

# The Occurrence of Apparent Bilateral Aldosterone Suppression in Adrenal Vein Sampling for Primary Aldosteronism

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**Context:** In adrenal venous sampling (AVS) for patients with primary aldosteronism (PA), apparent bilateral aldosterone suppression (ABAS), defined as lower aldosterone/cortisol ratios in the bilateral adrenal veins than that in the inferior vena cava, is occasionally experienced. ABAS is uninterpretable with respect to lateralization of excess aldosterone production. We previously reported that ABAS was not a rare phenomenon and was significantly reduced after adrenocorticotrophic hormone (ACTH) administration.

**Objective:** To validate the effects of ACTH administration and adding sampling positions in the left adrenal vein on the prevalence of ABAS in the larger Japan Primary Aldosteronism Study.

**Patients:** The data from 1689 patients with PA who underwent AVS between January 2006 and October 2016 were studied. All patients in the previous study, the West Japan Adrenal Vein Sampling study, were excluded.

Abbreviations: A/C, aldosterone/cortisol; ABAS, apparent bilateral aldosterone suppression; ACTH, adrenocorticotrophic hormone; APA, aldosterone-producing adenoma; ARC, active renin concentration; AVS, adrenal venous sampling; IVC, inferior vena cava; JPAS, Japan Primary Aldosteronism Study; LI, lateralization index; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; WAVES-J, West Japan Adrenal Vein Sampling.

**Outcome Measurements:** The prevalence of ABAS was investigated at two sampling positions in the left adrenal vein, the central vein and the common trunk, without and with ACTH administration.

**Results:** The prevalence of ABAS with ACTH administration was significantly lower than that without ACTH administration [without ACTH vs with ACTH: 79/440 (18.0%) vs 45/591 (7.6%);  $P < 0.001$ ]. With ACTH administration, the prevalence of ABAS was not different between the sampling position, at the central vein and at the common trunk [33/591 (5.6%) vs 32/591 (5.4%);  $P = 1.00$ ].

**Conclusions:** The effectiveness of ACTH administration for the reduction of ABAS in AVS regardless of the sampling position in the left adrenal vein was confirmed in the larger cohort.

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**Freeform/Key Words:** adrenal vein sampling, aldosterone suppression, apparent bilateral, hypertension, primary aldosteronism

Primary aldosteronism (PA) is the most common form of secondary endocrine hypertension, accounting for 5% to 10% of all hypertensive patients [1, 2]. In patients with PA, adrenal venous sampling (AVS) is recognized as the most reliable method for subtype diagnosis, and it is important for patients to have this procedure to determine the need for an adrenalectomy. To decide whether the disease is either unilateral or bilateral, two criteria are commonly used, the lateralization index (LI) and the contralateral ratio [3–6]. The LI is the ratio of aldosterone/cortisol (A/C) in the dominant adrenal vein relative to that in the non-dominant adrenal vein. The contralateral ratio is the ratio of A/C between the nondominant adrenal vein and either the inferior vena cava (IVC) or the peripheral vein. If the A/C ratio in one adrenal vein is lower than that in either the IVC or the peripheral vein, the diagnosis is unilateral disease of the other side, because of the presence of a contralateral suppression.

In some patients, the results of AVS were inconclusive because of the bilaterally lower A/C ratios in the adrenal veins than that in IVC despite successful cannulation [7]. Wolley *et al.* [8] reported that 2.6% of the patients who underwent AVS without adrenocorticotropic hormone (ACTH) administration showed the same phenomenon. Recently, we demonstrated using the data from the West Japan Adrenal Vein Sampling (WAVES-J) study that this phenomenon was observed in 9.5% of the patients who underwent AVS without ACTH administration, and that in 92% of these patients, it was resolved by ACTH administration [9]. In this study, we term this phenomenon as apparent bilateral aldosterone suppression (ABAS). ABAS was thought to be developed by the blood sampling in quiescent phase of aldosterone from aldosterone-producing adenoma (APA) accompanying the stress-induced ACTH secretion and to be eliminated by ACTH administration.

