In The Name Of God

Diagnosis and treatment of primary aldosteronis

Practical clinical perspectives

Introduction

- Hypertension, increased adrenal aldosterone secretion and suppressed renin are the three hallmarks of primary aldosteronism (PA), which was first fully described in 1955 [1]. Although estimates vary [2], the prevalence of PA is approximately 5% in patients with hypertension [3] and up to 20% in those with treatment-resistant hypertension [4, 5].

- Aldosterone-producing adenoma (APA) and bilateral idiopathic hyper aldosteronism (IHA) are the two most common subtypes of PA (Table 1) [11]. A less common form of PA, unilateral hyperplasia or primary adrenal hyperplasia (PAH), is caused by micronodular or macronodular hyperplasia of the zona glomerulosa of predominantly one adrenal gland. Familial hyper aldosteronism (FH) is rare, and germline mutations in four different genes have been described (see section on FH below).

Table 1 *Types of primary aldosteronism*

Type of primary aldosteronism	Cases
Aldosterone-producing adenoma (APA)	30%
Bilateral idiopathic hyperplasia (IHA)	60%
Primary (unilateral) adrenal hyperplasia	2%
Aldosterone-producing adrenocortical carcinoma	<1%
Familial hyperaldosteronism (FH)	
Glucocorticoid-remediable aldosteronism (FH type I)	<1%
FH type II (APA or IHA)	<6%
FH type III (germline *KCNJ5* mutations)	<1%
FH type IV (germline *CACNA1H* mutations)	<0.1%
Ectopic aldosterone-producing adenoma or aldosterone-producing carcinoma	<0.1%

Clinical Presentation

- *Primary aldosteronism* is usually diagnosed between 20 and 60 years of age. There is no reliable clinical phenotype to guide the clinician on which patients should be tested for PA. A hypokalaemia-induced renal-concentrating defect can result in polyuria and nocturia; this presentation is frequently mistaken for prostatism in men.
- *The degree of hypertension is typically moderate to severe and may be resistant to usual pharmacologic treatments* [12, 13]. The mean blood pressure (SD) was 184/112 mmHg in the first 262 patients with PA who were diagnosed at Mayo Clinic (1957–1986) [13]. *In general, patients with APA tend to have higher aldosterone levels and higher blood pressures than patients with IHA.*

- Because *hypokalaemia* is present in only 28% of patients with PA [14, 15], all patients with hypertension are potential candidates for this disorder. There is a unique subset of young patients (typically <35 years of age) who present with marked hypokalaemia but are not technically hypertensive with systolic/diastolic blood pressures of 130s/80s mmHg. These patients usually have APA and their pre-PA baseline blood pressures average 100/60 mmHg. Thus, although they do not meet the criteria for hypertension, there is a clinically significant change from baseline and presumably their young age and blood pressure counter regulatory mechanisms prevent hypertension, at least in the first year or two of the disease.

- *The prevalence of target-organ damage to the heart and kidney is increased in patients with PA compared to those with essential hypertension* [7, 10, 16]. Long-standing undiagnosed PA frequently leads to chronic kidney disease [17]. In a recent meta-analysis of 31 studies, including 3838 patients with PA and 9284 patients with essential hypertension, patients with APA and IHA had an increased risk of stroke [odds ratio (OR) 2.58], coronary artery disease (OR 1.77), atrial fibrillation (OR 3.52) and heart failure (OR 2.05) [10]. In addition, the diagnosis of PA increased the risk of diabetes (OR 1.33), metabolic syndrome (OR 1.53) and left ventricular hypertrophy (OR 2.29) [10]. *Thus, the cardiovascular toxicity in PA extends beyond hypertension; there is an aldosteronespecific toxicity.*
- *The risk of developing new-onset diabetes* mellitus was also demonstrated in a study of 2367 patients with PA who had no prior diagnosis of diabetes mellitus, in which 754 surgically treated patients with APA were matched with 3016 control subjects with essential hypertension [18]. The patients with PA who underwent adrenalectomy had a statistically significant reduced risk for incident diabetes and all-cause mortality compared with matched hypertensive controls [18].

- *Deep-seated renal cysts are found in up to 60% of patients with PA who have chronic hypokalaemia* [19].
- Because of a reset osmostat, the *serum sodium* concentration tends to be high–normal or slightly above the upper limit of normal [20]. This clinical sign is very useful in the initial assessment for potential PA, especially in patients treated with thiazide diuretics (where the serum sodium concentration tends to be low–normal).

Quality of life

Several studies have demonstrated the negative impact of PA on quality of life (QoL) [21–24]. Untreated patients with PA (APA and IHA) showed an impaired physical and mental QoL compared to the general population.

Symptoms of *anxiety, demoralization, stress, depression and nervousness* were more frequently reported in untreated patients with PA than in the general population and in patients with hypertension [25]. Adrenalectomy improved QoL and the symptoms of psychopathology.

After 1 year, almost all QoL measures had normalized for surgically managed patients, whereas most QoL measures had improved but not to the level of the general population for patients on medical treatment [26]. It is not clear whether these QoL differences between surgical and medical management were due in part to suboptimal dosages of MRAs in the medically managed cohort.

Prevalence

Before 1981, PA was thought to be a rare cause of hypertension [27–33]. Over time, it has been shown that most patients with PA are not hypokalaemic [11, 12, 14, 34] and that case detection testing can be completed without stopping antihypertensive medications [35]. Thus, *current prevalence estimates for PA are 5–10% of all patients with hypertension* [2, 3, 14, 15, 34, 36– 39]. In a recent study of 1672 unselected patients with hypertension, the prevalence of PA was 5.9% and was associated with the severity of hypertension: 3.9% and 11.8% in patients with stage 1 and stage 3 hypertension, respectively [15].

