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Management of hypertension in primary aldosteronism

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Abstract

Hypertension causes significant morbidity and mortality worldwide, owing to its deleterious effects on the cardiovascular and renal systems. Primary hyperaldosteronism (PA) is the most common cause of reversible hypertension, affecting 5%-18% of adults with hypertension. PA is estimated to result from bilateral adrenal hyperplasia in two-thirds of patients, and from unilateral aldosterone-secreting adenoma in approximately one-third. Suspected cases are initially screened by measurement of the plasma aldosterone-renin-ratio, and may be confirmed by additional noninvasive tests. Localization of aldosterone hypersecretion is then determined by computed tomography imaging, and in selective cases with adrenal vein sampling. Solitary adenomas are managed by laparoscopic or robotic resection, while bilateral hyperplasia is treated with mineralocorticoid antagonists. Biochemical cure following adrenalectomy occurs in 99% of patients, and hemodynamic improvement is seen in over 90%, prompting a reduction in quantity of anti-hypertensive medications in most patients. End-organ damage secondary to hypertension and excess aldosterone is significantly improved by both surgical and medical treatment, as

manifested by decreased left ventricular hypertrophy, arterial stiffness, and proteinuria, highlighting the importance of proper diagnosis and treatment of primary hyperaldosteronism. Although numerous independent predictors of resolution of hypertension after adrenalectomy for unilateral adenomas have been described, the Aldosteronoma Resolution Score is a validated multifactorial model convenient for use in daily clinical practice.

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Key words: Primary hyperaldosteronism; Hypertension; Adrenalectomy; Aldosteronoma; Treatment

Core tip: Primary hyperaldosteronism is the most common reversible form of secondary hypertension. After appropriate diagnosis and localization studies, adrenalectomy is the procedure of choice for unilateral aldosterone-secreting adenomas, while medical therapy is best for bilateral adrenal hyperplasia. Surgical resection improves or cures biochemical and hemodynamic perturbations in most patients, and halts or reverses many of the deleterious effects of hyperaldosteronism. Predicting which patients will benefit most from adrenalectomy is aided by the Aldosteronoma Resolution Score.

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INTRODUCTION

Hypertension is one of the most prominent risk factors for morbidity and mortality worldwide, accounting for 45% of deaths due to heart disease and 51% due to stroke^[1,2]. In the United States alone, 69 million adults

(29%) have hypertension, in whom it is significantly associated with myocardial infarction, cerebrovascular accidents, heart failure and renal disease^[3,4]. Given the large impact on global health, controlling hypertension is of utmost importance. Significant efforts have been made to characterize potentially curable, or secondary, types of hypertension such as renovascular hypertension, pheochromocytoma, Cushing's syndrome and primary hyperaldosteronism.

Primary hyperaldosteronism (PA) is the leading cause of secondary hypertension, and can be identified in 5% to 18% of hypertensive patients^[5,6]. First described by Conn in 1955 in a patient presenting with resistant hypertension and hypokalemia who was found to have an aldosterone-secreting adrenal adenoma^[7], PA can present in a myriad of clinical scenarios. Most recent epidemiologic studies have shown that approximately 60% of patients are found to have bilateral idiopathic hyperplasia, also known as idiopathic hyperaldosteronism (IHA), while 30% present with unilateral aldosterone-producing adenomas (APA)^[8]. One to two percent of patients present with primary or unilateral adrenal hyperplasia (UAH), 1% with aldosterone-secreting adrenocortical carcinoma, 1% with familial hyperaldosteronism, and 1% with ectopic aldosterone-producing adenoma or carcinoma^[6,9,10].

Classically, excessive aldosterone secretion not only results in difficult to manage hypertension in the majority of patients, but also produces biochemical effects of hypokalemia in 10%-30% of patients^[11]. More recent data, however, suggest that most patients with PA are actually normokalemic^[6,11,12]. In addition, aldosterone hypersecretion has been linked to significant and potentially reversible end-organ damage, particularly in the cardiovascular and renal systems^[13]. For instance, Tanabe *et al.*^[14] demonstrated that patients with PA have more pronounced cardiac hypertrophy compared to patients with essential or other secondary causes of hypertension. Fortunately, timely correction of aldosterone levels can prevent or reverse some of these effects^[15]. This review will describe the current methods of diagnosis and management of primary hyperaldosteronism, with a particular focus on the systemic effects of adrenalectomy as well as the predictors of resolution of hypertension after surgery.

