Evaluation of the Resistant Hypertension Patient

Budapest Nephrology School

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Case

- 51 year old man
- Hypertension x 12 years
- Diabetes x 5 years
- Tired, dry mouth
- MEDS: HCTZ & Valsartan, Diltiazem, Metoprolol, Clonidine, Metformin, Tricor, Statin
- 156-158/90 mm Hg (no orthostasis)
Definition of Resistant Hypertension

• Failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic** (JNC 7)
  
  < 140/90 mm Hg
  < 130/80 mmHg in DM or CKD or CHD

• In large clinical trials 10-30% fail to reach DBP < 90 mmHg and 40-60% fail to reach SBP < 140 mmHg
Diagnostic and Treatment Recommendations

1. Confirm Treatment Resistance
2. Exclude Pseudoresistance
3. Identify & Reverse Lifestyle Factors
4. Discontinue Interfering substances
5. Screen for Secondary HTN
6. Pharmacological Treatment
7. Refer to Specialist

Calhoun et al. Circulation 2008: 117; e510-e526
White Coat Hypertension

Visit to doctor - White Coat Effect

Blood Pressure (mmHg)

Day

Night

Systolic

Diastolic

Time (Hour)
Is the Hypertension Real?
MA Brown, et al. AJH 2001

Mean difference between referring doctor BP and ABP (mmHg) in patients with resistant HTN

Percent of patients with resistant HTN who had BP < 135/85 mmHg with ABP

Mean difference

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>% with controlled BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>14</td>
<td>28</td>
</tr>
</tbody>
</table>

SBP  DBP  % with controlled BP
Case

- Home blood pressure checked with a home BP monitor
- They run systolic values of 150-160 mm Hg for the last 6+ months
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Calhoun et al. Circulation 2008: 117; e510-e526
Big Arm + Small Cuff = High BP
Case

- Technique checked
- Monitor checked
  - √ OK
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Calhoun et al; Hypertension: 2008; 51; 000
Causes of Resistant Hypertension

- **Volume, volume, volume**
- Drug-related issues
  - Drug interaction
  - Intolerance due to known side effect
  - Suboptimal regimen
  - Interfering substance
- Nonadherence
- Secondary forms
Case

- Very aware of salt and sodium
- Has been working on weight, has lost 7 pounds
- Currently 209 pounds (30.9 kg/m²)
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Calhoun et al. Circulation 2008: 117; e510-e526
## Interfering Substances

### Table 2. Medications That Can Interfere With Blood Pressure Control

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonnarcotic analgesics</td>
<td>Nonsteroidal antiinflammatory agents, including aspirin</td>
</tr>
<tr>
<td></td>
<td>Selective COX-2 inhibitors</td>
</tr>
<tr>
<td>Sympathomimetic agents</td>
<td>(decongestants, diet pills, cocaine)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>(methylphenidate, dexamethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
<tr>
<td>Erythropoietin</td>
<td></td>
</tr>
<tr>
<td>Natural licorice</td>
<td></td>
</tr>
<tr>
<td>Herbal compounds</td>
<td>(ephedra or ma huang)</td>
</tr>
</tbody>
</table>
Apparent Mineralocorticoid Excess: Acquired

- 62 y/o woman with type 2 DM for 12 yrs and hypertension for 10 years
- Current Medication: Valsartan, Lasix, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation
- Home BP: am 180/110, midday 110/80, evening 150/100 mmHg
- Lab
  - Today: Na 144, K 2.6 TCO2 35, Cl 95
  - 6 months ago: Na 138, K 4.5 TCO2 26, Cl 101
Resistant Hypertension 62 y.o. Woman

Plasma aldosterone = 2 ng/dl

Plasma renin activity = 0.2 ng/ml/hr
Case

• Patient was not taking any interfering substances
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Circulation 2008: 117; e510-e526
Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension

PA = Primary aldosteronism

Whom to suspect?

