Patients with primary aldosteronism and inconclusive adrenal vein sampling

Kelvin Memeh MD

Fellow, Endocrine Surgery

Objectives

- Discussion of cases
- Overview of key terms in diagnostic work up of primary aldosteronism
- Highlight some difficulties inherent in interpreting AVS results
- Review some plausible solutions to some of the difficulties with AVS results
- Questions and further discussions

Patient 1

- 61year old male with medical history significant for HLD and HTN x 20 years.
- BP have been grossly well–controlled until about 8 years prior to presentation.
- About 5 years prior to presentation he was started on oral K supplementation for severe hypokalemia.
- PCP investigated further

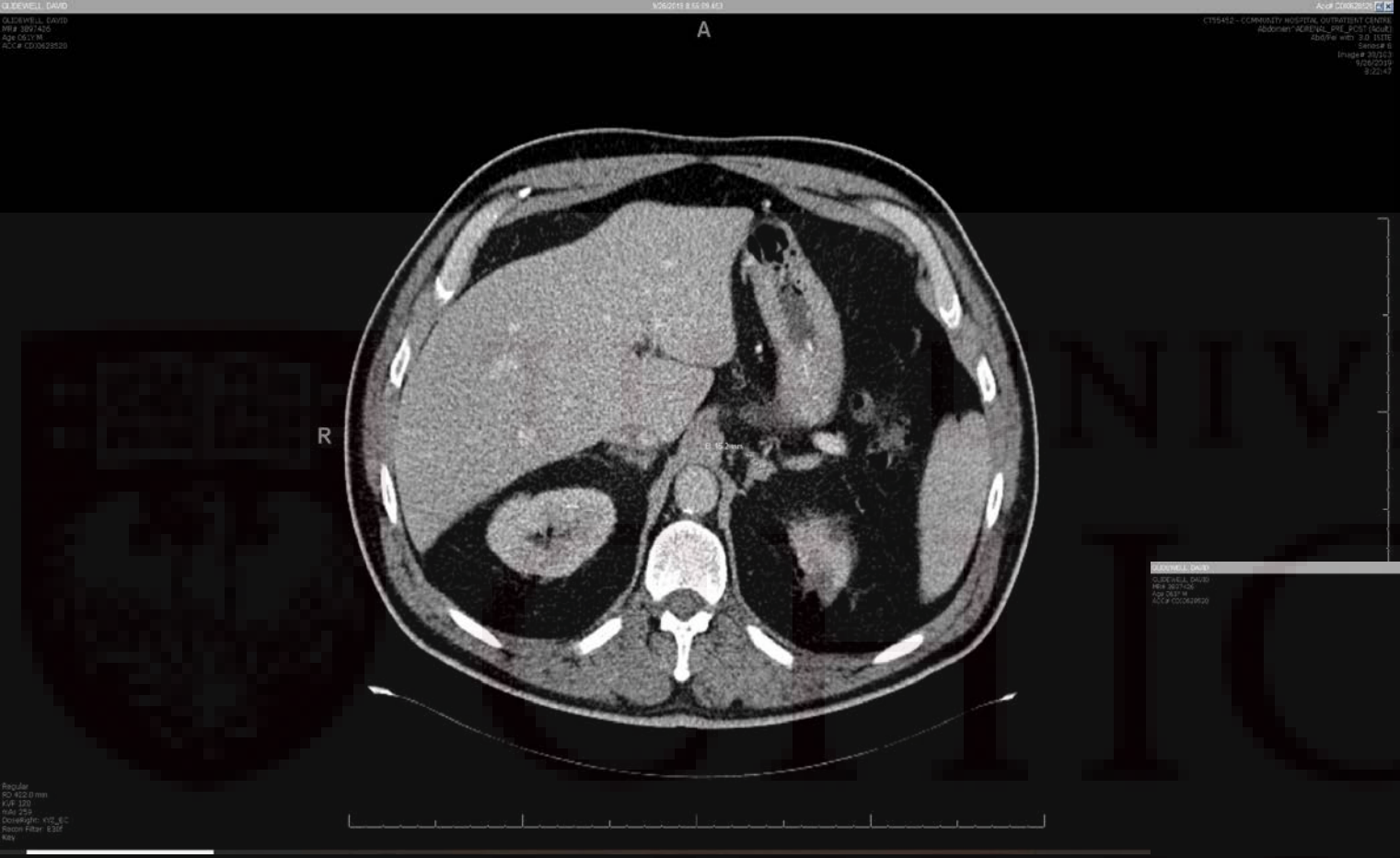
- Labs

  Aldosterone of 68.3 and renin 0.16.

  Plasma normetanephrine 42, Metanephrine 23

- MRI and subsequently CT scan with IV contrast showed a left adrenal nodule 1.2 x 1.6 cm.

