Adrenal Vein Sampling for Conn’s Syndrome: Diagnosis and Clinical Outcomes

Amy R. Deipolyi 1, Alexander Bailin 2, Stephan Wicky 2, Shehab Alansari 2 and Rahmi Oklu 2,*

1 Division of Vascular & Interventional Radiology, Department of Radiology, New York University Medical Center, New York, NY 10016, USA; E-Mail: amy.deipolyi@nyumc.org

2 Massachusetts General Hospital, Harvard Medical School, Division of Interventional Radiology, 55 Fruit Street, GRB-290A, Boston, MA 02114, USA; E-Mails: bhartealex@gmail.com (A.B.); stephan.wickyvandoyer@umassmemorial.org (S.W.); drshehabalansari@gmail.com (S.A.)

* Author to whom correspondence should be addressed; E-Mail: roklu@mgh.harvard.edu; Tel.: +617-726-8314.

Academic Editor: Andreas Kjaer

Received: 10 March 2015 / Accepted: 3 June 2015 / Published: 19 June 2015

Abstract: Adrenal vein sampling (AVS) is the gold standard test to determine unilateral causes of primary aldosteronism (PA). We have retrospectively characterized our experience with AVS including concordance of AVS results and imaging, and describe the approach for the PA patient in whom bilateral AVS is unsuccessful. We reviewed the medical records of 85 patients with PA and compared patients who were treated medically and surgically on pre-procedure presentation and post-treatment outcomes, and evaluated how technically unsuccessful AVS results were used in further patient management. Out of the 92 AVS performed in 85 patients, AVS was technically successful bilaterally in 58 (63%) of cases. Either unsuccessful AVS prompted a repeat AVS, or results from the contralateral side and from CT imaging were used to guide further therapy. Patients who were managed surgically with adrenalectomy had higher initial blood pressure and lower potassium levels compared with patients who were managed medically. Adrenalectomy results in significantly decreased blood pressure and normalization of potassium levels. AVS can identify surgically curable causes of PA, but can be technically challenging. When one adrenal vein fails to be cannulated, results from the contralateral vein can be useful in conjunction with imaging and clinical findings to suggest further management.
1. Introduction

Primary aldosteronism (PA) is a potentially curable cause of hypertension in 5%–14.4% of the hypertensive population [1–3]. In PA, excess aldosterone acts on renal aldosterone receptors, causing reabsorption of salt and water and excretion of potassium. This causes refractory hypertension and potentially hypokalemic metabolic acidosis. Cardiomyocytes, cardiac fibroblasts, and vascular smooth muscle cells also contain aldosterone receptors [4]. Chronically elevated aldosterone levels are associated with an increased risk of cardiac events [5]. There are at least seven subtypes of PA. Aldosterone-producing adenomas (APA) and bilateral adrenal hyperplasia (BAH, also referred to as “idiopathic aldosteronism”) account for 98% of cases [6]. The remaining 2% include rare familial subtypes, unilateral primary adrenal hyperplasia (PHA), and adrenal carcinoma. Management depends on differentiating these subtypes; unilateral etiologies may be cured surgically, whereas bilateral causes are managed medically with antihypertensives, including mineralocorticoid receptor antagonists. Patients with confirmed PA are evaluated with cross sectional imaging and biochemical assays. CT and MRI do not reliably distinguish unilateral from bilateral disease [7–12] but can help guide management in difficult cases and identify large adrenal masses concerning for malignancy. Prediction models have been developed to predict which patients have unilateral APAs, though have failed to distinguish such cases in the elderly [13]. Adrenal vein sampling (AVS), on the other hand, is the gold standard for localizing autonomous sources of aldosterone.

AVS is technically challenging with high reported failure rates, usually due to difficulty cannulating the right adrenal vein, which originates from the inferior vena cava [14,15]. When the adrenal vein is successfully cannulated, elevated cortisol levels are present in the adrenal vein sample. The cortisol level in the adrenal vein (CAV) is compared to peripheral samples, for example from the IVC (CIVC), to generate a ratio (CAV:CIVC). There is considerable lack of standardization in interpreting results, with a wide range of CAV:CIVC index cutoffs from 1.1 to 5 [16]. There is also controversy regarding the threshold determining unilateral from bilateral hypersecretion [12,15,17–19]. Most advocate for comparing the cortisol-corrected aldosterone output from each gland [12,15,19] whereas others advocate for identifying contralateral gland suppression [17,18]. There is also debate regarding the use of ACTH stimulation, omitted by some and advocated by others stressing the importance of ACTH to minimize aldosterone production fluctuations induced by stress [20]. In light of the difficulty in reliably cannulating both adrenal veins, some have considered using limited AVS data to identify surgical candidates [17,18].

This study retrospectively characterizes our single institution experience with AVS including concordance of AVS results with imaging and approaching a PA patient in whom bilateral AVS is unsuccessful.
2. Materials and Methods

2.1. Subjects

In this IRB-approved, HIPAA-compliant retrospective study, patients who underwent AVS between March 1990 and May 2014 were identified using the radiology department’s electronic searchable database using the keyword “adrenal vein sampling”. All patients were previously diagnosed with PA by specialized endocrinologists, according to accepted diagnostic standards [10]. Medical records were reviewed for demographics, blood pressure (BP, in mmHg), number of antihypertensive medications, potassium level (mEq/L), adrenal cross sectional imaging, AVS details and results, adrenalectomy, and pathologic findings. Pre-treatment BP and number of antihypertensive medications were assessed on initial presentation for medically managed patients or prior to adrenalectomy for surgically managed patients. Post-treatment BP and number of antihypertensive medications were assessed at the 1-month post-AVS clinic visit for medically managed patients, or at the 1-month post-adrenalectomy clinic visit for surgically treated patients.

2.2. Procedure

There were a total of 13 operators who performed AVS over the study period. AVS was performed in a sequential stimulated manner [12]. Briefly, medications including mineralocorticoid receptor antagonists were administered at least 2 weeks before AVS. The common femoral vein was catheterized for access to the adrenal veins, which were selected sequentially. Samples were taken separately from each adrenal vein and from the infrarenal inferior vena cava (IVC) or common femoral vein to measure cortisol (C) and aldosterone (A). Sequential adrenal vein sampling was performed at least 30 min after initiation of a continuous infusion of Cosyntropin (Mylan Institutional, Rockford, IL, USA), synthetic ACTH.

