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Aldosterone to Potassium Ratio after Adrenocorticotropin Stimulation in Unilateral Primary Aldosteronism Diagnosis

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Abstract

Background: It is important to identify patients with primary aldosteronism (PA) who have a high possibility of having aldosterone-producing adenoma (APA). However, the usefulness of the adrenocorticotropic hormone (ACTH) stimulation test for such purposes is controversial. This study aimed to evaluate the diagnostic accuracy of the ACTH stimulation test, corrected for serum potassium concentration, in the identification of unilateral lesion among patients with PA.

Methods: Seventy-nine patients with PA admitted to three medical centers were included in the study. ACTH stimulation tests and saline infusion tests (SITs) were performed. Plasma aldosterone concentration (PAC) was examined at 0, 30, and 60 min following ACTH stimulation and at 240 min following SIT. Receiver operator characteristic curve analysis was used to evaluate the diagnostic accuracy. Medical records were reviewed retrospectively.

Results: The area under the curve (AUC) at 240 min following SIT was 0.920, and the optimal cut-off value was 133.7 pg/mL, with a sensitivity of 92.3% and a specificity of 93.1%. For the ACTH stimulation test, the AUCs for the PAC-to-potassium concentration ratio at 0, 30, and 60 min were 0.979, 0.984, and 0.971, respectively. The most effective parameter for predicting unilateral lesion suggesting APA was the PAC-to-potassium

concentration ratio at 30 min, with a sensitivity of 100% and a specificity of 95.5%.

Conclusion: These results show that the PAC-to-potassium concentration ratio at 30 min in the ACTH stimulation test, as well as the PAC at 240 min in the SIT, is an excellent and practical indicator for identifying unilateral lesion in patients with PA.

抄録

背景：原発性アルドステロン症（PA）の症例で、アルドステロン産生腺腫（APA）の可能性が高い患者を同定することは重要である。但しその方法としての迅速副腎皮質刺激ホルモン（ACTH）刺激試験の有用性については議論の余地がある。本研究では迅速 ACTH 刺激試験の血漿アルドステロン値を血清 K 濃度で補正することによる APA を示唆する片側性病変の診断精度を評価することを目的とした。

方法：3 医療施設に入院し、迅速 ACTH 刺激試験と生理食塩水注入試験（SIT）を実施された PA 患者 79 人を対象とした。迅速 ACTH 刺激試験の 0、30、60 分の血漿アルドステロン濃度（PAC）および SIT 240 分の PAC を解析に用いた。診断精度の評価には受信者操作特性(ROC)曲線を使用した。データは後ろ向きに収集した。

結果：SIT 240 分の曲線下面積（AUC）は 0.920 であった。最適カットオフ値は 133.7 pg / mL で、感度 92.3%、特異度は 93.1%であった。 迅速 ACTH 刺激試験では、0、30、60 分の PAC/K の AUC は、それぞれ 0.979、0.984、および 0.971 であった。 APA を示唆する片側性病変の予測に最適であった指標は、30 分での PAC/K で、感度は 100%、特異性は 95.5%だった。

結論：迅速 ACTH 刺激試験での 30 分での PAC/K、および SIT での 240 分での PAC が、PA 患者において片側性病変を鑑別するのに優れた、実用的な指標であることが示唆された。

Ⅰ Introduction

Primary aldosteronism (PA), characterized by autonomous aldosterone hypersecretion and resultant renin suppression, is the most common cause of secondary hypertension and causes frequent cardiovascular complications[1)2)]. There are two major types of PA: aldosterone-producing adenoma (APA), which arises from the adrenal cortex, and idiopathic aldosteronism (IHA), which is caused by hyperplasia of the adrenocortical globular layer. It is critically important to determine whether aldosterone hypersecretion from the adrenal glands is unilateral or bilateral, because the therapeutic approach differs based on laterality [3)4)].

PA is suspected in cases of juvenile hypertension, treatment-resistant hypertension, hypokalemia, or an incidental adrenal mass lesion. Because PA accounts for 5–10% of all hypertension cases[5)6)], many endocrinologists believe that PA screening should be performed in all patients diagnosed with hypertension. In 1981, our laboratory proposed that the aldosterone-to-renin ratio could help screen for PA, and its utility has been recognized around the world[7)]. By using the aldosterone-to-renin ratio, we identified patients who should proceed with confirmatory tests such as the captopril test[3)8)9)], saline infusion test (SIT) [3)8)-10)], upright furosemide test[8)9)], and ACTH stimulation test[11)12)].