- Patient then self-referred to our clinic for surgical evaluation.
- Medication Hx:
  - Two anti-hypertensive agents; Lisinopril 20mg daily and Nifedipine 60mg ER tab.
  - Oral potassium chloride (KDUR) 20mEq ER daily
  - Atorvastatin 10 mg daily
- PSHX: Non-significant
- Fam Hx: Non contributory


A
R


A
R

- On our evaluation at UCM his BP were in the high 150's systolic and he confirmed that has been his baseline even on anti-BP meds

- We requested an adrenal vein sampling for lateralization/subtyping of the Aldosteronoma

AVS Result

				MEASURED VALUES		CALCULATED VALUES				
Sample	Draw Time	Accession #	Location	Aldosterone (ng/dL)	Cortisol (ug/dl)	Aldosterone (pmol/L)	Cortisol (nmol/L)	Adrnl/Fem Cortisol Ratio	Aldo/Cortisol Ratio	Aldo/Cortisol Ratio (Highest side/Lowest side)
1R	11:12	T65942	Right Adrenal Vein	33	25	914	684	0.7	1.3	NO RAV/FEM CORT GRADIENT
1L	11:18	T65968	Left Adrenal Vein	5840	370	161768	10215	11.1	15.8	
1F	11:20	T65983	Femoral Vein	111	33	3075	916			
2R	11:16	T66000	Right Adrenal Vein	16	26	443	726	0.9	0.6	NO RAV/FEM CORT GRADIENT
2L	11:19	T66021	Left Adrenal Vein	6540	396	181158	10941	13.3	16.6	
2F	11:20	T66188	Femoral Vein	119	30	3296	825			


WHAT`S
YOUR
PLAN?

Patient 2

- 58 year old woman with medical history significant for HTN diagnosed at age 38.
- She has been taking potassium on and off since 2014.
- 2017: Incidentally found to have a 1.2cm left adrenal nodule on a CT of the abdomen obtained for trauma work after MVC.
- 2017: worsening BP- difficult to control on usual medication and several combination by her PCP.
- Given ↓K and ↑BP PCP investigated further

- Labs:

  Cortisol was normal.

  Plasma (nor)metanephrines were also normal.

  Aldo/Renin ratio was high at 250.

Adrenal Vein Sampling results

May 7, 2019

09:00 am samples

RAV aldosterone/cortisol = 4500/701.3 = 6.42
LAV aldosterone/cortisol = 2100/1007.5 = 2.08
IVC aldosterone/cortisol = 37/20.4 = 1.81

Right-to-left lateralization ratio = 6.42/2.08 = 3.09

09:05 am samples

RAV aldosterone/cortisol = 4400/689.3 = 6.38
LAV aldosterone/cortisol = 1800/1032.4 = 1.74
IVC aldosterone/cortisol = 50/21.7 = 2.30

Right-to-left lateralization ratio = 6.38/1.74 = 3.67

Meds during testing: nebivolol 5 mg qd, spironolactone 50 qd (no KCl)

Adrenal Vein Sampling results

May 7, 2019

09:00 am samples

RAV aldosterone/cortisol = 4500/701.3 = 6.42
LAV aldosterone/cortisol = 2100/1007.5 = 2.08
IVC aldosterone/cortisol = 37/20.4 = 1.81

09:05 am samples

RAV aldosterone/cortisol = 4400/689.3 = 6.38
LAV aldosterone/cortisol = 1800/1032.4 = 1.74
IVC aldosterone/cortisol = 50/21.7 = 2.30

Meds during testing: nebivolol 5 mg qd, spironolactone 50 qd (no KCl)

