Primary Aldosteronism Practical Approach to Diagnosis and Management

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Primary Aldosteronism

Practical Approach to Diagnosis and Management

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ABSTRACT: Primary aldosteronism (PA) is the most common form of secondary hypertension. In many cases, somatic mutations in ion channels and pumps within adrenal cells initiate the pathogenesis of PA, and this mechanism might explain why PA is so common and suggests that milder and evolving forms of PA must exist. Compared with primary hypertension, PA causes more end-organ damage and is associated with excess cardiovascular morbidity, including heart failure, stroke, nonfatal myocardial infarction, and atrial fibrillation. Screening is simple and readily available, and targeted therapy improves blood pressure control and mitigates cardiovascular morbidity. Despite these imperatives, screening rates for PA are low, and mineralocorticoid-receptor antagonists are underused for hypertension treatment. After the evidence for the prevalence of PA and its associated cardiovascular morbidity is summarized, a practical approach to PA screening, referral, and management is described. All physicians who treat hypertension should routinely screen appropriate patients for PA.

A 68-year-old man requested a second opinion from a cardiologist for management of uncontrolled hypertension. Diagnosed with hypertension ≈35 years ago, he had taken up to 6 antihypertensive medications concurrently without adequate blood pressure control. In the ensuing years, he had developed stage 3 chronic kidney disease. A year before consultation, he was admitted to a hospital for new-onset atrial fibrillation in the setting of hypokalemia (serum potassium, 2.9 mEq/L). Potassium chloride was initiated at a daily dose of 60 mEq/d. A cardiologist was consulted during that hospitalization, and the medication regimen was adjusted to include a β-blocker and later clonidine for a diagnosis of primary hypertension. The patient did not tolerate clonidine. During the second-opinion consultation, the patient explained that he was avoiding nonsteroidal anti-inflammatory medications, had reduced his alcohol intake, had lost 30 pounds, and was exercising 3 to 4 times a week. He denied habitually eating confectionery licorice or taking nutritional supplements. He reported excellent adherence with his regimen of hydrochlorothiazide 50 mg daily, lisinopril 60 mg daily, amlodipine 5 mg daily, carvedilol 25 mg twice daily, potassium chloride 60 mEq daily, and apixaban 5 mg daily. Nonetheless, his blood pressure remained uncontrolled (156/89 mm Hg). Physical examination revealed 2+ lower-extremity edema but no abdominal bruits. Without interruption of his antihypertensive medications, plasma renin activity (PRA) and serum aldosterone concentrations were measured and were 0.2 ng·mL^{-1}·h^{-1} (normal range, 0.8–5.3 ng·mL^{-1}·h^{-1} upright) and 25.8 ng/dL

Key Words: adrenal cortex ■ aldosterone ■ hyperaldosteronism ■ hypertension ■ receptors, mineralocorticoid ■ renin ■ renin-angiotensin system

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(inappropriately high for this renin value), respectively. Evaluation for occult secondary causes of hypertension, including thyroid disease and pheochromocytoma, disclosed no other abnormalities. He was referred to an endocrinologist, who confirmed the diagnosis of primary aldosteronism (PA) and completed the evaluation. After laparoscopic adrenalectomy, his ambulatory blood pressure monitoring study showed a 24-hour mean blood pressure of 120 mm Hg systolic and 77 mm Hg diastolic during treatment with lisinopril, hydrochlorothiazide, and carvedilol.

INTRODUCTION

PA is defined as inappropriately elevated aldosterone production in the setting of low plasma renin. Once thought to be rare, PA is now known to be the most common cause of secondary hypertension, with a prevalence of 20% among patients with resistant hypertension,[1,2] 10% in those with severe hypertension (systolic blood pressure [SBP] ≥180, diastolic blood pressure ≥110 mm Hg),[3,4] and 6% in those with otherwise uncomplicated hypertension.[4] Only a small fraction of the patients with PA are diagnosed and treated.[5] Accumulating evidence suggests that PA amplifies cardiovascular morbidity and mortality beyond primary hypertension, even after controlling for the degree of blood pressure elevation.[6–9] Consequently, early identification and specific treatment of PA are essential, yet PA remains underrecognized by both internists and specialists. Screening for PA is simple and accessible and should be routinely implemented in patients with resistant hypertension, hypertension with hypokalemia, or early-onset hypertension. The purpose of this review is to highlight a recent explosion of knowledge about PA and to provide a practical approach to its diagnosis and treatment.

A contemporary understanding of PA is essential to the practice of cardiovascular medicine. Funder[5] has estimated that among US patients with PA, 1 in 550 is diagnosed and treated for the condition. This conservative estimate illuminates the magnitude of PA underdiagnosis. The recent expansion of knowledge addressing the prevalence, pathophysiology, and clinical approach to PA has provided an evidence-based understanding of this common condition. Although hypokalemia in the setting of hypertension should immediately and reflexively prompt consideration of PA, most patients with PA are not hypokalemic.[4,10,11] The screening process is much simpler than commonly perceived,[12] and the end-organ complications of hypertension caused by PA provide an imperative for making the diagnosis and implementing appropriate therapy.[13] Although the later stages of the evaluation are best performed in referral centers,[14] all providers with internal medicine training should be comfortable performing initial screening for PA when appropriate and initiating targeted medical therapy.

