

BRIEF REPORT

Measurement of 18-Hydroxycorticosterone during Adrenal Vein Sampling for Primary Aldosteronism

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Context: In primary aldosteronism, elevated serum 18-hydroxycorticosterone (18OHB) suggests aldosterone-producing adenoma (APA) rather than bilateral, idiopathic hyperaldosteronism (IHA), but little is known about the relative production of 18OHB and aldosterone (A) in APAs compared with IHA.

Objectives: We measured 18OHB, A, and cortisol (F) in blood from adrenal vein sampling (AVS) studies. We compared the discriminatory power of gradients in 18OHB/A and 18OHB/F ratios with A/F ratio gradients for distinguishing APA from IHA.

Design, Setting, and Subjects: We measured 18OHB and A in excess serum from 23 AVS studies performed at our university hospitals.

Main Outcome Measures: We calculated the ratios 18OHB/A, 18OHB/F, and A/F for all specimens, and determined the adrenal vein gradients for these ratios.

Results: The 18OHB/A ratios were much lower in blood draining APAs (2.17 ± 0.62) than in blood draining the contralateral adrenals (12.96 ± 12.76 ; $P < 0.001$) but similar to blood draining IHA adrenals (4.69 ± 4.32 ; $P = 0.02$). In contrast, the 18OHB/F ratios were elevated in specimens from APAs (26.03 ± 11.51) compared with IHA adrenals (9.22 ± 5.18 ; $P < 0.001$) or the contralateral adrenals (6.23 ± 2.97 ; $P < 0.001$). Using 18OHB/F gradient greater than two or 18OHB/A gradient less than 0.5 as criteria for lateralization, interpretations agreed with lateralizations based on A/F gradients in 21 of 23 cases.

Conclusions: High serum 18OHB in APA reflects augmented production of both 18OHB and A, not disproportionate 18OHB secretion relative to A. The 18OHB/A and 18OHB/F gradients are useful adjuncts but not as reliable as A/F gradients for A lateralization during AVS. (*J Clin Endocrinol Metab* 92: 2648–2651, 2007)

PRIMARY ALDOSTERONISM (PA) is a common secondary cause of arterial hypertension (HTN) (1, 2). The HTN associated with PA frequently resists correction with conventional antihypertensive medications and elicits greater end-organ complications than other forms of HTN, particularly for the kidney (3, 4) and heart (5). Consequently, timely diagnosis of PA remains important because of the potential for amelioration or cure of the HTN with surgery (6) or targeted medical therapy (7, 8). The diagnosis of PA is established by documenting sustained aldosterone (A) secretion despite volume expansion and suppression of plasma renin, and the management of PA is predicated on determining the source of A.

Various strategies have been used to distinguish unilateral

A production from an aldosterone-producing adenoma (APA) from bilateral or idiopathic hyperaldosteronism (IHA) (9). Computed tomography is very sensitive, but the small size of APAs and the high prevalence of incidental adrenal tumors compromise the predictive value of computed tomography scans (10–12). The failure of A to increase with upright posture (13) and high serum 18-hydroxycorticosterone (18OHB) (14, 15) both suggest APA, but posture studies are cumbersome, and clearly discriminating limits of serum 18OHB are not established. Consequently, adrenal vein sampling (AVS) is the definitive procedure for distinguishing APA from IHA (10–12).

A greater understanding of why serum 18OHB tends to be elevated in APA cases might improve the diagnostic use of 18OHB in PA. The conversion of 18OHB to A is the final step in A synthesis, and although the 18OHB/A ratio in mixed venous blood remains constant for APA patients (16), it is not known if the efficiency of this final step is altered in APAs. If so, the measurement of 18OHB in AVS specimens might help to distinguish APA from IHA. To test this hypothesis, we retrospectively measured 18OHB with A and cortisol (F) in AVS specimens obtained during cosyntropin infusion.