Although ACTH was administered, ABAS was still observed in a small number of patients. Some patients who did not show ABAS without ACTH administration demonstrated ABAS with ACTH administration. In the WAVES-J study, in most patients, the left adrenal vein samples were collected from the central vein during AVS. An additional sampling at the common trunk was performed in a subset of these patients. We reported a patient with ABAS without ACTH administration, where ABAS was resolved with an additional sampling at the common trunk.

In this study, we analyzed the data of the Japan Primary Aldosteronism Study (JPAS), a multicenter collaborative study for patients with PA in Japan, from which the WAVES-J study cohort had been derived. We excluded the data from the patients who had been included in the WAVES-J study to evaluate ABAS in the remaining, larger JPAS cohort. The JPAS also had many more patients sampled at both the central vein and the common trunk in AVS than that in the WAVES-J study.

In this study, we examined the effects of ACTH administration and the addition of a second blood sampling position in the left adrenal vein on resolving ABAS.

## 1. Patients and Methods

### A. Patients

Twenty-seven centers participated in the JPAS. The patients with confirmed PA who underwent AVS from January 2006 to October 2016 were enrolled in the study. The baseline clinical findings, the results of the AVS, and the posttreatment outcomes were electronically collected using the WEB registry system, and data security and maintenance of registered data were outsourced to EPS Corporation (Tokyo, Japan). The study protocol was approved by the ethics committees of each center.

The diagnostic procedure for PA was based on the guidelines of both the Japan Endocrine Society [10] and the Japan Society of Hypertension [11]. The screening for PA was performed based on the ratio of the plasma aldosterone concentration (PAC; pg/mL) to the plasma renin activity (PRA; ng/mL/h) (aldosterone renin ratio >200), after changing from potentially interfering antihypertensive drugs to calcium channel blockers and/or to  $\alpha$ -blockers where applicable. The diagnosis of PA was established by at least one positive result of confirmatory testing, including the captopril challenge test, the upright-furosemide loading test, and the saline loading test.

### B. AVS

Blood samples obtained via AVS were generally collected before and at 30 minutes after ACTH administration from both adrenal veins and from the IVC at a point distal to the renal vein. The tip of the catheter was placed into the left adrenal vein at a point distal to the division of the left inferior phrenic vein, termed the central vein, and at the junction of the inferior phrenic vein and the left adrenal vein as a common trunk [12]. The protocol for ACTH administration varied in each center. Eighteen centers used a bolus injection of 250  $\mu$ g of cosyntropin. Eight centers used a bolus injection of 200  $\mu$ g (or 250  $\mu$ g) followed by continuous infusion of 50  $\mu$ g (or 100 or 250  $\mu$ g) of cosyntropin. One center used a continuous infusion of cosyntropin. In four centers, sampling of the left and right adrenal veins was performed simultaneously, whereas in the other centers, the sampling was done sequentially. Catheterization was judged to be successful if the selectivity index (the ratio of cortisol concentration between the adrenal vein and the IVC) was either more than 2 without ACTH administration or more than 5 with ACTH administration.

Unilateral disease was defined if the LI was more than 4 both without and with ACTH administration. ABAS was defined if the A/C ratios in adrenal veins were bilaterally lower than that in the IVC.

### C. Analysis

The data from the JPAS were studied retrospectively. The prevalence of ABAS in AVS with and without ACTH administration was determined. ABAS was investigated in two different vein sampling combinations (the right adrenal vein and the central vein of the left adrenal vein or the right adrenal vein and the common trunk of the left adrenal vein). The baseline characteristics, the results of the AVS, and the percentages of patients who underwent a unilateral adrenalectomy with ACTH administration were compared.

We estimated the postoperative clinical and biochemical outcomes referring to the Primary Aldosteronism Surgery Outcome study over either a 6- or 12-month follow-up [13].

