2nd Thoughts?
Evaluation and Management of Secondary Hypertension

Daniel S. Richey, D.O.
Dallas Nephrology Associates
richeyd@dnhph.com

Disclosures
• None

Objectives
• Identify the most common etiologies based on patient age
• Understand the basic pathophysiology of renovascular hypertension and hyperaldosteronism
• Develop an evidence based strategy for diagnosis of the various etiologies of secondary hypertension
• Develop an evidence based strategy for management of the various etiologies of secondary hypertension

Hypertension
• Prevalence of hypertension among U.S. adults aged 18 and over was 29.1% (NHANES 2011–2012)
  — 75 million
• Prevalence of hypertension found to be 3.6% and the prevalence of pre-hypertension to be 3.4% in children and adolescents between the ages of 3 years and 18 years


Secondary Hypertension
• Definition
  — Secondary hypertension is a type of hypertension attributed to an underlying disease which may be correctable.
• Up to 10% of hypertensive patients have a secondary cause
• Clues
  — Age of onset < 30 or > 55
  — Documented, abrupt onset of HTN
  — Rapid worsening of previously well controlled BP
  — HTN refractory to an appropriate 3 drug regimen
  — Disease specific clues

Incidence
• Renal Parenchymal Disease (2-5%)
• Renovascular Hypertension (1%)
• Primary Hyperaldosteronism (5%)
• Obstructive Sleep Apnea
• Pheochromocytoma
• Cushings Syndrome
• Aortic Coarctation
• Thyroid Disorders
Secondary Hypertension

<table>
<thead>
<tr>
<th>Age</th>
<th>% of Hypertension with an underlying cause</th>
<th>Common etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (birth-12 years)</td>
<td>70-85%</td>
<td>Renal Parenchymal Disease</td>
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<tr>
<td></td>
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<td>Coarctation of the Aorta</td>
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<tr>
<td>Adolescents (12-18 years)</td>
<td>10-15%</td>
<td>Renal Parenchymal Disease</td>
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<td>Coarctation of the Aorta</td>
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<td>Young Adults (19-39 years)</td>
<td>5%</td>
<td>Renal Parenchymal Disease</td>
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<td>Thyroid Disorders</td>
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<tr>
<td></td>
<td></td>
<td>Fibromuscular Dysplasia</td>
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<tr>
<td>Middle Age Adults (40-64 years)</td>
<td>8-12%</td>
<td>Aldosteronism</td>
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<td></td>
<td></td>
<td>Thyroid Disorders</td>
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<tr>
<td></td>
<td></td>
<td>Obstructive Sleep Apnea</td>
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<tr>
<td></td>
<td></td>
<td>Cushings Syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Pheochromocytoma</td>
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<tr>
<td>Older Adults (65 years and older)</td>
<td>17%</td>
<td>Renal Parenchymal Disease</td>
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<tr>
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<td>Renal Artery Stenosis</td>
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</tbody>
</table>

Renal Parenchymal Disease

- Etiologies
  - DM
  - Glomerular Disease
  - Interstitial Disease
- HTN is both cause and consequence of renal disease
- Multifactorial Etiology
  - Decreased autoregulation
  - Glomerular Hypertension  Sclerosis
  - Activation of RAS
  - Activation of Renal Sympathetics
  - Dysregulated Vasodilatation
- Often your best clue to renal disease in an asymptomatic patient

Renovascular Hypertension

<table>
<thead>
<tr>
<th>Classification of Renal Artery Disease</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>60-80%</td>
</tr>
<tr>
<td>Fibromuscular Dysplasia</td>
<td></td>
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<tr>
<td>- Medial (30%)</td>
<td></td>
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<tr>
<td>- Perimedial (5%)</td>
<td></td>
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<tr>
<td>- Intimal (5%)</td>
<td></td>
</tr>
<tr>
<td>- Adventitial (&lt;1%)</td>
<td></td>
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<tr>
<td>- 20-40%</td>
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</tbody>
</table>

