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Adrenal venous sampling for stratifying patients for surgery of adrenal nodules detected using dynamic contrast enhanced CT

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PURPOSE
We aimed to assess the value of adrenal venous sampling (AVS) for diagnosing primary aldosteronism (PA) subtypes in patients with a unilateral nodule detected on adrenal computed tomography (CT) and scheduled for adrenalectomy.

MATERIALS AND METHODS
This retrospective study included 80 consecutive patients with PA undergoing CT and AVS. Different lateralization indices were assessed, and a cutoff established using receiver operating characteristic curve analysis. The value of CT alone versus CT with AVS for differentiating PA subtypes was compared. The adrenalectomy outcome was assessed, and predictors of cure were determined using univariate analysis.

RESULTS
AVS was successful in 68 patients. A cortisol-corrected aldosterone affected-to-unaffected ratio cutoff of 2.0 and affected-to-inferior vena cava ratio cutoff of 1.4 were the best lateralization indices, with accuracies of 82.5% and 80.4%, respectively. CT and AVS diagnosed 38 patients with aldosterone-producing adenomas, five patients with unilateral adrenal hyperplasia, and 25 patients with bilateral adrenal hyperplasia. Of the 52 patients with a nodule detected on CT, subsequent AVS diagnosed bilateral adrenal hyperplasia in 14 patients (27%). Compared to the results of combining CT with AVS, the accuracy of CT alone for diagnosing aldosterone-producing adenomas was 71.1% ($P < 0.001$). The cure rate for hypertension after adrenalectomy was 39.2%, with improvement in 53.5% of patients. On univariate analysis, predictors of persistent hypertension were male gender and preoperative systolic blood pressure.

CONCLUSION
To avoid inappropriate surgery, AVS is necessary for diagnosing unilateral nodules with aldosterone hypersecretion detected by CT.

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Primary aldosteronism (PA) is the most common form of secondary hypertension, with a prevalence of 5%–11% (1–3). PA is due primarily to the hypersecretion of aldosterone by an aldosterone-producing adenoma (APA) or unilateral (primary) adrenal hyperplasia (UAH), which constitute 30%–40% of cases; the remainder are presumed to be secondary to idiopathic bilateral adrenal hyperplasia (BAH) (1, 4, 5). APA and UAH are two forms of unilateral aldosterone hypersecretion, and both are curable with adrenalectomy. BAH induces bilateral aldosterone hypersecretion, and anti-aldosterone drugs are used in its medical management (5–7).

The plasma aldosterone-to-renin ratio is used to screen for PA in patients at high risk for PA (8). Recent guidelines recommend using computed tomography (CT) of the adrenal gland to categorize the subtype after confirming PA. However, CT cannot reliably visualize a microadenoma or distinguish between an incidentaloma or BAH and APA. It has been suggested that adrenal venous sampling (AVS) be performed to determine the subtype of PA and to differentiate between unilateral and bilateral production of aldosterone preoperatively (9). AVS to measure the adrenal vein aldosterone and cortisol is the gold standard for lateralizing aldosterone secretion (10). Lateralization is defined using several ratios. In patients with APA or UAH, a unilateral adrenalectomy results in a complete cure or improved hypertension and potassium normalization in approximately 30% of patients, with reported rates up to 86% (11–15).

This study assessed several lateralization ratios to establish the most predictive of unilateral disease. We also compared the CT results with those of bilateral AVS for differentiating the PA subtype, with the assumption that AVS is necessary before surgery, even in patients with nodules <10 mm detected with CT. Finally, we assessed the outcomes of adrenalectomy in our patients to identify preoperative predictors of a good outcome.

Materials and methods

Patient population

The records of consecutive patients referred to Keimyung University Dongsan Hospital, Endocrinology Department for suspected PA between January 2004 and June 2012 were reviewed retrospectively. A preliminary diagnosis of PA was based on clinical suspicion, including severe hypertension (blood pressure [BP] >180/110 mmHg despite drug treatment or drug resistance), hypertension with hypokalemia (serum potassium <3.6 mmol/L), or hypertension with an incidental adrenal nodule (9). Diuretics, beta-blockers, and antagonists of the renin-angiotensin system were withheld for two weeks, and aldosterone antagonists were stopped six weeks

before screening for PA. All patients underwent a saline suppression test after withdrawing interfering medications. A serum aldosterone >137 pM after infusing 2 L of 0.9% saline confirmed PA (16). All patients who were candidates for surgery underwent CT and AVS.

