Subtyping of Patients with Primary Aldosteronism: An Update

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ABSTRACT

Primary aldosteronism (PA) comprises two main subtypes: unilateral aldosteronism, mainly caused by aldosterone-producing adenoma; and bilateral adrenal hyperplasia. Establishing the correct subtype in patients with PA is indispensible for choice of treatment. In addition to established methods, alternative tests are evolving for subtyping. Computed tomography (CT) and adrenal venous sampling (AVS) are currently recommended in the guidelines for the diagnostic work-up of patients with PA. CT cannot be used as a stand-alone test for subtyping because of its limited accuracy but may be used in combination with other tests such as AVS or functional imaging. Nevertheless CT remains mandatory to exclude adrenocortical carcinoma. AVS provides the most accurate test to detect excessive secretion of aldosterone from an adrenal mass but has several practical limitations and disadvantages. Therefore, alternative non-invasive and patient-friendly methods are required to determine the need for adrenalectomy. Functional imaging with specific molecular positron emission tomographic ligands is a potential alternative method that may replace AVS for subclassifying patients with PA. The results of preliminary studies of ^{11}C-metomidate are promising but ligands incorporating radionuclides with longer half-lives that selectively bind to CYP11B2 are needed. Steroid profiling provides another method for subtyping and selecting patients for adrenalectomy, but this technology is in its infancy and prospective outcome-based studies are required to determine if this technique may provide an alternative to AVS.

Introduction

Among patients with primary aldosteronism (PA) excessive aldosterone secretion from a single adrenal may be caused by a unilateral adrenocortical aldosterone-producing adenoma (APA) (~40 % of all cases of PA) or more rarely by unilateral hyperplasia. Bilateral aldosterone excess results from micronodular or macronodular hyperplasia and is designated as bilateral adrenal hyperplasia (BAH) (~60 % of all cases of PA) [1, 2]. Due to differential expression of steroidogenic enzymes there can be variable secretion of steroids other than aldosterone. In particular, APAs often secrete higher amounts of corticosterone, deoxycorticosterone, and the hybrid steroids, 18-hydroxycortisol and 18-oxocortisol, compared to adrenals of BAH patients [3].

Although the concept of the distinct nature of both subtypes is controversial, definitive and reliable distinction of unilateral and bilateral disease is imperative for therapeutic management of patients with PA. Unilateral disease is usually treated by adrenalectomy (ADX) whereas bilateral disease is treated using mineralocorticoid receptor antagonists. Therefore the primary goal of adequate subtyping is not just to determine the correct diagnosis but to select correctly the patients with unilateral disease who can be expected to benefit from surgery (i. e., those with the best chance of complete clinical and biochemical remission). As a histological diagnosis is only possible for the removed adrenal, the diagnosis in the other gland remains obscure.

▶ Table 1 Advantages and disadvantages of the methods for subtyping of patients with primary aldosteronism.

	Advantages	Disadvantages
Computed tomography	– widely available – non-invasive – high spatial resolution – relatively cheap	– not specific: anatomical information – limited sensitivity – radiation exposure moderate – contraindication if contrast allergy
Adrenal venous sampling	– functional test – highly predictive of outcome	– limited availability – laborious and technically demanding – not standardized procedure – radiation exposure significant – contraindication if contrast allergy
Metomidate imaging	– proof of principle – specific binding to CYP11B2 – non-invasive technique	– limited availability (cyclotron needed) – radiation exposure moderate – lower selectivity of binding to CYP11B2 than to CYP11B1 – very limited data available
Steroid profiling	– non-invasive – high specificity (LC-MS/MS) – multiple hormones (one assay) – convenient: one blood sample	– LC-MS/MS: expensive – LC-MS/MS expertise required – no prospective data available – interpretation of results: expertise needed

LC-MS/MS: Liquid chromatography with tandem mass spectrometry.

