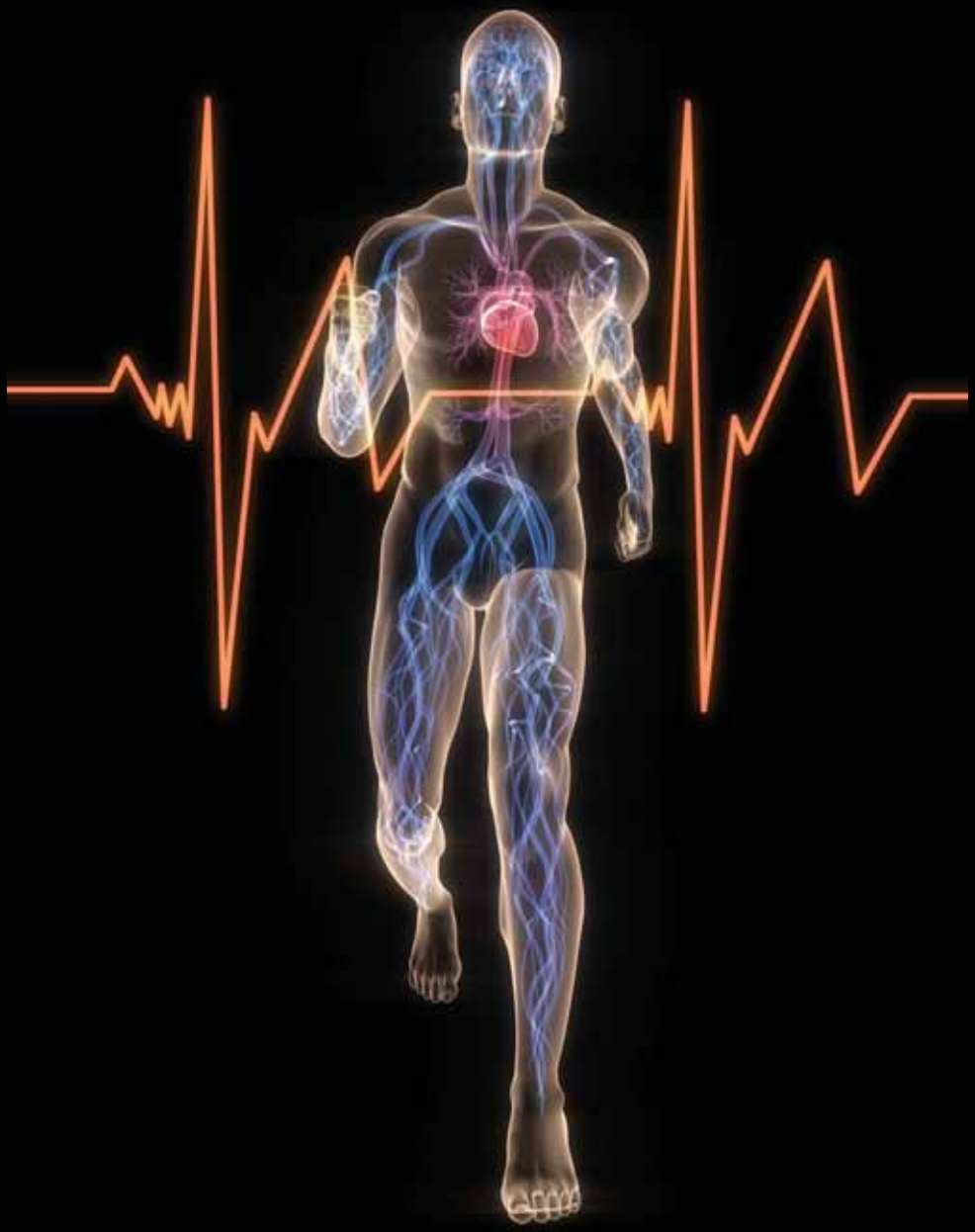
MICHIGAN HYPERTENSION CORE CURRICULUM

Education modules for training and updating physicians and other health professionals in hypertension detection, treatment and control



Developed by the Hypertension Expert Group
A Partnership of the
National Kidney Foundation of Michigan
and the
Michigan Department of Community Health
2010

Michigan Hypertension Core Curriculum

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National Kidney Foundation® of MICHIGAN

Michigan Department of Community Health
MDCH
Jennifer M. Granholm, Governor
Janet Olszewski, Director

April 2010

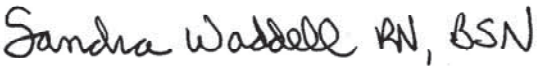
Dear Colleague:

In 2005, the Michigan Department of Community Health (MDCH) and the National Kidney Foundation of Michigan (NKFM) convened a group of hypertension experts to identify strategies that will improve blood pressure control in Michigan. Participants included physicians from across Michigan specializing in clinical hypertension, leaders in academic research of hypertension and related disorders, and representatives of key health care organizations that are addressing this condition that afflicts over 70 million U.S. adults. The Hypertension Expert Group has focused on approaches to reduce the burden of kidney and cardiovascular diseases through more effective blood pressure treatment strategies.

In an effort to improve hypertension control, the group developed educational programs on blood pressure management, diagnosis and treatment standards. The Expert Group has now turned their attention toward strengthening academic programs for health care providers in the area of clinical hypertension. It was suggested that while all universities and training programs have curricula focused on cardiovascular diseases, considerable variability exists on how each approaches the diagnosis and treatment of hypertension, in part because hypertension has not been the domain of any single medical subspecialty.

Thus, our goal was to develop a state-wide core curriculum designed to serve as a comprehensive guide for updating clinical knowledge of hypertension and related disorders. This core curriculum would ensure that trainees are adequately educated, focused on a basic understanding of pressure-related vascular pathophysiology and target-organ injury/dysfunction, optimal therapeutic strategies, and the most recent authoritative evidence-based guidelines and practice standards developed and promulgated by hypertension experts. The curriculum will be updated periodically and should continue to serve as a readily available current source for training.

Sincerely,



John Flack, MD, MPH
Chair, HTN Expert Committee
Wayne State University

Sandra Waddell, RN, BSN
Project Manager, HTN Expert Committee
National Kidney Foundation of Michigan

Acknowledgements

Hypertension Expert Workgroup Committee

Ziad Arabi, MD, Senior Staff Physician, Internal Medicine/Hospitalist Medicine, Henry Ford Hospital, Certified Physician Specialist in Clinical Hypertension*

Aaref Badshah, MD, Chief Medical Resident, Department of Internal Medicine
Saint Joseph Mercy-Oakland Hospital *

Jason I Biederman DO, FACOI FASN, Hypertension Nephrology Associates, PC*

Joseph Blount, MD, MPH, FACP, Medical Director, OmniCare Health Plan, Detroit, MI

Mark Britton, MD, PhD, Center of Urban and African-American Health Executive Committee, Wayne State University School of medicine, Wayne State University*

Paul Dake, MD, Family Medicine Residency Program Faculty McLaren Hospital

Benjamin Diaczok, MD, FACP, Program Director, Department of Internal Medicine, St. Joseph Mercy Oakland Hospital*

Mark D Faber MD, FACP, Program Director, Division of Nephrology and Hypertension
Henry Ford Hospital, Clinical Associate Professor, Wayne State University*

John M. Flack, MD, MPH, FAHA, FACP, Professor of Medicine and Physiology
Chair and Chief, Division of Translational Research and Clinical Epidemiology
Department of Internal Medicine, Wayne State University, Specialist in Chief for Internal Medicine, Detroit Medical Center* Editor in Chief

Arthur Franke, PhD, National Kidney Foundation of Michigan, Ann Arbor, MI

Crystal R. Gardner-Martin, MD, Hypertension Nephrology Associates, PC*

Patricia Heiler, MPH, CHES Michigan Department of Community Health,
Cardiovascular Health Section

Khaled Ismail MD, Hypertension Nephrology Associates, PC*

Diane Levine, MD, FACP, Associate Professor of Medicine, Vice Chair for Education
Department of Internal Medicine, Wayne State University

Michael Misuraca DO, Hypertension Nephrology Associates, PC*

Samar A. Nasser, PA-C, MPH, Division of Translational Research and Clinical Epidemiology, Department of Internal Medicine, Wayne State University*

Silas P. Norman, MD, Assistant Professor of Medicine, Division of Nephrology
Section of Transplantation, University of Michigan*

Acknowledgements

Kevin L. Piggott, MD, MPH, FAAFP Preventive Medicine Resident, University of Michigan School of Public Health and Family Physician*

Rosalind M. Peters, PhD, RN, Associate Professor, College of Nursing, Wayne State University*

William Repaskey, MD, Internal Medicine Hospitalist, University of Michigan Hospitals, Ann Arbor, MI*

Robert R. Ross, PA-C, Affiliate Professor, U of D Mercy PA Program

Robert D. Safian, MD, Director, Cardiac and Vascular Intervention Director, Cardiovascular Fellowship Training Program, Department of Cardiovascular Medicine, William Beaumont Hospital*

Ankur Sandhu MD, Nephrology and Critical Care Fellow, Henry Ford Hospital*

Kiran Saraiya DO, Hypertension Nephrology Associates, PC*

Linda Smith-Wheelock, ACSW, Chief Operating Officer, National Kidney Foundation of MI

Hani Al-Sharif MD, Nephrology Fellow, Henry Ford Hospital*

Susan P Steigerwalt MD, FACP, Director, Hypertension clinic SCSP; Member, Division of Nephrology and Hypertension, St John Hospital and Medical Center, Detroit, MI and Providence Hospital, Southfield, MI, ASH Clinical Hypertension Specialist*

Radhika Thalla MD, Nephrology Consultants P.C, William Beaumont Hospital, Royal Oak, MI*

Velma Theisen, MSN, RN, Manager, Heart Disease and Stroke Prevention Unit
Cardiovascular Health, Nutrition and Physical
Activity Section, Michigan Department of Community Health*

Joel M Topf, MD, Chief of Nephrology, St Clair Specialty Physicians , Director of the Chronic Kidney Disease Clinic, St John Hospital and Medical Center*

Sandra Waddell, RN, BSN, National Kidney Foundation of Michigan, Ann Arbor , MI

Steven A Yarows, MD, Chelsea Internal Medicine, Michigan Hypertension Center,
IHA, Adjunct Professor of Internal Medicine, Cardiovascular Division, University of Michigan Health System*

Jerry Yee, MD, Henry Ford Hospital, Nephrology

* Denotes contributing author

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10. Ms. LN returns 4 weeks after addition of an ACE-I and diuretic, and is symptomatic. What may be causing these symptoms, and how would you handle?

