Resistant Hypertension

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• No financial relationships
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Objectives

- Investigate type of patient demonstrating resistance
- Define resistant hypertension
- Recognize the role of history and physical examination in identifying secondary causes
- Evaluate the best lifestyle and pharmacological treatment for resistant hypertension
- Future therapies
Who is the Resistant Patient and Why?

- Women and minorities tend to react differently to medications
- Hormonal variations
- Different ways to metabolize medications
• More common and more severe in Blacks
• Hypertension in one or both parents
• Aging—sodium sensitivity increases with age
• Excess alcohol intake
• Obesity
• Dyslipidemia
• Type A? (e.g. the majority of us here)
Hypertension (HTN): Racial and Ethnic Disparities

• Highest amongst African Americans and Blacks
• Unlike stroke and coronary heart disease, HTN presence high regardless of gender and education status
• Black women: high prevalence of obesity

The Diabetic Hypertensive Is at Especially High Risk

• For CV disease
  – 65% of people with diabetes mellitus die of some form of heart or blood vessel disease

• For MI
  – Diabetic patients without a previous MI have as high a risk of MI as nondiabetic patients with a previous MI

• For CHF
  – In the DIGAMI* trial, 66% of total mortality among diabetics was due to heart failure

DIGAMI=Diabetes mellitus Insulin-Glucose Infusion in Acute MI; CHF=coronary heart disease; CV=cardiovascular; MI=myocardial infarction.
Benefits of 144/82 vs 154/87

HTN and Dyslipidemia Contributing to Endothelial Dysfunction

Hypertension

Dyslipidemia

Diabetes

Smoking

Endothelial dysfunction

↓ NO Synthesis
- Vasoconstriction
- Thrombosis
- Superoxide

↑ COX-1 Activity
- Thromboxane A₂
- Prostaglandin H₂
- Prostacyclin

Inflammation
- Leukocyte adhesion
- Endothelial permeability
- Foam cell formation
- T-cell activation

↑ Endothelin
- Vasoconstriction
- Calcium mobilization

Atherosclerosis

CVD

References:


Role of Neurohormonal Activation in CVD Risk and Progression

Insulin Resistance

Hyperinsulinemia

↑ Norepinephrine

↑ Angiotensin II

↓ Adrenal Medullary Activity

↓ HDL

↑ Triglycerides

Increased CV Risk, Atherogenesis, Progressive CVD

American Journal of Cardiology, Volume 95, Issue 9, Pages 8-13, 2 May 2005, Kanu Chatterjee, MB.
Deleterious Effects of Angiotensin II

Angiotensin II

- Increased Aldosterone
- Increased AVP
- Increased Efferent Constriction
- Increased Mesangial Contraction
- Increased Vessel Hypertrophy
- Increased Myocardial Hypertrophy
- Increased Sodium Retention
- Increased Norepinephrine Release
- CNS Dypsogenia
Pathophysiology

Injury to the Heart (eg, myocardial infarction)

↑ Levels of Norepinephrine

Negative Cardiac Effects

Negative Vascular Effects

Negative Renal Effects

Cardiac Injury
Hypertrophy
Arrhythmias

Vasoconstriction

Activation of RAS

Sodium Retention

Disease Progression
Objectives

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Definition of Resistant Hypertension
• Normal Blood Pressure: <120/80 mmHg
• Prehypertension: 120-139/80-89 mmHg
• Hypertension:
  – Generally: >140/>90 mmHg measured on 3 separate occasions
  – Stage 1: 140-159/90-99 mmHg
  – Stage 2: ≥160/100 mmHg
• Note Diabetics also have same goal, per new guidelines 12/2012
Malignant Hypertension

- Marked Hypertension with
  - Retinal hemorrhages
  - Exudates
  - Papilledema

- Hypertensive emergency – any end organ damage

- Usually associated with diastolic BP >120 mmHg

- Hypertensive encephalopathy can be seen at diastolic BP as low as 100 mmHg
  - Any end organ damage counts as malignant regardless of BP number
Resistant Hypertension

- Systolic or Diastolic hypertension despite ≥ 3 medications

  However, be aware of:

  - Suboptimal therapy (not at appropriate doses)
  - Pseudohypertension
  - Ingestion of other meds or substances that can elevate blood pressure
  - Office or “White coat” hypertension
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Secondary HTN

