

The Ratio of Plasma Aldosterone Concentration to Potassium in Adrenocorticotropin Stimulation Test is a Possible New Index for Diagnosis of Aldosterone-producing Adenoma in Patients with Primary Aldosteronism

Hiroaki ISHII, Yuki KOBAYASHI, Yusuke SHIBATA, Takahiro MIYAKOSHI
Wakana MIYAKOSHI, Jun-ichiro KITAHARA, Kousuke KATO, Naokazu YOKOTA
Yuko KAWAI and Mitsuhsisa KOMATSU*

*Division of Diabetes, Endocrinology and Metabolism, Department of Internal Medicine,
Shinshu University School of Medicine*

Primary aldosteronism (PA) is the most common form of secondary hypertension, and is characterized by high plasma aldosterone concentration (PAC) and low plasma renin activity (PRA), refractory hypertension, and occasional hypokalemia. Reliable parameters are required to identify aldosterone-producing adenoma (APA) in patients with PA, because APA is treatable with surgical resection if localization of aldosterone hypersecretion can be determined by adrenal venous sampling (AVS). The purpose of this study is to summarize the results of AVS in our institute and to evaluate the diagnostic accuracy of various parameters with adrenocorticotropin hormone (ACTH) stimulation test in identifying probable APA among patients with PA. Eighty-one patients with PA were admitted to Shinshu University Hospital from April 2009 to March 2013, and 59 patients who underwent AVS were included in the study. PAC and aldosterone to potassium ratio (APR) in ACTH stimulation tests were examined in 28 patients. Receiver operating characteristic (ROC) curve analysis was used to evaluate diagnostic accuracy. The response of PAC to ACTH in the probable APA group was stronger than that in the others. In ROC curve analysis, the area under the curve (AUC) of APR (PAC_{30min}/potassium) for diagnosis of probable APA was 0.9840 with an optimal cutoff value >102.6 corresponding to sensitivity and specificity of 94.1 % and 90.9 % for diagnosis of APA, respectively. This study indicated that APR after the ACTH stimulation test may be a useful and accurate parameter in cases of PA. In cases with APR ≥ 100 after ACTH stimulation, AVS is strongly recommended for localization of aldosterone hypersecretion. *Shinshu Med J 63 : 145–156, 2015*

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Abbreviations: APA, aldosterone-producing adenoma; APR, aldosterone potassium ratio; ARR, aldosterone renin ratio; AUC, area under the curve; AVS, adrenal venous sampling; CR, contralateral ratio; IHA, idiopathic hyperaldosteronism; LR, lateralized ratio; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ROC, receiver operating characteristic

* Corresponding author: Mitsuhsisa Komatsu
Division of Diabetes, Endocrinology and Metabolism,
Department of Internal Medicine, Shinshu University
School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano
390-8621, Japan
E-mail: mitsuk@shinshu-u.ac.jp

I Introduction

Primary aldosteronism (PA) is one of the most common causes of secondary hypertension and it should be treated with either surgical or medical

approaches depending on the etiology. PA was first reported by Conn, who proposed a predominant role of aldosterone hypersecretion in this syndrome¹⁾. PA was initially considered to be uncommon, but its incidence has now been established to be approximately 5%–10% of all hypertensive patients^{2)–6)}. With the widespread use of diagnostic imaging, such as abdominal ultrasonography and computed tomography (CT), the opportunities to find adrenal tumor(s) by chance have increased. Some such “incidentalomas” are finally diagnosed as PA after endocrinological tests. A recent study in Japan indicated that PA accounted for 5% of adrenal incidentalomas⁷⁾. PA is often resistant to conventional antihypertensive medication and causes cardiovascular and renal complications compared with essential hypertension^{8)–10)}. Therefore, it is necessary to screen for PA in all hypertensive patients.

The aldosterone/renin ratio (ARR) is known to be an excellent index for use in screening for PA¹¹⁾. When ARR screening is positive, confirmatory tests are added, such as the oral sodium loading test, captopril challenge test, saline infusion test, fludrocortisone suppression test, and upright posture with furosemide infusion test. The criteria for diagnosis of PA differ between referral centers, and as yet there is no global consensus. After provisional diagnosis of PA on confirmatory tests, it is necessary to decide on an appropriate therapeutic strategy. In this process, localization of aldosterone hypersecretion provides the most significant information for selecting among therapeutic options. PA can be roughly divided into two categories: aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA). APA can be treated surgically if the localization of aldosterone hypersecretion can be determined. At present, the adrenal venous sampling test (AVS) is the most useful means of determining the localization of aldosterone hypersecretion. However, AVS is expensive, relatively invasive, and requires a great deal of skill to perform; therefore, new methods are required as adjuncts for diagnosis of APA before AVS.