Blood Pressure Measurement

Rosalind Peters PhD, RN and Velma Theisen MSN, RN

Objectives:

At the end of this module, participants should be able to:

1. Describe the strengths and limitations of different methods of measuring BP.

2. Describe the steps necessary to ensure accurate measurement of BP in accordance with national guidelines.

3. Identify resources and references related to accurate home BP measurement.

Pre-Test questions:

1. The point at which the diastolic BP is recorded is
   a. the point where the sounds become muffled
   b. the last regular sound you hear
   c. the point where no sound is heard
   d. two millimeters below the last sound heard

2. The point at which the SBP is recorded is
   a. the point where the sounds are loudest
   b. the first sound you hear
   c. the point where the first of two consecutive sounds are heard
   d. two millimeters after the first sound heard

3. The correct cuff size for an individual is determined by
   a. the individual's age
   b. the size of the arm circumference
   c. the weight of the individual
   d. the body mass index of the individual

4. Evaluating the accuracy of the BP measurement device should be done
   a. every 3 years
   b. only when you suspect it might be inaccurate
   c. every 6 months
   d. every 12 months

5. Correct positioning the individual for BP measurement includes all of the following ***except***
   a. seated with feet flat on floor and legs uncrossed
   b. back supported
   c. arm supported at heart level
   d. seated on the side of an exam table

Measurement Methods

Early detection, treatment and control of hypertension require accurate blood pressure (BP) measurement.[1] This task, which too often is left to unlicensed assistive personnel, should be carefully done by the health care professional. Accuracy of measurement begins with understanding the three methods used to obtain a BP reading, and ensuring that the equipment to be used is accurate. The first method is auscultation with an approved and accurate BP device. The **mercury sphygmomanometer** is considered to provide the gold standard of BP measurement. However, due to concerns about environmental hazards these devices are being phased out, and in Michigan as of January 2009 mercury sphygmomanometers can only be used to check accuracy of other devices or used in a patient's home.[2]

As a result the mercury sphygmomanometers are being replaced with aneroid and/or oscillometric devices. **Aneroid** devices also use auscultation to detect blood flow through the artery. BP readings based on auscultation are subject to measurement error due to environmental factors (e.g., extraneous room noise), personnel factors (e.g., education, hearing ability, terminal digit preference), and device factors. Aneroid devices do not maintain stability over time and require frequent re-calibration (e.g., every 6 -12 months). The level of inaccuracy of BP measurements obtained with aneroid devices has been found to range from 1% to 44%.[3] To overcome the errors of auscultation, an ocillometric method may be used. The **ocillometric** method detects vibrations in the arterial wall that occur due to blood flow, and transforms the vibrations into an electrical signal which is displayed as a digital readout of BP. However, factors other than blood flow may affect the vibrations. Thus the oscillometric techniques will underestimate the true BP in patients with arterial stiffness or dysrrhythmias.[4] The ocillometric method has been used with a variety of measurement devices (e.g., upper arm, wrist, finger, and ambulatory devices). **Automated upper arm** devices that measure BP at the brachial artery have been shown to be reliable in clinical practice, and therefore their use is recommended over wrist or finger devices. **Finger** devices are not recommended due to inaccuracies related to peripheral vasoconstriction, alteration in BP at distal sites, and the error of limb position in relation to the heart during measurement.[4,3] **Wrist** devices are increasingly being used especially with obese people since the diameter of the wrist is usually not affected by obesity. However, wrist devices are subject to the same errors as finger devices, with the addition of altered readings due to the flexion/ hyperextension

of the wrist. Additionally, there is difficulty creating an accurate algorithm to estimate BP as there are two arteries at the wrist contributing to the oscillometric signal.[4] Wrist devices are not currently recommended for routine clinical practice or decision making.[3,4] **Ambulatory BP monitoring (ABPM)**, another type of ocillometric measurement, may be done when there is the possibility of white-coat hypertension or other concerns of measurement error. White-coat hypertension (persistent elevation in BP when measured in a clinical setting, but normal BP when the measurement is taken at home), affects as many as 1 in 3 in the general population but is higher in the elderly and pregnant women.[3,5] ABPM records BP every 15 to 30 minutes (or when triggered at the patient's request) for a 24 to 48 hour period. The data is stored in the device's memory until downloaded to a computer for interpretation by the physician.[5,6] The multiple recordings may provide greater diagnostic accuracy than isolated clinic measurements. However, when proper, standardized procedures are followed, the average of 4 duplicate clinic BP readings is as reliable as 24hr ABPM.[7] A third method of BP measurement uses **hybrid sphygmomanometers** which combines the features of both ausculatory and ocillometric devices. The hybrid combines manual BP measurement techniques but replaces the mercury column with an electronic pressure detection system.[3] These are relatively new devices with only a few certified to meet established standards.

BP measurements taken with ocillometric devices (automated or ABPM) are usually lower than with ausculatory methods. This difference must be reconciled with the fact that BP treatment guidelines are based on epidemiologic data obtained using ausculatory methods. Thus, lower thresholds for treatment should be considered if treatment decisions are based on automated measurements. BP measurements > 135/85 mmHg obtained with an ocillometric device (e.g., ABPM, home monitors) should be considered abnormal (hypertensive) and treated as such.[4]

Measurement Protocol

Accuracy of BP measurement requires careful attention to detail when any BP reading is obtained. Table 1 contains guidelines that should be followed to achieve maximal accuracy.

Measurement Locations

Blood pressure may be measured in numerous locations including professional settings (e.g., out-patient clinics, hospitals); community sites (e.g., pharmacies), and in patients' homes. In all of these locations, principles of accurate measurement must be followed including the use of appropriate equipment and adherence to BP measurement protocols. It is important that the individual measuring

the BP understands current national guidelines for identifying, referring, and managing high BP. In all settings the individual whose pressure is being recorded should be seated with the back supported, legs uncrossed, feet flat on the floor, and the arm supported at heart level. The setting should be as private and as quiet as possible.

In the clinical setting, a conscious decision must be made to establish an appropriate screening area. This is especially important as some individuals demonstrate "white coat hypertension" with the elevation of BP triggered by anxiety or nervousness usually in response to being in the healthcare setting. To evaluate the presence of white-coat hypertension, patients are encouraged to measure their BP at home. Home readings are useful for engaging patients in their own BP treatment program and also provide additional information for healthcare providers to better manage the therapy.

Patients who purchase a home BP unit need guidance so that they purchase an accurate upper arm machine, rather than finger or wrist device, and that the correct cuff size is obtained. Patients should be instructed to choose a monitor that has been tested and validated by either the Association for the Advancement of Medical Instrumentation, the British Hypertension Society, or the International Protocol for the Validation of Automated Blood Pressure Measuring Devices. A list of validated monitors is available on the British Hypertension Society website (www.bhsoc.org/blood_pressure_list.stm) or the Dabl Educational Trust website (www.dableducational.org/sphygmomanometers/devices_2_sbpm.html#ArmTable). (Dabl is a leading provider of healthcare management systems and research tools for the prevention and management of cardiovascular conditions including high BP). If the device is to be used for children or pregnant women, then patients need to know to select a monitor that has been validated for those conditions. Once the monitor is obtained, healthcare providers should assess the patient's accuracy in following measurement guidelines, and should compare home monitor readings with measurements taken in the provider's office. Providers should then give the patient directions as to the frequency and timing of the home measurements, as well as instructions as to what data should be reported to the provider.

Essential Points

1. Diagnosis and treatment decisions for high BP require **accurate** BP measurement – which should be done by the professional health care provider.

2. Many providers do not follow established protocols for BP measurement resulting in inaccurate diagnoses and treatment plans.

3. All measurement devices must be calibrated and/or validated for accuracy on a regular

basis. National guidelines recommend every six months for calibration assessment and accuracy assessed with every use.

4. ABPM readings will be lower than those obtained using office-based ausculatory methods. Accordingly, ABPM > 135/85 mm Hg is considered to be in the hypertensive range.

5. The American Heart Association provides national recommendations for accurate BP measurement by health professionals.

6. Home BP readings can enhance management of an individuals' hypertension, but should be implemented and monitored by a healthcare provider with adequate guidance and education provided to the patient and family.

Table 1: Guidelines for Obtaining Accurate Blood Pressure Readings[2]

I. **Prepare the equipment**:
   A. Use equipment that has been (1) validated as accurate against a mercury sphygmomanometer, (2) checked for disrepair of cuff (e.g., cracks or leaks in tubing, breaks in stitching or tears in fabric), (3) checked that gauge is intact (mercury meniscus or aneroid needle is at zero), (4) consistent with State Legislation.
   B. Obtain appropriate cuff size by measuring circumference of the patient's arm and choosing the cuff size that corresponds to that measurement.

II. **Prepare the patient**
   A. Assess (1) that patient has not recently had nicotine or caffeine and (2) that the patient has been sitting quietly for 5 minutes prior to measuring BP
   B. Position patient: (1) Use a sitting or semi-reclining position with the back supported and the arm at heart level (middle of the cuff should be at mid-sternum level). (2) Legs should be uncrossed with feet flat and supported on floor or foot rest (not dangling from examination table or bed)
   C. Bare the upper arm of any constrictive clothing (You should be able to get at least one finger under a rolled-up sleeve). Palpate brachial artery, position center of cuff bladder over the brachial artery

III. **Take the measurement**
   A. Support the patient's arm at heart level
   B. For ausculatory measurements:
      i. Obtain an *estimated systolic pressure* by palpation prior to auscultation
      ii. *Inflate* the cuff as rapidly as possible to maximum inflation level (30 mmHg above estimated systolic BP).
      iii. *Deflate* the cuff slowly at a rate of 2 to 3 mmHg/second; (1) note the first of 2 regular beats as systolic pressure (palpation helps to avoid under-estimating systolic pressure due to an ausculatory gap) (2) Use Kortokoff V (last sound heard) as the diastolic pressure (3) continue deflation for 10 mmHg past last sound to assure sound is not a 'skipped' beat.
      iv. The measurement should be recorded as an even number and to the nearest 2 mmHg (round upward)
   F. Neither the patient nor observer should talk during the measurement
   G. If two readings are measured, record the average of the readings

IV. **Record the measurement** – document the following:
   A. The obtained BP reading
   B. Patient position (sitting, semi-recumbent, lying, standing)
   C. Arm used, include arm circumference and cuff size used
   D. Type of device used to obtain the measurement (mercury, aneroid, automated)
   E. State of the individual (e.g., anxious, relaxed)
   F. Time of administration of any drugs that could affect BP

(*Source: [8,2,3])

Post-Test Questions:

1. High BP is defined as:
    a. An increase in systolic pressure of 15 mm Hg greater than baseline
    b. Absolute systolic pressure of 140 mm Hg or greater
    c. Absolute systolic pressure greater than 160 mm Hg
    d. Varied depending on the type of blood pressure measurement device used

2. Which BP device gives the most accurate BP reading?
    a. Ambulatory BP monitor
    b. Mercury sphygmomanometer
    c. Oscillometric monitor
    d. Aneroid sphygmomanometer

3. Arterial stiffness may lead to inaccuracies using which type of BP device?
    a. Ambulatory BP monitor
    b. Mercury sphygmomanometer
    c. Oscillometric monitor
    d. Aneroid sphygmomanometer

4. Which of the following organizations provides data regarding the validity of home BP monitors?
    a. American Heart Association
    b. British Hypertension Society
    c. National Heart, Lung, and Blood Institute
    d. American Society of Hypertension

5. Estimating SBP by palpation is an important step when using which method of blood pressure measurement?
    a. Auscultation
    b. Ocillometric
    c. Ambulatory
    d. All of the above

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Primary Hypertension

Steven Yarows, MD

Learning objectives

- Understand the correct method of taking BP and then correctly interpret and categorize the results.
- Since 1/3 of the US adult population has primary hypertension, understanding the important health and financial costs of this disease.
- Understand the three predominant hypertension phenotypes - isolated systolic, mixed systolic/diastolic and isolated diastolic hypertension.

