Primary Hyperaldosteronism
A Comprehensive Review of Pathophysiology, Diagnosis, and Treatment

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KEYWORDS

• Primary aldosteronism • Aldosterone • Endocrine hypertension • Adrenal • Renin
• Hyperaldosteronism • Adrenal venous sampling

KEY POINTS

- Primary hyperaldosteronism (PA) is the most common endocrine cause of hypertension. It encompasses a wide spectrum of autonomous, renin-independent aldosterone production with diverse histopathological etiologies.
- PA remains highly underdiagnosed and increases the risk for adverse cardiometabolic outcomes.
- Screening for PA by measuring aldosterone-to-renin ratio can be performed without discontinuing interfering medications. If renin levels are not suppressed, and there is a high clinical suspicion for PA, screening tests can be repeated after interfering medications and discontinued.
- Surgical adrenalectomy is the preferred treatment of lateralizing PA with the intention to reverse the pathophysiology of PA.
- A vast majority of PA is bilateral and will ultimately be treated with medical therapy. The goals of medical therapy as we understand them now are to normalize blood pressure, potassium levels and to treat with a large enough dose of mineralocorticoid receptor antagonists to cause a rise in renin levels.

INTRODUCTION

Primary hyperaldosteronism (PA) is a syndrome defined by autonomous aldosterone hormone secretion from the adrenal gland. This leads to sodium retention, hypertension (HTN), and cardiovascular damage. What was thought to be a binary disease caused by either an aldosterone producing adenoma or bilateral adrenal hyperplasia is now recognized as a spectrum of autonomous or abnormal aldosterone secretion with diverse histopathological etiology. Another major shift in our understanding of PA has been recognizing that its prevalence is much higher than previously thought, making it the most common secondary cause of HTN in the general population.

This review will highlight the pathophysiology of PA, our current understanding of its prevalence, clinical presentation, and discuss approaches to diagnosis and management of PA.

PATHOGENESIS

Aldosterone is secreted from the zona glomerulosa (ZG) of the adrenal cortex under the control of mainly angiotensin II and potassium, and to a lesser extent, adrenocorticotropic hormone (ACTH).

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Abbreviations

ACTH	Adrenocorticotropic hormone
ADH	Antidiuretic hormone
APDH	Aldosterone-producing diffuse hyperplasia
APM	Aldosterone-producing micronodule
APN	Aldosterone-producing nodule
ARR	Aldosterone-to-renin ratio
AVS	Adrenal venous sampling
DRC	Direct renin concentration
ENaC	Epithelial sodium channel
FH	Familial hyperaldosteronism
GRA	Glucocorticoid remediable aldosteronism
HISTALDO	Histopathology of primary aldosteronism
HRCT	High-resolution computed tomography
HTN	Hypertension
IHC	Immunohistochemistry
MACS	Mild autonomous cortisol secretion
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonists
NGS	Next generation sequencing
OSA	Obstructive sleep apnea
PA	Primary hyperaldosteronism
PAC	Plasma aldosterone concentration
PASNA	Primary aldosteronism with seizures and neurologic abnormalities
PRA	Plasma renin activity

A fall in glomerular filtration rate due to volume or sodium depletion causes secretion of renin from the juxtaglomerular cells of the kidney. Renin catalyzes the cleavage of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzymes.

Angiotensin II not only stimulates aldosterone production but also increases sodium and water reabsorption in the proximal tubule and loop of Henle. It also stimulates antidiuretic hormone (ADH) release from the hypothalamus, which leads to reabsorption of water at the distal nephron.

Aldosterone in turn activates the mineralocorticoid receptor (MR) in the principal cells of the kidney, leading to sodium reabsorption from the epithelial sodium channel (ENaC) in exchange for potassium or hydrogen ions. The above processes lead to restoration of homeostasis in sodium and water depleted states.

Extracellular hyperkalemia is another trigger for aldosterone secretion that is renin-independent. In volume expanded states where dietary potassium leads to extracellular potassium excess, angiotensin II levels are suppressed leading to low proximal tubule reabsorption of sodium and increased distal delivery of sodium. Aldosterone causes reabsorption of sodium in the distal tubule and increases potassium excretion, thereby restoring normal potassium homeostasis.[1]

In contrast to the normal physiology of aldosterone secretion as mentioned above, PA is characterized by dysregulated aldosterone production that is renin and Angiotensin II independent. This dysregulated aldosterone excess in PA is also not fully suppressed in the setting of a sodium load, volume expansion or hypokalemia.

