

# Influence of Adrenal Venous Sampling on Management in Patients with Primary Aldosteronism Independent of Lateralization on Cross-Sectional Imaging

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- BACKGROUND:** Patients with primary aldosteronism undergo imaging of the adrenal glands after confirmation of the disease. Adrenal venous sampling (AVS) is a useful adjunct to imaging, and advocates believe that AVS should be performed before surgical management. Others argue that patients with unilateral lesions on imaging do not require AVS. Although AVS accuracy has been established, few studies have evaluated how AVS alters management. Our study aimed to determine how AVS affected management of these patients.
- STUDY DESIGN:** Patient data were collected retrospectively from the electronic medical records at a single institution. Patients aged 18 years or older who underwent AVS with successful adrenal vein cannulation from 2007 to 2016 were included. The laterality of AVS was compared with laterality of preprocedural imaging for each patient. The management plan before AVS was determined by laterality on preprocedural imaging. The primary outcomes were management of primary aldosteronism, change in management compared with the plan before AVS, and antihypertensive medication use after therapy.
- RESULTS:** Seventy-four patients had successful adrenal venous cannulation. Thirty-three (44.6%) patients had AVS lateralization that was concordant with preprocedural imaging. Forty-one (55.4%) patients had AVS lateralization that was non-concordant with preprocedural imaging. There was a change in management in 29 (39.2%) patients.
- CONCLUSIONS:** Adrenal venous sampling can delineate the source of aldosterone hypersecretion, and often this is not concordant with cross-sectional imaging. We found that many patients avoided a potentially non-curative operation due to AVS. Adrenal venous sampling frequently alters the management of aldosteronomas and should be highly considered in patients before surgical intervention. (J Am Coll Surg 2019;229:116–124. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Up to 10% of cases of essential hypertension (HTN) are caused by primary aldosteronism (PA).<sup>1</sup> Primary aldosteronism might be due to a unilateral aldosterone-producing adrenal adenoma (APA) or bilateral adrenal

hyperplasia (BAH). A workup for PA is recommended for patients who have sustained HTN (>140/90 mmHg) on 3 or more medications, or controlled HTN (<140/90 mmHg) on 4 or more medications. When PA is suspected

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**Abbreviations and Acronyms**

APA	= aldosterone-producing adenoma
AVS	= adrenal venous sampling
BAH	= bilateral adrenal hyperplasia
HTN	= hypertension
PA	= primary aldosteronism

as the cause of HTN, patients should first have plasma aldosterone and renin levels compared. After confirming peripheral elevation of plasma aldosterone related to renin, patients typically undergo imaging of the adrenal glands by CT or MRI. In addition to high-resolution cross-section imaging, adrenal venous sampling (AVS) has become a useful adjunct for establishing or confirming the source of relative aldosterone hypersecretion from the adrenal glands.

Although AVS is the gold standard for differentiating between unilateral and bilateral PA, there is some controversy about the routine use of AVS. Advocates for AVS believe that most patients with PA should undergo AVS before definitive surgical management.<sup>2</sup> Others argue that patients younger than 35 years of age with a unilateral lesion consistent with an adrenal adenoma on imaging do not require AVS.<sup>1,3-6</sup> Adrenal venous sampling is an invasive procedure, and the usefulness and accuracy are operator dependent. Adrenal venous sampling is not readily available at all institutions. Primary aldosteronism is a rare diagnosis and, therefore, most patients are referred to institutions who perform AVS in high volumes. Even still, AVS is not always performed routinely on patients.

Although studies have demonstrated the accuracy of AVS, few studies have evaluated how AVS alters management.<sup>3,7,8</sup> In previous studies looking at AVS in patients with PA, the concurrence of AVS lateralization with preprocedural imaging has ranged from 53% to 62%.<sup>3,7,9</sup> A recent study showed only 3% to 12% of patients had unilateral lesions on preprocedural imaging, despite findings of unilateral lesions on AVS.<sup>10</sup> These data suggest that forming treatment plans without AVS can misappropriate patients to surgical or medical therapy. Accurate identification of the source of aldosterone hypersecretion is paramount to the likelihood of success rate of treatment intervention. Our study aimed to determine how often AVS was non-concordant with preprocedural imaging and, more importantly, how often it changed the medical or surgical management of these patients at our institution.

