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Adrenal Venous Sampling–Guided Adrenalectomy Rates in Primary Aldosteronism: Results of an International Cohort (AVSTAT)

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Abbreviations: ACTH, adrenocorticotrophic hormone; ADX, adrenalectomy; ARR, aldosterone-to-renin ratio; AVS, adrenal vein sampling; CR, contralateral ratio; LR, lateralization ratio; PA, primary aldosteronism; PAC, plasma aldosterone concentration.

Keywords: adrenalectomy, adrenal venous sampling, hyperaldosteronism, primary aldosteronism.

Abstract

Context

Adrenal venous sampling (AVS) is the current criterion standard lateralization technique in primary aldosteronism (PA). Japanese registry data found that 30% of patients with unilateral PA did not undergo adrenalectomy, but the reasons for this and whether the same pattern is seen internationally are unknown.

Objective

To assess the rate of AVS-guided adrenalectomy across an international cohort and identify factors that resulted in adrenalectomy not being performed in otherwise eligible patients.

Design, Setting, and Participants

Retrospective, multinational, multicenter questionnaire-based survey of management of PA patients from 16 centers between 2006 and 2018.

Main Outcome Measures

Rates of AVS implementation, AVS success rate, diagnosis of unilateral PA, adrenalectomy rate, and reasons why adrenalectomy was not undertaken in patients with unilateral PA.

Results

Rates of AVS implementation, successful AVS, and unilateral disease were 66.3%, 89.3% and 36.9% respectively in 4818 patients with PA. Unilateral PA and adrenalectomy rate in unilateral PA were lower in Japanese than in European centers (24.0% vs 47.6% and 78.2% vs 91.4% respectively). The clinical reasoning for not performing adrenalectomy in unilateral PA were more likely to be physician-derived in Japan and patient-derived in Europe. Physician-derived factors included non-AVS factors, such as good blood pressure control, normokalemia, and the absence of adrenal lesions on imaging, which were present before AVS.

Conclusion

Considering the various unfavorable aspects of AVS, stricter implementation and consideration of surgical candidacy prior to AVS will increase its diagnostic efficiency and utility.

Primary aldosteronism (PA) is the most frequent cause of secondary hypertension and is caused by an excess production of aldosterone from one or both adrenal glands (1-3). The etiologies of PA consist of 2 main subtypes: (i) a unilateral aldosterone-producing adenoma and (ii) bilateral adrenal hyperplasia (idiopathic hyperaldosteronism). While the unilateral subtype has a higher risk of developing cardiovascular sequela relative to the bilateral subtype (4-7), surgical removal of unilateral disease is expected to bring various benefits, including biochemical cure of hyperaldosteronism, resolution of hypertension (8, 9), lowering the risk for developing cardiovascular and chronic kidney disease (10-12), and quality of life improvements (13), compared with targeted medical treatment. Adrenal venous sampling (AVS) (14-16) is the criterion standard procedure strongly recommended by current clinical practice guidelines (17) for subtype testing of PA, especially to detect unilateral PA as an indication for adrenalectomy (ADX). However, from the

analysis of our PA registry in Japan, JPAS (Japan PA Study), 30% of patients with unilateral PA do not undergo ADX (18). Whether this same pattern is seen in other countries needs to be determined, as do the reasons for it. Given various unfavorable issues related to AVS, such as limited availability, technical demand, invasive nature, expense, and radiation exposure (19), AVS should be appropriately deployed so that its results are effectively utilized in detecting the unilateral subtype for ADX (16, 20, 21).

The primary objective of the International Multicenter Study on the Adrenal Venous Sampling Stats in Primary Aldosteronism (AVSTAT study) was to determine the rate of ADX in patients with PA following successful AVS, the reasons why ADX did not occur in patients with unilateral PA, and whether differences existed between Japanese and European centers.

Materials and Methods

Study design and patients

The AVSTAT study was conducted as a retrospective, multinational, multicenter questionnaire-based study. The AVSTAT registry was established at 16 centers, including 6 centers in Japan and 10 centers in Europe that were all part of the European Network for the Study of Adrenal Tumors (ENS@T). Patients with PA diagnosed in each center from 2006 to 2018 were included.