Technically successful cannulation of the adrenal vein was determined by a cortisol ratio criteria of \( \frac{CAV}{CIVC} > 3 \). A normalized aldosterone (A/C) in the dominant adrenal vein divided by the nondominant adrenal gland (lateralization index) of 4 or more was used to define the presence of APA or PHA. In the case of unsuccessful bilateral AVS, the decision to proceed with repeat AVS, surgery or medical management was based on correlation of medical imaging with unilateral AVS data, by the referring physician.

2.3. Imaging

Radiology reports from the most recent CT or MRI prior to AVS were evaluated. Imaging reports were categorized in one of four ways: left-sided lesion, right-sided lesion, bilateral lesions or nodularity, or no lesions. CT findings were compared with AVS findings, and ultimately with pathologic findings.

2.4. Outcomes and Data Analysis

Pathology records were reviewed for the patients who underwent surgery. Pathology was considered concordant when an adenoma was discovered on the side of a CT finding, or lateralization suggested by AVS. Patient outcome was analyzed on the basis of both decrease in BP and change in antihypertensive
drug prescriptions, assessed at the time of the 1-month post-procedure or post-surgical follow up visit. For both surgically treated and medically managed groups, the pre- and post-systolic BP (SBP), diastolic BP (DBP) and number of antihypertensive medications were compared with the Wilcoxon matched-pairs signed rank test within groups. Between groups, the post-treatment SBP and DBP were compared with unpaired \( t \) tests, \( \chi^2 \) tests, and the numbers of post treatment antihypertensive medications were compared with a Mann Whitney U test. All statistical tests were performed with Prism (Version 4.0, GraphPad Software Inc, San Diego, CA, USA). For all tests, \( p < 0.05 \) was considered statistically significant.

3. Results

3.1. Patient Demographics

A total of 85 patients (37 F, 48 M) with a mean age of 50.6 (range 29–76) years underwent 92 AVS procedures (Figure 1). In 5 patients, AVS was repeated once and in one patient AVS was repeated twice. All patients were hypertensive on initial presentation prior to AVS, with overall initial mean blood pressure of 160/93 (SE: 3.2/1.7).

Figure 1. Flow diagram illustrating study patients. There were 85 patients included in the study. Workup and outcomes are presented.

A total of 44 patients were managed surgically with adrenalectomy. Four patients (2 men, 2 women) had technically successful, lateralizing AVS, but were lost to follow up. The remaining 37 patients were managed medically. Demographic and laboratory assessment of these patients prior to AVS are presented in Table 1. Patients who were eventually managed surgically had significantly higher blood pressure according to unpaired \( t \) tests and were more likely to be hypokalemic according to \( \chi^2 \) tests than those managed medically. In both groups, patients were on a similar initial number of antihypertensive medications (3, range 0–6).
Table 1. Pre-AVS demographic and clinical data. Patients who eventually underwent surgery had significantly higher initial blood pressure (mmHg) and were more likely to be hypokalemic.

| Demographic and Clinical Variable | Surgical | Medical | p value |
|----------------------------------|----------|---------|---------|
| Mean Age (SE)                    | 51.2 (1.5)| 50 (1.6)| 0.7     |
| % Male                           | 45%      | 70%     | 0.04    |
| Pre-AVS Systolic BP (SE)         | 167 (4)  | 150 (4) | 0.009   |
| Pre-AVS Diastolic BP (SE)        | 96 (2)   | 89 (3)  | 0.03    |
| Pre-AVS BP meds (range)          | 3 (1–6)  | 2 (0–5) | 0.02    |
| % Hypokalemic                    | 86%      | 54%     | 0.003   |
| Pre-AVS Potassium (SE)           | 3.3 (0.1)| 3.6 (0.1)| 0.006  |
| Pre-AVS Aldosterone:Renin Ratio (SE) | 69 (14) | 94 (19) | 0.3     |

SE: Standard error of the mean; AVS: Adrenal vein sampling; BP: Blood pressure.

3.2. AVS Findings and Concordance to Imaging and Pathology

Using the $CAV:CIVC > 3$ threshold as technically successful AVS procedures, only 58 of 92 (63%) procedures met this criteria. Of the 34 (37%) technical failures, the majority were unsuccessful cannulations involving the right adrenal vein only (82%); the remainder involved the left adrenal vein only (6%) or both adrenal veins (12%). Over time, an increasing number of AVS procedures have been performed at our institution. Among the 13 operators who performed AVS, there has been wide variation in success rates; average technical success was 82% (SE 8%, range 0%–100%) between operators. Recently, however, rotational angiography (DynaCT Artis Zeego; Siemens, Malvern, PA, USA) was incorporated into practice; since 10/2012, there has been 100% technical success.

In total, 44 patients (44 AVS procedures) were eventually surgically managed, 37 patients were medically managed (43 AVS procedures), and 4 patients (4 procedures) were lost to follow up (Table 2). Among the 44 surgical patients, there were 32 technically successful AVS procedures. All of the 31 procedures lateralized to one side (17 left and 14 right). Therefore, there were a total of 31 procedures with subsequent pathologic evaluation among 31 patients. In one patient, CT showed a 1.5-cm left adrenal mass with enhancement that persisted on 10-min delays, but initial AVS was suggestive of a right-sided lesion. Given the contradictory findings, AVS was repeated and diagnosed a left-sided lesion; thus the patient went on to have a left adrenalectomy. Pathology showed a left cortical adenoma; BP decreased from 164/98 to 118/78 and the patient’s hypokalemia resolved, with no change in the number of antihypertensives (1).

Overall, 29 of 31 patients with diagnostic lateralizing AVS procedures had pathologically diagnosed adrenocortical adenomas, giving an accuracy of 94%. Of these, 4 were described as an adrenocortical adenoma with a background of nodular hyperplasia. The remaining 2 patients had multinodular adrenal hyperplasia, without a dominant nodule described. Among the 31 patients with diagnostic lateralizing AVS, 3 had CTs demonstrating no lesion and 1 had a CT demonstrating bilateral lesions; thus AVS provided essential diagnostic information beyond cross-sectional imaging in these 4 patients.

CT imaging was performed in all 44 surgically treated patients; one patient did not have documented surgical pathology, giving 43 patients with CT imaging and pathologic follow up. In 3 of these patients, no adrenal abnormalities were detected on cross-sectional imaging despite adenomas found at surgery,
giving a false negative rate of 7%. Of the 21 patients with diagnostic nonlateralizing AVS, 11 had unilateral lesions demonstrated on CT imaging. Thus in 14 of 63 patients (22%) with diagnostic AVS, AVS resulted in management.

