Prediction of unilateral hyperaldosteronism on adrenal vein sampling using captopril challenge test in patients with primary aldosteronism

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Abstract. Captopril challenge test (CCT) is a simple and safe confirmatory test for primary aldosteronism (PA). We investigated the effectiveness of the indices after captopril administration for prediction of unilateral hyperaldosteronism (UHA) on adrenal vein sampling (AVS). We studied 238 patients with PA who had CCT and successful AVS between July 2007 and December 2019 in Sapporo City General Hospital. Receiver operating characteristic (ROC) curve analysis showed that the diagnostic performance for prediction of UHA on AVS in regard to the reduction rate of plasma aldosterone concentration (PAC) after captopril administration was inferior to aldosterone to renin ratio (ARR) and PAC (area under the ROC curve 0.72 vs. 0.84, 0.72 vs. 0.89, respectively, both p < 0.01). Based on the optimal cut-off values in ARR (897 pg/mL/ng/mL/h, sensitivity 64.6%, specificity 93.0%) and PAC (203 pg/mL, sensitivity 73.9%, specificity 93.0%) after captopril administration, the patients were divided into three groups: (1) both positive, (2) one positive, and (3) both negative. The prevalence of UHA on AVS in the three groups were 90.0%, 52.9%, and 7.3%, respectively. In the first group, 31 of 32 patients with unilateral nodular lesion on CT had an ipsilateral unilateral AVS. In conclusion, the combination of post-captopril ARR and PAC is useful for prediction of laterality diagnosis on AVS. AVS is strongly recommended in patients with both positive or one positive results for the optimal cut-off values of post-captopril ARR and PAC and is weakly recommended in patients with both negative results.

Key words: Primary aldosteronism, Captopril challenge test, Adrenal vein sampling

PRIMARY ALDOSTERONISM (PA) is the most common form of secondary endocrine hypertension, accounting for 5–10% of all hypertensive patients [1, 2]. The two common subtypes of PA, aldosterone-producing adenoma (APA) and idiopathic hyperaldosteronism (IHA) should be differentiated, because the former requires adrenalectomy and the latter is treated with medication. Adrenal vein sampling (AVS) is recognized as the most reliable method for subtype diagnosis [3, 4]. Therefore, patients should undergo this procedure to determine the need for adrenalectomy. However, AVS is an invasive and costly procedure. It is necessary to predict laterality diagnosis of AVS using non-invasive examinations.

The captopril challenge test (CCT) is a confirmatory test for PA and is listed as a recommended test in the guidelines of the Endocrine Society [5] and the Japanese Endocrine Society (JES) [6], as well as the consensus statement of JES [7]. In addition, CCT is often performed first because it is simple, can be performed in a short time, and has few adverse effects [8].

Generally, CCT is done to confirm PA [5-7]. In contrast, there is no report using CCT to discriminate between APA and IHA. In general, patients with APA have higher basal PAC than patients with IHA [1]. Furthermore, from the study using posture test, aldosterone secretion in APA is independent on angiotensin II compared to that in IHA, although there are some cases with...
angiotensin-responsive APA [9]. Based on the above, we hypothesize that PAC and ARR after CCT, which is a suppression test of renin-angiotensin system, may be able to discriminate APA from IHA more effectively than basal PAC and ARR.

In this study, we investigated whether the results of CCT could be used to predict unilateral hyperaldosteronism (UHA) in patients who underwent AVS and were thought to have unilateral APA, among the patients who had a definite diagnosis of PA and underwent AVS.

**Patients and Methods**

**Patients**

Three hundred and eleven patients with PA who underwent AVS in Sapporo City General Hospital between July 2007 and December 2019 were investigated. The diagnostic procedure for confirmation of PA was performed following the guidelines and consensus statement of the JES [6, 7] and the guidelines of Japan Society of Hypertension [10]. Screening for PA was performed based on aldosterone to renin ratio (ARR). The cut-off value of ARR was >200 pg/mL/ng/mL/h, after changing from potentially interfering antihypertensive drugs to calcium channel blockers and/or α-blockers when applicable. The diagnosis of PA was established by at least one positive confirmatory test result, CCT, saline infusion test (SIT), and furosemide upright test (FUT) according to the consensus statement of the JES [7]. Patients with autonomous secretion of cortisol defined as serum cortisol level ≥1.8 μg/dL in an overnight 1 mg dexamethasone suppression test (1 mg DST) were excluded.