### D. Assay Methods

PAC and PRA were measured by commercially available kits. PAC was determined by radioimmunoassay (SPAC-S Aldosterone Kit; Fuji Rebio, Co., LTD, Tokyo, Japan) in all centers. The reference range of PAC in the supine position was 3.0 to 15.9 ng/dL. PRA was measured by radioimmunoassay or enzyme immunoassay. The reference range of PRA in the supine

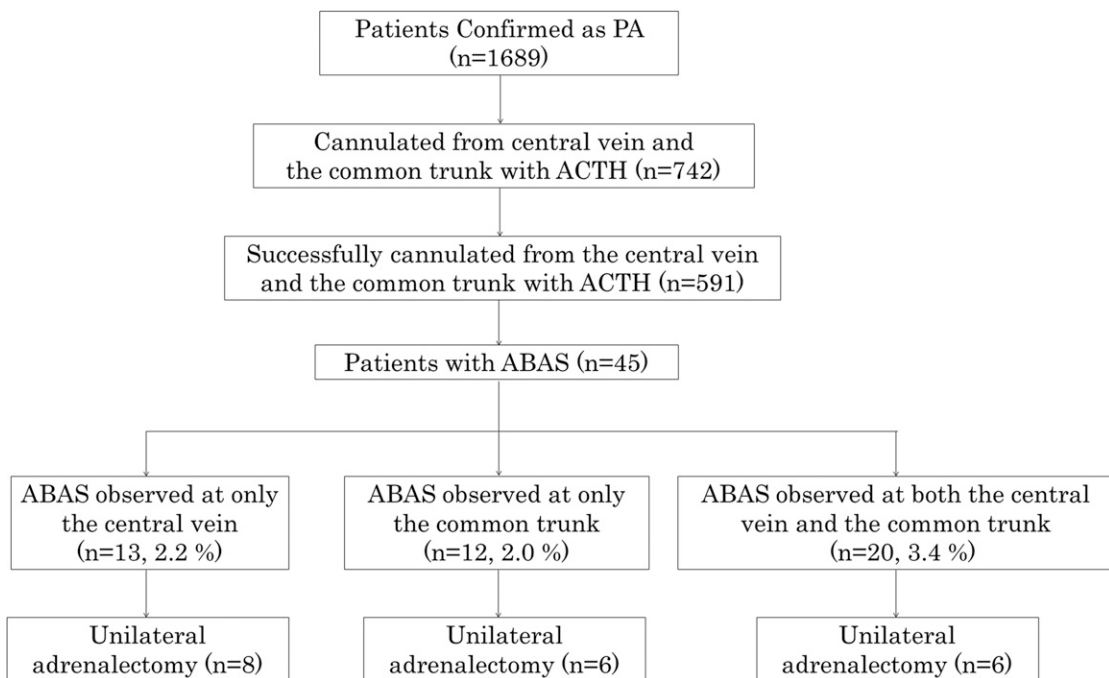
position was 0.3 to 2.9 ng/mL/h (PRA radioimmunoassay kits; Fuji Rebio, Co., LTD) in 15 centers, 0.2 to 2.3 ng/mL/h (PRA enzyme immunoassay kits; Yamasa, Co., LTD, Choshi, Japan) in seven centers, and 0.2 to 2.7 ng/mL/h (PRA radioimmunoassay kits; Yamasa, Co., LTD) in four centers. Plasma active renin concentration (ARC) was measured by immunoradiometric assay (Renin immunoradiometric assay kits, Fuji Rebio, Co., LTD) in one center. The reference range of ARC in the supine position was 2.5 to 21.4 pg/mL. ARC value was used for analysis after converting to PRA by dividing by 5 according to the Japan Endocrine Society guideline [10].

### E. Statistics

The data were analyzed and compared using BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan). Continuous variables were expressed as either mean  $\pm$  standard deviation or median and interquartile range. Continuous variables were analyzed by either the one-way analysis of variance or the Kruskal-Wallis test, as appropriate. Comparison of the frequency among two groups was estimated by either the  $\chi^2$  test or the Fisher's exact test, as appropriate. Statistical significance was achieved when the *P* value was  $<0.05$ .