Diagnosis of PA was confirmed according to the guidelines of the Japan Endocrine Society or the Endocrine Society Clinical Practice Guideline (22, 23). The subtype of PA was diagnosed by AVS with and/or without adrenocorticotrophic hormone (ACTH) stimulation. Adrenal vein cannulation was defined as successful if the selectivity index was >5 with ACTH stimulation or >2 without ACTH stimulation. Unilateral PA was defined by a lateralization ratio (LR) >4 with ACTH stimulation or >2 without ACTH stimulation (15). The LR is calculated by dividing the aldosterone-to-cortisol ratio on the dominant side by that on the nondominant side. The contralateral ratio (CR) was calculated by dividing the aldosterone-to-cortisol ratio on the nondominant side by that in the inferior vena cava.

Measurements

We assessed the numbers of AVS procedures, success rate of AVS, subtype of PA (unilateral or bilateral), and rate of ADX in each subtype. We made a comparison between Japan and European centers, and between the earlier study period (January 1, 2006 to December 31, 2011) and the later study period (January 1, 2012 to December 31, 2018). We also investigated why ADX did not occur in patients with unilateral PA. The reasons were divided into 3 categories: patient's decision, physician's decision, or both.

Statistical analysis

Stata/SE ver. 14 software developed by LightStone was used for statistical analyses. All data are shown as number (%). The P values comparing 2 groups were evaluated by χ^2 test. The correlation between AVS success rate and the number of AVS implementations was evaluated by the Pearson correlation test.

Ethics

The 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 the National Hospital Organization Kyoto Medical Center as the project lead center and by the institutional ethics committees of the participating centers in accordance with local ethical guidelines.

Results

A total of 4818 patients with confirmed PA were enrolled in the AVSTAT study. AVS was performed in 3194 patients (66.3%) and was successful in 2852 patients (89.3%; range, 73.1% to 100%). Thus, appropriate AVS data for exact subtype diagnosis were not obtained in 10.7% of the patients. Subtype diagnosis of PA was unilateral in 1055 patients (37.0%). ADX was performed in 1039 patients (36.4%) of patients with successful AVS and in 924 patients (87.6%) of patients with unilateral PA (Fig. 1). Comparison of PA cases, AVS results, and rates of adrenalectomy among individual centers are shown in Table 1.

Comparison of AVS performance between Japanese and European centers

Although the number of patients with PA were similar, the rate of AVS implementation was significantly lower in Japan than in European centers. The success rate of AVS was comparable between Japan and European centers. The rates of unilateral subtype, ADX in successful AVS, and ADX in unilateral patients with PA were all significantly lower in Japanese centers than those in European centers (Table 2).

Time-dependent changes in AVS, unilateral subtype, and ADX

Table 3 shows the comparison between the earlier period (2006-2011) and the later period (2012-2018) in Japanese and European centers. The rate of AVS performance in Japan significantly decreased from 65.7% to 54.6%, while that in Europe significantly increased from 70.1% to 78.7% during the observation period. The success rate of AVS showed a significant improvement in both regions. The rates of unilateral subtype (34.9% vs 21.0%; $P < 0.001$) and ADX in successful AVS (40.9% vs 19.3%; $P < 0.001$) in Japan significantly decreased during the observation period, while these rates in European centers did not show significant changes.

Reasons why ADX was not performed despite unilateral PA after successful AVS

We analyzed the reasons why some patients with unilateral PA did not undergo ADX. In this analysis, 108 out of 131 patients were included after excluding 23 patients without sufficient follow-up data (Table 4). The rate of ADX in confirmed unilateral PA was lower in Japan than in European centers (78.2% vs 91.4%; $P < 0.001$). Overall, the reasons why patients with confirmed unilateral PA did not undergo ADX were divided almost equally between decisions of the patients themselves, their caring physicians or jointly. The rate of patient's decision not to undergo ADX was significantly lower in Japan than that in European centers (20.7% vs 48.0%; $P < 0.001$). Although the rate of physician's decision and the rate of joint decisions were not significantly different between Japanese and European centers, these rates tended to be higher in Japan than those in European centers (37.9% vs 26.0%; $P = 0.187$ and 41.4% vs 26.0%; $P = 0.093$).