**METHODS**

This was a retrospective study conducted on patients who received AVS that had achieved successful selective

cannulation of the adrenal veins at Baylor Scott & White in Temple, TX between 2007 and 2016. The relevant patient data were collected from the institution's electronic medical records, and patients who were aged 18 years and older were included. This project was approved by the Baylor Scott & White Health IRB before data collection.

Patients were referred for AVS after PA was diagnosed with CT or MRI, and abnormalities were noted as nodules. In general, discrete mass lesions or nodules as small as 0.4 cm detected were identified by high-resolution scans. Asymmetrical thickening was not described as a discrete adrenal nodule. Lipid-rich (Hounsfield units <10) and lipid-poor (Hounsfield units >10) characteristics on non-contrast CT and rapid washout on contrast-enhanced CT were considered consistent with an adrenal adenoma.

Patients were referred for AVS from within our system by nephrologists, endocrinologists, and endocrine surgeons, and from outside of our system. The patients who were referred for AVS do not represent all patients with PA who are surgical candidates. The patients that were referred for AVS were determined to be potential surgical candidates by the referring physician. None of the patients referred for AVS were candidates to have operative resection based on lesion size or characteristics alone.

Adrenal venous sampling was performed using continuous cosyntropin infusion by a single interventional radiologist with AVS experience. Of all the patients undergoing AVS, only the studies that demonstrated successful cannulation of both the left and right adrenal veins were included in our study. This was determined by a 5:1 or greater ratio of adrenal to peripheral vein cortisol. In determining lateralization, we used the current recommendation from the Endocrine Society Clinical Practice Guidelines.<sup>1</sup> The cortisol-corrected aldosterone ratio was determined by the measured aldosterone divided by the measured cortisol. This cortisol-corrected aldosterone ratio was then compared from the high side to the low side, and a ratio of 4:1 indicated unilateral aldosterone excess.

Our primary end point was concordance. Concordance in this setting is defined as agreement of laterality between preprocedural imaging and AVS. Additional outcomes were the change in management and success of therapy. The initial management was determined by laterality on preprocedural imaging. Subsequent management was either mineralocorticoid antagonists or surgical therapy. Success of therapy was determined by the number of anti-hypertensive drugs. An international consensus determined which variables are useful to monitor outcomes for patients with PA after undergoing adrenalectomies.<sup>11</sup>

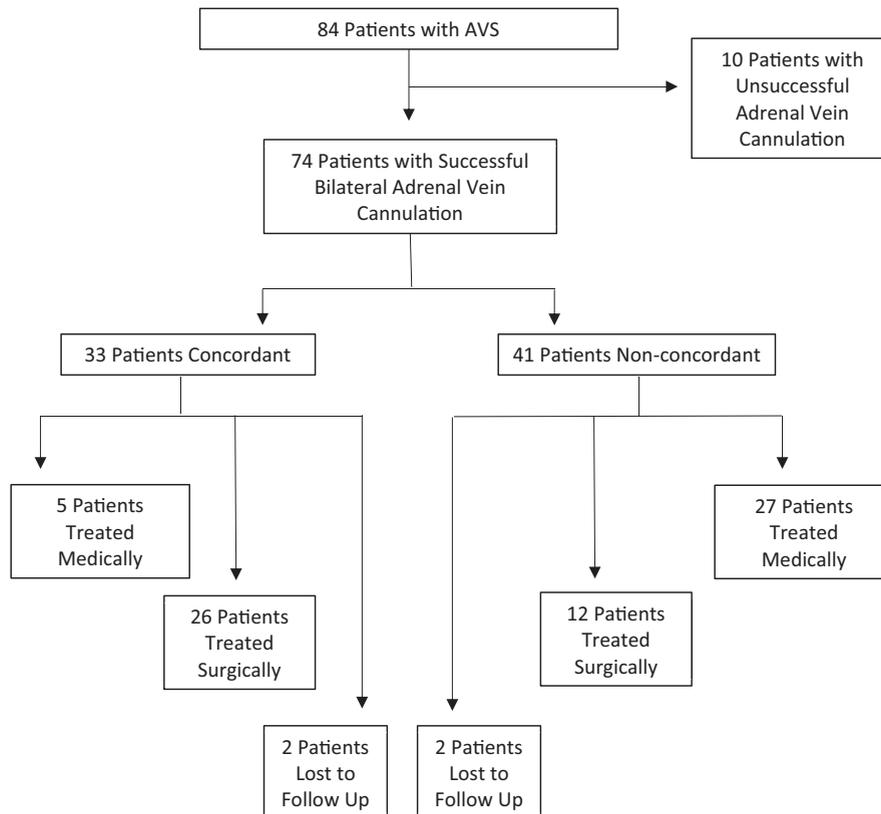
These variables are blood pressure, use of antihypertensive medications, plasma potassium, plasma aldosterone, and plasma renin concentrations. Many of our patients did not have repeat laboratory work, and the follow-up time frame for these plasma concentrations was variable in those patients that did have these data collected. Blood pressure measurements were not measured at a consistent time frame after treatment after AVS. Therefore, the number of blood pressure medications was chosen. It is common practice at our institution to de-escalate the number of blood pressure medications once the patient's blood pressure has become better controlled. Several other studies have used the use of antihypertensive medications as an end point to evaluate improvement in blood pressure control after treatment for PA.<sup>7,12</sup>

Descriptive statistics were used to describe sample characteristics. Analyses were performed to assess the association between variables of interest and concordance.

Chi-square tests (or Fisher's exact test when appropriate) were used to test this association for categorical variables. Because all of the continuous variables were not normally distributed, Wilcoxon-Mann-Whitney tests were used to test for associations between each continuous variable and concordance between AVS and cross-sectional imaging. Statistical significance was set at  $p < 0.05$ .

## RESULTS

A total of 86 patients who were aged 18 years or older underwent AVS during the study time period (Fig. 1). Seventy-four patients had AVS that achieved successful selective cannulation of the adrenal veins, and were included in the study. Seven of these 74 patients had unsuccessful cannulation of the adrenal vein on first attempt, but successful cannulation on second attempt, and were included in the study. Twelve patients did not have selective cannulation of the adrenal veins, and they were not



**Figure 1.** Patient cohort: patients who underwent adrenal venous sampling (AVS) from 2007 to 2016, and those who had successful adrenal vein cannulation. The flow chart also shows concordance and treatment groups. Concordance is defined as agreement between the laterality on preprocedural imaging and the laterality on AVS. Successful adrenal vein cannulation is imperative in determining laterality during AVS. Twelve patients did not have successful vein cannulation and, therefore, were excluded from the study. Two patients were lost to short-term follow-up from the concordant group, and 2 patients from the non-concordant group. Short-term follow-up was defined as the patient was lost to follow-up immediately after the AVS.

**Table 1.** Characteristics of 74 Patients with Successful Adrenal Vein Cannulation before Undergoing Therapy

Characteristic	Overall (n = 74)
Age, y, mean (SD)	55.6 (12.3)
Sex, n (%)	
Female	29 (39.2)
Male	45 (60.8)
HTN, n (%)	74 (100.0)
Diabetes, n (%)	26 (35.1)
Hyperlipidemia, n (%)	43 (58.1)
Cardiac comorbidity, n (%)	17 (23.0)
Respiratory comorbidity, n (%)	6 (8.1)
Obesity, n (%)	46 (62.2)
History of stroke, n (%)	4 (5.4)
Renal disease, n (%)	20 (27.0)
Liver disease, n (%)	1 (1.4)
Thromboembolic disease, n (%)	1 (1.4)
History of malignancy, n (%)	2 (2.7)
Pre-AVS renin, ng/mL, median (range)*	0.2 (0.0–2.3)
Pre-AVS aldosterone, ng/mL, median (range)	21.3 (3.2–1,040.0)
No. of HTN medications, median (range)	4 (1–7)
Hypokalemia, n (%)	51 (68.9)
Preprocedural imaging type, n (%)	
CT	66 (89.2)
MRI	8 (10.8)
Preprocedural imaging laterality, n (%)	
None	4 (5.4)
Right	19 (25.7)
Left	44 (59.5)
Bilateral	7 (9.5)
Lesion size, mm, median (range)	12.0 (0.0–39.0)
AVS laterality, n (%)	
None	39 (52.7)
Right	17 (23.0)
Left	18 (24.3)
Concordance, n (%)	33 (44.6)
Non-concordance, n (%)	41 (55.4)

\*Four patients did not have renin values.