Pre-test Questions

A 35 year old obese male comes to the office for a rash and has his routine BP measured with a standard cuff of 170/104 mmHg. He has a grandfather who died of a stroke at 83 years old, but he thinks his parents are in good health and only take 'a few' pills. You assess the rash and indicate it is tinea crura and advise an anti-fungal cream. You then address his BP by:

A. Have him return in the morning for another BP reading
B. Recheck his BP with a large cuff after sitting for 5 minutes
C. Start a diuretic and have him return for a physical
D. Advise him to lose weight and see him back in a year

The likelihood of isolated systolic hypertension (ISH) is higher in:

A. Over 70 years old
B. Under 50 years old

Which of the following is true?

A. Inadequate control of systolic BP is usually the reason for uncontrolled hypertension
B. Inadequate control of diastolic BP is usually the reason for uncontrolled hypertension
C. Inadequate control of systolic and diastolic BP are equally likely in individuals with uncontrolled hypertension

A 40 year old Black healthy male has been to your office twice in the past 2 months for upper respiratory infections and his average BP over these two visits was 160/102 mmHg; both BP readings were higher than150/96 mm Hg. His parents are both hypertensive on medication and he used their home BP monitor with a large cuff and it was 150/96 and 164/104 mmHg. What would be your starting therapy?

A. Hydrochlorothiazide (diuretic) 25mg qd
B. Valsartan (angiotensin receptor blocker) 320mg qd
C. Metoprolol XL (extended release beta blocker) 50mg qd
D. Amlodipine (dihydropyridine calcium channel blocker) 5mg qd
E. Amlodipine/lotensin (dihydropyridine calcium channel blocker + ACE inhibitor) 5/20mg qd

Essential (Primary) Hypertension:

Diagnosis of Hypertension

Essential hypertension is a misnomer. There is nothing 'essential' about hypertension; perhaps "essential BP", but not hypertension. This section will describe 'primary hypertension'.

Blood pressure (BP) is inherently variable within a reasonably predictable range. Hypertension is defined as elevated average BP over time, preferably with a minimum of 3 properly performed readings on different days and is never based on a single measurement. Your BP at rest is lower than your BP during activities. There is a natural diurnal variation for people with usual work-sleep cycles resulting in increased BP just prior to awakening continuing to be elevated in the morning while decreasing in the evening. BP also decreases in the early afternoon, which is why post-lunch lectures are difficult, and the nadir in BP occurs at 2-3AM, during sleep. This data is routinely obtained by 24-hour ambulatory blood pressure monitors. The decrease in BP during sleep is known as the 'dip' and is absent in some conditions and when absent results in increased cardiovascular (i.e., strokes, myocardial infarctions, death) events. Several selected conditions known to attenuate or eliminate the normal nocturnal decline in BP include: 1) chronic kidney disease (CKD), 2) obesity, 3) high sodium and/or low potassium diets, and 4) sleep disordered breathing.

Too much pressure is potentially deleterious for any system. For example, an overinflated car tire allows you to drive to the store without any difficulty; however the increased pressure prematurely wears out the tire. The human circulatory system is similar. Prolonged BP elevation results in accelerated atherosclerosis and vascular remodeling that heighten the risk of stroke (brain), myocardial infarction (heart), myocardial hypertrophy (heart), kidney failure (kidney), and abdominal aneurysms (general circulatory). Contrary to pervasive myths, there is no specific BP reading that prognosticates without fail a cardiovascular catastrophe. When marked BP pressures are detected, repeated measurements and careful short-term follow-up are critical.

Hypertension Phenotypes (Isolated Systolic, Isolated Diastolic, Isolated Systolic/Diastolic)

BP is represented by two numbers (i.e., 120/50 mmHg). The highest number is the systolic BP and the lower is the diastolic BP. The BP is typically measured by either the auscultatory or oscillometric methods. The following is a discussion of hypertension phenotypes. Hypertension is classified into distinctive phenotypes. Mixed systolic/diastolic hypertension is most common in middle aged patients when both the diastolic and systolic BP are elevated above 140/90 mmHg in the office. Isolated systolic hypertension (ISH) is most common after 50 years old, although there is an unusual, benign form in the youth.[1,2] ISH is also the most risky hypertension phenotype despite the fact that the diastolic BP is not elevated. Isolated diastolic hypertension is least prevalent (and also least risky) hypertension phenotype. The different categories of hypertension have different pathological mechanisms which will be discussed in the Pathophysiology Section.

Pre-hypertension is present when BP readings are between 120-139/80-89 mmHg.[3] These individuals are at risk for the development of hypertension. Thus, lifestyle modification (i.e., exercise, weight loss, salt and alcohol restriction) is recommended. Borderline or high normal BP is when the office readings are consistently between 135-140/85-90 mmHg in patients without CKD, diabetes, or ischemic heart disease.

White Coat Hypertension (office hypertension) is present when the office BP is >140/90 mmHg, yet the outside the office the BP is <135/85 mmHg during the daytime hours on 24-hour ambulatory BP monitor. These individuals have a slightly elevated cardiovascular risk compared to normotensives, however there are no guidelines recommending pharmacological drug therapy.

Masked Hypertension is when the office BP is normal (<140/90 mmHg) however the out of office BP is elevated (>135/85 mmHg). These individuals are at a greatly increased risk of cardiovascular events and medication treatment is advised. Nevertheless, this type of hypertension is very difficult to diagnose because ambulatory BP monitoring is not typically undertaken in patients with controlled office BP. Masked hypertension not infrequently occurs in patients with sleep apnea.

Epidemiology

The prevalence of hypertension in the United States is 73 million, which is approximately 1/3 of the adult population.[4,5] It is higher in men until 45 years of age and then is similar in both sexes until 55 years of age after which it occurs more commonly in women (Figures 1-3). The prevalence of hypertension is higher in African Americans, a demographic group that is afflicted with hypertension earlier in life that is more severe compared to whites. Hypertension incidence also markedly increases with age. A 55 year old has an 83-88% chance of becoming hypertensive over 20 years.[6] Higher hypertension prevalence has been observed in those with less education as well as greater obesity and physical inactivity. Hypertension prevalence also varies by geographic location of residence in the United States. In 2001–2003, age-standardized uncontrolled hypertension prevalence was highest in the District of Columbia, Mississippi, Louisiana, Alabama, Texas, Georgia, and South Carolina and lowest in Vermont, Minnesota, Connecticut, New Hampshire, Iowa, and Colorado.[7] Hypertension is also 2-3 times more prevalent in women taking birth control pills, especially obese, and older women.

Pharmacological treatment of hypertension in the United States in 2004 was 68.5% with 52.9% of those treated having their BP controlled, an increase from past surveys. BP control rates are higher in men than women and decrease with age, mainly due to uncontrolled isolated systolic hypertension (57.0%). Although treatment rates are higher in African Americans than whites, the control rates are worse (Table 1). Mexican-Americans have the lowest treatment rates, and the poorest control rates. Treatment rates are the highest for subjects 60 years old and greater; however, the control rates are below the middle age group, as a result of the higher incidence of isolated systolic hypertension. Hypertension is highly associated with other vascular diseases (77%), including diabetes (76.8%), metabolic syndrome (61.5%), stroke (69.5%), dyslipidemia (51.8%), CKD (81.8%), peripheral vascular disease (73.7%), coronary heart disease (73.0%), and both systolic and diastolic heart failure (71.4%).

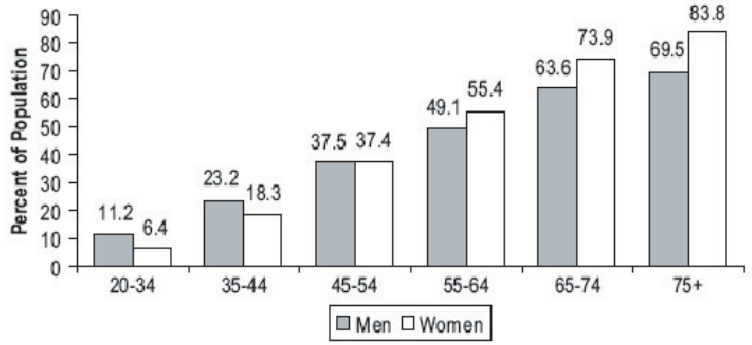


Chart 5-1. Prevalence of HBP in adults age ≥20 years by age and sex (NHANES: 1999–2004). Source: NCHS and NHLBI.

Figure 1- Rosamond W

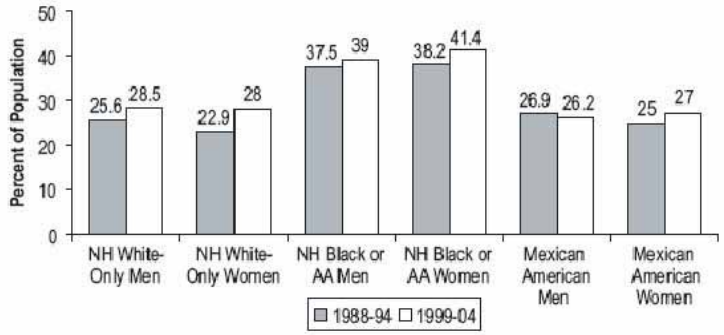


Chart 5-2. Age-adjusted prevalence trends for HBP in adults age ≥20 years by race/ethnicity, sex, and survey (NHANES: 1988–1994 and 1999–2004). Source: NCHS and NHLBI. NH indicates non-Hispanic; AA, African American.

Figure 2

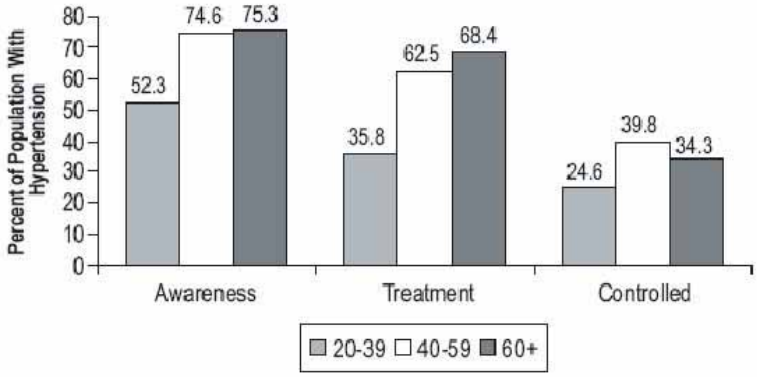


Chart 5-4. Extent of awareness, treatment, and control of HBP by age (NHANES: 1999–2004). Source: NCHS and NHLBI.