Next, we analyzed the main factors that contributed to physician decisions for patients with unilateral PA to not undergo ADX (Table 5). We identified both AVS-related and non-AVS-related factors. The non-AVS-related factors included advanced age, comorbidities, good blood pressure control, and investigational findings (eg, normokalaemia, no clear adrenal tumor or bilateral findings on computed tomography [CT], discrepancy of lateralization between adrenal scintigraphy and CT findings), many of which are known prior to AVS. The AVS-related factors included discrepancy between AVS and CT findings and lack of contralateral suppression and/or low plasma aldosterone concentration (PAC) on AVS. CT findings were diagnosed by radiologists in each center. Good blood pressure control was the most prevalent factor followed by a lack of contralateral suppression or low PAC on AVS and normokalemia. In Japan, lack of contralateral suppression or low PAC on AVS

were the most common factors, followed by normokalemia and good blood pressure control. In European centers, good blood pressure control was the main factor for the physician's decision.

Discussion

In the present study, we have investigated the results of AVS, including its success rate, subtype diagnosis, and rate of ADX across 16 international centers. We also investigated whether differences existed between Japanese and European centers over time. As summarized in Fig. 2, AVS findings did not result in ADX due to 3 major factors: (i) approximately 10% due to technically unsuccessful AVS, (ii) 50% due to bilateral subtype, and (iii) 4% due to a change in treatment decision after AVS. Thus, approximately 65% of patients underwent a time-consuming, expensive, and invasive AVS in view of its primary aim of identifying the unilateral subtype for ADX, although patients with bilateral PA benefited by avoiding unnecessary ADX from AVS. The success rate of AVS improved significantly over time, but it is still not 100% in many centers. It could be further improved by increasing experience, implementation in experienced centers, and introducing additional approaches such as the intraprocedural rapid cortisol assay (24).

In agreement with previous studies, unilateral PA accounts for only 30% of the total patients with PA who underwent AVS in the present study. The prevalence of bilateral PA was significantly higher in Japan than in European centers. The present results indicated that 4 AVS studies were needed to detect 1 unilateral patient with PA in Japan. Bilateral subtype, as the major subtype of PA (18), accounts for the high number of AVS procedures that need to be performed in order to identify patients with unilateral PA who stand to benefit from ADX. Lack of alternative established methods to distinguish bilateral from unilateral PA has been the fundamental reason for the application of AVS in a large number of patients with PA. Clinical prediction models of PA subtype (25-28), biochemical approaches such as urine steroid profile (29) and plasma microRNA analysis (30), and noninvasive positron emission tomography imaging (31-33) may improve the diagnostic efficiency of AVS in the subtype diagnosis of PA.

In addition, another factor which contributed to the inefficient use of the AVS results was the change in intended treatment decision after AVS. ADX was not performed in 12% of the patients with unilateral PA. One-third of those patients did not undergo surgery due to medical factors. The decision not to undergo ADX in unilateral PA was made predominantly by physicians in Japan, while it was more commonly the patient's decision in European centers. Reasons for physician decisions consisted of both non-AVS-related and AVS-related factors. In Japan, lack of CR suppression or low PAC on AVS as AVS-related factors were the most common factor, followed by normokalemia and good blood pressure control as the non-AVS-related factors. In European centers, however, good blood pressure control was the major factor for physician decision not to proceed to ADX. Besides the AVS-related factors, all of the non-AVS-related factors were highly likely to have been present before AVS. The decision to undergo AVS should therefore be carefully considered and take into account the various clinical, biochemical, and radiological findings to reserve AVS only for those patients who would be eligible and willing to undergo ADX if the AVS was supportive of unilateral disease.