Definition of primary aldosteronism

To interpret the results of AVS, an abnormal adrenal gland was defined based on the absolute aldosterone level or the cortisol-corrected aldosterone (Aldo/Cort). For CT, lateralization was defined as a unilateral adenoma (≥10 mm) with a completely normal contralateral gland, based on the possible cutoff for adrenalectomy without the use of AVS (15, 17).

Surgery was indicated when patients had clear lateralization on AVS and concordant CT. However, before making this decision, an affected-to-unaffected aldosterone ratio >2.2 with an unaffected-to-inferior vena cava (IVC) ratio <1.7 were used to define lateralization (18). Concordance was defined as CT showing a normal gland contralateral to the aldosterone lateralization. The gland to which the aldosterone lateralizes might have an abnormality of any size or might indeed appear normal, but be harboring a very small adenoma undetected by CT.

Based on the CT and AVS results, the PA was classified, and APA was defined using concordant results between the unilateral nodule on CT and lateralized aldosterone production as assessed by AVS. UAH was defined as a normal gland or unilateral hyperplasia on CT and lateralized aldosterone production as assessed by AVS. BAH was defined by normal glands or bilateral CT abnormalities and bilateral aldosterone secretion on AVS, or bilateral CT abnormalities and lateralized aldosterone secretion on AVS.

After adrenalectomy, the patients were grouped by their BP as either cured, improved, or no improvement. Cure was defined as a BP <140/90 mmHg with no antihypertensives. Improvement was defined as a BP <140/90 mmHg on the same or a reduced dose of antihypertensives. Those with no improvement met neither of these two criteria. Outcome was assessed as the best BP measured between 120 and 365 days after the adrenalectomy (19).CT

Adrenal CT was performed using various multidetector scanners (Sensation 16, 64; Somatom Definition Flash, Siemens, Erlangen, Germany). CT was performed at 3–5 mm collimation, 3–5 mm reconstruction intervals, 120 kVp, 250 mA, and a 1:1 table pitch. A maximum of 150 mL of nonionic contrast medium was injected intravenously at 2–3 mL/s with a power injector. Unenhanced and enhanced CT was acquired at 60 s and 15 min, respectively. The adrenal CT appearance was described as normal, hyperplasia when the gland volume was high or if its edges had lost their concave shape, and nodular when a circular adrenal lesion was detected. An adrenal adenoma was defined on CT using the following criteria: a nodular lesion that was negative or 10 Hounsfield units less on unenhanced CT and a homogeneous enhancing nodular lesion with an absolute percentage loss of enhancement >60% (20, 21).

Adrenal venous sampling

After obtaining informed consent, bilateral AVS was performed by one experienced vascular radiologist over the 10-year period using a percutaneous right transfemoral vein approach. Various 4 or 5 F glide catheters were used to catheterize both adrenal veins, and the catheter placement was confirmed fluoroscopically before sampling by injecting a small amount of contrast. Samples for measuring the serum aldosterone and cortisol were collected from both adrenal veins and the IVC. Accurate catheterization of the adrenal veins was assumed when the ratio of the cortisol levels in the adrenal vein to the IVC was >2.0.

Hormone assays

The serum and urine aldosterone concentrations were measured by radioimmunoassay (Abbott Architect, Maidenhead, UK) with a coefficient of variation of 9.5%. The plasma renin activity was measured by immunochemiluminometry (Liaison, DiaSorin, Dartford, UK) with a coefficient of variation of 6%. The plasma cortisol was measured using immunochemiluminometry (Cobas-6000, Indianapolis, Indiana, USA) with a coefficient of variation of 4.5%.

Statistical analysis

All data are shown as the mean±standard deviation. Patients with unilateral (APA and UAH) and bilateral (BAH) findings were compared using an unpaired Student's t test. Categorical variables were compared using the chi-square test.

