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Repeating adrenal vein sampling when neither aldosterone/cortisol ratio exceeds peripheral yields a high incidence of aldosterone-producing adenoma

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Abstract:	Objectives: In primary aldosteronism (PA), adrenal vein sampling (AVS) suggests unilateral aldosterone-producing adenoma (APA) when the aldosterone/cortisol (A/F) ratio is ≤ peripheral on one side and ≥2 times peripheral on the other. When A/F ratios are lower bilaterally than peripheral despite adequate samples (adrenal venous cortisol ≥3 times peripheral), we recommend repeat AVS. This study aimed to determine the frequency of this occurrence and outcomes in such cases. Methods: We performed a retrospective observational study of all cases of primary aldosteronism undergoing initial AVS over a 34 year period. Results: Initial AVS in 1397 patients returned satisfactory, discriminatory results in 1066 (76.3%) but 37 patients (2.6%) had adequate samples but bilateral A/F ratios no higher than peripheral. Of the 22 of these 37 who agreed to repeat AVS, 10 demonstrated unilateral aldosterone production, and eight of these had unilateral adrenalectomy disclosing APAs and resulting in cure (3) or improvement (5) in hypertension. Eight had bilateral aldosterone production. Four studies were inconclusive. Patients with initial unsatisfactory AVS because of bilaterally low A/F ratios had significantly (p=0.023) more unilateral disease [10 of 18 satisfactory repeat studies (55.6%) vs 326 of 1066 satisfactory initial studies (30.6%)] and a significantly higher (67.6% vs. 49.9%, p=0.034) percentage of males. Conclusions: Since the incidence of APAs was high in a subgroup with low A/F bilaterally on initial AVS, these patients should be offered repeat AVS. This might reflect both a greater dependence of aldosterone production on ACTH in APAs and the pulsatile nature of ACTH secretion.

REPEATING ADRENAL VEIN SAMPLING WHEN NEITHER ALDOSTERONE/CORTISOL RATIO EXCEEDS PERIPHERAL YIELDS A HIGH INCIDENCE OF ALDOSTERONE-PRODUCING ADENOMA

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ABSTRACT

Objectives: In primary aldosteronism (PA), adrenal vein sampling (AVS) suggests unilateral aldosterone-producing adenoma (APA) when the aldosterone/cortisol (A/F) ratio is ≤ peripheral on one side and ≥2 times peripheral on the other. When A/F ratios are lower bilaterally than peripheral despite adequate samples (adrenal venous cortisol ≥3 times peripheral), we recommend repeat AVS. This study aimed to determine the frequency of this occurrence and outcomes in such cases.

Methods: We performed a retrospective observational study of all cases of primary aldosteronism undergoing initial AVS over a 34 year period.

Results: Initial AVS in 1397 patients returned satisfactory, discriminatory results in 1066 (76.3%) but 37 patients (2.6%) had adequate samples but bilateral A/F ratios no higher than peripheral. Of the 22 of these 37 who agreed to repeat AVS, 10 demonstrated unilateral aldosterone production, and eight of these had unilateral adrenalectomy disclosing APAs and resulting in cure (3) or improvement (5) in hypertension. Eight had bilateral aldosterone production. Four studies were inconclusive. Patients with initial unsatisfactory AVS because of bilaterally low A/F ratios had significantly (p=0.023) more unilateral disease [10 of 18 satisfactory repeat studies (55.6%) vs 326 of 1066 satisfactory initial studies (30.6%)] and a significantly higher (67.6% vs. 49.9%, p=0.034) percentage of males.

Conclusions: Since the incidence of APAs was high in a subgroup with low A/F bilaterally on initial AVS, these patients should be offered repeat AVS. This might reflect both a greater dependence of aldosterone production on ACTH in APAs and the pulsatile nature of ACTH secretion.

Key Words:

Primary aldosteronism, adrenal vein sampling, aldosterone producing adenoma

INTRODUCTION

Recognition of higher than previously expected rates of primary aldosteronism (PA) among hypertensives [1,2] was a major stimulus for the creation by The Endocrine Society in 2008 of international guidelines for case detection and investigation of PA [3]. Adrenal venous sampling (AVS) is important in the diagnostic process, distinguishing unilateral from bilateral aldosterone overproduction, with additional treatment options. AVS is a challenging procedure, requiring an experienced radiologist, and reported rates of successful cannulation of both adrenal veins vary from 42% to 98% [4,5]. Cannulating the right adrenal vein is frequently more difficult than the left, due to the small vessel size and its direct entry into the inferior vena cava, while the left adrenal vein usually joins the left phrenic vein which drains into the left renal vein. Confirmation of successful catheter placement requires comparison of adrenal and peripheral venous cortisol levels in order to correct for dilution from non-adrenal blood, with adrenal vein/peripheral vein cortisol ratios of at least 3.0 indicating satisfactory catheter placement [6]. Aldosterone/cortisol (A/F) ratios are then compared between adrenal and peripheral samples in order to differentiate unilateral from bilateral adrenal aldosterone overproduction, the former suggested by an A/F ratio lower than peripheral on one side (contralateral suppression) and an A/F ratio on the other side at least two-fold higher than peripheral [6].

