THE UNIVERSITY OF CHICAGO
MEDICINE & BIOLOGICAL SCIENCES

"A 64 year old man referred for evaluation of suspected hyperaldosteronism "

Dr. Dickens does not have any relevant financial relationships with any commercial interests.

ENDORAMA: 64 year old man referred for evaluation of suspected hyperaldosteronism

Laura Dickens

September 7, 2017

Objectives

1. Understand the guidelines for primary hyperaldosteronism including screening, case confirmation, subtype classification, and management.
2. Recognize potential causes of hyperaldosteronism without suppressed renin.
3. Interpret adrenal vein sampling results.

Case Introduction

64 year old man with a PMH of Hodgkin lymphoma s/p chemo and XRT, squamous cell lung cancer s/p surgery, chemo, and XRT, pancreatic neuroendocrine tumor, hypertrophic obstructive cardiomyopathy, and HTN referred for evaluation for hyperaldosteronism.

HPI

- Longstanding history of HTN >10 years, previously on multiple antihypertensives. Currently only on Verapamil.
- Hypokalemia recognized for at least 2 years, requiring high dose supplementation (K-Dur 100 mEq daily).
- Recent K has ranged 3.2-3.7 on that dose.
- MRCP at OSH from July 2016 showed a 1.2 x 1.1 cm lesion of the left adrenal gland with imaging features consistent with lipid rich adenoma.
- OSH labs showed elevated aldosterone/renin ratio and patient was referred to UCMC for further evaluation

PMH:

- Hodgkin lymphoma
- Squamous cell lung cancer
- Pancreatic neuroendocrine tumor
- Acoustic neuroma
- Thyroid nodule
- Hypertrophic obstructive cardiomyopathy
- HTN

PSH: RUL lobectomy

ROS: +fatigue +SOB. Negative for headaches, sweating, palpitations, excessive weight gain, facial shape changes, or striae

Meds:

- Amiodarone
- Aspirin
- Nexium
- K-dur 100 mEq daily
- Viagra
- Verapamil-SR 480 mg daily

Allergies: NKDA

Social: Never smoker. Social ETOH use. No drugs. From Uruguay, works as an architect

Family: Breast cancer (mother), CVA (father)

Additional History

- **Hodgkin lymphoma:** Stage II, treated in 1976 with MOPP chemo x 8, and chest RT to 4400 rads. He had a relapse in the R neck/upper mediastinum in 1980 treated with additional radiation. NED since then
- **Acoustic neuroma:** Treated with gamma knife therapy in 2004
- **Squamous cell lung cancer:** In 2016 was incidentally found to have right lung mass, diagnosed on bronch/EBUS with squamous cell carcinoma. On 7/27/16, he underwent a cervical mediastinoscopy, R thoracotomy with RUL sleeve resection, and pulmonary artery plasty of interlobar PA. Final Stage pT3N1, IIIa. Postoperatively treated with chemo in Uruguay and then radiation at NWMH.
- **Pancreatic neuroendocrine tumor:** In 2016 was incidentally found to have a mass on the tail of the pancreas, 2.3 x 2.1 cm. Biopsy showed neuroendocrine tumor, grade I, strongly positive for synaptophysin and chromogranin. This CT scan also showed a Left Adrenal 1.1x1.2cm lipid rich adenoma.
- **Thyroid nodule:** In 7/2017 was seen to have a left thyroid nodule 4.0 x 3.5cm essentially replacing the left lobe, unchanged from 2016 scan. Mild displacement of trachea right of mid line. The thyroid nodule has been biopsied in the past and benign per patient.

Physical exam

VITALS: BP **123/67**, HR **63**, BMI **23.09**

General: Well appearing man in no distress

HEENT: Clear oropharynx. Non-injected sclera. Normal assessment of hearing

Neck: Neck supple, thyroid palpable L>R

CV: Normal rate, regular rhythm. No murmurs. No edema.

Pulm: Clear bilaterally. No increased work of breathing, wheezes, rales.

GI: Bowel sounds present. Soft, non-tender, non-distended

MSK: Normal gait and station

Skin: No rash. No hair loss

Lymphatic: No lymphadenopathy in the neck

Psych: Alert and oriented x3. Appropriate mood and affect.

Who to screen for Primary Aldosteronism (PA)

- Sustained BP > 150/100 on three measurements on different day
- BP > 140/90 on three conventional antihypertensive drugs including a diuretic
- BP < 140/90 on four or more antihypertensive drugs
- HTN and spontaneous or diuretic-induced hypokalemia
- HTN and adrenal incidentaloma *(and K < 3.5)*
- HTN with first degree relative with PA

