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REVIEW ARTICLE

Primary aldosteronism: renaissance of a syndrome

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Summary

Great strides have been made in our understanding of the pathophysiology of primary aldosteronism syndrome since Conn's description of the clinical presentation of a patient with an aldosterone-producing adenoma (APA) more than 50 years ago. It is now recognized that the APA is just one of the seven subtypes of primary aldosteronism. APA and bilateral idiopathic hyperaldosteronism (IHA) are the most common subtypes of primary aldosteronism. Although most clinicians had thought primary aldosteronism to be a rare form of hypertension for more than three decades, it is now recognized to be the most common form of secondary hypertension. Using the plasma aldosterone to plasma renin activity ratio as a case-finding test, followed by aldosterone suppression confirmatory testing, has resulted in much higher prevalence estimates of 5–13% of all patients with hypertension. In addition, there has been a new recognition of the aldosterone-specific cardiovascular morbidity and mortality associated with aldosterone excess. Although thought to be daunting and complex in the past, the diagnostic approach to primary aldosteronism is straightforward and can be considered in three phases: case-finding tests, confirmatory tests and subtype evaluation tests. Patients with hypertension and hypokalaemia (regardless of presumed cause), treatment-resistant hypertension (three antihypertensive drugs and poor control), severe hypertension (≥ 160 mmHg systolic or ≥ 100 mmHg diastolic), hypertension and an incidental adrenal mass, onset of hypertension at a young age or patients being evaluated for other forms of secondary hypertension should undergo screening for primary aldosteronism. In patients with suspected primary aldosteronism, screening can be accomplished by measuring a morning (preferably between 0800 and 1000 h) ambulatory paired random plasma aldosterone concentration (PAC) and plasma renin activity (PRA). An increased PAC:PRA ratio is not diagnostic by itself, and primary aldosteronism must be confirmed by demonstrating inappropriate aldosterone secretion. Aldosterone suppression testing can be performed with orally administered sodium chloride and measurement of urinary aldosterone or with intravenous sodium chloride loading and measurement of PAC. Unilateral adrenalectomy in patients with APA or unilateral adrenal hyperplasia results in normalization of hypokalaemia in all these patients; hypertension is improved in all and is cured in approximately 30–60% of them. In bilateral adrenal forms of primary aldosteronism, unilateral or bilateral adrenalectomy seldom corrects the hypertension and they should be treated medically with a mineralocorticoid receptor antagonist.

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Introduction: 'painting background'

In his presidential address at the Annual Meeting of the Central Society for Clinical Research (Chicago, IL; 29 October 1954), Dr Jerome W. Conn stated: 'I have prepared no comprehensive review of my personal philosophy of clinical investigation. Instead, I plan to make a scientific report to you about a clinical syndrome, the investigation of which has been most exciting to me since I initiated it in April of this year.'[1] Conn, a Professor of Medicine at the University of Michigan, had been active in government-funded research on the mechanisms of human acclimatization to humid heat. He established that the body's acclimatization response was to decrease renal salt and water loss and curtail the salt content in sweat and saliva, and he suggested that it was due to increased release of salt-retaining steroids from the adrenal glands. In April 1954, he was asked to see a 34-year-old woman with a 7-year history of muscle spasms, temporary paralysis, tetany, and weakness and a 4-year history of hypertension. She was found to have a blood pressure of 176/104 mmHg, severe hypokalaemia (1·6–2·5 mmol/l), mild hypernatraemia (146–151 mmol/l) and alkalosis (serum pH 7·62). Because there were no signs or symptoms of glucocorticoid or androgen excess, Conn suspected, based on his past research, that this clinical presentation could result from excess secretion of the adrenal salt-retaining corticoid. Conn studied the patient in the Metabolism Research Unit for 227 days. Using Streeten's bioassay technique to measure sodium retention in adrenalectomized rats after intraperitoneal injection of human urine, the patient averaged 22-fold more mineralocorticoid activity per day compared with normotensive controls. In his presidential address Conn stated: 'It is believed that these studies delineate a new clinical syndrome which is designated

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Table 1. Subtypes of primary aldosteronism

Aldosterone-producing adenoma (APA) – 35% of cases
Bilateral idiopathic hyperplasia (IHA) – 60% of cases
Primary (unilateral) adrenal hyperplasia –2% of cases
Pure aldosterone-producing adrenocortical carcinoma – < 1% of cases
Familial hyperaldosteronism (FH)
Glucocorticoid-remediable aldosteronism (FH type I) – < 1% of cases
FH type II (APA or IHA) –?% of cases
Ectopic aldosterone-producing adenoma or carcinoma – < 0·1% of cases

temporarily as primary aldosteronism.'[1] Conn planned for a bilateral adrenalectomy on 10 December 1954. In the 1995 Gittler and Fajans retelling of the surgical scene: 'To the immense delight of Conn and those in the operating room, the surgeon, Dr William Baum, encountered a right 13-g adrenal tumour which was removed while leaving the contralateral gland intact. The patient's postoperative studies showed an almost total reversal of the preoperative metabolic and clinical abnormalities. Conn … established for the first time the relationship among adrenal aldosterone-producing tumours, hypertension, and hypokalemia. A new era had arrived in the study of hypertension and adrenal mineralocorticoids.'[2]

By 1964, Conn had collected 145 cases,[3] and he suggested that up to 20% of patients with essential hypertension might have primary aldosteronism.[3] This suggestion was downplayed by others as a gross overestimate.[4,5] Later, Conn adjusted his predicted prevalence of primary aldosteronism to 10% of hypertensives,[6] a prediction that was substantiated nearly 40 years later.

