Confirmatory Testing in Primary Aldosteronism

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Context: Although confirmatory testing to verify aldosterone excess is a key step in the diagnosis of primary aldosteronism (PA), there is no consensus as to whether it is always needed and which of the tests need to be performed.

Objective: The objective of this study was to investigate the diagnostic significance of confirmatory tests in PA.

Design and Patients: In group A, 120 hypertensive patients who had positive case detection using the aldosterone to renin ratio (ARR) were subjected to at least one confirmatory test: the captopril challenge test (CCT), furosemide upright test (FUT), or saline infusion test (SIT). Among group A, 57 patients underwent all three confirmatory tests (group B), and 57 patients were differentiated as having either unilateral or bilateral PA based upon adrenal venous sampling, adrenal scintigraphy, and/or adrenal surgery (group C).

Results: The percentages of patients with positive CCT and FUT were 86 and 87% in group A, 88 and 88% in group B, and 96 and 94% in group C, respectively. The percentage of patients with positive SIT results was lower than that with other tests ($P < 0.01$). The percentage of patients with positive results for the three tests was higher in patients with baseline ARR of at least 1000 or plasma aldosterone concentration (PAC) of at least 250 pg/ml than in those with lower ARR or PAC in all three groups.

Conclusions: Most patients with positive case detection also had positive results on the CCT and FUT, especially when ARR was at least 1000 or PAC was at least 250 pg/ml under renin suppresion. Confirmatory testing for PA may not be needed in all patients with positive case detection. **(*J Clin Endocrinol Metab* 97: 1688–1694, 2012)**

Primary aldosteronism (PA) is the most common cause of endocrine hypertension. Although PA was previously considered to afflict fewer than 1% of patients with hypertension (1, 2), studies using the aldosterone to renin ratio (ARR) as a case detection test (3) led to a marked increase in detection of PA (4), with the prevalence ranging from 3–20% of hypertensive patients (5–10). In addition, the rate of complications of the cardiovascular system, brain, and kidneys has been shown to be greater in patients with PA than in those with essential hypertension (11–13). Thus, early detection and initiation of appropriate treatment is essential to prevent target organ damage in patients with PA.

Several guidelines and algorithms for the diagnosis and treatment of PA have been proposed over the past 4 yr (14–18). The diagnostic steps include case detection testing, confirmatory testing, subtype classification, and localization. Patients with a positive case detection test are recommended to undergo confirmatory testing to either confirm or exclude the diagnosis of PA (14, 15, 18, 19).

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Abbreviations: ARR, Aldosterone to renin ratio; AUC, area under the curve; AVS, adrenal venous sampling; CCT, captopril challenge test; FUT, furosemide upright test; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ROC, receiver operating characteristic; SIT, saline infusion test.

The Endocrine Society's clinical practice guidelines recommend the use of any of four confirmatory testing procedures, oral sodium loading, saline infusion test (SIT), fludrocortisone suppression, and captopril challenge test (CCT), and state that there is currently insufficient direct evidence to recommend one of these over the others (14). Investigators at the Mayo Clinic recommend confirmatory testing and use the oral sodium loading test (15, 19). Mulatero and colleagues (18) in Italy recommend confirmatory testing with either SIT or oral sodium loading and use the fludrocortisone suppression test as an additional confirmatory test.

Guidelines for the detection of PA from both the Japanese Society of Hypertension (20) and the Japan Endocrine Society (21) suggest three types of confirmatory tests: CCT, the furosemide upright test (FUT), and SIT. However, there is little evidence as to which confirmatory tests are optimal to confirm PA.

In the present study, we investigated the diagnostic significance of confirmatory tests in hypertensive patients who had abnormal case detection testing based on ARR.