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

Table 2. Groups With High Prevalence of PA

Patient Group	Prevalence
Moderate/severe hypertension: the prevalence rates cited here are from Mosso et al (27). Others have reported similar estimates (28, 67, 163, 206). We based the classification of BP for adults (aged >18 y) on the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (207), which establishes three different stages: Stage 1 = SBP 140–159 mm Hg, DBP 90–99 mm Hg; Stage 2 = SBP 160–179 mm Hg, DBP 100–109 mm Hg; Stage 3 = SBP >180 mm Hg, DBP = >110 mm Hg (23). When systolic and diastolic BPs were in different categories, the higher category was selected to classify the individual's BP status.	Overall, 6.1%. Stage 1 (mild), 2%. Stage 2 (moderate), 8%. Stage 3 (severe), 13%.
Resistant hypertension, defined as SBP >140 mm Hg and DBP >90 mm Hg despite treatment with three hypertensive medications (56, 193, 208–211).	17–23%
Hypertensive patients with spontaneous or diuretic-induced hypokalemia.	Specific prevalence figures are not available, but more frequently found in this group.
Hypertension with adrenal incidentaloma (141, 212–216), defined as an adrenal mass detected incidentally during imaging performed for extra-adrenal reasons.	Median, 2% (range, 1.1–10%). One retrospective study that excluded patients with hypokalemia and severe hypertension found APA in 16 of 1004 subjects (215).
Hypertension with obstructive sleep apnea (217, 218).	34% among newly hypertensive patients referred to a tertiary referral center and found to have obstructive sleep apnea.

Abbreviations: DBP, diastolic BP; SBP, systolic BP. [Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

How to Diagnose Primary Aldosteronism

- Three steps: (1) Screening (2) Case confirmation (3) Subtype classification

1. SCREENING: Plasma aldosterone/renin ratio (ARR)

- Testing conditions
  - Sample should be collected in the morning after patients have been out of bed for at least 2 hours and then seated for 5-15 minutes
  - Patients should be potassium replete and have unrestricted dietary salt intake
  - Mineralocorticoid receptor antagonists should be withdrawn for at least 4 weeks
- Interpretation
  - PA is suggested by suppressed renin and increased aldosterone
  - PAC/PRA > 20 ng/dL and PAC > 15 ng/dL

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

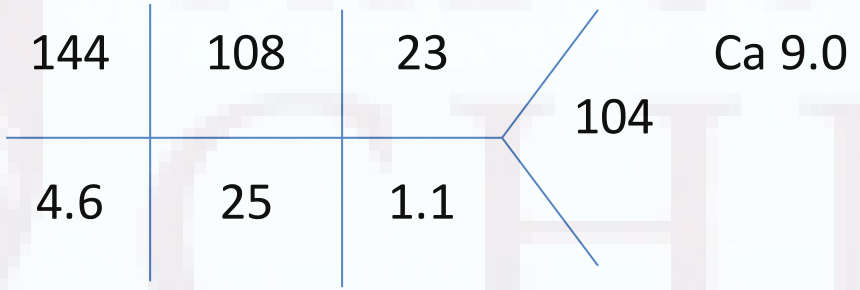
Table 5. Medications With Minimal Effects on Plasma Aldosterone Levels That Can Control Hypertension During Case Finding and Confirmatory Testing for PA

Drug	Class	Usual Dose	Comments
Verapamil slow-release	Non-dihydropyridine slow-release antagonist calcium channel	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow-release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations)
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two or three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

[Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

Labs



Aldosterone = 150 ng/dL
Renin = 1.0 ng/dL **
Plasma metanephrines = normal
Cortisol = 10.5 (3pm)
ACTH = 19.3

OSH Labs:
TSH 1.01

Renin Reference Range:
Na-deplete, upright:
Mean: 5.9
Range 2.9 – 10.8
Na-replete, upright:
Mean: 1.0
Range: < or = 0.6 – 3.0

Why Isn't Renin Suppressed?