Renovascular Hypertension is secondary elevation of blood pressure produced by any condition that interferes with arterial circulation to the kidney leading to renal ischemia.
Renovascular Hypertension

- Fibromuscular Dysplasia
  - Female
  - Age 15-40
  - Total Occlusion rare
  - Ischemic atrophy is rare
  - More responsive to percutaneous intervention
  - Good cure rate of HTN
  - Subtypes
    - Medial / Perimedial / Intimal / Adventitial

Fibromuscular Dysplasia

- Atherosclerotic Renal Artery Disease
  - Male and female
  - Age > 50
  - Total Occlusion common
  - Less responsive to percutaneous intervention
  - Poor cure rate of HTN

Decreased Renal Perfusion
Increased Renin
Increased Angiotensin II
Increased Aldosterone
Na Retention
Peripheral Vasoconstriction
Na Excretion


Renovascular Hypertension

- **Diagnosis of RVHT**
  - Demonstrate an anatomical stenosis by an imaging procedure
  - Prove hemodynamic significance of stenosis
  - Cure hypertension
    - Revascularization
    - Percutaneous angioplasty
    - Nephrectomy

- **Clinical Clues to Renovascular Hypertension**
  - Age of onset < 30 or > 55
  - Documented, abrupt onset of HTN
  - Rapid worsening of previously well controlled BP
  - HTN refractory to an appropriate 3 drug regimen
  - Abdominal Bruit
  - Flash Pulmonary Edema
  - Acute kidney injury after starting RAS blocking agent

- **Imaging**
  - Duplex Ultrasonography
    - Easy
    - Operator dependent
  - CT Angiography / MR Angiography
    - Good anatomical Information
    - Contrast Exposure
    - No data on hemodynamic significance of lesion
  - Renal Arteriography
    - Gold Standard
  - Captopril Renography
    - Provides evidence as to the hemodynamic significance of a stenotic lesion
    - Predicts reversibility following intervention

- **Treatment**
  - To stent or not to stent
  - Trials
    - ASTRAL (Angioplasty and Stenting for Renal Artery Lesion)
      - 806 total patients
      - At 1 year followup there were no changes in BP, renal function or cardiovascular events.
    - CORAL (Coronary Outcomes with Renal Atherosclerotic Lesions)
      - 947 total patients
      - Average 43 month followup for adverse cardiovascular/renal events

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*There is just this embedded belief that fixing an artery is a good thing*  
Dr. Eric Topol
Kaplan–Meier Curves for the Primary Outcome.

Renovascular Hypertension

- Predictors of response to revascularization
  - Kidney size > 9 cm
  - Perfusion preserved on Renal Flow Scan
  - Young Age
  - Recent onset of hypertension
  - Recent documented decrease in GFR
  - “Flash” pulmonary edema
    - Bilateral disease or solitary kidney

Primary Hyperaldosteronism

- Autonomous hypersecretion of aldosterone
  - Idiopathic Hyperaldosteronism (IHA)
  - Aldosterone Producing Adenoma (APA)
  - Adrenal Hyperplasia
    - Unilateral
    - Bilateral
- Most common at > 30 years of age
- Typical presentation
  - Refractory Hypertension
  - Hypokalemic Metabolic Alkalosis

Incidence of Primary Hyperaldosteronism

From: A Prospective Study of the Prevalence of Primary Aldosteronism in 1,125 Hypertensive Patients
Primary Hyperaldosteronism

• Diagnosis
  – Hypokalemia
    • Easily provoked by diuretics
    • 24 hour urine for K wasting?
  – 24 hour urine Aldosterone Excretion
    • Level > 14 is considered elevated
  – Plasma Aldosterone : Renin Ratio (ARR)
    • Based on the principle that suppressed renin and elevated aldosterone is pathophysiologic

Primary Hyperaldosteronism

• Aldosterone : Renin Ratio Rules
  – Measure plasma Aldosterone (ng/dL)
  – Measure plasma Renin Activity (ng/dL/hr)
    • Not Direct Renin Concentration
  – Serum Aldosterone must be > 15 ng/dL to consider
  – Patient not on ACE/ARB/DRI
  – Most literature suggests ARR in the range of 20-40 is highly suggestive of primary hyperaldosteronism