We also investigated to see whether there was a difference between Japanese and European centers over time. While the number of patients with confirmed PA increased significantly, the rate of AVS use in patients with PA, the rate of unilateral disease, and the rate of ADX in patients with successful AVS significantly decreased over the study time period in Japan. These results were in contrast to those in European centers, where the rate of AVS use increased, whereas the rate of unilateral subtype, ADX in patients with successful AVS, and ADX in patients with unilateral subtype remained unchanged over time. The reasons responsible for the difference in the rate of AVS use between Japan and European centers remain unknown. However, the results clearly indicated that larger number of patients with bilateral PA have been diagnosed and subjected to AVS for subtype diagnosis in Japan than in European centers. The reason for the difference of the ratio of unilateral

and bilateral subtype between Japan and European centers also remains to be elucidated. The differential somatic mutation burdens in aldosterone-producing adenomas in different ethnicities may be related to the difference (34). More likely, however, the different cutoff value of aldosterone-to-renin ratio (ARR) for screening might explain the difference: the recommended ARR cutoff in Japan is 20ng/dL per ng/mL/h (22, 23), whereas the most commonly adopted cutoff of ARR is 30ng/dL per ng/mL/h in the widely used Endocrine Society guidelines (17). This lower ARR cutoff was recommended by the 2011 Japanese guidelines and might lead to a significant increase in diagnosing PA with milder phenotype. It has been well known that PAC is lower in patients with bilateral PA than in patients with unilateral PA (5). The use of a lower ARR cutoff for screening may be responsible for the significant increase in the numbers of PA with bilateral subtype in Japan (25-31). However, further studies are needed to verify this hypothesis, since the diagnostic ARR data are not available in the present study.

Limitation

Our study has several limitations. The present study was retrospective and based on the questionnaire to each center, which could have the potential to bias all the estimates in the results (33, 34). Although the centers participated to this study are all referral centers in the clinical practice of PA in Japan and Europe, the numbers were limited and did not necessarily represent all the centers, which could bias the comparison between Japan and Europe.

The proportion of unilateral and bilateral PA could be affected by the method of AVS, with or without ACTH infusion, and the criteria for successful AVS and lateralization. Because confirmatory testing of PA and AVS is not standardized internationally, the diagnosis of PA and lateralization might not be the same between Japan and Europe.

Another factor which might affect the indication of adrenal surgery was the availability of an appropriate endocrine surgeons. Details of this factor remain unknown, since it was not included in the present questionnaires, However, since all the centers participated into the present study were the regional referral center with sufficient experience of AVS and laparoscopic ADX, it is unlikely that it was a major factor affecting the rate of ADX.

Conclusion

Despite significant increases in the number of diagnosed patients with PA, AVS implementation, and its technical development over the past decade, the overall rate of ADX corresponded only to one-third of the patients with PA subjected to AVS. The primary reason for patients not undergoing ADX was the bilateral subtype diagnosis, followed by unsuccessful AVS. In addition, some patients with unilateral PA did not undergo ADX due to the change of treatment policy by the doctors after successful AVS. Most of these reasons were non-AVS-related clinical and laboratory factors that were present even before AVS. Although AVS is strongly recommended as the criterion standard by the clinical guideline for subtype diagnosis of PA, its primary aim is to distinguish unilateral PA for ADX. Considering the various issues associated with AVS, such as its invasive and technically demanding nature, cost, and radiation exposure, there is a need for its diagnostic efficiency to be improved. The identification of those with unilateral PA who stand to benefit most from ADX remains essential and improvements in the noninvasive pre-AVS prediction of the bilateral subtype are required, especially in Japan.

Abbreviations

ACTH

adrenocorticotrophic hormone

ADX

adrenalectomy

ARR

aldosterone-to-renin ratio

AVS

adrenal vein sampling

CR

contralateral ratio

LR

lateralization ratio

PA

primary aldosteronism

PAC

plasma aldosterone concentration

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Table 1. Comparison of PA Cases, AVS Results, and Adrenalectomy Rates Among Each Center

