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Consensus

SFE/SFHTA/AFCE Consensus on Primary Aldosteronism, part 2: First diagnostic steps

Consensus SFE/SFHTA/AFCE sur l'hyperaldostéronisme primaire, groupe 2 : premières étapes diagnostiques

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Abstract

In patients with suspected primary aldosteronism (PA), the first diagnostic step, screening, must have high sensitivity and negative predictive value. The aldosterone-to-renin ratio (ARR) is used because it has higher sensitivity and lower variability than other measures (serum potassium, plasma aldosterone, urinary aldosterone). ARR is calculated from the plasma aldosterone (PA) and plasma renin activity (PRA) or direct plasma renin (DR) values. These measurements must be taken under standard conditions: in the morning, more than 2 hours after awakening, in sitting position after 5 to 15 minutes, with normal dietary salt intake, normal serum potassium level and without antihypertensive drugs significantly interfering with the renin-angiotensin-aldosterone system. To rule out ARR elevation due to very low renin values, ARR screening is applied only if aldosterone is > 240 pmol/l (90 pg/ml); DR values < 5 mIU/l are assimilated to 5 mIU/l and PRA values < 0.2 ng/ml/h to 0.2 ng/ml/h. We propose threshold ARR values depending on the units used and a conversion factor (pg to mIU) for DR. If ARR exceeds threshold, PA should be suspected and exploration continued. If ARR is below threshold or if plasma aldosterone is < 240 pmol/l (90 pg/ml) on two measurements, diagnosis of PA is excluded.

Keywords: Aldosterone-to-renin ratio (ARR); Screening; Primary aldosteronism; Standard conditions; Aldosterone; Renin

Résumé

Chez les patients suspects d'hyperaldostéronisme primaire (HAP), la première étape diagnostique, dite de dépistage, doit avoir une sensibilité et une valeur prédictive négative élevées. Le rapport aldostérone/rénine (RAR) est choisi car il présente une sensibilité meilleure et une variabilité moindre que les autres mesures (kaliémie, aldostéronémie, aldostéronurie). Le calcul du RAR est fait à partir de la mesure de l'aldostérone plasmatique (AP) et la mesure de la rénine : soit en activité (ARP), soit en mesure directe (RD). Ces mesures doivent être réalisées en conditions standardisées : le matin, plus de 2 heures après le lever, en position assise depuis 5 à 15 minutes, en régime normosodé, en normokaliémie et sans traitement interférant significativement avec le système rénine angiotensine. Pour éliminer les élévations du RAR liées essentiellement à des valeurs de rénine très basses, le calcul du RAR n'est appliqué que si l'aldostérone est > 240 pmol/L (90 pg/mL) et on majorera à 5 mU/L les valeurs de RD < 5mUI/L et à 0,2 ng/mL/h les valeurs d'ARP < 0,2 ng/mL/h. Il est alors proposé un seuil du RAR dont l'expression dépend des unités utilisées

Abbreviations: PA, Primary aldosteronism; ARR, Aldosterone-to-renin ratio; PRA, Plasma renin activity; DR, Direct renin; RAAS, Renin-angiotensin-aldosterone system; CEI, Converting enzyme inhibitor; NSAIDs, Non-steroidal anti-inflammatory drugs; SRI, Serotonin reuptake inhibitor; EP, Estrogen-progestin; RIA, Radioimmunoassay; LC-MS, Liquid chromatography-mass spectrometry; ARA-II, Angiotensin-II receptor antagonist.

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et, pour la mesure de la RD, du facteur de conversion (pg vs mUI). Si le RAR est supérieur à ce seuil, l'HAP est possible et les explorations devront être poursuivies. Si le RAR est en dessous de ce seuil ou si l'aldostérone plasmatique est, à deux reprises, en dessous de 240 pmol/L (90 pg/mL), le diagnostic d'HAP est exclu.