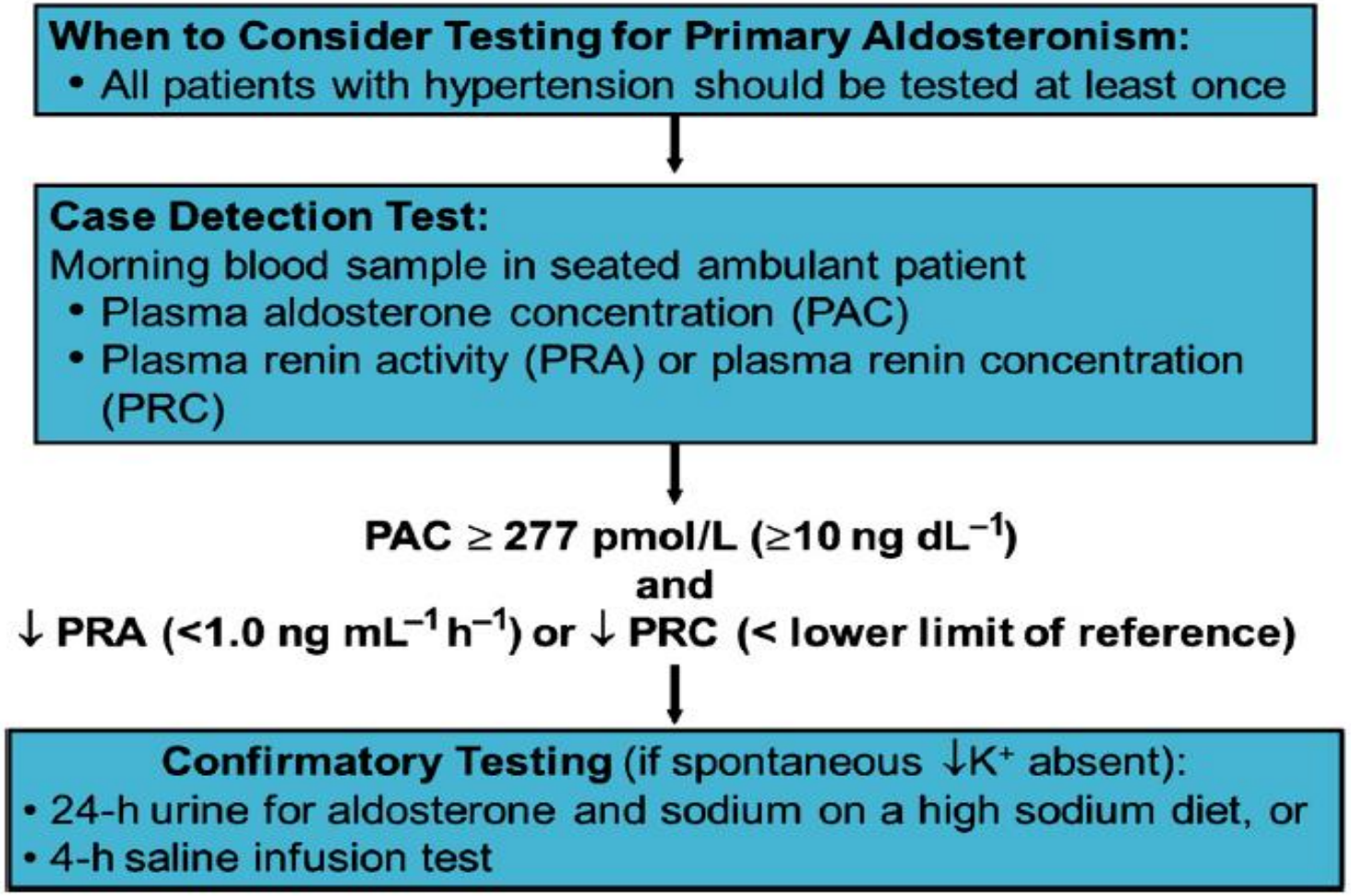
Who should be screened for PA?

- Unlike other adrenal disorders (e.g. Cushing syndrome), there is no typical PA phenotype to guide the clinician to suspect PA. Serum potassium status is not a reliable guide for screening for PA because 72% of patients with PA are normokalemic [11, 14, 15].
- In efforts to conserve medical costs and limit the consequences of false-positive case detection testing, the Endocrine Society guidelines on PA [11] recommend testing high-risk groups for PA. These groups include: (i) *patients with sustained blood pressure above 150/100 mmHg on each of three measurements obtained on different days*; (ii) ***patients with hypertension resistant to three conventional antihypertensive drugs (including a diuretic) or controlled blood pressure on four or more antihypertensive drugs***; (iii) *patients with hypertension and spontaneous or diuretic-induced hypokalaemia*; (iv) *patients with hypertension and adrenal incidentaloma; (v) patients with hypertension and sleep apnoea;* (vi***)*** *patients with hypertension and a family history of early onset hypertension or cerebrovascular accident at a young age (<40 years);* and (vii) *all hypertensive first-degree relatives of patients with PA* [11]. Unfortunately, these guidelines are not followed by practising clinicians. For example, in a recent Survey of 500 general practitioners in Italy and Germany, case detection testing for PA was performed in only 7–8% of 3135 patients with hypertension [40].

- Over more than three decades, it has been frustrating to see patients who were not tested for PA when they were first diagnosed with hypertension, but rather only after they have developed irreversible stage 4 to 5 chronic kidney disease.

- The diagnostic algorithm should be simplified, and **all patients with hypertension should be recommended for case detection testing for PA at least once** (Fig. 1). An initially normal case detection testing result for PA should be repeated if and when there is deterioration in hypertension control [43].

- Greater efforts need to be made to provide up-to-date information in medical schools and family practice and internal medicine residencies, focusing on the prevalence of PA, morbidity related to untreated PA and how to perform case detection testing.


When to Consider Testing for Primary Aldosteronism:
• All patients with hypertension should be tested at least once
Case Detection Test:
Morning blood sample in seated ambulant patient
• Plasma aldosterone concentration (PAC)
• Plasma renin activity (PRA) or plasma renin concentration (PRC)
PAC ≥ 277 pmol/L (≥10 ng dL−1)
and
↓ PRA (<1.0 ng mL−1 h−1) or ↓ PRC (< lower limit of reference)
Confirmatory Testing (if spontaneous ↓K+ absent):
• 24-h urine for aldosterone and sodium on a high sodium diet, or
• 4-h saline infusion test

Diagnosis

- The diagnosis of PA starts with **case detection**, followed by **confirmatory tests** and finally **subtype evaluation**. Each step may be completed, whilst the patient is taking antihypertensive medications [12].

- *Although hypokalaemia reduces the secretion of aldosterone, it rarely normalizes aldosterone secretion in patients with PA*; these patients are hypokalaemic because of excess aldosterone secretion. *Nevertheless, restoring the serum potassium level to normal before performing diagnostic studies is optimal (although not necessary in most cases).*

- The list of drugs and hormones capable of affecting the renin–angiotensin–aldosterone axis in patients without PA is extensive [48]. However, it is essential for clinicians to understand that although medications used to treat hypertension can potentiallycause false-negative testing results in patients with mild PA, *there is no medication that causes false-positive results, as long as a cut-off level for aldosterone is used*. Calcium channel blockers and a1-adrenergic receptor blockers do not affect the diagnostic accuracy in most cases [11]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have the potential to elevate PRA in patients with mild PA.

- ✓ Therefore, the finding of a PRA level ≥1.0 ng mL1 h1 or a PRC that is not suppressed in a patient taking an ACE inhibitor or ARB does not exclude the diagnosis of PA. However*, a PRA level <1.0 ng mL1 h1 or a PRC below the reference range in a patient taking an ACE inhibitor or ARB is diagnostic of low renin hypertension and possible PA*.
- ✓ MRAs (e.g. spironolactone and eplerenone) prevent aldosterone from activating the receptor, resulting sequentially in sodium loss, a decrease in plasma volume and an elevation in renin. **If PRA or PRC is not suppressed in a patient treated with an MRA, then no further PA-related testing can be performed and the MRA should be discontinued for 6 weeks before re-testing**. However, if the patient is hypokalaemic despite treatment with an MRA, then the mineralocorticoid receptors are not fully blocked and PRA or PRC should be suppressed in such a patient with PA.
- ✓ **Thus, for case detection testing, blood pressure medications, including MRAs, should not be discontinued**. Clinicians can proceed with case detection testing in all patients treated with MRAs, and the MRA does not need to be discontinued for confirmatory or subtype testing with adrenal vein sampling (AVS) if PRA or direct renin concentration is suppressed [49]. Other potassium-sparing diuretics, such as amiloride and triamterene, usually do not interfere with testing unless the patient is treated with high doses, which may result in elevated PRA or PRC.