- Interference from other factors

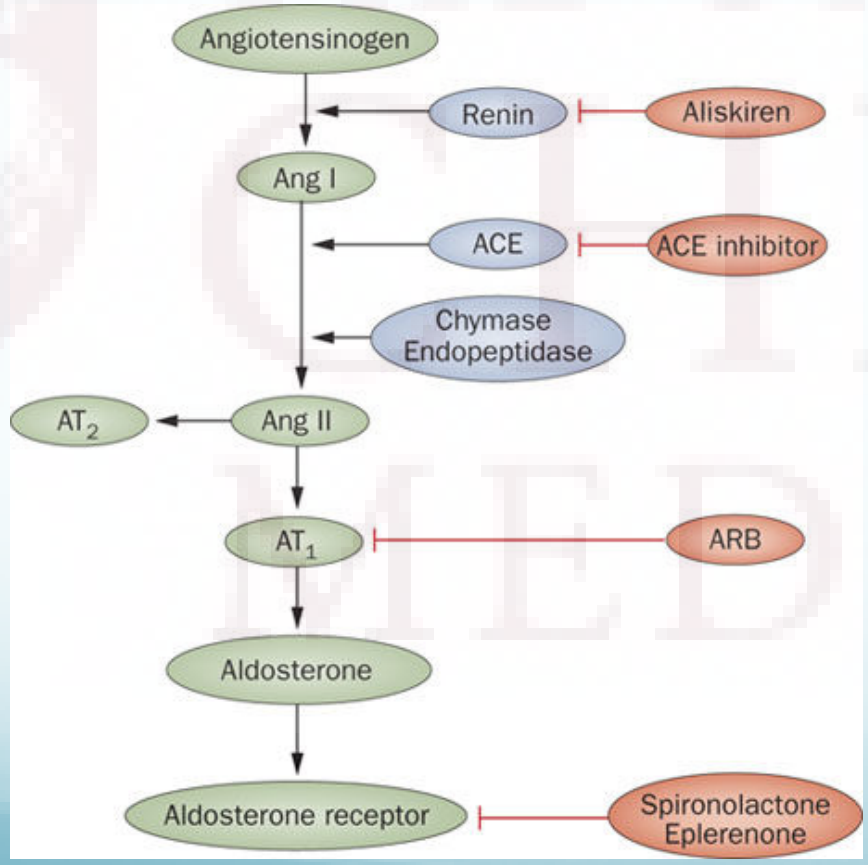


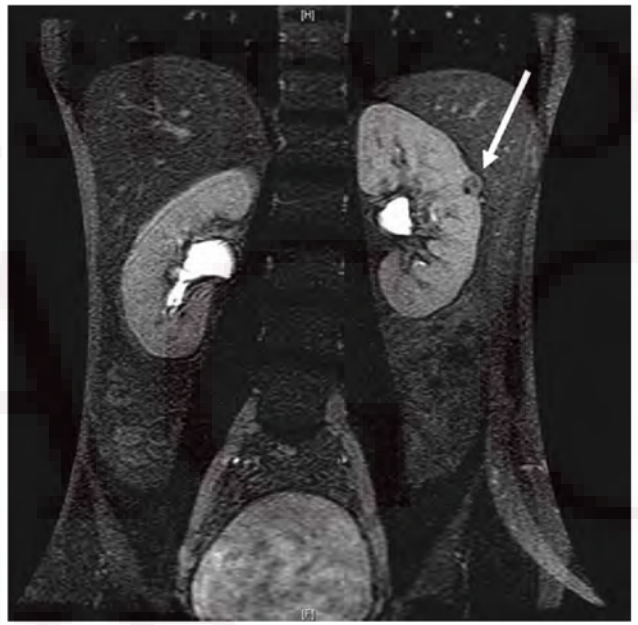
Table 3. Factors That May Lead to False-Positive or False-Negative ARR Results

Factor	Effect on Aldosterone Plasma Levels	Effect on Renin Levels	Effect on ARR
Medications[a]			
β-Adrenergic blockers	D	D D	U (FP)
Central agonists (eg, clonidine, α-methyldopa)	D	D D	U (FP)
NSAIDs	D	D D	U (FP)
K^+-wasting diuretics	R U	U U	D (FN)
K^+-sparing diuretics	U	U U	D (FN)
ACE inhibitors	D	U U	D (FN)
ARBs	D	U U	D (FN)
Ca^{2+} blockers (DHPs)	R D	U	D (FN)
Renin inhibitors	D	D U	U (FP) D (FN)
Potassium status			
Hypokalemia	D	R U	D (FN)
Potassium loading	U	R D	U
Dietary sodium			
Sodium restriction	U	U U	U (FN)
Sodium loading	D	D D	U (FP)
Advancing age	D	D D	U (FP)
Premenopausal women (vs males)[b]	R U	D	U (FP)
Other conditions			
Renal impairment	R	D	U (FP)
PHA-2	R	D	U (FP)
Pregnancy	U	U U	D (FN)
Renovascular HT	U	U U	D (FN)
Malignant HT	U	U U	D (FN)

Image: https://images.nature.com/full/nature-assets/nrneph/journal/v6/n6/images/nrneph.2010.58-f1.jpg
Table: Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

Why Isn't Renin Suppressed?

- **Reninoma**
  - Rare diagnosis, a review in 2007 cited 89 cases reported in the literature [1]
  - Mean PRA was 33.3 ng/mL per hour (range 2.8 - 150.9 ng/mL per hour)
  - Mean PRA was 12x upper limit of normal when reference range was included
  - Diagnosed by renal vein sampling + diuretics, ACE-I
  - Treatment is surgical



- **Paraneoplastic**
  - Also rare, has been associated with renal cell carcinoma, Wilms' tumor, adenocarcinoma and small cell carcinoma of the lung, hepatocellular carcinoma, pancreatic and small intestinal adenocarcinomas [2]
  - Characterized by increased ratio of pro-renin to renin

1. Wong et al. J Hypertens. 2008 Feb;26(2):368-73.
2. DeLellis et al. *Endocrine pathology*. Vol. 14. No. 4. Humana Press, 2003.

Why Isn't Renin Suppressed?

- Hypertensive kidney damage
  - JCEM paper in 2000 presented three cases of confirmed primary hyperaldosteronism with unsuppressed renin
  - One case had histologically proved renal arterioscelerosis, other two cases were suspected to have hypertensive kidney damage → leads to escape of the PRA from aldosterone suppression
  - Cr ranging 1.1 – 1.3 mg/dL

TABLE 1. Postural stimulation tests and urinary aldosterone excretion in three patients with primary hyperaldosteronism and unusually high renin activity

Patient no.	Urinary aldosterone (nmol/day)	Plasma cortisol (nmol/L)		Plasma aldosterone (ng/dL)		PRA (ng/mL·h)		P-Aldo/PRA	
		→	↑	→	↑	→	↑	→	↑
1	78					2.2	5.5		
2	53/58	727	610	54	52	1.6	1.8	33.7	28.9
3 (1995)	47	450	541	32	44	0.4	0.9	80.0	48.9
3 (1999)	291	535	309	120	103	2.5	4.2	48.0	24.5
Normal	8–44	180–700		5–25	7–36	0.5–4	1–6	<20	

Oelkers et al. J Clin Endocrinol Metab. 2000 Sep;85(9):3266-70.

