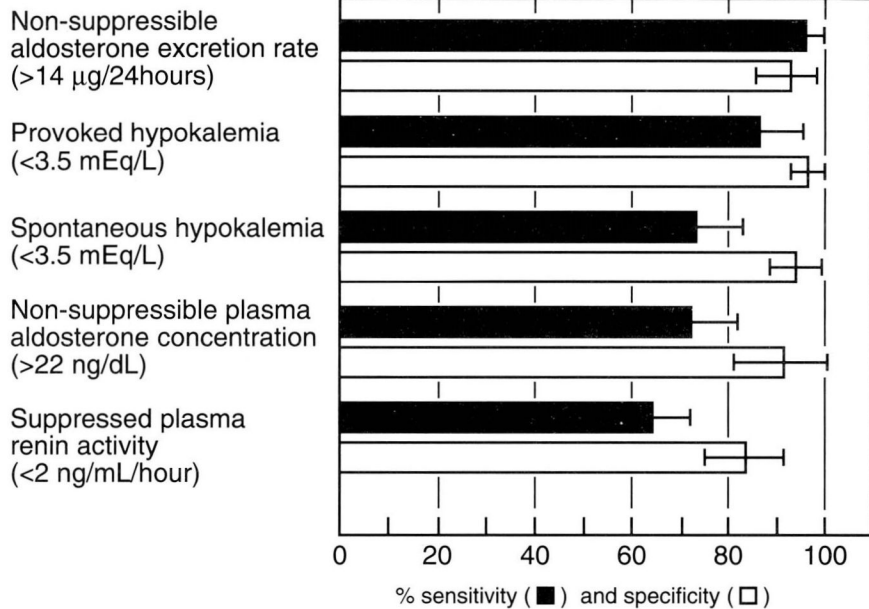


FIGURE 5. Sensitivity and specificity of tests used in the evaluation of primary aldosteronism. (From Bravo EL. Primary aldosteronism. *Cardiol Clin* 1988; 6:509-515. With permission from WB Saunders.)

ing, and requires considerable skill and experience. There is an appreciable incidence of complications, including adrenal and iliac venous thrombosis and extravasation of dye into the gland, leading to adrenal insufficiency. However, when technically successful and when both adrenal veins are entered, the accuracy of comparative adrenal venous aldosterone levels in confirming either a tumor or hyperplasia exceeds 95%.¹¹⁻¹³ The normal adrenal venous aldosterone concentration is 200 to 600 ng/dL. The ratio of ipsilateral to contralateral aldosterone is usually greater than 10 to 1. Correct placement of the catheter in the adrenal vein is essential. The accuracy of placement can best be evaluated by obtaining simultaneous ACTH-stimulated selective adrenal venous cortisol levels.¹⁴ An aldosterone ratio greater than 10 to 1 in the presence of symmetrical ACTH-induced cortisol response is diagnostic of an aldosterone-producing adenoma.

THERAPEUTIC APPROACHES

Medical therapy is indicated in patients with adrenal hyperplasia, in patients with adenoma who are poor candidates for surgery, and in patients with bi-

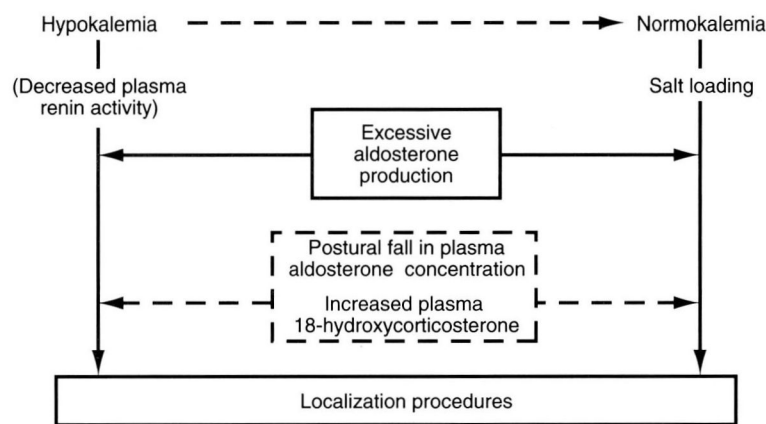


FIGURE 6. An algorithm for the diagnosis of primary aldosteronism. (From Bravo EL. Primary aldosteronism. In: Libertino and Novick, editors. *Urol Clin North Am*. Philadelphia: WB Saunders, 1989; 16(3):481-486. Reprinted with permission.)

