Difficult-to-Control & Resistant Hypertension

Anthony Viera, MD, MPH, FAHA
Professor and Chair
Objectives

• Define “resistant hypertension”
• Discuss evaluation strategy for patient with HTN that appears difficult to control
• Describe management options for patients with resistant HTN
Patient 1

- Mrs. D is a 59 y/o woman in for follow-up; BP last visit (4 weeks ago) was 188/93 mm Hg and you increased her amlodipine from 5-mg to 10-mg qd
- Other medications are lisinopril 20-mg BID, clonidine 0.2mg BID, tramadol 50-mg
- BUN/Cr have been normal
- Today’s office BP average is 170/90 mm Hg; she reports taking her medications.
- Does she have resistant hypertension?
Resistant hypertension

- BP level above goal despite adherence to a combination of at least three optimally dosed antihypertensive drugs of different classes, (ideally) one of which is a diuretic
Prevalence of resistant HTN

• Difficult to estimate
• Data from trials suggest 20% - 30%
  – UKPDS → 29% required 3 or more drugs to get to goal of <150/85 mm Hg
  – ALLHAT → 34% uncontrolled on 2 meds; 50% needed 3 or more agents
• Recent analyses (incl NHANES) suggest 12-13% among treated hypertensives
• Not all difficult-to-control HTN is resistant
Causes of poorly controlled BP

• Apparent drug resistance
  – Nonadherence to therapy
  – Suboptimal therapy
  – Isolated office hypertension (“white coat” phenomenon)

• True drug resistance
  – Physiologic resistance (volume overload)
  – Drug effects and interactions
  – Associated conditions
  – Secondary hypertension
Patient 2

• Mrs. G is a 74 year old woman with long history of severe hypertension who has had extensive evaluation for secondary hypertension that was unrevealing

• BP control improved, but still suboptimal, with gradual intensification of therapy; on ramipril, diltiazem, and hydrochlorothiazide/triamterene

• Further attempts at lowering BP resulted in side effects

• Office BP 174/68 mm Hg; creatinine 1.5 mg/dL; ECG remarkable for LVH

• What is your next step?
Problems with office BP measurements

• Poor technique
• Interobserver and intraobserver variability
• “White coat” phenomenon
• True inherent variability
Self-measurement of BP at Home in the Elderly: Assessment & Followup

- Office and home BP measured in 4939 elderly, treated hypertensive patients
- Office BP measured by physician
- Home BP measured 3 times, in AM and PM, on 4 consecutive days
- Thresholds defining uncontrolled hypertension:
  - 140/90 mmHg in office
  - 135/85 mmHg at home
- Mean follow-up: 3.2 years
- Endpoints: Cardiovascular mortality, cardiovascular events

JAMA 291:1342, 2004
SHEAF

• Mean blood pressures
  – Office: 152/85 mmHg
  – Home: 146/82 mmHg

• Categories of BP
  – Controlled: 685 pts (14%)
    • Ave SBP: Office 130 mmHg, Home 123 mmHg
  – White-coat hypertension: 656 pts (13%)
    • Ave SBP: Office 151 mmHg, Home 127 mmHg
  – Masked hypertension: 462 pts (9%)
    • Ave SBP: Office 134 mmHg, Home 144 mmHg
  – Uncontrolled: 3125 pts (63%)
    • Ave SBP: Office 160 mmHg, Home 155 mmHg

JAMA 291:1342,2004
SHEAF: CV events

JAMA 291:1342,2004
OvA (Office vs Ambulatory BP)

- Office and ambulatory BP measured in 1963 treated hypertensive patients
- Office BP measured 3 times on a single visit and averaged
- Ambulatory BP measured over 24 hours during normal activities
- Median follow-up: 5 years
- Endpoint: CVD events

NEJM 348:2407,2003
CVD events according to office and ambulatory pressures OvA

![Graph showing incidence of cardiovascular events by systolic blood pressure categories](image-url)
White coat effect in patients with hypertension: around 30%

