



Resistant Hypertension

Mitchell Rosner, MD
Henry B. Mulholland Professor of Medicine
Division of Nephrology
University of Virginia



Case Presentation



- 45 yo black male with poorly controlled hypertension.
- Symptoms of exertional fatigue and arthritis
- Family history of vascular disease, hypertension, kidney disease and diabetes
- Drinks heavily (5 beers per night)
- Office BP 162/98 mm Hg, pulse 88
- BMI: 39 (obese)

Case presentation



- Exam notable for:
 - Mild hypertensive retinopathy
 - LV hypertrophy with S4
 - No peripheral vascular disease
 - Significant edema

Case presentation



- Labs notable for:
 - Glucose 120 mg/dL
 - Low HDL, High LDL, High triglycerides
- Meds:
 - HCTz 25 mg/day
 - Lisinopril 40 mg/day
 - Metoprolol 100 mg/day
 - Aleve 450 mg twice a day

Questions:



- What are the predictors/causes of resistant hypertension in this patient?
- What is the approach to resistant hypertension?
- How should we modify this patients regimen to reach blood pressure goals?

Classification of BP for Adults JNC VII*



BP Classification	SBP mm Hg	or	DBP mm Hg
Normal	<120	or	<80
Prehypertension	120–139	or	80–89
Stage 1 Hypertension	140–159	or	90–99
Stage 2 Hypertension	≥160	or	≥100

*JNC 7 Report. JAMA 2003;289:2560-2572.

BP Control Rates

Trends in awareness, treatment, and control of high blood pressure in adults ages 18–74

National Health and Nutrition Examination Survey (%)				
	II 1976–80	II (Phase 1) 1988–91	II (Phase 2) 1991–94	1999–2000
Awareness	51	73	68	70
Treatment	31	55	54	59
Control	10	29	27	34

Sources: Unpublished data for 1999–2000 computed by M. Wozniak, National Heart, Lung, and Blood Institute, JNC VI.

Resistant Hypertension



- Definition:
- Hypertension should be considered resistant when blood pressure can NOT be reduced < 140/90 mmHg using an adequate and appropriate three-drug regimen, including an oral diuretic, with all three agents at or near maximal doses.
- Newer guidelines suggest that we should even use a cut-off of <130/80 mmHg

What is the appropriate work-up?

1. Look for non-adherence
2. Ensure that the regimen is adequate and appropriate
3. Rule out drug-drug interactions
4. Assess for associated conditions
5. Look for volume expansion
6. Consider pseudo-resistance
7. Reassess for secondary causes of hypertension
8. Modify the regimen empirically
9. Perform hemodynamic/neurohumoral assessment
10. Individualized and targeted therapy

• Courtesy Dr. Donald Vidt

Non-adherence



- From pharmacy records:
 - Nearly 40% of hypertensive patients discontinue their medications within 3 months of initiation
 - Nearly 70% of patients discontinued medication at the end of one year.
- Supervised (in-patient) observation may be the only method to reliably identify patients that are non-adherent yet adamantly deny this.

Reasons for non-adherence

- Cost of medication
- Inadequate patient education
- Complex dosing schedule
- Psychological factors (fear, denial)
- Forgetfulness
- Side effects and adverse effects on quality of life (real or perceived)
- Multiple drugs for concurrent illnesses

• Cramer et al JAMA 1989; 261: 3273

Is the regimen adequate?

- Biggest factor are regimens that do not include a diuretic or use a diuretic inappropriately (eg. thiazide with renal insufficiency).
- Some agents such as sympathetic antagonists or direct vasodilators promote sodium and water retention and can lead to "pseudo-tolerance" to these agents that is easily overcome with the addition of a diuretic.
- Does the agent last for 24 hours (peak/trough BP profile of the medication)?
- Use of inappropriate combinations: drugs from the same class, certain combinations.
- Use of combinations at lower dosages to avoid side-effects.

