

# Adrenal Vein Sampling With Gadolinium Contrast Medium in a Patient With Florid Primary Aldosteronism and Iodine Allergy

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## Abstract

We describe a 35-year-old woman who was allergic to iodine contrast medium and was diagnosed with primary aldosteronism (PA) based on functional confirmatory tests. She was suspected to have unilateral PA because of marked hypertension, spontaneous hypokalemia, high plasma aldosterone, reduced plasma renin activity, and a right hypodense adrenal tumor. She wanted to become pregnant and requested adrenalectomy instead of medical treatment with mineralocorticoid receptor antagonists. Localization of PA by adrenal vein sampling (AVS) was necessary, but angiography with iodine contrast medium was not possible because of her allergy. AVS was performed using gadolinium contrast agent (gadoterate meglumine) instead of iodine, in combination with computed tomography angiography (CTA). In AVS, before and after adrenocorticotropin (ACTH) loading, 12 blood samples were drawn from the right adrenal vein, left adrenal central vein, left adrenal common duct, left and right renal veins, and the lower inferior vena cava with only 5 mL of gadolinium medium. There were no complications during AVS. Examination revealed an elevated aldosterone/cortisol ratio on the right side, lateralized ratio of 7.4, and contralateral ratio of 0.76; the patient was diagnosed with right unilateral PA. She underwent right adrenalectomy and showed improvements in aldosterone level from 312.4 pg/mL to 83.0 pg/mL, potassium from 3.0 mEq/L to 3.9 mEq/L, and systolic blood pressure from 138 mm Hg to 117 mm Hg. In PA patients with iodine allergy, AVS can be performed safely and precisely using gadolinium contrast combined with CTA.

**Key Words:** gadolinium, adrenal vein sampling, primary aldosteronism, iodine allergy

**Abbreviations:** A/C, aldosterone/cortisol; ACR, American College of Radiology; ACTH, adrenocorticotropin; AVS, adrenal vein sampling; CT, computed tomography; CTA, computed tomography angiography; PA, primary aldosteronism; PAC, plasma aldosterone concentration.

Primary aldosteronism (PA) is a very common disease with a reported incidence of approximately 5% to 15% among hypertensive patients [1–3]. The treatment strategy for PA differs depending on its localization, as described in the clinical guidelines [3–5]. Specifically, unilateral PA is treated with unilateral adrenalectomy on the side with aldosterone hypersecretion, while bilateral PA is treated with mineralocorticoid receptor antagonists. Adrenal vein sampling (AVS) is the gold standard for localization diagnosis [6]. Unilateral PA is reportedly associated with a high risk of cerebrocardiovascular events [7]; accurate diagnosis by AVS is therefore important. In particular, patients with basal plasma aldosterone concentration (PAC) > 200 pg/mL, reduced plasma renin activity, and spontaneous hypokalemia exhibit clinical PA (ie, florid PA), which is often unilateral. However, it is difficult

to perform contrast-enhanced computed tomography (CT) and AVS in patients with iodine allergy, even in patients with florid PA, because of safety concerns. In addition, continuous treatment with mineralocorticoid receptor antagonists during pregnancy is difficult because of safety concerns for the fetus; it may be difficult to adequately control cardiovascular risk, particularly in patients with florid PA.

Iodine contrast medium is used for angiography in AVS; aldosterone and cortisol are measured to determine the lateral diagnosis. Based on a previous report [8], the American College of Radiology (ACR) suggested that prior steroid administration attenuates mild acute side effects [9]. Premedication with steroids in patients with iodine allergies affects cortisol measurements, making it difficult to calculate adrenal vein aldosterone/cortisol (A/C) ratio and to evaluate

