

## Case Report

# Adrenal Vein Sampling in a Patient With Primary Hyperaldosteronism and Severe Contrast Allergy

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**Abbreviations:** ACTH, adrenocorticotropic hormone; AVS, adrenal vein sampling; CO<sub>2</sub>, carbon dioxide; CT, computed tomography; HSR, hypersensitivity reaction; ICM, iodinated contrast media; PA, primary hyperaldosteronism; PAC, plasma aldosterone concentration; PCC, plasma cortisol concentration; SI, selectivity index.

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## Abstract

We report on a case of a 50-year-old female patient with primary hyperaldosteronism, in whom adrenal venous sampling was required to differentiate between unilateral and bilateral disease. Because of a history of severe allergy to iodinated contrast media, premedication with glucocorticoids was indicated. Exogenous glucocorticoids, however, can affect measurements of serum cortisol. To avoid this potential confounding effects on the cortisol assay, we decided to use dexamethasone instead of prednisolone or hydrocortisone. A high-dose adrenocorticotropin (ACTH) stimulation test with the simultaneous use of dexamethasone revealed an adequate adrenal cortisol response. ACTH-stimulated adrenal venous sampling showed reliable results, which provided a solid basis for further clinical decision-making.

**Key Words:** dexamethasone, adrenal vein sampling, primary hyperaldosteronism, contrast allergy, ACTH stimulation test

Primary hyperaldosteronism (PA) is defined as autonomous overproduction of aldosterone from the adrenal gland(s). PA results in excessive water and sodium retention, kaliuresis, and inflammation-induced fibrosis in target organs such as the heart and kidney. This may lead

to therapy-resistant hypertension and hypokalemia and is associated with an additionally increased risk of end-organ damage leading to cardiovascular and renal complications [1–10]. Early diagnosis and appropriate treatment is essential to prevent these deleterious outcomes [1,3,5,7,10–16].

PA is commonly caused by either an aldosterone-producing adenoma of the adrenal gland or idiopathic bilateral aldosterone hypersecretion. Other less frequent causes include unilateral hyperplasia, bilateral adenomas, and monogenetic variants. The distinction between bilateral and unilateral forms of PA is required for the selection of the most appropriate treatment. Imaging of the adrenal glands with computed tomography (CT) or magnetic resonance imaging is recommended to help delineate the subtype. The Endocrine Society Clinical Practice guidelines recommends adrenal vein sampling (AVS) as the preferred method in determining the etiology of hyperaldosteronism [17]. Unilateral disease is associated with a marked (4-fold greater than contralateral adrenal) increase in plasma aldosterone concentration (PAC) to plasma cortisol concentration (PCC) ratio on the affected side. In patients with bilateral hyperplasia there is little difference (less than 3-fold difference in PAC/PCC ratio without contralateral suppression) between the 2 sides. Correct and reliable PCC measurements are therefore paramount for a correct interpretation of AVS (see Table 1).

During the AVS procedure, intravenous iodinated contrast media (ICM) is used to confirm proper placement of the catheter. The use of ICM carries a risk of causing severe allergic reactions. Normally, premedication including glucocorticoids and antihistaminic agents are used to prevent potentially fatal reactions such as a compromised airway or anaphylactic shock [18]. However, use of a synthetic glucocorticoid could potentially interfere with the cortisol assay and may blunt the adrenocorticotrophic hormone (ACTH)-driven release of adrenal hormones [19]. This would influence all AVS parameters that rely on PCC

(selectivity index, lateralization index, and contralateral suppression index) (Table 1) and thereby negatively affect the reliability of AVS interpretation. Consequently, this premedication could lead to false AVS results and therefore inappropriate treatment in these patients with PA.

We here describe a case of a patient with PA and severe allergy to ICM. She underwent ACTH-stimulated AVS, with the concomitant use of dexamethasone to prevent a severe allergic reaction to the ICM. The AVS revealed accurate and reliable results.

