Evaluation of Resistant Hypertension in Clinical Practice

Matthew R. Weir, MD
Professor and Director
Division of Nephrology
University of Maryland School of Medicine
RESISTANT HYPERTENSION: DEFINITION PER JNC 7 (2003)

- Failure to reach goal BP (<140/90 mm Hg, <130/80 mm Hg with diabetes, chronic renal disease and CAD)
- At least a three-drug regimen, one of which is a diuretic...
- that the patient is taking

Learning Objectives

• To understand the spectrum of resistant hypertension
• To appreciate the importance of endocrine hypertension and obstructive sleep apnea as important etiologies of resistant hypertension
• To consider the importance of the adrenal gland in causing the majority of endocrine hypertension problems
THE SPECTRUM OF HYPERTENSION IN AMERICA

3-11 MILLION

65-70 MILLION

70-79 MILLION (37% at GOAL)
CLASSIFICATION OF RESISTANT HYPERTENSION

• Improper BP measurement and misclassification
• Specific identifiable disorder
  – Secondary HTN
• Exogenous substances
  – Too much salt
  – Too much food
  – Too much alcohol
• Complicating biologic factors
  – Sleep apnea
  – Metabolic Syndrome/Obesity
• Inappropriate or inadequate treatment
• Failure to adhere to the medical regimen

IDENTIFIABLE CAUSES OF HYPERTENSION

• Renal disorders
  – Parenchymal disease
  – Renovascular disease
• Endocrine disease
  – Thyroid disease
  – Mineralocorticoid excess
  – Glucocorticoid excess
  – Pheochromocytoma
  – Hypercalcemia
  – Acromegaly
• Sleep apnea
• Coarctation of the aorta
• CNS tumors
• Autonomic dysreflexia with spinal cord lesions
• Porphyria
• Carcinoid
• Exogenous substances
Learning Objectives

• To understand the spectrum of resistant hypertension
• To appreciate the importance of endocrine hypertension and obstructive sleep apnea as an important etiologies of resistant hypertension
• To consider the importance of the adrenal gland in causing the majority of endocrine hypertension problems
Sub-clinical Hypercortisolism

- N=423 adult resistant hypertensives (1/3 receiving spironolactone)
- All underwent an overnight (12 midnight) dexamethasone (1mg) suppression test
- Those patients with morning cortisol at or above 50 mmol/L had hypercortisolism confirmed by two salivary cortisol measures greater than or equal to 3.6 mmol/L collected at 11:00 PM

Sub-Clinical Hypercortisolism

• n= 112(26.5%) positive screening test
• n= 34(8.0%) had confirmed hypercortisolism
• Independent correlates of a positive DST were older age (p=0.007), male gender (p=0.012) presence of CVD (p=0.002) and CKD (p=0.016)
• Correlates of confirmed subclinical hypercorisolism were older age (p=0.02), DM (p=0.06) and non-dipping pattern of ABPM (p=0.04)

Thyroid Disease: Hypo

- Thyroid hormone plays a role in BP homeostasis
- Withdrawal of thyroid hormone in patients having had a total thyroidectomy results in an increase in serum norepinephrine and aldosterone with a consequent increase in BP, especially DBP
- DBP levels vary directly with TSH
- 20-40% of patients with hypothyroidism are hypertensive
Thyroid Disease: Hypo

- Cardiac output is reduced, reduction in heart rate
- Serum levels of renin are low (?effect of increased aldosterone)
- Increased SVR
- Elevation of BP is primarily diastolic with a reduced PP
Thyroid Disease: Hyper

- Increased CO, HR
- Reduced SVR
- SBP elevation more common
- Widened PP
- Almost the opposite of hypothyroidism!
Pheochromocytoma

