Adrenal Venous Sampling in Patients With Positive Screening but Negative Confirmatory Testing for Primary Aldosteronism

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Abstract—Adrenal venous sampling is considered to be the most reliable diagnostic procedure to lateralize aldosterone excess in primary aldosteronism (PA). However, normative criteria have not been established partially because of a lack of data in non-PA hypertensive patients. The aim of the study was to investigate aldosterone concentration and its gradient in the adrenal vein of non-PA hypertensive patients. We retrospectively studied the results of cosyntrropin-stimulated adrenal venous sampling in 40 hypertensive patients who showed positive screening testing but negative results in 2 confirmatory tests/captopril challenge test and saline infusion test. Plasma aldosterone concentration, aldosterone/cortisol ratio, its higher/lower ratio (lateralization index) in the adrenal vein with cosyntrropin stimulation were measured. Median plasma aldosterone concentration in the adrenal vein was 25,819 pg/mL (range, 5,154–69,920) in the higher side and 12,953 (range, 1,866–36,190) pg/mL in the lower side (P<0.001). There was a significant gradient in aldosterone/cortisol ratio between the higher and the lower sides (27.2 [5.4–66.0] versus 17.3 [4.0–59.0] pg/mL per μg/dL; P<0.001) with lateralization index ranging from 1.01 to 3.87. The aldosterone lateralization gradient was between 1 to 2 in 32 patients and 2 to 4 in 8 patients. None of the patients showed lateralization index ≥4. The present study demonstrated that plasma aldosterone concentration in the adrenal veins showed significant variation and lateralization gradient even in non-PA hypertensive patients. Adrenal venous sampling aldosterone lateralization gradients between 2 and 4 should be interpreted with caution in patients with PA because these gradients can be found even in patients with negative confirmatory testing for PA. (Hypertension. 2016;67:00-00. DOI: 10.1161/HYPERTENSIONAHA.115.06607.)

Key Words: aldosterone □ hyperaldosteronism □ hypertension □ primary hyperaldosteronism

Primary aldosteronism (PA) is the most common cause of endocrine hypertension associated with autonomous excess secretion of aldosterone.1–2 Early diagnosis is critical because of its potential curability by early treatment and high cardiovascular morbidity if not treated appropriately.3,4 Because a unilateral aldosterone-producing adenoma (APA) can be cured by an adrenalectomy and bilateral idiopathic hyperaldosteronism can be controlled with mineralocorticoid receptor antagonists, subtype diagnosis of PA by means of adrenal venous sampling (AVS) is a critical diagnostic step in selecting the treatment modality.5,6 However, decision criteria and diagnostic significance in AVS for subtype diagnosis have not been fully established partially because of the absence of data in non-PA patients.7–9

The lateralization index (LI), which reflects the gradient of the cortisol-corrected aldosterone concentration on the higher side relative to that on the lower side,10 is the most representative AVS criterion for identifying the laterality of aldosterone excess.11,12 An international multicenter study on AVS13 has demonstrated that a variety of cutoff values have been used in the referral centers in the world. Although LI≥4 after cosyntrropin stimulation is the most widely used for determining the side of aldosterone excess,13 many reference centers use a more permissive LI cutoff between 2 and 414 based on the finding that a few cases of unilateral APA had an LI<4.14 Those patients with such values in a gray zone could be mixed with APA and bilateral idiopathic hyperaldosteronism,15 thereby leaving the possibility of false-positive AVS results. When
considering that a bilateral idiopathic hyperaldosteronism is controlled by mineralocorticoid receptor antagonists and some of APAs can be controlled by mineralocorticoid receptor antagonists, an indication for adrenal surgery based on false-positive AVS results for unilateral subtype should be avoided, as described in an expert consensus statement.