In the present study, we systematically analyzed

various parameters in all patients diagnosed with PA in our hospital over a 4-year period. We confirmed the importance of the adrenocorticotropic hormone (ACTH) stimulation test to distinguish between APA and non-APA¹²⁾, and found that the ratio of plasma aldosterone concentration (PAC) to potassium (APR) in the ACTH stimulation test may be more useful for this purpose.

II Patients and Analysis

A Patients and methods

We retrospectively analyzed clinical data from patients with PA over the past 4 years. From April 2009 to March 2013, we diagnosed 81 patients as having PA at Shinshu University Hospital, Matsumoto, Japan, according to the protocol of The Japan Endocrine Society. In 59 out of 81 patients, we performed AVS because they desired surgical treatment if necessary. The study protocol was approved by the Ethics Committee of Shinshu University School of Medicine. The study was performed in accordance with the ethical principles of the Declaration of Helsinki. Most patients were referred from local hospitals or clinics for refractory hypertension, or detailed examination of adrenal incidentaloma or hypokalemia.

PAC and plasma renin activity (PRA) were measured in the supine position in the morning. ARR of 200 pg/mL per ng/mL/h or more was considered positive on PA screening. With regard to definitive diagnosis of PA, the Japan Endocrine Society recommends performing at least two different confirmatory tests. Therefore, we performed two distinct confirmatory tests: a captopril loading test and furosemide infusion test with the patient in the upright posture. In the captopril-loading test, cases were considered positive if ARR was over 200 pg/mL per ng/mL/h at 60 min or 90 min after administration of 50 mg of captopril. Furosemide (40 mg) was infused intravenously, and we determined PRA at 60 min and 120 min after infusion with the patient in the upright posture. The result was considered positive when PRA was less than 2.0 ng/mL/h at

both time points. When both of these confirmatory tests were positive, PA was diagnosed. In addition to the confirmatory tests, we performed the ACTH stimulation test in as many patients as possible because it has been reported to be useful as an adjunct for the diagnosis of PA¹²⁾. In the ACTH stimulation test, blood samples were taken before and after 30 and 60 min injection of 0.25 mg of ACTH in the morning. We measured PAC and plasma cortisol, and calculated the ratio of PAC to cortisol. In all 81 patients, 1 mg dexamethasone suppression test was performed in order to rule out autonomic cortisol hypersecretion or sub-clinical Cushing's syndrome. Three patients had subclinical Cushing's syndrome concomitant with PA.

AVS was performed to determine the localization of aldosterone hypersecretion. First, we obtained baseline samples from four points, i.e., right and left adrenal veins and the anterior-posterior inferior vena cava of the adrenal vein. Then, we injected 0.25 mg of ACTH intravenously and obtained blood samples from the same four sites 20 min later. Successful cannulation was confirmed by the criteria proposed by the Japan Endocrine Society. Unilateral hypersecretion was determined with two parameters: lateralized ratio (LR) and contralateral ratio (CR). LR was calculated by the values of PAC/cortisol from both sides. CR was calculated by the following equation: $CR = (\text{PAC/cortisol from opposite site}) / (\text{PAC/cortisol from anterior vena cava})$. When CR was less than 1.0, it was considered that aldosterone secretion from the opposite site of the adrenal gland was profoundly suppressed. We considered lateralization positive when LR was over 2.6 and CR was less than 1.0. Aldosterone hypersecretion was defined as $\text{PAC} \geq 14,000 \text{ pg/mL}$. When both aldosterone hypersecretion and $\text{LR} > 2.6$ were confirmed, we considered it as "unilateral aldosterone hypersecretion", which clinically indicates APA (defined as "probable APA" in this study). A diagnosis of bilateral aldosterone hypersecretion, which clinically suggested IHA (defined as "probable IHA" in this study) was made when the patients exhibited aldosterone hypersecretion from

the bilateral adrenal veins.

B Data analysis and statistical methods

We used the Mann-Whitney U test for statistical analyses of the ACTH test and furosemide infusion test results between the probable APA and other patients. The results are given as means \pm SEM. The diagnostic accuracy of various parameters was assessed by receiver operating characteristic (ROC) curve analysis and from the area under the curve (AUC). The differences in AUC in the ROC curves between each parameter were examined using MedCalc. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

III Results

A Patients' backgrounds

We diagnosed 81 patients with PA over the 4-year study period. PAC, ARR, and urinary aldosterone were markedly high and PRA was low in our patients with PA as expected. Among them 59 patients who underwent AVS were enrolled in the study. The characteristics and laboratory data of these patients are shown in **Table 1**. The average pre-treatment blood pressure was 144/88 mmHg. The average blood pressure was reduced to 131/82 from 144/88 mmHg one month after the treatment: 131/83 from 147/91 in the 33 patients treated with mineralocorticoid receptor antagonists and 130/81 from 142/86 in the 29 with surgical operation. All of the patients who received surgical resection had successful dose reduction or discontinuation of anti-hypertensive drugs. We performed potassium supplementation in 30 cases in which the serum potassium level at the initial visit to our hospital was less than 3 mEq/L with the goal of 3 mEq/L or more. However, in 9 cases with severe aldosteronism, the plasma potassium level did not exceed 3 mEq/L. The mean value of potassium in 59 patients was 3.4 mEq/L.