As aldosterone overproduction is an underlying pathophysiology of PA, aldosterone antagonists are effective for treatment. In cases of hypersecretion from the bilateral adrenal

glands, it is essential to continue treatment with aldosterone antagonists throughout the patient's lifetime. However, in cases of unilateral hypersecretion, most of which are cases of APA, surgical adrenalectomy of the affected side is recommended as a curative treatment.

Therefore, in medical practice, it is extremely important to identify both patients with PA among ubiquitous hypertensive patients, as well as those with a high possibility of unilateral lesion. In patients in whom a diagnosis of unilateral aldosterone hypersecretion is unclear, adrenal vein sampling (AVS) is strongly recommended to determine the laterality of the lesion. However, implementation of AVS requires technical skill and is invasive and involves substantial costs[13)14)]. Although it has recently been reported that SIT is useful not only as a confirmatory test of PA but also for the identification of unilateral PA[15)], the SIT has technical limitations including increasing plasma volume and being time-consuming[13)14)23)]. On the other hand, it has been reported that the ratio of PAC to potassium after ACTH loading in the ACTH loading test at the first visit to the hospital may be useful in diagnosing unilateral PA lesions.[12)] Therefore, it was estimated that the ratio of PAC to potassium after loading before testing in the rapid ACTH loading test might be useful for diagnosing unilateral lesions. Thus, we aimed to discover a novice clinical index with high diagnostic accuracy, and compare the diagnostic ability for unilateral PA lesions between SIT and the new index we found.

Ⅱ Materials and Methods

We assessed 79 patients with PA who underwent AVS after an ACTH stimulation test and SIT between April 2010 and March 2019 at Shinshu University Hospital, Nagano Municipal Hospital, and Ina Central Hospital, Japan. Fig. 1 illustrates the patient flow chart. Two patients were excluded because aldosterone antagonists were taken at the time of AVS. Five patients were excluded due to unsuccessful adrenal vein cannulation. Thus, 72 patients were included and assessed. We diagnosed PA following guidelines from the Japan Endocrine Society[16] and the Japan Society of Hypertension [9]. We screened for PA based on a value of >200 for the plasma aldosterone concentration (PAC: pg/ml)-to-plasma renin activity (ng/mL/hr) or a value of >40 for the PAC-to-active renin concentration (pg/ml). PA was diagnosed based on at least one positive result from the confirmatory tests, which included the captopril challenge test, the SIT, the upright furosemide test, and the oral salt loading test[3)9)17)]. Patients who had received prescriptions for antihypertensive drugs related to the renin angiotensin system were placed on calcium channel-blockers and α-adrenergic-blockers until 2 weeks (ACE inhibitor and ARB) or 4 weeks (aldosterone blocker) before the diagnostic tests were performed. Serum potassium levels at the time of diagnosis were measured routinely. In addition, serum potassium levels were measured within 24 hours of the start of the ACTH stimulation test in 39 patients. Hypokalemia was defined as a serum potassium concentration of <3.5 mEq/L before or at diagnosis of PA or if a patient was taking

a potassium supplement. If hypokalemia was present, we supplied the patient with oral potassium tablets.

A Assay methods

PAC was measured using commercial radioimmunoassay kits (SPAC-S Aldosterone Kit; Fuji Lebio, Tokyo, Japan) at Shinshu University Hospital until May 8, 2018, and at all other centers throughout the study. From May 9, 2018, PAC was measured using commercial chemiluminescence enzyme immunoassay kits (Accuraseed Aldosterone Kit; Wako Pure Chemical Industries, Osaka, Japan) at Shinshu University Hospital. The new method showed good correlation compared to the previous method ($r = 0.867$).

B SIT

Patients who had uncontrolled hypertension with medicine or had suspected heart failure did not undergo an SIT. In the remaining patients, the SIT was carried out as follows: 1) Tests were performed before breakfast; 2) Patients started this test from 8:00 AM after 30 min of lying in a supine position; 3) After drawing a blood sample, we infused 2 liters of saline for 4 hours into the patients; 4) At the end of the infusion, we obtained a blood sample; 5) During the test, we asked the patients to stay in a supine position, and we monitored blood pressure and symptoms. Patients who were receiving potassium supplementation took the potassium

after the test.

C ACTH stimulation test

We performed the test as follows: 1) Tests were performed before breakfast; 2) Patients started this test at 8:00 AM after lying in a supine position for 30 min, and we obtained a blood sample at the start; 3) Patients were given 250 μg of cosyntropin by intravenous injection; 4) blood samples were obtained at 30 min and 60 min after the injection; 5) patients were lying in the supine position during the test. Patients who were receiving potassium supplementation took the potassium after the test.

D Dexamethasone test

ACTH stimulation tests in this study did not include dexamethasone loading before testing. We performed a 1 mg dexamethasone loading test on another day.

