

# Comparison of the Central Adrenal Vein and the Common Trunk of the Left Adrenal Vein for Adrenal Venous Sampling

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## ABSTRACT

**Purpose:** To compare left adrenal venous sampling (AVS) in two locations: the central adrenal vein and the common trunk.

**Materials and Methods:** A total of 22 patients (12 men and 10 women; mean age, 50 y; range, 26–65 y) who were suspected of having primary aldosteronism (PA) and underwent successful AVS with cortisol concentration measurement and/or venography between November 2010 and August 2011 were retrospectively analyzed. In regard to the left adrenal vein, collections were done at two locations: at the common trunk below the confluence of the inferior phrenic vein and at the central adrenal vein, which was above the confluence. The effects of the inflow from the inferior phrenic vein on plasma aldosterone and cortisol levels were analyzed.

**Results:** Eight patients had bilateral hypersecreting lesions and 13 had a unilateral lesion. One was diagnosed as having secondary hypertension other than PA. The median cortisol levels below and above the confluence were 129  $\mu\text{g/dL}$  (range, 21–400  $\mu\text{g/dL}$ ) and 215  $\mu\text{g/dL}$  (range, 21–690  $\mu\text{g/dL}$ ), respectively. The median aldosterone levels were 2,120  $\text{pg/mL}$  (range, 164–42,700  $\text{pg/mL}$ ) and 4,275  $\text{pg/mL}$  (range, 119–59,000  $\text{pg/mL}$ ), respectively. The median aldosterone/cortisol (A/C) ratios were 244 (range, 34–2,401) and 278 (range, 25–2,251), respectively. Cortisol and aldosterone levels were significantly higher above the confluence ( $P = .0050$  and  $P = .0003$ , respectively), whereas the A/C ratio showed no significant difference ( $P = .12$ ).

**Conclusions:** Although higher levels of cortisol and aldosterone were obtained upstream, A/C ratio was not significantly different between the central adrenal vein and the common trunk.

## ABBREVIATIONS

A/C = aldosterone/cortisol, ACTH = adrenocorticotropic hormone, APA = aldosterone-producing adenoma, AVS = adrenal venous sampling, IHA = idiopathic hyperaldosteronism, IVC = inferior vena cava, PA = primary aldosteronism

It has been reported that approximately 3%–10% of hypertension is a result of primary aldosteronism (PA) (1–4). The most common two subtypes of PA are aldosterone-producing adenoma (APA) and bilateral idiopathic hyperaldosteronism (IHA) (5).

When PA has been confirmed, determining whether one or both adrenal glands produce excess aldosterone is the

next important procedure to help guide management of hypertension. Unilateral laparoscopic adrenalectomy is an excellent treatment option for patients with APA or unilateral hyperplasia: blood pressure control improves in nearly 100% of patients postoperatively, and average long-term cure rates of hypertension after unilateral adrenalectomy for APA range from 30% to 60% (1).

Although computed tomography (CT), magnetic resonance (MR) imaging, and scintigraphy can provide information about the presence of a nodule or enlargement of the adrenal gland, in many cases, they may show normal-appearing adrenal glands, minimal unilateral adrenal limb thickening, unilateral microadenomas ( $\leq 1$  cm), or bilateral macroadenomas. Several studies have found that CT contributes little to confirm lateralization in patients with PA, and that adrenal venous sampling (AVS) is essential to choose appropriate therapy in patients who have a high

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probability of APA and CT findings of unilateral adrenal limb thickening (1,5–7).

With respect to the sampling method of the right adrenal vein, many arguments have been made to explain its difficulty (8–10). On the contrary, there have been few reports about the method of sampling from the left adrenal vein (6,11). Because the left inferior phrenic vein joins the left adrenal vein in the majority of cases (8,12,13), this effluence may cause dilution and fluctuation of hormone levels. There are reports of blood collected upstream of the confluence (4) and in the lower stream (11), and the appropriate location for blood collection has not yet been established.

The present study was designed to examine the effect on AVS of the dilution caused by the inflow of the left inferior phrenic vein.