Mots clés : Rapport aldosterone/rénine ; RAR ; Dépistage ; Hyperaldostéronisme primaire ; Conditions standardisées ; Aldostérone ; Rénine

1. 1st diagnostic step in primary aldosteronism: rationale for aldosterone-renin ratio (ARR) as screening criterion

1.1. Aldosterone-renin ratio

After selecting a population for exploration for primary aldosteronism (PA) (see article 1) the first diagnostic step is screening. This requires a test with high sensitivity and negative predictive value, to confirm all situations liable to involve PA. In recent decades, several teams have sought an optimal criterion to screen for elevated aldosterone production and the corresponding inhibition of renin. The literature data of the last 20 years demonstrated that the aldosterone-renin ratio (ARR) is the parameter with the highest sensitivity (68–94%) for PA screening, compared to other biological variables: serum potassium, plasma aldosterone, or urinary aldosterone [1–6]. Its negative predictive value sometimes even approximates 100%, for diagnosis of Conn's adenoma [7]. Sensitivity, however, varies between reports, due to differences in ARR threshold values, assay methodology and sampling conditions. Nevertheless, ARR shows somewhat less variation related to environmental conditions (serum potassium, sodium load, age and posture) in a given patient than rival markers [8–10]. Correlations are excellent between measures taken in seated, prone and standing posture [11]. Reproducibility was also found to be acceptable in Rossi's 2010 study [9] of 1136 patients (plasma aldosterone/plasma renin activity [PRA]), although other studies reported variable reproducibility, even within PA populations [10]. Amar [12] reviewed the main studies reporting at least 1000 hypertension patients: 6.4 to 22.8% of patients showed ARR elevation, used as screening criterion (thresholds ranging from 20 to 40 ng/dl/ng.ml^{-1}.h^{-1} after withdrawal of interfering drugs); ARR elevation was associated with actual PA in 5.9 to 11.3% of patients. Depending on the team, the gold standard against which ARR was compared was one of the following dynamic tests (thresholds varying according to team): intravenous sodium load (aldosterone > 5 ng/dl or > 10 ng/dl), oral sodium load (urinary aldosterone > 12 μg/d), fludrocortisone (aldosterone > 6 ng/dl or > 5 ng/dl), or oral captopril (positive if ARR > 30 ng/dl/ng.ml^{-1}.h^{-1} 1 hour after 50 mg captopril) [13–19]. The drawback of ARR as criterion is that it is not yet perfectly standardized: values vary with assay technique, assay kit and unit used to express results, intra- and inter-patient variation coefficients vary, and environmental factors influence results: posture, medication, metabolic factors (serum potassium and sodium load), and factors related to comorbidity (kidney failure), age, or menstrual phase [20]. Finally, although sensitive for a given threshold, several reports have shown that ARR lacks specificity as an isolated diagnostic criterion for PA.

1.2. 24-hour urinary ionogram

Urinary ionograms seem to have two useful features: to demonstrate that hypokalemia is due to renal leakage, and to determine sodium load. It is useful at screening to have urinary potassium and sodium values, to determine sodium load. We therefore recommend implementing not only a blood ionogram and ARR estimate at screening, but also a 24-hour urinary ionogram (urinary sodium, potassium and creatinine).

1.3. Urinary aldosterone

Urinary aldosterone assay is used by several teams for screening or to confirm diagnosis, and seems to be a better indicator than plasma aldosterone alone [21,22]. Sensitivity, however, is lower than ARR (cf. Section 1.1), and the assay is burdensome and sometimes unreliable: 24-hour collection, margin of error up to 50%. It is not used as a PA screening criterion. Some teams have studied the aldosterone/creatinine ratio in urine samples compared to 24 h urine collection; in 102 patients with PA, confirmed on IV sodium load test, a threshold aldosterone/creatinine ratio of > 3.0 ng/mg allowed a 90.6% specificity for the diagnosis of PA vs essential hypertension, with a sensitivity (51%) similar to the sensitivity of 24 h aldosteronuria (44%), which remain mediocre [23].

1.4. N-terminal probrain natriuretic peptide (NT-proBNP)

N-terminal probrain natriuretic peptide (NT-proBNP) may in the future prove to be a PA marker in association with ARR. It correlates positively with ARR, negatively with renin level, and may be an independent marker of positive response to the IV saline suppression test, identifying patients at high risk of confirmed PA [24,25]. This assay, however, could only contribute to diagnosis in the absence of pathologies tending to elevate NT-proBNP (heart or kidney failure).

2. Assay methods

2.1. Plasma aldosterone assay

Plasma aldosterone may be assayed: