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A Case of Primary Aldosteronism Due to A Primary Adrenal Adenoma Diagnosed by Segmental Adrenal Venous Sampling (S-AVS) Using a Modified Catheter System and Lateral Cine Angiography

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 44
Final Diagnosis: Aldosterone producing adenoma
Symptoms: Hypertension
Medication: —
Clinical Procedure: Segmental adrenal venous sampling
Specialty: Cardiology

Objective: Unusual clinical course

Background: Before partial adrenalectomy for primary aldosteronism due to a primary adrenal adenoma, the aldosterone-producing tumor can be localized by segmental adrenal vein sampling (S-AVS). Cardiologists, who regularly perform percutaneous coronary intervention (PCI), or coronary angioplasty with stent, may not be familiar with the technique of S-AVS. A case of the use of S-AVS is reported in a patient who presented with primary aldosteronism and a right adrenal adenoma.

Case Report: A 44-year-old man with a history of hypertension presented with a man in the posterior part of the right adrenal gland. He had hypokalemia, and a high plasma aldosterone concentration/plasma renin activity ratio. A captopril stress test confirmed the diagnosis of primary aldosteronism. Pre-operative S-AVS was performed using a microwire and microcatheter, which were advanced into the segmental adrenal vein using a 6.5 French guiding catheter and a Y-shaped connector, under biplane cine angiography guidance. S-AVS showed a high plasma aldosterone concentration in the right superior tributary adrenal vein draining the adrenal mass. Right partial adrenalectomy was performed. Postoperatively, the patient's blood pressure and plasma aldosterone levels normalized.

Conclusions: S-AVS can be performed relatively easily before partial adrenalectomy using a catheter system with biplane cine angiography, which is a technique that is familiar to cardiologists.

MeSH Keywords: Adenoma • Hyperaldosteronism • Hypertension • Sampling Studies

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Background

Before partial adrenalectomy is performed to treat primary aldosteronism, the aldosterone-producing adrenal adenoma should be localized by segmental adrenal venous sampling (S-AVS) [1]. However, cardiologists who regularly perform percutaneous coronary intervention (PCI), or coronary angioplasty with stent, tend to be unfamiliar with S-AVS, and may be reluctant to attempt this procedure. The lack of familiarity with the procedure of adrenal venous sampling (AVS) may explain the high failure rate [2].

However, we have previously reported a modified method for AVS that allows it to be performed relatively easily [3,4]. When performing percutaneous coronary intervention (PCI), the cardiologist usually advances the wire and microcatheter while using a guiding catheter with a Y-shaped connector and confirming the progress of the procedure using fluoroscopy or biplane cine angiography. The modified procedure of S-AVS is more similar to that of PCI and could be used by cardiologists.

The case of a 44-year-old man who presented with primary aldosteronism due to an adrenal adenoma is reported, who underwent S-AVS using a catheter system familiar to cardiologists, with biplane cine angiography, before undergoing partial adrenalectomy. To our knowledge, this is the first case report describing this diagnostic technique.

Case Report

The patient was a 44-year-old Japanese man who was diagnosed with hypertension at the age of 39 years, at which time he had a left putaminal hemorrhage, which was treated conservatively. He was treated with oral antihypertensive therapy. During a routine medical examination, at the age of 43 years, an abdominal ultrasound identified a right adrenal mass, which was confirmed by computed tomography (CT) to measure 12 mm in diameter and located in the posterior part of the right adrenal gland **(**Figure 1).

Laboratory tests showed hypokalemia (3.1 mmol/L), a high plasma aldosterone concentration (PAC) (29.6 ng/dL), low plasma renin activity (PRA) (0.4 ng/mL/h), and high aldosterone/renin ratio of 74, which suggested primary aldosteronism. The patient was being treated with nifedipine (80 mg/day) and azilsartan (40 mg/day). After changing his antihypertensive therapy to the calcium antagonists, nifedipine 80 mg/day and amlodipine 10 mg/day, a captopril stress test confirmed the diagnosis of primary aldosteronism. The patient was scheduled for preoperative segmental adrenal venous sampling (S-AVS).

