Endocrine Journal 2008, **55** (5), 839–846

Diagnostic Accuracy of Adrenal Venous Sampling in Comparison with Other Parameters in Primary Aldosteronism

ISAO MINAMI, TAKANOBU YOSHIMOTO, YUKI HIRONO, HAJIME IZUMIYAMA, MASARU DOI AND YUKIO HIRATA

Department of Clinical and Molecular Endocrinology, Tokyo Medical and Dental University Graduate School, Tokyo 113-8519, Japan

Abstract. This retrospective study was aimed 1) to compare the difference of the findings between adrenal CT scan and adrenal venous sampling (AVS) in 35 cases with definite primary aldosteronism (PA) for assessment of the diagnostic efficacy of PA subgroup (unilateral and bilateral adrenal hypersecretion: UAH and BAH), and 2) to determine the clinical and biochemical parameters as potential predictors for PA subgroup. There were significant discordant results based on AVS and CT scan in subgrouping PA; 9 of 17 BAH patients (53%) had unilateral lesion on CT scan, while 4 of 18 UAH patients (22%) had no apparent or bilateral lesions on CT scan. Among three diagnostic criteria, absolute values of plasma aldosterone concentration (PAC) in both adrenal veins, lateralized and contralateral ratios of aldosterone/cortisol after ACTH stimulation during AVS to determine the laterality, none of them showed 100% diagnostic accuracy if applied alone. Among several clinical and biochemical parameters, hypokalemia (<3.4 mEq/l), younger age (<52 y) and poor response of PAC (<1.45) after furosemide-upright posture, proved to be significant predictors for UAH, with higher specificities (100%, 88%, 94%, respectively). Therefore, despite AVS as a gold standard method to determine the laterality of aldosterone hypersecretion in PA, our study shows that no single criterion could provide definite diagnostic value for its laterality by AVS. It is also suggested that most PA patients, if not all, with a distinct unilateral adrenal lesion on CT accompanied by hypokalemia, younger age and poor aldosterone response to renin stimulation, could undergo adrenalectomy without prior AVS.

Key words: Aldosterone, Primary aldosteronism, Adrenal venous sampling, Hypokalemia

(*Endocrine Journal* **55**: 839–846, 2008)

PRIMARY aldosteronism (PA) is characterized by autonomous aldosterone hypersecretion, thereby leading to suppressed plasma renin activity and hypertension. Nowadays, PA is considered to be more common secondary hypertension than previously believed; its prevalence among hypertensive patients has been reported to be 5–15% [1–6]. The most common two subtypes of PA are aldosterone-producing adenoma (APA) and bilateral idiopathic hyperaldosteronism (IHA), whereas far less common forms include unilateral adrenal hyperplasia, glucocorticoid remediable aldosteronism, familial hyperaldosteronism type II, adrenal cancer, and unilateral multiple adrenocortical micronodules. These PA subtypes can be divided into two subgroups; unilateral and bilateral adrenal lesions. It is important to distinguish unilateral from bilateral lesions, since patients with APA, which is usually unilateral, can be treated by adrenalectomy [7], whereas patients with IHA should be treated medically with antihypertensive drugs including mineralocorticoid receptor antagonists.

Diagnostic imaging tests by echography, computed tomography (CT) scan or magnetic resonance imaging (MRI) are very useful to determine the presence of nodule(s), mass and/or enlargement of adrenal glands. However, these imaging tests have often been inconclusive for the diagnosis of PA subtype [8]. Discordant results between CT findings and definite PA subtype are mainly attributable to non-functioning adrenal tumor,

Received: December 19, 2007
Accepted: April 21, 2008
Correspondence to: Takanobu YOSHIMOTO, Department of Clinical and Molecular Endocrinology, Tokyo Medical and Dental University Graduate School, 1-5-45 Yushima, Bunkyo-ku, Tokyo, 113-8519, Japan

small adrenal pathology, such as microadenoma and micronodules (less than 6 mm in size) not detectable even in thin-slice (3 mm) CT scan. Thus, these findings support the premise that PA patients should undergo adrenal venous sampling (AVS) to make the differential diagnosis between unilateral and bilateral lesions.

