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Consensus

SFE/SFHTA/AFCE consensus on primary aldosteronism, part 3: Confirmatory testing

Consensus hyperaldostéronisme primaire SFE/SFHTA/AFCE, groupe 3 : étape de confirmation diagnostique

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Abstract

Aldosterone/renin ratio (ARR) identifies patients at high or low risk of primary aldosteronism (PA), but sensitivity and especially specificity are suboptimal and confirmatory testing may therefore be necessary, in some but not all patients. In patients with elevated ARR and plasma aldosterone concentration above 550 pmol/L (20 ng/dL) on two assessments, PA can be diagnosed without confirmatory testing. Conversely, PA can be ruled out without confirmatory testing in patients with normal ARR and plasma aldosterone concentration below 240 pmol/L (9 ng/dL) on two assessments. In patients not corresponding to either of the previous conditions, dynamic confirmatory testing is mandatory. Several tests are available, based on aldosterone suppression by saline loading, fludrocortisone administration or converting enzyme inhibition by captopril. One test is based on renin stimulation by furosemide administration. Each of these tests has its limitations, and validation is incomplete. We recommend aldosterone suppression by saline infusion test. Renin stimulation by captopril may be used if sodium loading is contraindicated by impaired cardiac function.

Keywords: Primary aldosteronism; Aldosterone; Renin; Confirmatory testing

Résumé

La mesure du RAR permet d'identifier des patients à haut ou à faible risque d'HAP, cependant sa sensibilité et surtout sa spécificité ne sont pas parfaites, ce qui pose la question d'une étape supplémentaire avant d'affirmer ou de rejeter le diagnostic d'HAP. Nous estimons que cette étape supplémentaire n'est pas nécessaire chez tous les patients. Chez les patients qui présentent un RAR élevé à deux reprises, avec une aldostérone plasmatique supérieure à 550 pmol/L (20 ng/dL), le diagnostic d'HAP pourra être affirmé sans étape diagnostique supplémentaire. À l'inverse, chez les patients qui présentent un RAR normal à deux reprises, avec une aldostérone plasmatique inférieure à 240 pmol/L (9 ng/dL), le diagnostic d'HAP pourra être rejeté sans étape diagnostique supplémentaire. Chez les patients qui ne sont pas dans l'une de ces deux situations, une étape diagnostique supplémentaire est nécessaire, sous la forme d'un test dynamique de confirmation. Plusieurs tests sont basés sur la mesure de la freination d'aldostérone au cours d'une expansion volémique par charge sodée ou par administration de fludrocortisone, ou au cours d'une inhibition de l'enzyme de conversion par captopril. Un test est basé sur la stimulation de rénine par administration de furosémide. Chacun de ces tests a des limitations et leur validation reste incomplète. Nous recommandons d'utiliser le test de freination de l'aldostérone par charge sodée intraveineuse. Si ce test est contre-indiqué par une fonction cardiaque trop altérée nous recommandons d'utiliser le test de stimulation de la rénine par administration de captopril.

Mots clés : Hyperaldostéronisme primaire ; Aldostérone ; Rénine ; Test de confirmation

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1. Introduction

When screening by aldosterone/renin ratio (ARR) reveals a dissociation between plasma aldosterone and renin concentrations, diagnostic confirmation of primary aldosteronism (PA) may be undertaken in ambiguous cases, ideally using a method that is both sensitive and above all specific, so as to exclude any false positives on ARR. This is especially important if a low ARR threshold has been used to maximize sensitivity. Dynamic tests provide a confirmation step, exploring for an aldosterone suppression defect on saline loading test or acute captopril administration that would indicate autonomous aldosterone secretion. These tests should be conducted with the patient seated or supine.

2. Arguments for and against dynamic confirmatory testing

2.1. In favor of dynamic confirmatory testing

PA confirmation is a crucial step to avoid costly imaging or invasive examination. According to the literature, 30–50% of hypertension patients with positive ARR screening have elevated aldosterone levels at baseline, that can be suppressed on confirmatory testing and thus may correspond to false positives [1–3]. Less critically, there is also the question of false negatives on ARR, especially when the threshold was set high so as to enhance specificity.