Center number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Confirmed PA	682	577	570	476	445	433	337	330	241	240	190	196	766	588	399	297
AVS implementation (%)	38.3	58.9	40.0	82.8	79.5	60.0	10.0	98.7	99.9	55.7	61.3	89.9	66.8	74.4	66.7	40.7
Successful AVS (%)	91.2	91.6	86.0	90.6	84.1	95.0	29.9	98.7	83.1	82.1	87.9	78.7	82.0	88.1	73.1	90.9
Unilateral PA (LR > 4) (%)	34.5	15.8	39.8	31.9	86.6	27.1	47.7	64.4	53.6	28.7	57.0	63.6	58.5	55.1	41.1	60.0
Bilateral PA (LR ≤ 4) (%)	65.5	84.2	60.2	68.1	91.4	72.9	52.3	35.6	46.4	71.3	43.0	36.4	41.5	44.9	58.9	40.0
ADX in successful AVS (%)	30.3	16.1	37.8	29.1	10.0	32.2	43.1	60.7	65.5	28.8	49.9	59.9	55.2	62.2	23.3	70.0
ADX in unilateral PA (%)	70.7	93.9	89.7	86.8	68.0	86.6	95.7	99.3	85.5	50.0	88.0	88.2	87.5	10.0	65.5	10.0
ADX in bilateral PA (%)	90.0	15.5	34.4	29.1	68.8	13.3	0.6	0.0	34.8	81.1	41.1	77.7	0.0	17.6	0.0	25.0

AVS implementation rate was the number of AVS procedures divided by the number of confirmed PA. Successful AVS rate was the number of successful AVS divided by AVS implementation. ADX in successful AVS was the number of ADX in successful AVS divided by the number of successful AVS. Unilateral PA rate was the number of unilateral PA divided by the number of successful AVS. Abbreviations: ADX, adrenalectomy; AVS, adrenal venous sampling; LR, lateralization ratio; and PA, primary aldosteronism.

Table 2. Comparison of PA Cases, AVS Results, and Adrenalectomy Rates Between Japanese and European Centers

Parameters	Japanese centers	European centers	<i>P</i>
No. of centers	6	10	
Confirmed PA	2522	2296	
AVS implementation (%)	1437 (57.0)	1757 (76.5)	<0.001*
Successful AVS (%)	1282 (89.2)	1570 (89.4)	0.936
Unilateral PA (LR > 4) (%)	308 (24.0)	747 (47.6)	<0.001*
Bilateral PA (LR ≤ 4) (%)	974 (76.0)	823 (52.4)	<0.001*
ADX in successful AVS (%)	308 (24.0)	731 (46.6)	<0.001*
ADX in unilateral PA (%)	241 (78.2)	683 (91.4)	<0.001*
ADX in bilateral PA (%)	67 (6.9)	48 (5.8)	0.367

Data are shown as number (%).

P value comparing Japan and Europe, which are evaluated by χ^2 test.

AVS implementation rate was the number of AVS procedures divided by the number of confirmed PA. Successful AVS rate was the number of successful AVS divided by AVS implementation. ADX in successful AVS was the number of ADX in successful AVS divided by the number of successful AVS. Unilateral PA rate was the number of unilateral PA divided by the number of successful AVS. Abbreviations: ADX, adrenalectomy; AVS, adrenal venous sampling; LR, lateralization ratio; PA, primary aldosteronism.

Table 3. Historical Changes in AVS Results in Japanese and European Centers

Parameters	Japanese centers			European centers		
	2006-2011	2012-2018	<i>P</i>	2006-2011	2012-2018	<i>P</i>
Confirmed PA	542	1980		519	1738	
Performed AVS	356 (65.7)	1081 (54.6)	<0.001*	364 (70.1)	1367 (78.7)	<0.001*
Successful AVS	281 (78.9)	1001 (92.6)	<0.001*	288 (79.1)	1263 (92.4)	<0.001*
Unilateral PA (LR >4)	98 (34.9)	210 (21.0)	<0.001*	125 (43.4)	619 (49.0)	0.086
ADX in successful AVS	115 (40.9)	193 (19.3)	<0.001*	130 (45.1)	614 (48.6)	0.287
ADX in unilateral PA	81 (82.7)	160 (76.2)	0.204	113 (90.4)	570 (92.1)	0.531

Data are shown as number (%). *P* value comparing 2006-2011 and 2012-2018, which are evaluated by χ^2 test. The data of Center 1 were unavailable (missing). AVS implementation rate was the number of performed AVS procedures divided by confirmed PA. Successful AVS rate was the number of successful AVS procedures divided by AVS implementation. Unilateral PA rate was the number of unilateral PA divided by successful AVS procedures. Adrenalectomy rate was the number of adrenalectomy (ADX) divided by the number of successful AVS procedures. Abbreviations: AVS, adrenal venous sampling; LR, lateralized ratio; PA, primary aldosteronism.

