Resistant Hypertension: Diagnosis and Treatment

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Conflicts of Interest During Prior 12 Months

- Grant Support: NIH, Medtronic, RECOR
- Consulting: Valencia Technologies
- Honorarium: None
- Off-Label Use: None
A 54-year old white male presents with a 5-year history of poorly controlled hypertension despite use of multiple medications. Current treatment regimen includes HCTZ 25 mg, atenolol 50 mg, and losartan 50 daily. No prior drug intolerances. Renal function is normal (eGFR >60). Comorbidities include type 2 diabetes, OSA (untreated), and hyperlipidemia. In clinic, BMI is 32 kg/m^2 and office BP is 168/94 mmHg and heart rate is 84 bpm. No prior diagnostic testing has been done. Home BPs are 160-180s/90-100s.
The appropriate diagnostic testing at this point would be:

A. 24-hr ambulatory BP monitoring
B. Echocardiogram
C. Polysomnogram
D. Aldosterone/renin ratio
E. Renal doppler
Definition

- Resistant hypertension is defined as blood pressure that remains above goal in spite of concurrent use of 3 antihypertensive agents of different classes.

- Ideally, one of the 3 agents should be a diuretic and all agents should be prescribed at optimal dose amounts.

- As defined, resistant hypertension includes patients whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled, but required 4 or more medications to do so, should be considered resistant to treatment.

AHA Scientific Statement *Hypertension* 2008
• Prevalence of resistant HTN was 12.8% of all hypertensive individuals and 15.3% of those taking medications
• 7.9% were uncontrolled while taking ≥ medications
Prevalence of Resistant Hypertension in US NHANES 1988-2008

Roberie and Elliot, Curr Opinion Cardiol, in press
RESISTANT HYPERTENSION

UNCONTROLLED BLOOD PRESSURE

Apparent Resistant HTN

PSEUDORESISTANCE
- poor BP technique
- poor adherence
- whitecoat effect

True Resistant HTN
Prevalence of Resistant Hypertension in Spain

Spanish APBM Registry 2009
(n=68,045)

de la Sierra, Hypertension 2011
Persistence of White Coat Resistant Hypertension

Muxfeldt et al., Hypertension 2012
Resistant hypertension? Assessment of adherence by toxicological urine analysis

Oliver Jung\textsuperscript{a}, Janis L. Gechter\textsuperscript{a}, Cora Wunder\textsuperscript{b}, Alexander Paulke\textsuperscript{b}, Christine Bartel\textsuperscript{a}, Helmut Geiger\textsuperscript{a}, and Stefan W. Toennes\textsuperscript{b}

375 Patients Referred for Uncontrolled HTN on 3 Drugs

- Maximized Doses
- Excluded White Coat

108 Uncontrolled

- 15 with Secondary HTN
- 17 Controlled on 4 Drugs

76 Uncontrolled

- 40 Non-Adherent
  - (30% taking no meds and 85% <half)

36 True Resistant HTN (3.5% of referred patients)

J Hypertension 2013
Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network

Brent M. Egan, Yumin Zhao, Jiexiang Li, W. Adam Brzezinski, Thomas M. Todoran, Robert D. Brook and David A. Callhoun

Hypertension 2013
Resistant Hypertension in Hypertension Outcome Trials

ALLHAT
- 27% of participants were on 3 or more medications at study end.
- 50% of participants needed 3 more blood pressure medications.

ASCOT
- 49% of all subjects were diagnosed with resistant hypertension during median follow-up of 4.8 years.
- 34% of previously untreated subjects were diagnosed with resistant hypertension during median follow-up of 5.3 years.