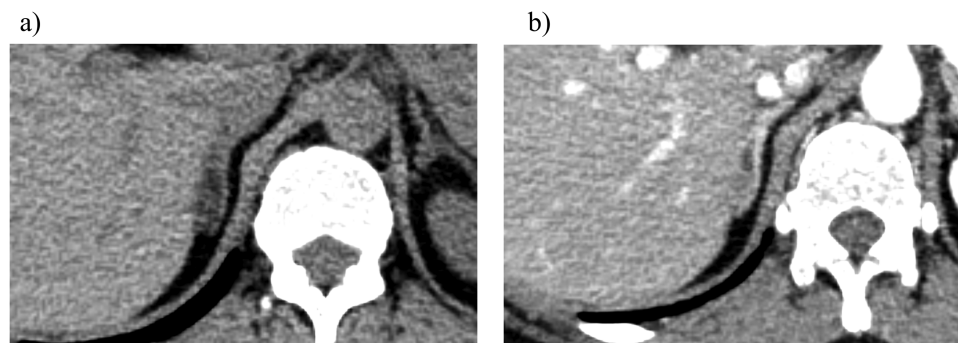
the laterality of PA. In addition, pretreatment with glucocorticoids may not always be safe for suppression of allergic reactions. Sasamura et al [10] reported successful use of gadolinium in AVS for a patient with iodine allergy in 2004. However, since 2006, nephrogenic systemic fibrosis has been reported as a side effect of exposure to gadolinium contrast medium [11]. Therefore, minimal gadolinium contrast medium should be used when possible. Here, we describe a young woman who wanted to become pregnant; she was diagnosed with unilateral PA by AVS, which included more blood sampling sites with a smaller amount of gadolinium contrast medium than reported previously. Unilateral right adrenalectomy cured hypertension both clinically and biochemically; it also ameliorated her hypokalemia, reduced plasma renin activity, and decreased the aldosterone level, without antihypertensive drugs.

## Case

A 35-year-old woman was admitted to Oita University Hospital with suspected pneumonia. Plain CT revealed an incidental finding of a 15-mm-diameter right adrenal gland nodule in the low absorption region of  $-30$  to  $10$  Hounsfield units (Fig. 1). The patient's past medical history included elevated blood pressure since age 33, food allergies, and suspected interstitial pneumonia. The patient's blood pressure was  $138/100$  mm Hg and her serum potassium level was  $3.0$  mEq/L. Her PAC was  $312.4$  pg/mL (normal:  $35.7$ - $240$  pg/mL), active renin concentration was  $1.1$  pg/mL (normal:  $3.2$ - $36.3$  pg/mL), and aldosterone-renin ratio was  $284$ . Therefore, PA was strongly suspected. For diagnosis of PA, functional confirmatory tests were performed in accordance with the clinical practice guidelines for PA of the Japan Endocrine Society [12] and the Japanese Society of Hypertension guidelines for the management of hypertension [5]. Specifically, the captopril test result was considered positive when the aldosterone-renin ratio was greater than or equal to  $40$  at  $90$  minutes after captopril administration, the saline infusion test result was considered positive when the PAC was greater than or equal to  $60$  pg/mL at  $4$  hours after the start of  $2$ -L saline infusion, and the oral salt loading test result was considered positive when the  $24$ -hour urinary aldosterone level was greater than  $8$   $\mu$ g/day (urinary  $\text{Na}^+ > 170$  mEq/d). In the captopril challenge test, the postcaptopril PAC was  $295.8$  pg/mL, active renin concentration was  $1.46$  pg/mL, and aldosterone-renin ratio was  $202.6$  after  $90$  minutes. In the saline infusion test, the PAC was  $231.4$  pg/mL after  $4$  hours. In the oral salt load-

