Primary aldosteronism: diagnostic and treatment strategies

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SUMMARY

Primary aldosteronism is caused by bilateral idiopathic hyperplasia in approximately two-thirds of cases and aldosterone-producing adenoma in one-third. Most patients with primary aldosteronism are normokalemic. In the clinical setting of normokalemic hypertension, patients who have resistant hypertension and hypertensive patients with a family history atypical for polygenic hypertension should be tested for primary aldosteronism. The ratio of plasma aldosterone concentration to plasma renin activity has been generally accepted as a first-line case-finding test. If a patient has an increased ratio, autonomous aldosterone production must be confirmed with an aldosterone suppression test. Once primary aldosteronism is confirmed, the subtype needs to be determined to guide treatment. The initial test in subtype evaluation is CT imaging of the adrenal glands. If surgical treatment is considered, adrenal vein sampling is the most accurate method for distinguishing between unilateral and bilateral adrenal aldosterone production. Optimal treatment for aldosterone-producing adenoma or unilateral hyperplasia is unilateral laparoscopic adrenalectomy. The idiopathic bilateral hyperplasia and glucocorticoid-remediable aldosteronism subtypes should be treated pharmacologically. All patients treated pharmacologically should receive a mineralocorticoid receptor antagonist, a drug type that has been shown to block the toxic effects of aldosterone on nonepithelial tissues.

REVIEW CRITERIA
We searched PubMed using terms including "aldosterone", "primary hyperaldosteronism", "aldosterone producing adenoma", "bilateral idiopathic hyperplasia", "renin", "potassium", "mineralocorticoid receptor antagonist", "spironolactone", "eplerenone", "adrenal vein catheterization", "adrenalectomy" and "essential hypertension". The search was not restricted by date or language of publication.

CME

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INTRODUCTION

The prevalence of hypertension has increased over the past several decades. It is estimated that approximately 85 million people (28.7% of total population) in the US are currently hypertensive.[1] Although most cases of hypertension are 'essential' or 'idiopathic', some cases have an identifiable cause, secondary hypertension. Identifying this latter subgroup is important as patients can be offered a curative therapy or targeted pharmacotherapy. The most common form of secondary hypertension is primary aldosteronism. Defined as hypertension associated with low renin and increased aldosterone levels that are not suppressed by appropriate testing (see below), primary aldosteronism was first described by Conn in 1955 in a 34-year-old woman with hypertension, intermittent paralysis, hypokalemia and metabolic alkalosis.[2] Further biochemical analyses detected increased activity of urinary salt-retaining corticoid. The patient was cured by removal of a benign adrenal adenoma.[3]

Conn initially suggested that primary aldosteronism might affect up to 20% of hypertensive patients, but later revised his estimate to 10%.[4] During the ensuing decades the prevalence of primary aldosteronism among hypertensive patients was found to be less than 3.5%.[5–10] In 1976, measurement of the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) was introduced as a test to screen for primary aldosteronism[11] but was not used routinely until the early 1980s when Hiramatsu and colleagues proposed it be the first-line case-finding test for the condition.[12] Use of the PAC : PRA ratio has substantially increased the number of confirmed cases of primary aldosteronism worldwide.[13] Clinical investigators have found the prevalence of primary aldosteronism among nonselected hypertensive persons to be

between 5% and 13%.[14–20] So, with an estimated prevalence of 10%, approximately 8.5 million people in the US have primary aldosteronism.

The prevalence of primary aldosteronism increases with severity of hypertension. Mosso and colleagues[14] showed that prevalence was 1.99% in subjects with STAGE 1 HYPERTENSION (according to the Joint National Committee 6); 8.02% in STAGE 2 HYPERTENSION; and 13.2% in STAGE 3 HYPERTENSION. Among patients with resistant hypertension, the prevalence of primary aldosteronism has been reported to be 17–20%.[21,22] African American and black South African subjects have lower renin levels than Caucasian subjects;[23,24] this could influence the result of the PAC : PRA ratio test, but ethnic differences have not been found to affect the prevalence of primary aldosteronism.[21] Consistent age effects are not evident. Compared with essential hypertension, primary aldosteronism has been reported by some to be more common among younger patients; others have detected no difference between age-groups.[14,16,21] No difference between the sexes has been reported.[14]

PATHOGENESIS

Aldosterone, produced in the ZONA GLOMERULOSA, is synthesized and released mainly in response to renin-dependent production of ANGIOTENSIN II; however, adrenocorticotropic hormone (ACTH), serum potassium, and dopamine also affect its production and secretion. Aldosterone exerts its effect by binding to the nuclear mineralocorticoid receptor. This ligand–receptor complex attaches to DNA and promotes gene expression. In epithelial tissues (e.g. renal tubular cells, distal colon and salivary glands) aldosterone enhances uptake of sodium; water follows, resulting in increased volume load and cardiac output. Sodium reabsorption is accompanied by potassium excretion. In the past, hypokalemia was thought to be a mandatory finding in primary aldosteronism but, as noted by Conn and colleagues in 1965,[25] the potassium levels in primary aldosteronism need not be below normal. Later studies confirmed that most patients with primary aldosteronism are normokalemic.[13–17,21,26,27]

In addition to causing hypertension, high levels of aldosterone have negative effects on nonepithelial tissues. These include increased oxidative stress and collagen remodeling, which result in endothelial dysfunction, left ventricular hypertrophy and fibrosis in the kidney, heart and blood vessels.[28] Both animal experiments and in vitro studies have shown that these effects are independent of hypertension. For example, long-term administration of aldosterone to rats increases collagen formation in both the right and left cardiac ventricles[29] and induces coronary inflammation with focal ischemic lesions.[30] Blockade of the mineralocorticoid receptor (which only partially normalizes blood pressure) substantially ameliorates the inflammatory reaction.[30] It has been suggested that left ventricular hypertrophy is a result of high sodium intake inducing a local increase in aldosterone synthase within myocardial cells.[31] It is clear, however, that PAC has a role; there is a positive correlation between cardiac collagen content (measured by ultrasonic backscatter) and plasma aldosterone levels in humans.[32]

The negative effect of circulating aldosterone on cardiac function was documented recently by Stowasser and colleagues.[33] These authors reported that in young, nonhypertensive subjects with glucocorticoid-remediable aldosteronism, left ventricular wall thickness is increased and diastolic function is reduced compared with age- and sex-matched controls. Indeed, cardiovascular events (stroke, myocardial infarction and atrial fibrillation) are more common in patients with primary aldosteronism than in subjects with essential hypertension, a finding that is independent of blood pressure.[34] Clinical multicenter studies (Randomized Aldactone Evaluation Study [RALES] and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study [EPHESUS]) have shown that addition of a mineralocorticoid receptor antagonist to treatment regimens decreases morbidity and mortality among patients with cardiovascular diseases.[35,36]

Aldosterone excess might also exert effects beyond blood pressure and the cardiovascular system. Although its pathogenesis is unclear, the metabolic syndrome is more common among patients with primary aldosteronism than among patients with essential hypertension.[37] Experimentally, aldosterone excess has been linked with bone loss due to concomitant increases in urinary calcium and magnesium excretion.[38]

SUBTYPES

The relative frequencies of the different forms of primary aldosteronism are listed in Table 1. The two major subtypes are bilateral idiopathic

Table 1 Subtypes of primary aldosteronism. Adapted from reference 45.