## MATERIALS AND METHODS

### Patient Selection

A total of 25 consecutive patients who were referred for suspected PA and underwent AVS at our institution or an associated facility from November 2010 to August 2011 was selected. Each patient underwent one or two confirmatory tests for aldosterone excess according to the guidelines of the Japanese Endocrine Society and Japanese Society of Hypertension: an oral sodium test, saline solution infusion test, captopril challenge test, and furosemide plus upright test. When PA had been confirmed, patients were referred to the radiology department for AVS. In the meanwhile, an enhanced CT scan was performed to detect the adrenal veins as well as to screen the adrenal glands (4,14). Three patients were excluded from the study because of unsuccessful blood sampling from the adrenal vein, leaving 22 patients (12 men and 10 women; mean age,  $50 \text{ y} \pm 12$ ) eligible for the present study.

Our institutional review board approved retrospective data collection and analysis for this research, and informed patient consent was waived.

### AVS Procedures

The patients were prepared from a pharmacologic standpoint by stopping diuretic agents,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers for at least 2 weeks before AVS and stopping mineralocorticoid receptor antagonists for at least 6 weeks before AVS, as previously reported (4,15,16). Patients who could not be left untreated for clinical reasons were allowed to take  $\alpha$ -blockers and/or a calcium channel blocker. Patients first signed an informed consent form that described the AVS procedure and its predictable complications such as groin hematoma, adrenal hemorrhage, thrombosis, and risk of nondiagnostic test results.

AVS was performed by three interventional radiologists (A.T., K.S., and Y.M.) with 11, 13, and 14 years of experience, respectively, and experience with at least 30

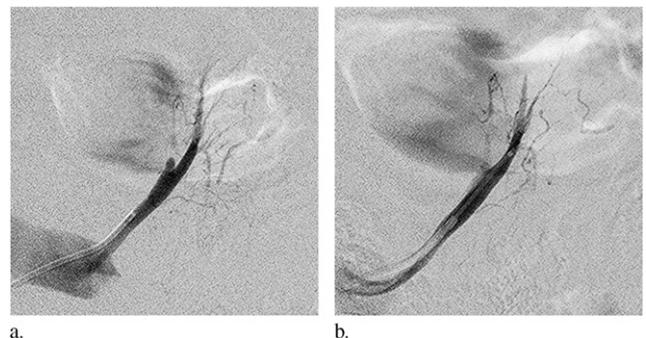
AVS cases each. Each operator performed AVS according to the technique and protocols described here.

Procedures were performed under local anesthesia. A 5-F sheath was inserted through the percutaneous femoral vein approach. Blood was obtained from the inferior vena cava (IVC) below the confluence of the renal veins by using the sheath or a 5-F catheter.

A 5-F reverse-curve catheter (LRA; Terumo—Clinical Supply, Gifu, Japan) was inserted into the left adrenal vein, and then venography was performed to confirm the confluence of the central adrenal vein and the left inferior phrenic vein, followed by sampling of blood at the common trunk, which is between the confluence of these veins and the orifice of the adrenal vein at the left renal vein. When the confluence of the left phrenic vein was not well identified or, in rare cases, the left adrenal and inferior phrenic veins entered the left renal vein separately, sampling was performed at the common trunk just above the orifice at the left renal vein. Subsequently, a high-flow-type microcatheter (Renegade Hi-Flo; Boston Scientific, Natick, Massachusetts) was inserted beyond the confluence of the inferior phrenic vein to reach the central adrenal vein, followed by venographic confirmation that the tip of the catheter had been placed proximal to the division of the lateral branch of the left adrenal vein (4). Blood was then collected there (Fig 1).

Finally a 4- or 5-F reverse-curve catheter or one with a steep curve on its tip (CJ1, RH, and RRA catheters; Terumo—Clinical Supply) was inserted into the right adrenal vein, followed by venographic confirmation, and blood was collected. When drawing blood was difficult through the 4- or 5-F catheter, a microcatheter was also inserted into the right adrenal vein. One sample was obtained from each vein in one AVS procedure, and blood was aspirated by gentle slow suction to avoid adrenal venous dilution.