AVS is currently regarded as the most reliable and accurate method to determine the source of aldosterone hypersecretion with highest diagnostic accuracy (79–100%) [5, 9], with ACTH stimulation further facilitating its accuracy [10, 11]. There have been several diagnostic criteria for lateralization by AVS; absolute PAC values in adrenal vein [6], gradient of aldosterone in the dominant over non-dominant adrenal vein (lateralized ratio), and/or that of aldosterone in the inferior vena cava over non-dominant vein (contralateral ratio) under basal and ACTH-stimulated conditions [10–14]. Successful sampling from both adrenal veins, especially the right adrenal vein which is often difficult to be cannulated due to its anatomical location [15, 16], demands considerable practical skills by expertise radiologists, limiting its application to major tertiary specialized center. Other drawbacks of AVS include its medical cost and complications, such as bleeding and adrenal infarction [11].

This retrospective study is aimed to compare the differences in the findings between adrenal CT scan and AVS to assess the diagnostic efficacy in PA subgrouping (unilateral and bilateral lesions) in 35 patients with definite PA, and then to determine any clinical and biochemical parameters as a potential predictor(s) for avoidance of AVS prior to operation.

Patients and Methods

Patients

From 2001 to 2008, 35 hypertensive patients with possible diagnosis of PA who had plasma renin activity (PRA) less than 1.0 ng/ml/hr and plasma aldosterone concentration (PAC) greater than 12 ng/dl and/or PAC to PRA ratio (ARR) greater than 20, were referred to our hospital. Confirmatory tests for the definite diagnosis of PA by furosemide-upright posture (FUP) and captopril tests, and subgrouping unilateral and bilateral adrenal lesions by AVS were performed after withdrawal of anti-hypertensive drugs for at least 2 weeks except for those patients with severe hypertension who received Ca channel blockers monotherapy for blood pressure control.

Confirmatory tests

FUP test was performed in 32 of 35 patients when hospitalized. Examination started between 0800–0900 h. After supine position for 30 min, blood was taken for measurements of basal PRA (Renin Riabead Kit: Dianabot) and PAC (SPAC-S Aldosterone Kit: TFB Inc.), followed by a bolus injection of 40 mg furosemide. After 2 h in upright posture (2 h-post FUP), blood was taken. The PAC ratio was defined as 2 h-post FUP PAC divided by basal PAC. Captopril test was performed in the remaining three patients in the supine position. PAC and PRA were measured before and 90 min after oral administration of captopril (50 mg). PRA less than 1.0 ng/ml/h at 2 h-post FUP or 90 min after captopril loading was considered as renin suppression; all 35 patients showed renin suppression and were diagnosed as definitive PA.

Imaging studies

All patients underwent 3 mm-thin slice adrenal CT scan. Based on adrenal CT findings, patients were divided into three groups; no 'apparent' lesion (CT-NAL), unilateral lesion (CT-UAL) and bilateral lesions (CT-BAL). A positive lesion on CT scan was defined as the presence of a distinct nodule(s) of at least greater than 8 mm in diameter and/or increased thickness of the adrenal glands. ^{131}I-Adosterol adrenal scintigraphy without dexamethasone pretreatment was performed in 19 of 23 CT-UAL patients. Symmetrical uptake of radioactivity by both adrenals was interpreted as no laterality, but preferential uptake of radioactivity by either adrenal as a unilateral lesion.

Adrenal venous sampling (AVS)

After obtaining informed consent, all patients underwent AVS. The adrenal veins were catheterized by the percutaneous approach, and the proper position of the catheter tip was verified by gentle injection of a small amount of contrast medium. PAC and cortisol levels were obtained from the inferior vena cava (IVC) below the level of the renal vein, the right and the left adrenal vein before and 15 min after a bolus injection of 250 μg ACTH (Cortrosyn®). Successful procedure of AVS