ALDOSTERONE IN NORMAL CARDIORENAL PHYSIOLOGY

Sodium is the primary determinant of plasma osmolarity, and total body sodium is the major determinant of plasma volume. Aldosterone regulates the final stages of sodium reabsorption in the distal renal tubule and collecting duct. Although aldosterone regulates absorption of just 1% to 5% of filtered sodium, the kidney filters the entire circulating plasma volume twice an hour, totaling ≈180 L plasma a day. The resulting large net daily burden of reabsorption underscores the strategic positioning of aldosterone in regulating plasma volume, as illustrated in the following clinically relevant example. In the setting of a 1500-mg sodium diet, as recommended in the 2017 American College of Cardiology/American Heart Association guidelines[15] for adults needing blood pressure reduction, equivalent to 0.75 teaspoon of table salt or 65 mEq of sodium, a healthy adult will filter 25 560 mEq (588 g) of sodium[16] and reabsorb ≈25 553 mEq (99.97% of the filtered load).

Molecular Mechanisms of Aldosterone Effects

Like other steroid hormones, aldosterone is lipophilic, and half of circulating aldosterone is weakly bound to plasma proteins. Aldosterone diffuses readily through cell membranes, where it binds to the mineralocorticoid receptor (MR), which in the unbound state resides in the cytoplasm. Upon ligand binding, MRs dimerize and translocate to the nucleus, where they act as ligand-activated transcription factors (Figure 1). MR is highly expressed in the epithelial cells lining the distal convoluted tubule and cortical collecting duct of the kidney, colonic mucosa, and eccrine sweat glands, which are all tissues that transport ions. In addition, MR is expressed in cardiomyocytes, vascular smooth muscle cells, endothelial cells, cells within brown adipose tissue, macrophages, and neurons in several brain regions, including the hippocampus, hypothalamus, and brainstem. The consequences of MR activation have been extensively studied in the kidney, where aldosterone promotes the expression of amiloride-sensitive epithelial sodium channels in the distal tubule and cortical collecting duct and their residence on the apical surface, resulting in sodium and water reabsorption. In addition, aldosterone mediates some of its effects in a rapid nongenomic fashion that likely involves MR and a receptor called G protein–coupled estrogen receptor 1.[17–19] Urinary sodium delivered to the distal tubule enters renal

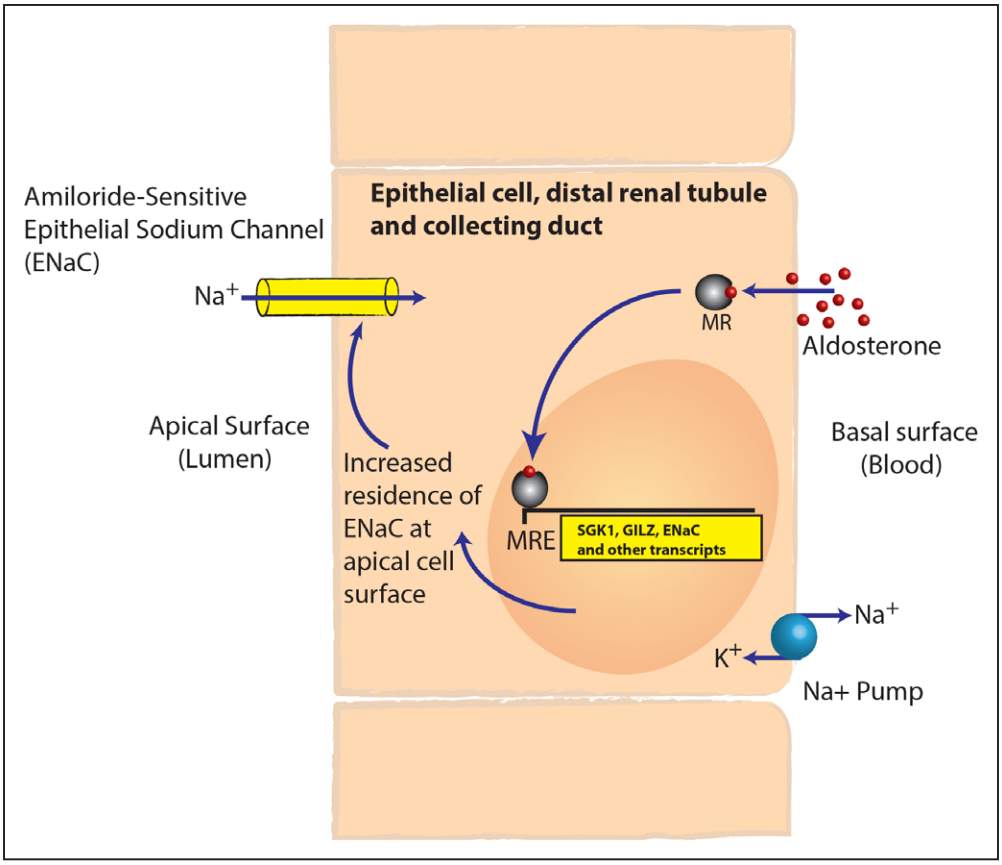

Figure 1. Illustration of the ligand-activated transcription factor activity of the mineralocorticoid receptor (MR).
The liposoluble steroid hormone aldosterone diffuses into cells and binds to and activates the MR. The MR then dimerizes and translocates to the nucleus, where it binds a hormone-response element and regulates the transcription of target genes. This process regulates the abundance of the amiloride-sensitive epithelial sodium channel on the apical surface of the epithelial cells in the distal-renal tubule and collecting duct, controlling the final 1% to 5% of sodium reabsorption. GILZ indicates glucocorticoid-induced leucine zipper; MRE, mineralocorticoid response element; and SGK1, serum- and glucocorticoid-inducible kinase.

tubular epithelial cells (principal cells) via apical epithelial sodium channels. From the epithelial cells, sodium is reabsorbed back into the interstitial fluid via Na^+ /K^+-ATPase pumps on the basolateral surface of the cells. As a result of the electrochemical gradient derived from sodium reabsorption, potassium is then secreted into the urine via apical potassium channels. Aldosterone also stimulates the urinary secretion of H^+ via the H^+-ATPase in the intercalated cells of the cortical collecting tubules. In concert, these renal actions of aldosterone contribute to intravascular volume expansion and renal loss of potassium and hydrogen ions.