The plasma aldosterone and cortisol levels of each vein were measured. In the early cases during the study period, adrenocorticotropic hormone (ACTH) stimulation was not performed, and ACTH stimulation was omitted in some cases with excessively autonomous aldosterone secretion based on review with endocrinologists.



**Figure 1.** (a) Venogram of common trunk of left adrenal vein with a 5-F catheter. (b) A microcatheter is inserted into the central adrenal vein beyond the confluence of the left inferior phrenic vein.

## AVS-derived Indices

To determine the side of aldosterone hypersecretion, the lateralized ratio and the contralateralized ratio were calculated (15,17). Before calculating these indices, the aldosterone/cortisol (A/C) ratio, which serves to correct adrenal venous aldosterone levels for differing degrees of dilution of adrenal versus nonadrenal venous blood, was calculated. The lateralized ratio is defined as the dominant A/C ratio divided by the nondominant A/C ratio, with the dominant and nondominant A/C ratios those on the sides with higher and lower aldosterone secretions, respectively. The contralateralized ratio is defined as the nondominant A/C ratio divided by the A/C ratio of the IVC. Catheterization of the adrenal vein was considered successful when the cortisol ratio of the adrenal veins to the IVC (ie, selectivity index) was 1.1 or more (18,19).

According to previous reports, a cutoff of the lateralized ratio of greater than 2 and a contralateralized ratio less than 1.0 indicates unilateral aldosterone secretion (16,18), and, in cases with ACTH stimulation, the laterality was confirmed in conjunction with it (4).

## Statistical Analysis

Results are expressed as means  $\pm$  standard error of the mean or as median and range when appropriate. Normality of distributions of plasma aldosterone and cortisol values, A/C ratio, and AVS-derived indices was verified by Shapiro–Wilk test. These values were compared between the two locations with a paired *t* test or Wilcoxon nonparametric test as appropriate. A two-sided *P* value lower than .05 was considered significant. Analysis was performed with StatPlus:mac (AnalystSoft, Alexandria, Virginia).

## RESULTS

The clinical features of all patients are shown in **Tables 1 and 2**. The subtype of PA and the final diagnosis were confirmed by endocrinologists in accordance with the Japanese Endocrine Society guidelines (4); in cases with difficulty in AVS diagnosis or a lack of ACTH stimulation, a comprehensive judgment was reached with CT and/or MR imaging findings. Thirteen patients (59%) had a unilateral adrenal lesion, which included unilateral APAs and unilateral hyperplasia, and the other eight patients (36%) had bilateral lesions. One patient was finally judged to have no aldosterone overproduction from either adrenal gland after AVS showed that the A/C ratio of the bilateral adrenal glands was lower than that of the IVC after ACTH stimulation and repeated loading tests did not prove aldosterone hypersecretion.

Twelve patients (55%) underwent adrenalectomy and were histologically diagnosed, whereas the remaining 10 patients (45%) were diagnosed based on the result of the AVS, imaging examinations including CT and/or MR imaging, and clinical course.

The median cortisol level of the left central adrenal vein was 215  $\mu\text{g/dL}$ , whereas that of the common trunk was 129  $\mu\text{g/dL}$ ; the difference was significant (**Fig 2a**). The median plasma aldosterone concentrations of the central adrenal vein and the common trunk were 4,275 and 2,120  $\text{pg/mL}$ , respectively; the difference was significant (**Fig 2b**). The median A/C ratios of the central adrenal vein and the common trunk were 278 and 244, respectively. Although the A/C ratio of the central adrenal vein was higher than that of the common trunk in 13 cases, the A/C ratio was not significantly different between the two locations (**Fig 3**). There were 11 cases in which the A/C ratio of the left adrenal vein was higher than that of the right adrenal vein, and the same number of cases showed a higher A/C ratio for the right adrenal vein. Therefore, the lateralized ratio was evaluated separately in these two groups. In the right adrenal–dominant group, the median lateralized ratios calculated based on the figures of the central vein and the common trunk were 4.40 and 9.19, respectively. Meanwhile, in the left adrenal–dominant group, the lateralized ratios were 10.70 and 10.96, respectively. Neither group showed a significant difference (**Fig 4**). In 11 cases in the right adrenal–dominant group, the contralateralized ratio was calculated using by the A/C ratios of the left adrenal vein and the IVC. The medians calculated based on the value of the central adrenal vein and the common trunk were 1.38 and 1.51, respectively; the difference by sampling location in the left adrenal vein was not significant (**Fig 5**).