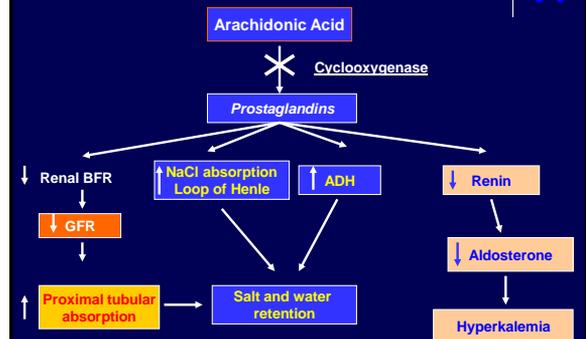
Drug interactions



1. Non-steroidal anti-inflammatory drugs

1. Cause sodium retention, enhance the vasoconstrictor responses to pressor hormones and antagonize the effects of other antihypertensives (with possible exception of calcium channel blockers and centrally acting alpha-antagonists)
2. Two recent meta-analyses suggest that NSAIDs lead to increases in mean arterial pressure of 4-5 mm Hg to as much as 10 mm Hg
3. Risk is greatest in the elderly, blacks and those with low-renin hypertension

NSAIDs-mechanism



Drug interactions

- Oral contraceptives- hypertension is 2-3 times more common in women taking OCPs. Especially in those who are obese and smoke. Not true for hormonal replacement
- Cocaine, Amphetamines
- Sympathomimetic amines- OTC nasal sprays, oral decongestants, appetite suppressants. Largely due to either direct stimulation of alpha receptors, or by indirect release of norepinephrine from storage sites.

Drug interactions

- Tricyclic antidepressants- specific to certain antihypertensive agents (clonidine, aldomet)
- Cyclosporine- potent renal vasoconstrictor with volume dependent hypertension
- Corticosteroids- mineralocorticoid activity promotes sodium and water retention
- Erythropoietin- increases systemic vascular resistance

Other lesser known drug interactions

- Lead, Mercury, Thallium, PCBs
- VEGF inhibitors
- Licorice (glycyrrhizic acid)
- Anabolic steroids
- Ma Huang "herbal extract"
- St. John's Wort
- Nicotine (?) and withdrawal from it
- Metoclopramide
- Venlafexadine
- Buspirone
- Sibutramine
- Lithium
- Naloxone (can also reverse effects of clonidine)

Salt



- Most convincing experimental evidence on free-living chimpanzees where on a graded sodium diet the difference in BP between the high and low-sodium intake group was 33/10 mm Hg (Denton et al)
- Correlation in 28 populations around the world with sodium intake and increasing blood pressure. Slope was 10 mm Hg rise in BP per 100 mmol of dietary sodium
- Slope of salt sensitivity increases with age
- Intersalt study in 10,079 subjects shows correlation with sodium intake and rising blood pressure

- Elliot P. Hypertension 1991; 17:3-8
- Intersalt Collaborative Research Group. BMJ 1988; 297:319

Salt-intervention trials

- Trials of Hypertension Prevention phase 2: moderate reduction of dietary sodium intake reduced blood pressure.
- Cutler et al. analyzed 22 trials of reduced sodium intake (1043 patients) and showed a reduction of 5.8/2.5 mm Hg for a 100 mmol/d reduction in sodium excretion
- Hofman et al randomized 486 newborn infants to a usual sodium diet or a low sodium diet for the first 6 months of life. BP was only 2.1 mm Hg lower in the low-sodium group at 6 months. However, 15 years later, the group on the low sodium diet had a BP 3.6/2.2 mm Hg lower.

Co-morbid conditions

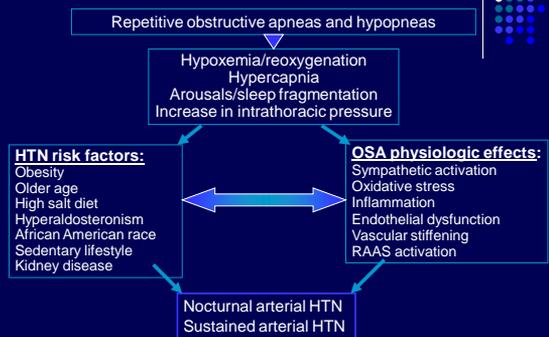
- Alcohol use and abuse: perhaps the most common cause of reversible hypertension. Limit intake to one ounce a day
- Cigarette Smoking: transient rises at least—depends on the number of cigarettes/day. Especially blunts effects of beta-blockers and leads to increased variability in blood pressure
- Sleep apnea: patients do not experience normal circadian fall in nocturnal BP. Dose response relationship between apnea-hypopnea index and development of hypertension. Recent trials support an antihypertensive effect of apnea therapy.