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Abbreviations: A, Aldosterone; APA, aldosterone-producing adenoma; AVS, adrenal vein sampling; F, cortisol; HTN, hypertension; IHA, idiopathic hyperaldosteronism; 18OHB, 18-hydroxycorticosterone; PA, primary aldosteronism.

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Subjects and Methods

Subjects and study protocol

Subjects were identified at the University of Texas Southwestern Medical Center during 2002–2005. The diagnosis of PA required: suppressed plasma renin (activity < 1 ng/ml·h = <0.3 ng/liter·sec) or direct immunoreactive renin (<5 μ U/ml); serum A more than 15 ng/dl (>416 pmol/liter); and failure to suppress A production with either oral salt loading (24 h urinary A > 14 μ g/24 h = >39 nmol/24 h) or saline infusion (serum A > 10 ng/dl = >278 pmol/liter after 2 liters iv over 4 h). Eligible PA subjects underwent technically successful AVS with measurement of A and F as part of their evaluation. Written informed consent was obtained to measure additional analytes from excess serum obtained from AVS. The study protocol was approved by the institutional review board at the University of Texas Southwestern.

Assays and calculations

Blood samples were transported on ice and promptly centrifuged for 10 min at 4 C and 2200 rpm. Serum F was measured by immunochemiluminometric assay with an ADVIA Centaur immunoassay analyzer (Bayer Diagnostics, Tarrytown, NY), neat and with dilutions. The assay range was 0.2–75 μ g/dl with between-run precision (coefficient of variation), 1.9–5.4% in the 3.9–37.2 μ g/dl range. Serum aliquots were sent to Mayo Medical Laboratories (Rochester, MN) for A assay by their proprietary RIA.

The A/F ratio in each sample was used to localize the source(s) of A (10–12). AVS was technically successful if the F concentrations in both the adrenal vein specimens were more than three times the F concentration in the IVC specimen (“adrenal vein F step-up”). Unilateral A production (APA or primary adrenal hyperplasia) was localized to the adrenal gland from which the higher A/F ratio derived if this A/F ratio was at least four times the A/F ratio of the other adrenal vein sample (“A/F gradient”); presumed IHA was deduced if the A/F ratios in the two adrenal vein samples differed by less than four (all less than two).

Serum 18OHB was measured by HPLC-tandem mass spectrometry after solvent extraction with [$^2\text{H}_4$]-dexamethasone internal standard. Serum controls and duplicate sets of calibrators were analyzed in each batch. The 18OHB was eluted using a methanol/water gradient through a 50 \times 2.1-mm reverse phase analytical HPLC column (particle size, 5 μ m). An MDS-SCIEX API4000 triple quadrupole mass spectrometer (Applied Biosystems, Foster City, CA), operating in negative ion atmospheric pressure chemical ionization mode, was used for detection using selected reaction monitoring. The imprecision of the assay (coefficient of variation) ranged from 1.7–6.3% when measured at four levels from 5–5000 ng/dl. Accuracy was demonstrated by spiking 18OHB into serum with recovery of 101–112%. A was measured, neat and with dilution, in the same aliquots by RIA after methylene chloride extraction. Intraassay precision ranged from 7.2–9.6%, while interassay precision ranged from 6.7–9.2% in serum controls with A concentrations of 3.8–37 ng/dl.

AVS procedure

AVS was performed under a continuous infusion of 50 μ g/h cosyntropin (Amphastar, Rancho Cucamonga, CA) in 5% dextrose as described (12). All 27 subjects with successful AVS and retrievable specimens gave their consent for the study. An interpretation was rendered despite a F step-up less than three in four cases, but only data from the 23 AVS studies with F step-ups more than three were included for the study to prevent misclassifications. Excess serum was stored in less than 0.5-ml aliquots at –80 C until batch assayed.

Statistical analyses

Statistical analyses used SAS/STAT software, version 9.1 (SAS Institute Inc., Cary, NC). *P* values for comparisons between APA and contralateral 18OHB, A, F, 18OHB/A, and 18OHB/F adrenal vein samples were based on signed rank tests. *P* values for comparisons of 18OHB, A, F, 18OHB/A, and 18OHB/F between APA and IHA adrenal vein samples were based on rank sum tests. Tests of differences and ratios yielded the same judgment of significance.