There were no local or general complications during or after AVS based on chart review or examination report.

## DISCUSSION

The rate of PA among patients with hypertension has increased to 3%–9% since Gordon et al (20) reported that the prevalence was higher than previously thought based on the use of the aldosterone-to-renin ratio as a screening test (1–3). When the diagnosis has been confirmed, adrenal gland appearance is checked on CT to find an adrenal mass lesion or adrenomegaly. If the patient can physically tolerate, and wishes to undergo, surgical treatment for PA, AVS is necessary to determine whether aldosterone hypersecretion is bilateral or unilateral, and, if unilateral, which adrenal gland is responsible (4).

AVS has become widely used in the diagnosis of PA since Melby et al first reported AVS (21), along with the evolution of diagnostic imaging and catheters. Many reviews of sampling from the right adrenal vein have been performed because of the difficulty in catheterization (9,19,22). However, studies on the location from which to draw blood from the left adrenal vein or the effect of dilution by the left inferior phrenic vein have been scarce.

There are reports that most left adrenal veins join the left renal vein, and the left adrenal vein and the inferior phrenic vein enter the left renal vein separately in 1%–10% of

**Table 1.** Clinical Data

Pt. No.	Age (y)/Sex	CT/MR Findings	Final Diagnosis	Operator	Catheter Type (R/L)	Adrenal Vein Anomaly (R/L)
Left-dominant group						
1	61/M	Normal	IHA	A.T.	CJ1/LRA	None/none
2	47/F	Normal	IHA	A.T.	CJ1/LRA	None/none
3	43/M	L adenoma	L APA	A.T.	CJ1/LRA	None/none
4	39/M	L adenoma	L APA	A.T.	CJ1/LRA	None/none
5	26/M	L adenoma	L APA	A.T.	RH/LRA	None/none
6	53/M	L adenoma	L APA	K.S.	CJ1/LRA	None/none
7	45/F	L adenoma	L APA	A.T.	CJ1/LRA	None/none
8	28/F	L adenoma	L APA	A.T.	CJ1/LRA	None/none
9	45/M	L adenoma	L APA	A.T.	CJ1/LRA	None/none
10	57/M	L adenoma, R hyperplasia	L APA	K.S.	RRA/LRA	None/none
11	63/M	L adenoma	L APA	K.S.	RRA/LRA	None/none
Right-dominant group						
12	60/F	Bilateral adenomas	R APA	A.T.	CJ1/LRA	None/none
13	48/F	Normal	IHA	A.T.	CJ1/LRA	Open to accessory HV/none
14	54/F	Normal	IHA	A.T.	RRA/LRA	None/AV and IPV merge to renal vein separately
15	47/F	L hyperplasia	R UAH	A.T.	CJ1/LRA	None/none
16	29/F	Normal	IHA	A.T.	RRA and microcatheter/LRA	Open to accessory HV/AV and IPV merge to renal vein separately
17	65/F	L hyperplasia	IHA	A.T.	CJ1/LRA	None/none
18	64/F	Normal	R UAH	A.T.	CJ1/LRA	None/none
19	60/M	L adenoma	Bilateral APA	A.T.	CJ1/LRA	Open to accessory HV/none
20	58/M	Bilateral hyperplasia	IHA	A.T.	RRA/LRA	None/none
21	61/M	Normal	Secondary hypertension	A.T.	CJ1/LRA	None/none
22	40/M	Normal	R APA	A.T.	RRA/LRA	None/none

