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Consensus

SFE/SFHTA/AFCE consensus on primary aldosteronism, part 4: Subtype diagnosis

Consensus hyperaldostéronisme primaire SFE/SFHTA groupe 4 : diagnostic étiologique des hyperaldostéronismes primaires

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Abstract

To establish the cause of primary aldosteronism (PA), it is essential to distinguish unilateral from bilateral adrenal aldosterone secretion, as adrenalectomy improves aldosterone secretion and controls hypertension and hypokalemia only in the former. Except in the rare cases of type 1 or 3 familial hyperaldosteronism, which can be diagnosed genetically and are not candidates for surgery, lateralized aldosterone secretion is diagnosed on adrenal CT or MRI and adrenal venous sampling. Postural stimulation tests and ^{131}I-norcholesterol scintigraphy have poor diagnostic value and ^{11}C-metomidate PET is not yet available. We recommend that adrenal CT or MRI be performed in all cases of PA. Imaging may exceptionally identify adrenocortical carcinoma, for which the surgical objectives are carcinologic, and otherwise shows either normal or hyperplastic adrenals or unilateral adenoma. Imaging alone carries a risk of false positives in patients over 35 years of age (non-aldosterone-secreting adenoma) and false negatives in all patients (unilateral hyperplasia). We suggest that all candidates for surgery over 35 years of age undergo adrenal venous sampling, simultaneously in both adrenal veins, without ACTH stimulation, to confirm the unilateral form of the hypersecretion. Sampling results should be confirmed on adrenal vein cortisol assay showing a concentration at least double that found in peripheral veins. Aldosterone secretion should be considered lateralized when aldosterone/cortisol ratio on the dominant side is at least 4-fold higher than contralaterally.
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Keywords: Aldosterone; Aldosterone-secreting adenoma; Aldosteronism; Primary; Adrenal vein sampling

Résumé

L'enquête étiologique des hyperaldostéronismes primaires doit distinguer les cas avec ou sans hypersécrétion latéralisée, les premiers pouvant bénéficier d'une surrénalectomie unilatérale pour supprimer l'hypersécrétion, contrôler l'hypertension et s'il y a lieu l'hypokaliémie. En dehors des cas exceptionnels d'hyperaldostéronisme familial de type 1 ou 3, pour lesquels il y a un diagnostic génétique mais pas d'indication opératoire, le diagnostic de latéralisation repose sur l'imagerie en coupes et sur le cathétérisme veineux surrénal. En effet les tests de posture n'ont pas de valeur décisionnelle, la scintigraphie au 131I-norcholesterol a une performance insuffisante et la tomographie par émission de positons au 11C-metomidate n'est pas encore disponible. Nous suggérons la pratique d'une imagerie en coupes dans tous les cas d'hyperaldostéronisme documenté. L'imagerie montre exceptionnellement un carcinome corticosurrénal où l'objectif opératoire est carcinologique. Elle peut montrer des surrénales normales

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ou hyperplasiques ou un adénome unilatéral. Elle expose à des faux positifs (association d'un incidentalome après 35 ans) et à des faux négatifs (hyperplasie primaire unilatérale). Nous suggérons de la compléter, chez les candidats à la chirurgie de plus de 35 ans, par un cathétérisme veineux surrénal pour confirmer que l'hypersécrétion est unilatérale. Nous suggérons un cathétérisme simultané des deux surrénales, sans stimulation par l'ACTH ; de confirmer sa sélectivité par une cortisolémie au moins double dans chaque veine surrénale que dans le sang veineux mêlé ; et de considérer que l'hypersécrétion est latéralisée si l'aldostéronémie standardisée par la cortisolémie est au moins quatre fois plus élevée du côté dominant que du côté opposé.
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Mots clés : Adénome sécrétant de l'aldostérone ; Aldostérone ; Cathétérisme veineux surrénal ; Hyperaldostéronisme primaire

1. Rationale

Etiological diagnosis concerns only those patients in whom primary aldosteronism (PA) has been confirmed (see previous chapters). Etiology is known in 2 rare single-gene forms of PA in which aldosterone hypersecretion is related either to abnormalities in synthesis regulation (familial hyperaldosteronism type 1, FH1), or to hereditary activation (FH3) [1]; these forms account for less than 1% of cases. Even rarer is adrenocortical carcinoma (ACC), with prevalence of 1–9 per million and only 3% showing isolated aldosterone hypersecretion, most predominantly involving cortisol secretion [2].