## Case Presentation

A 50-year-old female patient was referred to our outpatient clinic because of biochemically confirmed PA. She had a 3-year history of difficult-to-control hypertension, along with intermittent headaches, palpitations, decreased energy, and easy fatigability for the past year. She experienced a wide range of cognitive symptoms, malaise, and was unable to work. Plasma renin concentration before saline infusion at the referring hospital was 3.2 ng/L and PAC was 514 pmol/L. The aldosterone/renin ratio was 160 pmol/ng. After salt loading the plasma renin concentration was 1.2 ng/L and the PAC was 296 pmol/L. A CT of the abdomen showed no adrenal abnormalities. To distinguish between bilateral and unilateral forms of PA, AVS was required. Unfortunately, she had a history of severe allergy to ICM, which had previously caused an episode of dyspnea and swollen throat. Due to this history of a prior severe allergic reaction to ICM, pre-treatment with glucocorticoids and antihistaminic agents was required.

**Table 1.** Interpretation of adrenal venous sampling

Index	Formula	Interpretation
Selectivity index	$PCC_{side}/PCC_{IVC}$	Values $\geq 3$ confirm that the sample was obtained in the adrenal vein.
Lateralization index	$(PAC_{dominant}/PCC_{dominant}) / (PAC_{nondominant}/PCC_{nondominant})$	Values $>3$ to 4 indicate lateralized aldosterone excess.
Contralateral suppression index	$(PAC_{nondominant}/PCC_{nondominant}) / (PAC_{IVC}/PCC_{IVC})$	Values below the cutoff [1] indicate suppression of aldosterone secretion in the nondominant gland.

In adrenal venous sampling (AVS), aldosterone and cortisol concentrations are measured in blood samples from 3 sites [right adrenal vein, left adrenal vein, and vena cava inferior (IVC)], often under continuous cosyntropin [synthetic adrenocorticotrophic hormone (ACTH)] infusion. Absolute values and accurate laboratory assays for cortisol and aldosterone are essential for successful interpretation of the data. The plasma cortisol concentrations (PCC) from the adrenal veins and IVC are used to confirm successful cannulation of both adrenal veins. The calculated selectivity index (SI) is the most popular technique to confirm the success of AVS [43]. The finding of a concentration gradient between a blood sample in an adrenal vein and the IVC indicates the correct placement of the catheter's tip into the adrenal vein. Most centres use an SI cut-off of 3 or greater for AVS performed during ACTH stimulation [43]. The lateralization index (LI; high-side adrenal vein PAC/PCC divided by low-side adrenal vein PAC/PCC) is the index used for assessment of lateralization of aldosterone excess and is the primary endpoint of AVS. Because of the dilutional effect of the samples by nonadrenal blood, the adrenal aldosterone levels are corrected by the plasma cortisol concentration. Most centers use LI between 3 and 4 during ACTH stimulation. Ratios  $\leq 3$  are consistent with bilateral aldosterone secretion [21,43]. In patients with unilateral disease the aldosterone/cortisol ratio for the nondominant adrenal is less than or equal to the corresponding ratio for the peripheral vein [21,44-46]. This is called "contralateral suppression" and confirms unilateral disease of the other adrenal gland.

Abbreviations: dominant, side with higher plasma aldosterone concentration; IVC, inferior vena cava, nondominant, side with lower plasma aldosterone concentration; PAC, plasma aldosterone concentration; PCC, plasma cortisol concentration.

To avoid the potential confounding effects on the cortisol assay, we decided to use dexamethasone as anti-allergic premedication. Since it was unclear whether the adrenal response to ACTH would be intact if the patient was using high-dose dexamethasone, a high-dose ACTH stimulation test with the simultaneous use of dexamethasone was performed first.

Per protocol, the patient was administered dexamethasone 8 mg (as an equivalent of 50 mg prednisolone) orally both at 9 PM and the next morning at 7 AM. The cortisol concentration was 218 nmol/L, measured at the moment of admission at the hospital, before the administration of dexamethasone. One hour before the second dexamethasone dose, an intravenous bolus of 250 µg ACTH (Synacthen®) was administered. After 60 min, the serum cortisol concentration rose adequately to 812 nmol/L. Reference values for a normal cortisol response was >430 nmol/L after 250 µg ACTH (Roche Elecsys Cortisol gen2 ECLIA, Roche Diagnostics, Mannheim, Germany; AB\_2811288) [20]. This confirmed a normal cortisol response to ACTH stimulation despite the use of high dose dexamethasone. The PAC prior to dexamethasone administration was 540 pmol/L (18.53 ng/dL; reference: 110-1200 pmol/L). After the bolus ACTH and 1 dose of dexamethasone, it was 740 pmol/L. The same day, the patient underwent AVS using continuous ACTH stimulation. AVS was successful and uncomplicated; results are shown in Table 2. The mean selectivity index was 17 on the right side and 32.6 on the left side. The mean aldosterone/cortisol ratio in the adrenal veins of the 2 samples was 1.8 on the right and 2.29 on the left, amounting to a left-to-right lateralization index of 1.30. The aldosterone/cortisol ratio in each adrenal vein was greater than the corresponding ratio in the inferior vena cava, further confirming bilateral aldosterone overproduction. Altogether, the AVS produced reliable results and indicated bilateral adrenal excessive aldosterone production, with a slight dominance to the left adrenal gland.

