Secondary Forms of Hypertension: Diagnosis and Management

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Disclosures

• No conflicts of interest
### Types and Causes of Hypertension

#### Systolic and diastolic hypertension

**Primary, essential, or idiopathic**

**Identifiable causes**

**Renal**
- Renal parenchymal disease
- Acute glomerulonephritis
- Chronic nephritis
- Polycystic disease
- Diabetic nephropathy
- Hydronephrosis

**Renovascular disease**
- Renal artery stenosis
- Other causes of renal ischemia

**Renin-producing tumors**

**Renoprival**

- Primary sodium retention: Liddle's syndrome, Gordon's syndrome

**Endocrine**
- Acromegaly
- Hypothyroidism
- Hyperthyroidism
- Hypercalcemia (hyperparathyroidism)

**Adrenal disorders**
- Cortical disorders
  - Cushing's syndrome
- Primary aldosteronism
- Congenital adrenal hyperplasia
- Medullary tumors: pheochromocytoma

**Extra-adrenal chromaffin tumors**
- 11β-hydroxysteroid dehydrogenase deficiency or inhibition (licorice)

**Carcinoids**

**Exogenous hormones**
- Estrogen
- Glucocorticoids
- Mineralocorticoids
- Sympathomimetics
- Erythropoietin

**Neurological disorders**
- Increased intracranial pressure
- Sleep apnea
- Quadriplegia
- Acute porphyria
- Familial dysautonomia
- Lead poisoning
- Guillain-Barré syndrome

**Acute stress**
- Psychogenic hyperventilation
- Hypoglycemia
- Burns
- Alcohol withdrawal
- Sickle cell crisis
- After resuscitation
- Perioperative

- Increased intravascular volume (polycythemia)
- Alcohol
- Nicotine
- Cyclosporine, tacrolimus
- Other agents (see Table 15-5)

#### Systolic hypertension

**Increased cardiac output**
- Aortic valvular insufficiency
- Arteriovenous fistula, patent ductus
- Thyrotoxicosis
- Paget's disease of bone
- Beriberi

**Arterial rigidity**

**Foods containing tyramine with monamine oxidase inhibitors**

**Coarctation of the aorta and aortitis**

**Pregnancy-induced**

**Other causes of hypertension**

**Coexisting conditions**

**Direct effects of hypertension**

**Secondary causes**

**Etiological factors**

**Risk factors**

**Outcome measures**

**Prevention**

**Management**

**Pharmacological therapy**

**Surgical treatment**

**Nonpharmacological therapy**

**References**
Conditions Contributing to BP Elevation: Potentially Reversible

- Lifestyle-Nutritional Factors
  - Obesity
  - Dietary salt
  - Life stress
  - OSA

- Classic Forms of Secondary Hypertension
  - Renovascular Disease
  - Primary Aldosteronism
  - Pheo
  - Renal Parenchymal Disease
  - Cushings Disease

- Prescription or OTC Drugs
Agents that can interfere with blood pressure control

<table>
<thead>
<tr>
<th>Non-narcotic analgesics (non-steroidal anti-inflammatory agents, selective COX-2 inhibitors, aspirin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetic agents (decongestants, diet pills, cocaine)</td>
</tr>
<tr>
<td>Stimulants (methylphenidate, dexamfetamine, dextroamphetamine, amphetamine, methamphetamine)</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Erythropoietin</td>
</tr>
<tr>
<td>Natural licorice</td>
</tr>
<tr>
<td>Herbal compounds (ephedra or ma huang)</td>
</tr>
</tbody>
</table>
Clinical features of the different causes of secondary hypertension