- Classic Picture: Paroxysmal elevation of BP associated with pounding headache, palpitations and sweating
- Must exclude pseudopheochromocytoma which is also paroxysmal in nature, often associated with tachycardia, and associated with increased plasma catechols during attacks, and increases in baseline plasma epinephrine and metanephrine, often with a past history of emotional trauma.
Pheochromocytoma

• Very rare, 0.2% of patients with hypertension
• Symptoms related to tumoral hyperscretion of norepinephrine, epinephrine, and dopamine
• Increased SNS activity may also contribute
• Can be asymptomatic (some series suggest 10%)
Pheochromocytoma: When to suspect

- Episodes of non-exertional palpitations, diaphoresis, headache, tremor
- Resistant hypertension
- Family history of pheochromocytoma or MEN syndrome
- Incidental adrenal tumor
- New onset hypertension especially at a younger age, or atypical DM
- Pressor response during anesthesia
- DCM
Pheochromocytoma: Testing

- Often negative
- Most metabolism of catechols is intratumoral with formation of metanephrine, normetanephrine
- Most recommend
  - 24 hour urine fractionated catecholamines and metanephrines by HPLC with electrochemical detection or tandem mass spectroscopy (sensitivity 98%, specificity 98%)
  - Measurement of creatinine to ensure completeness of collection
Other Causes of Paroxysmal Hypertension

- Anxiety
- Hyperthyroidism
- Migraine Headache
- Renovascular Hypertension
- CNS lesions
- Seizure disorder
- Carcinoid
- Baroreflex failure
- Factitious
- Medications: Cocaine, LSD, amphetamine, clozapine, tyrosine injection with MAOI
Hyperparathyroidism

• Increased PTH and Ca ++
• Hypertension is common; causal nature is unknown, as PTHx does not cure the hypertension
• Observational studies link hyper PTH with LVH, diastolic dysfunction, increased carotid IMT, and increases in indirect measures of aortic stiffness
Aldosterone breakthrough

- Driven by residual AT1 receptor stimulation by AngII
- Driven by rise in potassium which stimulates aldosterone secretion

RAAS Pathway

Myocardial fibrosis
Cardiac hypertrophy

Vascular inflammation
Endothelial dysfunction

Central hypertensive effects

Sodium retention
Potassium excretion
PREVALENCE OF PRIMARY ALDOSTERONISM IN SUBJECTS WITH RESISTANT HYPERTENSION

PA = Primary aldosteronism.

ASCOT Study

- 1411 patients who received spironolactone as a fourth line agent for uncontrolled BP.
- Mean age: 63 years
- Median dose of spironolactone: 25 mg
- Duration of treatment: 1.3 years
- Only 6% discontinued treatment due to adverse events

Effect of Spironolactone on Blood Pressure in Subjects With Resistant Hypertension

Neil Chapman, Joanna Dobson, Sarah Wilson, Björn Dahlof, Peter S. Sever, Hans Wedel, Neil R. Poulter, on behalf of the Anglo-Scandinavian Cardiac Outcomes Trial Investigators
Molecular Mechanisms Of Aldosterone Vascular Toxicity: Summary

- Functional MRs
  - AngII Activation of MR
  - Vascular Calcification

- SMCs
  - ICAM Expression and Leukocyte Adhesion
  - ROS-Dependent, Pro-atherogenic Vascular MR-Regulated Genes

- ECs
  - Aldosterone Promotes SMC Proliferation in Vascular Injury Models via PGF

- Whole Vessel
  - Is Vascular MR Responsible?
Hypothetical Mechanisms for Relatively High Aldosterone, Despite Low Renin, in Hypertensives

a. aldosterone stimulating factor in visceral adipose tissue
b. other aldosterone stimulating factors
c. secretion of aldosterone by adipocytes
d. decreased NO bioavailability
e. “autonomous” aldosterone production
f. variation in aldosterone synthetase (CYP11B2)
Steroid Biosynthesis