One of the most critical defects in AVS is the lack of data in non-PA hypertensive patients. AVS results in non-PA patients could strengthen the currently used LI cutoff and minimize the number of patients undergoing surgery as a consequence of incorrect lateralization of AVS. In the present study, we investigated AVS parameters and LI in non-PA hypertensive patients who showed positive case detection but negative results in 2 standard confirmatory testing recommended by the Endocrine Society.

Patients and Methods

Patients
This retrospective study was conducted as a multicenter collaborative study involving 9 referral centers in Japan (West Adrenal Vein Sampling in Japan [WAVES-J] study). The WAVES-J database included clinical and laboratory data of hypertensive patients who underwent AVS between January 2006 and December 2013. Case detection was performed on the basis of a ratio of plasma aldosterone concentration (PAC) in μg/mL/plasma renin activity (PRA) in ng/mL per hour; ARR ≥200 in accordance with the guidelines of the Japan Society of Hypertension and the Japan Endocrine Society. The screening was performed after changing antihypertensive agents to α-adrenergic blockers, calcium channel blockers, and angiotensin II type I receptor blockers, as appropriate, until the final diagnosis. Of 550 patients in the WAVES-J database, 40 who showed positive case detection but negative results in both captopril challenge test (CCT) and saline infusion test (SIT) as confirmatory tests, but had successful cosyntropin-stimulated AVS data, were studied. The CCT was considered to be positive if the ARR was ≥300 after oral administration of 50-mg captopril. The SIT was considered to be positive if the PAC was ≥50 pg/mL after intravenous administration of 2 L of 0.9% NaCl.

All 40 patients were clinically diagnosed and informed as having PA or suspected PA by positive Furosemide-upright test (PRA <2 ng/mL per hour as positive; n=21), positive rapid cosyntropin test (maximal PAC/cortisol ratio ≥28.5 pg/mL per μg/dL as positive; n=17), or clinical findings suggesting PA such as a tendency to hypokalemia (≤3.7 mEq/L; n=2) under the clinical setting of positive case detection. AVS was indicated for subtype diagnosis in all these patients after confirming patient’s desire for surgery by the respective attending physicians and conducted absolutely as a part of routine clinical practice after informed consent for AVS. Additional factors such as age and adrenal tumor on computed tomography were also taken into account for AVS indication. Because furosemide-upright testing is used as one of the confirmatory testing only guidelines of the Japan Society of Hypertension and the Japan Endocrine Society and significance of rapid cosyntropin stimulation test as a confirmatory testing has not been established, patients who showed positive case detection testing but negative results in both of CCT and SIT as globally recommended confirmatory tests were defined as non-PA in the present study.

Adrenal Venous Sampling
Details of the AVS protocol have been previously described. Briefly, cosyntropin was given as a bolus infusion before cannulation in 5 centers, and by a bolus infusion followed by a continuous infusion throughout the procedure in the remaining centers. Catheter cannulation was performed using the percutaneous femoral vein approach. The adrenal vein cannulation was considered to be successful if the selectivity index was ≥2.5. The selectivity index was defined as the plasma cortisol concentration (PCC) in the adrenal vein relative to the PCC in the IVC. The LI was defined as the PAC/PCC (A/C) ratio on the higher side divided by that on the lower side. The contralateral ratio was defined as A/C ratio on the lower side in adrenal vein relative to the A/C ratio in the IVC. The ipsilateral ratio was defined as A/C ratio on the higher side in the adrenal vein relative to the A/C ratio in the IVC. The contralateral adrenal aldosterone suppression was defined as contralateral ratio <1.

Analysis and Statistics
AVS parameters including PAC, PCC, A/C ratio, and LI were analyzed and compared between the higher and the lower sides. The numbers of patients with LI cutoffs of ≥2, ≥3, and ≥4 were investigated. Clinical manifestations were compared between the LI <2 and LI ≥2. The contralateral ratio and ipsilateral ratio were analyzed, and number of patients with contralateral adrenal aldosterone suppression were investigated.