- 611 patients with office BP > 140/90 mmHg
- Referred for ABPM
- Medications
  - 0: 277
  - 1 or 2: 216
  - 3 or more: 118

Am J Hypertens 14:1263,2001
Spanish ABPM Registry

• 8295 patients with resistant HTN by office BP

• ABPM: 37.5% white-coat phenomenon (white-coat resistance)

• Key point from OvA and Spanish study: 1/3 of patients with suspected resistant HTN have normal BP on ABPM
Mrs. G’s ABPM

<table>
<thead>
<tr>
<th>Period</th>
<th>Time</th>
<th>Samples</th>
<th>Mean Sys mmHg (+/- Std.Dev.)</th>
<th>Mean Dia mmHg (+/- Std.Dev.)</th>
<th>Mean HR BPM (+/- Std.Dev.)</th>
<th>BP Load Sys %</th>
<th>BP Load Dia %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10:12-11:39 (25:27)</td>
<td>40</td>
<td>131 (16.0)</td>
<td>79 (10.1)</td>
<td>76 (9.4)</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Awake Period</td>
<td>06:00-22:00</td>
<td>32</td>
<td>135 (15.4)</td>
<td>82 (7.4)</td>
<td>79 (8.4)</td>
<td>31</td>
<td>19</td>
</tr>
<tr>
<td>Asleep Period</td>
<td>22:00-06:00</td>
<td>8</td>
<td>116 (8.4)</td>
<td>64 (5.9)</td>
<td>67 (7.0)</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Asleep Dip: Sys</td>
<td>= 13.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dia = 21.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ambulatory monitoring can save lives

Intra-arterial ambulatory blood pressure monitoring can save your life – or, acute haemodynamic response to a murderous assault

Mary E. Heber ¹, Edward B. Raftery ¹ and Derek Thompson ²

¹ Department of Cardiology and Clinical Sciences, Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex, U.K.; ² Renal Unit, St. Paul’s Hospital, London, U.K.

(Received 2 December 1987; accepted 21 December 1987)

A patient undergoing intra-arterial blood pressure monitoring was attacked by a burglar armed with a knife. The knife was turned aside by the transducer/perfusion unit, which continued to monitor his heart rate and blood pressure throughout. A pronounced “fight or flight” response was recorded.
Ambulatory monitoring can save lives
Ambulatory monitoring can save lives

Fig. 2. Print-out from tape of blood pressure recording at the time of the attack. A–B, before discovery of intruder; B, discovery of intruder; C, drop in blood pressure; D, sympathetic-mediated rise in blood pressure.
Out-of-office BP assessment strategy

Office BP elevated

- Home BPs normal
  - Perform ABPM
    - 24-hr ABP < 130/80 mmHg
      - Continue current therapy
    - 24-hr ABP > 130/80 mmHg
      - Intensify therapy
- Home BPs elevated
  - Intensify therapy

24-hr ABP < 130/80 mmHg

24-hr ABP > 130/80 mmHg
Step 1: Confirm HTN is truly resistant

- Repeat office measurements
  - Ensure correct cuff size
- Confirm adherence to treatment plan
  - This can be a challenge
- Consider out-of-office monitoring
- In elderly, consider pseudohypertension, but this is difficult to confirm
Step 2: Eliminate or reduce contributing factors

• Make adherence to drugs as simple as possible
  – Once-daily
  – Fixed dose combinations
• Discontinue or reduce things that interfere with BP control
  – Drugs
  – Supplements
  – Foods / drinks
Interfering substances

- Corticosteroids
- Cyclosporine
- Erythropoietin
- NSAIDS
- OCPs
- Some antidepressants (e.g., bupropion, TCAs)
- Sympathomimetics
  - Decongestants, cocaine, diet pills
- Chewing tobacco
- Excessive alcohol intakes
- Excessive sodium intake
- Excessive licorice
- Some herbals
  - Ginseng
  - Ephedra
  - Bitter orange
Patient 3