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Suggestive clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Severe or resistant hypertension</td>
</tr>
<tr>
<td></td>
<td>An acute rise in blood pressure over a previously stable value</td>
</tr>
<tr>
<td></td>
<td>Proven age of onset before puberty</td>
</tr>
<tr>
<td></td>
<td>Age less than 30 years with no family history of hypertension and no obesity</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>An acute elevation in serum creatinine of at least 30 percent after administration of angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB)</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema</td>
</tr>
<tr>
<td></td>
<td>Onset of stage II hypertension after age 55 years</td>
</tr>
<tr>
<td></td>
<td>Systolic or diastolic abdominal bruit (not very sensitive)</td>
</tr>
<tr>
<td>Primary renal disease</td>
<td>Elevated serum creatinine concentration</td>
</tr>
<tr>
<td></td>
<td>Abnormal urinalysis</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>New elevation in blood pressure temporally related to use</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Paroxysmal elevations in blood pressure</td>
</tr>
<tr>
<td></td>
<td>Triad of headache (usually pounding), palpitations, and sweating</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>Unexplained hypokalemia with urinary potassium wasting; however, more than one-half of patients are normokalemic</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Cushingoid facies, central obesity, proximal muscle weakness, and ecchymoses</td>
</tr>
<tr>
<td></td>
<td>May have a history of glucocorticoid use</td>
</tr>
<tr>
<td>Sleep apnea syndrome</td>
<td>Primarily seen in obese men who snore loudly while asleep</td>
</tr>
<tr>
<td></td>
<td>Daytime somnolence, fatigue, and morning confusion</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>Hypertension in the arms with diminished or delayed femoral pulses and low or unobtainable blood pressures in the legs</td>
</tr>
<tr>
<td></td>
<td>Left brachial pulse is diminished and equal to the femoral pulse if origin of the left subclavian artery is distal to the coarct</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Symptoms of hypothyroidism</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>Elevated serum thyroid stimulating hormone</td>
</tr>
</tbody>
</table>
PHEO: Symptoms

Cleveland Clinic
73/76: 1 or more
55/76: at least 2

- Headache
- Sweats
- Palpitation
Pheo: Screening

• Spot urine:
  metanephrine/creatinine: mcg/mg = mg/24 hour

• Plasma Metanephrine
  100% sensitive (52/52)
  100% negative predictive value (162/162)
Cushing’s Syndrome: Screening

Overnight Dexamethasone Suppression

- Dexamethasone 1 mg hs
- Plasma cortisol @ 8:00 AM
- Normal suppression: cortisol < 5 mcg/dl
- 10-20 % false positive
RVH: Clinical Clues

• Severe HTN… > 180/120
• Unexplained loss of GFR with antihypertensive therapy, especially:
  – ↑ creat > 30-50% 1-4 weeks following ACE-I or ARB
• Severe HTN and
  – diffuse atherosclerosis + > 50 y/o
  – unexplained small kidney (<9cm) or asymmetry
  – Recurrent episodes (flash) pulmonary edema
• Systolic-Diastolic bruit
## Atherosclerotic RAS: Prevalence of 50% or Greater Narrowing

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall:</td>
<td>11-42%</td>
</tr>
<tr>
<td>Autopsy:</td>
<td>4-50%</td>
</tr>
<tr>
<td>Under age 60:</td>
<td>5.5%</td>
</tr>
<tr>
<td>Over age 60:</td>
<td>16.4%</td>
</tr>
<tr>
<td>During cardiac cath:</td>
<td></td>
</tr>
<tr>
<td>⊗ Coronary Stenosis</td>
<td>29%</td>
</tr>
<tr>
<td>⊗ Coronary Stenosis</td>
<td>10%</td>
</tr>
<tr>
<td>During aortic angiography:</td>
<td></td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>38%</td>
</tr>
<tr>
<td>Aortic occlusive disease</td>
<td>33%</td>
</tr>
<tr>
<td>Lower limb occlusive disease</td>
<td>39%</td>
</tr>
</tbody>
</table>
RAS + HTN $\rightarrow$ STENT ?

RAS + CKD $\rightarrow$ STENT ?
Renal and Cardiovascular Events in ASTRAL

STARS: Decline GFR or Death
RAS + HTN $\rightarrow$ STENT

RAS + CKD $\rightarrow$ STENT
Hypertensive patients with atherosclerotic renal artery disease, who have stable renal function and well managed blood pressure on medical therapy derive no proven benefit by revascularization.
Criticism of ASTRAL Trial

**Selection bias:**
- Patients excluded if “definitely needed” revascularization

**Many “stent” patients unlikely to benefit**
- 17% never stented ….minimal RAS
- 39% showed only 50-70% stenosis

Cross over and **Intention to Treat Analysis**
- 6% of medical group crossed over for revascularization
STAR: Criticism