July 31, 2019 : Repeat AVS

09:00 am samples

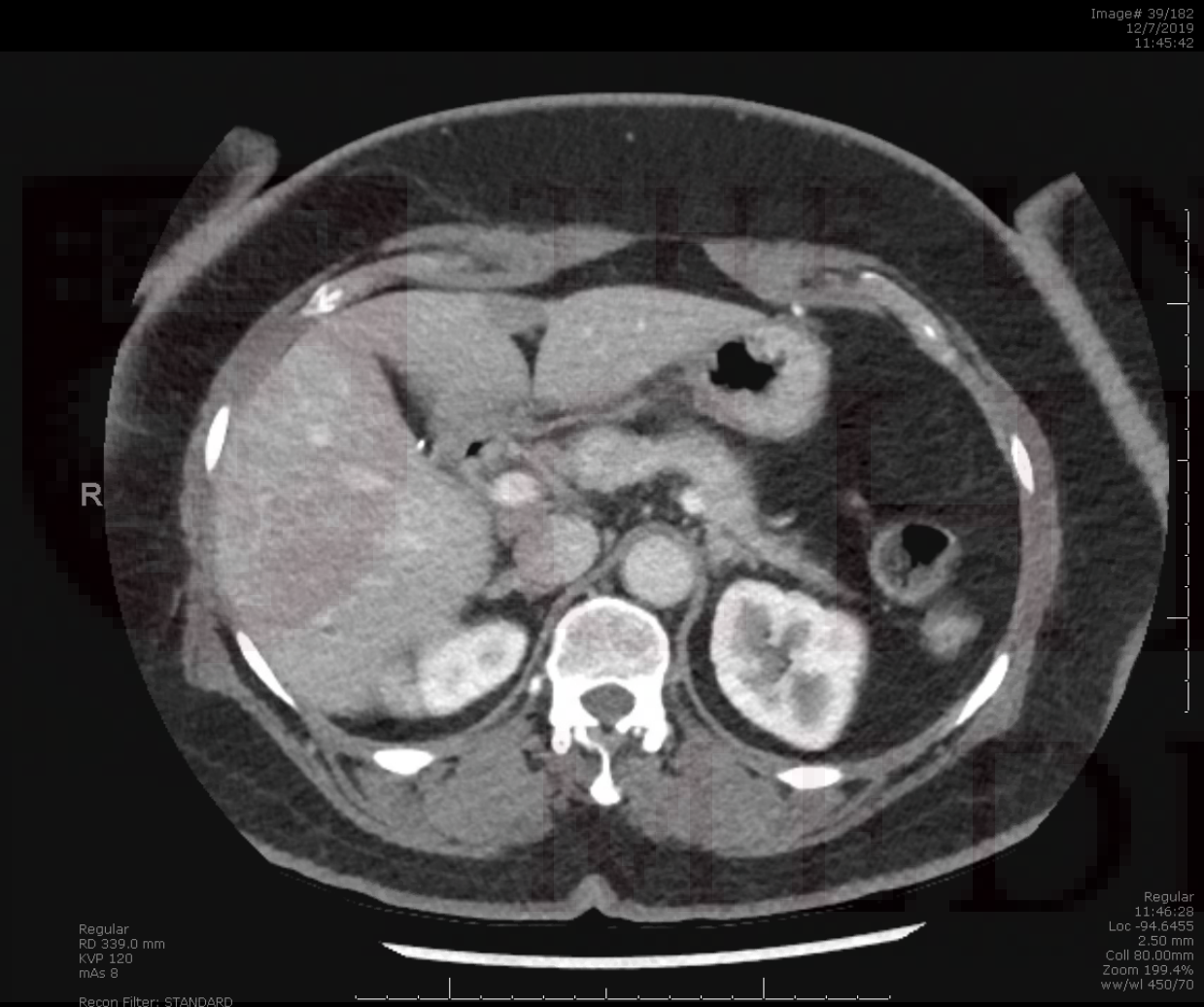
RAV aldo/cortisol = 5580/540.5 = 10.32
LAV aldo/cortisol = 1650/845.6 = 1.95
IVC aldo/cortisol = 41/22.1 = 1.86