Results

A/F gradients identified APAs in 16 subjects (Table 1), and in all cases, an adrenal adenoma was identified after laparoscopic adrenalectomy (12). The remaining seven cases were managed with spironolactone or eplerenone plus other therapies. Using excess serum, 18OHB was measured by HPLC-tandem mass spectrometry, and A was remeasured by RIA after extraction for the study data set (Table 1; and supplemental Table 1, published as supplemental data on The Endocrine Society’s Journals Online web site at <http://jcem.endojournals.org>). Localization of A production using A values from repeat assays agreed with initial interpretations in all cases.

As expected, values for both 18OHB and A in adrenal vein blood draining APAs were substantially higher compared with blood draining the contralateral adrenals (mean 18OHB = 14,424 \pm 8,041 *vs.* 4,643 \pm 4,913 ng/dl, *P* < 0.001; mean A = 7211 \pm 4480 *vs.* 496 \pm 532 ng/dl, *P* < 0.001, respectively), although F values were similar (624 \pm 385 *vs.* 677 \pm 506 μ g/dl; *P* = 0.9). The 18OHB/A ratios in adrenal vein blood draining APAs were all remarkably similar (mean 2.17 \pm 0.62; range 1.36–3.40), consistent with prior studies of the 18OHB/A ratio in PA mixed venous blood (16). Contrary to expectations, the 18OHB/A ratios in adrenal vein blood contralateral to the APAs were considerably higher in all cases (mean 12.96 \pm 12.76; *P* < 0.001; range 3.26–40.20).

The 18OHB (5867 \pm 3050 ng/dl) and A (2009 \pm 1465 ng/dl) values for adrenal vein blood from IHA adrenals were both lower than for APAs (both *P* < 0.001), but F values (695 \pm 330 μ g/dl) were similar (*P* = 0.5). The 18OHB/A ratios for blood draining IHA adrenals (mean 4.69 \pm 4.32; range 1.14–14.37) clustered near values similar to those obtained for APA specimens, except for much higher values in subject No. 18 (Table 1; *P* = 0.02 IHA *vs.* APA). The 18OHB/A ratios for the right and left adrenal vein specimens from individual IHA subjects were strikingly similar, within a factor of 1.7 except for subject No. 1. Using an 18OHB/A gradient less than 0.5 as criterion for lateralization, the 18OHB/A gradients agreed with the A/F gradients in 21 of 23 cases (Table 1). These data demonstrate that APAs actually produce abundant 18OHB relative to A.

The 18OHB/F ratios were elevated in blood draining APAs (26.03 \pm 11.51) compared with blood draining IHA adrenals (9.22 \pm 5.18; *P* < 0.001) or the contralateral adrenals (6.23 \pm 2.97; *P* < 0.001). Using an 18OHB/F gradient of more than two as criterion for lateralization, the 18OHB/F gradients also agreed with the A/F gradients in 21 of 23 cases (Table 1).

Discussion

The major new finding of our study is that, while the 18OHB/F ratio is elevated in adrenal vein blood draining APAs, the 18OHB/A ratio is paradoxically lower in these samples than for the contralateral adrenal glands. Our data suggest that the high serum 18OHB in APAs derives from augmented production of both 18OHB and A by the tumors, rather than disproportionate secretion of 18OHB relative to A. However, the relative secretion of 18OHB and A by APAs might be different in the basal state than under cosyntropin