- Primary renal disease (esp vascular)
- Oral agents (oral contraceptive pills and NSAIDS)
- Pheochromocytoma
- Primary Aldosteronism (HTN, hypokalemia, and metabolic alkalosis)
- Cushings’s syndrome
- Thyroid disease
- Sleep Apnea (!!!)
Approach

• Family History
• Medication History
  – ACE-I inhibition can worsen renal artery disease
  – OCP or other hormonal treatment
  – NSAIDS
• Social History
  – Alcohol (note binge and amount)
  – Exercise
  – Diet
  – Stress
  – Compliance!!!!
  – Sleep hygiene
Physical Examination

• Blood Pressure Readings on both upper extremities
• Significant difference implies a vascular problem:
  – Consider carotid or subclavian evaluation, insight into other vascular problems
• Waist circumference (part of the metabolic syndrome panel)
Physical Exam – Key Findings

• Repeat BP *yourself!*
• Repeat BP on the other upper extremity
Physical examination, con’t

• HEENT: Look in pupils, reactivity, edema
• Look for JVD, carotid bruits
• Cardiac examination: listen for an S4 gallop and new murmurs
• Listen for renal artery bruits, feel for an aneurysm
• Feel for distal pulses and assess for edema, look for splinter hemorrhages
Laboratory Tests Recommended Before Initiating Therapy

- Urinalysis
- Complete blood count
- Blood chemistry
  - Basic metabolic panel
  - TSH
- Lipid profile
- 12-lead electrocardiogram
Consider:

- Diagnosis of Sleep Apnea (get a sleep study)
- Consider an echocardiogram if an S4 or new murmur is heard
- Diagnosis of Metabolic Syndrome
Metabolic Syndrome (AKA Syndrome X)

At least 3 of these 5:

- Fasting blood glucose $\geq 100$ mg/dL
- HDL-C $< 50$ mg/dL for women, $< 40$ for men
- Triglycerides $> 150$ mg/dL
- Systolic BP $> 130$ mmHg
- Waist circumference $> 35$” for woman, $> 40$” for men
Abdominal Obesity

- More metabolically active
- Greater endocrine activity
- Releases more free fatty acids and inflammatory mediators
- Increases incidence of diabetes
- Therefore increases the incidence of CVD
Consider: “White Coat Hypertension”

- Home Blood Pressure measurements
  - And
- Ambulatory Blood Pressure monitors
  - Better predictors than office BP of target organ damage
Ambulatory BP Monitoring

- 24 hour measure
- Reliable and accurate
- Not subject to bias or preference
- Not subject to “white coat” phenomenon
- Can measure mean / nocturnal BP
- More predictive of outcomes
- Other measures would take weeks
Ambulatory BP Monitoring

- Also Useful for:
  - Monitoring the effectiveness of therapy
  - Measuring borderline HTN or hypotension
  - Pregnancy induced HTN
Ambulatory BP Monitor

- Example:
Objectives

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Treatment

• First, remove offenders
  – Avoid binge drinking
  – Cut back on stimulants (caffeine, diet pills, stress)
  – Look for hormonal therapy (be certain to address herbal medications and MVI formulations)
Women and Hormones

• Estrogens
  – Hormone Replacement Therapy (HRT)
  – Oral (and transdermal) Contraception

• Testosterone, endogenous and exogenous

• Adipokines (adiponectin, leptin, TNF, interleukins) – abdominal obesity
Estrogen

- Overall, only 41.5 cases of HTN per 10,000 person-years due to oral estrogen
- Works via renin-angiotensin system
  - Estrogen stimulates the hepatic production of renin substrate (angiotensinogen)
- Mean elevation in BP of 3-6/2-5 mmHg,
  - ~5% of women develop overt hypertension
Estrogen: oral contraceptives

• Meta analysis 14 independent studies
  – 1980 thru 2003
  – Relative risk of MI & stroke increased 2-fold in pts with low dose (<50 mcg ethinyl estradiol)

• Main concern OCP’s:
  – Development of persistent HTN and subsequent premature CVD
  – Women >35 years and in women who smoke higher risks
Estrogen: Hormone Replacement Therapy

- Much lower doses of estrogen
- Women’s Health Initiative (WHI)
  - 16,000 women placebo controlled, evaluating effects of estrogen-progesterone replacement in postmenopausal women
  - At 5.2 years, only a small increase in SBP compared to placebo
- PEPI trial
  - ERT, with and without progestins, did not affect BP at 3 years
Estrogen: HRT