DIAGNOSIS

Patients with hypertension and hypokalemia, regardless of suspected cause (diuretics, incidentaloma), and patients with medically-resistant hypertension, should be considered for screening for primary hyperaldosteronism^[16]. Initial evaluation of patients involves biochemical testing with plasma aldosterone (ng/dL) to renin (ng/mL per hour) ratio (ARR). This test identifies excessive aldosterone secretion with simultaneous suppression of plasma renin activity. Although ARR is regarded as the ideal screening tool for PA, there exists some controversy regarding the clinical conditions under which the ARR is obtained, as well as the test's diagnostic accuracy. Certain drugs, including beta-blockers, angiotensin-converting enzyme inhibi-

tors (ACE-I), selective-serotonin reuptake inhibitors and oral contraceptives, have been shown to affect the results of the test^[17,18]. Ideal testing conditions involve discontinuation of such medications two weeks prior^[10,17,18]. However, in a recent study, Fisher *et al.*^[19] showed that doing so is impractical, and most patients are unable to be taken off their anti-hypertensive medications without the need for substitution by other agents to adequately control blood pressure or serious side effects such as hospitalization. Others suggest that only use of spironolactone will absolutely interfere with the interpretation of this ratio^[16]. In addition, there is some disagreement regarding the requirement of a minimum plasma aldosterone level and the critical ARR cutoff for diagnosis. Most authors recommend an ARR of 20-40, and researchers found that ARR of at least 35 has 100% sensitivity and 92.3% specificity in diagnosing primary hyperaldosteronism^[17,20,21]. Furthermore, biochemical testing should be done in the morning, in a seated position after an initial two-hour ambulatory period^[18]. False negative and positive results can occur, as affected by age, smoking, medications, posture, and renal function, so it is generally advisable to repeat biochemical testing in patients with high pretest probability of PA, typically four weeks later^[18].

Patients with suspected primary aldosteronism identified by screening ARR may undergo confirmatory testing or go on to localization studies. Confirmatory testing includes: the oral sodium loading test, the saline infusion test, the fludrocortisone suppression test, and the captopril challenge test^[22]. Time, cost, patient compliance, and certain physiologic parameters need to be considered in choosing the specific confirmatory test. For instance, in patients with severe hypertension, cardiac or renal insufficiency, clinicians should avoid the oral sodium loading test and the saline infusion tests. In general, such additional testing often proves burdensome and in 30%-50% of cases does not prove to be abnormal in patients with high ARR suggestive of PA^[10,22,23]. Currently, there is lack of evidence encouraging the use of any one of these tests as a gold standard and many physicians, including those in our own practice, no longer recommend confirmatory testing.

LOCALIZATION

The etiology of aldosterone hypersecretion is established by imaging and adrenal vein sampling (AVS). The distinction between unilateral APA from bilateral hyperplasia is a key factor in determining the appropriate management. APAs are best managed by surgical resection, whereas the treatment for IHA is medical therapy. Current high-resolution computed tomography (CT) imaging has enhanced the classification of subtypes of hyperaldosteronism and the ability to identify APAs. The sensitivity and specificity of adrenal imaging with 1.25-3 mm cuts for APA is 78% and 75%, respectively^[22,24]. Findings on adrenal CT include normal-appearing adrenals, unilateral macroadenomas (greater than 1 cm), unilateral microadenomas (less than 1 cm), bilateral micro- or macroadeno-