APA = aldosterone-producing adenoma, AV = adrenal vein, HV = hepatic vein, IHA = idiopathic hyperaldosteronism, IPV = inferior phrenic vein, UAH = unilateral adrenal hyperplasia.

cases (11,12); a cadaver study reported that only 34% of left inferior phrenic veins join the left adrenal vein (23), and there have been reports of anomalous cases in which the left adrenal vein unites with the circumaortic left renal vein or directly with the IVC (8,13). The majority of left adrenal veins receive a left inferior phrenic vein and renal capsular vein tributaries (12). When collecting blood from the left adrenal vein with the use of a reverse-curve catheter, we obtain blood at the left adrenal vein immediately above the confluence of the renal vein in view of the restriction in its shape in many cases. There are reports (4,24) that recommend that blood be collected at the central adrenal vein, which is upstream of the confluence of the inferior phrenic vein. However, the effect of the sampling location on the examination data is unclear. Therefore, we assumed that it was important to determine the optimal location to sample blood from the left adrenal vein to identify adrenal hypersecreting lesions precisely.

In the present study, the absolute cortisol and aldosterone levels were higher in the central adrenal vein than in the common trunk. This is considered to have resulted from the blood of the central adrenal vein having been diluted by the effluence of the inferior phrenic vein. There are reports that a cortisol ratio of at least 1.1–3 between the adrenal vein and IVC is considered successful without ACTH stimulation (15,16,18,25), and, when judging this cortisol ratio, this attenuating effect cannot be disregarded.

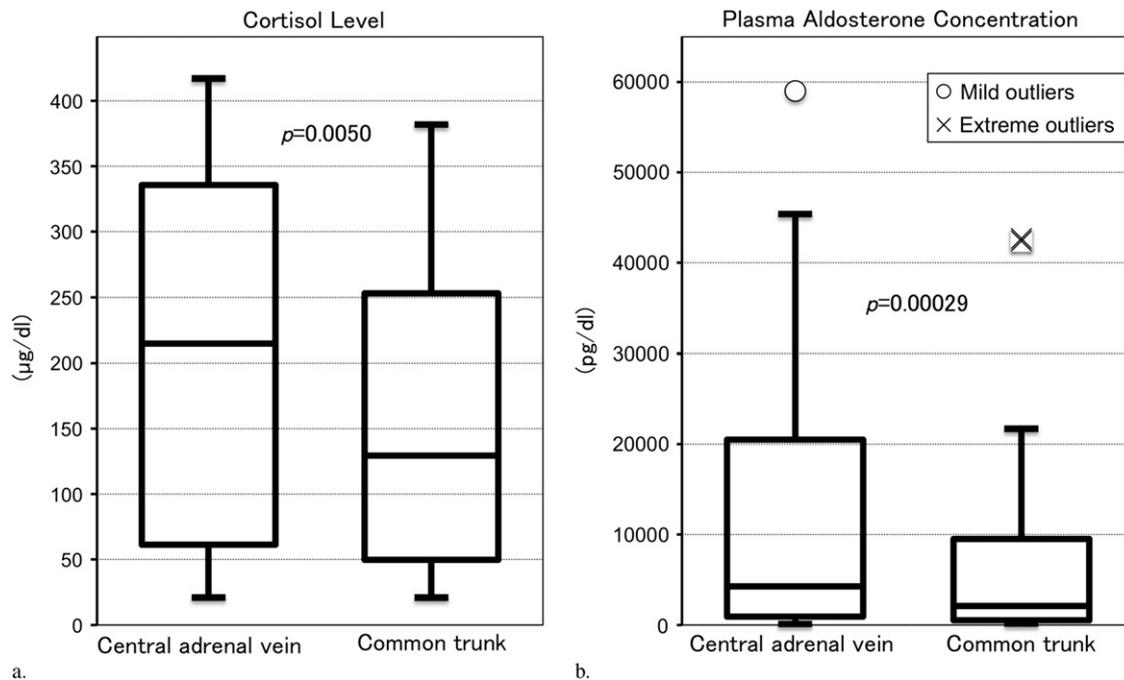
According to Japan Endocrine Society guidelines, if the adrenal vein plasma aldosterone concentration after ACTH stimulation is at least 14,000 pg/mL, the adrenal gland on this side is judged to be hypersecreting aldosterone. If the adrenal vein plasma aldosterone concentration is bilaterally at least 14,000 pg/mL, IHA is most likely (4). As ACTH loading was not performed in all cases in the present study, the values after ACTH stimulation were not included in the