Relationships of Plasma Renin Levels with Renal Function in Patients with Primary Aldosteronism

Cristiana Catena, GianLuca Colussi, Elisa Nadalini, Alessandra Chiuch, Sara Baroselli, Roberta Lapenna, and Leonardo A. Sechi

Hypertension Unit, Division of Internal Medicine, Department of Experimental and Clinical Pathology and Medicine, University of Udine, Udine, Italy

- Study enrolled 56 patients with primary aldosteronism and 323 control patients with essential HTN
  - Mean follow up was 6.2 years
  - 30 of 56 patients with PA were found to have adrenal adenomas
  - 25 treated with adrenalectomy, 31 treated with spironolactone
- Outcomes included measures of renal function (Cr clearance, albuminuria), blood pressure and number of antihypertensives, potassium level, renin/aldosterone levels

Catena et al. Clin J Am Soc Nephrol. 2007 Jul;2(4):722-31.

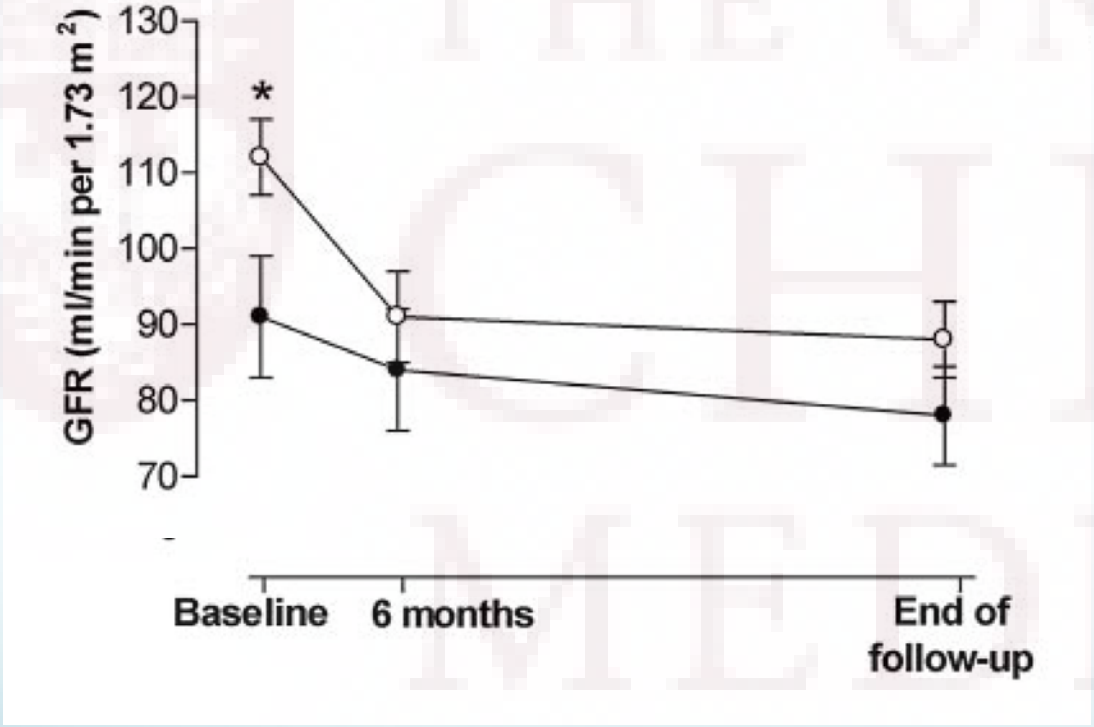
Comparison of Patients with Suppressed vs Non-suppressed Renin

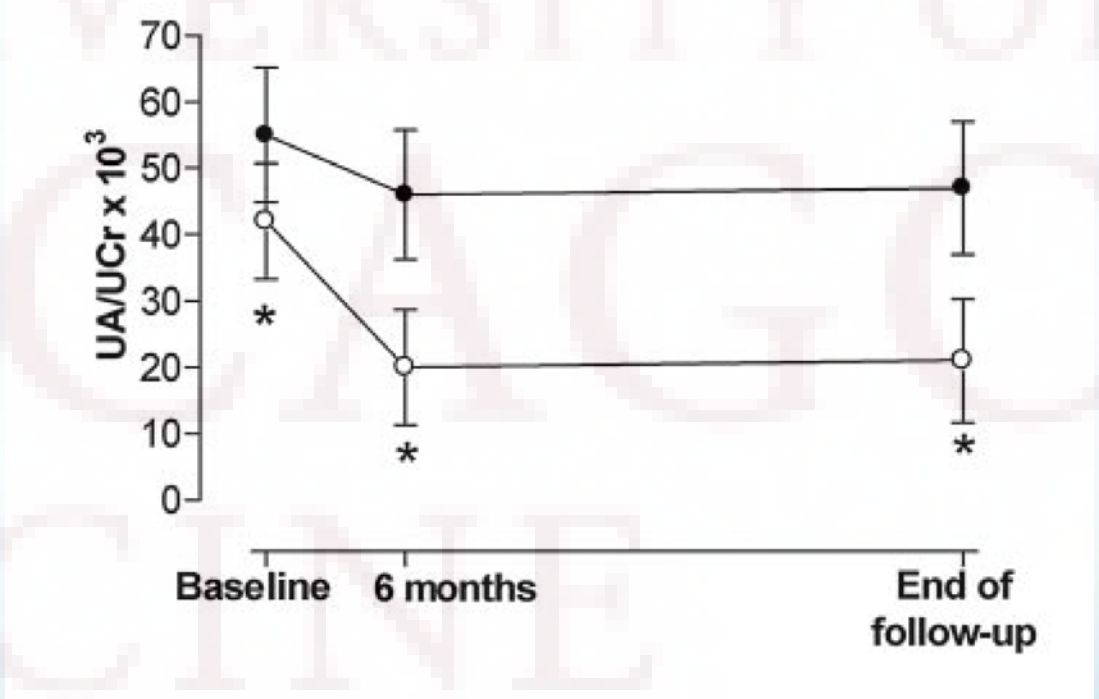
Table 2. Characteristics of patients with primary aldosteronism and plasma active renin concentrations that were lower or higher than the limit of detection with our method[a]

