Utility of adrenocorticotrophic hormone in adrenal vein sampling despite the occurrence of discordant lateralization

Short title: ACTH in adrenal venous sampling

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Summary: Background: Adrenal vein sampling (AVS) is crucial for accurate lateralization of aldosterone excess but it is technically challenging due to the difficulty of adrenal vein cannulation. The use of adrenocorticotrophic hormone (ACTH) to improve cannulation success is controversial and can lead to discordant lateralization outcomes. **Objective:** To evaluate the utility of ACTH in two centres with different levels of AVS expertise and formulate a strategy for interpreting discordant results. **Design:** A retrospective cross-sectional analysis of AVS results and post-operative patient outcomes. **Setting:** Two large tertiary hospitals with harmonized AVS protocols where adrenal venous samples are collected both before and after ACTH stimulation. **Measurements:** Cannulation success (measured by selectivity index, SI), lateralization (measured by lateralization index, LI) and post-operative biochemical cure. **Results:** Number of AVS procedures judged to have successful bilateral

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adrenal vein cannulation increased from 53% pre- to 73% post-ACTH. The increase in cannulation success was significantly higher in centre where AVS was performed by multiple radiologists with a lower basal success rate. In both centres, the proportion of cases deemed to display lateralization significantly decreased with the use of ACTH (70% pre- to 52% post-ACTH). Based on post-operative outcomes of patients with discordant results who underwent unilateral adrenalectomy, the combination of LI > 3 pre-ACTH and LI > 2 post-ACTH was predictive of a biochemical cure. **Conclusion:** ACTH can increase the rate of cannulation success during AVS at the expense of reduced lateralization. The criteria for lateralization should be carefully determined based on local data when ACTH is used.

Keywords: primary aldosteronism, aldosterone-renin ratio, adrenal vein sampling, selectivity index, lateralization index, discordant lateralization, hypertension

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Introduction

Primary aldosteronism (PA), or Conn's syndrome, is a clinical syndrome of hypertension, suppressed renin activity and increased aldosterone production once considered rare.

However, studies in recent years demonstrated that PA is the most common endocrine cause of hypertension, affecting almost 10% of general hypertensive patients and up to 30% of those with refractory hypertension ¹. Early diagnosis and treatment of PA is crucial to prevent the cardiovascular and renal complications arising from hypertension and aldosterone excess *per se* ².

In PA, aldosterone production can be unilateral, from an aldosterone-producing adenoma (APA), or bilateral, caused by bilateral adrenal hyperplasia (BAH). These two subtypes account for the majority of cases of PA with adrenal carcinoma and familial PA being much rarer. The distinction between unilateral and bilateral aldosterone excess is important as management differs for each condition. APA can potentially be cured surgically with unilateral adrenalectomy whereas BAH requires lifelong treatment with mineralocorticoid-receptor antagonists (MRA).

The gold standard for differentiating APA from BAH is through adrenal vein sampling (AVS) using digital subtraction or fluoroscopic guidance. Adrenal imaging alone may sometimes miss APA (false negative) or identify non-functioning adrenal incidentalomas (false positive) which are not uncommon in patients over 40 years of age ³. When guided by AVS, adrenal surgery provides a higher rate of hypertension cure than CT guidance alone ⁴. AVS can even guide the selection of side of adrenalectomy in patients with poorly controlled bilateral disease ⁵. However, AVS is a technically challenging diagnostic procedure, especially during the catheterization of the right adrenal vein (RAV), which is shorter than the left adrenal vein (LAV) and typically empties directly into the inferior vena cava at variable locations. Success rates for bilateral adrenal veins cannulation range between 30% and 96%, depending on the level of expertise ⁶. Given the invasive nature, cost and time required of AVS, increasing its success and accuracy is paramount for the best management of PA.