Table 2. Sampling Data

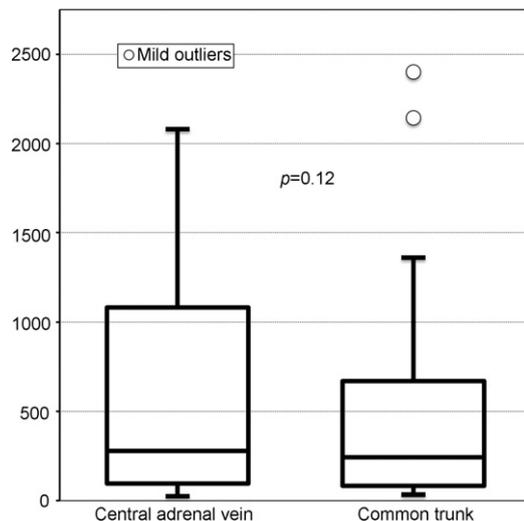
Pt. No.	Left Central Adrenal Vein						Left Common Trunk						Right Adrenal Vein				IVC			Interval*
	A (pg/mL)	C (μg/dL)	A/C Ratio	SI	LR	CR	A (pg/mL)	C (μg/dL)	A/C Ratio	SI	LR	CR	A (pg/mL)	C (μg/dL)	A/C Ratio	SI	A (pg/mL)	C (μg/dL)	A/C Ratio	
Left-dominant group																				
1	15,000	690.0	217	103.0	1.5	NA	10,100	400.0	253	59.7	1.7	NA	496	33.3	149	4.97	120	6.7	179	32
2	935	62.0	151	4.7	1.8	NA	315	38.1	83	2.9	1.0	NA	2,130	260.0	82	19.55	91	13.3	68	25
3	2,900	26.3	1,103	3.0	9.4	NA	2,020	20.9	967	2.4	8.2	NA	236	20.1	117	2.31	254	8.7	292	8
4	22,300	219.0	1,018	19.7	14.6	NA	7,050	86.6	814	7.8	11.7	NA	682	97.8	70	8.81	224	11.1	202	16
5	9,950	196.0	508	10.0	10.7	NA	7,800	150.0	520	7.7	11.0	NA	925	195.0	47	9.95	149	19.6	76	71
6	41,100	401.0	1,025	22.0	8.1	NA	16,500	381.9	432	21.0	3.4	NA	443	34.8	127	1.91	276	18.2	152	10
7	45,400	371.4	1,222	21.6	53.0	NA	42,700	314.0	1,360	18.3	58.9	NA	685	296.8	23	17.26	304	17.2	177	32
8	43,700	210.1	2,080	11.3	12.7	NA	42,400	176.6	2,401	9.5	14.7	NA	827	50.5	164	2.72	874	18.6	470	13
9	31,400	224.5	1,399	23.9	6.0	NA	21,700	301.7	719	32.1	3.1	NA	2,170	93.1	233	9.90	288	9.4	306	22
10	59,000	417.1	1,415	24.8	46.2	NA	7,650	146.7	521	8.7	17.0	NA	106	34.6	31	2.06	348	16.8	207	16
11	5,650	25.1	2,251	3.0	18.3	NA	5,100	23.8	2,143	2.9	17.4	NA	212	17.2	123	2.07	98.4	8.3	119	14
Right-dominant group																				
12	572	192.0	30	36.2	212.5	0.05	269	32.2	84	6.1	75.8	0.15	176,000	278.0	6,331	52.45	294	5.3	555	18
13	2,830	236.0	120	8.6	3.8	3.36	2,220	256.0	87	9.3	5.2	2.43	1,820	40.5	449	1.47	98.6	27.6	36	48
14	985	337.0	29	14.7	11.3	1.38	260	73.0	36	3.2	9.3	1.68	5,300	160.0	331	6.99	48.5	22.9	21	39
15	119	47.9	25	5.5	81.0	0.32	164	48.7	34	5.6	59.8	0.43	6,300	31.3	2,013	3.60	67.6	8.7	78	33
16	13,900	411.0	338	27.0	8.4	2.61	10,900	351.0	311	23.1	9.2	2.40	7,250	25.4	2,854	1.67	197	15.2	130	46
17	1,210	83.4	145	5.3	2.5	2.02	726	66.7	109	4.2	3.4	1.51	2,350	64.0	367	4.08	113	15.7	72	43
18	10,500	225.0	467	56.3	1.3	2.77	953	191.0	50	47.8	12.1	0.30	7,150	118.0	606	29.50	67.5	4.0	169	33
19	459	21.0	219	1.3	1.9	6.09	384	21.6	178	1.4	2.4	4.95	866	20.4	425	1.29	56.7	15.8	36	17
20	478	54.3	88	5.4	4.4	0.69	1,240	52.8	235	5.2	1.6	1.84	643	16.6	387	1.64	129	10.1	128	73
21	1,060	332.4	32	19.0	1.2	0.82	827	244.4	34	14.0	1.2	0.87	1,270	321.3	40	18.36	67.9	17.5	39	13
22	321	61.1	53	3.5	38.7	0.32	450	111.8	40	6.3	50.6	0.24	5,250	25.8	2,035	1.46	291	17.7	164	18