In strategies based purely on baseline levels of aldosterone and renin, PA may be diagnosed from elevated ARR associated with elevated plasma aldosterone (or, for some teams, elevated 24-h urinary aldosterone). This straightforward diagnostic strategy is valid when ARR and aldosterone elevation are clear, but lacks sensitivity: PA, when confirmed, may be associated with baseline plasma aldosterone and/or urinary aldosterone values within normal limits, resulting in false negatives. The false negative rate revealed in dynamic confirmatory testing may be as high as 36–43%, although in some series no intraoperative confirmation of PA diagnosis was reported [1,4].

Aldosterone shows pulsatile secretion making ARR intrinsically variable, so that repeating ARR measures is mandatory [5]. In a Japanese series of 71 surgically confirmed Conn adenomas, plasma aldosterone and ARR on repeated measures under baseline conditions were normal on at least 1 reading in 39% and 31% of patients, respectively [6].

Thus, dynamic confirmatory testing is required after ARR screening in order to provide a strong negative predictive value, thereby excluding false positives (i.e., hypertensive patients with low renin and high ARR, who do not actually have PA).

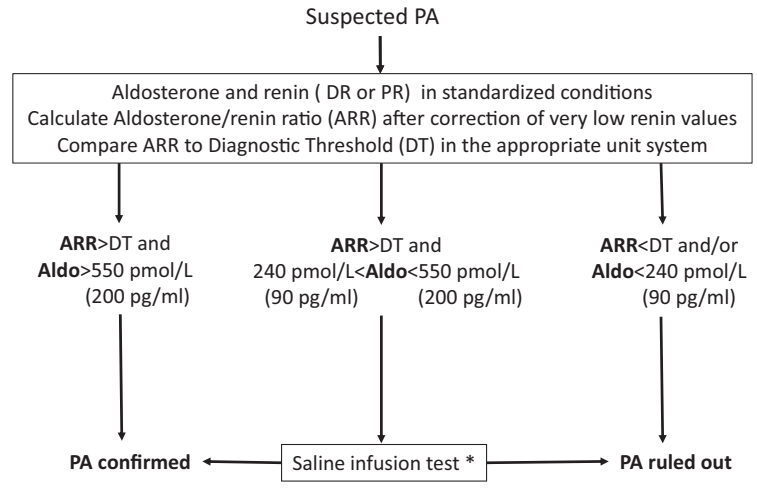
The test's positive predictive value is less critical but can confirm PA when there is no frank elevation of baseline aldosterone concentration, although such a hormone profile generally does not select the right candidates for surgery [7].

Overall, dynamic testing seems unwarranted when baseline plasma aldosterone concentrations are sufficiently low (< 240 pmol/L ([9 ng/dL]) [1] as the risk of false negatives on ARR is slight and PA can be ruled out without further exploration. Likewise, it is unwarranted when plasma aldosterone under standardized conditions is higher than 550 pmol/L (20 ng/dL) on at least two measurements, and is associated with low renin level. The risk of false positives in that case is very slight [8,9] and PA can be diagnosed without further exploration. Fig. 1 shows a flowchart for this diagnostic strategy.

2.2. Limitations of confirmatory testing

Reviewing the literature finds no established or consensual reference test for confirming PA. Data for dynamic testing come from studies with low levels of evidence due to:

- small series;
- no validated PA reference test;
- non-consensual positivity thresholds for the dynamic tests;



First diagnosis steps and confirmatory testing in patients with suspected PA
Premières étapes diagnostiques chez les patients suspects d'hyperaldostéronisme primaire

Fig. 1. Positive diagnosis of primary aldosteronism?