Patients and Methods

Patients

Hypertensive patients (n = 120) with elevated ARR [>200; plasma aldosterone concentration (PAC) in picograms per milliliter and plasma renin activity (PRA) in nanograms per milliliter per hour] in case detection testing were subjected to at least one of the three confirmatory tests (group A). Of the 120 patients, 57 were subjected to all three confirmatory tests (group B), and 57 were differentiated as having either unilateral or bilateral PA based upon adrenal venous sampling (AVS), adrenal scintigraphy, and/or adrenal surgery (group C). In group A, there was no significant difference in clinical characteristics, number of antihypertensive drugs used, serum potassium, prevalence of hypokalemia, PAC, PRA, or ARR among the patients who underwent the different confirmatory tests (CCT *vs.* FUT, CCT *vs.* SIT, or FUT *vs.* SIT).

Twenty-three patients in group B were not included in group C. Of these patients, 15 did not undergo AVS because they opted against surgical treatment. Although the remaining eight patients underwent AVS, the results did not meet the criteria for adequate catheterization or subtype classification described below in *Adrenal venous sampling*.

In group C, 34 patients were subjected to all three confirmatory tests, 12 patients were subjected to two confirmatory tests, and 11 patients were subjected to one confirmatory test. Of the 57 patients in group C, 34 patients were diagnosed as PA with unilateral lesion based upon the results of AVS and/or adrenal scintigraphy and underwent adrenalectomy, whereas 23 underwent medical treatment. Significant improvement in blood pressure and normalization of serum potassium, PAC, and PRA were achieved in all patients after adrenalectomy.

This retrospective study was approved by the institutional ethics review committee of Kyoto Medical Center.

Confirmatory testing

CCT (22–24), FUT (25), and SIT (26–28) were used as confirmatory tests according to the Guidelines of the Japanese Society of Hypertension (20) and the Japan Endocrine Society (21). Each confirmatory test was done after an overnight fast. Antihypertensive agents were replaced for at least 2 wk before testing with calcium channel antagonists or α-blockers to minimize interference with PAC, PRA, and ARR measurement in all but two patients. Angiotensin receptor blocker treatment to control blood pressure could not be discontinued in one patient. The other patient was taking a mineralocorticoid receptor antagonist for 1 yr, and this medication was withdrawn 3 wk before confirmatory testing. Hypokalemia was corrected by potassium supplementation before confirmatory testing. The cutoff values for each confirmatory test were based on the guidelines of Japan Endocrine Society for detection of PA (21).

For the CCT, patients received 50 mg captopril orally after lying in a supine position for at least 30 min. Blood samples were drawn for measurement of PAC and PRA before captopril administration (time zero) and at 60 and 90 min after captopril administration. The CCT was considered positive if the ARR was over 200 at 60 or 90 min after administration of captopril (21).

For the FUT, patients stayed in a supine position for at least 30 min before venipuncture was performed for measurement of basal PRA. Patients were then given an iv bolus injection of 40 mg furosemide. After 2 h in an upright posture, venipuncture was repeated for measurement of PRA after FUT. A positive FUT was defined as post-FUT PRA below 2 ng/ml · h (21).

For the SIT, patients were kept in a supine position for at least 30 min, and then venipuncture was performed for measurement of basal PAC. Then 2 liters of 0.9% NaCl was administered iv over 4 h and PAC was measured again. A positive SIT was defined as post-saline infusion PAC (PAC after SIT) over 60 pg/ml (21).

Adrenal venous sampling

AVS was performed to determine whether the site of aldosterone hypersecretion was unilateral or bilateral. Cosyntropin was used for AVS. Criteria for adequate catheterization in AVS were an adrenal venous cortisol concentration after cosyntropin administration of at least 200 μg/dl and an adrenal venous cortisol concentration after cosyntropin infusion at least five times the cortisol concentration in blood from the inferior vena cava (21). When the adrenal venous blood aldosterone/cortisol ratio was at least 2.6 after cosyntropin administration, a unilateral lesion was considered to be present on the high-value side (21).