As shown in **Fig. 1**, AVS was attempted in 59 out of the 81 patients with PA, and the technical failure of AVS occurred in 2 patients. Thus AVS was successfully performed in 57 patients. As the remaining 22 patients intended to continue oral

Table 1 Characteristics and Laboratory Data in 59 Patients with Primary Aldosteronism

	Mean±SEM		Number
Age (yr)	53.3±1.5	Localization of tumor	
Sex (male : female)	27 : 32	Right	22
Pre-treatment systolic BP (mmHg)	144±3	Left	23
Pre-treatment diastolic BP (mmHg)	88±2	Bilateral	7
Post-treatment systolic BP (mmHg)	131±2	None	7
Post-treatment diastolic BP (mmHg)	82±2		
PAC (pg/mL)	377.8±49.6	Size of tumor	
PRA (ng/mL/hr)	0.14±0.02	Right	14.0 mm
ARR (pg/mL per ng/mL/hr)	2101±500	Left	16.1 mm
Serum potassium (mEq/L)	3.4±0.1		Number
Urinary aldosterone (μ g/day)	13.4±1.9		
HbA1c (%)	5.5±0.1	Operation	26 (44 %)

BP, blood pressure ; PAC, plasma aldosterone concentration ; PRA, plasma renin activity ; ARR, aldosterone renin ratio

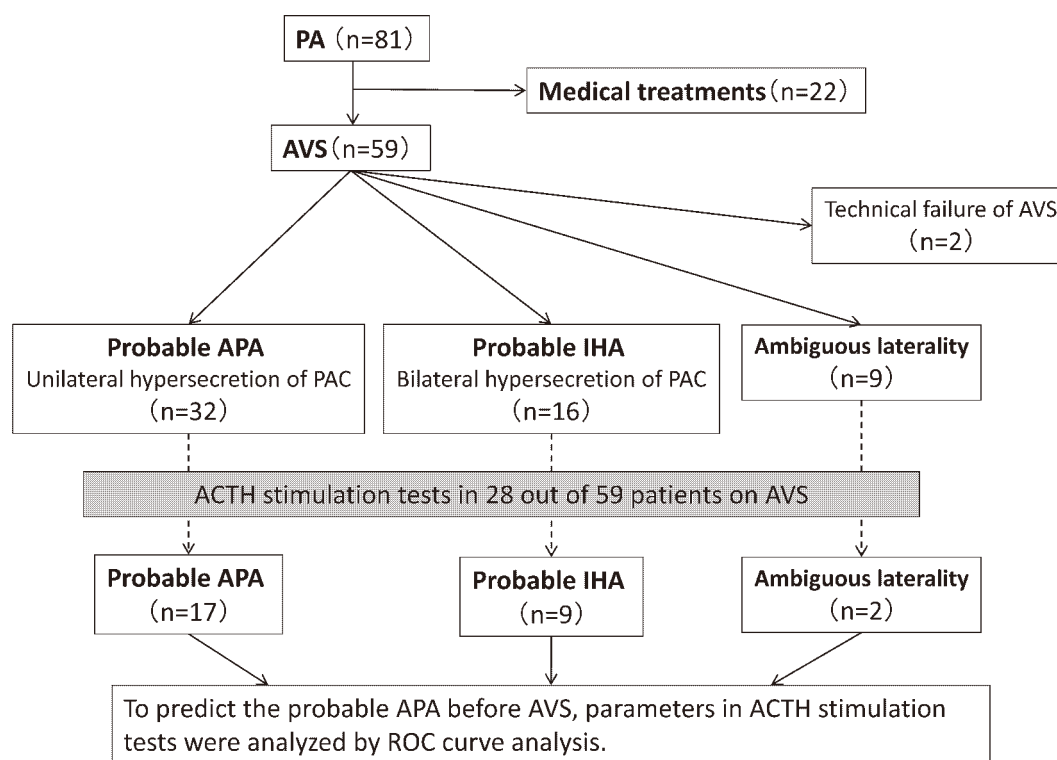


Fig. 1 Proportion of the patients. Overall classification of the patients reviewed in the study.