ing test, the urinary aldosterone concentration was  $23.5$   $\mu$ g/day (urinary  $\text{Na}^+ 350$  mEq/d). All functional confirmatory test results were positive, and a diagnosis of PA was made. The patient requested surgical treatment, rather than medical treatment, because of her desire to become pregnant. Her renal function was normal with creatinine of  $0.53$  mg/dL and estimated glomerular filtration rate of  $104.4$  mL/min/ $1.73$  m<sup>2</sup>, and contrast imaging was considered feasible. Localization of PA by AVS was necessary; iodine contrast-enhanced CT with iohexol was performed to confirm the locations of the bilateral adrenal veins and their branches. Facial redness and eyelid swelling occurred after contrast-enhanced CT; dermatological examination suggested allergy to iodine contrast medium. AVS was required for localization, but iodine contrast medium could not be used because of the patient's allergy. Because AVS with gadolinium contrast medium is an off-label use in Japan, we obtained permission from the quality management office of Oita University Hospital to perform angiography using gadoterate meglumine. During the AVS procedure,  $2$  microcatheters (Goldcrest 2.2 Fr,  $110$  cm) were inserted,  $1$  into each of the left and right femoral veins. In total,  $12$  blood samples were collected from  $6$  locations: left adrenal central vein and common duct, right adrenal vein, lower inferior vena cava, and left and right renal veins before and after adrenocorticotropic (ACTH) loading (Table 1, Fig. 2);  $5$  mL of gadolinium was used. For ACTH loading, tetracosactide was first administered by a rapid intravenous infusion of  $0.25$  mg, followed by a continuous intravenous drip infusion started at  $0.25$  mg/h. Adrenal venous blood sampling was resumed  $15$  minutes after rapid intravenous injection of tetracosactide. AVS results were interpreted based on the localization diagnostic criteria of the Japanese Endocrine Society [12]. Catheter insertion success was determined by assessment of the cortisol level: Before ACTH loading, it was  $3$ -fold higher than in the inferior vena cava; after ACTH loading, it was  $5$ -fold higher than in the inferior vena cava. For localization, the A/C ratio was calculated; a diagnosis of unilateral PA was made when the A/C ratio was  $4$ -fold greater on the high side than on the low side (lateralized ratio  $\geq 4$ ) and the A/C ratio on the low side was less than in the inferior vena cava (contralateral ratio  $< 1$ ).

The hormone values in AVS are shown in Table 1. The results before ACTH loading showed that catheter insertion in the left adrenal central vein was unsuccessful; the results after ACTH loading showed that catheter insertion in the left and right adrenal veins was successful. The hormone levels after ACTH loading, which were considered successful in all



**Figure 1.** Adrenal gland image on computed tomography (CT). CT shows a nodule with a diameter of  $15$  mm and  $-10$  Hounsfield units in the right adrenal gland. A, Plain CT image. B, Iodine contrast CT image.

catheter insertions, were used for localization diagnosis. For the left adrenal vein, the hormone level of the common duct, where the A/C ratio was higher than in the central vein, was used. The results showed lateralized ratio 7.4 and contralateral ratio 0.76 after ACTH loading; a diagnosis of right unilateral PA was made. No complications, including allergic reactions, were observed during or after AVS. Based on the results of AVS, the patient was considered suitable for surgery and was scheduled for right adrenalectomy in the urology department. She was treated with 5 mg of esaxerenone for blood pressure control and potassium correction until surgery, because it was scheduled for 2 months after diagnosis. Laparoscopic right adrenalectomy was performed with no perioperative blood pressure elevation or potassium fluctu-

ations; no complications occurred. Histopathological diagnosis revealed positive CYP11B2 findings (Fig. 3C and 3D); thus, a diagnosis of aldosterone-producing adrenocortical adenoma was made. Postoperatively, the patient required no antihypertensive medication; compared with preoperative findings, her PAC level was decreased, active renin concentration level was increased, hypokalemia had resolved, and blood pressure improved (Table 2).

