*Original Article*

# Localization of Aldosterone-Producing Adrenocortical Adenomas: Significance of Adrenal Venous Sampling

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**Accurate localization of aldosterone-producing adenoma (APA) is essential for the treatment of primary aldosteronism (PA). In order to confirm the clinical usefulness of adrenal venous sampling (AVS), we retrospectively studied 87 cases of PA in whom AVS was conducted. We collected right and left adrenal venous effluents simultaneously before and after adrenocorticotropic hormone (ACTH) stimulation for measurements of aldosterone concentration (A) and cortisol concentration (C). Based on AVS results, we judged 66 cases as having unilateral aldosterone hypersecretion and the remaining 21 cases as having no apparent laterality. Of the above 66 subjects, 61 underwent laparoscopic removal of the adrenal gland through a retroperitoneal approach. The presence of APA was histopathologically confirmed, and blood pressure decreased significantly with normalization of plasma aldosterone concentration (PAC) in all cases. The receiver operator characteristics (ROC) curve analysis between the operated and no–apparent-laterality groups revealed that the ratio of A/C on the higher side to A/C on the lower side (A/C ratio) after ACTH stimulation is a useful index, with a cutoff value of 2.6, a sensitivity of 0.98 and a specificity of 1.0. The ROC curve analysis between the APA side and contralateral side within the operated patients revealed that the cutoff value of A was 1,340 ng/dL, with a sensitivity of 0.92 and a specificity of 1.00. Our results indicate the usefulness of simultaneous AVS and ACTH stimulation for localizing APA. (*Hypertens Res* 2007; 30: 1083–1095)**

***Key Words*: aldosterone-producing adenoma, localization, adrenal venous sampling**

## Introduction

Primary aldosteronism (PA) is one of the major causes of secondary hypertension. Recent studies have suggested that PA is much more common than previously thought, and in hypertensive patients the prevalence rate of PA has been reported to be approximately 5–15% (*1–10*). The two most common causes of aldosteronism are unilateral adenoma, aldosterone-producing adenoma (APA), and bilateral hyperplasia, idiopathic hyperaldosteronism (IHA). In cases of APA, hypertension can be cured by surgical resection, whereas surgery may be of little value in cases of IHA (*11*). Therefore, in patients with PA, it is critical to investigate the possibility of a functioning APA and to localize it.

CT, MRI, adrenal scintigraphy, and/or adrenal venous sam-

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pling (AVS) are usually employed to localize an APA. Adrenal imaging using state-of-the-art CT scan is one of the most useful methods to localize an APA; however, an adenoma of 5 mm or less in diameter may not be detected. Even APAs of more than 5 mm are not always detected by CT. Regarding adrenal scintigraphy, adrenal iodomethyl-norcholesterol (NP-59) uptake depends primarily on the size of the APA rather than on its functional activity (*12*). This test might not be useful for detecting a small APA, because the tracer uptake is poor in APAs of less than 1.5 cm in diameter (*13–15*). In addition, PA may be associated with non–aldosterone-secreting nodules in the ipsilateral or contralateral adrenal gland (*16–18*). Bilateral idiopathic hyperplasia may be associated with a unilateral non-functioning macro-nodule which can demonstrate an intense uptake on adrenal scintigraphy even under dexamethasone suppression, and this may lead to an incorrect diagnosis of a unilateral APA (*19*).

Of late, AVS has been reported to be a more sensitive and specific diagnostic method for localizing an APA than CT or scintigraphy (*20*). Many cases of small APAs undetected on CT have been reported to be diagnosed by AVS and surgically treated (*21*). Rossi *et al*. reported positive AVS findings in 104 patients with PA and equivocal CT or MRI findings. With blood samples obtained from bilateral adrenal veins (bilateral selective AVS), a value of ≥2.0 for the ratio of aldosterone/cortisol (A/C) on one side to A/C on the contralateral side (the A/C ratio) identified a unilateral source of excess aldosterone in 80% of the patients (*22*). AVS with adrenocorticotropic hormone (ACTH) stimulation is generally used to eliminate fluctuation and facilitate localization of unilateral APA (*17*, *23–25*). With ACTH stimulation, the diagnostic accuracy increases, especially for differential diagnosis from IHA (*17*).

We performed CT and AVS with ACTH stimulation in 87 consecutive patients with PA, and compared the findings of CT scans with those of AVS. The present study was undertaken to establish the clinical usefulness of AVS in localizing an APA.

## Methods

### Subjects

The study group consisted of 43 men and 44 women (mean age, 52 years; range, 31 to 75 years) enrolled over a period of 4.5 years, in whom AVS was successfully carried out. The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine. Informed consent was obtained from all the patients. The patients were referred to our hypertension/endocrine clinic because of uncontrollable hypertension, hypertension associated with hypokalemia, or adrenal tumors on CT or suspected PA. Blood pressure was measured with a mercury sphygmomanometer after at least 15 min of rest in a sedentary position, and the average value of three consecutive measurements was recorded. The

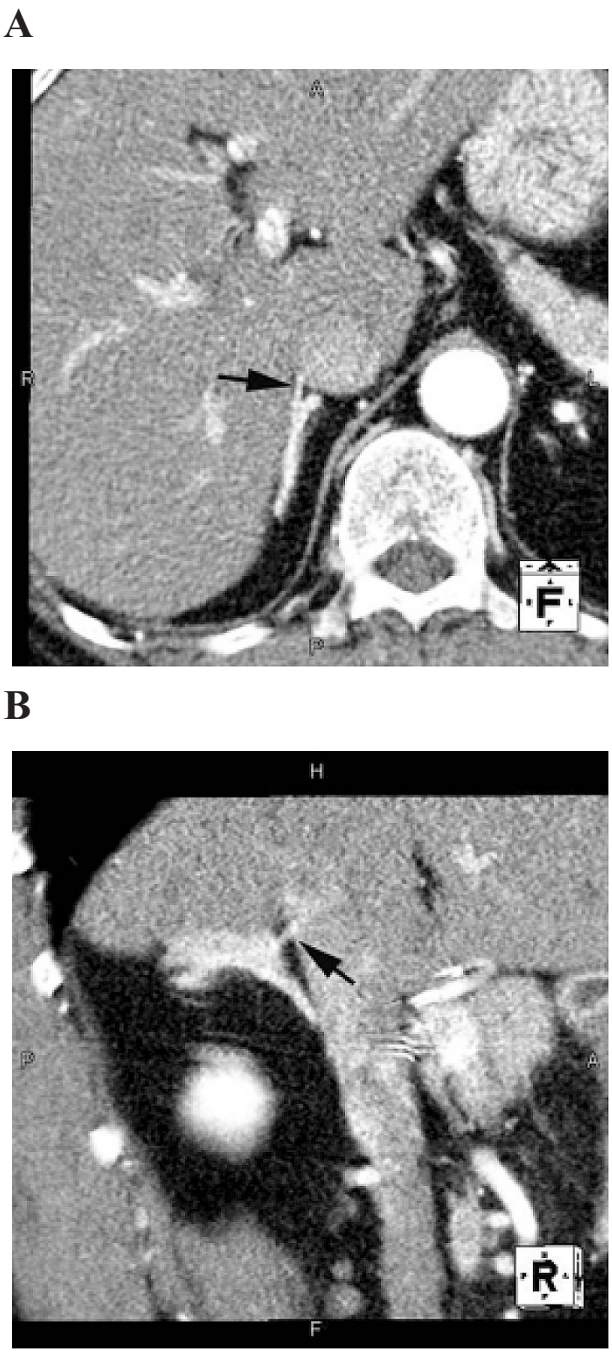


**Fig. 1.** *A right adrenal vein imaged by multi-detector row CT (MDCT). Anatomical variances of the right adrenal veins were detected by MDCT to facilitate cannulation for AVS. A: An axial view as obtained by MDCT. B: A sagittal MDCT view. The arrow indicates a right adrenal vein.*

patients were treated with a calcium channel blocker and/or an $\alpha_1$-blocker before and during endocrinological examinations (*26*). None of the patients received diuretics, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin

**Table 1. Clinical Data of the Patients with Primary Aldosteronism**

| | Total (cases 1–87) ($n$=87) | APA (cases 1–61) ($n$=61) | Medically treated | |
|---|---|---|---|---|
| | | | APA suspected (cases 62–66) ($n$=5) | No apparent laterality (cases 67–87) ($n$=21) |
| Age (years) | 52.4±1.3 | 52.0±1.3 | 61.4±3.1 | 51.4±2.1 |
| Sex (male/female) | 43/44 (87) | 31/30 (61) | 2/3 (5) | 10/11 (21) |
| Duration (years) | 12.9±2.1 | 13.8±1.2 | 16.6±4.3 | 10.5±2.7 |
| Systolic blood pressure (mmHg) | 149.7±2.6 | 153.2±2.7 | 154.8±13.8 | 141.5±4.3* |
| Diastolic blood pressure (mmHg) | 90.5±1.7 | 91.4±2.2 | 83.2±6.3 | 89.6±3.8 |
| Antihypertensive drugs[a] | 4.9±0.5 | 5.2±0.4 | 3.0±0.8 | 3.9±0.7 |
| Na (mEq/L) | 142.4±0.6 | 143.2±0.3 | 139.8±2.9 | 142.1±0.6 |
| K (mEq/L) | 3.43±0.07 | 3.30±0.07 | 3.62±0.27 | 3.59±0.12 |
| Urinary Na (mEq/g Cr) | 111.7±7.59 | 112.8±8.4 | 141.4±30.7 | 102.4±13.4 |
| Urinary K (mEq/g Cr) | 48.78±3.09 | 56.0±3.8 | 41.7±8.02 | 38.1±5.17 |
| Urinary K/Na ratio | 0.579±0.049 | 0.60±0.05 | 0.43±0.11 | 0.471±0.12 |
| PRA (ng/mL/h) | 0.21±0.02 | 0.19±0.02 | 0.24±0.08 | 0.25±0.04 |
| PAC (ng/dL) | 23.8±1.18 | 27.6±2.11† | 15.1±1.37 | 14.6±1.25 |
| PAC/PRA | 173±10.3 | 202±17.5† | 96.7±32.8 | 105±18.3 |

Values are the mean±SEM. APA, aldosterone producing adenoma; Cr, creatinine; PRA, plasma renin activity; PAC, plasma aldosterone concentration. [a]Number of tablets of antihypertensive drugs per day at the first visit to our Clinic. *Significantly lower than in the other two groups, $p<0.05$; †higher than in the other two groups, $p<0.05$.

receptor blockers. Blood samples for aldosterone concentration (PAC) and plasma renin activity (PRA) were obtained after a 30-min rest in the supine position in the morning (9:00–10:00 AM) (normal range: PAC 2.5–12 ng/dL; PRA 0.4–2.0 ng/mL/h). The patients were fed 10 g of sodium chloride per day in the hospital. PAC and PRA were measured by radioimmunoassay; PAC was measured by SPAC-S Aldosterone Kit (TFB Inc., Tokyo, Japan), and PRA was measured by Renin Riabead Kit (Dainabot, Tokyo, Japan). Plasma cortisol concentrations were measured by fluorescence polarization immunoassay (Abbott Japan Co., Chiba, Japan).

## CT Scan

CT scans were performed with a 16 channel multi-detector row CT (MDCT), Somatom Cardiac Sensation (Siemens, Germany) that analyzed adrenal regions in contiguous 1.0-mm–thick slices. A nonionic iodinated contrast agent was routinely administered intravenously. All scans were reviewed by three radiologists experienced in adrenal imaging, and discordant interpretation was resolved by consensus. They were aware that all the patients had been diagnosed as having PA based on endocrinological examinations, but all other information was concealed. In addition to the analysis of the adrenal glands, adrenal veins were also visualized by CT, and the axial and sagittal images of adrenal veins were used to assess the anatomical variations of right adrenal veins and simulate catheterization (Fig. 1). Accordingly, the success rate of AVS was 98% (87/89).

## Simultaneous Bilateral Adrenal Venous Sampling

Bilateral adrenal veins were simultaneously catheterized in all the patients regardless of CT findings. The adrenal venous blood was sampled between 1:00 and 3:00 PM in all the subjects. After a 60-min rest in the supine position, two venous catheters were introduced *via* the bilateral femoral veins. After baseline samples were simultaneously obtained from both adrenal veins, all patients received an intravenous bolus injection of 0.25 mg ACTH. A second set of blood samples was collected from the same sites 15 min after the ACTH injection. The proper placement of the catheter tip was confirmed just before and after sampling using a very small amount of contrast medium. Furthermore, successful adrenal venous cannulation was confirmed based on the cortisol level after ACTH stimulation in the adrenal venous sample, which was more than five times higher than that in the vena cava sample (range, 7.24 to 93.9) in all the patients (*25*). Venous blood from the left adrenal gland was obtained at the left adrenal vein immediately adjacent to the entrance of the inferior phrenic vein. No serious complications, such as hemorrhage, were observed in any patient.

The adrenal venous aldosterone concentration (A) was divided by the cortisol concentration (C) in order to correct non-uniform dilution effects between the right and left adrenal veins. We calculated the ratio of A to C (A/C), the ratio of A/C on the higher side to A/C on the lower side (A/C ratio) and the ratio of A on the higher side to A on the lower side (A ratio). We highly suspected "unilateral aldosterone hypersecretion," when the A/C ratio after ACTH was found to be

**Table 2. Plasma Aldosterone Concentrations, Aldosterone (A) Ratio and A/C Ratio before and after ACTH Stimulation in 61 Patients with Surgically-Proven Aldosteronoma**