Thirteen patients underwent adrenalectomy despite technically unsuccessful AVS. One patient’s pathology was not available, giving a total of 12 patients who underwent 12 AVS with subsequent surgical resection. In all of these patients, the right adrenal vein was not adequately sampled based on cortisol ratio criteria, \( C_{AV}:C_{IVC} < 3 \), with average selectivity indices of 1.3 (SE 0.1, range 0.8–2.6). In one patient, large respiratory tidal volume led to significant motion causing limited cannulation time of the right adrenal vein for sampling. Surgery was performed based on cross-sectional imaging in these patients, in conjunction with compelling clinical and laboratory findings. Overall, for the 12 patients with technically unsuccessful right adrenal vein cannulations, CT was concordant with pathology in 11 of 12 cases (92%). Among patients with technically unsuccessful right adrenal vein cannulation and left-sided adenomas found on imaging and at surgery, the left adrenal vein aldosterone:cortisol ratio was on average 22.6 (SE 8.9, range 2.1–58.4). In contrast, among patients with technically unsuccessful right adrenal cannulation and right-sided adenomas found on imaging and at surgery, the left adrenal vein aldosterone:cortisol ratio was on average 4.5 (SE 4.0, range 0.3–24.4). Therefore, high left adrenal venous aldosterone:cortisol ratios in conjunction with corroborating imaging evidence may help suggest a left-sided APA in challenging cases, where lower ratios would suggest a right-sided lesion.

Among the 37 patients who were managed medically, there were 43 AVS procedures. Four patients had 2 AVS procedures and one patient had 3 procedures, due to technical failures on first attempts. Two of these patients with 2 procedures and the one patient with 3 procedures eventually had successful bilateral AVS, while the other 2 patients had 2 technically unsuccessful procedures. In total, there were 21 technically unsuccessful AVS cases among the medically managed patients. Of these, 16 involved the right adrenal vein only, 2 involved the left adrenal vein only, and 3 were bilateral failures. In two of the patients with repeated studies, initial AVS lateralized to the left adrenal vein, though no adenoma had been detected on CT. They both went on to have further AVS showing no lateralization, prompting medical therapy. In 18 patients, AVS was technically successful and non-lateralizing, and thus were medically managed, despite 5 of these patients having suggestive CT findings. In the 14 patients with unsuccessful AVS who did not undergo repeat sampling, the absence of contralateral adrenal suppression was taken as evidence for absence of operable lesions.
Table 2. AVS, pathologic, imaging and clinical data for all patients. SI: sensitivity index; LI: lateralization index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HypoK: hypokalemia; Preop: pre-adrenalectomy; Postop: post-adrenalectomy; meds: blood pressure medications. Hypokalemia was considered resolved in potassium levels increased from a value below normal to a value within normal range or higher (normal range 3.5–5.0 mEq/L). *** indicates patients who underwent repeated AVS.

| CT Findings                      | SI (L) | SI (R) | L1 (L) | L1 (R) | SBP pre | DBP pre | SBP Post | DBP Post | Preop Meds | Postop Meds | HypoK Resolved | Adrenal Resected | Pathology                                      |
|----------------------------------|--------|--------|--------|--------|---------|---------|----------|----------|------------|-------------|----------------|-----------------|-----------------------------------------------|
| Lateralizing AVS, Adrenalectomy  | (n = 31) |        |        |        |         |         |          |          |            |             |                |                  |                                               |
| Left adrenal adenoma             | 9.5    | 51.3   | 127.8  | 0.01   | 204     | 102     | -        | -        | 2          | -           | yes            | yes             | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 32.7   | 30.8   | 58.0   | 0.02   | 170     | 90      | 150      | 92       | 4          | 0           | yes            | yes             | Adrenocortical adenoma                         |
| Left adrenal lesion too          | 108.5  | 100.2  | 54.1   | 0.02   | 174     | 108     | 120      | 70       | 4          | 3           | yes            | yes             | Adrenocortical adenoma                         |
| small to characterize            |        |        |        |        |         |         |          |          |            |             |                |                  | Adrenocortical adenoma                         |
| Normal                           | 19.3   | 48.8   | 28.3   | 0.04   | 144     | 90      | 118      | 68       | 4          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 52.6   | 70.8   | 27.2   | 0.04   | 130     | 80      | 107      | 73       | 6          | 0           | yes            | Left            | Adrenocortical adenoma                         |
| Normal                           | 38.9   | 54.9   | 26.0   | 0.04   | 130     | 80      | 118      | 78       | 2          | 0           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 12.0   | 19.7   | 22.9   | 0.04   | 170     | 98      | 140      | 60       | 2          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 23.3   | 31.1   | 22.6   | 0.04   | 154     | 96      | 102      | 78       | 5          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 18.6   | 48.7   | 13.6   | 0.1    | 158     | 108     | 120      | 70       | 2          | 0           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 44.7   | 50.8   | 13.6   | 0.1    | 164     | 98      | 109      | 67       | 1          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma ***         |        |        |        |        |         |         |          |          |            |             |                |                  | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 50.6   | 39.8   | 10.1   | 0.1    | 155     | 90      | 110      | 60       | 2          | 0           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 5.8    | 5.5    | 9.4    | 0.1    | 130     | 85      | 130      | 85       | 4          | 2           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 30.5   | 8.0    | 5.0    | 0.2    | 200     | 115     | 134      | 90       | 2          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal adenoma             | 35.4   | 22.1   | 3.9    | 0.3    | 200     | 100     | 120      | 70       | 2          | 1           | yes            | Left            | Adrenocortical adenoma                         |
| Left adrenal thickening          | 6.1    | 10.6   | 33.0   | 0.0    | -       | -       | -        | -        | -          | 5           | 2              | yes             | Left            | Adrenocortical adenoma with mixed macro- and micronodular pattern |
| Left adrenal adenoma             | 49.2   | 39.1   | 11.8   | 0.1    | 160     | 88      | 117      | 76       | 3          | 0           | yes            | Left            | Adrenocortical adenoma with a background of nodular cortical hyperplasia |
Table 2. Cont.