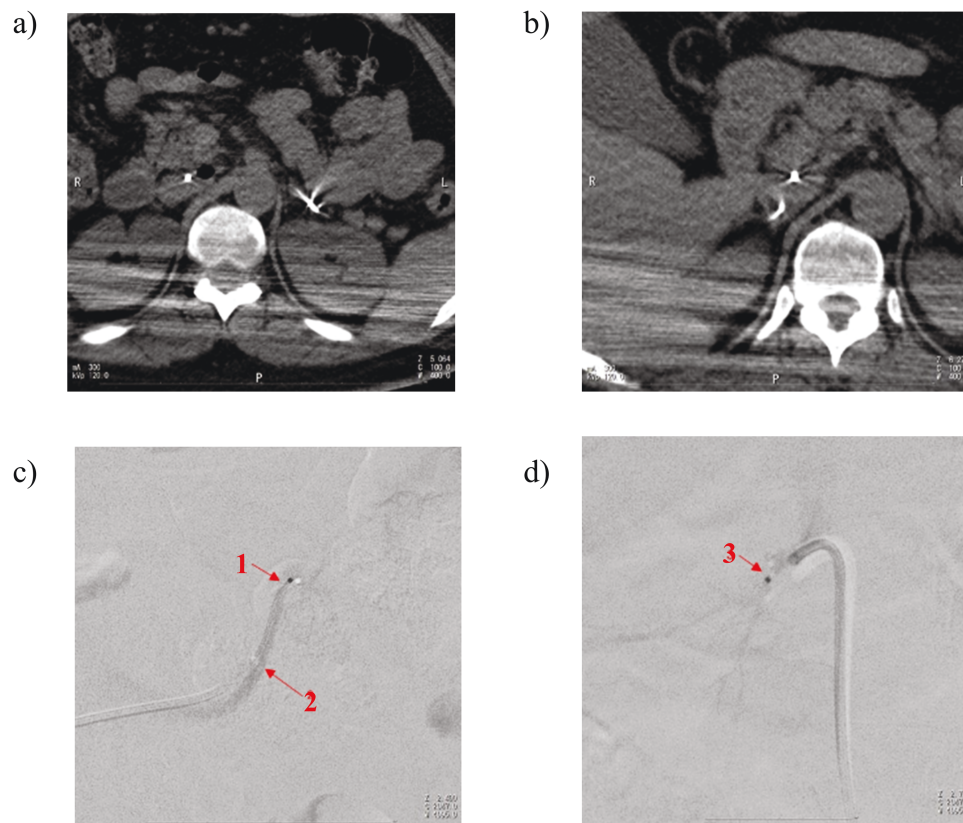
## Discussion

Here, we described a 35-year-old woman with refractory hypertension, spontaneous hypokalemia, and a 15-mm-diameter right adrenal hypodense tumor detected on CT.

**Table 1.** Results of adrenal vein sampling

	Before adrenocorticotropic hormone loading			After adrenocorticotropic hormone loading		
	Aldosterone, pg/mL	Cortisol, µg/dL	A/C	Aldosterone, pg/mL	Cortisol, µg/dL	A/C
Right adrenal vein	4646.4	330.0	14.1	69535.5	597.0	120.1
Left adrenal vein						
Central vein	2315.1	41.4	55.9	8447.4	785.0	10.8
Common duct	1214.4	52.0	23.4	12835.8	787.0	16.3
Inferior vena cava	262.7	15.2	17.3	423.9	19.7	21.5
Right renal vein	220.1	11.4	19.3	417.9	18.2	23.0
Left renal vein	313.2	41.4	7.6	399.1	18.1	22.0

Abbreviation: A/C, aldosterone to cortisol ratio.



