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New Advances in the Diagnostic Workup of Primary Aldosteronism

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Primary aldosteronism is an important and common cause of hypertension that carries a high burden of morbidity. Outcomes, however, are excellent if diagnosed and treated appropriately. The diagnostic workup for primary aldosteronism is complex and comprises three steps: (1) screening, (2) confirmatory testing, and (3) subtype differentiation. In this review, we discuss recent advances in the diagnostic workup for primary aldosteronism. The development of accurate mass spectroscopy–based assays for measuring aldosterone will lead to improved confidence in all diagnostic aspects involving measurement of aldosterone, and accurate measurement of angiotensin II may soon advance us beyond the measurement of renin. We now have a greater understanding of hormonal influences on the aldosterone/renin ratio, which are particularly important when screening premenopausal women or those taking estrogen-containing preparations. Confirmatory testing is important, but there are limitations to the commonly used methods that have recently become more apparent, with new approaches offering a way forward. Adrenal venous sampling (AVS) is a challenging procedure but is important for deciding on treatment options. Success rates may be improved by the use of Synacthen stimulation and of rapid intraprocedural measurement of cortisol. Better understanding of AVS interpretation criteria allows improved prognostication and aids treatment decisions. The use of labeled metomidate positron emission tomography computed tomography scanning may also offer an alternative to AVS in some units. Although the diagnostic approach to patients with primary aldosteronism remains a complex multistep process in which attention to detail is important, recent advances will improve patient care and outcomes.

Freeform/Key Words: primary aldosteronism, adrenal vein sampling, alodsterone producing adenoma

Primary aldosteronism is now recognized as the most common secondary endocrine cause of hypertension, with a prevalence exceeding 10% in patients assessed at specialist hypertension centers [1, 2]. A growing body of research also suggests that primary aldosteronism has greater deleterious cardiovascular and renal consequences in comparison with essential hypertension [3–5]. It is for these reasons that the diagnostic workup for patients with primary aldosteronism has assumed increasing importance in recent years. The recently updated Endocrine Society Guidelines [6] outline the consensus approach to diagnosis, a multistep process consisting of case detection and screening, followed by a confirmation step in most patients, and then subtype differentiation in subjects who could be considered candidates for surgical treatment if a unilateral lesion were to be found. Aspects of the diagnostic process remain controversial, and research continues to be published. In this review, we will discuss recent advances of relevance to clinicians involved in investigation and management of patients with primary aldosteronism, including less well-established

Abbreviations: ACTH, adrenocorticotropic hormone; ARB, angiotensin II receptor blocker; ARR, aldosterone/renin ratio; AVS, adrenal venous sampling; CT, computed tomography; DRC, direct renin concentration; FST, fludrocortisone suppression testing; LI, lateralization index; PET, positron emission tomography; PRA, plasma renin activity; RST, recumbent saline suppression test.

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aspects and some that are still on the horizon in terms of possible introduction to clinical practice.

1. Search Methods

We conducted PubMed searches from 2010 onwards using variations of the following search string:

primary aldosteronism AND
(adrenal venous sampling OR
fludrocortisone suppression test OR
saline suppression test OR
aldosterone/renin ratio OR
diagnosis OR
metomidate OR
CT OR
lateralisation index OR
contralateral suppression)

This identified a large number of publications that were then reviewed for content. Additional relevant publications were identified from references included in the publications from the initial search.

2. Case Detection and Screening for Primary Aldosteronism

Case detection for primary aldosteronism in the modern era relies on assessment of the aldosterone/renin ratio (ARR). This was introduced by Hiramitsu *et al.* [7], and its application as a screening test in the wider hypertensive population is in part responsible for the subsequent marked rise in recognition of this condition in normokalemic (as well as hypokalemic) individuals [8–11].