| CT Findings                              | SI (L) | SI (R) | LI (L) | LI (R) | SBP pre | DBP pre | SBP post | DBP post | Preop meds | Postop meds | HypoK Resolved | Adrenal Resected | Pathology                                                                 |
|------------------------------------------|--------|--------|--------|--------|---------|---------|----------|----------|------------|-------------|----------------|------------------|----------------|--------------------------------------------------------------------------|
| Left adrenal lesion too small to characterize | 18.5   | 35.2   | 12.6   | 0.1    | 150     | 100     | 102      | 72       | 3          | 2           | yes             | Left             | Adrenocortical adenoma with a background of nodular cortical hyperplasia |
| Right adrenal adenoma                     | 9.4    | 21.9   | 0.04   | 23.6   | 188     | 90      | 140      | 100      | 3          | 3           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 16.2   | 18.8   | 0.2    | 4.5    | 168     | 88      | 140      | 100      | 3          | 3           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 42.0   | 65.6   | 0.2    | 4.7    | 166     | 90      | 138      | 68       | 5          | 2           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 9.3    | 38.7   | 0.2    | 5.1    | 160     | 98      | 148      | 88       | 2          | 1           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 22.1   | 39.2   | 0.1    | 10.3   | 200     | 110     | 130      | 82       | 4          | 2           | yes             | Right            | Adrenocortical adenoma                                                 |
| Normal                                    | 39.3   | 31.7   | 0.1    | 11.6   | 180     | 110     | 118      | 80       | 2          | 2           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 17.5   | 11.7   | 0.1    | 14.3   | 150     | 90      | 130      | 80       | 5          | 4           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 85.6   | 49.7   | 0.1    | 14.7   | -       | -       | -        | -        | -          | 2           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 16.5   | 39.7   | 0.1    | 17.9   | 226     | 141     | 140      | 84       | 2          | 0           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 8.5    | 23.3   | 0.03   | 36.3   | 162     | 85      | 122      | 76       | 4          | 1           | yes             | Right            | Adrenocortical adenoma                                                 |
| Right adrenal adenoma                     | 50.3   | 9.1    | 0.1    | 16.5   | 170     | 90      | 134      | 80       | 1          | 1           | yes             | Right            | Adrenocortical adenoma with a background of nodular cortical hyperplasia |
| Right adrenal adenoma                     | 11.7   | 25.6   | 0.04   | 22.7   | 140     | 90      | 117      | 83       | 1          | 1           | yes             | Right            | Adrenocortical adenoma with a background of nodular cortical hyperplasia |
| Right adrenal adenoma                     | 10.7   | 10.7   | 0.1    | 14.1   | 190     | 110     | 120      | 90       | 3          | 1           | yes             | Right            | Adrenocortical adenoma with a background of nodular cortical hyperplasia |
| Bilateral adrenal thickening              | 16.9   | 10.8   | 0.03   | 31.7   | 160     | 90      | -        | -        | 2          | 1           | yes             | Right            | Multinodular adrenal cortical hyperplasia                               |

- **SBP** and **DBP** refer to systolic and diastolic blood pressures respectively.
- **Preop** and **Postop** refer to preoperative and postoperative levels.
- **HypoK** indicates whether the patient had hypokalemia.
- **Resolved** indicates whether the hypokalemia resolved.
- **Adrenal Resected** indicates whether the adrenal was resected.
- Pathology includes specific diagnoses such as Adrenocortical adenoma with a background of nodular cortical hyperplasia.
Table 2. Cont.

| CT Findings       | SI (L) | SI (R) | LI (L) | LI (R) | SBP pre | DBP pre | SBP Post | DBP Post | Preop meds | Postop meds | HypoK Resolved | Adrenal Resected | Pathology                                |
|-------------------|--------|--------|--------|--------|---------|---------|----------|----------|------------|-------------|----------------|-----------------|------------------------------------------|
| Bilateral adrenal adenomas | 4.8    | 1.2    | 2.9    | 0.3    | -       | -       | 136      | 90       | 3          | 1           | yes            | Bilateral (subtotal right) | Bilateral nodular cortical hyperplasia |
| Left adrenal adenoma | 13.6   | 0.8    | 34.9   | 0.0    | 150     | 90      | 119      | 77       | 3          | 1           | yes            | Left            | Adrenocortical adenoma                     |
| Left adrenal adenoma | 17.2   | 0.9    | 31.4   | 0.0    | 142     | 71      | 123      | 68       | 4          | 2           | yes            | Left            | Adrenocortical adenoma                     |
| Bilateral adrenal adenomas | 7.6    | 1.2    | 6.1    | 0.2    | -       | -       | 121      | 66       | 3          | 0           | yes            | Left            | Adrenocortical adenoma                     |
| Left adrenal adenoma | 33.1   | 2.6    | 12.4   | 0.1    | 177     | 117     | 100      | 70       | 3          | 0           | yes            | Left            | Cortical nodular hyperplasia with two dominant nodules |
| Normal            | 2.3    | 1.0    | 4.4    | 0.2    | -       | -       | 115      | 66       | -          | 4           | no             | Left            | Not documented                                |
| Left adrenal adenoma | 7.3    | 1.5    | 2.1    | 0.5    | 148     | 96      | 130      | 80       | 2          | 1           | yes            | Left            | Nodular hyperplasia with a dominant adrenocortical adenoma |
| Bilateral adrenal adenomas | 3.1    | 1.5    | 48.9   | 0.0    | 150     | 87      | 124      | 76       | 3          | 3           | yes            | Right           | Adrenal cortical hyperplasia with a dominant nodule |
| Right adrenal adenoma | 17.4   | 1.0    | 1.4    | 0.7    | 120     | 73      | 116      | 70       | 3          | 2           | -              | Right           | Adrenocortical adenoma                     |
| Right adrenal adenoma | 7.1    | 1.5    | 0.5    | 2.1    | 154     | 92      | 155      | 105      | 2          | 0           | yes            | Right           | Adrenocortical adenoma                     |
| Right adrenal adenoma | 43.9   | 1.0    | 0.3    | 3.7    | 240     | 120     | 122      | 86       | 2          | 1           | yes            | Right           | Adrenocortical adenoma                     |
| Right adrenal adenoma | 23.6   | 1.2    | 0.1    | 12.8   | 240     | 120     | 138      | 68       | 5          | 2           | yes            | Right           | Adrenocortical adenoma                     |
| Right adrenal adenoma | 16.8   | 1.8    | 0.0    | 47.7   | 133     | 77      | 124      | 78       | 3          | 0           | no             | Right           | Adrenocortical adenoma                     |
### Table 2. Cont.