- **cholesterol**
  - **pregnenolone**
    - **progesterone**
      - **11-deoxycorticosterone**
        - **corticosterone** *(CYP 11B2)*
          - **18-hydroxycorticosterone** *(CYP 11B2)*
            - **aldosterone**
  - **17-hydroxyprogrenolone**
    - **17-hydroxyprogesterone**
      - **deoxycortisol** *(CYP 11B1)*
        - **cortisol**
Plasma Renin Activity and Plasma Aldosterone in the Metabolic Syndrome

Plasma Renin Activity (ng/ml/hr)

- Supine: Metabolic Syndrome
- Supine: No Metabolic Syndrome
- Standing: Metabolic Syndrome
- Standing: No Metabolic Syndrome

P-values:
- Plasma Renin Activity (Supine): P=0.07
- Plasma Renin Activity (Standing): P=0.3
- Plasma Aldosterone (Supine): P<0.01
- Plasma Aldosterone (Standing): P<0.0002

Plasma Aldosterone (ng/dL)

- Supine: Metabolic Syndrome
- Supine: No Metabolic Syndrome
- Standing: Metabolic Syndrome
- Standing: No Metabolic Syndrome
Plasma Aldo by Body Weight and BP Status

Plasma Aldo (ng/dl)

- Normal Weight
- Overweight
- Obese

Normotensive
Hypertensive
Left Ventricular Mass in Patients with Resistant Hypertension

Du Cailar et al, Hypertension, 2010
Protein Excretion in Patients with Resistant Hypertension

Pimenta et al, Hypertension, 2008
Aldosterone and Essential Hypertension: Summary

- BP and hypertension are associated with relatively high aldosterone, despite low PRA in African Americans
- Metabolic syndrome is associated with higher aldosterone in African American males
- Aldosterone induced oxidative stress leads to vascular remodeling and tissue injury
- Aldosterone induced hypertension and vascular injury are potentiated by a high NaCl diet
Aldosterone: Heart Disease and Proteinuria

- High plasma aldosterone on admission is associated with death in patients with acute ST-elevation MI (Beygui et al, Circ 2006)

- Spironolactone, in addition to standard therapy, reduces morbidity and mortality in patients with severe CHF (Pitt et al, NEJM 1999)

- Eplerenone, in addition to “optimal” therapy, reduces morbidity and mortality in patients with MI complicated by LV dysfunction and CHF (Pitt et al, NEJM 2003)

- Spironolactone, in addition to standard therapy, decreases proteinuria in patients with chronic renal disease (Sato et al, Am J Hypertens 2005)
Primary Aldosteronism

- Adrenal hypersecretion of aldosterone – independent of renin:
  - hypertension
  - increased aldosterone levels
  - low plasma renin activity levels
- Two most common causes:
  - Unilateral aldosterone-producing adenoma (APA) – Conn 1955
  - Bilateral idiopathic hyperaldosteronism (IHA)
Primary Aldosteronism Prevalence

Screening “Essential Hypertensives”:

- 1994 -- Australia -- 8.5% (n = 199)
- 1994 -- India -- 8.7% (n = 103)
- 1999 – Slovakia – 13.0% (n = 115)
- 1999 -- UK -- 14.4% (n = 135)
- 1999 -- S. Africa -- 6.4% (n=303)
- 2000 -- Singapore -- 4.6% (n = 350)
- 2000 -- Chile -- 5.2% (n = 305)
- 2002 – Italy – 6.3% (n = 1,043)
- 2002 -- Olmsted County, USA – 12.0% (n = 117)
- 2004 – Japan – 5.9% (n = 1,020)

1° Aldo is common: 5 – 10% of Hypertensives!
High Prevalence of Unrecognized Sleep Apnoea* in Drug-Resistant Hypertension

Logan et al. J Hypertens 2001;19:2271

* >10 events/hr
Prevalence of OSA

<table>
<thead>
<tr>
<th>% OSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
</tr>
<tr>
<td>90</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>70</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>30</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

Middle-Aged Adults
- Young et al. NEJM 1993. AHI ≥5 events/hr.

