



Pitfalls in the preoperative and postoperative workup of patients with primary aldosteronism

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We were highly interested in the findings of Vignaud *et al.*'s study (1), which showed that preoperative workup was consistent with guidelines for only 40% of the patients with primary aldosteronism (PA). In addition, they found that complete biological success was not sufficiently assessed after surgery, and no differences in surgical outcomes were observed between patients operated based on the results of adrenal computed tomography (CT) scanning or adrenal venous sampling (AVS).

It is known that PA is the most frequent cause of endocrine arterial hypertension and it is associated with a higher cardiometabolic risk than primary hypertension (2,3). However, despite its importance, PA remains highly underdiagnosed (4), and the PA management guidelines are poorly applied for its detection and management (2,3). At the moment, the real-life situation is that only 1.9% of the expected cases of PA are diagnosed and as a consequence, just 1% of the expected adrenalectomies are performed (4). In addition, discrepant recommendations were identified at all management steps (screening, confirmation, classification, treatment and follow-up) among 12 guidelines for the diagnosis and treatment of PA, published between 2006 and 2016 (5).

In terms of the preoperative work-up, no consensus

exists about which aldosterone to renin ratio should be used for PA screening, nor what confirmatory test is the most reliable to confirm autonomous aldosterone secretion (2,3). Nevertheless, as Vignaud *et al.* (1) highlighted, the most challenging diagnostic step is the subtyping of PA since CT and magnetic resonance imaging (MRI) are considered unreliable procedures to differentiate between unilateral and bilateral PA, with a reported discordance between these techniques and AVS of 38% (6). Thus, the last guidelines recommend that when surgical treatment is desired by the patient, an experienced radiologist should use an AVS to make the distinction between unilateral and bilateral disease (3). The exceptions proposed by the guidelines for performing AVS are to suspect an adrenocortical carcinoma, cortisol co-secretion or an age <35 years old and clear unilateral adrenal nodule in CT/MRI (2,3). However, there is a gap between clinical guidelines recommendations and current clinical practice. In this regard, as it has been reported by Vignaud *et al.* (1), only 31% of the patients with PA underwent AVS before surgery and preoperative AVS was "adequately" performed in just 40% of the cases (2,3). These results are in agreement with the described in the SPAIN-ALDO study, where only 35% of the patients had

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an available AVS (7). The criteria for using AVS are quite heterogeneous across centers. For example, in the Vignaud series (1), some centers hardly ever used the procedure, others limited AVS use to specific situations such as bilateral lesions on imaging, small lesions on imaging or large number of preoperative antihypertensive treatments, and others followed strictly the French recommendations. Nonetheless, in this study, there was no correlation between complete clinical success and the completeness of preoperative workup. These results are in line with the described in the unique prospective randomized study published comparing CT-based and AVS-based management (8). However, we have to take into account that SPARTACUS study has several limitations, including that they selected the most severe group of patients with PA; the four cases in whom AVS failed were included in the CT cohort; the difficulties in reconciling CT diagnoses between cooperating institutions and the study was not generated to evaluate secondary endpoints (hypertension cure and biochemical cure) (8).

Other factors that may justify the existence of a heterogeneous use of AVS is the lack of consensus about which is the best approach in the AVS: (I) some authors defend the use of adrenocorticotrophic hormone (ACTH) stimulation during AVS since its use results in a higher proportion of successful samples, while other authors found that its use may lead to an inversion of the lateralization index (LI) to the wrong side (9); (II) adrenal venous samples might be obtained simultaneously or sequentially; but, although with simultaneous sampling thought to potentially avoid problems related with ACTH fluctuation, simultaneous sampling increased technical difficulty of the AVS; (III) discontinuing renin angiotensin-system-interfering medications is not always feasible, so some authors have proposed the possibility of continuing some of these medications such as mineralocorticoid receptors antagonist during the procedure as long as renin levels remained unsuppressed (10). Furthermore, the interpretation of the results is not easy nor is it standardized, varying the cutoff values of the selectivity index (SI), LI and contralateral suppression index between centers. Theoretically, the AVS, despite correct implementation and interpretation, can fail in certain situations: (I) abnormal adrenal venous drainage (accessory hepatic vein, double veins or cannulation of veins not draining the aldosterone producing adenoma); (II) bilateral PA with asymmetrical production of aldosterone or cortisol; (III) Conn's syndrome may lead to a higher rate of misclassified AVS;

(IV) stress reaction starting the procedure may alter the LI. All these factors may contribute to the quite low use of the AVS in the subtyping diagnosis of PA. This finding challenges the current recommendation to perform AVS in all patients with PA. On the other hand, NP59 scintigraphy or positron emission tomography (PET)-metomidate could be considered in certain clinical situations, especially when the AVS is unsuccessful or the results are indeterminate (11).