62% (40 of 64) randomized to stenting and analyzed (ITT) were unlikely to benefit:

- 12 < 50% stenosis
- 22 50-70% stenosis
- 6 never stented

Bias in patient selection:

- Resistant hypertension (BP>140/90) excluded
- Flash pulmonary edema, rapid loss GFR excluded

Mann & Sos
J Clin Hyp 2010
Considerations for RVH Screening

• What is probability of finding RAS?
• Will I intervene if RAS identified?
• Is BP controlled?...renal function stable? on medical therapy
• Will BP respond to intervention?
  – Short duration of ↑↑BP best predictor of BP response
  – No lab/radiology predictor of BP response
• What are risks of diagnostics?
• What are risks of intervention?
DUPLEX
CT Angiography
# Diagnostic Tests for Renal Artery Stenosis

<table>
<thead>
<tr>
<th></th>
<th><strong>duplex</strong></th>
<th><strong>CTA</strong></th>
<th><strong>MRA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>principle</strong></td>
<td>records velocity</td>
<td>Helical CT angiography</td>
<td>MR image</td>
</tr>
<tr>
<td><strong>advantages</strong></td>
<td>Noninvasive</td>
<td>Noninvasive</td>
<td>Noninvasive</td>
</tr>
</tbody>
</table>
| **limitations**| •Time consuming  
•Technically difficult  
•not widely available | •IV contrast  
•Poor imaging in FMD | •Gadolinium-NSF |
| **positive test** | •PSV >200cm/sec  
•RAR >3.5 | Stenosis >75 %  
OR  
>50% + PSD |                                  |
| **Sensitivity / specificity** | 85% / 92% | 96% / 97% | 100% / 96% |
Candidates for RAS Screening-Intervention

- Short duration of BP elevation
- Resistant HTN + clinical clues for RVH
- Intolerance to optimal medical therapy
- Progressive CKD + bilateral RAS or stenosis SFK
- Fibromuscular disease in young patient
- Recurrent flash pulmonary edema or refractory CHF
Clinical Clues RVH
+
Candidate for Intervention

CKD ?

yes

no

Duplex Available ?

no

yes

CTA

Duplex

CTA + contrast prophylaxis
New-Onset CV Event After Diagnosis of ARAS

Kalra
Kidney Int.
2005
ACE inhibitors Improve Survival in ARAS

Number at risk
On ACEi 62 45 33 18 12 6
Without ACEi 133 112 66 38 22 6

Nephrol Dial Transplant 2005
ACE Inhibitors Effectively Control Hypertension in ARAS

- Franklin (1986): Enalapril + HCTZ vs TT..
goal BP 96% v 82%
- In 4 other trials, 80-100% reach goal BP
- Discontinuation due to ↑ creat 0%- 3.5%

Textor
Role of Renin-Angiotensin System Blockade In Atherosclerotic Renal Artery Stenosis and Renovascular Hypertension
Hypertension, 2007
Medical Management of ARAS

Monitoring
- GFR, proteinuria, lipids, glycemic control, K⁺
- Duplex surveillance: Stenotic/Nonstenotic Kidney?
  - Kidney size,
  - renal artery PSV (RAR)

Drug Therapy
- Treat BP to goal … <140/90 with ACE/ARB + add-on Rx
- Treat lipids to LDL < 80
- ASA/fish oil

Cardiovascular Lifestyle Modification
- Manage CV comorbidities
- Glycemic control
- Cessation of cigarette smoking is essential
“Blood pressure should be reduced to levels less than 130/80 in patients with chronic kidney disease”
JNC 7, March 2003

• Target BP in CKD is < 130/80
KDOQI 2004
Guidelines 2013?
The Importance of Proteinuria
Aggressive BP control preserves renal function in proteinuric patients

