Adrenal Venous Sampling in Primary Hyperaldosteronism

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Abstract Adrenal venous sampling (AVS) is used to distinguish unilateral from bilateral aldosterone hypersecretion as a cause of primary hyperaldosteronism (PHA). This distinction is critical because unilateral disease is treated, and often cured, by adrenalectomy, whereas bilateral hypersecretion should be managed medically. In this article, we review the epidemiology and etiologies of PHA, present screening guidelines for hypertensive patients with suspected PHA, assess the utility and pitfalls of cross-sectional imaging, and discuss the indications for and interpretation of AVS.

Keywords Primary hyperaldosteronism · Aldosterone-producing adenoma · Idiopathic hyperaldosteronism · Adrenal vein sampling · Adrenal venous sampling · Screening · Diagnostic imaging · Selectivity index · Laterality index

Introduction

Primary hyperaldosteronism (PHA) is a treatable, and possibly curable, etiology of secondary hypertension. The most common causes of PHA include aldosterone-producing adenoma (APA) and bilateral adrenal hyperplasia or idiopathic hyperaldosteronism (IHA). Less common causes of PHA include adrenocortical carcinoma, unilateral

hyperplasia, familial hyperaldosteronism, and ectopic aldosterone-secreting tumors.

APA, first described by Conn [1] in 1956, accounts for 30–35 % of cases of PHA, and IHA represents the majority of the remaining cases. Compared to IHA, patients with an APA generally have higher aldosterone secretion rates often manifested by more severe hypertension and hypokalemia [2, 3]. Although historical studies suggest a prevalence of PHA of <1 % among hypertensive patients, more recent studies note a prevalence of 5–13 % among all hypertensive patients [4–6, 7•, 8–15].

Precise determination of the etiology of hyperaldosteronism is necessary to guide operative intervention for APA or medical therapy for IHA. The ultimate treatment goal for either strategy is to prevent the morbidity and mortality from longstanding hypertension including renal insufficiency and cardiovascular pathology [10, 16–18]. Surgery for unilateral pathology corrects hyperaldosteronism and hypokalemia and improves blood pressure control in nearly all patients, with 35–60 % requiring no further antihypertensive agents [19–24]. The aldosteronoma resolution score (ARS) was developed to stratify the likelihood of normotension following adrenalectomy for APA. This scoring system accounts for the number of antihypertensives at the time of adrenalectomy (two points for two or fewer medications) and important clinical factors (one point for each favorable clinical feature: body mass index of ≤ 25 kg/m², duration of hypertension of <6 years, and female gender). A score of 1 or less predicts a 27 % likelihood of resolution, while a score greater than 3 predicts resolution in 75 % of cases [25].

Clinical Presentation

PHA should be suspected in patients with hypertension, unexplained hypokalemia, and metabolic alkalosis [17].

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Despite this classic description, less than half of patients with PHA are hypokalemic at the time of presentation, and hypokalemia is seen in <20 % of patients with bilateral hyperplasia [4, 15, 26]. Occasionally patients with PHA may present with hypokalemia and normal blood pressure [27].

Screening

Because APA can be a reversible cause of hypertension, screening for APA is recommended in hypertensive patients with hypokalemia, severe or resistant hypertension, and/or an adrenal incidentaloma [28]. More specific criteria for screening of hypertensive patients were developed by the Endocrine Society: hypertension and hypokalemia (either spontaneous or on low-dose diuretic therapy); severe hypertension (defined as systolic blood pressure >160 mmHg/diastolic blood pressure >100 mmHg, or hypertension refractory to three or more pharmacologic agents); patients with an incidental finding of an adrenal mass; patients with a family history of early onset hypertension or cerebral vascular accident under age 40 years; all patients with a first degree relative with PHA [7•].

Initial evaluation of this selected population includes an early morning, ambulatory biochemical assay of plasma aldosterone concentration (PAC) and plasma renin activity (PRA) or plasma renin concentration (PRC). For accurate interpretation of these studies, mineralocorticoid receptor antagonists such as spironolactone and eplerenone should be suspended for 6 weeks prior to testing. In normal subjects, the PRA is <1 ng/ml, and the PRC is undetectable. In patients with PHA, the PAC is generally elevated to >15 ng/dl, but the PAC/PRA ratio is a more sensitive indicator. A PAC/PRA ratio of >20 is suggestive of PHA, while some clinicians advocate utilizing a cutoff of 30 for greater specificity [29, 30]. One study of 434 hypertensive patients found that utilizing criteria of both a PAC >20 ng/dl and PAC/PRA ratio of >30 demonstrated a 90 % sensitivity and 91 % specificity for PHA [31].