A receiver operating characteristic (ROC) curve analysis of published lateralization ratios and novel ratios was used to assess the efficacy of each method and to establish appropriate cutoff values. The ratio of the affected to unaffected side and unaffected-to-peripheral ratio were analyzed.

The sensitivity, specificity, and predictive values of CT alone for the diagnosis of APA were calculated and compared to results combining CT with AVS. The positive predictive values according to nodule size were compared using Fisher's exact test. The accuracy of CT alone and CT combined with AVS was compared using McNemar's test. The statistical power for detecting a difference with 72.4%–100% accuracy using a sample of 68 paired observations exceeded 99%.

Univariate analysis was performed on all possible variables of hypertensive cure using the paired Student's t test and chi-square test for continuous and categorical variables, respectively. Statistical analyses were per-formed using a computer software (Statistical Package for Social Sciences, Version 17.0, SPSS Inc., Chicago, Illinois, USA). *P* values that were less than 0.05 was deemed to indicate statistical significance.

Results

Baseline patient characteristics

Eighty patients with PA were identified, all of whom underwent adrenal CT and AVS. The mean patient age was 46 years (range, 22–70 years) and 52 were males (65%). The mean systolic and diastolic BP were 155±5.7 and 93±2.4 mmHg, respectively. Drug-resistant hypertension was observed in 48 patients (60%), and there were no local or general complications during or after AVS. Cortisol levels were detectable in 68 patients with bilateral AVS (85%), while the results were incomplete in 12 patients (15%) due to difficulty catheterizing the right adre-

nal vein; the latter were treated medically. The diagnosis was APA in 38 patients, presumed BAH in 30, and UAH in five.

No significant differences in age, gender, systolic or diastolic BP, duration of hypertension, family history of hypertension, plasma renin activity, or urinary aldosterone were observed in patients with APA, UAH, or BAH (Table 1). The potassium levels were slightly lower in the APA group, although this was not significant (APA/UAH, 2.9±0.1 mmol/L vs. BAH, 3.1±0.1 mmol/L; P = 0.085). The plasma aldosterone level and plasma aldosterone-to-renin ratio did not differ significantly between the two groups.

Lateralization ratios

Only those patients with successful bilateral adrenal sampling were included. We compared the published lateralization ratios in patients with unilateral and bilateral disease and preformed ROC curve analysis for each ratio (Table 2). Only those ratios in which the area under the curve (AUC) was highly significant were included in further analysis. The AUC was highest for Aldo/Cort A:U (AUC=0.882, P = 0.0007) and Aldo/Cort U:IVC (AUC=0.851, P = 0.0009). The optimum cutoff for lateralization was considered for these two ratios. The cutoff values for Aldo A:IVC (P = 0.825) and Aldo/Cort A:IVC (P = 0.093) were not significant.

The ROC curve for Aldo/Cort A:U had a cutoff >2.0, giving the optimum sensitivity with minimal loss of specificity. Using cross-tabulation, the sensitivity was 100% (43/43 APA or UAH), specificity 56.0% (14/25 BAH), and diagnostic accuracy 82.5%. For Aldo/Cort U:IVC, a cutoff <1.4 gave an optimum sensitivity of 95.3% (41/43 APA or UAH), specificity of 48.0% (12/25 BAH), and diagnostic accuracy of 80.2%.

CT findings of the adrenal gland

Fifty-two patients (76.4%) were diagnosed with a unilateral nodular abnormality, of whom 30 patients (55.6%) had a nodule at least 10 mm, four (5.8%) had unilateral hyperplasia, six (8.8%) had bilateral abnormalities, and six (8.8%) had a normal CT.

Table 1. Demographics of patients with unilaterality and bilaterality in primary aldosteronism

	APA/UAH (n=43)	BAH (n=25)	*P*
Age (years)	46.3±1.8	48.2±1.5	0.086
Gender (male/female)	25/18	14/11	0.863
Systolic BP at referral (mmHg)	153.2±3.3	156.8±3.0	0.158
Diastolic BP at referral (mmHg)	95.4±2.5	92.5±2.1	0.330
Duration of hypertension (years)	7.25±0.8	8.0±1.0	0.072
Family history of hypertension	15/27 (55.5%)	10/20 (50.0%)	0.834
Plasma potassium (mmol/L)	2.9±0.1	3.1±0.1	0.085
Plasma renin activity (ng/L)	6.0±1.5	7.0±1.5	0.081
Plasma aldosterone (ng/100 mL)	26.0±4.5	22.5±3.5	0.076
Plasma aldosterone-to-renin ratio	112.5±34.7	88.5±23.8	0.061
Urinary aldosterone (mg/day)	22.5±3.5	20.3±2.8	0.090