The question as to who should be screened for primary aldosteronism is a controversial one. Although a very high prevalence of primary aldosteronism in drug-resistant hypertension is well-established, screening is much easier in untreated hypertensive patients because it avoids the confounding effects of antihypertensive medications. Additionally, it is very clear from 2follow-up studies of treated patients that treatment outcomes are better in subjects with a shorter duration of hypertension and milder disease [12–14]. Some would therefore argue that all patients with hypertension should be screened, and preferably at an early stage. The wider application of screening has implications for the resources required to further investigate and manage patients with primary aldosteronism, particularly important for the highly specialized step of adrenal vein sampling and for adrenal surgery. Where it is not possible or desirable to proceed to adrenal vein sampling or adrenalectomy, empiric treatment with mineralocorticoid receptor antagonists is a reasonable approach that may ameliorate some concerns.

Regardless of potential concerns about resource limitations, current screening rates in nonspecialist centers appear to be very low. A recent survey in Italy and Germany found that only 7%–8% of general practitioners ordered aldosterone and renin measurements, and the prevalence of diagnosed primary aldosteronism was only 1% of hypertensive patients [15, 16]. The optimal approach to improving the rate of screening for primary aldosteronism is not clear, but increasing awareness among general practitioners and primary care physicians who are likely to be the first contact for hypertensive patients is probably the most important factor. Easy to use guidelines and accessible tools such as diagnostic algorithms might also be helpful.

A. Hormone Measurement Issues

Assessment of the ARR requires accurate biochemical measurement of both aldosterone and renin as well as controlling for the many factors that may influence the ratio, potentially causing

false-negative or false-positive test results. The quality of the assays used is therefore of major importance in the screening process.

Accurate measurement of aldosterone is relatively challenging because of its low circulating concentration in comparison with other steroid hormones such as cortisol. Aldosterone measurement is most commonly performed by radioimmunoassay, pioneered many years ago [17], though this has been replaced by automated chemiluminescent assays in some centers [18]. Substantial variability in results from aldosterone radioimmunoassays have been demonstrated however, and chemiluminescent assays are likely to have similar issues [19]. Accurate aldosterone measurement is vital not only in case detection and confirmatory testing, but also during adrenal venous sampling (AVS), when very high aldosterone levels may require dilution. Ideally, an assay method should have excellent specificity and sensitivity in both circumstances, and the recent development of accurate methods of measuring aldosterone via high-performance liquid chromatography and tandem mass spectrometry offers this advantage (among others) [19, 20]. This method can now be considered the gold standard in aldosterone measurement, analogously to how it has overtaken other approaches for most human steroids [21]. Advances in semiautomation for the platform have additionally made it practical and economical (after initial set-up costs) for high-volume clinical applications. High-performance liquid chromatography and tandem mass spectrometry measurement should therefore be the target measurement method in reference laboratories involved in the diagnosis of primary aldosteronism, provided the initial cost outlay can be overcome and that robust quality control is maintained. Radioimmunoassays and/or chemiluminescent techniques, however, will likely continue to have a place in wider community-based screening for cost and resource reasons.

The current situation with renin measurement is less clear. Historically, renin has been assayed by the labor-intensive method of measuring plasma renin activity (PRA), which measures enzymatic activity (the amount of angiotensin I generated from its endogenous substrate, angiotensinogen, over a period of time). This has now been replaced in most laboratories by the more cost- and time-effective methods of measuring direct renin concentration (DRC) by automated immunometric approaches. Accuracy at low renin levels using these methods is variable, however, and because renin is the denominator in the ARR, small variations in renin measurement can cause large changes in the ratio. Furthermore, in many situations, PRA is a superior measurement, because DRC can be influenced by other factors such as estrogen administration, which increases angiotensinogen and leads to a compensatory fall in DRC, but not PRA [22]. It is unlikely that PRA will reenter regular clinical use, given the labor and time commitment required, so is there an alternative? One promising approach is to measure angiotensin II [23, 24]. Because it is responsible for directly stimulating aldosterone synthesis, angiotensin II is arguably a more relevant factor to measure in regard to assessing autonomous aldosterone production than renin. An optimist might speculate that we may be using the aldosterone/angiotensin II ratio in the near future, with both hormones measured by rapid and accurate mass spectrometric assay methods.