A conclusive final diagnosis of unilateral disease is feasible when the post-surgical follow-up data show complete biochemical cure [4]. Patients with bilateral disease (BAH) will not be intentionally operated and therefore a conclusive diagnosis can never be established for this group. A glimpse into the histopathology of BAH may be provided from patients operated for supposedly unilateral disease who subsequently show persistent aldosteronism following ADX. In addition, some patients with BAH and 'asymmetric' aldosterone secretion may also undergo ADX as a consequence of their severe phenotype and a last resort for treatment [5].

There are several methods potentially useful for differentiating unilateral (APA) from bilateral disease (BAH): 1. adrenal computed tomography (CT) or magnetic resonance imaging (MRI); 2. adrenal venous sampling (AVS); 3. targeted functional imaging using a radiolabeled metomidate PET tracer; and 4. measurements of peripheral venous steroid profiles. Currently AVS is the only method recommended according to the Endocrine Society guideline to distinguish both subtypes and for selecting patients eligible for ADX [6]. Functional imaging and steroid profiling are evolving and promising methods but their true value for reliable subtyping requires validation. In this article, we summarize these four methods and review their pro's and con's for their role in subtyping patients with PA.

Anatomical Imaging by CT and MRI

Starting in the 1970's when CT became available, this anatomic imaging modality enjoyed continuous use for locating adrenal adenomas in patients with a biochemical diagnosis of PA. CT is relatively inexpensive and non-invasive and provides high spatial resolution for imaging an adrenal mass. Subsequently MRI has provided an alternative anatomical imaging modality but apart from lack of radiation exposure carries no advantages over CT for subtyping PA patients [6].

Multidetector CT scanning has several serious drawbacks for selecting PA patients for ADX (▶ **Table 1**). First, CT (and also MRI) provide an anatomical and not a functional diagnosis, so that these imaging modalities cannot establish whether an adrenal adenoma is actually the source of any excessive aldosterone production. This is important since non-functional adenomas are not uncommon, particularly with advancing age when prevalences increase to 10 % in patients older than 50 years [7]. For this reason CT suffers from limited specificity. Diagnostic sensitivity remains also far from optimal. Although CT is generally reported to be unable to detect microadenomas (< 1 cm) with any degree of certainty, modern CT scans using thinner slices may detect microadenomas of less than 1 cm. Many APAs have a size of 1–2 cm but it has also been shown that adenomas of less than 1 cm account for nearly 25–50 % of all APAs [8–9]. Thus, a substantial number of patients with APAs who might be cured by ADX can be missed by CT.

The value of CT for subtype diagnosis has been addressed in numerous studies, but most have been retrospective with poorly standardized clinical and biochemical follow-up criteria to classify outcomes. Additionally, most studies used AVS as the reference standard. A systematic review showed that in nearly 38 % of PA patients, results from CT or MRI indicated the incorrect APA or BAH subtype and would have resulted in inappropriate treatment [10]. Nevertheless, this high proportion was obtained under the assumption that AVS provides the perfectly correct subtype classification.

As outlined later, this assumption is not fully justified. Nevertheless, in contrast to the outlined retrospective studies, a recent prospective study showed persistent PA in 9 of 46 patients (20 %) who underwent ADX based on CT scan [11]. Volumetric analysis of the adrenal glands demonstrated that mean adrenal gland volume in APA patients was not significantly different from BAH adrenal volume [12]. Moreover, volumes of the contralateral adrenal in APA patients were significantly larger in comparison to non-PA control adrenals.

Despite all above considerations, CT should still be carried out as the initial imaging test in PA patients for two reasons: a CT scan helps to rule out the occasional adrenocortical carcinoma that produces aldosterone [6]. Second, contrast enhanced CT provides useful information on the venous anatomy, which facilitates cannulation in those patients who need to undergo AVS [13, 14].