AVS, adrenal venous sampling; HTN, hypertension.

included in this study. Fifty-nine of these 74 patients were referred from within the institution. Fifteen patients were referred from outside the institution.

Patient characteristics are shown in [Table 1](#). Of these 74 patients with selective cannulation, 66 had a preprocedural CT scan and 8 had an MRI. All of the abnormalities on preprocedural imaging were noted as nodules ranging from 0.4 to 3.9 cm. Four patients had no adrenal abnormalities on preprocedural imaging. On cross-sectional imaging, adrenal nodules were identified in 19 patients on the right, 44 patients on the left, and bilaterally in 7 patients. Adrenal venous sampling results indicated no lateralization in 39

patients, lateralization to the right in 17, and to the left in 18. Thirty-three (44.6%) had AVS lateralization that was concordant with preprocedural imaging. Forty-one (55.4%) patients had AVS lateralization that was not concordant with preprocedural imaging.

Concordance of preprocedural imaging and AVS is demonstrated in [Table 2](#). Of those patients that had non-concordance, the AVS did not lateralize in 35 (85.8%) patients when preprocedural imaging demonstrated a unilateral source, lateralized unilaterally when the imaging was bilateral in 3 (7.3%) patients, lateralized to the contralateral side of imaging in 2 (4.9%) patients, and was unilateral on AVS but nonlateralized on imaging in 1 (2.4%) patient.

Bivariate analysis between the concordant and non-concordant groups was performed ([Table 3](#)). A statistically significant difference was detected between the percentage of diabetes between the non-concordant and concordant groups (45.2% compared with 21.9%;  $p = 0.0370$ ). The concordant group had a higher rate of hypokalemia compared with the non-concordant group (84.4% compared with 58.5%).

Non-concordance between AVS and imaging led to a change in management in 70.7% of the non-concordance patients and 39.2% of all the 74 patients who had successful AVS cannulation ([Table 4](#)). There were 12 patients who had non-concordance, but did not have a change in management. Two of these patients were lost to follow-up. Two patients had no masses on preprocedural imaging with bilateral results on AVS, and subsequently were treated medically. Eight of these non-concordant patients had bilateral AVS results but underwent adrenalectomy. Seven of these resections were unilateral, and 1 was bilateral. The 7 patients who underwent unilateral resection had AVS laterality ratio between 3:1 and 4:1, and clinically were considered to be lateralized. The patient who underwent bilateral adrenalectomy had bilateral oversecretion of cortisol. The patient was initially referred to our institution with an aldosterone of 52.4 ng/mL and a unilateral adrenal nodule on preprocedural imaging. When his AVS did not lateralize, his aldosterone and renin were collected again. At this point his aldosterone was 22 ng/mL, renin was 1.5 ng/mL, and additional workup revealed adrenocorticotropic hormone-dependent Cushing syndrome. He was intended to treat, and therefore, we included him in this study.

The change in number of blood pressure medications was used to determine success of therapy. In the non-concordant group who did not have a change in management, there were 2 patients treated medically and 8 patients treated surgically. In the medically treated patients in this group, 1 (50%) patient had improvement. In the surgically treated patients in this group, 7 of 8 (87.5%) patients

**Table 2.** Concordance between Preprocedural Imaging and Adrenal Venous Sampling

Preprocedural imaging laterality	AVS Right	AVS Left	AVS Bilateral	Total
None	0	1	3	4
Right	12*	0	7	19
Left	2	17*	25	44
Bilateral	3	0	4*	7
Total	17	18	39	74

The  $\kappa$  statistic for this table is 0.2759 with a 95% CI of 0.1485–0.4034.

\*Concordant. All others are non-concordant ( $n = 33$ ).

AVS, adrenal venous sampling.

showed improvement. In the non-concordant patients who did have a change in management, 25 were treated medically and 4 were treated surgically. In the medically treated group, 9 patients improvement in blood pressure management (36%). In the surgically treated group, all had improvement in blood pressure management. In the concordant group that was treated medically, 2 (40%)

patients had improvement in blood pressure control. In the concordant group that was treated surgically 20 (76.9%) patients had improvement in blood pressure control.

A total of 38 patients underwent adrenalectomy (Table 5). The most frequent laterality was the left side on preprocedural imaging (57.9%) and on AVS (42.1%). Thirty-five of the 38 patients treated surgically had improvement in the number of blood pressure medications post-therapy. In this group, non-concordance was present in 12 (31.6%) patients.