E AVS diagnostic criteria

Patients with confirmed PA who wanted to undergo surgery underwent thin-slice contrast-enhanced computed tomography (CT) and AVS with ACTH stimulation. We diagnosed the subtype of PA based on the AVS results. Adrenal vein cannulation was defined as successful if the selectivity index was >5 [18]. The selectivity index was defined as the ratio of cortisol

concentration in the adrenal vein to that in the inferior vena cava. A lateralization index (LI) of >4 from AVS was used to define the presence of unilateral hyperaldosteronism[19]. The LI was calculated by dividing the aldosterone-to-cortisol ratio (A/C) on the dominant side by that on the nondominant side. All patients who did not meet the criteria of unilateral hypersecretion were considered to have bilateral hypersecretion of aldosterone.

F Statistical methods

We assessed the diagnostic accuracy of several outcomes using a receiver operating characteristic (ROC) curve analysis, and we calculated the area under the curve to determine the best level for determining the subtype. Statistical analyses were performed using EZR statistical software (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [20]. Continuous variables were expressed as median values and interquartile ranges. Categorical variables were expressed as numbers and percentages. Patient characteristics were compared between unilateral and bilateral lesions. We analyzed continuous variables using the Mann-Whitney U test and categorical variables using the Fisher exact test: i.e. the Mann-Whitney U test was used for age, body mass index, systolic blood pressure, diastolic blood pressure, initial PAC, serum potassium and eGFR, and the Fisher exact test was used for sex and pottasium supplement. A p-value <.05 was considered statistically significant.

The study protocol was approved by the ethics committees of our hospitals in

accordance with the Declaration of Helsinki. Informed consent from the patients was obtained using the opt-out method.

Ⅲ Results

A Baseline characteristics

Patient characteristics are summarized in Table 1. Patients were classified as having either unilateral or bilateral PA based on the AVS findings. In the unilateral group, initial PAC was higher and initial potassium concentration was significantly lower than that in the bilateral group. The number of patients who needed potassium supplementation was also higher in the unilateral group. Table 2 shows the adrenal CT findings by group. In the unilateral group, 23 of 27 patients exhibited unilateral adrenal tumors >8 mm in diameter. Nineteen out of 45 patients had no abnormalities on the CT scan.

B SIT and AVS results

PAC after 240 min of saline infusion (PAC_{240}) is reported to be a good indicator for discrimination of unilateral and bilateral hypersecretion of aldosterone[19]. As shown in Fig. 2A, PAC_{240} was significantly higher in the unilateral group. Fig. 2B shows the ROC for PAC_{240} indicating unilateral hypersecretion of aldosterone, suggesting APA. The AUC of PAC_{240} was 0.920 and the optimal cut-off value for PAC_{240} was 133.7 pg/mL, with a

sensitivity of 92.3% and a specificity of 93.1%. Thus, this was consistent with previous results[21)22)], indicating that PAC_{240} was a useful parameter for discriminating between unilateral and bilateral aldosteronism.

C ACTH stimulation test

The rapid ACTH stimulation tests were performed among 58 patients with PA. Fig. 3 shows the serial change of PAC, PAC/cortisol, and PAC/potassium during the ACTH stimulation test. The values in the unilateral group were higher than those in the bilateral group at all time points. Upon stimulation with ACTH, PAC values increased in both groups, and the unilateral group exhibited a high concentration of PAC at 0, 30, and 60 min following ACTH stimulation (Fig. 4A-C). When we examined the PAC-to-cortisol ratio (PAC/cortisol), the values in both groups after ACTH stimulation were distinct (Fig. 4D-F), and the curve for the unilateral group was higher at all time points. When we plotted the PAC-to-basal potassium concentration ratio, the between-group difference was more evident (Fig. 4G-I).

D ROC curve analysis of the ACTH stimulation test for distinguishing between unilateral and bilateral primary aldosteronism

We next analyzed ACTH stimulation data using an ROC curve analysis for PAC, PAC/cortisol, and PAC/potassium at each time point (PAC_0, PAC_{30}, and PAC_{60} at 0, 30, and