Etiological diagnosis mainly aims to distinguish PA with and without lateralized secretion [3]. The former can be managed surgically, and comprises aldosterone-secreting adenoma (ASA) or in some cases no visible adenoma (unilateral primary hyperplasia). Surgery has the aim of controlling the consequences of hypersecretion (hypertension, and possibly hypokalemia), rather than the oncologic aim in ACC. PA without lateralized secretion is managed medically. Etiological exploration distinguishes candidates for adrenalectomy (lateralized PA) and those (non-lateralized) in which it would serve no purpose.

Even in lateralized PA, the risk/benefit ratio of surgery may be poor: comorbidity exacerbates operative risk and prevents postoperative termination of treatment, hypertension continues to need controlling, and patients may prefer medical treatment. Etiological exploration is thus warranted only in candidates for surgery. Patients presenting FH1 or FH3 have bilateral secretion, and are not candidates for surgery and etiological testing is not suitable.

Etiological tests to detect or predict lateralized hypersecretion comprise CT and MRI, adrenal vein sampling (AVS), functional imaging and posture tests.

2. CT/MRI

R 4.1 CT (or MRI when CT is contraindicated) should be performed in all cases of PA.
(Weak, level of evidence: +)

2.1. Technique

Fine imaging is required, as ACCs are small (around 10 mm). Rapid CT ($\geq$ 64-row) is the first choice. MRI has poorer resolution and slower acquisition, with risk of respiratory artifacts, and is reserved to contraindications for CT.

2.2. Performance

Systematic analysis of the literature (38 articles published between 1982 and 2008; 950 patients) compiled CT and MRI results in patients undergoing AVS, with lateralization on AVS as gold-standard [4]. In 38% of cases, imaging was discordant with respect to AVS, either failing to detect the origin of lateralized secretion (19.1%), or indicating a unilateral lesion when AVS found no lateralization (14.6%) or even a lesion contralateral to the lateralization found on AVS (3.9%). Several subsequent studies confirmed the frequency of false positives and false negatives on CT [5–8], but few described the typical image corresponding to ASA [6,7,9–11]. Table 1 presents articles with precisely reported CT data with comparison to AVS or PA resolution after adrenalectomy [6,7,10,11].

2.3. Indications

The surgeon needs CT (or MRI) in order to choose the surgical approach; some find it useful for AVS, locating the right adrenal vein. These indications are restricted to candidates for surgery, and involve contrast enhancement. The Endocrine Society considers imaging indicated in all cases of PA, to rule out ACC [3]. This recommendation leads to multiple examinations in patients without indications or who are not candidates for surgery, as the rate of PA in specialized centers is around 10%, whereas that of ACC with mineralocorticoid expression is nearer 10^{-6}.

3. Adrenal vein sampling

R 4.2 We do not recommend AVS in non-candidates for surgery.
(Strong, level of evidence: +)

Table 1
Predictive value of CT for unilateral secretion.

Author	*n*	Definition of CT data	Endpoint and result
Minami et al. (2008) [10]	33	A: 2 normal adrenals; B: distinct unilateral nodule ≥ 8 mm or increased thickness; C: as B, but bilateral	LI > 4 on AVS in 1 case A out of 7, 14 cases B out of 23, and 3 cases C out of 5
Lau et al. (2012) [6]	55	Scale: 1 (confirmed bilateral lesions) to 5 (single nodule, other arm of the adrenal < 5 mm)	PA resolved if surgery or LI > 5 on AVS. Se and Sp 100% if grade 5
Kupers et al. (2012) [11]	87	Typical nodule: hypodense (< 10 HU), diameter ≥ 8 mm, the rest of the AG and contralateral adrenal being thin and regular	LI > 4 on AVS. Typical nodule Se and Sp, 55% and 87%
Riester et al. (2014) [7]	194	Typical nodule: hypodense (<10 HU), diameter ≥ 10 mm, the rest of the adrenal and contralateral adrenal being thin and regular	LI > 4 on AVS. Typical nodule Se and Sp, 39% and 64%[a]

AVS: adrenal vein sampling; HU: Hounsfield unit; LI: lateralization index; Se and Sp: sensitivity and specificity.
[a] Estimated from incomplete data.