Five patients were 35 years old or younger. The mean age of these patients was 33.4 years. Four of the patients had a left-sided lesion on preprocedural imaging, and 1 patient had a right-sided lesion. The mean size was 12.1 mm. Three patients had concordance between AVS and preprocedural imaging, and all were treated surgically. Two of these patients had a decrease in HTN medication use. Two of the patients were non-concordant and had bilateral localization on AVS. The nodules in these 2

**Table 3.** Comparison of Preprocedural Clinical Variables Between Concordant and Non-Concordant Patients

Characteristic	Non-concordant		Concordant		p Value
	n	%	n	%	
Hypertension*	41	100.0	33	100.0	
Diabetes	19	46.3	7	21.0	0.0244
Hyperlipidemia	26	63.4	17	51.5	0.3024
Cardiac comorbidity	11	26.8	6	18.2	0.3794
Respiratory comorbidity	5	12.2	2	6.1	0.2163
Obesity	23	56.1	23	67.7	0.2305
Stroke	2	4.9	2	6.1	1.0000
Renal	10	24.4	10	30.3	0.5691
Thromboembolic disease	0	0.0	1	3.0	0.4459
Liver disease	1	2.4	0	0.0	1.0000
Malignancy	1	2.4	1	3.0	1.0000
Hypokalemia	26	65.0	25	75.8	0.3188
Preoperative imaging laterality <sup>†</sup>					—
None	4	9.8	0	0.0	
Right	7	17.1	12	36.4	
Left	27	65.9	17	51.5	
Bilateral	3	7.3	4	12.1	
AVS laterality <sup>‡</sup>					<0.0001
Right	5	12.2	12	36.4	
Left	1	2.4	17	51.5	
Bilateral	35	85.4	4	12.1	
Type of treatment <sup>†</sup>					<0.0001
Operation	12	29.3	26	78.8	
Medical	27	65.9	5	15.2	
Lost to follow-up	2	4.9	2	6.1	

\*Because all patients had hypertension, no test was done.

<sup>†</sup>Chi-square or Fisher's exact test was used.

AVS, adrenal venous sampling.

**Table 4.** Change in Management and Success of Therapy.

Characteristic	Non-concordance, n (n = 41)	Concordance, n (n = 33)
Change in management		
Change to operative management	4	0
Improved HTN	4	—
Change to medical management	25	0
Improved HTN	9	—
No change in HTN	9	—
Worsened HTN	5	—
Lost to long-term follow-up	2	—
No change in management		
Treated operatively	8	26
Improved HTN	7	20
No change in HTN	1	3
Lost to long-term follow-up	0	3
Treated medically	2	5
Improved HTN	1	2
No change in HTN	1	2
Worsened HTN	0	1
Lost to short-term follow-up	2	2

Short-term follow up was immediately after the adrenal venous sampling (within the first month), and long-term follow-up was months to years after the adrenal venous sampling. HTN, hypertension.

patients were 1.4 cm and 2.4 cm. One of these non-concordant patients had surgical intervention due to a high side to low side ratio of 3.3, and this patient had improvement in use of HTN medications. The other non-concordant patient was treated medically and had worse HTN control.

## DISCUSSION

Bilateral adrenal hyperplasia is the most common subtype of PA, and APA is the second most common.<sup>13</sup> On imaging, patients with BAH can have adrenal glands that appear normal or slightly thickened due to micro- or macrohyperplasia. In addition, patients with BAH might have mild bilateral adrenal thickening and an incidental non-functioning adrenal adenoma that can cause confusion.<sup>1</sup> A systemic review of 38 studies and 950 patients with PA showed that CT and MRI misdiagnosed the cause of PA in 37.8%.<sup>9</sup> Another study reported that in 203 patients that underwent CT and AVS, CT was only 53% accurate.<sup>3</sup> Twenty-two percent would have been excluded from adrenalectomy, and another 25% would