Finally, although there is plenty of evidence about the positive effect of adrenalectomy for PA on cardiometabolic outcomes, the reported rates of complete clinical cure are as low as 30–40% in most of the series (3,12), even though it has been reported that some patients classified as cured may developed hypertension after a relative short-term follow-up. For example, in the Vignaud study (1), 16% of the patients considered as cured at the first follow up (median 43 days) had contradictory results at the second follow-up visit (median 377 days) due to the resumption of antihypertensive drugs. The criteria to classify outcomes of adrenalectomy for unilateral PA are quite heterogeneous. Thus, it is essential to standardize the way of publishing the outcomes (*Table 1*) (13), which implies hormonal determination once the patient has undergone surgery, as well as a minimum follow-up time. The outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) are the most widely used (*Table 1*) (13). Based on them, complete clinical success is defined by normal blood pressure without antihypertensive medication after surgery. At the last follow-up, it was achieved in 31% of patients in the series of Vignaud (1). These results are in accordance with the reported in our Spanish registry, of 38% (14). Nevertheless, it should be noted that even biochemical cure without hypertension cure is associated with an improvement in the cardiometabolic risk and a major increase in health-related quality of life (HRQoL) after surgery. In this way, it has been recently described that correction of hypokalemia and control of diastolic blood pressure are essential factors contributing to the improvement in the HRQoL in patients with PA (15).

The ideal situation will be to predict before surgery which PA patients are going to have hypertension cure. In this regard, several prognostic models have been proposed to predict outcome after adrenalectomy. In agreement with the results of the Eurocrine Study Group (1), the SPAIN-ALDO score includes female sex, use of two or fewer antihypertensive medications, hypertension grade 1, no type 2 diabetes and non-obesity as the predictive variables of hypertension cure. The chance of hypertension cure was

Table 1 Outcomes after adrenalectomy for unilateral primary aldosteronism (PASO criteria) (13)

Outcome	Clinical	Biochemical
Complete success (remission)	Normal BP without antihypertensive medication	1. Hypokalemia correction (if present before operation) and 2. Normalization of ARR or 3. Aldosterone suppressed during confirmatory testing if ARR increased postoperatively
Partial success (improvement)	Stable BP with less antihypertensive medication or lower BP with an equal or a smaller number of antihypertensive drugs	1. Correction of hypokalemia (if present before surgery) and increased postoperative ARR And at least one of the following (compared with presurgical): 2. Decreased $\geq 50\%$ in basal aldosterone levels or 3. Abnormal but improved postoperative aldosterone during confirmatory testing
Absence of success (persistence)	Unchanged or higher BP with equal or greater n° of antihypertensive drugs	1. Persistent hypokalemia (if present before operation) or 2. Persistent increase in ARR after surgery and 3. Failure to suppress aldosterone secretion during confirmatory testing

BP, blood pressure; ARR, aldosterone-to renin ratio.

80.4% if all these variables were present before surgery (14). Nevertheless, in the Vignaud *et al.* (1) study, body mass index, duration of hypertension, and number of antihypertensive drugs were the important predictive variables of hypertension cure identified on the multivariate analysis.

In conclusion, there are still several pitfalls and limitations in the diagnosis of PA, including case detection, confirmatory and subtyping diagnosis. The rates of complete clinical cure are still quite low, probably related to the selection of surgical patients. AVS is the best lateralization test at present, although it has several limitations, including that it is not universally available, it is not a standardized test, neither the technique nor the interpretation of the results and has a modest correct catheterization rate in multiple studies and therefore not easily reproducible. The available evidence should act as a wake-up call to improve the way we select patients' candidates for surgical treatment.

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