AN INDIVIDUALIZED APPROACH TO THE EVALUATION AND MANAGEMENT OF PRIMARY ALDOSTERONISM

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ABSTRACT

Objective: With the increased emphasis on personalized and individualized medicine, the American Association of Clinical Endocrinologists Adrenal Scientific Committee has developed a series of articles to update members on personalized medicine as it applies to adrenal diseases.

Methods: We synthesized literature reviews, guidelines from professional societies, and personal experience.

Results: Since Conn described primary aldosteronism (PA) over 60 years ago, debate has raged about the prevalence of PA in the hypertensive population, the wisdom of broadly screening for PA, and prudent approaches to evaluate and manage these patients. Accumulated data from multiple centers around the globe have begun to crystallize the clinical characteristics about these patients, which allows for an individualized approach before the diagnosis of PA is even established. Evidence-based criteria for screening, improved and widely available clinical assays, and validated algorithms for evaluation empower all endocrinologists to address this complex disease in an effective manner.

Conclusion: Breakthroughs in the pathogenesis and evolution of PA illustrate why our thinking about this disease must remain flexible: PA is not a rare and uniform condition, but rather a common syndrome with protean manifestations. (Endocr Pract. 2017;23:680-689)

Abbreviations:
A/C = cortisol-corrected aldosterone concentration;
ACE = angiotensin-converting enzyme; APA = aldosterone-producing adenoma; APCC = aldosterone-producing cell cluster; ARB = angiotensin receptor blocker; ARR = aldosterone-to-renin ratio; AVS = adrenal venous sampling; CT = computed tomography; ENaC = epithelial sodium channel; GRA = glucocorticoid remediable aldosteronism; IHA = idiopathic hyperaldosteronism; LI = lateralization ratio; MR = mineralocorticoid receptor; MRI = magnetic resonance imaging; PA = primary aldosteronism; PRA = plasma renin activity; SRA = surgical remediable aldosteronism

INTRODUCTION

As we advance into the Digital Age, endocrinology has increasingly become a game of numbers. Numerical criteria dominate our diagnostic algorithms, treatment goals, and thought processes. Patients expect us to order laboratory tests and bristle if we dismiss trivial deviations from the reference ranges. In contrast, the Age of Personalized and Individualized Medicine calls for an infusion of rational thinking, tailoring our approach to the patient based on their characteristics, goals, and limitations. In these articles on adrenal disorders, “personalized medicine” refers...
to the role of genetic analysis in the care of the patient. For the purposes of this article on primary aldosteronism (PA), we use the term “individualized medicine” to refer to the application of nongenetic patient characteristics to optimize care of the individual patient. In this article, we will consider the example of PA and how a personalized or individualized approach can be employed to improve diagnosis and treatment.

INDIVIDUALIZING THE APPROACH TO PA

Why Has Our Approach to PA Changed?

Prevalence

Numerous studies around the world from primary care settings to referral-based hypertension practices universally find a prevalence of PA from 5 to 20% among hypertensive populations. In general, prevalence estimates are higher in populations enriched for hypertension and more specifically severe or resistant hypertension. Further, the prevalence may vary depending on the specific testing and standards used to define PA.

High-Prevalence Populations

As discussed below, hypokalemia, older age, known adrenal tumor, family history of PA or young-onset hypertension, and most importantly resistant hypertension identify high-risk populations who may benefit most from screening.

Simplified Screening

So much has been written about medication interference and proper procedures for testing that many endocrinologists feel paralyzed about even embarking on the evaluation. Some factors matter more than others, and the more severe the disease, the less preparation for testing influences the interpretation. PA screening can usually be performed in the ambulatory clinic setting with minimal or no preparation; however, the conditions of testing and a clinical assessment of disease severity for each individual is essential for proper interpretation of screening data and to minimize the risk of false-negatives and false-positives.

Growth of Specialized Centers

Access to centers that successfully perform adrenal vein sampling (AVS) and laparoscopic or retroperitoneoscopic adrenalectomy has expanded considerably over the last 2 decades. Many rural communities and some metropolitan areas, however, still lack these services.