Regulation of Aldosterone Production

In normal physiology, the renin-angiotensin-aldosterone system is the primary regulator of aldosterone production. In the setting of volume depletion or other states of decreased renal perfusion or sodium delivery, the juxtaglomerular cells release renin. Renin cleaves angiotensinogen to form angiotensin I, and angiotensin-converting enzyme catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II receptors on the adrenal zona glomerulosa (ZG) cells signal primarily through depolarization and increased intracellular calcium to induce the enzymatic machinery necessary to synthesize aldosterone, including aldosterone synthase (cytochrome P450 11B2 or CYP11B2).[20] Besides angiotensin II, high plasma potassium concentration stimulates and low plasma potassium inhibits aldosterone production; in addition, high potassium potentiates the effect of angiotensin II as an aldosterone secretogogue.[21] Adrenocorticotropic hormone transiently stimulates aldosterone synthesis. The net effect of this physiology is that renin and aldosterone normally rise and fall in parallel.

Throughout most of human history, aldosterone protected our interior environment against the threat of salt or volume depletion during stresses such as salt and water deprivation, high-heat environments, diarrhea, or fever. Historic data from the Yanomamo people of northeastern Brazil are illustrative of this protective role of aldosterone and the broad dynamic range over which aldosterone secretion occurs. In the 1970s, the Yanomamo excreted ≈1 mEq of sodium per day, balancing roughly 1 mEq (23 mg) of daily sodium intake. Their urinary aldosterone levels were 27 times higher and urinary sodium excretion 100-fold lower than members of a research team consuming an ordinary

diet that included table salt.[22] In contrast, homeostasis of body sodium content and plasma volume requires little or no aldosterone in adults living in developed societies and consuming a high-sodium diet today. Consistent with a reduced need for aldosterone production in societies consuming a high-sodium diet, the adult ZG contains very little aldosterone synthase compared with infant ZG.[23] Today, the average daily sodium intake in US adults is 3592 mg, >4.5 times greater than the 768 mg/d consumed in hunter-gatherer societies.[24] Thus, the modern environment challenges the adult adrenal ZG to minimize aldosterone production, diametrically opposite to sodium preservation, for which it evolved. Consequently, even mild degrees of aldosterone production can be viewed as inappropriate for the high sodium intake in salt-loaded societies and detrimental to health.

Pathogenic Mechanisms of PA: How Can PA Be So Common?

Broadly, PA can be dichotomized to unilateral aldosterone production from the right or left adrenal gland (aldosterone-producing adenoma [APA]) or bilateral hyperaldosteronism (BHA). In contrast to normal physiology, in PA, the adrenal gland produces aldosterone in an autonomous fashion. Whereas APA is a tangible form of disease, BHA is an elusive concept, which has lacked a pathophysiological mechanism for many years. The development of highly specific antibodies for aldosterone synthase and sophisticated genomic sequencing techniques has led to major advancements in our understanding of PA pathogenesis in the recent years. The simple nomenclature of APA versus BHA derives from basic histology of resected adrenal glands, in conjunction with imaging and adrenal vein sampling. Recent studies using immunohistochemical staining of aldosterone synthase have demonstrated that the PA pathology spans a wide spectrum that includes bilateral adenomas, unilateral hyperplasia,[25,26] micronodules, and microscopic aldosterone-producing cell clusters (APCCs)[27] in various combinations. Such immunohistochemistry studies have revealed that in unilateral PA, an adrenal gland hosting a macroscopic nodule might contain additional sources of autonomous aldosterone secretion[28] and that the largest ("dominant") nodule is sometimes not a source of aldosterone at all.[29,30]

The genesis and progression of PA are not yet fully understood, but several hypotheses have derived from recent studies. In 2010, Nishimoto and colleagues[31] described APCCs as discrete subcapsular cell clusters expressing aldosterone synthase in the normal adrenals, in contrast to the continuous ZG observed in rodent adrenals and young human adrenals.[32] APCCs were also noted adjacent to APAs,[27,29,31] despite suppressed renin, suggesting their autonomous aldosterone synthesis. Immunohistochemistry studies of adrenal glands obtained from deceased kidney donors have shown an age-dependent increase in the number of APCCs, in stark contrast to the decline of the total aldosterone synthase–expressing area, further supporting the autonomy of APCCs in aldosterone production.[33,34]

The genetic landscape of aldosterone-producing states has yielded further progress in our understanding the molecular mechanisms of PA pathogenesis, starting with studies of familial forms of PA. Three types of familial hyperaldosteronism (FHA) are currently recognized. FHA type I (FHA-I), also known as glucocorticoid-remediable aldosteronism, was first described by Sutherland et al[35] in 1966 and has an autosomal dominant inheritance. In 1992, Lifton and colleagues[36] elucidated the molecular basis of FHA-I, residing in a chimeric gene, which fuses the 5′ end including the promoter of the 11β-hydroxylase gene (*CYP11B1*) and the 3′ end of the *CYP11B2* gene. The enzyme encoded by this hybrid gene produces aldosterone under the regulation of adrenocorticotropic hormone in the zona fasciculata, where cortisol is normally made. The hypertension of FHA-I tends to be milder than average for PA but is associated with a high incidence of hemorrhagic strokes.