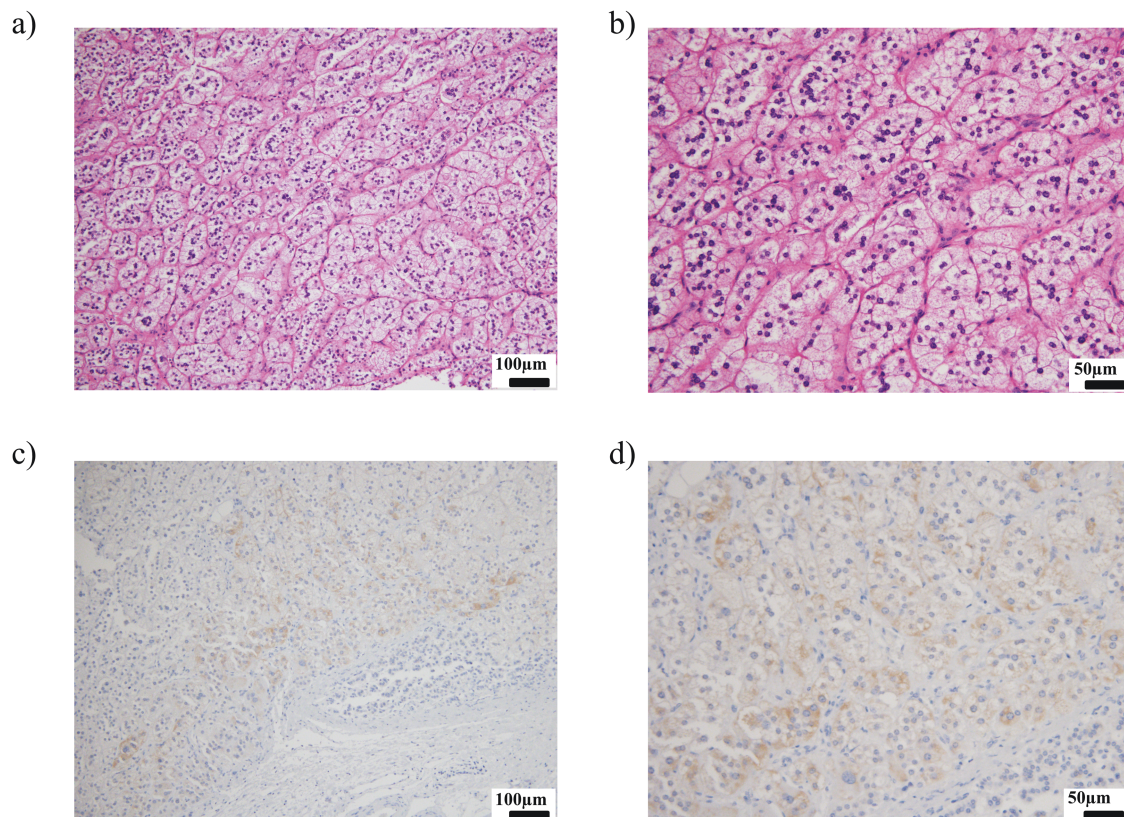
**Figure 2.** Computed tomography angiography (CTA) and venography with gadoterate meglumine. CTA was used to confirm that guidewires were inserted into the A, left, and B, right adrenal veins. Angiography of the C, left, and D, right adrenal veins was performed using gadoterate meglumine. 1, central vein of the left adrenal gland; 2, lower left diaphragmatic vein; 3, right adrenal vein.

In previous retrospective reports, all patients younger than 35 years with high plasma aldosterone (> 200 pg/mL), reduced plasma renin activity, spontaneous hypokalemia, and a unilateral adrenal mass detected on CT were diagnosed with unilateral PA [13, 14]. Although our patient was age 35 years at the time of diagnosis, she had hypokalemia and a right adrenal tumor was detected on CT; she was therefore presumed to have unilateral PA, before confirmation by AVS. Although we considered right adrenalectomy without AVS, we performed AVS because the patient requested a localized diagnosis.