Analysis

The positive rate for each confirmatory test was determined for groups A, B, and C and compared among groups. In addition, in group C, positive confirmatory test rates and respective cutoff values were compared between patients with unilateral PA and those with bilateral PA. All statistical analyses were performed using JMP version 5 (SAS Institute Inc., Cary, NC). Differences in measured parameters between groups were evaluated using the *t* test and χ^2 test. A P value <0.05 was considered significant.

TABLE 1. Characteristics of the study population

	Group A	Group B	Group C	Group A − B	Group A − C
n	120	57	57	63	63
Age (yr)	55 ± 12	52 ± 10	53 ± 10	58 ± 13[a]	57 ± 13[c]
Number of drugs	1.4 ± 0.9	1.2 ± 0.6	1.5 ± 0.9	1.5 ± 1.1	1.2 ± 0.9
Serum potassium (mEq/liter)	3.7 ± 0.5	3.8 ± 0.3	3.6 ± 0.5	3.6 ± 0.6	3.8 ± 0.5[c]
Prevalence of hypokalemia (%)	41	32	51	49[b]	33[c]
PAC (pg/ml)	241 ± 176	208 ± 105	271 ± 201	271 ± 219	215 ± 147
PRA (ng/ml · h)	0.3 ± 0.2	0.4 ± 0.2	0.3 ± 0.3	0.3 ± 0.2	0.3 ± 0.2
ARR	1330 ± 1787	1013 ± 1008	1482 ± 2013	1616 ± 2244	1192 ± 1559

Data are expressed as mean ± SD or proportion of patients (percentage). For group A, at least one confirmatory test was performed; for group B, all three confirmatory tests were performed; for group C, AVS, adrenal scintigraphy, and/or adrenal surgery were performed; for group A − B, one or two confirmatory tests were performed; and group A − C includes patients who were not differentiated as having either unilateral or bilateral PA by AVS, adrenal scintigraphy, and/or adrenal surgery. Hypokalemia refers to spontaneous hypokalemia.

[a] $P < 0.01$ *vs.* group B.

[b] $P < 0.05$ *vs.* group B.

[c] $P < 0.05$ *vs.* group C.

Results

Clinical characteristics of each group are summarized in Table 1. Hypokalemia was designated as serum potassium lower than 3.5 mEq/liter or if potassium supplementation was prescribed. Diuretic-induced hypokalemia was not included. Age and prevalence of hypokalemia were significantly higher ($P < 0.01$ and $P < 0.05$, respectively) in group A minus B than in group B. Age and serum potassium were significantly higher ($P < 0.05$) and the prevalence of hypokalemia was significantly lower ($P < 0.05$) in group A minus C than in group C.

Means ± SD for ARR after CCT were 1169 ± 1448 (range, 53–10,500) in group A, 850 ± 787 (range, 54–4640) in group B, and 1463 ± 1784 (range, 94–10,500) in group C. The means ± SD for PRA after FUT were 1.2 ± 1.4 ng/ml · h (range, 0.1–8.2) in group A, 1.0 ± 1.0 ng/ml · h (range, 0.1–4.2) in group B, and 1.1 ± 1.5 ng/ml · h (range, 0.1–8.2) in group C. The means ± SD for PAC after SIT were 111 ± 103 pg/ml (range, 14–458) in group A, 111 ± 108 pg/ml (range, 14–458) in group B, and 125 ± 128 pg/ml (range, 20–458) in group C. ARR after CCT was significantly higher ($P < 0.05$) in group C than in group B. There was no significant difference among the three groups in the other respective indexes for each confirmatory test.

Positive rates for each confirmatory test are shown in Table 2. The positive rates for CCT and FUT were more than 85% in both groups A and B, whereas that for SIT was less than 65% in both groups. In group C, the positive rates were more than 90% for CCT and FUT, but only 60% for SIT. Thus, the rate of positive results was lowest for SIT among all three groups.