PA is a salt sensitive disease. This is because low Angiotensin II levels in PA lead to increased distal delivery of sodium, further perpetuating the cycle of sodium reabsorption facilitated by aldosterone and worsening HTN.[1]

Histopathology of Primary Hyperaldosteronism

Significant progress has been made in the last 5 to 10 years in understanding the histopathologic characteristics of PA.[2] Development of specific monoclonal antibodies to aldosterone synthase or CYP11B2 led to the ability to use immunohistochemistry (IHC) to visualize the areas of aldosterone excess in resected adrenal glands, and demonstrated highly variable histopathological features in patients with unilateral PA.[3]

This subsequently led to the development of the HISTALDO (histopathology of primary aldosteronism) consensus to standardize nomenclature and achieve consistency among pathologists for the histopathologic diagnosis of unilateral PA. Based on hematoxylin and eosin (H&E) staining and functional IHC staining with CYP11B2, adrenal cortical lesions are classified as aldosterone-producing adenoma (APA), aldosterone-producing nodule (APN), aldosterone-producing micronodule (APM) (formerly known as “aldosterone-producing cell cluster”), aldosterone-producing diffuse hyperplasia (APDH), multiple aldosterone-producing nodules or multiple aldosterone-producing micronodules (formally known as micronodular hyperplasia) and rarely, aldosterone-producing adrenocortical carcinoma.[4]

Since the use of functional IHC staining there have been multiple reports of the source of aldosterone excess, as evidenced by CYP11B2 staining, being different from the presumed source based on H&E or imaging.[3–5] Incorporating CYP11B2 staining in histopathological diagnosis has also been shown to enhance the prediction of surgical outcomes in PA.[6]

Genetics of Primary Hyperaldosteronism

Studies done using next generation sequencing (NGS) have led to the insight that PA is largely a genetic disorder.[2] The vast majority of PA cases are sporadic with approximately 6% being due to a familial cause.[7]

Familial and inherited forms of primary hyperaldosteronism

There are 4 types of familial PA that have been described so far, classified as familial hyperaldosteronism (FH) Type I-IV. The characteristics of familial and inherited forms of PA have been summarized in **Table 1**.[8]

FH-I was the first form of FH to be described, also called glucocorticoid remediable aldosteronism or GRA. It has an autosomal dominant pattern of inheritance resulting in severe HTN at a young age. FH-1 is caused by a chimeric CYP11B1/B2 gene that fuses the regulatory regions of genes that encode the enzymes responsible for the last steps of cortisol and aldosterone synthesis. The unequal crossing over event leading to this chimeric gene formation leads to ectopic aldosterone synthase expression in the zona fasciculata and stimulation of aldosterone production by ACTH. Because aldosterone production is under the control of ACTH, glucocorticoids are the treatment in these patients.

Familial forms of PA associated with germline CLCN2 mutations that code for chloride channel 2 or CIC-2 are classified as having FH-II. The phenotypic presentation is variable and indistinguishable from that of primary aldosteronism without familial inheritance. CLCN2 mutations induce a gain of function of ClC-2 channels, leading to sustained chloride efflux from the cell. This efflux leads to activation of calcium signaling and increased CYP11B2 expression. No targeted treatments for FH-II are currently available.

FH-III is due to mutations in the potassium channels encoded by the KCNJ5 gene. These mutations are responsible for a change in the channel selectivity, with a loss of potassium selectivity and an increased sodium influx, leading to cell membrane depolarization, opening of voltage-gated calcium channels, and increased aldosterone production. FH-III can cause severe early-onset HTN associated with profound hypokalemia and massive bilateral adrenal hyperplasia; however, variable severity of hyperaldosteronism was observed among FH-III kindreds. CYP11B2 was often coexpressed with 11β-hydroxylase or 17α-hydroxylase, or with both, which explains the increased levels of the hybrid steroids 18-hydroxycortisol and 18-oxocortisol in these patients. No targeted treatments for FH-III are available so far, but macrolides specifically block the mutated channels and might represent potential pharmacologic options.