Measurement of renin

- Renin can be measured based on its enzymatic activity (PRA) or on its mass (PRC).
- Normal morning PRA for seated individuals ranges from approximately 1–4 ng mL1 h1 (0.8–3.0 nmol L1 h1). The corresponding normal reference range for PRC is 8 to 35 mU L1.
- In general, there is a good correlation between PRA and PRC [51, 52].
- However, PRC can be affected by oestrogen status in women. For example, false-positive results on case detection testing for PA can occur when PRC is measured in women receiving oestrogen-containing preparations [48, 53, 54]. In addition, the preovulatory surge in oestrogen in premenopausal women is associated with false-positive case detection testing when using PRC, but not PRA [54].
- Thus, although both methods to measure renin are suitable for case detection testing for PA, use of PRA is preferred.

Case detection tests

- Case detection testing involves the measurement of PAC and PRA (or PRC) in a random morning ambulatory blood sample (Fig. 1).
- In 1981, Hiramatsu and colleagues proposed the PAC/PRA ratio as a case detection test for PA [35].

- In a patient with hypertension and hypokalaemia, secondary hyperaldosteronism (e.g. renovascular hypertension) should be considered if both PAC and PRA are increased and the PAC/PRA ratio is <277 (with PAC measured in pmol L1 and PRA in ng mL1 h1; PAC/PRA ratio <10 if PAC is measured in ng dL1 and PRA in ng mL1 h1).
- If both PAC and PRA (or PRC) are suppressed in a patient with hypertension and hypokalaemia, an alternate source of agonism at the mineralocorticoid receptor should be considered (e.g. hypercortisolism, licorice use).

Interpretation of the PAC/PRA ratio has proven to be confusing due to the wide variation in the lower limits of detection for PRA. Thus, it is more practical to use absolute values for PAC and renin (PRA or PRC) (Fig. 1). **The measurement of PAC and PRA or PRC is widely accepted as the case detection test of choice for PA** [11, 55, 56]. A PAC >277 pmol L1 (>10 ng dL1) and a PRA <1.0 ng mL1 h1 or a PRC lower than the lower limit of the reference range is a positive case detection test result, a finding that warrants further testing (Fig. 1) [11].

Confirmatory tests

With one exception, a high PAC and low PRA test result is not diagnostic by itself, and PA must be confirmed by demonstration of inappropriate aldosterone secretion [11].

- ✓ **The one exception to the requirement for formal confirmatory testing in a patient with hypertension is the clinical setting of spontaneous hypokalaemia with PAC >555 pmol L1 (>20 ng dL1) and PRA <1 ng mL1 h1 (or PRC below the lower limit of the reference range); this presentation is diagnostic of PA** [11].

All other patients should have PA confirmed by demonstration of aldosterone secretory autonomy with aldosterone-suppression testing, which can be performed with orally administered sodium chloride and measurement of urinary aldosterone excretion or with intravenous sodium chloride loading and measurement of PAC [12, 57].

Oral sodium loading test

- Before initiating the high-sodium diet, it is important to normalize serum potassium concentration and achieve hypertension control. Patients should receive a high-sodium diet for 3 days. The goal is a sodium intake of 5000 mg (equivalent to 218 mmol sodium or 12.8 g sodium chloride), an amount that most patients can achieve with dietary changes [13].

- The serum potassium concentration should be monitored daily and oral potassium chloride supplements administered as needed.

- On the morning of the third day of the high-sodium diet, a 24-h urine collection is started for the measurement of aldosterone, sodium and creatinine. *In normal individuals, when the 24-h urinary sodium excretion exceeds 200 mEq there is no reason to release renin or secrete aldosterone.*

- ✓ **Thus, a urinary aldosterone excretion of more than 33.2 nmol day1 (>12 mcg/24 h) in the setting of low PRA (or PRC) is consistent with autonomous aldosterone secretion** [13]. The sensitivity and specificity of the oral sodium loading test are 96% and 93%, respectively [58].

Intravenous saline infusion test

- ✓ The intravenous saline infusion test may also be used to demonstrate aldosterone secretory autonomy [34, 57].

- ✓ Following an overnight fast, 0.9% sodium chloride solution (2 L) is infused intravenously over 4 h with the patient in the seated position [59]. Heart rate and blood pressure are monitored during the infusion. At the completion of the infusion, blood is collected for measurement of PAC. PAC levels in normal subjects decrease to less than 139 pmol L1 (<5 ng dL1**), whereas levels are not suppressed to less than 277 pmol L1 (<10 ng dL1) in most patients with PA.** *Postinfusion PAC values between 139 pmol L1 (5 ng dL1) and 277 pmol L1 (10 ng dL1) are indeterminate and may be seen in some patients with IHA and less often in patients with APA*.

Other confirmatory tests

- The fludrocortisone suppression and captopril stimulation tests are less commonly used confirmatory tests. These are described in detail elsewhere [13].

Subtype studies

- The optimal treatment of PA depends on whether the aldosterone secretory autonomy is based on one or both adrenal glands. Thus, the goal of subtype testing is to determine whether the source of aldosterone excess is from the right, left or both adrenal glands.
- When localized to one adrenal gland (APA or PAH), unilateral adrenalectomy results in normalization of hypokalaemia in all patients; hypertension is improved in all patients and is cured in 30–60% [60–65].
- In patients with bilateral adrenal aldosterone hypersecretion (IHA and familial forms of hyperaldosteronism), unilateral adrenalectomy debulks the disease but does not cure the excess aldosterone secretion [13]. Thus, IHA and the familial forms of hyperaldosteronism should be treated medically.
- **APAs are usually small (mean diameter 1.6 cm; <1.0 cm in 16.5% of patients) [65] adrenal nodules with low computed tomography (CT) attenuation [<10 Hounsfield units (HU)] on noncontrast CT and are golden yellow in colour when resected** (Fig. 2). The adrenal glands in patients with IHA may be normal on CT, may show thickening or nodular changes, or may show incidental nonfunctioning adrenal cortical nodules.
- *When PA is caused by an aldosterone- producing adrenal carcinoma, it is usually characterized by marked biochemical abnormalities (e.g. serum potassium <2.5 mmol L1), severe hypertension and a unilateral adrenal mass larger than 4 cm in diameter with high noncontrast CT attenuation (e.g. >20 HU) [66].*

Computed tomography

- **Adrenal-directed CT scan should be the first test in the subtype evaluation of PA** (Fig.3). However, because of the age-related prevalence of nonfunctioning adrenocortical nodules [For67], the reliability of CT in localizing APAs declines with patient age.For example, if a solitary small (>1 cm and <2 cm) unilateral nodule with low CT attenuation (<10 HU) on noncontrast CT is found in conjunction with normal contralateral adrenal morphology in a young patient (<35 years) with severe PA [e.g. spontaneous hypokalaemia and PAC >832 pmol L1 (>30 ng dL1)], unilateral adrenalectomy is a reasonable treatment option (Fig. 3) [11, 65, 68].

