Resistant Hypertension

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Hypertension and Age

Causes of Hypertension

>90% will have Essential hypertension

≤10 will have a secondary cause of hypertension

9/10 will have:
- Primary renal disease
- Renovascular hypertension
- Obstructive sleep apnea
- Primary hyperaldosteronism

1/10 will have:
- Pheochromocytoma
- Cushing's syndrome, etc.
Resistant hypertension is defined as blood pressure that remains above goal despite confirmed administration of 3 antihypertensive medications at therapeutic dosages including a diuretic.

Poorly controlled hypertension is suboptimal BP control in treated patients and results from:
1. Noncompliance
2. Inadequate therapeutic regimen
3. Undiagnosed secondary hypertension
4. Resistant hypertension

Case 1

- 50 year-old male who was referred for evaluation resistant hypertension. He denied any complaints
- Medications: Amlodipine 10 mg/d, Coreg ER 40 mg/d, eplerenone 50/d, Lasix 40 bid, lisinopril 40 mg/d, Catapres TTS-2 one patch/wk, and minoxidil 5 mg bid
- P/E: BP 170/100, P 84/min, wt 202 Lbs. Otherwise, unremarkable
- Labs: Na 140, K 3.6, CO2 28, BUN 26, Cr 1.96, plasma renin 4.25, plasma aldo 24, pl metanephrine 0.22, plasma normetanephrine 0.74
- 24-hr.urine: Cr. 1.58 gm, prot 240 mg, Na 180 mmol
- Renal artery doppler: Unremarkable
- Abdominal CT: Normal adrenal glands

Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories

| Patients: | 4783 patients with hypertension, who participated in clinical studies (1989-2006) |
| Primary outcome: | Persistence with prescribed drug therapy and execution of their once a day drug dosing regimens |
| Results: | About half of patients had stopped taking their meds within one year |


Pseudo-Resistant Hypertension

- Poor BP measurement technique
- Noncompliance
- White-coat HTN
- Inadequate dosing or inappropriate combinations of antihypertensive medications
# Kidney Disease and Hypertension

- Kidney disease is the most common secondary cause of hypertension
- HTN is present in > 80% of patients with kidney disease
- Volume expansion and increased peripheral vasoconstriction are usually present
- HTN increases kidney injury further, increasing proteinuria and causing loss of GFR
- HTN is the second most common cause of ESRD
- More patients die than progress to ESRD

## Kidney Disease and HTN Pathogenesis

- Activation of RAAS
- Activation of SNS
- Renal ischemia, vasoconstriction
- Volume expansion
- Iatrogenic factors: EPO, Cyclosporin, Steroids

## Kidney Disease and HTN Treatment

- Activation of RAAS
  - Ace Inhibition, Angiotensin receptor blockade, Renin inhibitors
- Volume Expansion
  - Diuretics
- Activation of SNS volume Expansion
  - Sympathetic blockade (alpha and beta blockers)
- Iatrogenic factors- EPO, Cyclosporin, Steroids
  - Adjustment of dosages of these agents
Kidney Disease and HTN Treatment

- Lack of diuretic use has been shown in referral practices to be the primary cause of resistant hypertension
- Employing goal-oriented management can translate BP control results achieved in clinical trials into outpatient practice


Kidney Disease and HTN Treatment

- If BP not at goal after 2 to 4 weeks, reassess the following:
  - Medication compliance (are prescriptions filled on schedule?)
  - Regular use of "over-the-counter drugs" that can raise BP (decongestants, vasoconstrictive nose spray or eye drops, NSAIDS) or alcohol more than 2 drinks daily). Excessive salt intake (measure 24-hr urine Na (or Cl) if on NaHCO3
  - Sleep apnea
  - New major life stressors
  - If the above assessment is unrevealing, consider ambulatory blood pressure monitoring