| APA case | Age | Sex | CT tumor size (mm) | | Pre-ACTH | | | | Post-ACTH | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Aldosterone (ng/dL) | | A ratio | A/C ratio | Aldosterone (ng/dL) | | A ratio | A/C ratio |
| | | | Right | Left | Right | Left | | | Right | Left | | |
| 1 | 51 | M | 25 | n.d. | 7,550 | 36 | 210.3 | 98.8 | 19,300 | 350 | 55.1 | 447.0 |
| 2 | 57 | M | 14 | n.d. | 1,680 | 53 | 31.8 | 39.3 | 65,200 | 616 | 105.8 | 135.1 |
| 3 | 59 | F | n.d. | 23 | 162 | 16,300 | 100.6 | 72.6 | 208 | 22,800 | 109.6 | 96.2 |
| 4 | 54 | F | 12 | n.d. | 47 | 12 | 3.8 | 7.7 | 4,040 | 248 | 16.3 | 58.2 |
| 5 | 49 | M | n.d. | 13 | 25 | 582 | 23.4 | 32.3 | 84 | 4,350 | 51.8 | 57.4 |
| 6 | 56 | F | 13 | n.d. | 393 | 18 | 22.2 | 16.4 | 1,840 | 426 | 4.3 | 54.5 |
| 7 | 35 | F | 10 | n.d. | 3,050 | 75 | 40.7 | 90.1 | 3,710 | 158 | 23.5 | 53.7 |
| 8 | 52 | F | n.d. | 17 | 28 | 257 | 9.2 | 13.2 | 567 | 3,830 | 6.8 | 40.3 |
| 9 | 36 | F | 9 | n.d. | 978 | 31 | 31.9 | 21.1 | 22,100 | 306 | 72.0 | 36.7 |
| 10 | 66 | F | 10 | n.d. | 2,780 | 143 | 19.4 | 23.6 | 18,600 | 273 | 68.1 | 34.9 |
| 11 | 46 | M | n.d. | 19 | 33.9 | 459 | 13.5 | 23.9 | 287 | 7,680 | 26.8 | 34.1 |
| 12 | 36 | M | 20 | n.d. | 2,570 | 38 | 68.0 | 37.0 | 17,000 | 335 | 50.7 | 31.9 |
| 13 | 40 | M | 12 | n.d. | 2,590 | 27 | 96.6 | 57.5 | 16,100 | 193 | 83.4 | 29.6 |
| 14 | 44 | M | n.d. | 12 | 19 | 361 | 18.8 | 18.4 | 381 | 4,800 | 12.6 | 29.1 |
| 15 | 42 | F | n.d. | 22 | 88 | 2,710 | 30.9 | 11.3 | 576 | 25,300 | 43.9 | 28.0 |
| 16 | 42 | M | 7 | 8 | 15 | 129 | 8.8 | 10.7 | 376 | 4,620 | 12.3 | 27.5 |
| 17 | 58 | M | n.d. | 14 | 27 | 934 | 34.9 | 48.2 | 324 | 5,880 | 18.1 | 27.3 |
| 18 | 75 | M | 15 | n.d. | 356 | 25 | 14.3 | 4.9 | 14,000 | 125 | 112.0 | 26.4 |
| 19 | 44 | M | n.d. | 16 | 31 | 370 | 11.9 | 12.5 | 281 | 6,320 | 22.5 | 25.2 |
| 20 | 53 | M | n.d. | 13 | 4,580 | 70 | 65.9 | 20.5 | 11,200 | 146 | 76.7 | 24.5 |
| 21 | 55 | F | n.d. | 7 | 52 | 777 | 14.9 | 11.0 | 486 | 8,100 | 16.7 | 22.3 |
| 22 | 61 | F | 22 | 12 | 43 | 588 | 13.8 | 33.4 | 615 | 6,460 | 10.5 | 21.9 |
| 23 | 41 | M | n.d. | 29 | 82 | 521 | 6.3 | 6.5 | 362 | 2,830 | 7.8 | 20.3 |
| 24 | 47 | M | 35 | n.d. | 4,420 | 71 | 62.1 | 12.5 | 14,000 | 243 | 57.7 | 19.0 |
| 25 | 67 | F | 6 | 10 | 38 | 400 | 10.5 | 14.6 | 188 | 1,424 | 7.6 | 18.0 |
| 26 | 53 | M | 20 | n.d. | 25 | 165 | 6.7 | 14.7 | 351 | 668 | 1.9 | 18.0 |
| 27 | 53 | F | n.d. | 10 | 58 | 291 | 5.0 | 6.9 | 121 | 1,090 | 9.0 | 16.9 |
| 28 | 43 | F | n.d. | 17 | 85 | 391 | 4.6 | 16.7 | 474 | 9,670 | 20.4 | 15.5 |
| 29 | 49 | F | n.d. | 9 | 234 | 2,150 | 9.2 | 22.0 | 408 | 3,270 | 8.0 | 14.8 |
| 30 | 60 | F | n.d. | n.d. | 46 | 3,060 | 67.3 | 31.4 | 298 | 5,480 | 18.4 | 14.8 |
| 31 | 58 | F | n.d. | 10 | 28 | 408 | 14.8 | 19.3 | 158 | 1,230 | 7.8 | 14.7 |
| 32 | 61 | F | 7.5 | n.d. | 2,470 | 45 | 55.1 | 14.1 | 7,060 | 188 | 37.6 | 14.6 |
| 33 | 63 | F | 19 | n.d. | 352 | 19 | 18.8 | 9.9 | 14,500 | 507 | 28.6 | 13.9 |
| 34 | 43 | M | 7 | n.d. | 5,400 | 48 | 112.5 | 7.2 | 5,500 | 120 | 45.8 | 13.9 |
| 35 | 49 | F | n.d. | 12 | 112 | 2,140 | 19.1 | 37.0 | 732 | 4,490 | 6.1 | 13.1 |
| 36 | 32 | M | n.d. | 12 | 58 | 346 | 6.0 | 5.1 | 347 | 2,150 | 6.2 | 11.5 |
| 37 | 59 | F | n.d. | 14 | 358 | 6,410 | 17.9 | 16.9 | 708 | 6,780 | 9.6 | 11.5 |
| 38 | 64 | F | 7 | n.d. | 1,100 | 75 | 14.7 | 17.9 | 2,740 | 157 | 17.5 | 10.2 |
| 39 | 57 | F | 15 | n.d. | 865 | 45 | 19.3 | 23.0 | 2,400 | 163 | 14.7 | 10.1 |
| 40 | 42 | M | n.d. | 22 | 36 | 4,780 | 133.9 | 18.1 | 72.9 | 12,200 | 167.4 | 9.3 |
| 41 | 37 | F | n.d. | 17 | 30 | 2,810 | 94.2 | 22.2 | 394 | 5,490 | 13.9 | 9.1 |
| 42 | 53 | M | 15 | 15 | 8,470 | 60 | 140.9 | 50.9 | 10,000 | 310 | 32.3 | 8.9 |
| 43 | 70 | F | n.d. | n.d. | 140 | 31 | 4.5 | 3.9 | 7,270 | 563 | 12.9 | 8.0 |
| 44 | 52 | F | n.d. | n.d. | 393 | 13 | 30.9 | 40.1 | 2,890 | 545 | 5.3 | 7.7 |
| 45 | 64 | M | 12 | n.d. | 2,200 | 14 | 160.6 | 49.7 | 4,630 | 239 | 19.4 | 7.7 |
| 46 | 72 | F | n.d. | 8 | 241 | 331 | 1.4 | 6.0 | 363 | 689 | 1.9 | 7.2 |
| 47 | 55 | M | n.d. | 17 | 47 | 10 | 4.6 | 8.0 | 2,905 | 340 | 8.5 | 7.0 |
| 48 | 62 | F | 7 | n.d. | 990 | 71 | 13.9 | 13.1 | 2,950 | 488 | 6.0 | 6.8 |
| 49 | 35 | M | n.d. | 14 | 19 | 545 | 28.2 | 42.8 | 403 | 2,670 | 6.6 | 6.5 |

**Table 2. Continued**

| APA case | Age | Sex | CT tumor size (mm) | | Pre-ACTH | | | | Post-ACTH | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Aldosterone (ng/dL) | | A ratio | A/C ratio | Aldosterone (ng/dL) | | A ratio | A/C ratio |
| | | | Right | Left | Right | Left | | | Right | Left | | |
| 50 | 51 | M | n.d. | n.d. | 108 | 884 | 8.2 | 1.1 | 1,350 | 7,370 | 5.5 | 5.8 |
| 51 | 43 | F | n.d. | n.d. | 47 | 101 | 2.2 | 5.5 | 464 | 1,420 | 3.1 | 5.5 |
| 52 | 52 | F | n.d. | 20 | 24 | 126 | 5.3 | 13.3 | 175 | 974 | 5.6 | 5.3 |
| 53 | 63 | M | n.d. | n.d. | 1,450 | 9 | 170.6 | 2.4 | 3,680 | 394 | 9.3 | 4.9 |
| 54 | 61 | M | 7 | n.d. | 1,360 | 13 | 108.8 | 2.6 | 2,330 | 96 | 24.4 | 4.6 |
| 55 | 54 | M | n.d. | 13 | 129 | 206 | 1.6 | 7.6 | 879 | 1,540 | 1.7 | 4.0 |
| 56 | 31 | F | n.d. | n.d. | 2,950 | 611 | 4.8 | 4.8 | 5,140 | 1,000 | 5.1 | 3.9 |
| 57 | 46 | M | n.d. | n.d. | 360 | 92 | 3.9 | 3.2 | 990 | 3,230 | 3.3* | 3.8* |
| 58 | 57 | M | n.d. | 21 | 207 | 15 | 14.2 | 8.1 | 3,410 | 560 | 6.1 | 3.4 |
| 59 | 67 | M | 7 | n.d. | 33 | 13 | 2.5 | 2.9 | 2,910 | 549 | 5.3 | 3.2 |
| 60 | 39 | M | 14 | n.d. | 275 | 39 | 7.0 | 6.5 | 3,060 | 709 | 4.3 | 3.1 |
| 61 | 53 | F | 9 | n.d. | 1,330 | 50 | 26.8 | 6.4 | 3,330 | 334 | 10.0 | 2.4 |

ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma; M, male; F, female; A, aldosterone; C, cortisol; A ratio, the value of aldosterone of the higher side divided by that of the lower side; A/C ratio, the value of A/C (aldosterone/cortisol) of the higher side divided by that of the lower side; n.d., not detected. *The side showing a higher A/C or aldosterone ratio differed before and after ACTH loading.

higher than 3.0, since Young *et al*. reported that this value of 3.0 or less would be consistent with bilateral hypersecretion (*25*). However, we also took into account the absolute A value (*27*), the A/C, and the A ratio in judging whether or not an operation was indicated.

### Pathological Examinations

Sixty-one adrenal gland specimens were retrieved from the surgical pathology files of Tohoku University Hospital. Adrenocortical adenomas were morphologically defined as encapsulated, solitary adrenocortical masses of different sizes. All the lesions were diagnosed as benign adenomas based on the histological criteria of Weiss (*28*). Immunohistochemical analysis for steroidogenic enzymes, including 3β-hydroxysteroid dehydrogenase (3β-HSD) and P450c17, was also performed in all the cases to examine the autonomous neoplastic production of corticosteroids or to differentiate APA from hyperplasia or IHA (*27*, *29*, *30*). Immunoreactivity for 3β-HSD is positive in the hyperplastic zona glomerulosa in IHA, whereas it is likely to be negative in the adjacent nontumorous hyperplastic area of the zona glomerulosa of APA (*27*, *29*, *30*).

### Statistical Analysis

Results are expressed as the means±SEM, when appropriate. Group differences were compared by unpaired *t*-test. We performed receiver operator characteristics (ROC) curve analysis of the A/C ratio and A ratio in 61 operated patients with histologically proven APA and 21 patients who were considered to have no apparent laterality. We also performed ROC curve analysis of A and A/C between the APA side and contralateral side within the operated patients with proven APA. In each analysis, the cutoff values, sensitivity, and specificity were determined. Data were computed by ANOVA, followed by Dunnett's test for multiple comparisons. Values of $p<0.05$ were considered to indicate statistical significance. Analyses were carried out with the SPSS for Windows statistical package (version 14.0; SPSS Inc., Chicago, USA).

## Results

### Clinical Data of the Patients with PA

The average blood pressure was 149.7/90.5 mmHg despite treatment with antihypertensive drugs. Forty-nine patients had hypokalemia (3.1±0.05 mEq/L, mean±SEM), whereas 38 patients were normokalemic (3.9±0.5 mEq/L). The recumbent PRA was low (0.21±0.02 ng/mL/h; range, 0.1–0.8). The recumbent PAC was high (23.5±1.18 ng/dL; range, 8.0–83.5). The mean PAC/PRA ratio was 173 (range, 20–835). The PAC/PRA ratio was more than 20 at both 1 and 2 h after oral administration of 50 mg captopril in all patients. There were significant differences in several clinical parameters among the three groups of patients: systolic blood pressure was significantly lower in the group of patients with no apparent laterality ($p<0.05$), while PAC and PAC/PRA ratio were significantly higher in the group of patients with APA ($p<0.05$) than in the other two groups (Table 1).

### CT Scan and AVS

Of the 87 patients with PA, 66 met our criteria of unilateral

**Table 3. Plasma Aldosterone Concentration, Aldosterone (A) Ratio and A/C Ratio before and after ACTH Stimulation in the Medically Treated Patients**

| Case | Age | Sex | CT tumor size (mm) | | Pre-ACTH | | | | Post-ACTH | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Aldosterone (ng/dL) | | A ratio | A/C ratio | Aldosterone (ng/dL) | | A ratio | A/C ratio |
| | | | Right | Left | Right | Left | | | Right | Left | | |
| Non-operation group | | | | | | | | | | | | |
| 62 | 59 | F | n.d. | 10 | 9 | 659 | 73.2 | 80.0 | 504 | 34,300 | 68.1 | 78.1 |
| 63 | 60 | M | 20 | n.d. | 2,600 | 37 | 69.9 | 28.5 | 6,270 | 168 | 37.4 | 18.1 |
| 64 | 66 | M | 12 | 14 | 26 | 87 | 3.3 | 3.0 | 6,650 | 612 | 10.9* | 6.3* |
| 65 | 70 | F | n.d. | 8 | 270 | 3,380 | 12.5 | 92.0 | 991 | 6,810 | 6.9 | 6.2 |
| 66 | 52 | M | n.d. | n.d. | 94 | 340 | 3.6 | 1.6 | 1,120 | 6,350 | 5.7 | 3.2 |
| 67 | 52 | M | n.d. | 10 | 263 | 366 | 1.4 | 1.3 | 860 | 2,340 | 2.8 | 2.6 |
| 68 | 47 | F | n.d. | 6 | 157 | 279 | 1.8 | 4.7 | 2,400 | 4,600 | 1.9 | 2.5 |
| 69 | 50 | F | 5 | 8 | 47 | 212 | 4.6 | 5.2 | 2,050 | 3,780 | 1.8 | 2.1 |
| 70 | 55 | M | 22 | n.d. | 32 | 22 | 1.4 | 1.3 | 2,140 | 577 | 5.0 | 1.9 |
| 71 | 40 | F | n.d. | 7 | 408 | 69 | 5.9 | 6.3 | 6,620 | 2,150 | 3.1 | 1.8 |
| 72 | 45 | M | n.d. | 10 | 31 | 33 | 1.1 | 1.3 | 1,730 | 599 | 2.9* | 1.7* |
| 73 | 62 | F | n.d. | n.d. | 550 | 86 | 6.4 | 2.5 | 3,020 | 1,090 | 2.8 | 1.7 |
| 74 | 44 | F | n.d. | n.d. | 65 | 44 | 1.5 | 1.0 | 1,680 | 2,230 | 1.3* | 1.6* |
| 75 | 41 | M | n.d. | 15 | 203 | 79 | 2.6 | 1.7 | 2,030 | 3,010 | 1.5* | 1.5* |
| 76 | 42 | M | n.d. | n.d. | 91 | 39 | 2.3 | 2.0 | 2,380 | 1,340 | 1.8 | 1.5 |
| 77 | 52 | F | n.d. | n.d. | 646 | 1,740 | 2.7 | 1.7 | 3,090 | 3,930 | 1.3 | 1.4 |
| 78 | 73 | M | 10 | n.d. | 577 | 155 | 3.7 | 4.7 | 4,540 | 2,780 | 1.6 | 1.4 |
| 79 | 51 | M | n.d. | 5 | 650 | 217 | 3.0 | 4.1 | 1,440 | 4,020 | 2.8* | 1.4* |
| 80 | 48 | F | 8 | 6 | 1,140 | 1,330 | 1.2 | 3.1 | 3,000 | 3,910 | 1.3 | 1.3 |
| 81 | 58 | M | n.d. | 16 | 655 | 57 | 11.6 | 15.3 | 2,850 | 449 | 6.3 | 1.3* |
| 82 | 51 | M | n.d. | 8 | 935 | 874 | 1.1 | 6.9 | 2,540 | 1,920 | 1.3 | 1.3* |
| 83 | 75 | F | n.d. | 17 | 637 | 253 | 2.5 | 2.2 | 2,350 | 2,430 | 1.0* | 1.1* |
| 84 | 41 | F | n.d. | n.d. | 56 | 27 | 2.1 | 1.6 | 3,260 | 2,650 | 1.2 | 1.1* |
| 85 | 55 | F | n.d. | n.d. | 602 | 557 | 1.1 | 1.3 | 2,590 | 2,280 | 1.1 | 1.1 |
| 86 | 49 | M | n.d. | 11 | 1,620 | 407 | 4.0 | 6.6 | 4,320 | 3,420 | 1.3 | 1.1* |
| 87 | 49 | F | n.d. | n.d. | 156 | 48 | 3.3 | 1.4 | 4,050 | 2,750 | 1.5 | 1.1* |