Hypertension

Resistant Hypertension
- M
- F

1Young et al. NEJM 1993. AHI ≥5 events/hr.
## Sleep Apnea Syndrome: A Possible Contributing Factor to Resistant Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Uncontrolled</th>
<th>Controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>33.7</td>
<td>33.4</td>
</tr>
<tr>
<td>Neck (cm)</td>
<td>43.5</td>
<td>42.6</td>
</tr>
<tr>
<td>Waist/hip ratio</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>AHI (events/hr)</td>
<td>44</td>
<td>32*</td>
</tr>
<tr>
<td>HI (%)</td>
<td>36</td>
<td>29</td>
</tr>
</tbody>
</table>

Lavie and Hoffstein. Sleep 2001;24:721
CPAP in Patients with Resistant Hypertension

Logan et al, Euro Respir Care 2003
Aldosterone Levels and Risk of OSA in Subjects with Resistant Hypertension

Calhoun et al. CHEST 2003
Apnea-hypopnea index and hypoxic index correlates with plasma aldosterone in resistant hypertension subjects

Rho = 0.44, p = 0.0002

Rho = 0.38, p = 0.001
Apnea-hypopnea index and hypoxic index does not correlate with plasma aldosterone in control subjects

Figure 2

Rho = 0.12, p = 0.52

Rho = 0.002, p = 0.99
Positive Relationship of Sleep Apnea to Hyperaldosteronism in an Ethnically Diverse Population

Sim J et al, J Hypertens, 2011
Effect of Spironolactone on AHI in Patients with Resistant Hypertension and Moderate-Severe OSA

![Graph showing the effect of spironolactone on AHI in patients with resistant hypertension and moderate-severe OSA. The graph compares the baseline and 3-months AHI values for spironolactone and control groups.](image)
Primary Aldosteronism

1. When to test for PA
2. Case detection testing
3. Confirmatory testing
4. Subtype testing
5. Treatment

And 3 key clinical “tips”
Primary Aldosteronism—Step 1

When to test for PA:

- Pts with ↑BP & ↓K⁺--regardless of presumed cause
- Rx-resistant hypertension (3 antihypertensive drugs & poor control)
- Severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic)
- Hypertension & an incidental adrenal mass
- Onset of hypertension at a young age
- Whenever performing a secondary hypertension evaluation (eg, when testing for renovascular disease or pheochromocytoma)
Primary Aldosteronism—Step 2

Case Detection Testing:

- Morning (8-10 a.m.) ambulatory paired plasma aldosterone concentration (PAC) & plasma renin activity (PRA)

- May be performed while the pt is taking BP meds & without posture stimulation

- ↓K⁺ reduces the secretion of aldo & it is optimal to restore serum K⁺ to nl before performing dx tests

- Mineralocorticoid receptor (MR) antagonists (eg, spironolactone & eplerenone), & high-dose (> 5 mg/d) amiloride are the only meds that absolutely interfere & should be D/C at least 6 wks before testing
Primary Aldosteronism—Step 2

Tip #1:
However, if the patient is hypokalemic or requiring KCl supplements while treated with a MR antagonist, then complete MR blockade is absent and case detection testing and confirmatory testing can be done while on low-dose MR antagonist (eg, SPL 25 mg/d or EPL 50 mg/d)
Primary Aldosteronism

Case Detection Testing:

- ACE inhibitors, ARBs, & diuretics have the potential to "falsely elevate" PRA in a pt with PA—therefore, in a pt Rx with an ACE inhibitor, ARB, or diuretic the finding of a detectable PRA level or a low PAC/PRA ratio does not exclude 1° aldo

- However, when a PRA level is undetectably low in a pt taking an ACE inhibitor, ARB or a diuretic, 1° aldo should be highly suspect