Treatment with spironolactone was added to her baseline medication, which consisted of doxazosin 8 mg, metoprolol 100 mg, nifedipine 60 mg, and perindopril 8 mg. Her cognitive symptoms did not improve, and she experienced troubling side effects. Therefore, despite evidence of bilateral aldosterone production, she elected to undergo unilateral adrenalectomy (left side) to reduce the degree of aldosterone excess and, consequently, the severity of the PA phenotype.

She underwent uncomplicated laparoscopic unilateral adrenalectomy, and histopathology revealed micronodular adrenal hyperplasia. The postsurgical saline infusion test showed suboptimal suppression of aldosterone [nadir: 185 nmol/L (6.67 ng/dL)], and low-dose eplerenone was initiated. Cognitive functioning normalized and remained normal now up to 2 years after surgery, but hypertension persisted so she received low-dose eplerenone in addition to 2 antihypertensive drugs, consisting of amlodipine 10 mg and perindopril 8 mg.

## Discussion

Here we demonstrate that successful and reliable AVS is possible in patients with severe PA and a known allergy to ICM if high-dose dexamethasone with concomitant continuous ACTH infusion is used.

Distinguishing the subtype of PA is key to determine the best treatment options. AVS is generally required to differentiate between unilateral and bilateral disease [17,21]. ICM is essential for successful angiographic localization of the adrenal veins. ICM is generally safe, but adverse hypersensitivity reactions (HSR) after the administration of ICM are a continuous challenge in clinical practice. Adverse events after ICM exposure are classified into immediate HSR (onset immediately up to 1 h after administration of the agent and presents with symptoms of anaphylaxis) and nonimmediate HSR (start more than

**Table 2.** Adrenal venous sampling results

	Aldosterone (nmol/L)	Aldosterone (ng/dL)	Cortisol (nmol/L)	Cortisol (µg/dL)	Selectivity Index (mean)	Adrenal aldosterone: cortisol ratio (mean)	Lateralization Index
Right adrenal vein					17.0	1.8	0.77
Sample 1	30.1	1085.0	21,212	768.9			
Sample 2	36.0	1297.6	16,431	595.6			
Left adrenal vein					32.6	2.29	1.30
Sample 1	82	2955.7	35,708	1294.4			
Sample 2	83	2991.7	36,346	1317.5			
Inferior vena cava							
Sample 1	0.67	24.2	1,122	40.7			
Sample 2	0.66	23.8	1,112	40.3			
Sample 3	0.75	27.0	1,078	39.1			

1 h up to 10 days after administration and presents with exanthems), with different mechanisms. Reported data of previous studies have shown that the incidence of acute adverse reactions to ICM varied widely because of different definitions. Reported incidence rates are 0.15% to 2% with low-osmolarity contrast agents, with >98% being mild and self-limiting [22-29]. Battistel et al found that 2.6% of patients with PA selected for AVS reported a history of severe ICM allergy requiring premedication [30]. Several risk factors for developing repeat reaction to ICM are being discussed. The commonly agreed-on risk factor is a history of an immediate adverse reaction to the ICM [28,29,31,32]. Park et al found that patients with severe initial HSR exhibit a higher recurrence rate of severe HSR compared to patients with moderate initial HSR [29].

Alternative methods that permit invasive imaging of adrenal veins are required in patients with contraindication to ICM. One potential method is the use of gadolinium as an alternative contrast agent. The use of gadolinium contrast to visualize visceral, peripheral, carotid, or coronary arteries has been reported in patients with contraindications for ICM or renal insufficiency [33-35]. Sasamura et al reported the use of gadolinium for venography of the adrenal veins in a patient with ICM allergy without any side effects [36]. A reaction to both ICM and gadolinium is believed to be a rare event [37] because they are chemically distinct compounds with structural differences. In 1 study, the incidence rate of acute allergic-like reactions to both agents in patients who have received both types of contrast media for imaging studies was reported [37]. The overall incidence rates of reaction to ICM and gadolinium were 0.48% and 0.17%, respectively; 0.024% of patients had reactions to both ICM and gadolinium. None of the reactions was reported to be moderate or severe.