Genetics and Pathogenesis

We now understand that somatic mutations in ion channels or ion pumps contribute to the pathogenesis of aldosterone-producing adenomas (APAs). Further, even biochemically and morphologically “normal” adrenal glands harbor pockets of cells that bear similar somatic mutations and express aldosterone synthase. These abnormal cells might be precursors for the development of APAs and/or idiopathic hyperaldosteronism (IHA, also frequently referred to as bilateral adrenal hyperplasia).

Outcomes Data

When counseling a patient about adrenalectomy, preoperative characteristics are useful for estimating postoperative outcomes. This information allows individualized counseling not only about treatment but when to pursue later stages of the evaluation.

Spectrum of Disease

Many textbooks refer to strict cut-off criteria for PA diagnosis and dichotomize PA as either APA or IHA. Today, we realize that patients with low-renin hypertension and low-to-moderate serum aldosterone also show very good blood pressure reduction with mineralocorticoid receptor (MR) antagonists, and some patients with PA have IHA plus APA. Furthermore, PA need not be recognized as only a severe disease of aldosterone excess; rather, patients may have milder or early forms of PA that may still be recognized and addressed with interventions to prevent exposure to aldosterone excess and increased risk for cardiovascular disease.

Detection of “Overt” PA

“Overt” PA refers to cases of PA that display clear biochemical evidence of autonomous (renin-independent) aldosterone secretion with an apparent clinical syndrome of excessive MR activation (hypertension and/or hypokalemia). An individualized approach to identifying overt cases of PA is recommended by The Endocrine Society clinical practice guidelines, which recommend screening all patients for whom PA is likely based on clinical grounds (Table 1) (1). In these selected groups of patients, the prevalence of PA can exceed 20%; therefore, the yield of testing and positive predictive values are high, and the benefits of making the diagnosis are large. For these patients, PA is highly probable, and the diagnosis should be pursued until ruled out. Focusing screening for PA on patients who meet any of the aforementioned criteria provides an example of individualized case detection; however, these criteria target attention on those patients that are most likely to have overt and severe forms of PA that are clinically apparent. As discussed below, patients with milder forms of PA might not meet these screening criteria yet would still benefit from prompt diagnosis.

When PA is suspected, the recommended biochemical testing to screen for renin-independent aldosteronism is a serum aldosterone and plasma renin activity (PRA, or renin mass) and calculating the aldosterone-to-renin ratio (ARR) (1). The most sensitive criteria for a positive screen (maximizing case-detection while minimizing missed cases of PA) include a fully suppressed renin activity (<0.3 ng/mL/h) paired with a serum aldosterone of at least 6 ng/dL,
such that the ARR is greater than 20 (1). An ARR ≥30 in the context of a suppressed renin suggests renin-independent aldosteronism and is the most accepted criteria for a positive screen for PA. An ARR ≥20 with a suppressed renin is also indicative of a positive screen and may increase the likelihood of detecting mild-to-moderate cases of PA at the expense of false-positive screening. Dynamic testing to confirm autonomous aldosterone excess should be performed. When serum aldosterone is very high (>20 ng/dL) with concomitant suppression of renin such that the ARR is much greater than 20 and hypokalemia is present, the diagnosis of PA is established without further confirmatory testing. Testing to confirm PA involves 1 of 4 recommended methods to demonstrate autonomous and nonphysiologic aldosterone secretion: oral or intravenous salt loading, fludrocortisone suppression, or captopril challenge (1). Each of these confirmatory tests assesses for substantial renin-independent aldosteronism and has its own pros and cons. For example, the oral salt suppression test can be conducted in the ambulatory setting, whereas intravenous saline infusion requires several hours of direct observation and support in a facility. It is important to note that the most effective “gold standard” for PA is the resolution of renin-independent aldosteronism following surgical resection; clear and consistent biochemical biomarkers, histopathologic patterns, or radiographic characteristics are not available as a gold standard (2). For this reason, the criteria used to define each confirmatory test as positive or negative are imperfect and are generally established to detect the most severe of cases (to ensure high sensitivity); however, they may miss milder forms of renin-independent aldosteronism that we currently do not define as PA (3-5).