Adrenal Venous Sampling

Adrenal venous sampling (AVS) is recommended by the Endocrine Society guideline to distinguish APA and BAH subtypes [6]. Except for young patients (< 35 years) with clear-cut PA and an unilateral adenoma, all patients should undergo AVS to select those amenable for unilateral ADX. AVS is a functional test as opposed to CT and the concept that this technique is able to establish the source of aldosterone excess is intuitively appealing. It is not surprising that use of AVS has shown a steep increase in major referral centers worldwide. This technique involves selective cannulation of the adrenal veins and one peripheral vein for measurements of plasma aldosterone and cortisol concentrations [15–17]. The technical success rates of correct adrenal vein cannulation is over 90 % in hands of experienced radiologists and the reported complication rate is less than 2.5 % [6].

Accurate placement of catheters is essential for reliable assessment of adrenal aldosterone secretion. However, selective cannulation, particularly of the right adrenal vein, is notoriously difficult and complicated by considerable anatomic variation [14]. Commonly, the ratio of plasma concentrations of cortisol in the adrenal vein (AV) to a peripheral vein (PV) is used to verify and document accurate catheter placement. This ratio, also called selectivity index (SI), is calculated as cortisol AV/PV. An additional purpose of measuring cortisol is to correct for dilution from non-adrenal blood contamination. There are several drawbacks of using cortisol for these purposes. First, in comparison to aldosterone, cortisol is protein-bound (transcortin) and has a long circulating half-life. Thus, the step-ups in peripheral to adrenal vein cortisol concentrations are relatively modest and subject to interpretative error. An additional disadvantage is that some APAs can co-secrete cortisol [18, 19]. Potentially this may further invalidate the use of cortisol to determine the correct catheter position. Finally, cortisol is subject to pulsatile stress-mediated increments, thus impairing its usefulness for correct catheter positioning.

To minimize stress induced variations in cortisol secretion, cosyntropin stimulation is used at many centers [20]. There are two advantages of cosyntropin stimulation: it increases the selectivity index and thereby the technical success rates of AVS and it obviates the need for simultaneous adrenal vein blood sampling. However, cosyntropin stimulation makes the procedure more complex, there is no consensus about the optimal stimulation protocol and in terms of outcome it is still controversial whether its use affects the accuracy of subtyping [16, 17].

Since 2015 several alternatives to cortisol have been identified to provide improved assessment of selectivity of adrenal vein sampling. Measurements of plasma metanephrine, the O-methylated metabolite of epinephrine, in particular show much larger step-ups from peripheral to adrenal venous plasma than cortisol and in many cases have clearly indicated selective sampling when measurements of cortisol suggested incorrect catheter placement [20]. Measurements of metanephrine is also particularly useful for APAs that cosecrete cortisol [21, 22]. Since metanephrine is produced continuously within adrenal medullary cells from epinephrine leaking from chromaffin storage granules, a process that is independent of catecholamines secretion, these measurements should also not be affected by stress. Several steroids, including dehydroepiandrosterone, androstenedione, 11-deoxycortisol, and 17-hydroxyprogesterone also produce much larger step-ups from peripheral to adrenal venous plasma than cortisol and as such also provide superior biomarkers than cortisol to assess the selectivity of adrenal vein sampling [23–25]. It is time to give up on use of cortisol as an indicator of adrenal vein sampling selectivity. Apart from metanephrine and the four steroids outlined above, almost all steroids produced as part of the adrenal biosynthetic backbone produce higher selectivity indices than cortisol and are thereby also likely to offer superior assessments of correct catheter placement than cortisol [23].

Lateralization of aldosterone hypersecretion is currently commonly assessed by calculation of the lateralization index (LI) using the higher ratio of aldosterone to cortisol in one vein compared to the other. The cut-off level of the LI depends on whether cosyntropin stimulation is used or not but most centers use an LI of > 4 to diagnose unilateral PA and of < 3 to diagnose bilateral PA [16]. In patients with an LI between 3.0–4.0, lateralization can be diagnosed when the contralateral suppression index (defined as the ratio of aldosterone/cortisol between the non-dominant adrenal vein and a peripheral vein) is ≤ 1.0. Many centers use the contralateral suppression index as an extra criterion for lateralization but there are no outcome studies to show unequivocally that contralateral suppression is a useful diagnostic criterion [16, 20].

