

## Endocrine Hypertension

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### Disclosure

**Michael McDermott** has no conflict of interest or relationships to disclose in relation to this educational activity.

### Learning Objectives

- Explain the evaluation and management of primary aldosteronism.
- Discuss the evaluation and management of pheochromocytomas and paragangliomas.
- Review the clinical features and evaluation of Cushing's syndrome and Acromegaly.

### Case

A 31 year old man has hypertension which remains elevated on 3 antihypertensive medications. No family history of hypertension.

**Meds:** Ramipril 10 mg, Amlodipine 10 mg, Metoprolol XL 50 mg

**Exam:** BP 158/92 P 68 Ht 6'1" Wt 235 lb.

Physical examination is normal otherwise.

**Labs:** Na 142 mEq/L, K 3.1 mEq/L, Creatinine 0.9 mg/dl

**You decide to evaluate for causes of secondary hypertension.**

**What initial evaluation would have the highest yield?**

1. Plasma metanephrines
2. Plasma aldosterone and plasma renin activity
3. 24 hour urine cortisol excretion
4. Renal artery doppler ultrasound

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Plasma Aldosterone 38 ng/dl (normal: 1-21)

Plasma Renin Activity < 0.6 ng/ml/hr (normal: 0.6-4.3)

**What is your interpretation of these results?**

1. Diagnostic of primary aldosteronism
2. Possible false positive due to ACE inhibitor
3. Possible false positive due to calcium channel blocker
4. Possible false positive due to beta blocker

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**What do you recommend now?**

1. Stop current medications. Repeat aldosterone and renin levels
2. Confirmatory testing: measure aldosterone after saline infusion
3. Abdominal CT scan
4. Adrenal vein sampling

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**Abdominal CT:** 2.6 cm lipid rich left adrenal adenoma

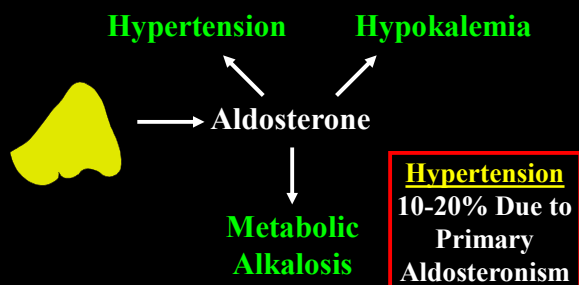
**What do you recommend now?**

1. Adrenal vein sampling for aldosterone and cortisol
2. CT guided biopsy of left adrenal mass
3. Long-term treatment with an aldosterone receptor antagonist
4. Surgery to remove left adrenal adenoma

**Primary Aldosteronism**

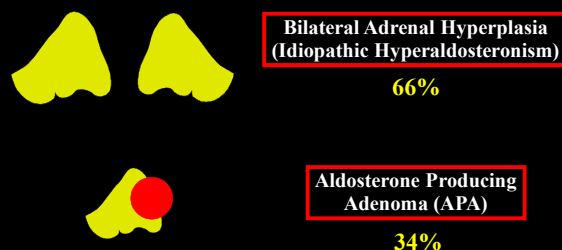
Primary Aldosteronism

Pathophysiology



Primary Aldosteronism

Main Subtypes



Primary Aldosteronism

Which Hypertensive People to Screen

- BP > 150/100 Sustained
- BP > 140/90 on 3 BP Drugs
- BP controlled on  $\geq$  4 BP Drugs
- Hypokalemia (spontaneous or diuretic induced)
- All hypertensive patients –recommend by many
- Adrenal incidentaloma

Young WF. J Intern Med 2019; 285:126-148.  
Vaidya A. J Clin Endocrinol Metab 2020; 105:3771-83.  
Mehdi A. Cleve Clin J Med 2021; 88(4):221-7.

Primary Aldosteronism

Screening Tests

Random Sample

Plasma Aldosterone (PA)

Plasma Renin Activity (PRA)

Positive Screen

- PA > 5 ng/dl and PRA < 1 ng/ml/hr
- PA/PRA Ratio > 20

**For Direct Renin Assay**  
PRA = Direct Renin / 8

**Primary Aldosteronism**  
False Positive Tests do not Occur

Significant **↑ Aldosterone** and **↓ Renin**

Nothing Else Causes This  
Positive Results = **Positive Results**

You Can Test Any Patient Any Time  
Without Stopping Medications

Young WF. J Intern Med 2019; 285:126-148.  
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Mehdi A. Cleve Clin J Med 2021; 88(4):221-7.

