Secondary Hypertension
The Primary Care Perspective

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What Is Hypertension (JNC 7)

CLASSIFICATION OF BLOOD PRESSURE (BP)*

CATEGORY	SBP MMHG		DBP MMHG
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Hypertension, Stage 1	140–159	or	90–99
Hypertension, Stage 2	≥160	or	≥100

BLOOD PRESSURE MEASUREMENT TECHNIQUES

METHOD	NOTES
In-office	Two readings, 5 minutes apart, sitting in chair. Confirm elevated reading in contralateral arm.
Ambulatory BP monitoring	Indicated for evaluation of "white coat hypertension." Absence of 10–20 percent BP decrease during sleep may indicate increased CVD risk.
Patient self-check	Provides information on response to therapy. May help improve adherence to therapy and is useful for evaluating "white coat hypertension."

What is Hypertension

- For Children/Adolescents:
  - Average SBP/DBP >/= 95th percentile for age, gender, and height.
  - "Prehypertension" is >/= 90th percentile
  - 3 separate readings on 3 separate visits.
  - Incidence appears to be increasing over time.

What is Essential/Primary Hypertension

- HTN with no identifiable cause
- Often develops gradually over years
- Much of HTN still falls in this category - up to 85% in many reports.
- Likely a complex interaction between multiple risk factors/causes in many cases.

What is Secondary Hypertension?

- Meets Criteria for HTN
- Results from an identifiable, potentially correctable cause
- Accounts for significant number of Resistant HTN cases
- Estimated to account for 5-15% of cases of HTN
- Prevalence of hypertension in adults between 20-30% (50-70 million people). Conservatively, probably 3-5 million people in U.S. affected.

Associations with Hypertension

- Family History – first degree relatives
- Race – more common in African Americans
- Physical Inactivity
- Dyslipidemia
- Obesity
- Vitamin D deficiency

Unclear Association with HTN

- Caffeine
  - May cause short spike in BP
  - No sustained effect noted
  - May be more significant in older/overweight
- Stress/Anxiety/Type A
  - Clearly causes short-term increases
  - Unclear if sustained stress can truly cause HTN

When to Suspect Secondary HTN

- Early age of onset
  - Young adult without family history or risk factors
  - Onset prior to puberty
- Severe or resistant HTN
  - Remember – fewer than 50% of patients well controlled on a single medication
- Acute onset or change in control when previously stable
- Malignant/End-organ changes
- Abnormal exam findings (e.g. abdominal bruit)

Evaluation for type of HTN

- Confirm Diagnosis
- History
- Physical Exam

- Diagnostic Testing (Blood Tests, Urine, ECG, Imaging)

Confirm elevated blood pressures

- In office
  - Proper Cuff/Technique
- Outside of office
  - Useful to identify “White Coat” hypertension
    - May account for 20-30% of HTN by some estimates
  - Ambulatory BP monitor
  - Home BP monitor
    - Discuss optimal conditions for measurement
    - Discuss proper equipment
    - Correlates well with Ambulatory Monitors

History

- Birth History
  - More premature babies reaching adulthood
  - Use of Umbilical artery catheters may post some risk
  - Aware of any prolonged hospital stay when born
- Childhood History
  - Recurrent UTI's, urinary reflux
  - Traumas/Infections - PSGN

History

- Family history
  - HTN, Endocrine disorders, early heart disease, strokes, kidney failure, blindness, sleep apnea, etc.
- Current known medical conditions
- Pregnancy status
- Compliance with medications

Social History

- Diet
  - Salt Intake
    - No one ‘adds’ salt
    - Ask about fast food or processed foods
  - Licorice – excessive ingestion
- Tobacco Use
- Alcohol Consumption
- Illicit drugs
  - Cocaine, amphetamines, ecstasy (MDMA)
- Toxic/Environmental Exposures
  - Lead
  - Arsenic

Medications - OTC

- NSAIDS, Aspirin
- Cough/Cold Medications
  - Pseudoephedrine, phenylephrine, dextromethorphan
- Herbals
  - Ginseng
  - St. John’s Wort
  - Ephedra, ma huang
- Energy Drinks
  - Often contain caffeine or herbal ingredients