In addition to the aldosterone-producing adenoma (APA) described by Conn, six other subtypes of primary aldosteronism have been described over the subsequent four decades. APA and bilateral idiopathic hyperaldosteronism (IHA) are the most common subtypes of primary aldosteronism (Table 1). A much less common form, unilateral hyperplasia or primary adrenal hyperplasia (PAH), is caused by micronodular or macronodular hyperplasia of the zona glomerulosa of predominantly one adrenal gland. Familial hyperaldosteronism (FH) is also rare and two types have been described: FH type I and type II. FH type I, or glucocorticoid-remediable aldosteronism (GRA), is autosomal dominant in inheritance and associated with variable degrees of hyperaldosteronism, high levels of hybrid steroids (e.g. 18-hydroxycortisol and 18-oxocortisol), and suppression with exogenous glucocorticoids.[7] FH type II refers to the familial occurrence of APA or IHA or both.[8] Ectopic aldosterone-secreting tumours (e.g. neoplasms in the ovary or kidney) are exceedingly rare.[9]

Prevalence: evolving recognition

In the past, clinicians would not consider the diagnosis of primary aldosteronism unless the patient presented with spontaneous hypokalaemia, and then the diagnostic evaluation would require discontinuing antihypertensive medications for at least 2 weeks. The spontaneous 'hypokalaemia/no antihypertensive drug' diagnostic approach resulted in predicted prevalence rates of less than 0·5% of hypertensive patients.[4,5,10–14] However, it is now recognized that most patients with primary aldosteronism are not hypokalaemic[15,16] and that screening can be completed with a simple blood test [plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio] while the patient is taking most antihypertensive drugs.[17–19] Using the PAC:PRA ratio as a case-finding test, followed by aldosterone suppression confirmatory testing, has resulted in much higher prevalence estimates (5–13% of all patients with hypertension) for primary aldosteronism.[20–26]

Clinical presentation: a new understanding of aldosterone-dependent morbidity

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decade of life. Few symptoms are specific to the syndrome. Patients with marked hypokalaemia may have muscle weakness and cramping, headaches, palpitations, polydipsia, polyuria, nocturia, or a combination of these. The polyuria and nocturia are a result of hypokalaemia-induced renal concentrating defect and the presentation is frequently mistaken for prostatism in men. There are no specific physical findings. Oedema in not a common finding because of 'mineralocorticoid escape'. The degree of hypertension is usually moderate to severe and may be resistant to usual pharmacological treatments.[27] In the first 262 cases of primary aldosteronism diagnosed at Mayo Clinic (1957–86), the highest blood pressure was 260/155 mmHg; the mean (± SD) was 184/112 ± 28/16 mmHg.[27] Hypertensive emergencies are not uncommon.[28] Patients with APA tend to have higher blood pressures than those with IHA.[29] Hypokalaemia is frequently absent; thus, all patients with hypertension are candidates for this disorder. In other patients, the hypokalaemia may become evident with addition of a potassium-wasting diuretic. Because of a reset osmostat, the serum sodium concentration tends to be high-normal or slightly above the upper limit of normal. This clinical clue is very useful when initially assessing the potential for primary aldosteronism.

Several studies have shown that patients with primary aldosteronism may be at higher risk than other patients with hypertension for target-organ damage of the heart and kidney.[30,31] When matched for age, blood pressure and duration of hypertension, patients with primary aldosteronism have greater left ventricular mass measurements than patients with other types of hypertension (e.g. pheochromocytoma, Cushing's syndrome or essential hypertension).[32] In patients with APA, the left ventricular wall thickness and mass decreases markedly after 1 year from the time of adrenalectomy.[33] A case–control study of 124 patients with primary aldosteronism and 465 patients with essential hypertension (matched for age, sex, and systolic and diastolic blood pressure) found that patients presenting with either APA or IHA had a significantly higher rate of cardiovascular events (e.g. stroke, atrial fibrillation and myocardial infarction) than the matched essential hypertension patients.[31] A negative effect of circulating aldosterone on cardiac function was found in young nonhypertensive subjects with GRA that had increased left ventricular wall thickness and reduced diastolic function compared with age- and sex-matched controls.[30] In addition, arterial wall stiffness was independently increased in 36 patients with primary aldosteronism compared to 28 patients with essential hypertension that were

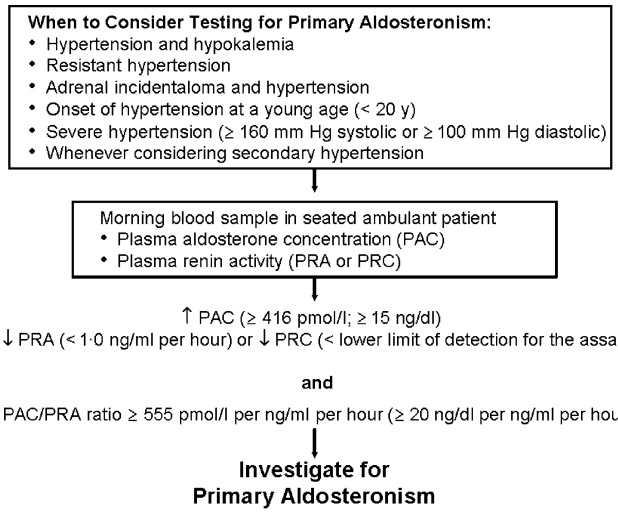


Fig. 1 When to consider testing for primary aldosteronism and use of the plasma aldosterone concentration-to-plasma renin activity ratio as a case-finding tool. PAC, plasma aldosterone concentration; PRA, plasma renin activity; PRC, plasma renin concentration.

matched for blood pressure, age, body mass index, cholesterol, triglyceride, blood glucose levels.[34]

In a large study from Italy, patients with APA or IHA had a higher urinary albumin excretion rate than comparable patients with essential hypertension.[35] Others have shown partially reversible renal dysfunction in which elevated albuminuria is a marker of a dynamic rather than structural renal defect.[36] In a study of 85 patients with primary aldosteronism and 381 patients with essential hypertension, the prevalence of metabolic syndrome was higher in primary aldosteronism than in essential hypertension (41·1% *vs.* 29·6%; $P < 0{\cdot}05$).[37] The aldosterone-dependent cardiovascular morbidity is one of the factors used to justify the cost-effectiveness of increased efforts at case-finding. A prospective study to determine the cost-effectiveness of more widespread testing for primary aldosteronism has not been done.

Diagnosis: a simplified approach

Although thought to be daunting and complex in the past, the diagnostic approach to primary aldosteronism is straightforward and can be considered in three phases: case-finding tests, confirmatory tests and subtype evaluation tests.

Case-finding testing

Spontaneous hypokalaemia is uncommon in patients with uncomplicated hypertension and, when present, strongly suggests associated mineralocorticoid excess. However, several studies have shown that most patients with primary aldosteronism have baseline blood levels of potassium in the normal range.[15,20,38–40] Therefore, hypokalaemia is not and should not be the criterion used to make the diagnosis of primary aldosteronism. Patients with hypertension and hypokalaemia (regardless of presumed cause), treatment-resistant hypertension (three antihypertensive drugs and poor control), severe hypertension (≥ 160 mmHg systolic or ≥ 100 mmHg diastolic), hypertension and an incidental adrenal mass, and onset of hypertension at a young age should undergo screening for primary aldosteronism (Fig. 1). In addition, the diagnosis of primary aldosteronism should be considered whenever performing a secondary hypertension evaluation (e.g. when testing for renovascular disease or pheochromocytoma).