60 min, respectively). The AUC for PAC was larger after ACTH stimulation, and the AUCs for PAC_0, PAC_{30}, and PAC_{60} were 0.888, 0.926, and 0.948, respectively (Fig. 5A-C). Figures 5D-F illustrate ROC curves for PAC/cortisol during the ACTH stimulation test. The AUCs for PAC_0/cortisol, PAC_{30}/cortisol, and PAC_{60}/cortisol were 0.887, 0.888, and 0.922, respectively. These findings suggest that contrary to a previous report [22], PAC/cortisol did not improve the AUC in comparison with PAC alone. In contrast, the PAC/potassium ratio was an excellent parameter for discriminating unilateral primary aldosteronism from bilateral primary aldosteronism. As shown in Fig. 5G-I, the AUCs of PAC_0/potassium, PAC_{30}/potassium, and PAC_{60}/potassium were 0.979, 0.984, and 0.971, respectively. The most effective parameter appeared to be PAC_{30}/potassium, with a sensitivity of 100% and a specificity of 95.5%. This result suggests that unilateral primary aldosteronism can be completely excluded and a diagnosis of bilateral primary aldosteronism confirmed if PAC_{30}/potassium is less than the cutoff value of 136.8 pg/mEq. Fig. 5 shows the ROC and indicates the sensitivity, specificity, and cutoff value for each time point. It should be noted that use of the potassium value before potassium supplementation resulted in a PAC_0/initial potassium that was a relatively weak parameter, with an AUC of 0.912, sensitivity of 88.5%, specificity of 84.1%, and cutoff value of 48.58 pg/mEq. Therefore, potassium supplementation is required for hypokalemia.

E ROC curve analysis of PAC and potassium for distinguishing between unilateral and bilateral primary aldosteronism

We next compared the initial PAC, PAC 0 min in ACTH stimulation tests, initial potassium, and corrected potassium before the ACTH stimulation test in the patients with bilateral and unilateral PA. The AUC for PAC before the ACTH stimulation test was similar to the initial PAC, but the AUC for corrected potassium was larger than that for initial potassium. AUCs for the initial PAC, PAC 0 min in ACTH stimulation tests, initial potassium, and corrected potassium were 0.918, 0.888, 0.907, and 0.953, respectively.

F Comparison of ROC curves for PAC_{240} after SIT and PAC_{30}/potassium after ACTH stimulation

We performed both SIT and ACTH stimulation tests on 22 patients. Thus, we directly compared ROC curves of PAC_{240} after SIT and PAC_{30}/potassium after the ACTH stimulation test (Fig. 5); AUCs were 0.929 and 0.964, respectively ($p = 0.627$).

Ⅳ Discussion

This study identifies a simple, useful indicator that distinguishes cases of unilateral aldosterone hypersecretion in patients with PA. Namely, in patients with PA for whom

hypokalemia exists after potassium is used to normalize potassium concentrations, unilateral adrenal lesions can be diagnosed by dividing the PAC_{30} by the potassium concentration following ACTH stimulation; this approach has a sensitivity of 100% and a specificity of 95.5%.

SIT has long been used to diagnose PA[15)21)] as intravenous injections do not sufficiently suppress PAC in patients with PA. Furthermore, in recent years, such an approach has also been proposed for the diagnosis of APA, as there is less PAC suppression than in IHA[21)22)]. The present study confirms that SIT is useful for diagnosing unilateral lesions. PAC_{240} in the SIT had a cutoff value of 133.7 pg/mEq, sensitivity of 92.3%, and specificity of 93.1%. However, SIT has two disadvantages compared to the ACTH stimulation test in that first, there is some risk of increased plasma volume and second, it is time-consuming[13)14)23)].

The ROC curve analysis showed that PAC_0/potassium at the start of the ACTH stimulation test is also a good indicator, with a sensitivity of 94.1%, a specificity of 95.5%, and a cutoff value of 73.3 pg/mEq. The higher test accuracy gained by considering potassium in relation to PAC_0 indicates that aldosterone secretion is affected by the concentration of potassium at that time: potassium directly stimulates aldosterone secretion via cell membrane depolarization[24)]. Generally, in APA, autonomic aldosterone secretion is higher than that in IHA[25)], but the potassium concentration decreases due to the action of aldosterone, and the apparent concentration of PAC decreases. As a result, there may be cases where it is difficult

to distinguish APA from IHA; therefore, use of only PAC without consideration of potassium levels may result in misidentification.

In APA, ACTH stimulates aldosterone secretion [24], and diurnal fluctuation of ACTH often leads to diurnal fluctuation of PAC [26]. Building on these data, reports show that ACTH stimulation test results can be used to distinguish APA from IHA[12)23)26)-28)]. Furthermore, we considered that it would be better to correct the PAC value relative to cortisol levels. Moreover, Sonoyama *et al.* proposed an ACTH stimulation test wherein dexamethasone was used to suppress endogenous ACTH secretion beforehand[11)]; however, Inoue *et al.* reported that dexamethasone pre-administration did not improve diagnostic ability[29)]. Umakoshi *et al.* argued that the accuracy of the ACTH stimulation test was lower than that of SIT, and the usefulness of the ACTH stimulation test is still under discussion[30)]. However, as we clarified in the current study, the significance of the ACTH stimulation test is largely affected by correction for potassium concentration.