was confirmed by cortisol level more than 200 μg/dl in the adrenal vein after ACTH stimulation [17]. To determine the source of aldosterone hypersecretion, the following three diagnostic criteria were evaluated; 1) absolute value of PAC in bilateral adrenal venous effluents, 2) lateralized ratio (LR) defined as the gradient of aldosterone-cortisol ratio (A/C) in the dominant adrenal vein over that in the non-dominant adrenal vein, and 3) contralateral ratio (CR) defined as A/C in the non-dominant adrenal vein over that in IVC. Since 12 of 35 cases failed to conduct IVC sampling after ACTH stimulation, we did not adopt the combination of LR and CR as one criterion to determine laterality. Instead, each of LR and CR was adopted as a single independent criterion. The diagnosis of unilateral aldosterone hypersecretion (UAH) was made when at least two of the three criteria were fulfilled; 1) PAC more than 1400 ng/dl at one side [6], 2) LR more than 4 [13, 14], and 3) CR less than 1 [11–14]. Those patients diagnosed as UAH underwent ipsilateral adrenalectomy, while those who failed to fulfill these criteria were diagnosed as bilateral aldosterone hypersecretion (BAH) and received medical treatment.

Statistical analysis

All data are expressed as mean ± SD. The differences of transformed parametric variables were assessed by Mann-Whitney U-test. Categorical variables were assessed with χ^2 test. Variables of categorical and biochemical data including serum potassium, age and PAC ratio were derived to establish potentially predictive values for UAH.

Results

Clinical and endocrine features

The clinical and endocrine features of 35 PA patients studied are summarized in Table 1. There were no statistical differences in age, sex or systolic and diastolic blood pressure between UAH and BAH patients as determined by AVS. Serum potassium levels were significantly ($p<0.001$) lower in UAH than in BAH. Creatinine clearance was not different between either group, but morbidity of left ventricular hypertrophy assessed by ultrasound cardiography or

Table 1. Clinical and endocrine features of 35 patients with PA

	UAH (18)	BAH (17)
Age (years)	51.4 ± 11.7	57.4 ± 10.0
Sex (male/female)	8/10	4/13
Systolic blood pressure (mmHg)	148 ± 23	134 ± 16
Diastolic blood pressure (mmHg)	87 ± 18	84 ± 14
Serum potassium (mEq/l)	3.1 ± 0.5	4.0 ± 0.3**
Left ventricular hypertrophy	9/18	2/17*
Creatinine clearance (ml/min)	99 ± 32	103 ± 35
Basal PAC (ng/dl)	28.5 ± 16.6	13.3 ± 6.0**
Basal PRA (ng/ml/h)	0.3 ± 0.3	0.3 ± 0.2
Basal ARR	171 ± 148	74 ± 67
Furosemide upright posture test	(16)	(16)
PAC	37.7 ± 19.6	28.4 ± 8.6
PRA	0.8 ± 1.0	0.6 ± 0.3
PAC ratio	1.53 ± 0.55	2.37 ± 0.91**
Adrenal CT imaging		
No apparent lesion (CT-NAL) (7)	1	6
Unilateral lesion (CT-UAL) (23)	14	9
Bilateral lesions (CT-BAL) (5)	3	2
Treatment	Adrenalectomy (left/right)	Medication
	18(10/8)	17

PAC, (plasma aldosterone concentration); PRA, (plasma renin activity); ARR, (aldosterone-renin ratio); UAH, (unilateral aldosterone hyperesecretion); BAH, (bnilateral aldosterone hyperesecretion). Parenteses (total number of patients).

*p<0.05, **p<0.01 compared with UAH.

electrocardiography was significantly ($p = 0.0149$) greater in UAH than in BAH. Basal PAC was significantly ($p = 0.0062$) higher in UAH than in BAH, while either basal PRA or ARR was not different. There was no statistical difference in 2 h post-FUP PRA and PAC between UAH and BAH, whereas PAC ratio 2 h post FUP was significantly higher ($p = 0.0079$) in BAH than in UAH.

Imaging studies

Based on the findings by adrenal CT imaging of 35 PA patients studied (Table 1), a solitary unilateral adrenal nodule and/or mass was detected in 23 patients (CT-UAL), bilateral adrenal nodules and/or enlargement in 5 patients (CT-BAL), and no adrenal lesion in either adrenal gland in 7 patients (CT-NAL).

Among 19 patients who underwent adrenal scintigraphy, 12 patients showed unilateral uptake at the ipsilateral side (10) and at the contralateral side (2) as detected by CT scan, and 7 patients showed bilateral uptake.