There are several limitations to the AVS technique that need to be considered (▶ **Table 1**). It is a complex, technically demanding, time consuming and an invasive technique that is not convenient for patients or medical staff [16, 17]. Invasiveness includes not only catheter manipulations but also exposure to radiation, although this depends on the proficiency of the interventional radiologist. More importantly, the procedure is not standardized and this applies in particular to the use of the cut-off levels to determine selectivity and lateralization. Lack of medical staff with the necessary technical expertise is one of the main reasons why AVS is insufficiently available to accommodate all patients that should undergo AVS according to the Endocrine Society guideline. Moreover, currently only a small fraction of hypertensive patients with PA are identified and if all patients with PA were actually identified through hypertensive population screening it is highly unlikely that any center could cope with the subsequent demand for AVS.

A major consideration to all the above concerns the accuracy of AVS to establish the correct subtype of PA. The increasing use has gradually led to the contention that AVS is the 'gold' standard test but AVS has never been scrutinized according to the recommendations of the GRADE consortium [26]. Under conditions in which no 'gold' standard test is available, a prespecified outcome representing the benefits for the patients should be determined. In cases of patients who undergo ADX for unilateral disease (APA) the biochemical and clinical remission rates reflect the endpoints that determine the long-term outcome for patients. The many published studies that reported on the diagnostic accuracy of AVS have a retrospective design with an inherent potential for bias. In addition, most studies suffered from incomplete or non-standardized follow-up data to assess outcome. Even more importantly, management of patients in comparative studies was determined by the result of AVS. That AVS is not a 'gold' standard test can also be derived from recently published data. An international multicenter study using standardized follow-up data showed that the biochemical cure of 94 % (range: 83–100) was lower than the 96–100 % as published in a recent systematic review [27]. A recently published randomized controlled outcome trial comparing management based on AVS versus CT could not establish a better clinical and biochemical outcome after one year of follow-up [11]. Although AVS is currently still the best performing test for subtyping of patients with PA, further and better designed studies are required to determine its true value for selecting patients with PA for ADX.

Functional Imaging Using Radiolabeled Metomidate PET Tracers

Prior to the development of new radiolabeled tracers for molecular imaging, one of the first agents used for functional imaging of APAs was the norcholesterol derivative, ^{131}I-6β-iodomethyl-19-norcholesterol, also named NP-59 [28]. One retrospective study suggested that NP-59 might be helpful as functional imaging agent to select patients for ADX [29]. However, this was a small group of selected patients with PA in whom CT and AVS were inconclusive. This technique has major disadvantages that explain why this technique has been abandoned for subtyping patients with PA: it is time consuming, it is associated with a high radiation exposure (30 mSv) to the adrenal glands, the tracer is not widely available and most importantly, uptake of the tracer is poor in small APAs and the spatial resolution to detect these small adenomas is insufficient, even if SPECT/CT imaging is used.

In more recent years, an extensive search has evolved for agents suitable for highly specific molecular PET imaging of adrenocortical tissue. One of the first agents was ^{11}C-metomidate that has the capacity to bind with high specificity and avidity to the enzymes exclusively expressed in the adrenal cortex and involved in steroid synthesis, including CYP11B1 and CYP11B2 [30]. However ^{11}C-metomidate has a low selectivity for CYP11B2 over CYP11B1. This agent was shown to be potent for differentiating adrenocortical from non-adrenocortical tissue and has been used in several studies to identify the adrenal lesion [31].