Twenty-two of the present patients underwent both SIT and ACTH stimulation tests. We performed an ROC curve analysis for each of these patient groups. While there was no statistical difference between the two in terms of index, PAC_{30}/potassium had higher sensitivity and specificity. Accordingly, we believe that both approaches have the same ability to distinguish unilateral lesion. However, SIT has disadvantages in that the saline load given to patients with PA leads to heart failure in some cases and the test takes over 4 hours to

complete [31]. Therefore, we conclude that it is better to perform an ACTH stimulation test rather than SIT.

Simple abdominal CT is an important examination in the process of PA diagnosis and treatment policy decisions. In the present study, all 27 patients with unilateral lesions diagnosed by AVS had abnormal adrenal glands. However, there were three cases in which CT showed bilateral lesions, and there were no cases in which aldosterone hypersecretion was observed on the side contralateral to where the mass was confirmed. Nonetheless, it is important to remember that a clear mass on CT does not clearly indicate it as the cause of aldosterone hypersecretion[31].

The limitation of this study is that not all cases were able to undergo both the ACTH stimulation test and SIT, so the number of cases was insufficient to directly compare the two approaches. Furthermore, to clarify and extend these findings, it is necessary to define protocols in advance and collect data at multiple facilities. In this study, SIT was performed in the supine position, but the results may be different if performed in the sitting position[32]. In addition, unilateral or bilateral determination was made based on AVS alone, so a small APA may have been missed due to insufficient pathological examination in non-operative cases. Moreover, because the AVS diagnostic criteria were based solely on criteria after ACTH loading, some APAs may have been missed[33]. Finally, this study may include indication bias by treatment because AVS was performed only on patients who wanted

surgery according to guidelines[8)9)16)].

In conclusion, we showed that PAC_{30}/potassium following an ACTH stimulation test in patients with PA is an excellent indicator to screen for unilateral lesions. Furthermore, we confirmed that the PAC_{240} in the SIT is also a good indicator. Both indicators exhibited good sensitivity and specificity. For diagnosis of unilateral PA, the ACTH stimulation test seems to be appropriate in consideration of safety and required time.

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Table

Table 1　Baseline characteristic

Charactaristics	Total (n=72)	Unilateral (n=27)	Bilateral (n=45)	p value
Age, years	51 (41.8-57)	54 (44-60)	51 (41-54)	0.094
Male, n (%)	31 (43.1)	11 (40.7)	20 (44.4)	0.81
Body mass index, kg/m^2	24.5 (22.0-28.9)	24.2 (21.3-25.8)	25.0 (22.4-30.5)	0.147
Systolic blood pressure, mmHg	138 (128.8-150)	136 (129-148)	141 (129-153)	0.396
Diastolic blood pressure, mmHg	85 (77-93)	81 (77-88)	86 (77-98)	0.188
Initial PAC, pg/ml	177.4 (127.8-309.2)	376.3 (251.9-553.3)	138 (96.8-179.9)	<0.001
Serum potassium, mEq/l	3.7 (3.2-4)	3.1 (3-3.45)	4 (3.7-4.1)	<0.001
Pottasium supplement n (%)	15 (20.8)	12 (44.4)	3 (6.7)	<0.001
eGFR, ml/min/1.73 m^2	78 (69-87)	73 (64.2-87)	78 (70-88)	0.254

Data are presented as median (interquartile range) unless otherwise indicated. PAC:Plasma aldosterone concentration. eGFR; estimated glomerular filtration rate

Table 2　Localization of CT findings and diagnosis by AVS

CT findings	Diagnosis by AVS	
	Unilateral(n=27)	Bilateral(n=45)
Not found	0	19
Unilateral tumor (<8 mm)	1	4
Unilateral tumor (≧8 mm)	23	20
Bilateral tumor or swelling	3	2

Figure legends

Fig. 1 Study flow chart

AVS: adrenal vein sampling

Fig. 2 A, Box plot of PAC values at 240 min in the SIT of patients with bilateral and unilateral lesions (n = 42). B, ROC curve of PAC values at 240 min in the SIT for differential diagnosis of bilateral and unilateral lesions. Data points represent the Youden index cutoff (specificity, sensitivity). PAC: plasma aldosterone concentration; SIT: saline infusion test; ROC, receiver operator characteristic; AUC: area under the curve

Fig. 3 Time course of the ACTH stimulation test. PAC (A, n = 58), PAC/COR (B, n = 58), and PAC /potassium (C, n = 39). Data are presented as medians.

