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A Case of Adrenal Vein Sampling in Primary Aldosteronism With Homolateral Suppression

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Context: Adrenal venous sampling (AVS) is regarded as the gold standard for diagnosis of primary aldosteronism (PA) subtypes, although some authors have questioned its diagnostic accuracy and highlighted the lack of standardized procedure protocols and interpretation criteria for AVS. In particular, the usefulness of cosyntropin stimulation and benefit of superselective adrenal vein catheterization have been hotly debated.

Objective: We report a case that highlights the potential pitfalls of superselective sampling and demonstrates a negligible effect of cosyntropin stimulation on aldosterone secretion in nonadenomatous adrenal tissue when an aldosterone-producing adenoma (APA) is present.

Intervention and Results: A 38-year-old man with PA and a single right macroadenoma underwent AVS at our center. The procedure was performed both under basal conditions and during cosyntropin stimulation. Right adrenal vein angiography demonstrated two branches of the main adrenal vein trunk, one draining the nodule and one draining the right adrenal gland. Hormonal assays confirmed adrenal origin of left-sided and all right-sided samples, and were consistent with lateralization on the right side, with suppression of aldosterone secretion in the left adrenal gland and in the nonadenomatous right adrenal tissue. Cosyntropin-stimulated AVS results were similar to those of the unstimulated procedure.

Conclusions: Cosyntropin stimulation does not significantly affect aldosterone secretion from nonadenomatous adrenal tissue when an APA is present and can therefore be used during AVS for PA. Superselective AVS should be performed with caution and interpreted by expert clinicians.

Freeform/Key Words: aldosterone, aldosterone-producing adenoma, adrenal vein sampling, endocrine hypertension

Diagnostic work-up in primary aldosteronism (PA) requires subtype differentiation, which is key for determining the optimal therapeutic plan [1]. Adrenal venous sampling (AVS) is the recommended procedure to distinguish unilateral from bilateral forms of PA. Unfortunately, AVS still lacks a standardized protocol, despite recent efforts to achieve consensus on this matter [2, 3]. Different centers adopt different approaches and schedules in performing the sampling (*e.g.*, bilateral simultaneous sampling vs sequential cannulation of adrenal veins; central vein vs superselective sampling from secondary adrenal vein branches; use of

Abbreviations: ACR, aldosterone/cortisol ratio; APA, aldosterone producing adenoma; AVS, Adrenal venous sampling; IVC, inferior vena cava; LI, lateralization index; PA, primary aldosteronism.

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cosyntropin stimulation) and several different cutoff values with respect to the selectivity index and lateralization ratio have been proposed to define successful adrenal vein cannulation and lateralized aldosterone overproduction [2, 3].

The case we report here enables discussion and provides useful answers concerning two debated issues related to the performance and interpretation of AVS, namely, the use of superselective adrenal vein cannulation and the benefit of cosyntropin stimulation.

1. Case Report

We report the case of a 38-year-old man who was referred to our Hypertension Unit with a confirmed PA diagnosis (Table 1). Contrast-enhanced abdominal computed tomography scanning revealed a normal left adrenal gland and an exophytic right adrenal nodule measuring 22 mm in diameter (Fig. 1). AVS was performed under basal conditions and during continuous cosyntropin infusion (50 μg/h). On the right side, the radiologist initially placed the catheter just at the outlet of the main adrenal vein trunk in the inferior vena cava (IVC), and was therefore able to stain by venography two secondary adrenal vein branches: the first, in the cranial position, seemed to drain the body and the limbs of the gland, whereas a second branch, caudally directed, seemed to drain only the right nodule (Fig. 2). Samples were obtained initially by placing the catheter tip at the outlet of the main adrenal vein trunk in the IVC (sample 1; Table 2), and then by deeply inserting the catheter in both of the secondary branches (sample 2 from the upper branch draining the body and the limbs, and sample 3 from the caudal branch draining the nodule; Table 2). Two of the three samples from the right side (one collected from the main right adrenal vein trunk and one from the nodule-draining secondary branch) showed a high cortisol-corrected aldosterone concentration, whereas the other (the one collected from the whole gland-staining secondary branch) showed an aldosterone/cortisol ratio (ACR) that was lower than that measured in the IVC. The left-sided sample also showed a low cortisol-corrected aldosterone concentration that was inferior to that measured in the IVC. Interestingly, both in the unstimulated and in the cosyntropin-stimulated procedures, this condition of "suppression" of aldosterone production could be observed. The lateralization index (LI, defined as the ACR from the dominant adrenal over the ACR from the nondominant adrenal), using sample 3 on the right side, was 7.2 under basal conditions and 13.8 during cosyntropin infusion; the ACR, using sample 2 on the right side, was found to be inferior to the ACR from the IVC, which indicated suppression of aldosterone production, both under basal and cosyntropin-stimulated conditions, and was similar to the findings for the left adrenal vein. The patient underwent right total laparoscopic adrenalectomy.