In patients with suspected primary aldosteronism, screening can be accomplished by measuring a morning (preferably between 0800 and 1000 h) ambulatory paired random PAC and PRA (Fig. 1). This test may be performed while the patient is taking antihypertensive medications [with some exceptions (see below)] and without posture stimulation.[19,20,41–44] Hypokalaemia reduces the secretion of aldosterone, and it is optimal to restore the serum level of potassium to normal before performing diagnostic studies. Mineralocorticoid receptor antagonists (e.g. spironolactone and eplerenone)[44] and high-dose amiloride are the only medications that absolutely interfere with interpretation of the ratio and should be discontinued at least 6 weeks before testing. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists (ARB) and diuretics have the potential to 'falsely elevate' PRA. Therefore, in a patient treated with an ACE inhibitor, ARB or diuretic the finding of a detectable PRA level or a low PAC:PRA ratio does not exclude the diagnosis of primary aldosteronism. However, a very useful clinical point is that when a PRA level is undetectably low in a patient taking an ACE inhibitor, ARB or a diuretic, primary aldosteronism should be highly suspect. Thus, ACE inhibitors, ARBs and non-potassium-sparing diuretics do not need to be discontinued.[44] A second important clinical point is that the PRA is suppressed (< 1·0 ng/ml per hour) in almost all patients with primary aldosteronism. Adrenergic inhibitors (e.g. beta-adrenergic blockers and central alpha-2 agonists) suppress renin secretion,[44] but also in turn suppress aldosterone secretion (although to a lesser degree than renin) in normal individuals; thus, although the PAC/PRA may rise in hypertensive patients without primary aldosteronism treated with adrenergic inhibitors, the PAC remains less than 416 pmol/l (15 ng/dl) and the case finding test is not significantly affected.[44]

The PAC:PRA ratio is based on the concept of paired hormone measurements. For example, in a hypertensive hypokalaemic patient (i) secondary hyperaldosteronism should be considered when both PRA and PAC are increased and the PAC:PRA ratio is less than 277 in SI units [10 in convential units (e.g. renovascular disease)]; (ii) an alternate source of mineralocorticoid receptor agonism should be considered when both PRA and PAC are suppressed (e.g. hypercortisolism); and (iii) primary aldosteronism should be suspected when PRA is suppressed (< 1·0 ng/ml per hour) and PAC is increased. At least 14 prospective studies have been published on the use of the PAC:PRA ratio in screening for primary aldosteronism.[45] Although there is some uncertainty about test characteristics and lack of standardization (see below), the PAC:PRA ratio is widely accepted as the screening test of choice for primary aldosteronism. It is important to understand that the lower limit of detection varies among different PRA assays and can have a dramatic effect on the PAC:PRA ratio. Thus, the cut-off for a 'high' PAC:PRA ratio is laboratory-dependent and, more specifically, PRA assay-dependent. In a retrospective study, the combination of a PAC:PRA ratio of more

than 832 (30 in conventional units) and PAC of more than 555 pmol/l (20 ng/dl) had a sensitivity of 90% and a specificity of 91% for APA.[46] At the Mayo Clinic, a PAC (in pmol/l) : PRA (in ng/ml per hour) ratio of 555 (20 in conventional units) or more and PAC of at least 416 pmol/l (15 ng/dl) are found in more than 90% of patients with surgically confirmed APA. A PAC of > 416 pmol/l (15 ng/dl) is the high normal range (normal range, 28–583 pmol/l; 1–21 ng/dl). In patients without primary aldosteronism, most of the variation in PAC:PRA ratios occurs within the normal range.[47] A high PAC:PRA ratio is a positive screening test result, a finding that warrants further testing.

It is important for the clinician to recognize that the PAC:PRA ratio is only a case-finding tool, and all positive results should be followed by a confirmatory aldosterone suppression test to verify autonomous aldosterone production before treatment is initiated. In a recent study of 118 subjects with essential hypertension, neither antihypertensive medications nor acute variation of dietary sodium affected the accuracy of the PAC:PRA ratio adversely, with a sensitivity on and off therapy of 73% and 87%, respectively, and a specificity of 74% and 75%, respectively.[20] In a study of African American and Caucasian subjects with resistant hypertension, the PAC:PRA ratio was elevated (> 555; > 20 in conventional units) in 45 of 58 subjects with primary aldosteronism and in 35 of 207 patients without primary aldosteronism (sensitivity of 78% and specificity of 83%).[42] Furosemide and upright posture do not improve the post-test probability for APA more than the use of the baseline PAC:PRA ratio.[48]

The measurement of PRA is time consuming, shows poor inter-laboratory variability, and requires special pre-analytical prerequisites. To overcome these disadvantages, a monoclonal antibody against active renin is being used by several reference laboratories to measure plasma renin concentration (PRC) instead of PRA. However, few studies have focused on comparing the different methods in the testing for primary aldosteronism and these studies lack confirmatory testing.[49,50] In one study with 76 normotensive volunteers and 28 patients with confirmed primary aldosteronism, the PAC:PRC ratio performed as well as the PAC:PRA ratio in differentiating primary aldosteronism patients from normal volunteers.[51] Before a recommendation to replace PRA with PRC in the testing for primary aldosteronism can be made, more studies with larger cohorts are needed. Until such studies are completed it would be reasonable to consider a positive PAC/PRC test when the PAC is more than 416 pmol/l (15 ng/dl) and the PRC is below the lower limit of detection for the assay (Fig. 1).

Confirmatory testing

An increased PAC:PRA ratio is not diagnostic by itself, and primary aldosteronism must be confirmed by demonstrating inappropriate aldosterone secretion. The list of drugs and hormones capable of affecting the renin–angiotensin–aldosterone axis is extensive, and frequently in patients with severe hypertension, a 'medication-contaminated' evaluation is unavoidable. Certain calcium channel blockers (e.g. verapamil) and α_1-adrenergic receptor blockers do not affect the diagnostic accuracy in most cases. It is impossible to interpret data obtained from patients receiving treatment with mineralocorticoid receptor antagonists (e.g. spironolactone, eplerenone) or high-dose amiloride when PRA is not suppressed. Therefore, treatment with a mineralocorticoid receptor antagonist should not be initiated until the evaluation has been completed and the final decisions about treatment have been made. If primary aldosteronism is suspected in a patient receiving treatment with a mineralocorticoid receptor antagonist or high-dose amiloride, the treatment should be discontinued for at least 6 weeks before further diagnostic testing. Aldosterone suppression testing can be performed with orally administered sodium chloride and measurement of urinary aldosterone or with intravenous sodium chloride loading and measurement of PAC.