Mutations in CACNA1H, encoding the calcium channel Cav3.2, are responsible for FH-IV. These mutations result in changes in calcium current properties, leading to an increased intracellular

Table 1
Familial and inherited forms of primary hyperaldosteronism

Disease	Age of Onset	Specific Features	Gene	Transmission	Treatment
FH-I	Variable Often before 20 y	Cerebrovascular events at young age (<30 y)	Chimeric *CYP11B1/B2*	Autosomal dominant	Glucocorticoids, MR antagonist
FH-II	Variable Young onset in patients with *CLCN2* mutations	None	*CLCN2*	Autosomal dominant	MR antagonist
FH-III	Before 20 y Variable in mild forms	Massive bilateral adrenal hyperplasia in severe cases	*KCNJ5*	Autosomal dominant	MR antagonist Bilateral adrenalectomy in severe cases
FH-IV	Variable Most frequent before 20 y	Developmental disorder in some cases	*CACNA1H*	Autosomal dominant	MR antagonist
PASNA	Childhood	Seizures and neurologic abnormalities	*CACNA1D*	? (*de novo*)	MR antagonist Calcium channel blocker

From Fernandes-Rosa FL, Boulkroun S, Zennaro M. Genetic and genomic mechanisms of primary aldosteronism. Trends Mol Med. 2020;26(9):819–832; with permission.

concentration of calcium and aldosterone production. Patients develop early onset HTN with the associated developmental delay or complex neurologic disorders. Specific calcium channel blockers acting on mutated Cav3.2 channels could be a useful development for patients with FH-IV.

Primary aldosteronism with seizures and neurologic abnormalities (PASNA) is caused by de novo germline pathogenic variants in CACNA1D and has been reported in 3 children and is exceedingly rare.

Somatic mutations in primary hyperaldosteronism

Using a combination of CYP11B2 IHC to identify the site of aldosterone excess and NGS, 88% to 93% of patients with APAs were found to have pathogenic somatic mutations.[9–11]

Somatic mutations in the genes associated with FH can also lead to the formation of APAs. The most common abnormalities are mutations in KCNJ5, with varying frequencies across different studies.[2]

The prevalence of certain pathogenic mutations seems to vary based on the sex and ethnicity of the population studied. KCNJ5 mutations are more common in Asian populations and in women.[12,13] Somatic *CACNA1D* mutations are the most frequent mutations found in APAs in African American patients.[11] Somatic mutations of CTNNB1 have been reported in a small number of patients with APA thought to be associated with pregnancy or menopause.[14]

Somatic mutations were also identified in patients with multinodular adrenal glands without APA. It was noted that the micronodules from the same adrenal specimen could harbor different mutations.[10]

Pathogenic model of aldosterone-producing adenoma development

Two different models of APA development have been proposed as detailed below.[8]

In the aldosterone-producing cell cluster (APCC) model, somatic mutations in different APA driver genes lead to the development of APCCs. APCCs have been found in normal adrenal glands, in adrenal glands that also contain APA and in patients with bilateral adrenal hyperplasia. APCCs may then develop into APA through formation of a translational lesion.

In the two-hit model, genetic and environmental factors lead to abnormal cell proliferation in the ZG creating a favorable environment for a *second hit* which is the occurrence of somatic mutations in APA driver genes. This two-hit model suggests that the high prevalence of PA is largely driven by a diffuse bilateral process of acquired somatic mutations causing less severe PA.

In both hypotheses, somatic mutations that affect ion channels or pumps ultimately lead to activation of calcium signaling, increased CYP-11B2 expression, and autonomous aldosterone production.

EPIDEMIOLOGY

The prevalence of PA is much higher than previously recognized and is challenging to truly estimate. We now understand that PA encompasses a wide spectrum of renin-independent aldosterone production, and the prevalence of PA varies depending on the criteria used to define a positive screening or confirmatory test as well as the population studied.

For example, lowering the threshold for a positive screening test from an aldosterone-to-renin ratio (ARR) of greater than 30 ng/dL per ng/mL/h and a minimum serum aldosterone of 10 ng/dL to an ARR of greater than 20 ng/dL per ng/mL/h without any requirement for a minimum aldosterone concentration changed the prevalence of PA in 1 study looking at hypertensive patients from 13.8% to almost 33%.[15]

A recent cross-sectional study enrolled both normotensive and hypertensive participants who then completed an oral sodium suppression test regardless of aldosterone or renin levels, as a confirmatory test for PA. This study clearly demonstrated the continuum of renin-independent aldosterone production with the severity of aldosterone production being correlated with the degree of HTN. The prevalence of biochemically overt PA was noted to be 11.3% in normotensive individuals and as high as 22% in participants with stage II HTN. In referral centers for HTN, when patients with resistant HTN and suppressed renin are considered, up to 50% might have overt PA.[16]

Despite the high prevalence and considerable clinical and public health implications of untreated PA, it remains highly underdiagnosed. This could be related to complicated testing protocols, guidelines that are often challenging to follow, and even a lack of awareness throughout the medical community about the prevalence and health impact of PA.