- Possible that HRT may slow the rise in SBP over longer f/up
- However—increases in coronary, stroke, and venous thromboembolic risk demonstrated in WHI, HRT is not given orally for cardiovascular protection
- Transdermal estradiol with many fewer side effects and risks (lack of first pass) still in study
Testosterone and Androgens

• Testosterone:
  – Given to both men & women to treat sexual dysfunction
  – Need to watch increases in cholesterol, esp LDL
  – BP not specifically a problem unless weight gain a problem
Active Treatment

- Lifestyle
- Antihypertensive medications
- Meta Analysis of 7 major antihypertensive drug trials
Algorithm for Treatment of Hypertension

Begin Lifestyle Modifications

- Lose weight
- Limit alcohol
- Increase physical activity
- Reduce Sodium
- Maintain potassium, calcium, magnesium
- Stop smoking
- Reduce saturated fat, cholesterol

Not at Goal Blood Pressure
Treatment

Healthy lifestyle:
• Decrease emotional stress!!!! Seriously
• Limit alcohol intake: For women, >2 drinks/day associated with increased incidence of HTN
• Monitor periodically for end organ damage
Treatment- Lifestyle

Exercise:

- Nurses’ Health Study, ages 40-65, inverse relationship to risk of coronary event
- Starting in mid-later life had lower incidence CHD events compared to those remaining sedentary
- WHI-light to moderate exercise
- *Duration the key: goal of 2 or more hours/week*

NEJM 2001;344:3-9
Hypertension: New Guidelines and Treatment

• Why is it important to treat?
  – Strokes
  – Renal Failure
  – Hypertensive heart disease
  – Diabetic complications, including retinopathy (leading cause of blindness in the US)
Update HTN 6/2008

- Obesity and Older Age most common RF
- Sleep Apnea
- Chronic renal disease
- Diabetes Mellitus

**JNC 8 & ATP 4: Still waiting**
Treatment: Medications

- Trials that set the Standard
  - Capicorn
  - ALLHAT
  - SHEP
  - ACCORD BP (most recent 3/2010)
Lessons From CAPICORN

- Different types of beta blockers
- Alpha blocker + beta blocker = significantly improved anti-hypertensive effect
- Vasodilating beta blockers have better overall profile for treatment in CV disease—studies still pending
Beta Blockers Revisited: Harmful or Helpful?

• Reducing Heart rate in HTN: Is it Harmful?

• Not all beta blockers are the same:
  – Traditional beta blockers cause increases in central venous pressure
  – Newer generation beta blockers:
    • Reduce central venous pressure
    • Cause vasodilation

Bangalore S, Sawhney S, Messerli FH
If just treating HTN, BB may not be the best choice

- In contrast to patients w/MI and heart failure, beta blocker reduction in heart rate w/atenolol increased CV events for Hypertensive patients.

- Current study used only atenolol, and further studies need to be done, especially on vasodilating BB.
These are not your father’s beta blockers

- Increased central pressure thought to worsen outcomes
- Beta blockers that are vasodilators *do not* increase central pressure
  - Carvedilol (Coreg)
  - Nebevilol (Bystolic)
  - Ivabradine (Procoralan)
Treatment: Medications

• Trials that set the Standard
  – Capicorn
  – ALLHAT
  – SHEP
ALLHAT Trial Design

• Randomized, double-blind, multi-center clinical trial
• Determine whether occurrence of fatal CHD or nonfatal MI is lower for high-risk hypertensive patients treated with newer agents (CCB, ACE-I, alpha-blocker) compared with a diuretic
• Known ASCVD, DM, smoker, LVH, low HDL
• 42,418 high-risk hypertensive patients ≥ 55 years
ALLHAT
JAMA 2002 Dec. 18

- 33357 men and women - diverse races
- HTN & at least one other CHD risk factor
- Compared: Thiazide, Lisinopril, Amlodipine, and previously stopped doxazosin arm
- Primary outcome Fatal CHD or non-fatal MI
- Secondary outcomes:
  - Total Mortality - CVA
  - Combined CHD - CHF
ALLHAT Conclusions

• Amlodipine (representing CCB), lisinopril (representing ACE-I) and chlorthalidone (representing thiazide-type diuretics)
  – Comparable in preventing major coronary events or increasing overall survival.