**Confirmatory tests**

In this study, the diagnosis of PA was confirmed when at least one of the three confirmatory tests, namely CCT, SIT, and FUT, was positive. Generally, the confirmatory tests were performed during hospitalization, taking 12 g of dietary salt per day. The confirmatory tests were started at 0830 h after resting for 30 min in the supine position. CCT and SIT were continued in the supine position. The criterion of each test was based on the guidelines and the consensus statement of the JES [6, 7]. For CCT, positive results were defined as ARR >200 pg/mL/ng/mL/h or PAC >120 pg/mL after 60 or 90 min of oral administration of 50 mg captopril. In SIT, positive results were defined as PAC >60 pg/mL after intravenous infusion of 2 L saline for 4 h. In FUT, positive results were defined as PRA <2.0 ng/mL/h after intravenous injection of 40 mg furosemide and 2 h of standing.

**AVS and imaging**

The procedure for AVS is described elsewhere by Miyoshi et al. [11]. Blood samples obtained via AVS were collected from both adrenal veins and the inferior vena cava (IVC) at a point distal to the renal vein, administering 0.25 mg of cosyntropin (ACTH 1-24) for approximately 30 min. Successful cannulation in the right adrenal vein was determined through imaging using the C-arm computed tomography (CT). Successful AVS was defined as a selectivity index (SI) >5 after ACTH stimulation. UHA on AVS was defined as LI >4 after ACTH stimulation. Bilateral hyperaldosteronism (BHA) on AVS was defined as LI ≤4 after ACTH stimulation [6, 7]. The contralateral ratio (CR) calculated by dividing aldosterone/cortisol in the non-dominant adrenal vein by that in the IVC was also investigated. Contralateral suppression was defined as CR <1 on the non-dominant side. If the aldosterone/cortisol was bilaterally lower in the adrenal veins than that the IVC (apparent bilateral aldosterone suppression; ABAS), AVS was considered inconclusive [12].

CT was performed in all patients. The diagnosis of CT was performed by experienced radiologists. In this study, unilateral nodular lesions on CT was limited to a unilateral single nodule with findings of a typical adenoma.

The indication for adrenalecctomy was determined individually for each patient.

**Analysis**

The data were evaluated retrospectively. The accuracy of indices among CCT, ARR, PAC 60 min after captopril administration, and reduction rate of PAC from baseline to 60 min after captopril administration for prediction of UHA on AVS after ACTH stimulation were compared. In addition, we investigated whether the combination of the results of two indices with higher ability for prediction of UHA on AVS was useful in determining the strength of recommendation of AVS.

This study was approved by the ethics committee of Sapporo City General Hospital (approval number: R02-059-677).

**Assay methods**

PAC and PRA were measured using commercially available kits: radioimmunoassay for the former (SPAC-S Aldosterone Kit; Fuji Rebio, Co., Ltd, Tokyo, Japan), with a 30–159 pg/mL reference range and radioimmunoassay for the latter (PRA radioimmunoassay kits; Yamasa, Co., Ltd), with a 0.2–2.7 ng/mL/h reference range, all in the supine position.

**Statistics**

Data were analyzed and compared using BellCurve for
Continuous variables were analyzed using t-test or Mann-Whitney U test, as appropriate. The comparison of frequencies between the two groups was estimated by either the χ² test or Fisher’s exact test, as appropriate. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value and the sensitivity, and the specificity of the indices related to CCT for prediction of UHA on AVS after ACTH stimulation. The area under the ROC curve (AUC) was evaluated to compare the diagnostic performance of the indices. Statistical significance was achieved at a p-value of <0.05.

Results

A flowchart of this study is summarized in Fig. 1. We investigated 311 patients who underwent AVS between July 2007 and December 2019 at Sapporo City General Hospital. Patients who did not undergo CCT or who did not have available data on CCT were excluded. Patients who had serum cortisol ≥1.8 μg/dL after 1 mg DST, unsuccessful cannulation of the adrenal vein in AVS, and those without available data on the left or right central veins or IVC were excluded. Patients with ABAS on AVS were also excluded because appropriate laterality on AVS could not be interpreted. Finally, 238 patients were studied.

Table 1 shows the characteristics, the biochemical findings, and the parameters before and after CCT in all patients and patients with UHA and BHA. In the 238 patients who were analyzed in this study, the mean age was 50 years, majority were female (56.7%), 66 were diagnosed as UHA on AVS, and 66 underwent adrenalectomy. Twelve patients in BHA group underwent adrenalectomy. The reasons for indication of surgery were large unilateral tumor on CT (n = 2), severe hypertension (n = 7), and detecting the tributary of adrenal vein with high PAC on segmental AVS (n = 3). Comparing between patients with UHA (n = 66) and BHA (n = 172), PAC and ARR at baseline, as well as PAC, ARR 60 min after captopril administration were significantly higher in the UHA group (both p < 0.01). Reduction rate of PAC 60 min after captopril administration was significantly lower in the UHA group (p < 0.01).