A = aldosterone, C = cortisol, CR = contralateralized ratio, LR = lateralized ratio, NA = not applicable, SI = selectivity index.

\* Sampling interval of left and right adrenal veins.



**Figure 2.** Cortisol and plasma aldosterone concentrations. Box-and-whisker plots show medians, interquartile range, and extreme cases of cortisol (**a**) and plasma aldosterone (**b**) concentrations of the central adrenal vein and the common trunk. The cortisol and aldosterone levels in the central adrenal vein are significantly higher in the common trunk.



**Figure 3.** Box plot (median, interquartile range, and extreme values) shows the A/C ratio of the central adrenal vein and the common trunk. No significant difference was found between them.

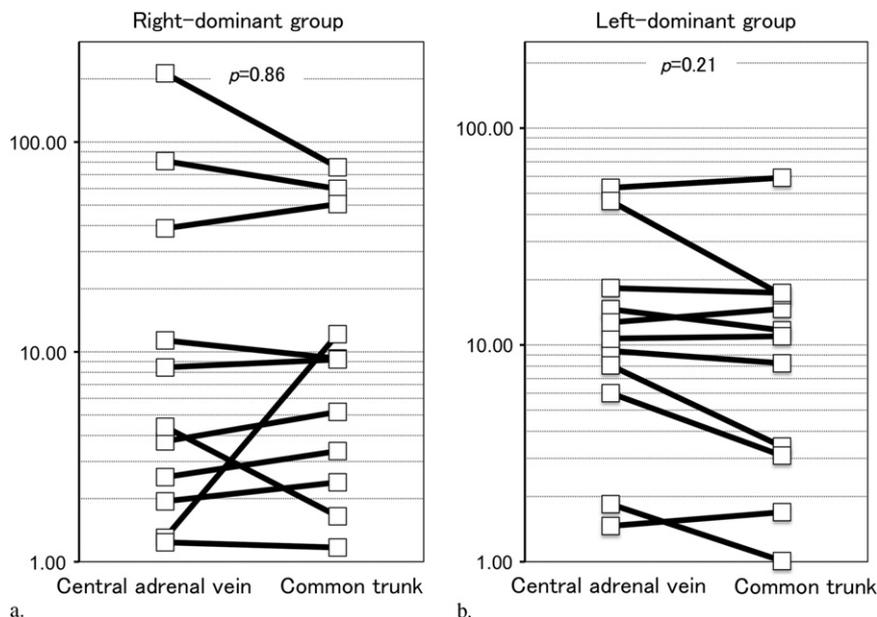
analysis. Even without ACTH stimulation, the average aldosterone value of the central adrenal vein was 65% higher than that of the common trunk, and, if this criterion was used after ACTH stimulation, the difference in the location of blood collection location might affect the diagnosis. Further investigation is required with respect to this point.