- Mr. B is a 55 year old man with 5 year history of refractory hypertension
- Home SBP 130-160 mmHg despite therapy with 6 antihypertensive agents
- Creatinine 0.7 mg/dL; potassium 4.1 mEq/L
- BMI 44 kg/m² and office BP 156/90 mmHg
- What is your plan?
Step 3: Reconsider secondary causes

• Address chronic kidney disease if present
• Consider checking for primary aldosteronism
• Consider testing for obstructive sleep apnea
• Consider rarer causes as appropriate
Obstructive sleep apnea

• Consider sleep study
• Epworth Sleepiness Scale or Sleep Apnea Clinical Score coupled with nighttime pulse oximetry when sleep study not available
• Treatment with CPAP may be helpful in reducing BP; certainly has other benefits
Evaluation for hyperaldosteronism

**Initial studies**
Aldo (ng/dL)/PRA (ng/mL/h)
ARR > 20 and aldo > 15 ng/dL

**Confirmatory tests**
Salt loading
24-hour aldo excretion

**Imaging**
High-resolution CT
Patient 4

- Mr. J is a 68 year old man with labile BP which has proven difficult to control
- Creatinine 1.1 mg/dl, renal ultrasound and urine catecholamines normal
- K+ is normal
- Current regimen: chlorthalidone 25-mg qd, losartan 50 mg bid, amlodipine 10mg qd
- BP in clinic ~176/80 mmHg repeatedly, confirmed elevated by out-of-office
- What medication do you add next?
Number of drugs needed to achieve BP goals

- UKPDS
- HOT
- AASK
SBP reduction by drug

BMJ 326:1427, 2003
SBP reduction with a single drug

BMJ 326:1427,2003
SBP reduction with combinations

Three drugs at half dose = ↓ 20/10 mmHg

Number of drugs at half-standard doses

BMJ 326:1427,2003
Adverse effects by dose

BMJ 326:1427, 2003
Combination drug therapy

- The efficacies of 5 categories of drugs are similar at standard doses
- The drugs are effective from all pretreatment levels of blood pressure
- Efficacy is only 20% lower at half-standard doses than at standard doses
- Adverse effects are much less common at half-standard doses than at standard doses
- Reductions in BP with drugs in combination are additive
Effective drug combinations

- V + R drug
- First three drugs will generally be
  - Thiazide diuretic
  - ACEI or ARB
  - Dihydropyridine CCB
Spironolactone in resistant hypertension

Reduces BP ~ 20/10 mmHg

SBP – filled bars
DBP – open bars

BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT*

*Anglo-Scandannavian Cardiovascular Outcomes Trial

\[ \Delta \text{SBP} = -21.9 \]
\[ \Delta \text{DBP} = -9.5 \]

Pre PrePost Post
SBP 156.9 135.1
DBP 85.3 75.8

6% discontinuation rate due to adverse effects

N=1411

Spironolactone

• Several small studies
• PATHWAY-2  Lancet. 2015;386:2059-2068.
  – Randomized, double-blind, crossover, 335 patients
  – Home BP as outcome, intention-to-treat
  – Spironolactone compared to doxazosin and bisoprolol
  – Home BP -9 mm Hg vs placebo and -4 mm Hg vs other two
Step 4: Intensify therapy

• Reiterate importance of lifestyle modifications
• Increase diuretic dose (HCTZ → chlorthalidone) or change to loop if GFR <30 mL/min
• If no contraindications, add spironolactone
• Beta-blocker
• Use a combined alpha-beta blocker (possibly a vasodilating beta-blocker like carvedilol)
• Add clonididine, start with pill → transition to patch
Step 4 (cont)

- Consider hydralazine
- Combine nondihydropyridine and dihydropyridine CCB
- Consider long-acting nitrate in elderly
- Minoxidil (plus loop) or reserpine
Take-home points

• Confirm poor BP control with home and/or ambulatory blood pressure monitoring
• Eliminate or reduce interfering substances or factors (including anything contributing to volume overload)
• Reconsider the common secondary causes of hypertension
• Use effective combinations of antihypertensive agents (including a diuretic)
• Spironolactone is an evidence-based tx for resistant HTN, but watch K+