PA, primary aldosteronism ; AVS, adrenal venous sampling ; APA, aldosterone-producing adenoma ; IHA, idiopathic hyperaldosteronism ; ACTH, adrenocorticotrophic hormone

antihypertensive therapy and did not wish to undergo AVS, they were treated with aldosterone

receptor antagonists. The two patients in whom AVS failed were also treated with aldosterone rece-

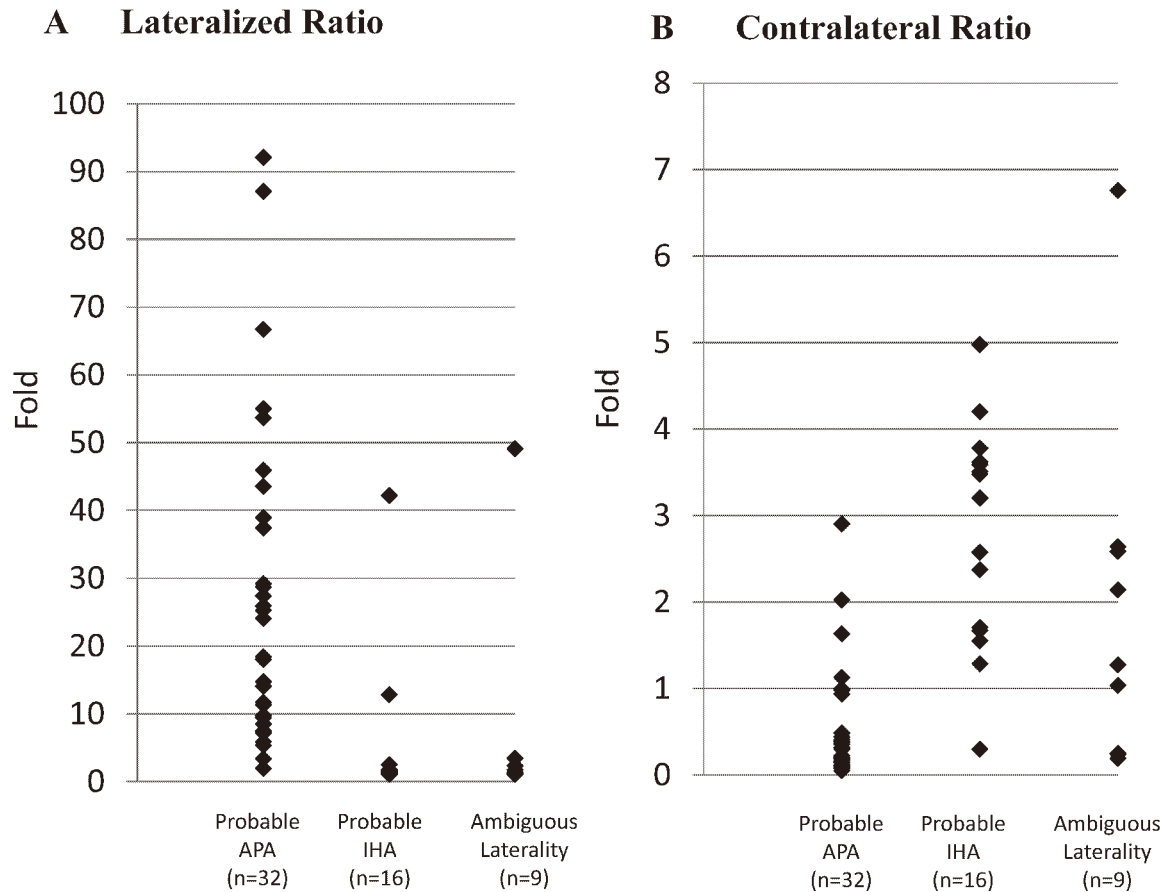


Fig. 2 Scattergram of lateralized ratio (A) and contralateral ratio (B) among 3 groups in patients with PA successfully undergoing AVS.

APA, aldosterone-producing adenoma ; IHA, idiopathic hyperaldosteronism

ptor antagonists. Based on the results of AVS, we clinically diagnosed 32 and 16 patients as “probable APA” and “probable IHA”, respectively. The remaining 9 patients showed marginal hypersecretion of aldosterone, and did not satisfy the criteria for diagnosis of the laterality (**Fig. 1**).

Fig. 2 shows LR and CR in the 57 patients in whom AVS was successfully performed. The LR was ≥ 2.6 in all except one of the probable APA patients (**Fig. 2A**). Among the 32 patients with probable APA, 4 had CR > 1 (**Fig. 2B**), and 2 patients did not agree to surgical resection. Thus, 26 patients were treated by surgery. Among the 26 patients, 25 were histologically diagnosed as having adenomas and one was diagnosed as having hyperplasia. The CR of the patient showing hyperplasia was exactly 1.0 in AVS, suggesting suppression of aldosterone secretion from the opposite site of the adrenal gland would be a valuable addition to clinical diagnosis of

APA.