Low BP: MAP 92 = 125/75
Usual BP: MAP 102 = 140/90

NEJM 1994
### Relative Risk of Major Complications of Chronic Kidney Disease

#### Cardiovascular mortality

<table>
<thead>
<tr>
<th>eGFR</th>
<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
<th>ACR ≥300</th>
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</thead>
<tbody>
<tr>
<td>&gt;105</td>
<td>0.9</td>
<td>1.3</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td>90-105</td>
<td>Ref</td>
<td>1.5</td>
<td>1.7</td>
<td>3.7</td>
</tr>
<tr>
<td>75-90</td>
<td>1.0</td>
<td>1.3</td>
<td>1.6</td>
<td>3.7</td>
</tr>
<tr>
<td>60-75</td>
<td>1.1</td>
<td>1.4</td>
<td>2.0</td>
<td>4.1</td>
</tr>
<tr>
<td>45-60</td>
<td>1.5</td>
<td>2.2</td>
<td>2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>30-45</td>
<td>2.2</td>
<td>2.7</td>
<td>3.4</td>
<td>5.2</td>
</tr>
<tr>
<td>15-30</td>
<td>14</td>
<td>7.9</td>
<td>4.8</td>
<td>8.1</td>
</tr>
</tbody>
</table>

#### Kidney failure (ESRD)

<table>
<thead>
<tr>
<th>eGFR</th>
<th>ACR &lt;10</th>
<th>ACR 10-29</th>
<th>ACR 30-299</th>
<th>ACR ≥300</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;105</td>
<td>Ref</td>
<td>Ref</td>
<td>7.8</td>
<td>18</td>
</tr>
<tr>
<td>90-105</td>
<td>Ref</td>
<td>Ref</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>75-90</td>
<td>Ref</td>
<td>Ref</td>
<td>3.8</td>
<td>48</td>
</tr>
<tr>
<td>60-75</td>
<td>Ref</td>
<td>Ref</td>
<td>7.4</td>
<td>67</td>
</tr>
<tr>
<td>45-60</td>
<td>5.2</td>
<td>22</td>
<td>40</td>
<td>147</td>
</tr>
<tr>
<td>30-45</td>
<td>56</td>
<td>74</td>
<td>294</td>
<td>763</td>
</tr>
<tr>
<td>15-30</td>
<td>433</td>
<td>1044</td>
<td>1056</td>
<td>2286</td>
</tr>
</tbody>
</table>

**KDIGO Report**

*Kidney Int.  2010*
ACCORD BP Trial

- 4700, Type 2 DM
- Established CVD ..or
- 2 additional risk factors
- Baseline BP 139/76

**Intensive therapy**
Target SBP < 120
Achieved SBP 119.3

**Standard Therapy**
Goal SBP <140
Achieved SBP 133.5

5 years

No difference in:
- 1º composite outcome (nonfatal MI, nonfatal stroke, CV death)
- Annual all cause mortality

Differences:
- Fewer strokes in IT (0.32%) vs ST (0.53%), HR 0.63
  *Absolute benefit 1 in 89*
- More serious ADE in IT (3.3 vs 1.3 %)..syncope, renal failure, bradycardia, hyperkalemia

*NEJM 2010*
## BP Targets in CKD: Importance of Proteinuria and Clinical Atherosclerosis

<table>
<thead>
<tr>
<th>CKD</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>diabetes</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>proteinuria</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>atherosclerosis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age &gt;80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Target BP:</strong></td>
<td><strong>140/90</strong></td>
<td><strong>140/90</strong></td>
<td><strong>130/80</strong></td>
<td><strong>130/80</strong></td>
<td><strong>130-135</strong></td>
<td><strong>150</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 attempt SBP 130-135 if no side effects

| 2 avoid DBP <60-65 in CAD |
Drug Therapy in CKD

Goal BP depends on proteinuria
- > 500mg/day → 130/80
- < 500 mg/day → 140/90

Measure Home BP, ABP?