APA, aldosterone producing adenoma; BAH, bilateral adrenal hyperplasia; BP, blood pressure; UAH, unilateral adrenal hyperplasia.
Data are given as mean±standard deviation or n (%).

Table 2. Results of ROC curve analysis of different lateralization indices

Lateralization index	AUC	*P*
Aldo A:U	0.705	0.019
Aldo U:IVC	0.740	0.007
Aldo A:IVC	0.470	0.825
Aldo/Cort A:U	0.882	< 0.001
Aldo/Cort U:IVC	0.850	< 0.001
Aldo/Cort A:IVC	0.652	0.093

A, affected adrenal gland; Aldo, aldosterone; Aldo/Cort, cortisol corrected aldosterone; AUC, area under the curve; IVC, inferior vena cava; ROC, receiver operating characteristic; U, unaffected adrenal gland.

Diagnosis of aldosterone-producing adenoma using CT and adrenal venous sampling

Using the CT and AVS results, APA was diagnosed in 38 patients (55.8%) (Table 3, Fig.). Of these, 28 APA underwent an adrenalectomy, and adenomas were confirmed in 25 patients histologically. In patients 6, 11, and 28, the histology showed adrenal hyperplasia. Patients 6 and 11 had a nonsignificant Aldo/Cort A:U of 1.6 and 1.4 and an Aldo/Cort U:IVC of 2.1 and 2.6, respectively. Nevertheless, they requested surgery to try to cure hypokalemia. Patient 28 had severe, drug-resistant hypertension, which warranted radical treatment despite the small nodule size and hyperplastic nature of the adrenal gland as assessed by CT. Twelve patients with APA preferred medical treatment and an annual follow-up to immediate surgery.

Diagnosis of unilateral adrenal hyperplasia using CT and adrenal venous sampling

Five patients (7.4%) were diagnosed with UAH, three of whom had a normal CT, and two had unilateral adrenal hyperplasia (Table 3, Fig.). All three patients have been treated medically in our institution, with annual CT and laboratory follow-up.

Diagnosis of bilateral adrenal hyperplasia using CT and adrenal venous sampling

Benign adrenal hyperplasia was diagnosed in 25 patients (36.7%). The mean Aldo/Cort A:U was significantly higher in APA patients than in BAH patients (APA 3.2±0.5 vs. BAH 2.1±0.4, P < 0.001), and the Aldo/Cort U:IVC was significantly lower (APA 0.9±0.2 vs. BAH 1.9±0.3, P < 0.001). Three patients had normal CT and six had bilateral abnormalities (Table 4).

Table 3. Characteristics of aldosterone-producing adenoma and unilateral adrenal hyperplasia using CT and adrenal venous sampling