Primary Hyperaldosteronism

• Confirmatory Testing
  – Oral Sodium loading
  – Saline Infusion Test
  – Fludrocortisone Suppression Test
  – Captopril Suppression Test

Primary Hyperaldosteronism

Plasma Aldosterone is measured as a baseline, then following some combination of Na loading and/or medication dosing. Most literature suggests Aldosterone should be suppressed to < 10 ng/dL

Primary Hyperaldosteronism

• Imaging vs AVS
  – Retrospectively reviewed the medical records of patients who underwent AVS for PH during a 4-year period (2000-2004).
    • Mean Age 52 years
    • Mean adenoma size 1.5 cm
  – Overall, only 22 (55%) of 40 patients had concordance between CT and AVS

Primary Aldosteronism

• Imaging
  – Cases in which APA is highly likely
    • patients < 40 years of age with marked primary aldosteronism
    • a well-defined, hypodense adrenal mass (> 1 cm on CT scan)
    • AVS can be bypassed and the patient can undergo unilateral laparoscopic adrenalectomy.


Cushing's Syndrome

- Cortisol
  - Leads to essentially the same clinical findings as hyperaldosteronism
  - Only occurs in setting of glucocorticoid overproduction (Cushing's / ectopic ACTH) or interference with cortisol → cortisone conversion (Licorice)
- Diagnosis
  - 24 urine free cortisol
  - Dexamethasone suppression
  - ACTH level
- Treatment
  - Mineralocorticoid Blockade

Pheochromocytoma

- Adrenal chromaffin cell tumor resulting in excess secretion of catecholamines
  - Adrenal (85%)
  - Extra-adrenal (15%)
- Patients suffer “paroxysmal” spikes in blood pressure
  - Symptoms tend to be episodic as well

Pheochromocytoma

- Diagnosis
  - Biochemical confirmation should occur first
    - Clonidine suppression test
      - Differentiation between Pheo and sympathetic overactivation
      - Normetanephrine value at baseline and 3 hours after giving Clonidine
    - Glucagon Stimulation
      - Stimulates release of catecholamines
    - Imaging
      - Only after biochemical diagnosis
      - CT/MRI
      - 18F-MIBG w/wo SPECT
    - Bilateral Disease
      - Von Hippel Lindau
      - Multiple Endocrine Neoplasia type II
      - Neurofibromatosis
- Plasmatic Metanephrines
  - 99
  - 92
  - Specificity
  - 89
  - 85
  - Plasma Catecholamines
  - 83
  - 88
  - 53
  - Urinary Catecholamines
  - 76
  - 94
  - 76
  - Urinary Metanephrines
  - 63
  - 94
  - 94
  - Urinary Vanillylmandelic Acid
  - Plasma concentrations of normetanephrine or metanephrine (more than 4-6 and 2-5 fold above the upper reference limits) is associated with close to 100% probability of the tumor

Pheochromocytoma

• Treatment
  – Resection
    • Before the introduction of adrenergic blockade surgical mortality rates ranged from 24% to 50%
  – Sympathetic Blockade
    • Phenoxybenzamine
      – Start 10-14 days before surgery
    • Beta Blockade
  – alpha-Methyl-paratyrosine
    • Decreases catecholamine synthesis

Obstructive Sleep Apnea

• Published reports estimate 50% of patients with OSA have HTN
• Mechanism
  – Chemoreceptors
    • Sense p02
    • Decreased levels leads to increase sympathetic outflow
• Clinical
  – Daytime somnolence
  – Headaches
  – snoring
• Diagnosis
  – Sleep study
• Treatment
  – CPAP

Figure 2. Changes in mean (MAP), systolic, and diastolic blood pressure with effective (closed bars) and subtherapeutic (open bars) CPAP. *Significant difference.