Glucocorticoid remediable aldosteronism (GRA) is an autosomal dominant disorder caused by an unequal crossing over event during meiosis that inserts a promoter sensitive to adrenocorticotropic hormone signaling from the CYP11B1 proximal to the aldosterone synthase gene (CYP11B2) (6). GRA should be considered in young individuals with PA and in patients with a family history of PA or history of early onset hypertension and hemorrhagic stroke (7). Unfortunately, genetic testing for this disorder is not available in a commercial laboratory in the United States and must be performed in a research laboratory. A 3-day dexamethasone suppression test (1 mg twice daily for 3 days; aldosterone <4 ng/dL is a positive result) can be used to screen for GRA with good but not perfect diagnostic accuracy (8). The treatment of GRA is medical and usually involves low-dose glucocorticoids and MR antagonists. Other monogenic forms of mineralocorticoid excess should be considered in children with hypertension, and these disorders have been reviewed elsewhere (9).

It is important to recognize that even “overt PA” is not a monolithic disease. There exists a spectrum of PA severity that is dictated by the degree of aldosterone autonomy. Therefore, clinical and biochemical biomarkers of MR activation tend to correlate with the severity of overt PA in each patient. Markers of MR activation include the degree of renin suppression, the degree of hypokalemia, the fractional excretion of urinary potassium, and blood pressure. For example, mild cases of overt PA have higher renin activity, higher serum potassium, lower urinary potassium excretion, and lower blood pressure compared to cases of more severe overt PA (10). Furthermore, dietary sodium intake significantly influences PA screening results for patients with milder disease. When PA screening is conducted under high dietary sodium intake mild and severe forms of PA are equally detected and confirmed (10); however, when PA screening is conducted with dietary sodium restriction, as is routinely recommended (10), a substantial proportion of bona fide PA cases are missed (10). For this reason, it is strongly recommended that PA screening with the ARR be conducted during a period of high sodium intake typical of most unrestricted diets (1,10).

Do medications need be discontinued prior to screening? The most common cause of a false-negative result is the use of a medication that raises renin substantially (the denominator in the ARR), such as MR antagonists, epithelial sodium channel (ENaC) inhibitors, and the acute action of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). Other antihypertensives (including diuretics) lower blood pressure either via vasodilation or volume depletion, both of which can raise renin. As a rule of thumb, if the renin is suppressed, the
ARR is interpretable, and the screen is valid despite the use of potentially interfering medications including MR antagonists. Therefore, screening with the ARR should be considered in the ambulatory setting regardless of medication use. If the renin is low but not suppressed due to medication effect, yet the serum aldosterone and ARR are high, PA cannot be excluded. In this scenario, washout of the interfering medication may be necessary (often for 4-6 weeks) while blood pressure is controlled neutral agents such as alpha antagonists, calcium channel blockers, and/or hydralazine. The individualized approach requires the use of the clinical assessment of disease severity, how difficult it is for the patient to undergo additional testing, and the risk of medication discontinuation to determine when conditions are adequate to interpret screening results. Floridly abnormal screens obviate the need for confirmatory testing. Some caveats to ARR testing include laboratories that report renin down to 0.1 ng/mL/h, which inflates the ARR even when serum aldosterone concentrations are low. Some commercial PRA assays are being phased out in favor of renin mass assay, for which the units are different, and the correlation of the 2 assays is not strictly linear. Table 2 highlights some common scenarios encountered with ARR testing and their interpretations.

“Subclinical” or “Nonclassical” PA

Clinical interest and professional society guidelines generally focus on detecting overt cases of PA, given their substantially higher risk of cardiovascular disease. However, growing evidence has extended the spectrum of PA to milder forms that do not meet accepted criteria for diagnosis but might also contribute to adverse cardiovascular outcomes. “Subclinical PA” refers to PA cases that display intermediate or overt biochemical evidence of renin-independent aldosteronism but lack an obvious clinical syndrome of excessive MR activation. For example, patients with normal blood pressure or mild stage I hypertension are not generally considered to have excessive MR activation (4,10), but a notable proportion of these populations may still have biochemical evidence suggestive of PA as a continuum with low-renin essential hypertension. Some evidence suggests that much of “low-renin” hypertension may in fact represent occult forms of PA, and these patients often benefit from treatment with MR antagonists (2). On the other hand, the low-renin phenotype of essential hypertension is much more common with older age; therefore, older patients with hypertension and a low-renin phenotype may be considered for PA screening or treated empirically with an MR antagonist for a form of hypertension that may preferentially respond to this medication class.