**Primary Aldosteronism**  
False Negative Tests – Medications

↓ Aldosterone/Renin Ratio

| Medication         | Aldosterone | Renin | ARR |
|--------------------|-------------|-------|-----|
| ACE Inhibitor      | ↓           | ↑↑    | ↓   |
| AR Blocker         | ↓           | ↑↑    | ↓   |
| Ca Channel Blocker | →↓          | ↑     | ↓   |
| K Wasting Diuretic | →↑          | ↑↑    | ↓   |
| K Sparing Diuretic | ↑           | ↑↑    | ↓   |

**Primary Aldosteronism**  
Medications That Can Be Used During Testing

- Hydralazine
- Prazosin
- Doxazosin
- Terazosin
- Verapamil Slow Release

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**Primary Aldosteronism**  
False Negative Tests – Other Conditions

↓ Aldosterone/Renin Ratio

| Condition        | Aldosterone | Renin | ARR |
|------------------|-------------|-------|-----|
| Hypokalemia      | ↓           | →↑    | ↓   |
| Pregnancy        | ↑           | ↑↑    | ↓   |
| Renovascular HTN | ↑           | ↑↑    | ↓   |
| Malignant HTN    | ↑           | ↑↑    | ↓   |

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**Primary Aldosteronism**  
Confirmatory Testing

**Sodium Loading Tests**

Oral Salt Load (High NaCl Diet x 3 Days)  
IV Saline Infusion (2 L NS over 4 Hours)

**Positive Diagnosis**

**Oral Salt Load**

- 24 hr Urine Aldosterone (3<sup>rd</sup> day) > 12 ug

**IV Saline Infusion**

- Plasma Aldosterone > 10 ng/dl

Medication Restrictions:  
Spironolactone

**Primary Aldosteronism**  
Confirmatory Testing – When Not Needed

All 3 Present

- Spontaneous Hypokalemia
- Plasma Renin Suppressed
- Plasma Aldosterone > 20 ng/dl

Nothing Else Causes This

Young WF. J Intern Med 2019; 285:126-148.  
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### Primary Aldosteronism Subtype Classification

**Only If Surgery is Being Considered**

- CT Adrenal Glands – All Patients
- Adrenal Vein Sampling – Many Patients

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### Primary Aldosteronism Adrenal Vein Sampling

IVC  
Femoral Vein

**Calculations**  
Aldosterone Side to Side Gradient  
Aldosterone to Cortisol Gradient

### Primary Aldosteronism Adrenal Vein Sampling – When Not Needed?

**All 3 Present**

- Age: < 35 Years
- Plasma Aldosterone: Markedly Elevated
- CT Scan: Unilateral Cortical Adenoma

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### Primary Aldosteronism Evaluation and Management

PA > 5 ng/dl and ARR > 20

Needed → Confirmatory Testing

Not If → Spontaneous ↓ K, Suppressed Renin, Aldosterone > 20 ng/dl

CT Adrenal

Needed → Adrenal Vein Sampling

Not If → Age < 35, PA Markedly ↑, Cortical Adenoma

Bilateral → Medical Therapy  
Unilateral → Adrenalectomy

Adapted from: Funder J, J Clin Endocrinol Metab. 2016;101(5):1889-1916

### Primary Aldosteronism Bilateral Adrenal Hyperplasia - Medical Treatment

**Mineralocorticoid Receptor Antagonists (MRA) Plus Additional BP Meds as Needed**

ACE-I  
ARB  
CCB

↑ Aldosterone

**MRA: Spironolactone +/- Eplerenone**

**MRA Doses Sufficient to Maintain K in Upper 1/2 Normal Range Without K Supplements**

### Primary Aldosteronism Aldosterone Producing Adenoma – Surgery (+ Pre-op)

**Pre-Operative: MRA Then Adrenalectomy**

↑ Aldosterone

**MRA: Spironolactone +/- Eplerenone**

**MRA Doses Sufficient to Maintain K in Upper 1/2 Normal Range Without K Supplements**

**Case**

A 21 year old man present with recent onset of hypertension and headaches. He also acknowledges having intermittent palpitations and episodes of profuse sweating. He informs you that his sister had similar symptoms and a rare adrenal tumor was found.

**Medications:** None

**Exam:** BP 178/98 P 88 Ht 5'8" Wt 171 lb

Physical examination is normal otherwise.

You decide to evaluate for causes of secondary hypertension.