Figure 3

TABLE 1. Prevalence of Awareness, Treatment, and Control of Hypertension by Descriptive Factors in the REGARDS Cohort [8]

		Awareness of Hypertension Among All Hypertensives			Treatment of Hypertension Among Aware Hypertensives				Control of Hypertension Among Treated Hypertensives	
	All REGARDS Participants	No. of Hypertensive Participants	Aware of Hypertension			On Medication		No. Treated	Controlled Blood Pressure	
			No.	%	No. aware	No.	%		No.	%
All	11 606	6023	5477	90.9	5477	4866	88.8	4858	3198	65.8
Race										
White	57.2%	3070	2738	89.2	2738	2373	86.7	2371	1663	70.1
Black	42.8%	2953	2739	92.8	2739	2493	91.0	2487	1535	61.7

Post-test Answers

A 35 year old obese male comes to the office for a rash and has his routine blood pressure measured with a standard cuff of 170/104 mmHg. He has a grandfather who died of a stroke at 83 years old, but he thinks his parents are in good health and only take 'a few' pills. You assess the rash and indicate it is tinea crura and advise an anti-fungal cream. You then address his BP by:

A. Have him return in the morning for another BP reading
B. Recheck his BP with a large cuff after sitting for 5 minutes
   Since he is obese and just had a single reading, potentially not performed properly, it should be repeated correctly. If elevated, he should have another blood pressure check, although it does not have to be the next day, unless he has rare hypertensive urgency. (**Correct answer)**
C. Start a diuretic and have him return for a physical
D. Advise him to lose weight and see him back in a year

The likelihood of isolated systolic hypertension increases in:

A. Over 70 years old
   This is more common after 50 years of age **(Correct answer)**
B. Under 50 years old

Which of the following is true?

A. Inadequate control of systolic BP is usually the reason for uncontrolled hypertension **(Correct answer)**
B. Inadequate control of diastolic BP is usually the reason for uncontrolled hypertension
C. Inadequate control of systolic and diastolic BP are equally likely in individuals with uncontrolled hypertension

A 40 year old Black healthy male has been to your office twice in the past 2 months for upper respiratory infections and his average BP over these two visits was 160/102 mmHg; both BP

readings were higher than150/96 mm Hg. His parents are both hypertensive on medication and he used their home BP monitor with a large cuff and it was 150/96 and 164/104 mmHg. What would be your starting therapy?

A. Hydrochlorothiazide (diuretic) 25mg qd
B. Valsartan (angiotensin receptor blocker) 320mg qd
C. Metoprolol XL (extended release beta blocker) 50mg qd
D. Amlodipine (dihydropyridine calcium channel blocker) 5mg qd
E. Amlodipine/lotensin (dihydropyridine calcium channel blocker + ACE inhibitor) 5/20mg qd **(Correct answer)**

Essential Points:

- Blood pressure is inherently variable within a predictable range. Hypertension is defined as elevated average BP over time, preferably with a minimum of 3 properly performed readings on different days and is never based on a single measurement
    - Proper measurement of BP includes that the patient is seated in a chair with a backrest and have their feet resting on the floor and be resting for a minimum of 5 minutes. Most importantly, a proper sized cuff should be used and unfortunately most Americans now need the larger cuff due to the increase in obesity.
- Hypertension is classified into different categories.
    - Pre-hypertension are BP readings between 120-139/80-89 mmHg
    - Mixed systolic/diastolic hypertension is most common in middle aged patients when both the diastolic and systolic BP are elevated above 140/90 mmHg at the office. It is due to increased arteriolar resistance in the distal smaller vessels.
    - Isolated systolic hypertension is most common after 50 years old. It is due to increased large conduit (aorta) vessel stiffness.
    - Isolated diastolic hypertension is the least common and least risky hypertension phenotype.
    - White Coat Hypertension (office hypertension) when the patient has elevated office BP (>140/90 mmHg), however outside the office the BP is <135/85 mmHg during the daytime hours as measured by a 24-hour ambulatory BP monitor
    - Masked Hypertension is when the office BP is normal (<140/90 mmHg) however the out of office BP is elevated (>135/85 mmHg).
- The prevalence of hypertension in the United States is 73 million, which is approximately 1/3 of the adult population
    - Hypertension is the largest risk factor for a stroke. Outcome studies with isolated systolic hypertension have shown that decreasing systolic BP by approximately 10 mmHg lowers the risk of a nonfatal stroke by 40%, fatal stroke by 60% and congestive heart failure by 50%.
    - Uncontrolled hypertension (>140/90 mmHg) accounts for 77% of people who have a first stroke, 74% who have congestive heart failure, and 69% who have a first heart attack.
    - Normotensive men and women at 50 years of age live approximately 5 years longer than their normotensive counterparts.

Blood Pressure, Circulatory Physiology, and Hemodynamically-Mediated Target-Organ Injury

John M. Flack, M.D., M.P.H., F.A.H.A., F.A.C.P., F.A..C.G.S.
Professor and Chairman
Chief, Division of Translational Research and Clinical Epidemiology
Department of Internal Medicine
Specialist in Clinical Hypertension
Wayne State University
Specialist in Chief for Internal Medicine, Detroit Medical Center

Learning Objectives

At the end of this lecture the student will be able to:

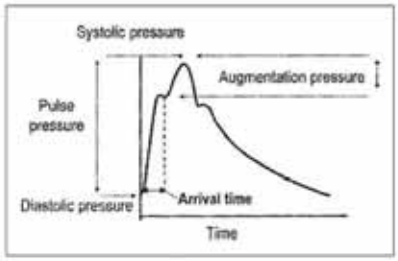
1. Articulate the determinants of arterial blood pressure in the younger as well as aged circulatory system.
2. Describe the circadian variation in blood pressure.
3. Identify the mechanisms of blood pressure-related target organ injury.
4. List the organs injured by blood pressure elevations and the clinical manifestations of such injury.
5. Describe how cerebral ischemia disrupts normal cerebral autoregulation of blood flow.
6. Discuss the microcirculatory adaptations in the kidney to high systemic arterial pressures.

1. Determinants of Arterial Blood Pressure

BP depends is determined by both physical and physiological factors. Physiological factors interface with physical factors to determine BP level. Systole accounts for ~ one-third of the cardiac cycle. Stroke volume (SV) is typically ejected during the initial one-half of the systolic phase of the cardiac cycle - or, stated slightly differently, SV is normally ejected during the initial one-sixth of the overall cardiac cycle given that systole accounts for ~ one-third of the total cardiac cycle. Cardiac output is cyclic, yet under normal physiological circumstances flow through the arterial tree is continuous.

The distensibility of the aorta, a large conduit vessel, determines the degree of the systolic blood pressure elevation, for a given amount ejected blood (stroke volume) during systole. During ejection of the SV the highly elastic aorta expands, thus dissipating the rise in blood pressure. The expansion of the aorta during systole stores energy. After ejection of stroke volume has ceased the aortic elastic recoil releases stored energy thereby propelling blood forward in the arterial vasculature after the rapid systolic ejection period. Thus, the aortic elastic properties explain continuous blood flow through the arterial circulation, even after the active systolic ejection phase. Though the elastic aorta distends, and thus dampens the rise in SBP, during systole, SBP does, however, rise during the systolic phase of the cardiac cycle. Another significant contributor to the rise in BP during systole relates to reflected pressure waves from the peripheral arterial vasculature.

Figure 1. Arterial Waveform

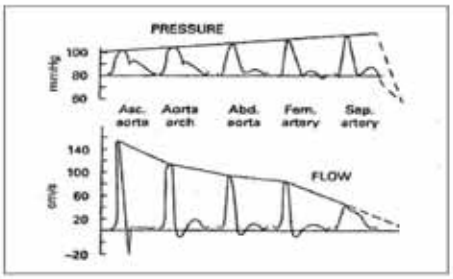


Central pressure waveform. The height of the late systolic peak above the inflection defines the augmented pressure, and the ratio of augmented pressure to PP defines the augmentation index

Agabiti-Rosei E et al. Hypertension 2007;50:154-160.

These reflected waves "sum up" with the pressure generated from ejected blood into arterial system and are therefore the major determinants of systolic BP; thus, the arterial waveform (at any location) consists of both forward traveling and reflected waveforms. Normally, because of the reflected waves, SBP and pulse pressure (PP) are amplified or increase by ~ 10 – 14 mm Hg when moving from the aorta to the brachial artery. However, DBP and mean arterial pressure (MAP) change very little (figure 2).

Figure 2. Change in contours in pressure and flow waves



Change in contours in pressure wave (top) and flow wave (bottom) between the ascending aorta and the saphenous artery

Agabiti-Rosei E et al. Hypertension 2007;50:154-160.

After the systolic ejection phase, the fall in DBP is dampened as the elastic recoil of the large capacitance vessels propels forward the blood volume that was stored during systole. The reflected waveforms largely emanate from the peripheral resistance arterioles and timing wise, arrive back in the aorta during diastole thereby augmenting coronary perfusion pressure.

The difference between SBP, peak BP during the cardiac cycle, and DBP, the lowest BP during the cardiac cycle, is the pulse pressure (PP). Pulse pressure is predominantly influenced by the amount of blood ejected during systole (SV) and the magnitude of the change in pressure inside the arterial vasculature for a given change in arterial volume (arterial compliance). Arterial compliance will be discussed in more detail later.

A. **Physical Factors**: *Blood volume* (BV) and *arterial compliance* are important physical factors that determine BP levels. Blood volume is distributed unevenly between the arterial and venous (capacitance vessels) sides of the vascular system. Approximately two-thirds to three-quarters of the BV is contained within the venous capacitance vessels; the remaining one-quarter to one-third is contained in the arterial

side of the vascular tree. Arterial BV is determined by the difference in the BV ejected by the heart/unit of time (cardiac output, C.O.) and the outflow through the arterial resistance vessels into the venous capacitance vessels (peripheral runoff). When C.O. and peripheral runoff are balanced, arterial BV and arterial pressure remain constant. If C.O. increases but peripheral runoff doesn't rise commensurately, then arterial BV rises and BP also increases.

Arterial elasticity is an important determinant of the rise in SBP that occurs for any given increase in BV. Generally speaking, arterial elasticity is inversely related to age; that is, younger persons have greater arterial elasticity and with advancing age arterial elasticity declines. *Arterial compliance* is determined by elastic properties of the large conduit vessels. Arterial compliance is **dV/dP** - the change in pressure that occurs with a given change in arterial volume. It should be clear that the greater the arterial elasticity, the smaller the rise in systolic pressure during the systolic ejection phase of the cardiac cycle. Conversely, lesser arterial elasticity causes a greater rise in systolic BP during the systolic ejection phase. This also places an extra burden of work on the myocardium to maintain cardiac output, in part because the systolic ejection phase is prolonged under these circumstances.

B. Physiological Factors: *Cardiac output (stroke volume [SV] * heart rate [HR]) and peripheral arterial resistance*, largely determined at the level of the arterioles, are the major physiological factors involved in the determination of arterial BP.

C. Age-Related Changes in the Aortic Conduit Vessel

There is an age-related reduction in arterial elasticity. This means that the rise in SBP is going to be greater because, for a given stroke volume, less of the SV is "stored" in the stiffer aorta. Pressure waves travel faster in stiff/less elastic arterial blood vessels leading to increased pressure wave reflection from the peripheral arterial vasculature. Thus, SBP rises to a greater degree than would be seen in a younger person with greater arterial elasticity for any given level of stroke volume. Also, because less of the SV is "stored" in the aorta during the systolic ejection phase, there is a greater run-off of the stroke volume to the periphery. Thus, BP falls to a lower level during diastole. These physiologic changes in the vasculature underlie the higher levels of SBP, lower levels of DBP, and widening of the pulse pressure that have been well documented with advancing age. Accordingly, the stiffening of the vasculature places an increased work burden on the myocardium, in part attributable to lengthening of the systolic ejection phase.