## 2. Results

A flowchart of this study is summarized in Fig. 1. In the JPAS, 1689 patients were confirmed as having PA. Seven hundred and forty-two patients underwent attempted cannulation of the right adrenal vein and both the central vein and the common trunk with ACTH administration. Five hundred and ninety-one patients were successfully cannulated at the right adrenal vein and both positions in the left adrenal vein. The prevalence of ABAS at either the central vein or the common trunk with ACTH administration was 45/591 (7.6%). The characteristics of patients with ACTH administration are summarized in Table 1. The percentages of male were higher in the patients with ABAS at both the central vein and the common trunk than that in the patients without ABAS (75% vs 48%; *P* = 0.02). The percentages of males were significantly higher than that of females in the patients who were



**Figure 1.** Flowchart of patients with ABAS with ACTH administration.

**Table 1. Baseline Characteristics of the Patients With and Without ABAS in AVS**

	ABAS at Only the Central Vein (n = 13)	ABAS at Only the Common Trunk (n = 12)	ABAS at Both the Central Vein and the Common Trunk (n = 20)	Without ABAS (n = 546)
Age (y)	53.8 ± 11.8	57.7 ± 11.2	56.6 ± 15.6	55.6 ± 10.9
Sex (male/female)	8 (62%)/5 (38%)	9 (75%)/3 (25%)	15 (75%) <sup>a</sup> /5 (25%)	261 (48%)/285 (52%)
BMI	28.2 [21.6–31.0]	24.3 [22.3–28.1]	24.7 [22.7–25.8]	24.1 [21.8–27.2]
Duration of hypertension (y)	19.6 ± 9.0 <sup>a</sup>	14.8 ± 11.6	10.0 ± 9.2	8.4 ± 9.0
Systolic BP (mm Hg)	153.2 ± 23.7	152.8 ± 28.9	159.0 ± 31.0	154.9 ± 24.3
Diastolic BP (mm Hg)	88.3 ± 13.8	98.4 ± 25.5	89.1 ± 18.6	92.8 ± 15.7
PRA (ng/mL/h)	0.4 [0.3–0.5]	0.2 [0.1–0.5]	0.2 [0.1–0.4]	0.3 [0.2–0.6]
PAC (pg/mL)	231 [184–399]	279 [194–425]	250 [132–298]	184 [126–282]
ARR	752 [467–1065]	1765 [603–2860]	960.9 [554–1639]	521 [306–1125]
Serum potassium levels (mEq/L)	3.5 [3.3–3.6] <sup>b</sup>	3.0 [3.0–3.6] <sup>b</sup>	3.7 [3.2–4.0]	3.8 [3.5–4.1]
Potassium supplementation	6 (46%) <sup>a</sup>	7 (58%) <sup>a</sup>	10 (50%) <sup>a</sup>	103 (19%)
Blood urea nitrogen levels (mg/dL)	14.3 ± 4.3	14.8 ± 4.0	14.3 ± 3.7	13.4 ± 3.9
Serum creatinine levels (mg/dL)	0.86 [0.7–0.9]	0.76 [0.7–0.9]	0.80 [0.7–0.9] <sup>a</sup>	0.71 [0.6–0.9]
Adrenal nodule in CT	10 (77%)	11 (92%) <sup>a</sup>	13 (65%)	306 (56%)
Adrenalectomy	8 (62%) <sup>a</sup>	6 (50%)	6 (30%)	158 (29%)

Data are expressed as the mean ± standard deviation, median [interquartile range], or number (percentage). *P* value represents the patients with ABAS vs the patients without ABAS.

Abbreviations: ARR, aldosterone renin ratio; BMI, body mass index; BP, blood pressure; CT, computed tomography.

<sup>a</sup>Significantly higher than the patients without ABAS, *P* < 0.05.

<sup>b</sup>Significantly lower than the patients without ABAS, *P* < 0.05.

diagnosed as the unilateral subtype in AVS and did not have ABAS with ACTH administration (data not shown). Duration of hypertension was significantly longer in the patients with ABAS at the central vein than that in the patients without ABAS (19.6 ± 9.0 vs 8.4 ± 9.0 years; *P* < 0.001). The percentages of patients taking potassium supplementation was significantly higher in the patients with ABAS at either the central vein or the common trunk or with ABAS at both the central vein and the common trunk than that in the patients without ABAS (46%, 58%, 50% vs 19%; *P* = 0.03, *P* < 0.01, *P* < 0.01, respectively). The percentages of patients having an adrenalectomy was significantly higher in the patients with ABAS at only the central vein than that in the patients without ABAS (62% vs 29%; *P* = 0.03). The protocols of ACTH administration in AVS were not different between patients with and without ABAS (data not shown).