Before S-AVS, infusion of synthetic adrenocorticotropic hormone (ACTH) (tetracosactide acetate) was commenced at 0.1 mg/hour. S-AVS was performed using a system that is easily available to cardiologists [1]. The S-AVS procedure combined a 6.5 French guiding catheter with a Y-shaped connector [3], and biplane cine angiography [4]. Engagement in the adrenal vein was achieved and imaging was performed following injection of contrast medium through the guiding catheter. During S-AVS, an OM type 2.2 Fr Gold Crest split-tip microcatheter (Koshin Medical, Co. Ltd.; Tokyo, Japan) was advanced into the segmental adrenal vein through the 6.5 French guiding catheter, which allowed sampling to be performed at 15 sites [4].

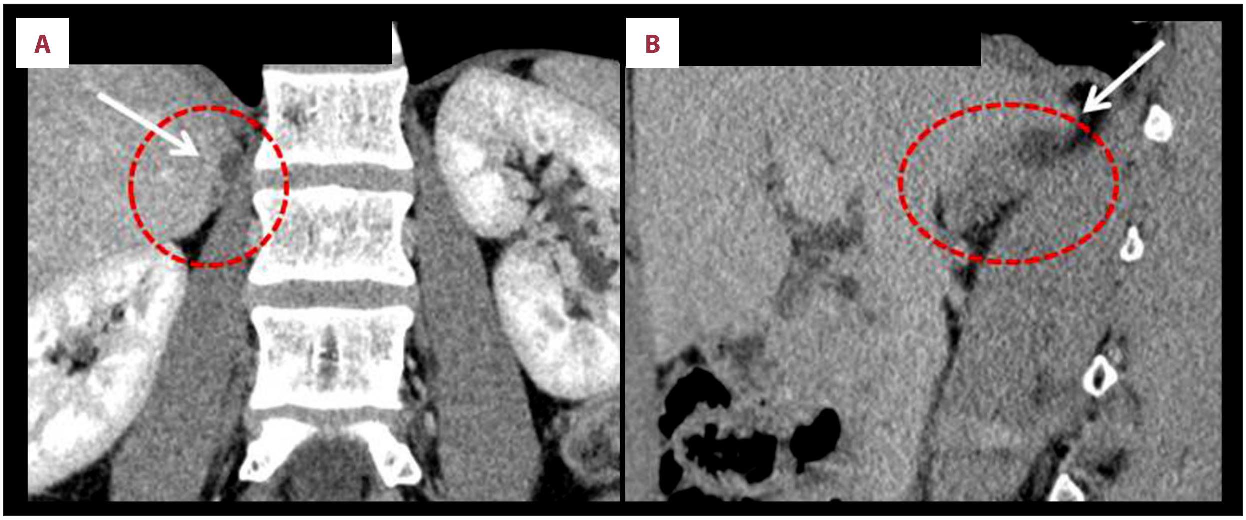

Figure 1. Preoperative enhanced computed tomography (CT) imaging of the right adrenal adenoma in a 44-year-old man with primary aldosteronism. (**A**) (Coronal enhanced CT) Coronal view of the preoperative enhanced computed tomography (CT) image shows a right adrenal mass, indicated by arrows. (**B**) (Sagittal enhanced CT) Sagittal view of the preoperative enhanced CT shows a 12 mm mass in the posterior part of the right adrenal gland, indicated by arrows.