In efforts to improve the success rate of AVS, some centres use synthetic adrenocorticotrophic hormone (ACTH) during AVS to maximise the gradient between adrenal and peripheral vein cortisol levels which is critical for the confirmation of adrenal vein catheterization, termed “cannulation success” ⁷⁻¹⁰. Despite these benefits, the use of ACTH in AVS remains controversial and is routinely used by only 50% of specialist centres around the world ⁶. There

are concerns that ACTH may reduce the rate of successful lateralization ¹¹ possibly due to stimulated aldosterone secretion from non-autonomous adrenal cortical areas. There are currently no clear guidelines on whether ACTH should be routinely used in AVS, and when ACTH is used, the interpretation of discordant data pre- versus post-ACTH is uncertain.

By evaluating all AVS procedures performed both before and after ACTH stimulation at two large tertiary hospitals in Melbourne, Australia, we aimed to: 1) determine the value of ACTH for improving cannulation success in two centres with different level of expertise; 2) assess the impact of ACTH on rates of lateralization; 3) formulate clinical guidelines on how to interpret AVS data when they differ pre- and post-ACTH.

Methods

Patients and study design

A retrospective clinical audit was conducted at Austin Health between January 2001 and May 2018 and at Monash Health between January 2010 and May 2018 on a total of 207 AVS procedures performed on 201 patients. Only AVS performed both pre- and post-ACTH were included in the study. Clinical information was retrieved from the hospitals' medical records, or correspondence from private physicians where possible.

Diagnosis of primary aldosteronism

The diagnosis of PA was made in accordance with The Endocrine Society guidelines ¹². In the majority of patients, interfering antihypertensive medications (beta-blockers, diuretics, dihydropyridine calcium channel antagonist, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors) were stopped for 4 to 6 weeks before the aldosterone:renin ratio (ARR) screening test and oral potassium supplementation was prescribed to achieve a target serum potassium at or above 4.0mM. To control hypertension, patients were switched to non-interfering antihypertensive medications including verapamil, hydralazine, moxonidine and prazosin. Screening was considered positive when the ARR was greater than 70 pmol/L:mU/L on at least two independent samples. The diagnosis of PA was confirmed when plasma aldosterone remained above 140 pmol/L after a conventional recumbent saline suppression test ¹² where 2 litres of normal saline was infused intravenously over 4 hours.

Serum potassium, cortisol, direct renin concentration and plasma aldosterone concentration were measured at baseline and after the saline infusion.

Adrenal imaging and adrenal vein sampling

All PA patients underwent an adrenal CT scan with contrast and fine cuts (< 3 mm) using standard criteria for adrenal gland investigations including non-contrast CT attenuation measured in Hounsfield units to assist subtype differentiation and adrenal vein localisation. All images are reviewed by the duty radiologist as well as the radiologist performing AVS. At Monash Health, from 2013 onwards, the majority of AVS procedures were performed by one dedicated interventional radiologist who developed a focussed expertise in the technique while AVS at Austin Health was performed by a range of radiologists. Both centres performed sequential cannulation of the adrenal veins and peripheral / external iliac vein through a percutaneous femoral vein approach under fluoroscopic guidance. After baseline aldosterone and cortisol samples were collected from the peripheral vein, LAV and then the RAV, a 250µg intravenous bolus of ACTH₁₋₂₄ was administered peripherally followed by an infusion at 50µg/hour. During the infusion, the catheter remained in the RAV. After 15 minutes, a second set of samples were collected from the RAV, then the LAV and finally the peripheral vein. Cortisol was used to correct for any dilutional effect caused by the position of catheter tip. Only AVS studies with paired adrenal vein and peripheral samples pre- and post-ACTH were included in this analysis. Aldosterone and cortisol values from samples pre- and post-ACTH were assessed for successful cannulation and lateralization.