Patient (gender/age [years])	CT	Aldo/Cort A:U	Aldo/Cort U:IVC	Lateralization
Aldosterone-producing adenoma				
1 (M/39)	Nodule (right, 6 mm)	2.8	1.2	Right
2 (F/40)	Nodule (right, 10 mm)	3.0	1.1	Right
3 (M/42)	Hyperplasia (left, 7 mm)	3.2	1.0	Left
4 (F/44)	Nodule (left, 16 mm)	3.5	0.8	Left
5 (M/47)	Hyperplasia (right)	3.1	1.1	Right
6 (M/48)	Nodule (left, 8 mm)	1.6	2.1	Left
7 (M/38)	Nodule (right, 15 mm)	5.5	0.4	Right
8 (F/42)	Nodule (left, 8 mm)	2.5	1.4	Left
9 (M/43)	Nodule (left, 10 mm)	3.8	0.7	Left
10 (M/41)	Nodule (left, 25 mm)	6.2	0.1	Left
11 (F/49)	Nodule (right, 18 mm)	1.4	2.6	Right
12 (M/44)	Nodule (left, 15 mm)	5.2	0.3	Left
13 (F/38)	Nodule (right, 7 mm)	3.5	0.7	Right
14 (M/41)	Nodule (left, 16 mm)	4.2	0.5	Left
15 (M/40)	Nodule (right, 15 mm)	2.4	1.6	Right
16 (F/42)	Nodule (left, 22 mm)	5.8	0.3	Left
17 (M/45)	Nodule (left, 24 mm)	6.2	0.2	Left
18 (F/46)	Nodule (left, 14 mm)	2.5	1.5	Left
19 (M/44)	Nodule (right, 12 mm)	2.9	1.4	Right
20 (F/43)	Nodule (left, 8 mm)	3.5	1.2	Left
21 (M/41)	Nodule (left, 16 mm)	4.2	0.7	Left
22 (F/38)	Nodule (left, 25 mm)	7.5	0.1	Left
23 (M/50)	Nodule (right, 26 mm)	2.5	1.4	Right
24 (M/49)	Nodule (left, 32 mm)	2.4	1.5	Left
25 (F/47)	Nodule (left, 28 mm)	2.8	1.4	Left
26 (F/44)	Nodule (left, 7 mm)	3.5	1.1	Left
27 (M/42)	Nodule (left, 15 mm)	3.2	1.2	Left
28 (M/41)	Nodule and hyperplasia (left, 4 mm)	4.0	1.0	Left
29 (M/40)	Nodule and hyperplasia (left, 6 mm)	4.2	1.0	Left
30 (F/44)	Nodule (left, 18 mm)	3.5	1.2	Left
31 (F/45)	Nodule (left, 24 mm)	3.1	1.3	Left
32 (F/44)	Nodule (right, 28 mm)	3.8	1.4	Right
33 (M/43)	Nodule (left, 26 mm)	2.4	1.6	Left
34 (F/42)	Nodule (left, 24 mm)	5.2	0.9	Left
35.M/45	Nodule (right, 20 mm)	6.5	0.3	Right
36 (M/46)	Nodule (left, 10 mm)	2.3	1.5	Left
37 (F/48)	Nodule (left, 15 mm)	4.5	0.7	Left
38 (M/45)	Nodule (right, 16 mm)	4.2	0.9	Right
Unilateral adrenal hyperplasia				
1 (F/44)	Normal	4.5	0.5	Left
2 (M/43)	Hyperplasia (left)	5.8	0.3	Left
3 (M/41)	Normal	4.0	0.8	Right
4 (M/42)	Hyperplasia (right)	2.4	1.4	Right
5 (F/45)	Normal	3.5	1.2	Left

A, affected adrenal gland; Aldo, aldosterone; Aldo/Cort, cortisol corrected aldosterone; F, female; IVC, inferior vena cava; M, male; U, unaffected adrenal gland.

Sixteen (64%) patients had a unilateral nodular CT abnormality. Of these, 12 (75%) had nodules ≥10 mm, and four patients had nodules <10 mm. Twelve patients had Aldo/Cort A:U >2.2 and Aldo/Cort U:IVC <1.7, but bilateral CT abnormalities in three patients or a contralateral CT nodule in nine patients led to a diagnosis of BAH.

Assessment of unilateral adrenalectomy using CT and the adrenal venous sampling results

Fifty-two patients (76.4%) had a unilateral nodule on CT. Of the patients undergoing AVS, 38 (73.0%) were confirmed to have APA, and 14 (27.0%) were diagnosed with BAH due to bilateral or contralateral aldosterone production. Fifteen of these 18 patients (83.3%) had a nodule ≥10 mm on CT. The patients were referred for a unilateral adrenalectomy using the above criteria. Compared to CT combined with AVS (Cort A:U >2.0, Aldo/Cort U:IVC <1.4) to diagnose APA, CT alone had 100% sensitivity (38/38), 42.8% (6/14) specificity, 65.6% positive predictive value (21/32), 100% negative predictive value (20/20), and 71.1% (37/52) diagnostic accuracy for APA, which differed significantly ($P < 0.001$) from the 98.0% (51/52) diagnostic accuracy obtained when CT was combined with AVS. Overall, most patients would have been classified appropriately as having either unilateral or bilateral disease.