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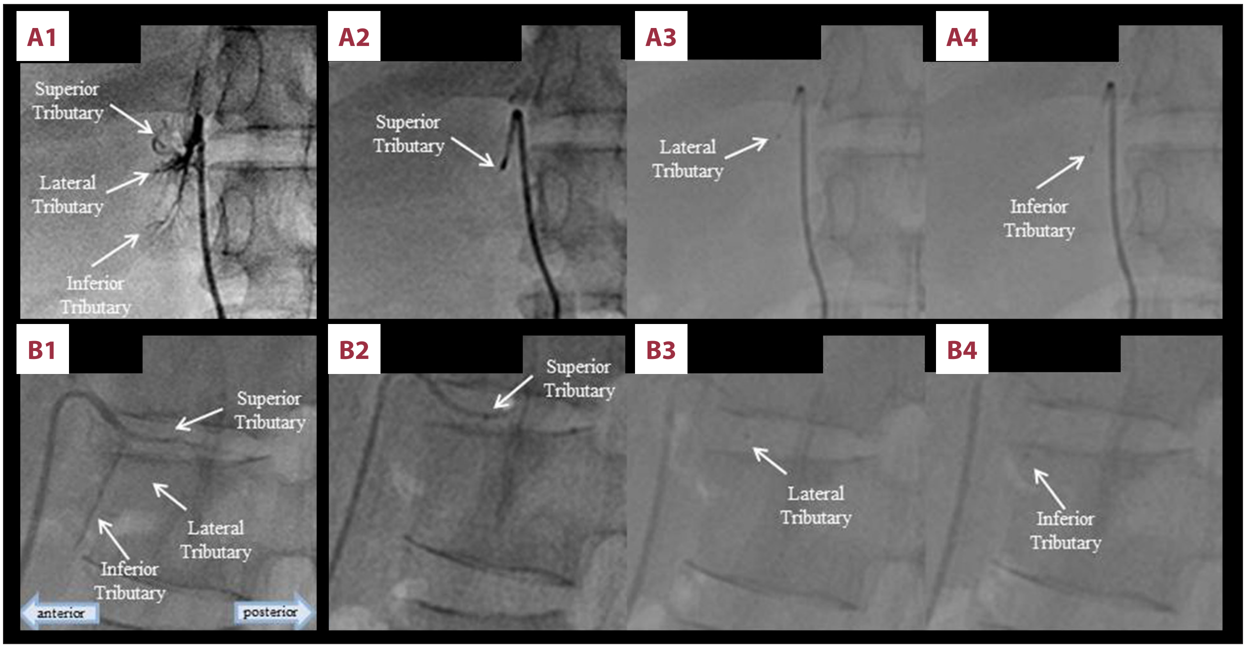

Figure 2. Comparison between frontal and lateral views during right segmental adrenal venous sampling (S-AVS) in a 44-year-old man with primary aldosteronism. The guiding catheter was engaged in the right central adrenal vein and the venous anatomy was confirmed by injection of contrast medium. The central adrenal vein was enhanced by contrast medium from the guiding catheter. (**A**) [**A1**, **A2** (No. 11), **A3** (No. 12), **A4** (,O. 13)]. Frontal views of all tributary veins, the superior tributary vein, the lateral tributary vein, and the inferior tributary vein. (**B**) [**B1**, **B2** (No 11), **B3** (No. 12), **B4** (No. 13)] Lateral views of all tributary veins, the superior tributary vein, the lateral tributary vein, and the inferior tributary vein. CRA – cranial angulation; LAO – left anterior oblique.

First, a total of five samples were collected from the segmental veins of the left adrenal gland, including the superior tributary vein (No. 2), lateral arcuate tributary vein (No. 3), common stem (No. 4) and inferior phrenic vein (Nos. 5 and 6). These three tributary veins of the left adrenal gland were easily separated in the frontal imaging view. Right S-AVS was performed with engagement in the right adrenal vein confirmed by cone beam CT (CBCT) with two-fold diluted contrast medium. The guiding catheter in the central adrenal vein was used for retrograde contrast enhancement of the three tributary adrenal veins in the right adrenal gland.

Figure 2 shows the images obtained in the frontal and lateral views, 0 degrees cranial and 90 degrees left anteroposterior oblique. Five samples were collected from the segmental right adrenal veins, including the superior tributary vein, the lateral tributary vein, the inferior tributary vein, and the central right adrenal vein. In the frontal view, the superior tributary vein and the lateral tributary vein were too close to each other for these veins to be distinguished. However, the lateral view showed the superior tributary vein arising from the posterior part of the adrenal gland, while the lateral tributary vein ran diagonally from the inferior-posterior region, so the two veins were easy to distinguish. The inferior tributary vein was readily identified because it descended immediately in both the frontal view and the lateral view.

The results of S-AVS at the 15 sites are shown in Figure 3. Engagement of the catheter in the adrenal vein was confirmed by detecting a plasma cortisol concentration (PCC) ≥200 μg/dL following ACTH stimulation [5]. Based on this, blood collection sites No. 2, 3, 4, 11, 12, 13, 14, and 15 were considered to be inside the adrenal gland. Using the criteria that the PCC in the adrenal vein (31.5×5=157.5 μg/dL in this patient) was >5 times higher than that in the inferior vena cava [6]. Sampling sites 2, 3, 4, 6, 11, 12, 13, 14, and 15 were inside the adrenal gland. When hypersecretion of aldosterone was defined as a plasma aldosterone concentration (PAC) ≥1400 ng/dL in the adrenal vein following ACTH stimulation [7], aldosterone hypersecretion was found at sites No. 11, 12, 13, 14, and 15. Based on a right/left ratio ≥2.6 for the PAC/PCC ratio [7], sites No. 11, 13, 14, and 15 showed hypersecretion of aldosterone.