Fortunately only rarely, in our experience, A/F ratios bilaterally are found to be no higher than peripheral, despite cortisol gradients confirming successful adrenal vein cannulation, a result that is uninterpretable in regard to lateralisation of aldosterone production. The frequency of this occurrence, the best subsequent management and the likely outcomes have to our knowledge never been documented. The aim of this study therefore was to retrospectively analyse our AVS database to identify such cases of primary aldosteronism where adequate cannulation of both adrenal veins was demonstrated but no increase in the

A/F ratio on either side found during adrenal vein sampling. We further examined these cases to identify the results of further testing and outcomes.

METHODS

Setting and subjects

This study was performed in the Hypertension Units of the Greenslopes and Princess Alexandra Hospitals, Brisbane, Australia. Using a prospectively updated database, results of AVS between January 1978 and February 2012 were searched for those with bilaterally low A/F ratios on initial sampling.

Diagnosis of primary aldosteronism

The diagnosis of PA was established according to our previously published criteria [7]. Interfering medications (diuretics, beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and dihydropyridine calcium channel antagonists) were stopped, if possible, at least 4 weeks prior to testing (6 weeks in the case of diuretics including spironolactone). Patients with an elevated aldosterone/renin ratio on at least 2 occasions (>70 with plasma aldosterone in picomoles/liter and plasma active renin in milliunits/liter or >590 with plasma renin activity in ng/ml/hr) underwent fludrocortisone suppression testing to confirm PA. Fludrocortisone suppression testing was regarded as positive if the aldosterone level at 10:00 am after at least 2 hours of upright posture was ≥165pmol/L after 4 days of oral salt loading with concurrent fludrocortisone administration (0.1mg 6 hourly), providing that (1) upright renin was suppressed to less than 8.4mU/L, (2) plasma potassium was within the normal range (sufficient oral potassium chloride 6 hourly to keep plasma potassium measured at least three times daily as close as possible to

4.0mmol/L) and (3) plasma cortisol was lower at 1000 h than at 0800h, excluding an acute increase in ACTH preventing suppression of aldosterone.

Adrenal vein sampling

This study was restricted to those in whom bilateral adrenal vein cannulation was attempted. Adrenal vein sampling was performed between 8 and 11am after overnight recumbency and without ACTH stimulation. Sequential cannulation of both adrenal veins was performed by no more than three experienced radiologists in either hospital (six in total). Usually a short time (<15mins) elapsed between sampling of the left and right adrenal veins. Gradients of ≥3 between adrenal and peripheral venous cortisol concentrations were taken to indicate adequate sampling. If the A/F ratio on one side was ≥2 times the simultaneously collected peripheral ratio and on the other side was the same or less than peripheral (contralateral suppression), the study was considered to demonstrate lateralization of aldosterone production. Adrenal venous A/F ratios higher than peripheral on both sides were taken to indicate bilateral aldosterone production. When results of AVS were inconclusive (comprising unsuccessful cannulation of either adrenal vein or A/F ratios no higher than peripheral bilaterally), repeat AVS was offered to the patient. Computed tomography (CT) of the adrenals with slices 2-3 mm apart was always performed prior to adrenal vein sampling in order to identify any adrenal lesions and to localize adrenal veins and thus assist in successful cannulation [5].

Outcomes

Hospital records were examined to determine patient outcome. Data were collected on patient demographic details, AVS results, serum potassium on presentation and follow up, blood pressure and medications before and after unilateral adrenalectomy or commencement of aldosterone blocking medications.

Hypertension was defined as 'cured' if BP was 140/90 mm Hg or less without antihypertensive medications and 'improved' if fewer medications were needed, provided that the dosage of none of the medications was increased, or if the dosage of one or more medications could be reduced, provided that no additional medications were added. Patients were regarded as 'not improved' if the same or a greater number or antihypertensives were needed to achieve the same BP or if the BP was higher. When patients had a repeat FST after unilateral adrenalectomy (commencing February 1996), demonstration of normal suppressiblity of aldosterone was taken to indicate biochemical cure of PA [8].