Sodium restriction
- 2 gram Na+ = 5 gram salt ≈ 100 meq Na+

Diuretics
- GFR > 30 → thiazide … CTD > HCTZ
- GFR < 30 →
  - Loop diuretics … furosemide bid, torsemide daily
  - High dose thiazides ? … CTD 50, HCTZ 50 bid

ACE or ARB in proteinuria, not both

Nocturnal administration of some agents
**Sequence of Antihypertensive Therapy in CKD**

<table>
<thead>
<tr>
<th>Edema</th>
<th>Proteinuria*</th>
<th>No proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1st drug</th>
<th>2nd drug</th>
<th>3rd drug</th>
<th>4th drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI + D</td>
<td>nonDHP</td>
<td>NonDHP</td>
<td>Spironolactone, loop + thiazide diuretic</td>
</tr>
<tr>
<td>AI</td>
<td>DHP or AI</td>
<td>D</td>
<td>Labetalol, metoprolol**</td>
</tr>
<tr>
<td>D</td>
<td>DHP</td>
<td>DHP or AI</td>
<td>D</td>
</tr>
</tbody>
</table>

**Notes:**
- AI: angiotensin inhibitor
- D: diuretic
- NonDHP: nondihydropyridine (diltiazam, verapamil)
- DHP: dihydropyridine (amlodipine, nifedipine)

* >500 mg protein per day
** compelling indication
Proteinuria Threshold for Intensive BP Control

**KDIGO**
- ACR < 30 mg/g → < 140/90, no preferred agent
- ACR 30-300 mg/g → <130/80, ACE-I or ARB

**Up-to-Date (Bakris)**
- PER < 500 mg/day → <140/90
- PER ≥ 500 mg/day → <130/80, ACE-I or ARB

**Equivalents and Reconciliation of Guideline**
- ACR 30mg/g creat = PCR 150 mg/g creat
- 80 kg male x 25mg creat excretion per kg = 2g creat
- 150 mg protein/g creat x 2 g = 300 mg protein
## Limitations of Using PCR Exclusively in CKD Management

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>100</th>
<th>67</th>
<th>67</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td>male</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td>Creat excretion (mg/kg)</td>
<td>20-25</td>
<td>15-20</td>
<td>15-20</td>
</tr>
<tr>
<td>Projected creat excretion (mg)</td>
<td>2500</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Projected creat excretion (G)</td>
<td>2.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Protein excretion rate “PER” (mg)</td>
<td>1000</td>
<td>400</td>
<td>1000</td>
</tr>
<tr>
<td>protein-creat ratio “PCR” (mg/G)</td>
<td>400</td>
<td>400</td>
<td>1000</td>
</tr>
</tbody>
</table>
Management of Proteinuria

• ACE-I or ARB, no role for combination
• BP goal <130/80…. or lower
• Proteinuria goals
  – Nephrotic: < 3.5 Grams, ↓50% baseline,
  – Nonnephrotic < 1000 mg, ↓50% baseline
• Evaluation and monitoring
  – 24 hour urine for initial assessment
  – Calculate PCR off 24º urine
  – Monitor PCR and adjust therapy
PRIMARY ALDOSTERONISM
Primary Aldosteronism: Prevalence & Epidemiology

- 1955 - “20% → 10%” …Conn
- <3%

1980 PAC:PRA case-finding 1980

- Nonselect patients, 10%
- Resistant HTN 20%
- Prevalence ≈ severity HTN
  - Stage 1….2%
  - Stage 2….8%
  - Stage 3….13%
- No age, sex, racial differences
Primary Aldo: Clinical Features

- Hypertension: often severe, rarely malignant
- No Edema
- Hypokalemia is inconsistent
  - 50% APA
  - 17% IHA
  - normal K in most GRA
- Metabolic alkalosis
- Mild hypernatremia
## Subtypes of primary aldosteronism

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Relative Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic Hyperaldosteronism</td>
<td>65</td>
</tr>
<tr>
<td>Aldosterone-producing adenoma</td>
<td>30</td>
</tr>
<tr>
<td>Unilateral adrenal hyperplasia</td>
<td>3</td>
</tr>
<tr>
<td>Aldo-producing adrenal carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Familial hyperaldosteronism</td>
<td></td>
</tr>
<tr>
<td>Type I glucocorticoid-remediable aldosteronism</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Type II</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Ectopic Aldo-producing tumors</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>
Indications for Screening in Hypertensive Subjects