A unilateral adenoma ≥10 mm with a completely normal contralateral gland has been suggested as a criterion for surgery (22). In comparison, the positive predictive value of CT alone for diagnosing APA with nodules ≥10 mm was no different from that for small nodules detected using CT (65% vs. 75%; $P = 0.900$).

Outcome after adrenalectomy

Of the 38 patients with unilateral disease, 35 had long-term outcome data. Of the remaining three patients, follow-up records were unavailable for two, while the remaining patient awaits review after a recent adrenalectomy. After adrenalectomy, the hypertension was cured in 39.2% (11/28) of the patients and improved in 53.5% (15/28). Two patients did not meet

Table 4. Characteristics of bilateral adrenal hyperplasia using CT and adrenal venous sampling

Patient (gender/age [years])	CT	Aldo/Cort A:U	Aldo/Cort U:IVC	Lateralization
1 (M/51)	Normal	1.5	2.8	None
2 (F/49)	Normal	1.2	2.3	None
3 (M/39)	Hyperplasia (bilateral)	1.3	2.5	None
4 (F/44)	Nodules (bilateral; right, 16 mm; left, 11 mm)	4.0	0.8	Right
5 (M/46)	Nodule (right, 0.8 mm)	1.9	2.6	None
6 (M/45)	Hyperplasia (bilateral)	2.8	1.5	Left
7 (M/51)	Nodule (right, 0.7 mm)	1.8	2.8	None
8 (F/45)	Nodule (left, 15 mm)	2.5	1.5	Right
9 (M/46)	Hyperplasia (bilateral)	3.2	1.2	Left
10 (F/44)	Nodules (bilateral right, 12 mm; left, 11 mm)	1.4	2.6	None
11 (M/48)	Hyperplasia (right) Nodule (left, 20 mm)	3.5	1.0	Left
12 (M/45)	Nodule (right, 16 mm)	3.5	1.0	Left
13 (F/43)	Nodule (left, 0.6 mm)	1.4	2.7	None
14 (M/44)	Nodule (left, 13 mm)	2.8	1.5	Right
15 (M/47)	Nodule (right, 15 mm)	3.2	1.2	Left
16 (M/46)	Nodule (left, 0.8 mm)	2.5	1.5	None
17 (F/45)	Nodule (right, 12 mm)	2.0	2.1	None
18 (M/42)	Nodule (left, 16 mm)	2.1	2.4	Right
19 (M/44)	Nodule (right, 10 mm)	2.0	1.8	None
20 (M/46)	Nodule (right, 25 mm)	3.2	1.4	Left
21 (F/45)	Nodule (left, 15 mm)	2.7	1.3	Right
22 (F/44)	Nodule (right, 17 mm)	1.8	1.9	None
23 (F/46)	Nodule (left, 19 mm)	2.0	1.9	Right
24 (F/47)	Nodule (left, 28 mm)	3.1	1.1	Right
25 (F/45)	Normal	1.1	4.1	None

A, affected adrenal gland; Aldo, aldosterone; Aldo/Cort, cortisol corrected aldosterone; F, female; IVC, inferior vena cava; M, male; U, unaffected adrenal gland.

Table 5. Univariate analysis of preoperative predictors of postadrenalectomy hypertension

	Cure (n=11)	No cure (n=17)	*P*
Age (years)	43.8±2.7	46.2±2.5	0.131
Gender (male/female)	3/8	12/5	0.025
Preoperative systolic BP (mmHg)	155.2±4.5	158.8±3.6	0.01
Preoperative diastolic BP (mmHg)	93.4±4.3	95.5±2.7	0.630
Size of nodules (mm)	2.0±0.3	1.4±0.2	0.142
Family history of hypertension	3	9	0.248
Duration of hypertension (years)	4.17±1.3	6.4±0.9	0.196
Plasma potassium (mmol/L)	3.0±0.1	2.7±0.1	0.158
BMI (kg/m^2)	27.1±1.5	28.8±1.4	0.208
Aldo postsaline suppression test[a]	648.5±109.1	528.6±78.5	0.309
Number of antihypertensives	2.1±0.3	2.5±0.3	0.311