Oral sodium loading test. After hypertension and hypokalaemia are controlled, patients should receive a high sodium diet (supplemented with sodium chloride tablets if needed) for 3 days, with a goal sodium intake of 218 mmol of sodium (equivalent to 12·8 g sodium chloride).[27] The risk of increasing dietary sodium in patients with severe hypertension must be assessed in each case.[52] Because the high salt diet can increase kaliuresis and hypokalaemia, vigorous replacement of potassium chloride may be needed and the serum level of potassium should be monitored daily. On the third day of the high sodium diet, a 24-h urine specimen is collected for measurement of aldosterone, sodium and creatinine. To document adequate sodium repletion, the 24-h urinary sodium excretion should exceed 200 mmol. Urinary aldosterone excretion more than 33 nmol/d (12 μg/24 h) in this setting is consistent with autonomous aldosterone secretion.[53] The sensitivity and specificity of the oral sodium loading test are 96% and 93%, respectively.[54]

Intravenous saline infusion test. The intravenous saline infusion test has also been used widely for the diagnosis of primary aldosteronism.[55–58] Normal subjects show suppression of PAC after volume expansion with isotonic saline; subjects with primary aldosteronism do not show this suppression. The test is done after an overnight fast. Two litres of 0·9% sodium chloride solution are infused intravenously with an infusion pump over 4 h into the recumbent patient. Blood pressure and heart rate are monitored during the infusion. At the completion of the infusion, blood is drawn for measurement of PAC. PAC levels in normal subjects decrease to less than 139 pmol/l (5 ng/dl)[58]; most patients with primary aldosteronism do not suppress to less than 277 pmol/l (10 ng/dl); postsaline infusion PAC values between 139 and 277 pmol/l (5 and 10 ng/dl) are indeterminate and can be seen in patients with IHA.[12,55,56,59]

Fludrocortisone suppression test. In the fludrocortisone suppression test, fludrocortisone acetate is administered for 4 days (0·1 mg every 6 h) in combination with sodium chloride tablets (2 g three times daily with food). Blood pressure and serum potassium need to be monitored daily. In the setting of low PRA, failure to suppress the upright 1000 h PAC to less than 166 pmol/l (6 ng/dl) on day 4 is diagnostic of PA.[60] It should be noted that increased QT dispersion on the electrocardiogram and deterioration of left ventricular function have been reported during fludrocortisone suppression tests.[52] Most centres no longer use the fludrocortisone suppression test.

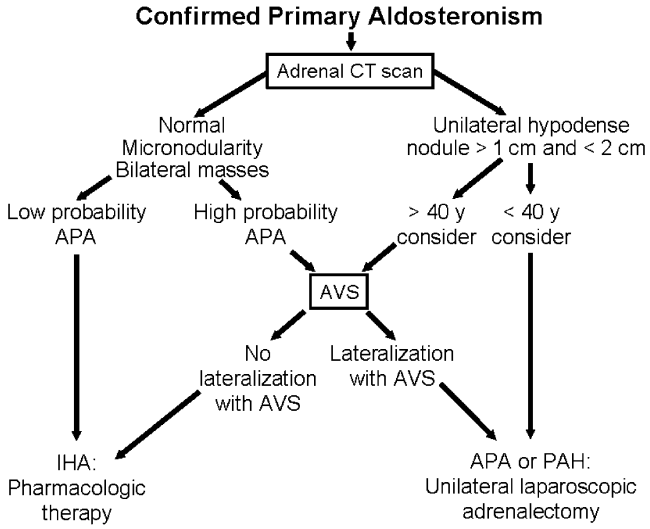


Fig. 2 Subtype evaluation of primary aldosteronism. See text for details. APA, aldosterone-producing adenoma; AVS, adrenal venous sampling; CT, computed tomography; IHA, idiopathic hyperaldosteronism; PAH, primary adrenal hyperplasia. (Modified from Young & Hogan.[64])