B ACTH stimulation test

The ACTH stimulation test was performed in 28 patients with PA (17 patients with probable APA, 9 patients with probable IHA, and 2 patients with ambiguous laterality) (**Fig. 1**). The ACTH stimulation test data are shown in **Table 2**. We compared the results of the ACTH stimulation test in between the probable APA patients and the combined patients with probable IHA and ambiguous laterality. The latter group was referred to as “probable non-APA”. Serum potassium level was lower in the probable APA patients than in the probable non-APA patients. There were significant differences between the probable APA and the probable non-APA patients with regard to PAC before and after 30 and 60 min of ACTH stimulation. There were no significant differences in cortisol levels at any time point. The response of PAC to the ACTH stimula-

Table 2 Adrenocorticotropin Stimulation Test

	Number of patients	K (mmol/L)	PAC 0 min (pg/mL)	PAC 30 min (pg/mL)	PAC 60 min (pg/mL)	COR (ng/dL)	COR 30 min (ng/dL)	COR 60 min (ng/dL)
Probable APA	17	3.1±0.1	438±81	852±137	847±131	10.7±0.7	23.3±0.9	26.2±1.0
Probable non-APA (Probable IHA+ Ambiguous laterality)	11	4.0±0.1	118±10	242±24	267±23	9.8±1.2	22.0±1.0	25.9±1.1
P value (VS non APA)		<0.001	<0.001	<0.001	<0.001	0.466	0.466	0.906

Data are expressed as means ± SEM. PAC, plasma aldosterone concentration; COR, plasma cortisol concentration; K, potassium; APA, aldosterone-producing adenoma; IHA, idiopathic hyperaldosteronism

tion test in the probable APA group was stronger than that in the probable non-APA, however there were no significant differences between the two groups (**Fig. 3A**). In contrast, the PAC increment from the basal level was robust in the probable APA group (**Fig. 3B**). As a high value of PAC/cortisol ratio after the ACTH stimulation test is one of the hallmarks of PA¹³), we next analyzed the changes in PAC/cortisol ratio as shown in **Fig. 3C**. As expected, the values were higher in the probable APA patients than in the probable non-APA (**Fig. 3C**). As the potassium levels were low and PACs were high in the probable APA patients, we expected that the aldosterone potassium ratio (APR) would be a useful parameter in the diagnosis of APA. Accordingly, we analyzed the changes in APR in the ACTH stimulation test. APR was markedly higher in the probable APA patients than in the probable non-APA (**Fig. 3D**).

C ROC curve analysis for diagnosis of APA

We performed ROC curve analysis and calculated the sensitivity and specificity of various parameters in the diagnosis of APA in the patients with PA (**Fig. 4**). With a PAC_{0min} cutoff value of 152 pg/mL, we obtained a sensitivity of 88.2 % and specificity of 90.9 %. The AUC of PAC_{0min} for diagnosis of APA was 0.8984 (**Fig. 4A**). Among PAC (**Fig. 4A-C**), PAC/cortisol (**Fig. 4D-F**), and PAC/potassium (**Fig. 4G-I**), PAC/potassium had the highest AUC and PAC/cortisol was the lowest AUC, although the differences in these AUCs did not reach statistical

significance. In general, ACTH stimulation improved the ROC curves as shown in **Fig. 4**. It should be noted that 30 min after stimulation might be a better time point than 60 min after stimulation. The ROC curves, cutoff values, sensitivities, and specificities of various parameters are shown in **Fig. 4A-I**. With a PAC_{30min}/potassium ratio cutoff of 102.6, sensitivity was 94.1 % and specificity was 90.9 %. The AUC of this parameter reached 0.9840 (95 % CI: 0.848-1.00) (**Fig. 4H**). The AUC of APR (PAC_{60min}/potassium) for diagnosis of APA was 0.9733 (95 % CI: 0.831-1.00) with an optimal cutoff value >97.7 corresponding to sensitivity and specificity of 94.1 % and 90.9 % for diagnosis of APA, respectively.

IV Discussion

In this study, we retrospectively analyzed the characteristic features of 59 patients with PA who underwent AVS in our hospital over a 4-year period. PA is the most common etiology of secondary hypertension, and APA, which is one of the subtypes of PA, is surgically treatable. Therefore, there is a need for a simple and accessible method to detect APA. In this study, we confirmed the importance of the ACTH stimulation test before adopting AVS to identify probable APA among patients with PA¹²). In addition, we found that APR in the ACTH stimulation test was a potentially powerful and reliable parameter in the test. Among the various parameters in the ACTH stimulation test, APR at