Details on positivity rates for each confirmatory test in patients who underwent all three tests (group B) are as follows: 28 of 57 patients (49%) had positive findings on all three tests. Of the 21 patients who had positive results on two confirmatory tests, 20 of 57 patients (35%) showed positive results for FUT and CCT (but not SIT) and one of 57 (2%) showed positive results for FUT and SIT (but not CCT). None of the patients in this group showed positive results for CCT and SIT (but not FUT).

Correlations between basal ARR and prevalence of positive confirmatory test results are shown in Table 3. In each of the three patient groups, data were analyzed for those with ARR below 1000 and those with ARR of 1000 or higher. Positive confirmatory test results were more common in patients with ARR of 1000 or higher than in those with ARR below 1000 in all three groups. Furthermore, under renin suppression, the cutoff value of PAC of at least 250 pg/ml showed similar rates of positive results in confirmatory testing (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

In group C, 39 patients were diagnosed with unilateral PA, and 18 with bilateral PA by AVS, adrenal scintigra-

TABLE 2. Positive rates for each confirmatory test

	Group A	Group B	Group C
n	120	57	57
CCT	86% (102/119)	88% (50/57)	96% (54/56)
FUT	87% (69/79)	88% (50/57)	94% (43/46)
SIT	63%[a] (42/67)	60%[a] (34/57)	60%[a] (21/35)

[a] $P < 0.01$ *vs.* CCT or FUT.

TABLE 3. Positive rates for each confirmatory test in patients with ARR below 1000 and ARR of 1000 or higher

	Group A		Group B		Group C	
	ARR < 1000 (n = 73)	ARR ≥ 1000 (n = 47)	ARR < 1000 (n = 37)	ARR ≥ 1000 (n = 20)	ARR < 1000 (n = 34)	ARR ≥ 1000 (n = 23)
CCT	81% (58/72)	94%[a] (44/47)	87% (32/37)	90% (18/20)	94% (31/33)	100% (23/23)
FUT	82% (41/50)	97%[a] (28/29)	84% (31/37)	95% (19/20)	90% (27/30)	100% (16/16)
SIT	56%[b] (24/43)	75%[c] (18/24)	51%[b] (19/37)	75% (15/20)	48%[b] (11/23)	83%[a,d] (10/12)

[a] $P < 0.05$ *vs.* ARR < 1000.

[b] $P < 0.01$ *vs.* CCT or FUT.

[c] $P < 0.05$ *vs.* CCT or FUT.

[d] $P < 0.05$ *vs.* CCT.

phy, and/or adrenal surgery. The proportion of positive confirmatory test results was compared between patients with unilateral and bilateral PA (Table 4); there were no significant differences between these groups. However, the positive rate in SIT in 34 patients with the confirmed diagnosis of unilateral PA by adrenalectomy was comparable to that in CCT and FUT and significantly higher than that in patients with bilateral PA. In addition, ARR after CCT and PAC after SIT were significantly higher ($P < 0.01$) in patients with unilateral PA than in patients with bilateral PA (mean ± SD of ARR after CCT, 1904 ± 2012 *vs.* 533 ± 365; mean ± SD of PAC after SIT, 174 ± 151 *vs.* 61 ± 24 pg/ml, respectively). There was no significant difference in PRA after FUT between patients with unilateral and bilateral PA (1.2 ± 1.9 *vs.* 0.9 ± 0.6 ng/ml · h) (Fig. 1). Two patients in the unilateral PA group showed negative results for FUT. In one of these patients, angiotensin receptor blocker was used to control blood pressure and could not be discontinued, and the other patient took a mineralocorticoid receptor antagonist for 1 yr until 3 wk before confirmatory testing.

We further assessed the validity of ARR after CCT and PAC after SIT as predictors of PA subtype (unilateral or bilateral adrenal disease). Receiver operating characteristic (ROC) curve analysis was performed to find the optimal cutoff value for diagnosis of unilateral PA (Fig. 2). An ARR after CCT value of 990 had a sensitivity of 55.3% and specificity of 94.4%, and a value of 1720 had 44.7% sensitivity and 100.0% specificity [area under the curve (AUC) = 0.784]. A PAC after SIT value of 109 pg/ml had a sensitivity of 55.0% and specificity of 100.0% (AUC = 0.738).