Five cases (cases 62–66) were highly suspected to have aldosteronomas, but rejected surgical treatment. Twenty one cases (cases 67–87) showed no apparent laterality of aldosterone secretion and were supposed to have bilateral adrenal diseases, such as idiopathic hyperaldosteronism, and bilateral aldosteronomas. ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma; M, male; F, female; A, aldosterone; C, cortisol; A ratio, the value of aldosterone of the higher side divided by that of the lower side; A/C ratio, the value of A/C (aldosterone/cortisol) of the higher side divided by that of the lower side; n.d., not detected. *The side showing a higher A/C or aldosterone ratio differed before and after ACTH loading.

aldosterone hypersecretion by AVS. Among them, 61 (Table 2) underwent laparoscopic removal of the adrenal gland through a retroperitoneal approach, and the presence of APA was histologically confirmed in all 61 of these patients. On the other hand, 5 patients (cases 62–66 in Table 3) did not agree to surgery and underwent medical treatment. CT findings and AVS results were concordant in 46 (75%) of the 61 surgically proven cases. In 15 (25%) of the 61 patients, CT was of no diagnostic value. Reasons for the failure were as follows: undetectable tumors (1.5–7 mm in diameter on histological examination) in either the adrenal gland in 8 cases (cases 30, 43, 44, 50, 51, 53, 56 and 57), bilateral nodules in 4 cases (cases 16, 22, 25 and 42), and presence of non-functional nodules (13–21 mm in diameter on CT) on the contralateral side of aldosterone hypersecreting microadenomas not visualized on CT (3–7 mm in diameter on histological examination) in 3 cases (cases 20, 47 and 58). The 21 patients with no apparent laterality of aldosterone secretion diagnosed by AVS (cases 67–87 in Table 3) included 7 patients without nodules, 12 patients with unilateral adrenal nodules, and 2 patients with bilateral nodules on CT. In 9 patients (cases 68, 69, 71, 78–82, and 86), data before ACTH stimulation suggested unilateral lesion, but the A/C ratio after ACTH stimulation indicated bilateral disease.

Figure 2 shows the A/C ratio of 61 patients with surgically proven APA (cases 1–61) and 21 patients with no apparent laterality of aldosterone secretion (cases 67–87). The A/C ratio after the ACTH loading was higher than 3.0 in 60 of the

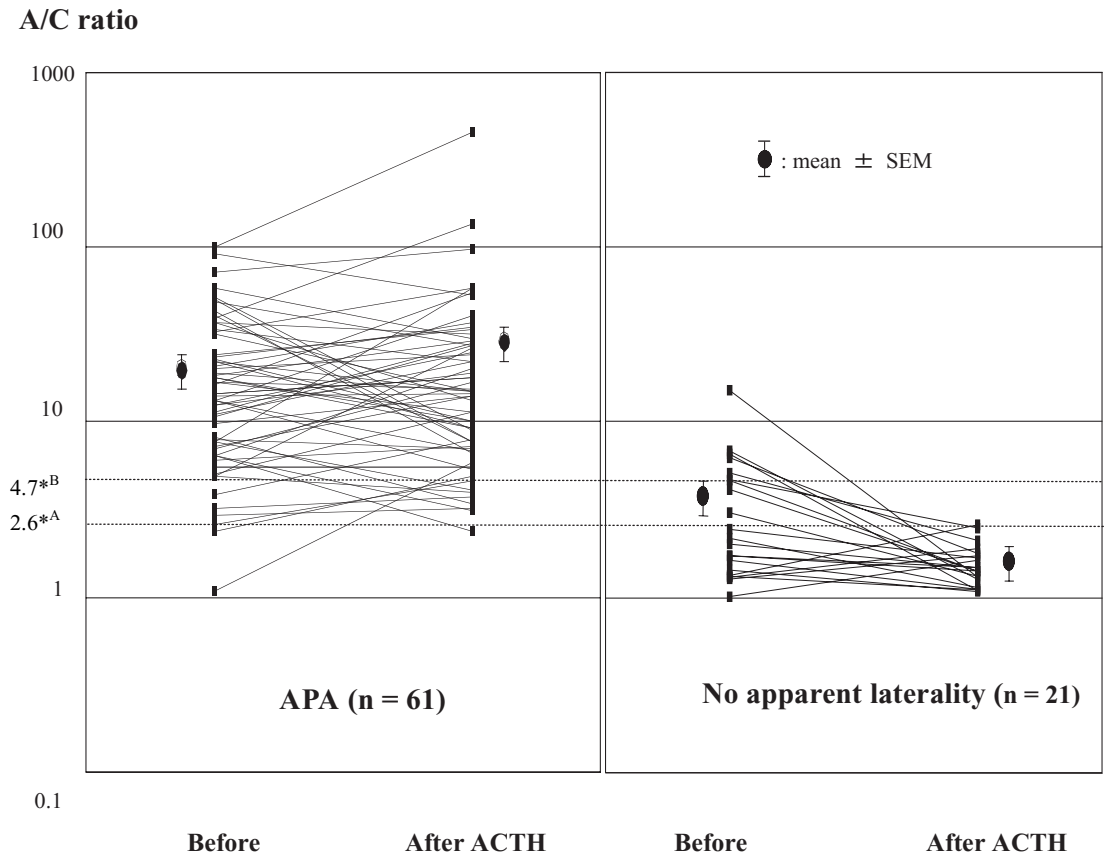


**Fig. 2.** *Ratio of higher adrenal vein aldosterone/cortisol (A/C) to lower adrenal vein A/C before and 15 min after ACTH loading in 61 patients with surgically-proven aldosterone producing adenoma (APA) (cases 1–61) and 21 medically treated patients with no apparent laterality of aldosterone secretion (cases 66–87). A/C ratio, ratio of higher adrenal vein aldosterone/cortisol (A/C) to lower adrenal vein A/C. *B and *A show the cutoff values of A/C ratio before and after ACTH determined by ROC curve analysis respectively.*

**Table 4. Sensitivity and Specificity for the Cutoff Values of AVS-Derived Indexes Determined by ROC Curve Analysis**

| | Before ACTH | | | After ACTH | | |
|---|---|---|---|---|---|---|
| | Cutoff values | Sensitivity | Specificity | Cutoff values | Sensitivity | Specificity |
| A/C ratio | 4.7 | 0.902 | 0.762 | 2.6 | 0.984 | 1.000 |
| A ratio | 4.0 | 0.902 | 0.810 | 3.1 | 0.934 | 0.905 |
| Aldosterone (ng/dL) | 112 | 0.918 | 0.865 | 1,340 | 0.918 | 1.000 |
| A/C | 3.5 | 0.934 | 0.934 | 2.0 | 0.951 | 0.934 |

AVS, adrenal venous sampling; ROC, receiver operator characteristics; ACTH, adrenocorticotropic hormone; A/C ratio, the value of A/C (aldosterone/cortisol) of the higher side divided by that of the lower side; A ratio, the value of aldosterone of the higher side divided by that of the lower side.