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Aortic Coarctation

• Congenital defect
  – Male > Female
• Clinical
  – Differential BP in upper extremities vs lower extremities
    • Radiosymembral Delay
    • Diminished/absent femoral pulse
  – May have differential BP in arms if defect is proximal to the left subclavian artery
  – Often asymptomatic
• Surgical Treatment
  – long term survival better if corrected early
  – If uncorrected 67% will develop LV failure by age 40 and 75% will die by age 50

Aortic Coarctation

• Thyroid Disorders
  – Hyperthyroid⇒Systolic Hypertension
  – Hypothyroid⇒Diastolic Hypertension
• Hyperparathyroidism and hypercalcemia
  – Hypertension is observed in about 20% of patients with primary hyperparathyroidism
• Acromegaly
  – Hypertension is noted in about 40% of patients with acromegaly
Drugs

- Oral Contraceptives
- Erythropoetin
- NSAIDs and Cox-2 inhibitors
- Cocaine and Amphetamines
- Weight loss supplements
  - Rx and OTC
- Anti-Depressants (MAOIs, SSRI, TC)
- VEGF inhibitors (Bevacizumab)
- Calcineurin Inhibitors (Cyclosporine, Tacrolimus)
- Ethanol

Drugs

- Caffeine
  - Meta-analysis of 16 studies
  - Results
    - A significant rise of 2.04 mmHg (95% confidence interval [CI]), 1.10-2.99 in systolic BP and 0.73 mmHg (95% CI, 0.14-1.31) in diastolic BP was found after pooling of coffee and caffeine trials.
    - Coffee trials (median intake: 725 ml/day) and caffeine trials (median dose: 410 mg/day) were analysed separately.
      - BP elevations appeared to be larger for caffeine [systolic: 4.16 mmHg; diastolic: 2.41 mmHg] than for coffee (systolic: 1.22 mmHg and diastolic: 0.49 mmHg).

Question 1

- What is the most common form of Secondary Hypertension?
  A) Primary Hyperaldosteronism
  B) Renovascular Hypertension
  C) Renal Parenchymal Hypertension
  D) Obstructive Sleep Apnea

Question 2

- You see a 65 year old Caucasian male with a past medical history of hypertension and coronary artery disease for initial evaluation. He notes his blood pressure had been previously well controlled on Metoprolol and Hydrochlorothiazide. He says over the last couple of months his pressures have been increasing. He underwent a Doppler ultrasound at a recent ER visit which showed evidence of renal artery stenosis on the left. He was told he may need a stent placed.
  What is the best test to differentiate renovascular hypertension (RVHT) from anatomic renal artery stenosis (RAS)?
  A) Computed Tomography Angiography
  B) Magnetic Resonance Angiography
  C) Renal Arteriography
  D) Captopril Renography

Question 3

- Which single test has the highest sensitivity for establishing a biochemical diagnosis of a pheochromocytoma?
  A) Serum Metanephrines
  B) Plasma Catecholamines
  C) 24 hour urine Metanephrines
  D) 24 hour urine Catecholamines

Question 4

- You see a 42 year old female for evaluation of hypokalemia. She recently began taking a thiazide diuretic for some lower extremity edema and was found to have a K level of 2.7 mEq/L on repeat lab testing. She has no history of hypertension but her blood pressure in your office is noted to be 165/82. You prescribe K replacement and repeat labs 2 weeks later. The labs are as follows; Na-144, K-3.2, Cl-102, HCO3-34, BUN-12, Cr-0.8.
  What would be the first step towards confirming your diagnosis?
  A) 24 hour urine collection for K excretion
  B) Serum Aldosterone and Renin Activity levels
  C) Adrenal CT
  D) Adrenal Vein Sampling
You see a patient with a known history of hypertension who has been on the same 3 drug therapy for several years. Baseline creatinine is 1.3 mg/dL and has been stable. Abdominal ultrasound done during a recent ER visit showed evidence of left renal artery stenosis. This finding was confirmed with a CT angiogram. Most recent evidence suggests:

- Stent placement will likely improve BP control but not renal function
- Stent placement offers no advantages over intensive medical therapy
- Stent placement will likely improve renal function but not blood pressure
- Stent placement will improve both renal function and blood pressure