- However, more than95%of patients with PA are older than 35 years of age [65]. In addition, in young patients with PA, normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenomas (≤1 cm) or bilateral macroadenomas may be observed on adrenal CT. If the patient wants to pursue the surgical option, a more accurate subtype test than adrenal CT is required.\
- *In general, compared to patients with IHA, those with APAs have more severe disease, which includes marked hypertension, spontaneous hypokalaemia and higher levels of plasma aldosterone [e.g. >832 pmol L1 (>30 ng dL1)] and urinary aldosterone [>83 nmol day1 (>30 mcg/24 h)] [13,69].*

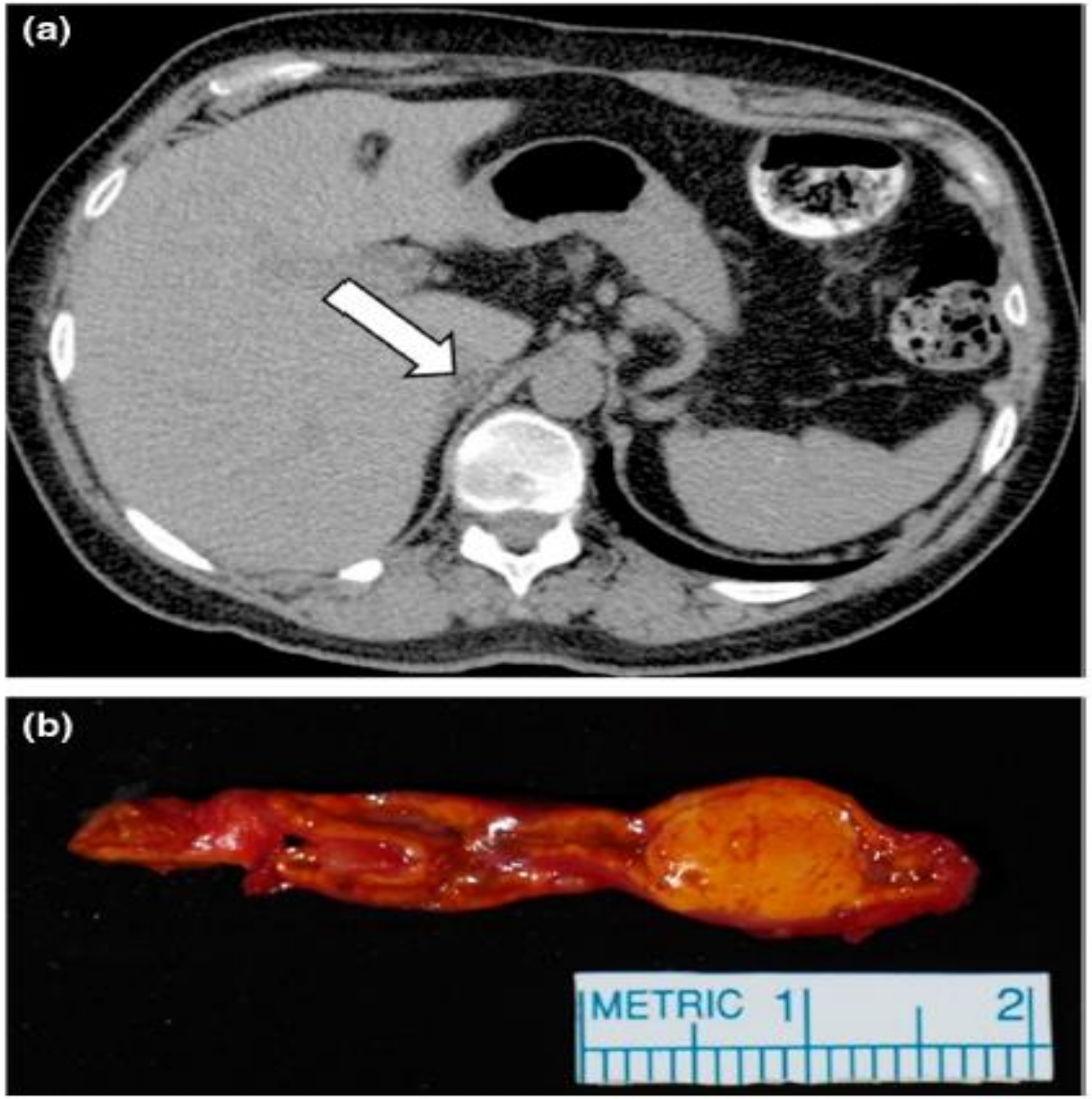


Fig. 2 A 53-year-old woman with primary aldosteronism.
(a) Noncontrast axial computed tomography (CT) scan
image shows a small nodule (arrow) in the right adrenal
gland with a CT attenuation of 3 Hounsfield units. Adrenal
venous sampling demonstrated that the right adrenal glandwas the source of aldosterone hypersecretion.

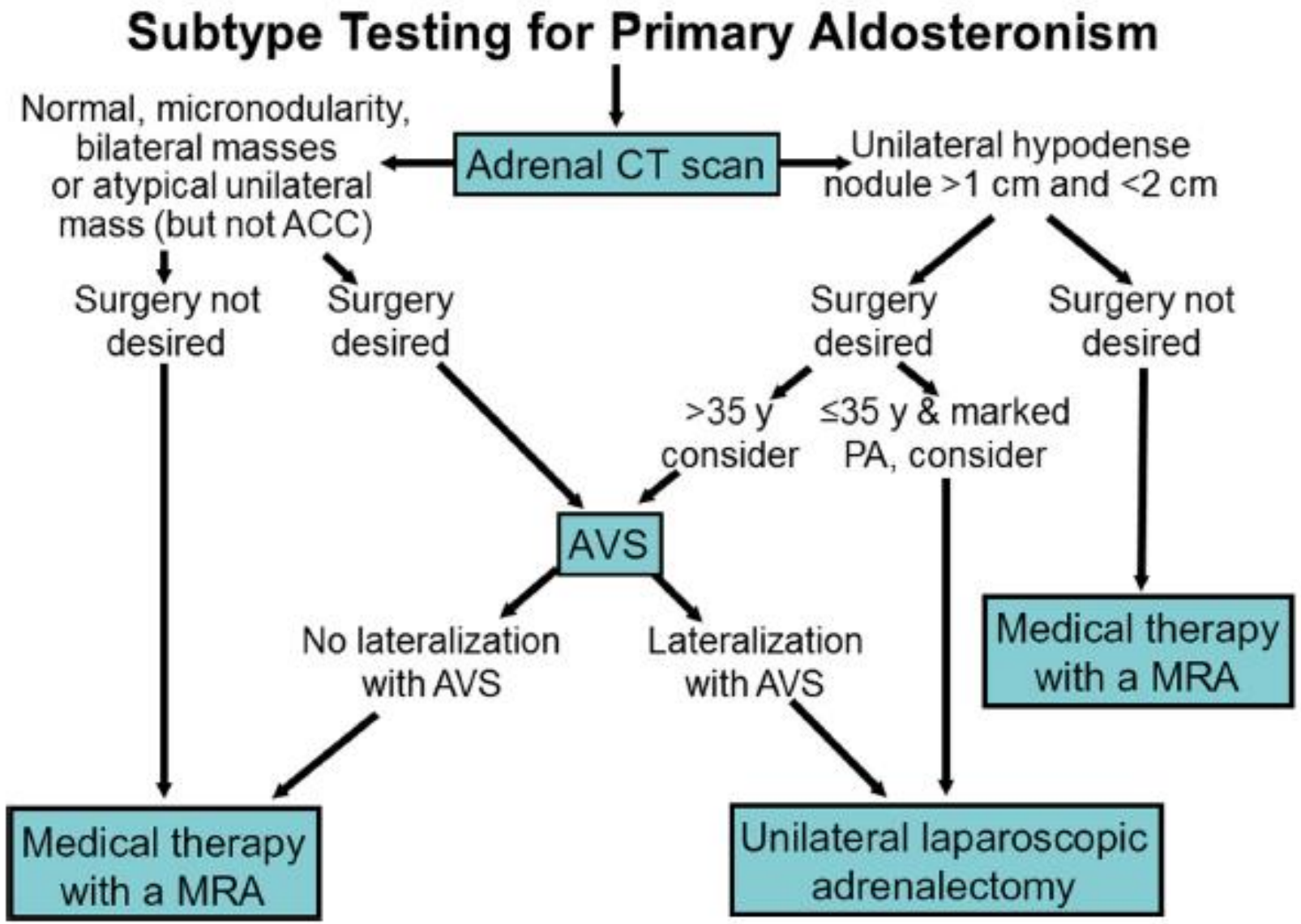
(b) Grossadrenal pathology specimen showing a golden yellowaldosterone-producing adenoma (1.5 9 1.4 9 0.8 cm).