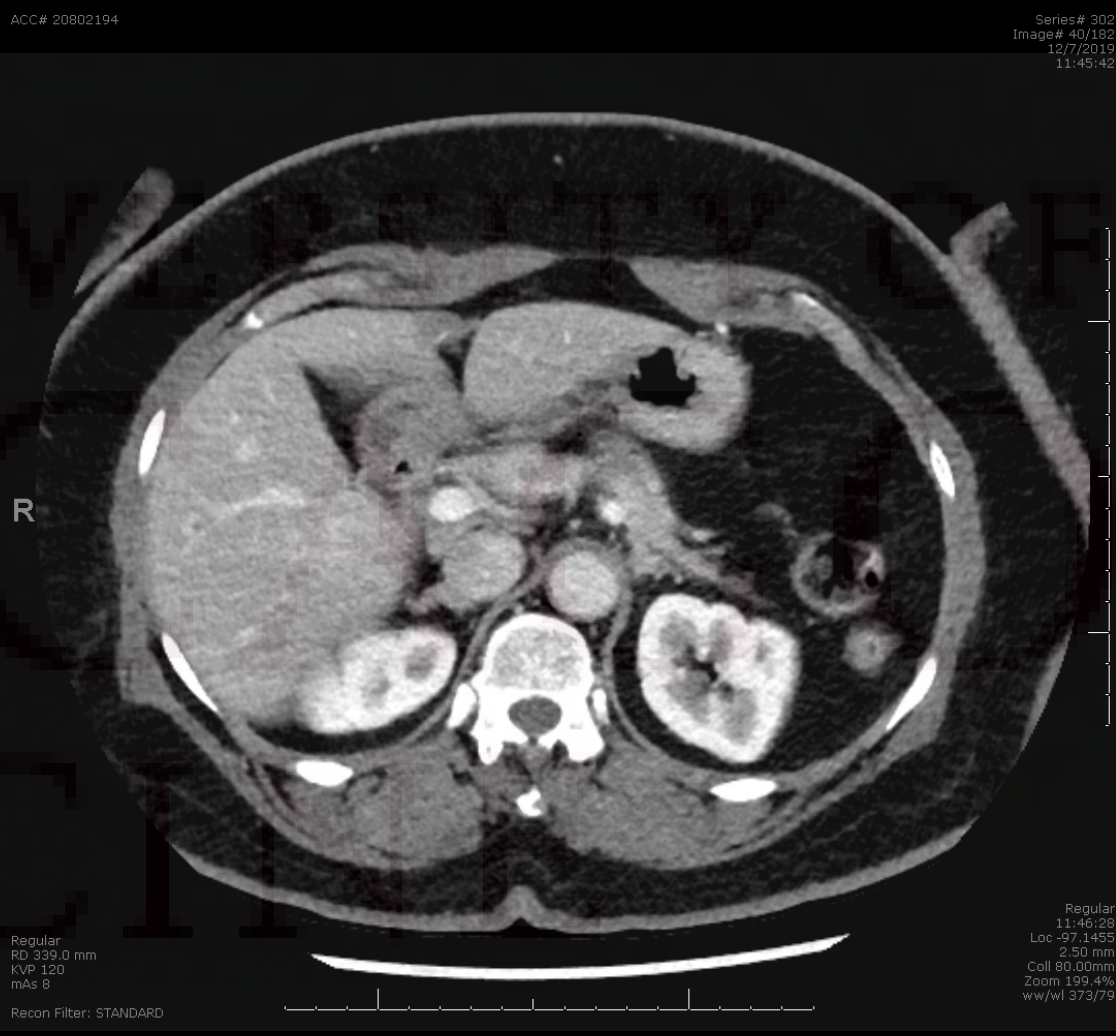
09:05 am samples

RAV aldo/cortisol = 6080/549.0 = 11.07
LAV aldo/cortisol = 1660/696.9 = 2.38
IVC aldo/cortisol = 38/21.1 = 1.80

Right-to-left lateralization ratio = 11.07/2.38 = 4.65

Meds during testing: HCTZ 12.5 mg qd, nebivolol 10 mg qd, (off spironolactone since 5/22/19), KCl 20 mEq tid


Image# 39/182
12/7/2019
11:45:42
R
Regular
RD 339.0 mm
KVP 120
mAs 8
Recon Filter: STANDARD
Regular
11:46:28
Loc -94.6455
2.50 mm
Coll 80.00mm
Zoom 199,4%
ww/wl 450/70


ACC# 20802194
Series# 302
Image# 40/182
12/7/2019
11:45:42
R
Regular
RD 339.0 mm
KVP 120
mAs 8
Recon Filter: STANDARD
Regular
11:46:28
Loc -97.1455
2.50 mm
Coll 80.00mm
Zoom 199,4%
ww/wl 373/79

- Left side lesion on imaging
- Two consecutive AVS lateralized to right- the contra-lateral side of the lesion

Evaluation of primary aldosteronism

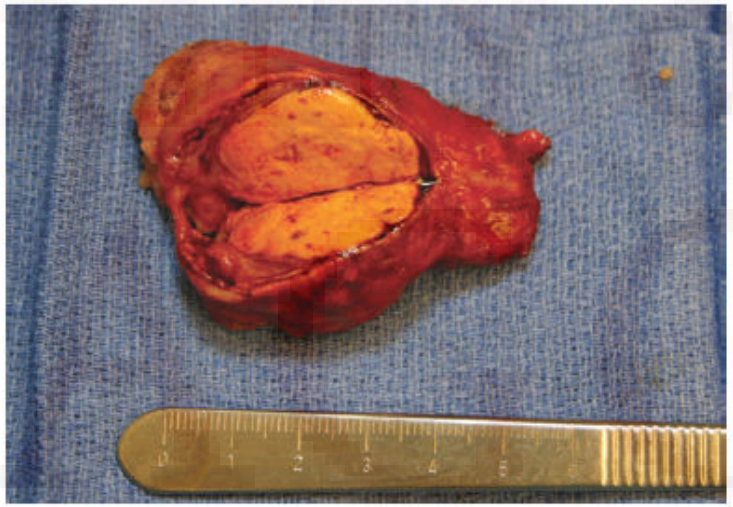
Primary Aldosteronism(PA)

According to Endocrine Society:

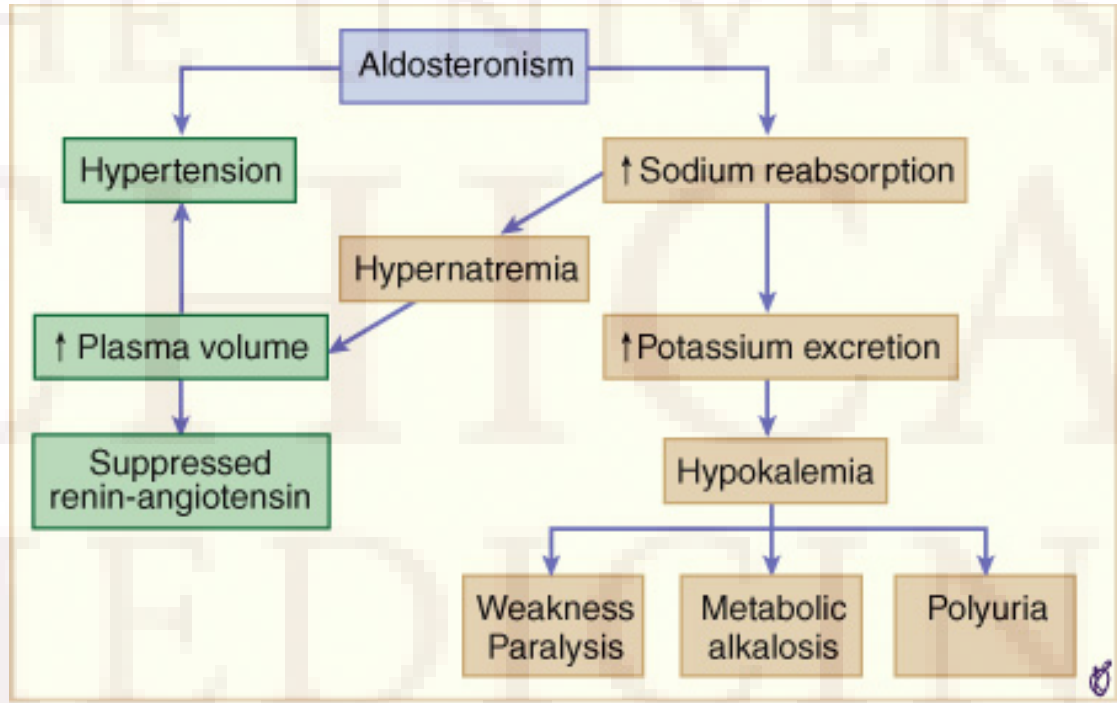
- PA is a group of disorders in which aldosterone production is inappropriately high for sodium status, relatively autonomous of the major regulators of secretion (angiotensin II, plasma potassium concentration), and non-suppressible by sodium loading.

- The excess aldosterone causes hypertension, cardiovascular damage, sodium retention, suppression of plasma renin, and increased potassium excretion that (if prolonged and severe) may lead to hypokalemia

- First described by Jerome Conn in 1954.
- Mean age at diagnosis = 50years
- M> F (slightly).



- 5- 10 % of patients with HTN have primary mineralocorticoid excess.
- Common causes: adrenal adenoma, unilateral or bilateral adrenal hyperplasia (BAH).
- Rare causes: adrenal carcinoma or inherited conditions of familial hyperaldosteronism.



- Classic Triad: hypertension, unexplained hypokalemia , and metabolic alkalosis

- 9-35 % of patients with primary mineralocorticoid excess are normokalemic

Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-1916. doi:10.1210/jc.2015-4061

- Less clear- cut cases, rule out other differential diagnosis : surreptitious vomiting, diuretic therapy, and Bartter syndrome

- Identifying and screening at-risk population: Patients with hypertension.

Especially in

- severe HTN (>150 mmHg systolic or >100 mmHg diastolic) or drug-resistant hypertension (sub-optimally controlled HTN on a three-drug program that includes an adrenergic inhibitor, vasodilator, and diuretic).

- Hypertension with adrenal incidentaloma.

- Hypertension with sleep apnea.

- Hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years).

- All hypertensive first-degree relatives of patients with primary aldosteronism.

Funder JW, Carey RM, Mantero F, et al. The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-1916. doi:10.1210/jc.2015-4061.

Käyser SC, Dekkers T, Groenewoud HJ, et al. Study Heterogeneity and Estimation of Prevalence of Primary Aldosteronism: A Systematic Review and Meta-Regression Analysis. *J Clin Endocrinol Metab*. 2016;101(7):2826-2835. doi:10.1210/jc.2016-1472

- Detection testing(target at-risk patients)

- Suppressed plasma renin activity (PRA) or Plasma renin concentration (PRC): typically <1
- Inappropriately elevated plasma aldosterone concentration(PAC) for the PRA (typically >15 ng/dL [416 pmol/L].

- Some(if not most) patient should have a confirmatory test to establish the diagnosis

Exceptions

Spontaneous hypokalemia

Undetectable PRA or PRC

PAC ≥20 ng/dL (555 pmol/L)