61 patients with APA. In 4 of these 61 patients (cases 50, 53, 54 and 59; Table 2, Fig. 2), the A/C ratio before ACTH was less than 3.0 but increased above 3 after ACTH. In case 61 (Table 2, Fig. 2), after ACTH stimulation, the A/C ratio was less than 3.0, but the absolute A values were 3,330 and 334 ng/dL with the A ratio of 10.0, suggesting strong unilateral hypersecretion of aldosterone, and we therefore advised the patient to undergo unilateral adrenalectomy.

Table 4 shows the sensitivity and specificity for the cutoff values of AVS-derived indexes determined by ROC curve analysis. The ROC curve analysis between the operated group and no–apparent-laterality group revealed that the A/C ratio after ACTH stimulation provided the best discriminating power, with a cutoff value of 2.6, a sensitivity of 0.98, and a

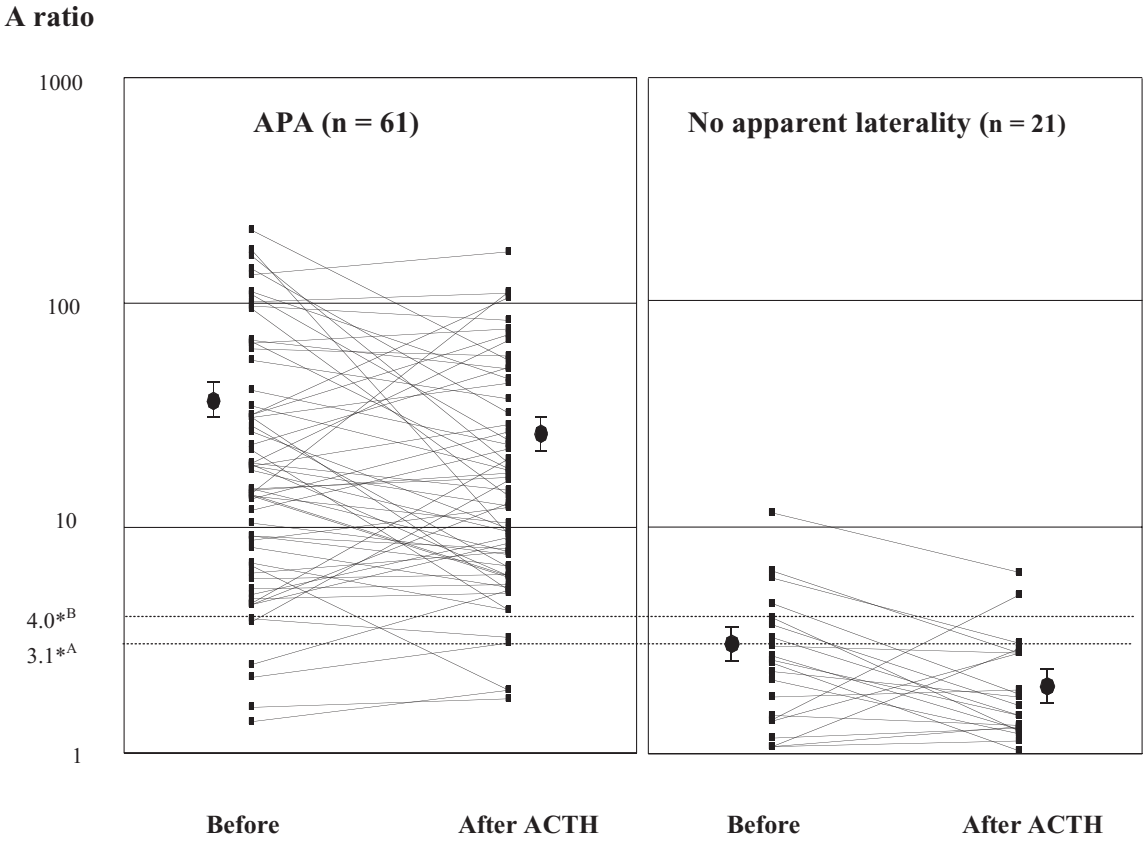


**Fig. 3.** *Ratio of higher adrenal vein aldosterone (A) to lower adrenal vein A before and 15 min after ACTH loading in 61 patients with surgically-proven aldosterone producing adenoma (APA) (cases 1–61) and 21 medically treated patients with no apparent laterality of aldosterone secretion (cases 66–87). *B and *A show the cutoff values of A ratio before and after ACTH determined by ROC curve analysis respectively.*

specificity of 1.0. The ROC curve analysis between the APA side and contralateral side in the operated patients revealed that the absolute A value after ACTH simulation provided the best discriminating power, with a cutoff value of 1,340 ng/dL, a sensitivity of 0.92, and a specificity of 1.0. In each of the indexes, the discriminating power was higher after than before ACTH stimulation.

Figures 2–5 show the relationship between the AVS-derived indexes and their cutoff values determined by ROC curve analysis. Figure 3 shows that the A/C ratio before ACTH was higher than 4.7 (cutoff value in Table 4) in 55 cases (90%) and that after ACTH was higher than 2.6 (cutoff value) in 60 (98%) of 61 cases with surgically proven APA. Figure 3 shows that the A ratio before ACTH was higher than 4.0 (cutoff value in Table 4) in 55 cases (90%) and that after ACTH was higher than 3.1 (cutoff value in Table 4) in 57 (93%) of 61 operated patients with APA. Figure 4 shows the absolute A values of the 61 patients with APA (cases 1–61). The absolute A values of the APA side increased to 668–65,200 ng/dL 15 min after ACTH, whereas the levels in the contralateral side increased only to 1,340 ng/dL and only 2 cases (cases 50 and 56) showed a value equal to or higher than 1,000 ng/dL. The absolute A values of the APA side before ACTH stimulation were higher than 112 ng/dL (cutoff value in Table 4) in 59 cases (97%), and those after ACTH were higher than 1,340 ng/dL (cutoff value) in 56 (92%) of 61 operated cases. There was substantial overlap in the absolute A values between the APA and the contralateral side before ACTH, while the overlap was much less after ACTH. Figure 5 shows that the A/C before ACTH was higher than 3.5 (cutoff value in Table 4) in 57 cases (93%) and that after ACTH was higher than 2.0 (cutoff value) in 58 (95%) of 61 operated cases. There was substantial overlap in the A/C values both before and after ACTH between the APA and the contralateral side.

## Treatment

Sixty-one patients underwent surgical treatment (retroperitoneoscopic adrenalectomy) based on the results of AVS. The post-operative clinical data collected about 1 month after adrenalectomy are summarized in Table 5. Blood pressure