**Table 5.** Characteristics of 38 Patients Who Underwent Adrenalectomy

Characteristic	Data
Hypokalemia pretherapy, n (%)	33 (86.8)
Preprocedural imaging, n (%)	
Right	14 (36.8)
Left	22 (57.9)
Bilateral	2 (5.3)
AVS, n (%)	
Right	14 (36.8)
Left	16 (42.1)
Bilateral	8 (21.1)
Non-concordance, n (%)	12 (31.6)
Estimated blood loss, mL, median (range)	25.0 (3.0–400.0)
Length of stay, d, median (range)	1.0 (1.0–6.0)
Postoperative complication, n (%)	
Acute renal injury	1 (2.6)
Uncontrolled HTN	1 (2.6)
Pneumonia	1 (2.6)

AVS, adrenal venous sampling; HTN, hypertension.

have had an operation that was not indicated or inappropriate.<sup>3</sup> A retrospective review on 41 patients with PA who underwent AVS showed concordance to preprocedural imaging in 22 (55%).<sup>7</sup> Due to misdiagnosis, some centers routinely perform AVS on all PA patients.<sup>2</sup>

A recent study from a center that routinely performs AVS demonstrated that management was changed in 43% of patients.<sup>14</sup> The majority of patients with non-localizing imaging had unilateral disease on AVS. Without AVS, these patients would likely have been misdiagnosed as having BAH. This might have led to earlier identification of a surgically curable disease, reducing the cardiovascular risks that are associated with long-term uncontrolled PA. In patients 40 years or younger, 30% had a change in management. In all age groups, wrong-side operation was avoided in 3%, and unnecessary operation was avoided in 30%.

The SPARTACUS trial<sup>15</sup> is the only randomized controlled trial comparing the outcomes of CT-based management with AVS-based management for patients with PA. The study accrued 200 patients, with 184 completing follow-up. Ninety-two patients were randomized to receive treatment based on CT findings, and 92 to receive AVS-based treatment. This study failed to demonstrate any difference in intensity of antihypertensive management between the 2 treatment groups after 1 year of follow-up. Although these findings challenge the use of AVS in all patients with PA, there are potential limitations of this study, including that a significant selection bias might have occurred with this study cohort, and that this might not represent the general PA population.

In addition, the primary end point of defined daily dose of antihypertensive might not be the appropriate measure of cure for patients with PA. Nevertheless, this study is significant because of its randomized prospective design.

Our study demonstrates findings similar to those described in previous studies. Almost half of our patients with successful cannulation were found to have non-concordance, leading to a change in management in 39.2% of patients. This illustrates that quality patient care can be improved by obtaining AVS before operating on a patient with a unilateral lesion on imaging. Adrenal venous sampling can also help clarify the laterality of the aldosterone hypersecretion, and it can determine when the PA is due to bilateral disease, thereby determining patients that should be treated medically.

Unilateral adrenalectomy results in improved control of HTN in almost all patients, and a cure in 30% to 60%.<sup>1</sup> The cure rate is usually defined by a cessation of all antihypertensive medications. A recent study showed the improvement rate of HTN control was as high as 95.5% in patients who were appropriately identified as having unilateral PA.<sup>16</sup> The majority of their patients (80.3%) underwent AVS before surgical therapy. A study was performed that compared 25 patients who underwent AVS and then adrenalectomy with 7 patients who had adrenalectomy without AVS. In the AVS group, 4 (16%) patients stopped taking all antihypertensive medications. In the non-AVS group, 2 (29%) stopped taking all anti-hypertensive medications. One patient in the non-AVS group had recurrent HTN and hypokalemia.<sup>7</sup>

Similarly, we found that surgically treated patients nearly always had improvement in their blood pressure management. However, this is likely because surgical therapy was used in patients who had unilateral APA. This type of PA is curable, unlike BAH, which is managed with medical therapy.

We used the current recommendation of a 4:1 ratio of aldosterone between high side and low side to determine laterality on AVS.<sup>1</sup> When the 4:1 ratio is used, there is a 95% sensitivity and 98.6% specificity that the AVS is lateralized.<sup>17</sup> Several patients with a ratio between 3:1 and 4:1 were considered lateralized clinically. If we had used 3:1 ratio, this would have changed 12 patients from being non-lateralized on AVS to unilateral. One of these patients would have gone from the concordant group to the non-concordant group, and 7 of these patients would be recategorized from non-concordant to concordant. Only 5 of these 12 patients had a change in management. Lowering the threshold would make the change in management 32.43% of our patients, instead of 39.2%.