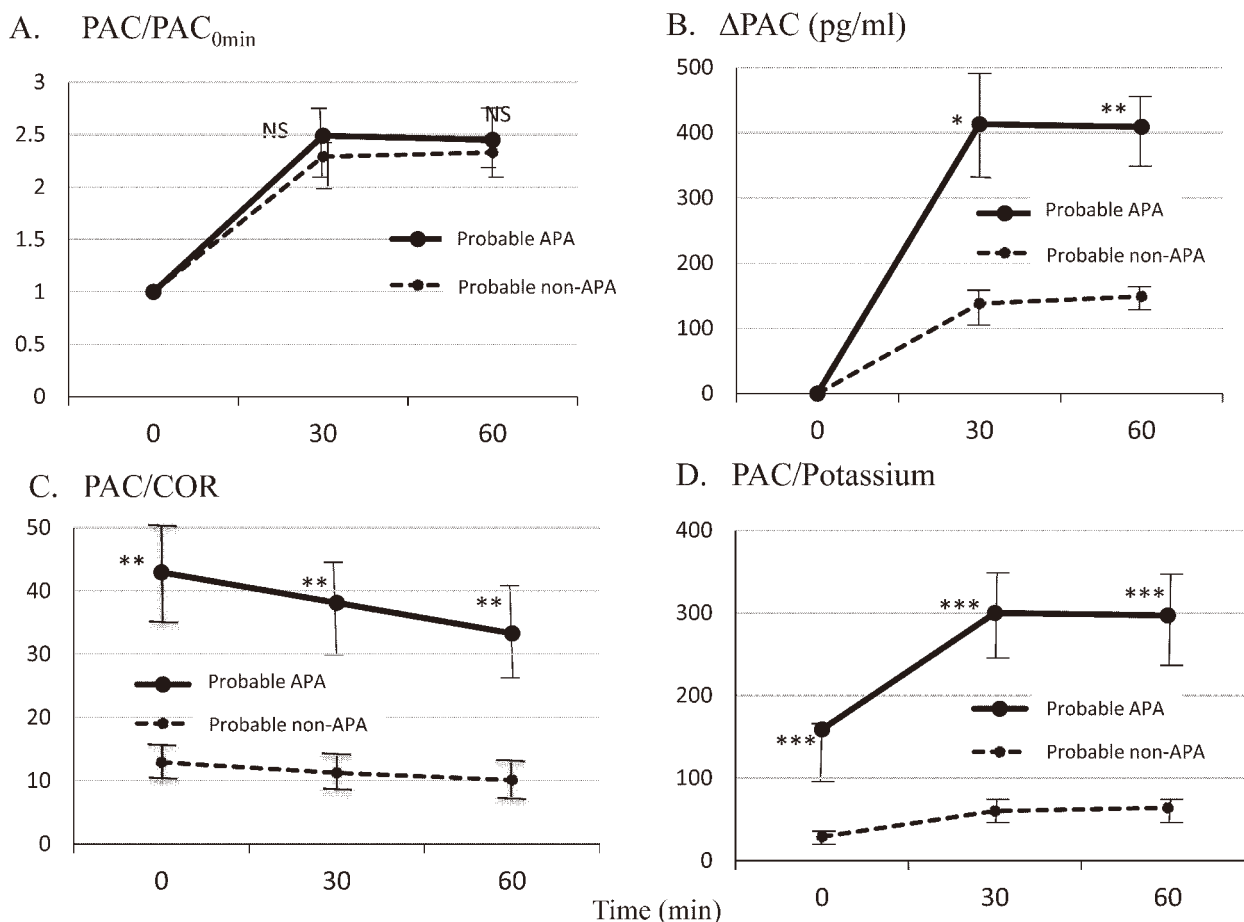


Fig. 3 Changes in PAC/PAC_{0min} (A), increments in PAC (B), PAC/COR ratio (C), and PAC/potassium ratio (D) after ACTH injection in the probable APA group (continuous line) and the probable non-APA group (dashed line).

Data are shown as means \pm SEM. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ vs. probable non-APA group. ACTH, adrenocorticotrophic hormone; PAC, plasma aldosterone concentration; PAC_{0min}, PAC at 0 min; Δ PAC, absolute increases of PAC from 0 min, COR, cortisol

30 min after stimulation was suggested to be an excellent parameter to detect APA by ROC curve analysis. By consensus, the ratio of maximum PAC to cortisol after ACTH stimulation is a well-known parameter in the test. However, our results suggested that PAC itself is more useful than the PAC to cortisol ratio. In addition, APR may be a more useful parameter for identifying APA. Obviously, accumulation of larger numbers of cases is required to confirm our hypothesis that APR is an unequivocally useful parameter in comparison with PAC itself after the ACTH stimulation test.