Obstructive Sleep Apnea (OSA) & HTN

- OSA and HTN commonly co-exist...
 - About 50% of patients with OSA are hypertensive
 - About 30-40% of HT patients have OSA
- High AHI is associated with greater likelihood of HTN (WSCS/SHHS)
- Pathophysiologic mechanisms
- CPAP therapy – modest BP effect (2 – 5 mmHg)

Budhiraja R, et al. *Resp Care* 2010;55(10):322.
Calhoun DA. *Curr Hypertens Rep* 2010;12:189.

Mechanisms in the etiology of OSA



Adapted from: Calhoun DA. *Curr Hypertens Rep* 2010;12:189.
Rosas SE. *Clin J Am Soc Nephrol* 2011;6:954.

Summary of meta-analyses of randomized controlled CPAP trials

Study	Number of trials/patients	BP end point	Minimum CPAP duration	Outcome
Alajmi et al.	10/587	Office/ambulatory	4 wk	SBP: -1.38 mm Hg (not significant)
				DBP: -1.52 mm Hg (not significant)
				More benefit in more severe OSA; trend for better SBP reduction with better CPAP adherence
Bazzano et al.	16/818	Office/ambulatory	2 wk	SBP: -2.46 mm Hg
				DBP: -1.83 mm Hg
				More benefit in patients with higher baseline BP, higher BMI, and more severe OSA
Haenijens et al.	12/572	Ambulatory	1 wk	24-h SBP: -1.64 mm Hg
				24-h DBP: -1.48 mm Hg
				More benefit in more severe OSA and with better CPAP adherence
Mo and He	7/471	Ambulatory	4 wk	24-h SBP: -0.95 mm Hg (not significant)
				24-h DBP: -1.78 mm Hg

BMI/body mass index, BP blood pressure, CPAP continuous positive airway pressure, DBP diastolic blood pressure, OSA obstructive sleep apnea, SBP systolic blood pressure

Calhoun DA. *Curr Hypertens Rep* 2010;12:189.

Relationship between obesity and hypertension

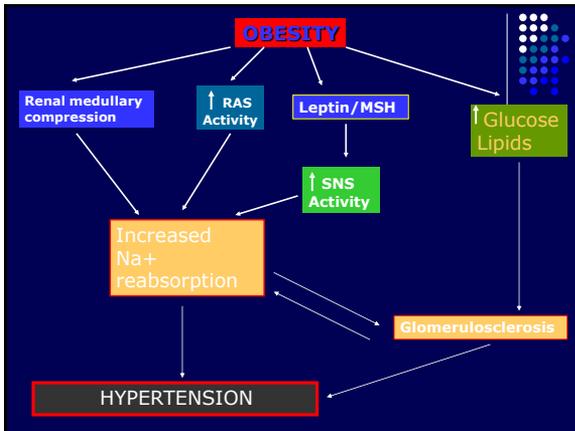
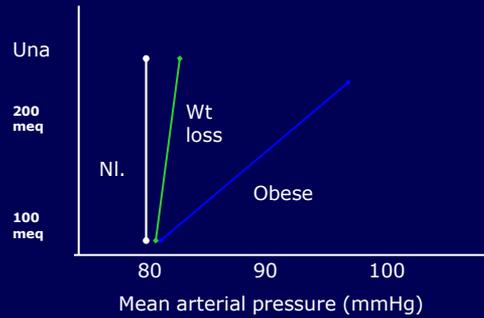
- Excess weight is the most common cause of hypertension:
 - Framingham study:
 - 78% of hypertension in males and 65% in females directly attributable to hypertension
 - Association seen in all population groups across the world (not a genetic effect)
 - Much of weight gain seen with increased age is related to weight gain
 - Obviously, not all obese patients are hypertensive—the distribution curve is shifted towards higher BP.