Mistuba et al described 2 cases of PA patients in which gadopentetate dimeglumine, gadolinium chelated by diethylenetriamine pentaacetate, was used as an alternative contrast agent for AVS [38]. The results showed reduced, but acceptable quality. No adverse reaction occurred.

Battistel et al demonstrated the feasibility of another strategy to circumvent the need for ICM [30]. They used carbon dioxide (CO<sub>2</sub>) administration to visualize the inferior vena cava and the adrenal veins and to verify the correct placement of the catheter's tip within the vessels. Similar to gadolinium, CO<sub>2</sub> has been used as a radiocontrast agent, and it can be used in patients with renal dysfunction or ICM allergy. The AVS procedure was successful. However, CO<sub>2</sub> gas is technically difficult to use, and the image resolution may be inferior [39].

The visualization of the adrenal veins in these reports was considerably poorer than the images obtained using conventional contrast media. We did not choose these

methods because of the reduced image quality and a lack of experience with the use of these contrast media for AVS at our center.

We are the first to report on a simplified strategy to safely perform AVS with continuous ACTH infusion in patients with ICM allergy using dexamethasone as premedication, instead of prednisolone or hydrocortisone.

The Elecsys Cortisol II assay in our clinical laboratory is an automated competitive immunoassay using a monoclonal antibody, which is highly specific for cortisol. Of all automated immunoassays, the Elecsys Cortisol II is probably the least affected by interference with synthetic glucocorticoids. However, therapy with prednisolone, 6- $\alpha$ -methylprednisolone or prednisone can still result in falsely elevated concentrations of cortisol, due to their close similarity to cortisol [19]. Dexamethasone and other fluorinated corticosteroids exert no significant cross-reactivity in this assay and in all other cortisol immunoassays used in clinical practice. Therefore, it is the glucocorticoid of choice in suppression tests of the hypothalamic-pituitary-adrenal axis to assess hypercortisolism.

Dexamethasone binds to glucocorticoid receptors in hypothalamic paraventricular nuclei and in pituitary corticotroph cells, and as such, glucocorticoids exert negative feedback effects on the hypothalamic-pituitary-adrenal axis via direct suppression of corticotropin-releasing hormone and ACTH secretion. Under physiological circumstances, a supraphysiologic dose of any glucocorticoid, including dexamethasone, is sufficient to suppress pituitary ACTH secretion and thus cortisol production. It is, however, not clear if there is a direct inhibitory effect of dexamethasone on the adrenal cortex, although dexamethasone has been shown to inhibit the transcription of steroidogenic genes through a mechanism that involved glucocorticoid receptor- and steroidogenic factor 1-mediated induction of DAX-1 [40]. To our knowledge, there are no published reports on the concomitant use of dexamethasone and ACTH, 2 agents with opposite mechanism of action on adrenal cortisol production. Therefore, a high-dose ACTH stimulation test during short-term treatment with dexamethasone was performed according to clinical practice guidelines of the Endocrine Society [41]. A peak of serum cortisol >430 nmol/L is considered normal using the restandardized Roche Elecsys Cortisol II assay, which is calibrated against the international reference method for cortisol [19,42]. The observed peak stimulated cortisol of 812 nmol/L in our patient indicated excellent adrenal secretory response despite the presence of high-dose dexamethasone.

The main limitation of this report is that our analysis is restricted to 1 patient. Our finding thus requires further confirmation. Another limitation is that there is a lack of

research on how administration of dexamethasone affects the release of aldosterone.

## Conclusion

AVS is the gold standard test to differentiate between unilateral and bilateral causes of PA. However, ICM is needed in this procedure, posing a problem for patients with a severe allergy to ICM. The use of exogenous glucocorticoids can affect measurements of serum cortisol and may also influence adrenal cortisol secretion. Here we demonstrate that AVS utilizing continuous ACTH infusion can still be reliably and safely performed when using dexamethasone as premedication for ICM allergy.

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## Additional Information

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**Data Availability:** Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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