Hyperaldosteronism: Diagnostic Dilemmas and Future Directions

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Hyperaldosteronism: Misconceptions

1. “Primary Aldosteronism (PA) is rare”
   ▪ Actually, PA prevalence is ~5% in all HTN, up to 20% in resistant HTN

2. “I only need to test for PA if hypokalemia is present”
   ▪ Hypokalemia is only seen in 25% of PA pts

3. “Hypertensive pts are appropriately screened for PA”
   ▪ In the US, only ~1 in 550 pts with PA are dx’ed and treated

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Hyperaldosteronism: Case 1

45 y/o female with longstanding HTN

- Currently on 4-drug antihypertensive therapy with good BP control
  - Chlorthalidone, lisinopril, amlodipine, and hydralazine
- Screening for PA performed
  - PAC (aldosterone) 21 ng/dL, PRA (renin) < 0.6 ng/mL/h, Serum [K] 3.6
- Pt not interested in surgical evaluation
  - “My BP is great, and I don’t mind taking a few pills.”
- It is reasonable to continue the pt’s antihypertensives since BP at target?
Hyperaldosteronism: Target Organ Damage

**Stroke**

<table>
<thead>
<tr>
<th>Matched studies</th>
<th>Events</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monticone et al. (2017)</td>
<td>6</td>
<td>99</td>
</tr>
<tr>
<td>Muntia et al. (2017)</td>
<td>29</td>
<td>192</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>35</td>
<td>291</td>
</tr>
<tr>
<td>OR 2.58 (1.93-3.45)</td>
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**CAD**

<table>
<thead>
<tr>
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<tr>
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<tr>
<td>Muntia et al. (2017)</td>
<td>7</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>11</td>
<td>391</td>
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<tr>
<td>OR 1.77 (1.1-2.83)</td>
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References:

### Atrial Fibrillation

<table>
<thead>
<tr>
<th>Primary aldosteronism</th>
<th>Essential hypertension</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Events</td>
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<tr>
<td>Monticone et al. (2017)</td>
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</tr>
<tr>
<td>Murata et al. (2017)</td>
<td>8</td>
<td>4.13 (1.5-11.28)</td>
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<tr>
<td>Reid et al. (2018)</td>
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<td>1.14 (0.46-2.82)</td>
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<tr>
<td>Subtotal (ESI CI)</td>
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<td>3.52 (2.06-5.99)</td>
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<tr>
<td>Total events</td>
<td>33</td>
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<tr>
<td>Heterogeneity $t^2$ 0.6; $\chi^2_1=6.52$; df=1 (p=0.06); I^2=64%</td>
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</table>

### Heart Failure

<table>
<thead>
<tr>
<th>Primary aldosteronism</th>
<th>Essential hypertension</th>
<th>OR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Monticone et al. (2018)</td>
<td>0</td>
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<tr>
<td>Murata et al. (2017)</td>
<td>6</td>
<td>1.12 (0.46-2.82)</td>
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<td>Subtotal (ESI CI)</td>
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<td>2.05 (1.11-3.78)</td>
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<tr>
<td>Total events</td>
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<tr>
<td>Heterogeneity $t^2$ 0.0; $\chi^2_1=0.0$; df=1 (p=0.07); I^2=0%</td>
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</tbody>
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Hyperaldosteronism: Case 1, Revisited

45 y/o female with longstanding HTN

- Currently on 4-drug antihypertensive therapy with good BP control
  - Chlorthalidone, lisinopril, amlodipine, and hydralazine

- Positive PA screen

- Pt not interested in surgical evaluation
  - “My BP is great, and I don’t mind taking a few pills.”

- It is reasonable to continue the pt’s antihypertensives since BP at target?

No. Risk of CV events and organ damage increased in PA independent of BP
Hyperaldosteronism: Case 2

- 39 y/o man on 4-drug antihypertensive therapy with appropriate control
- Is screening for PA necessary?
Hyperaldosteronism: Whom to Screen?

Endocrine Society Guidelines, 2016

- Patients with sustained blood pressure above 150/100 mmHg, grade 2 and grade 3 hypertension
- Patients with resistant hypertension (blood pressure not controlled by three conventional drugs including a diuretic) or controlled BP (<140/90 mmHg) on four or more antihypertensive drugs
- Patients with hypertension and spontaneous or diuretic induced hypokalemia
- Patients with hypertension and an adrenal incidentaloma
- Patients with hypertension and sleep apnea
- Patients with hypertension and a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 years)
- All first-degree relatives of patients with PA

VS

When to Consider Testing for Primary Aldosteronism:
- All patients with hypertension should be tested at least once

The Time has Come for Systematic Screening for Primary Aldosteronism in All Hypertensives*

Giuseppe Maiolino, MD, PhD, a Lorenzo A. Calò, MD, PhD, b Gian Paolo Rossi, MD a

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http://dx.doi.org/10.1016/j.jacc.2017.02.041
Hyperaldosteronism: Case 2, revisited