PAC: plasma aldosterone concentration; COR: plasma cortisol concentration (μg/dL)

Fig. 4 Box plot of values of PAC at 0 min (A), PAC/COR at 0 min (B), PAC/potassium at 0 min (C), PAC at 30 min (D), PAC/COR at 30 min (E), PAC/potassium at 30 min (F), PAC at 60 min (G), PAC/COR at 60 min (H), and PAC/potassium at 60 min (I) in ACTH stimulation tests of patients with bilateral and unilateral lesions.

PAC: plasma aldosterone concentration; COR: plasma cortisol concentration (μg/dL)

Fig. 5 ROC curve for PAC at 0 min (A), 30 min (B), and 60 min (C); PAC/COR at 0 min (D), PAC/COR at 30 min (E), PAC/COR at 60 min (F), PAC/potassium at 0 min (G), PAC/potassium at 30 min (H), and PAC/potassium at 60 min (I) for differential diagnosis of bilateral and unilateral lesions in patients with PA. Data points represent the Youden index cutoff values (specificity, sensitivity). ROC: receiver operator characteristic; PAC: plasma aldosterone concentration; COR: plasma cortisol concentration (μg/dL)

Fig. 1

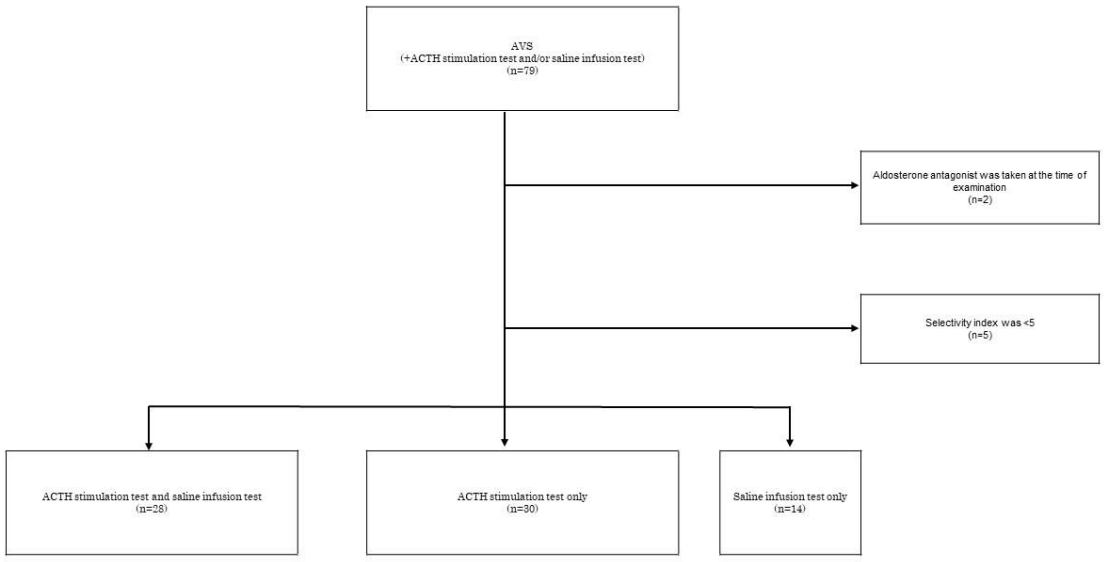


Fig. 2

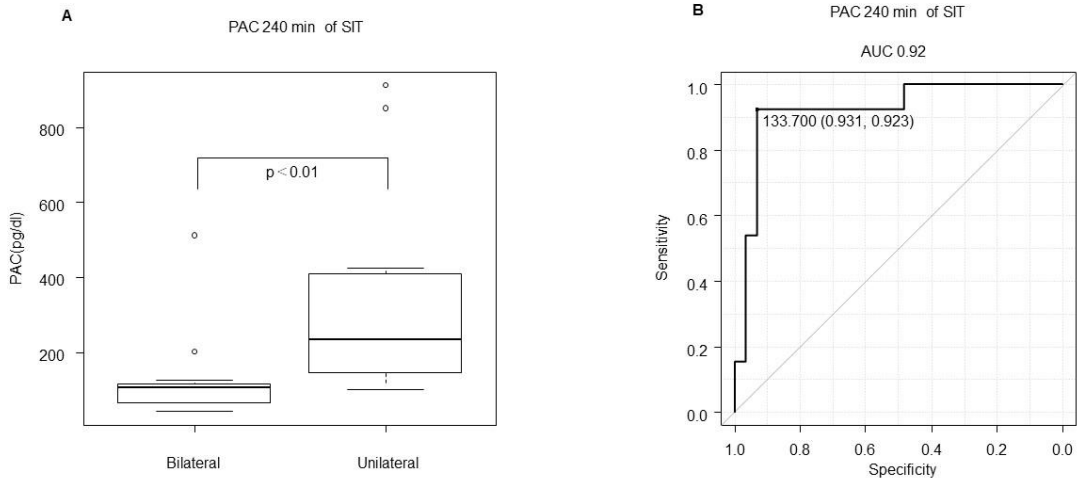

A
PAC 240 min of SIT
PAC(pg/dl)
800
600
400
200
p < 0.01
Bilateral
Unilateral
B
PAC 240 min of SIT
AUC 0.92
Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
133.700 (0.931, 0.923)
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