CLINICAL PRESENTATION

There is no specific and reliable clinical phenotype of PA, and clinical presentation of the disease can be quite varied. In the past, difficult to control HTN was considered an important clinical manifestation of PA. We now know that milder phenotypes of PA are much more prevalent with approximately 11% of patients with biochemical PA being normotensive.[16] This, in addition to poor compliance with

existing guidelines that can be complicated to follow has led to a push for all patients with HTN to be screened for PA at least once by some experts.[17]

Hypokalemia has long been considered a hallmark sign of PA, however, less than 30% of patients who have PA will present with hypokalemia.[18] Having said that, the prevalence of PA in patients with hypokalemia and HTN referred to a tertiary care HTN unit was noted to be 28%, highlighting the importance of screening for PA in hypertensive patients with hypokalemia.[19]

PA is associated with a wide spectrum of cardiovascular, renal and metabolic diseases as detailed later in this review.

Mild autonomous cortisol secretion (MACS) has been reported with a prevalence ranging from 4% to 27% in PA. The presence of concomitant cortisol excess is important to consider during AVS for 2 reasons. Firstly, to be able to ascertain whether plasma metanephrine levels should be measured during AVS to determine lateralization.[20] Secondly, in patients with PA and MACS, secondary adrenal insufficiency requiring glucocorticoid replacement may occur in up to 30% to 50% of cases following a curative unilateral adrenalectomy.[21]

DIAGNOSIS

There is a lack of international consensus for defining PA which can make the diagnosis challenging. According to the Endocrine Society, the diagnosis of PA should follow a three-step approach in most cases: screening, confirmation or exclusion, and finally a subtype diagnosis to distinguish unilateral from bilateral disease.[22]

Screening

Clinical practice guidelines recommend screening for PA in individuals with resistant or uncontrolled HTN, early onset HTN, spontaneous or diuretic induced hypokalemia, a strong family history of HTN, or if there is a diagnosis of an adrenal incidentaloma or obstructive sleep apnea (OSA).[22]

The widely accepted screening test for PA is measurement of plasma ARR. A normal or elevated plasma aldosterone concentration (PAC) together with a low or suppressed renin concentration is characteristic of PA and gives rise to an elevated ARR. Direct renin concentration (DRC) assays and plasma renin activity (PRA) assays are both acceptable methods for measurement of renin levels.[22]

There are several factors that can lead to false positive or false negative ARRs, which need to be considered prior to screening. Medications such as beta blockers, clonidine, alpha methyl dopa, nonsteroidal anti-inflammatory drugs, estrogen containing oral contraceptive pills, and direct renin inhibitors can cause false positive results. Other medications such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists (MRA), dihydropyridine calcium channel blockers, and diuretics can cause false negative results.[23] Hypokalemia and sodium restriction can both raise renin levels causing false negative results, so potassium levels should be normalized, and patients should be instructed to liberalize salt intake in diet prior to screening for PA.[24,25]

In patients with suspected PA, screening can be performed without changing antihypertensive medications. This is especially true for patients with uncontrolled HTN where discontinuation of certain medications might be unsafe. Performing ARR testing while on interfering medications can be informative in some cases. For example, an elevated ARR while a patient is on an ACE inhibitor, diuretic, or MRA is highly suggestive of PA. If renin is not suppressed in patients with a high pretest probability of PA, then it is suggested to discontinue the interfering medication for 2 to 4 weeks. Antihypertensives that do not affect ARR as much such as verapamil, hydralazine or doxazosin could be used to control blood pressure while undergoing diagnostic tests.[22]

The sensitivity and specificity of ARR as a screening test varies considerably depending on the ARR cutoff used and whether a minimum PAC cutoff value is used in addition to having a suppressed PRA. The suggested ARR cutoff value for a positive screening test varies from 20 to 35 ng/dL per ng/mL/h depending on the society guidelines referenced.