Laboratory measurements

Plasma aldosterone and direct renin concentration were measured using chemiluminescent immunoassays on a DiaSorin Liaison analyser in both institutions. For aldosterone, the within-run coefficients of variation (CV) were 3.5% at 188 pmol/liter and 1.8% at 798 pmol/liter. The total CV were 9.6% at 188 pmol/liter and 5.6% at 798 pmol/liter. For renin, the within-run CV were 6.6% at 24.0 mU/liter and 1.4% at 92.4 mU/liter. The total CV were 10.0% at 24.0 mU/liter and 4.5% at 92.4 mU/liter. At Austin Health, plasma renin activity was measured before 2nd April 2013. For consistency in units of measurement, plasma renin activity was converted to direct renin concentration (1 ng/mL/hr PRA is equivalent to approximately 12 mU/L DRC). Plasma cortisol was measured using chemiluminescent immunoassay on a

Beckman Coulter UniCel Dxl 800 analyzer at Monash Health and using a Roche Cobas e602 analyzer at Austin Health. For plasma cortisol measurements at Monash Health, the within-run CV were 6.7% at 166 nmol/liter, 4.4% at 665 nmol/liter and 4.4% at 1060 nmol/liter. The total CV were 7.9% at 166 nmol/liter, 6.0% at 665 nmol/liter and 6.4% at 1060 nmol/liter. At Austin Health, the within-run CV for plasma cortisol measurement were 2.5% at 90 nmol/liter and 2.9% at 690 nmol/liter.

AVS data interpretation and criteria for adrenalectomy

As recommended by the Endocrine Society Guidelines ¹², the selectivity index (SI) was calculated by dividing adrenal vein cortisol by peripheral vein cortisol levels. Successful cannulation of the adrenal veins was indicated when $SI > 2$ pre-ACTH, or $SI > 3$ post-ACTH. The aldosterone: cortisol ratio (ACR) was determined for each cannulation site. The lateralization index (LI) was defined as $ACR (\text{dominant adrenal vein}) : ACR (\text{non-dominant adrenal vein})$. LI was calculated for all patients, but comparisons of pre- and post-ACTH were only made when bilateral successful cannulation of adrenal veins was achieved both pre- and post-ACTH. The diagnosis of unilateral APA was made when $LI > 3$ pre-ACTH or $LI > 4$ post-ACTH. The diagnosis was supported by a contralateral suppression index (CSI) ($ACR (\text{non-dominant adrenal vein}) : ACR (\text{peripheral vein}) < 1$) although this was not a prerequisite for proceeding with surgery. Patients with successful lateralization of aldosterone excess were offered unilateral adrenalectomy. Patients with discordant lateralization but characteristics suggestive of APA, including young age, hypokalaemia or strong family history, were also offered surgical treatment.

Follow up and postoperative outcome evaluation

After AVS procedures at both centres, all surgically treated patients were evaluated at 1, 3, 6 and 12 months for blood pressure, antihypertensive medications and renin assessment, where feasible. The histology of the resected adrenals and long-term outcomes were analyzed. Post-operative outcomes for unilateral primary aldosteronism patients with adrenalectomy were assessed using the Primary Aldosteronism Surgical Outcome (PASO) consensus criteria ¹³. Complete clinical success was defined as normal blood pressure without the aid of antihypertensive medications. Complete biochemical success referred to normalisation of hypokalaemia (if present before surgery) and ARR ¹³. Patients with failed

cannulation in AVS were either offered a repeat AVS or treated with MRA (spironolactone in the majority; eplerenone if spironolactone is not tolerated). Patients with bilateral disease were treated with MRA.

Statistical methods

Continuous data were analysed for normality using the Kolmogorov-Smirnov test. Values were either presented as mean $\pm$ standard deviation, or median (interquartile range). Comparison between groups were performed using student t-test or nonparametric (Mann Whitney *U*) test as appropriate. Categorical data were reported as counts and/or percentages and comparisons were assessed using Chi-square test. McNemar's test was used for comparison of successful cannulation and unilateral lateralization of AVS before and after ACTH. Statistical significance was assigned at a P value of <0.05 . IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, N.Y., USA) was used to perform the analyses.