The adrenal mass was located in the posterior part of the right adrenal gland on CT imaging. The vein draining the tumor was identified as the right superior tributary adrenal vein (site No. 11), where an extremely high PAC (16,500 ng/dL) and PAC/PCC ratio (150) were found. Although the PAC was also high in the lateral tributary vein (No. 12) and the inferior tributary vein (No. 13), it was assumed that these samples were contaminated by aspiration of backflow from the superior tributary vein or central adrenal vein. This hypothesis was supported

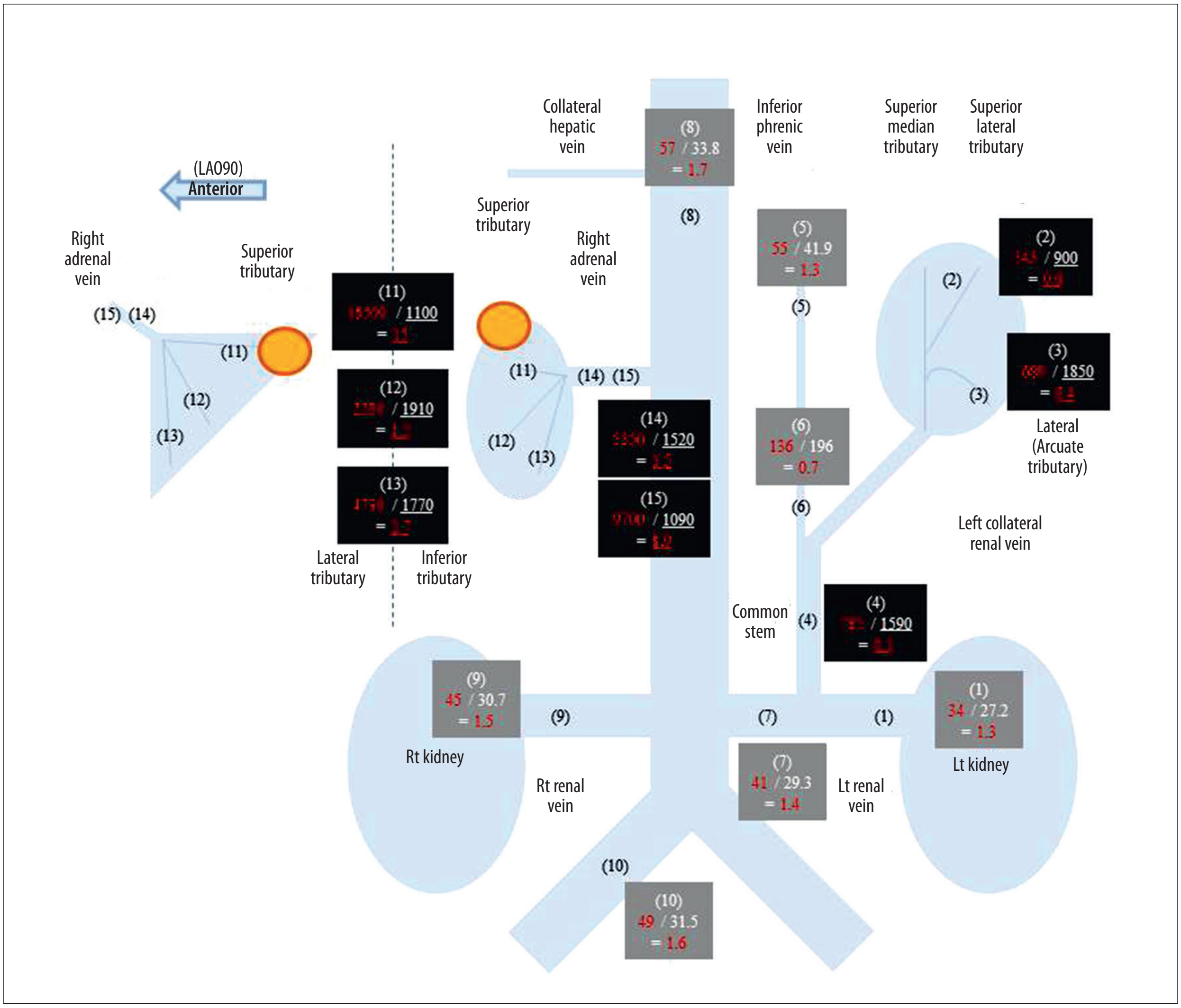

Figure 3. Diagrammatic representation of the results of right segmental adrenal venous sampling (S-AVS) in a 44-year-old man with primary aldosteronism. Blood samples were collected at 15 sites. The site number, plasma aldosterone concentration (PAC), plasma cortisol concentration (PCC), and PAC/PCC ratio following adrenocorticotropic hormone (ACTH) stimulation are indicated. PAC (ng/dL)/PCC (μg/dL)=the aldosterone/cortisol ratio

by the finding that the PAC/PCC ratio and PAC level were higher in the central adrenal vein (No. 14 and 15) when compared with sites No. 12 and 13. It was concluded that sites No. 12 and 13 were located in tributary adrenal veins draining normal adrenal tissue and that primary aldosteronism was caused by the right adrenal adenoma previously detected by CT imaging.