Subtype	Relative frequency (%)
Idiopathic hyperaldosteronism	65
Aldosterone-producing adenoma	30
Primary unilateral adrenal hyperplasia	3
Aldosterone-producing adrenocortical carcinoma	1
Aldosterone-producing ovarian tumor	<1
Familial hyperaldosteronism type I (glucocorticoid-remediable aldosteronism)	<1
Familial hyperaldosteronism type II (familial occurrence of aldosterone-producing adenoma and/or idiopathic hyperaldosteronism)	Unknown

hyperaldosteronism (IHA) and aldosterone-producing adenoma (APA; Figure 1). As most patients with primary aldosteronism are normokalemic and the PAC : PRA ratio is increasingly being used as a case-finding test, IHA is now the most frequently diagnosed subtype.[18,39] In general, IHA patients are older, have milder hypertension and are more frequently normokalemic than those with APA.[40] Unilateral adrenal hyperplasia is an unusual subtype. Nonetheless, this diagnosis should be considered when adrenal vein sampling shows lateralization but an APA is not detected during histological examination.[41] Approximately 1% of patients with primary aldosteronism are shown to have an aldosterone-producing adrenocortical carcinoma. In a summary based on 58 case reports, Seccia and colleagues found that mean survival time was approximately 1.5 years. There was wide variation in tumor size. In less than half of the patients who had undergone preoperative CT, the imaging findings were indicative of malignancy (e.g. heterogeneous density, calcification).[42]

Familial forms of primary aldosteronism include familial hyperaldosteronism type 1 (FH-1) or glucocorticoid-remediable aldosteronism (GRA), and FH-2 (familial occurrence of APA, IHA or both). GRA, which is inherited in an autosomal dominant fashion, is caused by recombination between *CYP11B1* and *CYP11B2*, which encode members of the cytochrome P450 superfamily of enzymes. The chimeric gene formed via recombination has aldosterone synthase activity. It is expressed throughout the adrenal cortex and regulated primarily by ACTH.[43] In addition to increased PAC, levels of 18-OH-cortisol and 18-oxo-cortisol are increased in GRA. Severity of hypertension is associated with gender and with the position at which the genes cross over. FH-2 occurs more frequently than GRA, and familial studies indicate autosomal dominant inheritance. In some families, FH-2 is linked to a mutation in the 7p22 region. Such a linkage has not been found in other families, indicating that FH-2 is a genetically heterogeneous disease.[44]

CASE FINDING

Testing for primary aldosteronism should be considered in any of the following circumstances: (i) hypertension and spontaneous hypokalemia or hypokalemia provoked by administration of a low-dose diuretic; (ii) severe hypertension (i.e. Joint National Committee 7 stage 2 hypertension, ≥160 mmHg systolic and/or ≥100 mmHg diastolic; (iii) a patient requires three or more antihypertensive drugs; (iv) hypertension manifests at a young age (e.g. <20 years); (v) adrenal incidentaloma is present; (vi) whenever an evaluation for secondary hypertension is considered (e.g. when testing for renovascular disease or PHEOCHROMOCYTOMA); and (vii) hypertensive relatives of patients with primary aldosteronism.

Ratio of plasma aldosterone concentration to plasma renin activity

After correcting hypokalemia (if present), the blood of patients who are likely to have primary aldosteronism should be sampled for measurement of PAC and PRA, and the PAC : PRA ratio should be calculated. As a clinical guideline, a PAC : PRA ratio ≥20 ng/dl per ng/ml per hour (554 pmol/l per ng/ml per hour) in combination with a PAC ≥15 ng/dl (416 pmol/l) in a morning blood sample from an ambulant patient is indicative of primary aldosteronism. Confirmatory testing (see section below) should be performed. It is important to note that the PAC : PRA ratio threshold is

laboratory-dependent. Mineralocorticoid receptor antagonists (spironolactone and eplerenone) and high-dose amiloride (e.g. >5 mg daily) should be discontinued 6 weeks before blood sampling to avoid direct interference with the results. Blood pressure and serum potassium levels need to be monitored closely during drug withdrawal.[39,45] An algorithm of case findings and further evaluation is presented in Figure 2.

The use of the PAC : PRA ratio has been questioned because it is primarily an indicator of low renin levels[46] and might be affected by patient age, ethnicity, β-adrenergic blockers, angiotensin-receptor blockers, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, posture and diurnal hormone cycles.[26,47,48] When the effects of the antihypertensive drugs atenolol, amlodipine, doxazosin, fosinopril and irbesartan on the PAC : PRA ratio were investigated in a group of patients with suspected primary aldosteronism, amlodipine and irbesartan were shown to contribute to a false-negative ratio.[26] In a recent study of 118 subjects with essential hypertension, Schwartz and Turner[19] showed that neither antihypertensive medications nor acute variation of dietary sodium adversely affected the accuracy of the PAC : PRA ratio. Sensitivity of the ratio during periods with and without therapy was 73% and 87%, respectively; specificity was 74% and 75%, respectively. Furosemide and upright posture do not improve the post-test probability of APA to a greater extent than using the baseline PAC : PRA ratio.[49] It is important to recognize, however, that the PAC : PRA ratio is only a screening test. A confirmatory aldosterone suppression test must be conducted to verify autonomous aldosterone production before treatment is initiated.