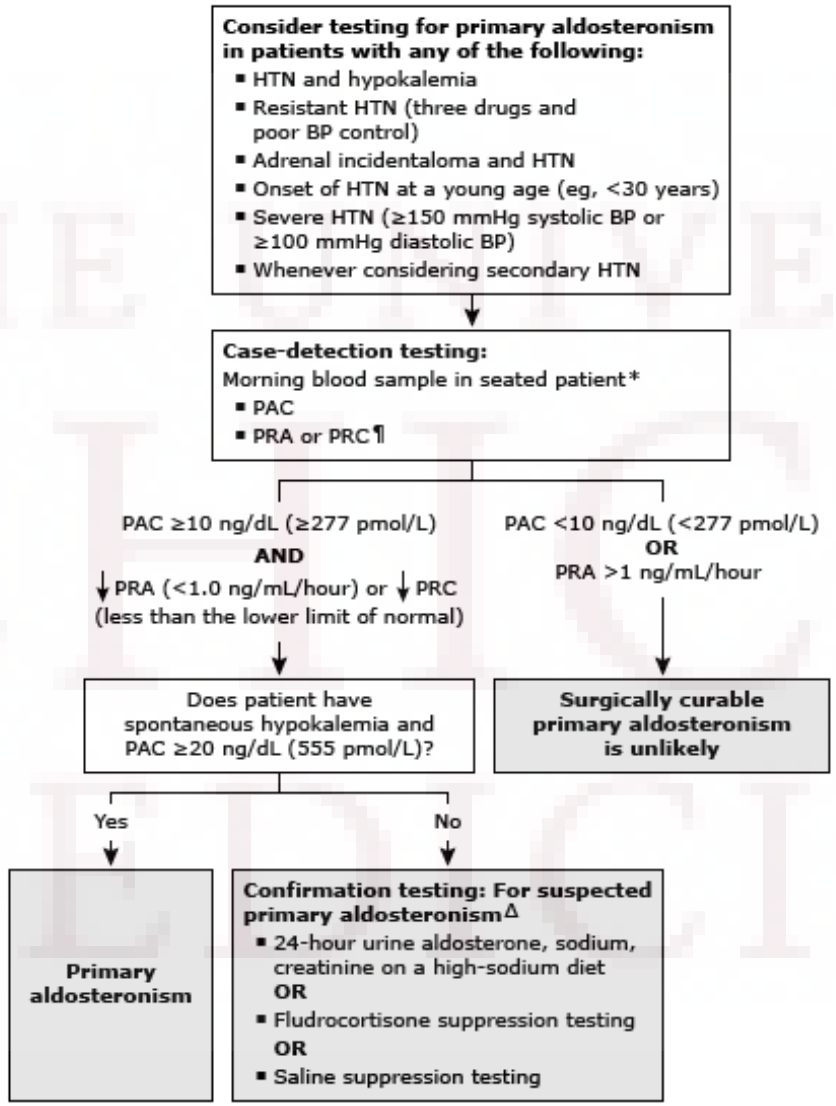
False Positive AVS

Medication/conditions	Effect of Aldosterone	Effect on Renin	Overall effect on ARR
B- blocker	↓	↓↓	↑ (False positive)
Central agonist (e.g clonidine, α-methyl dopa)	↓	↓↓	↑
NSAIDS	↓	↓↓	↑
High dietary sodium	↓	↓↓	↑
Renal impairment	minimal	↓	↑

False Negative AVS

Medication/conditions	Effect of Aldosterone	Effect on Renin	Overall effect on ARR
Diuretic(K wasting or sparing)	↑	↑↑	↓(False Negative)
Calcium Channel blocker	Minimal or ↓	↑	↓
ACE-Inhibitor	↑	↑↑	↓
AR-Blocker	↑	↑↑	↓
Hypokalemia	↓	Minimal or ↑	↓

Case-detection testing for diagnosis of primary aldosteronism



HTN: hypertension; BP: blood pressure; PAC: plasma aldosterone concentration; PRA: plasma renin activity; PRC: plasma renin concentration.

* Patient out of bed for at least two hours and seated for at least 5 to

Aldosterone resolution score:

Aldosterone Resolution Score: 4 Variable Model		
	Points	
Predictor	**Present**	**Absent**
No. antihypertensive medications ≤2	2	0
Body mass index ≤25	1	0
Years of hypertension ≤6	1	0
Female	1	0
Total*	5	0