The phenotype of low-renin essential hypertension has been well recognized for several decades. This prevalent subgroup of hypertensives (~30-40%) exhibits a suppressed PRA; however, they do not display overt clinical signs of PA and do not have biochemical evidence of PA. Nevertheless, multiple intervention studies for severe or resistant hypertension in populations with a low renin have shown that MR antagonists are equivalent or superior to alternatives such as ARBs (12,13), ACE inhibitor (14), diuretics (13), and adrenergic antagonists (15). These intervention studies implicate less-than-classical aldosterone (or other mineralocorticoid) excess and MR activation in the pathophysiology of the low-renin hypertension phenotype. Furthermore, longitudinal evidence suggests that subclinical PA may exist even in normotensive individuals with no clinically apparent syndrome of elevated blood pressure or PA (16,17). In other words, even antecedent to the development of hypertension, there may be a syndrome of renin-independent aldosteronism, characterized by low renin that increases risk for vascular disease and possibly progression to more overt forms of PA.

The observation that subclinical PA may exist in large subsets of normotensives and mild hypertensives suggests that either PA is more prevalent than we recognize or that only a small fraction of normotensives with subclinical PA progress to more overt forms of the disease (3-5,10,18,19). One theory that has been proposed to account for these clinical observations is that aldosterone-producing cell clusters (APCCs) may be a prevalent cause of subclinical PA that has largely been unrecognized (20). APCCs are foci of high aldosterone synthase (CYP11B2) expression in morphologically normal adrenal glands (21,22). Remarkably, even in adrenal glands with no histopathologic tumors or hyperplasia, Nishimoto and colleagues were able to identify large and often multiple clusters of dense CYP11B2 staining that invaded the zona fasciculata, suggesting high and pathologic aldosterone synthesis (21,22). Although they did not have biochemical evidence to support aldosterone autonomy (since these adrenal specimens were obtained postmortem), they observed APCCs even adjacent to known aldosterone-producing adenomas (APAs), a surprising observation since zona glomerulosa CYP11B2 activity adjacent to APAs is expected to be suppressed due to the lack of stimulation by angiotensin II (21). Further, they demonstrated that APCCs were present in ~50% of all morphologically normal adrenal glands analyzed and that they harbored mutations in channels known to increase secretion of aldosterone in APAs (22). Collectively, these findings suggested that APCCs may be a common cause of autonomous renin-independent aldosterone excess (20). Thus, APCCs may represent an early precursor to neoplastic PA and may account for the fact that subclinical PA and the low-renin phenotype appear to be prevalent (3,5,20).

Individualized Imaging and Localization

When the diagnosis of PA has been confirmed, localization of the source of autonomous aldosterone secretion is considered to ensure the most effective and individualized treatment. Patients with a positive screen for PA who
are not interested in or are capable of undergoing surgery need not necessarily proceed with confirmatory testing and imaging to localize the source; they can be treated with an MR antagonist without further diagnostics. The combination of cross-sectional imaging (computed tomography [CT] and/or magnetic resonance imaging [MRI]) in combination with AVS can provide accurate localization. Surgical adrenalectomy is most appropriate for those with unilateral excessive aldosterone production: either an adenoma or unilateral hyperplasia. These patients have surgically remediable hyperaldosteronism (SRA). Patients with bilateral hyperplasia or IHA, are generally treated medically rather than surgically.

Visualization of a unilateral adrenal adenoma on CT or MRI in young patients (<40 years) with confirmed PA who have hypokalemia and normal kidney function is usually considered sufficient localization since the likelihood of a unilateral source of PA is almost certain (23,24). However, in many cases adrenal abnormalities may be small, often <1 cm in diameter, and may therefore be missed on conventional CT or MRI imaging. Furthermore, nonfunctional adrenal adenomas are common “red herrings” that inappropriately direct surgical management. Therefore, it is not surprising that several studies have found CT and MRI imaging to be less sensitive and specific than AVS for the prediction of SRA (1,25,26), and that current guidelines recommend AVS for the most accurate selection of patients with SRA (1).