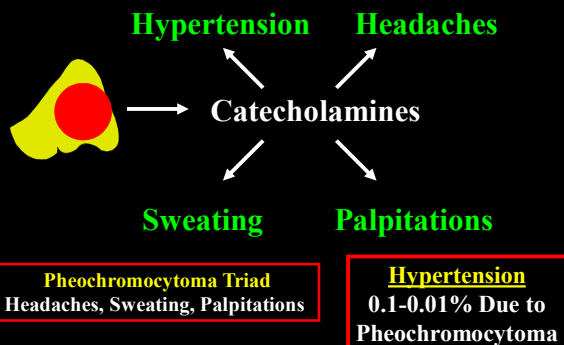
What initial tests would have the highest yield?

1. Plasma metanephrines
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**Pheochromocytoma  
Paraganglioma**

**Pheochromocytoma / Paraganglioma**

**Pathophysiology**



**Pheochromocytoma / Paraganglioma**

**General**

Prevalence is Low

1/1,000-10,000 of Hypertensive Patients

Frequently Sought, but Rarely Present

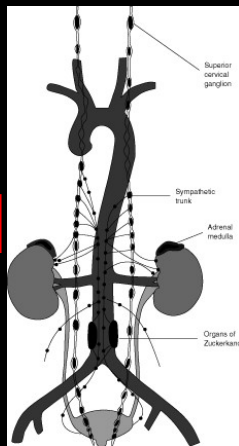
1/200 of Those Investigated

Pheochromocytoma Not Difficult to Find

Majority > 4 cm, Round, HU > 20

Paraganglioma May Take More Investigation

**Pheochromocytoma**  
Adrenal Medulla



**Paraganglioma**  
Sympathetic  
Ganglia

Petri BJ. Br J Surg  
2009; 96:1381-92

**Pheochromocytoma / Paraganglioma**

Familial Syndromes: 30-40% are Inherited

- Multiple Endocrine Neoplasia Type 2A/2B
- Von Hippel Lindau Syndrome
- Neurofibromatosis Type 1
- Succinate Dehydrogenase Mutations

**Genetic Testing is Indicated in All Patients**

### Pheochromocytoma / Paraganglioma

**Malignancy Rate: 15-25%**

- Malignant Diagnosis Cannot be Made by Histology
- Diagnosis Only Made When Metastases Appear
- Some Mutations Predictive (SDH B)
- Latency May Be Up To 20 Years

Hamidi O. J Clin Endocrinol Metab 2017; 102:3296-3305

### Pheochromocytoma / Paraganglioma

**Which Hypertensive Patients Should Be Screened?**

- Headaches, Sweating, Palpitations
- Severe or Resistant Hypertension
- Familial Syndrome
- Adrenal Incidentaloma with HU > 10

### Pheochromocytoma / Paraganglioma

**Diagnostic Tests**

| Test                      | Sporadic                  | Hereditary                |
|---------------------------|---------------------------|---------------------------|
|                           | Sensitivity / Specificity | Sensitivity / Specificity |
| Plasma Metanephrine       | 99% / 82%                 | 97% / 96%                 |
| Urine Metanephrine (24H)  | 97% / 45%                 | 96% / 82%                 |
| Plasma Catecholamine      | 92% / 72%                 | 69% / 89%                 |
| Urine Catecholamine (24H) | 91% / 75%                 | 79% / 96%                 |
| VMA (24H)                 | 77% / 86%                 | 46% / 99%                 |

**Best Tests**

- Plasma Metanephrine
- Urine Metanephrine (24H)

Adapted from: Lenders JW, JAMA 2002;287:1427-34

### Pheochromocytoma / Paraganglioma

**Diagnostic Tests – True Positives**

**Plasma Metanephrine**

2-4 Fold > Ref Range

**Urine Metanephrine**

3-5 Fold > Ref Range

### Pheochromocytoma / Paraganglioma

**Diagnostic Tests – False Positives**

**Mild Elevations**

**Epecially Common**

- Mildly ↑ Norepinephrine
- Mildly ↑ Normetanephrine

### Pheochromocytoma / Paraganglioma

**False Positive Tests – Medications**

| Drug             | Plasma |    | Urine |    |
|------------------|--------|----|-------|----|
|                  | NMN    | MN | NMN   | MN |
| MAO Inhibitors   | ++     | ++ | ++    | ++ |
| Cocaine          | ++     | +  | ++    | +  |
| Acetaminophen    | ++     | -- | ++    | -- |
| Methyldopa       | ++     | -- | ++    | -- |
| Phenoxybenzamine | ++     | -- | ++    | -- |
| Sulfasalazine    | ++     | -- | ++    | -- |
| Tricyclics       | ++     | -- | ++    | -- |
| Levodopa         | +      | +  | ++    | +  |
| Sympathomimetics | +      | +  | +     | +  |
| Bupirone         | --     | ++ | --    | ++ |
| Labetalol        | --     | -- | ++    | ++ |
| Sotalol          | --     | -- | ++    | ++ |