ACTH-AVS

Bilateral AVS was successful in 33 of 35 patients (94%), except for two patients with left adrenal nodule on CT scan, in spite of the failure of cannulation into the right adrenal vein. They had PAC more than 1400 ng/dl in the left adrenal vein after ACTH stimulation, and thus were diagnosed as UAH. Among 33 cases in whom bilateral AVS was successful, 16 patients were diagnosed as UAH and the rest of 17 patients as BAH (Table 1). Based on the results from ACTH-AVS, 14 of 23 CT-UAL patients were diagnosed as UAH from the ipsilateral lesion, but the rest of 9 patients as BAH. Two of 5 CT-BAL and 6 of 7 CT-NAL were diagnosed as BAH by ACTH-AVS, but the rest of 3 CT-BAL and 1 CT-NAL as UAH.

Among 19 CT-UAL patients after adrenal scintigraphy, 6 of 10 patients with unilateral uptake at the ipsilateral lesion were diagnosed as UAH, but the rest of 4 as BAH. When combined with adrenal scintigraphy and CT scan results, 6 of 12 patients with unilateral uptake were diagnosed as ipsilateral UAH (sensitivity 50%), but 3 of 7 patients with bilateral uptake as BAH (specificity 43%).

Diagnostic accuracy of three criteria for localization of aldosterone hypersecretion by ACTH-AVS is shown in Table 2. The first criterion on "PAC more than 1400 ng/dl at one side after ACTH stimulation" gave the highest sensitivity (100%), but low specificity (71%) due to 5 false-positive BAH patients who had LR ≤4 and/or CR ≥1. The second criterion on "LR more than 4" gave sensitivity (81%) and specificity (94%), while the third criterion on "CR less than 1" showed the highest diagnostic accuracy, with sensitivity (100%) and specificity (93%). There were two CT-UAL patients with discrepant LR and CR results, one (LR>4, CR≥1) and another (LR≤4, CR<1); both of them were diagnosed as BAH based on the first criterion (PAC>1400 ng/dl) in both sides.

Table 2. Diagnositic accuracy of three different criteria for lateralization of aldosterone hypersecretion by ACTH-AVS in PA patients

		UAH/BAH	Predictive value		
			sensitivity	specificity	P
1. PAC	(33)				
positive	(21)	16/5	100%	71%	0.00003
negative	(12)	0/12			
2. LR	(33)				
positive	(14)	13/1	81%	94%	0.00001
negative	(19)	3/16			
3. CR	(23)				
positive	(10)	9/1	100%	93%	0.00001
negative	(13)	0/13			

Three criteria for localization of aldosterone hypersecretion after ACTH-AVS include 1) "PAC more than 1400 ng/dl at one side", 2) "lateralized ratio more than 4 (LR>4)", and 3) "contralateral ratio less than 1 (CR<1)", respectively. Parentheses (total number of patients studied and those with positive and negative finding in each criterion). Number of patients with unilateral adrenal hypersecretion and bilateral adrenal hypersecretion are shown as UAH/BAH.

Treatment

All 18 UAH patients diagnosed by ACTH-AVS underwent unilateral adrenalectomy; a solitary adenoma was identified in either adrenal gland resected. PAC and serum potassium levels were normalized with concomitant improvement in blood pressure control 6 months after surgery. The remaining 17 BAH patients were treated medically with antihypertensive drugs, including calcium channel blockers, α-blockers, and spironolactone or eplerenone.

Clinical and biochemical parameters for a possible predictor(s) for UAH

Due to the unreliability of adrenal CT in differential diagnosis between UAH and BAH, cut-off values of several clinical and laboratory parameters were assessed for a potential predictor for UAH in 35 cases. Based on the overlapped distributions of each parameter between UAH and BAH, cut-off lines giving a maximal diagnostic accuracy [true positive plus true negative cases/all cases)] for UAH were calculated by 2 × 2 table generated from scattergram (Fig. 1), and each variable are shown in Table 3. Age (52 y), systolic blood pressure (148 mmHg), serum potassium level (3.4 mEq/l), urinary aldosterone (9.0 μg/day), basal PAC (18 ng/dl), and 2 h post-FUP PAC ratio (1.45) yielded significant cut-off lines, respectively, whereas no significant cut-off lines could be obtained from basal PRA and post-FUP PRA (Fig. 1). The predictive values based on these cut-off values of each parameter are summarized in Table 3. Among them, serum potassium (<3.4 mEq/l) or potassium supplements, yielded the greatest diagnostic accuracy as a predictor for UAH (sensitivity 83%; specificity 100%), while age (<52 y) and PAC ratio (<1.45) showed high specificity (88% and 94%), but low sensitivity (56% and 50%), respectively. We also analyzed whether these cut-off values of each parameter are also applicable for 23 CT-UAL cases (Table 3). In consistent with the analytical results from all cases, serum potassium was found to be most efficient UAH predictor (sensitivity 86%; specificity 100%), while age and PAC ratio showed high specificity (100% and 88%), but low sensitivity (57% and 67%), respectively.