Some investigators have suggested including a PAC cutoff along with an elevated ARR as part of the screening criteria. However, patients with PA can sometimes present with lower aldosterone levels and can be missed if a specific PAC cutoff of greater than 10 to 15 ng/dL is chosen.[26] A retrospective study was performed to characterize the intraindividual variability in aldosterone concentrations and ARRs over multiple measurements in patients with confirmed PA. Plasma aldosterone values were checked on different days and they found a wide degree of variation, with almost a third of PA patients having at least 1 aldosterone value below the conventional threshold of 10 ng/dL and a quarter having at least 1 ARR below 20 ng/dL per ng/mL/h.[27] A threshold of aldosterone less than 5 ng/dL has been proposed by 1 group to rule out PA to minimize the risk of false negatives and is well accepted.[28]

It is also suggested that aldosterone and renin values are evaluated independently rather than relying on the ARR alone. Having a suppressed rennin (PRA <1.0 ng/ml/h or corresponding DRC <10 mU/l) in a high-risk patient should increase the suspicion of nonsuppressible aldosterone production.[26]

Dynamic/Confirmatory Testing

Once PA is suspected on a positive screening test, confirmatory testing is done due to the low specificity of ARR and to prevent patients with false positive results from undergoing unnecessary, expensive, and potentially invasive testing. Current guidelines recommend that patients with spontaneous hypokalemia, PAC>20 ng/dL, plus PRA or DRC below detection level, may be diagnosed with PA without further confirmatory tests.[22]

Confirmatory tests are based on the principle that volume expansion or blockade of angiotensin II production, such as in the captopril test, should decrease aldosterone production in normal physiology. The 2 most common tests in clinical practice are oral salt or IV sodium loading tests described further in **Table 2**.[22]

Subtyping

Once PA is confirmed on biochemical testing, it is appropriate to proceed with imaging the adrenal glands. High-resolution computed tomography (HRCT) or MRI of the adrenal glands are the initial imaging studies of choice.

CT is superior to MRI in terms of spatial resolution. It is also useful to exclude the presence of an extremely rare aldosterone-producing carcinoma and to provide information for the interventional radiologist on the location and anatomy of the adrenal veins. While MRI is better able to characterize lipid-rich adenomas without exposure to ionizing radiation, both HRCT and MRI have limitations in detecting microadenomas and poor accuracy in predicting unilateral disease.[29] The absence of morphologic adrenal abnormalities should not exclude patients from being considered a candidate for surgical management.[22]

Despite newer diagnostic imaging modalities, AVS remains the gold standard for distinguishing unilateral from bilateral PA.

The prevalence of adrenal adenomas increases with age and imaging alone is not reliable in distinguishing unilateral from bilateral PA. Adrenal imaging and AVS results are discordant in roughly 40% of patients with PA. The accuracy of CT imaging in younger patients less than 35 years old is higher due to incidentalomas being less common, and AVS can be forgone in these patients.[30]

AVS should be offered to patients with a diagnosis of PA only if they are willing to consider adrenalectomy and have no major contraindications to the procedure. It is also important to consider that a vast majority of PA is bilateral and surgically remediable aldosteronism is more likely in patients with higher PAC and more severe forms of disease. There are several limitations to AVS including high cost, technical dependence, risk of complications, and lack standardization of the procedure which is described in greater detail in the article written by Drs Tendler and Shteyman in this adrenal focused issue.

BURDEN OF DISEASE

Untreated PA results in disproportionately higher rates of cardiovascular, renal and metabolic disease when compared to essential HTN. Although the degree of HTN could be a contributing factor, several observational studies have demonstrated an increased cardiovascular risk in patients with PA, independent of blood pressure. This includes an elevated risk of coronary artery disease (CAD), Left Ventricular Hypertrophy, heart failure, atrial fibrillation and stroke.[31,32]

Patient with PA also have an increased glomerular filtration rate, higher rates of albuminuria, and increased risk for CKD when compared to essential HTN.[33–35]

PA has been associated with an increased risk of Type 2 diabetes and metabolic syndrome. This could be related to insulin resistance, decreased insulin secretion and increased insulin clearance in PA.[36] Concurrent glucocorticoid co-secretion in PA could be another factor.[37]

There is a high prevalence of PA in patients with OSA of up to 30% as reported in 1 prospective screening study highlighting the importance of screening patients who have OSA for PA.[38]

PA is also associated with an increased risk of osteoporosis and fractures which are thought to be related to hypercalciuria.[39]

TREATMENT

The management strategy for PA depends on whether a patient has unilateral or bilateral PA. As previously discussed, a vast majority of PA is likely to be caused by heterogenous bilateral processes and therefore not be amenable to cure by surgery.