B. Extraneous Influences on the ARR

B-1. Sex hormone influences

Progesterone is a potent antagonist of the mineralocorticoid receptor, causing natriuresis with secondary stimulation of renin and aldosterone [25]. Because progesterone rises significantly during the luteal phase of the menstrual cycle, the ARR might be expected to vary in premenopausal women. Additionally estrogen tends to increase angiotensinogen causing a rise in angiotensin II, which, by negative feedback, reduces synthesis of renin enzyme by the juxtaglomerular cells of the kidney. It is thus perhaps to be expected that there are sex differences in the ARR, and several reports suggest a clinically important influence of the menstrual cycle on the ARR. Several observational studies demonstrate that the ARR increases during the luteal phase of the cycle, resulting in frankly abnormal ratios in a number

of cases [26, 27]. Interestingly this only occurs when using DRC rather than PRA to calculate the ratio, again suggesting that PRA may be superior to the DRC in some situations. Care must therefore be taken in interpreting the ARR in premenopausal women, with preference for testing the ARR in the follicular phase of the cycle or using PRA if possible. At the very least, the demonstration of a repeatedly elevated ARR over time should be mandatory before proceeding to confirmation test.

B-2. The influence of medications

Many drugs are known to affect the renin angiotensin system and are capable of interfering with the ARR (Table 1). Drugs that stimulate renin production may cause a false-negative ratio; this category includes diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers (ARBs), and dihydropyridine calcium channel blockers [28]. Clinically, diuretics are the most important of these medications because they can profoundly influence renin levels, and in some cases screening can still be productive while taking angiotensin-converting enzymes/ARBs or calcium channel blockers. Other medications that are not antihypertensive agents also appear to stimulate renin in some cases. Two selective serotonin uptake inhibitors, sertraline and escitalopram, both simulated renin, causing a reduction in ARR in one recent study [29].

Given the influence of the female sex hormones on ARR, it is not surprising that oral contraceptive medications can cause changes in the ARR, depending on how this is measured. False-positive ratios have been reported in women taking oral contraceptives combining ethinyl-estradiol and drospirenone [22, 30]. This may be partly because drospirenone is a progestogenic agent with mineralocorticoid antagonistic effects that therefore stimulate renin and aldosterone. Typically, the ARR increases only when renin is measured as DRC rather than PRA. This is because DRC (but not PRA) falls, presumably, as a feedback effect of the rise in angiotensin II induced by estrogen in the combined contraceptive [22]. Not all contraceptives share this effect, with a progestin-only subdermally implanted contraceptive not causing changes in the ratio [22]. Furthermore, hormone replacement therapy in post-menopausal women may also have effects on the ARR. This was demonstrated in a recent investigation in which administration of the combined oral hormone replacement therapy caused an increase in the ARR (with renin measured by DRC) in 15 normotensive women, which was frankly elevated in 3/15 by 6 weeks [31].

That many antihypertensive medications affect aldosterone and renin can make control of hypertension difficult while undergoing screening for primary aldosteronism. Slow-release verapamil, the direct vasodilator hydralazine, and α blockers are thought to have minimal effect on the ratio, but it is often difficult to control blood pressure with tolerable doses of these medications alone. Recently, moxonidine, a centrally active agonist of the imidazoline

Table 1. Drugs and Other External Influences of the ARR

Drug or Other Influence	Possible Confounding Effect on ARR
β-Blockers	Increase
Diuretics	Reduce
ACE inhibitors/ARBs	Reduce
Dihydropyridine calcium channel blockers	Reduce
Clonidine	Increase
Methyldopa	Increase
Selective serotonin reuptake inhibitors	Reduce
COCs containing ethinyl-estradiol and drospirenone	Increase (if measuring renin with DRC)
Hormone replacement therapy	Increase (if measuring renin with DRC)
Luteal phase of menstrual cycle	Increase (if measuring renin with DRC)

ACE, angiotensin-converting enzyme; COC, combined oral contraceptive.

receptor, has been demonstrated to have no appreciable effect on the ARR in healthy nonhypertensive males despite a reduction in blood pressure [32]. This drug may therefore be a useful addition to the armamentarium.