In a systematic review of 16 studies (3,136 total participants) Montori and Young[50] found that the threshold PAC : PRA ratios used varied between 7.2 and 100.0 ng/dl per ng/ml per hour (200 and 2,774 pmol/l per ng/ml per hour). Sensitivity and specificity for APA varied between 64% and 100%, and 87% and 100%, respectively. Descriptions of reference standards and attribution of diagnosis at the end of the studies were, however, incomplete. In addition, origin of the study cohort, ongoing antihypertensive medications, use of high versus low salt diet, and circumstances during blood sampling were not standardized. The authors concluded that none of the studies provided valid estimates of PAC : PRA ratio test characteristics
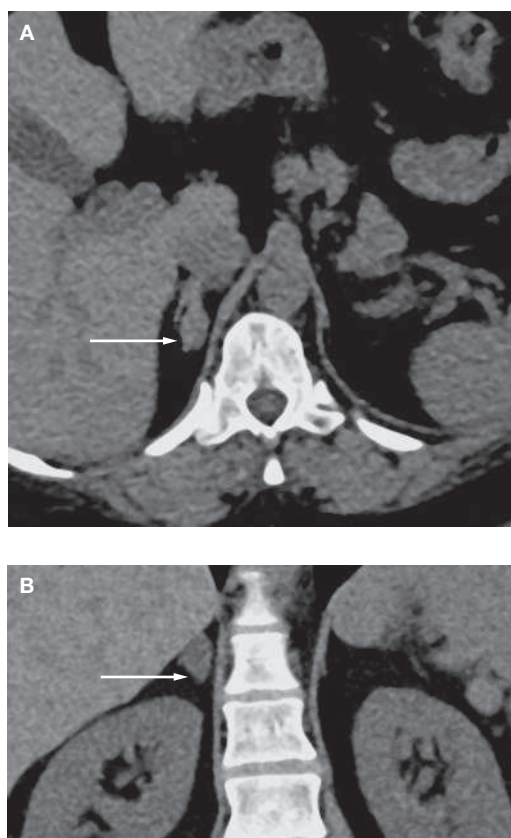
Figure 1 CT of a right adrenal mass in a 35-year-old woman with a 7-year history of hypertension. (**A**) Axial image showing 2-cm right adrenal nodule (arrow), Hounsfield unit score 8. (**B**) Coronal image. As adrenal venous sampling performed at a local hospital was not conclusive, the patient was referred to Mayo Clinic (Rochester, MN) for a second opinion. Laboratory study results included the following: serum potassium, 3.3 mEq/l (3.3 mmol/l [during replacement with potassium chloride 96 mEq daily]); plasma aldosterone concentration (PAC), 46 ng/dl (1,276 pmol/l); and plasma renin activity, <0.6 ng/dl per hour. Repeat adrenal venous sampling showed that right adrenal vein PAC was 19,795 ng/dl (549,113 pmol/l [right adrenal vein PAC : plasma cortisol ratio, 19.8]); left adrenal vein PAC was 543 ng/dl (15,062 pmol/l [left adrenal vein PAC : plasma cortisol ratio, 0.71]); and inferior vena cava PAC was 104 ng/dl (2,885 pmol/l [inferior vena cava PAC : plasma cortisol ratio, 4.5]). The right-to-left lateralization ratio was 27.9:1.0 (right PAC : cortisol divided by left PAC : cortisol) and consistent with a right aldosterone-producing adenoma. Laparoscopic right adrenalectomy was recommended.

(sensitivity, specificity and likelihood ratio at different cutoff levels).

In a retrospective study of 62 patients (45 with primary aldosteronism and 17 with essential
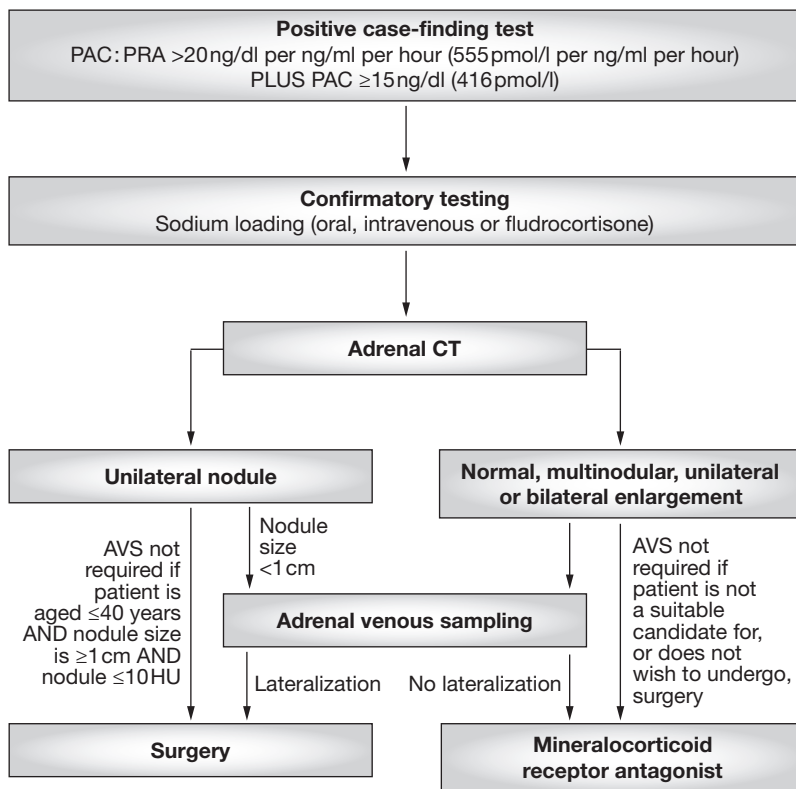
Figure 2 Algorithm for using the ratio of plasma aldosterone concentration to plasma renin activity as a case-finding tool, and for subtype evaluation, of primary aldosteronism. This algorithm should be modified on the basis of clinical circumstance; common sense should prevail.
AVS, adrenal vein sampling; HU, Hounsfield units; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

hypertension), Tiu and colleagues[51] showed that the PAC : PRA ratio has a larger area under the RECEIVER OPERATING CHARACTERISTIC CURVE than PAC or PRA alone, thus justifying the use of the PAC : PRA ratio as a first-line case-finding test. The cutoff levels corresponding to the highest accuracy for the PAC : PRA ratio varied with posture and time of day, and this test should be standardized both within and between centers to minimize variability. Adding PAC as a single variable to the PAC : PRA ratio provides a higher sensitivity and specificity for identifying primary aldosteronism.[52]