- 35–41% of patients with a high probability of APA clinical phenotype and a normal adrenal CT scan prove to have unilateral aldosterone hypersecretion [61, 69*].Indeed Adrenal CT is not able to distinguish accurately between APA and IHA [61, 65, 69, 70].*

- In one study of 203 patients with PA who were evaluated with both CT and AVS, CT was accurate in only 53% of patients; based on the CT findings, 42 patients (22%) would have been incorrectly excluded as candidates for adrenalectomy and 48 (25%) might have had unnecessary or inappropriate surgery [61].

- In a systematic review of 38 studies involving 950 patients with PA, adrenal CT and magnetic resonance imaging (MRI) results did not agree with the findings from AVS in 359 patients (38%); based on CT/MRI, 19% of the 950 patients would have undergone noncurative surgery and 19% would have been offered medical therapy instead of curative adrenalectomy [70].

- In patients seeking a surgical cure for PA, AVS is an essential step.


Subtype Testing for Primary Aldosteronism
Adrenal CT scan
Normal, micronodularity, bilateral masses or atypical unilateral mass (but not ACC)
Unilateral hypodense nodule >1 cm and <2 cm
Surgery not desired
Surgery desired
Surgery desired
Surgery not desired
>35 y consider
≤35 y & marked PA, consider
AVS
No lateralization with AVS
Lateralization with AVS
Medical therapy with a MRA
Medical therapy with a MRA
Unilateral laparoscopic adrenalectomy

Adrenal vein sampling

- ✓ This method remains the gold standard test to distinguish unilateral from bilateral disease in patients with PA [11, 34, 61, 65, 69, 70, 75]. AVS is a technically demanding procedure because the right adrenal vein is small and may be difficult to locate and cannulate; the success rate depends on the expertise and engagement of the interventional radiologist [72, 74]. The success rate for cannulation of the right adrenal vein in 384 patients from 47 studies was 74% [13]..

- ✓ Several years ago, we reported five key factors for a successful AVS programme: (i) appropriate patient selection; (ii) careful patient preparation; (iii) focused technical expertise; (iv) a defined written protocol; and (v) accurate data interpretation [72]

- ✓ In addition, a centre-specific, written protocol should be developed by an interested group of endocrinologists, hypertension specialists, internists, interventional radiologists and laboratory personnel [72, 78].

- At Mayo Clinic, we use *continuous cosyntropin infusion (50 mcg h_1 starting 30 min before sampling and continuing throughout the procedure) during sequential AVS*.

- The rationale for cosyntropin- stimulated AVS includes:

✓ to minimize stress-induced fluctuations in aldosterone secretion during sequential sampling of the adrenal veins; (ii)

✓ to maximize the adrenal-to-IVC cortisol gradient and thus confirm successful sampling of the adrenal veins [69, 80, 81]; and (iii)

✓ to maximize the secretion of aldosterone from an APA [61, 72, 80].

- The percutaneous femoral vein approach is used to obtain blood from both adrenal veins and from the external iliac vein (labelled 'IVC'), which are assayed for aldosterone and cortisol concentrations.

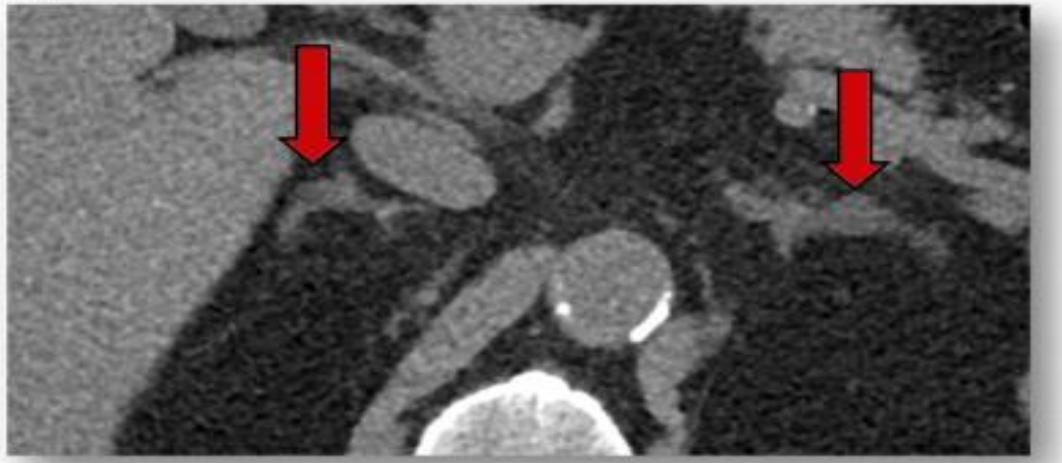
- The left adrenal vein blood sample is typically obtained from the common phrenic trunk immediately adjacent to the entrance to the left adrenal vein, whereas the blood sample from the right adrenal vein is obtained just at the orifice of the vein.
- *The cortisol concentrations from the adrenal veins and IVC are used to confirm successful catheterization (the minimal adrenal-to-IVC cortisol gradient is ≥5 : 1).* At Mayo Clinic the mean adrenal-to-IVC cortisol gradient was 33.9 : 1 on the right side and 23.8 : 1 on the left [61].

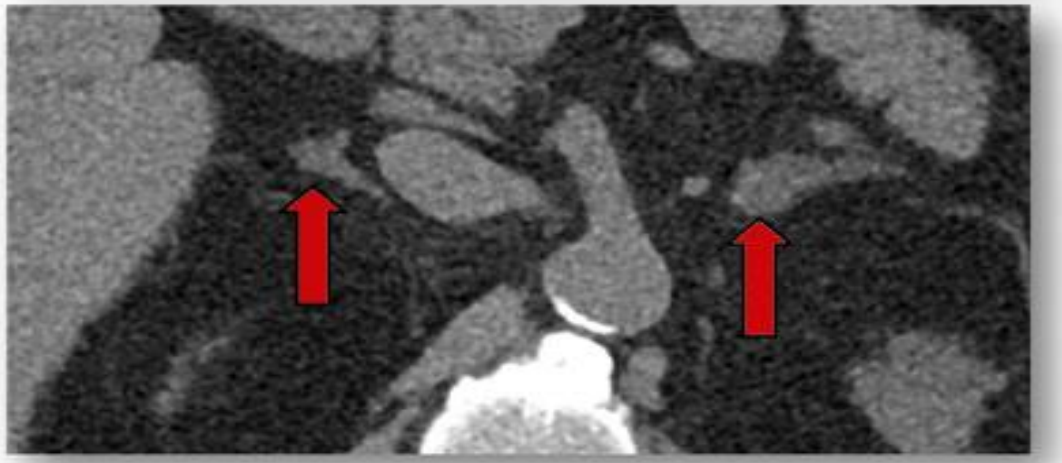
- To correct for the dilutional effect of the inferior phrenic vein flow into the common phrenic trunk, the right and left adrenal vein PAC values are divided by their respective cortisol concentrations; these are cortisol-corrected ratios and are used to determine the aldosterone lateralization ratio (ALR) (Fig. 4).
- *In patients with APA, the mean cortisolcorrected ALR (i.e. the ratio of PAC/cortisol from the APA side to that from the normal side) is 18 : 1 [61]. An ALR cut-off of ≥4 : 1 is used to indicate unilateral aldosterone excess (Fig. 4). In patients with IHA, the mean cortisol corrected ALR is 1.8 : 1 (high side to low side), and a ratio of <3 : 1suggests bilateral aldosterone hypersecretion* [61].

