


Clinical outcomes from surgical management of primary aldosteronism based on inconclusive adrenal vein sampling

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Dear Editor,

Adrenal vein sampling (AVS) is the gold standard procedure for subtyping primary aldosteronism (PA). Successful AVS (bilateral cannulation) remains a challenge for the majority of centres with low procedure volume. Diagnostic algorithms based on inconclusive AVS indices (defined as unsuccessful bilateral cannulation) and imaging finding to aid surgical decision making is lacking. In our institution, clinical decision-making has varied between clinicians when faced with inconclusive AVS: a purist approach of uninterpretability of available ratios and ongoing conservative management or a pragmatic approach. The latter approach considers the option of unilateral ipsilateral adrenal surgery in case of unilateral cannulation index of aldosterone:cortisol (A/C) of cannulated adrenal vein to inferior vena cava ratio (AV/IVC) >1 or contralateral adrenal surgery in case of A/C AV/IVC <1, with a careful patient discussion of estimates of biochemical remission from published literature depending on imaging findings.^{1,2} We reviewed the clinical outcomes after unilateral adrenalectomy based on successful and inconclusive AVS results at our institution over a 15-year period.

AVS was performed under continuous stimulation with adrenocorticotrophic hormone: 50 µg/h, started 30 min before sampling, and continued throughout the procedure. Blood was sampled from AV and IVC sequentially for cortisol and aldosterone measurements. Successful adrenal vein cannulation is defined as achieving a selectivity ratio of 5:1 (cortisol ratio of each AV/IVC). Unilateral disease was considered if lateralisation index was ≥4:1 (A/C between the dominant and

nondominant AV in case of bilateral successful AV cannulation) or if contralateral suppression index was <1 (A/C ratio between cannulated contralateral AV to IVC) in case of bilateral or unilateral successful cannulation.³ Biochemical remission, following unilateral adrenalectomy, was defined by aldosterone:renin <30 pmol/mlU or random aldosterone ≤140 pmol/L and normokalaemia. Clinical remission was defined as achieving normal blood pressure (<140/90 mmHg) with normokalaemia without any antihypertensive therapy postadrenalectomy. Data are expressed as mean (±SD) or percentages and statistical analysis was performed using Fisher's Exact test for categorical variables between groups.

Sixty-nine patients underwent AVS for biochemically-proven PA since 2009. Four patients had repeat AVS due to failure to achieve bilateral cannulation at the first attempt, but for two patients, AVS was still inconclusive on the second attempt. One patient suffered an adrenal haemorrhage during AVS and was excluded from the analysis due to the unreliability of AVS indices. The mean age of our cohort was 53 (±12) years with a male preponderance of 3:1. Patients were on an average of 3 anti-hypertensive medications and 77% had a history of hypokalaemia. The majority of patients had unilateral adrenal lesions (62%) on computed tomography (CT) imaging, while bilateral lesions or normal adrenals were equally distributed among the rest.

Overall, successful AVS was achieved in 38/68 (55%) cases over a 15-year period, but over the last 12 months, 12/14 (86%) AVS were successful when performed by a single dedicated radiologist,

demonstrating technical proficiency achieved with increasing volume. 2/13 patients with bilateral aldosterone excess were offered unilateral adrenalectomy due to a unilateral adrenal lesion on imaging; both achieved biochemical remission. 6/7 patients with

left-sided aldosterone excess on AVS underwent left adrenalectomy and 5 achieved biochemical remission. 15/18 patients with right-sided aldosterone excess underwent right adrenalectomy whilst another two are awaiting surgery. The two patients, not offered

TABLE 1 Comparing AVS indices and clinical outcomes for patients undergoing unilateral adrenal surgery for PA based on inconclusive AVS (group A and B) and those managed conservatively with medical therapy (Group C).

Group	Patient	Sex	Age (years)	Adrenal lesion on CT	Successful cannulation side	AC cannulated AV/IVC	AC uncannulated AV/IVC	Unilateral adrenalectomy	Biochemical remission	SBP (mmHg)	DBP (mmHg)
A	1	M	49	BL	L	0.4	-	R	Y	148	78
	2	M	75	L	L	0.7	-	R	Y	110	61
	3	M	54	L	L	2.7	-	L	Y	120	80
	4	F	53	L	R	5.4	-	R	Y	158	90
	5	M	69	R	L	0.1	-	R	Y	115	65
B	6	M	65	BL	L	-	0.3	L	Y	130	68
	7	M	61	L	L	3.4	0.3	L	Y	130	82
	8	M	51	L	L	1.9	0.9	L	Y	148	97
	9	M	36	L	None	-	0.1 (R)	L	Y	125	79
	10	M	67	L	L	7.3	0.1	L	Y	117	73
	11	F	31	None	L	25	0.9	L	Y	108	79
	12	F	50	None	L	0.9	0.1	L	Y	123	73
	13	M	36	None	L	4.1	0.4	L	Y	150	107
	14	M	36	None	L	2.1	0.3	L	Y	112	76
	15	F	45	None	L	3.9	0.3	L	N	144	76
	16	F	58	R	R	>1.1	0.9	R	Y	120	80
Biochemical remission rate:									94%		
									Mean (SD)	128 (±15)	79 (±11)
C	17	M	58	BL	L	1.7	3.9			132	82
	18	M	79	L	None	-	-			155	69
	19	M	42	BL	L	6.5	2.0			130	80
	20	F	39	BL	L	-	0.2			145	75
	21	M	55	BL	L	0.9	0.2			140	97
	22	M	48	BL	L	0.01	0.5			141	102
	23	M	57	L	L	1.8	1.1			129	79
	24	M	71	L	L	2.3	0.4			171	104
	25	M	68	L	L	0.2	-			116	76
	26	M	55	L	L	17	1.0			128	78
	27	M	64	None	L	6	0.14			150	90
	28	M	59	None	L	3.8	-			115	71
	29	M	69	R	L	0.06	-			120	80
Mean (SD)									136 (±15)	83 (±11)	

Note: Group B includes those patients with inconclusive AVS but suppressed AC uncannulated AV/IVC. Biochemical remission defined as aldosterone:renin <30 pmol/mIU, or random aldosterone ≤140 pmol/and normokalaemia.