Results

A total of 207 AVS procedures (103 from Austin Health and 104 from Monash Health) were performed on 201 patients. Three patients from each hospital respectively were evaluated twice due to failed AVS on the first attempt.

The baseline characteristics of patients who underwent AVS were comparable between the two hospitals (Table 1). The mean age was 53 ± 12 (range 19-78 years) and 106 were men with 95 women. Patients from Monash Health had higher systolic and diastolic blood pressure than those from Austin Health (160/98 mmHg vs 150/88 mmHg), while those from Austin Health required more potassium replacement (61% vs 42%) and were found to have more adrenal masses on CT (83% vs 56%), but no difference was observed in their ARR.

Effect of ACTH stimulation on cannulation success

At Austin Health, the percentage of successful bilateral cannulations increased from 33% (34/103) pre-ACTH to 64% (66/103) post-ACTH (Figure 1A). Likewise, an overall increase in the proportion of AVS where bilateral cannulation success was achieved was also demonstrated at Monash Health from 73% (76/104) pre-ACTH to 83% (86/104) post-ACTH

(Figure 1A). The percentage of cannulations of the LAV and RAV deemed to be successful increased after ACTH stimulation (Figure 1B). When results from both centres were combined, ACTH increased the selectivity of LAV from 78% pre-ACTH to 97% post-ACTH and the RAV from 60% pre-ACTH to 76% post-ACTH (Figure 1B). Overall, the rate of cannulation success of both adrenal veins was significantly higher after ACTH stimulation (Figure 1B).

Effect of ACTH stimulation on lateralization index (LI)

Analysis of lateralization was performed on the 102 AVS procedures where both pre- and post-ACTH cannulation success was achieved (Table 2). Overall, there was a significant decrease in LI post-ACTH compared to pre-ACTH (Figure 2). Using a cut-off of LI >3 pre-ACTH or LI >4 post-ACTH for lateralization, the proportion of cases considered to have unilateral aldosterone excess decreased from 70% pre-ACTH to 54% post-ACTH (Figure 3).

Overall there was a 23% global discordance in lateralization among patients who had successful bilateral cannulation (Table 2). Twenty patients showed lateralization pre-ACTH (17 lateralized to the right; 3 to the left) but bilateral aldosterone production after ACTH stimulation; three patients demonstrated bilateral aldosterone production pre-ACTH but lateralized to the left post-ACTH. There was only one patient who lateralized from the right basally to the left post-ACTH.

Evaluation of discordant lateralization and postoperative outcome

Of the 24 patients (20 from Monash Health, 4 from Austin Health) with discordant lateralization of aldosterone production, seven (all from Monash Health) proceeded to unilateral adrenalectomy based on lateralization pre-ACTH and a combination of features suggestive of APA, including young age, typical adrenal adenoma on CT imaging and/or hypokalaemia¹⁴ (Table 3). A contralateral suppression index (CSI) <1 pre-ACTH was present in all seven patients as it was also considered consistent with APA^{15,16}.

Over a follow-up period of 4 to 78 months, three of the seven operated patients had complete biochemical success with normalisation of their ARR. Patient #1 most probably experienced a cure given her normal blood pressure off all antihypertensive medications post-operatively, however follow-up and biochemical testing was not possible due to relocation overseas. All four cured patients had post-ACTH LI>2. Three other patients (#3, 5 and 7) had persistently

elevated ARR>70 post-operatively despite a pre-ACTH LI >3.0 together with contralateral suppression. They shared the common characteristic of post-ACTH LI <2.0.

Discussion

The combined data from two large tertiary centres that share a common rigorous protocol for AVS demonstrated that ACTH stimulation can affect both the selectivity of adrenal veins during AVS and the magnitude of lateralization of aldosterone excess.