- lack of data comparing tests (most studies compared 2 tests, one of which was arbitrarily used as the reference test);
- false negatives on dynamic tests: i.e., aldosterone suppression on dynamic test together with lateralized aldosterone secretion on adrenal vein sampling, which may be seen in as many as 12% of screened cases [10,11];
- all confirmatory tests presuppose that aldosterone secretion in PA is independent and dissociated from renin secretion, which in reality is far from always the case [12,13];
- moreover sodium loading tests can be dangerous, notably in case of severe hypertension or heart failure.

3. Description of tests

Table 1 shows confirmatory tests. Three are based on sodium loading:

- by acute venous administration (intravenous saline infusion test);
- by oral administration of sodium 6 g per day for 3 days, or;
- by a standardized mineralocorticoid intake (fludrocortisone suppression test);
- alternatively, the captopril test is considered to lower plasma aldosterone by acute angiotensin converting enzyme inhibition. In all tests, non-suppression of aldosterone is indicative of autonomous secretion. For confirmatory testing, the antihypertensive treatment that is continued will preferably be that which interferes least with the renin-angiotensin system (non-dihydropyridinic calcium channel blockers and/or alpha-blockers), although testing is also reliable when only thiazide or loop diuretics and mineralocorticoid receptor antagonists are interrupted [14]. For certain tests lasting several days (fludrocortisone suppression test, 3-day oral salt loading test), it is important to check complete renin suppression if aldosterone suppression is to be reliably interpreted. An essential factor in dynamic test performance is the choice of aldosterone and renin assay methods and thresholds. Renin-angiotensin-system hormone measurements vary widely between assay techniques, and normal values and thresholds should ideally be determined specifically in each laboratory, although this is not always feasible in clinical practice [15]. The following data, collected by the working group, are therefore basically descriptive, and the resulting guidelines have low levels of evidence.

4. Which dynamic test should be used?

An ideal test should meet several criteria: effectiveness (high positive and negative predictive values), safety of execution, and low cost. None of the dynamic tests available meet all three.

The main purpose of confirmatory testing is to eliminate false positives on ARR. The best test is therefore that with the highest negative predictive value, such as the intravenous saline infusion test or the fludrocortisone test rather than the captopril test or the oral salt loading test.

There are few studies comparing the various dynamic tests. For some authors, the fludrocortisone suppression test is the reference [3,16]. Studies reporting good performance have mainly come from a single Australian team [4,16–18]. The test is expensive and burdensome, requiring hospital admission to detect and correct severe hypokalemia induced by high-dose fludrocortisone. In a series of 98 patients screened for PA, Mulatero et al. reported 88% concordance between intravenous saline infusion and fludrocortisone suppression results [3]. Willenberg et al. likewise found equivalent sensitivity and specificity between intravenous saline infusion and fludrocortisone suppression, but with differing thresholds [19]. In the prospective PAPY study of 120 Conn adenomas diagnosed on strict criteria in a large population of 1125 hypertension patients, intravenous saline infusion showed moderate diagnostic performance (82% sensitivity, 75% specificity) but a strong negative predictive value of 95% [20]. There is no consensus between teams as to the aldosterone suppression threshold for intravenous saline infusion [3,18–21]. Some authors reported poorer saline infusion performance in PA patients without history of hypokalemia [22]. The Brisbane team reported poorer performance for oral salt loading or intravenous saline infusion than for fludrocortisone suppression, with about 30% sensitivity in patients with normal serum potassium levels [16,17]. The same team recently showed that implementing saline infusion in seated position improved performance, identifying 96% of PA cases previously identified on fludrocortisone suppression, versus 30% for supine position [18]. Oral salt loading was thoroughly studied by the Mayo Clinic team, showing about 70% sensitivity and 91% specificity in a series of Conn adenoma identified on adrenal vein sampling [23,24].