• Chlorthalidone = amlodipine in overall CVD event prevention
  – However, chlorthalidone > amlodipine in preventing heart failure.
Because of the effectiveness of thiazide-type diuretics in preventing one or more major forms of CVD and their lower cost, they should be the drugs of choice for first-step antihypertensive drug therapy, unless there are other compelling indications.
Treatment: Medications

• Trials that set the Standard
  – Capicorn
  – ALLHAT
  – SHEP
  – ACCORD BP
SHEP Study

- Treatment of elderly patients with HTN
- Thiazide diuretic
- Stroke, total mortality, CVD events
- 63% patients had BP controlled with diuretic alone
- CVA reduced 36% (3/100) and CVD events reduced 6 per 100 in 4.5 years

JAMA1991;265;3255-3264
HTN in the Elderly Trial

- ACE (enalapril) vs. HCTZ
- 6083 adults with HTN aged 65 - 84 years
- Australia Family Practice clinics
- Open-label study in multiple practices
- BP reduction was the same: 26/12 mm Hg
- All CVD events or death reduced for men (17% or approximately 4 / 100)
- No difference in events for women

NEJM 2003;348:583-592
• Conducted as part of the ACCORD glycemia trial, as there was no clinical evidence to support recommendations to support <130 mmHg SBP in DM2 (as advised in JNC7)
ACCORD BP

• 4733 patients, randomized, nonblinded:
  – SBP <120 mmHg (average 3.5 meds)
  – SBP <140 mmHg
  – F/up 4.7 years

• After 1 year: mean systolic BP
  – 119.3 mmHg intensive group
  – 133.5 mmHg standard group
ACCORD BP

• No significant difference in nonfatal MI, major coronary events, and mortality
• Significant difference in stroke, less in intensive arm, ~40% reduction
  =Treat 89 people for 5 years to prevent one
• Adverse events higher in intensive therapy group: 3.3% vs 1.3%

JNC 7 Algorithm for Tx of Hypertension

Not at Goal Blood Pressure (<140/90 mm Hg)  
(<130/80 mm Hg for those with diabetes or chronic kidney disease)

Initial Drug Choices

Without Compelling Indications

Stage 1 Hypertension
(SBP 140-159 or DBP 90-99 mm Hg)
**Thiazide-type diuretics** for most  
May consider ACEI, ARB, BB, CCB,  
or combination

Stage 2 Hypertension
(SBP ≥160 or DBP ≥100 mm Hg)
**2-drug combination** for most  
(usually thiazide-type diuretic and  
ACEI, ARB, BB, or CCB)

With Compelling Indications

Drug(s) for the compelling indications
Other antihypertensive drugs  
(diuretic, ACEI, ARB, BB, CCB)  
as needed

Lifestyle Modifications

Optimize dosages or add additional drugs  
until goal blood pressure is achieved  
Consider consultation with hypertension specialist

Algorithm for Treatment of Hypertension (continued)

Initial Drug Choices*

Compelling Indications

- Heart failure
  - ACE inhibitors
  - Diuretics
- Myocardial infarction
  - β-blockers (α/β best)
  - ACE inhibitors (with systolic dysfunction)
- Diabetes mellitus (type 1) with proteinuria
  - ACE inhibitors
- Isolated systolic hypertension (older persons)
  - Diuretics preferred
  - Long-acting dihydropyridine calcium antagonists

*Based on randomized controlled trials.
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Renal Sympathectomy

- Treatment for HTN, even in 1970’s
- Open surgery for those with resistive HTN
- Poorly tolerated:
  - Orthostatic hypotension
  - Palpitations
  - Anhydrosis
  - Intestinal disturbances
  - Loss of ejaculation
  - Thoracic Duct Injuries

Renal Sympathetic Activation: Efferent Nerves
Kidney as Recipient of Sympathetic Signals

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow
Renal Sympathetic Activation: Afferent Nerves
Kidney as Origin of Central Sympathetic Drive

Vasoconstriction
Atherosclerosis
Insulin Resistance

Sleep Disturbances

Renal Afferent Nerves

↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

Hypertrophy
Arrhythmia
Oxygen Consumption

↑ Renin Release
Renal Denervation


• Simplicity 2 (2010/11): ~100 patients with a control groups (50/50); with device, 20-25 mmHg additional systolic BP reduction

SYMPLICITY Clinical Trial Program follows over 5000 patients across multiple indications