Since these three parameters did not correlate with each other, their diagnostic efficacy in combination was tested for UAH predictor among 23 CT-UAL patients (Table 3). Any combination of these parameters gave the comparable sensitivity at the specificity of 100%; serum potassium and age (57.1%), serum

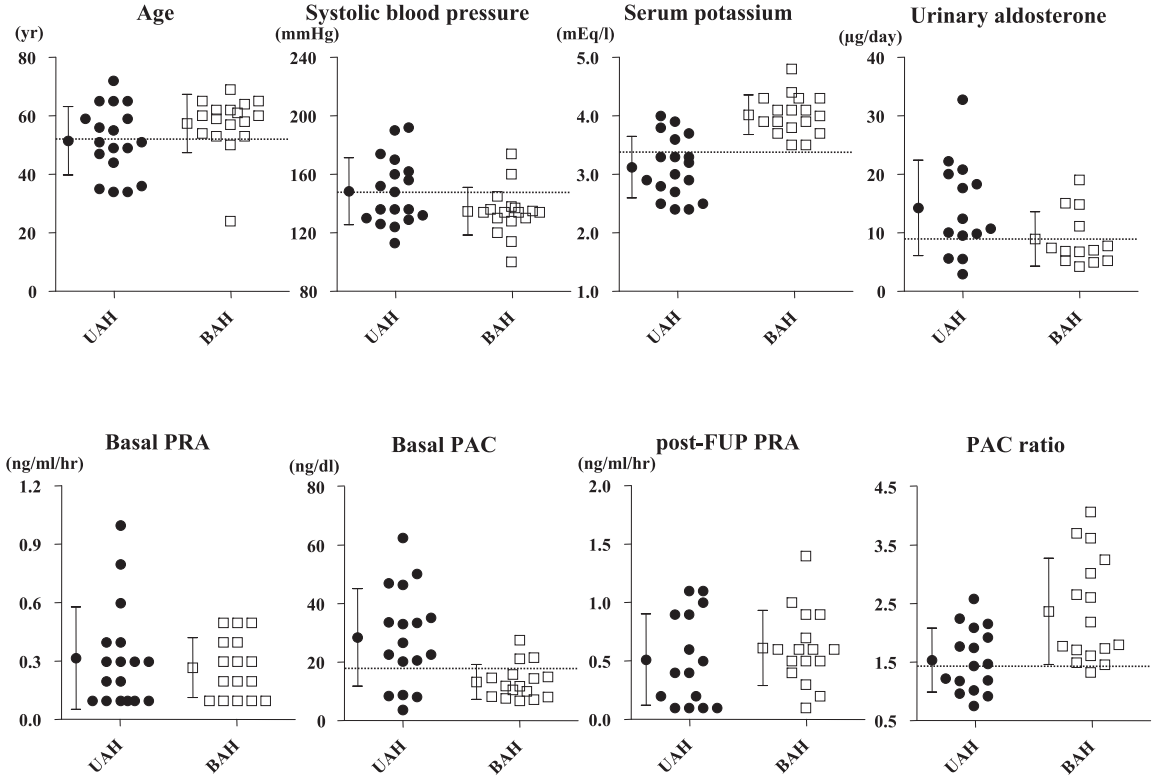

Fig. 1. Comparison of clinical and biochemical parameters between UAH and BAH. The distribution of each parameter for UAH (•) and BAH (□) were shown by scattergrams; each point with bar shows mean ± SD. The dotted lines indicate cut off values calculated by 2 × 2 Table for gaining maximum diagnostic accuracy; age (52 y), systolic blood pressure (148 mmHg), serum potassium level (3.4 mEq/l), urinary aldosterone (9.0 μg/day), basal PAC (18 ng/dl), and post FUP PAC ratio (1.45).