Immunoreactive renin concentration
As estimates of PRA depend on physiological ANGIOTENSINOGEN levels, several pathological and physiological conditions can influence PRA concentration. Technical difficulties are associated with the laboratory assay for PRA. For example, the sample must be stored and transported

on ice. Also, there is a lack of methodological standardization between different laboratories. To overcome these problems, a monoclonal antibody directed against active renin has been developed and several laboratories currently measure immunoreactive renin concentration (ARC) instead of PRA. To date, few studies have focused on comparing the different methods in testing for primary aldosteronism. In one study, a PAC : ARC ratio cutoff of 90 pg/ml (2.13 pmol/l) was found to have a sensitivity of 100.0% and specificity of 98.6% ($n = 83$, ten patients known to have APA).[53] In a prospective study of 36 hypertensive patients, Ferrari and colleagues[54] found that a PAC : ARC ratio greater than 5.4 ng/dl per ng/l (corresponding to a PAC : PRA ratio >27 ng/dl per ng/ml per hour [749 pmol/l per ng/ml per hour]) was indicative of primary aldosteronism. Olivieri *et al.*[55] used a PAC : ARC ratio when screening for primary aldosteronism in a primary care setting and found that 32.4% of hypertensive subjects had a PAC : ARC ratio >32 pg/ml (0.76 pmol/l; corresponding to a PAC : PRA ratio of 50 ng/dl per ng/ml per hour [1,387 pmol/l per ng/ml per hour]). Notably, the diagnosis of primary aldosteronism was not subsequently confirmed with a suppression test in any of these studies. More studies with larger cohorts are needed before ARC can be recommended as a replacement for PRA when testing for primary aldosteronism.

CONFIRMATORY TESTING
The most widely used confirmatory tests for primary aldosteronism are intravenous saline loading, oral sodium loading and the fludrocortisone suppression test (FST). The principle underlying these tests is that an increase in intravascular volume should decrease renin release and subsequent aldosterone production in patients without primary aldosteronism. Sodium suppression testing is performed by one of two methods. First, oral administration of sodium chloride (12 g per day for 4 days) and measurement of urinary aldosterone level and sodium excretion on days 3 to 4 (normal suppression is defined as a 24-h urinary aldosterone concentration <12 μg, concomitant with urinary sodium >200 mmol/day). Some patients already consume a diet with such high sodium content that administration of sodium chloride tablets is unnecessary. The second technique is intravenous infusion of 2 l of normal saline over 4 h, and measurement of PAC at baseline and

4-h time points (normal suppression is defined as PAC <10 ng/dl [277 pmol/l]). Intravenous sodium loading should start during the morning, as the circadian rhythm of ACTH will lower PAC in some patients with adenoma and GRA, thereby generating false-negative results.

In the FST, fludrocortisone acetate is administered for 4 days (0.1 mg every 6 h) concomitant with a high sodium diet and slow-release sodium chloride 30 mmol (1.8 g) three times per day. Plasma potassium level should be measured daily and the patient given sufficient supplements to maintain normal levels. Failure to suppress upright PAC (measured at 10:00 h) to a level less than 6 ng/dl (166 pmol/l) at day 4 is diagnostic of primary aldosteronism, provided that PRA is <1 ng/ml/h, serum cortisol concentration is less at 10:00 h than at 07:00 h, and plasma potassium is within normal range.[56] It should be noted that increased QT DISPERSION in combination with deterioration of ventricular function has been reported during the FST.[57] For this reason, this test should be used with care, and the authors do not recommend it as a first choice.

The captopril suppression test (CST) has also been introduced as a potential confirmatory technique for primary aldosteronism. Captopril inhibits the conversion of angiotensin I to angiotensin II, thereby inhibiting aldosterone production and increasing renin levels in healthy subjects. CST is performed by measuring plasma aldosterone levels before and 2 h after oral administration of 25 mg captopril. Normal suppression is defined as PAC less than 15 ng/dl (416 pmol/l) and a PAC : PRA ratio less than 50 ng/dl per ng/ml per hour (1,387 pmol/l per ng/ml per hour).[58] In a comparative study of CST and oral salt loading in 49 subjects, Agharazii and colleagues[59] detected comparable sensitivity. The authors noted that because the CST did not depend on sodium intake, it could be performed in patients for whom salt loading is contraindicated (such as those with cardiac failure) and is an efficient alternative test. Additional confirmatory studies and a better assessment of test characteristics are needed before the CST can be recommended as a replacement for the current standard confirmatory tests. It should also be noted that administration of captopril can result in profound hypotension in some patients. Careful blood pressure monitoring is required.

It should be noted that all of the confirmatory tests mentioned above have risks and should be used with care in patents with compromised left ventricular cardiac function.

SUBTYPE EVALUATION

As treatment options differ for different forms of primary aldosteronism, it is important to determine the disease subtype. After the diagnosis of primary aldosteronism has been confirmed, the patient should undergo CT (with or without contrast enhancement) with 2–3-mm thick slices of the adrenal glands. The probability of identifying an adrenal mass on CT is approximately 6%;[60] however, most adrenal nodules found on CT are nonfunctional and benign.[61] As such, the anatomic identification of an adrenal mass on CT in a patient with primary aldosteronism does not establish a cause-and-effect relationship. Of 203 patients who underwent both CT and adrenal vein sampling (AVS), 51% of those with a unilateral micronodule (≤1 cm) produced aldosterone at the contralateral side and 41% of those producing aldosterone unilaterally had normal CT findings.[62] So, adrenal CT lacks the overall accuracy to distinguish between unilateral and bilateral disease.