First-in-Man (AU)

Series of Pilot Studies (EU, US & AU)

Symplicity HTN-2 Initial RCT (EU & AU)

SYMPPLICITY HTN-3
US Pivotal Trial (US)

Global SYMPPLICITY Registry (Approved Regions)

Expand HTN Indication (Approved Regions)

Pilot Studies in New Indications (Approved Regions)

SYMPPLICITY HF

Post-Market Registry (US)

Trials under way
• Simplicity 3: Add in big players such as aldosterone blockers, now in the US
• Need more Racial and Cultural heterogeneity
Radiofrequency catheter positioning in the renal artery aiming at circumferential application of radiofrequency spaced apart by approximately 5 mm.

Figure Legend:
Figure Legend:

Fluoroscopic Images of Catheter Positions in the Renal Artery
(Left) Radiofrequency catheter positioned in the right renal artery. (Right) Contrast injection into the right renal artery.
Brief Procedure with a Low Complication rate (n=153)

- 38 minute median procedure time
  - Average of 4 ablations per artery
- Intravenous narcotics & sedatives used to manage pain during delivery of RF energy
- No catheter or generator malfunctions
- No major complications
- Minor complications 4/153:
  - 1 renal artery dissection during catheter delivery (prior to RF energy), no sequelae
  - 3 access site complications, treated without further sequelae

Symplicity HTN-1: BP Reductions through 3 years

P<0.01 for ∆ from BL for all time points

1 M (n=143) 3 M (n=148) 6 M (n=144) 12 M (n=130) 18 M (n=107) 24 M (n=59) 30 M (n=24) 36 M (n=24)

Systolic BP
Diastolic BP

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
Conclusions from Symplicity HTN-1

• The magnitude of clinical response is significant and sustained through 3 years
• Increasing responder rates indicate:
  – no loss of treatment effect out to 36 months
  – BP non-response at 6 months does not predict failure to respond at 12 months or later
• The treatment effect was consistent across subgroups (age, diabetes status, and baseline renal function)
• No late adverse events were seen

*Expanded results presented at the American College of Cardiology Annual Meeting 2012 (Krum, H.)
Symplicity HTN-2: Lancet Conclusions

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, *resulted in significant reductions in BP*.
- Magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality
- No major complications.
- Catheter-based renal denervation is beneficial for patients with treatment-resistant essential hypertension.

Challenges and Opportunities
Challenges and Opportunities

Challenges

• Prevention (esp high risk grps Black, Hisp)
• Symptom recognition (both by pts & healthcare providers)
• Diagnostic testing
• Treatment and intervention
• Outcomes
Challenges and Opportunities

Opportunities

• Education to patients and their healthcare providers
• Early recognition of symptoms and aggressive prevention and treatment strategies can improve outcomes
• Start young!!
  – Health classes in community and classrooms
  – Healthier choices at a lower socioeconomic level
  – Healthier choices at school
New stress tests being evaluated:
- Anger
- Mathematical stress
- Emotional stress
In Terms of Medications

• Switch a beta blocker to an alpha-beta blocker (metoprolol to carvedilol, labetolol) or other vasodilating beta blocker

• Make certain on a thiazide diuretic
  – Increase dosage
  – Combination with others key

• Recent trials suggest that Spironolactone may be a good choice for those w/OSA

• Consider the renin system:
  – ACE-I inhibitors and ARB’s
  – Spironolactone (Decreased LV EF and OSA)
  – Look for renal artery stenosis if increased BP or not controlled with 3 or more
  – Consider Renal Denervation – Trials in Milwaukee and Madison
• Non-traditional vasodilators
  – Hydralazine (possible with NTG for afterload reduction)
  – Minoxidil (watch for edema, twice daily usually at initial low dose e.g. 2.5 mg BID)
Calcium Channel Blockers

• Dihydropyridines (amlodipine, felodipine)
  – Vasodilators
  – Increased vascular permeability

• Nondihydropyridines (verapamil, diltiazem)
  – Reduce vascular permeability
  – Affect cardiac contractility and conduction
Patient Motivation

• Get exercise: walk, dance, swim
• Shift focus away from what NOT to eat to something tasty to eat:
  – Nuts
  – Get the grill out
  – Dark chocolate
• Breathe
  – Listen to music, smile, compliment another person
Thank You!!!

Questions?