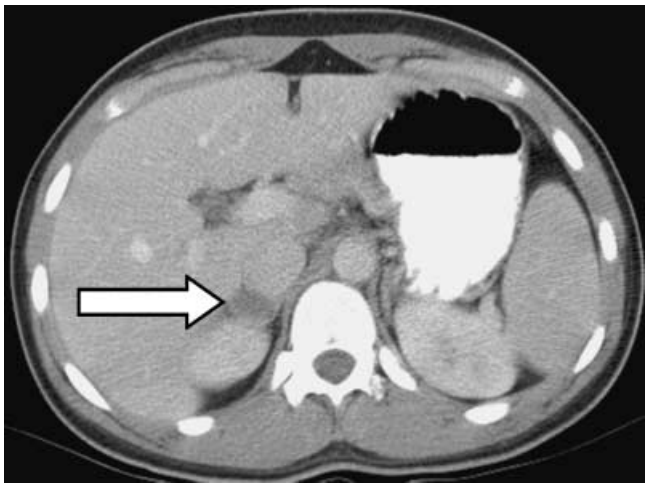


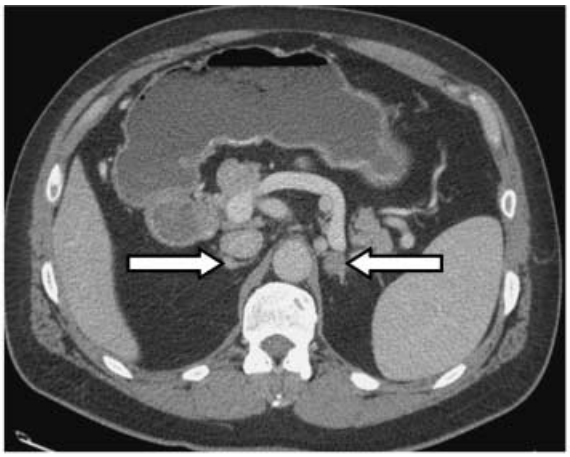
Fig. 3 Appearance of a 2·2-cm right adrenal nodule (arrow) on contrast-enhanced computed tomography in a 17-year-old woman. The patient presented with new-onset hypertension and hypokalaemia (1·4 mmol/l) with inappropriate kaliuresis. She required 300 mEq of oral potassium chloride daily to maintain serum potassium in the normal range. The screening test for primary aldosteronism was positive, with a plasma aldosterone concentration (PAC) of 1414 pmol/l and low plasma renin activity (PRA) at < 0·6 ng/ml per hour (PAC:PRA ratio > 2350). The confirmatory test for primary aldosteronism was also positive, with 24-h urinary excretion of aldosterone of 116 nmol/d on a high sodium diet (urinary sodium = 206 mmol/d). The patient had a laparoscopic right adrenalectomy to remove a 2·2 × 2·2 × 1·1-cm adenoma. Postoperatively, the plasma aldosterone concentration was < 28 pmol/l. Hypertension and hypokalaemia were cured.

Subtype studies

Following case-finding and confirmatory testing, the third management issue guides the therapeutic approach by distinguishing APA and PAH from IHA and GRA. Unilateral adrenalectomy in patients with APA or PAH results in normalization of hypokalaemia in all; hypertension is improved in all and is cured in approximately 30–60% of them.[61–63] In IHA and GRA, unilateral or bilateral adrenalectomy seldom corrects the hypertension.[27] IHA and GRA should be treated medically. APA is found in approximately 35% of cases and bilateral IHA in approximately 60% of cases (Table 1). APAs are usually small hypodense nodules (< 2 cm in diameter) on computed tomography (CT) and are golden yellow in colour when resected. IHA adrenal glands may be normal on CT or show nodular changes. Aldosterone-producing adrenal carcinomas are almost always > 4 cm in diameter and have an inhomogeneous imaging phenotype on CT.

Adrenal CT. Primary aldosteronism subtype evaluation may require one or more tests, the first of which is imaging the adrenal glands with CT (Fig. 2). When a solitary, unilateral, small, and hypodense macro-adenoma (> 1 cm and < 2 cm) and normal contralateral adrenal morphology are found on CT in a young patient (< 40 years) with primary aldosteronism, unilateral adrenalectomy is a reasonable therapeutic option (Fig. 3). However, in many cases, CT may show normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral micro-adenomas (≤ 1 cm), or bilateral macro- or micro-adenomas or a combination of the two (Fig. 4a). In these cases, additional testing is required to determine the source of excess aldosterone secretion. Small APAs may be labelled incorrectly as 'IHA' on the basis of CT findings of bilateral nodularity or normal-appearing adrenals. Also, apparent adrenal micro-adenomas may actually represent areas of hyperplasia, and unilateral adrenalectomy would be inappropriate. In addition, nonfunctioning unilateral adrenal macro-adenomas are not uncommon, especially in older patients (> 40 years).[65] Unilateral PAH may be visible on CT or the PAH adrenal may appear normal on CT. In general, patients with APAs have more severe hypertension, more frequent hypokalaemia, higher plasma (> 694 pmol/l; > 25 ng/dl) and urinary (> 83 nmol/d; > 30 μg/24 h) levels of aldosterone, and are younger (< 50 years) than those with IHA.[27,29] Patients fitting these descriptors are considered to have a 'high probability of APA' regardless of the CT findings (Fig. 2); 41% of patients with 'high probability of APA' and a normal adrenal CT scan prove to have unilateral aldosterone hypersecretion.[66]

Adrenal CT is not accurate in distinguishing between APA and IHA. In one study, CT contributed to lateralization in only 59 of 111 patients with surgically proven APA; CT detected fewer than 25% of the APAs that were smaller than 1 cm in diameter.[67] In a another study of 203 patients with primary aldosteronism who were evaluated with both CT and adrenal vein sampling, CT was accurate in only 53% of patients[66]; based on CT findings, 42 patients (22%) would have been incorrectly excluded as candidates for adrenalectomy and 48 (25%) might have had unnecessary or inappropriate surgery. In a recent study, adrenal vein sampling was performed in 41 patients with primary aldosteronism and concordance between CT and adrenal vein sampling was only 54%.[68] Therefore, adrenal venous sampling is essential to direct appropriate therapy in patients with primary aldosteronism who have a high probability of APA and who seek a potential surgical cure.



Results of Bilateral Adrenal Venous Sampling

Vein	Aldosterone (A), pmol/l	Cortisol (C), nmol/l	A/C ratio	Aldosterone ratio*
R adrenal vein	405226	32004	12·7	23·8
L adrenal vein	15063	28252	0·5	
Inferior vena cava	1526	690	2·2	

*R adrenal vein A/C ratio divided by L adrenal vein A/C ratio.

Fig. 4 A 55-year-old man had a 12-year history of hypertension and hypokalaemia. The screening test for primary aldosteronism was positive, with a plasma aldosterone concentration (PAC) of 600 pmol/l and low plasma renin activity (PRA) at < 0·6 ng/ml per hour (PAC:PRA ratio > 1000). The confirmatory test for primary aldosteronism was also positive, with 24-h urinary excretion of aldosterone of 91·5 nmol/d on a high sodium diet (urinary sodium, 227 mmol/d). (a) Adrenal computed tomography with a 12-mm mass (arrow) in the left adrenal and two nodules (6 mm and 4 mm) within the right adrenal gland (arrow). (b) Adrenal venous sampling lateralized aldosterone secretion to the right, and two cortical adenomas (11 and 5 mm) were found at laparoscopic right adrenalectomy. The postoperative plasma aldosterone concentration was < 28 pmol/l. Hypokalaemia was cured and blood pressure was normal without the aid of antihypertensive medications.