Table 3. Predictive values of clinical and biochemical parameters for unilaterality by ACTH-AVS in PA patients

All cases (n = 35)	UAH	BAH	Predictive value		
			sensitivity	specificity	P
Age (<52 y)	10 (18)	2 (17)	56%	88%	0.006374
Systolic blood pressure (≥148 mmHg)	9 (18)	2 (17)	50%	88%	0.014878
Serum potassium (<3.4 mEq/l)	15 (18)	0 (17)	83%	100%	<0.000001
Urinary aldosterone (≥9.0 μg/day)	11 (14)	3 (13)	79%	69%	0.012502
Basal PAC (≥18 ng/dl)	13 (17)	3 (16)	76%	81%	0.000914
PAC ratio (<1.45)*	8 (16)	1 (16)	50%	94%	0.005919
CT-UAL cases (n = 23)	UAH	BAH	Predictive value		
			sensitivity	specificity	P
Serum potassium (<3.4 mEq/l)	12 (14)	0 (9)	86%	100%	<0.000001
Age (<52 y)	8 (14)	0 (9)	57%	100%	0.004983
PAC ratio (<1.45)*	8 (12)	1 (8)	67%	88%	0.01706
Serum potassium/Age	8 (14)	0 (9)	57%	100%	0.004983
Serum potassium/PAC ratio	7 (12)	0 (8)	58%	100%	0.007374
Age/PAC ratio	6 (12)	0 (8)	50%	100%	0.016827
Serum potassium/Age/PAC ratio	6 (12)	0 (8)	50%	100%	0.016827

Number of patients with positive variable for UAH is shown in each parameter.
Parentheses (total number of UAH and BAH patients from whom the data were available.)
*After furosemide upright posture test

potassium and PAC ratio (58.3%), age and PAC ratio (50.0%), combination of all three parameters (50.0%), respectively (Table 3).

Discussion

We reviewed 35 patients with definitive PA in order to evaluate, 1) the diagnostic accuracy between CT and AVS, and 2) the potential predictive power of clinical and biochemical parameters in distinguishing UAH from BAH.

Our study showed relatively high proportion (51%) of UAH among PA patients. Although the proportion of APA and IHA has been reported to differ, higher incidence (53–85%) of APA has been recently shown from several institutes where AVS is routinely performed for PA subgrouping [6, 11, 13]. Several studies have reported that adrenal CT scan is not a reliable method for PA subgrouping [5, 11, 14]. In the present study using ACTH-AVS, 9 of 23 CT-UAL patients were finally diagnosed as BAH, and one of 7 CT-NAL patients and 3 of 5 CT-BAL patients were finally diagnosed as UAH. In other words, 39% of CT-UAL patients might have had inappropriate surgery, and 33% of CT-NAL and CT-BAL patients would have been incorrectly excluded from the candidates for adrenalectomy, if based on CT findings alone. Adrenal scintigraphy with low sensitivity and specificity could not increase diagnostic accuracy even in the combination of CT scan. This is simply due to a large number of discrepant results between CT scan and adrenal scintigraphy.

The present study therefore confirmed that AVS is the most reliable and accurate method to determine the laterality of aldosterone hypersecretion. It should be noted that AVS is the exclusive diagnostic procedure for CT-NAL and CT-BAL patients to distinguish surgically remediable UAH from BAH. In this study, we adopted the combination of three criteria for AVS localization (absolute values of PAC in adrenal vein after ACTH stimulation, LR and CR) to differentiate between UAH and BAH. Each criterion, if applied alone, did not show 100% diagnostic accuracy; "PAC more than 1400 ng/dl at one side after ACTH stimulation" with 100% sensitivity but relatively lower specificity, "LR more than 4" with higher specificity, but lower sensitivity, and "CR less than 1" with the highest diagnostic accuracy, except for one false-negative case out of 23. Therefore, it is recommended to adopt combination of more than one criterion by ACTH-AVS to increase its diagnostic accuracy.