When the patient and clinician wish to pursue surgical treatment (see section below), AVS should also be performed in most patients. AVS is technically difficult and requires a radiologist with experience. A subtype study that clinicians can use is [iodine-131]6-β-iodomethyl-19-norcholesterol (NP-59) scintigraphy. Although advocated by some groups,[63] the sensitivity of NP-59 scintigraphy depends heavily on the size of the adenoma.[64,65] Because tracer uptake was poor in adenomas less than 1.5 cm in diameter, this method was not often 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 US include the following: (i) NP-59 is not approved by the 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 can 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 centers in the US currently offer NP-59 scintigraphy.
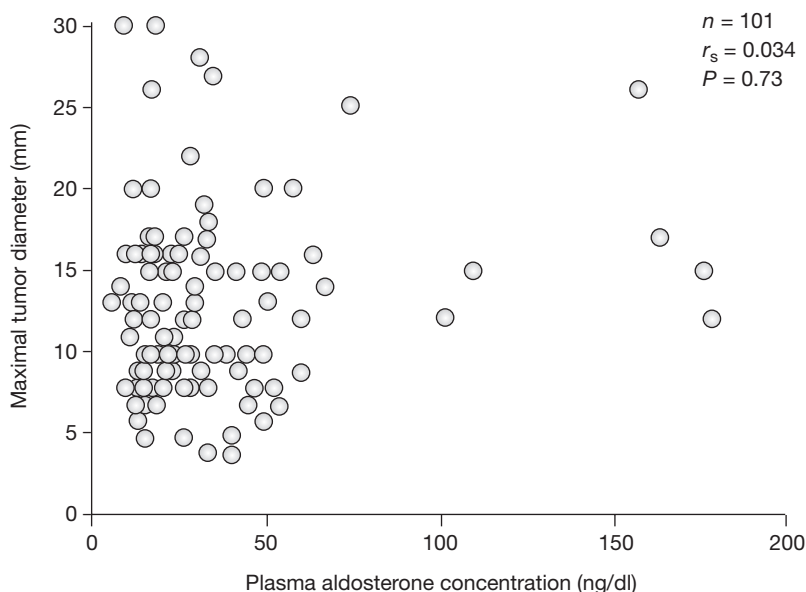
Figure 3 Relationship between maximal diameter of aldosterone-producing adenoma at pathology examination and plasma aldosterone concentration ($n = 101$). Only subjects with adrenal vein sampling-predicted and surgically confirmed solitary unilateral aldosterone-producing adenoma were included. r_s, Spearman rank correlation coefficient.

On CT, benign cortical adenomas are uniform, round and hypodense (e.g. Hounsfield unit score ≤10).[66] So, for cases in which APA is highly likely (patients ≤40 years of age with marked primary aldosteronism, e.g. PAC ≥30 ng/dl [832 pmol/l]) and a well-defined, hypodense adrenal mass (>1 cm on CT scan) is identified, AVS can be bypassed and the patient can undergo unilateral laparoscopic adrenalectomy.[39,67] A review by Kloos *et al.* included discussion of age-dependent prevalence of adrenal cortical adenomas. In patients with primary aldosteronism, the likelihood that an adrenal mass is related to the primary aldosteronism is much greater in a 20-year-old than in a 70-year-old; in the latter patient group, the prevalence of clinically nonfunctioning cortical adenomas exceeds 7%.[61] So, when CT shows a unilateral nodule in a patient who is older than 40 years, the physician should not assume that the mass is the source of excess aldosterone. Finding an irregular adrenal mass or a dense adrenal mass (Hounsfield unit score >10 detected by adrenal CT) in a patient with primary aldosteronism is not typical of a benign aldosterone-producing adenoma; the adrenal mass might not be the source of aldosterone hypersecretion. When large adrenal masses (>4 cm) that are dense

or have mixed attenuation on CT are found in patients with primary aldosteronism, a diagnosis of adrenocortical carcinoma should be considered. If surgical treatment is to be pursued in this clinical setting, then AVS is mandatory. In 101 patients with AVS-predicted and surgically confirmed solitary APA at the Mayo Clinic, Rochester, no significant correlation was found between PAC and tumor size (Figure 3).

Cerebrovascular complications at a young age can affect up to 18% of patients with GRA.[68] As such, patients with primary aldosteronism who have early-onset hypertension (i.e. before the age of 20 years), a family history of primary aldosteronism or a family history of stroke (<40 years of age) should undergo screening tests for GRA. Because aldosterone production is ACTH-dependent, the dexamethasone suppression test can be used in the diagnostic work-up, although germline mutation testing is the best single test.[69] In clinical practice, FH-2 is indistinguishable from APA and IHA, and the diagnosis can be made only by documenting primary aldosteronism in other family members and excluding GRA with genetic testing.

TREATMENT
Surgical intervention
Unilateral laparoscopic adrenalectomy is the optimal treatment for patients diagnosed with APA or unilateral hyperplasia. PAC should be measured the day after surgery to confirm surgical cure. Serum potassium levels should be analyzed the day after the operation. In most cases, potassium supplementation should be withdrawn and doses of antihypertensives decreased when the patient is discharged from hospital. Because aldosterone production in the contralateral adrenal might be suppressed during the first postoperative weeks, a sodium-rich diet should be recommended. Serum potassium levels should be monitored weekly for 4 weeks. In a small number of patients with APA, marked hyperkalemia develops postoperatively and short-term fludrocortisone supplementation might be required.

In almost all patients with surgically managed APA, control of blood pressure improves and serum potassium levels normalize. Between 33% and 35% become normotensive (blood pressure <140/90 mmHg) without the aid of antihypertensive drugs.[40,70–72] Other investigators, who defined cure as blood pressure less than

160/95 mmHg without medication, have reported a cure rate of 56–77%.[73–75] Removal of an APA has also been shown to restore the normal diurnal rhythm of blood pressure.[76] Factors reported to be associated with cure of the disease postoperatively include lack of a family history of hypertension, preoperative use of no more than two antihypertensive drugs, young age, short duration of hypertension (<5 years), positive response to spironolactone, high preoperative PAC : PRA ratio and a high urinary aldosterone excretion.[70,72,73,75] Pre-existing apparent polygenic hypertension is probably the most common reason for persistently increased blood pressure.[75]

In a summary of studies on laparoscopic adrenalectomies (limited to reports with ≥40 patients), primary aldosteronism was found to be the most common indication.[77] In a series of 245 adrenalectomies performed at Mayo Clinic, 41% of patients had primary aldosteronism.[60] The most common surgical approach is unilateral laparoscopic adrenalectomy. Compared with open adrenalectomy, laparoscopic adrenalectomy is associated with fewer complications and fewer hospitalization days.[78–80] According to a retrospective study from the University of Calgary, the frequency of adrenalectomy for primary aldosteronism increased from 13% to 27% after the introduction of laparoscopic surgery.[81] Selected by ICD-9-CM code, the annual rate of adrenalectomies for hyperaldosteronism increased from 0.15 to 0.28 per 100,000 discharges between 1988 and 2000 ($P = 0.015$) in the US.[82] This significant increase can also be attributed to heightened awareness and more frequent case-finding testing for primary aldosteronism among physicians. Ishidoya and colleagues[83] compared outcomes after partial and total adrenalectomy and reported that all patients ($n = 63$) were cured after total adrenalectomy, whereas 2 of 29 patients who underwent partial adrenalectomy were still hypertensive with elevated PAC in the postoperative period. Multiple nodules were found in 27% of the extirpated adrenals. This finding indicates that primary aldosteronism can be multinodular, and that it is not feasible for the surgeon to macroscopically identify and enucleate all adenomas. The potential advantages of partial adrenalectomy are minimal (e.g. fewer ports, shorter operative time, preservation of adrenal tissue) and must be weighed against the risk of persistent primary aldosteronism.