- Therefore, most patients with a unilateral source of aldosterone have cortisol-corrected ALRs ≥4.0, and ALRs greater than ≥3.0 but <4.0 represent a zone of overlap.

- In addition to the AVS ALR, a contralateral suppression index (CSI) can be calculated: the contralateral (nondominant adrenal) aldosterone/ cortisol ratio is divided by the IVC aldosterone/ cortisol ratio. In the early Mayo Clinic series, the CSI was <1.0 in 93.4% of patients with surgically confirmed APA [61]. Although a supportive finding, if the ALR is ≥4.0, a CSI <1.0 is not associated with better postoperative blood pressure outcomes and should not be a requirement for surgery [83, 84]. However, there are several situations in which the CSI can be very helpful.For example,
- When the ALR is in the grey zone (3.0–<4.0), a CSI of <1.0 ispredictive of good surgical outcomes .
- In addition, if AVS is not bilaterally successful, a CSI of <0.5 is highly predictive of contralateral disease [86].
- Also, patients with a CSI of <0.47 are at increased risk for postoperative hyperkalemia (see treatment section below) [87].

(A)





(B)

Adrenal Vein Sampling*

Vein	Aldosterone (A) pmol/L	Cortisol (C) nmol/L	A/C Ratio	Aldosterone Ratio
RT Adrenal Vein	249660	20470	12.2	11 : 1
LT Adrenal Vein	13315	12608	1.1	
IVC	1110	552	2.0	

*Cosyntropin infusion 50 mcg/hr

Familial hyperaldosteronism

- *FH should be considered when PA is diagnosed before the age of 20 years or when PA is diagnosed in more than one family member.* To date, four forms of FH have been described [94].

➢ FH type1:CYP11B1/CYP11B2 germline chimeric gene

Glucocorticoid-remediable aldosteronism(GRA;FH type1 is a form of hyperaldosteronism in which the hypersecretion of aldosterone can be reversed with physiologic doses of glucocorticoid to suppress corticotropin secretion [95]. FH type I was first described in a single family in 1966 [96]. The aetiology was discovered 26 years later: a nonhomologous crossing over on chromosome 8q24.3 between CYP11B1 gene (encoding 11-beta-hydroxylase) and CYP11B2 (encoding aldosterone synthase) resulting in the CYP11B1/CYP11B2 chimeric gene where mineralocorticoid production is regulated by corticotropin instead of the normal secretagogue Angiotensin.

The CYP11B1/CYP11B2 chimeric gene is characterized by early onset hypertension that can be mild to severe. The diurnal nature of the aldosterone excess in these patients might explain the infrequency of hypokalaemia.

- In the absence of treatment with a corticosteroid, the CYP11B1/ CYP11B2 chimeric gene results in overproduction of aldosterone and 18-hydroxycortisol and 18- oxycortisol.

- **Genetic testing for the CYP11B1/ CYP11B2 chimeric gene should be considered for patients with PA who have a family history of the disease, onset of PA at a young age (<20 years) or a family history of strokes at a young age.**

Table 2 *Forms of familial hyperaldosteronism*

Familial hyperaldosteronism type	Germline mutation and future classification	Other terminology	OMIM classification
Type I	*CYP11B1/CYP11B2* germline chimeric gene	Glucocorticoid-remediable aldosteronism	103900
Type II	Germline *CLCN2* chloride channel mutations		
Type III	Germline *KCNJ5* mutations		613677
Type IV	Germline *CACNA1H* mutations		607904
	Germline *CACNA1D* mutations	Primary aldosteronism with seizures and neurologic abnormalities (PASNA)	615474
	Germline armadillo repeat containing 5 (*ARMC5*) mutations	Bilateral macronodular adrenal hyperplasia (BMAH)	615954

➢ *FH typeII:CLCN2chloride channel germline mutations*

- FH type II was first reported in 1991 and is inherited in an autosomal dominant manner [99–102]. Families with FH type II have had APAs and IHA. FH type II is more common than FH type I, but accounts for fewer than 6% of all patients with PA [98].

the authors found germline CLCN2 chloride channel mutations in eight of the probands

➢ FH type III: germline KCNJ5 mutations

- FH type III (OMIM #613677) was first described in1959 in a 5-year-old boy which caused by mutation in germline KCNJ5
- germline KCNJ5 mutations is 0.3% in patients with PA and 8% among patients with familial PA [109]. Most patients with germline KCNJ5 mutations present with polyuria, polydipsia and refractory hypertension in childhood; investigations show both marked hypokalaemia and PA. In most cases, the degree of aldosterone hypersecretion is so high that bilateral adrenalectomy is required.

➢ FH type IV: germline CACNA1H gene mutations

- FH type IV (OMIM #617027) is inherited in an autosomal dominant fashion caused by mutations in the

CACNA1H gene.

The treatment of patients with germline CACNA1H mutations should be identical to that of patients with apparent sporadic PA due to IHA. However, inselected cases of refractory disease associated with massive bilateral adrenal hyperplasia, bilateral laparoscopic adrenalectomy may need to be

PA with seizures and neurologic abnormalities(PASNA) is caused by de novo germline mutations
in CACNA1D.
The severe neurologic abnormalities do not allow these individuals to reproduce and thus, although due to a germline mutation, it is not technically a familial form of PA.

Aldosterone-producing cell clusters

- Aldosterone synthase (CYP11B2) expression is limited to the zona glomerulosa of the adrenal gland. However, CYP11B2 and CYP11B1 immunohistochemical staining studies have detected focal subcapsular nests of adrenocortical cells that extend into the zona fasciculata and stain strongly for CYP11B2 and are termed aldosterone-producing cell clusters (APCCs) [140]. APCCs have been identified in normal adrenal glands and in pathology specimens from patients with PA, where APCCs may occur adjacent to APAs [140].
- It is interesting that the presence of APCCs increases with age and may in part reflect the ageing adrenal gland [142, 143]. Studies to determine the clinical relevance of APCCs are underway.