- 39 y/o man on 4-drug antihypertensive therapy with good BP control

- Is screening for PA necessary? Yes

- Aldosterone 11 (16:30), renin < 0.6, serum [K] 3.1

- After KCl supplementation and change to 09:00 collection
  - Aldosterone 16, renin < 0.6, serum [K] 3.9
Hyperaldosteronism: Simplified Algorithm

Hyperaldosteronism: Case 2, revisited

39 y/o man on 4-drug antihypertensive therapy

- Positive biochemical screen for PA

- 24 hr urine: Na 240 mmol, aldosterone 13.4 mcg, creat 1.5
Hyeraldosteronism: Case 2, revisited
Hyperaldosteronism: Case 2, revisited

39 y/o man on 4-drug antihypertensive therapy

- Positive biochemical screen for PA
- CT abd/pelvis with right-sided 1.5 cm adenoma

- Is AVS needed?
Hyperaldosteronism: Limitation of CT Abd

- High Prevalence of Adrenal Incidentaloma in General Population

# Hyperaldosteronism: Poor CT Abd Performance

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Subjects</th>
<th>Accuracy of CT for Aldo Hypersecretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim V, et al (2014)</td>
<td>143</td>
<td>59%</td>
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</table>
Hyperaldosteronism: Adrenal Venous Sampling

- Adrenal veins cannulated by IR sequentially
- Aldosterone and cortisol levels are measured simultaneously from L + R adrenal veins and IVC

“Are catheters in correct position?” – Selectivity Index (SI)
  - Adrenal:IVC cortisol ≥ 3 shows correct catheterization

“Does aldo production lateralize?” – Lateralization Index (LI)
  - Dominant Aldo:cortisol/Non-dominant aldo:cortisol ≥ 4
Hyperaldosteronism: Case 2, revisited

- 39 y/o man with primary aldosteronism
- CT abd/pelvis with right-sided 1.5 cm adenoma

- AVS performed…
“Are catheters in correct position?”
Adrenal:IVC cortisol ≥ 3 shows correct catheterization

“Does aldosterone production lateralize?”
Dominant aldosterone:cortisol/Non-dominant aldosterone:cortisol ≥ 4

<table>
<thead>
<tr>
<th>Cortisol</th>
<th>(mcg/dL)</th>
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<tr>
<td>IVC</td>
<td>L adrenal vein</td>
<td>R adrenal vein</td>
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<tr>
<td>36.1</td>
<td>581.2</td>
<td>840</td>
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<table>
<thead>
<tr>
<th>Aldosterone</th>
<th>(ng/dL)</th>
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</thead>
<tbody>
<tr>
<td>IVC</td>
<td>L adrenal vein</td>
<td>R adrenal vein</td>
</tr>
<tr>
<td>23.2</td>
<td>3400</td>
<td>362</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aldo/Cortisol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IVC</td>
<td>L adrenal vein</td>
</tr>
<tr>
<td>0.64</td>
<td>5.85</td>
</tr>
</tbody>
</table>
Hyperaldosteronism: Case 2, revisited

Pt underwent L adrenalectomy
- Post-operatively, potassium supplements and ACE-I held

One week later
- HTN improved (4 BP drugs -> amlodipine monotherapy)
- Hyperkalemia to 6.1 -> treated with fludrocortisone x 6 wks
Hyperaldosteronism: Case 3

56 y/o man with HTN

- BP controlled while on spironolactone 50 mg daily, amlodipine 10 mg daily
- Screening for PA performed
  - PAC 21 ng/dL, PRA < 0.6 ng/mL/h, [K] 3.4

- Can these results be interpreted while on BP meds?
  - Yes! No BP med will cause false positive testing for PA
  - But if PAC elevated and PRA not suppressed, hold BP meds (or switch to alpha blocker or CCB) and repeat testing in 2 wks
Hyperaldosteronism: Med Effect on Aldo/Renin

Aldo Interpretation Based on Renin Levels

Adenoma with suppressed renin

Adenoma without suppressed renin
Aldo Interpretation Based on Renin Levels

Adenoma with suppressed renin

Adenoma without suppressed renin
Hyperaldosteronism: Case 4

65 y/o man with longstanding HTN
• Positive testing for PA
• CT abdomen unremarkable
• AVS discussed with the patient, but he is concerned about complications
• He asks, “Could this be managed with a medication instead?”
Hyperaldosteronism: Challenges

1. Spironolactone Tolerability
   • Incidence of gynecomastia
     • 10% with 25 mg daily$^1$
     • 30% with 100 mg daily$^2$
     • 62% with 200 mg daily$^2$

$^1$Pitt B, et al. NEJM, 1999 Sep 2;341(10):709-17
1. Spironolactone Tolerability
   - Incidence of gynecomastia
     - 10% with 25 mg daily\(^1\)
     - 30% with 100 mg daily\(^2\)
     - 62% with 200 mg daily\(^2\)