Several studies have assessed the diagnostic value of ^{11}C-metomidate in patients with PA, but most studies were not designed to evaluate its role in subtyping [32]. One study addressed the value ^{11}C-metomidate PET/CT in patients with PA in a head-to-head design using AVS as the reference test [33]. The sensitivity and specificity of ^{11}C-metomidate PET/CT, employing a ratio of tumor SUVmax (standardized uptake value) to normal adrenal background SUV of > 1.25 for diagnosing APA, was 76 % and 87 % respectively. This small series of patients is promising but the applicability of this tracer is limited because one needs an on-site cyclotron due to the short 20-min half-life of ^{11}C. Radioisotopes with a longer half-life are more desirable. For subtyping of patients with PA, one would need a molecular tracer capable of binding specifically to CYP11B2 (aldosterone synthase). This is not only a crucial enzyme in aldosterone synthesis but its expression in smaller APAs is increased as compared to CYP11B1 (▶ **Table 1**). Potential fluorine-18 labeling of such compounds will make them of practical use for PET scanning. Several new promising compounds for this purpose are currently under investigation in in vitro and in animal studies. A preliminary report of such compound (CDP2230) showed a more than 15 times higher selectivity for CYP11B2 over CYP11B1 compared to ^{11}C-metomidate [34]. These data suggest that this compound has the potential to become a promising new agent for subtyping patients with PA.

Steroid Measurements

A new emerging method for subtyping of patients with PA involves measurements of additional steroids to aldosterone, including the hybrid steroids 18-hydroxycortisol and 18-oxocortisol. This has been fostered by the development of liquid chromatography with tandem mass spectrometry (LC-MS/MS) technology [35]. This technology is not only more accurate than immunoassays but also enables simultaneous measurements of multiple steroids in a single sample [23].

Several studies have examined whether adrenals from APAs and BAH are associated with a specific steroid signature as measured in urine or in adrenal venous plasma while more recently a few studies addressed the value of steroid profiling in a peripheral venous blood sample for subtyping. Some studies focused on one hormone, others used a panel of steroids.

The first evidence that patients with APAs differed from patients with BAH in steroid secretion came from the group of Biglieri in 1979, showing that the use of a peripheral venous plasma 18-hydroxycorticosterone level of > 100 ng/dl was highly predictive for an APA [36]. This could be confirmed several years later by other groups [37, 38]. More recently the basis for this finding was provided by a small study reporting a nearly 3-fold higher concentration of 18-hydroxycorticosterone in adrenal veins draining from APAs than in those from BAH [39]. The additional finding of a high concordance between the 18-hydroxycorticosterone/cortisol ratio and the aldosterone/cortisol ratio in the APA patients indicated however that measurement of 18-hydroxycorticosterone was not more useful for lateralization than aldosterone itself. Given the lack of larger prospective studies, measurement of 18-hydroxycorticosterone in adrenal or peripheral venous plasma has not made its way into routine clinical practice and cannot be recommended for selecting patients for ADX.

Most recently we carried out a retrospective study in a large group of 216 patients with PA, comprising 126 patients with an APA and 90 patients with BAH [40]. Aldosterone, 18-oxocortisol and 18-hydroxycortisol were all higher in adrenal venous samples from APAs compared to BAH. The hybrid steroids were not overly helpful for lateralization as they showed lateralization in only 76 % (n = 90) (18-oxocortisol) and 35 % (18-hydroxycortisol) of cases where lateralization was apparent using aldosterone. Another retrospective study confirmed also higher 18-oxocortisol levels in adrenal blood from APAs than BAH but found no evidence that the use of the 18-oxocortisol/cortisol ratio was superior to the aldosterone/cortisol ratio for subtyping patients with PA [41].

As far back as 1992, Ulick and co-workers established that patients with APA showed higher urinary excretion of the hybrid steroids, 18-hydroxycortisol and 18-oxocortisol, than patients with BAH [42]. A later study that assessed both plasma and urinary steroids came to a similar conclusion although they noticed considerable overlap between both groups [38]. Although the sensitivity of the urinary 18-hydroxycortisol excretion for the APA diagnosis was only 30 %, an excretion rate of > 510 µg/day was diagnostic for APA, suggesting that such patients with proven PA and a unilateral adenoma on CT could be sent straight for ADX.