FHA type II (FHA-II), first described in 1991,[37] is clinically indistinguishable from sporadic PA. Although FHA-II appears to be the most common form of inherited PA, the underlying mutations remain unknown, and it is likely a genetically heterogeneous condition. In 2 FHA-II kindreds, mutations in the CLCN2 chloride channel have been identified.[38,39]

FHA type III (FHA-III) was initially reported in 2008 in a family with early-onset, severe PA and marked bilateral adrenal hyperplasia.[40] In 2011, Choi and colleagues[41] revealed the causative germline mutation in this family to be located in the *KCNJ5* gene encoding the Kir3.4 (also called GIRK4) potassium channel. These mutations alter the selectivity filter of the channel, allowing sodium conductance through what is ordinarily an inward-rectifying potassium channel, which maintains ZG cell hyperpolarization. This change in sodium conductance leads to cell depolarization and calcium entry, which in turn drives aldosterone production.

Germline mutations in *CACNA1D* (encoding the L-type calcium channel Cav1.3)[42] and *CACNA1H* (encoding the T-type calcium channel Cav3.2)[41] have now also been described in families with PA. Many of these cases, which can be considered FHA type IV (FHA-IV), have additional neurological and cognitive dysfunction.

Recent clinical investigation has provided a greater understanding of the pathogenesis of PA and has unexpectedly revealed a high frequency of somatic mutations in genes involved in aldosterone production, which helps to explain the increasing prevalence of PA with age.[42–44] Somatic mutations in the same genes causing FHA-III and FHA-IV have been identified in a

high proportion of APAs. Choi et al[41] were the first to report *KCNJ5* somatic mutations in APAs, findings that several other groups have subsequently confirmed. The percentage of APAs with a mutation in *KCNJ5* varies by region and is as high as 80% in Asian populations.[45] Since this discovery, several teams have expanded the spectrum of somatic mutations in APAs that appear to be causally linked to aldosterone production. The somatic mutations in genes encoding other ions channels and pumps include *ATP1A1* (encoding a Na^+/K^+ ATPase α subunit), *ATP2B3* (encoding a Ca^{2+} ATPase), as well as *CACNA1D*.[42,44,46,47] In addition, activating somatic mutations of *CTNNB1* (β-catenin, an intracellular signal transducer in the *Wnt*-signaling pathway) have been reported in APAs of pregnant or postmenopausal women, who were found to exhibit dramatic overexpression of ectopic luteinizing hormone/chorionic gonadotropin and gonadotropin-releasing hormone receptors, presumably induced by the β-catenin mutations.[48] Such aldosterone driver mutations (*CACNA1D* and *ATP1A1*) were identified in 8 of 23 APCCs (35%) isolated from kidney donors' adrenal glands but were not present in the adjacent normal tissue,[33] supporting the hypothesis that some APCCs might be precursors of APAs.

Transcriptome analyses have identified several genes with an expression that is upregulated in APAs compared with normal adjacent tissues, unveiling more possible mechanisms involved in the pathogenesis of PA. Such relevant genes with increased expression in APAs include enzymes and cofactors required for aldosterone synthesis, including *CYP11B2, CYP21A2*, adrenodoxin (*FDX1*), and P450-oxidoreductase (*POR*)[49–52]; genes encoding G-protein–coupled receptors such as luteinizing hormone/chorionic gonadotropin receptor (*LHR*), adrenocorticotropic hormone receptor (melanocortin receptor type-2 [*MC2R*]), gonadotropin-releasing hormone receptor (*GNRHR*), and serotonin receptor 4 (*HTR4*)[53]; genes encoding transcription factors involved in steroidogenesis and differentiation[50,52]; and calmodulin kinase (*CAMK),* encoding a protein involved in Ca^{2+} signaling.[51] All of these proteins enhance the steroidogenic capacity of adrenal cells.

Despite this increasingly detailed understanding of APAs, the origins of BHA remain poorly understood. One possibility is that BHA derives from the accumulation of a clinically significant number of APCCs in both adrenal glands. In mice, deletion of the TWIK-related acid-sensitive potassium channels types 1 and 3 (TASK-1, TASK-3) causes bilateral PA.[54] TASK-2 expression is decreased in some adrenal nodules from patients with PA[55]; however, the significance of altered TASK function as an etiologic factor in BHA remains speculative. Whereas in unilateral PA adrenal glands are often removed to treat APAs, surgery is rarely used for BHA, which limits access to BHA tissue samples and represents a comparative challenge for molecular studies of BHA pathogenesis.

PA is not a yes/no dichotomy in hypertensive patients but rather a spectrum of MR antagonist–responsive disease, particularly in patients with resistant hypertension and mildly elevated or even ostensibly normal aldosterone levels. Calhoun and colleagues[56] have explored this phenotype extensively, and Baudrand and colleagues[57] have further characterized this continuum using comprehensive dynamic testing. Additional evidence for this mild PA phenotype comes from the PATHWAY-2 trial (Prevention And Treatment of Hypertension With Algorithm based Therapy - 2). Patients with resistant hypertension often responded well to MR antagonists in PATHWAY-2, despite the exclusion of patients with classic PA from the study and regardless of baseline aldosterone levels.[58] It is not known whether MR-responsive hypertension in the setting of ostensibly normal circulating aldosterone indicates a relative excess of aldosterone or hypersensitivity to aldosterone, MR activation via occult ligands, or other mechanisms.