Characteristic	Primary Aldosteronism		*P*
	Plasma Active Renin <2.5 pg/ml (n = 40)	Plasma Active Renin >2.5 pg/ml (n = 16)	
Clinical characteristics			
age (yr)	52 ± 11	54 ± 14	NS
female/male gender (n [%])	9/31 (22/78)	7/9 (44/56)	NS
adenoma/idiopathic	21/19	9/7	NS
BMI[b]	28.7 ± 3.7	27.9 ± 4.1	NS
SBP (mmHg)[c]	163 ± 15	175 ± 19	0.015
DBP (mmHg)[c]	101 ± 9	108 ± 9	0.011
estimated duration of hypertension (yr)	9 ± 5	13 ± 6	0.014
Laboratory variables			
plasma sodium (mmol/L)	141 ± 2	140 ± 2	NS
plasma potassium (mmol/L)[d]	3.1 ± 0.4	3.5 ± 0.4	<0.001
urinary sodium (mmol/24 h)	106 ± 39	101 ± 63	NS
urinary potassium (mmol/24 h)	52 ± 16	47 ± 23	NS
serum creatinine (μmol/L)	88 ± 18	94 ± 22	NS
creatinine clearance (ml/min per 1.73 m^2)	112 ± 30	91 ± 33	0.025
urinary albumin/creatinine ratio (median [IQR])	0.042 (0.017 to 0.082)	0.055 (0.031 to 0.122)	0.015
plasma active renin (pg/ml)	<2.5	10.5 ± 6.6	<0.001
plasma aldosterone (pg/ml)	261 ± 149	218 ± 254	NS

Catena et al. Clin J Am Soc Nephrol. 2007 Jul;2(4):722-31.