There are a few retrospective studies that aimed to evaluate the role of steroids in a peripheral venous blood sample. Satoh et al. reported on 18-hydroxycortisol and 18-oxocortisol levels measured in peripheral venous samples using LC-MS/MS [43]. They established much higher plasma levels of both steroids in patients with APA than in those with BAH with relatively stronger increments for 18-oxocortisol (12.5-fold) than for 18-hydroxycortisol (2.5-fold). Plasma 18-oxocortisol displayed a sensitivity and specificity of 83 % and 99 % using a cut-off level of 4.7 ng/dl. All patients with an APA showed 18-oxocortisol levels of > 1.2 ng/dl while no patient with BAH showed a level of > 6.1 ng/dl. If combined with plasma aldosterone concentration, 84 % of the patients with APA with a unilateral adenoma had a plasma aldosterone concentration of > 32.7 ng/dl and a plasma 18-oxocortisol concentration of > 6.1 ng/dl. These results suggest that in nearly 50 % of all patients with PA, AVS could be circumvented because these patients could have been sent straight for ADX.

The value of a peripheral venous steroid profile for predicting the correct subtypes (APA vs. BAH) was reported in a recent large retrospective study of 216 patients with PA [40]. In 80 % (172/216) of patients it was possible to classify the PA subtype correctly (based on post-ADX outcome as reference method) using a panel of 12 steroids (aldosterone, 18-oxocortisol, 18-hydroxycortisol, 11-dexycortisol, 21-deoxycortisol, corticosterone, 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, androstenedione, DHEA, and DHEAS). This classification, shows promise but requires further improvements. It should be noted, however, that that study used an AVS procedure with cosyntropin stimulation in some patients, thus potentially introducing bias.

In a related study, we measured a panel of 15 steroids in 79 patients with PA who were genotyped for mutations in the KCNJ5, ATP1A1, ATP2B3, and CACNA1D genes [44]. A remarkable finding was that the APAs with KCNJ5 mutations showed the highest peripheral plasma levels of 18-oxocortisol compared with all other mutations and the wild-type group. A subpanel of 7 steroids (aldosterone, 18-oxocortisol, 18-hydroxycortisol, 11-deoxycorticosterone, corticosterone, cortisol, and 21-deoxycortisol) measured in peripheral venous plasma correctly predicted the genotype in 73 of 79 patients with APAs (92 %). In 26/27 patients the presence of a somatic KCNJ5 mutation could be reliably predicted by the venous steroid profile. If validated this indicates that measurement of such a panel of 7 steroids may circumvent the need for AVS in patients with BAH because only patients with APA would require AVS to determine which adrenal gland overproduces aldosterone for selecting for ADX. The relatively small size and the retrospective nature of this study precludes any definite conclusions until these results are confirmed by a larger prospective study with standardized follow-up for outcome to verify the final subtype diagnosis.

Conclusions and Perspectives

Of the four discussed methods, CT and AVS are recommended for the diagnostic work-up of patients with PA. CT with its limited sensitivity and specificity cannot be used as a stand-alone test but only in combination with other techniques such as AVS or functional imaging (PET scanning). CT scanning is nonetheless mandatory in every patient to exclude a potential adrenocortical carcinoma. AVS is a highly attractive test because it tests the functionality of an adrenal mass, even if small. This technique has, however, several limitations and disadvantages, urging the development and investigation of alternative non-invasive patient-friendly methods to determine which patients should be sent for ADX. Functional imaging with highly specific molecular PET ligands is a potentially promising method that may replace AVS in some or even all patients. Although the results of preliminary studies of ^{11}C-metomidate are encouraging, more specific and fluorinated ligands that selectively bind to CYP11B2 are needed. Steroid profiling as a method for subtyping and selecting patients for ADX is still in its infancy and more prospective outcome-based studies are required to see if this technique is a better alternative to AVS.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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