Medications - Prescription

- Antidepressants
- Anti-inflammatories, including Cox-2
- Hormones
  - Contraception
  - Testosterone Supplement
- Glucocorticoids
- Stimulant medications (ADHD, etc)
- Migraine medications
- Transplant Medications (cyclosporine/tacrolimus)
- Weight Loss medications
- Erythropoietin

Review of Systems

- General
  - Weight Changes
  - Fatigue/Weakness
  - Sleep Quality
  - Diaphoresis
  - Flushing/Pallor
- HEENT
  - Headaches
  - Dizziness
  - Blurred Vision
  - Snoring
  - Nasal Congestion
  - Nosebleeds
- Cardiovascular
  - Chest Pain
  - Palpitations
  - Paroxysmal Nocturnal Dyspnea
- Respiratory
  - Shortness of breath/Dyspnea on Exertion
  - Gasping during sleep/Choking

Review of Systems

- **Abdominal**
  - **Nausea**
  - **Vomiting**
  - **Abdominal Pain**
  - **Fullness/swelling of abdomen**
- **Musculoskeletal**
  - **Muscle Weakness**
  - **Leg Cramps**
- **Neurologic**
  - **TIA symptoms**
- **Vascular**
  - **Cold Feet**
  - **Claudication**
- **Skin changes**
  - **Striae**
  - **Pigmentation**
  - **Excessive dryness, hair loss**

Physical Exam

- **General**
  - **Height/Weight/BMI/Percentiles**
  - **In children, poor growth may be sign of chronic disease such as renal insufficiency, hypothyroidism, etc**
  - **Obesity – typical vs central/cushingoid**
- **HEENT:**
  - **Acromegaly, Moon facies, Hirsuitism**
  - **Eyes – Papilledema, AV Nicking, Hemorrhages, Exudates**
  - **Obstructed Nasal Passages**
  - **Tonsillar/Uvular enlargement**
  - **Nasal Congestion, suggestion of Adenoid Hypertrophy**
  - **Crowded Mouth**
  - **Overbite/Retrognathia/Micrognathia**

Physical Exam

- Neck
  - Goiter
  - Neck size >/= 17 inches in men (>/= 16 inches in women) associated with OSA
- Cardiovascular Exam
  - Murmurs
  - PMI displacement
  - RV heave
  - Radial/femoral delay
  - Tachycardia
- Abdominal Exam
  - Bruit
  - Mass (PCKD, Wilms tumor, neuroblastoma)
  - Bladder enlargement (obstructive lesion with hydronephrosis).

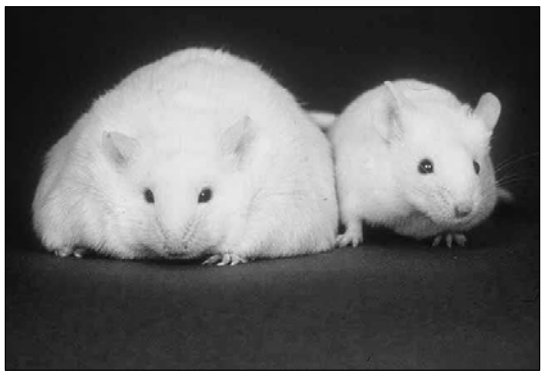
Physical Exam

- Musculoskeletal
  - Joint swelling
  - Muscle weakness
- Skin –
  - Striae
  - Acne
  - Malar rash
  - Flushing/Pallor/Sweating
  - Petechiae/Purpura

Lab/Test Evaluation

- **Blood**
  - **Glucose, H/H, lipid panel, potassium, creatinine, calcium, TSH**
- **Urine**
  - **Urinalysis, consider urine albumin/creatinine ratio**
  - **Urine HCG**
- **ECG**

Obesity



Lifestyle Changes

LIFESTYLE MODIFICATION RECOMMENDATIONS

MODIFICATION	RECOMMENDATION	AVG. SBP REDUCTION RANGE†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m²).	5–20 mmHg/10 kg
DASH eating plan	Adopt a diet rich in fruits, vegetables, and lowfat dairy products with reduced content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to ≤100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week.	4–9 mmHg
Moderation of alcohol consumption	Men: limit to ≤2 drinks* per day. Women and lighter weight persons: limit to ≤1 drink* per day.	2–4 mmHg

* 1 drink = 1/2 oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).