The PAC, PRA, and PCC were assessed using a radioimmunoassay. Each of the following reference ranges was determined in the supine position. The reference range of PAC was 30 to 159 pg/mL (SPAC-S Aldosterone kits; TFB, Tokyo Japan). The reference range of PRA was 0.3 to 2.9 ng/mL per hour (PRA kit) in 7 centers, 0.1 to 2.0 ng/mL per hour (Renin RIA kit) in 2 centers, and 0.2 to 2.7 ng/mL per hour (Renin RIA kit) in 1 center. The reference range of PCC was 6.2 to 19.4 μg/dL (Roche Diagnostics Japan, Tokyo, Japan).

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as number and percentages. Continuous variables were analyzed by the Mann–Whitney U test and categorical variables by Fisher exact test. All tests were 2 tailed, with differences reported as significant when P<0.05.

This retrospective study was conducted according to the guidelines for clinical studies published by the Ministry of Health and Labor, Japan, and was approved by the ethics committee of Kyoto Medical Center as the project leader institute and by the institutional ethics committees of the participating hospitals.

Results

Baseline clinical characteristics of the patients are shown in Table 1. Blood pressure was moderately controlled with 2 different classes of antihypertensive medications. Because all the patients showed positive case detection with ARR, PAC tended to be high normal and the PRA was low (median [interquartile range] of PAC and PRA, 145 [125–175] pg/mL and 299 [221–419].

Table 1. Clinical Characteristics in Non–Primary Aldosteronism Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>10/30</td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (53–65)</td>
</tr>
<tr>
<td>BP systolic, mm Hg</td>
<td>142 (131–153)</td>
</tr>
<tr>
<td>BP diastolic, mm Hg</td>
<td>84 (73–93)</td>
</tr>
<tr>
<td>Serum K, mEq/L</td>
<td>4.0 (3.7–4.1)</td>
</tr>
<tr>
<td>PAC, pg/mL</td>
<td>147 (125–180)</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>ARR</td>
<td>299 (221–419)</td>
</tr>
<tr>
<td>Adrenal nodule on CT (%)</td>
<td>21/40 (52.5)</td>
</tr>
</tbody>
</table>

Data shown as the median (interquartile range) or number (percent of cohort). ARR indicates aldosterone/renin ratio; BP, blood pressure; CT, computed tomography; K, potassium; PAC, plasma aldosterone concentration; PRA, plasma renin activity.
0.5 [0.4–0.6] ng/mL per hour). In addition, 51% of the patients had an adrenal nodule on computed tomography.

The PAC and PCC in the adrenal vein after cosyntropin administration ranged from 1866 to 69920 pg/mL and from 207 to 2320 μg/dL, respectively. Median PAC of the higher side was 25819 pg/mL ranging from 5154 to 69920 pg/mL, whereas that of the lower side was 12953 pg/mL ranging from 1866 to 36190 pg/mL. There was a significant difference in PAC between the higher and the lower sides (P<0.001; Figure 1A). Median PCC of the higher side was 1015 μg/dL ranging from 331 to 2320 μg/dL, whereas that of the lower side was 658 μg/dL ranging from 207 to 1450 μg/dL. There was a significant difference in PCC between the higher and the lower sides (P<0.001; Figure 1B). Median A/C of the higher side was 27.2 ranging from 5.4 to 66.0 and that of the lower side was 17.3 ranging from 4.0 to 59.0. A/C showed a significant difference between the higher and lower sides (P<0.001; Figure 1C).

The LI showed a median of 1.42 and ranged from 1.01 to 3.87. Of 40 patients, 32 had an LI between 1 and 2, 4 showed a value between 2 and 3, and the remaining 4 showed a value between 3 and 4. None of the patients showed LI≥4 (Figure 2). Accordingly, 8 patients (20%) showed a laterality of aldosterone secretion when an LI cutoff of 2 was used for subtype diagnosis (Table 2). There was, however, no significant difference in any of the clinical and laboratory findings, including serum potassium levels and the prevalence of an adrenal nodule on computed tomography, between the patients with LI<2 and LI≥2 (Table 3).