The normal aortic distension that occurs when blood is ejected from the heart is mediated by the aortic elastin fibers located in the media of the vessel wall. However, with advancing age and elevated blood pressure, aortic elastin fibers fragment thus transferring the pulsatile aortic stress to collagen fibers. This leads to aortic stiffening, a process that is further accelerated by diabetes mellitus and arterial wall calcification. Plausibly the fragmented elastin fibers with their plethora of calcium binding sites plausibly contribute to arterial wall calcification. Chronic kidney disease, smoking, and diabetes mellitus also contribute to calcium deposition in the media of the arterial wall. Figure 3 displays the hemodynamic consequences of aortic stiffening

Figure 3. Hemodynamic Consequences of Aortic Stiffening

Hemodynamic Consequences of Aortic Stiffening

- Increases pulse wave velocity (PWV) resulting in faster reflection of waves from peripheral resistance vessels
  - Summing of peripheral wave reflections with the forward wave earlier in the cardiac cycle augmenting SBP
  - Increased myocardial work
  - Decreased coronary perfusion pressure
- Enhances BP sensitivity to increases in intravascular volume
- Decreased baroreceptor responsiveness
- Increased central aortic pressure
- Wide pulse pressure or isolated systolic hypertension

Adapted from Williams B. JACC 2009;5(5):452-454.

2. Blood Pressure Measurement

A variety of techniques are available for the measurement of arterial BP. The primary, though not exclusive, method used in clinical settings is indirect estimation of brachial artery pressure using an appropriately sized sphygmomanometer. The arm should be at the level of the heart with the palm facing upward. The BP cuff is inflated above the level of systolic BP by ~ 20 mm Hg. How do you know how high to inflate the BP cuff to determine the SBP level ~ 20 mm Hg above where the systolic BP likely is? Before you listen for Korotkoff sounds, apply an appropriate size cuff to the arm, inflate it until the radial pulse is no loner palpable. Now you are ready to listen for Korotkoff sounds – inflate the cuff ~ 20 mm Hg above the systolic pressure level where the radial pulse was no longer palpable. This stops all blood flow in the brachial artery. Next the cuff is gradually deflated and as the pressure inside the brachial artery exceeds that in the cuff, tapping (Korotokoff phase 1) sounds become audible. The cuff is continually deflated. However, the flow of blood through the brachial artery remains episodic until the pressure in the brachial artery during diastole exceeds the external pressure supplied exerted by the cuff. When this occurs, blood flow during becomes continuous and the tapping sounds disappear (Phase V Korotokoff sound). In some patients the Korotokoff sounds may muffle before they disappear - the BP level of this muffling is (Phase IV Korotokoff sounds). In adults, the Phase I and V Korotokoff sounds are what are recorded as the SBP and DBP, respectively.

Systolic blood pressure may vary by 10 or more mm Hg between the arms in ~ 25% of hypertensives. Blood pressure values over the popliteal artery are either as high or more than 20 mm Hg higher than BP determinations obtained over the brachial artery (arm).

3. Central Aortic Blood Pressure

Central aortic blood pressure is typically lower than the BP level obtained clinically in the brachial artery. Central aortic blood pressure is likely to be a more important determinant of cardiovascular complications such as stroke and heart failure than peripheral (brachial) blood pressures. This is because aortic SBP is the pressure that the left ventricle ejects blood against and aortic DBP is a major determinant of coronary perfusion pressure. Moreover, central aortic pressure is the pressure that the vasculature in the brain is exposed to. Several non-invasive devices that can be used in clinical settings now allow estimation of central aortic pressure from either radial or carotid pulse waveforms using a validated generalized transfer function. Antihypertensive drugs have been shown to differentially affect central aortic blood pressure.

B. Elevated or Hypertensive BP Levels

Blood pressure elevations are considered hypertension at different levels of elevation dependent

upon the other co-morbidities present. This is the diagnostic algorithm for hypertension that is used by the Joint National Committee on the Detection Evaluation and Treatment of High Blood Pressure 7th Report (also known as the JNC 7). In persons with diabetes mellitus, chronic kidney disease (estimated glomerular filtration rates [EGFR] < 60 ml/min/1.73 m^2 and/or spot urine albumin:creatinine ratio of > 200 mg/g), BP is considered elevated and diagnostic of hypertension when the systolic BP is $\geq$ 130 and/or the diastolic BP is $\geq$ 80 mm Hg. In all other persons, the BP elevation that is diagnostic of hypertension is $\geq$ 140/90 mm Hg. It should be noted that it takes more than one accurate BP measurement to diagnose hypertension in most instances. However, in the clinical setting some patients with and without the aforementioned co-morbidities will have BP levels below these diagnostic thresholds yet still be considered hypertensive because they are taking antihypertensive medications that have lowered their BP readings to below these thresholds.

4. Circadian Blood Pressure Variation

Throughout the 24-hour time period, in normal persons BP levels typically follow a predictable pattern. BP has a circadian rhythm. Blood pressure is approximately 10 – 20 % lower at night (2400 - 0599h) than between (0600 - 2200h). The BP nadir occurs early in the morning, a few hours after midnight, and begins to increase from this low level several hours before awakening. The rise in BP during the early morning hours occurs in parallel with a rise in pulse rate, increase in blood viscosity, and increased platelet aggregation. Some individuals - persons with chronic kidney disease/low estimated glomerular filtration rates, overweight African American women consuming high sodium diets, persons with low dietary potassium intakes, those with sleep disordered breathing, hyperactive sympathetic nervous systems - have been shown to have a blunted BP circadian rhythm. That is, BP (either systolic, diastolic, or both) do not fall at least 10% below average daytime levels at night. These persons are called “non-dippers”. There are also persons who are hyper-dippers (nighttime BP is > 20 mm Hg lower than the daytime BP) such as some stroke survivors. Both non-dippers and hyper-dippers have higher risks for pressure-related cardiovascular injury (e.g., stroke, heart failure) than persons with normal nocturnal declines in BP of ~ 10 – 20%. Twenty four hour BP readings are easily obtained in the clinical setting. Ambulatory BP monitoring is accomplished with specialized portable BP measurement devices that provide typically 2 – 3 BP measurements per hour that are stored in the device and are available for retrieval and analysis when the ambulatory BP monitoring device is returned to the clinic. It is, however, important to note that in hypertensive individuals ambulatory BP levels are typically lower than office cuff BP determinations. Accordingly, the threshold for elevated or abnormal ambulatory BP levels is numerically lower than for cuff BPs (Table 1).

Table 1. Suggested Values for the Upper Limit of Normal Ambulatory Blood Pressure

Suggested Values for the Upper Limit of Normal Ambulatory Blood Pressure

	OPTIMAL	*NORMAL*	*ABNORMAL*
Daytime	< 130 / 80	< 135 / 80	> 140 / 90
Nighttime	< 115 / 65	< 120 / 70	> 125 / 75
24 hour	< 125 / 75	< 130 / 80	> 135 / 85

Pickering TG et al. *Circulation* 2005;111:697-716.

4. Cardiovascular-Renal Complications of Hypertension

Table 2 displays BP sensitive target organs. That is, these are the organs that clinically manifest dysfunction and/or anatomic changes that can be detected clinically. Yet, with prevention of hypertension or, once hypertension develops, control of BP, pressure-related dysfunction of these organs is either preventable or, alternatively, can be forestalled.

Table 2. Blood Pressure Target Organs

Blood Pressure Target Organs

1. Brain
2. Retina
3. Heart
4. Arterial vasculature
   a. Macro-vasculature
      - Aorta
      - Arteries
   b. Micro-vasculature
      - Capillaries

Elevated BP, particularly SBP, is associated with multiple microvascular (eg, retinopathy, nephropathy) and macrovascular (eg, myocardial infarction, atherothrombotic stroke) cardiovascular-renal complications. Target-organ dysfunction, such as left ventricular systolic dysfunction (systolic and/or diastolic heart failure), can occur because of micro- and macro-vascular disease/dysfunction resulting in chronic ischemia of the myocardium. *In addition to these organ-specific complications, hypertension causes premature morbidity and mortality*. Though persons without hypertension can experience these complications, on average, persons with hypertension experience them relatively prematurely; hypertensives also are at higher overall risk for these complications than normotensive persons. The risk for virtually all cardiovascular-renal complications can be reduced with effective antihypertensive treatment. <u>It is, however, important to note that the risk for pressure-related cardiovascular-renal complications at BP levels well below hypertension diagnosis thresholds</u>. Risk approximately doubles for each 20/10 mm Hg higher BP above the level of 115/75 mm Hg.

5. Clinical Detection of Pressure-Related Target Organ Injury

It is not infrequent that clinicians encounter patients in whom they do not have prior medical records that document important historical trends in BP. Patients are also often unaware of their prior level of BP control. Nevertheless, there are relatively easily detectable clues to the prior level of BP control. Documentation of any or all of the findings in table 3 would suggest that BP control has been less than optimal.

Table 3. Clinically Available Clues Indicative of Poorly Controlled BP

Clinically Available Clues Indicative of Poorly Controlled BP

EXAMINATION

1. Retinopathy
   a. Arteriolar narrowing, A-V nicking
   b. Focal and general arteriolar narrowing, arteriolar silver wiring
   c. Hemorrhages, exudates, cotton-wool spots, papilledema and/or microaneurysms
2. Cardiac examination
   a. Laterally displaced and/or enlarged PMI
   b. S4 gallop
3. Electrocardiogram
   a. Inverted or bi-phasic P-wave in V1
   b. Voltage criteria for LVH

6. Mechanisms of Blood Pressure-Related Target Organ Injury

"Damage" to target-organs such as the heart, kidney, brain, and peripheral vasculature can occur at BP levels that are within the so-called normal range. This is because BP cut-points for the diagnosis of hypertension such as $\geq$ 140/90 mm Hg are arbitrary. SBP is more closely linked to target-organ injury and adverse clinical complications than DBP. Hypertension or incrementally higher levels of BP (even within the normal BP range) can injure target-organs via several mechanisms. Elevated BP can disrupt the functional and/or anatomic integrity of the vascular endothelium leading to accumulation of lipids, macrophages/monocytes, and inflammatory mediators in the subendothelium; this is the early stage of atherogenesis. As a vascular plaque grows elevated BP can create enough hemodynamic stress on the plaque to either contribute to or cause plaque rupture. Even in the absence of overt atherosclerosis, elevated BP leads to vascular remodeling/hypertrophy of arterial resistance vessels (arterioles) and causes abnormal vascular function (e.g., raised peripheral arterial resistance, endothelial dysfunction) and chronic ischemia of the involved target-organ such as the brain and kidney. Even if an atherosclerotic plaque does not rupture, its growth can be facilitated by elevated BP and it may compromise blood flow enough to cause intermittent (angina pectoris, transient ischemic attack [TIA]) or chronic ischemia of a target-organ. Sometimes the raised BP leads to weakening of the arteriolar vessel wall resulting in aneurysmal dilation of the vessel. Aneurysms are prone to rupture. Elevated BP, particularly SBP, is a major cause of left ventricular hypertrophy and ultimately both LV systolic dysfunction and diastolic heart failure.