CLINICAL CONSEQUENCES OF PA

PA resulting from an APA is called Conn syndrome. The German Conn Syndrome Registry, which includes all forms of PA, is a multicenter registry intended to study PA with adequate statistical power despite low screening rates. In the German Conn Syndrome Registry, overall mortality was higher in patients with PA compared with nonhypertensive control patients but not different from patients with primary hypertension. Death resulting from cardiovascular causes was more common among patients with PA compared with matched control patients with primary hypertension.[59]

Fibrosis of the heart, adrenal glands, pancreas, and lungs has been found at autopsy in patients with PA.[60] Although PA is most often detected in patients with hypertension, who are more likely to be screened, PA likely affects the cardiovascular system even in normotensive individuals with early and mild PA. Stowasser and colleagues[7] studied a small number of normotensive patients with familial forms of PA, who were found to have concentric left ventricular hypertrophy and poorer diastolic function compared with age- and sex-matched normotensive control participants. Freel et al[61] found that patients with PA more often have a diffuse, noninfarct pattern of late gadolinium enhancement on cardiac magnetic resonance imaging compared with control study participants with primary hypertension, a finding that was independent of blood pressure. In addition, patients with PA more often have exercise-induced myocardial ischemic defects on single-photon emission computed tomography and echocardiography compared with patients with primary hypertension.[62] This evidence of myocardial fibrosis is concordant with

animal studies of secondary hyperaldosteronism in the setting of a high-salt diet.[63,64] In addition, to the extent that myocardial fibrosis contributes to arrhythmias and sudden death in heart failure, these imaging data are consistent with the observation that spironolactone or eplerenone improves mortality in heart failure (eg, RALES [Randomized Aldactone Evaluation Study] and EPHESUS [Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study]).[65,66] More than simply affecting the heart and kidneys, PA is associated with vascular remodeling characterized by a marked increase in media:lumen ratio.[67]

These small-scale studies of intermediate phenotypes have led to larger studies of health outcomes in PA. Milliez et al[6] found that compared with patients with primary hypertension, patients with PA were more likely to have experienced stroke, nonfatal myocardial infarction, or atrial fibrillation (odds ratios, 4.2 [95% confidence interval, 2.0–8.6], 6.5 [95% confidence interval, 1.5–27.4], and 12.1 [95% confidence interval, 3.2–45.2], respectively). These findings were also independent of blood pressure. Hence, the man in our vignette illustrates several common consequences of long-standing PA, manifesting in his case with atrial fibrillation and hypokalemia after years of uncontrolled hypertension. To avoid the enrichment for unusual diseases expected in specialty referral centers, Monticone et al[4] prospectively screened for PA in unselected patients with hypertension recruited from primary care clinics. Metabolic syndrome was more common among the 5.9% of patients diagnosed with PA compared with other hypertensive patients, consistent with earlier studies suggesting an effect of PA on metabolism.[68] A meta-analysis of 3838 patients with PA compared with 9284 patients with primary hypertension also demonstrated adverse cardiovascular outcomes in PA.[69]

Diagnosis of PA

Although the later stages of the evaluation and subtyping are commonly deferred to endocrinologists or other skilled hypertension specialists at referral centers, screening for PA is simple, widely available, and relatively inexpensive. However, PA remains underrecognized, and the diagnosis is often delayed for many years. In view of the cardiorenal and cerebrovascular implications of PA when left untreated, it is imperative to suspect and to screen for PA early. Thus, all providers treating hypertension, including primary care practitioners, cardiologists, and nephrologists, should routinely perform PA screening in appropriate patients.

Screening for PA

The 2017 American College of Cardiology/American Heart Association hypertension guidelines recommend screening for PA in high-risk populations, including patients with resistant hypertension, hypertension and spontaneous or diuretic-induced hypokalemia, hypertension and an adrenal mass, or hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years).[15] These guidelines have revised the definition of resistant hypertension to be an office SBP/diastolic blood pressure ≥130/80 mm Hg and prescription of ≥3 antihypertensive medications at optimal doses, including a diuretic if possible, or an office SBP/diastolic blood pressure <130/80 mm Hg for a patient requiring ≥4 antihypertensive medications. The Endocrine Society clinical practice guidelines include a few additional high-risk populations for PA (Table 1).[12] For example, obstructive sleep apnea is common in patients with resistant hypertension, and this population has a high prevalence of PA.[70,71] Note that all of these recommendations were based on studies conducted before the introduction of the lower threshold for hypertension in the new American College of Cardiology/American Heart Association 2017 guidelines.

Serum (or plasma) aldosterone and plasma renin are used in PA screening with a simple blood draw. The aldosterone-to-renin ratio (ARR) has been widely recommended as a screen for PA, but we suggest first identifying a low renin (PRA <1 ng·mL^{-1}·h^{-1}) and then requiring an aldosterone >10 ng/dL for the following reasons.[72] When PRA is used, the ARR (aldosterone in nanograms per deciliter and renin in nanograms per milliliter per hour) in the population is not normally distributed, having a median of ≈5 and few values >10.[73,74] An ARR >20, which is commonly used as the threshold for positive PA screening, had a sensitivity of 78% and a specificity of 83% in study participants with resistant hypertension.[75] The most important pitfall of PA screening is that some laboratories report PRA values to a lower limit of 0.1 ng·mL^{-1}·h^{-1}. In this circumstance, the ARR is disproportionately influenced by its denominator[76] and can meet the threshold of 20 even when aldosterone is as low as 2 ng/dL. These values are not diagnostic of PA. Thus, caution should be used in interpreting the ARR when PRA is reported to values <0.6 ng·mL^{-1}·h^{-1}. Another potential pitfall in using the ARR is that many clinical laboratories are transitioning to replacing PRA with direct renin concentration (DRC), which yields different ARR values. The DRC in picograms per milliliter is often roughly a factor of 10 higher and has a much wider linear dynamic range at high values.