Cortisol co-secretion

- Patients with PA have been shown to be at increased risk for insulin resistance and metabolic syndrome [144–149], depression [23, 24] and osteoporotic fractures [150–152]. These associations would seem to be consistent with glucocorticoid secretory autonomy or excess. A steroid metabolome study compared the following patient groups: 174 patients with PA (103 APA, 71 IHA); 162 healthy controls; 56 patients with endocrine inactive adrenal adenoma; 104 patients with mild subclinical glucocorticoid secretory autonomy; and 47 patients with adrenal-dependent Cushing syndrome [153].
- **The key findings were that**: **(i)** patients with PA (APA and IHA) had significantly increased cortisol and total glucocorticoid metabolite excretion compared to controls and patients with subclinical Cushing syndrome ($P < 0.001$); **(ii)** surrogate parameters of metabolic risk correlated with glucocorticoid but not mineralocorticoid excretion; and **(iii)** unilateral adrenalectomy in patients with APA resolved both mineralocorticoid and glucocorticoid excess [153].

- These findings suggest that some degree of cortisol co-secretion is highly prevalent in patients with PA and is linked to metabolic risk, which may indicate that treatment with MRAs in patients with IHA and APA may not prevent glucocorticoid-dependent metabolic risk [153]. However, these data should be interpreted with caution because this study was not simply identifying cortisol co-secretion from APAs, but rather increased corticosteroid metabolome in patients with APA and IHA. The hypothalamic– pituitary–adrenal axis is not suppressed in these patients, and there is no adrenal crisis or steroidwithdrawal in surgically treated patients with APAs.

- **When should clinicians test for cortisol cosecretion in patients with APAs?**
- In general, clinically important cortisol secretion from an adrenal adenoma is correlated with **tumour size**. Unlike aldosterone secretion from an adenoma, clinically important cortisol secretion requires a 'large factory' **(typically with adenoma diameters >2 cm)** [155]. *Thus, it is reasonable to test patients with PA for cortisol co-secretion when the adrenal adenoma is >1.5 cm in diameter. Such testing includes baseline dehydroepiandrosterone sulphate and an overnight 1-mg dexamethasone suppression test* [156].

- When glucocorticoid secretory autonomy is observed in a patient with PA who has a single cortical adenoma >1.5 cm in diameter, it could be argued that AVS is not needed. Clinicians do not have a good long-term medical management option for Cushing syndrome, whereas PA can be treated effectively with MRAs. Rarely, PA and Cushing syndrome can co-exist due to separate aldosterone- and cortisol-secreting adenomas [157].

Principles of treatment

- The treatment objectives for patients with PA include *resolution of hypokalaemia as well as prevention of the morbidity and mortality associated with hypertension, progressive chronic kidney disease and further cardiovascular damage.* The cause of PA dictates the optimal treatment option.

- It is essential for clinicians to understand that normalization of blood pressure is not the only goal. In the presence of sodium excessive, autonomous secretion of aldosterone is associated with an increased risk of cardiovascular disease and morbidity. Thus, either curative surgery or optimized mineralocorticoid receptor blockade should be part of the management plan for all patients with PA.

- As highlighted above, a recent QoL study found that the beneficial effects of surgical treatment were greater than for treatment with MRAs [26]. Thus, surgical management is the optimal treatment approach for patients with unilateral disease. By contrast, in patients with PA caused by bilateral adrenal disease, bilateral adrenalectomy is not a ‘good trade’ due to the resultant primary adrenal insufficiency and need for lifelong glucocorticoid and mineralocorticoid replacement.

Surgical treatment of APA and unilateral hyperplasia

- *The optimal treatment of APA or unilateral hyperplasia is curative surgery because hypertension control is improved in all patients and no blood pressure medications are required in 30–60% of individuals* [60, 65, 84, 158–161].
- APAs are small and may be multiple and not distinguishable by the surgeon intra-operatively, the entire adrenal gland should be removed .

- Prior to surgery, blood pressure should be controlled and hypokalaemia corrected with potassium supplements or an MRA. PAC should be measured the morning after the operation to confirm a biochemical cure [65]. Following surgery, MRAs and potassium supplements should be discontinued. In general, the number and dosages of antihypertensive medications can be cut by 50% postoperatively. Any medications that may contribute to hyperkalemia (e.g. ACE inhibitors and ARBs) should be discontinued. The proportion of hypertension that was associated with aldosterone excess resolves in 1–3 months after surgery.

Risk for postoperative hyperkalemia

- Postoperatively, there is a risk of short-term hypoaldosteronism leading to clinically important hyperkalemia [87, 166, 167]. In a multicentre study of 142 surgically treated patients, the prevalence of postoperative hyperkalemic was 9.9%;
- thehyperkalemic patients were older and had worse renal function than the nonhyperkalemic patient group [168].
- In a study of 192 patients with PA who were treated surgically, 12 (6.3%) developed postoperative hyperkalemia (median serum potassium5.5 mmol L1, range 5.2–6.2 mmol L1); median time to onset was 13.5 days (range 7–55 days) [87].
- On univariate analysis, hyperkalemic patients had slightly greater preoperative serum creatinine levels (106.1 vs.

88.4 mol L1, P = 0.01), higher postoperative creatinine (115 vs. 88.4 mic mol L1, P = 0.02), lower median AVS CSI (0.14 vs. 0.27, P = 0.03) and larger adenomas (1.9 vs. 1.4 cm, P = 0.02). Multivariable logistic regression showed that the CSI remained the only significant predictor of postoperative hyperkalemia (P = 0.04) with an optimal cut-off of <0.47 [87].

- At Mayo Clinic, we monitor serum potassium weekly for 4 weeks after surgery, and a high-sodium diet should be followed to avoid the hyperkalemia of hypoaldosteronism. Shortterm fludrocortisone supplementation may be required if the serum potassium concentration rises above 5.2 mEq L1. In some exceptional cases, long-term mineralocorticoid replacement may be needed.

Renal function after surgery

- Clinicians should recognize that most patients withlong-standing PA have some degree of renal insufficiency that is masked by the glomerular hyperfiltration associated with aldosterone excess [169–171].

- Approximately 40% of patients with PA show a clinically important decrease in renal function after surgery [172]. Glomerular hyperfiltration pre-operatively masks mild to moderate underlying renal failure.

- In one study, the average decrease in estimated glomerular filtration rate was 16.7 mL min1/1.73 m2 (a decrease of 19.7%) [173]. Effective treatment of PA with either surgery or an MRA will unmask the underlying chronic kidney disease.

Pharmacologic treatment

- *Medical management with MRAs is the treatment of choice for IHA and GRA.* Although not the optimal treatment option, MRAs may also be used to treat patients with PA that is caused by an APA [26, 174]. The general guidance that should be provided to all patients with hypertension is also appropriate for patients with PA: maintain ideal body weight, avoid tobacco, participate in a regular exercise programme and follow a sodium-restricted diet.
- In a longitudinal study assessing 602 patients with PA treated with MRAs matched with 41,853 patients with essential hypertension (with comparable cardiovascular disease risk profiles and blood pressure control), the incidence of cardiovascular events was higher in patients with PA treated with MRAs than in those with essential hypertension [56.3 vs. 26.6 events per 1000 person-years, adjusted hazard ratio (HR) 1.91] [176].