[a]Aldosteron level after saline suppression test. BMI, body mass index; BP, blood pressure; UAH, unilateral adrenal hyperplasia. Data are given as mean±standard deviation or n.

the criteria for cured or improved hypertension, although they had postadrenalectomy BPs of 140/90 mmHg on three antihypertensives, which was a decrease from 175/115 mmHg preoperatively on five agents. The potassium normalized in all patients from a mean of 3.0±0.1 to 4.8±0.1 mmol/L ($P < 0.001$). BP improved substantially from 152.2/93.4±3.2/2.4 preoperatively to 128.1/82.2±1.7/1.2 postoperatively ($P < 0.001$), with a reduction in the number of antihypertensives taken. The predictors of persistent hypertension in the univariate analyses are summarized in Table 5. Significant predictors included male gender ($P = 0.025$) and preoperative systolic BP ($P = 0.012$).

Discussion

In this study, AVS showed bilateral or contralateral aldosterone production in 27% of patients with PA with a unilateral nodule on CT. Focusing on patients with nodules ≥10 mm in diameter, 35% had similar bilateral or contralateral aldosterone production. Therefore, the accuracy of CT alone was inadequate for diagnosing APA, even for large nodules. Consequently, we examined the efficiency of AVS for reliably categorizing nodules detected by CT as PA and identifying the need for surgery.

A number of studies have applied various lateralization methods to patients in whom bilateral AVS was successful. In our series, Aldo/Cort A:U >2.0 and Aldo/Cort U:IVC <1.4 gave the best diagnostic accuracy of 82.5% and 80.2%, respectively, with 56.0% and 48.0% specificity. This is similar to the cutoff based on the Endocrinonolgy Society guidelines (9, 22–24). The absolute aldosterone concentration was not as useful as the cortisol-corrected values, which correct for the dilutional effects of the inferior phrenic vein flow into the left adrenal vein and for IVC blood when sampling at or near the orifice of the right adrenal vein (12–14, 25). In addition, the contralateral-gland-to-IVC ratio was accurate, suggesting that not all patients with unilateral disease have complete contralateral aldosterone suppression.

We found that adrenal CT was also insufficient for differentiating PA subtypes. In our study, CT correctly categorized 71.1% of the patients. A recent

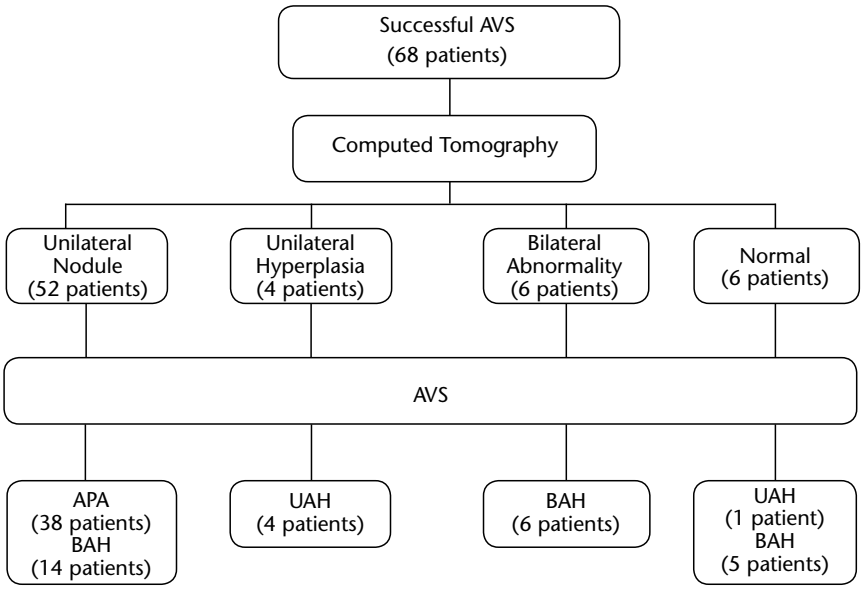

Figure. Schema showing recruitment pathway of findings in CT and adrenal venous sampling for causes of primary aldosteronism. APA, adenoma-producing aldosterone; AVS, adrenal venous sampling; BAH, bilateral adrenal hyperplasia; UPH, unilateral primary hyperplasia.