There are some reports that a venous sample from the left side is typically obtained from the common trunk because passage deeper into the gland increases the risk,

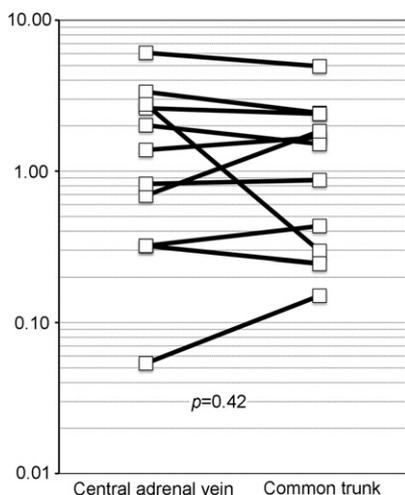
and studies with nondiagnostic results are very uncommon (6,11,15). On the contrary, according to Japan Endocrine Society guidelines, the tip of the catheter is inserted precisely into the left adrenal central vein distal to the division of the left inferior phrenic vein and proximal to the division of the lateral branch of the left adrenal vein, and blood is sampled (4). Although the present study showed that the hormone level of the central adrenal vein was higher than that of the common trunk, there were no significant differences in the indices based on A/C ratio. Microcatheters were used to sample blood at the central adrenal vein to reduce the risk of vascular injury and to allow fine adjustment of the catheter tip. However, considering the results of the present study, sampling at the common trunk without the use of a microcatheter may be sufficient based on these indices.

Simultaneous blood collection from both adrenal veins was omitted in the present study, so, even if the blood drawing interval between the right and left adrenal veins was minimized, a disproportion caused by a transient increase of aldosterone from “burst-like” aldosterone secretion cannot be excluded (26). We believe hormone secretion fluctuation and stress effect could have played little role in left AVS results, as central vein samples were obtained immediately following samples collected through the common trunk via a microcatheter that was advanced coaxially.

The present study has some limitations. First, as the results of AVS were part of the workup used to make the final diagnosis, a tautology may have existed in our evaluation of AVS for diagnostic purposes. Those who



**Figure 4.** Graph shows lateralized ratio calculated with the figures of the central adrenal vein and common trunk. No significant difference was found between these two locations in the right-dominant group (a) or left-dominant group (b).



**Figure 5.** Graph shows contralateralized ratio calculated with the figures of the central adrenal vein and common trunk in the right-dominant group. No significant difference was found between them.

underwent ACTH stimulation and those who did not were intermingled, and laterality was determined based on the result of AVS without ACTH stimulation in some of the latter. In other words, it could be that a few small APAs were missed in the group of patients considered to have IHA. Second, to reduce invasion and avoid repeat examinations, a selectivity index of greater than 1.1 was set in this study; however, there are reports that a selectivity index greater than 2 or greater than 3 can provide more accurate information on the determination of laterality (7,16,27). Applying this relatively lenient criterion might cause a decrease in the concordance rate between results of AVS and the final diagnosis. Third, the sample size is

small, and there is only one sample in each AVS location. Therefore, there may be a potential bias of sample data and a lack of reproducibility as a result of variants of venous anatomy and position of the catheter tip.

In conclusion, although the left adrenal vein was diluted by the effluence of the left inferior phrenic vein, the A/C ratio and indices based on A/C ratio were not significantly different between AVS of the central adrenal vein and the common trunk.

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