Some studies reported better performance of intravenous saline infusion, oral salt loading and fludrocortisone suppression tests compared to the captopril test [25,26], but others did not [9,27–29]. The PAPY study found that the captopril test had a lower positive predictive value when implemented under low-sodium diet (< 7.6 g NaCl/day) compared to the intravenous saline infusion test. Conversely, the two tests had equivalent positive predictive values when implemented under high sodium diet [10]. A single-center Japanese study recommended the furosemide test in case of acute sodium depletion in standing posture to detect renin suppression as a confirmation of PA: the furosemide test showed equivalent or better performance than intravenous saline infusion [9]; these findings, however, have not been replicated.

Overall, dynamic tests show only moderate sensitivity and positive predictive values but high specificity and negative predictive values, and thus serve mainly to rule out PA after screening [30]. The literature seems to testify that the intravenous saline infusion and fludrocortisone suppression tests have better negative predictive values than the captopril or oral salt loading tests.

The choice of PA confirmation test should take account of the potential risks incurred by sodium loading. In case of poorly controlled hypertension or heart failure, the captopril test should replace sodium loading or fludrocortisone tests although its performances are controversial. Suppression tests are preferable whenever possible.

Table 1
Dynamic aldosterone suppression tests.

Confirmatory test	Protocol	Performance	Comments
Intravenous saline infusion	Supine position, 1 h Infusion of 2 L of 0,9% saline in 4 h (08:00–12:00) Aldosterone and renin sampling at T0 and T4 h Hourly measurement of plasma aldosterone and heart rate	Agharazii et al. (2001) [29] ($n = 44$) Se: 100%, Sp: ND Aldosterone threshold, pmol/L (ng/dL): 246 (8.5) Diagnostic criteria: CT/scintigraphy/AVS/surgery Giacchetti et al. (2006) [25] ($n = 61$, case/control) Se: 88%, Sp: 100% Aldosterone threshold, 196 pmol/l (7 ng/dL) Diagnostic criteria: surgery/AVS Mulatero et al. (2006) [3] ($n = 98$) Se: 90%, Sp: 84% Aldosterone threshold, 140 pmol/L (5 ng/dl) Diagnostic criterion: fludrocortisone suppression Rossi et al. (2007) [10,20] (PAPY, $n = 120$ HAP) Se: 82%, Sp: 75% Aldosterone threshold, 196 pmol/L (7 ng/dL) Diagnostic criterion: CT/AVS Nanba et al. [9] (2012) ($n = 57$) Se: 60%, Sp: ND Aldosterone threshold, 170 pmol/L (6 ng/dL) Diagnostic criterion: surgery/AVS/scintigraphy Willenberg et al. (2012) [19] ($n = 33$) Se: 82%, Sp: 92% Aldosterone threshold, 88 pmol/L, (3.15 ng/dL) Diagnostic criterion: surgery/AVS Ahmed, Stowasser (2014) [18] ($n = 66$) Se: 96% (seated), 33% (supine), Sp: ND Aldosterone threshold, 165 pmol/L (6 ng/dL): seated; 140 pmol/L (5 ng/dL) : supine Diagnostic criterion: fludrocortisone suppression	Contraindicated in severe hypertension, kidney failure, heart failure, cardiac arrhythmia, severe uncorrected hypokalemia
3-days oral salt loading	Oral sodium intake > 200 mmol (6 g)/day for 3 days, checked by 24-h urine sodium content Potassium chloride supplementation to maintain normal plasma potassium 24 h urinary aldosterone assay from day 3 at 08:00 until day 4 at 8:00	Young (2002) [23], Bravo et al. (1983) [24] Se: 70%, Sp: 91% 24 h urinary aldosterone threshold, 12–14 mcg/day (33–39 nmol/day)	Contraindicated in severe hypertension, kidney failure, heart failure, cardiac arrhythmia, severe uncorrected hypokalemia. In case of kidney failure, aldosterone assay may be performed by HPLC-MS/MS
Fludrocortisone suppression	Hospital admission Fludrocortisone 0.1 mg every 6 h for 4 days Potassium chloride supplementation and plasma potassium assay every 6 h NaCl supplementation (30 mmol × 3/day). Seated plasma aldosterone and renin assay on day 4 at 10:00, cortisol assay at 07:00 and 10:00 am	Mulatero et al. (2006) [3] ($n = 98$) Se: 100%, Sp: ND Aldosterone threshold, 140 pmol/L (5 ng/dL) Diagnostic criterion: fludrocortisone suppression Willenberg et al. (2012) [19] ($n = 33$) Se: 87%, Sp: 97% Aldosterone threshold, 150 pmol/L (5.35 ng/dL) Diagnostic criteria: surgery/AVS Ahmed, Stowasser (2014) ($n = 66$) Se: 100%, Sp: ND Aldosterone threshold, 165 pmol/L (6 ng/dL) Diagnostic criterion: fludrocortisone suppression	Burdensome test: hospital admission, sodium chloride and potassium chloride monitoring and plasma potassium checked several times daily Reference test for some authors