CT scan and MRI have limitations. Small APAs can incorrectly appear as BAH on CT.<sup>1</sup> In addition, nonfunctioning unilateral adrenal macroadenomas are not rare and can be misinterpreted as a functioning tumor. The finding in our study of a marked predominance of left-sided adrenal adenomas is supported by previous reports. A population study of 1,376 patients in 2018 found left-sided adrenal adenomas occurred 3 times more frequently than right-sided ones.<sup>18</sup> In addition, in 61% of patient with bilateral adrenal adenomas the left-sided adenoma was significantly larger. This marked discrepancy in incidence between sides suggest that left-sided adrenal adenomas are substantially more likely to be recognized based on their anatomic location, which can preclude identification of right-sided adrenal adenomas until they are much larger. This detection bias could explain why bilateral adrenal disease is more accurately identified by AVS then by cross-sectional imaging. The differential detection of left vs right adrenal adenomas and the potential added accuracy provided by AVS is supported by the results of this study.

Adrenal venous sampling has its limitations. It can be challenging to successfully cannulate the right adrenal vein due to the direct take off from the inferior vena cava. Previous studies have demonstrated rates of successful cannulation of the right adrenal vein as low as 74%. Experience subsequently increased the success rate up to 96%. The learning curve for AVS appears to be about 30 cases for individuals experienced in endovascular techniques.<sup>3,9,16,19</sup> The need for AVS is low, given that PA is not a common disease process, and many centers do not have high volumes of patients. Therefore, it might not be practical for all patients to have AVS due to the limited number of centers performing this procedure.

Medical and surgical therapy is not guided by AVS alone. Oftentimes, the study is useful in guiding discussion about treatment options with patients. Two of our patients who were surgical candidates underwent AVS and had concordant results. It is unclear why they did not follow-up, which demonstrates that patients might not always follow what practitioners recommend. Nevertheless, the results themselves can lead to a more insightful conversation between patient and practitioner. Patients do not always have their mind made up about surgical intervention. They might opt for nonoperative management after AVS, despite a result that would suggest the patient is a surgical candidate. However, AVS is associated with risks, and should not be performed in patients who refuse or who are not candidates for surgical intervention.

There are limitations to our study. This study was subject to the inherent bias of a retrospective review. Patients were referred for AVS based on individual providers. Usually these referrals were from nephrologist, endocrinologists, or endocrine surgeons within our institution. Patients were referred for AVS with an adrenal nodule seen on cross-sectional imaging. None of our patients were noted to have adrenal thickening or nodularity only. As such, our population does not capture all surgical candidates with PA that came through our institution or even that came through our catchment area. This study was performed at a single center and with a single AVS operator. Therefore, our results might not be generalizable to all patient populations. Adrenal venous sampling is not a common procedure and, therefore, our sample size was limited. We might have been limited by the threshold for determining laterality on AVS. If we had used a lower threshold, several patients would have been recategorized from non-concordant to concordant. This would explain why several patients went on to adrenalectomy and, therefore, did not have the expected change in management.

Additional studies should be aimed at evaluating the long-term outcomes for blood pressure management in patients who had AVS and were treated with adrenalectomy or mineralocorticoid-receptor antagonists based on localization of aldosterone hypersecretion. There is a need for additional prospective randomized controlled trials and multicenter studies to accrue sufficient numbers of patients to determine long-term outcomes and provide results that might be more generalized to broader populations of patients with PA.

## CONCLUSIONS

Our study indicates that AVS affects the management of patients with PA, and should be strongly considered before proceeding with therapy. Adrenal venous sampling can confirm bilateral aldosterone hypersecretion in some patients with an apparent unilateral adrenal abnormality on imaging and, therefore, avoid a non-curative and unnecessary adrenalectomy. In patients with bilateral adrenal abnormalities on imaging, AVS can identify those patients with a unilateral source of aldosterone hypersecretion and thereby identify PA that is amenable to surgical treatment and cure. Adrenal venous sampling should not be performed in patients who refuse or who are not candidates for operation. Patients younger than 35 years of age with marked PA and a unilateral adrenal adenoma on imaging do not require AVS before adrenalectomy, according to previous guidelines, and our data did not disprove this.