- Thus, ACE inhibitors, ARBs, renin inhibitors & non-potassium sparing diuretics do NOT need to be discontinued
Primary Aldosteronism

- **Case Detection Testing:**
  - **Key point:** PRA is suppressed (< 1.0 ng/mL per hr) in almost all patients with 1° aldo
  - Adrenergic inhibitors (eg, β-adrenergic blockers & central α₂ agonists) suppress renin secretion, but also in turn suppress aldo secretion (although to a lesser degree than renin) in nl individuals; thus, although the PAC/PRA may rise in hypertensive patients without 1° aldo Rx with adrenergic inhibitors, the PAC remains less than 15 ng/dL (416 pmol/L) & the case finding test is not significantly affected
Step 1. Consider Testing for Primary Aldosteronism:
- Hypertension and hypokalemia
- Resistant hypertension (3 drugs and poor BP control)
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<30 y)
- Severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

Step 2. Case Detection Testing:
Morning blood sample in seated ambulant patient
- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)

\[ \uparrow \text{PAC (≥15 ng/dL; ≥416 pmol/L)} \]
\[ \downarrow \text{PRA (<1.0 ng/mL/hr) or } \downarrow \text{PRC (< lower limit of detection for the assay)} \]

and

\[ \text{PAC/PRA ratio } \geq 20 \text{ ng/dL per ng/mL/hr (≥555 pmol/L per ng/mL/hr)} \]

Step 3. Confirmatory Testing
Primary Aldosteronism—Step 3

Confirmatory Testing:

- An ↑ed PAC/PRA ratio is not diagnostic by itself, & PA must be confirmed by demonstrating inappropriate aldosterone secretion.

- As long as PRA is suppressed, most antihypertensive drugs can be used during this step.

- We perform Aldo suppression testing with orally admin NaCl & measurement of urinary aldosterone and Na^+.
Tip #2:

However, if the patient has spontaneous hypokalemia and a high PAC (eg >30 ng/dL; >832 pmol/L) and undetectable PRA (eg, <0.6 ng/mL/hr), there is no other diagnosis except PA to explain these findings—in this UNIQUE setting confirmatory testing is not needed.
Confirmatory Testing:

In the patient with undetectable PRA, and when the 24-hr urinary Na⁺ is >200 mEq, a 24-hr urinary aldosterone of >12 μg (> 33 nmol/d) confirms PA.
Primary Aldosteronism—Step 4

Subtype Testing:
- Unilateral adx in pts with APA or unilateral adrenal hyperplasia (primary adrenal hyperplasia [PAH]) results in normalization of $\downarrow K^+$ in all; hypertension is improved in all and is cured in approx 30% to 60%

- In IHA, unilat or bilat adx seldom corrects the hypertension. IHA & glucocorticoid remediable aldosteronism (GRA) should be treated medically

- $\therefore$ for those pts that want to pursue a surgical cure, the accurate distinction between the subtypes of 1° aldo is a critical step
Tip #3: 72% of patients with PA are normokalemic!!!!
AVS Summary

- 203 patients; 1990 -- 2003
- 96% success rate
- Based on CT:
  - 46 patients (24%) would have been bypassed for surgery
  - 42 pts (22%) would have had unnecessary surgery

Accuracy of CT = 53%!
Step 4: Subtype Testing

Adrenal CT scan

- Normal, micronodularity, bilateral masses, or atypical unilateral mass (eg >2 cm)
  - Surgery not desired

- Unilateral hypodense nodule >1 cm and <2 cm
  - Surgery desired
  - >40 y: consider AVS
  - <40 y: consider AVS

AVS

- No lateralization with AVS
  - IHA or GRA: Pharmacologic therapy
  - APA or PAH: Unilateral laparoscopic adrenalectomy