Because of these potential pitfalls in interpreting the ARR, we recommend the following straightforward approach to interpreting the aldosterone and renin when screening for PA. Our approach is based on the logic of the ARR but is designed to guard against false positives caused by very low renin measurements while maintaining simplicity. Clinically, a PRA <1 ng·mL^{-1}·h^{-1} or DRC <10 pg/mL is considered suppressed and indicative of volume expansion, and a simultaneous aldosterone

Table 1. Indications for Primary Aldosteronism Screening

Hypertension resistant to 3 conventional antihypertensive drugs
Hypertension and hypokalemia (spontaneous or diuretic induced)
Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 y)
Hypertension and an adrenal tumor
Controlled blood pressure on ≥4 antihypertensive drugs
Sustained blood pressure >150/100 mm Hg, measured on 3 different days
Hypertension and sleep apnea
All hypertensive first-degree relatives of patients with primary aldosteronism

>10 ng/dL raises suspicion of PA. As previously mentioned, hypokalemia inhibits aldosterone production, so an even lower aldosterone could be present in hypokalemic PA. For that reason, correction of hypokalemia to a plasma K^+ of 4.0 before testing is recommended. A practical approach to PA screening and triaging for patients with inadequate hypertension control is shown in Figure 2.

Some technical aspects of the assays used to diagnose PA are worth knowing. Blood samples for measurement of aldosterone and renin (either PRA or DRC) are ideally collected simultaneously in the morning after patients have been ambulatory for at least 2 hours. Although several factors can influence aldosterone and renin results, aldosterone and renin still rise or fall concurrently in patients without PA. Most antihypertensive drugs except β-blockers tend to raise renin and aldosterone, although not proportionately. When the ARR is used, false positives occur in 14% to 22% of screening tests in resistant hypertension patients, depending on which antihypertensive medications are used.[75] To avoid false positives, we recommend that positive PA screens be defined as those with both low renin and high aldosterone, rather than a specific ARR.[72] Table 2 lists the major causes of false negatives and false positives for PA screening.

Discontinuation of antihypertensive medications to facilitate testing for PA has some risks. Thus, on first of suspicion of PA, we recommend screening patients in the office without discontinuing medications. Patients with PA demonstrate persistent volume expansion and resistance to typical antihypertensive medications, and screening results can still be interpreted as long as renin is suppressed.[77] In fact, emerging evidence suggests that even the later stages of the evaluation can be performed successfully if renin remains suppressed despite MR antagonist therapy.[78] Although mild cases might be missed when screening is performed during medication treatment, most patients with significant PA who will maximally benefit from further evaluation will still have suppressed renin (ie, PRA <1 $ng \cdot mL^{-1} \cdot h^{-1}$ or DRC <10 pg/mL). When renin is not suppressed but the ARR and index of suspicion are high, interfering medications should be reduced or discontinued, and antihypertensive agents with no or minimal interference with the renin-angiotensin-aldosterone system substituted such as the α-adrenergic blockers hydralazine and vera-

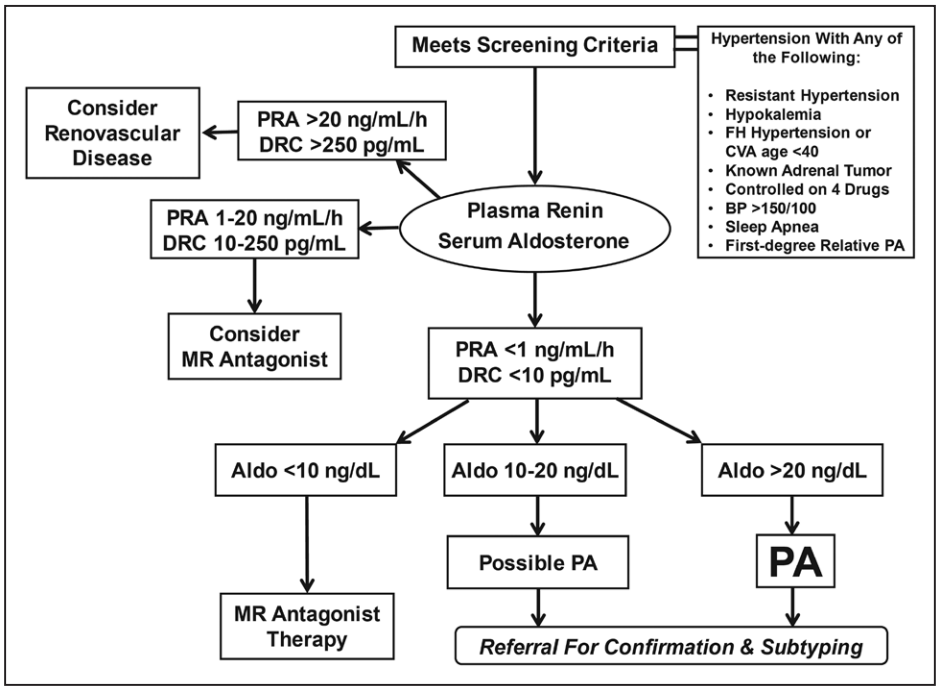

Figure 2. Simplified algorithm for primary aldosteronism (PA) screening and triaging based primarily on plasma renin and secondarily on serum aldosterone.

Patients with low renin and aldosterone >10 ng/dL are referred for confirmatory testing and subtyping; most patients with aldosterone >20 ng/dL have PA, and those with hypokalemia do not require confirmatory testing. Aldo, aldosterone; BP, blood pressure; CVA, cerebrovascular accident; DRC, direct renin concentration; FH, family history; MR, mineralocorticoid receptor; and PRA, plasma renin activity.