| CT Findings                                      | SI (L) | SI (R) | LI (L) | LI (R) | SBP pre | DBP pre | SBP post | DBP post | PreAVS meds | PostAVS meds |
|--------------------------------------------------|--------|--------|--------|--------|---------|---------|----------|----------|-------------|--------------|
| Normal                                           | 27.3   | 41.9   | 0.3    | 3.6    | 110     | 78      | 128      | 90       | 4           | 6            |
| Normal                                           | 39.5   | 76.2   | 0.5    | 2.1    | 163     | 108     | 120      | 90       | 3           | 3            |
| Normal                                           | 48.7   | 33.7   | 0.5    | 2.0    | 154     | 100     | 118      | 88       | 0           | 2            |
| Normal                                           | 84.3   | 92.9   | 0.5    | 1.9    | 158     | 80      | 116      | 64       | 2           | 3            |
| Normal                                           | 24.7   | 101.9  | 0.5    | 1.8    | 144     | 100     | 154      | 89       | 2           | 4            |
| Normal                                           | 35.1   | 43.0   | 1.6    | 0.6    | 130     | 72      | 150      | 95       | 1           | 3            |
| Normal                                           | 30.1   | 22.9   | 3.5    | 0.3    | 140     | 100     | 140      | 105      | 1           | 2            |
| Bilateral adrenal adenomas                       | 78.2   | 53.6   | 0.5    | 2.0    | 146     | 70      | 124      | 76       | 3           | 5            |
| Bilateral adrenal adenomas                       | 70.1   | 87.7   | 0.9    | 1.1    | 155     | 96      | 132      | 77       | 3           | 4            |
| Bilateral adrenal thickening                     | 11.9   | 22.0   | 0.8    | 1.3    | 150     | 80      | 148      | 75       | 1           | 4            |
| Right adrenal adenoma                            | 23.5   | 27.9   | 0.4    | 2.3    | 150     | 97      | 128      | 71       | 3           | 4            |
| Right adrenal adenoma                            | 7.0    | 7.0    | 1.0    | 1.0    | 150     | 74      | 140      | 74       | 3           | 6            |
| Right adrenal adenoma                            | 23.1   | 35.5   | 1.0    | 1.0    | 240     | 120     | 100      | 80       | 1           | 3            |
| Right adrenal thickening                         | 52.3   | 59.2   | 0.4    | 2.6    | 155     | 88      | 140      | 70       | 1           | 4            |
| Left adrenal adenoma                             | 37.7   | 46.4   | 0.3    | 3.4    | 160     | 90      |          |          | 2           |              |
| Left adrenal adenoma                             | 75.2   | 74.4   | 2.0    | 0.5    | 137     | 86      | 134      | 82       | 3           | 4            |
| Left adrenal adenoma                             | 23.4   | 38.0   | 3.2    | 0.3    | 140     | 86      | 158      | 100      | 4           | 4            |
| Left adrenal adenoma and right adrenal thickening| 40.2   | 39.5   | 0.3    | 3.3    | 148     | 102     | 136      | 84       | 2           | 7            |
Table 2. Cont.

| CT Findings          | SI (L) | SI (R) | LI (L) | LI (R) | SBPpre | DBPpre | SBPpost | DBPpost | PreAVS meds | PostAVS meds | Rationale for Medical Management |
|----------------------|--------|--------|--------|--------|--------|--------|---------|---------|-------------|-------------|--------------------------------|
| Left adrenal adenoma | 23.7   | 1.1    | 2.0    | 0.5    | 170    | 90     | 125     | 74      | 2           | 4           | Lateralizing AVS, no Follow Up or Medically Managed (n = 4) |
| Left adrenal adenoma | 8.6    | 0.9    | 0.6    | 1.6    | 171    | 117    | 142     | 91      | 3           | 4           | Lost to follow up |
| Left adrenal adenoma | 1.4    | 35.1   | 6.2    | 0.2    | 158    | 94     | 140     | 76      | 2           | 4           | Lost to follow up |
| Nondiagnostic AVS, Medically Managed (n = 16) |        |        |        |        |        |        |         |         |             |             |                            |
| Bilateral adrenal thickening | 21.4   | 0.9    | 0.2    | 6.1    | 201    | 124    | 140     | 90      | 0           | 3           | Clinical/imaging data not compelling, AVS not repeated |
| Left adrenal adenoma | 87.6   | 1.5    | 0.2    | 6.4    | 158    | 103    | 130     | 71      | -           | -           | Clinical/imaging data not compelling, AVS not repeated |
| Left adrenal thickening | 31.8   | 0.9    | 1.0    | 1.0    | 134    | 70     | 150     | 88      | 2           | 4           | Clinical/imaging data not compelling, AVS not repeated |
| Left adrenal thickening | 1.5    | 11.2   | 5.2    | 0.2    | 118    | 83     | 110     | 78      | 2           | 2           | Clinical/imaging data not compelling, AVS not repeated |
| Normal                | 1.4    | 2.3    | 2.8    | 0.4    | 120    | 72     | 106     | 70      | 2           | 3           | Clinical/imaging data not compelling, AVS not repeated |
Table 2. Cont.

| CT Findings          | SI (L) | SI (R) | LI (L) | LI (R) | SBPpre | DBPpre | SBPpost | DBPpost | PreAVS meds | PostAVS meds | Rationale for Medical Management |
|----------------------|--------|--------|--------|--------|--------|--------|---------|---------|-------------|-------------|----------------------------------|
| Normal               | 35.4   | 0.9    | 2.6    | 0.4    | 144    | 96     | 135     | 85      | 2           | 2           | Clinical/imaging data not compelling, AVS not repeated |
| Normal               | 27.2   | 1.5    | 1.1    | 0.9    | 140    | 80     | 134     | 70      | 2           | 3           | Clinical/imaging data not compelling, AVS not repeated |
| Normal               | 53.4   | 1.0    | 1.3    | 0.7    | 120    | 80     | 140     | 78      | 4           | 4           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal adenoma| 10.0   | 0.9    | 2.9    | 0.3    | 100    | 70     | 114     | 70      | 2           | 3           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal adenoma| 25.6   | 1.5    | 0.6    | 1.5    | 160    | 70     | 133     | 74      | 5           | 6           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal adenoma| 2.5    | 2.5    | 0.1    | 7.7    | 150    | 80     | 131     | 62      | 5           | 6           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal thickening| 42.0  | 1.4    | 0.3    | 3.3    | 140    | 96     | 134     | 84      | 2           | 3           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal thickening| 1.0   | 1.0    | 0.9    | 1.1    | 144    | 64     | -       | -       | 5           | -           | Clinical/imaging data not compelling, AVS not repeated |
| Right adrenal adenoma| 49.2   | 1.3    | 0.1    | 10.3   | 210    | 114    | 165     | 95      | 2           | 3           | Refused repeat AVS or further workup |
| Right adrenal adenoma ***| 15.8  | 2.5    | 3.3    | 0.3    | 136    | 80     | 129     | 78      | 2           | 1           | Repeated AVS also failed; no compelling imaging/clinical |
| Normal ***           | 35.0   | 2.4    | 0.2    | 5.9    | 160    | 80     | -       | -       | 3           | 2           | Failed AVS twice, refused further AVS |
3.3. Response to Therapy