Although most guidelines recommend the use of AVS in addition to CT or MRI to optimize localization of PA, this recommendation has been recently challenged by the first large randomized controlled trial to assess the utility of AVS for predicting SRA (27). In brief, the SPARTACUS trial showed that patients who had PA treatment decisions made using CT alone, versus CT with AVS together, had nearly the same clinical outcome 1 year later (27). Patients treated with CT had an 80% rate of biochemical cure compared to 89% with AVS, and after 1 year of follow-up, there were no differences in the number of antihypertensive medications used or in blood pressure control. Clinical outcomes beyond 1 year were not available to assess the long-term durability of the results. The SPARTACUS study highlights the complexity of the decision-making process with regard to PA localization. For clinicians at large medical centers with experience and expertise with AVS, the use of AVS is common prior to adrenalectomy, since a failure rate of 20% is generally viewed as unacceptable. Furthermore, most of these centers have observed that the sensitivity of AVS exceeds that of CT and that the rate of biochemical cure following AVS directed adrenalectomy is >95%.

### Table 2
Interpretation of Screening for PA

<table>
<thead>
<tr>
<th>Serum aldosterone (ng/dL)</th>
<th>PRA (ng/mL/h)</th>
<th>ARR</th>
<th>Serum potassium (mmol/L)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>2.0</td>
<td>2.5</td>
<td>3.8</td>
<td>Negative screen for PA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PRA not suppressed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Serum aldosterone too low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ARR too low</td>
</tr>
<tr>
<td>3.0</td>
<td>0.10</td>
<td>30</td>
<td>4.2</td>
<td>Unlikely to be PA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Serum aldosterone too low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ARR likely inflated by extremely low PRA</td>
</tr>
<tr>
<td>12</td>
<td>0.70</td>
<td>15</td>
<td>2.8</td>
<td>Positive screen for PA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Unexplained hypokalemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ARR suggestive and PRA relatively suppressed</td>
</tr>
<tr>
<td>24</td>
<td>&lt;0.60</td>
<td>&gt;40</td>
<td>3.3</td>
<td>PA confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Positive PA screen with aldosterone &gt;20 ng/dL</td>
</tr>
<tr>
<td>40</td>
<td>2.0</td>
<td>20</td>
<td>3.5</td>
<td>Negative screen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• PRA not suppressed (not consistent with renin-independent aldosteronism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Consider secondary aldosteronism or medication effect (such as MR antagonist). If medication effect implicated, consider value in repeat testing after medication adjustments.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARR = aldosterone-to-renin ratio; PA = primary aldosteronism; MR = mineralocorticoid receptor; PRA = plasma renin activity.

The table describes scenarios in which the serum aldosterone and PRA are interpreted.
What factors in the participant population and study design account for the results of SPARTACUS? In the CT-guided therapy arm (n = 92), only patients with a >7 mm mass in 1 adrenal gland and a normal contralateral gland were offered surgery. Only 50% of patients in that group met this criterion, and only 80% of those patients were cured, or a disappointing 40% cure rate overall. The other patients were treated with MR antagonist, which has been shown to normalize blood pressure not only in IHA but in most APA patients as well (28). Consequently, it is unknown how many patients in the CT-guided therapy arm were denied surgical cure because CT showed bilateral nodules or normal glands and AVS was not performed. In fact, 21 patients who lateralized in the AVS-guided treatment arm had bilateral nodules on CT, and results of CT and AVS were discordant in 50% of patients with conclusive data from both studies. In the AVS-guided treatment arm (n = 92), only 50% of patients lateralized, limiting the number of cases who underwent adrenalectomy. PA “persisted” in 5/46 patients treated with AVS-guided adrenalectomy, but although the information was difficult to extract from the appendix and tables, hypokalemia resolved in all, and PA was significantly improved in all 5 cases. The 2 major lessons from SPARTACUS are: (1) even patients with robust lateralization on AVS can still have a component of IHA, which we cannot identify using currently available tests; and (2) when in doubt, treat with an MR antagonist. In summary, although this recent study could not conclusively demonstrate the superiority of AVS over CT scanning, most published experience suggests that AVS is the preferred method to identifying SRA in appropriately skilled and experienced referral centers.