- Patients with PA also had higher adjusted risks for incident mortality (HR 1.34), diabetes (HR 1.26) and atrial fibrillation (HR 1.93).
- Of interest, the excess risk for cardiovascular events and mortality was limited to patients with PA who had suppressed PRA on medical treatment, suggesting inadequate dosing of MRAs [176].
- Thus, if medical management is to be pursued, it is essential that the MRA dosage is adequate to fully block the toxic effects of hyperaldosteronism. Due to concomitant low-renin essential hypertension in some patients with PA, measurement of PRA may not be optimal to guide management*; a high–normal serum potassium without the aid of oral potassium supplements may be a more practical treatment target to determine the effective MRA dosage.*

- Spironolactone was approved by the US Food and Drug Administration (FDA) in the 1960s and has been the drug of choice to treat PA. Available as 25- , 50- and 100-mg tablets, the initial dosage is 12.5– 25 mg per day and increased to 400 mg day1 if necessary to achieve a high–normal serum potassium concentration without the aid of oral potassium chloride supplementation.
- During the first 6 weeks of treatment, serum potassium and creatinine should be monitored frequently (e.g. weekly). Concomitant therapy with salicylates should be avoided as they decrease the effectiveness of spironolactone. Because spironolactone is not selective for the mineralocorticoid receptor, side effects are common. Due to antagonism at the androgen receptor, spironolactone at dosages of more than 50 mg per day may result in painful gynaecomastia, erectile dysfunction and decreased libido in men. Agonist activity at the progesterone receptor may result in menstrual irregularity in women [177].
- Eplerenone, a competitive and selective MRA, was approved by the FDA for the treatment of uncomplicated essential hypertension in 2003. 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. A shared decision-making discussion with the patient determines the optimal initial MRA. Eplerenone is available as 25- and 50-mg tablets and should be administered twice daily because of its short half-life; a typical starting dosage is 25 mg twice daily with the plan to titrate upward for a target high–normal serum potassium concentration without the aid of potassium supplements. Although the maximum dose approved by the FDA for hypertension is 100 mg per day, potency studies have shown that eplerenone is 25–50% less potent compared with spironolactone. When titrated for a serum potassium concentration between 4.0 and 5.0 mmol L1, typical doses of eplerenone are 200–300 mg per day in patients with PA. In the initial phase of treatment, it is important to closely monitor blood pressure and serum levels of potassium and creatinine

- Because the hypertension in patients with IHA is multifactorial and frequently coincident with essential hypertension, a second antihypertensive agent is often needed to achieve good blood pressure control. Nonloop diuretics (e.g. 12.5–50 mg hydrochlorothiazide daily) are very effective in combination with the MRA.

- In patients with GRA confirmed by germline mutation testing, chronic treatment with physiologic doses of a glucocorticoid corrects hypokalaemia and normalizes blood pressure. However, the clinician should be mindful to avoid iatrogenic Cushing syndrome with excessive doses of glucocorticoids. Shorter-acting glucocorticoids such as hydrocortisone should be prescribed, using the smallest effective dose in relation to body surface area (e.g. hydrocortisone 10–12 mg m2 per day).
- Another treatment option for patients with GRA includes MRAs; this option avoids iatrogenic subclinical or clinical Cushing syndrome.
- Aldosterone synthase inhibitors, although not yet available for clinical use, are in development [179].

PA in the setting of pregnancy

- PA is uncommon in pregnancy and fewer than 50 cases have been reported in the literature; most pregnant patients with PA have APA [180–185].
- PA in pregnancy can lead to preterm delivery,intrauterine growth retardation, placental abruption and intrauterine foetal demise [185–187].
- An unusual feature of PA during pregnancy is that the degree of disease may be either improved or aggravated. In some women with PA, the high blood concentrations of pregnancy-related progesterone are antagonistic at the mineralocorticoid receptor and partially block the action of aldosterone; these patients in fact have an improvement in the degree of hypertension and hypokalaemia during pregnancy [188, 189]. In other pregnant women, increased expression of the luteinizing hormone–choriogonadotropin receptor in APAs the degree of hypertension and hypokalaemia can be aggravated by the increased pregnancy-related blood levels of human chorionic gonadotropin [190, 191].

- Pregnancy does not impact the performance of case detection testing for PA. As in the nonpregnant woman, a morning blood sample should be obtained for the measurement of PAC and renin (PRA or PRC).
- Confirmatory testing in the setting of pregnancy can be challenging because the captopril stimulation test is contraindicated in pregnancy and the saline infusion test may not be well tolerated because of oedema. The optimal confirmatory test in the setting of pregnancy is measurement of aldosterone excretion in a 24-h urine collection on an ambient sodium diet.
- In order to avoid exposure to radiation or contrast material, subtype testing in pregnancy should start with abdominal MRI without gadolinium. Unilateral APA can be diagnosed in the unique clinical setting of pregnancy with marked PA [spontaneous hypokalaemia and PAC >832 pmol L1 (>30 ng dL1)] and a clear unilateral adrenal adenoma on MRI [65].

- The severity of hypertension and hypokalaemia dictates the treatment of PA in pregnancy. For example, in the subset of patients who have remission in the degree of PA, surgery or treatment with an MRA can be avoided until after delivery.
- However, surgical and/or medical intervention is indicated if hypertension and hypokalaemia are marked. Unilateral laparoscopic adrenalectomy during the second trimester can be considered in those women with severe PA and documented unilateral APA (see above).
- Spironolactone is listed by the FDA as a pregnancy ategory C drug because feminization of newborn male rats has been documented.
- Eplerenone is listed by the FDA as a pregnancy category B drug. When PA is managed medically in pregnant women, the hypertension should be treated with standard antihypertensive drugs that are approved for use during pregnancy. Hypokalaemia should be treated with oral potassium supplements. **In those cases of severe PA in pregnancy where surgery is not an option, low dose eplerenone may be considered [180, 193].**

Summary of practical considerations

- PA is a relatively common cause of hypertension and the hypertension can be either cured with surgery or specifically targeted with pharmacologic therapy.
- Undetected or ineffectively treated PA results in increased cardiovascular morbidity and nephrotoxicity.
- All patients with hypertension should be tested for PA at least once.
- Case detection testing for PA should be performed by measuring a morning blood sample for PAC and renin (PRA or PRC). This test should be performed without changing blood pressure medications. No blood pressure medication causes a false-positive testing result as long as a cut-off for PAC is used [e.g. >277 pmol L1 (>10 ng dL1)].

- Case detection testing is not diagnostic of PA unless the patient has spontaneous hypokalaemia and the PAC is >555 pmol L1 (>20 ng dL1); formal confirmatory testing is not needed in this setting.
- Because most patients with PA do not have spontaneous hypokalaemia, formal confirmatory testing should be performed to establish aldosterone secretory autonomy.
- Subtype testing should start with an adrenaldedicated abdominal CT scan to exclude adrenocortical carcinoma and to detect APAs in young patients (<35 years of age).

- AVS may not be needed in young patients (<35 years of age) with marked PA [spontaneous hypokalaemia and PAC >832 pmol L1 (>30 ng dL1)] who have unilateral adrenal macroadenoma (>1 cm and <2 cm) and a normal contralateral adrenal gland.
- For most patients with PA who want to pursue the surgical option, AVS is indicated to accurately localize the source of aldosterone hypersecretion.
- Surgery for an APA should be unilateral adrenalectomy (not partial adrenalectomy) because the surgeon cannot reliably identify small APAs intra-operatively.
- Because of the risk for postoperative hyperkalemia, all patients should be followed with serum potassium monitoring weekly for 4 weeks.
- All patients with PA who are not treated surgically should be treated with an MRA. For effective mineralocorticoid receptor blockade, the dosage of the MRA should be titrated to a high–normal level of serum potassium without oral potassium supplements.

Thanks For your Attention