Outcomes

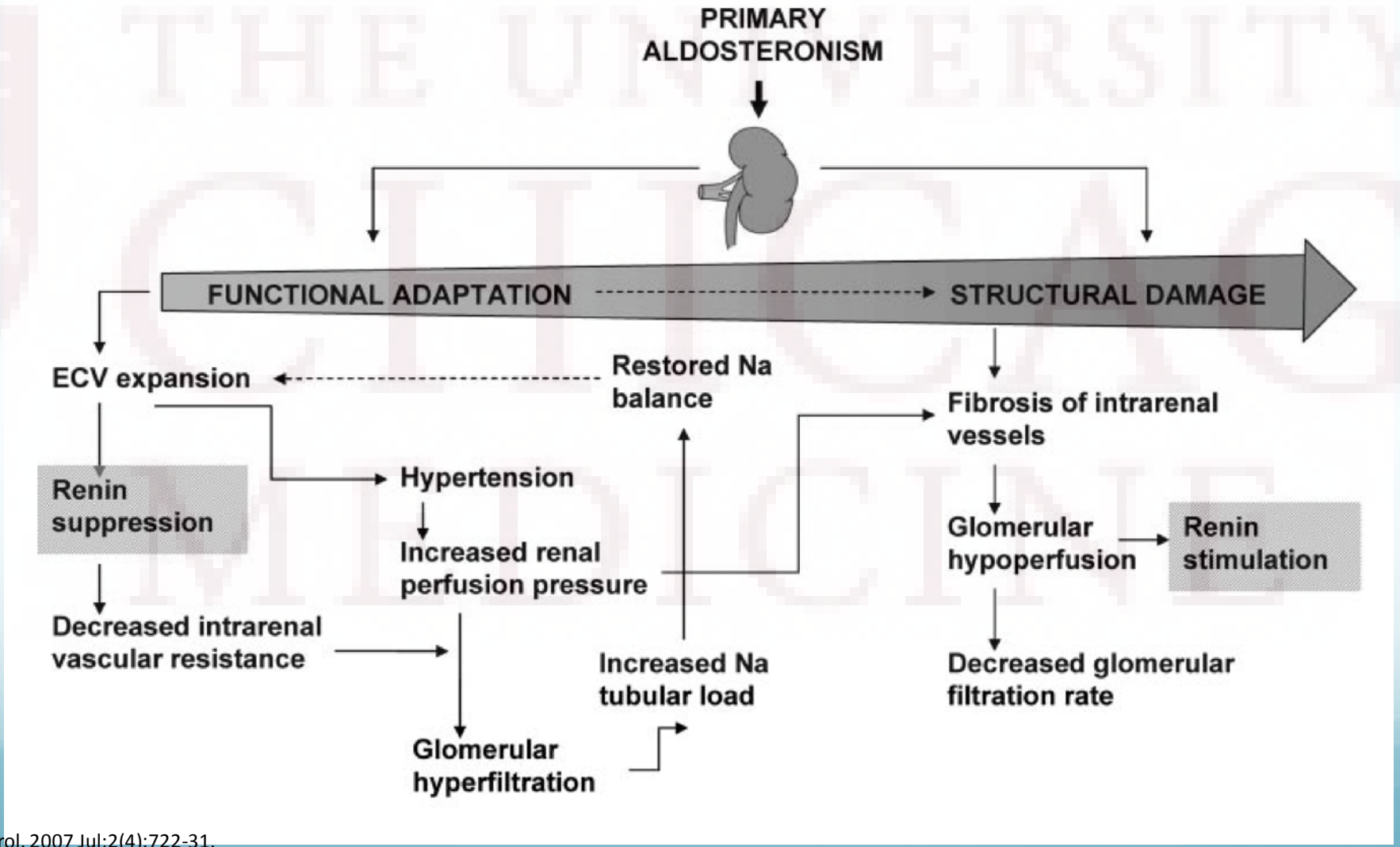




GFR

Albuminuria

Proposed Mechanism: Renin Escape from Aldosterone Suppression



Catena et al. Clin J Am Soc Nephrol. 2007 Jul;2(4):722-31.

Primary Aldosteronism

2. CASE CONFIRMATION

- Recommended for patients with positive ARR to definitively confirm or exclude diagnosis
- EXCEPT in the setting of spontaneous hypokalemia, undetectable plasma renin, and PAC >20
- No “gold standard” confirmatory test, four are common
  - Oral sodium loading
  - Saline infusion
  - Fludrocortisone suppression
  - Captopril challenge

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

Table 7. PA Confirmatory Tests

Test and Procedure	Interpretation	Concerns
Oral sodium loading test Patients should increase their sodium intake to >200 mmol (~6 g)/d for 3 d, verified by 24-h urine sodium content. Patients should receive adequate slow-release potassium chloride supplementation to maintain plasma potassium in the normal range. Urinary aldosterone is measured in the 24-h urine collection from the morning of day 3 to the morning of day 4.	PA is unlikely if urinary aldosterone is <10 μg/24 h (28 nmol/d) in the absence of renal disease where PA may coexist with lower measured urinary aldosterone levels. Elevated urinary aldosterone excretion (>12 μg/24 h [>33 nmol/d] at the Mayo Clinic; >14 μg/24 h [39 nmol/d] at the Cleveland Clinic) makes PA highly likely.	This test should not be performed in patients with severe uncontrolled hypertension, renal insufficiency, cardiac arrhythmia, or severe hypokalemia. 24-h urine collection may be inconvenient. Laboratory-specific poor performance of the RIA for urinary aldosterone (aldosterone 18-oxo-glucuronide or acid labile metabolite) may blunt diagnostic accuracy—a problem obviated by the currently available HPLC-tandem mass spectrometry methodology (223). Aldosterone 18-oxo-glucuronide is a renal metabolite, and its excretion may not rise in patients with renal disease.
		to provoke non-renin-dependent alterations of aldosterone levels; c) it allows for the potentially confounding effects of potassium to be controlled, and for ACTH (via cortisol) to be monitored and detected; and d) it is safe when performed by experienced hands.
Captopril challenge test Patients receive 25–50 mg of captopril orally after sitting or standing for at least 1 h. Blood samples are drawn for measurement of PRA, plasma aldosterone, and cortisol at time zero and at 1 or 2 h after challenge, with the patient remaining seated during this period.	Plasma aldosterone is normally suppressed by captopril (>30%). In patients with PA it remains elevated and PRA remains suppressed (58, 60, 163, 227). Differences may be seen between patients with APA and those with IAH, in that some decrease of aldosterone levels is occasionally seen in IAH (228).	There are reports of a substantial number of false-negative or equivocal results (59, 229).

[Adapted from J. W. Funder et al: Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:3266–3281 (3), with permission. © Endocrine Society.]