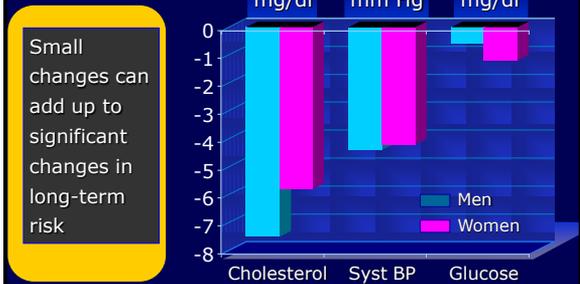
Obesity and pressure-natriuresis

- Animals and humans fed a high-fat diet develop sodium retention, increase cardiac output and hypertension.
- Now several lines of evidence has shown that pressure natriuresis in obese individuals is shifted to higher blood pressures. Furthermore, the curves have a decreased slope c/w salt sensitivity in many, but not all, obese individuals.

Pressure natriuresis in obesity



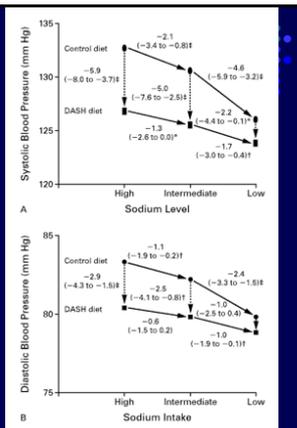
Metabolic Response to 10-lb Weight Loss: Framingham Data



Higgins M et al. Acta Med Scand Suppl 1988;723:23-36.

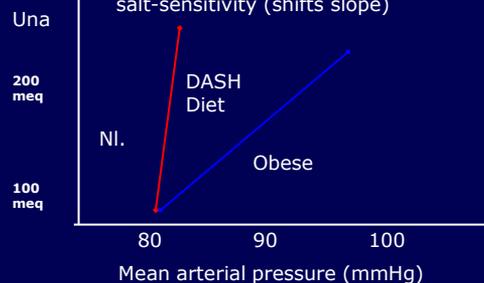
DASH Diet

Sodium restriction along with low fat diet rich in fruits and vegetables lowers blood pressure



Change in pressure-natriuresis with DASH

DASH diet acts like a diuretic to remove salt-sensitivity (shifts slope)



Assess for volume expansion

- The most common physiological cause for resistant hypertension is volume overload.
- Excessive sodium intake: with the exception of calcium-channel blockers, all antihypertensive drugs are more effective on a sodium-restricted diet.
- Diuretic choice is important:
 - Thiazide for those with normal renal function
 - Loop diuretics for those with kidney disease- should be dosed bid or even tid.

Pseudoresistance

- Pseudo-hypertension: BP cuff pressure is inappropriately high as compared to intra-arterial pressure because of extensive atheromatous changes. Suspect if:
 - Marked hypertension in the absence of target-organ damage
 - Antihypertensive therapy produces symptoms consistent with hypotension
 - Calcifications of arterial tree
 - Severe and isolated systolic hypertension

Overview of secondary hypertension

- **Renal:**
 - Renal parenchymal disease
 - Renovascular hypertension (RVHT)
 - Renin secreting tumors
- **Adrenal:**
 - Primary aldosteronism (PA)
 - Syndromes of mineralocorticoid excess
 - Pheochromocytoma (PHEO)
 - Cushing's
- **Hormonal:**
 - Thyroid disorders,
 - Primary hyperparathyroidism
 - Acromegaly
- **Genetic mutations:**
 - Liddle's
 - Gordon's
- **Drug-induced**
- **Sleep apnea**

SECONDARY CAUSES OF RESISTANT HYPERTENSION

Estimated Prevalence (%)

- | | |
|-------------------------------------|-----------------------|
| • Renal parenchymal disease | 1.0 – 8.0 |
| (depending on | the creatinine level) |
| • Renal artery disease | 3.0 – 4.0 |
| • Aldosteronism | 1.5 – 15.0 |
| (higher in recent series) | |
| • Pheochromocytoma | <0.5 |
| • Cushing's syndrome | <0.5 |
| • Hyperthyroidism or hypothyroidism | 1.0 – 3.0 |
| • Sleep apnea | NA |
| • Coarctation of the aorta | <1.0 |

Moser M & Setaro JF. N Engl J Med 2006;355:385.