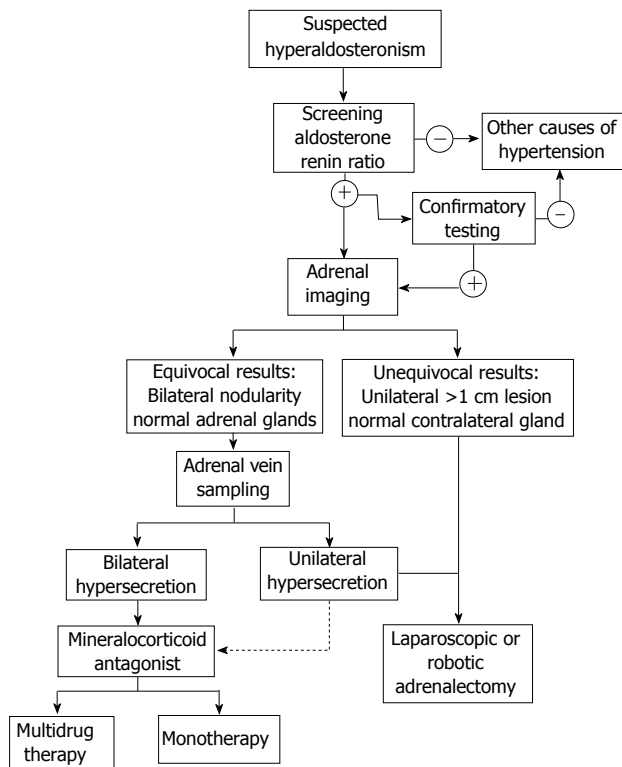


Figure 1 Treatment algorithm.

mas, and minimal unilateral adrenal limb thickening^[22]. Imaging in IHA can reveal normal-appearing adrenal glands or show nodular changes. As a result, radiologists can misread APAs as IHA, whereas microadenomas can be incorrectly labeled as areas of hyperplasia^[22]. Several studies have shown that CT alone may lead to misdiagnosis in PA. In a systematic review, Kempers *et al*^[25] found that 37.8% of patients who showed lateralization on CT/magnetic resonance imaging (MRI) had conflicting results on AVS. If imaging alone was used for localization, 14.6% of patients would have undergone inappropriate adrenalectomy, while 19.1% would have been inappropriately excluded from surgery. Furthermore, in 3.9% of patients, CT/MRI lateralized to the opposite side. These considerations have prompted many to regard AVS as a gold standard for lateralization. However, mandatory use remains a contentious topic. The United States Endocrine Society and Japan Endocrine Society guidelines recommend that AVS be performed in all patients who have diagnosed PA and are considering surgical resection^[22,25,26]. However, the Adrenal Vein Sampling International Study showed that AVS is utilized routinely in only a few centers worldwide^[27]. AVS requires highly skilled radiologists for successful cannulation of both adrenal veins and the procedure is not without complications. AVS is unsuccessful in up to 20% due to failure to cannulate the right adrenal vein, and even in experienced centers, the complication rate averages 0.5%–2.5%^[24,25,28,29].

Despite recommendations from the endocrine societies, several groups continue to advocate for selective use. Zarnegar *et al*^[30] and Tan *et al*^[31] both demonstrated the

effectiveness of AVS in cases of equivocal findings on initial imaging studies. Specifically, Zarnegar *et al*^[30] compared outcomes after adrenalectomy for patients with > 1 cm adenomas with normal contralateral adrenal glands on CT to those who required AVS and CT (< 1 cm). They found similar outcomes in both groups as measured by biochemical and hemodynamic resolution, advocating for selective use of AVS for patients with smaller tumors or indeterminate imaging findings. A recently-issued consensus statement recommends certain patients with PA do not necessarily require AVS, including: patients who are < 40 years old with marked PA and clear unilateral adrenal adenoma and normal contralateral gland on imaging; patients who are not surgical candidates due to unacceptably high operative risk; patients with suspected adrenocortical carcinoma; or patients who have proven familial hyperaldosteronism^[32].

MANAGEMENT

Treatment of PA is aimed at prevention of morbidity and mortality associated with hypertension, hypokalemia and direct aldosterone-associated organ damage. Once the cause of hyperaldosteronism is established, the proper management strategy can be instituted (Figure 1). Adrenalectomy is the procedure of choice for documented unilateral secretion of aldosterone (APA or UAH), while medical therapy is warranted for bilateral aldosterone hypersecretion as with IHA and bilateral APA, or for patients who refuse surgery or are poor surgical candidates.

Medical management involves antagonism of the mineralocorticoid (MR) receptor with spironolactone or eplerenone. Spironolactone has been utilized for over four decades as a first-line agent at doses ranging 25–400 mg/d^[22,33]. Hypokalemia typically resolves immediately, but blood pressure reduction may take several months to occur^[6]. Anti-androgen side effects such as gynecomastia and dysmenorrhea can result from spironolactone due to cross-antagonism of the sex-steroid receptors, usually in a dose-dependent fashion^[34,35]. Eplerenone is more specific for the aldosterone receptor and therefore causes fewer undesired side effects. It is, however, less potent^[36]. A recent randomized trial comparing the two therapies showed that spironolactone from 75 to 225 mg/d was more efficacious than eplerenone at 100–300 mg/d for hypertension control^[36]. In addition, since spironolactone is cheaper and more widely available, clinicians should weigh these factors when recommending the appropriate agent for medical management of PA^[10,36]. It is noteworthy that hypervolemia can be prohibitive in using MR antagonists as sole agents for PA, and in approximately 50% of patients, a second agent such as a low-dose thiazide diuretic can help achieve adequate blood pressure control^[37]. Other agents including sodium channel blockers (amiloride, triamterene), calcium channel blockers, ACE-I, and angiotensin-receptor blockers (ARB) have also been employed as secondary agents in PA, with variable effects on blood pressure and plasma aldosterone levels^[37,38].