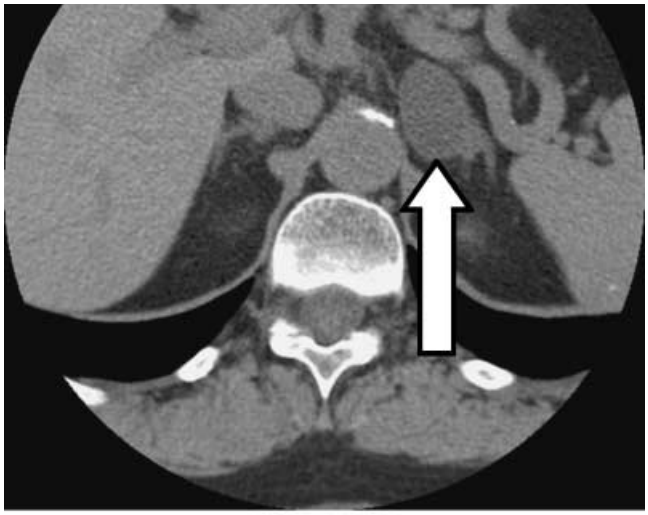
Adrenal venous sampling. Adrenal venous sampling is the reference standard test to differentiate unilateral from bilateral disease in patients with primary aldosteronism.[66,67] Adrenal venous sampling is a difficult procedure because the right adrenal vein is small; the success rate depends on the proficiency of the angiographer. According to a review of 47 reports, the success rate for cannulating the right adrenal vein in 384 patients was 74%.[27] With experience, the success rate rises to 90–96%.[66,69,70] Some centres perform adrenal venous sampling in all patients who have the diagnosis of primary aldosteronism.[66] A more practical approach is the selective use of adrenal venous sampling[66,71] outlined in the Fig. 2. Many groups advocate the use of continuous cosyntropin infusion during adrenal venous sampling for the following reasons: (i) to minimize stress-induced fluctuations in aldosterone secretion during nonsimultaneous adrenal vein sampling; (ii) to maximize the gradient in cortisol from adrenal vein to inferior vena cava and thus confirm successful sampling of the adrenal vein; and (iii) to maximize the secretion of aldosterone from an APA.[57,66,72] An infusion of 50 μg of cosyntropin per hour is initiated 30 min before adrenal vein catheterization and continued throughout the procedure.[57,66,70] However, some groups have suggested that, when given as a bolus injection and when the adrenal veins are sampled simultaneously, cosyntropin administration does not improve the diagnostic accuracy of adrenal venous sampling.[73]

The adrenal veins are catheterized through the percutaneous femoral vein approach; blood is obtained from both adrenal veins and the inferior vena cava (IVC) below the renal veins and assayed for aldosterone and cortisol concentrations. To be sure there is no cross-contamination, the 'IVC' sample should be obtained from an iliac vein. The venous sample from the left side typically is obtained from the inferior phrenic vein immediately adjacent to the entrance of the adrenal vein. The right adrenal vein may be especially difficult to catheterize because it is short and enters the IVC at an acute angle.[70] The cortisol concentrations from the adrenal veins and IVC are used to confirm successful catheterization; the adrenal vein/IVC cortisol ratio is typically more than 10 : 1 with the continuous cosyntropin infusion protocol,[66] and more than 3 : 1 without the use of cosyntropin.[69]

Dividing the right and left adrenal vein PACs by their respective cortisol concentrations corrects for the dilutional effect of the inferior phenic vein flow into the left adrenal vein; these are termed 'cortisol-corrected ratios' (Fig. 4b). In patients with APA, the mean cortisol-corrected aldosterone ratio (APA-side PAC/cortisol : normal adrenal PAC/cortisol) is 18 : 1.[66] A cut-off of the cortisol-corrected aldosterone ratio from high side to low side of more than 4 : 1 is used to indicate unilateral aldosterone excess (Fig. 4b).[66] In patients with IHA, the mean cortisol-corrected aldosterone ratio is 1·8 : 1 (high side : low side); a ratio less than 3 : 1 is suggestive of bilateral aldosterone hypersecretion (Fig. 5).[66] Therefore, most patients with a unilateral source of aldosterone will have cortisol-corrected aldosterone lateralization ratios greater than 4·0; ratios greater than 3·0 but less than 4·0 represent a zone of overlap. Ratios no more than 3·0 are consistent with bilateral aldosterone secretion. The test characteristics of adrenal vein sampling for detecting unilateral aldosterone hypersecretion (APA or PAH) are sensitivity of 95% and specificity of 100%.[66] At centres with experience with adrenal vein sampling, the complication rate is 2·5% or less.[66,69] Complications can include symptomatic groin haematoma, adrenal haemorrhage and dissection of an adrenal vein. Adrenal venous sampling is essential to direct appropriate therapy for patients with primary aldosteronism who have a clinically high probability of APA.

In clinical settings where adrenal vein sampling is not available, pharmacological therapy should be considered (see below).

Subtype studies for GRA – familial hyperaldosteronism type I. This syndrome is inherited in an autosomal dominant fashion and is responsible for fewer than 1% of cases of primary aldosteronism (Table 1).[7] GRA is characterized by hypertension of early onset that is usually severe and refractory to conventional antihypertensive therapies, aldosterone excess, suppressed PRA, and excess production of 18-hydroycortisol and 18-oxycortisol. GRA is caused by a chimeric gene duplication that results from unequal crossing over between the



Results of Bilateral Adrenal Venous Sampling

Vein	Aldosterone (A), pmol/l	Cortisol (C), nmol/l	A/C ratio	Aldosterone ratio*
R adrenal vein	4855	9215	0·52	
L adrenal vein	9903	11119	0·89	1·71
Inferior vena cava	527	1435	0·37	

*L adrenal vein A/C ratio divided by R adrenal vein A/C ratio.

Fig. 5 A 64-year-old woman had a 7-year history of hypertension and spontaneous hypokalaemia. The screening test for primary aldosteronism was positive, with a plasma aldosterone concentration (PAC) of 472 pmol/l and low plasma renin activity (PRA) at < 0·6 ng/ml per hour (PAC:PRA ratio > 785). The confirmatory test for primary aldosteronism was also positive, with 24-h urinary excretion of aldosterone of 44·4 nmol/d on a high sodium diet (urinary sodium, 323 mmol/d). (a) Adrenal computed tomography with a 3·3 × 2·1-cm low-density mass (arrow) in the medial limb of the left adrenal gland. (b) Adrenal venous sampling did not lateralize aldosterone secretion above a cut-off of 4 : 1 and was consistent with bilateral idiopathic hyperaldosteronism. She was treated medically with a mineralocorticoid-receptor antagonist. The right adrenal mass was followed as an adrenal incidentaloma: testing for pheochromocytoma and autonomous cortisol secretion was negative. Serial imaging showed no change in the adrenal mass over 2 years.