Discussion

Confirmatory testing is an important step for hypertensive patients with positive case detection testing for PA by ARR. The aim of confirmatory testing is to assure the autonomous secretion of aldosterone and thus to confirm the diagnosis of PA. There is no consensus as to a single optimal confirmatory test for PA analogous to the dexamethasone suppression test for Cushing's syndrome. Instead, multiple confirmatory tests based upon different principles and underlying mechanisms have been used: CCT (22–24), FUT (25), SIT (26–28), the oral salt loading test (14, 15), fludrocortisone suppression test (14), and rapid ACTH test (25). Protocols involving either single or multiple confirmatory tests vary by location and institution. The Endocrine Society Guidelines recommend the use of either the oral sodium loading test, SIT, fludrocortisone suppression test, or CCT (14). However, there is no consensus as to which confirmatory tests should be used to confirm PA.

CCT, FUT, and SIT are the confirmatory tests recommended by the Japanese Society of Hypertension (20) and Japan Endocrine Society (21). In CCT, PAC remains elevated and PRA remains suppressed in patients with PA,

TABLE 4. Positive rates for each confirmatory test in patients with unilateral PA and bilateral PA in Group C

	Unilateral PA		
	All patients (n = 39)	Operated patients (n = 34)	Bilateral PA (n = 18)
CCT	97% (37/38)	97% (32/33)	94% (17/18)
FUT	93% (27/29)	92% (22/24)	94% (16/17)
SIT	70%[a,b] (14/20)	81%[d] (13/16)	47%[c] (7/15)

[a] $P < 0.01$ *vs.* CCT.

[b] $P < 0.05$ *vs.* FUT.

[c] $P < 0.01$ *vs.* CCT or FUT.

[d] $P < 0.05$ *vs.* bilateral PA.