Surgically managed patients experienced significantly improved potassium levels and blood pressure after adrenalectomy (Table 3). Mean potassium level increased from 3.3 (SE 0.1) mEq/L prior to the procedure to 4.1 (SE 0.1) mEq/L after adrenalectomy, which was significant according to a paired t test ($p < 0.0001$). SBP significantly decreased from 167 (SE 5) mmHg to 124 (SE 2) mmHg according to a paired t test ($p < 0.0001$), as did DBP from 97 (SE 2) mmHg to 78 (SE 2) mmHg ($p < 0.0001$). Finally, the mean number of antihypertensive medications decreased from 3 (range 1–6) drugs to 1 (range 0–4) drug, which was significantly different according to a Mann-Whitney test ($p < 0.0001$). At least 11 of 35 patients (31%) with documented post-surgical medication lists required no antihypertensive medications at all. Among patients who had adrenalectomy performed on the side indicated by AVS lateralization, all patients had a 10% or greater reduction in SBP; average decrease was 25% (SE 2%, range 10%–47%). All patients had resolution of hypokalemia after adrenalectomy. Post-operative follow up was on average 3.4 years (SE 10 months, range 1 month–17 years).

Table 3. Clinical and laboratory findings in patients before and after adrenalectomy. After surgery, blood pressure decreased on fewer antihypertensive medications, and potassium normalized. Potassium presented as mEq/L; BP as mmHg.

| Outcome Measure       | Before Surgery | After Surgery | $p$ value |
|-----------------------|----------------|---------------|-----------|
| Potassium (SE)        | 3.3 (0.1)      | 4.1 (0.1)     | $< 0.0001$|
| Systolic BP (SE)      | 167 (5)        | 124 (2)       | $< 0.0001$|
| Diastolic BP (SE)     | 97 (2)         | 79 (2)        | $< 0.0001$|
| # BP meds (range)     | 3 (1–6)        | 1 (0–4)       | $< 0.0001$|

Table 3. Clinical and laboratory findings in patients before and after adrenalectomy. After surgery, blood pressure decreased on fewer antihypertensive medications, and potassium normalized. Potassium presented as mEq/L; BP as mmHg.

Subset analysis of the 13 patients with technically unsuccessful AVS who nonetheless underwent adrenalectomy showed that SBP significantly decreased from 174 (SE 15) mmHg to 124 (SE 3) mmHg ($p = 0.01$) and DBP decreased from 102 (SE 5) mmHg to 79 (SE 3) mmHg ($p = 0.01$). The number of antihypertensive medications also decreased from 3 to 1 ($p = 0.002$). Potassium level significantly increased from 3.2 (SE 0.1) mEq/L to 4.1 (SE 0.2) mEq/L ($p = 0.0002$).

Medically managed patients also had improved blood pressure, with systolic pressure decreasing from 152 (SE 4) mmHg to 133 (3) mmHg after AVS, which was significantly different by paired $t$ test ($p = 0.002$). Similarly, diastolic blood pressure also decreased from 84 (4) mmHg to 77 (3) mmHg ($p = 0.001$). The mean number of antihypertensives increased from 3 (range 0–6) to 5 (range 1–7) ($p = 0.0007$).

We also performed a subset analysis, including only patients with diagnostic AVS, who were either surgically ($n = 31$) managed after lateralizing study or medically managed ($n = 21$) after nonlateralizing study. While there was no difference between surgically and medically managed patients in SBP (167 vs. 154 mmHg; $p = 0.05$ by $t$ test), DBP (97 vs. 92 mmHg, $p = 0.2$ by $t$ test), or number of pre-AVS blood pressure medications (3 vs. 2, $p = 0.07$ by Mann Whitney $U$ test), there was lower SBP (125 vs. 134 mmHg, $p = 0.04$ by $t$ test) and reduced blood pressure medications (1 vs. 4, $p < 0.0001$ by Mann Whitney $U$ test) for patients who underwent surgery compared to those that did not.
4. Discussion and Conclusion

PA is the most common cause of secondary hypertension. PA is often a result of APA and PAH, potentially curable causes of PA; surgery can normalize hypokalemia in nearly 100% patients and correct hypertension in 30%–60% of patients [21,22]. We found significant improvement in patients’ blood pressure, with nearly a third of surgically treated patients no longer requiring antihypertensive medications, and a concomitant normalization of potassium levels.

The PA treatment algorithm primarily involves distinguishing unilateral from bilateral disease, as surgery is so effective in treating unilateral causes [20]. While some have suggested that confirmatory laboratory testing may not be necessary in the diagnostic algorithm [23], AVS remains a critical part of the evaluation of patients with PA, as cross-sectional imaging is not always reliable. At least 25%–30% of adrenal adenomas are not detected on abdominal CT [24]. Furthermore, incidental adrenal nodules are discovered on high resolution CT in 4.4% of people [25], and on autopsy in as many as 9% of normotensive and 12% of hypertensive patients [26]. Not only may an adrenal mass not be detected, but if one is discovered, it is likely nonfunctioning.

In this study, we found pathologic concordance for diagnostic lateralizing AVS of 94%. In 22% of patients, diagnostic AVS led to management contradictory to that suggested by pre-procedure CT. In one study of over 200 patients, adrenal CT or MRI was concordant with surgical pathology in only 58.6% of cases, though performed better in patients under 35 years of age [27]. In a systematic review from 2009, CT and MRI were accurate in only 62% of 950 patients [7]. However, more recent studies have shown sensitivity and specificity on the order of 80% [28]. The findings in our study reaffirm the superiority of AVS in accurately diagnosing unilateral aldosterone-producing lesions, and confirms that AVS remains the gold standard in diagnosis.