Despite the usual recommendation that AVS be performed to identify SRA, there is no agreement as to the protocol that optimizes sensitivity and specificity. In a recent review of AVS performed worldwide, approximately one-third of centers performed bilateral AVS sequentially following cosyntropin stimulation, one-third performed bilateral AVS simultaneously without cosyntropin stimulation, and about one-third performed bilateral AVS simultaneously following cosyntropin stimulation (29). Cosyntropin increases the blood flow through the adrenal gland, so that the adrenal veins are dilated and slightly more easily catheterized. Furthermore, when cosyntropin is administered at a constant rate, then aldosterone and cortisol production is, in theory, constant, so that AVS can be performed in the right and left adrenal veins sequentially, making the procedure even less challenging. The high cortisol concentrations in the adrenal veins following cosyntropin also provide greater confidence that the adrenal veins have been successfully catheterized.

The question remains as to whether AVS should be performed with or without cosyntropin stimulation. One large study often cited as establishing the importance of AVS performed AVS sequentially following stimulation with cosyntropin (30). In contrast, an early description of AVS described bilateral simultaneous AVS both before and after cosyntropin administration (31,32). The studies are difficult to compare, since some use pathologic findings as the primary end point to document cure, while other studies use biochemical cure as the primary end point. One recent study reported simultaneous bilateral AVS both before and after cosyntropin administration in a large number of patients and concluded that the 2 protocols are complementary (33). In that study, AVS with cosyntropin identified about 75% of SRA patients; however, data from AVS without cosyntropin was required to identify all patients with SRA. This study used biochemical cure as the primary end point, which might be more reliable than other studies that used adrenal pathology as the primary end point for defining cure. A preliminary AVS review at the institution of one of the authors (C.D.M.) has confirmed these findings (34).

The AVS criteria that best predict SRA continue to be refined. The serum aldosterone concentrations from each adrenal vein and from the peripheral vein are divided by the respective cortisol concentrations to calculate the cortisol-corrected aldosterone concentration (A/C). The ratio of dominant A/C to nondominant A/C is referred to as the lateralization index (LI). Under cosyntropin stimulation, an LI <2 demonstrates bilateral disease, while an LI >4 is usually considered predictive of a good response to adrenalectomy (1). Others have suggested that a nondominant A/C that is suppressed below the peripheral vein A/C, called “contralateral suppression (35), or nondominant aldosterone suppressed below the peripheral vein aldosterone (33), are predictive of good responses to adrenalectomy. Most patients with SRA meet both these criteria. Because aldosterone and cortisol values are generally much lower, LI criteria without cosyntropin are generally lower, as low as 2 for lateralization (29).

The main controversy is what to do for patients with an LI of 2 to 4. Once again, an individualized approach is required in counseling the patient on treatment recommendations. First, if the LI is 3 to 4 and significant contralateral suppression is observed, adrenalectomy is likely to yield significant clinical benefits. Second, measurement of additional biomarkers in the AVS samples such as 18-hydroxycorticosterone can provide additional evidence of lateralization. Third, several factors are known to predict the clinical response to adrenalectomy, including age, duration of hypertension, number of antihypertensive medications, and hypokalemia. Thus, medical therapy with an MR antagonist is the safe and conservative choice for patients who lack favorable prognostic factors.

**Individualized Treatment**

Treatment decisions in PA can be individualized depending on disease severity, type of disease (unilateral APA vs. IHA), and the goals of patient care. The ideal goal of treatment is to cure hyperaldosteronism and thereby
cure or improve hypertension and its consequences, and resolve hypokalemia if applicable.

Surgery is the preferred therapeutic intervention when PA is localized to a unilateral source, the patient is willing to undergo a surgical procedure, and the age and comorbidities associated with the procedure are reasonable. Minimally invasive surgical approaches are now widely available and are associated with a shorter and safer surgery than the open surgical approach alternative. Anterior laparoscopic surgery is commonly practiced, while specialized centers may also offer retroperitoneoscopic approaches that afford even shorter recovery times (36). Although not widely practiced, a more recent option that is becoming available is radiofrequency ablation of adrenal adenomas. Small studies have shown similar rates of hypertensive cure or improvement and similar rates of complications and hospital length of stay, suggestive that ablative techniques may represent a potential nonsurgical alternative for the treatment of unilateral PA (37,38). One minor limitation to radiofrequency ablation is the inability to collect histopathology; therefore, these procedures should only be considered when radiography is strongly suggestive of a benign cause of PA. Although the dogma suggests that surgery be reserved for unilateral PA, in certain instances of bilateral PA where blood pressure and/or potassium balance is difficult to control with maximal MR antagonist therapy, unilateral surgery may be effective, especially if there is substantial asymmetry observed on AVS (39). There are no long-term studies demonstrating that surgical therapy is superior to medical therapy for patients with unilateral aldosteronism. Therefore, the decision to proceed to adrenalectomy is based upon the patient’s individual priorities as guided by his physician. Many patients prefer laparoscopic adrenalectomy with an overnight hospital stay and rapid recovery since it reduces the number of required antihypertensive medications and eliminates the need for potassium replacements. In contrast, not all physicians have easy access to skilled laparoscopic surgeons and to centers with experience and skill with AVS. In the absence of such expertise, medical therapy may be preferable.