The patient opted for partial adrenalectomy. Accordingly, laparoscopic partial right adrenalectomy was performed to remove approximately one-quarter of the right adrenal gland, together with the mass, while the remainder of the gland was preserved, including the central vein (Figure 4). At one month after surgery, the patient's blood pressure (BP) was normalized without oral medication. Following partial adrenalectomy, the PAC decreased from 28.4 ng/dL to 2.6 ng/dL and the aldosterone/renin ratio decreased from 95 to 13. The postoperative captopril stress test was negative.

The macroscopic appearance of the right adrenal resection specimen was consistent with an adrenal adenoma, and was well-circumscribed and encapsulated with a brown/yellow color (Figure 5). The histology showed clear cells with vacuolated cytoplasm and a few compact cells with eosinophilic cytoplasm, arranged in nests and cords. These histologic features were consistent with a diagnosis of adrenal cortical adenoma.

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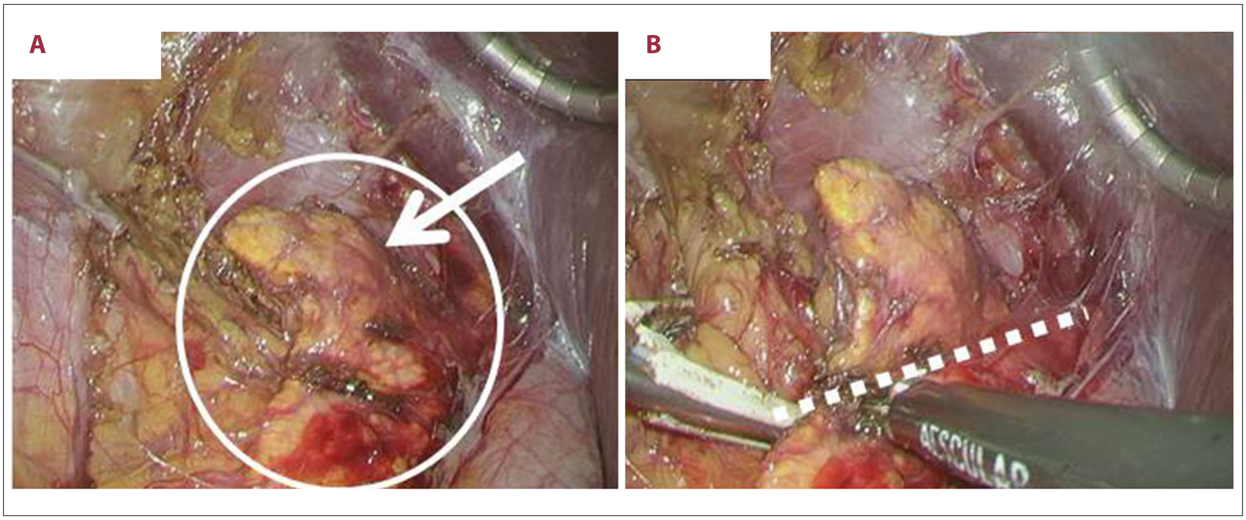

Figure 4. Findings during laparoscopic right partial adrenalectomy in a 44-year-old man with primary aldosteronism. (**A**) The arrow indicates the adrenal adenoma. (**B**) After dissection around the right adrenal gland, one-quarter of the adrenal gland containing the mass was excised (shown by the dotted line), avoiding the central vein.