Few long-term studies have compared adrenalectomy with medical treatment in APA. In a retrospective study of 24 patients with APA treated for at least 5 years with spironolactone or potassium-sparing diuretics, Ghose and colleagues[84] found that blood pressure decreased by a mean of 46/27 mmHg. Despite this, most patients required additional hypertensive drugs and several of those taking spironolactone reported adverse effects (e.g. breast tenderness, breast engorgement, muscle cramps, decreased libido, menstrual irregularity, erectile dysfunction, axillary hair loss and irritability). In the long term, adrenalectomy is less expensive than medical therapy.[71]

Pharmacological therapy

Patients with IHA, and those with APA or unilateral hyperplasia who are not candidates for or who decline surgery, should receive a mineralocorticoid receptor antagonist. Two drugs of this class are currently available: spironolactone and eplerenone. Spironolactone can, however, be of limited value because of its affinity for androgen and progesterone receptors. This affinity can induce adverse effects such as gynecomastia and sexual dysfunction in men, and menstrual irregularities in women. Gynecomastia was reported in 6.9% of men who received 50 mg of spironolactone daily and in 52.0% of those who received 150 mg daily.[85]

Substitution of the 17α-thioacetyl group of spironolactone with a carbomethoxy group generates eplerenone. The affinity of eplerenone for progestin and androgen receptors is as much as 500-fold lower than that of spironolactone, thus nullifying the adverse effects associated with progesterone agonism and androgen antagonism. Eplerenone has no active metabolites and a shorter half-life than spironolactone. These characteristics probably underlie the reduced risk of hyperkalemia associated with eplerenone.[86] In a study of men with mild to moderate essential hypertension, 50 mg eplerenone twice daily for 8 weeks reduced blood pressure by a mean of 11.7/7.8 mmHg.[86] On a molecular basis, eplerenone is 50–75% as potent as spironolactone.[87] From a health economics perspective, however, spironolactone is recommended as first-line drug; the average wholesale price for a year of eplerenone therapy (50 mg twice daily) is US$2,759 compared with $603 for spironolactone (50 mg twice daily).[88]

Amiloride has been used as an alternative to mineralocorticoid receptor antagonists on account of its potassium-sparing effect. *In vitro*

studies have found that amiloride prevents aldosterone-induced endothelial swelling.[89] In experiments with rats, the drug inhibited myocardial scarring induced by excess aldosterone.[90] To date there have been no clinical studies showing that amiloride protects against the negative effects of aldosterone on nonepithelial tissues. For pharmacotherapy of primary aldosteronism, a mineralocorticoid receptor antagonist is highly recommended, even if used only at a low dose (e.g. spironolactone 12.5 mg daily).

GRA is also treated pharmacologically, with a glucocorticoid to partially suppress pituitary ACTH secretion. To avoid iatrogenic CUSHING'S SYNDROME, the lowest effective dose of glucocorticoid should be used. As glucocorticoid treatment does not always result in normalization of blood pressure, the addition of a mineralocorticoid receptor antagonist should be considered. Other antihypertensive agents might be used as third-line and fourth-line agents for adequate blood pressure control.[91]

CONCLUSION

Primary aldosteronism is a common and potentially curable cause of hypertension. Measurement of the PAC : PRA ratio and PAC are inexpensive, low-risk case-finding tools that are available at most medical centers. Optimal treatment (from both individual and cost-effective perspectives) for APA is unilateral laparoscopic adrenalectomy. All pharmacologically managed patients should receive a mineralocorticoid receptor antagonist to prevent the negative effects of aldosterone on nonepithelial tissues.

KEY POINTS

■ Primary aldosteronism is present in 5–13% of people with hypertension

■ Diagnosis of primary aldosteronism is based on an increased ratio of plasma aldosterone concentration to plasma renin activity, and results of a subsequent aldosterone suppression test

■ There are several subtypes of primary aldosteronism—bilateral idiopathic hyperplasia and aldosterone-producing adenoma are the most common

■ Determination of subtype is essential to direct therapy

■ Surgical (e.g. laparoscopic adrenalectomy) and pharmacological (e.g. mineralocorticoid receptor antagonists) interventions are commonly used

References

1 Hajjar I and Kotchen TA (2003) Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA* **290:** 199–206
2 Conn JW (1955) Presidental address: part I painting background; part II primary aldosteronism, a new clinical syndrome. *J Lab Clin Med* **45:** 3–17
3 Conn JW and Conn ES (1961) Primary aldosteronism versus hypertensive disease with secondary aldosteronism. *Recent Prog Horm Res* **17:** 389–414
4 Conn JW (1966) The evolution of primary aldosteronism: 1954–1967. *Harvey Lect* **62:** 257–291
5 Andersen GS *et al.* (1988) The incidence rate of phaeochromocytoma and Conn's syndrome in Denmark, 1977–1981. *J Hum Hypertens* **2:** 187–189
6 Berglund G *et al.* (1976) Prevalence of primary and secondary hypertension: studies in a random population sample. *Br Med J* **2:** 554–556
7 Fishman LM *et al.* (1968) Incidence of primary aldosteronism uncomplicated "essential" hypertension: a prospective study with elevated aldosterone secretion and suppressed plasma renin activity used as diagnostic criteria. *JAMA* **205:** 497–502
8 Streeten DH *et al.* (1979) Reliability of screening methods for the diagnosis of primary aldosteronism. *Am J Med* **67:** 403–413
9 Tucker RM and Labarthe DR (1977) Frequency of surgical treatment for hypertension in adults at the Mayo Clinic from 1973 through 1975. *Mayo Clin Proc* **52:** 549–545
10 Kaplan NM (1967) Hypokalemia in the hypertensive patient, with observations on the incidence of primary aldosteronism. *Ann Intern Med* **66:** 1079–1090
11 Dunn PJ and Espiner EA (1976) Outpatient screening tests for primary aldosteronism. *Aust NZ J Med* **6:** 131–135
12 Hiramatsu K *et al.* (1981) A screening test to identify aldosterone-producing adenoma by measuring plasma renin activity: results in hypertensive patients. *Arch Intern Med* **141:** 1589–1593
13 Mulatero P *et al.* (2004) Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. *J Clin Endocrinol Metab* **89:** 1045–1050
14 Mosso L *et al.* (2003) Primary aldosteronism and hypertensive disease. *Hypertension* **42:** 161–165
15 Gordon RD *et al.* (1994) High incidence of primary aldosteronism in 199 patients referred with hypertension. *Clin Exp Pharmacol Physiol* **21:** 315–318
16 Loh KC *et al.* (2000) Prevalence of primary aldosteronism among Asian hypertensive patients in Singapore. *J Clin Endocrinol Metab* **85:** 2854–2859
17 Fardella CE *et al.* (2000) Primary hyperaldosteronism in essential hypertensives: prevalence, biochemical profile, and molecular biology. *J Clin Endocrinol Metab* **85:** 1863–1867
18 Lim PO *et al.* (2000) High prevalence of primary aldosteronism in the Tayside hypertension clinic population. *J Hum Hypertens* **14:** 311–315
19 Schwartz GL and Turner ST (2005) Screening for primary aldosteronism in essential hypertension: diagnostic accuracy of the ratio of plasma aldosterone concentration to plasma renin activity. *Clin Chem* **51:** 386–394
20 Hamlet SM *et al.* (1985) Is aldosterone/renin ratio useful to screen a hypertensive population for primary aldosteronism? *Clin Exp Pharmacol Physiol* **12:** 249–252
21 Calhoun DA *et al.* (2002) Hyperaldosteronism among black and white subjects with resistant hypertension. *Hypertension* **40:** 892–896