B-3. Confirmatory tests

After the detection of an elevated ARR, current consensus guidelines recommend definitive confirmation of autonomous aldosterone production in most patients by one of four suppression tests [6]. Hypertensive patients with spontaneous hypokalemia combined with renin below the limit of detection and an elevated aldosterone concentration (>550 pmol/L) may be an exception to this rule. There are a number of options for confirmatory testing and no clearly evident gold standard. The recumbent saline suppression test (RST) is most commonly used worldwide, with alternatives including the fludrocortisone suppression test, the oral salt loading test, the captopril challenge test, and the less frequently used frusemide upright test. The fludrocortisone suppression test is generally regarded as the most sensitive test, certainly compared with the RST [33], but is cumbersome and expensive and requires a 5-day inpatient hospital stay. The more commonly used RST is prone to false negatives, even with generous cutoff values. This is supported by two recent studies. In one study, patients were diagnosed with primary aldosteronism by a repeatedly elevated ARR with high aldosterone levels and went on to AVS regardless of the results of recumbent saline infusion testing [34]. Of 41 patients who suppressed aldosterone to <139 pmol/L with RST (thus "excluding" primary aldosteronism), 12 (29%) lateralized with AVS; this proportion increased to 38/104 (37%) who suppressed below the higher cutoff of 277 pmol/L. The RST would have therefore excluded a substantial proportion of lateralizing and therefore potentially curable cases.

In another study, the RST missed 16/24 cases of primary aldosteronism diagnosed by fludrocortisone suppression testing (FST) [35]. This preliminary study also compared saline suppression testing in the seated and recumbent positions, based on the premise that posture responsive forms of primary aldosteronism may be missed by testing in the recumbent position. In comparison with recumbent saline infusion, a similar protocol in the seated position was positive in 23/24 of the cases positive by FST, suggesting it is much more sensitive than RST, especially for posture responsive forms of primary aldosteronism.

The influence of the menstrual cycle on the ARR may also affect the results of suppression testing. In a preliminary observational study, progesterone and aldosterone levels were significantly higher in nine women studied with FST during the luteal phase of the cycle, in comparison with 12 women studied during the follicular phase. All luteal phase studies were positive, compared with only 9/12 of the follicular phase studies [36]. Although it is unclear if some of these FST results were false positive or false negative, these results suggest that further study is warranted, ideally with repeat suppression tests in different phases of the cycle in the same individuals.

B-4. Subtype differentiation

Subtype differentiation is important for determining treatment options. Unilateral disease usually responds well to unilateral adrenalectomy, whereas bilateral disease resulting from bilateral adrenal hyperplasia is usually treated medically with medications that block aldosterone action. Correct lateralization is imperative to spare patients unnecessary and ineffective surgery and to identify patients who will benefit from surgery and who may be able to avoid lifelong drug therapy.

Cross-sectional imaging with computed tomography (CT) has been demonstrated as being poorly sensitive and specific for unilateral disease, misclassifying a sizeable proportion of patients [37–39]. Consensus guidelines therefore suggest that most patients should undergo AVS [6]. A proposed exception is younger patients (~<30–35 years of age) with florid primary aldosteronism and a clear unilateral lesion on CT because this is an age group in which