Table 2. Major Sources of Error in Primary Aldosteronism Screening

Factor	Mechanism
False positives	
Hyperkalemia	Directly stimulates aldosterone production
Calculating aldosterone/renin ratio	Artificially inflates ratio with renin values <0.6 ng·mL^{-1}·h^{-1}
Direct renin inhibitors	Lowers plasma renin activity
Oral contraceptives or estrogen	Lowers direct renin concentration
False negatives	
Hypokalemia	Impairs aldosterone production
Mineralocorticoid receptor antagonists	Raise renin in patients with primary aldosteronism and can increase aldosterone
Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers	Increase renin disproportionate to aldosterone
Diuretics and sodium restriction	Rarely raise renin in patients with primary aldosteronism
Pregnancy	Disproportionately raises renin, especially plasma renin activity

pamil.[12] In such an instance, screening with aldosterone and renin measurement should be repeated after ≥2 weeks on the new regimen. Before repeat testing, serum potassium should be normalized, and dietary sodium should be high.[79]

Confirmatory Testing for PA

Patients who screen positive for PA should be referred to an endocrinologist or hypertension specialist for confirmatory testing and subtyping. To confirm the diagnosis of PA, most centers in the United States use salt-loading tests to induce volume expansion, which suppresses aldosterone production in normal individuals but not in patients with PA, in whom the aldosterone secretion is autonomous. The 24-hour urine aldosterone measurement is collected on the third day of oral salt loading; alternatively, a serum aldosterone is collected after intravenous saline infusion of 2 L over 4 hours. Additional options include the fludrocortisone suppression test and captopril challenge test, which are less standardized, more difficult to perform safely (fludrocortisone suppression test), and prone to equivocal results (captopril challenge test). Patients with spontaneous hypokalemia, suppressed renin, and plasma aldosterone concentration >20 ng/dL are diagnosed with unequivocal PA from screening alone (Figure 2).[12]

Subtyping of PA

Unilateral disease is most often caused by an APA (typically <2 cm), rarely a carcinoma (often >6 cm), and occasionally larger (2–4 cm) adenomas that coproduce aldosterone and cortisol. Laparoscopic adrenalectomy is highly successful for treating APA, with complete biochemical success in 94% of patients and ≈85% partial or complete clinical success at specialized centers.[80] In contrast, unilateral adrenalectomy is about half as successful for BHA as for APA,[81] and surgical removal of both adrenal glands is not recommended for BHA because of the resultant morbid state of adrenal insufficiency. Once the diagnosis of PA is established, the patient should be counseled about the potential for surgical remediation with adrenalectomy for unilateral disease. If the patient is not a surgical candidate or is unwilling to pursue further evaluation and surgery, medical therapy with MR antagonist (spironolactone or eplerenone) is the treatment of choice. If the patient is a surgical candidate and wishes to pursue the necessary preoperative evaluation, additional testing known as subtyping is necessary.

Current guidelines for the workup of PA recommend that all patients with PA undergo adrenal imaging to rule out adrenal carcinoma. Adrenal imaging is inaccurate in determining which adrenal glands are the sources of PA (ie, "laterality") because small adrenal adenomas are common and imaging features cannot distinguish APAs from nonfunctional tumors. The test of choice for PA subtyping is adrenal vein sampling, not cross-sectional imaging.[12] After the diagnosis of PA is confirmed and adrenal imaging has been done, adrenal vein sampling should be performed in patients who would be interested in adrenalectomy to ameliorate their PA if the source is determined to be 1 (not both) adrenal gland. The discussion of whether to undertake adrenal vein sampling should be in consultation with an endocrinologist or hypertension expert who can delineate the risks and benefits of laparoscopic adrenalectomy. Adrenal vein sampling is technically challenging and should be performed in a tertiary referral center by an experienced interventional radiologist using consistent protocols and interpretation criteria.[82]

MEDICAL THERAPY FOR PA: PEARLS AND PITFALLS

If the patient is not a surgical candidate or has BHA, medical therapy with spironolactone or eplerenone is indicated. Spironolactone is effective for treating PA in most patients, inexpensive, and widely available, but be-

cause of some uncertainties about long-term outcomes with MRA therapy, surgery remains the treatment or choice for appropriate candidates. Spironolactone has a slow onset of action relative to vasodilators. Thus, a low dose (12.5–25 mg once daily) added to current antihypertensive medications is a good starting dose of spironolactone for PA. Electrolytes, creatinine, and blood pressure are reassessed in 4 to 8 weeks (before the dose is titrated upward), but these tests must be assessed sooner in patients with renal insufficiency, who are prone to develop hyperkalemia with MR antagonists. Because PA induces a hyperfiltration state, a small rise in serum creatinine is expected in patients with PA after surgical cure or with MR antagonist therapy, reflecting effects on glomerular hemodynamics, not glomerular injury. The daily spironolactone dose is typically increased by 25 to 50 mg every 4 to 8 weeks until the patient maintains a serum potassium in the upper half of normal without supplements. Spironolactone can be divided twice daily once a total daily dose of ≥100 mg is reached. Nonadherence and incomplete adherence are common in resistant hypertension, including patients ultimately found to have PA.[83] Consideration should be given to therapeutic drug monitoring before the dose is advanced,[84] particularly when hypokalemia remains uncorrected. The literature describes spironolactone doses of up to 200 mg daily for PA.[85] We are aware of anecdotal reports of 200- to 400-mg daily doses used long term for PA. In studies outside the setting of PA, daily doses as high as 500 mg have been used.[86]

One study of 602 patients with PA treated medically found that the adverse cardiovascular outcomes are mitigated if the MR antagonist dose is titrated to also raise PRA to >1 $ng \cdot mL^{-1} \cdot h^{-1}$.[87] Some authorities monitor PRA and titrate the spironolactone dose to a normal PRA. If in the judgment of the clinician the blood pressure falls too far below the goal of 130/80 mm Hg during titration, other antihypertensive medications are discontinued on the basis of side-effect profiles and mechanisms of action. If the blood pressure remains elevated after potassium is normalized or the maximum tolerated dose is reached, additional antihypertensive medications are adjusted to achieve target blood pressure.