R 4.3 When AVS is indicated, both adrenal veins should be sampled simultaneously, without adrenocorticotropic hormone (ACTH) stimulation, with selectivity index threshold ≥ 2 and lateralization index threshold ≥ 4.
(Strong, level of evidence: ++)

R 4.4 We suggest performing AVS in candidates for surgery aged > 35 years, whatever the imaging findings.
(Strong, level of evidence: ++)

3.1. Principle

AVS compares aldosterone/cortisol ratio between the two adrenal veins (lateralization index: LI) to screen for lateralized secretion. Treatments (antihypertensive agents, potassium supplementation) should be adapted in advance, as in peripheral aldosterone assay. AVS is the gold-standard test, as adrenalectomy, if performed, aims to suppress unilateral hypersecretion rather than unilateral nodules.

3.2. Technique

AVS consists in measuring cortisol and aldosterone concentrations in the two adrenal veins and downstream blood (inferior vena cava or a peripheral vein). Variants comprise simultaneous or sequential sampling in the two adrenal veins [12,13], and associated pharmacologic stimulation (ACTH bolus or infusion, or metoclopramide; see [12] for a review). Stimulation sets a ceiling to and thus neutralizes ACTH-dependent variation in stress-induced steroids [14], and is therefore warranted in sequential AVS. The ratio between adrenal vein and inferior vena cava or peripheral vein cortisol levels represents a selectivity index (SI) to check that AVS was selective. LI is calculated only if SI reaches a predetermined threshold; most centers use an SI threshold of ≥ 2 without ACTH or ≥ 3 with ACTH, and an LI threshold of ≥ 2 without ACTH and ≥ 2.6 with ACTH [6,7,10–12,15].

3.3. Results

A recent international consensus statement [12] proposed an SI threshold of ≥ 2 to validate AVS and an LI threshold of ≥ 2 to confirm lateralization of hypersecretion [12], adding that a stricter LI threshold "undoubtedly leads to selection of a population with a higher chance of being cured with adrenalectomy". Various SI and LI threshold values were compared in a cooperative study in which the endpoint was concordant between two AVSs in a single patient; however, the second AVS was performed because the first was "non-satisfactory", which biased the findings [15]. As expected, stricter thresholds gave lower rates of lateralization: 67% for SI ≥ 1.1 + LI ≥ 2, versus 36% for SI ≥ 2 + LI ≥ 4. The respective performance of these thresholds was not validated against adrenalectomy. Despite the lack of good-quality data, we suggest an LI threshold of ≥ 4, for reasons of efficacy (increased probability of cure by adrenalectomy, as seen above [12]) and of safety (stricter thresholds reducing the number of patients exposed to operative risk, in a procedure aiming not at tumor prevention but functional improvement that stands comparison with medical management). Simultaneous and sequential AVS was compared in 2 articles; but sample sizes were unclear and there was no assessment criterion independent of AVS itself, so that no conclusion can be drawn [13,14]. Studies assessing SI and LI before and after ACTH or metoclopramide stimulation generally reported increase in SI but not LI and mentioned no impact on the decision to operate (Table 2, adapted from [12]).

3.4. Predictive value of AVS for outcome of surgery

Assessing the performance of AVS requires an independent assessment criterion, i.e. the results of adrenalectomy on hypersecretion, blood pressure and kalemia. This allows assessment of specificity, but not of sensitivity, as patients without lateralization do not undergo surgery. Few studies have applied this criterion in patients in whom adrenalectomy was indicated on

Table 2
Contribution of aldosterone stimulation in AVS.

	n validated AVSs	Simultaneous bilateral AVS	Impact on SI	Impact on LI
ACTH				
Monticone et al. (2012) [23]	76	No	Increased	Unchanged
Mathur et al. (2010) [24]	114	Yes	Reduced on right Unchanged on left	Unchanged on right Increased on left
Seccia et al. (2012) [14]	63	Yes	Increased	Unchanged
Tanemoto et al. (2009) [25]	10	Yes	Unchanged	Unchanged
Rossi et al. (2008) [26]	46	Yes	Increased	Reduced
Satoh et al. (2007) [27]	87	Yes	Increased	Reduced
Harvey et al. (2006) [28]	12?	Yes	Increased	NR
Carr et al. (2004) [13]	11	Yes	NR	NR
Metoclopramide				
Wu et al. (2001) [29]	20	Yes	NR	Unchanged

AVS: adrenal vein sampling; LI: lateralization index; SI: selectivity index; NR: not reported; see detail and individual study references in [7].

the basis of positive AVS [5–8]; the number of patients followed up after positive AVS, the definition of positivity and the results of surgery were poorly defined, hindering the calculation of specificity. Specificity is not 100%, as PA may persist after adrenalectomy indicated by lateralized AVS [4,5,8].