Diagnostic Imaging

Once the diagnosis of PHA has been confirmed with biochemical testing, diagnostic imaging should be obtained as the first modality to differentiate APA from IHA and localize the lesion(s). Computed tomography (CT) is the recommended primary imaging modality [7•, 32]. CT may identify a unilateral lesion, bilateral lesions, bilateral hyperplasia, or less frequently unilateral hyperplasia. Patients with hyperplasia may also have normal-appearing adrenal glands [4]. Magnetic resonance imaging (MRI) may replace CT as the primary imaging modality for patients with a contraindication to ionizing radiation.

Despite technological advances and improved spatial resolution of cross-sectional imaging, CT and MRI are

limited diagnostic modalities for HPA since they provide only anatomic and not functional information. The presence or absence of adrenal lesions on cross-sectional imaging can demonstrate a significant amount of discordance with a functional test such as adrenal venous sampling (AVS). Retrospective reviews demonstrate that CT is accurate in only 50–53 % of patients and if utilized as the sole lateralization study would have incorrectly excluded 22 % from adrenalectomy and lead to unnecessary adrenalectomy in 25 % [33–35]. Another retrospective study of 71 patients found a sensitivity of 87 % with a specificity of 71 % for the diagnosis of APA on CT alone [36]. A systematic review of 950 patients across 38 studies found CT and MRI to be discordant with AVS localization in 37.8 % of patients, and, if operative intervention had been based on imaging alone, would have led to inappropriate adrenalectomy in 18.5 % and inappropriate medical management in 19.1 % of cases [37•]. Additionally, the absence of a mass on CT does not exclude APA; even with thin helical collimation, CT may miss lesions <3 mm in diameter [38, 39].

Indications for AVS

AVS was introduced in the 1960s to differentiate unilateral from bilateral aldosterone hypersecretion [40]. AVS remained the primary diagnostic modality for 2 decades until cross-sectional imaging with CT and MRI became more widely available [41]. Additionally, CT and/or MRI can aid in operative planning for patients who will eventually require adrenalectomy following confirmatory lateralization by AVS.

Given the limitations of CT and MRI in PHA, the Endocrine Society recommends AVS in all patients with biochemical laboratory findings of PHA who are candidates for adrenalectomy to determine whether the etiology is bilateral or unilateral [7•]. Most clinicians recommend selective AVS for all patients over the age of 40. Patients under the age of 40 with a solitary unilateral lesion greater than one centimeter by CT or MRI do not necessarily require AVS [4, 42]. This selective approach is justified by the increasing incidence of adrenal hyperplasia with age. Others recommend selective AVS based on the biochemical characteristics of good-risk operative candidates—a serum potassium level of <3.5 mmol/l or an estimated glomerular filtration rate of >100 ml/min with at least an 8-mm low-attenuation adrenal mass by CT was 53 % sensitive and 100 % specific for an APA [43].

Adrenal Venous Sampling

Procedure

There is not a standardized approach to AVS for HPA; however, certain requirements must be met to ensure an

accurate interpretation of the results. The inferior vena cava (IVC) and bilateral adrenal veins are accessed percutaneously via the common femoral vein by the specialist. The adrenal veins may be cannulated for specimen collection either simultaneously or sequentially [44, 45]. Sequential adrenal venous cannulation is more common, being used by more than half of performing centers with similar success as the more technically challenging simultaneous access technique [44, 46•].

Aldosterone and cortisol levels are measured in both adrenal veins and the IVC, which serves as a baseline comparator. The specimens are assayed with serial dilution from 1:1 to 1:10 and 1:50 [2, 33, 47, 48]. Although early technical guides to the procedure recommended duplicate collection of all samples, more recent data demonstrate no benefit to duplicate specimens but longer procedure time and higher cost [49].

In experienced hands, AVS is a low-risk procedure with a complication rate of <2.5 %. The most common complication is a hematoma at the femoral venous access site, occurring in 2 % of patients undergoing AVS. Fortunately, adrenal vein dissection, adrenal rupture, and adrenal hemorrhage are rare events [33, 35, 47, 50, 51].