adrenal incidentalomas are rare and where AVS and CT-based diagnoses have a much higher proportion of concordance [40]. Despite this well-acknowledged risk of misclassification by CT, a recent provocative study found similar short-term blood pressure outcomes from a CT-based diagnostic algorithm when compared with an AVS-based approach [41]. This prospective randomized study comprised almost 200 patients with a relatively florid phenotype (prevalence of hypokalemia, 68%). Surprisingly, despite a clear signal that the CT-based approach was inaccurate in many cases (there was discordance between AVS and CT in 50% of the 90 patients with both successful AVS and CT, and there was a large preponderance of left-sided adrenal enlargement [40% vs 12%] in the CT group vs the expected equal right-left split in the AVS group), blood pressures at 12 months' follow-up were similar in both the CT- and AVS-diagnosed groups. Notably of the patients treated with adrenalectomy, more diagnosed by CT (20%) had persistent primary aldosteronism when compared with those diagnosed by AVS (10%), although this was not statistically significant. Notwithstanding the possible issues of insufficient power, selection bias toward patients with more florid primary aldosteronism, and a relatively short follow-up, one possible conclusion might be that patients with bilateral aldosterone production may in many cases also benefit from adrenalectomy, as has been suggested in limited fashion previously [42]. These findings deserve cautious consideration, but replication in other cohorts and longer follow-up is needed before supplanting the current consensus approach.

Although AVS is a technically difficult procedure, in experienced hands a large proportion of studies are successful. Despite the invasive nature of AVS, it is also a relatively safe procedure, with the major complication, adrenal hemorrhage, occurring rarely [43]. In a recent case series examining 24 adrenal hemorrhages associated with AVS, this complication occurred more commonly in the right adrenal gland and did not appear to be directly related to radiologist experience [44]. Reassuringly in this series, no invasive management was required and outcomes were generally excellent.

The quality of AVS samples is judged on cortisol gradients between the adrenal and peripheral samples (selectivity index), with a gradient of at least 2–3 typically used in most centers for non–adrenocorticotropic hormone (ACTH)-stimulated studies [43, 45]. Lateralization is often assigned on the basis of the lateralization index (LI), defined as the aldosterone/cortisol gradient in blood from one adrenal vein compared with that on the other side. An alternative approach is to compare aldosterone/cortisol gradients with peripheral gradients, in which case a gradient of at least twice the peripheral gradient on one side, with a gradient no higher than peripheral on the other side (contralateral suppression), is usually considered diagnostic of unilateral disease. One potential problem with judging sample adequacy is that cortisol secretion is not constant, and sampling at a time of quiescent cortisol secretion can result in poor cortisol gradients and uncertainty about the success of adrenal vein cannulation. Exogenous ACTH stimulation has been proposed as a method to iron out fluctuations in hormone secretion during AVS. There is controversy around the use of ACTH, with some authors concerned about possible confounding effects on lateralization [46]. The weight of the evidence from recent studies comparing stimulated and nonstimulated AVS procedures is fairly reassuring, however, suggesting that ACTH improves AVS success without compromising lateralization in the great majority of cases; nevertheless, this remains a valid concern and should be kept in mind. ACTH is likely to be particularly useful in centers where the baseline AVS success rate is relatively low.

In one small study of 32 patients with surgically treated primary aldosteronism who had pre- and post-ACTH samples taken without repositioning of the catheters, the proportion of samples that achieved adequate (selectivity index >3) gradients increased after ACTH from 44% to 88% on the right and from 47% to 100% on the left, suggesting that about one-half of the baseline samples were taken from a satisfactory position but did not achieve adequate gradients [47]. Based on the lateralization criteria, 27/32 (84%) procedures had concordant lateralization between pre- and post-ACTH samples. In another multicenter study comprising 76 patients who underwent AVS with pre- and post-ACTH samples taken, either ACTH bolus or continuous infusion (depending on the center) increased the rate of successful

AVS significantly [48]. Concordance between the pre- and post-ACTH studies was 78% to 88% depending on ACTH method, and the use of strict interpretation criteria (using high cutoff values for cortisol gradients to define successful samples and a high LI to define unilateral disease) was important to maintaining concordant diagnoses between the stimulated and nonstimulated procedures.