If we discuss ACTH responsiveness in detail, there is a wide degree of heterogeneity of Conn's adenoma responsiveness to ACTH^{14)–16)}. However,

it is generally considered that APA patients show an ACTH-dependent aldosterone response, whereas IHA patients tend to have an angiotensin II-dependent aldosterone response¹⁷⁾¹⁸⁾. Since the 1970s, several lines of evidence have suggested that PAC in the upright posture usually decreases in patients with APA, and increases in those with IHA^{18)–20)}. Biglieri reported that an upright posture is useful for differentiating between APA and IHA²¹⁾, although there were some equivocal findings²²⁾²³⁾. As background for these findings, it was reported that adrenal sensitivity to angiotensin II was increased in IHA patients²⁴⁾. In addition, angiotensin II was reported to fail to stimulate aldosterone secretion in patients with APA²⁵⁾. Meanwhile, Tunny et al. re-

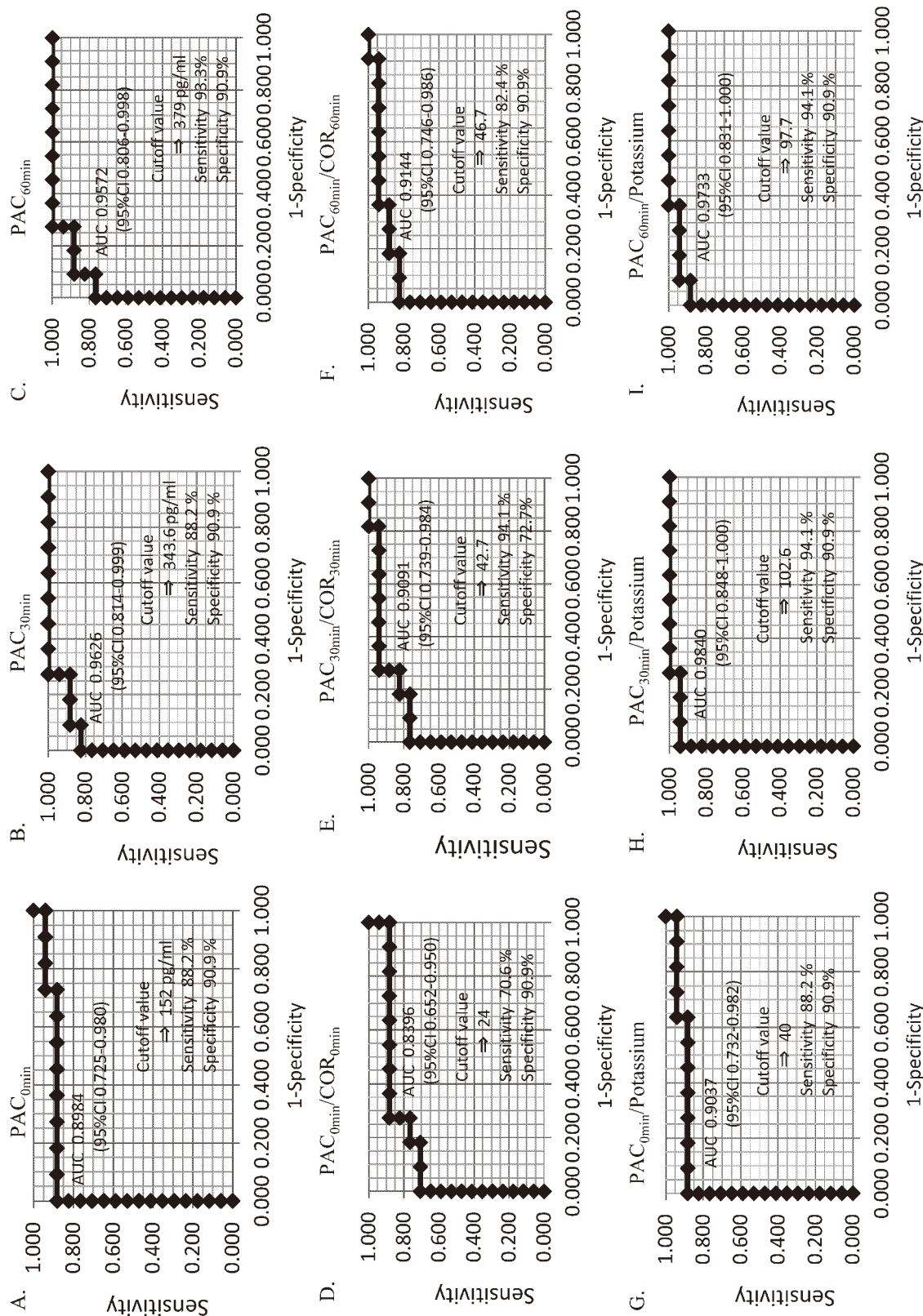


Fig. 4 ROC curve analysis of various parameters in ACTH stimulation test.