22 Gallay BJ *et al.* (2001) Screening for primary aldosteronism without discontinuing hypertensive medications: plasma aldosterone–renin ratio. *Am J Kidney Dis* **37:** 699–705

23 Pratt JH *et al.* (1999) Levels of mineralocorticoids in whites and blacks. *Hypertension* **34:** 315–319

24 Rayner BL *et al.* (2001) Screening for primary aldosteronism—normal ranges for aldosterone and renin in three South African population groups. *S Afr Med J* **91:** 594–599

25 Conn JW *et al.* (1965) Normokalemic primary aldosteronism: a detectable cause of curable "essential" hypertension. *JAMA* **193:** 200–206

26 Mulatero P *et al.* (2002) Drug effects on aldosterone/ plasma renin activity ratio in primary aldosteronism. *Hypertension* **40:** 897–902

27 Rossi E *et al.* (2002) High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. *Am J Hypertens* **15:** 896–902

28 Brown NJ (2005) Aldosterone and end-organ damage. *Curr Opin Nephrol Hypertens* **14:** 235–241

29 Brilla CG *et al.* (1990) Remodeling of the rat right and left ventricles in experimental hypertension. *Circ Res* **67:** 1355–1364

30 Rocha R *et al.* (2002) Aldosterone induces a vascular inflammatory phenotype in the rat heart. *Am J Physiol Heart Circ Physiol* **283:** H1802–1810

31 Takeda Y *et al.* (2001) Effects of high sodium intake on cardiovascular aldosterone synthesis in stroke-prone spontaneously hypertensive rats. *J Hypertens* **19:** 635–639

32 Kozakova M *et al.* (2003) Myocardial ultrasonic backscatter in hypertension: relation to aldosterone and endothelin. *Hypertension* **41:** 230–236

33 Stowasser M *et al.* (2005) Evidence for abnormal left ventricular structure and function in normotensive individuals with familial hyperaldosteronism type I. *J Clin Endocrinol Metab* **90:** 5070–5076

34 Milliez P *et al.* (2005) Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* **45:** 1243–1248

35 Pitt B *et al.* (2003) Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* **348:** 1309–1321

36 Zannad F *et al.* (2000) Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). *Circulation* **102:** 2700–2706

37 Fallo F *et al.* (2006) Prevalence and characteristics of the metabolic syndrome in primary aldosteronism. *J Clin Endocrinol Metab* **91:** 454–459

38 Chhokar VS *et al.* (2005) Hyperparathyroidism and the calcium paradox of aldosteronism. *Circulation* **111:** 871–878

39 Young WF Jr (2003) Minireview: primary aldosteronism—changing concepts in diagnosis and treatment. *Endocrinology* **144:** 2208–2213

40 Blumenfeld JD *et al.* (1994) Diagnosis and treatment of primary hyperaldosteronism. *Ann Intern Med* **121:** 877-885

41 Mansoor GA *et al.* (2002) Unilateral adrenal hyperplasia causing primary aldosteronism: limitations of I-131 norcholesterol scanning. *Am J Hypertens* **15:** 459–464

42 Seccia TM *et al.* (2005) Aldosterone-producing adrenocortical carcinoma: an unusual cause of Conn's syndrome with an ominous clinical course. *Endocr Relat Cancer* **12:** 149–159

43 Mulatero P *et al.* (2004) Genetics of primary aldosteronism. *J Hypertens* **22:** 663–670

44 So A *et al.* (2005) Familial hyperaldosteronism type II is linked to the chromosome 7p22 region but also shows predicted heterogeneity. *J Hypertens* **23:** 1477–1484

45 Young WF Jr (2003) Primary aldosteronism—treatment options. *Growth Horm IGF Res* **13 (Suppl A):** S102–S108

46 Montori VM *et al.* (2001) Validity of the aldosterone–renin ratio used to screen for primary aldosteronism. *Mayo Clin Proc* **76:** 877-882

47 Kaplan NM (2004) The current epidemic of primary aldosteronism: causes and consequences. *J Hypertens* **22:** 863–869

48 Lamarre-Cliche M *et al.* (2005) Effects of circadian rhythms, posture, and medication on renin-aldosterone interrelations in essential hypertensives. *Am J Hypertens* **18:** 56–64

49 Hirohara D *et al.* (2001) Performance of the basal aldosterone to renin ratio and of the renin stimulation test by furosemide and upright posture in screening for aldosterone-producing adenoma in low renin hypertensives. *J Clin Endocrinol Metab* **86:** 4292–4298

50 Montori VM and Young WF Jr (2002) Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism: a systematic review of the literature. *Endocrinol Metab Clin North Am* **31:** 619–632

51 Tiu SC *et al.* (2005) The use of aldosterone-renin ratio as a diagnostic test for primary hyperaldosteronism and its test characteristics under different conditions of blood sampling. *J Clin Endocrinol Metab* **90:** 72–78

52 Weinberger MH and Fineberg NS (1993) The diagnosis of primary aldosteronism and separation of two major subtypes. *Arch Intern Med* **153:** 2125–2129