- Low K+
- Drug Resistance
- Negative Family History of Hypertension
- Obesity and sleep apnea
- Serendipitous occasions
  - The unexpected adenoma
PAPY Study
## Table. Obstructive Sleep Apnea (OSA) Effects on Blood Pressure (BP)

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>BP Method</th>
<th>Findings, SBP/DBP, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coughlin et al 27</td>
<td>N=104: 61 obese OSA, 43 obese control</td>
<td>Clinic</td>
<td>BP ↑ 11.4/5.2 in OSA vs control (P&lt;.004)</td>
</tr>
<tr>
<td>Moller et al 19</td>
<td>N=42: 24 overweight OSA, 18 overweight control</td>
<td>24 hour</td>
<td>Daytime BP ↑ 20/12 in OSA vs control; nighttime BP ↑ 22/22 in OSA vs control (P&lt;.001)</td>
</tr>
<tr>
<td>Davies et al 28</td>
<td>N=90: 45 obese OSA, 45 obese control</td>
<td>24 hour</td>
<td>Daytime and nighttime DBP ↑ 4.6 and 7.2 in OSA vs control (P&lt;.001 and 0.04, respectively); nighttime SBP ↑ 9.2 in OSA vs control (P=.01)</td>
</tr>
<tr>
<td>Pankow et al 29</td>
<td>N=93: 38 overweight severe OSA, 35 overweight moderate OSA, 20 overweight control</td>
<td>24 hour</td>
<td>Daytime BP ↑ 13/10 and 8/7 for severe OSA and moderate OSA respectively vs control (P&lt;.005); nighttime BP ↑; 21/15 and 7/6 for severe OSA and moderate OSA respectively vs control (P&lt;.001)</td>
</tr>
<tr>
<td>Pankow et al 30</td>
<td>N=50: 25 overweight OSA, 25 overweight control</td>
<td>24 hour</td>
<td>Daytime BP ↑ 7.9/6.9 in OSA vs control (P&lt;.05); nighttime BP ↑ 14.3/9.1 in OSA vs control (P&lt;.01)</td>
</tr>
</tbody>
</table>

SBP indicates systolic BP; DBP, diastolic BP; and control, study group free from OSA.
Potential mechanisms by which OSA contributes to the development of resistant hypertension

- Calhoun et al have demonstrated increased aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea.

- Stimulation of the catecholamine axis through repeated exposure to hypoxia
BP responses to CPAP

• Usually in the range of 10/5 mm Hg
Atherosclerotic Renal Artery Stenosis (ARAS): Clinical Characteristics

- Older, men > women
- Generalized atherosclerosis
- Correlates:
  - HTN
  - Chronic kidney disease (ischemic nephropathy)
  - Usually have a cigarette history
  - Volume overload
    - “Flash” pulmonary edema
ARAS: Treatment options

- Medical therapy
- Revascularization
  - Surgical
  - Percutaneous
- Best therapy, particularly for bilateral disease with some renal function impairment, is still debated
Case

- Non-smoker
- No bruits
- Renal CT angio was not done
- Plasma metanephrines were normal (and an MRI was also done, adrenal glands appeared normal)
- There are no symptoms of snoring, no daytime somnolence, but NO sleep study was done
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Circulation 2008: 117; e510-e526
SODIUM CHLORIDE
BLOOD
PRESSURE
AUTONOMIC NERVE SYSTEM
AUTOREGULATION

Townsend  Disease a Month 1998;44:243-253
BASICS of BLOOD PRESSURE

- Autoregulation
  - CCB
  - Hydralazine
  - Minoxidil

- SALT
  - Diuretic

- Humoral
  - ACE-I
  - ARB

- Adrenergic (α)
ASCOT: BP Response to Spironolactone

$\Delta$ SBP = 21.9
(95%CI 20.8, 23.0)

Mean blood pressure (mmHg)

Pre SBP 156.9
Post SBP 135.1

$\Delta$ DBP = 9.5
(95%CI 9.0, 10.1)

Pre DBP 85.3
Post DBP 75.8

Chapman Hypertension 2007; 49:839-845
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Calhoun et al. Circulation 2008: 117; e510-e526
Resistant or Difficult-to-Control Hypertension

Marvin Moser, M.D., and John F. Setaro, M.D.