With regards to adrenal vein selectivity, the use of ACTH led to a 20% increase in the number of cannulations judged to be successful, which is consistent with international literature^{9,10,17-19}. If only the basal AVS results were recorded, of the 201 patients studied in this series, 77 or 38% would have undergone an invasive procedure without producing interpretable results. This improvement was most notable in the centre without a dedicated interventional radiologist – a 31% increase in successful cannulation was observed at Austin Health compared to 10% at Monash Health. The higher cannulation success rate at Monash Health, even before ACTH, can be attributed to having a dedicated interventional radiologist which is recognized as key to AVS success⁶. Whilst ACTH does not replace the need for a dedicated radiologist with specific AVS expertise, ACTH is a valuable tool to enhance the potential success of AVS.

The use of ACTH in AVS remains controversial and has recently been reviewed by Deinum *et al*²⁰. An earlier review by Rossi *et al.* demonstrated increased cannulation success at the expense of reduced lateralization²¹. In agreement with Rossi's review and a meta-analysis¹¹, our study also showed a decrease in lateralization indices between baseline and post-ACTH at both centres (13% at Austin Health and 17% at Monash Health). A similar finding of discordant lateralization has been reported in 10-30% of cases from expert centres around the world^{9,10,22,23}. However, there are no published guidelines on the management of these patients. In our series of seven cases where unilateral adrenalectomy was performed despite discordant lateralization, four patients experienced a surgical cure. They share the common characteristics of LI > 2 post-ACTH, which is not considered typical of lateralization based on current criteria. We therefore suggest that a lower, rather than higher, LI threshold may be

needed post-ACTH, compared to pre-ACTH, for the interpretation of lateralization. The three patients who did not experience a surgical cure had post-ACTH LI < 2.

The mechanism underlying the decrease in lateralization post-ACTH is not well defined. In cases where pre-ACTH lateralization correctly predicted surgical success, it is postulated that lateralization post-ACTH is masked due to ACTH disproportionately stimulating aldosterone production from the contralateral normal adrenal gland. It is known that binding of ACTH to melanocortin type 2 receptor (MC2R) in normal adrenals stimulates both aldosterone and cortisol secretion acutely^{10,24}. Enhanced aldosterone production from the normal contralateral gland may therefore diminish the LI and lead to the false impression of bilateral aldosterone excess. Furthermore, the incremental increase in aldosterone after ACTH stimulation is time-dependent with a significant rise between 5- and 10-minutes post-ACTH although it appears to plateau between 10 and 15 minutes²⁵. If post-ACTH adrenal vein sampling begins less than 15 minutes after an ACTH bolus or infusion, there may be a time-mismatch between the two sides such that sampling captures differentially stimulated aldosterone responses. This may explain why AVS protocols utilising simultaneous sampling experience less discordance^{18,26}. In sequential sampling protocols, after ACTH stimulation, the RAV is almost always sampled first and the LAV is sampled some minutes later. For the Monash Health cohort, the mean time difference between sampling of RAV and LAV post-ACTH is 11.89 minutes (± 7.1 SD). This small time lag may permit greater aldosterone production from the left compared to the right adrenal gland, thereby masking right-sided APA. Basal right-sided lateralization was observed in all four cured patients in our current series, as well as ten out of thirteen discordant AVS cases at Monash Health since the conclusion of the current study (Appendix 1) and five out of seven cases from Ghorayeb *et al*⁹. These data suggest that where simultaneous adrenal vein sampling is not feasible, the AVS team should allow sufficient time lag of greater than 15 minutes after ACTH administration, and minimise the time between cannulating the right and left adrenal veins.