The contralateral ratio showed a median of 2.10 ranging from 0.60 to 4.40. Two of 40 patients (5.0%) showed contralateral aldosterone suppression with contralateral ratio of 0.60 and 0.90 with their LI of 3.87 and 3.11. The ipsilateral ratio showed a median of 2.78 ranging from 1.83 to 5.60 (Table 4). Although these 2 patients had undergone adrenalectomy, postoperative outcome did not show any definite cure of hypertension and endocrine profile: no improvement of blood pressure in one patient and mild but sustained elevation of PAC in the other patient, respectively.

**Discussion**

Although PAC and its gradient between both sides of the adrenal vein are the most important biochemical measures in the subtype diagnosis of PA, the specificity of the diagnostic criteria has not been established, partially because of the lack of data in non-PA patients. The AVS cutoffs used in the different centers are derived from postoperative retrospective data and from receiver operating characteristic curves obtained in patients who were selected for adrenalectomy on the basis of different clinical criteria. However, the cutoffs derived in this way cannot be considered reliable. Theoretically, optimal AVS cutoffs should be determined by prospective studies in patients who underwent unilateral adrenalectomy, irrespective of their AVS results, but such studies are not ethically available.12 Our study is the first to demonstrate AVS data in hypertensive patients who were defined as non-PA according to the clinical practice guideline of the Endocrine Society. These hypertensive patients showed positive case detection testing for PA but showed negative results both in CCT and SIT, which are recommended as confirmatory testing by the

**Table 2. Numbers of Patients in Different Quartile of LI of Adrenal Venous Sampling in Non–Primary Aldosteronism Hypertensive Patients**

<table>
<thead>
<tr>
<th>LI</th>
<th>&lt;2</th>
<th>≥2 to &lt;3</th>
<th>≥3 to &lt;4</th>
<th>≥4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>32 (80)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

LI indicates lateralized index.
Endocrine Society guideline. Our results of the present study circumvent problems of AVS lateralization criteria and provide a considerable advancement in the knowledge of PA. It was clearly demonstrated that PAC in the adrenal vein showed a wide range of variation reaching as high as 60000 pg/mL, a level comparable with that seen in PA patients (median, 28 600 pg/mL; range, 3851–262 000; our unpublished data from 157 PA patients). Our findings suggest that the absolute adrenal vein PAC dose not by itself identify pathological adrenal aldosterone hypersecretion.

Although there was a small but significant difference in both PAC and A/C ratio between the higher and the lower sides of the adrenal vein, none of the non-PA patients showed an LI $\geq$ 4. Taken together, the previous finding by Young et al$^{24}$ that no patient with bilateral idiopathic hyperaldosteronism had an LI $\geq$ 4 after cosyntropin stimulation, our present results provided evidence for the specificity of the LI cutoff of > 4 as a unilateral subtype of PA. Although 80% (32/40) of the patients showed an LI<2, 20% (8/40) patients showed an LI between 2 and 4, there exists a significant aldosterone gradient in the adrenal vein even in non-PA patients. It should be noted that there was no significant difference of clinical features including age, blood pressure, serum potassium, PAC, PRA, and ARR between the patients with LI $\geq$ 2 and < 2. Mechanisms responsible for such aldosterone gradient in the adrenal vein in non-PA patients remain to be elucidated. Whether aldosterone-producing cell clusters with CYP11B2 expression$^{26,27}$ has a pathological significance in the higher side of adrenal in these 8 patients requires further investigation. The aldosterone gradient in the gray zone (LI=2–4) should be carefully interpreted in the subtype diagnosis of PA to avoid inappropriate adrenalectomy.$^{13}$ Additional criteria such as contralateral adrenal aldosterone suppression$^{15}$ and clinical and biochemical findings$^{21}$ should be taken into account when considering patients for adrenal surgery.