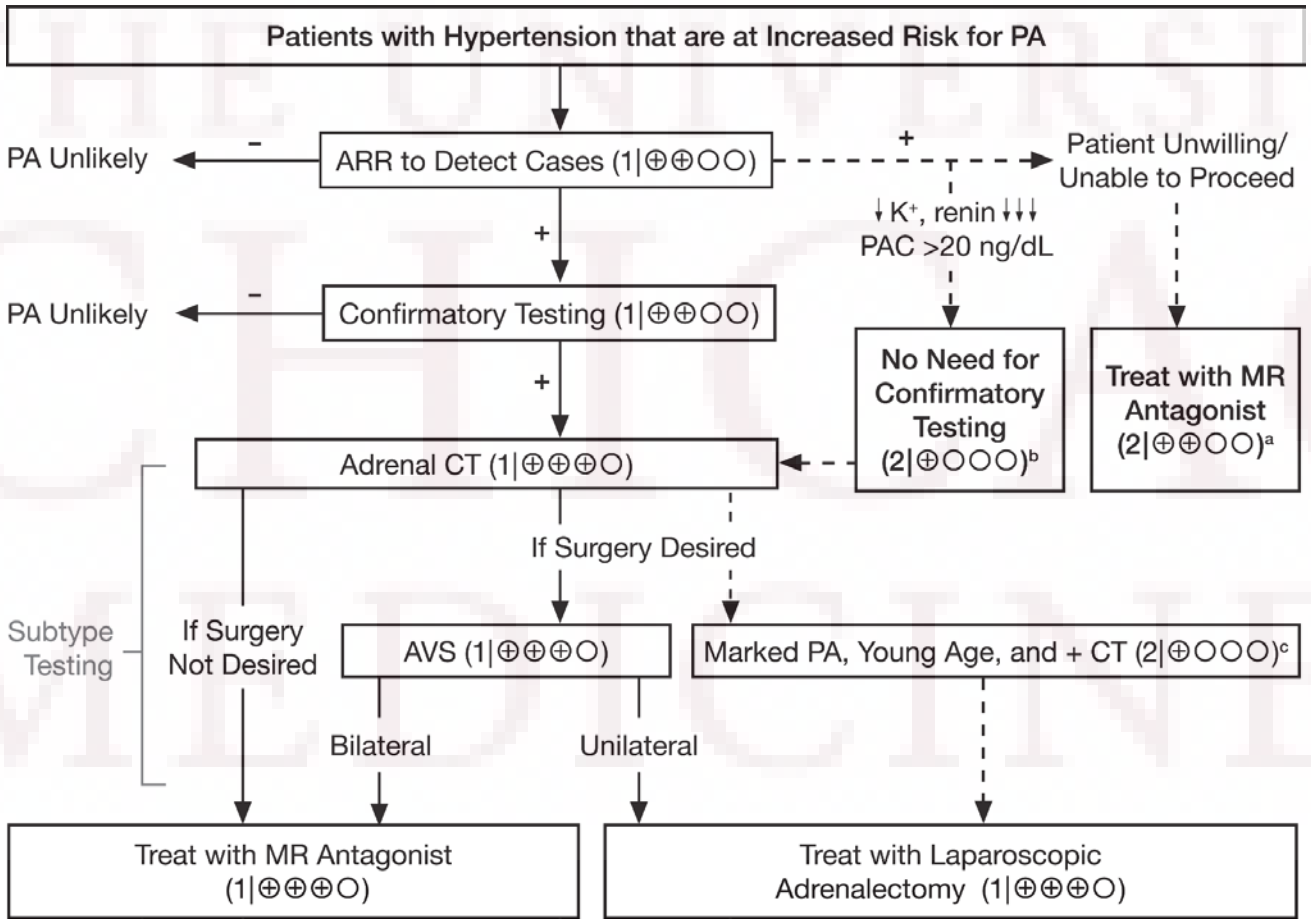
*Possible score range from 0 to 5.

Aldosterone Resolution Score: 4 Variable Model

Aldo Resolution Score	% Resolution of after adrenalectomy
0 - 1	**13.7%**
2-3	**44.1%**
4-5	**80%**

Zarnegar et. al., Annals of Surgery, Volume 247(3), March 2008 pp 511-518

Algorithm for the detection, confirmation, subtype testing, and treatment of PA.



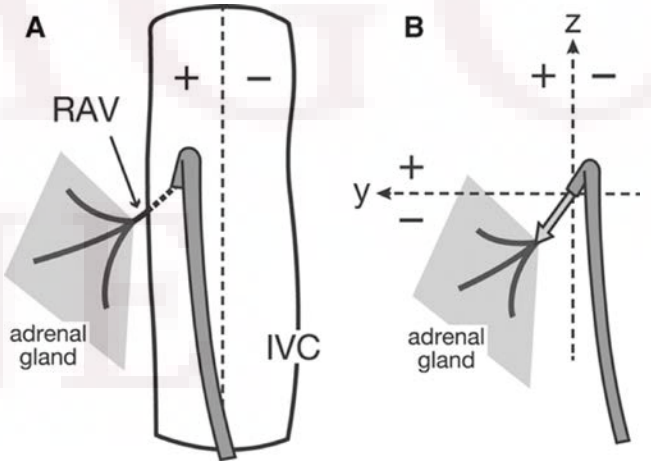
J Clin Endocrinol Metab, Volume 101, Issue 5, 1 May 2016, Pages 1889–1916, https://doi.org/10.1210/jc.2015-4061

Adrenal Vein Sampling

Image guided catheter placement in the adrenal veins and then sample blood for adrenal hormones

1. Confirm placement by comparing cortisol level in the said AV and that in the IVC or femoral vein. AV : IVC(or FV) = 5:1 or more. This is the lateralization index.
2. Next, samples are sent for Aldosterone.
3. Catheter is then placed in the contra-lateral AV and steps 1 and 2 are repeated.

* Difficulty: right >>left AV



Interpretation of AVS

- Selectivity index: AV cortisol divided IVC(or FV) cortisol

> 5 (or 3) denoted correct catheterization

- Lateralization index : Ipsilateral A/C ratio divided by contralateral A/C ratio

>4 denotes unilateral Aldosterone producing adenoma/ hyperplasia

< 2 denotes idiopathic aldosteronism

2- 4: borderline

What if IR are unable to cannulate the right adrenal vein?

Should we discard the result of the AVS?