Nitric oxide is synthesized from its precursor L-arginine via the action of endothelial NO synthase (eNOS). Nitric oxide (NO) is necessary for normal vascular function. The integrity of the vasculature, both functionally and anatomically, is dependent on adequate NO effect. Pulsatile blood flow in the arterial system leads to NO release from endothelial cells. Accordingly, pulsatile blood flow during exercise leads to even greater NO release from the vascular endothelium. However, with ageing, for example, the arterial vasculature stiffens, in part because of remodeling/hypertrophy of the arterial media. This is characteristically associated with increases in peripheral arterial resistance. This stiffening of the vasculature also has another important effect on endothelial function. The endothelium of stiff blood vessels produces less NO than elastic/pliable vessels do. The lack of NO effect has also been termed endothelial dysfunction which can be measured, though with some difficulty, non-invasively. In several states of endothelial dysfunction, the primary physiological problem is not a lack of NO production but rather enhanced destruction via the mediators of high levels of oxidative stress. Two examples of states of high oxidative stress are obesity and diabetes.

The higher the level of BP, the more likely pressure-related target-organs will sustain injury. Injury to pressure-sensitive target organs is occurs via multiple mechanisms as displayed in table 4. Endothelial dysfunction, vascular remodeling causing target-organ ischemia, accelerated atherosclerosis, cardiac remodeling/left ventricular hypertrophy and vascular rarefaction are examples of chronic pressure-related injury. An arterial tear as seen in aortic dissection or rupture of an aneurysm are very dramatic manifestations of pressure-related target-organ injury. **Table 4. Mechanisms of Blood Pressure-Related Target Organ Injury**

Mechanisms of Blood Pressure-Related Target Organ Injury

1. Endothelial dysfunction → impaired coronary vasodilatory reserve (one manifestation)
2. Vascular remodeling / chronic target-organ ischemia → organ dysfunction
3. Vascular rarefaction
4. Arterial tear (aortic dissection) or rupture (aneurysms)
5. Endothelial injury / activation of inflammatory and coagulation pathways (malignant / accelerated HTN), leaky arterioles (cerebral edema)
6. Accelerated atherosclerosis
7. Atherosclerotic plaque rupture
8. Cardiac remodeling → left ventricular hypertrophy → heart failure (systolic and diastolic) and/or ventricular arrhythmias / sudden death

7. Mechanisms of Pressure-Related Hemodynamically-Mediated Renal Injury

Hypertension has been linked both to chronic kidney disease as well as end-stage renal disease (ESRD). In fact, hypertension is the second leading cause of ESRD behind diabetes mellitus. The distinction between hypertension and diabetes mellitus is not entirely distinct. About 70 - 80% of persons with diabetes mellitus have hypertension (BP $\geq$ 130/80 mm Hg and/or taking antihypertensive medications), and obesity augments the risk for both hypertension and diabetes mellitus.

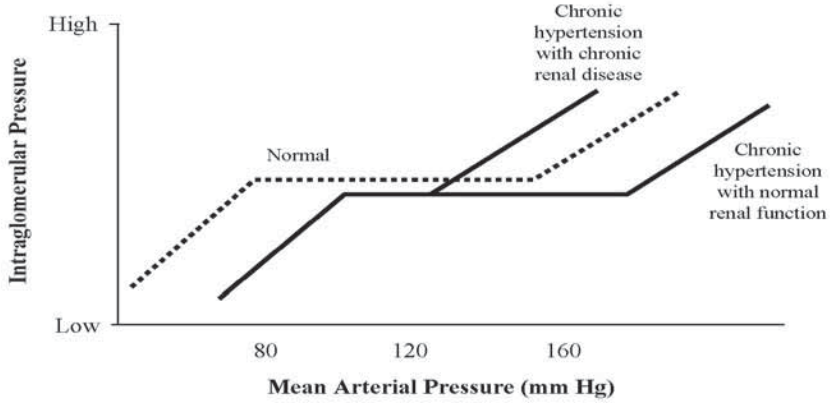
Transmission of systemic arterial pressure into the glomerulus, the functional unit of the kidney, is a major cause of renal injury. Under normal conditions the glomerulus protects itself from inordinate transmission of arterial pressure into the glomerular capillary loop. The mechanism by which systemic arterial transmission to the glomerulus is dampened is called autoregulation of renal GFR and blood flow. The afferent arteriole brings blood flow into the glomerulus from the renal artery where blood is filtered, urine is formed, and blood leaves the glomerulus via the efferent arteriole. Blood subsequently flows from this glomerular capillary network into another one, the peritubular capillaries. That is, the efferent arteriole branches into a peritubular capillary network that surrounds the tubules.

Autoregulation of GFR and renal blood flow are accomplished via several mechanisms. Increases in afferent arteriolar luminal pressure cause constriction of this vessel; decreases in luminal pressure cause dilation of this vessel. These afferent luminal caliber changes in response to changes in pressure are accomplished via the <u>myogenic reflex</u>. <u>Tubuloglomerular feedback (TGF)</u> is another mechanism through which afferent arteriolar tone can be affected. This mechanism changes afferent arteriolar tone according to changes in sodium chloride delivery to the macula densa in the distal nephron. Increased NaCl delivery leads to increased afferent arteriolar tone while decreased delivery causes afferent arteriolar dilation. Finally, local activation of the RAS system as typically occurs in the setting of reduced renal mass (↓ nephron number) leads to Ang II -mediated efferent >> than afferent arteriole constriction that raises intraglomerular pressure.

In the setting of chronic hypertension, the afferent arteriole anatomically remodels and becomes functionally incapable of maximally dilating (figure 4). This causes the lower end of the normal sigmoidal relationship between MAP and intraglomerular pressure to move to a higher level of BP. In contradistinction to the effect of chronic hypertension on the cerebral blood flow autoregulatory curve, as kidney function deteriorates and nephron number drops, the upper limit of autoregulation moves to a lower BP level resulting in intraglomerular pressure (and GFR) varying in a more direct relationship with systemic arterial pressure. In other words, the relationship between glomerular pressure and GFR becomes more linear.

Figure 4

Maintenance of Relatively Constant Intraglomerular Pressure by Renal Autoregulation despite Variations in Mean Arterial Pressure



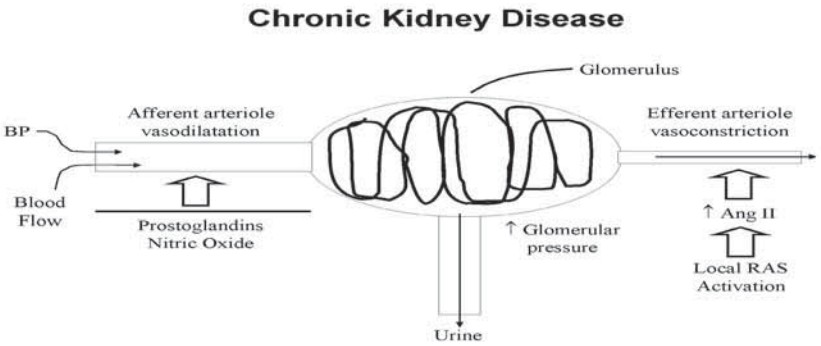
In chronic hypertension, the curve showing the relation of the intraglomerular pressure to the renal perfusion pressure (or mean arterial pressure) is shifted to the right. With the development of chronic renal failure, renal autoregulation changes in such a way that the intraglomerular pressure begins to vary more directly with changes in the mean arterial blood pressure. When this change occurs, the normal sigmoidal relation becomes progressively more linear. As a result, increases in the mean arterial pressure cause exaggerated increases in the intraglomerular pressure, whereas declines in the mean arterial pressure cause exaggerated decreases. Because of the rightward shift in the lower end of the curve, antihypertensive therapy may be accompanied by a decline in the glomerular filtration rate at a level of blood pressure that would not affect a normal person. Renal dysfunction in this setting is hemodynamic in origin and reflects a lower intraglomerular pressure.

Palmer BF. N Engl J Med 2002;347(16):1256-1261.

As nephron number falls, the demands on the remaining glomeruli increase to make up for the lost glomeruli. GFR is maintained, at the expense of high intraglomerular pressure, as a consequence of local activation of the RAS system that causes Ang II-mediated efferent arteriolar constriction; at the afferent arteriole, vasodilatory prostaglandins and nitric oxide mediate vasodilatation. These changes in afferent and efferent arteriolar tone, in aggregate, lead to intraglomerular capillary hypertension. There is also increased glomerular endothelial permeability resulting in excess filtration of plasma proteins in direct relation to the increased glomerular pressure that is, in turn, elevated because of transmission of systemic arterial pressure into a dilated afferent arteriole. A final common pathway leading to further nephron destruction is glomerusclerosis and tubulointerstitial fibrosis.

To understand the above pathophysiology is to also understand how to protect the kidney from further loss of functioning mass. Attainment of low levels of BP as well as lowering intraglomerular pressure with drugs such as angiotensin converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB's) are proven ways to protect kidney function (figure 5).

Figure 5. Chronic Kidney Disease



Ang= angiotensin; BP= blood pressure; RAS= renin-angiotensin system.

The aforementioned renal pathophysiology has important therapeutic implications. A note of caution, given that intraglomerular pressure in persons with reduced kidney function is more directly linked to systemic arterial pressure, lowering BP and/or lowering intraglomerular pressure can lead to a rise in serum creatinine that occurs as a result of lowering of GFR. Essentially the compromised kidney is letting you know that it can't autoregulate its GFR, at least over the short-term. Nevertheless, the compromised kidney maintains function longer, even if GFR falls in the short-term, when BP is lowered and intraglomerular pressure falls. In fact, the very conditions where autoregulation of GFR is abnormal - reduced renal mass, diabetes mellitus, proteinuric kidney disease - are indications for the type of pharmacological interventions (angiotensin converting enzyme inhibitor or angiotensin receptor blocker therapy) that may lead to a rise in serum creatinine. Thus, due to systemic circulatory and renal micro-circulatory effects, lowering BP with regimens containing ACE inhibitors, angiotensin receptor blockers, and direct renin inhibitors, will often lead to a rise in the serum creatinine indicative of a drop in the global GFR. If the patient has been over-diuresed and has a contracted plasma volume, the rise in creatinine will be even more prominent.

7. Clinically Recognizable Manifestations of BP-Related Target-Organ Injury

Table 5 displays common clinically recognizable manifestations of BP-related target-organ injury. These complications represent micro- and macro-vascular complications as well as target-organ dysfunction/failure. Careful clinical assessment and examination will detect many of these complications. The fundoscopic examination is often either poorly executed or not done in clinical situations, yet it provides great insight into the prior level of BP control and is one of the easiest ways to determine the presence of BP-related target-organ injury. Though retinopathy is linked to the level of BP, most retinal abnormalities are not specific, per se, to hypertension as some of these changes also occur, for example, in diabetes mellitus. Control of BP can prevent or forestall virtually all of these complications.