The frequency of ABAS is shown in Table 2. The prevalence of ABAS at either the central vein or the common trunk with ACTH administration was significantly lower than that without ACTH administration [without ACTH administration vs with ACTH administration; 79/440 (18.0%) vs 45/591 (7.6%), *P* < 0.001]. In contrast, there were no differences in the prevalence of ABAS at the central vein and at only the common trunk between without and with ACTH administration [without ACTH administration vs with ACTH administration;

**Table 2. Frequency of ABAS Without and With ACTH Administration**

	Without ACTH Administration	With ACTH Administration	<i>P</i> Value
ABAS at only the central vein	14/440 (3.2%)	13/591 (2.2%)	0.4356
ABAS at only the common trunk	11/440 (2.5%)	12/591 (2.0%)	0.7705
ABAS at both the central vein and the common trunk	54/440 (12.3%)	20/591 (3.4%)	<0.001
ABAS at either the central vein or the common trunk	79/440 (18.0%)	45/591 (7.6%)	<0.001

Data are expressed as numbers and percentages of patients with ABAS only at the central vein, only at the common trunk, both at the central vein and the common trunk, and either the central vein or the common trunk.

ABAS at only the central vein, 14/440 (3.2%) vs 13/591 (2.2%); ABAS at only the common trunk, 11/440 (2.5%) vs 12/591 (2.0%);  $P = 0.33$ ,  $P = 0.67$ , respectively]. With ACTH administration, the prevalence of ABAS between only the central vein and only the common trunk was not different [13/591 (2.2%) vs 12/591 (2.0%);  $P = 1.00$ ]. When the patients with ABAS at both the central vein and the common trunk were added, the prevalence of ABAS between the central vein and the common trunk was not significantly different [33/591 (5.6%) vs 32/591 (5.4%);  $P = 1.00$ ].

The details of AVS of patients with ABAS with ACTH administration are shown in [Table 3](#). With ACTH administration, 11 of the 13 (85%) patients with ABAS at only the central vein showed an LI more than 4 at the common trunk. Similarly, 11 of the 12 (92%) patients with ABAS at only the common trunk showed an LI more than 4 at the central vein. Unilateral adrenalectomy was performed on eight (62%) of the patients with ABAS at only the central vein and on seven (58%) of the patients with ABAS at only the common trunk. All the patients had a left-side adrenalectomy.

The AVS data of the patients with ABAS at both the central vein and the common trunk are shown in [Table 4](#). In 16 of the 20 patients with ABAS at both the central vein and the common

**Table 3. The Laterality in the Results of AVS and CT Findings in the Patients With ABAS With ACTH Administration**

	ABAS at Only the Central Vein (n = 13)	ABAS at Only the Common Trunk (n = 12)	ABAS at Both the Central Vein and the Common Trunk (n = 20)
Without ACTH administration			
At the central vein			
LI > 4	3 (L3, R0)/5 (60%)	4 (L4, R0)/7 (57%)	5 (L1, R4)/11 (45%)
LI > 4 and concordant with CT	3 (L3, R0)/5 (60%)	3 (L3, R0)/7 (43%)	4 (L1, R3)/11 (36%)
At the common trunk			
LI > 4	4 (L4, R0)/5 (80%)	2 (L2, R0)/7 (29%)	5 (L2, R3)/11 (45%)
LI > 4 and concordant with CT	3 (L3, R0)/5 (60%)	1 (L1, R0)/7 (14%)	3 (L1, R2)/11 (27%)
With ACTH administration			
At the central vein			
LI > 4	2 (L2, R0)/13 (15%)	11 (L11, R0)/12 (92%)	1 (L0, R1)/20 (5%)
LI > 4 and concordant with CT	2 (L2, R0)/13 (15%)	9 (L10, R0)/12 (75%)	1 (L0, R1)/20 (5%)
At the common trunk			
LI > 4	11 (L11, R0)/13 (85%)	2 (L2, R0)/12 (17%)	3 (L2, R1)/20 (9%)
LI > 4 and concordant with CT	9 (L9, R0)/13 (69%)	1 (L1, R0)/12 (8%)	3 (L1, R1)/20 (9%)
CT findings	Left nodule (9)/bilateral nodules (1)	Left nodule (8)/right nodule (2)/bilateral nodules (1)	Left nodule (6)/right nodule (5)/bilateral nodules (2)
The side of adrenalectomy	Left (8)	Left (6)	Left (4)/right (2)