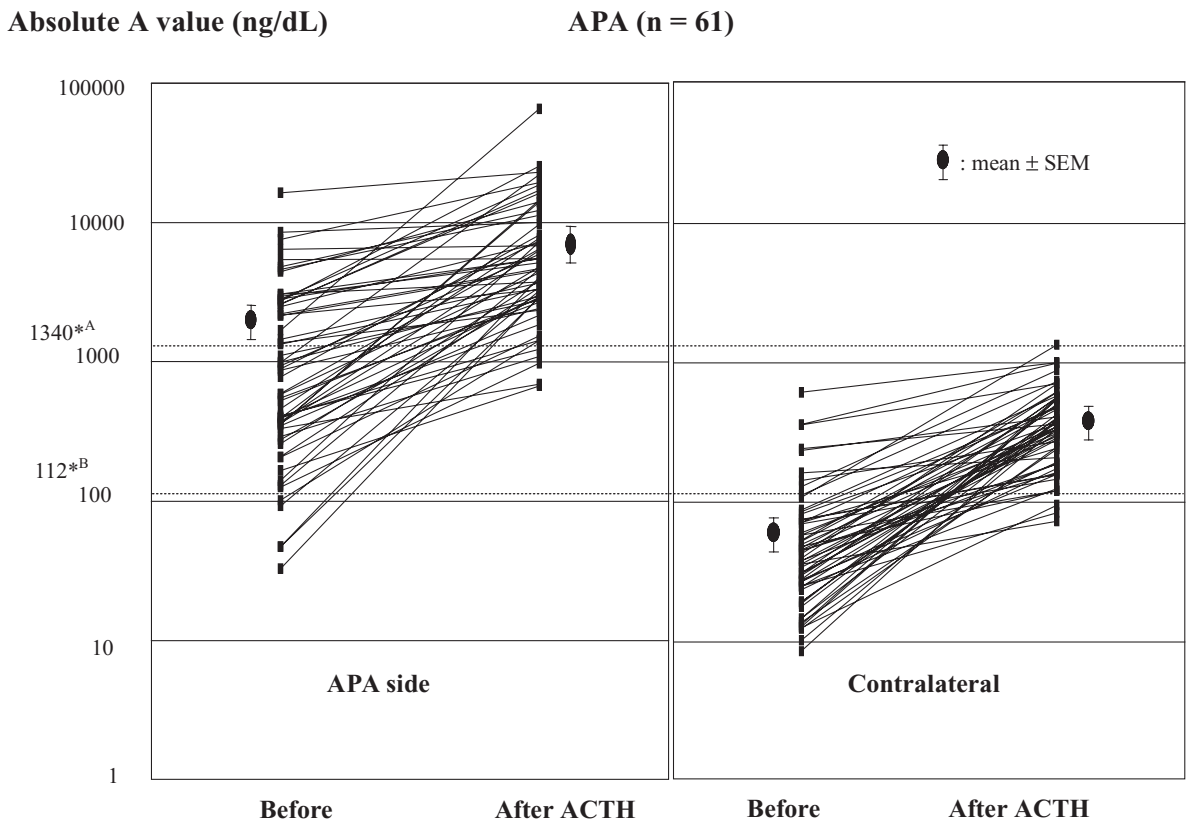


**Fig. 4.** *Adrenal venous aldosterone concentration (A) before and 15 min after ACTH loading in 61 patients with surgically-proven aldosterone producing adenoma (APA). The left panel shows the absolute A value in the adrenal vein, in which higher aldosterone levels were found by AVS (APA side), and the right panel shows that in the adrenal vein of the other side (contralateral). *B and *A show the cutoff values of absolute A value before and after ACTH determined by ROC curve analysis respectively.*

decreased in all these patients, and 23 of them became free from antihypertensive agents. PAC fell down to 5.07±0.25 ng/dL (range, 2.1–10.7), and the PAC/PRA ratio to 10.8±1.48 (range, 0.31–16.8). Five patients (cases 62–66 in Table 3) with a diagnosis of unilateral hyperaldosteronism who did not agree to surgery and 21 patients (cases 67–87 in Table 3) with no apparent laterality of aldosterone secretion as diagnosed by AVS received medical treatment, including spironolactone, and their hypertensive states improved.

### Histopathological Examination

The presence of APA was confirmed by histopathological examination in the 61 patients who were diagnosed to have APA by AVS. 3β-HSD was negative in the adjacent non-tumorous hyperplastic area of the zona glomerulosa in the adrenals obtained from these 61 patients, consistent with the diagnosis of APA (*27*, *29*, *30*). In particular, in the 8 patients in whom nodules were not detected by CT, APAs of 1.5 to 7 mm in diameter were confirmed in the surgically removed adrenals by histological and immunohistochemical examinations. Furthermore, in 3 cases adrenal nodules of 13–21 mm in diameter were detected by CT in the contralateral side of aldosterone hypersecretion diagnosed by AVS. Based on the AVS results, adrenal glands with no apparent tumors on CT were resected, and APAs of 3–7 mm in diameter were confirmed by histological and immunohistochemical examinations.

## Discussion

The present study demonstrates the usefulness of AVS. In comparison with other AVS-derived indexes, unilateral hypersecretion of aldosterone was clearly diagnosed based on the A/C ratio after ACTH stimulation, with a cutoff value of 2.6, providing the best compromise between sensitivity and specificity. Furthermore, the A/C ratio after, but not before, ACTH revealed the correct laterality of APA in several operated cases, suggesting the usefulness of ACTH loading for AVS.

However, there are reports that question the usefulness of ACTH loading (*31*), and we could not rule out the possibility

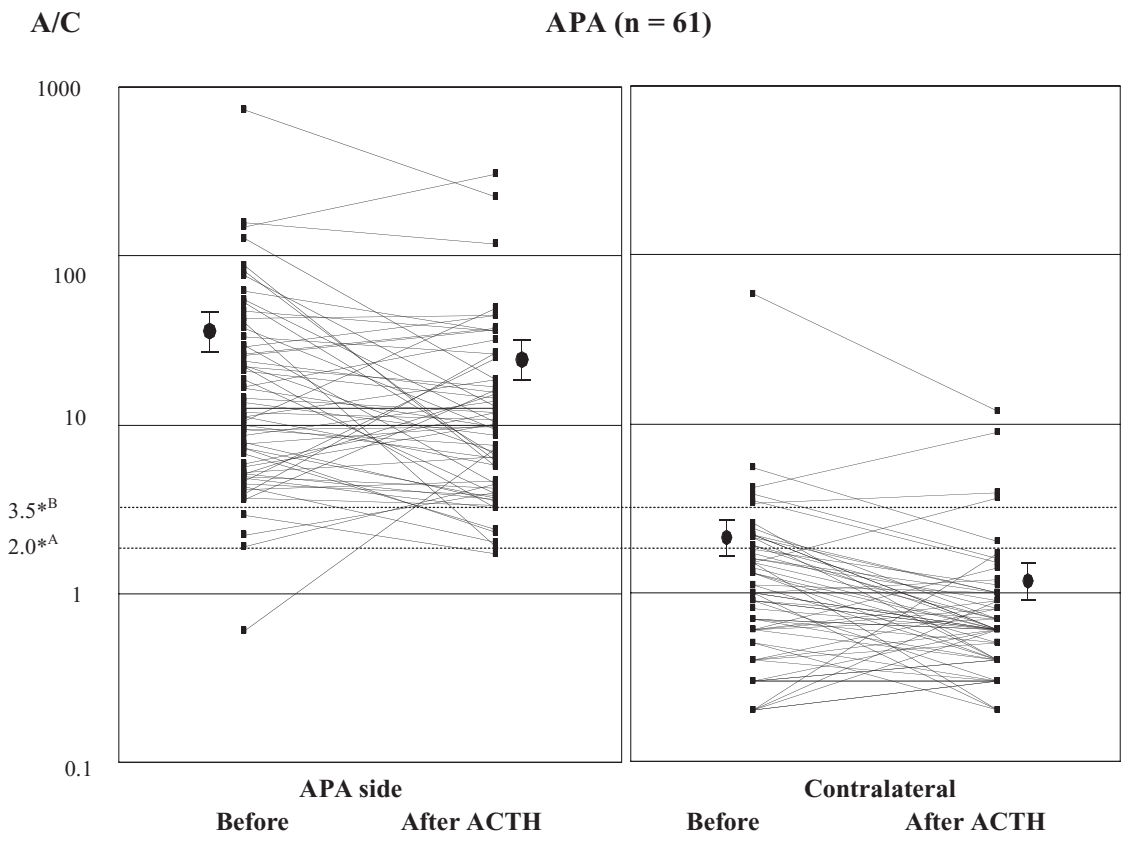


**Fig. 5.** *Aldosterone/cortisol (A/C) in the adrenal vein before and 15 min after ACTH loading in 61 patients with surgically-proven aldosterone producing adenoma (APA). The left panel shows the A/C in the adrenal vein, in which higher A/C levels were found by AVS (APA side), and the right panel shows those in the adrenal vein of the other side (contralateral). *B and *A show the cutoff values of A/C before and after ACTH determined by ROC curve analysis respectively.*