Table 5

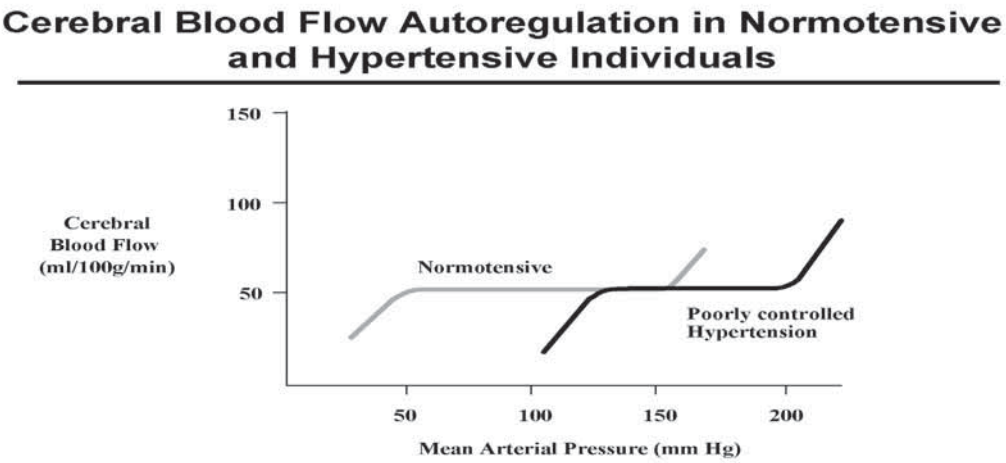
Examples of Clinically Recognizable BP-Related Target Organ Injury

1. Brain
   - Stroke
   - Transient Ischemic Attack
   - Dementia
2. Retina
   - Retinopathy
3. Heart
   - Left Ventricular Hypertrophy (LVH)
   - Left Atrial Enlargement (LAE)
   - Diastolic Dysfunction
   - Heart Failure (systolic and diastolic)
4. Arterial vasculature
   - Atherosclerosis
   - Arteriosclerosis
   - Dissection (aorta)
   - Aneurysm

8. Autoregulation of Cerebral Blood Flow

Under normal circumstances, cerebral blood flow (CBF) is ~ 50 ml/100g/min. CBF is proportional to cerebral oxidative metabolism and is highly sensitive to pCO_2; higher levels of carbon dioxide cause higher CBF. The cerebral circulation does, however, have a physiological protective mechanism - cerebral autoregulation - that maintains CBF relatively constant across a broad range of systemic perfusion pressures. In normal, non-hypertensive persons, cerebral autoregulation keeps CBF constant between mean arterial pressures (MAP) of 50 - 150 mm Hg (figure 6).

Figure 6



This is accomplished by dilatation and constriction of cerebral resistance vessels in response to reductions and elevations, respectively, in systemic BP. In chronic hypertension, when BP is poorly controlled, the entire autoregulatory curve is shifted to the right. The curve is shifted rightward, in part, because the pressure-related hypertrophy of the cerebral resistance vessels that diminish their capacity for maximum dilation (necessary to maintain blood flow when systemic pressure falls). However, the hypertrophy of these same arterial resistance vessels allows the arteriole to withstand higher than normal BP levels before its structural and functional integrity is compromised. Accordingly, in chronic hypertension that is not well controlled, the lower and upper limits of cerebral autoregulation move to higher BP levels.

Clinical Implications: *In the setting of chronic, poorly controlled hypertension rapid reductions in BP can lead to cerebral ischemia attributable to reductions in cerebral blood flow at BP levels that are within the hypertensive range.*

A. Reductions in MAP below the Lower Limit of CBF Autoregulation

As systemic perfusion pressure falls below the lower limits of CBF autoregulation, cerebral resistance vessels have dilated maximally but are no longer able to maintain cerebral blood flow. As CBF falls, cerebral oxidative metabolism is supported by augmentation of oxygen extraction from the declining cerebral blood flow. At this point symptoms of cerebral hypoperfusion such as lethargy, confusion, somnolence, etc. can appear. When CBF falls below ~10 ml/100g/min, the ionic gradient across neuronal cell membranes becomes disrupted leading to calcium influx and potassium efflux and neuronal cell injury/death occur. Unlike the heart where oxygen extraction is maximal at rest, the brain can extract greater amounts of oxygen from blood traversing it when cerebral blood flow falls. This provides at least some measure of cushion against cerebral ischemia.

B. Increases in MAP above the Upper Limit of CBF Autoregulation

As systemic perfusion pressure rises cerebral resistance vessels normally constrict. When systemic perfusion pressure rises above the upper limits of CBF autoregulation then CBF increases dramatically and there is increased permeability of the cerebral vasculature leading to cerebral edema and increased intracranial pressure. Raised intracranial pressure has two important physiological effects. First, systemic BP increases further. Secondly CBF may fall though this tendency is counterbalanced by the reflex rise in systemic perfusion pressure. Symptoms of CNS dysfunction again can occur such as seizures, lethargy, stupor, coma, etc. The clinical term for this life-threatening clinical situation is hypertensive encephalopathy. Table 6 displays clinical symptoms that characterize hypertensive encephalopathy.

Table 6

Clinical Manifestations of Pressure-Mediated Brain Injury During Severe BP Elevations

- Hypertensive Encephalopathy
  - Severe BP elevation or a rapid rise in BP
  - Headache
  - Nausea, vomiting
  - Transient neurological dysfunction (i.e., agitation, altered sensorium seizures)
  - Visual disturbances
  - Papilledema usually, but not always present

9. Blood Pressure and Cerebral Blood Flow Regulation during Acute Brain Ischemia

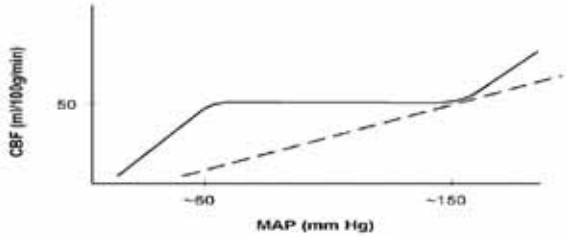
Hypertension is the major risk factor for stroke. Approximately 80% of patients with acute stroke have elevated BP at the time of hospital admission. The observation of elevated BP at the time of admission has also been made in persons without antecedent hypertension.

Blood pressure reflexively rises during acute cerebral ischemia and brain trauma. During acute cerebral ischemia, cerebral blood flow autoregulation is disrupted in the ischemic areas of the brain surrounding the already infarcted area. Disruption of CBF autoregulation is greater for brainstem ischemic lesions than for hemispheric lesions; severe hemispheric lesions cause greater disruption of autoregulation than minor hemispheric lesions; and subcoritcal lesions

cause greater disruption of CBF autoregulation than cortical lesions. This disruption of CBF autoregulation can last for weeks. The disruption of autoregulation in the ischemic areas of the brain leads to a dependence of systemic perfusion pressure for blood flow and therefore oxygen delivery into these areas (figure 7).

Figure 7. Relation of Systemic Perfusion Pressure to Cerebral Blood Flow

Figure 1. Relation of Systemic Perfusion Pressure to Cerebral Blood Flow



In non-hypertensives between MAP 60 - 150 mm Hg, there is little variation in CBF in response to changes in MAP. Chronic hypertension shifts the entire CBF autoregulatory curve to the right. In both normotensives and hypertensives the overall shape of the CBF autoregulatory curve is sigmoidal.

The dotted line depicts the distortion of the normal CBF autoregulatory curve into essentially a linear relation within the "ischemic penumbra" during acute brain ischemia. The ischemic penumbra is the non-infarcted and injured but potentially viable brain tissue that is adjacent to the infarcted area.

CBF=cerebral blood flow; MAP=mean arterial pressure.

Flack JM, et al. in Transient Ischemic Attacks, Blackwell Futura Publishing, Ch 14, pp 309-323.

On the other hand, excessive blood flow as can occur with very elevated systemic BP can facilitate formation of cerebral edema. Effective cranial perfusion pressure (CPP) is the difference between MAP and intracranial pressure (ICP). A significant proportion of persons with acute stroke have elevated ICP; therefore, the rise in systemic perfusion pressure might also help maintain CBF in the ischemic area of the brain when ICP is elevated. The highest levels of systemic BP appear to be associated with intracranial hematomas. Interestingly, this is also the one stroke subtype where autoregulation of CBF may not be impaired, particularly when the intracranial hematoma is small (< 45 ml).

Blood pressure perceptibly falls during the first 4 days after acute stroke and continues to fall spontaneously through 7 - 10 days post-stroke. In one large series of acute stroke patients, the fall in BP by day 10 averaged 20/10 mm Hg. Diurnal variation in BP is abnormal during acute stroke. The normal nocturnal declines in BP, both systolic and diastolic, are markedly attenuated to absent.

The therapeutic and clinical implications of the abnormal autoregulation of CBF in acute cerebral ischemia are profound. Though elevated BP is a risk factor for stroke and, in the setting of acute stroke, might facilitate cerebral edema formation, the dependence of CBF in ischemic brain areas on systemic perfusion pressure makes antihypertensive treatment risky. Even moderate reductions in BP might be associated with worsening cerebral ischemia and infarct extension, particularly in the ischemic penumbra (the damaged but still viable brain tissue surrounding the infarct).

Clinical Implications: *The clinician must resist the temptation to acutely lower BP in patients presenting with stroke or other manifestations of acute cerebral ischemia or head trauma. This is extremely difficult because clinicians have been conditioned to the fact that elevated BP cases stroke. Therefore when clinicians encounter elevated BP in the setting of stroke there is a strong inclination to acutely lower the BP via pharmacological means. Unless the systolic BP exceeds ~ 230 mm Hg and/or the DBP exceeds ~ 130 mm Hg, the clinician should refrain from intervening with pharmacological agents to acutely lower BP. Blood flow and therefore oxygen delivery into the watershed area (ischemic penumbra) is dependent on systemic perfusion pressure. Also, in ~ 40% of patients with acute stroke, intracranial pressure is increased. Raised intracranial pressure is also an impediment to cerebral blood flow and therefore cerebral oxygen delivery. The major exception to this recommendation of therapeutic restraint is when there are signs of new/ worsening target-organ injury that is likely related to elevated BP (e.g., heart failure, worsening kidney function, etc.). It is wise to keep the BP lower than ~ 185/110 mm Hg when thrombolytic therapy will be utilized in acute stroke patients.*

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Introduction to Special Populations

Silas P. Norman, MD

The term Special Populations refers to the group of patients who either have hypertension (HTN) in the setting of, or caused by other diseases. Such groups are typified by patients with diabetes mellitus, pregnancy and members of ethnic minority groups. Treating individuals who have HTN and other special circumstances can be especially challenging. In order to treat patients most effectively, the practitioner must have a good sense of the confounding situation and understand how blood pressure medications and treatments are affected by the situation. A provider must also be able to share and coordinate care with other specialty providers when necessary to ensure the best outcomes.

In treating patients from special populations, the basic premises of HTN care remain true. The goal of care is to minimize end-organ damage and to do so without harming the patient. Practitioners should ideally try to utilize the fewest medications possible to achieve blood pressure goals and be conscious of how dosing schedules and medication costs can affect medication adherence. Care should be culturally competent and the provider should seek to engender trust in the patient-provider relationship. In the following sections we detail a number of specific medical situations that exemplify the common special populations and outline an approach for treatment and control of cardiovascular risk broadly and HTN specifically in each group considered.