2. Goals of therapy not entirely straightforward
   - BP control not enough, need adequate MR blockade
   - Serum [K] > 4.5, PRA > 1

Hyperaldosteronism: Treat to Renin > 1

- 602 PA pts treated with MR antagonists
- 41,853 age-matched pts with essential HTN
- 1\textsuperscript{st} outcome – incident CV event
  - MI, revascularization, CHF admit, CVA
- Found 2x risk in PA vs essential HTN
- UNLESS treated to PRA > 1 (no diff)

Hyponaldosteronism: Pearls of Med Therapy

1. High doses of spironolactone generally not needed
   ▪ MR blockade achieved in > 90% of PA pts with 50 mg spironolactone\(^1\)

2. In case of antiandrogenic side effects, switch to eplerenone
   ▪ Eplerenone must be given twice daily (3-6hr half life)
   ▪ So, if pt intolerant of spironolactone 50 mg daily, use eplerenone 50 mg bid

3. PA is a hyperfiltration state: eGFR will decrease with MRA therapy\(^2\)
   ▪ Mean decrease in eGFR of 15 ml/min per 1.73 m\(^2\)

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Hyperaldosteronism: Not Just a Salt Problem

1. Spironolactone Tolerability
   • Incidence of gynecomastia
     • 10% with 25 mg daily\(^1\)
     • 30% with 100 mg daily\(^2\)
     • 62% with 200 mg daily\(^2\)

2. Goals of therapy not entirely straightforward
   • BP control not enough, need adequate MR blockade
   • Serum [K] > 4.5, PRA > 1

3. Is MR blockade enough?
   • How do we deal with glucocorticoid excess in PA?

Hyperaldosteronism: Not Just Salt

Mineralocorticoid

Glucocorticoid

Hyperaldosteronism: Not Just Salt

- Is MRA therapy enough?

Hyperaldosteronism: Medical vs Surgical Rx

12 studies including 6148 PA pts
- Surgery (versus medical therapy)
  - Lower incidence of composite CV outcomes
  - Less persistence of HTN

High Affinity, Selective, MRAs
• Esaxerenone

Future Subtype Studies for PA
• Peripheral “hybrid” steroids (18-Oxocortisol)
• Nuclear Imaging (68Ga-Pentixafor)
Hyperaldosteronism: Esaxerenone

<table>
<thead>
<tr>
<th>Chemical structure</th>
<th>Spironolactone</th>
<th>Eplerenone</th>
<th>Esaxerenone</th>
</tr>
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<tbody>
<tr>
<td>Molecular formula</td>
<td>$\text{C}<em>{24}\text{H}</em>{32}\text{O}_4\text{S}$</td>
<td>$\text{C}<em>{24}\text{H}</em>{36}\text{O}_6$</td>
<td>$\text{C}<em>{22}\text{H}</em>{21}\text{F}_3\text{N}_2\text{O}_4\text{S}$</td>
</tr>
<tr>
<td>Oral bioavailability</td>
<td>60–90%</td>
<td>69%</td>
<td>90%</td>
</tr>
<tr>
<td>EC_{50} or IC_{50} (nM) (rats or rabbits)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>36</td>
<td>713</td>
<td>9.4</td>
</tr>
<tr>
<td>GR</td>
<td>764</td>
<td>3060</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>AR</td>
<td>133</td>
<td>&gt;100,000</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>PR</td>
<td>1200</td>
<td>&gt;100,000</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>Human: &gt;12 h</td>
<td>Human: 3–5 h</td>
<td>Human: 18.6–25.1 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monkey: 10–13 h</td>
</tr>
</tbody>
</table>

Change in sitting BP (mmHg)

- SBP: n=44, $-17.7^*$
- DBP: n=44, $-9.5^*$

Hyperaldosteronism: 18-Oxocortisol

Peripheral 18-Oxocortisol to Distinguish APA from BHA

Hyperaldosteronism: 18-Oxocortisol

Peripheral 18-Oxocortisol to Distinguish APA from BHA

68Ga-Pentixafor Targets CXCR4 in Aldo-Producing Adenomas

Hyperaldosteronism: Summary

- PA associated with cardiac/renal injury if aldosterone excess not addressed
  - EVEN if BP controlled with other antihypertensives

- When screening hypertensive pts for PA
  - Positive screen is aldo > 10 ng/dL and PRA < 1 (early morning collection)
  - If aldo > 10 but PRA > 1,
    - Hold other BP meds (can use α- or CCB) and recheck aldo:renin in 2 wks
    - Within 6 weeks, renin should fall if PA present

- Can do screening, confirmatory, and AVS testing for PA if spironolactone used
  - BUT ONLY if renin is suppressed (i.e., PRA < 1)

- Most effective tx for APA is adrenalectomy; if bilateral, use MR antag.

- If treating medically, must have adequate MR blockade
  - Target serum [K] of ~4.5, PRA > 1