Fig. 3

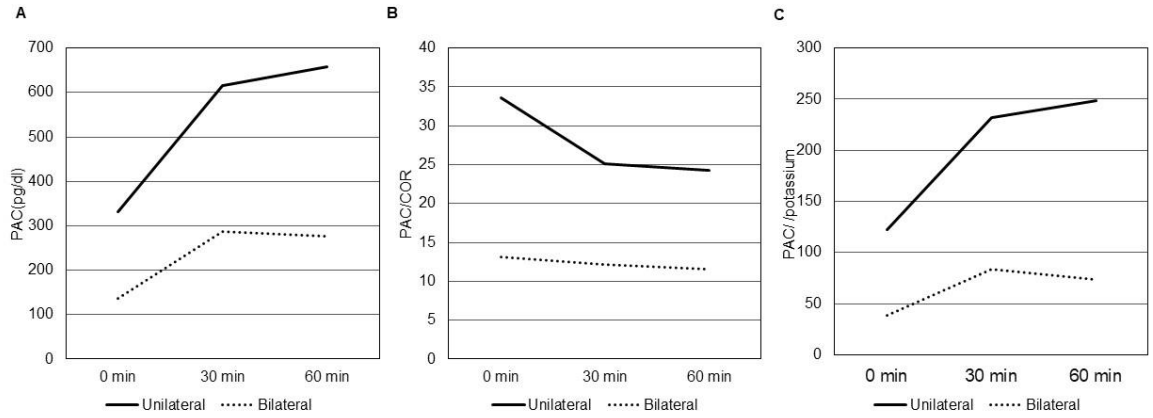

A
PAC(pg/dl)
700
600
500
400
300
200
100
0
0 min
30 min
60 min
Unilateral
Bilateral
B
PAC/COR
40
35
30
25
20
15
10
5
0
0 min
30 min
60 min
Unilateral
Bilateral
C
PAC/ /potassium
300
250
200
150
100
50
0
0 min
30 min
60 min
Unilateral
Bilateral