Figure 5. The macroscopic appearance of the resected adrenal adenoma in a 44-year-old man with primary aldosteronism. The macroscopic appearance is that of a circumscribed and encapsulated tumor with a yellow/brown color on cut section. The histology confirmed the diagnosis of a benign adrenal adenoma.

Discussion

In this case, partial adrenalectomy was performed following diagnostic information obtained by segmental adrenal venous sampling (S-AVS), using a catheter system familiar to cardiologists, together with biplane cine angiography. In patients with primary aldosteronism, excessive aldosterone production occurs. There are several causes of primary aldosteronism, including aldosterone-producing adenoma, aldosterone-producing microadenoma, and idiopathic hyperaldosteronism. Although non-functioning adrenal adenoma can occur, as in this case, adrenal adenoma can lead to primary aldosteronism. The first-line treatment for primary aldosteronism due to adrenal adenoma is adrenalectomy, but surgery will fail in 37.8% of patients if localization is based solely on imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) [8]. Therefore, it is essential to perform adrenal venous sampling (AVS) before adrenalectomy to improve diagnosis [5,9–11]. Conventional AVS involves the collection of blood samples from both central adrenal veins and only identifies the laterality of excess unilateral hypersecretion of aldosterone, often resulting in total adrenalectomy.

S-AVS was developed as a method of collecting blood samples from the segmental adrenal tributary veins [1]. The adrenal segmental tributary veins include the superior, lateral, and inferior tributary veins for the right adrenal gland, while the left adrenal gland has the superior-median, superior-lateral, and lateral tributary veins. The precise localization of the site of excess aldosterone secretion in the adrenal gland can be achieved by performing S-AVS with an advanced micro-catheter [12–14]. If excess hormone production by the tumor is confirmed, partial resection of the adrenal gland that includes the tumor can be performed to preserve the residual healthy part of the adrenal gland. In patients with bilateral lesions, it has been reported that bilateral subtotal adrenalectomy can be effective without leading to postoperative adrenal failure [15,16]. At several centers, S-AVS now is used to allow partial adrenalectomy to be performed [13].

However, S-AVS is more difficult than conventional AVS, and catheter engagement is challenging, particularly on the right side [2], because the right adrenal vein has a small diameter and directly enters the inferior vena cava. Physicians such as cardiologists may be reluctant to perform AVS due to lack of experience with the technique and its high failure rate [2,3]. While AVS is not usually associated with complications, adrenal hemorrhage can occur [4], and this is more likely on the right side [17]. Physicians may be reluctant screen patients for primary aldosteronism, and it has been proposed that patients with primary aldosteronism who are considering adrenalectomy should be referred to specialized centers for diagnostic AVS, but there are too few such facilities compared with the number of patients requiring treatment.

Primary aldosteronism is the major cause of secondary hypertension and is relatively common [18]. Patients with primary aldosteronism can develop cardiovascular events that are not dependent on a high blood pressure [19]. Therefore, cardiologists are increasingly involved in managing patients with primary aldosteronism among the cardiovascular patient population. It was recently reported that renal sympathetic denervation (RDN) can reduce blood pressure [20], which suggests that catheter intervention could become a treatment option for patients with hypertension. However, it is essential to exclude secondary hypertension before performing RDN, since there may be patients with primary aldosteronism among those with treatment-resistant hypertension, more cases are likely to be found by screening for secondary hypertension after the introduction of RDN. Thus, it is likely that cardiologists will encounter more patients with primary aldosteronism in the future and opportunities for them to perform AVS may increase. However, unlike PCI, there is no widespread consensus about the optimum AVS procedure.