Diagnostic utility of data from adrenal venous sampling for primary aldosteronism despite failed cannulation of the right adrenal vein

Jesse D. Pasternak, MD,[a] Irene Epelboym, MD,[b] Natalie Seiser, MD,[a] Matt Wingo, BS,[b] Max Herman, BA,[b] Vanessa Cowan, MD,[b] Jessica E. Gosnell, MD,[a] Wen T. Shen, MD,[a] Robert K. Kerlan, Jr, MD,[c] James A. Lee, MD,[b] Quan-Yang Duh, MD,[a] *and* Insoo Suh, MD,[a]
San Francisco, CA, and New York, NY

Primary aldosteronism: making sense of partial data sets from failed adrenal venous sampling-suppression of adrenal aldosterone production can be used in clinical decision making

Veljko Strajina [a,*], Zahraa Al-Hilli [a], James C. Andrews [b], Irina Bancos [c], Geoffrey B. Thompson [a], David R. Farley [a], Melanie L. Lyden [a], Benzon M. Dy [a], William F. Young [c], and Travis J. McKenzie [a]

[a] *Department of Surgery, Mayo Clinic, Rochester, MN*
[b] *Department of Radiology, Mayo Clinic, Rochester, MN*
[c] *Division of Endocrinology, Metabolism, Nutrition & Diabetes, Mayo Clinic, Rochester, MN*

- AV/IVC index: $\frac{\text{Aldosterone level in AV divided by cortisol level in the AV}}{\text{Aldosterone level in the IVC divided by cortisol level in the IVC}}$

a. If value ≥ 5.5, then there is lateralization to the ipsilateral side

b. If value ≤ 0.5 , then there is lateralization to the contralateral side

- When (a) is applied, no inappropriate adrenalectomy was performed.

- When b is applied, 17 % of adrenalectomy was inappropriate
  - mostly because of bilateral disease.

- When combine imaging findings and (b), the inappropriate adrenalectomy rate decreased to 8%

What if the AVS lateralizes to a gland that is contra-lateral to the CT finding?

What if the AVS lateralizes to a gland that is contra-lateral to the CT finding?

Few studies suggests follow the AVS and ignore the CT finding.

Nwariaku FE, Miller BS, Auchus R, et al. Primary hyperaldosteronism: effect of adrenal vein sampling on surgical outcome. *Arch Surg*. 2006;141(5):497-503. doi:10.1001/archsurg.141.5.497

Back to our patient

Patient 1:

				MEASURED VALUES		CALCULATED VALUES				
Sample	Draw Time	Accession #	Location	Aldosterone (ng/dL)	Cortisol (ug/dl)	Aldosterone (pmol/L)	Cortisol (nmol/L)	Adrnl/Fem Cortisol Ratio	Aldo/Cortisol Ratio	Aldo/Cortisol Ratio (Highest side/Lowest side)
1R	11:12	T65942	Right Adrenal Vein	33	25	914	684	0.7	1.3	NO RAV/FEM CORT GRADIENT
1L	11:18	T65968	Left Adrenal Vein	5840	370	161768	10215	11.1	15.8	
1F	11:20	T65983	Femoral Vein	111	33	3075	916			
2R	11:16	T66000	Right Adrenal Vein	16	26	443	726	0.9	0.6	NO RAV/FEM CORT GRADIENT
2L	11:19	T66021	Left Adrenal Vein	6540	396	181158	10941	13.3	16.6	
2F	11:20	T66188	Femoral Vein	119	30	3296	825			

Failed cannulation of the right adrenal vein due.

Calculated the AV/IVC index = **4.72**

- On post op visit: off his lisinopril; 30 mg Nifedipine(half of previous dose), K was 4 without supplementation

Back to our patient

- Patient 2:

Discordant AVS and CT findings:

- CT showed left adenoma, AVS suggests right side PA.

Options:

- Already have good BP control with optimization of BP meds so ? utility of surgery.
- Repeat AVS here at UCM, if want to pursue surgery.

New Paradigm in outcomes after Adrenalectomy for Primary Aldosteronism

The Primary Aldosteronism Surgery Outcome (PASO) study.

- International study from 28 centers.

- Create a consensus criteria for clinical and biochemical outcomes and follow-up after adrenalectomy for unilateral primary aldosteronism and

Using the Delphi method, they reached consensus on

- six outcome criteria; complete, partial, and absent clinical and biochemical success
- two recommendations for the time and interval of follow-up after unilateral adrenalectomy

- Applied these criteria in a retrospective analysis of a large prospective cohort of patients who had undergone adrenalectomy to determine frequency of remission and identify preoperative determinants of successful outcome

- follow up ranged 3 – 18 months

- Results

- 37% of patients had complete clinical success(off BP meds after surgery)
- 47% of patients had partial clinical success (less medication to attain normal BP and/or off K supplementation)
- 94% of patients had complete biochemical success.
- Female sex and younger age were independently associated with clinical success

- Conclusions

- More to be done on the “true’ outcome of adrenalectomy for this group of patients
- Longer follow up for clinical and biochemical outcomes. Recommend 3months, 6 months and annually


Thank
you!!