Resistant Hypertension

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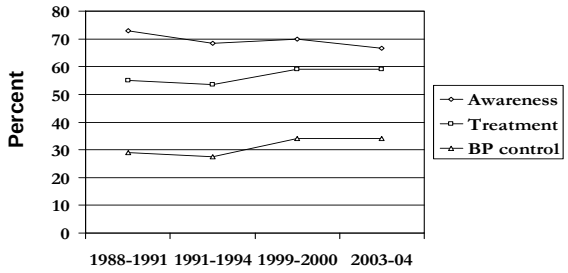
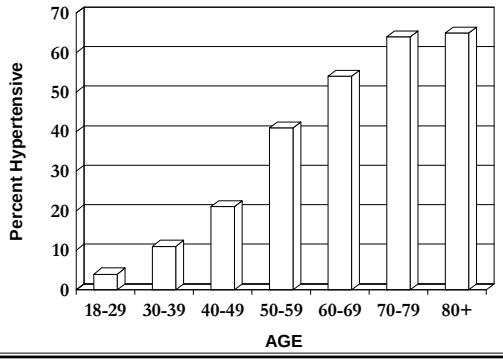
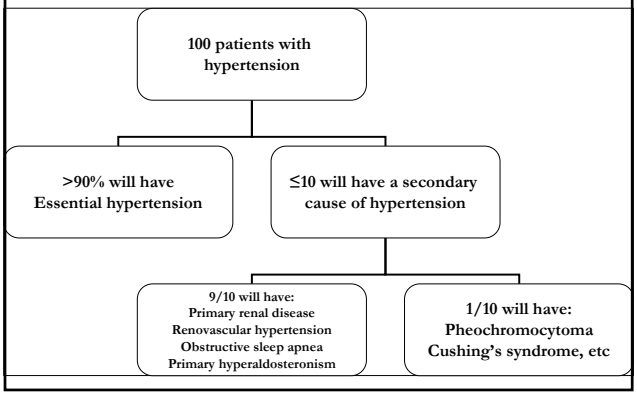
Trends in the Awareness, Treatment, and Control of Hypertension (NHANES)



Hypertension and Age



Causes of Hypertension



- **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**

Pseudo-Resistant Hypertension

- **Poor BP measurement technique**
- **Noncompliance**
- **White-coat HTN**
- **Inadequate dosing or inappropriate combinations of antihypertensive medications**

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**

Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. Vrijens et al. BMJ;17:336(7653):1114-7; May, 2008

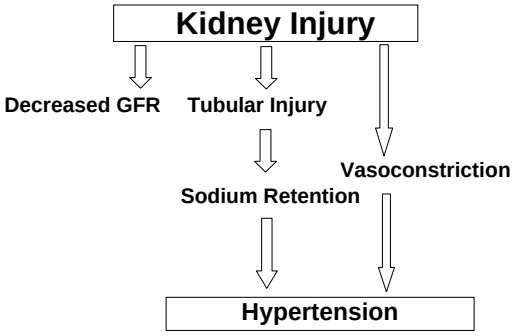
Kidney Disease and Hypertension

- 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 Hypertension



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**

Singer et al. Goal-Oriented Hypertension Management: translating clinical trials to practice. Hypertension;40:464-469, 2002

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**

- **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**

Mean Difference in Blood pressure

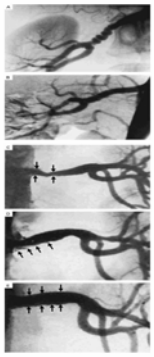
Intervention	Systolic	Diastolic
Diet	5.0 (7.0 to 3.1)	3.7 (5.1 to 2.4)
Exercise	4.6 (7.1 to 2.0)	2.4 (4.0 to 0.7)
Sodium restriction	3.6 (4.6 to 2.5)	2.5 (3.3 to 1.8)
Alcohol restriction	3.8 (6.1 to 1.4)	3.2 (5.0 to 1.4)
K supplements	3.9 (8.6 to 0.8)	1.5 (6.2 to 3.1)
Mg supplements	1.3 (4.0 to 1.5)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

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, Diovan160 /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)**



Safian et al. N Engl J Med 2001;344:431

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)**

Scoble et al. Clin Nephrol. 1989;31:119
Hansen et al. J vasc Surg 2002;36:443
Olin , et al. AJM 1990
Safian and Textor, NEJM2001;344:431
Davis et al;NEJM 79:301:1273
Mann and Pickering. Ann Int Med 92;117:845