Adrenalectomy is the preferred treatment strategy for

patients with demonstrable unilateral hypersecretion of aldosterone. The standard approach employed by most centers is lateral transperitoneal laparoscopic adrenalectomy as first described in 1992 by Gagner *et al*^[39]. However, some surgeons prefer a posterior retroperitoneoscopic approach or robotic-assisted surgery. Proponents of the retroperitoneoscopic approach recommend this technique for smaller tumors (< 6 cm), prior abdominal surgery and lower body mass index (BMI)^[40-42]. Several recent meta-analyses comparing transabdominal to retroperitoneal laparoscopic adrenalectomy found no significant differences between the two approaches^[43,44]. Additionally, Brandao *et al*^[45] systematically reviewed robotic-assisted adrenalectomy and found that it is equally safe and may even result in less blood loss and shorter hospital stay, compared to laparoscopic approaches.

OUTCOMES

Aldosterone hypersecretion causes hypertension and biochemical abnormalities with potassium hemostasis by activation of the renin-angiotensin-aldosterone-system (RAAS). It has been shown that abnormal activation of the RAAS correlates directly with end-organ damage in the cardiovascular and renal systems and it is well-documented that blockade of the angiotensin-II arm by ACE-I or ARB provides significant cardiovascular protection^[13]. Pathophysiologically, aldosterone works to increase sodium absorption in the kidneys, leading to increased intravascular volume and thereby increased blood pressure. Cardiovascular damage occurs from increased left ventricular mass and hypertrophy as well as aldosterone-driven fibrosis and collagen production in the interventricular septum. Furthermore, perivascular inflammation, vascular remodeling in the heart and kidney, and direct damage to the nephron anatomy and physiology, are thought to contribute to sustained deleterious end-organ effects from aldosterone excess that may occur independent of hypertension^[46-48]. In fact, compared to patients with essential hypertension, patients with primary hyperaldosteronism are at increased risk for these adverse effects, which are significantly reduced by surgical or medical management^[49-51]. Milliez *et al*^[52] demonstrated in a retrospective study a markedly increased incidence of stroke (12.9% *vs* 3.4%), non-fatal MI (4.0% *vs* 0.6%), and atrial fibrillation (7.3% *vs* 0.6%) in patients with PA compared to those with essential hypertension. There was no difference in the PA subtype. Additionally, Ribstein *et al*^[53] reported significant decrease in proteinuria in patients with PA with treatment of aldosterone excess by adrenalectomy or spironolactone compared to control essential hypertension patients.

The treatment of aldosterone hypersecretion either by medical or surgical means is very effective. Nearly 100% of patients will experience a biochemical cure with normalization of hypokalemia and aldosterone levels^[54,55]. These effects follow surgery relatively quickly. It is recommended that potassium supplements and MR antagonists should be discontinued on post-operative day 1, and anti-

hypertensive medications reduced simultaneously. Patients are also instructed to eat a diet generous in salt for the first month after surgery to account for a suppressed contralateral adrenal gland^[56]. Interestingly, a minority of people can develop prolonged zona glomerulosa insufficiency causing hyperkalemia after adrenalectomy. Reported by Fischer *et al*^[57], this outcome had an incidence of 5% of adrenalectomized PA patients in their cohort and required long-term fludrocortisone treatment post-operatively.