Aldosterone Receptor Antagonists

- Have substantial antihypertensive, cardioprotective and antiproteinuric effects
- Improve blood pressure control in patients with poorly controlled hypertension
- In the ASCOT-BPLA study, the addition of spironolactone as a fourth-line antihypertensive drug for uncontrolled hypertension decreased the mean blood pressure by 22/10 mm Hg
- The potential risk of hyperkalemia should be monitored closely

Mean Difference in Blood pressure

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Systolic</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>5.0 (7.0 to 3.1)</td>
<td>3.7 (5.1 to 2.4)</td>
</tr>
<tr>
<td>Exercise</td>
<td>4.6 (7.1 to 2.0)</td>
<td>2.4 (4.0 to 0.7)</td>
</tr>
<tr>
<td>Sodium restriction</td>
<td>3.6 (4.6 to 2.5)</td>
<td>2.5 (3.3 to 1.8)</td>
</tr>
<tr>
<td>Alcohol restriction</td>
<td>3.8 (6.1 to 1.4)</td>
<td>3.2 (5.0 to 1.4)</td>
</tr>
<tr>
<td>K supplements</td>
<td>3.9 (8.6 to 0.8)</td>
<td>1.5 (6.2 to 3.1)</td>
</tr>
<tr>
<td>Mg supplements</td>
<td>1.3 (4.0 to 1.5)</td>
<td>2.2 (3.4 to 0.9)</td>
</tr>
<tr>
<td>Relaxation</td>
<td>4.0 (6.4 to 1.6)</td>
<td>3.1 (4.7 to 1.5)</td>
</tr>
<tr>
<td>Fish oil</td>
<td>2.3 (4.3 to 0.2)</td>
<td>2.2 (4.0 to 0.4)</td>
</tr>
<tr>
<td>Combined interventions</td>
<td>5.5 (8.8 to 2.3)</td>
<td>4.5 (6.9 to 2.0)</td>
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</table>
Case 2

- 32 year-old white female was referred for poorly controlled BP. Apart from intermittent headache and some fatigue, no other complaints
- Medications: Labetalol 400 mg bid, Procardia XL 60 mg/day, Diovan 160 mg/day, HCTZ 25 mg/day, and KCL 20 meq/day
- P/E: BP 160/90, P 66/min, wt 140 Lbs. Positive abdominal bruit. Otherwise, unremarkable
- Labs: Na 141, K 3.6, Cl 102, CO2 29, BUN 14, cr 0.88, pl. renin 4.9, pl. aldo 38
- 24-hour urine: Cr. 0.9 gm, prot 190 mg, Na 150 mmol, K 50 mmol
- Renal U/S: Unremarkable with nl. Size of both kidneys
- Renal arteries duplex us: Right RAS

RAS: Atherosclerosis and FMD

- Atherosclerotic - 65%
  - Mostly men >65 years
- Fibromuscular dysplasia
  - Mostly young females
    - 35-40% (children)
    - 10-15% (adults)

Renal Artery Stenosis Prevalence

- Mild to moderate HTN: <1%
- Acute, severe or refractory HTN: 10-45%
- 6.8% of general population above 65 years had > 60% stenotic lesions
- Cardiac cath with HTN: 20-30%
- Cardiac cath with HTN and CRI: 30-50%
- Starting hemodialysis: 14%
- PVD: 40-60% (13% bilateral)

RAS: Who to Screen

1. Onset of HTN < age 30 or > age 55
2. Systolic-diastolic abdominal bruit
3. Accelerated or resistant HTN
4. Recurrent (flash) CHF/pulmonary edema
5. Renal failure of uncertain etiology
6. Coexisting diffuse PVD, especially heavy smokers
7. Rapid decrease of renal function with ACE inhibitors or ARB (more than 30% increase in creatinine)
8. Asymmetric kidneys with HTN

JNC VI: Clinical clues for RAS
Renovascular Hypertension

Fibromuscular vs Atherosclerotic

• Young female with hypertension and abdominal bruit - suspect fibromuscular dysplasia