Table 1 (*Continued*)

Confirmatory test	Protocol	Performance	Comments
Captopril test	Seated or standing 1 h before 50 mg oral captopril Seated throughout test Blood sampling at T0, T1 h and T2 h for aldosterone, renin and cortisol assay	Agharazii et al. (2001) [29] ($n = 44$) Se: 97%, Sp: ND Aldosterone threshold, 246 pmol/l (8.5 ng/dl) Diagnostic criteria: CT/scintigraphy/AVS/surgery Rossi et al. (2007) [10,20] (PAPY, $n = 137$ HAP) Se: 79%, Sp: 74% Aldosterone threshold, 390 pmol/L (13.9 ng/dl) Diagnostic criteria: CT/AVS Nanba et al. (2012) [9] ($n = 57$) Se: 96%, Sp: ND Aldosterone threshold, 336 pmol/L (12 ng/dl) Diagnostic criteria: surgery/AVS/scintigraphy	High false negative rate Simple and risk-free, even in severe hypertension or heart failure Performance often considered poorer than sodium loading

5. Recommandations

R 3.1: Like in ARR screening, aldosterone assay on dynamic tests should be performed under standardized conditions: in the morning, more than 2 hours after awakening, in seated position for 5–15 minutes, under normal sodium diet and, if necessary, after recovery of normal potassium concentration.

Strong recommendation; Level of evidence ++.

R 3.2: As antihypertensive drugs impact ARR, at least 2 weeks' interruption (or 6 weeks for anti-aldosterone compounds) is necessary ahead of dynamic testing. Long-action non-dihydropyridine calcium channel blockers and alpha-blockers can be maintained.

Strong recommendation; Level of evidence +++.

R 3.3 (equivalent to R 2.3): PA can be ruled out without dynamic testing by an ARR below threshold, and/or a plasma aldosterone measured below 240 pmol/L (9 ng/dL)[1] on two occasions.

Weak recommendation; Level of evidence ++.

R 3.4: PA can be positively diagnosed without dynamic testing by elevated ARR and a plasma aldosterone measured above 550 pmol/L (20 ng/dL), on two occasions.

Strong recommendation; Level of evidence ++.

R 3.5: Diagnosis of PA can be neither confirmed or ruled out when plasma aldosterone is measured between 240 pmol/L (9 ng/dL)[1] and 550 pmol/L (20 ng/dL) on two occasions. In such a situation, dynamic testing is recommended to confirm PA.

Weak recommendation; Level of evidence ++.

R 3.6: Intravenous saline infusion shows the best trade-off between performance and limitations. If considered risky in a patient with impaired left ventricle function, a captopril test may be used.

Weak recommendation; Level of evidence ++.

[1] Threshold defined for the Diagnosis Products Corporation kit (Los Angeles, CA, USA) for aldosterone assay in Mosso et al. [1].

6. Conclusions

The above guidelines are based on expert consensus, and are intended to avoid systematic recourse to heavy and costly testing. The experience and various practices of expert teams from referral centers may include more radical attitudes, some of them further restricting dynamic testing, others offering systematic dynamic testing as recommended by recent consensus statements [31,32].

Disclosure of interest

The authors declare that they have no competing interest.

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