ACTH bolus improved the diagnostic success of AVS in another recent study because of both an improvement in bilateral successful sampling and the attainment of a clear diagnosis in cases where the pre-ACTH sampling had been technically successful but nondiagnostic [49]. Concordance between diagnostic studies pre- and post-ACTH was 91%. AVS can sometimes be nondiagnostic despite adequate cortisol gradients because of poor aldosterone secretion at the time of sampling, even in the case of a unilateral aldosterone-producing adenoma. Aldosterone/cortisol gradients bilaterally lower than peripheral were documented as occurring in 2.6% of unstimulated AVS procedures in a large case series. Although this may seem an infrequent issue, the significance of this phenomenon lay in the relatively large proportion (56%) of these subjects who, on repeat AVS, were found to have unilateral, surgically correctable primary aldosteronism [50]. Furthermore, the occurrence of bilaterally low aldosterone/cortisol gradients was considerably higher at 9.5% of unstimulated procedures in another recent publication from Japan [51]. ACTH clearly reduces the occurrence of this phenomenon [49, 51].

Another aspect that may affect the use of cortisol to judge sample accuracy and as a denominator to correct aldosterone is autonomous cosecretion of cortisol. The exact prevalence of autonomous cortisol secretion in primary aldosteronism is unclear, with reports ranging from as much as 21% in a small Japanese cohort [52] to 4% in a larger Italian study [53]. Apart from interfering with AVS interpretation, cortisol cosecretion may be associated with a period of postadrenalectomy adrenal insufficiency [54, 55]. It would therefore seem prudent to incorporate a routine dexamethasone suppression test or similar into the pre-AVS workup.

Other proposed methods to improve the accuracy of AVS include the use of metoclopramide, which induces an acute increase in aldosterone secretion from the adrenals. However, this did not improve diagnostic success in one recent study, although there was perhaps some value in aiding AVS interpretation where only one side could be cannulated [56]. Another group has recently demonstrated benefit from intraprocedural CT scanning to assist with correct catheter placement, with incorrect right-sided catheter placement identified by CT in 16/100 procedures, after which 12/16 were able to be successfully repositioned during the procedure [57].

Intraprocedural cortisol measurement can give rapid feedback to the radiologist performing AVS, and several studies have suggested that this improves AVS success [58,59]. Most reported “rapid” methods, however, require a lengthy (~30 minutes) delay and formal laboratory procedures. A recent report using an immunochromatographic approach in the form of a simple test strip that can be read semiquantitatively within 5 minutes did demonstrate a substantial improvement in AVS success in a multicenter trial; this may prove to be a more practical approach suitable for widespread application [60]. Again, this is likely to be of most assistance in units where the baseline success rate is relatively low.

Beyond obtaining satisfactory samples, the optimal criteria for determining lateralization based on AVS samples are somewhat contentious. Although the direct comparison of cortisol-corrected aldosterone levels from adrenal venous effluent from each gland (the LI) is intuitively important in assigning lateralization, relative suppression of aldosterone by the gland contralateral to an aldosterone producing adenoma was held by some authors in early publications to be the most reliable predictor of success after adrenalectomy [61]. Current evidence is mixed. In one study of 80 patients with an LI ≥2 (non–ACTH-stimulated) who had surgical adrenalectomy, 83% had contralateral suppression, and its presence was a powerful predictor of cure of hypertension and biochemical cure of primary aldosteronism as assessed by repeat suppression testing [62]. In contrast, in another recent multicenter study of 234 AVS procedures in patients considered to have unilateral primary aldosteronism, contralateral

suppression was present in 82%, but its presence or absence did not correlate with outcome because both patients with or without contralateral suppression experienced a 52% cure rate [63]. However, this study was essentially restricted to patients with an LI of at least four.