In most cases of bilateral PA, the initial treatment of choice is medical therapy with MR antagonists. The 2 most commonly available options are spironolactone and eplerenone. Spironolactone has approximately twice the potency of eplerenone at equivalent doses and is generally cheaper. For men, however, spironolactone carries a significant risk of gynecomastia that increases with higher doses and longer durations of use. It should be noted that there are no large and longitudinal studies that have assessed treatment targets or for titrating MR antagonist therapy or demonstrated that long-term MR antagonist therapy is superior to surgery and/or other antihypertensive medication classes for cardiovascular events or other hard endpoints. Should MR antagonists be titrated to achieve normal blood pressure and serum potassium alone? Alternatively, should MR antagonists be titrated until a biomarker of MR antagonism is observed, such as a rise in plasma renin? Most clinicians presumptively target a combination of these endpoints; however, it is important to note the lack of prospective studies comparing the efficacy of MR antagonists in PA when compared to alternative agents, or when compared to essential hypertensives treated with MR antagonists, on a variety of cardiovascular and metabolic endpoints (1). Until such data become available, one individualized approach is to first titrate MR antagonists to achieve a normal serum potassium and a rise of PRA to greater than 1 ng/mL/h, as crude metrics of adequate MR antagonism. If the blood pressure remains elevated, other antihypertensives should then be added until the blood pressure is at goal. Since excessive MR activity is associated with cardiovascular disease above and beyond the effect of blood pressure alone, this recommendation may provide an individualized approach to counter the compounded detrimental effects of hypertension plus excess MR activation in PA to elicit end-organ damage.

When MR antagonists alone are insufficient to normalize blood pressure, the use of other antihypertensives should be considered. Calcium channel blockers and alpha- and beta-adrenergic antagonists are obvious choices. ACE inhibitors and ARBs are worth considering; however, the combination of these medications with MR antagonists may result in hyperkalemia and decreased renal blood flow if overdone. When hypokalemia remains a persistent problem, ENaC inhibitors such as amiloride can be effective add-ons.

**Compare These Cases**

**Case 1**

P.A. is a 44-year-old man with difficult-to-control hypertension. High blood pressure was first recorded during a dental exam 10 years ago, and he was controlled with amiodipine monotherapy for 4 years. Hydrochlorothiazide was added but discontinued after a few months due to hypokalemia. He now takes amlodipine, valsartan, metoprolol, and hydralazine at maximal doses plus 80 mEq/day of KCl. He complains of leg swelling, erectile dysfunction, and exercise intolerance. He has no other medical problems and no family history of hypertension. On exam, his body mass index is 26 kg/m², blood pressure is 148/93, heart rate 56 with 1+ pedal edema. Screening laboratory data show the following: serum aldosterone, 28 ng/dL; PRA, <0.6 ng/mL/h; serum potassium, 3.3 mEq/L; serum creatinine, 1.2 mg/dL; urine microalbumin, 22 mg/g creatinine. What would you recommend as the next steps?

**Case 2**

E.H. is a 76-year-old woman who has had hypertension for 35 years. She also has type 2 diabetes mellitus, obstructive sleep apnea, chronic renal insufficiency, and is
status post ST-elevation myocardial infarction with placement of 2 coronary artery stents and congestive heart failure. She had a CT scan for abdominal pain, and a 1.6-cm lipid-rich adenoma of the right adrenal gland was noted. Her medications include amlodipine, valsartan, labetalol, atorvastatin, metformin, sitagliptin, and furosemide. She has a strong family history of type 2 diabetes mellitus and hypertension. On exam, her body mass index is 44 kg/m², blood pressure is 136/88, heart rate 76 with 1+ pedal edema. Screening laboratory data show the following: serum aldosterone, 15 ng/dL; PRA, 0.8 ng/mL/h; serum potassium, 4.2 meq/L; serum creatinine, 1.8 mg/dL; urine microalbumin, 185 mg/g creatinine; glycated hemoglobin, 6.9%. What would you recommend as the next steps?