ACCOMPLISH
- 25-28% of all participants remained uncontrolled after a mean follow-up of 3 years.
Risk Factors for Having Resistant Hypertension
Kaiser-Permanente Southern California

470,386 Hypertensives
60,327 Resistant

Sim et al., Mayo Clinic Proceedings 2013
Biochemical test results:
- Serum aldosterone 10 ng/dL
- PRA is 0.6 ng/ml/hr
- 24-hr aldosterone 13 mcg
- 24-hr sodium 202 meq

Based on above test results:
A. The patient has primary aldosteronism
B. The patient does not have primary aldosteronism
C. Low ARR excludes primary aldosteronism
D. Urinary sodium too low to diagnose primary aldosteronism
Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension

<table>
<thead>
<tr>
<th>Location</th>
<th>Prevalence of PA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>17%</td>
</tr>
<tr>
<td>Birmingham</td>
<td>20%</td>
</tr>
<tr>
<td>Oslo</td>
<td>22%</td>
</tr>
<tr>
<td>Prague</td>
<td>19%</td>
</tr>
</tbody>
</table>

PA = Primary aldosteronism.

24-hr Urinary Aldosterone and BMI in Patients with Resistant Hypertension

Quartiles of BMI

Men p<0.0001

Women p<0.0013
Percent suppressed PRA, high ARR, and High Aldo in Resistant Hypertension vs. Controls

Gaddam et al., Arch Intern Med 2008
BNP and ANP Levels in Patients with Resistant Hypertension vs. Control Subjects

Gaddam et al., Arch Intern Med 2008
BNP and ANP Levels in Patients with High and Normal Aldosterone and Resistant Hypertension vs. Control Subjects

Gaddam et al., Arch Intern Med 2008
Potential Mechanisms of Refractory Fluid Retention in Patients with Resistant Hypertension

- Hyperaldosteronism
- Obesity
- African American race
- Chronic kidney disease
- High dietary salt intake
Audience Response Question 3

Most effective medication change would be:

A. Titrate HCTZ to 50 mg
B. Substitute lisinopril 40 for losartan
C. Substitute chlorthalidone 25 mg for HCTZ
D. Substitute amlodipine 5 mg for atenolol
On a combination of lisinopril 40 mg, amlodipine 10 mg, and chlorthalidone 25 mg the patients office BP is 154/88 mmHg. The next appropriate therapeutic step is:

A. Add diltiazem CD 180 mg qday
B. Titrate chlorthalidone to 50 mg qday
C. Add spironolactone 25 mg qday
D. Add hydralazine 25 mg tid
Blood Pressure Response to Spironolactone in Subjects With Resistant Hypertension

BP Response to Spironolactone in PA and Non-PA Subjects

SBP = systolic blood pressure; DBP = diastolic blood pressure
BP Response with Spironolactone 25-50 mg

ASCOT Results

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Results

![Graph showing the effects of different medications on blood pressure in response to changes in renin levels.](image)

Lancet 2015
## Results

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure (mm Hg)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>$-3.86,(-5.28\text{ to }-2.45)$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>$-0.88,(-2.32\text{ to }0.56)$</td>
<td>$0.23$</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>$-1.49,(-2.94\text{ to }-0.04)$</td>
<td>$0.04$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-0.68,(-2.10\text{ to }0.75)$</td>
<td>$0.35$</td>
</tr>
</tbody>
</table>

Difference in mean home systolic blood pressure after treatment with the lower (week 6) and higher doses (week 12) of each treatment.

*Table 4: Home systolic blood pressure dose response (higher vs lower dose)*

Lancet 2015
Chlorthalidone 25 mg vs. HCTZ 50 mg daily

Ernst et al. *Hypertension* 2006;47:352

After 8 weeks

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone</td>
<td>-12.4</td>
<td>-7.4</td>
</tr>
<tr>
<td>HCTZ</td>
<td>-7.1</td>
<td>-5.1</td>
</tr>
</tbody>
</table>

$\Delta$ in 24-hour BP (mm Hg)

$P=0.054$

$P=0.297$
Chlorthalidone 25 mg vs. HCTZ 50 mg daily

After 8 weeks

- SBP: Chlorthalidone -13.5 mm Hg, HCTZ -6.4 mm Hg
  - P = 0.009
- DBP: Chlorthalidone -7.2 mm Hg, HCTZ -4.6 mm Hg
  - P = 0.288

Ernst et al. *Hypertension*. 2006;47:352
Generalized Treatment Approach for Resistant Hypertension

- ACE inhibitor or ARB in combination with long-acting calcium channel blocker (amlodipine). I tend to dose bid to maximize duration of effect and minimize adverse effects, especially amlodipine-associated peripheral edema.

