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A CASE OF ADRENAL VEIN SAMPLING IN PRIMARY ALDOSTERONISM WITH "HOMOLATERAL SUPPRESSION"

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ABSTRACT

Context: Adrenal venous sampling (AVS) is regarded as the gold standard in primary aldosteronism (PA) subtype diagnosis, although some authors have questioned its diagnostic accuracy and highlighted its lack of standardization of procedure protocol and interpretation criteria. In particular, the usefulness of cosyntropin stimulation and benefit of super-selective adrenal vein catheterization have been hotly debated.

Objective: we report herein a case that highlights the potential pitfalls of super-selective sampling and demonstrates a negligible effect of cosyntropin stimulation on aldosterone secretion in non-adenomatous adrenal tissue when an aldosterone producing adenoma (APA) is present.

Case Report: a 38-year old man with PA and a single right macro-adenoma underwent AVS at our Centre. 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 non-adenomatous 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 non-adenomatous adrenal tissue when an APA is present and can therefore be used during AVS for PA. Super-selective AVS should be performed with caution and interpreted by expert clinicians.

INTRODUCTION

Diagnostic work-up in primary aldosteronism (PA) requires subtype differentiation that represents the key for optimal therapeutic plan [1]. Adrenal venous sampling (AVS) is the recommended procedure to distinguish unilateral from bilateral forms. Unfortunately AVS still lacks of a standardized protocol, despite recent efforts to achieve consensus on this topic [2,3]. Different Centres adopt different schedules in performing the sampling (e.g., bilateral simultaneous sampling versus sequential cannulation of adrenal veins; central vein versus super-selective sampling from secondary adrenal vein branches; use of cosyntropin stimulation) and several different cut-off values of selectivity index and lateralization ratio have been proposed to define successful adrenal vein cannulation and lateralized aldosterone overproduction [2,3].

The case we report herein allows discussion and provides useful answers about two debated issues on performance and interpretation of AVS, namely the use of super-selective adrenal veins cannulation and the benefit of cosyntropin stimulation.

CASE REPORT

We report the case of a 38-years-old man 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 a exophytic right adrenal nodule 22 mm in diameter (Figure 1). AVS was performed under basal conditions and during continuous cosyntropin infusion (50 μg/h). On the right side the radiologist placed the catheter at first just at the outlet of the main adrenal vein trunk in the inferior vena cava (IVC), being able to stain by venography two secondary adrenal vein branches: one, in the cranial position, seemed to drain the body and the limbs of the gland, whereas a second branch, caudally directed, seemed to drain just the right nodule (Figure 2). Samples were obtained initially 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 (the one collected from the main right adrenal vein trunk and the 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 IVC. The left-sided sample showed a low cortisol-corrected aldosterone concentration as well, that was again inferior to that measured in 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 dominant adrenal over the ACR from non-dominant adrenal) using sample 3 on the right side was 7.2 under basal conditions and 13.8 during cosyntropin infusion; the ACR using the sample 2 on the right side resulted inferior to the ACR from the IVC, indicating suppression of the aldosterone production, both under basal and cosyntropin-stimulated conditions, similarly to the left adrenal vein. The patient underwent right total laparoscopic adrenalectomy.

Immunohistochemical staining of the adrenal nodule and of the surrounding adrenal gland, using specific antibodies for 11β-hydroxylase and aldosterone synthase (from Prof. Celso Gomez-Sanchez, University of Mississippi, Jackson, MS) [4] showed non-homogeneous aldosterone synthase staining exclusively present in the adrenal nodule, and it was absent in the surrounding adrenal cortex (Supplemental Figure S1A), 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 Figure S1B). After surgery, blood pressure and potassium levels were normalized and the patient is now free from medication. The study was approved by the local ethic 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 the main nodule is provided in the supplemental file (supplemental Table S1 and Figure S2).