Next, we investigated clinical effectiveness of the combination of determination using the optimal cut-off values of ARR (897 pg/mL/ng/mL/h) and PAC (203 pg/mL) from ROC curve analysis 60 min after captopril administration. Table 3 shows the prevalence of UHA on AVS in the following three groups: (1) patients with both positive results of ARR and PAC, (2) patients with one positive result, and (3) patients with both negative results. The positive rates of UHA on AVS in the three
groups were 90.0%, 52.9%, and 7.3%, respectively. In 40 patients with both positive results according to the two indices 60 min after captopril administration, 36 (90.0%) had UHA on A VS. In this group, out of 32 patients with unilateral nodular lesion on CT, 31 (96.9%) had UHA on A VS. In the patient with unilateral nodular lesion on CT and BHA on A VS, the LI on A VS was 3.72. The patient underwent unilateral adrenalectomy, and the resected adrenal tumor was pathologically a cortical adenoma. Of the 164 patients with both negative results according to the two indices 60 min after captopril administration, 12 (7.3%) had UHA on A VS. In addition, in 92 patients with normal CT findings and normal serum potassium level, only 4 (4.3%) had UHA on A VS.

**Table 1** Characteristics and biochemical findings in all patients, as well as patients with UHA and BHA on AVS

|                           | All patients (n = 238) | UHA (n = 66) | BHA (n = 172) | p-value |
|---------------------------|------------------------|--------------|---------------|---------|
| Age (year)                | 50 ± 11                | 51 ± 13      | 50 ± 11       | 0.46    |
| Female gender (n, %)      | 135, 56.7              | 30, 48.5     | 105, 61.0     | 0.03    |
| Duration of hypertension (year) | 6 ± 7                  | 9 ± 8        | 5 ± 6         | <0.01   |
| Number of antihypertensive drugs | 1.4 ± 1.1             | 1.9 ± 1.2    | 1.2 ± 1.0     | <0.01   |
| Systolic blood pressure (mmHg) | 139 ± 15               | 140 ± 14     | 139 ± 15      | 0.83    |
| Diastolic blood pressure (mmHg) | 85 ± 13                | 81 ± 11      | 86 ± 13       | 0.01    |
| Serum potassium (mEq/L)   | 3.7 ± 0.5              | 3.2 ± 0.6    | 3.9 ± 0.3     | <0.01   |
| PRA (ng/mL/h) at baseline | 0.3 [0.2 0.5]          | 0.2 [0.1 0.4] | 0.3 [0.2 0.5] | <0.01   |
| PAC (pg/mL) at baseline   | 173 [132 272]          | 325 [210 529] | 155 [120 204] | <0.01   |
| 60 min after captopril administration | 131 [97 204] | 300 [196 476] | 117 [90 143] | <0.01 |
| ARR (pg/mL/ng/mL/h) at baseline | 565 [342 1,150] | 1,658 [775 2,610] | 477 [310 755] | <0.01 |
| 60 min after captopril administration | 388 [214 841] | 1,390 [511 2,303] | 306 [197 528] | <0.01 |
| Reduction rate of PAC (%) 60 min after captopril administration | 21 [5 34] | 6 [–9 25] | 25 [14 38] | <0.01 |
| Unilateral nodular lesion on CT (n, %) | 90, 37.8 | 52, 78.8 | 38, 22.1 | <0.01 |
| Adrenalectomy (n, %)       | 66, 27.7              | 54, 81.8     | 12, 7.0       | <0.01   |

The data are presented as mean ± standard deviation or median and interquartile range, or number and percentage. UHA, unilateral hyperaldosteronism; BHA, bilateral hyperaldosteronism; AVS, adrenal vein sampling; PRA, plasma renin activity; PAC, plasma aldosterone concentration; ARR, aldosterone to renin ratio; CT, computed tomography. 
P-values are compared between UHA group and BHA group.

**Table 2** The results of ROC curve analysis of ARR, PAC, and reduction rate of PAC 60 min after captopril administration for prediction of UHA on AVS

|                  | ARR (pg/mL/ng/mL/h) | PAC (pg/mL) | Reduction rate of PAC (%) |
|------------------|---------------------|-------------|---------------------------|
| AUC (95% CI)     | 0.84 (0.78–0.91)    | 0.89 (0.84–0.94) | 0.72<sup>a</sup>,<sup>b</sup> (0.64–0.79) |
| Optimal cut-off value | 897                 | 203         | 15                        |
| Sensitivity (%)  | 64.6                | 73.9        | 64.6                      |
| Specificity (%)  | 93.0                | 93.0        | 73.3                      |

ROC, receiver operating characteristic; ARR, aldosterone to renin ratio; PAC, plasma aldosterone concentration; UHA, unilateral hyperaldosteronism; AUC, area under the ROC curve; CI, confidence interval. <sup>a</sup>: p < 0.01, ARR vs. reduction rate of PAC; <sup>b</sup>: p < 0.01, PAC vs. reduction rate of PAC.