In the patient described in the present report, it was difficult to understand the adrenal vein anatomy in the frontal view, especially for the right adrenal gland (Figure 2). In this case, it was not clear which vein was the superior tributary vein, or the lateral tributary vein, based on the frontal view on imaging. Therefore, S-AVS was easier to perform by using biplane cine angiography, which allowed switching between the frontal and lateral views while advancing the catheter. By performing S-AVS with imaging in both the frontal and lateral views after determining the location of the target mass on coronal and sagittal CT scans, it was possible to identify the vein draining the adenoma as the superior tributary vein in the lateral imaging view. Although using biplane cine angiography makes AVS much simpler, there have been no current recommendations regarding this procedure, which may be due to the fact that biplane cine angiography only recently became widespread and the fact that AVS is currently rarely performed by clinicians.

Previously, we proposed the use of a catheter system for AVS that can be safely and reliably used by cardiologists because of its similarity to PCI systems [3]. At many centers, a 5 French catheter is generally used for AVS. Although a method of AVS using a 5 French catheter has been previously reported [1], because it was unfamiliar to cardiologists, the present modified method was developed. When the guidewire and microcatheter are advanced together, the microcatheter fills the inner lumen of a 5 French catheter and contrast injection cannot be performed, but while contrast imaging or blood sampling is possible if the guidewire is withdrawn from the microcatheter, a 5 French catheter can easily become disengaged when the wire is withdrawn [4]. In contrast, AVS becomes much easier if a 6 French or larger guiding catheter is used in combination with a Y-shaped connector. With the S-AVS system, it was possible to advance the microcatheter to a segmental adrenal branch vein by using a 0.018 mm guide wire, while injecting contrast medium through the guiding catheter, which improved the stability and safety of the AVS method. Since cardiologists are familiar with this system, an increase of the success rate might be expected. A 6 French RDC-1, 6 French ITA-1, or 6.5 French tapered-tip AVS catheter are suitable for this system. We recommend using an OM type microcatheter (2.2 French Gold Crest®) for S-AVS because this type of microcatheter has two side holes at the tip that prevent obstruction by the vein wall.

Assessment of whether engagement has been successfully achieved is important when performing S-AVS. Because the procedural time is quite long for beginners, intravenous infusion of synthetic ACTH is strongly recommended rather than one-shot intravenous injection. Rapid measurement of the cortisol levels during AVS is effective for confirming cannulation of the adrenal vein [21,22], but is not available at most centers. Cone beam CT (CBCT) rotational angiography with retrograde venous contrast enhancement is useful for locating the adrenal gland [23], especially the right adrenal gland, and we use this method for right S-AVS. If the contrast medium is injected at a standard concentration, the enhancement may be too strong, and so it is necessary to dilute the contrast agent with saline.

Preparation of specimen tubes is also important. During S-AVS, additional blood sampling tends to be required. In addition, the blood sampling sequence may easily be changed, which can cause confusion that will lead to failure of the procedure in the treatment of primary aldosteronism. Such problems might be more common in clinical practice than is generally realized. Therefore, writing the blood collection numbers on the tube labels before AVS is not recommended, and it is more appropriate to write these numbers on the tube labels during AVS and to also record a diagram with the blood collection numbers in the operation notes.

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The strategy of resecting an adrenal gland for a benign disease such as primary aldosteronism can be difficult for physicians and patients to accept psychologically. However, surgery is strongly recommended for some patients with primary aldosteronism and partial adrenalectomy may be a more acceptable treatment for primary aldosteronism. Partial adrenalectomy is not a difficult procedure for urologists to perform and is effective for the treatment of primary aldosteronism. Although cardiologists have previously been reluctant to perform AVS procedures, despite the prevalence of primary aldosteronism, the opportunity to perform S-AVS is expected to increase in the future.

Conclusions

There have been no previous case reports describing the diagnostic performance of segmental adrenal venous sampling (S-AVS) before partial adrenalectomy using this catheter system and biplane cine angiography. Since cardiologists can perform S-AVS relatively easily by this method, due to its similarities with percutaneous coronary intervention (PCI), or coronary angioplasty with stent, it is hoped that treatment of primary aldosteronism will be facilitated through the more frequent adoption of AVS procedures by cardiologists in the future.

Conflict of interest

The authors have received honoraria from Otsuka Holdings and grant support for a clinical trial of treatment for resistant hypertension with an ultrasonic renal denervation system.

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