## Pheochromocytoma / Paraganglioma False Positive Tests

### Other Medications and Situations That May Cause False Positives

- Serotonin Norepinephrine Reuptake Inhibitors
- Selective Serotonin Reuptake Inhibitors
- Ethanol Abuse and Withdrawal
- Clonidine Withdrawal

## Adrenal Masses CT Imaging

### Benign Conditions

|                  | NCCT        | CCT           | DCECT       | RWP   |
|------------------|-------------|---------------|-------------|-------|
| Adenoma          | < 10 HU     | Enhances      | < 30 HU     | > 50% |
| Pheochromocytoma | > 20 HU     | Indeterminate | > 30 HU     | < 50% |
| Myelolipoma      | Visible Fat | Visible Fat   | Visible Fat |       |

NCCT = Non Contrast CT – HU  
CCT = Contrast CT  
DCECT = Delayed Contrast Enhanced CT  
RWP = Relative Washout Percentage

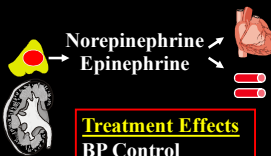
## Pheochromocytoma / Paraganglioma Treatment

### Pre-Operative

Alpha Blocker (1<sup>st</sup>)  
Beta Blocker (2<sup>nd</sup>) or  
Calcium Channel Blocker

Then

### Adrenalectomy



### Treatment Effects

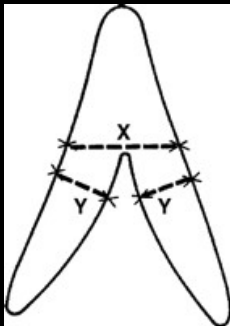
BP Control  
Volume Expansion  
Vasodilation  
Rate Control



### Paraganglioma Surgery

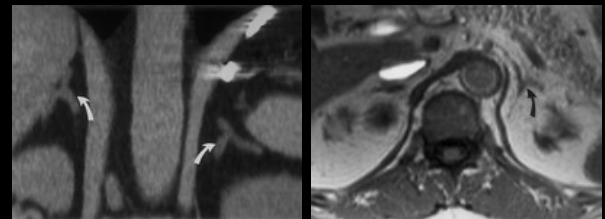
## Adrenal Imaging

## Normal Adrenal Glands



- Normal body size (X): 5-8 mm
- Normal limb size (Y): 2-3 mm
- Total gland width: 2-3 cm

## Normal Adrenal Glands



### Adrenal Imaging

#### Lipid Content

#### CT Scan (Non-Contrast) – Hounsfield Units (HU)

Low HU: High Lipid Content = Benign

- Non-Functioning Adenoma
- Cortisol Producing Adenoma
- Aldosterone Producing Adenoma

High HU: Low Lipid Content = Benign or Malignant

- Lipid Poor Adenoma
- Pheochromocytoma
- Adrenal Carcinoma
- Metastatic Carcinoma

**MRI: Signal Drop Out = Benign**

### Adrenal Imaging

#### Evaluation

Low HU: High Lipid Content = Benign

- Overnight 1 mg Dexamethasone Suppression Test
- Plasma Aldosterone and Renin

High Low Lipid: High HU = Benign or Malignant

- Overnight 1 mg Dexamethasone Suppression Test
- Plasma Aldosterone and Renin
- Plasma Metanephrines
- Examine Image for Features of Carcinoma

**MRI: Signal Drop Out = Benign (same as above)**

### Case

A 42 year old woman complains of weight gain, fatigue, muscle weakness, and abnormal menses.

**Medications:** None

**Exam:** BP 140/90 P 76 Ht 5'4" Wt 155 lb.

Central obesity, facial plethora and rounding, fullness of supraclavicular fat pads, and purple abdominal striae.

**Labs:** K 3.6 mEq/L, Na 142 mEq/L, Creatinine 0.8 mg/dl

You decide to evaluate for causes of secondary hypertension.

What initial evaluation would have the highest yield?

