DIAGNOSIS AND TREATMENT OF RESISTANT HYPERTENSION

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Faculty Disclosure
Suzanne Oparil, MD

The below relationships listed are potential conflict of interest, but are NOT considered to influence this presentation. Disclosures are listed below (previous 12 months):


Increasing Interest in “Resistant Hypertension”

*There were 7 publications between 1958 – 1975.
PUBMED search conducted 5/24/2013 for “resistant hypertension”
Definition of TRH – American Heart Association (AHA)

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

- "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 require 4 or more medications to do so should be considered resistant to treatment."


<table>
<thead>
<tr>
<th>Number of Medications</th>
<th>Controlled BP</th>
<th>Uncontrolled BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
Prevalence of aTRH - NHANES

<table>
<thead>
<tr>
<th>Year</th>
<th>Percentage with aTRH*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1994</td>
<td>5.5</td>
</tr>
<tr>
<td>1999-2004</td>
<td>8.5</td>
</tr>
<tr>
<td>2005-2010</td>
<td>11.8</td>
</tr>
</tbody>
</table>

*Among all US adults with hypertension

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Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis

Dharan J. Kumbhari1, P. Gabriel Sorg1,2, Christopher P. Cannon1,3, Kari A. Egi1,4, Stephen C. Smith3,5, Kevin Crowley4,5, Shinya Goto6, E. Magnus Ohman3,7, George L. Bakris1, Todd S. Portele8, Scott Korable9,10, and Deepak L. Bhatt5,11

On behalf of the REACH Registry Investigators

Tennessee, Vanderbilt University, Nashville, TN; The American Heart Association, Dallas, TX; Brigham and Women’s Hospital, Boston, MA; University of California, San Francisco, CA; Emory University, Atlanta, GA; University of Florida, Gainesville, FL; University of North Carolina, Chapel Hill, NC; University of Washington, Seattle, WA; Kaiser Permanente Medical Care Program, Los Angeles, CA; Mayo Clinic, Rochester, MN; University of Chicago, Chicago, IL; The University of Texas Health Science Center at Houston, Houston, TX; Mount Sinai Medical Center, Miami, FL; The Hospital of the University of Pennsylvania, Philadelphia, PA; The University of Kentucky, Lexington, KY; University of Minnesota, Minneapolis, MN; University of California, Los Angeles, CA; University of California, San Diego, CA; and the University of Colorado, Denver, CO

European Heart Journal 34, 1204–1214, 2013.

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Reduction of Atherothrombosis for Continued Health (REACH) Registry

Population: 53,530 hypertensive patients in 44 countries ≥ 45 yrs old and 3 or more CVD risk factors or established CAD, CVD, PAD

- 46,740 (87.3 %) non-resistant hypertension on < 3 antihypertensive agents
- 6,790 (12.7%) resistant hypertension
- 3,316 (6.2%) on 3 antihypertensive agents
- 2,471 (4.6%) on 4 antihypertensive agents
- 1,003 (1.9%) on ≥ 5 antihypertensive agents

4 year followup (2004 – 2008)

**Evaluation Objectives**

- **Confirm true treatment resistance**
  - Patient adherent with 3 or more medications
  - Accurate BP measurement
  - Exclude white coat “resistant hypertension”
- **Screen for secondary causes of hypertension**
  - Primary aldosteronism
  - Renal artery stenosis
  - Obstructive sleep apnea
- **Document degree of target-organ damage**
  - LVH, retinopathy, CKD, proteinuria
Definition of TRH - Operationalized

- Treatment-resistant hypertension (TRH) is defined as SBP/DBP \( \geq 140/90 \) mmHg with concurrent use of \( \geq 3 \) antihypertensive medication classes or use of \( \geq 4 \) antihypertensive medication classes regardless of blood pressure.

- In epidemiology studies, the term apparent TRH (aTRH) has been used when pseudoresistance can be determined.