Unilateral Primary Hyperaldosteronism

In patients with PA that lateralizes to one adrenal gland, adrenalectomy with curative intent is treatment of choice if the patient is a good surgical

Table 2
Confirmatory tests for primary hyperaldosteronism

Test	Protocol	Cut off Value	Sensitivity	Specificity	Specific Considerations	Contraindication
Recumbent Saline infusion test	Infusion of 2L of 0.9% NaCl over 4 h with measurement of PAC preinfusion and postinfusion in recumbent position	Postinfusion PAC: >10 ng/dL: highly likely to be PA 5–10 ng/dL: intermediate results	38%	94%	BP and pulse should be monitored hourly. Potassium needs to be replaced to avoid hypokalemia	Patients with uncontrolled hypertension, renal impairment, arrhythmia, heart failure, and severe hypokalemia.
Seated Saline infusion test	Infusion of 2L of 0.9% NaCl over 4 h with measurement of PAC pre infusion and postinfusion in seated position	Postinfusion PAC: >6 ng/dL: diagnostic of PA	87%	94%	BP and pulse should be monitored hourly. Potassium needs to be replaced to avoid hypokalemia	Patients with uncontrolled hypertension, renal impairment, arrhythmia, heart failure, and severe hypokalemia.
Oral sodium loading test	NaCl intake ~6 g/day for 3 consecutive days followed by checking 24-h urinary aldosterone and sodium excretion on day 4.	PAC in the 24-h urine with 24-h urinary sodium excretion >200 mmol/day: >12–14 μg/24h: highly suggestive of PA <10 μg/24h in the absence of renal disease makes the diagnosis of PA unlikely	96%	93%	24-h urinary sodium excretion of >200 mmol/day is required prior to interpreting PAC in urine to ensure adequate sodium intake in diet Urinary aldosterone should be performed by HPLC-MS to provide adequate test performance. Renal failure can make interpretation of the results difficult by producing false negative values	Patients with uncontrolled hypertension, renal impairment, arrhythmia, heart failure, and severe hypokalemia.

candidate and is willing to undergo surgery. Adrenalectomy is now routinely performed via laparoscopy or a retroperitoneoscopic approach.[22]

A complete adrenalectomy is the recommended surgical procedure in unilateral PA because AVS is only able to determine the side of aldosterone excess.[22] Experience with CYP11B2 staining has shown that the site of aldosterone excess within the adrenal gland might differ from what was anticipated to be the source before surgery.[3–5]

Segmental selective AVS has been described as a strategy to guide partial adrenalectomy in patients with PA. However, biochemical success rates after partial adrenalectomy remain low. The expertise required to perform segmental selective AVS and applicability of the data studying mainly Asian patients is also limited.[40]

There is limited data on percutaneous ablative procedures for the management of unilateral PA and how it compares to surgical adrenalectomy. However, it can be safe and effective when done at centers with experience in the procedure. In a randomized controlled trial comparing catheter based adrenal ablation to spironolactone, complete clinical response was seen in 27% and partial clinical response was seen in 54% of patients who underwent ablation. Complete biochemical success was seen in over 50% of patients.[41] It is unclear which patients would be best suited to undergo ablative procedures and how their outcomes would compare to surgery.

Postoperative management and outcomes

In the first week following surgery patients should be closely monitored for hyperkalemia. This is thought to be related to suppression of both renin levels as well as aldosterone secretion from the contralateral adrenal gland.[42] Although treatment of PA improves long-term renal outcomes, following both surgical and medical treatment of PA, a decline in glomerular filtration rate is noted in the first few months following therapy. This is due to correction of kidney hyperfiltration and unmasking underlying kidney impairment. This should be anticipated and discussed with the patient ahead of time especially in those with preexisting chronic kidney disease.[33]

The primary aldosteronism surgical outcome (PASO) study led to the development of consensus criteria to define clinical and biochemical outcomes following unilateral adrenalectomy. Complete clinical success was defined as a normal blood pressure without needing any antihypertensive medications. Partial clinical success was defined as having either a lower blood pressure with the same amount of or lower medication or having the same blood pressure with lower medication. Complete biochemical success was defined as normalization of ARR and potassium levels. Partial biochemical success was defined as normalization of potassium levels with improvement in ARR, and a >/=50% decrease in aldosterone levels after surgery. The final outcome should be assessed at 6 to 12 months postsurgery and reassessed annually.