that lateralization might be masked by the stimulation of the contralateral gland by a large bolus dose of ACTH. Moreover, responses to ACTH may vary, probably due to heterogeneity of APA (*32*, *33*). For example, in case 61 the ratio of A/C before ACTH was 6.4, but it decreased to 2.4 (below 3) after ACTH. In this case, we advised the patient to undergo operation, taking into account various other parameters, such as the A/C ratio before ACTH, absolute A value, A ratio, *etc.* On the other hand, in cases 68, 69, 71, 78, 79, 81, 82, and 86, the A/C ratio was higher than 4 before ACTH but less than 3 after ACTH stimulation. In such cases, ACTH at a dose lower than that used in the present study may reveal lateralization; this issue needs further investigation. Although it was possible that these patients had aldosteronomas, we could only recommend surgery to those patients with clear laterality. Indeed, all the patients who underwent surgery based on our criteria had histopathologically proven aldosteronomas.

In the present study, we obtained a higher concordant ratio of AVS and CT scan findings (about 75%; 46/61) than that reported by others (*25*, *34*). Magill *et al*. reported that of 38 patients with aldosteronism subjected to non-contrast CT imaging and bilateral venous sampling, 15 had APA. Only 8 of these 15 APA patients had concordant non-contrast CT imaging and AVS findings (*34*). Young *et al*. detected unilateral aldosterone secretion by AVS in 24 of 47 patients with a unilateral micronodule (≤10 mm) on CT and in 21 of 32 with a unilateral macronodule (>10 mm) on CT (*25*). Our higher concordant ratio may be the result of the improved quality of the CT scanner we employed and the use of contrast CT imaging. The present study has shown, however, that AVS is more useful in showing lateralization than contrast CT imaging using the most modern scanner.

It is sometimes difficult to localize APA because it can be bilateral (*35*, *36*); patients with IHA may have a unilateral macronodule detectable by CT or MRI (*16*, *37–40*); or there may be a microscopic APA undetectable by CT or MRI. Moreover, in patients with microscopic APA, a non-functional adenoma can be accidentally found (by CT or MRI) on the ipsilateral or contralateral adrenal gland (*16*, *18*, *20*, *24*, *38*, *41*). Patients with PA having a definite unilateral adrenal nodule and a normal contralateral adrenal on CT might be recommended for surgery. However, if AVS is not performed, the adrenal gland with a non-functioning nodule on the opposite side of a functioning tumor could be mistakenly

**Table 5. Post-Operative Clinical Data of the Patients with APA**

| | APA (cases 1–61) ($n$=61) |
|---|---|
| Systolic blood pressure (mmHg) | 128.4±3.6 |
| Diastolic blood pressure (mmHg) | 80.4±2.2 |
| Antihypertensive drugs* | 1.5±0.3 |
| Na (mEq/L) | 141.1±0.25 |
| K (mEq/L) | 4.38±0.05 |
| Urinary Na (mEq/g Cr) | 139.3±7.24 |
| Urinary K (mEq/g Cr) | 52.2±4.87 |
| Urinary K/Na ratio | 0.38±0.03 |
| PRA (ng/mL/h) | 2.87±0.43 |
| PAC (ng/dL) | 5.07±0.25 |
| PAC/PRA | 10.8±1.48 |

Values are the mean±SEM. APA, aldosterone producing adenoma; Cr, creatinine; PRA, plasma renin activity; PAC, plasma aldosterone concentration. *Number of tablets of antihypertensive drugs per day.

removed. It is also possible to overlook patients with no detectable tumors on CT.

Doppman *et al*. reported that the A/C ratio after ACTH stimulation in patients with APA should be greater than 5 (*16*, *17*). Young *et al*. reported 2 patients with APA and 1 with primary adrenal hyperplasia whose A/C ratio was less than 5 (3.7, 4.3 and 4.5), and found that the highest ratio in surgically confirmed IHA was 3.5. They commented that most patients with a unilateral source of aldosterone hypersecretion would have an A/C ratio greater than 4.0; a ratio of 3.0 or less would be consistent with IHA; and a ratio between 3 and 4 would likely represent an overlap zone (*38*). Consistent with these studies, in the present study most patients, 55 patients out of 61 (90%), with surgically proven APA had values higher than 4.0. On the other hand, Omura *et al*. diagnosed aldosterone hypersecretion when the absolute A value was higher than 1,400 ng/dL at 30 min after ACTH stimulation (*27*, *42*). This value is remarkably similar to the cutoff value for unilateral hypersecretion obtained in the present study, and indeed 56 (92%) of the 61 patients fulfilled this criterion. However, in 5 cases, the absolute A value was below 1,400 ng/dL.

The ROC curve analysis of the present cases indicates that the A/C ratio after ACTH is the best index to determine the laterality of aldosterone hypersecretion with a cutoff value of 2.6. This value is substantially lower than the value at which we highly suspected unilateral hypersecretion. On the other hand, there were patients with a value equal or close to this cutoff even among the patients in whom we judged as having no apparent laterality. Some of these patients had other AVS indexes higher than the cutoff value determined by the ROC curve analysis in the present study, such as the absolute A value. In cases 67, 70, 72 and 81, the absolute A values in the unilateral adrenal venous samples after ACTH were lower than 1,340 ng/dL (cutoff value), but the A/C ratios after ACTH stimulation were 2.6 or lower (range: 1.3–2.6). Thus, it may be possible that these patients had unilateral hypersecretion. However, we would like to point out the fact that in the present study, among the patients with a cutoff value of 2.6 or lower, there was only one patient in whom an operation was conducted and the presence of APA was confirmed histologically. Clearly, we should await further investigation for clarification of the cutoff values of AVS parameters or their combinations.

Based on the results of the current and previous studies, an A/C ratio of 3.0 after ACTH stimulation may be taken as clear evidence of unilateral hypersecretion, whereas an A/C ratio of less than 2.0 may indicate bilateral hypersecretion. We think that those patients with an A/C ratio between 2.0 and 3.0 should be judged individually, considering other parameters such as the absolute A value after ACTH, A/C after ACTH, A ratio, *etc.*

The results of AVS with ACTH stimulation are important when deciding between surgery and medication for hyperaldosteronism. However, this modality has the disadvantage of technical difficulty. This method requires well-trained angiographers who are skilled in catheterizing the right adrenal vein, which may be difficult. Careful imaging of the adrenal veins by CT would be helpful to improve the success rate of AVS.

Hormonal investigations such as AVS are influenced by various factors, including diurnal variations and stress. In the present study, we performed AVS in the early afternoon when the availability of medical staff and facilities are appropriate. In addition, we catheterized both veins at one time and collected samples simultaneously to reduce time-dependent variations, and also used a bolus injection of ACTH to reduce the time required for the procedure. From the clinical course of the patients after surgery and the results of histopathological examinations, the criterion we propose for diagnosing unilateral hypersecretion seems reasonable. PA is one of the curable forms of hypertension, and the prevalence of PA has been reported to be higher than previously thought. Although there is no consensus on how to treat patients with PA, a clear determination of unilateral hypersecretion is imperative when the patients hope for surgery.

Finally, we would like to acknowledge that there were many limitations in this study. The study had a retrospective design, and thus there may have been a bias for patient selection. Moreover, there is no consensus on the diagnostic criteria for aldosterone hypersecretion in patients with PA. Further investigation is clearly needed in order to determine the best method for the diagnosis of unilateral hypersecretion of aldosterone and therefore the proper indications for surgical intervention.

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