review of 38 studies and 950 patients suggested that CT or magnetic resonance imaging misdiagnosed the cause of PA in 37.8% of patients when AVS was used as the reference test to diagnose the laterality of aldosterone secretion (26–28). Most of our patients were older than 40 years of age. CT likely detected nonfunctioning adrenal incidentalomas or nodules, which are much more prevalent with increasing age. Due to the low prevalence of incidentalomas in the under-40 age group, it has been suggested that such patients with PA could proceed to adrenalectomy without AVS (28).Despite the inaccuracy of using CT alone, we consider it essential and interpret the results together with AVS. Using the best lateralization criteria from our study and interpreting AVS together with CT, 98.0% of the patients were categorized correctly, which was significant when compared to either diagnostic test alone. Patients with unilateral disease might have bilateral abnormalities on CT and would be missed. However, given the low specificity of AVS in our study, we included the more specific CT in our categorization of unilateral disease to avoid unnecessary surgery on patients with bilateral disease. These patients were treated conservatively with medication.

Previous studies determined the clinical impact of adrenalectomy chosen based on CT alone or CT plus AVS (5, 14, 17–19). Those authors reported that the reduction in BP, number of hypertensive medications, plasma aldosterone, and potassium normalization at follow-up were equivalent in the two groups and concluded that CT could be used to diagnose nodules >10 mm reliably and that AVS should be used when CT is normal or both adrenal glands are abnormal (29, 30).

Adrenal venous sampling is essential for long-term benefits. We used AVS to evaluate the suppression of aldosterone secretion in the gland contralateral to the CT abnormality or a marked increase in aldosterone in a gland with a definite ipsilateral abnormality. Therefore, when considered together with CT, it can play a role in decision-making regarding unilateral adrenalectomy. These results should be interpreted with caution and highlight a major difficulty with AVS, which many clinicians face regularly.

Classical clinical and biological abnormalities should help to differentiate the subtype of PA. Younger age, recent onset of hypertension, high BP, hypokalemia, and a high aldosterone-to-renin ratio are frequently associated with APA (5–7, 17, 20–22). However, we did not find a significant difference between the APA and BAH groups, as described earlier (19). These results underline the key role of AVS compared to using clinical and biological parameters to distinguish APA and BAH.

When patients were selected carefully for surgery using the results of both AVS and CT, 92.7% of the patients had either cured hypertension or improved BP control. On univariate analysis, significant predictors of persistent postoperative hypertension were of male gender and a high preoperative systolic BP (23–27).There are some limitations to this study. First, 15% of the patients had incomplete AVS due to technical difficulties. The reported failure rates of AVS range from 10%–20% (19–21). The right adrenal vein can be difficult to cannulate and aspirate from because it is small and enters the IVC posteriorly at an angle. By contrast, the left adrenal vein drains into the left renal vein and is more readily catheterized. Although experienced vascular radiologists have recently improved the success rate, the technique needs standardization. Second, determination of the true diagnostic accuracy, sensitivity, and specificity of each cutoff is impossible, as surgery is not performed in patients with apparent bilateral disease. Consequently, the accuracy of AVS is based on a group of patients in whom surgery was indicated using AVS results. Therefore, we cannot rule out the possibility that there were some incorrectly categorized patients in our series, which weakens our analysis. Consequently, the results should be interpreted with caution. Finally, there was no strict follow-up period and a lack of histology from all adrenalectomies using APA. The effects of treatment were not available for all follow-up studies.

In conclusion, to predict unilateral disease, the best lateralization ratios were Aldo/Cort A:U >2.0 and Aldo/Cort U:IVC <1.4. AVS together with CT has significantly better diagnostic accuracy than CT alone. AVS and CT are complementary techniques that can distinguish the subtypes of PA and en-

able the selection of appropriate therapy. AVS should be performed before an adrenalectomy regardless of the nodule size on CT, since it potentially enabled the correct diagnosis and avoided inappropriate surgery in patients with a unilateral or larger nodule assessed using only CT. In addition, either a cure or improved BP control is seen when patients are selected carefully for surgery using the results of AVS and CT.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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