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. Both in the left-sided sample and in the right-sided sample the ACR was less than that in 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]. These findings can be interpreted considering that blood in the different samples from the right adrenal vein come 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 non-adenomatous tissue aldosterone production was suppressed.

We obtained right blood samples at the outlet of the main right adrenal vein trunk; we then inserted the catheter at first in the gland-staining cranial secondary branch, and then in the nodule-staining caudal secondary branch to perform a “super-selective” 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]. Super-selective adrenal venous sampling has been already described in literature and advocated as accurate method to allow the localization of adrenal tissue involved in aldosterone hypersecretion [7]. As shown in Figure 2, deep insertion and staining of the catheter just in the cranial vein branch

would have apparently demonstrated 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 just from the outlet of the adrenal vein in the IVC, we were able to obtain a high aldosterone concentration and consequently not miss the right aldosterone overproduction. Therefore, super-selective AVS is a useful technique in some selected situations but should be performed with the caution of not missing any adrenal vein branches. Furthermore, super-selective AVS increases the occurrence of adrenal hemorrhage [7], a complication that is very rare in standard AVS procedure [8].

Cosyntropin stimulation has a proposed 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 affect significantly LI and gives a similar diagnosis as with unstimulated AVS [9]. In the present clinical case we observed, both under basal conditions and after cosyntropin stimulation, a consistent pattern of suppression not only on the side contralateral to the adenoma, but also from a sampling site on the same side of the node, draining the extra-nodal adrenal tissue. This observation reinforces suggests that cosyntropin stimulation does not significantly affect aldosterone gradients between the two adrenal glands when an adenoma is present and, therefore, it does not interfere with the final diagnosis [6].

Finally, the immunohistochemical analysis demonstrated that the APA was also cosecreting some cortisol, still suppressible during overnight 1 mg dexamethasone suppression test and not sufficient to inhibit both ACTH secretion and 11β-hydroxylase expression outside 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. APA cosecreting cortisol have been described previously [10,11]. It has been suggested that this phenomenon is more frequent in

APA of greater size and therefore in these cases a dexamethasone suppression test before AVS performance is warranted.

AVS, and particularly super-selective AVS, is a challenging technique not available in most centres. In future, non-invasive procedures able to distinguish between unilateral and bilateral PA, such as PET-CT scanning using CYP11B2-specific radiolabelled tracer (12), may substitute AVS in PA subtype differentiation.

CONCLUSION

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

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Clinical and biochemical parameters	At diagnosis	Normal values
SBP/DBP (mmHg)	175/115	≤140/90
Number 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 a.m. (μg/dL)	28.4	5-25
Cortisol after DST (μg/dL)	0.1	≤1.8
Serum Aldosterone post-SLT (ng/dL)	49.7	≤5

Table 1. Clinical and biochemical parameters of the patient. SBP= Systolic Blood Pressure; DBP= diastolic blood pressure; DRC= direct renin concentration; ACTH= adrenocorticotropic hormone; DST= dexamethasone suppression test.

AVS hormonal values					
Unstimulated AVS	**Routine Cortisol (µg/dl)**	**Aldosterone (ng/dl)**	**SI**	**ACR**	**IR**
Infra-renal inferior vena cava	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**
Infra-renal inferior vena cava	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

Table 2. Hormonal measurements from adrenal venous sampling. AVS= Adrenal Venous Sampling; SI= Selectivity Index; ACR= Aldosterone/Cortisol Ratio; IR= Ipsilateral Ratio.

LEGENDS TO FIGURES

Legend to figure 1. CT-scan images of the right adrenal gland. A: frontal view; arrow-head: adrenal gland body; arrow: right adrenal nodule. B: sagittal view; arrow-head: adrenal gland body; arrow: right adrenal nodule. CT: see text.

Legend to figure 2. Venography during AVS. A: cannulation of the right adrenal vein branch draining the right adrenal gland; arrow-head 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 at adrenal vein branches surrounding the right adrenal nodule.