Abbreviations: AC, aldosterone: cortisol; AV/IVC: adrenal vein/inferior vena cava; AVS, adrenal vein sampling; BL, bilateral; DBP, diastolic blood pressure; F, female; L, left; M, male; N, no; PA, primary hyperaldosteronism; R, right; SBP, systolic blood pressure; SD, standard deviation; Y, yes.

surgery despite lateralisation on successful AVS, was due to the clinician's judgement based on finding normal adrenals on CT. Overall, 10/23 (43%) of patients with successful AVS and unilateral adrenalectomy achieved clinical remission, and 22/23 (96%) achieved biochemical remission.

16/30 patients with inconclusive AVS underwent unilateral adrenalectomy based on AVS results and imaging findings after careful discussion within a multidisciplinary team (MDT). The remainder continued on long-term medical therapy as per the clinician's judgment ($N = 13$), whereas one patient with bilateral unsuccessful cannulation was offered adrenalectomy based on CT findings alone. The clinical characteristics and surgical outcomes of the 29 patients are included in Table 1. Unilateral adrenalectomy was performed in 13 patients with left-sided successful cannulation. Notably, a left adrenal lesion was only present in five patients and a right-sided adrenalectomy was performed on one of them due to left-sided suppression on AVS (A/C AV/IVC < 1). The other patients had either normal adrenals ($N = 5$), bilateral adrenal lesions ($N = 2$) or a right adrenal lesion ($N = 1$) on imaging. Two patients with unilateral right-sided cannulation underwent right adrenalectomy and one patient with a left adrenal lesion was offered left adrenalectomy based on unsuccessful cannulation of both adrenal veins (patient 9). 15/16 (94%) patients achieved biochemical remission. Blood pressure management was comparable between the surgical (Groups A and B) cohort postoperatively and the medical (Group C) cohort. The latter cohort was on a median number of 3 antihypertensive agents with 9/13 patients taking a mineralocorticoid receptor antagonist and their mean serum potassium was $4.2 (\pm 0.5)$ mmol/L.

We further analysed the A/C of the uncannulated AV/IVC in patients with inconclusive AVS (Table 1—Group B). These samples are those labelled as coming from the adrenal vein, but the mathematical assessment of cortisol later informed us that the adrenal vein was not cannulated (cortisol ratio AV:IVC < 5). The blood was sampled in the vicinity of the adrenal vein as it drains into the IVC, whereas our peripheral samples are taken inferior to the renal veins within the IVC. Interestingly, 11 patients had ratios < 1 and contralateral adrenalectomy achieved biochemical remission in 10 of them (91%). Of note, a unilateral ipsilateral adrenal lesion was present in only five of those patients having unilateral adrenalectomy based on inconclusive AVS.

Overall, 19/40 (48%) offered surgery, based on successful and inconclusive AVS, in our cohort achieved clinical remission, comparable to the estimated 37% previously reported.⁴ For the 19 patients requiring ongoing antihypertensive therapy, despite biochemical remission, we noted a significant reduction in the mean number of antihypertensive therapy required to control blood pressure (2.9 preoperatively vs. 1.8 postoperatively, $p < .002$). Two patients had evidence of ongoing PA postunilateral adrenalectomy due to bilateral disease.

Our data challenges a purist approach to only consider unilateral adrenalectomy once successful AVS confirms lateralisation of aldosterone excess. Whilst offering adrenalectomy based on CT finding of unilateral adrenal lesion achieves biochemical remission in

80% of cases,⁵ in our cohort inconclusive AVS results influenced surgical decision-making in 16 patients, with variable CT findings, and achieved a surprising 94% biochemical remission rate, comparable to the previously reported estimates from successful AVS.⁴ Therefore an MDT approach to interpreting inconclusive AVS along with imaging findings effectively allows for careful selection of appropriate patients for surgical management and avoids inappropriate surgery. Importantly, inconclusive AVS with unilateral AV cannulation avoids offering adrenalectomy to a suppressed side in unilateral disease (A/C AV/IVC < 1), but necessarily carries a risk of undertaking unilateral surgery in bilateral disease. Nevertheless, emerging data on clinical and biochemical outcomes in the latter is encouraging and unilateral surgery may no longer be considered inappropriate.⁶ Such occurrence was rare in our cohort (5%). Our data further identifies the clinical utility of finding a suppressed A/C AV/IVC (< 1) in the uncannulated AV to suggest unilateral aldosterone excess in the contralateral adrenal gland in 90% of cases, albeit within the limitation of our small cohort size. This suggests that blood sampled within the vicinity of the AV, from a suppressed adrenal gland, as it drains into the IVC, has a gradient for equilibrating aldosterone levels within the IVC. Further retrospective analysis of larger datasets of inconclusive AVS is needed to further validate this finding.

Finally, patients with PA who are not candidates for surgical management (e.g., frailty or patient choice) should not undergo AVS, especially those who, in some clinicians' judgment, would not be considered for surgery due to anatomically normal adrenal glands on imaging, albeit not a universally agreed criterion.

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