In the PASO study complete clinical success was achieved in 37% patients, partial clinical success in an additional 47% who underwent adrenalectomy. Complete biochemical success was seen in 94% of patients. Younger patients and those on fewer medications preoperatively had a higher likelihood of clinical success.[43]

Surgical vs. medical management for unilateral primary hyperaldosteronism

Surgical adrenalectomy is the treatment of choice for unilateral PA. While there are no randomized controlled trials showing that surgical adrenalectomy is superior to MRA therapy, several observation studies have demonstrated a clinical and biochemical benefit of adrenalectomy over MRA in unilateral PA. In a recent metanalysis performed including 16 studies comparing surgery vs medical therapy, surgery was associated with an overall 66% relative reduction in the risk of death and 45% decrease in the risk of MACE compared to medical therapy. We need to be careful in interpreting these results due to not knowing whether the group on medical therapy was being treated with an adequate dose of MRAs.[44]

In terms of biochemical outcomes, surgery addresses the source of aldosterone excess and reduces endothelial dysfunction, inflammation and fibrosis that is seen with aldosterone excess. Theoretically, MRA could achieve similar results by blocking the downstream effects of aldosterone but are dependent on adequate dosing, tolerance and compliance with medications.[45]

Recurrence following surgery

PA is broadly categorized into unilateral or bilateral PA based on results of AVS, with lateralized PA being synonymous with the presence of an APA. Recent data show that lateralized PA could be a result of multifocal asymmetric bilateral PA caused by multiple CYP11B2 positive areas and is indistinguishable from unilateral PA due to an APA. The implications of these findings are that unilateral adrenalectomy for lateralizing PA may not always result in biochemical cure due to residual PA from the contralateral gland. Certain characteristics in individuals with PA such as black race, lateralization on AVS only at baseline and not post-cosyntropin stimulation and having discrepant

imaging and AVS results place them at a higher risk for residual PA following adrenalectomy.[46]

In a retrospective study looking at long term disease recurrence in patients with unilateral PA, the recurrence rates differed based on histopathology classified as classical or nonclassical histopathology according to HISTALDO criteria. Classical histopathology included APA and a dominant APN. Nonclassical histopathology included multiple APNs or APMs and APDH. Long term biochemical PA recurrence was seen in 23% of the 57 patients studied 7.5 years after unilateral adrenalectomy with an overrepresentation of those patients with nonclassical histopathology. 60% of nonclassical histopathology patients and 14% of classical histopathology patients had a recurrence. These findings emphasize the role of histopathology and the requirement for continued outcome assessment in the management of surgically treated patients for PA.[47]

Bilateral Primary Hyperaldosteronism

Role of surgery

The role of unilateral adrenalectomy in patients with bilateral PA is unclear. Based on retrospective and anecdotal data, unilateral adrenalectomy is an option when clinical targets are challenging to achieve with medical management alone and where marked asymmetry was noted on AVS.[48] Bilateral adrenalectomy is not recommended for bilateral PA due to the risks associated with the need for lifelong glucocorticoid and mineralocorticoid replacement outweighing the potential benefits.

Medical Management

In patients with bilateral PA or those with unilateral PA who do not undergo adrenalectomy, sodium restriction and MRA therapy are the mainstays of treatment.

PA is a salt-sensitive disease and sodium restriction to <1.5-2 g/day of sodium should be recommended in addition to treatment with MRA. The effect of moderate salt restriction to 5 g/day on blood pressure was well demonstrated in a small study of 41 patients with PA, on MRA therapy with unsuppressed renin levels. In 12 weeks, the study cohort experienced a reduction of SBP of 9 mm Hg, which is a greater effect than what was observed in trials on patients with essential HTN for the same degree of dietary sodium restriction. These results suggest a greater influence of dietary sodium intake on HTN in PA than essential HTN.[49]

The most commonly prescribed MRAs in clinical practice are spironolactone and eplerenone. Spironolactone is the preferred agent due to being more potent and longer acting requiring only once a day dosing when compared to eplerenone. However, antiandrogen and progesterone agonist effects can lead to gynecomastia, decreased libido, and menstrual irregularities limiting its use, particularly in men. Eplerenone being a selective MRA might be preferred to spironolactone in men.[22]