- Lateralization with AVS
  - Surgery not desired
  - Pharmacologic therapy

Primary Aldosteronism—Step 5

- **Treatment:**
  - The Rx goal is to prevent the morbidity & mortality associated with ↑BP, ↓K⁺, & CV damage.
  - Normalization of BP should not be the only goal in managing the patient with PA. Excess aldo is assoc with ↑CV toxicity.
  - ∴ normalization of circulating aldo or aldo receptor blockade should be part of the management plan for all pts with PA.
Subtype-Directed Treatment for 1° Aldo

IHA

CV Toxicity

APA

Other Antihypertensive Agents

• Amiloride
• HCTZ
• ACE-I
• ARB
• CCB

Mineralocorticoid-Receptor Antagonist (MR-A)

Selective MR-A: Eplerenone

Nonselective MR-A: Spironolactone

Laparoscopic Adrenalectomy

CV Toxicity

APA

IHA
Primary Aldosteronism—Step 1

When we test for PA:

- Pts with ↑BP & ↓K⁺—regardless of presumed cause
- Rx-resistant hypertension (3 antihypertensive drugs & poor control)
- Severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic)
- Hypertension & an incidental adrenal mass
- Onset of hypertension at a young age
- Whenever performing a secondary hypertension evaluation (eg, when testing for renovascular disease or pheochromocytoma)
Primary Aldosteronism—Step 2

Case Detection Testing:

- Morning (8-10 a.m.) ambulatory paired plasma aldosterone concentration (PAC) & plasma renin activity (PRA)
- May be performed while the pt is taking BP meds & without posture stimulation
- $\downarrow K^+$ reduces the secretion of aldo & it is optimal to restore serum $K^+$ to nl before performing dx tests
- Mineralocorticoid receptor (MR) antagonists (eg, spironolactone & eplerenone), & high-dose (> 5 mg/d) amiloride are the only meds that absolutely interfere & should be D/C at least 6 wks before testing
Primary Aldosteronism—Step 3
Confirmatory Testing:

- An \( \uparrow \) ed PAC/PRA ratio is not diagnostic by itself, & PA must be confirmed by demonstrating inappropriate aldosterone secretion.
- As long as PRA is suppressed, most antihypertensive drugs can be used during this step.
- We perform Aldo suppression testing with orally admin NaCl & measurement of urinary aldosterone and Na\(^+\).
Primary Aldosteronism—Step 4

Subtype Testing:

- We start with adrenal-dedicated abdomen CT.
- When a solitary, hypodense, and unilateral macroadenoma (>1 cm & <2 cm) & normal contralateral adrenal morphology are found on CT in a young patient (<40 yrs), unilateral laparoscopic adrenalectomy is a reasonable treatment option.
- However, in many cases, CT may show normal-appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenomas (<1 cm), or bilateral macroadenomas—in these cases, if the patient wants to pursue the surgical option, additional testing is needed.
Primary Aldosteronism—Step 5

Treatment:

- The Rx goal is to prevent the morbidity & mortality associated with ↑BP, ↓K⁺, & CV damage.
- Normalization of BP should not be the only goal in managing the patient with PA. Excess aldo is assoc with ↑CV toxicity.
- Normalization of circulating aldo or aldo receptor blockade should be part of the management plan for all pts with PA.
Subtype-Directed Treatment for \(1^\circ\) Aldo

- **IHA**
  - CV Toxicity
  - Other Antihypertensive Agents
    - Amiloride
    - HCTZ
    - ACE-I
    - ARB
    - CCB
  - Mineralocorticoid-Receptor Antagonist (MR-A)
    - Selective MR-A: Eplerenone
    - Nonselective MR-A: Spironolactone
  - Laparoscopic Adrenalectomy

- **APA**
Learning Objectives

- To understand the spectrum of resistant hypertension
- To appreciate the importance of endocrine hypertension and obstructive sleep apnea as important etiologies of resistant hypertension
- To consider the importance of the adrenal gland in causing the majority of endocrine hypertension problems
Future Discussion

The role of renal denervation!