TABLE 1. Steroid ratios, gradients, and means for AV samples

Subject no.	Lateralized AVS								
	APA			Contralateral			Gradients and lateralization ^a		
	18OHB/A	18OHB/F	A/F	18OHB/A	18OHB/F	A/F	18OHB/A	18OHB/F	A/F
2	2.00	35.36	17.72	3.26	8.27	2.53	0.61 R ^b	4.2 R	7.0 R
3	1.93	36.25	18.78	4.85	3.58	0.74	0.40 L	10 L	25 L
4	1.36	22.23	16.35	5.09	1.85	0.36	0.27 L	12 L	45 L
5	1.51	25.96	17.16	4.75	5.01	1.05	0.32 L	5.3 L	16 L
6	1.97	34.98	17.77	4.29	4.27	1.00	0.46 R	8.2 R	18 R
7	2.87	54.60	19.05	40.20	9.55	0.24	0.07 R	5.7 R	80 R
8	1.78	25.25	14.22	5.10	5.97	1.17	0.35 L	4.3 L	12 L
11	3.03	10.25	3.39	35.19	6.64	0.19	0.09 L	1.5 L ^b	18 L
12	1.69	17.43	10.34	35.92	6.15	0.17	0.05 L	2.8 L	60 L
14	2.39	22.71	9.52	10.58	10.69	1.01	0.23 L	2.1 L	9.4 L
15	2.32	31.03	13.40	5.84	6.92	1.18	0.40 L	4.5 L	11 L
16	1.49	24.73	16.57	4.06	5.38	1.33	0.37 R	4.6 R	12 R
17	1.82	12.98	7.13	6.74	4.85	0.72	0.27 R	2.7 R	10 R
20	3.05	34.06	11.17	20.87	13.11	0.63	0.15 L	2.6 L	18 L
22	3.40	11.52	3.39	10.58	4.74	0.45	0.32 R	2.4 R	7.6 R
23	2.12	17.15	8.07	9.95	2.68	0.27	0.21 R	6.4 R	30 R
Mean	2.17	26.03	12.75	12.96	6.23	0.81			
SD	0.62	11.51	5.31	12.76	2.97	0.60			
Subject no.	Bilateral AVS								
	Right			Left			Gradients and lateralization ^a		
	18OHB/A	18OHB/F	A/F	18OHB/A	18OHB/F	A/F	18OHB/A	18OHB/F	A/F
1	1.14	2.13	1.86	8.18	20.80	2.54	0.14 R ^b	10 L ^b	1.4 L
9	4.53	8.71	1.93	3.51	8.32	2.37	0.77 L	1.0 R	1.2 L
10	2.35	3.27	1.39	2.26	5.65	2.49	0.96 L	1.7 L	1.8 L
13	1.98	11.13	5.61	2.52	14.06	5.57	0.79 R	1.3 L	1.0 R
18	13.74	9.38	0.68	14.37	7.74	0.54	0.96 R	1.2 L	1.3 R
19	2.46	13.60	5.53	4.17	14.48	3.47	0.59 R	1.1 L	1.6 R
21	2.40	4.03	1.68	2.05	5.73	2.79	0.85 L	1.4 L	1.7 L
Mean	4.69	9.22	2.75						
SD	4.32	5.18	1.72						

Data for 18OHB and A are in ng/dl, and F in μ g/dl. The 18OHB/A ratio is dimensionless, and the 18OHB/F and A/F ratios are ng/ μ g. To convert 18OHB and A to pmol/liter, multiply by 27.59 or 27.75, respectively; to convert F to nmol/liter, multiply by 27.59. Means and SD values for "Bilateral AVS" sets include both right and left adrenal vein samples. L, Left-side dominant; R, right-side dominant.

^a Criteria for lateralization are: A/F, gradient > 4; 18OHB/F, gradient > 2; and 18OHB/A, gradient < 0.5.

^b Discordant result with A/F gradient interpretation.

infusion as reported here, and the responsiveness of APAs to cosyntropin is variable (17).

We propose that 18OHB from adrenals contralateral to APAs primarily derives from the zona fasciculata (Fig. 1). Under cosyntropin stimulation, the "suppressed" adrenal still synthesizes a trace of 18OHB and A from the zona glomerulosa. Cosyntropin simultaneously increases intra-adrenal corticosterone, which provides substrate for the minor 18-hydroxylase activity of CYP11B1 (18), yielding 18OHB. This model is consistent with previous indirect demonstrations that the zona fasciculata still produces 18OHB when A synthesis is suppressed (19). Consequently, the residual 18OHB production from the adrenal contralateral to an APA attenuates the 18OHB/F gradients mustered by the tumor and generates inverted 18OHB/A gradients, which are both useful for confirming APA lateralization.