• Patient with renal dysfunction and evidence of atherosclerotic disease (Carotid bruit, CAD, PVD) or with risks of atherosclerosis (Smoking, Family history, elevated cholesterol, diabetes) – suspect atherosclerotic RAS

RAS: Detection of Anatomic Stenosis

• Duplex US
• Spiral CT
• MRA
• Renal arteriogram
• CO₂ angiography
• Intra vascular ultrasound (IVUS)

Renovascular Hypertension

Therapy

Objective
- Preserve renal mass
- Help control blood pressure

Surgical intervention
- Recommended for hemodynamically significant lesions (>75% luminal occlusion) especially in the presence of recurrent episodes of flash pulmonary edema and/or renal dysfunction post ACE inhibitor/ARB therapy
(ASTRAL) Angioplasty and Stent for Renal Artery Lesions: Randomized unblinded trial

Patients: 806 patients with atherosclerotic RAS
Primary outcome: Renal function
Secondary outcomes: BP, the time to renal and major CV events, and mortality
Treatment: Medical therapy vs medical therapy + angioplasty ± stent placement
Follow-up: 5 years (median 34 months)
Outcomes: No evidence of a worthwhile clinical benefit revascularization in patients with RAS

Primary Hyperaldosteronism

- Prevalence varies with hypertension
  - 5-13% of all hypertensives
  - 17-20% of patients with resistant hypertension
- Excessive secretion of aldosterone from:
  - Adrenal adenoma (~30%)
  - Bilateral adrenal hyperplasia (~65%)
  - Adrenocortical carcinoma (1%)
- Usually develops between age 30-50, slightly more common in females and Caucasians

Case 3

- 45 year-old female, who was referred for HTN and hypokalemia. Her main complaint was general weakness and intermittent headache
- Meds: Norvasc 5 mg/day, lisinopril/HCTZ 20/12.5/day, Toprol XL 100 mg/day, KCl 20 meq/day
- P/E: BP 150/95, P 60/min, wt 155 Lbs. Otherwise, unremarkable
- Labs: Na 143, K 3.4, Cl 103, CO2 29, BUN 18, Cr 0.92, pl. renin 0.1, aldo 42
- 24-hour urine: Cr. 1.1 gm, prot 210 mg, Na 150 mmol, K 48 meq.
- Abd. CT: No discrete adrenal mass

Primary Hyperaldosteronism

- Suspect in a patient with the triad of hypertension, hypokalemia (spontaneous or easily provoked by a diuretic or is difficult to correct with K supplements), and metabolic alkalosis
- Accelerated or malignant hypertension is rare
Primary Hyperaldosteronism

### Diagnosis

- Suppressed plasma renin activity and elevated serum or urine aldosterone levels are the hallmarks of primary overproduction of aldosterone
- Elevated aldosterone to renin ratio (>20)
- Evidence of renal K wasting (high urinary K or TTKG)
  - Urine K+ >20 meq in 24 hr
- Confirmation by showing inappropriate aldo secretion
  - Infuse saline 2 L over 4 hours then measure plasma aldosterone (abnormal if plasma aldosterone is >10)
  - High sodium diet (250 meq daily for 3 days and collect 24 hour urine for aldosterone (abnormal if urine Na >200 mmol and urine aldo >14 mcg/24 hr)

### Treatment

- Surgical
  - Laparoscopic adrenalectomy
  - Treatment of choice for adenoma or unilateral hyperplasia
- Pharmacologic
  - Spironolactone is usually first line
  - Eplerenone if side effects prohibit spironolactone
### Case 4

- 57 year old male referred for evaluation of difficult to control hypertension. The patient
- Meds include: Verapamil 480mg QD, HCTZ 50mg QD, Terazosin 10mg QD, Minoxidil 10mg QD
- P/E: BP 150/98, P 96/min, wt 206 Lbs. Otherwise, unremarkable
- Labs: Na 142, K 3.8, Cl 104, CO2 31, BUN 9, Cr 0.99, Aldo 9.6, PAC/PRA 68, thyroid studies normal
- 24-hour urine: Prot 157 mg, Na 150 mmol, K 37 meq
- Abd. CT: No discrete adrenal mass

### Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Neurohormonal effects of obstructive sleep apnea</th>
</tr>
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<tbody>
<tr>
<td>✓ Increased sympathetic activity</td>
</tr>
<tr>
<td>✓ Activation of renin-angiotensin-aldosterone axis</td>
</tr>
<tr>
<td>✓ Increased reactive oxidation species</td>
</tr>
<tr>
<td>✓ Impaired endothelial function</td>
</tr>
<tr>
<td>✓ Elevated Endothelin-1 levels</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Prevalence of sleep related breathing disturbances approximately 2-4% in the general population</th>
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<tbody>
<tr>
<td>Estimated prevalence of 25 to 35% in the hypertensive population</td>
</tr>
<tr>
<td>Estimated prevalence of 85% in patients with resistant hypertension</td>
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<tr>
<td>Longitudinal studies show a significant association between severity of OSA and development of hypertension within 4 years</td>
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</tbody>
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<th>Results of studies of CPAP on correcting BP have been equivocal</th>
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<td>May be a better preventive strategy</td>
</tr>
<tr>
<td>Patients with more severe hypertension may benefit more</td>
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<td>Anti-aldosterone agents may be more effective in this population</td>
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</tbody>
</table>
Obstructive Sleep Apnea

Factors Contributing to Resistant Hypertension
(Sarafidis and Bakris, JACC 52(22): 1749-57)

- Drug-induced
  - Nonsteroidal anti-inflammatory drugs (including cyclo-oxygenase-2 inhibitors)
  - Sympathomimetics (decongestants, anorectics)
  - Cocaine, amphetamines, other illicit drugs
  - Oral contraceptive hormones
  - Adrenal steroid hormones
  - Erythropoietin
  - Cyclosporine and tacrolimus
  - Licorice (included in some chewing tobacco)
  - Over-the-counter dietary and herbal supplements (e.g., ginseng, yohimbine, ma huang, bitter orange)

- Excess alcohol intake


Factors Contributing to Resistant Hypertension
(Sarafidis and Bakris, JACC 52(22): 1749-57)

- Volume overload
  - Excess sodium intake
  - Volume retention from kidney disease
  - Inadequate diuretic therapy
- Associated conditions
  - Obesity
  - Diabetes mellitus
  - Older age
- Identifiable causes of hypertension
  - Renal parenchymal disease
  - Renovascular disease
  - Primary aldosteronism
  - Obstructive sleep apnea
  - Pheochromocytoma
  - Cushing’s syndrome
  - Thyroid diseases
  - Aortic coarctation
  - Intracranial tumors

Treatment of Resistant Hypertension

- Exclusion of other causes of pseudo-resistance
- Treatment of a secondary etiology, when possible
- Identification and modification of factors contributing to resistant hypertension
- Targeting different mechanisms of hypertension (volume overload, Renin-Angiotension-Aldosterone system, vascular resistance)

When to look for secondary hypertension?

- Onset of hypertension before puberty or over the age of 55
- Severe or difficult to treat hypertension
- A change in the ability to control blood pressure
- Hypertension in the absence of a family history
- A high index of suspicion based on knowing the way in which various forms of secondary hypertension occur
  - Symptoms - palpitations, sweating
  - Signs - body habitus, bruits
  - Laboratory evaluation – elevated Cr, hypokalemia

Summary

- A minority of patients with hypertension have an identifiable cause known as secondary HTN
- Identification of the cause and its treatment has potential to significantly improve BP control and sometimes, cure it
- Endocrine abnormalities are important in causing secondary hypertension
- Renovascular disease is significantly more common cause of HTN than understood