Unilateral PA is sometimes difficult to diagnose because of adrenal vein anomalies, which result in a bilateral adrenal suppression pattern on AVS that may be related to blood sampling from nontumorous lesions of both adrenal glands [15]. In patients with suspected unilateral PA, the current recommendations are to collect blood multiple times [15-17] and/or before and after ACTH loading [15] when performing AVS. In patients with suspected left unilateral PA, Ogata et al [18] recommend that blood be drawn from the left adrenal vein at 2 locations: the central vein and the common duct. This is because left unilateral PA often shows a 4-fold difference in the A/C ratio between the left adrenal central vein and the common duct; this finding is helpful when catheterization of the right adrenal vein cannot be performed. In addition, the veins into which the adrenal veins flow often have unusual vascularization; some branches flow from the adrenal glands into the renal veins without passing through the central veins [19]. To successfully perform AVS only once, because our patient was allergic to iodine, additional blood sampling was performed before ACTH loading, from the left adrenal vein at 2

locations (central vein and common duct) and from the right and left renal veins. As a result, the only blood sampling sites required for diagnosis were the right and left adrenal veins and the inferior vena cava after ACTH loading; a diagnosis of right unilateral PA was made.

Compared to iodine, gadolinium has a higher x-ray attenuation due to its higher atomic weight, but the concentration of commercially available gadolinium contrast media is nearly 5 times lower than that of iodine contrast media [20]. For this reason, when comparing gadolinium and iodine contrast media at the same dose in angiography, gadolinium contrast media have been reported to have an inferior contrast to iodine [21]. In this case, the amount of gadolinium was 5 mL; blood was collected a total of 12 times before and after ACTH loading. In contrast, Sasamura et al [10] reported using 6 mL of gadolinium and collected blood a total of 4 times; we were able to successfully collect more blood with less gadolinium. The amount of gadolinium was minimized to avoid the onset of nephrogenic systemic fibrosis as a side effect; it also avoided gadolinium allergy because the patient was allergic to many antigens. In Japan, meglumine gadoterate can be used up to 0.2 mL/kg in magnetic resonance imaging. Since the weight of this patient was 71.8 kg, a maximum dose of 14.4 mL could be used. The 5 mL of gadolinium used in this AVS was well below the maximum dose and is considered to be safe. Gadolinium use was minimized despite multiple blood samplings for AVS because computed tomography angiography (CTA)—a method of confirming successful intravascular insertion using a guidewire (Fig. 2A and 2B) that has reduced the use of contrast medium—was used, and catheters were inserted into both the left and right inguinal regions. Onozawa



**Figure 3.** Histopathology of an aldosterone-producing adenoma. The excised adrenal tissue was stained with A and B, hematoxylin, or C and D, CYP11B2. A, 100× magnification; B, 200× magnification (hematoxylin staining); C, 100× magnification; and D, 200× magnification (CYP11B2 staining).

**Table 2.** Clinical features before and after adrenalectomy

	Before MRA	After MRA Before Ax	After Ax
SBP, mm Hg	138	133	117
DBP, mm Hg	100	102	80
K, mEq/L	3.0	4.2	3.9
PAC, pg/mL	312.4	316.0	83.0
ARC, pg/mL	1.1	2.8	1.9
ARR, PAC/ARC	284	113	44
Antihypertensive drug	None	Esaxerenone 5 mg	None

Abbreviations: ARC, active renin concentration; ARR, aldosterone to renin ratio; Ax, adrenalectomy; DBP, diastolic blood pressure; MRA, mineralocorticoid receptor antagonist; PAC, plasma aldosterone concentration; SBP, systolic blood pressure.

et al [22] reported that the use of CTA increased the success rate of catheter insertion from 86.4% to 95.7%. CTA is an excellent method to reduce the amount of contrast medium used and increase the success rate of catheter insertion. In addition, by using 2 catheters inserted into the left and right adrenal veins, we avoided the need to reinsert the catheters into the adrenal veins before and after ACTH loading, thereby reducing the amount of gadolinium required. However, the use of 2 catheters resulted in high catheter costs.