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**

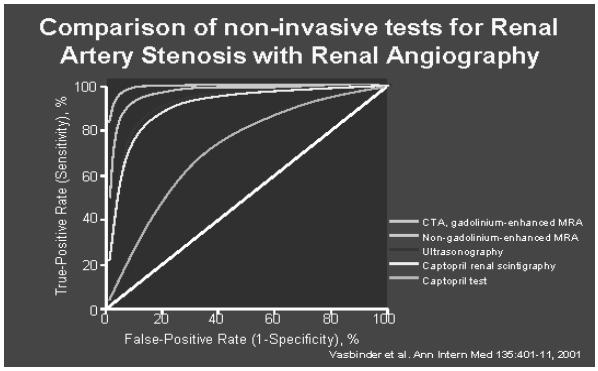
JNC VI: Clinical clues for RAS

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**

Renovascular Hypertension



RAS: Detection of Anatomic Stenosis

- **Duplex US**
- **Spiral CT**
- **MRA**
- **Renal arteriogram**
- **CO_2 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**

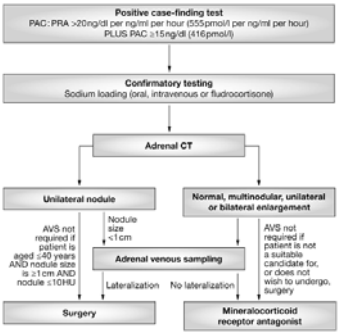
Primary Hyperaldosteronism

- **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+ >20meq 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)**

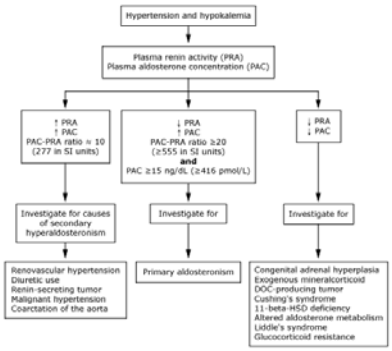
Algorithm for using the ratio of plasma aldosterone concentration to plasma renin activity as a case-finding tool, and for subtype evaluation, of primary aldosteronism



Mattsson C and Young WF Jr (2006) Primary aldosteronism: diagnostic and treatment strategies. *Nat Clin Pract Neprol* **2:** 198–208 doi:10.1038/ncpneph0151

NATURE CLINICAL PRACTICE NEPHROLOGY

Primary Hyperaldosteronism



UpToDate, 2009

Primary Hyperaldosteronism *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

- Neurohormonal effects of obstructive sleep apnea
  - ✓ Increased sympathetic activity
  - ✓ Activation of renin-angiotensin-aldosterone axis
  - ✓ Increased reactive oxidation species
  - ✓ Impaired endothelial function
  - ✓ Elevated Endothelin-1 levels

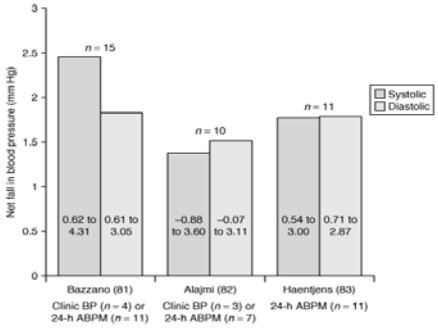
Obstructive Sleep Apnea

- Prevalence of sleep related breathing disturbances approximately 2-4% in the general population
- Estimated prevalence of 25 to 35% in the hypertensive population
- Estimated prevalence of 85% in patients with resistant hypertension
- Longitudonal studies show a significant association between severity of OSA and development of hypertension within 4 years

Obstructive Sleep Apnea

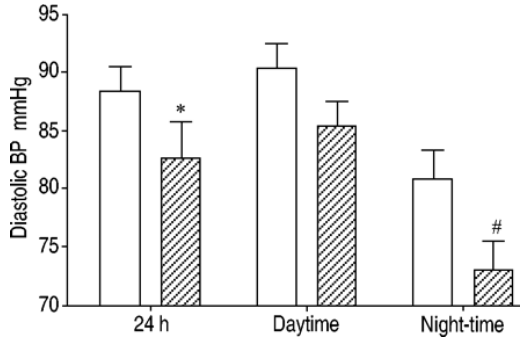
- Results of studies of CPAP on correcting BP have been equivocal
- May be a better preventive strategy
- Patients with more severe hypertension may benefit more
- Anti-aldosterone agents may be more effective in this population

Obstructive Sleep Apnea



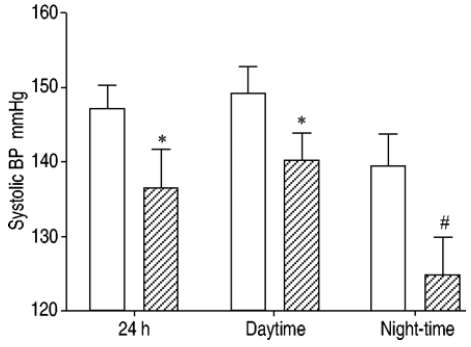
Friedman and Logan. The price of obstructive sleep apnea-hypopnea: hypertension and other ill effects. Am J Hypertens. 2009 May;22(5):474-83.

Obstructive Sleep Apnea



Logan, et al. Refractory hypertension and sleep apnoea: effect of CPAP on blood pressure and baroreflex. Eur Respir J. 2003 Feb;21(2):241-7.

Obstructive Sleep Apnea



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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