In patients 3, 5 and 7 who did not receive a surgical cure, their pre-ACTH results appeared to demonstrate false lateralization while ACTH unveiled bilateral adrenal disease. A potential explanation for the augmented aldosterone-secretory response to ACTH in BAH is the upregulation of MC2R in hyperplastic tissue. One study evaluated the expression of G-protein coupled receptors (GPCR) in 15 adrenal tumours, including 14 APA and one adrenal sample

with hyperplastic tissue ²⁷. The study revealed 20-fold higher expression of MC2R mRNA in the “hyperplastic” adrenal tissue than normal adrenal tissue (100 copies/0.1 microgram total RNA) or APA (31-739 copies/0.1 microgram total RNA). One may postulate that in the setting of BAH, the contralateral hyperplastic gland may be significantly stimulated by ACTH and therefore become unmasked. The great variability of MC2R expression in APAs may also influence the response to ACTH stimulation, resulting in either appropriately high aldosterone secretion (true lateralization) or relatively low aldosterone secretion compared to contralateral hyperplasia (unmasked BAH). One study demonstrated that MC2R is under-expressed in about two-thirds of the APA as compared to the normal adrenal cortex which may explain the loss of lateralization ²⁸. There are also reports of aldosterone-producing cell clusters (APCCs) in the adrenal gland in patients with or without PA ²⁹⁻³¹. However, it is unclear if APCCs respond to ACTH to cause discordant AVS results.

In our study, ACTH unsuppressed the contralateral gland in three cases, with the CSI increasing to above 1 post-ACTH. However, one of these patients still experienced biochemical cure. Pre-ACTH, all seven patients had suppressed CSI < 1, but their post-operative outcomes were different. When interpreting ACTH-stimulated AVS, only a few centres use CSI as a criterion for lateralization. Wolley *et al* ¹⁶ reported that contralateral suppression is an important predictor of surgical success while Monticone *et al* ¹⁵ argued that contralateral suppression is less important for patients with robust lateralization based on LI >4.0. The effect of ACTH on CSI is not commonly studied, although it has been noted to be minimal by some studies ^{10,17}. In our series, CSI was not a robust predictor of surgical cure.

Overall, our study found that ACTH was useful for increasing the number of AVS procedures judged to have successful cannulation. In cases of discordant AVS result post-ACTH stimulation, the best management approach remains unclear. Based on the clinical and biochemical outcomes of operated patients who had long-term follow-up, we demonstrated that the combination of pre-ACTH LI > 3 and post-ACTH LI > 2 is a robust predictor of surgical success. This recommendation is different to current guidelines which suggest that the post-ACTH LI should be higher than the pre-ACTH LI. However, our criteria for lateralization is limited by the sample size because only a small number of patients with discordant AVS results underwent adrenalectomy. As with all AVS studies, definitive diagnosis of the true

subtype cannot be ascertained in cases where surgery is not performed. For that reason, we only used data from patients who underwent adrenalectomy to form our recommendation. Another limitation is the lack of histochemical confirmation of aldosterone synthase staining adenomatous tissue in the resected samples. However, almost all patients had repeat biochemical testing to assess for a biochemical cure. Evaluation for somatic mutations in the resected lesions may be interesting in light of recent study findings that the underlying genetic mutation determines the response of LI to ACTH, with *KCNJ5* mutations associated with descending LI, while *ATP1A1* and *ATP2B3* mutations associated with an ascending LI ³². Ongoing research which explores alternative strategies, such as nuclear medicine imaging and venous steroid profiling, for subtyping in the setting of discordant AVS results will also facilitate the accurate diagnosis of unilateral versus bilateral PA.

Conclusion

ACTH can increase the number of AVS procedures considered to have successful cannulation, especially in centres where a dedicated radiologist is not available. However, ACTH can reduce the number of cases assessed to have lateralization. This may represent masking of true lateralization of unilateral disease or unmasking of bilateral disease. For physicians who need to make a clinical decision based on discordant results, we recommend that a lower, rather than higher, threshold for the lateralization index be used for subtype assessment after ACTH stimulation. More prospective studies are needed on strategies to maximise the benefits of ACTH on cannulation while producing robust lateralization results for accurate PA subtyping.