Immunohistochemical staining of the adrenal nodule and the surrounding adrenal gland, using specific antibodies for 11β-hydroxylase and aldosterone synthase (provided by Celso Gomez-Sanchez, University of Mississippi, Jackson, MS) [4], showed nonhomogeneous aldosterone

Table 1. Clinical and Biochemical Parameters of the Patient

Clinical and Biochemical Parameters	At Diagnosis	Normal Values
SBP/DBP (mm Hg)	175/115	<140/90
No. of drugs	2	—
Serum potassium (mmol/L)	2.6	3.5–5.5
Creatinine (mg/dL)	1.03	0.7–1.4
DRC (μU/mL]	3.8	7–76
Serum aldosterone (ng/dL)	34.8	7–30
ACTH (pg/mL)	19.1	17–70
Cortisol at 8:00 AM (μg/dL)	28.4	5–25
Cortisol after DST (μg/dL)	0.1	≤1.8
Serum aldosterone post-SLT (ng/dL)	49.7	≤5

Abbreviations: ACTH, adrenocorticotropic hormone; DBP, diastolic blood pressure; DRC, direct renin concentration; DST, dexamethasone suppression test; SBP, systolic blood pressure; SLT, intravenous saline load test.

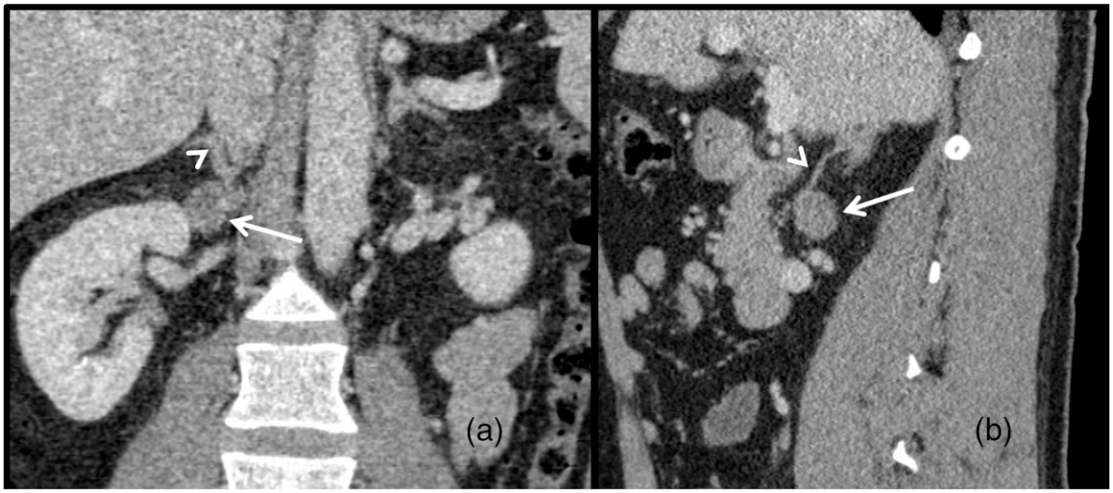

Figure 1. Computed tomography scan images of the right adrenal gland. (a) Frontal view. Arrowhead: adrenal gland body; arrow: right adrenal nodule. (b) Sagittal view. Arrowhead: adrenal gland body; arrow: right adrenal nodule.

synthase staining exclusively present in the adrenal nodule, and it was absent in the surrounding adrenal cortex [Supplemental Fig. 1(A)], indicating that the source of aldosterone excess was the nodule and that aldosterone production in the surrounding adrenal zona glomerulosa was suppressed. 11β-hydroxylase staining was present both in the adrenal surrounding the nodule and, less strongly, inside the nodule [Supplemental Fig. 1(B)]. After surgery, blood pressure and potassium levels were normalized and the patient is now free from medication. The study was approved by the local ethics committee and the patient gave his written consent.