Increased distal delivery of sodium and upregulation of distal tubular ENaCs is a major mechanism in the pathophysiology of PA. Treatment with Amiloride or Triamterene which are 2 ENaC antagonists can lower blood pressure and raise potassium levels. Blood pressure goals can be challenging to achieve with monotherapy, often due to concomitant essential HTN. Using a thiazide diuretic, amiloride, or triamterene in conjunction with MRAs can reduce the dose of MRA drug needed to achieve clinical or biochemical targets for the treatment of PA.[22]

It is important to closely monitor blood pressure, potassium, and serum creatinine levels with each medication change and especially in the first 4 to 6 weeks of starting medical therapy.

The management of familial forms of PA varies depending on the type, as noted in **Table 1**.

Goals of medical therapy

The goal of medical therapy is to normalize blood pressure readings and potassium levels. Another important goal of medical therapy is to treat with a large enough dose of MRA to increase PRA levels to >1 ng/mL/hr which seems to improve cardiovascular outcomes in patients who are medically managed. In a large, matched cohort study of patients with PA and essential HTN, the incidence of CV events was higher in patients with PA on MRAs than in patients with essential HTN. The excessive CV events in the PA group were limited to patients whose PRA remained suppressed at <1 ng/mL/hr, whereas patients who were treated with higher MRA doses and had an unsuppressed renin of >/=1 ng/mL/hr had no significant excess risk.[31]

Another cohort study was performed by the same group of investigators comparing the risk of incident atrial fibrillation between patients with essential HTN, medically and surgically treated PA. They found that patients with medically treated PA who had a PRA of <1 ng/mL/hr had a significantly higher risk for incident atrial fibrillation when compared to groups with essential HTN, surgical adrenalectomy, and those on MRA with an unsuppressed renin, who all had a similar risk for atrial fibrillation.[50]

FUTURE DEVELOPMENTS

Despite making huge strides in understanding the pathophysiology and epidemiology of PA, the diagnosis of PA remains a challenge. Devising a more streamlined and practical approach to the diagnosis of PA would aid in increasing the screening rates and increase the use of MRA for renin independent HTN in clinical practice.

In the next several years we expect to see more noninvasive imaging modalities for subtyping PA like the ^{11}C-metomidate PET-CT and ^{68}Ga-pentixafor PET-CT which have already shown promise.[51] Adrenal steroid profiling is another promising tool that may help in the diagnosis of PA as well as determining the subtype of PA.[52,53]

Novel medications such as nonsteroidal MRA and aldosterone synthase inhibitors are being evaluated in the management of PA. There is a lot of enthusiasm surrounding aldosterone synthase inhibitors and their ability to attenuate aldosterone hormone production, and potentially provide superior outcomes when compared to MRAs.[54]

As more cases of PA are diagnosed, future clinical practice guidelines will hopefully address some of the challenges in the management of PA outlined in this article and provide broader strategies for implementing medical therapy in the more prevalent bilateral forms of PA.

CLINICS CARE POINTS

- Primary hyperaldosteronism is characterized by autonomous dysregulated aldosterone production from the adrenal gland that is independent of renin and is relatively nonsuppressible by sodium loading or volume expansion. It encompasses a wide spectrum of renin-independent aldosterone production with diverse histopathological etiologies.
- A vast majority of PA is caused by bilateral disease, remains highly underdiagnosed, and increases the risk for adverse cardiometabolic outcomes.
- Screening for PA by measuring ARR can be performed without discontinuing interfering medications. If renin levels are not suppressed, and there is a high clinical suspicion for PA, screening tests can be repeated after interfering medications are discontinued.
- AVS remains the gold standard for subtyping PA, despite challenges such as access to centers with the expertise in performing the procedure, high cost, and lack standardization of the protocol.
- Surgical adrenalectomy is the preferred treatment of lateralizing PA with the intention to reverse the pathophysiology of PA.
- A vast majority of PA is bilateral and will ultimately be treated with medical therapy. The goals of medical therapy as we understand them now are to normalize blood pressure, potassium levels and to treat with a large enough dose of MRA to cause a rise in renin levels.
- There are several noninvasive imaging modalities and steroid biomarkers being developed to assist in the diagnosis of PA. Aldosterone synthase inhibitor medications currently under evaluation could be a game changer in the treatment of PA.

DISCLOSURES

The authors have nothing to disclose.

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