Synthetic Adrenocorticotrophic Hormone (ACTH) Stimulation

The purposes of ACTH stimulation during AVS are to minimize the stress-induced fluctuations in aldosterone secretion due to sequentially cannulated adrenal veins, to maximize the gradient in cortisol from the adrenal vein to the IVC for confirmation of successful cannulation, and to maximize aldosterone secretion from an APA [33]. Some studies suggest that synthetic ACTH stimulation does not increase the diagnostic accuracy of AVS [50, 52, 53], while others recommend either a bolus dose or continuous infusion for improved technical success, selectivity, and lateralization rates [45, 51, 54, 55]. One recent retrospective review of 220 AVS procedures found an increase in technical success from 44 to 82 % with the addition of ACTH stimulation [56]. A study comparing bolus dose ACTH to continuous infusion found no difference in success rate by infusion strategy [57•].

Selectivity Index (SI)

The SI measures the adequacy of the cannulation of the adrenal veins and is the ratio between cortisol levels in the respective adrenal vein and in the IVC. Because of the small size of the adrenal veins, blood sampled at the time of AVS is often obtained near the orifice of the vein and may be diluted. This dilution as well as difficulty cannulating the vein introduce error in the measurement of

adrenal vein aldosterone levels, which most often occurs in the case of the right adrenal vein. The simultaneous measurement of cortisol concentrations allows for correction of this dilution by providing a normalizing factor. The success of cannulation determined by SI differs for non-stimulated and ACTH-stimulated AVS samples: without stimulation, an SI of greater than three confirms cannulation (though some centers report an SI as low as 1.1), and with ACTH-stimulation, an SI of more than five is considered adequate [47, 51, 58, 59•]. Some clinicians advocate the addition of catecholamine sampling for confirmation of both selectivity and laterality, but this method is not commonly used and requires further validation [60–62].

Successful biochemical assay generally depends upon the ability to selectively cannulate the right adrenal vein, which is technically more challenging than the left adrenal vein due to its small length and near perpendicular take-off from the IVC. Experienced interventionalists obtain right adrenal venous cannulation in 81–96 % of patients [33, 37•, 38, 63]. Lower volume centers or less experienced clinicians may have lower success rates of 40–80 % [11, 50, 64]. Intraprocedural measurement of cortisol to determine SI can significantly increase the success rate of AVS to 85–90 %, especially in lower volume centers, but requires up to 30 min of additional procedure time [65–68]. CT venography or cone beam CT during AVS is an additional adjunct that can improve right adrenal vein cannulation to up to 98 %, but is not widely available [54, 69–71]. A systematic, multidisciplinary approach to the collection and interpretation of adrenal venous samples also improves yield [72].

Laterality Index

Once successful cannulation has been confirmed, localization of aldosterone hypersecretion via the laterality index is calculated by comparing the aldosterone-to-cortisol ratio between the left and right adrenal veins. It is important to use the aldosterone-to-cortisol ratio in order to control for dilutional effects, particularly of the inferior phrenic vein into the left adrenal vein. When comparing the aldosterone-to-cortisol ratios of the dominant to non-dominant side, a threshold value of four is the most commonly used criteria to determine hypersecretion from one gland [46•, 59•, 66], though some studies report criteria as low as two and up to five as a cutoff value [4, 33, 50, 73]. Using a laterality index of four as the threshold for APA yields a sensitivity of 81–98 % and a specificity of 94–100 % [33, 50, 52, 59•, 64, 74–78].

Additional confirmatory biochemical assays may be useful adjuncts to the laterality index. Contralateral suppression of aldosterone secretion may be evident in the setting of an APA (i.e., the nondominant adrenal vein

aldosterone-to-cortisol ratio may be less than the IVC aldosterone-to-cortisol ratio). This non-dominant aldosterone suppression can be used to confirm contralateral APA in 93 % of cases [33]. Recently, the measurement of 18-oxocortisol levels in adrenal vein samples has shown promise in localizing APA, but requires further study [79].

Conclusions

AVS is used to distinguish unilateral from bilateral aldosterone hypersecretion as a cause of PHA. Patients treated with adrenalectomy for APA or unilateral aldosterone hypersecretion have significantly improved hypokalemia and blood pressure levels. Following biochemical confirmation of PHA by a PAC/PRA ratio of >20, lateralization should proceed with cross-sectional imaging by CT. Select good-risk surgical candidates under 40 years of age with a unilateral adenoma of low attenuation by CT may proceed directly to adrenalectomy. However, all others should undergo AVS with ACTH stimulation for a functional evaluation of lateralization. Cannulation success rates may be increased with intraprocedural cortisol assays or CT guidance. With the use of ACTH stimulation, a selectivity index of three to five should be used to confirm adrenal vein cannulation, while a laterality index of 4 or greater is indicative of unilateral disease. Results should ideally be interpreted by a multidisciplinary team.

Compliance with Ethics Guidelines Conflict of Interest Abbey L. Fingeret and James A. Lee declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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