A case with similar findings and "homolateral suppression," despite the presence of an aldosterone-producing cell cluster outside of the main nodule, is provided in the supplemental file (Supplemental Table 1; Supplemental Fig. 2).

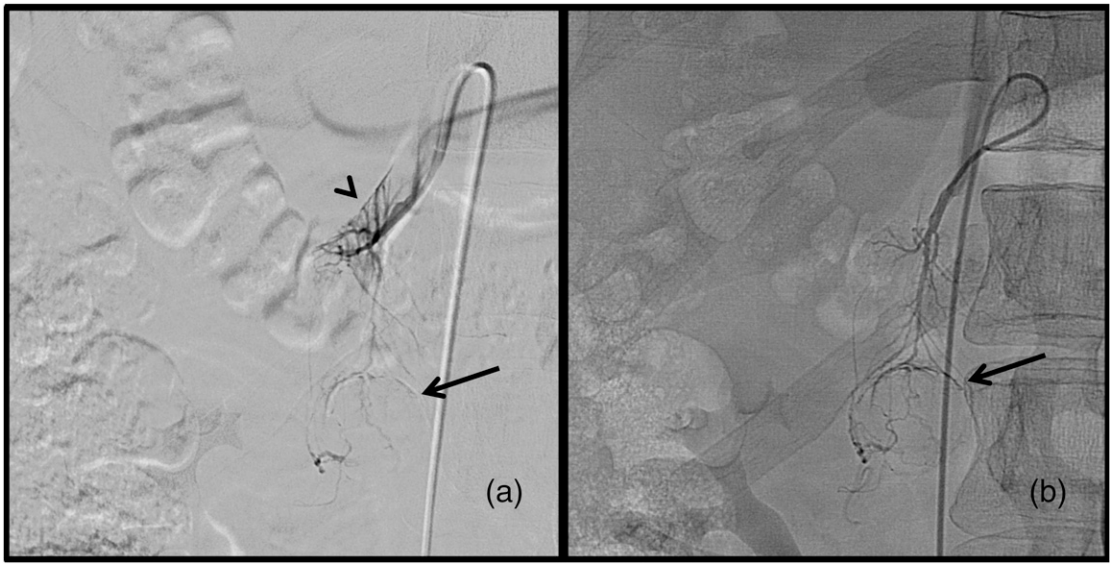

Figure 2. Venography during AVS. (a) Cannulation of the right adrenal vein branch draining the right adrenal gland; arrowhead indicates adrenal gland venography; a pale staining of right adrenal vein branches surrounding right adrenal adenoma is also seen (due to partial passage of contrast medium in the other adrenal vein branch). (b) Selective cannulation of the right adrenal vein branch draining the right adrenal nodule; the arrow points to adrenal vein branches surrounding the right adrenal nodule.

Table 2. Hormonal Measurements From AVS

AVS Hormonal Values					
Unstimulated AVS	**Routine Cortisol (μg/dL)**	**Aldosterone (ng/dL)**	**SI**	**ACR**	**IR**
Infrarenal IVS	18.3	27.6	—	1.5	—
Left adrenal vein	112	52	6.1	0.5	0.3
Right adrenal vein, sample 1	519	1277	28.4	2.5	1.6
Right adrenal vein, sample 2	428	86	23.4	0.2	0.1
Right adrenal vein, sample 3	625	2237	34.2	3.6	2.4
Cosynthropin-Stimulated AVS	**Routine Cortisol (μg/dL)**	**Aldosterone (ng/dL)**	**SI**	**ACR**	**IR**
Infrarenal IVS	32.1	60	—	1.9	—
Left adrenal vein	312	139	9.7	0.4	0.2
Right adrenal vein, sample 1	840	2927	26.2	3.5	1.8
Right adrenal vein, sample 2	718	209	22.4	0.3	0.2
Right adrenal vein, sample 3	1019	5581	31.7	5.5	2.9

Abbreviations: IR, ipsilateral ratio; SI, selectivity index.