## Author Contributions

Study conception and design: Campbell, Snyder, Milan, Lairmore, McDonald  
 Acquisition of data: Campbell, Young  
 Analysis and interpretation of data: Campbell, Shaver  
 Drafting of manuscript: Campbell, Young, Shaver  
 Critical revision: Campbell, Young, Snyder, Milan, Lairmore, McDonald

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## Discussion



**DR QUAN-YANG DUH** (San Francisco, CA): About half of the patients with primary aldosteronism are curable by adrenalectomy. The other half have bilateral disease and are treated medically. It is sometimes difficult to distinguish between the medical vs surgical primary aldosteronism because aldosteronomas tend to be small, and incidental nonfunctioning adenomas can be found in 1% of patients at age 30 years and 7% at age 70 years. The potential inaccuracy of CT scan is a reason why the adrenal vein sampling is used. In this study, Dr Lairmore and his colleagues from Baylor showed that routine adrenal vein sampling (AVS) can change the management in almost half of their patients with primary aldosteronism. I agree with them that venous sampling changes the management in many patients.

For me, the question is not whether to do venous sampling, but when to do it. And I believe that we can do it selectively. If AVS were without problems, routine use would be a no-brainer. However, it is expensive, and it is associated with several problems. First, the failure rate—in this case at 14%—is in the range of what we expect for most good centers. Second, venous sampling can cause right adrenal vein infarction in about 1% of patients. Third, even when AVS successfully lateralizes, adrenalectomy still failed to achieve biochemical cure in about 3% of patients. When you add these numbers together, 15% to 20% of the patients would not benefit from AVS, and this may explain why the only prospective randomized study for the SPARTACUS trial from the Netherlands did not show any difference in outcomes between the strategy of routine AVS vs relying on CT imaging alone.

Because of these issues, we should not do AVS if the results would not change patient management. The examples are patients

who are not surgical candidates or who do not want surgery; patients who already have another reason, independent indication for adrenalectomy; and patients who already have a high probability of success when adrenalectomy is guided by CT alone. These include patients in whom we can predict with high probability, 80% to 90%, that adrenalectomy will lead to a biochemical cure. The variables that increase this likelihood of success include young age, unilateral tumor larger than 1 cm, hypokalemia, and creatinine clearance greater than 100 mL. With these things in mind, I have 3 questions for Dr Lairmore, all related to patient selection.

For the 8 patients who had an adrenalectomy despite nonlateralizing AVS, did you consider just doing the adrenalectomy without the venous sampling? What were the added values of venous sampling for these patients? In addition, were there other patients whose venous sampling did lateralize, but you would have gone ahead with the operation anyway for other reasons? If you were to have performed AVS only selectively, for example, not doing it in those patients with unilateral lesions larger than 1 cm, how many patients, and what percentage of patients in your study, would have had wrong-side operation or unnecessary adrenalectomy? Given your findings, are there patients with primary aldosteronism who are surgical candidates for whom you would not recommend AVS?

**DR TERRY LAIRMORE** (Temple, TX): You asked about the 8 patients in the study who went on to have an adrenalectomy despite having nonlateralizing findings on venous sampling. Unfortunately, the retrospective nature of our study does not allow me to drill into the specific prospective surgical decision-making in these patients. However, as Dr Campbell said, a majority of these patients had a cortisol-corrected venous sampling ratio that approached the 4:1 significance but did not meet it, so these data were strongly suggestive of the unilateral source without meeting the criteria. In addition, the standard criteria, independent criteria for taking out adrenal glands, including size, criteria, as well as atypical findings on CT scan, remain in place, so adrenalectomy could still be considered for these patients. I think it is important to point out that even in patients who have an independent reason to remove an adrenal mass, an effective strategy should address both the aldosterone hypersecretion and the abnormal mass. The added benefit of AVS in this subset of patients then would be to provide biochemical data. Cross-sectional imaging provides anatomic data, and the AVS gives us functional or biochemical data to allow us to address both of those issues.

Dr Duh asked the important question of how many patients had a clear unilateral mass greater than 1 cm and then were reclassified as having bilateral disease on venous sampling. In our study, this was a significant number of patients. It was 19 out of a total of 86 patients who had an apparent unilateral mass on CT and then were reclassified as having bilateral hypersecretion on venous sampling.

I agree with Dr Duh that the most important question is who should undergo AVS, or, conversely, who should not. I think that in patients who are younger than age 35 years, who have marked primary aldosteronism, hypokalemia, and a large unilateral mass, it is certainly reasonable to proceed with laparoscopic adrenalectomy