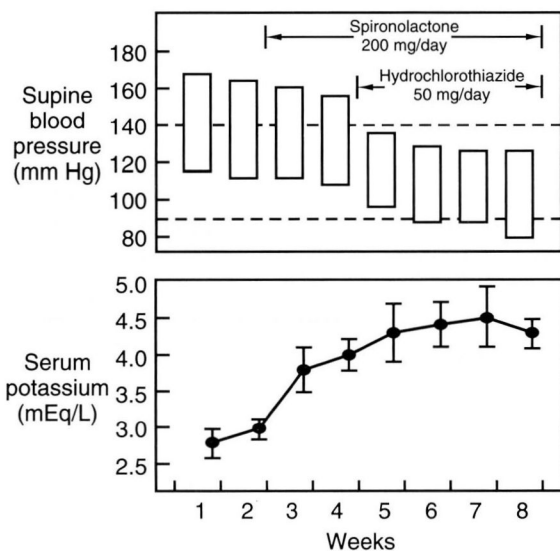


FIGURE 7. The effect of spironolactone combined with hydrochlorothiazide on blood pressure and serum potassium concentration in patients with aldosterone-producing tumors. (From Bravo EL, Dustan HP, Tarazi RC. Spironolactone as a nonspecific treatment for primary aldosteronism. *Circulation* 1973; 98:491-498. Reproduced with permission. Copyright 1973, the American Heart Association.)

lateral adenomas that may require bilateral adrenalectomy. The long-standing experience has been that the hypertension associated with primary aldosteronism is salt-dependent and water-dependent and is best treated by sustained salt and water depletion.¹⁵ Usual doses of diuretics are hydrochlorothiazide 25 to 50 mg/day or furosemide 80 to 160 mg/day, in combination with either spironolactone 100 to 200 mg/day or amiloride 10 to 20 mg/day. This usually results in prompt correction of hypokalemia and normalization of blood pressure within 2 to 4 weeks (Figure 7). In some cases, the addition of

either a beta-adrenergic blocker, a vasodilator, or both may be needed to normalize arterial pressure completely. Other alternatives, such as the sole use of nifedipine 40 to 60 mg/day, are not as effective as diuretic therapy and fail to correct the metabolic abnormalities.¹⁶ Potential side effects of spironolactone include gynecomastia, impotence, nausea, vomiting, pigmentation, and lassitude. Hyperkalemia may occur in those patients with significant impairment of renal function.

In the majority of cases, surgical excision of aldosterone-producing adenomas leads to normotension and reversal of the biochemical defects. At the very least, surgery renders arterial pressure easier to control with medications in those who have residual hypertension. In addition, neither duration and severity of hypertension nor the degree of end-organ involvement has any relationship to the arterial pressure response after surgery¹⁷ (Figures 8 and 9).

Patients undergoing surgery should receive drug treatment for at least 3 to 6 months before surgery, both to decrease blood pressure and to correct metabolic abnormalities. These patients also have a significant potassium deficit that must be corrected preoperatively because hypokalemia increases the risk of cardiac arrhythmias during anesthesia. Prolonged reduction of arterial blood pressure permits the use of intravenous fluids during surgery without

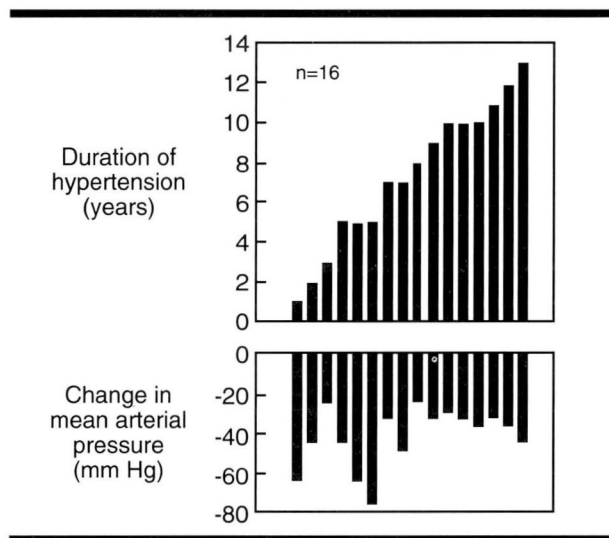


FIGURE 8. The relationship between duration of hypertension and blood pressure response after removal of an aldosterone-producing tumor. Postoperative blood pressure readings represent values obtained at 6 to 12 months after surgery. (From Bravo EL. Pheochromocytoma and mineralocorticoid hypertension. In: Glasscock RJ, editor. Current therapy in nephrology and hypertension. Philadelphia: BC Decker, 1991:386–391. Reprinted with permission.)