2. Discussion

In this case report, AVS results showed low cortisol-corrected aldosterone concentration, not only on the left side, contralateral to the adenoma, but also in one of two different sites of blood sampling on the right side, both of adrenal origin. In both the left-sided sample and in the right-sided sample, the ACR was less than that in the IVC. This has been called "contralateral suppression" when applied to the side contralateral to an adrenal adenoma [2, 3]. Contralateral suppression has been proposed as an additional criterion to detect lateralized aldosterone production [2, 3], and some authors consider it a necessary prerequisite before adrenalectomy [5, 6]. The findings in our patient can be interpreted in light of the fact that blood in the different samples from the right adrenal vein comes from different regions of the gland, among which only one was producing high amounts of aldosterone; consequently, not only left-sided adrenal tissue aldosterone production, but also right nonadenomatous tissue aldosterone production, was suppressed.

We obtained right blood samples at the outlet of the main right adrenal vein trunk; we then initially inserted the catheter in the gland-staining cranial secondary branch, and then in the nodule-staining caudal secondary branch to perform a "superselective" adrenal vein cannulation, retrieving different samples of blood from different portions of the right-sided adrenal tissue. Selective adrenal vein cannulation has been shown to be necessary when right adrenal vein and accessory hepatic veins share the same point of entry into the IVC, to avoid excessive dilution of adrenal blood [3]. Superselective AVS has already been described in the literature and recommended as an accurate method to allow the localization of adrenal tissue involved in aldosterone hypersecretion [7]. As shown in Fig. 2, deep insertion and staining of the catheter just in the cranial vein branch would have apparently provided findings for the whole right adrenal gland. An inexperienced radiologist could have sampled blood from this site only, thereby missing the actual aldosterone-producing site, resulting in a misleading AVS finding of bilateral suppression of aldosterone production. Instead, when we sampled blood from just the outlet of the adrenal vein in the IVC, we were able to obtain a high aldosterone concentration and consequently did not miss the right aldosterone overproduction. Therefore, superselective AVS is a useful technique in selected situations, but should be performed cautiously so as to not miss any adrenal vein branches. Furthermore, superselective AVS increases the occurrence of adrenal hemorrhage [7], a complication that is very rare in standard AVS procedures [8].

Cosyntropin stimulation has been proposed to have a favorable effect in maximizing the adrenal-to-peripheral cortisol gradient, stimulating aldosterone secretion from the adenoma, increasing the LI, and reducing time-dependent fluctuations in hormone secretion. Recently, a

multicentric study demonstrated that cosyntropin administration during AVS does not significantly affect LI and results in a diagnosis similar to that of unstimulated AVS [9]. In the present clinical case, we observed a consistent pattern of suppression, both under basal conditions and after cosyntropin stimulation, not only on the side contralateral to the adenoma, but also from a sampling site on the same side of the node, wherein the extranodal adrenal tissue was drained. This observation reinforces the suggestion that cosyntropin stimulation does not significantly affect aldosterone gradients between the two adrenal glands when an adenoma is present and, therefore, cosyntropin stimulation does not interfere with the final diagnosis [6].

Finally, the immunohistochemical analysis demonstrated that the aldosterone producing adenoma (APA) was also cosecreting some cortisol, which was still suppressible during an overnight, 1-mg dexamethasone suppression test and was not sufficient to inhibit both adrenocorticotropic hormone secretion and 11β-hydroxylase expression outside of the adenoma. Of particular interest, the cosecretion of cortisol from the APA did not interfere with the diagnosis of unilateral PA, both under basal conditions and during cosyntropin infusion. APAs cosecreting cortisol have been described previously [10, 11]. It has been suggested that this phenomenon is more frequent in APAs of larger size; therefore, in these cases, a dexamethasone suppression test before performing AVS is warranted.

AVS, and particularly superselective AVS, is a challenging technique that is not available in most centers. In future, noninvasive procedures that are able to distinguish between unilateral and bilateral PA, such as positron emission tomography–computed tomography scanning using CYP11B2-specific radiolabeled tracer (12), may replace AVS in PA subtype differentiation.

3. Conclusion

In conclusion, this case demonstrates some potential pitfalls and offers insights into the use and interpretation of AVS in the diagnostic PA workup. This case shows the possible risks of superselective cannulation when it is not accurately performed; it may potentially result in a misleading diagnosis. In addition, we observed that cosyntropin stimulation did not stimulate aldosterone production from extranodal tissue homolateral to the adenoma; rather, cortisol-corrected aldosterone concentration appeared consistent with suppression both in veins draining the extranodal tissue homolateral to the adenoma and the contralateral adrenal gland. This observation reinforces the suggestion that cosyntropin stimulation does not affect the diagnosis of unilateral PA and can therefore be used during AVS.

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