3.5. Should AVS be systematic?

The lack of a gold-standard means that whether AVS is warranted can be judged only theoretically and not on hard data. The procedure is invasive, and entails a risk of adrenal vein lesion (estimated at 0.6% in expert center reports [16]). It is costly: at least 1 day's hospital stay, with interventional radiology using a single-use probe, and at least 6 steroid assays. It is complicated to perform: the right adrenal vein is difficult to catheterize; and the 6 samples, 6 blood tubes and 6 plasma tubes need to be meticulously labeled. Consequently, AVS is routine in only a few centers. A risk/benefit analysis should be enabled by the ongoing SPARTACUS [17] randomized controlled trial, comparing hormonal and blood pressure results of adrenalectomy indicated by CT alone or by CT confirmed by AVS; meanwhile, different situations may be distinguished.

3.5.1. CT finds a typical unilateral nodule

A typical unilateral nodule is a hypodense ≥ 10 mm or ≥ 8 mm nodule with normal contralateral adrenal ([7,9,11] and Table 1). In this situation, failing to perform AVS entails a risk of unnecessary surgery due to an associated non-secreting adenoma [3,4]. However, incidentaloma rate is age-dependent, and recent studies indicate that, in PA, a typical unilateral nodule before the age of 40 [11,18] or 35 years [8] is very probably an ASA. AVS can be omitted in this age range, although the above findings were based on small patient samples and the double criterion (typical nodule + young age) applies to less than 10% of cases (Table 3).

3.5.2. CT does not find a typical unilateral nodule

The aspect may be of normal adrenals, bilateral nodules or a unilateral nodule that is atypical in being small (< 10 or < 8 mm) or associated with an abnormal contralateral adrenal. In this situation, failing to perform AVS entails a loss of opportunity in 19–35% of cases [4,19]. The decision to operate, and therefore to perform AVS, depends on operative risk, expected benefit of surgery, and the patient's wishes. If the risk/benefit ratio is negative, AVS should not be performed. Otherwise, exploration should be continued to the end and the patient referred to a center experienced in AVS.

3.5.3. Special cases

AVS is not contributive in suspected ACC (usually, ≥ 4 cm heterogeneous nodule, often with co-secretion of cortisol or androgens), as tumor resection is in any case mandatory. Nor is it useful in FH1 or FH3, as unilateral adrenalectomy is not curative in these cases. In FH2, the situation is, in the present state of knowledge, unclear, as PA may be associated with a unilateral typical nodule.

To sum up, AVS is not useful in patients who are not candidates for adrenalectomy, including those with FH1 or FH3, or who present a large tumor or tumor associated with cortisol or

Table 3
Frequency of unilateral secretion in typical adenoma before 40 years of age.

	Total	With typical nodule ≤ 40 yrs	Lateralization criterion	*n* lateralized
Mulatero et al. (2008) [18]	70	5	IS ≥ 2, IL ≥ 4	5/5
Kupers et al. (2012) [11]	87	9	IS ≥ 2, IL ≥ 4	9/9
Riester et al. (2014) [7]	193	6	IS ≥ 2, IL ≥ 4	5/6
Lim et al. (2014) [8]	133	21	PA resolved by adrenalectomy	15/21[a]
Total	483	41/483 (8%)		34/41 (83%)

[a] Including 6/6 under 35 years of age.

androgen secretion, as surgery is indicated regardless of AVS. Abstention is also probably possible in under 35-year-olds with typical nodules. Otherwise, the indication for surgery should be confirmed by AVS, whether adrenal nodules are present or not. The literature is silent on how to proceed after invalid AVS. One option is to repeat the AVS, as in some cases in the study by Mulatero et al. [15]; alternatively, isolated medical treatment may be pursued. In either case, the patient must be informed.