† Effects are dose and time dependent.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

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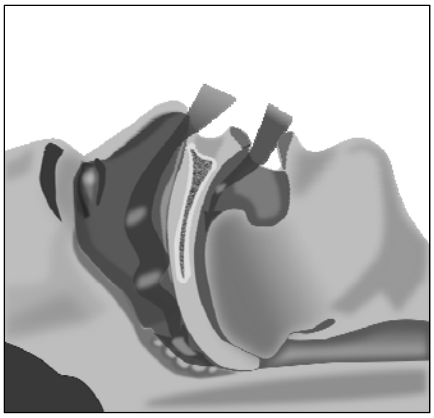
Obstructive Sleep Apnea

- **True prevalence of sleep apnea difficult to determine. Estimated that 4-9% of people are symptomatic with sleep apnea, and another 10% may meet criteria but be relatively asymptomatic.**
- **In one study of resistant HTN, 83% had unsuspected sleep apnea.**

Obstructive Sleep Apnea

- **Intermittent hypoxemia and/or increased upper airway resistance cause increased sympathetic nervous system activity.**



Treatment: CPAP for OSA

- **Mixed results, but some studies show 9-14 mmHg decrease in SBP and 7-9 mmHg decrease in DBP.**
- **Largest benefit in severe OSA and in patients also on BP medications.**

Referral

- **Because many / most of the other causes of secondary and resistant hypertension directly or indirectly involve the kidneys, referral to Nephrologist common for uncontrolled/resistant/secondary HTN**

Secondary Hypertension

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Disclosure

- **I am the Site Co-PI for Symplicity HTN – 3, a clinical trial of renal denervation to treat resistant hypertension sponsored by Medtronic Ardian LLC, Mountain View, CA.**

Resistant Hypertension (RH)

- **BP above goal in spite of concurrent use of 3 antihypertensive agents of different classes.**
- **One should be a diuretic.**
- **All should be at optimal doses.**
- **Includes patients who are controlled on 4 or more meds.**
- **Goal – 140/90 or 130/80 if DM or CKD.**

Secondary HTN

- **12.7% of patients over age 50 referred to a HTN clinic had a secondary cause.**
- **Causes**
  - **Renal artery stenosis (35% of those with a secondary cause)**
  - **Primary Aldosteronism (17-23% of RH cases), GRA**
  - **Renal parenchymal disease**
  - **OSA**
  - **Pheochromocytoma**
  - **Cushing's disease**
  - **Thyroid disease**
  - **Coarctation of Aorta**

Renal Artery Stenosis

- **Randomized trials have not shown benefit in terms of renal function or BP with intervention as compared to medical therapy.**
- **>90% are atherosclerotic (older age, smokers, known PAD).**
- **<10% are FMD, commonly women under age 50.**

Renal Artery Stenosis

- **MRA is highly sensitive, but may suggest that a minimal lesion is moderate or severe.**
- **Value of renal artery doppler or CT angiogram depends on institutional expertise.**
- **ACEI or ARB use is advised with RAS, but do not tolerate >30% rise in Cr.**

Treatment of Renal Artery Stenosis

- **Angioplasty almost always improves/cures HTN if FMD.**
- **Angioplasty/stenting not superior to medical therapy if atherosclerotic.**
- **Consider angioplasty/stenting of atherosclerotic RAS if drugs not effective or recurrent flash pulmonary edema.**

Primary Aldosteronism

- **17-23% of RH cases**
- **Only 9-37% have hypokalemia**
- **Several Subtypes**

Subtypes of PA

- **Aldosterone Producing Adenoma (Conn 1954)**
- **Unilateral or Bilateral Adrenal Hyperplasia**
- **Glucocorticoid Remediable Aldosteronism**
- **Aldo producing adrenal carcinoma**
- **Aldo producing ovarian or renal tumor**

Evaluation - Primary Aldosteronism

- **Aldo/renin ratio is elevated (>25) and aldo level >15 ng/dl.**
- **ARR is an effective screening test if spironolactone, eplerenone, amiloride, triamterene are not in use.**

Evaluation of Primary Aldosteronism

- **Adrenal CT is recommended.**
- **Carcinomas are usually >4cm.**
- **Adenoma may be < 1cm and not visualized.**
- **If surgery is an option, adrenal vein sampling is necessary.**

Treatment of AP adenoma

- **Laparascopic adrenalectomy**
- **After surgery 40-65% will have persistent essential HTN**