promoter sequence of CYP11B1 gene (encoding 11β-hydroxylase) and the coding sequence of CYP11B2 (encoding aldosterone synthase).[7] This chimeric gene contains the 3′ corticotropin-responsive portion of the promoter from the 11β-hydroxylase gene fused to the 5′ coding sequence of the aldosterone synthase gene. The result is ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata. Thus, mineralocorticoid production is regulated by corticotropin instead of the normal secretagogue, angiotensin II; aldosterone secretion can be suppressed by glucocorticoid therapy. Genetic testing is a sensitive and specific means of diagnosing GRA. However, in view of its rarity, it is not recommended that all patients with primary aldosteronism undergo genetic testing for GRA,[74,75] but rather, genetic testing for GRA should be considered for primary aldosteronism patients with a family history of primary aldosteronism or onset of primary aldosteronism at a young age (e.g. < 20 years), or in primary aldosteronism patients who have a family history of strokes at a young age.[75,76]

Subtype studies for FH type II. FH type II is autosomal dominant and may be monogenic.[8] The hyperaldosteronism in FH type II does not suppress with dexamethasone and GRA mutation testing is negative. Although FH type II is more common than FH type I, the true prevalence is unknown. The molecular basis for FH type II is unclear, although a recent linkage analysis study showed an association with chromosomal region 7p22.[8]

Subtype tests used in the past. [131I]-19-Iodocholesterol scintigraphy was first used in the early 1970s and improved agents (e.g. [6β-131I]iodomethyl-19-norcholesterol [NP-59] and 75Se-selenomethyl-cholesterol) were introduced in the late 1970s.[77] The NP-59 scan, performed with dexamethasone suppression, had the advantage of correlating function with anatomical abnormalities. However, the sensitivity of this test depended heavily on the size of the adenoma.[78,79] Because tracer uptake was poor in adenomas smaller than 1·5 cm in diameter, this method often was not helpful in interpreting micronodular findings obtained with high-resolution CT. In addition to its poor sensitivity, other reasons that NP-59 is rarely used in the USA include (i) NP-59 is not approved by the Food and Drug Administration (FDA), and its use requires institutional review board approval; (ii) dexamethasone is administered at 1 mg every 6 h starting 7 days before NP-59 injection and continued throughout the scanning period; (iii) imaging starts on day 4 after NP-59 injection and may continue daily through day 10; (iv) a lateralizing scan can be seen in adrenal cortical adenomas that do not secrete aldosterone; and (v) only three or four centres in the USA currently offer NP-59 scintigraphy.

The posture stimulation test, also developed in the 1970s, was based on the finding that PAC in patients with APA showed diurnal variation and was relatively unaffected by changes in angiotensin II levels, whereas IHA was characterized by enhanced sensitivity to a small change in angiotensin II that occurred with standing.[80] After an overnight recumbency, an indwelling catheter is inserted at 0700 h and a blood sample is collected to 0800 h for measurement of PAC, PRA, cortisol and potassium. Blood is collected again at 1200 h, after the patient has been upright and ambulatory since 0800 h, for these same measurements. PAC in recumbent and hypertensive controls and normal subjects are normal and increase two- to fourfold after 4 h in the upright posture. Patients with IHA typically have a postural increase in PAC of at least 33% over baseline. In a patient with primary aldosteronism, the absence of the normal postural increase in PAC supports the diagnosis of APA or GRA. The posture stimulation test is valid only if the normal diurnal decrease in ACTH is confirmed by a decrease in the cortisol levels between 0800 h and 1200 h. If both PAC and cortisol increase in these 4 h, the test should be considered invalid. In a review of 16 published reports, the accuracy of the posture stimulation test was 85% in 246 patients with surgically verified APA.[27] However, it became clear that some APAs were sensitive to angiotensin II and that some patients with IHA had diurnal variation in aldosterone secretion. In addition, although the

posture stimulation test may have predicted which patient had APA, it did not assist in localization.

18-Hydroxycorticosterone (18-OHB) is considered either the immediate precursor of aldosterone or a separate end product formed after 18-hydroxylation of corticosterone. Patients with APA generally have recumbent plasma 18-OHB levels greater than 100 ng/dl at 0800 h, whereas patients with IHA have levels that are usually less than 100 ng/dl.[81] 18-OHB actually proved to be a surrogate for PAC, which also tends to be higher in patients with APA than in those with IHA. However, the accuracy of supine morning 18-OHB and PAC in distinguishing between patients with APA and IHA is less than 80%.[27]

Treatment

The treatment goal is to prevent the morbidity and mortality associated with hypertension, hypokalaemia and cardiovascular damage.[38] The cause of the primary aldosteronism helps to determine the appropriate treatment. Normalization of blood pressure should not be the only goal in managing a patient who has primary aldosteronism. In addition to the kidney and colon, mineralocorticoid receptors occur in the heart, brain and blood vessels. Excessive secretion of aldosterone is associated with increased risk of cardiovascular disease and morbidity. Therefore, normalization of circulating aldosterone or mineralocorticoid receptor blockade should be part of the management plan for all patients with primary aldosteronism.[38]

Surgical treatment of aldosterone-producing adenoma and unilateral hyperplasia

Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia.[82] Although blood pressure control improves in nearly 100% of patients postoperatively, average long-term cure rates of hypertension after unilateral adrenalectomy for APA range from 30% to 72%.[61,63,83] Persistent hypertension following adrenalectomy is correlated directly with having more than one first-degree relative with hypertension, use of more than two antihypertensive agents preoperatively, older age, increased serum creatinine level, and duration of hypertension and is most likely due to coexistent primary hypertension.[61,63,83,84]

Laparoscopic adrenalectomy is the preferred surgical approach and is associated with shorter hospital stays and less long-term morbidity than the conventional open approach.[82,85] Because APAs are small and may be multiple, the entire adrenal gland should be removed.[86] To decrease the surgical risk, hypokalaemia should be corrected with potassium supplements and/or a mineralocorticoid receptor antagonist preoperatively. The mineralocorticoid receptor-antagonist and potassium supplements should be discontinued postoperatively. PAC should be measured 1–2 days after the operation to confirm a biochemical cure. Serum potassium levels should be monitored weekly for 4 weeks after surgery and a generous sodium diet should be followed to avoid the hyperkalaemia of hypoaldosteronism that may occur because of the chronic suppression of the renin–angiotensin–aldosterone axis. In approximately 5% of APA patients, clinically significant hyperkalaemia may develop after surgery and short-term fludrocortisone supplementation may be required. Typically, the hypertension resolves in 1–3 months postoperatively. It has been found that adrenalectomy for APA is significantly less expensive than long-term medical therapy.[87]