Two of 40 (5%) patients showed contralateral adrenal aldosterone suppression with contralateral ratio 0.60 and 0.90 with their LI 3.87 and 3.11, respectively. Diagnostic significance of contralateral adrenal aldosterone suppression in addition to LI in the subtype diagnosis of PA has been demonstrated by various previous studies. Young et al$^{24}$ demonstrated that contralateral adrenal aldosterone suppression is seen in 95% of the patients with unilateral PA. In addition, Umakoshi et al$^{28}$ demonstrated a clinical significance of contralateral adrenal aldosterone suppression for prediction of unilateral PA especially when LI is <4. It is, therefore, suggested that the 2 patients with contralateral adrenal aldosterone suppression could be PA with false-negative results in both of CCT and SIT. It was, however, demonstrated that contralateral adrenal aldosterone suppression was also seen in 30% of the patients with bilateral PA.$^{24}$ The present study may provide evidence that contralateral adrenal aldosterone suppression occurs even in non-PA patients. Theretofore, limitation of the specificity of contralateral adrenal aldosterone suppression should be taken into account in the interpretation of AVS data.

There are limitations in our study. The patients investigated in the present study were defined as non-PA based on the negative results in 2 confirmatory testing recommended by the Endocrine Society Guideline.$^{17}$ Although the rather low ARR cutoff for case detection by the guideline may strengthen the probability of non-PA nature of the patients, whether these patients, especially 8 patients who showed LI between 2 and 4, are definitely not PA remain unknown. Negative results of SIT, oral salt-loading test, CCT, or fludrocortisone suppression test (FDST), however, have been demonstrated to reliably exclude PA patients.$^{20,28}$ Of these testing, lack of 24-hour urine aldosterone data after oral salt-loading test and FDST as the most reliable confirmatory testings$^{17}$ is a significant limitation.

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### Table 3. Comparison of Clinical Findings Between Those With LI≥2 and LI<2 of Adrenal Venous Sampling in Non–Primary Aldosteronism Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>LI≥2 (n=8)</th>
<th>LI&lt;2 (n=32)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>56 (47–66)</td>
<td>61 (53–65)</td>
<td>0.5</td>
</tr>
<tr>
<td>BP systolic, mmHg</td>
<td>142 (131–150)</td>
<td>142 (130–155)</td>
<td>0.9</td>
</tr>
<tr>
<td>BP diastolic, mmHg</td>
<td>84 (75–87)</td>
<td>86 (73–93)</td>
<td>0.4</td>
</tr>
<tr>
<td>Serum K, mEq/L</td>
<td>4.0 (3.8–4.2)</td>
<td>4.0 (3.7–4.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>PAC, pg/mL</td>
<td>157 (131–163)</td>
<td>143 (125–197)</td>
<td>0.9</td>
</tr>
<tr>
<td>PRA, ng/mL per h</td>
<td>0.6 (0.4–0.6)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.9</td>
</tr>
<tr>
<td>ARR</td>
<td>299 (223–433)</td>
<td>299 (221–419)</td>
<td>1.0</td>
</tr>
<tr>
<td>Adrenal nodule on CT (%)</td>
<td>6/8 (75)</td>
<td>15/32 (46.9)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Data shown as the median (interquartile range) or number (percent of cohort). ARR indicates aldosterone/renin ratio; BP, blood pressure; CT, computed tomography; K, potassium; LI, lateralized index; PAC, plasma aldosterone concentration; PRA, plasma renin activity.