Table 4. Reasons for Not Undergoing Adrenalectomy in Patients With Unilateral PA

Parameters	All	Japanese centers	European centers	<i>P</i>
No. of centers	16	6	10	
Total number of patients	108	58	50	
Patient's decision only (%)	36 (33.3)	12 (20.7)	24 (48.0)	0.003*
Physician's decision only (%)	35 (32.4)	22 (37.9)	13 (26.0)	0.187
Joint decision (%)	37 (34.3)	24 (41.4)	13 (26.0)	0.093

Data are shown as number (%). *P* value comparing Japan and ENS@T, evaluated by χ^2 test.

Table 5. Factors Contributing to Physician's Decisions for Patients With Unilateral PA Not to Undergo Adrenalectomy

Parameters	All	Japanese centers	European centers
No. of centers	16	6	10
Total number of patients	108	58	50
Non-AVS-related factors			
Elderly (%)	6 (5.6)	2 (3.4)	4 (8.0)
Comorbidities (%)	14 (13.0)	7 (12.1)	7 (14.0)
Good blood pressure control (%)	32 (29.6)	14 (24.1)	18 (36.0)
Normokalemia (%)	23 (21.3)	17 (29.3)	6 (12.0)

Parameters	All	Japanese centers	European centers
Bilateral or no clear adrenal tumor on CT (%)	18 (16.7)	11 (19.0)	7 (14.0)
Discrepancy of lateralization between scintigraphy and CT findings (%)	3 (2.8)	1 (1.7)	2 (4.0)
AVS-related factors			
Discrepancy between AVS and CT findings (%)	9 (8.3)	8 (13.8)	1 (2.0)
Lack of CR suppression or low PAC on AVS (%)	27 (25.0)	22 (37.9)	5 (10.0)

Figure 1. Investigation and management of PA cases in the AVSTAT study.

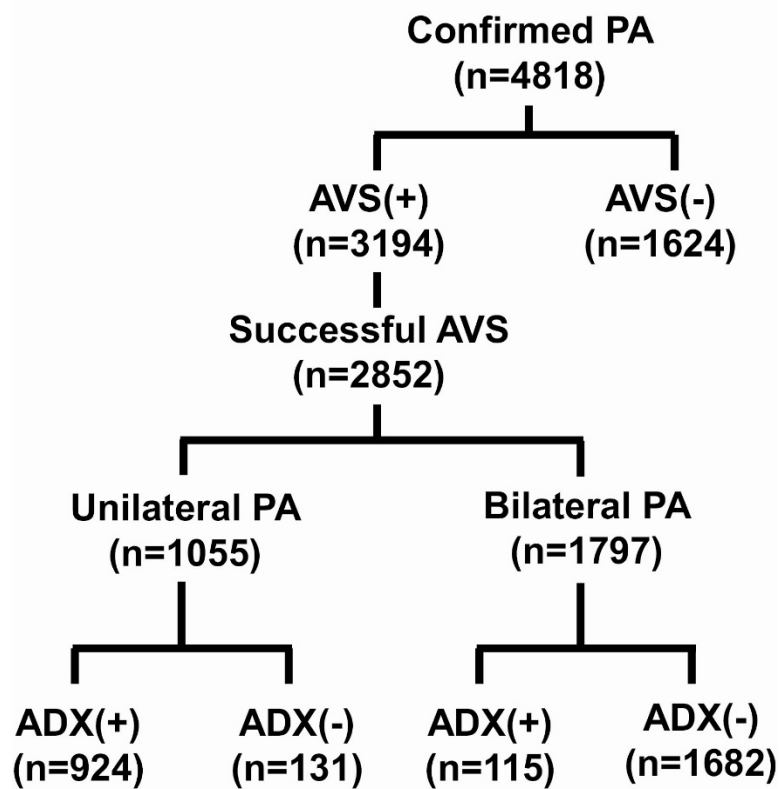


Figure 2. AVS outcomes based on subtype diagnosis and adrenalectomy in all patients, at Japanese centers and at European centers. a.) unsuccessful AVS, b.) unilateral subtype with ADX, c.) unilateral subtype without ADX, d.) bilateral subtype with ADX, e.) bilateral subtype without ADX.