In each group (ABAS at only the central vein, ABAS at only the common trunk, and ABAS at both the central vein and at the common trunk), the percentages of the patients determined to have unilateral disease (LI > 4 or LI > 4 and concordant with CT) and the dominant side are expressed using the data without or with ACTH administration, at either the central vein or the common trunk. In the 13 patients with ABAS at only the central vein, 11 patients were sampled at the two positions in the left adrenal vein without ACTH administration, and five patients were successfully cannulated at the right adrenal vein and both of the two positions in the left adrenal vein without ACTH administration. In the 12 patients with ABAS at only the common trunk, nine patients were sampled at the two positions in the left adrenal vein without ACTH administration, and seven patients were successfully cannulated at the right adrenal vein and both of the two positions in the left adrenal vein without ACTH administration. In the 20 patients with ABAS at both the central vein and at the common trunk, 16 patients were sampled at the two positions in the left adrenal vein without ACTH administration, and 11 patients were successfully cannulated at the right adrenal vein and at both the two positions in the left adrenal vein without ACTH administration. Abbreviations: L, left; R, right.

**Table 4. The Details of AVS in the 20 Patients With ABAS at Both the Central Vein and the Common Trunk With ACTH Administration**

Patient	Without ACTH Administration				With ACTH Administration			
	RAV	Central Vein	Common Trunk	IVC	RAV	Central Vein	Common Trunk	IVC
1	<b>15,800/165 (95.6)<sup>a</sup></b>	848/177 (4.8)	4860/915 (5.3)	1840/44 (41)	76,700/2102 (36.5) <sup>a</sup>	6300/1017 (6.2)	8850/2032 (4.4)	3400/60 (56.9)
2	2040/441 (4.6)	<b>18,200/390 (46.7)<sup>a</sup></b>	<b>2600/120 (21.7)<sup>a</sup></b>	347/11 (30.7)	11,300/1989 (5.7)	49,900/2264 (22.0)	18,100/1452 (12.5)	784/30 (26.3)
3	251/43 (5.8)	1090/85.3 (12.8)	1430/95 (15.0)	141/9 (15.3)	2660/591 (4.5)	3000/295 (10.2)	2220/298 (7.4)	378/30 (12.8)
4	626/52 (12.0)	29,400/37 (801.3)	13,300/33 (409.1)	514/22 (23.0)	3830/1523 (2.5)	3560/1768 (2)	16,600/1949 (8.5)	759/37 (21)
5	2212/608 (3.6)	3482/31 (113.1)	2409/28 (87.5)	701/14 (50.8)	4194/940 (4.5)	4756/823 (5.8)	26,102/944 (27.6) <sup>a</sup>	1556/26 (60)
6	n.d.	n.d.	n.d.	n.d.	6020/559 (10.8)	1530/337 (4.5)	1450/325 (4.5)	306/18 (17.4)
7	1983/109 (18.2)	5189/85 (61.2)	<b>6853/68 (100.8)<sup>a</sup></b>	124/10 (13.1)	10,451/1710 (6.1)	14,321/1990 (7.2)	7690/620 (12.4)	175/14 (12.8)
8	<b>3530/58 (61.2)<sup>a</sup></b>	1450/148 (9.8)	2910/165 (17.6)	409/20 (20.2)	13,300/1100 (12.0)	4450/799 (5.6)	4530/1052 (4.3)	569/32 (18.0)
9	<b>1850/42 (43.7)<sup>a</sup></b>	2540/882 (2.9)	2680/604 (4.4)	215/11 (19.0)	17,400/1611 (10.8)	6440/1292 (5.0)	5250/1149 (4.6)	288/21 (13.6)
10	<b>4960/30 (167.6)<sup>a</sup></b>	1210/426 (2.8)	625/161 (3.9)	201/9 (21.6)	16,400/1835 (8.9)	4120/1383 (3.0)	896/177 (5.1)	269/18 (15.1)
11	1510/26 (58.2)	1110/23 (48.2)	936/18 (50.7)	86/7 (12.8)	20,700/1395 (14.8)	17,600/1127 (15.6)	11,100/819 (13.6)	149/8 (18.3)