Treatment of PA with Bilateral Hyperplasia

- **Mineralocorticoid antagonist**
  - **Spironolactone (Aldactone) 25-400mg daily**
    - **Also progesterone agonist and androgen antagonist**
    - **Breast tenderness, irregular menses, impotence**
    - **$16-35.00 a month**
  - **Eplerenone (Inspra) 25-100mg daily**
    - **Selective for MC receptor**
    - **$100.00 a month**
    - **Should be used BID**

Glucocorticoid Remediable Aldosteronism

- Ectopic expression of aldosterone synthase in the adrenal zona fasciculata.
- Cells of the zona fasciculata produce both cortisol and aldosterone.
- Increased levels of 18-OH cortisol.
- Exogenous glucocorticoid suppresses activity of the zona fasciculata.

Adrenal Histology

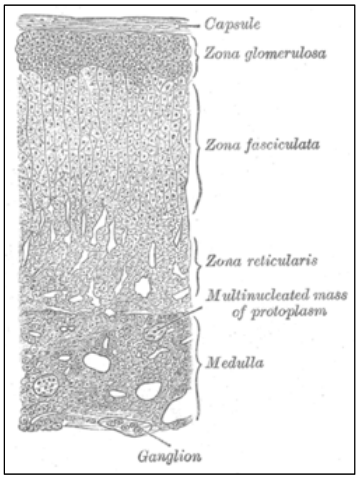


Image from http://en.wikipedia.org/wiki/Adrenal_gland

Glucocorticoid-Remediable Aldosteronism

- Familial, autosomal dominant.
- FH of primary aldosteronism or stroke before age 40.
- Onset of HTN before age 21.
- Dx by genetic testing.
- Treatment is prednisone 2.5 to 5mg QHS.

Glucocorticoid-Remediable Aldosteronism Genetic Testing

- International Registry for Glucocorticoid-Remediable Aldosteronism
- Phone: 1-800-722-5520, ext. 25011
- Internet: http://www.brighamandwomens.org/Departments_and_Services/medicine/services/endocrine/Services/gra/default.aspx

Renal Parenchymal Disease

- **Less than 15% of CKD patients in Nephrology clinics had BP <130/80 despite an average of 3 different medications.**
- **Sodium and fluid retention lead to treatment resistance.**
- **Failure to use diuretics, inadequate dose of diuretic, and use of thiazides with low GFR are common problems.**

Pheochromocytoma

- **0.1% to 0.6% of HTN.**
- **10% of pheochromocytomas are malignant.**
- **Increased BP variability which is a risk factor for CV morbidity/mortality.**
- **Paroxysmal HTN may be due to this or an intracranial tumor.**
- **Average 3 years from symptoms to Dx.**

Pheochromocytoma

- **In autopsy studies 75% were not clinically suspected.**
- **Episodic headaches, palpitations, sweating has diagnostic specificity of 90%.**
- **Plasma free metanephrines – 91% sensitive and 99% specific.**

24 hr Urine Studies for Pheochromocytoma

- **100% sensitive and 94% specific**
- **Diagnostic findings:**
  - **Norepinephrine > 170 mcg**
  - **Epinephrine > 35 mcg**
  - **Dopamine > 700 mcg**
  - **Normetanephrine > 900 mcg**
  - **Metanephrine > 400 mcg**

Treatment of Pheochromocytoma

- **Control BP and prevent intraoperative hypertensive crisis.**
- **Alpha blocker > 14 days before surgery.**
- **After 3 days of alpha blockade, 5g Na diet and volume expansion to prevent orthostasis and catecholamine induced volume contraction.**

Treatment of Pheochromocytoma

- **Start beta blocker 3 days before surgery.**
- **If beta blocker is used first, unopposed alpha receptor stimulation can increase BP.**

Surgery for Pheochromocytoma

- **Laparascopic adrenalectomy is possible in 90%**
- **16% recur**
- **Annual biochemical screening indicated**

Cushing's Syndrome: Clinical

- **Central obesity, hypertension, glucose intolerance**
- **Moon face**
- **Abdominal striae**
- **Menstrual irregularity**

Cushing's Syndrome

- **Overstimulation of the mineralocorticoid receptor by cortisol.**
- **70+% of Cushing's patients have HTN.**
- **Sleep apnea and insulin resistance also contribute to high BP.**