Common side effects of spironolactone in menstruating women include spotting between menses and breast tenderness at high doses. Spironolactone should be combined with contraception for women of reproductive potential because of potential teratogenic effects on a male fetus. Men can develop gynecomastia and sexual dysfunction as a result of the antagonism of testosterone by spironolactone, but this effect is dose dependent and takes weeks to months to develop, usually well after blood pressure has nadired. The incidence of gynecomastia may be as high as 30% at 100 mg daily and 62% at 200 mg daily.[88] If adverse effects of spironolactone develop, eplerenone is substituted, usually given twice daily at a dose twice that of spironolactone, for example, 50 mg eplerenone twice daily exchanged for 50 mg spironolactone once daily. Eplerenone is generally more expensive than spironolactone and can be considered as initial MRA therapy if cost is not prohibitive. The principles of titrating eplerenone dosing are the same as for spironolactone. Published studies of eplerenone for hypertension used doses up to 400 mg/d despite the package insert limiting doses to 50 mg twice daily, reflecting concerns over hyperkalemia in patients with heart failure and renal insufficiency.[89,90] The most common mistakes made in prescribing spironolactone for PA are starting at too high a dose and titrating up too quickly. The most common mistake in prescribing eplerenone for PA is not using a high enough dose and not dividing the dose twice daily.

Studies of proteinuria and left ventricular hypertrophy regression in patients with PA have shown similar improvements in patients treated surgically or medically. Although these findings might be reassuring for patients managed with an MR antagonist, some uncertainty remains as to how to adequately titrate medical therapy. Once blood pressure and serum potassium are normal, can one assume that all MR in the heart, kidney, brain, and vasculature is also adequately antagonized? Can residual aldosterone have detrimental MR-independent effects? What about low amounts of autonomous cortisol cosecretion from smaller tumors? Some unsettling data on these concerns have begun to appear. One large prospective study of patients with PA treated medically or surgically found higher cardiovascular mortality among those treated medically, with the caveats that patients were not randomized and that surgery might not be offered to patients with poor prognosis.[8] A study from Taiwan found evidence of glucose tolerance deterioration in patients with PA treated medically,[91] possibly reflecting failure to address glucocorticoid production from some of these tumors.[92] Until more data from prospective studies are available, medical therapy remains a good option, but surgical therapy might have advantages, in addition to being more cost-effective in young patients.[93]

WHAT ABOUT PATIENTS WHO SCREEN NEGATIVE FOR PA?

The prevalence of PA in patients with resistant hypertension might be as high as 20%, but then 80% of that group will screen negative for PA. Some of these patients might have a mild form of PA, not meeting criteria for a formal diagnosis yet possibly contributing to their hypertension.[94] Some of these patients might progress to overt PA over time, but such prospective studies have not been conducted. Regardless, patients

with resistant hypertension respond well to spironolactone, with placebo-adjusted reductions in ambulatory SBP averaging 5.4 mm Hg[95] and placebo-adjusted home SBP reductions averaging 8.7 mm Hg.[58] The PATHWAY-2 study demonstrated the superiority of spironolactone to bisoprolol or doxazosin added to existing regimens in patients with resistant hypertension, except in patients with the highest DRC.[58] Close monitoring of electrolytes is essential when MR antagonists are used. Therefore, we recommend treatment with an MR antagonist for those resistant hypertension patients who meet the criteria for PA screening and whose renin is normal or low but whose aldosterone is not high enough for a positive PA screen.

FUTURE DIRECTIONS

Some major causes of clinical inertia and impediments to screening for PA include the complexity and cost of the later stages of the evaluation. Although some data support the cost-effectiveness[94] of the diagnostic process we have suggested here, approaches to reduce the cost of PA evaluation are anticipated. The majority of patients with PA identified through expanded screening are patients with BHA, who ultimately require MR antagonist therapy yet still often undergo computed tomographic imaging and adrenal vein sampling without finding a surgical target. To streamline the evaluation, noninvasive strategies for PA subtyping have recently been proposed. Steroid profiling of adrenal vein and peripheral serum samples from PA patients has led to the identification of biomarkers with potential to discriminate APAs from BHA. For example, peripheral plasma concentrations of 18-oxocortisol, a "hybrid steroid" (bearing both aldosterone and cortisol functionalities), are higher in patients with APA than in those with BHA, whereas those of cortisol, corticosterone, and dehydroepiandrosterone are lower.[97–99] The utility of peripheral 18-oxocortisol and 18-hydroxycortisol in discriminating between APA and BHA is particularly high in Japanese populations, in whom *KCNJ5* mutations in APAs are frequent.[97] The targeted implementation of these evolving diagnostic tools is likely to reduce the need for adrenal vein sampling in patients with BHA, to reduce the cost of the evaluation, and to encourage broader screening for PA in populations with a high prevalence of this common form of hypertension, which is highly amenable to targeted therapy or even cure.

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