A-I, ROC curve of PAC_{0min} (A), PAC_{30min} (B), PAC_{60min} (C), PAC_{0min}/cortisol_{0min} (COR_{0min}) (D), PAC_{30min}/COR_{30min} (E), PAC_{60min}/COR_{60min} (F), PAC_{0min}/potassium (G), PAC_{30min}/potassium (H), and PAC_{60min}/potassium (I) in the diagnosis of probable APA among patients with PA. PAC, plasma aldosterone concentration; PAC_{0min}, PAC at 0 min; PAC_{30min}, PAC at 30 min; PAC_{60min}, PAC at 60 min; COR_{0min}, cortisol at 0 min; COR_{30min}, cortisol at 30 min; COR_{60min}, cortisol at 60 min; AUC, area under curve; ACTH, adrenocorticotropic hormone; APA, aldosterone-producing adenoma

ported that 40 % of APA patients had a response to angiotensin II²⁶). In the present study, we assessed PAC response in the upright posture with the furosemide infusion test substituting for angiotensin II infusion to determine whether APA patients show responses to angiotensin II. These results indicated that there were significant differences in the PAC response between APA and IHA patients, but ROC curve analysis failed to show excellent sensitivity and specificity. In this study, we confirmed the findings reported by Sonoyama et al. indicating that the ACTH stimulation test is useful for the diagnosis of APA among patients with suspected PA¹²).

Physiologically, aldosterone secretion from the adrenal cortex is regulated by several factors, including angiotensin II, ACTH, and potassium. Therefore, we considered that the concentration of potassium might affect the reactivity of the ACTH stimulation test; in fact, it was lower in APA patients than the IHA patients in the present study. This can be understood from the tendency toward strong aldosterone hypersecretion in patients with APA. As potassium supplementation is performed for hypokalemia in some patients, the potassium concentration itself was not sufficient to distinguish between IHA and APA in our study, but it would be one factor determining the PAC response. Further, we assumed that the PAC response to the ACTH stimulation test would be enhanced to a greater extent if hypokalemia had been corrected. Based on this concept, we considered the ratio of aldosterone and potassium as an index. Accordingly, our results suggested that APR may be a very useful indicator in the diagnosis of APA among patients with PA.

Dexamethasone treatment before the ACTH stimulation test was initially proposed by Kem et al.²⁷). Indeed, Sonoyama et al. performed dexamethasone pretreatment in their study¹²). If the serum ACTH levels in the morning are suppressed by pretreatment with 1 mg of dexamethasone overnight, it is possible that the difference in PAC before and after the ACTH stimulation test might become more apparent. However, Sonoyama *et al.* found that the PAC itself after stimulation was more

useful than the degree of increment in PAC¹²). They also failed to obtain a favorable ROC curve of PAC before stimulation with ACTH. For example, with PAC_{omin}, the AUC, sensitivity, and specificity were 0.623, 47.8 %, and 69.4 %, respectively, in the diagnosis of APA in PA patients. This was probably due to overnight suppression of ACTH with dexamethasone. Therefore, dexamethasone loading may be unnecessary for differential diagnosis of APA from PA.

We performed the rapid ACTH test without the dexamethasone suppression test, but several days after admission when endocrinological stabilization had been achieved. This is why pre-stimulated PAC was a relatively good marker to identify clinical APA in our study. Nevertheless, post-stimulated PAC seems to be a more specific and sensitive parameter in ROC analysis. This issue should be confirmed in future studies. With regard to the PAC/cortisol ratios before and after ACTH stimulation, we also performed the analysis using respective peak values, and the sensitivity and specificity were essentially the same as the values calculated 30 min or 60 min after stimulation.

Several attempts have already been made to localize unilateral aldosterone hypersecretion without AVS: single-photon emission CT with [¹³¹I]-iodocholesterol²⁸), [¹¹C]-metomidate positron emission tomography-CT²⁹), clinical prediction score³⁰), and parathormone levels³¹). Nevertheless, AVS is currently considered the gold standard method to identify the laterality of aldosterone hypersecretion. Therefore, selection of appropriate patients for AVS by the ACTH stimulation test is plausible.

The future possibilities of APR may be broader than the spectrum explored in this study. Many patients with suspected secondary hypertension had already received antihypertensive drugs, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and beta-blockers, which affected screening for PA. In the next step, we will apply the ACTH stimulation test and evaluate APR under various conditions.

This study was performed in a single medical center and with retrospective analysis. One of the drawbacks of our study was the limited number of patients receiving the ACTH stimulation test. However, this was not due to selection bias, but was simply due to the absence of the ACTH stimulation test as a mandatory examination in suspected PA in our hospital during the study period. To overcome these limitations, it will be necessary to perform a prospective and multi-center study to confirm the diagnostic accuracy and usefulness of APR in the clinical diagnosis of APA.

In conclusion, we confirmed the usefulness of the ACTH stimulation test in the diagnosis of APA, and suggested that post-ACTH APR may be a new and

reliable parameter in cases of suspected PA. Even when CT does not reveal a tumor or swelling of the adrenal glands, we propose that the ACTH stimulation test should be performed in refractory hypertensive patients to identify APA.

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Disclosure Statement

The authors have no potential conflicts of interest associated with this research.

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