Feedback

Case 1

P.A. developed hypertension at age <35, and he now has uncontrolled hypertension despite 4 medications without a strong family history or obesity. He is hypokalemic and experiencing several medication side effects. The chances he has PA are very high, and missing or delaying the diagnosis increases his risk of developing worsening cardiovascular disease.

Individualized Approach to His Evaluation

Do not stop any medications. Conduct screening testing now. His PA screen shows a suppressed renin despite 2 vasodilator medications and an aldosterone >20 ng/dL. Despite hypokalemia (ARR >47). This testing is confirmatory for PA. Treatment of his PA is very likely to improve his blood pressure control and normalize his potassium. Given the severity of his PA, it is most likely that he has an APA. A CT (or MRI) should be performed. If a clear adenoma is visualized, it is highly likely (>95% chance) that this is the culprit lesion. It is not unreasonable to proceed with unilateral surgery; however, at hospital centers that offer experienced and competent AVS, more certain localization can be confirmed with a subsequent AVS procedure.

Case 2

In contrast, E.H. has a marginally positive screen (ARR 19) with a PRA that is not fully suppressed (0.8 ng/mL/h). Taken together, these results neither confidently confirm nor exclude PA. It can be debated whether screening for PA should have ever been conducted; E.H. is >70 years old, has heart failure and resistant hypertension, and might be best served by empirically adjusting her antihypertensives to include an MR antagonist. Alternatively, if her physical status was considered to be high despite her comorbidities, screening could be repeated on another day. Proceeding directly to confirmatory testing should be considered with extreme caution since she has severe hypertension and heart disease, and sodium loading could severely exacerbate these problems. She is at high risk for cardiovascular complications during surgery, and given her normal potassium and other clinical characteristics, it is unlikely that she will have much clinical improvement if she does have an APA. Furthermore, her renal insufficiency places her at risk for a rise in serum creatinine and prolonged hyperkalemia postoperatively (40). Therefore, unless her screening studies on repeat testing confirm overt and severe PA, the most effective and safe decision would entail the use of MR antagonist therapy.

Individualized Approach to Her Evaluation

Counsel her about the process and the risks and benefits of each step. Salt loading might exacerbate her heart failure symptoms, and contrast agents can damage her kidneys. PA leads to more end-organ complications such as cardiac fibrosis, atrial fibrillation, and worsening heart and kidney failure. The issue of PA must be addressed, but she might benefit from chronic MR antagonist treatment, even if she does have an APA that might be cured with surgery. Her inclination towards surgery should be explored based on her personal preferences and her medical and surgical risks. She might express a strong desire to stop as many medications as possible and pursue AVS and surgery, but if not, a safe approach is to forego the rest of the evaluation and proceed directly to MR antagonist therapy.

CONCLUSIONS & FUTURE DIRECTIONS

Although, renin, potassium handling, and blood pressure, are valuable biomarkers of MR activity, there is a need for newer methods to objectively quantify MR activation. A new metric for MR activity that may have future potential is measurement of urinary exosomal excretion of ENaC subunits. Recent studies have demonstrated the ability to detect urinary exosomes containing ENaC and the ability of this assay to correlate with MR activity in PA (41,42). Future work to refine the measurement of urinary ENaC excretion and calibration to correlate these measures with MR activation may provide a unique method to assess individual aldosterone excess. Steroid biomarkers characteristic of APA, such as 18-oxo-cortisol, might be employed to exclude APA and obviate the need for imaging and AVS in carefully selected patients with PA (43). Finally, a new generation of potent and selective MR antagonists might provide similar blood pressure control as spironolactone and eplerenone but with a much lower risk of hyperkalemia, particularly in patients with impaired renal function. Consequently, the importance of PA, even in its evanescent forms, combined with the broader use of MR antagonists looms large as we navigate the Era of Personalized and Individualized Medicine.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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