4. Functional imaging: ^{131}I-norcholesterol and ^{11}C-metomidate

> R4.5 We suggest not using functional imaging for etiologic diagnosis of PA.
> (Weak, level of evidence: +)

Two radiopharmaceuticals (RP) have been described: ^{131}I-methylnorcholesterol, which accumulates in the adrenocortical gland under the influence of ACTH, and ^{11}C-metomidate, an 11β hydroxylase and aldosterone-synthase inhibitor.

4.1. Technique

^{131}I-methylnorcholesterol (Norchol®) scintigraphy is performed under dexamethasone (DXM) suppression. Spironolactone, diuretics and oral contraceptives should be interrupted 4–6 weeks ahead of examination. The thyroid should be presaturated with iodine. Images are acquired at D2 and D4 or D5 on tomoscintigraphy coupled to CT. Normal adrenals are not seen before D4-5. Early unilateral fixation suggests ASA.

^{11}C-metomidate PET-scan uses a short half-life radiopharmaceutical, and therefore needs to be conducted near the site producing the RP. In the only clinical study to date [20], 150–500 MBq ^{11}C-metomidate was injected, with dynamic recording for the first 45 min. DXM suppression increased adrenal tumor uptake (versus normal adrenal tissue) by 25%.

4.2. Performance

The published ^{131}I-methylnorcholesterol scintigraphy studies are all old, retrospective, with varying assessment criteria, and poor resolution. A single, retrospective study reported a comparison against CT, in 27 PA patients, all with CT and 8 with non-conclusive AVS [21]. The assessment criteria were histologic results and response to surgery. Sensitivity was better on scintigraphy than CT (82% vs. 41% for histology, 100% vs. 40% for response to surgery), but specificity did not differ (respectively, 67% and 67% for histology, 54% and 62% for response to surgery).

Burton et al. assessed ^{11}C-metomidate PET in 44 patients: 39 with PA and 5 with incidentaloma [20]. In the 25 patients with unilateral adenoma, ^{11}C-metomidate uptake [SUVmax] was greater in tumoral than normal adrenal tissue. At a 1.25 tumoral/normal adrenal SUVmax ratio threshold, PET showed 76% sensitivity and 87% specificity.

4.3. Indications

^{131}I-methylnorcholesterol scintigraphy is indicated in case of failure of AVS. It is long, costly and requires several days' prior DXM suppression. It is not without risk: DXM raises blood pressure and lowers kalemia in hypertensive and hypokalemic patients. ^{11}C-metomidate is not commercially available, and its contribution remains to be determined.

5. Postural stimulation tests

> R4.6 We do not recommend posture tests for etiological diagnosis of PA.
> (Weak, level of evidence: ++)

5.1. Technique

We are concerned here with the contribution of postural stimulation tests to etiological rather than positive diagnosis of PA: 40 mg/iv furosemide response after 2 hours' walking and response to upright stance after 2 or 4 hours' walking.

5.2. Performance

Lau et al., in a prospective study, compared CT (1.25 mm slices with and without contrast enhancement) versus postural stimulation test (≥ 30% reduction in aldosterone concentration after 4 hours' walking as indicating ASA) in 50 consecutive patients with non-suppressible PA [6]. The endpoints were hormonal resolution in the 24 operated patients and AVS lateralization after 1 hour's 50 μg/h synacthen (SI ≥ 5 and LI ≥ 4) in the 26 non-operated patients. Sensitivity and specificity were respectively < 56% and 75% on postural test, versus 77% and 80% for CT. CT sensitivity and specificity were 100% in case of > 10 mm unilateral nodule without contralateral abnormality. The authors concluded that the posture test contributed nothing to CT, the latter being contributive in all surgery candidates. They briefly analyzed and discounted previous studies, which had been retrospective.

Nanba et al. [22] compared the captopril test, postural stimulation + furosemide test and intravenous saline infusion in 120 patients. In a subgroup of 57 patients, they reported sensitivity and specificity for a composite lateralization criterion consisting of AVS after synacthen (SI ≥ 5 and LI ≥ 2.6) or scintigraphy (without details) or response to surgery (without details). Sensitivity was 93% for postural test + furosemide, but with incomplete data, specificity could not be calculated in a subgroup of 48% of the patients.

Disclosure of interest

The authors declare that they have no competing interest.

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