Statistics

The data were analysed using Statistica 10 (Statsoft. Inc Tulsa).Standard descriptive statistics were employed for demographic data. For non-parametrically distributed data medians were compared using the Mann-Whitney U test. Proportions between groups were compared using the chi-square test. A "p" value <0.05 was considered statistically significant.

RESULTS

Patient characteristics and frequency of bilateral low A/F ratios.

Of 1397 patients with PA who underwent an initial AVS, 37 (2.6%) had adrenal venous A/F ratios the same or lower than peripheral on both sides. Of the remaining initial studies, 1066 were conclusive and 294 (21%) were inconclusive.

The demographics, results of CT examination, presence of pre-treatment hypokalemia, results of repeat AVS, histology and outcomes in terms of BP and repeat fludrocortisone suppression testing (if performed) after unilateral adrenalectomy for the 37 patients are shown in table 1.

There was a significantly (p=0.034) higher percentage of males among the 37 with low A/F ratios bilaterally than among the remaining patients undergoing AVS [25/37 (67.6%) vs. 679/1360 (49.9%)]. Median ages were similar (54.0 vs 53.5 years, p=0.38).

Outcomes

While 15 patients declined a repeat study, 22 of the 37 patients with bilaterally low initial A/F ratios underwent repeat AVS. Ten of these were consistent with unilateral and eight with bilateral aldosterone production. Four studies were again inconclusive, two due to failure to successfully cannulate one or both adrenal veins and two due to bilateral low A/F ratios for a second time.

A similar proportion of those who declined repeat AVS compared to those who repeated AVS had hypokalemia (9/15 vs. 11/22 p=0.55), evidence of adrenal adenoma on CT where available (8/12 vs. 12/19 p=0.82), and were of male gender (9/15 vs 16/22 p=0.42).

Eight of the ten patients showing unilateral aldosterone production went on to unilateral adrenalectomy. Four of the five who had follow-up FST had a biochemical cure and the fifth had residual but reduced unsuppressible aldosterone production. The five who had been hypokalemic became normokalemic, and hypertension was cured in three and improved in the other five.

The possibility of unilateral APA was considered and discussed with five additional patients with unsatisfactory initial AVS on the basis of a unilateral mass lesion on CT and hypokalaemia (patients 19, 23, 24, 25 and 26). Four had declined a second AVS and one had an inconclusive second AVS. They all chose unilateral adrenalectomy. Two had a follow up FST which confirmed biochemical cure. Hypertension was cured in two and improved in three.

When repeat AVS was consistent with bilateral aldosterone production (n=8), specific medical treatment was commenced with either spironolactone or amiloride or both, with correction of hypokalemia in the four initially hypokalemic and improvement of hypertension in all. Three of these patients eventually went on to unilateral adrenalectomy because of a poor long term blood pressure response or intolerance to medical therapy. In these cases the side with higher aldosterone production was removed.

There was a significantly higher frequency of unilateral disease (10/18 [55.6%] vs. 326/1066 [30.6%], p=0.023) in the subgroup with bilaterally low A/F on initial AVS than in the 1066 with initial diagnostic AVS.

DISCUSSION

As far as we are aware, this is the first report suggesting that repeat AVS in cases where the initial study was compromised by bilateral low adrenal venous A/F ratios yields a high incidence of unilateral PA with worthwhile clinical and biochemical responses to unilateral adrenalectomy. A higher percentage of males in this subgroup was an additional unexpected finding.

There is no immediately obvious explanation for the higher incidence of unilateral disease in the PA patients with failed AVS due to bilaterally quiescent secretion of aldosterone. ACTH is secreted episodically in pulses, reflected in the pattern of cortisol levels revealed by frequent, 20 minute sampling [9]. Aldosterone secretion in patients with APA has been shown to have an episodic or pulsatile pattern of release, and it has been suggested that this is more “disorderly” than in normal subjects [10]. While it has been suggested that APAs are

more responsive to ACTH than the adrenals of patients with bilateral overproduction of aldosterone [11,12], there is also published evidence contradicting this [13].

If renin-angiotensin is chronically severely suppressed in PA, which happens more commonly in APA than in bilateral PA, then responses to other regulators such as ACTH and potassium may become more prominent and recognisable. Secretion normally resulting from angiotensin stimulation will be minimal, significantly lowering adrenal venous concentrations, so that any periods of quiescence in episodic ACTH secretion will be accompanied by very low aldosterone secretion and be more recognisable. This is perhaps what we are seeing in the patients with failed AVS despite good cannula placement, and might explain why more of them than expected have unilateral APAs.