Gadolinium-enhanced angiography has been used for patients with iodine allergy in the field of interventional radiology [23-25]. Gadolinium contrast medium has been approved for use as a contrast agent for magnetic resonance imaging, but not for use as an angiographic contrast agent in Japan. In this case, gadolinium was used as an angiographic agent after approval from the appropriate committee in our hospital. Although AVS by gadolinium was performed safely in this case, it is important to carefully consider whether its use would be beneficial in other cases. The patient showed facial redness and swelling in response to iodine during contrast CT, which is classified as a moderate allergic reaction in the ACR manual [9]. In Japan, administration of iodine contrast media to patients with iodine hypersensitivity is contraindicated, so AVS with gadolinium was performed in this case, although it was used off-label.

There have been many reports of carbon dioxide angiography in patients allergic to iodine; these have involved AVS and various other types of angiography. However, carbon dioxide is lighter than blood and its buoyancy must be considered [26], which requires advanced examination techniques [27]. AVS has also been carried out using carbon dioxide gas [28], but AVS is difficult even with iodine contrast medium; thus, AVS using carbon dioxide may not be available at some institutions because of the technical requirements. In fact, we attempted to use carbon dioxide in this case, but it could not be placed into the adrenal vein. However, because gadolinium contrast medium is a liquid (similar to iodine contrast medium), it is technically easy for examiners familiar with the use of iodine to perform imaging with gadolinium. Furthermore, angiography using carbon dioxide has been pointed out to have the risk of air embolization due to air contamination [29]. Air embolization can cause extensive organ damage. There is also the danger that it is difficult to distinguish between carbon dioxide and air in angiography. This suggests that carbon dioxide should not be used for angiography.

Before we performed AVS with gadolinium contrast medium, we considered AVS with iodine contrast medium after

prior steroid administration. Based on a report by O'Malley et al [8], the ACR stated that prior steroid administration attenuates minor acute side effects when iodine contrast agents are used in patients at moderate risk of allergy [9]. However, the ACR indicated that the report by O'Malley and colleagues did not consider high-risk patients and did not adequately evaluate moderate to severe acute side effects. Thus, the ACR does not recommend prior steroid administration for high-risk patients (such as our patient) who have already exhibited adverse reactions to iodine contrast medium. In addition, while other types of angiography can be performed with steroids to reduce allergies, AVS requires calculation of the A/C ratio; steroid administration can affect these results. Prins et al [30] performed AVS using dexamethasone, rather than prednisolone or hydrocortisone, to avoid steroid-induced effects on cortisol levels. They performed AVS after ACTH loading rather than before ACTH loading to reduce the effect of dexamethasone administration on adrenal vein cortisol levels. However, they noted that dexamethasone may suppress aldosterone secretion and prevent the accurate determination of hormone levels. When performing AVS after prior administration of corticosteroids, it is necessary to select a cortisol assay kit in which given corticosteroids do not have cross-reactivity with cortisol measurement. A previous study reported that the incidences of allergy to contrast media were 0.48% for iodine and 0.17% for gadolinium; the incidence of allergy to gadolinium was not high. Furthermore, 0.024% of patients were allergic both to iodine and gadolinium contrast media [31]. Although gadolinium contrast medium is not entirely safe, it is presumably safer than iodine contrast agents. We also considered measuring adrenal medullary hormone instead of cortisol after corticosteroid administration. Freel et al [32] provided reference values for epinephrine, norepinephrine, and dopamine in right and left adrenal veins based on AVS data from nonpheochromocytoma patients. However, they pointed out that it is difficult to determine the localization of pheochromocytoma by AVS because these catecholamines and their metabolites have a large difference and variability between the left and right adrenal veins. Based on this report, we believe that the localization of primary aldosteronism using the aldosterone/catecholamine ratio is also difficult to diagnose.

In conclusion, we performed AVS using gadolinium as a contrast agent in combination with CTA in a PA patient with iodine allergy. This method is safe, accurate, and generally easy to perform.

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## Disclosures

The authors have nothing to disclose.

## Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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