Our Patient: Case Confirmation

<u>24 hour urine:</u>

Volume = 2750 mL

Urine Cr = 1018 mg

Aldosterone = 83 mcg (normal 2.0 – 20 mcg/24 hours)

Urine Na = 193 mmol

Urine K = 215 mmol

Primary Aldosteronism

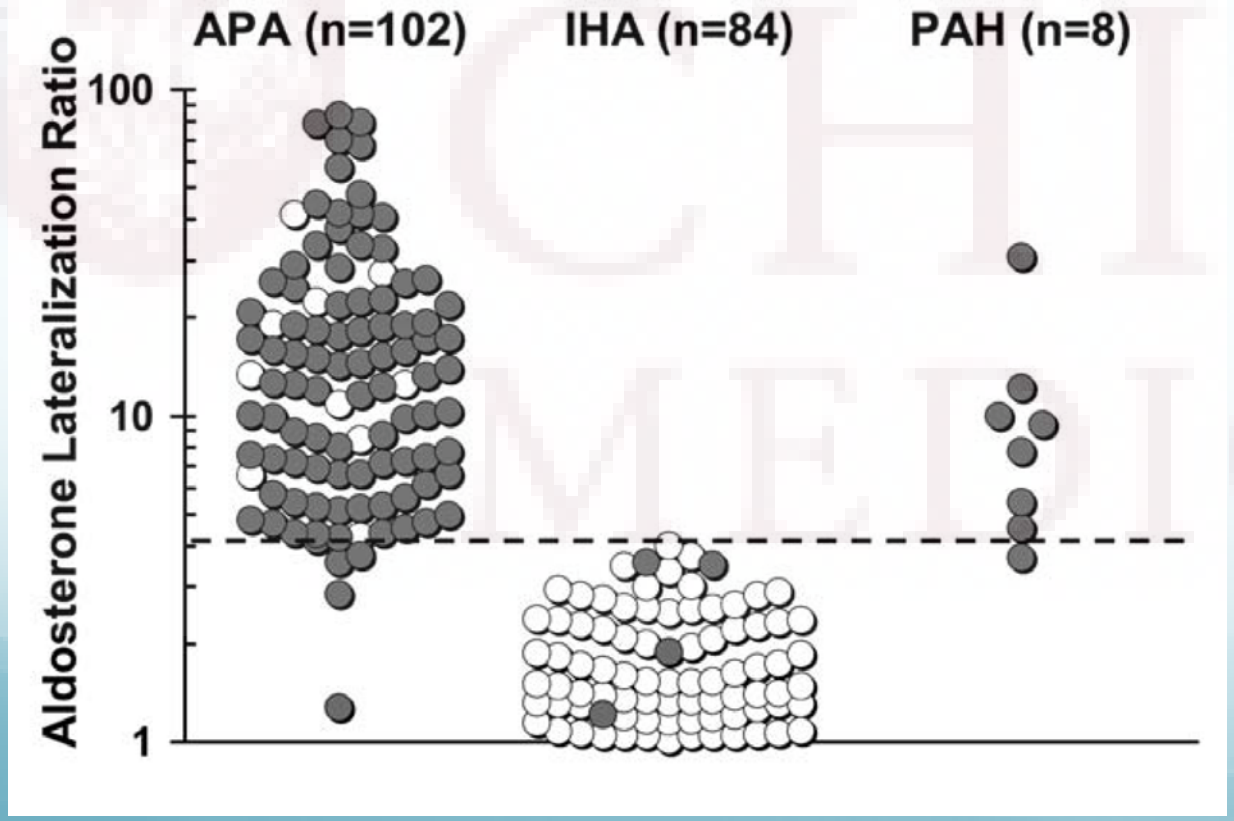
3. SUBTYPE CLASSIFICATION

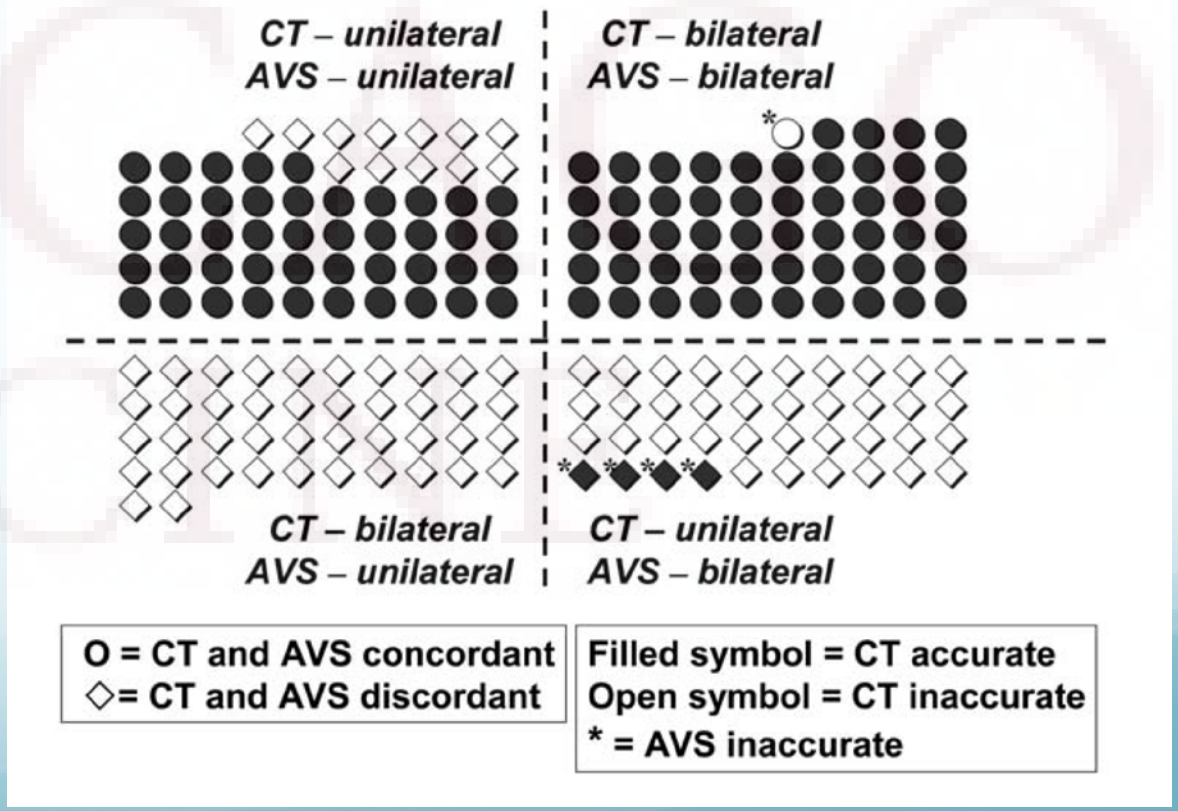
- Subtype classification
  - Imaging: Adrenal CT
  - Lateralizing: If surgery is feasible and desired by patient, do AVS
    - EXCEPT in younger patients (<35 years) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal lesions with radiological features consistent with a cortical adenoma on adrenal CT
    - Sensitivity and specificity for unilateral aldosterone excess are 95% and 100%, respectively
- Genetic testing
  - Familial hyperaldosteronism type I (glucocorticoid remediable aldosteronism)
  - Familial hyperaldosteronism type II
  - Familial hyperaldosteronism type III

