Resistant Hypertension: Core Curriculum 2008

Mark G. Parker, MD

INTRODUCTION

A patient with difficult-to-control hypertension commonly is referred to a nephrologist for evaluation and therapy. Resistant hypertension is defined as blood pressure that remains under suboptimal control despite the adherent use of 3 full-dose antihypertensive medications, inclusive of a diuretic.

Classic teaching dictates that initial subspecialty referral and assessment must demand a careful history, physical examination, and laboratory investigation to exclude secondary causes of hypertension, including renovascular disease, chronic kidney disease, and endocrinopathies (Table 1). Nonetheless, these causes are identified in as little as 10% of resistant hypertension referrals. A greater prevalence of secondary causes is noted with increasing age or coexistent atherosclerosis. An earlier Core Curriculum on Hypertension by David Warnock and Stephen Textor outlines secondary hypertension causes.

Suboptimal therapy is the most common cause of resistant hypertension. Suboptimal therapy may be defined as failure to use rational pharmacological combinations, attend to comorbid conditions, properly intervene for excess extracellular volume, or some combination of these. Furthermore, evaluation may be confounded by inaccurate blood pressure measurement, pseudohypertension, white coat effect, medical nonadherence, and concomitant ingestion of interfering or antagonizing substances.

An intriguing line of investigation is emerging with regard to the importance of obesity, sleep apnea, and hyperaldosteronism in patients with resistant hypertension. An interrelated pathophysiological process of these disorders has been postulated. Careful assessment for these conditions may expose additional avenues for successful treatment of patients with resistant hypertension.

Therapy for patients with resistant hypertension involves lifestyle modification, effective treatment of comorbid conditions, and rational pharmacological combinations. Individual lifestyle interventions have a small impact in isolation, but are useful in aggregate. A rational medication approach emphasizes appropriate drug class combinations at optimal doses, particular attention to adequate diuretic use, and a potential role for mineralocorticoid blockade.

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I. Accurate blood pressure assessment: technique
   A. Variables affecting clinic blood pressure measurement
      1. Arm position
         a. Midcuff, upper arm, right atrium level
      2. Cuff size
         a. Largest error when cuff too small relative to arm circumference (falsely increased readings)

Originally published online as doi:10.1053/j.ajkd.2007.11.040 on August 11, 2008.

Address correspondence to Mark G. Parker, MD, Division of Nephrology, Maine Medical Center, 22 Bramhall St, Portland, ME 04102. E-mail: parkem@mmc.org

0272-6386/08/5204-0023$34.00/0
doi:10.1053/j.ajkd.2007.11.040

Table 1. Classic Disease States as Secondary Causes of Hypertension

Coarctation of the aorta
Glucocorticoid-excess diseases
Cushing syndrome
Mineralocorticoid-excess diseases
Hyperaldosteronism
Pheochromatocytoma
Renal parenchymal disease
Renal vascular disease
Sleep apnea
Thyroid disorders

   b. Bladder length should be at least 80% and width at least 40% of arm circumference
3. Sphygmomanometer type and maintenance
   a. Mercury remains gold standard, although aneroid now more common; this requires periodic calibration
   b. Oscillometric automated monitors require no transducer and are less susceptible to external noise
      i. Less reliable in patients with stiff arteries
      ii. Require periodic validation
4. Frequency of readings
5. Patient factors
   a. Anxiety; white coat effect
   b. Recent food, exercise, nicotine, caffeine intake; modest impact

B. Pseudohypertension
1. Poor arterial compliance caused by advanced atherosclerosis or vascular calcification
2. Osler's maneuver as clinical sign
   a. Palpable brachial or radial artery distal to fully inflated cuff
   b. Poor reproducibility
3. Intra-arterial monitoring as gold standard, but not often practical

C. White coat effect
1. Pressor response associated with blood pressure measured in physician's office
2. Evidence of end-organ damage is often used to discriminate true hypertension from white coat effect
   a. Left ventricular hypertrophy
   b. Microalbuminuria
   c. Retinal changes
3. Not completely benign?
   a. Hypertension and Ambulatory Recording Venetia Study (HARVEST)
      i. Left ventricular mass index and wall thickness greatest in patients with true hypertension, but these indexes in patients with white coat hypertension exceed those in patients with normotension
      ii. Microalbuminuria observed only in patients with true hypertension
   b. Discrimination of white coat from true resistant hypertension
      i. Home monitoring; average of 3 consecutive readings once or twice daily used in investigative studies
      ii. Twenty-four–hour ambulatory blood pressure monitoring (ABPM)

D. Blood pressure monitoring in resistant hypertension assessment
1. Importance of repeated measures
   a. Optimal frequency uncertain
2. Exclusion of white coat hypertension requires home monitoring or ABPM
3. Better cardiovascular risk prediction achieved with ABPM
   a. Night-time variation
      i. Nondipping as predictor of adverse cardiovascular events
   b. Relevance of load (percentage of abnormal values/total)
4. Adjunct assessment to therapy response
5. Cost-benefit advantage of 24-hour ABPM versus home monitoring or office/clinic monitoring is uncertain