In our experience, CT and AVS are assessed in conjunction, with each modality providing complementary information. In cases where findings are contradictory, AVS may be repeated for further characterization. Furthermore, when AVS is technically unsuccessful in one adrenal gland, CT findings in conjunction with compelling clinical data can be used to interpret measurements from the contralateral gland, or to guide the decision to repeat AVS or continue with surgery despite nondiagnostic AVS. The management of the 13 patients with technically unsuccessful AVS who nonetheless went on to undergo adrenalectomy demonstrates how cross-sectional, laboratory, and AVS findings may be interpreted together to guide management. All of these patients had adenomas resected, and had significant improvement in blood pressure and potassium levels. These findings are in line with previous studies suggesting that technical failure in assessing one adrenal vein during AVS may not necessarily lead to a clinical failure [29].

Furthermore, patients who were eventually medically managed due to absence of lateralization on AVS had less severe hypertension and hypokalemia compared with the patients with unilateral lesions who were surgically managed. These findings are similar to those in previous reports [30] and suggest that clinical and laboratory evaluation can further help distinguish patients who are surgical candidates in cases where AVS is technically unsuccessful.

The relatively low technical success rate of 63% is multifactorial and represents the experience of one institution over a period of decades. As experience accumulated, technology improved, and performance of the procedure was restricted to fewer operators, technical success improved. These
findings are in line with recommendations to consolidate experience in referral centers with greater numbers of cases [20].

The role of contralateral gland suppression as additional data from AVS was not evaluated in our study. Among patients with diagnostic lateralizing AVS who underwent surgical resection, all experienced resolution of hypokalemia, and there was a substantial improvement in hypertension. There were two patients with cortical hyperplasia without a dominant adrenal adenoma on pathology, and were therefore considered as discordant with AVS results. These patients had significant contralateral suppression and significant clinical improvement after surgery. There were no patients with lateralization indices <4 in this study who were considered for surgery; therefore our results do not inform previous suggestions of the important of contralateral suppression in this patient population [31].

The primary limitations of this study are its retrospective nature, entailing loss of some patients to follow up and lack of standardization among referring providers and interventional radiologists performing the procedure. Because most patients were referred from outside institutions, the laboratory evaluation of the patient leading to diagnosis of PA prior to AVS is not available. Furthermore, as thresholds for determining placement of the catheter within the adrenal vein and for determining lateralization are somewhat controversial, interpretation of AVS results may differ between clinicians, leading to variation in management decision-making over the course of the study. Finally, because all adrenal glands are not pathologically sampled or removed, it is not possible to determine sensitivity and specificity, as false negatives are not detected.

In conclusion, AVS is a technically challenging procedure that is critical in the evaluation for surgically curable causes of secondary hypertension. However, even technically unsuccessful sampling procedures offer diagnostic value, when interpreted in the context of clinical, laboratory, and cross-sectional imaging findings.

Author Contributions

Rahmi Oklu and Amy R. Deipolyi conceived and designed the study; Shehab Alansari, Amy R. Deipolyi, and Alexander Bailin performed the data collection; Amy R. Deipolyi, Rahmi Oklu, and Stephan Wicky analyzed the data; Amy R. Deipolyi and Rahmi Oklu wrote the paper.

Conflicts of Interest

The authors declared no conflicts of interest.

References

1. Milliez, P.; Girerd, X.; Plouin, P.F.; Blacher, J.; Safar, M.E.; Mourad, J.J. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J. Am. Coll. Cardiol. 2005, 45, 1243–1248.
2. Mosso, L.; Carvajal, C.; Gonzalez, A.; Barraza, A.; Avila, F.; Montero, J.; Huete, A.; Gederlini, A.; Fardella, C.E. Primary aldosteronism and hypertensive disease. Hypertension 2003, 42, 161–165.
3. Plouin, P.F.; Amar, L.; Chatellier, G. Trends in the prevalence of primary aldosteronism, aldosterone-producing adenomas, and surgically correctable aldosterone-dependent hypertension. *Nephrol. Dial. Transplant.* 2004, 19, 774–777.

4. Briet, M.; Schiffren, E.L. Vascular actions of aldosterone. *J. Vasc. Res.* 2012, 50, 89–99.

5. Xanthakis, V.; Vasan, R.S. Aldosterone and the risk of hypertension. *Curr. Hypertens. Rep.* 2013, 15, 102–107.

6. Vonend, O.; Ockenfels, N.; Gao, X.; Allolio, B.; Lang, K.; Mai, K.; Quack, I.; Saleh, A.; Degenhart, C.; Seufert, J. Adrenal venous sampling: Evaluation of the German Conn’s registry. *Hypertension* 2011, 57, 990–995.

7. Kempers, M.J.; Lenders, J.W.; van Oudheusden, L.; van der Wilt, G.J.; Schultzke Kool, L.J.; Hermus, A.R.; Deinum, J. Systematic review: Diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism. *Ann. Intern. Med.* 2009, 151, 329–337.

8. Nwariaku, F.E.; Miller, B.S.; Auchus, R.; Holt, S.; Watumull, L.; Dolmatch, B.; Nesbitt, S.; Vongpatanasin, W.; Victor, R.; Wians, F.; et al. Primary hyperaldosteronism: Effect of adrenal vein sampling on surgical outcome. *Arch. Surg.* 2006, 141, 497–502.

9. Schwab, C.W., 2nd; Vingan, H.; Fabrizio, M.D. Usefulness of adrenal vein sampling in the evaluation of aldosteronism. *J. Endourol.* 2008, 22, 1247–1250.

10. Seiler, L.; Rump, L.C.; Schulte-Monting, J.; Slawik, M.; Borm, K.; Ravenstädt, H.; Beuschlein, F.; Reincke, M. Diagnosis of primary aldosteronism: Value of different screening parameters and influence of antihypertensive medication. *Eur. J. Endocrinol.* 2004, 150, 329–337.

11. Vonend, O.; Stegbauer, J.; Kokulinsky, P.; Adams, S.; Liermann, D.; Hahn, K.; Rump, L.C. [Comparison of adrenal imaging and selective adrenal vein sampling in primary hyperaldosteronism]. *Dtich. Med. Wochenschr.* 2007, 132, 2436–2441.