CKD is the most common form of secondary hypertension

- Historical view:
 - 4429 patients referred to resistant hypertension clinic from 1978 to 1993
 - ~10% had identified forms of secondary hypertension
 - Hypertension resistance:
 - Patient
 - Physician
 - Disease

Anderson GH Jr, et al. J Hypertens 1994;12:609.

Features of "Inappropriate" Hypertension...

- Age of onset: <20 or >50 years
- Level of blood pressure : >180/110 mmHg
- Organ damage
 - Funduscopy: moderate or malignant
 - Serum creatinine >1.5 mg/dL
 - Cardiomegaly or left ventricular hypertrophy (LVH) as determined by electrocardiography
- Presence of features indicative of secondary causes
 - Unprovoked hypokalemia
 - Abdominal bruit
 - Variable pressures with tachycardia, sweating, tremor
 - Family history of renal disease
- Poor response to generally effective therapy

Kaplan, NM. Kaplan's Clinical Hypertension, 10th ed. Philadelphia:Lippincott Williams & Wilkins 2010:150.

Office hypertension



- A pressor response ("white coat effect") is seen in 15-20% of patients in the doctor's office. Must be persistent to qualify as a "white coat effect."
- Mechanisms not understood- no clear psychological profile or behavioral factors
- More common in older hypertensives with isolated systolic hypertension
- BP measured by nurses/techs is typically lower than that of a physician
- Ambulatory blood pressure monitoring is critical to exclude this effect and monitor drug therapy

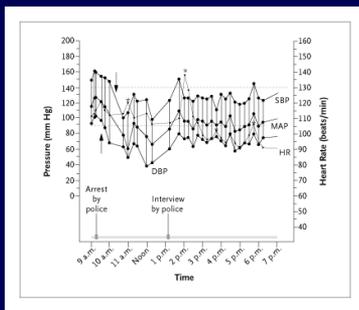
• Pickering TG et al. JAMA 259: 225, 1988

Role of psychosocial stress

- Involves both activity of the sympathetic nervous system and hypothalamic-pituitary-adrenocortical system in both short-term, acute pressor responses and more long-term BP effects.
- Very variable effects depending upon gender, race, age, etc.



Role of Stress



Yosefv et al. NEJM 350 (22): 2315

Hemodynamic/neurohumoral assessment

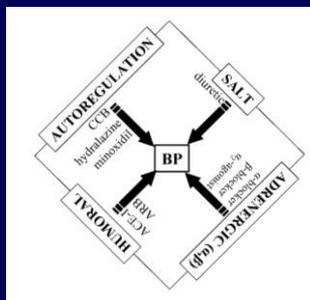
Hemodynamic Measurement

- Cardiac output increased
- Elevated peripheral resistance
- Plasma volume increase
- Plasma catecholamine increase
- Plasma renin increase
- Plasma/urinary aldosterone increase

Management

- Beta-blocker or NDHPCCB
- ACE-inhibitor, ARB, vasodilators
- Loop diuretic, +/- thiazide
- Rigid sodium restriction
- Clonidine, alpha/beta-blockers
- ACE-inhibitor, ARB or beta-blocker
- Spirolonactone, eplerenone, amiloride

Pharmaceutical approach



Townsend Disease a Month 1998;44:243-253

Renin Profiling and Choice of Antihypertensive Drugs

- 40% low renin; 15%-20% high renin; 40% medium renin
- Small studies demonstrate efficacy of diuretics and calcium channel blockers in low-renin HTN. ACE inhibitors and β -blockers demonstrate efficacy in high-renin HTN
- Small clinical trial (Egan et al) demonstrates feasibility and efficacy of strategy
- Large studies evaluating this strategy have not been done

Back to our patient...



- What are the predictors/factors associated with resistant hypertension in this patient?
 - Physical inactivity
 - Alcohol use
 - Inadequate medical regimen
 - Obesity
 - Volume overload
 - +/- Stress
 - +/- Secondary hypertension
 - +/- Sleep apnea
 - NSAID use

How would you treat him?