- Hypokalemia: spontaneous or induced by low dose diuretic
- Severe or resistant HTN
- adrenal incidentaloma
- FH early onset HTN or stroke (<40 y/o)
- 1st degree relatives with primary aldo
Hormonal Profile in Primary Aldosteronism

\[ \uparrow \text{Aldo} + \downarrow \text{renin} \]

\[ \uparrow\uparrow \text{Aldo:Renin Ratio} \]

ARR
Screening: aldosterone to renin ratio

PAC/PRA

- Morning (?), ambulatory, paired PAC+PRA
- Most BP meds can be continued
  - Low PRA of 1º Aldo unresponsive to diuretics, ACE/ARB
  - High Aldo of 1º Aldo not suppressed by ACE/ARB
  - Captopril stimulation test in screening
  - Dihydropyridines have minimal effect
  - β blockers may ↓PRA but would not stimulate Aldo
- Avoid SPN, eplerenone 4-6 weeks… amiloride OK?
- Interpretation in context of medication
- PRC = PRA x 7
Primary Aldosteronism: Diagnosis

Plasma Aldosterone: Plasma Renin Activity

• PA:PRA > 25

and

• Aldosterone >15 ng/dl

Non suppression of Aldosterone with salt load

• IV: 2 liter NS/4 hour (serum Aldo > 10 ng/dl)
• Oral: 1 tsp salt x 6 days (urine Aldo >14 mcg/24 hr)
Hypertension and Hypokalemia

↑ Aldo, ↓ PRA: Primary Aldo

↑ Aldo, ↑ PRA: 2º HTN
  - Renovascular disease
  - Diuretic use
  - Renin-secreting tumor, Malignant HTN, coarctation

↓↓ Aldo, ↓ PRA: other mineralocorticoid effect
  - DOCA: tumors, CAH ↓17α OHase, ↓11β OHase
  - Cushing’s, Exogenous steroids
  - Congenital hyperplasia
  - Liddle’s syndrome: gain-of-function mutation ENaC
  - Apparent Mineralocorticoid Excess, licorice: ↓ 11β-HSD
## Interpretation of Aldo-Renin Ratio

<table>
<thead>
<tr>
<th>PAC, ng/dL</th>
<th>PRA, ng/mL/h</th>
<th>ARR</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>15</td>
<td>10</td>
<td>Secondary aldosteronism</td>
</tr>
<tr>
<td>15</td>
<td>3</td>
<td>5</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>&lt; 0.6</td>
<td>10</td>
<td>Low-renin HTN, not PA</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>60</td>
<td>Low-renin HTN, not PA</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>15</td>
<td>Possible PA</td>
</tr>
<tr>
<td>15</td>
<td>&lt; 0.6</td>
<td>25</td>
<td>Probable PA</td>
</tr>
<tr>
<td>27</td>
<td>&lt; 0.6</td>
<td>45</td>
<td>Very likely PA</td>
</tr>
</tbody>
</table>

ARR—aldosterone-renin ratio; HTN—hypertension; PA—primary aldosteronism; PAC—plasma aldosterone concentration; PRA—plasma renin activity.
Primary Aldosteronism: Diagnosis

Plasma Aldosterone: Plasma Renin Activity

- **PA:PRA > 25**
- **Aldosterone >15 ng/dl**

Non suppression of Aldosterone with salt load
- **IV: 2 liter NS/4 hour (serum Aldo > 10 ng/dl)**
- **Oral: 1 tsp salt x 6 days (urine Aldo >14 mcg/24 hr)**
Oral salt load for 24 hour urine

- 1 teaspoon table salt daily…OR
- Salt tablets:
  - 1 gram NaCl, 2 tid = 6000 mg NaCl = 100 meq daily …OR
- High salt diet:
  - 5000 mg Na = 12 g NaCl = >200 meq Na / day
- 3 days of salt loading → 24º urine on day 4
  - measure sodium, creatinine, aldosterone
- Explicit instructions on 24 Hr urine
- Goal: 24 hour urinary Na⁺ > 200 meq/day
- Diagnosis: urinary aldosterone > 12 mcg/24 hours
Normal Adrenal
Adrenal adenoma
Bilateral Adrenal Hyperplasia
High Probability of APA