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II. Ingestions/antagonizing substances
  A. Magnitude of effect not rigorously studied
  B. Salt
    1. Increased sensitivity; diets greater than 100 mmol/d
      a. Most consistent correlations with increased age, obesity, African American race, chronic kidney disease
      b. Induction of salt sensitivity by dietary potassium deficiency in African Americans
      c. Possible association with indolent tubulointerstitial renal injury
    2. Utility of 24-hour urine sodium to estimate salt intake
    3. Reduction to target intake impacts on systolic blood pressure from 2 to 8 mm Hg
  C. Drugs
    1. Class effects (Table 2)
    2. Nonsteroidal anti-inflammatory agents
      a. Inhibition of renal vasodilatory prostaglandin production
      b. Impaired sodium excretion
      c. Magnitude of effect on mean blood pressure approximately 5 mm Hg
    3. Sympathomimetics
      a. Prescription and over-the-counter preparations, including weight-control agents
        i. For decongestants, magnitude of effect small; 1.0 to 1.2 mm Hg
      b. Illicit drugs, including cocaine and amphetamines
    4. Miscellaneous
      a. Sibutramine, venlafexadine, metoclopramide, buspirone
    5. Abrupt withdrawal of β-blockers or clonidine
  D. Moderate to severe alcohol use (>2 drinks/d)
  E. Other ingestions
    1. Caffeine, nicotine, licorice
    2. Heavy metal exposure
      a. Lead, mercury

Table 2. Medications That Can Increase Blood Pressure or Antagonize Antihypertensive Therapy

Anabolic steroids
Anti–vascular endothelial growth factor therapy (bevacizumab)
Bronchodilators
Calcineurin inhibitors
Corticosteroids
Decongestants
Herbals (St John's wort, ma huang)
Erythropoietic-stimulating agents
Monoamine oxidase inhibitors
Nonsteroidal anti-inflammatory drugs
Oral contraceptives
Tricyclic antidepressants

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III. Nonadherence
- A. Causes and frequency
  1. Side effects
     - a. Most common with central α agonists, direct arterial vasodilaters, β-blockers, diuretics
     - b. Studies of long-term follow-up with monotherapy of patients with essential hypertension show best adherence with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)
  2. Perceived lack of efficacy
  3. Complex regimens
     - a. Inclusion of short half-life, frequently dosed medications
     - b. Increased nonadherence with greater number of medications or pills
       - i. Anecdotal; not systematically studied
     - c. Inclusion of medications with greater side-effect incidence
- B. Assessment
  1. Patient interview; historical elements that corroborate medication use
     - a. Fatigue (β-blockers, α_1-antagonists, central α-agonists)
     - b. Edema (calcium channel blockers, minoxidil)
     - c. Dry mouth (central α-agonists)
  2. Physician judgment
     - a. Sensitivity of physician estimate of compliance as low as 10% in some studies
  3. Pill counts
     - a. Easily manipulated by patients; not formally studied
  4. Prescription renewal confirmation
     - a. Poor reliability
  5. Electronic monitoring systems; predominantly a research tool
     - a. Improved blood pressure control in two-thirds of patients during 2-month observation in 1 cohort
  6. In-hospital direct observation in selected circumstances
- C. Intervention
  1. Conflicting results regarding the actual impact of adherence on outcomes in patients with resistant hypertension
     - a. One prospective case-control study of electronic monitoring in patients with resistant hypertension versus those with responsive hypertension failed to show a difference in adherence (>80% both groups)
       - i. Follow-up only 4 weeks
  2. Comprehensive pharmacy care programs show promise
     - a. Standardized education, regular pharmacist follow-up, and controlled medication dispense mechanisms shown to improve blood pressure in an elderly cohort