Uncontrolled Blood Pressure

**Pseudoresistance**
- Poor BP technique
- Poor adherence
- Whitecoat effect
- Inadequate doses of medications
- Inappropriate combinations of medications

**Resistant Hypertension**

Nonadherence

- Common Problem
- Difficult to Detect
  - Pill counts
  - Pharmacy fill data
  - Microchip equipped pill bottles
  - **Biochemical testing**
  - When all else fails, **FRANK DISCUSSION WITH PATIENT**
Adherence in patients with “Resistant” Hypertension

Toxicological Urine Analysis

76 patients with aTRH (BP uncontrolled on ≥ 4 drugs)
Confirmed regular drug intake in days prior to testing
HPLC-MS analysis of spot urine samples for antihypertensive drugs

Adherent: n=36
Nonadherent: n=40

87.5% confessed when given test results

Percentage of Prescribed Drugs Taken by Nonadherent Patients

Patient Adherence to Therapy
Potential Mechanisms of Refractory Fluid Retention in Patients with Resistant Hypertension

- Hyperaldosteronism
- Obesity
- African American race
- Chronic kidney disease
- High dietary salt intake

Generalized Treatment Recommendations

- Life style modifications (weight loss, exercise, low-salt/high fiber diet)
- Standard triple regimen of ACE inhibitor or ARB, thiazide diuretic, and long-acting calcium channel blocker
- Preferential use of chlorothalidone
- Consider use of aldosterone antagonist (spironolactone, eplerenone, amiloride) as fourth drug
- Vasodilating beta-blocker as fifth drug
- Centrally-acting agent as fifth drug (clonidine, guanfacine)
- Vasodilating agents (hydralazine, minoxidil) as last resort

Potential Mechanisms of Refractory Fluid Retention in Patients with Resistant Hypertension

- Hyperaldosteronism
- Obesity
- African American race
- Chronic kidney disease
- High dietary salt intake
### Pharmacokinetic/Pharmacodynamic Comparison of HCTZ and Chlorthalidone

<table>
<thead>
<tr>
<th></th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Half-life (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCTZ</strong></td>
<td>2</td>
<td>4-6</td>
<td>6-9 (long-term dosing)</td>
<td>12 (single dose) 16-24 (long-term dosing)</td>
</tr>
<tr>
<td><strong>Chlorthalidone</strong></td>
<td>2-3</td>
<td>2-6</td>
<td>40 (single dose) 44-48 (long-term dosing)</td>
<td>24-48 (single dose) 48-72 (long-term dosing)</td>
</tr>
</tbody>
</table>


### Chlorthalidone 25 mg vs HCTZ 50 mg Daily

After 8 weeks

CHLORTHALIDONE

<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>

P=0.054  P=0.297


### Clinical Trials

#### Primary Endpoint
- Hospitalization for Hypokalemia
- Hospitalization for Hyponatremia
**Diuretic Use: Practical Considerations**

**Chlorthalidone**
- Dosing: 12.5-25 mg daily
- Metabolic complications worse, especially hypokalemia
- We typically dose with spironolactone

**Spironolactone**
- Dosing: 12.5-100 mg daily
- Hyperkalemia uncommon if good renal function
- CKD, ACEi/ARB, renin inhibitor, NSAIDs increase risk
- Generally well tolerated up to 25 mg
- Breast tenderness/gynecomastia dose dependent

**Loop diuretics**
- Usually not needed until GFR <30
- Use with minoxidil or hydralazine
- Long acting agent or twice daily dosing of furosemide

**Potential Mechanisms of Refractory Fluid Retention in Patients with Resistant Hypertension**

- Hyperaldosteronism
- Obesity
- African American race
- Chronic kidney disease
- High dietary salt intake

**Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension**

![Graph showing prevalence of primary aldosteronism across different locations](graph.png)
Percent Suppressed PRA, High ARR, and High Aldo in Resistant Hypertension vs Controls

Blood Pressure Response to Spironolactone in Subjects With Resistant Hypertension

Change in ABPM Levels with Spironolactone in Patients with True Resistant Hypertension
BP Response to Spironolactone in PA and Non-PA Subjects