1. Plasma ACTH
2. AM serum cortisol
3. 24 hour urine cortisol excretion
4. AM serum cortisol and Plasma ACTH

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**Labs:** K 3.6 mEq/L, Na 142 mEq/L, Creatinine 0.8 mg/dl

Urine cortisol 354 ug/24 hr (nl, 10-60)

What do you recommend now?

1. Plasma ACTH
2. Midnight salivary cortisol
3. MRI pituitary
4. CT abdomen

### Case 4

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Urine cortisol 354 ug/24 hr (nl, 10-60)

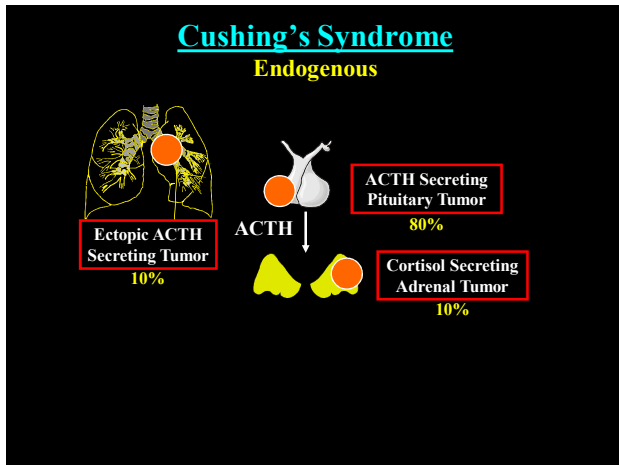
Plasma ACTH 45 pg/ml (normal: 10-85)

What is the most likely underlying disorder?

1. Ectopic ACTH syndrome
2. Iatrogenic Cushing's syndrome
3. Pituitary ACTH secreting tumor
4. Cortisol producing adrenal adenoma

**Cushing's  
Syndrome**





### Cushing's Syndrome

Screening

| Screening Tests             | Positive Result                |
|-----------------------------|--------------------------------|
| • 24 Hour Urine Cortisol    | Elevated ( $\geq 2 \times$ nl) |
| • Bedtime Salivary Cortisol | Elevated                       |
| • 1 mg DST*                 | Cortisol $> 1.8$ ug/dl         |

\*DST = Dexamethasone Suppression Test  
**Take:** 1 mg Dex at 10-11 PM  
**Measure:** serum cortisol next morning at 8:00 AM

Nieman L, J Clin Endocrinol Metab 2008; 93:1526-40  
Endocrine Society Clinical Practice Guidelines

### Cushing's Syndrome

Differential Diagnosis

| Condition                        | ACTH (Plasma)  | DST (8 mg)     |
|----------------------------------|----------------|----------------|
| Pituitary ACTH Secreting Tumor   | Normal/High    | Suppression    |
| Ectopic ACTH Secreting Tumor     | High/Very High | No Suppression |
| Adrenal Cortisol Secreting Tumor | Low            | No Suppression |

Nieman L, J Clin Endocrinol Metab 2008; 93:1526-40  
Endocrine Society Clinical Practice Guidelines

# Acromegaly

## Acromegaly Clinical Features



## Acromegaly Clinical Features



## Acromegaly Clinical Features



## Acromegaly Clinical Features

- **Hypertension:** Resistant to Therapy
- **CVD/CHF Mortality:** Very High

Acromegaly. Clinical Practice Guidelines – Endocrine Society  
Katznelson L. J Clin Endocrinol Metab 2014; 99: 3933-51

## Acromegaly Diagnostic Testing

- **IGF-1:** Elevated - Best Overall Test
- **GH During OGTT:** Failure to Suppress GH

Acromegaly. Clinical Practice Guidelines – Endocrine Society  
Katznelson L. J Clin Endocrinol Metab 2014; 99: 3933-51

**Hyperthyroidism**

**Hypothyroidism**

Thyroid Disorders  
Hypertension

**Hyperthyroidism**

- Systolic Hypertension

**Hypothyroidism**

- Diastolic Hypertension

McDermott MT. Ann Intern Med 2009; 151 (11):ITC61  
McDermott MT. Ann Intern Med 2012; 157:ITC-1-14.

Thyroid Function Testing

Screening / Case Finding

TSH

↓ TSH

Hyperthyroidism

Free T4  
Total T3

↑ TSH

Hypothyroidism

Free T4

McDermott MT. Ann Intern Med 2009; 151 (11):ITC61  
McDermott MT. Ann Intern Med 2012; 157:ITC-1-14.

**Thank You**