12	5300/1100 (4.8)	8076/1160 (7.0)	6420/1120 (5.7)	82/13.3 (6.2)	13,500/1906 (7.1)	7430/1050 (7.1)	4190/830 (5.0)	186/25 (7.4)
13	350/67 (5.2)	1060/168 (6.3)	711/111 (6.4)	72/8 (9.1)	4180/680 (6.1)	3680/617 (6.0)	3810/656 (5.8)	198/20 (10.2)
14	2299/132 (17.4)	573/50.2 (11.4)	576/45 (12.9)	414/10 (40.6)	9150/572 (16.0)	10,128/641 (15.8)	6732/514 (13.1)	541/17.3 (31.3)
15	328/17 (19.8)	512/145 (3.5)	502/112 (4.5)	211/10 (20.9)	2670/566 (4.7)	2060/353 (5.8)	1950/323 (6.0)	331/20 (16.6)
16	n.d.	n.d.	n.d.	n.d.	2400/4068 (0.6)	2010/1172 (1.7)	7800/495 (15.8) <sup>a</sup>	718/39 (18.3)
17	136/18 (7.6)	932/40 (23.3)	1030/64 (16.1)	238/19 (12.5)	4780/948 (5.0)	8300/911 (9.1)	7350/748 (9.8)	356/23 (15.8)
18	110/26 (4.2)	185/42 (4.4)	344/57 (6.0)	114/23 (5.0)	1930/882 (2.2)	864/420 (2.1)	723/186 (3.9)	118/21 (5.5)
19	n.d.	n.d.	n.d.	n.d.	25,300/1734 (14.6)	9510/846 (11.2)	10,900/981 (11.1)	449/27 (16.6)
20	n.d.	n.d.	n.d.	n.d.	16,700/857 (19.5)	14,300/815 (17.5)	15,900/862 (18.4)	389/20 (19.9)

Data are shown as A/C ratio (pg/mL, µg/dL, pg/mL per µg/dL, respectively). The number 1 to 3 and 7 to 14 patients showed the selectivity index > 2 without ACTH administration at the right adrenal vein, the central vein, and the common trunk. The AVS data in the adrenal vein with a higher A/C ratio than that in the IVC are shown in bold characters. The number 1 to 6 patients underwent a unilateral adrenalectomy. The number 1, 2, and 7 to 10 patients were determined as having unilateral disease from the AVS data without ACTH administration. The number 3, 13, and 14 patients showed ABAS at both the central vein and the common trunk without ACTH administration. The number 5 and 16 patients with ABAS with ACTH administration were determined as having unilateral disease from the AVS data at the common trunk in the left adrenal vein without ACTH administration. Patient no. 1 was determined as having unilateral disease at the right adrenal vein with ACTH administration.

Abbreviations: n.d., no data; RAV, right adrenal vein.

<sup>a</sup>The AVS data are determined as unilateral disease because of an LI more than 4.

trunk, blood sampling was also performed without ACTH administration. Eleven of the 16 patients were successfully cannulated at both the two positions in the left adrenal vein, and six patients were determined as having unilateral disease (right dominant: four patients; left dominant: two patients). Two of the six patients underwent unilateral adrenalectomies. Three patients showed ABAS at both the central vein and the common trunk even without ACTH administration.

In 2 of the 20 patients who had ABAS at both the central vein and the common trunk, a repeat AVS was performed. In one patient (patient no. 3; Table 4), an alternative drainage vein from the left adrenal tumor to the left renal vein through the accessory left adrenal vein with higher A/C ratio than that in the IVC was detected. In the other patients (patient no. 6; Table 4), an alternative drainage vein to the right renal vein with higher A/C ratio than that in the IVC was detected.