Contralateral suppression was found to correlate with better outcomes from surgery in several other recent studies [64, 65], although it appears to be more important in cases in which the LI is relatively low. Conversely, an interesting study recently examined the results of ACTH-stimulated AVS in 40 hypertensive patients in whom primary aldosteronism was excluded, finding that the median LI was 1.42, but that four patients (10%) had an LI between three and four [66]. This argues that, for ACTH-stimulated AVS, a cutoff of at least four should be applied. Overall, there is no clearly superior method of AVS interpretation, but a sensible approach would be to take account of both the LI and the presence of contralateral suppression, particularly where the non–ACTH-stimulated LI is between two and four.

Contralateral suppression is also useful in situations where only one adrenal vein has been successfully cannulated, because it can predict unilateral disease on the other side. One recent study examined the predictive value of only left adrenal vein sampling results compared with the diagnosis achieved from bilateral sampling, using a source and then validation cohort [67]. Using a left adrenal vein indicated a peripheral aldosterone/cortisol ratio of 0.5 or lower to indicate right unilateral primary aldosteronism and of at least 5.5 to indicate a left source had a positive predictive value of 100%. Thus, even when cannulation of one side has been unsuccessful, AVS may be diagnostic in the right circumstances.

Another advance in AVS that has recently been reported is the use of "segmental" or "superselective" sampling, which is sampling from several tributaries to the central adrenal vein [68]. This has been demonstrated to map the precise segment of the adrenal responsible for autonomous aldosterone and may allow for adrenal-sparing surgery. The technical skill and time required for this technique will likely limit its uptake however.

Because of the technically demanding aspects of AVS, there has been interest in other methods of determining lateralization. Positron emission tomography CT (PET-CT) is potentially promising and has been evaluated using labeled metomidate in several studies. Metomidate is an inhibitor of 11-β hydroxylase and can be labeled as a PET tracer. In one study, 39 patients with primary aldosteronism and five with nonfunctional adenomas had PET-CT with metomidate; this was compared with AVS, which was used as a gold standard [69]. The study determined that a maximum standardized uptake value ratio of 1.25:1 between adrenals had a specificity of 87% and sensitivity of 76% for unilateral disease, and specificity increased further in patients where the maximum standardized uptake value of the higher side was >17. Although this requires further confirmation, PET-CT could therefore be a useful adjunct for lateralization where AVS is unavailable or unsuccessful. There are however, substantial technical barriers to the use of ^{11C}metomidate, primarily the short half-life of 20 minutes, which requires close proximity to a cyclotron; hopefully, more practical isotopes will be available in the future. Single-photon emission CT/CT using ^{131}I-6β-iodomethyl-19-norcholesterol may also be useful in certain circumstances, offering much improved resolution comparative to scintography alone, although the protocol required remains cumbersome [70].

3. Conclusion

Since the first description of primary aldosteronism by Jerome Conn in 1955, there has been steadily growing recognition of the importance of this condition, which has only accelerated with time [71]. Despite this, screening and case detection among nonspecialist centers appear to be suboptimal [15, 16]. Improving awareness and improving the diagnostic workup for primary aldosteronism will increase detection rates, with the end result of improving hypertension control in this often treatment-resistant group, and reducing morbidity and mortality.

The diagnostic process now is largely well-established, and improving it has recently consisted mainly of the following refinements: ensuring we minimize false-positive and false-negative

Table 2. Methods to Improve AVS Success

Method
1. Control of posture and time of day (morning and supine posture preprocedure preferred) [72, 73]
2. Preprocedure CT scanning to visualize adrenal veins and adrenal anatomy [72, 73]
3. Maximizing radiologist experience [72, 73]
4. Pre/intraprocedural synthetic ACTH administration [47–49, 51]
5. Intraprocedural rapid cortisol measurement [58–60]
6. Intraprocedural CT scanning [57]

screening results by better appreciating the influence of drugs and hormones on the ARR and using superior laboratory methods; streamlining confirmation testing with diagnostic procedures that are simple and have good specificity and sensitivity; and optimizing AVS to ensure the highest possible success rate (Table 2). With a focus on continual improvement of the diagnostic process, patient outcomes can only improve.

Acknowledgments

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