Errors arising during assay of aldosterone and cortisol can never be completely excluded but evidence to suggest this was not found in the cases in question. Explanations such as anomalous venous drainage of the adrenals [5,14–16], accidental 'super-selective' adrenal sampling [17], or extra-adrenal aldosterone producing tumours are unlikely given the results of repeat AVS.

The preponderance of males in those with bilaterally low A/F ratios during AVS is an unexpected finding and has no obvious explanation. Possibly this was a chance finding due to the small number of cases.

A significant limitation of this study is its retrospective nature which, for example, may have increased the risk of selection bias when considering subjects for repeat AVS. The percentages of patients with adrenal lesions on CT and/or with hypokalemia in the sub-groups accepting repeat AVS and those not accepting were not different. This makes it improbable that stronger arguments in favour of repeat AVS were used for those thought at the time more likely to have an APA.

The principal finding in the present study was that, despite failure of the initial AVS to contribute to a diagnosis, repeat AVS was usually successful. Eighteen of 22 repeat AVS were diagnostic. This is perhaps surprising, and suggests that the initial sampling during quiescent aldosterone secretion was presumably due to chance (and episodic ACTH secretion) rather than a permanent idiosyncratic particularity of adrenal function in these patients.

Some units employ ACTH stimulation of aldosterone secretion with an intravenous bolus immediately before, or a continuous infusion during, AVS sampling [18,19]. The aim is to maximise the sensitivity of the procedure, ensuring active secretion of both cortisol and aldosterone by both adrenals during sample collection. Rossi et al reported that an ACTH bolus (250mcg) before AVS consistently increased aldosterone production by the contralateral adrenal but less consistently from the ipsilateral APA, reducing successful lateralization [20]. The same group studied varied bolus doses of ACTH, reporting a favourable increase in the "selectivity index" with higher doses of ACTH, but again counterbalanced, unfortunately, by a confounding effect on correct lateralisation of APA [21]. There has been some criticism of this study because of unusually permissive criteria for successful sampling and lateralisation [22]. A multicentre study (three Units, 76 patients) employing either ACTH bolus or infusion found that ACTH stimulation increased rates of successful bilateral cannulation from 49% to 87%, without significantly reducing accuracy of discrimination between unilateral and bilateral disease [23].

While we cannot answer the question whether ACTH stimulation during AVS would have reduced the already low incidence of bilaterally quiescent aldosterone secretion, it is reasonable to suggest that it might have. We have therefore recently changed our protocol for repeat AVS only, following bilateral low adrenal vein/peripheral vein aldosterone/cortisol ratios at initial AVS. This involves collection of two full sets of samples, the first without

ACTH stimulation and the second with ACTH stimulation. If the first samples without ACTH stimulation are satisfactory, those results are accepted as definitive, since any possible compromise due to loss of contralateral suppression following ACTH stimulation is avoided. The additional samples collected after ACTH are only utilised in diagnosis if those before ACTH again showed low aldosterone cortisol ratios versus peripheral bilaterally.

To conclude, in this study we examined an infrequent but difficult clinical problem; when, despite unequivocal evidence of primary aldosteronism, adrenal vein sampling fails to demonstrate elevated aldosterone/cortisol ratios on either side. It appears that persistence in pursuing a diagnosis in this group yields unexpectedly high rates of potentially curable APA. It seems likely that the problem is associated with quiescent periods in ACTH secretion, which may be more common in males than females. We recommend always encouraging the patient to have repeat AVS in this situation. We are prospectively examining the use of ACTH stimulation in repeat studies, with sampling both before and after ACTH.