- High plasma aldosterone (>25 ng/dl)
- High urinary aldosterone (>30 mcg/24 hr)
- More severe hypertension
- More frequent hypokalemia
- Younger age (<50)
Subtype evaluation of primary aldosteronism

- **Subtype testing**
  - Adrenal CT scan

  - **Normal, micronodularity, bilateral masses, or atypical unilateral mass (eg, >2 cm)**
    - Surgery not desired
    - Surgery desired
      - AVS
        - No lateralization with AVS
          - IHA or GRA: Pharmacologic therapy
        - Lateralization with AVS
          - APA or PAH: Unilateral laparoscopic adrenalectomy

  - **Unilateral hypodense nodule >1 cm and <2 cm**
    - Surgery desired
      - >40 y consider
      - <40 y consider
        - Pharmacologic therapy
Medical Therapy: Mineralocorticoid Antagonists

- IHA and nonsurgical APA patients
- Spironolactone: 1\textsuperscript{st} line
  - 25-100 mg single daily dose
  - Androgen/progesterone receptor affinity $\rightarrow$ gynecomastia, ED, menstrual irregularity
- Eplerenone: 2\textsuperscript{nd} line
  - SPN derivative
  - Low progestin/androgen affinity $\rightarrow$ few side effects
  - Short duration, lower MR affinity $\rightarrow$ bid, $1/2$ potency SPN
  - $$$, 10x cost of SPN
- Amiloride: 3\textsuperscript{rd} line
  - Blocks ENaC, not MR
  - 10-20 mg daily
- Adjunctive therapy
  - Thiazide
  - IHA $\rightarrow$ ACE-I, APA $\rightarrow$ amlodipine
Obstructive Sleep Apnea
Obstructive Sleep Apnea

- OSA in RH: 71-85%
- Severity of apnea \( \approx \) severity of hypertension
- Mechanism:
  - Hypoxia + \( \uparrow R_{\text{airway}} \rightarrow \uparrow \text{SNS outflow} \)
- Screen: obesity, loud snoring, daytime sleepiness
- Response to CPAP variable
  - 5.5 hrs/night \( \rightarrow \downarrow \text{SBP}_{\text{amb}} \ldots \ldots \) 14mm \( \text{night} \) 9mm \( \text{day} \)
Prevalence of secondary causes of hypertension associated with resistant hypertension.

- OSA: 64.0%
- Primary Hypertension: 34.4%
- Primary Aldosteronism: 5.6%
- Renal Artery Stenosis: 2.4%
- Oral Contraceptives: 1.6%
- Renal Parenchymal Disease: 1.6%
- Thyroid Disease: 0.8%

Effect of CPAP in Resistant HTN *

<table>
<thead>
<tr>
<th></th>
<th>CPAP ($n = 29$)</th>
<th>Conventional Rx ($n = 35$)</th>
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<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Day SBP</td>
<td>133.4</td>
<td>133</td>
</tr>
<tr>
<td>Day DBP</td>
<td>78.9</td>
<td>79</td>
</tr>
<tr>
<td>Night SBP</td>
<td>122.2</td>
<td>120.3</td>
</tr>
<tr>
<td>Night DBP</td>
<td>71.4</td>
<td>68.3</td>
</tr>
</tbody>
</table>

* All patients who completed follow-up

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## Effect of CPAP in Resistant HTN **

<table>
<thead>
<tr>
<th></th>
<th>CPAP (n = 20)</th>
<th></th>
<th>Conventional Rx (n = 21)</th>
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<tbody>
<tr>
<td></td>
<td>baseline</td>
<td>Follow-up</td>
<td>baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Day SBP</td>
<td>140.7</td>
<td>134.4</td>
<td>140.6</td>
<td>140</td>
</tr>
<tr>
<td>Day DBP</td>
<td>82.4</td>
<td>78.8</td>
<td>82.1</td>
<td>82.4</td>
</tr>
<tr>
<td>Night SBP</td>
<td>128.2</td>
<td>122</td>
<td>129.6</td>
<td>129.1</td>
</tr>
<tr>
<td>Night DBP</td>
<td>74</td>
<td>68.5</td>
<td>75.5</td>
<td>74.8</td>
</tr>
</tbody>
</table>

** 24 hour BP < 125/80

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