- Chlorthalidone 12.5-25 mg daily

- Spironolactone 12.5-50 mg daily

- Combined alpha-beta antagonist (I prefer labetalol over carvedilol)

- Centrally-acting agent (guanfacine)

- Vasodilator (minoxidil). May require use of loop-diuretic to blunt fluid retention.
The most effective non-pharmacologic change would likely be:

A. Dietary sodium restriction <100 meq/day
B. CPAP use >4 hrs night
C. Weight loss
D. Daily exercise
EFFECTS OF SALT REDUCTION (6 g/day)

He and MacGregor. Cochrane Database of Systematic Reviews 2004
Resistant Hypertension
High/Low Dietary Salt Cross-Over Evaluation

12 patients

6 patients low-salt diet 1 week

6 patients high-salt diet 1 week

wash-out 2 weeks

6 patients low-salt diet 1 week

6 patients high-salt diet 1 week

Pimenta et al. Hypertension 2009
## Results: High-Low Salt Cross-Over

<table>
<thead>
<tr>
<th></th>
<th>High-salt (n=12)</th>
<th>Low-salt (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>94.3 ± 18.6</td>
<td>92.7 ± 17.6*</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>35.1 ± 32.1</td>
<td>12.5 ± 10.8*</td>
</tr>
<tr>
<td>Serum K (mEq/L)</td>
<td>3.8 ± 0.3</td>
<td>4.1 ± 0.5</td>
</tr>
<tr>
<td>PAC (ng/dL)</td>
<td>11.1 ± 4.8</td>
<td>15.5 ± 9.3*</td>
</tr>
<tr>
<td>PRA (ng/mL/h)</td>
<td>0.9 ± 0.5</td>
<td>14.3 ± 32.6</td>
</tr>
<tr>
<td>Ualdo (mcg/24-hr)</td>
<td>11.7 ± 5.1</td>
<td>18.6 ± 11.2*</td>
</tr>
<tr>
<td>UK (mEq/24-hr)</td>
<td>56.9 ± 21.8</td>
<td>69.2 ± 27.7*</td>
</tr>
<tr>
<td>UNa (mEq/24-hr)</td>
<td>261.5 ± 70.4</td>
<td>48.6 ± 27.2*</td>
</tr>
<tr>
<td>TFC (kohms⁻¹)</td>
<td>29.3 ± 3.7</td>
<td>26.5 ± 3.5</td>
</tr>
</tbody>
</table>

* Different from high-salt, p<0.05

Pimenta et al. Hypertension 2009
Reduction in Blood Pressure High to Low Salt Ingestion

Pimenta et al. Hypertension 2009
Effect of CPAP on BP in Patients with OSA and Resistant HTN

Martinez-Garcia, JAMA 2013

71 subjects with CPAP > 4 hrs/night
Effect of CPAP on BP in Subjects with OSA and Resistant HTN

Martinez-Garcia JAMA 2013
RENAL DENERVATION – SIMPLICITY HTN-2 TRIAL

Baseline BP=178/97 mm Hg on 5.2 medications

n=106

RENAL DENERVATION – SIMPLICITY HTN-2 TRIAL

Home BP
-20/12 mmHg (n=32)

24-hr ABPM
-11/7 mmHg (n=20)

RENAL DENERVATION – SIMPLICITY HTN-3 TRIAL

Simplicity HTN-3 Investigators. NEJM April 2014
Generalized Treatment Approach for Resistant Hypertension

- Dietary sodium restriction, weight loss, exercise, (CPAP).
- ACE inhibitor or ARB in combination amlodipine.
- Chlorthalidone 12.5-25 mg daily
- Spironolactone 12.5-50 mg daily
- Combined alpha-beta antagonist (I prefer labetalol over carvedilol)
- Centrally-acting agent (guanfacine)
- Vasodilator (minoxidil). May require use of loop-diuretic to blunt fluid retention.