Cushing's Syndrome

- **24hr urine cortisol is 3 times upper limit of normal.**
- **Urine and late night salivary cortisol should be checked twice.**

Cushing's Syndrome - Treatment

- **MC receptor antagonist like spironolactone or eplerenone works best.**
- **Excision of an ACTH producing pituitary tumor or cortisol producing adrenal tumor lowers BP.**

Hypothyroidism

- **Found in 3.6% of referred HTN patients.**
- **There is decreased release of endothelial derived relaxation factor which increases peripheral vascular resistance.**
- **Sodium restriction, diuretics, CCB are treatment of choice.**

Hyperthyroidism

- **Results in increase in heart rate, cardiac contractility, and stroke volume.**
- **Systolic HTN is common.**
- **Salt sensitive.**
- **Use B blocker if tolerated.**

Coarctation of the Aorta

- **Congenital or acquired (Takayasu arteritis)**
- **More common in males**
- **30-40% have a bicuspid aortic valve**
- **10% have an intracranial aneurysm**

Coarctation of the Aorta

- **HTN in the upper extremities and diminished femoral pulses (brachial –femoral delay).**
- **Measure brachial and popliteal BP.**
- **Headache, cold feet, pain in legs with exercise.**
- **Cardiomegaly and LV strain on EKG.**
- **Diagnosis made by Echo with doppler.**

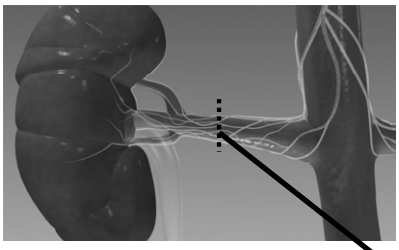
Coarctation Management

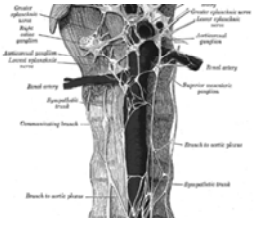
- **Adults should have CT or MRA of thoracic aorta and intracranial vessels.**
- **Angioplasty/Stent is preferred at some centers.**
- **Surgery – resection +/- bypass graft.**

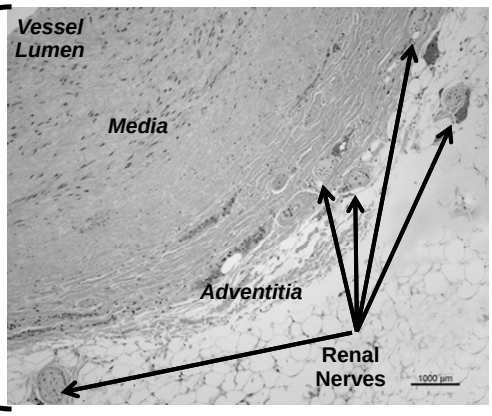
Renal Denervation

Targeting Renal Nerves

- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia







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Images provided courtesy of Medtronic

Renal Denervation

- **Renal sympathetic nerves contribute to elevated SNS activity and HTN.**
- **Denervation reduces sympathetic control of renal function and removing renal afferent contribution to BP elevation.**

Renal Denervation

- **Limited to investigational use.**
- **Catheter based delivery of low level RF energy through the wall of the renal artery to denervate the kidney.**

Symplicity HTN -2

- **RCT of 106 patients**
- **At 6 months mean decrease in BP 32/12 mmHg.**
- **At 12 months mean decrease in BP 28/10.**
- **3% complication rate: renal artery dissection, femoral artery hematoma, pseudoaneurysm.**

Symplicity HTN 3

- **Bilateral Renal Denervation in Patients with Uncontrolled Hypertension.**
- **Prospective, single blind, randomized, controlled.**
- **Primary Endpoint is blood pressure.**
- **All patients have renal angiogram, randomized 2:1 to denervation vs. sham.**
- **Inclusion Criteria**
  - **Age 18-80**
  - **SBP > 160mmHg**
  - **GFR>45 ml/min**
  - **Full doses of 3 meds including diuretic (25mg HCTZ, 80mg furosemide)**

Symplicity HTN 3 Referrals

- **Phone: 614-292-5315 – Denise Fadorsen**
- **EPIC: Ambulatory Referral Nephrology or Cardiology for Resistant Hypertension**