The postoperative outcomes of the 20 patients with ABAS who underwent unilateral adrenalectomy were evaluated. Of the 15 patients with available outcome data after surgery, complete clinical success, partial clinical success, and absent clinical success was 33.3% (five patients, including patient no. 6; Table 4), 53.3% (eight patients, including patient no. 3; Table 4), and 13.3% (two patients), respectively. Of the 13 patients with available biochemical data, complete biochemical success and absent biochemical success was 92.3% (12 patients, including patients no. 3 and 6; Table 4) and 7.7% (one patient), respectively.

### 3. Discussion

In this study, we used a sample size that was much larger than that of the WAVES-J study. Because we investigated the left adrenal vein data at the two sampling positions, the

frequency of ABAS was higher than that of the studies by Wolley *et al.* [8] and the WAVES-J study. ABAS was more prevalent in male patients with PA. The exact reason for the sex difference remains unknown. However, it could simply be attributed to APA being more common in the patients with ABAS and male sex being more common in the patients with APA in the current study.

The current study demonstrated that ACTH administration reduces the frequency of ABAS, as suggested in the WAVES-J study. From the results of this study, it is recommended to perform ACTH administration to reduce the inconclusive results of AVS by ABAS.

The prevalence of ABAS was not different between the procedures of the sampling position in the left adrenal vein, at the central vein and at the common trunk. Umakoshi *et al.* [12] reported that the concordance rate of subtype diagnosis in the central vein and the common trunk was more than 95%, using the data of the WAVES-J study. They concluded that in a view of its better diagnostic accuracy, technical ease, lower cost, and lower risk of vein rupture, sampling from the common trunk of the left adrenal vein might be preferable as the standard method of AVS [12]. Performing an additional sampling at the central vein after encountering ABAS in AVS sampled at only the common trunk could be a worthwhile method.

In the WAVES-J study, we reported that a patient who showed ABAS both without and with ACTH administration had an alternative drainage vein from APA that was discovered by a repeat AVS. A higher aldosterone concentration and a higher A/C ratio in the alternative drainage vein was found in the patient [9]. There are also some reports of an alternative drainage vein from an adrenal tumor [14, 15]. In this study, 2 of the 20 patients with residual unresolved ABAS with ACTH administration received a repeat AVS. In one patient, an alternative drainage vein that flowed into the left renal vein was found, and in the other patient, an alternative drainage vein that flowed into the right renal vein was found.

In this study, the six patients who had ABAS at both the central vein and the common trunk with ACTH administration did not show ABAS and had conclusive results of AVS without ACTH administration. The current study demonstrated that the phenomenon occurs on both sides of the adrenal vein. It is suggested that the phenomenon could be attributed to a different catheter position without and with ACTH administration. Carr *et al.* [16] reported that the catheter shifted during the sampling without and with ACTH administration due to the respiratory movements. Because a sequential procedure requires recannulation into the adrenal vein, the position of the catheter may shift more frequently during the procedure. In this study, a sequential AVS was performed in 17 of the 20 patients with ABAS at both the central vein and the common trunk. It is however not clear whether the results of AVS may change by a simultaneous procedure.

Some patients showed ABAS only at the central vein or at the common trunk. ABAS only at the central vein could be attributed to an incidentally too-selective cannulation into the tributary that is not drained by APA [17–20]. ABAS only at the common trunk could be attributed to a dilution into the common trunk turn by a blood flow with low aldosterone concentration from the left inferior phrenic vein.

The strength of this study is that we could show the frequency of ABAS with a much larger cohort than the WAVES-J study with ACTH administration. In addition, we could show the frequency of ABAS at the central vein and at the common trunk in the left adrenal vein. The limitation of this study is that the variation in the protocols of AVS among participating centers might have effects on the occurrence of ABAS. The effect on ABAS between a sequential and a simultaneous AVS could not be clarified.

In conclusion, the effectiveness of ACTH administration for the reduction of ABAS in the AVS procedures, regardless of the sampling positions in the left adrenal vein, was proven in a large cohort.

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