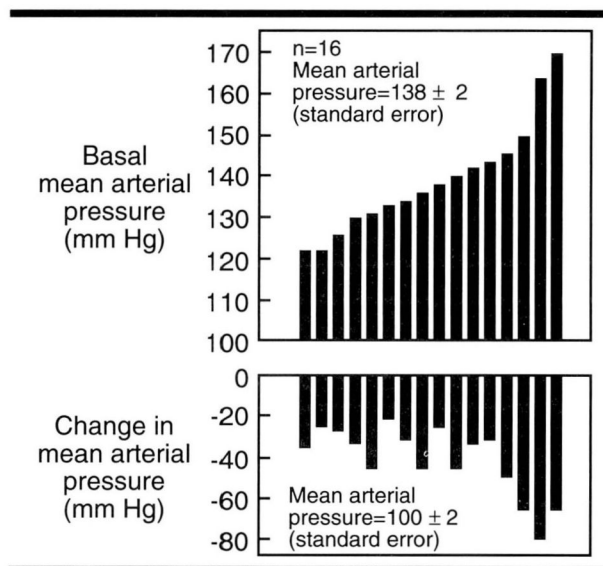


FIGURE 9. The relationship between severity of hypertension and blood pressure response after removal of an aldosterone-producing tumor. Postoperative blood pressure readings represent values obtained at 6 to 12 months after surgery. (From Bravo EL. Pheochromocytoma and mineralocorticoid hypertension. In: Glasscock RJ, editor. Current therapy in nephrology and hypertension. Philadelphia: BC Decker, 1991:386–391. Reprinted with permission.)

producing hypertension and decreases morbidity. Administration of medications is usually continued until surgery, and glucocorticoid administration is not needed before surgery.

During the immediate postoperative period, anti-hypertensive agents are generally not required if the patient was normotensive for at least 3 months before surgery while receiving diuretic therapy. If hypertension becomes a problem, diuretics should be tried first and other types of antihypertensive agents later.

After the removal of an aldosterone-producing adenoma, selective hypoaldosteronism usually occurs, even in patients whose plasma renin activity had been stimulated with chronic diuretic therapy.¹⁸ One likely explanation for this effect is that spironolactone may inhibit aldosterone biosynthesis by the adrenal cortex. Therefore, if indicated, potassium supplementation should be given cautiously and serum potassium values should be monitored closely. However, sufficient residual mineralocorticoid activity is often left to prevent excessive renal retention of potassium, provided that sodium intake is adequate. If hyperkalemia occurs, all forms of potas-

sium chloride supplementation should be discontinued and administration of furosemide in doses of 80 to 160 mg/day should be started. Treatment with fludrocortisone is often not needed. If it is needed, however, 0.1 mg/day may be used as the initial dose. Abnormalities in aldosterone production can persist for as long as 3 months.

SUMMARY

The clinical manifestations of primary aldosteronism are not distinctive, but certain hypertensive patients require additional studies. These include patients with either spontaneous or diuretic-induced hypokalemia and those with refractory hypertension without an obvious secondary cause. The best test for identifying patients with primary aldosteronism is measuring the aldosterone excretion rate during salt loading. A rate exceeding 14.0 $\mu\text{g}/24$ hours provides the highest sensitivity and specificity. The presence of hypokalemia or suppressed plasma renin activity provides corroborative evidence, but their absence does not preclude the diagnosis. An adenoma is likely in the presence of

significant spontaneous hypokalemia (serum potassium ≤ 3.0 mEq/L), a paradoxical decrease in ambulatory plasma aldosterone concentration, and plasma 18-hydroxycorticosterone values of 100 ng/dL or greater.

The adrenal CT scan (3- to 5-mm cuts) should be considered the initial step in localization. Medical

therapy is indicated for patients with hyperplasia and for patients with bilateral adenomas that may require total bilateral adrenalectomy. Whenever feasible, surgical excision is recommended for unilateral tumors. Neither the duration and severity of hypertension nor the degree of end-organ involvement are contraindications for surgery.

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