53 Unger N *et al.* (2004) Comparison of active renin concentration and plasma renin activity for the diagnosis of primary hyperaldosteronism in patients with an adrenal mass. *Eur J Endocrinol* **150:** 517–523

54 Ferrari P *et al.* (2004) Active renin versus plasma renin activity to define aldosterone-to-renin ratio for primary aldosteronism. *J Hypertens* **22:** 377–381

55 Olivieri O *et al.* (2004) Aldosterone to renin ratio in a primary care setting: the Bussolengo study. *J Clin Endocrinol Metab* **89:** 4221–4226

56 Stowasser M and Gordon RD (2004) Primary aldosteronism—careful investigation is essential and rewarding. *Mol Cell Endocrinol* **217:** 33–39

57 Lim PO *et al.* (2001) Adverse cardiac effects of salt with fludrocortisone in hypertension. *Hypertension* **37:** 856–861

58 Young WF Jr and Klee GG (1988) Primary aldosteronism: diagnostic evaluation. *Endocrinol Metab Clin North Am* **17:** 367–395

59 Agharazii M *et al.* (2001) Captopril suppression versus salt loading in confirming primary aldosteronism. *Hypertension* **37:** 1440–1443

60 Thompson GB and Young WF Jr (2003) Adrenal incidentaloma. *Curr Opin Oncol* **15:** 84–90

61 Kloos RT *et al.* (1995) Incidentally discovered adrenal masses. *Endocr Rev* **16:** 460–484

62 Young WF *et al.* (2004) Role for adrenal venous sampling in primary aldosteronism. *Surgery* **136:** 1227–1235

63 Lumachi F *et al.* (2003) Non-invasive adrenal imaging in primary aldosteronism: sensitivity and positive predictive value of radiocholesterol scintigraphy, CT scan and MRI. *Nucl Med Commun* **24:** 683–688

64 Hogan MJ *et al.* (1976) Location of aldosterone-producing adenomas with 131I-19-iodocholesterol. *N Engl J Med* **294:** 410–414

65 Nomura K *et al.* (1990) Iodomethylnorcholesterol uptake in an aldosteronoma shown by dexamethasone-suppression scintigraphy: relationship to adenoma size and functional activity. *J Clin Endocrinol Metab* **71:** 825–830

66 Choyke PL (1998) From needles to numbers: can noninvasive imaging distinguish benign and malignant adrenal lesions? *World J Urol* **16:** 29–34

67 Young WF Jr *et al.* (2003) Adrenalectomy for primary aldosteronism; authors' reply. *Ann Intern Med* **138:** 157–159

68 Litchfield WR *et al.* (1998) Intracranial aneurysm and hemorrhagic stroke in glucocorticoid-remediable aldosteronism. *Hypertension* **31:** 445–450

69 Stowasser M and Gordon RD (2001) Familial hyperaldosteronism. *J Steroid Biochem Mol Biol* **78:** 215–229

70 Sawka AM *et al.* (2001) Primary aldosteronism: factors associated with normalization of blood pressure after surgery. *Ann Intern Med* **135:** 258–261

71 Sywak M and Pasieka JL (2002) Long-term follow-up and cost benefit of adrenalectomy in patients with primary hyperaldosteronism. *Br J Surg* **89:** 1587–1593

72 Meyer A *et al.* (2005) Long-term follow-up after adrenalectomy for primary aldosteronism. *World J Surg* **29:** 155–159

73 Celen O *et al.* (1996) Factors influencing outcome of surgery for primary aldosteronism. *Arch Surg* **131:** 646-650

74 Lo CY *et al.* (1996) Primary aldosteronism: results of surgical treatment. *Ann Surg* **224:** 125–130

75 Proye CA *et al.* (1998) Essential hypertension: first reason for persistent hypertension after unilateral adrenalectomy for primary aldosteronism? *Surgery* **124:** 1128–1133

76 Zelinka T *et al.* (2004) Diurnal blood pressure variation in pheochromocytoma, primary aldosteronism and Cushing's syndrome. *J Hum Hypertens* **18:** 107–111

77 Assalia A and Gagner M (2004) Laparoscopic adrenalectomy. *Br J Surg* **91:** 1259–1274

78 Rossi H *et al.* (2002) Primary hyperaldosteronism in the era of laparoscopic adrenalectomy. *Am Surg* **68:** 253–256

79 Gonzalez R *et al.* (2004) Laparoscopic approach reduces likelihood of perioperative complications in patients undergoing adrenalectomy. *Am Surg* **70:** 668–674

80 Jacobsen NE *et al.* (2003) Laparoscopic versus open adrenalectomy for surgical adrenal disease. *Can J Urol* **10:** 1995–1999

81 Chavez-Rodriguez J and Pasieka JL (2005) Adrenal lesions assessed in the era of laparoscopic adrenalectomy: a modern day series. *Am J Surg* **189:** 581–585

82 Saunders BD *et al.* (2004) Trends in utilization of adrenalectomy in the United States: have indications changed? *World J Surg* **28:** 1169–1175

83 Ishidoya S *et al.* (2005) Laparoscopic partial versus total adrenalectomy for aldosterone producing adenoma. *J Urol* **174:** 40–43

84 Ghose RP *et al.* (1999) Medical management of aldosterone-producing adenomas. *Ann Intern Med* **131:** 105–108

85 Jeunemaitre X *et al.* (1987) Efficacy and tolerance of spironolactone in essential hypertension. *Am J Cardiol* **60:** 820–825

86 Sica DA (2005) Pharmacokinetics and pharmacodynamics of mineralocorticoid blocking agents and their effects on potassium homeostasis. *Heart Fail Rev* **10:** 23–29

87 Weinberger MH *et al.* (2002) Eplerenone, a selective aldosterone blocker, in mild-to-moderate hypertension. *Am J Hypertens* **15:** 709–716

88 Fleming T (Ed.; 2005) *Red Book: Pharmacy's Fundamental Reference*, 438 and 614. Montvale: Thomson PDR

89 Oberleithner H *et al.* (2004) Human endothelium: target for aldosterone. *Hypertension* **43:** 952–956

90 Campbell SE *et al.* (1993) Myocardial fibrosis in the rat with mineralocorticoid excess: prevention of scarring by amiloride. *Am J Hypertens* **6:** 487–495

91 Dluhy RG and Lifton RP (1999) Glucocorticoid-remediable aldosteronism. *J Clin Endocrinol Metab* **84:** 4341–4344