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Figure 1. Treatment of Resistant Hypertension.
NSAIDs denotes nonsteroidal antiinflammatory drugs.
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**Figure 1. Treatment of Resistant Hypertension.**

NSAIDs denotes nonsteroidal antiinflammatory drugs.
Causes of Resistant HTN
Garg et al AJH 2005

Drug-related 58%
Psychologic 9%
Office resistance 6%
Nonadherence 16%
Unknown 6%
Secondary HTN 5%
Nonadherence 16%
Unknown 6%
Secondary HTN 5%
Reasons for Inadequate BP Control

- Acceptance of inadequate control by physician
- Difficulty achieving BP control with one agent/suboptimal regimens
- BP goals are more aggressive than in previous years
- Lack of compliance due to:
  - perceived side effects of antihypertensive medication(s)
  - frequency of dosing/multiple agents to attain control
Strategies for Improving Adherence to Regimens

- Clinician empathy increases patient trust, motivation, and adherence to therapy
- Once daily dosing, combination therapies
- Physicians should consider their patients’ cultural beliefs and individual attitudes in formulating therapy
Case

- Plasma renin activity = 0.1 ng/mL/hr
- Serum aldosterone = 8.0 ng/dL
Novel Therapies
Symplicity Renal Denervation

• Symplicity ® System (Medtronic) uses radiofrequency ablation delivered by a catheter directly applied to the lumen of both renal arteries (sequentially) through a femoral access procedure that usually takes less than hour to complete.

• This procedure reduces sympathetic inflow into [efferent], and out from [afferent], the kidneys.

• The recent report of the Simplicity HTN-2 trial indicates sustained BP reduction in most patients at 6 months
Renal Nerves as a Therapeutic Target

- Arise from ~ T10-L2
- Follow the renal artery to the kidney
- Primarily lie within the adventitia

Diagram showing:
- Vessel Lumen
- Media
- Adventitia
- Renal Nerves
Rheos Device

• Rheos ® System (CVRx), utilizes the known effects of baroreceptor stimulation to reduce sympathetic output and lower BP
• Requires surgical implantation of a pacemaker-like device that has an electrode tunneled from its subclavicular location to the carotid body on each side of the neck
• When the pacemaker is turned on it activates baroreceptor input into the brainstem resulting in BP reduction that appears to be sustained for several years
### Rheos System

**Office-based baseline (mean±SD) and Annual Changes (mean±SE)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Δ 1 year</th>
<th>Δ 2 year</th>
<th>Δ 3 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>190 ± 30</td>
<td>-38 ± 8 (p&lt;0.001)</td>
<td>-34 ± 8 (p&lt;0.001)</td>
<td>-37 ± 10 (p=0.003)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>111 ± 22</td>
<td>-25 ± 5 (p&lt;0.001)</td>
<td>-20 ± 6 (p=0.005)</td>
<td>-23 ± 7 (p=0.005)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>79 ± 9</td>
<td>-12 ± 3 (p&lt;0.001)</td>
<td>-11 ± 4 (p=0.008)</td>
<td>-6 ± 4 (p=0.14)</td>
</tr>
</tbody>
</table>

Scheffers  Journal of Hypertension 2009;27(supp4):S421
ABPM

Change in SBP (mm Hg)

N=379

Change in DBP (mm Hg)

Conclusion

• Most resistant hypertension is due to drug management issues (lack of adequate regimen, non-compliance, side effects, physician apathy)

• Secondary hypertension only accounts for 5-10 % of hypertension

• Hyperaldosteronism is present in approx 20 % of patients with resistant hypertension