12. Young, W.F.; Stanson, A.W.; Thompson, G.B.; Grant, C.S.; Farley, D.R.; van Heerden, J.A. Role for adrenal venous sampling in primary aldosteronism. *Surgery* 2004, 136, 1227–1235.

13. Riester, A.; Fischer, E.; Degenhart, C.; Reiser, M.F.; Bidlingmaier, M.; Beuschlein, F.; Reincke, M.; Quinkler, M. Age below 40 or a recently proposed clinical prediction score cannot bypass adrenal venous sampling in primary aldosteronism. *J. Clin. Endocrinol. Metab.* 2014, 99, E1035–E1039.

14. Reznik, R.H.; Armstrong, P. The adrenal gland. *Clin. Endocrinol.* 1994, 40, 561–576.

15. Young, W.F., Jr.; Klee, G.G. Primary aldosteronism. Diagnostic evaluation. *Endocrinol. Metab. Clin. North Am.* 1988, 17, 367–395.

16. Magill, S.B.; Raff, H.; Shaker, J.L.; Brickner, R.C.; Knechtges, T.E.; Kehoe, M.E.; Findling, J.W. Comparison of adrenal vein sampling and computed tomography in the differentiation of primary aldosteronism. *J. Clin. Endocrinol. Metab.* 2001, 86, 1066–1071.

17. Doppman, J.L.; Gill, J.R., Jr.; Miller, D.L.; Chang, R.; Gupta, R.; Friedman, T.C.; Choyke, P.L.; Feuerstein, I.M.; Dwyer, A.J.; Jicha, D.L.; et al. Distinction between hyperaldosteronism due to bilateral hyperplasia and unilateral aldosteronoma: Reliability of CT. *Radiology* 1992, 184, 677–682.

18. Espiner, E.A.; Ross, D.G.; Yandle, T.G.; Richards, A.M.; Hunt, P.J. Predicting surgically remedial primary aldosteronism: Role of adrenal scanning, posture testing, and adrenal vein sampling. *J. Clin. Endocrinol. Metab.* 2003, 88, 3637–3644.
19. Rossi, G.P.; Sacchetto, A.; Chiesura-Corona, M.; de Toni, R.; Gallina, M.; Feltrin, G.P.; Pessina, A.C. Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: Results in 104 consecutive cases. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 1083–1090.

20. Rossi, G.P.; Auchus, R.J.; Brown, M.; Lenders, J.W.; Naruse, M.; Plouin, P.F.; Satoh, F.; Young, W.F., Jr. An expert consensus statement on use of adrenal vein sampling for the subtyping of primary aldosteronism. *Hypertension* **2014**, *63*, 151–160.

21. Blumenfeld, J.D.; Sealey, J.E.; Schlussel, Y.; Vaughan, E.D.; Sos, T.A.; Atlas, S.A.; Muller, F.B.; Acevedo, R.; Ulick, S.; Laragh, J.H. Diagnosis and treatment of primary hyperaldosteronism. *Ann. Intern. Med.* **1994**, *121*, 877–885.

22. Young, W.F., Jr.; Hogan, M.J.; Klee, G.G.; Grant, C.S.; van Heerden, J.A. Primary aldosteronism: Diagnosis and treatment. *Mayo Clin. Proc.* **1990**, *65*, 96–110.

23. Kline, G.A.; Pasieka, J.L.; Harvey, A.; So, B.; Dias, V.C. High-probability features of primary aldosteronism may obviate the need for confirmatory testing without increasing false-positive diagnoses. *J. Clin. Hypertens.* **2014**, *16*, 488–496.

24. Raman, S.P.; Lessne, M.; Kawamoto, S.; Chen, Y.; Salvatori, R.; Prescott, J.D.; Fishman, E.K. Diagnostic Performance of Multidetector Computed Tomography in Distinguishing Unilateral From Bilateral Abnormalities in Primary Hyperaldosteronism: Comparison of Multidetector Computed Tomography With Adrenal Vein Sampling. *J. Comput. Assist. Tomogr.* **2015**, *39*, 414–418.

25. Bovio, S.; Cataldi, A.; Reimondo, G.; Sperone, P.; Novello, S.; Berruti, A.; Borasio, P.; Fava, C.; Dogliotti, L.; Scaglotti, G.V.; *et al.* Prevalence of adrenal incidentaloma in a contemporary computerized tomography series. *J. Endocrinol. Investig.* **2006**, *29*, 298–302.

26. Hedeland, H.; Ostberg, G.; Hokfelt, B. On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes. *Acta Med. Scand.* **1968**, *184*, 211–214.

27. Lim, V.; Guo, Q.; Grant, C.S.; Thompson, G.B.; Richards, M.L.; Farley, D.R.; Young, W.F., Jr. Accuracy of adrenal imaging and adrenal venous sampling in predicting surgical cure of primary aldosteronism. *J. Clin. Endocrinol. Metab.* **2014**, *99*, 2712–2719.

28. Lau, J.H.; Sze, W.C.; Reznek, R.H.; Matson, M.; Sahdev, A.; Carpenter, R.; Berney, D.M.; Akker, S.A.; Chew, S.L.; Grossman, A.B.; *et al.* A prospective evaluation of postural stimulation testing, computed tomography and adrenal vein sampling in the differential diagnosis of primary aldosteronism. *Clin. Endocrinol.* **2012**, *76*, 182–188.

29. Trerotola, S.O.; Asmar, M.; Yan, Y.; Fraker, D.L.; Cohen, D.L. Failure mode analysis in adrenal vein sampling: A single-center experience. *J. Vasc. Interv. Radiol.* **2014**, *25*, 1611–1619.

30. Melby, J.C.; Spark, R.F.; Dale, S.L.; Egdaahl, R.H.; Kahn, P.C. Diagnosis and localization of aldosterone-producing adenomas by adrenal-vein cateterization. *N. Engl. J. Med.* **1967**, *277*, 1050–1056.
31. Umakoshi, H.; Tanase-Nakao, K.; Wada, N.; Ichijo, T.; Sone, M.; Inagaki, N.; Katabami, T.; Kamemura, K.; Matsuda, Y.; Fujii, Y.; et al. Importance of contralateral aldosterone suppression during adrenal vein sampling in the subtype evaluation of primary aldosteronism. *Clin. Endocrinol.* **2015**, *doi:10.1111/cen.12761.*

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