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### Table 4. CL and IL Ratio and Number of Patients With CL Adrenal Aldosterone Suppression in Non-PA Hypertensive Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL ratio</td>
<td>2.10 (0.60–4.40)</td>
</tr>
<tr>
<td>IL ratio</td>
<td>2.78 (1.83–5.60)</td>
</tr>
<tr>
<td>No. of patients with CL adrenal aldosterone suppression (%)</td>
<td>2/40 (5)</td>
</tr>
</tbody>
</table>

Data shown as the median (range) or number (percent of cohort). The CL adrenal aldosterone suppression was defined as CL ratio < 1. CL indicates contralateral; and IL, ipsilateral.
of the present study in the specificity of the diagnosis of PA and non-PA. We have demonstrated that negative results in both of CCT and SIT were seen only in 1 (1.7%) of the 57 hypertensive patients with positive case detection.29 Mulatero et al21 also reported that SIT is a reliable alternative to the FDST for confirming the diagnosis of PA. In addition, we used a PAC cutoff of 50 pg/mL for the SIT, a more permissive value for PA and stricter one for non-PA than used in previous studies.17 Mulatero et al21 have shown that supine SIT identified 60 of 67 (90%) patients confirmed as having PA by FDST when a PAC cutoff of 50 pg/mL after SIT was used. By contrast, Ahmed et al30 have recently demonstrated a high false-negative rate (16/24; 67%) by the conventional supine SIT when compared with 4% by seated SIT in PA patients based on FDST. Although the reason for discrepancy of the sensitivity between the 2 studies21,30 remains unknown, the findings by Ahmed et al29 also suggest a possible diagnosis of PA in our patients. In addition, Rossi et al2 demonstrated sensitivity of ARR cutoff of 300 after CCT was shown to be only 59% in patients with general hypertensive patients although its sensitivity was higher (ie, false-negative rate lower) among the patients with highly suspected PA (eg, spontaneous hypokalemia, high ARR).15 Therefore, the diagnosis of PA could not be completely excluded in all the patients even without positive SIT and CCT, especially in those with contralateral adrenal aldosterone suppression. The diverse specificity of the confirmatory testing should wait further establishment of the gold standard testing in future.

Two patients showed LI between 3 and 4 with contralateral aldosterone suppression in the present study. Exact evaluation of the postoperative outcome was not feasible because of lack of sufficient data including additional confirmatory testing such as oral salt-loading test and FDST for assessment of biochemical cure. However, no significant improvement of blood pressure in one case and mild but sustained elevation of PAC in the other case did not provide definite evidence for diagnosis of unilateral PA. In addition, given the finding that some of the PA patients with bilateral disease have been shown to be cured of hypertension after adrenalectomy,32 subtype diagnosis may not be specifically answered even after adrenalectomy. Possibility of PA in these 2 patients were, therefore, not completely excluded. In another important limitation, it is uncertain that our present results could be extended even if AVS is done without cosyntropin stimulation.

Perspectives
We found that the absolute concentration of aldosterone in the adrenal veins showed a wide variation and moderate gradients between the adrenal glands in patients without PA. Considering the possibility of a false-negative unilateral diagnosis, additional evidence such as contralateral suppression of aldosterone secretion and clinical findings characteristic to PA should be taken into account when contemplating surgery for patients whose LI values are in the gray zone (LI=2–4).

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Disclosures
None.

References

**Novelty and Significance**

**What Is New?**

- This is the first study to investigate plasma aldosterone concentration in the adrenal vein in non-primary aldosteronism (non-PA) hypertensive patients.
- Aldosterone showed wide range of concentrations and significant gradients between the right and left adrenal veins even in non-PA patients although none of them shows a lateralization index (LI) value ≥4.

**What Is Relevant?**

- Permissive criteria of adrenal venous sampling may lead to an inappropriate surgical indication because even non-PA patient show unilateral subtype.
- By currently recommended confirmatory testing, clinicians are not missing surgically curable PA with LI ≥4.

**Summary**

We investigated plasma aldosterone concentration in the adrenal vein of 40 non-PA hypertensive patients. It was clearly demonstrated that plasma aldosterone concentration in the adrenal vein showed significant variation and gradient even in non-PA patients. Caution should be taken in the interpretation of plasma aldosterone concentration in the adrenal vein and LI in the gray zone (LI=2–4) for subtype diagnosis of PA. Conversely, none of the patients showed an LI value of ≥4, suggesting its specificity to identify surgically curable PA.
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