In this study, we investigated the utility of CCT for predicting patients with UHA diagnosed by AVS. CCT is generally performed to distinguish PA from essential hypertension (EHT). Although some studies have been performed to identify patients with APA from patients with EHT [13, 14], there were no reports that were able to discriminate patients with APA from patients with IHA.

There are three indices in CCT, which is ARR, PAC [6, 7], and reduction rate of PAC [5]. For diagnosis of PA, there are various cut-off values of ARR and PAC after CCT [15]. Meng et al. reported that reduction rate
of PAC after CCT (cut-off value: 30%) had a lower accuracy for the diagnosis of PA [16].

In this study, we compared the diagnostic performance of ARR, PAC, and reduction rate of PAC after CCT for the prediction of UHA on AVS that was a surrogate indicator of unilateral APA. It was demonstrated that ARR and PAC were comparable, and that the reduction rate of PAC was inferior to other indices. However, even with ARR and PAC, the diagnostic performance to identify UHA on AVS was not sufficient for a practical use considering its sensitivity and specificity. Therefore, we examined the prediction of UHA on AVS by the combination of judgments using the optimal cut-off values of two indices after captopril administration, ARR and PAC. UHA on AVS was approximately 90% when the two indices were positive, and BHA on AVS was approximately 90% when the two indices were negative. UHA and BHA on AVS were almost half when one index was positive.

Table 4 shows our proposal for the combination of the judgments using ARR and PAC after captopril administration and the strength of recommendation for AVS implementation. The cut-off values of ARR and PAC were modified to be definite and close to the optimal values calculated by the ROC curve analysis. AVS is strongly recommended if both indices are positive or one index is positive. Furthermore, if both indices are positive and CT shows a unilateral nodular lesion, the laterality of CT and AVS is almost concordant. In such a case, adrenalectomy without AVS may be considered. If one index is positive, AVS is mandatory if surgery is considered. AVS is weakly recommended if both indices are negative. Furthermore, since the probability of UHA on AVS is extremely low when CT finding are normal and serum potassium level is normal, it may be considered to omit AVS and to start medical therapy using mineralocorticoid receptor antagonists.

Some studies have predicted subtype diagnosis without AVS [17-20]. Unlike these studies, the purpose of our study was to examine the usefulness of CCT alone for predicting subtype diagnosis of PA. Compared to the studies using a prediction score [17-19], the method we...
used in this study was simple. Umakoshi et al. reported a simple method for predicting subtype diagnosis on AVS using a combination of CT findings and serum potassium levels [20]. Compared to the report of Umakoshi, the method we used in this study could extract both the group with a high prevalence of UHA and the group with a high prevalence of BHA.

There are several limitations in this study. First, this was a single center study, and had relatively smaller number of patients. In addition, this was a retrospective study resulting in some biases to be included. Second, measurement of renin and aldosterone is not standardized. Since this study used RIA kits, PRA radioimmunoassay kits and SPAC-S Aldosterone Kit, the results of other assays cannot be applied. It is hoped that the measurement of renin and aldosterone will be standardized in the future. Third, the laterality of AVS could not be completely consistent with subtype of PA. It was possible that there were patients with unilateral APA with LI ≤4 on AVS. In addition, the patients with BHA on AVS might contain those with bilateral APA.

In conclusion, the combination of judgements in ARR and PAC after captopril administration is useful for the prediction of UHA and BHA on AVS. AVS is strongly recommended in patients with both positive or one positive result for the optimal cut-off values of ARR and PAC after captopril administration and is weakly recommended in patients with both negative results. It was suggested that the results of this study could help to reduce the number of the patients who needed to be performed AVS.

**Disclosure Summary**

The authors have nothing to disclose.

![Supplementary Fig. 1](image)

**Supplementary Fig. 1** The ROC curve of ARR (A), PAC (B), and reduction rate of PAC (C) 60 min after captopril administration for prediction of UHA on AVS

ROC, receiver operating characteristic; ARR, aldosterone to renin ratio; PAC, plasma aldosterone concentration; UHA, unilateral hyperaldosteronism; AVS, adrenal vein sampling; AUC, area under the ROC curve; CI, confidence interval. Arrow indicates the optimal cut-off value.

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