Pharmacological treatment

IHA and GRA should be treated medically. In addition, APA patients may be treated medically if the medical treatment includes mineralocorticoid receptor blockade.[88] A sodium-restricted diet (< 100 mEq of sodium per day), maintenance of ideal body weight, tobacco avoidance and regular aerobic exercise contribute significantly to the success of pharmacological treatment. No placebo-controlled randomized trials have evaluated the relative efficacy of drugs in the treatment of primary aldosteronism.[89] Spironolactone has been the drug of choice to treat primary aldosteronism for more than three decades.[90] It is available as 25-, 50- and 100-mg tablets. The dosage is 12·5–25 mg per day initially and is increased to 400 mg per day if necessary to achieve normokalaemia without the aid of oral potassium chloride supplementation. Hypokalaemia responds promptly, but hypertension may take as long as 4–8 weeks to be corrected. After several months of therapy, this dosage often can be decreased to as little as 25–50 mg per day; dosage titration is based on a goal serum potassium level in the high-normal range. Serum potassium and creatinine should be monitored frequently during the first 4–6 weeks of therapy (especially in patients with renal insufficiency or diabetes mellitus). Spironolactone has increased the half-life of digoxin, and for patients taking this drug, the dosage may need to be adjusted when treatment with spironolactone is started. Concomitant therapy with salicylates should be avoided because they interfere with the tubular secretion of an active metabolite and decrease the effectiveness of spironolactone. However, spironolactone is not selective for the aldosterone receptor. For example, antagonism at the testosterone receptor may result in painful gynecomastia, erectile dysfunction and decreased libido in men; agonist activity at the progesterone receptor results in menstrual irregularity in women.

Eplerenone is a steroid-based antimineralocorticoid that acts as a competitive and selective aldosterone receptor antagonist and was approved by the FDA for the treatment of uncomplicated essential hypertension in late 2003.[90] The 9,11-epoxide group in eplerenone results in a marked reduction of the molecule's progestational and anti-androgenic actions compared with spironolactone; eplerenone has 0·1% of the binding affinity to androgen receptors and less than 1% of the binding affinity to progesterone receptors compared with spironolactone. Treatment trials comparing the efficacy of eplerenone *vs.* spironolactone for the treatment of primary aldosteronism have not been published. Presumably, eplerenone will be the superior drug if it is shown to be as effective as spironolactone for the treatment of mineralocorticoid-dependent hypertension, because it lacks the limiting anti-androgen side-effects of spironolactone. Eplerenone is available as 25-mg and 50-mg tablets. It is approximately five times more expensive than spironolactone. For primary aldosteronism, it is reasonable to start with a dose of 25 mg twice daily (twice daily because of the shorter half-life of eplerenone

compared to spironolactone) and titrated upward for normokalaemia and blood pressure effect. The maximum dose approved by the FDA for hypertension is 100 mg daily. Potency studies with eplerenone show equal or 25–50% less milligram per milligram potency when compared with spironolactone. As with spironolactone, it is important to follow blood pressure, serum potassium and serum creatinine levels closely. Eplerenone is contraindicated in the setting of hyperkalaemia (serum potassium > 5·5 mEq/l), clinically significant renal insufficiency (serum creatinine > 2·0 mg/dl in men and > 1·8 mg/dl in women), diabetes mellitus with microalbuminuria, concomitant administration of strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole), or concomitant treatment with potassium-sparing diuretics. Side-effects include dizziness, headache, fatigue, diarrhoea, hypertriglyceridaemia and elevated liver enzymes.

Patients with IHA frequently require a second antihypertensive agent to achieve good blood pressure control. Hypervolaemia is a major reason for resistance to drug therapy, and low doses of a thiazide (e.g. 12·5–50 mg of hydrochlorothiazide daily) or a related sulphonamide diuretic are effective in combination with the aldosterone receptor antagonist. Because these agents often lead to further hypokalaemia, serum potassium levels should be monitored.

Before initiating treatment, GRA should be confirmed with genetic testing. In the GRA patient, chronic treatment with physiological doses of a glucocorticoid normalizes blood pressure and corrects hypokalaemia. The clinician should be cautious about iatrogenic Cushing's syndrome with excessive doses of glucocorticoids, especially with the use of dexamethasone in children. The smallest effective dose of shorter acting agents such as prednisone or hydrocortisone should be prescribed in relation to body surface area (e.g. hydrocortisone, 10–12 mg/m^2 per day). Target blood pressure in children should be guided by age-specific blood pressure percentiles. Children should be monitored by paediatricians with expertise in glucocorticoid therapy, with careful attention paid to preventing retardation of linear growth by overtreatment. Treatment with mineralocorticoid receptor antagonists in these patients may be just as effective and avoids the potential disruption of the hypothalamic–pituitary–adrenal axis and risk of iatrogenic side-effects. In addition, glucocorticoid therapy or mineralocorticoid receptor blockade may even have a role in normotensive GRA patients.[30]

Conclusions

Over the past 53 years, there has been a remarkable renaissance in our understanding of the syndrome of primary aldosteronism. It is now recognized as the most common form of secondary hypertension with prevalence estimates of ≈10% of all patients with hypertension. The recognition of aldosterone-specific cardiovascular morbidity and mortality associated with aldosterone excess should stimulate clinicians to increase efforts at case-finding. With more practical diagnostics, case-finding has become a simple two-step process; starting with a morning (preferably between 0800 and 1000 h) ambulatory paired random plasma aldosterone concentration (PAC) and plasma renin activity (PRA). A positive PAC:PRA ratio should be followed by aldosterone suppression testing to confirm the syndrome. The development of laparoscopic adrenalectomy has been a major advance for patients with unilateral adrenal disease. The availability of two mineralocorticoid receptor antagonists gives clinicians and patients a pharmacological therapy choice based on side-effects and cost.

However, the work on the syndrome that Conn started 53 years ago is not yet done. Many uncertainties remain. Will plasma renin concentration replace PRA in the testing algorithm? Where does low-renin hypertension stop and primary aldosteronism start? What is the aetiology of primary aldosteronism due to bilateral IHA? What mutation is responsible for FH type II and how common is it? What is the underlying pathophysiology of primary aldosteronism due to unilateral hyperplasia? Will eplerenone be just as effective as spironolactone in preventing long-term morbidity related to aldosterone excess? These and other questions will be answered in the coming decades as the renaissance continues.

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