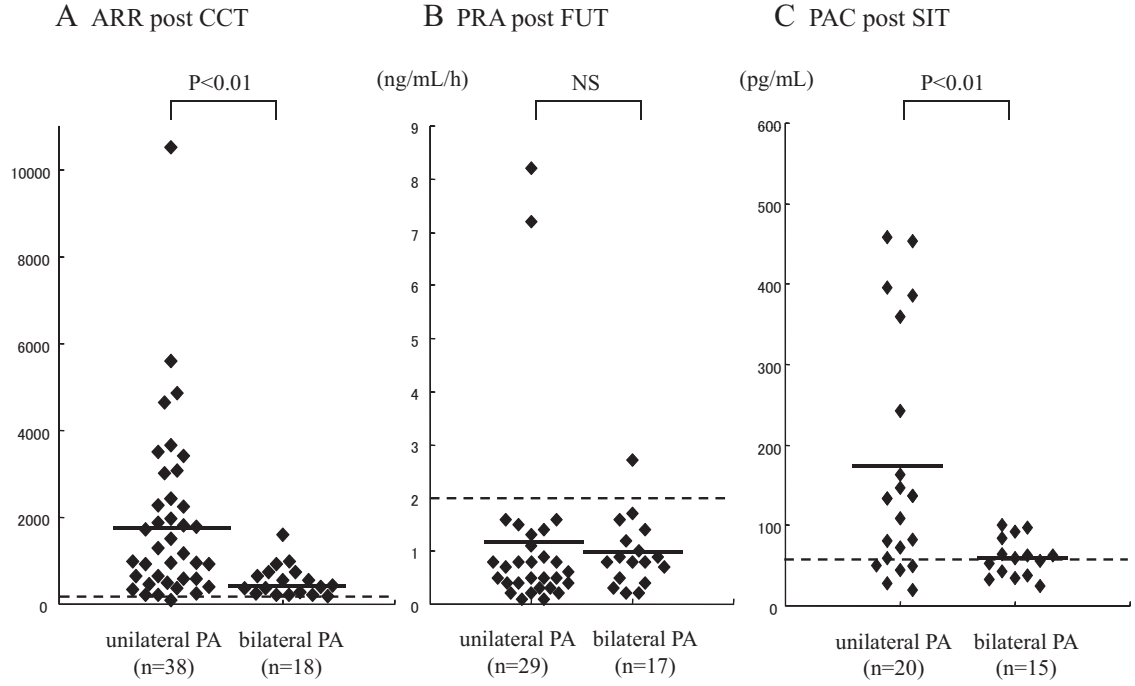

FIG. 1. Comparison of indexes for each confirmatory test among patients with unilateral and bilateral PA in group C. Panel A, ARR after CCT; means ± SD of ARR post CCT were 1904 ± 2012 for unilateral PA and 533 ± 365 for bilateral PA ($P < 0.01$). Panel B, PRA after FUT; means ± SD of PRA after FUT were 1.2 ± 1.9 ng/ml · h for unilateral PA and 0.9 ± 0.6 ng/ml · h for bilateral PA [not significant (NS)]. Panel C, PAC after SIT; means ± SD of PAC after SIT were 174 ± 151 pg/ml for unilateral PA and 61 ± 24 pg/ml for bilateral PA ($P < 0.01$). *Black lines* indicate the mean values. *Dashed lines* indicate the cutoff values for each confirmatory test.

whereas PAC is suppressed in normal subjects (14). The diagnostic significance of CCT has been demonstrated in a number of previous studies (22–24, 29), although the sensitivity and specificity varied depending on the biochemical markers and cutoff points used, and a substantial number of false-positive and false-negative results have been reported (30, 31). Although FUT indirectly detects excess plasma aldosterone through suppression of plasma renin, it has been used as a confirmatory test for the diagnosis of PA in Japan (25). SIT has been used widely for diagnosis of PA. Plasma aldosterone is suppressed in normal subjects but not in patients with PA. Rossi *et al.* (31) demonstrated that a PAC of 6.75 ng/dl after SIT was the optimal cutoff for diagnosis of aldosterone-producing adenoma, resulting in 82.6% sensitivity and 75.1% specificity. In another study, a PAC of 5 ng/dl after SIT used as a cutoff showed 88.0% sensitivity and 88.0% specificity for diagnosis of PA (28).

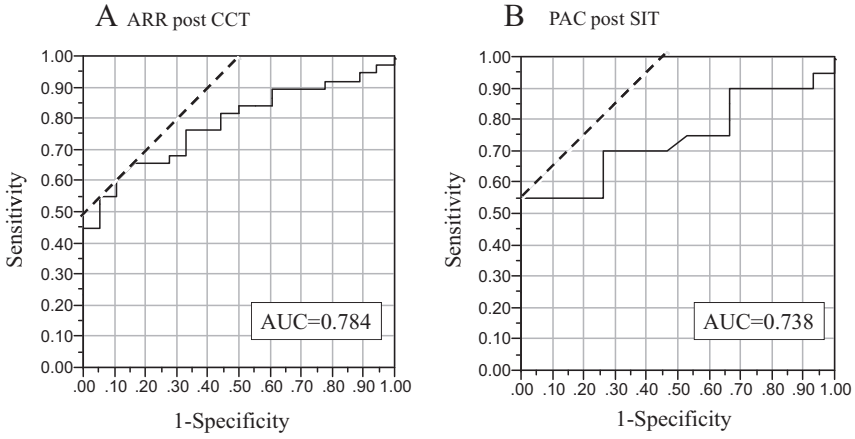

FIG. 2. ROC curve for ARR after CCT and PAC after SIT for the diagnosis of unilateral PA in group C. Panel A, ROC curve for ARR after CCT (AUC = 0.784); panel B, ROC curve for PAC after SIT (AUC = 0.738). An ARR after CCT value of 990 had 55.3% sensitivity and 94.4% specificity, and a value of 1720 had 44.7% sensitivity and 100.0% specificity. A PAC after SIT value of 109 pg/ml had 55.0% sensitivity and 100.0% specificity. *Dashed lines* are drawn at a 45° angle tangent to the ROC curve.