Funder et al. J Clin Endocrinol Metab. 2016 May;101(5):1889-916.

Importance of Localization with AVS

- Study from Mayo clinic 1990-2003 recruited 203 patients with primary hyperaldosteronism to undergo AVS





Young et al. Surgery. 2004;136:1227–1235.

Adrenal Vein Sampling (AVS)

- Three types of protocols:
  - Unstimulated sequential or simultaneous bilateral
  - Unstimulated sequential or simultaneous bilateral THEN bolus cosyntropin-stimulated sequential or simultaneous bilateral
  - Continuous cosyntropin infusion with sequential bilateral AVS
- Confirm successful catheterization with **adrenal/peripheral vein cortisol ratio**
  - For continuous cosyntropin administration, cutoff of more than 5:1 indicates successful catheterization
- Determine lateralization based on **cortisol-corrected aldosterone ratios**
  - For continuous cosyntropin administration, cutoff of high-side to low-side of more than 4:1 indicates unilateral aldosterone excess.

	Right Adrenal Vein	Right Adrenal Vein	Left Adrenal Vein	Left Adrenal Vein	Femoral Vein	Femoral Vein
ALDOSTERONE	2070	1590	6700	6500	210	213
Cortisol	604.3	356.6	265.5	281.5	32.2	31.8
Average cortisol	480.5		273.5		32	
Adrenal to IVC cortisol ratio	15			8.5		
Cortisol corrected aldosterone	3.4	4.5	25.2	23.1		
Average cortisol corrected aldosterone	3.95		24.15			

L / R ratio = 24.2 / 4.0
= 6.1
= LEFT lateralization

Treatment

- Hyperaldosteronism has adverse cardiovascular effects at least partly independent of HTN
- Treatment recommendations
  - Unilateral primary aldosteronism → unilateral laparoscopic adrenalectomy
  - Bilateral adrenal disease → medical treatment with mineralocorticoid antagonist
    - Spironolactone primary agent, Eplerenone alternative

Case Conclusion (for now)

- Started on spironolactone 25mg daily
- Met with Dr. Grogan
- Plans for laparoscopic left adrenalectomy and resection of pancreatic neuroendocrine tumor in 6 months when patient returns from Uruguay

References

- Funder JW, Carey RM, Mantero F, Murad MH, Reincke M, Shibata H, Stowasser M, Young WF Jr. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016 May;101(5):1889-916. doi: 10.1210/jc.2015-4061. Epub 2016 Mar 2. PubMed PMID: 26934393.
- Wong L, Hsu TH, Perlroth MG, Hofmann LV, Haynes CM, Katznelson L. Reninoma: case report and literature review. J Hypertens. 2008 Feb;26(2):368-73. doi: 10.1097/HJH.0b013e3282f283f3. Review. PubMed PMID: 18192852.
- DeLellis, Ronald A., and Ling Xia. "Paraneoplastic endocrine syndromes: a review." *Endocrine pathology*. Vol. 14. No. 4. Humana Press, 2003.
- Oelkers W, Diederich S, Bähr V. Primary hyperaldosteronism without suppressed renin due to secondary hypertensive kidney damage. J Clin Endocrinol Metab. 2000 Sep;85(9):3266-70. PubMed PMID: 10999820.
- Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA. Relationships of plasma renin levels with renal function in patients with primary aldosteronism. Clin J Am Soc Nephrol. 2007 Jul;2(4):722-31. Epub 2007 Apr 25. PubMed PMID: 17699488.
- Young WF, Stanson AW, Thompson GB, Grant CS, Farley DR, van Heerden JA. Role for adrenal venous sampling in primary aldosteronism. *Surgery*. 2004;136:1227–1235.