253 Table 1. Demographic details and outcomes in patients with bilaterally low A/F ratios on initial AVS

Patient	Age at diagnosis (y)	Gender	Result of second attempt at AVS*	Nodule on Adrenal CT[+]	Hypokalemia	Treatment[#]	Blood pressure outcome	Tumor size (cm)[×]	Post op FST[†]
1	63	M	Right	Y	N	Adrenalectomy	Improved	1.1	-
2	43	M	Right	Y	Y	Adrenalectomy	Cure	0.8	Cure
3	56	F	Right	-	Y	Medical	Improved	-	-
4	64	F	Right	Y	Y	Adrenalectomy	Improved	1.3	-
5	41	M	Right	N	N	Adrenalectomy	Improved	NH	Improved
6	48	M	Left	Y	N	Adrenalectomy	Cure	0.5	Cure
7	46	M	Left	Y	N	Adrenalectomy	Cure	0.8	Cure
8	52	M	Right	Y	N	Adrenalectomy	Improved	1.8	-
9	54	M	Right	N	Y	Medical	Improved	-	-
10	56	M	Left	Y	Y	Adrenalectomy	Improved	1.8, 1.0	Cure
11	42	M	Bilat	N	N	Adrenalectomy	Improved	NH	-
12	54	M	Bilat	Y	Y	Medical	Improved	-	-
13	57	F	Bilat	-	N	Medical	Improved	-	-
14	55	F	Bilat	N	N	Medical	Improved	-	-
15	21	M	Bilat	-	N	Medical	Improved	-	-
16	57	F	Bilat	Y	Y	Adrenalectomy	Improved	0.8	-
17	47	F	Bilat	N	Y	Medical	Improved	-	-
18	59	M	Bilat	Y	Y	Adrenalectomy	Improved	1.0	-
19	55	M	Unsuccessful	Y	Y	Adrenalectomy	Improved	1.8	-
20	61	M	Low	Y	Y	Medical	Improved	-	-
21	35	M	Low	N	N	Medical	Improved	-	-
22	49	M	Unsuccessful	N	N	Medical	Improved	-	-
23	58	F	-	Y	Y	Adrenalectomy	Improved	1.8	-
24	47	M	-	Y	Y	Adrenalectomy	Cure	NH	Cure

25	54	F	-	Y	Y	Adrenalectomy	Improved	2.0	-
26	53	M	-	Y	Y	Adrenalectomy	Cure	1.0	Cure
27	61	F	-	N	N	Medical	Improved	-	-
28	56	F	-	Y	Y	Medical	Improved	-	-
29	64	M	-	N	Y	Medical	Improved	-	-
30	45	M	-	-	Y	Medical	Improved	-	-
31	38	M	-	Y	N	Medical	Improved	-	-
32	60	M	-	-	N	Medical	Improved	-	-
33	58	F	-	N	N	Medical	Improved	-	-
34	45	M	-	-	Y	Medical	Improved	-	-
35	52	M	-	Y	Y	Medical	Not Improved	-	-
36	55	M	-	N	N	Medical	Improved	-	-
37	46	F	-	Y	N	Medical	Improved	-	-

*"Right/Left" indicates AVS lateralised to one side, "Bilat" indicates bilateral production, "Low" indicates bilaterally low A/F ratios, "Unsuccessful" indicates that one side was not successfully cannulated.

[+]"Y" indicates abnormal appearances on an adrenal CT consistent with an adenoma, on the same side if AVS "lateralised.

[#] "Medical" indicates treatment with specific aldosterone blocking drug; spironolactone, amiloride or both.

[×]"NH" indicates nodular hyperplasia.

[†]"Cure" indicates normal suppression of plasma aldosterone during postoperative fludrocortisone suppression testing, "Improved" indicates failure of normal suppression of plasma aldosterone during postoperative FST (consistent with residual autonomous aldosterone production) but with day four FST plasma aldosterone levels lower than pre-operatively.

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Reviewers' Summary Evaluations

Referee 1

Adrenal sampling (AVS) is an essential tool in assessment of primary aldosteronism (PA) in order to diagnose an aldosterone-producing adenoma (APA) suitable form for surgery. When the aldosterone/cortisol (A/F) ratio is lower bilaterally than peripheral, AVS should be repeated; the Authors showed high incidence of APAs in patients with prior AVS incomplete, suggesting the significance of repeat AVS.

Referee 2

Primary aldosteronism is a frequent cause of identifiable and resistant hypertension. Screening for this potentially curable disorder has evolved with better endocrinologic criteria and adrenal imaging. Laparoscopic surgery is highly effective for excision of Conn's tumors. However, surgical cure depends on pre-operative localization, by adrenal venous sampling, to avoid 'wrong-side' surgery. The summary by Wolley et al of their very large series tells an important lesson: "If at first, you don't succeed, try, and try again." However, the expertise that a large experience conveys implies that interventional management of primary aldosteronism is best conducted in appropriate referral centers.

Condensed abstract

This retrospective observational study of adrenal vein sampling (AVS) for primary aldosteronism reviewed 1397 AVS done with consistent protocols over a 34 year period to examine the frequency of cases where adequate samples were obtained but bilaterally low aldosterone production was demonstrated. This occurred in 37 (2.6%) cases and 22 of these underwent a repeat study, demonstrating 10 unilateral aldosterone producing adenoma (APA), 8 cases of bilateral disease and 4 inconclusive repeat studies. Since the incidence of APA was high in this subgroup, these patients should always be offered a repeat AVS.

Abbreviations definitions list

PA = Primary aldosteronism

AVS = Adrenal vein sampling

APA = Aldosterone producing adenoma

A/F ratio = Aldosterone/cortisol ratio

ACTH = Adrenocorticotrophic hormone

CT = Computed tomography

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