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Table 1. Patient characteristics at baseline

	Monash Health	Austin Health	P-value (Monash vs Austin)
AVS procedures	104	103	
Patients (<i>n</i>)	101	100	
Male (%)	49% (49/101)	57% (57/100)	0.43
Age (years)	52 ±11 (range 19-76)	54 ±12 (range 25-78)	0.17
Systolic blood pressure (mmHg)	160 (150,180)	150 (136,160)	<0.001
Diastolic blood pressure (mmHg)	98 (90,105)	88 (80,91)	<0.001
Number of anti-hypertensive agents	3 (2,4)	3 (2,3)	0.29
Serum potassium level (mmol/L)	3.8 (3.5,4.2)	3.5(3.0,4.1)	0.002
Plasma aldosterone (pmol/L)	532 (421,750)	750 (535,1183)	0.001
DRC (mU/L)	2.4 (2.0,4.8)	3.4 (2.0,5.3)	0.10
ARR (pmol/mU)	197 (117,319)	233 (118,431)	0.34
Patients requiring potassium replacement (%)	43% (43/101)	60% (46/77)	0.013
Patients with adrenal masses on CT (%)	56% (57/101)	82% (65/79)	<0.001

AVS, adrenal vein sampling; CT, computed tomography; DRC, direct renin concentration; ARR, aldosterone-renin ratio. Data are expressed as median (interquartile range) or percentage (number affected/total number) unless specified as mean ± SD.

Table 2. Percentage of patients with concordant (unshaded) vs discordant (shaded) lateralization outcomes before and after ACTH

		Post-ACTH LI>4 Lateralization Outcome		
Pre-ACTH LI>3 Lateralization Outcome	n = 102	Bilateral	Right	Left
	Bilateral	27% (n=28)	0	3% (n=3)
	Right	16% (n=17)	25% (n=25)	1% (n=1)
	Left	3% (n=3)	0	25% (n=25)

Table 3. Baseline characteristics and post-operative outcomes of patients with discordant lateralization in the setting of ACTH use in AVS

Pt #	Sex	Age (years)	Baseline			K (mmol/L)	ARR (pmol/mU)	Adrenal mass on CT	Side of lateralization on AVS pre-ACTH	LI		CSI		Histology	Last Review			Duration of follow up post-op (months)	Repeat ARR post-op (pmol/mU)
			SBP (mmHg)	DBP (mmHg)	No of meds					Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH		SBP (mmHg)	DBP (mmHg)	No of meds		
1	F	42	140	80	3	3.2	1010	R	R	6.72	3.05	0.65	0.91	A	106	70	0	4	-
2	F	52	140	80	1	2.8	112.5	R	R	47.74	3.52	0.18	0.56	A	139	78	1	78	16
3	F	58	110	70	2	3.6	538	L	L	3.02	1.27	0.26	0.50	H	112	80	1	71	143
4	F	54	225	125	4	4.1	>172	R	R	21.54	2.12	0.77	0.68	A	135	80	3	50	16
5	F	49	152	105	2	3.7	84	None	L	4.65	0.82	0.56	4.21	H	118	91	1	41	88
6	F	45	170	100	3	4.3	183	None	R	27.63	2.60	0.80	1.76	A	140	88	2	42	47
7	M	58	140	80	4	4.8	265	R	R	12.91	1.63	0.72	1.49	A	120	80	0	18	73

Pt, patient; F, female; M, male; R, right; L, left; A, adenoma; H, hyperplasia; CT, computed tomography; LI, lateralization index; CSI, contralateral suppression index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARR, aldosterone to renin ratio.

Figure legends

Figure 1A. Effect of ACTH on the proportion of bilateral successful cannulation at each hospital, using the cut-off of SI>2 pre-ACTH or SI>3 post-ACTH.

*P value <0.05 comparing percentage of successful cannulation post-ACTH to pre-ACTH.