Change in SBP with Spironolactone vs ACEi/ARB in Patients with True Resistant Hypertension

REAL LIFE EXPERIENCES FROM THE KIRKLIN CLINIC
**J.M. 69 Year-old Black Woman**  
**Retired Substitute Teacher**  
**Initial Visit 07/12/2013**  

- **Referred for resistant HTN**
- **Diagnosed in 2004:**
  - BP uncontrollable when husband died in 2012. BP readings:
    - 140/70 → 160-200/80 mm Hg
- **Previous evaluation:**
  - CT angiogram of kidneys
  - RAS stented 2008—patent stent
  - “small arteries” in parenchyma
- **Comorbidities**
  - Hypercholesterolemia
  - Hypothyroidism
  - Diverticulitis

**Current medications**
- Olmesartan Medoximil/Amlodipine/Hydrochlorothiazide 40/10/25 mg QD
- Enalapril 20 mg BID
- Metoprolol ER 50 mg QD
- Levothyroxine 25 mg QD
- Clonidine 0.1mg BID
- Furosemide 20 mg BID
- Potassium Chloride 20 mEq QD
- Aspirin 81 mg QD

**Cont’d – J.M. Initial Visit 07/12/2013**

<table>
<thead>
<tr>
<th>No complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE: BP 206/82 mm Hg (seated)</td>
</tr>
<tr>
<td>HR 76</td>
</tr>
<tr>
<td>BMI 34.8</td>
</tr>
<tr>
<td>Lab: Creatinine 0.76</td>
</tr>
<tr>
<td>eGFR &gt;60 ml/min/1.73 m²</td>
</tr>
<tr>
<td>Glucose 79</td>
</tr>
<tr>
<td>K⁺ 4.7</td>
</tr>
<tr>
<td>Plan: Begin chlorthalidone 25 mg QD</td>
</tr>
<tr>
<td>Increase metoprolol to 100 mg QD</td>
</tr>
<tr>
<td>D/C enalapril and furosemide</td>
</tr>
<tr>
<td>Order SA, PRA, 24hr urine for aldosterone/cortisol/Nat/K⁺</td>
</tr>
<tr>
<td>RTC 1 month</td>
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</table>

**J.M. Return Visit 08/30/2013**

| Complaints: Dry mouth, ankle swelling, cough, cost of Olmesartan Medoximil/Amlodipine/Hydrochlorothiazide |
| Home BPs: ~170-180 mm Hg |
| PE: BP 176/62 mm Hg (seated) |
| HR 56 |
| No edema |
| Lab: Serum aldol 15 |
| 24-hr urine aldol 7.9 |
| PRA 3.9 |
| Plan: D/C Olmesartan Medoximil/Amlodipine/Hydrochlorothiazide Substitute Amlodipine 10 mg/valsartan 320 mg QD Add Spironolactone 25 mg QD Stop K⁺ replacement |
| RTC 3 months |
Missed 2 visits due to vacation

Complaints:
- Lightheaded when BP < 135 mmHg

Home BPs:
- ~130/80 mm Hg

Plan:
- Wean Clonidine
- Stop K+ replacement
- RTC 3 months

Current Medications:
- Amlodipine 10mg/Valtsaran 320mg QD
- Metoprolol ER 100 mg QD
- Spironolactone 25 mg QD
- Levothyroxine 25 mg QD
- Aspirin 81 mg QD

University of California, San Francisco Medical School

J.M. Return Visit 11/14/2013

No complaints

Home BPs: 144/80 mm Hg (highest recorded home BP since last visit)

PE:
- BP 124/68 mm Hg (seated)
- HR 58
- No edema

Plan:
- Continue taking current medications
- RTC 6 months

Conclusions

Clinical implications:
- Important to identify and manage patients with aTRH.
- Interventions to prevent aTRH and reduce the risk for adverse outcomes among individuals with aTRH are needed.
- Future studies are needed to identify approaches for preventing aTRH as well as reducing the risk for CVD and renal outcomes once patients develop aTRH.
Thank you!