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IV. Comorbid conditions influencing blood pressure control
  A. Obesity
    1. High prevalence in resistant hypertension
    2. Association with insulin-resistance, obstructive sleep apnea (OSA), hyperaldosteronism
    3. Consistent benefit of weight reduction on blood pressure control
  B. OSA
    1. Association with hypertension suggested in population-based studies
      a. An independent variable even after accounting for body mass index, sex, age, alcohol, cigarettes, ethnicity
    2. Mechanisms
      a. Increased muscle sympathetic nerve activity (MSNA) in OSA
        i. Not observed in obese patients who do not have OSA
      b. Association of OSA with increased plasma aldosterone concentration (PAC)
    3. High prevalence reported in resistant hypertension
    4. OSA therapy impact
      c. Reduced MSNA and improvement in blood pressure shown when effective nocturnal continuous positive airway pressure delivered
        ii. Greatest benefit in most severe cases
  C. Hyperaldosteronism
    1. Classically listed as "secondary" cause of hypertension, particularly in context of discrete adenoma (low incidence)
    2. May be more prevalent in cases of resistant hypertension than previously appreciated; as high as 20% in some reports
      a. PAC/plasma renin activity (PRA) ratio as a screen
        i. High PAC absolute (>15 mg/dL) and high PAC/PRA (>20 to 30) consistent with diagnosis
        ii. Interference of ACE inhibitors, ARBs, and mineralocorticoid blockade with interpretation
      b. Often normokalemic
      c. Prevalence may be overestimated by selection bias
    3. Linked to obesity and OSA
      d. Evidence that oxidized fatty acid derivatives common in obesity may stimulate aldosterone secretion
      e. PAC increased in patients with OSA
    4. Benefit of mineralocorticoid blockade in patients with resistant hypertension
  D. Diabetes mellitus
    1. Association of insulin resistance with hypertension
    2. Interaction with salt sensitivity
  E. Metabolic syndrome

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V. Treatment
  A. Attention to extracellular volume status

1. Techniques to assess plasma volume have shown that occult volume expansion is underappreciated in patients with hypertension
   a. Isotopic albumin labeling labor intensive, not practical for routine use
   b. Thoracic bioimpedence technique derives stroke volume from low voltage current applied through skin electrodes that detect thoracic fluid volume during systole
      i. Stroke volume, heart rate, blood pressure used to calculate systemic vascular resistance and cardiac output
      ii. Impedence cardiography emerging as potential noninvasive tool to guide therapy; remains expensive
      iii. Direct comparison of hypertension specialist clinical assessment with bioimpedence method showed physician tendency to underestimate need for diuretic therapy in patients with resistant hypertension
2. Emphasis on dietary salt restriction
3. Consideration of mineralocorticoid blockade as primary or adjunct diuretic therapy in patients with resistant hypertension
   a. Relative risk of hyperkalemia with concurrent use of ACE inhibitors, ARBs, β-blockers, direct renin inhibitors, or impaired kidney function

B. Nonpharmacological interventions
   1. Not studied in specific context of resistant hypertension; studies in primary prevention and standard hypertensive care presumed to be applicable
   2. Weight reduction
      a. Potentially the greatest impact as an isolated variable
      b. Systolic blood pressure reduction 5 to 20 mm Hg/10 kg weight loss
   3. Salt restriction to less than 100 mEq ($<$2.4 g)/d
      a. 3 to 6 mm Hg/100 mmol reduction in sodium intake
   4. Diet; possible impact of Dietary Approaches to Stop Hypertension (DASH)
      a. 8 to 14 mm Hg reduction in systolic blood pressure
   5. Aerobic exercise; 30 min/d
      a. 4 to 9 mm Hg reduction in systolic blood pressure
   6. Limit alcohol use to fewer than 2 drinks/d
      a. 2 to 4 mm Hg reduction in systolic blood pressure
   7. Smoking cessation

C. Pharmacological therapies
   1. Suboptimal medical regimen may be most common cause of resistant hypertension
      a. Accounted for 43% of causes in 1 tertiary care clinic study
   2. Complementary class effect interventions for easily controlled hypertension outlined in Joint National Commission 7 Report and previous Hypertension Core Curriculum
      a. Common initial regimens typically include some combination of angiotensin-interfering agents (ACE inhibitors or ARBs), β-blockers, calcium channel blockers, and diuretics
      b. Regimens tailored, when appropriate, to comorbid condition indications for diabetes, coronary artery disease, congestive heart failure, chronic kidney disease, and cerebrovascular disease
      c. Necessity of appropriate dosing
   3. Additional considerations in resistant hypertension; not systematically investigated
      a. Intensification of diuretics, including a combination with mineralocorticoid antagonism
         i. Half-life longer and antihypertensive efficacy enhanced with thiazides
         ii. If loop diuretics used, necessity for increased frequency or selection of longer acting agents (eg, torsemide)
      b. Combined renin-angiotensin system interruption

i. ACE inhibitor plus ARB
ii. Mineralocorticoid blockade
iii. Utility of direct renin inhibitors?
iv. Risk of hyperkalemia and acute kidney injury

c. α_1-Antagonists
d. Dual calcium channel blockade (dihydropyridine plus nondihydropyridine)
e. Direct vasodilators: hydralazine or minoxidil
i. Need for concurrent β-blocker and diuretic

D. Caution regarding unfavorable or antagonistic drug combinations
1. β-Blockers and verapamil or diltiazem
a. Negative chronotropy
2. Direct vasodilators with insufficient β-blockade and diuretic
3. Lack of additive effect of calcium channel blockers with diuretics

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ACKNOWLEDGEMENTS

Support: None.
Financial Disclosure: None.