Resolution of hypertension in primary hyperaldosteronism is etiology-specific. For cases not appropriate for surgical resection, blood pressure control is best achieved by mineralocorticoid antagonists, as previously discussed. Conversely, for localized APAs adrenalectomy results in improvement in blood pressure control in over 90% of patients, and complete resolution, as defined by BP < 140/90 mmHg without the need for antihypertensive medications, in 30%-60%^[6,58]. Patients that are not cured generally experience lower mean blood pressures and take fewer antihypertensive medications after surgery^[59]. Persistent hypertension after adrenalectomy may result from misdiagnosis of unilateral aldosterone hypersecretion, or more likely, coexistent essential hypertension with underlying end organ damage. Chronic aldosterone excess has been shown to increase arterial stiffness, and may contribute to enduring hypertension in these patients^[60]. Blood pressure typically normalizes or shows maximal improvement in one to six months after adrenalectomy, though it can continue to decrease for up to one year following surgery^[60].

Multiple studies have looked at outcomes of adrenalectomy for APA to characterize predictive factors for resolution of hypertension. Factors that have been correlated with favorable results include younger age, female sex, lower BMI, fewer pre-operative antihypertensive medications, shorter duration of hypertension preoperatively, fewer first-degree family members with hypertension, better renal function as evidenced by higher glomerular filtration rate, lower creatinine and less proteinuria, lower serum aldosterone and higher urine aldosterone, histopathologic features, and smaller tumor size^[58,61-64]. Recently, in a large series, Zhang *et al*^[65] showed by multivariate regression that shorter duration of hypertension and lower serum aldosterone level were predictive of resolution of hypertension after adrenalectomy. Furthermore, several studies have linked the *TT* genotype of *CYP11B2* gene encoding aldosterone synthase to successful outcomes after adrenalectomy for PA^[66-68].

To better predict which of these features result in resolution of hypertension after adrenalectomy in patients with APA, Zarnegar *et al*^[55] proposed the Aldosteronoma Resolution Score (ARS) which takes into account four readily available pre-operative clinical parameters including BMI ≤ 25 kg/m², female sex, duration of preoperative hypertension ≤ 6 years, and number of preoperative antihypertensive medications ≤ 2. Each parameter receives a score of 1, with the exception of number of preoperative medications, which is scored by 2 points due to its relative significance in the prediction model. A score

of 0-1 predicts a low likelihood of resolution, while patients with ARS 4-5 have a high likelihood of resolution of hypertension after adrenalectomy. In the study, 27.6% of patients with ARS 0-1 were cured, whereas 75% with ARS 4-5 had complete resolution of hypertension. Using an external cohort, the authors also demonstrated external validity of the model. Utsumi *et al.*^[61] further validated the accuracy of the ARS model using a Japanese population, confirming the utility of the ARS as a clinical tool for counseling patients on expected surgical outcomes.

While surgery abolishes the source of excess aldosterone secretion and significantly improves or resolves biochemical disturbances and blood pressure control, the long-lasting effects of exposure on the vasculature, heart, brain and kidney have yet to be completely delineated^[63]. Nonetheless, several studies have shown that the progression of at least some of these effects are slowed or even reversed by adrenalectomy. Strauch *et al.*^[60] showed that resection of APA reduced arterial stiffness parameters compared to medical management. Rossi *et al.*^[15] showed regression of left ventricular hypertrophy in patients with primary hyperaldosteronism after appropriate medical or surgical intervention compared to optimally treated patients with primary hypertension, while Lin *et al.*^[69] showed adrenalectomy reversed myocardial fibrosis in these patients. Renal function has also been shown to improve after resection with resolution of microalbuminuria in APA patients compared to those with essential hypertension owing to the resolution of relative glomerular hyperfiltration in PA from the volume-expanding and hypertensive effects of the hormone^[50,70].

CONCLUSION

Primary hyperaldosteronism is a common and treatable cause of secondary hypertension. Aldosterone excess has been linked to systemic disturbances in the cardiovascular, renal, and vascular systems, in addition to causing hypokalemia and hypertension. Multiple studies have shown worse morbidity with higher rates of myocardial infarction, stroke and renal dysfunction compared to patients with essential hypertension. Depending on the subtype, medical or surgical treatment is effective at halting or even reversing some, if not all, of these effects. Diagnosis and subtype differentiation relies on ARR, possible confirmatory testing, and localization studies with CT and adrenal venous sampling. Unilateral adrenalectomy for patients with APA successfully reverses biochemical disturbances, resolves or significantly improves hypertension, and halts progression of systemic perturbations. Though a variety of parameters have been found to be associated with resolution of hypertension after resection of APA, the ARS is currently the most accurate prediction model for resolution. Adrenalectomy for APA is a safe procedure that should be performed for appropriate candidates to improve long-term outcomes.

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