Fig. 4

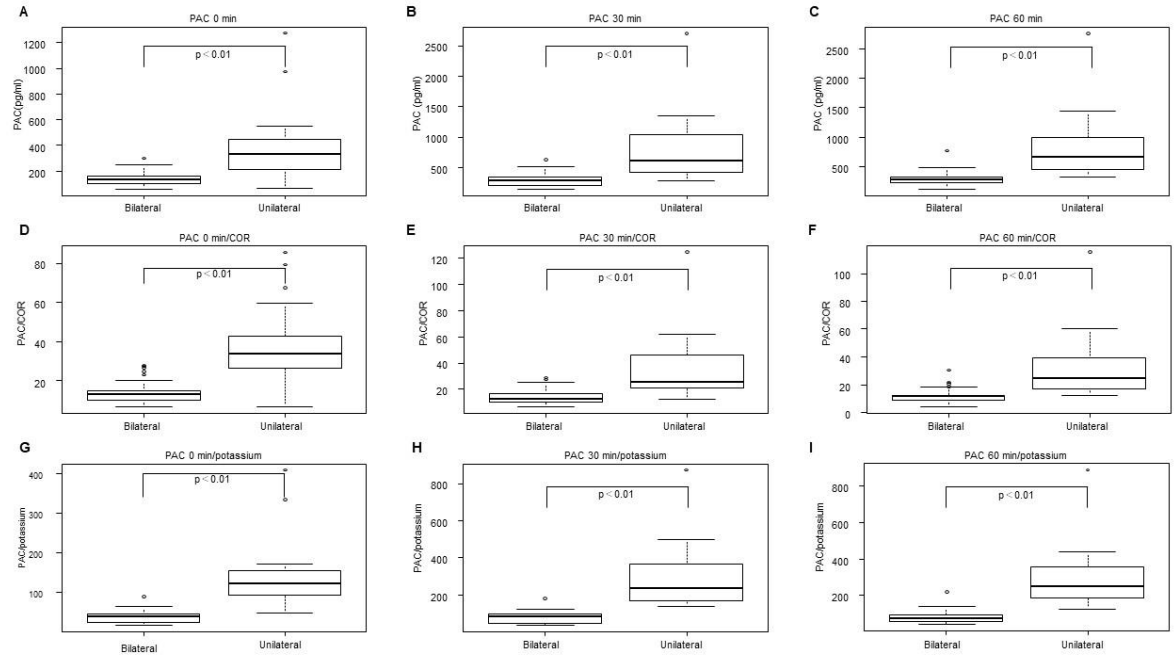
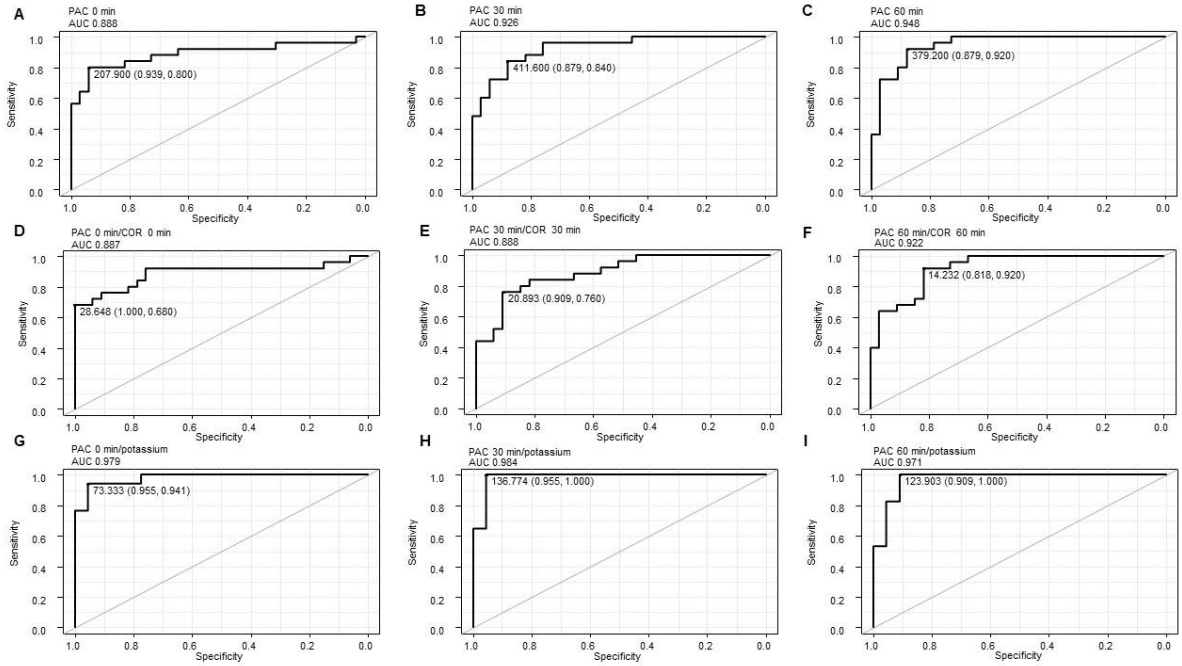

A
PAC 0 min
p < 0.01
PAC(pg/ml)
Bilateral
Unilateral
B
PAC 30 min
p < 0.01
PAC (pg/ml)
C
PAC 60 min
p < 0.01
PAC (pg/ml)
D
PAC 0 min/COR
p < 0.01
PAC/COR
E
PAC 30 min/COR
p < 0.01
PAC/COR
F
PAC 60 min/COR
p < 0.01
PAC/COR
G
PAC 0 min/potassium
p < 0.01
PAC/potassium
H
PAC 30 min/potassium
p < 0.01
PAC/potassium
I
PAC 60 min/potassium
p < 0.01
PAC/potassium

Fig. 5


A
PAC 0 min
AUC 0.888
207.900 (0.939, 0.800)
B
PAC 30 min
AUC 0.926
411.600 (0.879, 0.840)
C
PAC 60 min
AUC 0.948
379.200 (0.879, 0.920)
D
PAC 0 min/COR 0 min
AUC 0.887
28.648 (1.000, 0.680)
E
PAC 30 min/COR 30 min
AUC 0.888
20.893 (0.909, 0.760)
F
PAC 60 min/COR 60 min
AUC 0.922
14.232 (0.818, 0.920)
G
PAC 0 min/potassium
AUC 0.979
73.333 (0.955, 0.941)
H
PAC 30 min/potassium
AUC 0.984
136.774 (0.955, 1.000)
I
PAC 60 min/potassium
AUC 0.971
123.903 (0.909, 1.000)
Sensitivity
Specificity