In the present study, we investigated the proportion of patients with positive findings on three confirmatory tests (CCT, FUT, and SIT) in three patient groups. The proportion of positive results for CCT and FUT was more than 85%. In contrast, less than 65% of patients had positive results on the SIT, and this proportion was significantly lower than for CCT and FUT in all three patient groups ($P < 0.01$). Although the mechanisms responsible for the low sensitivity of SIT remain unknown, it could be attributed at least in part to the retrospective study design; patients with severe hypertension, cardiovascular complications including congestive heart failure, or untreated hypokalemia

were not subjected to SIT in the present study, leading to selection bias. The relatively high dietary salt intake in the Japanese population could affect SIT results. Another factor that should be taken into account is the subtype of PA. In the present study, the positive rate in SIT in surgically confirmed unilateral PA was comparable to that in CCT and FUT and significantly higher ($P < 0.05$) than that in patients with bilateral PA (Table 4). The results agree with the previous study by Rossi *et al.* (31), in which both CCT and SIT were shown to be sensitive tests for the identification of aldosterone-producing adenoma, and their accuracy did not significantly differ under adequate sodium intake conditions. Although SIT is one of the most popular confirmatory tests for PA, the test duration of over 4 h in addition to various adverse effects on the cardiovascular function and/or electrolyte metabolism limits its application in general practice.

The majority of the hypertensive patients with positive ARR also showed positive results on confirmatory tests for PA, supporting the idea that one test is sufficient for confirmation of PA. The similar findings for CCT and FUT in all three patient groups suggest that one of these two tests rather than both is sufficient to confirm PA. For practical purposes, CCT is preferable to FUT because of the potential adverse effects of FUT (*e.g.* orthostatic hypotension associated with volume contraction and aggravation of hypokalemia). Furthermore, the number of confirmatory tests could be minimized in patients with basal ARR of at least 1000 and PAC of at least 250 pg/ml under renin suppression.

The subtype classification of PA into unilateral or bilateral adrenal PA determines the course of therapy. Multiple methods have been reported for achieving subtype classification. In the present study, there was no significant difference between unilateral and bilateral PA in the proportion of patients with positive findings on the CCT and FUT (Table 4). However, the positive rate in SIT was significantly higher in those surgically confirmed unilateral PA than patients with bilateral PA. In addition, ARR after CCT and PAC after SIT were significantly higher ($P < 0.01$) in patients with unilateral PA than in patients with bilateral PA. ROC curve analysis for the diagnosis of unilateral PA showed that an ARR after CCT value of 990 had 55.3% sensitivity and 94.4% specificity and a value of 1720 had 44.7% sensitivity and 100.0% specificity. A PAC after SIT value of 109 pg/ml showed 55.0% sensitivity and 100.0% specificity. Taking all these together, the degree of abnormality of confirmatory test appears to be somewhat predictive in determining the subtype of PA. The extent of overlap between the subtypes, however, would limit its usefulness and would not permit substitution for AVS in subtype classification and lateralization of the side of PA before surgery, even in those patients highly likely to have unilateral PA.

In conclusion, CCT and FUT performed optimally as confirmatory tests for PA. The proportion of patients with positive confirmatory test results was high among those with ARR of at least 1000 and PAC of at least 250 pg/ml under renin suppression. The SIT appears to be a suboptimal confirmatory test relative to the CCT and FUT. In view of our findings, we suggest that confirmatory testing for PA could be minimized to one test to reduce time, cost, and risk for patients. However, because these studies were conducted in Japanese patients, additional studies in other populations as well as those using a prospective study design are needed to determine which confirmatory test is best for the diagnosis of PA.

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