Lifestyle Modification

<u>Modification</u>	Approximate SBP reduction (range)
Weight reduction	5–20 mmHg/10 kg weight loss
Adopt DASH eating plan	8–14 mmHg
Dietary sodium reduction	2–8 mmHg
Physical activity	4–9 mmHg
Moderation of alcohol consumption	2–4 mmHg

COULD EXPECT AS MUCH AS 20 mmHG FALL IN BLOOD PRESSURE

Treatment changes:

- 1. Change to combination medications:
 - ACE-inhibitor plus calcium-channel blocker might be a good choice
 - Trandolapril/verapamil
 - Could also use combination with a diuretic, but..

Treatment Changes:

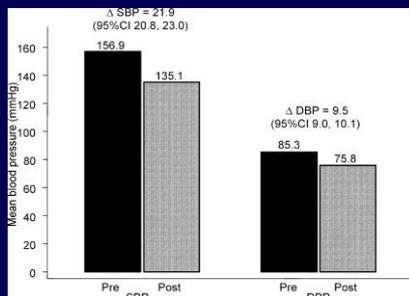
- Need to add a loop diuretic:
 - Start lasix 40 mg bid along with sodium restriction.
- Continue beta-blocker—given resting pulse of 80-90, could increase the dose.

Chlorthalidone vs HCTZ

Dorsch et al 2011

- Retrospective cohort analysis of MRFIT study
- Despite lower potassium and higher uric acid, there was a slight increase in CV events in HCTZ group
- Chlorthalidone is more potent, lowered SPB more than HCTZ and is longer acting
- LDL and glucose levels were lower on Chlorthalidone

Effects of Spironolactone in 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm

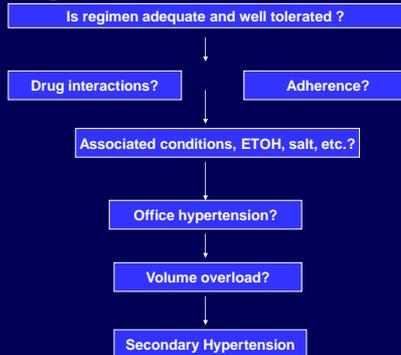


Chapman, N. et al. Hypertension 2007;49:839-845

Other issues:

- Probably screen for sleep apnea
- Would exclude hyperaldosteronism (renin/aldosterone level, 24 hr urine aldosterone)
- Check 24 hr urine protein
- Renal ultrasound (possibly doppler study)
- Follow closely over the next 6 months.

Algorithm



CONTROVERSIES (1)

Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- PA:PRA is highly sensitive but has a high false positive rate of 35% to 50%.
- Wide variation in sensitivity (64% to 100%) and specificity (87% to 100%)
- Reported ratios are all laboratory-dependent (especially low PRA)
- Proper preparation
 - Restore serum K+
 - Blood pressure medications acceptable including ACE/ARB, diuretic, adrenergic inhibitor
 - Hold MR antagonists for 2 weeks

CONTROVERSIES (2)

Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- Better diagnostic accuracy is obtained if the absolute plasma aldosterone concentration is included as a second criterion in combination with PA:PRA ratio.
- The combination of a PA:PRA ratio >30 and a PA value >20 ng/dL had a sensitivity of 90% and specificity of 91% for APA (Weinberger 1993)
- A PA:PRA ratio ≥20 and PA >15 ng/dL were found in >90% of patients with surgically-confirmed APA (Young 1999)

Drugs affecting renin/aldosterone

	PRC	PRA	Aldosterone
ACE-I	↑	↑	↓
ARB	↑	↑	↓
Direct renin inhibitors	↑	↓	↓
Aldo receptor blockers	↑	↑	↑
Beta blockers	↓	↓	↓

CONTROVERSIES (3)

PA:PRA ratio in the evaluation of primary aldosteronism

- Mainly a reflection of the level of PRA and does not reflect aldosterone autonomy
(Montori et al. *Mayo Clin Proc* 2001;76:877)
- Lacks sensitivity and specificity and primarily reflects the level of PRA which usually falls with age and is not associated with aldosterone excess.
(Schwartz et al. *Am J Hypertens* 2002)
- PA:PRA ratio is a screening test suggestive of primary aldosteronism

Questions?