Although AVS is the most accurate diagnostic procedure available for subgrouping PA, it demands

considerable practical skill and therefore limits its application in general. Since prevalence of PA among patients with hypertension is now considered to be increasing [18], it is difficult and not practical to extend the application of AVS to all PA patients for its localization. In fact, several algorithms have been proposed for subgrouping PA to circumvent routine AVS [5, 11–13, 19]. It has been reported that combination of upright posture test and adrenal imaging can be predictive for APA with 100% specificity, but only 29–37% sensitivity [12, 13].

Therefore, we examined several clinical and biochemical parameters as any potential predictor for subgrouping PA to decide application of AVS. Among several clinical and biochemical parameters, hypokalemia (<3.4 mEq/l), younger age (<52 yr), and low response of PAC ratio (<1.45) after FUP showed higher specificity (88–100%) for UAH prediction. Hypokalemia (<3.4 mEq/l) with highest specificity (100% for all cases and CT-UAL cases) for predicting UAH as shown in our study is consistent with the contention that APA patients show lower serum potassium, higher PAC and severe hypertension than IHA patients [20, 21]. Thus, PA patients with hypokalemia combined with positive CT-UAL are more likely to have a solitary unilateral APA.

Younger age (<52 yr) with high specificity (88% for all cases and 100% for CT-UAL cases) for UAH prediction as shown in our study is in accordance with an algorithm proposed by Young *et al.* [19] that PA patients younger than 40 yr with a solitary unilateral adrenal tumor can undertake unilateral adrenalectomy without AVS, since incidentaloma is quite uncommon in young patients. Therefore, PA patients of younger age would be one of the potential predictive factors for UAH.

The upright posture test has been used to differentiate PA subgroup. Although FUP is the most potent stimulatory test for renin secretion, post FUP PAC ratio in our study showed low sensitivity (50% for all cases and 67% for CT-UAL cases) with high specificity (94% for all cases and 88% for CT-UAL cases) for UAH prediction. This may be explained by the relatively high proportion of renin-responsive cases in our APA patients.

Since these three parameters (hypokalemia, younger age, and/or low PAC ratio), although highly specific, showed significant overlapped distributions (Fig. 1), they could not be sufficient or definite enough to predict UAH without AVS. Since these three predictors do not correlate with each other, we reasoned that their combination could increase diagnostic accuracy for subgrouping PA. Approximately half of UAH cases had two or more predictors among CT-UAL patients, whereas most BAH cases among CT-UAL patients (8 of 9) had no UAH predictor. Only one BAH case had one UAH predictor (poor response of PAC after FUP). Collectively, most PA patients, if not all, with a distinct unilateral adrenal lesion on CT scan who have all three predictors are likely to undergo ipsilateral adrenalectomy without prior AVS for PA subgrouping.

There is a limitation in our present study. Our interpretation may be biased due to the study design from small number of referral patients. In fact, 43% (15/35) of our PA patients showed hypokalemia, but several recent studies have shown that 60–90% of PA patients are normokalemic [4, 22, 23]. Since most of our patients were referred for further evaluation of adrenal incidentaloma or probable PA, it is possible that we are mainly dealing with "typical" APA. Therefore, it remains undetermined whether these factors could discriminate unilateral microadenoma (<8 mm) from macroadenoma (≥8 mm) detectable by CT scan. In fact, it has been reported that biochemical findings (serum potassium, ARR and PAC) in aldosterone-producing microadenoma (microAPA) were similar to those of IHA [17].

Therefore, AVS is the gold standard method to determine the laterality of aldosterone hypersecretion for subgrouping PA, but due to its invasive procedure, complication, technical difficulties and medical cost, we suggest that most PA patients, if not all, with a distinct unilateral adrenal lesion by CT scan accompanied by profound hypokalemia, younger age and poor response of PAC after FUP, may exempt AVS for PA subgrouping. Further larger scale prospective studies are required to establish more efficient algorithm including AVS for diagnosis and treatment of PA subgroup.

Acknowledgments

This study was supported in part by the Grant-in-aid from the Ministry of Education, Science, Sports and Culture, and the Ministry of Health, Welfare, and Labor of Japan.

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