Several studies document higher serum 18OHB in mixed venous blood of APA subjects than IHA (9, 14, 15), yet few studies have measured A precursors in adrenal vein samples. One study showed that several precursors, including 18OHB and 19-oxygenated 11-deoxycorticosterone metabolites, are present in high abundance (20), but this study included only

eight sets of samples and did not evaluate 18OHB as an adjunct to A localization.

We used strict criteria for PA diagnosis, adrenal vein F step-ups, and A/F lateralization gradients to prevent misclassification in this pilot study. AVS was performed with cosyntropin stimulation to mitigate fluctuations in F production and to maximize adrenal vein F step-ups. Our results might be different if less stringent criteria for PA or AVS lateralization were used. Furthermore, bilateral simultaneous AVS without cosyntropin infusion (17) would most accurately reflect relative 18OHB and A production from the APAs. Some specimens might have been altered by storage at -80°C for many months. Nevertheless, given the remarkable internal consistency of results and *P* values, these limitations should not detract from our main conclusions.

Our retrospective pilot study cannot demonstrate whether 18OHB measurements during AVS either improved A localization or patient outcomes. We suggest that 18OHB measurements might prove particularly useful for AVS studies with unsuccessful access of the right adrenal vein or suboptimal adrenal vein F step-ups, which ordinarily preclude conclusive interpretations.

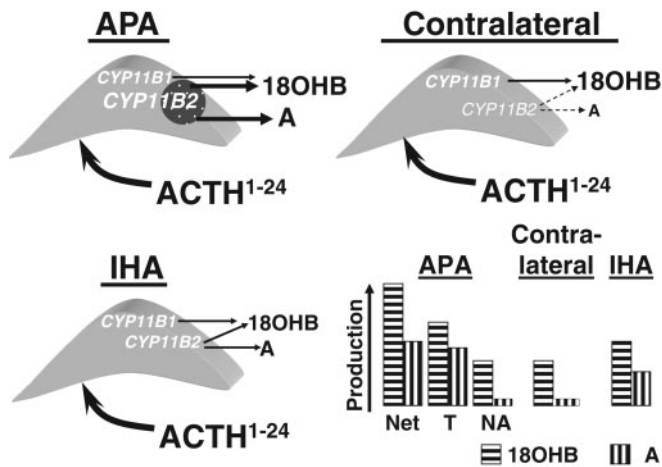


FIG. 1. Model explaining the inverted 18OHB/A gradients in AVS studies from subjects with APAs. The tumors (*top left*) express abundant CYP11B2 activity, which yields large amounts of A plus 18OHB as an obligate intermediate. Any residual 18OHB derived from the zona fasciculata (*thin line*) is small compared with the amount derived from the tumor (*thick lines*). In the contralateral adrenal (*top right*), CYP11B2 and, consequently, A synthesis are suppressed (*dashed lines*), but under cosyntropin stimulation, “normal” amounts of 18OHB derive from the zona fasciculata via the 18-hydroxylase activity of CYP11B1. IHA adrenals produce 18OHB and A with features generally similar to APAs, although the proportions vary among individual subjects. Relative production of 18OHB and A is cartooned based on our data on the *bottom right*. Net adrenal vein blood from gland with the APA (Net) with an approximate 2:1 ratio of 18OHB/A reflects both contributions from the tumor (T) and surrounding normal adrenal (NA), the latter of which is probably similar to proportions derived from the contralateral adrenal. By this analysis, the 18OHB/A ratio derived from the APA under cosyntropin stimulation is likely to be less than 2:1.

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Conflicts of Interest: D.W.C. declares stock ownership in LabCorp; all other authors declare no conflicts of interest.

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