Figure 1B. Effect of ACTH on the proportion of successful cannulation of LAV and RAV.

*P value <0.05 comparing percentage of successful cannulation of RAV and LAV pre- and post-ACTH.

RAV, right adrenal vein; LAV, left adrenal vein.

Figure 2. Change in lateralization index from pre- to post-ACTH.

*P value = 0.04 comparing average LI pre-ACTH to post-ACTH.

Figure 3. Change in percentage of patients with lateralization pre- vs post-ACTH, based on 102 AVS cases with bilateral successful cannulation defined by SI>2 pre-ACTH and SI>3 post-ACTH.

*P value = 0.03, pre-ACTH vs post-ACTH.

Appendix 1. Characteristics of non-operated AVS patients with discordant lateralization pre- and post-ACTH at Monash Health from January 2016 to May 2018

Sex	Age (years)	Baseline			K (mmol/L)	Aldo (pmol/L)	Renin (mU/L)	ARR (pmol/mU)	Adrenal mass on CT	LI		CSI		Side of lateralization on AVS pre-ACTH	Last Review			Dosage of MRA (mg)	Latest		Duration of follow up after starting MRA (months)
		SBP (mmHg)	DBP (mmHg)	No of meds						Pre-ACTH	Post-ACTH	Pre-ACTH	Post-ACTH		SBP (mmHg)	DBP (mmHg)	No of meds		K (mmol/L)	Renin (mU/L)	
F	43	168	128	1	4.4	428	3.3	129.7	None	9.19	0.83	1.63	3.38	R	123	87	1	50 [#]	4.6	16	22
M	65	150	86	1	4.9	504	<2	252	L	7.00	2.32	1.07	1.74	R	120	78	2	25 [#]	4.7	31	29
M	64	170	85	5	3.7	306	3.6	85	R	3.31	4.6 Left lateralization	2.57	1.66	R	130	60	5	25 [#]	5.3	42	27
F	40	155	105	4	4.2	259	1.6	161.88	None	3.99	1.07	1.71	2.32	R	108	73	1	50 [#]	4.7	11.6	27
M	67	160	94	4	4.2	378	1.7	222.35	None	13.85	2.27	0.62	5.05	R	133	77	3	10 [^]	4.2	5.6	26
M	61	135	70	4	3.2	445	2.7	164.81	None	0.54	12.58 Left lateralization	1.61	0.3	Bilateral	117	73	2	50 [#]	4.4	21.3	28
F	48	158	93	4	3.6	600	4	150	R	0.35	133.83 Left lateralization	2.79	0.45	Bilateral	135	80	3	37.5 [#]	4.5	19	21
F	58	190	90	2	4.2	332	<2	-	R	1.49	11.34 Left lateralization	3.25	0.53	Bilateral	119	71	1	25 [#]	4.5	5	19
F	60	161	90	1	4.0	231	3	77	L	10.97	1.06	0.63	1.78	R	130	90	1	50 [#]	4.6	30	24
F	43	155	100	0	4.4	610	4.1	149	None	3.21	1.06	2.87	2.66	R	122	86	1	25 [#]	4.4	6.2	22
F	34	160	100	1	4.2	344	<2	>172	L	11.21	1.04	1.43	3.14	R	126	86	1	100 [^]	4.6	22	23
F	54	170	70	1	4.6	408	4	102	None	9.47	0.93	0.52	1.63	R	133	91	1	75 [#]	5.1	28	22
F	61	153	90	2	4.4	2210	29	76	L	3.09	3.07	0.94	1.23	R	159	87	1	50 [#]	4.1	10	14

Pt, patient; M, male; F, female; R, right; L, left; CT, computed tomography; LI, lateralization index; CSI, contralateral suppression index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ARR, aldosterone to renin ratio; MRA, mineralocorticoid receptor antagonist; #, spironolactone; *, eplerenone; ^, amiloride.

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