Chronic Kidney Disease

Silas Norman, MD

Learning Objectives:

1. To understand the prevalence of chronic kidney disease (CKD) in the U.S. population.
2. To understand the mechanisms of HTN in individuals affected by CKD.
3. To understand the importance of renin-angiotensin-aldosterone blockade in the treatment of HTN in CKD individuals.
4. To understand the leading causes of CKD in the U.S.
5. To understand the basic screening procedure for CKD in HTN individuals.

Pre-Test Questions:

1. What is the leading cause of end-stage kidney disease (ESRD) in the U.S.?
    a. Diabetes mellitus **(correct answer)**
    b. Glomerulonephritis
    c. Hypertension
    d. Non-steroidal anti-inflammatory drugs
2. Which of the following is an appropriate screening test for individuals suspected to have CKD?
    a. Serum blood urea nitrogen
    b. Serum creatinine
    c. Urinary protein
    d. A and B
    e. B and C **(correct answer)**

Chronic kidney disease (CKD) is an important but often unrecognized cause of HTN. Chronic kidney disease stages 3-5, defined by the K/DOQI guidelines as GFR $\leq$ 59 ml/min affects an estimated 6.2 million Americans with an increasing prevalence in some populations.[1] As CKD progresses the likelihood of HTN also increases such that the virtually all patients that approach end-stage kidney disease (ESRD) are hypertensive. In addition, clinically, the management and control also becomes progressively difficult for reasons described below. Chronic kidney disease does not affect all populations equally, with African- and Hispanic-Americans more likely to develop and experience progression of CKD than their white counterparts.[2-4]

Hypertension in CKD is related to the primary function of the kidneys themselves. Clearance of metabolic waste products is the primary focus for kidneys and this clearance is accomplished utilizing blood pressure driven filters (glomeruli). As the absolute number of glomeruli decrease from any cause of injury, the remaining filters need to incrementally increase their filtering function to keep net waste removal constant. One mechanism to accomplish increases in filtration is to promote increases in BP. Increased BP across glomeruli results in an increase perfusion pressure and increase single nephron glomerular filtration. In the short term, this is a successful adaptation, but over time, exposure

to elevated BP causes progressive glomerular damage. The damage and loss of additional glomeruli further exacerbates the situation such that remaining glomeruli may promote even higher BP in order to maintain waste clearance.

An additional issue that is well recognized by providers is the difficulty in controlling HTN in the CKD population. In part, this difficulty is a result of trying to interrupt the maladaptive compensation of kidneys to inadequate glomerular mass. Maintenance of HTN is occurs through multiple mechanisms. A significant number, though not all, of these mechanisms are renin-angiotensin-aldosterone system (RAAS)-related. Sympathetic nervous activity increases as glomerular filtration rate falls. Renin production from the juxtaglomerular cells of the kidney is stimulated by sympathetic activity and renal hypoperfusion. Renin, the rate-limiting enzyme in the synthesis of angiotensin II, converts angiotensinogen to angiotensin I which is ultimately converted by angiotensin converting enzyme (ACE) to the penultimate product of the RAAS system, angiotensin II. Angiotensin II is a potent vasoconstrictor and in addition promotes sodium and water reabsorption from the renal proximal tubule.

Aldosterone production from the adrenal gland occurs in part from stimulation from angiotensin II. Aldosterone promotes sodium chloride retention and as a result water, thus increasing vascular volume and as a consequence, blood pressure. The RAAS is the most important intrinsic renal contribution to HTN. In addition, the contribution of the RAAS to HTN as well as to the pathogenesis of CKD makes clear why interruption with direct renin inhibitors, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have an important role in both lowering of BP as well as in the preservation of kidney function control.

Kidney disease perpetuates HTN in part because of the diseases that cause CKD. Diabetes mellitus is the leading cause of CKD in the U.S. and is responsible for over 40% of all end-stage kidney disease (ESRD) cases.[1] The progressive macro and microvascular damage that occurs as a consequence of glycemic and non-glycemic CVD risk factors (e.g., hypertension, dyslipidemia) in persons with diabetes directly promotes HTN. Diabetes further contributes to HTN through direct kidney injury in the form of diabetic nephrosclerosis. The loss of nephron mass contributes to HTN as described previously. In addition, the proteinuria associated with diabetic nephropathy further injures nephrons causing more kidney damage and further exacerbating the situation.

The second leading cause of advanced CKD and ESRD is essential HTN itself.[1] The

development of essential HTN can set in motion a self-perpetuating cycle of damage. Hypertension causes kidney injury, which exacerbates HTN, causing further kidney injury. Of note, not all CKD attributed to HTN is initially cause by HTN. There are likely many individuals, particularly young people who develop unrecognized, self-limited glomerular disease that results in kidney injury and HTN. For these individuals with asymptomatic initial kidney injury, by the time they present for medical care will have HTN, abnormal kidney function and normal serologic markers. As such, these individuals tend to be characterized as having CKD caused by HTN rather than HTN caused by CKD.

There are a number of additional causes of CKD that are worth discussing because although they are not preventable, early detection and treatment can significantly reduce the morbidity associated with such diseases. Autosomal dominant polycystic kidney disease (ADPKD) affects 1 in 500 (approximately 600,000 in the U.S.) and contributes to approximately 10% of advanced CKD cases. Polycystic kidney disease individuals develop HTN from the same mechanisms as described above. In addition, HTN may be further exacerbated by the fact that ADPKD individuals with advanced CKD tend to have less anemia than non-ADPKD individuals. People affected with ADPKD may also have HTN from essential HTN or obesity, just like the general population. There are additional causes of CKD (Table 1) that can directly or indirectly contribute to HTN that should be kept in mind in assessing individuals with HTN.

Chronic kidney disease is important not just because of the risk for HTN and ESRD, but also because of the increased risk for cardiovascular (CV) events.[5-7] Individuals with CKD have a significantly increased risk for CV mortality, starting with relatively small decrements in overall renal function.[8-10] Hypertension accelerates and further exacerbates this situation. As expected, in the individual who has the not uncommon combination of CKD, HTN and DM is at extraordinarily high risk of CV death. Treatment of individuals with CKD is essential to effect what are certainly preventable excess deaths in this population. Numerous studies demonstrate that control of blood pressure can slow progression of CKD, particularly in patients with significant proteinuria at the onset of therapy. Further, and perhaps more importantly, HTN and CKD control can decrease CV events and death.

An analysis of the Fourth National Health and Nutrition Examination Survey (NHANES IV) reveals that only 37% of subjects had blood pressures controlled to a goal of < 130/< 80 mmHg.[11] The major issue was inadequate control of systolic blood pressures. African Americans were more than twice as likely and the elderly almost five times more likely to have uncontrolled blood pressures

than other groups. Similarly, Wong et al. demonstrated that patients with CKD, along with other CV co-morbidities had poor control rates, despite higher rates of treatment than the general population.[12] This apparent paradox of more intensive treatment not leading to greater control highlights the population often affected by CKD. CKD has been proven to confer resistance to the BP lowering effect of antihypertensive agents. Large numbers of CKD patients come from underserved populations and populations with limited economic resources and access to quality health care. As practitioners approach the patient with CKD, recognition of the CV risk and the overall poor control should be prominent in care considerations.

As noted more thoroughly elsewhere in this book, individuals presenting with HTN should be screened for secondary and reversible causes. With relatively simple, inexpensive testing, unrecognized CKD can be diagnosed and appropriate treatments prescribed. The work up should include renal ultrasound to define kidney sizes, character and blood flow, urine dipstick and microscopy along with a spot determination of urinary albumin/creatinine ratio or protein/creatinine ratio and assessment of renal function and serum glucose. In addition, providers need to be aware that there are not only differences in prevalence of disease among race and gender groups, but also differences in rates of HTN control that may affect outcomes.[13-17] Providers must also prepare themselves to follow up and re-evaluate patients as often as is necessary to ensure good outcomes.

Although the development of CKD can seem complicated, the treatment is often relatively straightforward. First and foremost, BP must be controlled. There is a clear relationship between increasing blood pressures and CV death.[18] In addition, increasing BP clearly contributes to progressive declines in renal function.[19] Practitioners should adhere to recommendations from the Joint National Committee on Hypertension (JNC-7).[20] Important for outcome is an appreciation that close to target is not on-target and that we maintain therapeutic inertia towards achieving good HTN control. The cornerstone of drug therapy for CKD are the ACE-I (and increasingly ARB's).[21,22] Angiotensin converting enzyme inhibitors have been shown to improve blood pressure, slow progression of CKD and reduce proteinuria.[23-25] There is an increasing literature supporting ARB use, particularly in those with type 2 DM.[26,27] In addition, diuretic therapy and dietary sodium reduction should be standard in the approach to treatment of HTN in CKD. As CKD affected individuals will often have multiple co-morbidities (HTN, DM, obesity, hyperlipidemia), a holistic approach involving coordination of providers will be necessary to achieve optimal results.

Figures:
Figure 1. Pie-chart with major diseases causing ESRD
Figure 2. Graphic showing HTN control in CKD

Tables:
Table 1. List of “all” causes of CKD
Table 2. List of screening test for CKD
Table 3. Calculators for CKD (CG, MDRD and Swartz)
Table 4. Staging of CKD

Essential points check:

1. Chronic kidney disease is common in the U.S.
2. Chronic kidney disease is often unrecognized or underestimated.
3. Diabetes is the leading cause of CKD.
4. Renin, angiotensin and aldosterone are important contributors to HTN
5. Appropriate screening for CKD can reduce morbidity and provide opportunities for early intervention.

Post-Test Questions:

1. In patients with CKD and diabetes, the first line anti-hypertensive agent is
    a. Calcium channel blocker
    b. Beta blocker
    c. Angiotensin converting enzyme inhibitor **(correct answer)**
    d. Alpha blocker

Table 1

Prerenal Disease	
	True volume depletion
	Gastrointestinal tract, renal or sweat losses or bleeding
	Heart failure
	Hepatic cirrhosis
	Nephrotic syndrome
	Hypotension
	Non-steroidal anti-inflammatory drugs
	Bilateral renal artery stenosis
Obstructive uropathy	
	Prostate disease
	Malignancy
	Calculi
	Congenital abnormalities
Vascular disease	
	Vasculitis
	Malignant hypertension
	Scleroderma
	Thromboembolic disease
	Nephrosclerosis
Glomerular disease	
	Glomerulonephritis
	Nephrotic syndrome
Tubular disease	
	Multiple myeloma
	Hypercalcemia
	Uric acid nephropathy
	Polycystic kidney disease
	Medullary sponge kidney
Interstitial disease	
	Pyelonephritis
	Interstitial nephritis
	Analgesic abuse

Pathophysiology of Renal Disease. Table 2-1 pg. 42
Burton David Rose. Second ed. McGraw Hill 1987

Table 2

Screening Test for CKD

- Estimation of GFR
  - Age, weight and plasma creatinine for Cockroft-Gault
  - Age, race, gender and plasma creatinine for MDRD
  - Age, height, gender and plasma creatinine for Schwartz
- Evaluation of the urine
  - Urinalysis
  - Dipstick for protein, blood, glucose
  - Microalbumin or protein/creatinine ratio
- Radiologic Imaging
  - Renal ultrasound with doppler

Table 3

Cockroft-Gault = http://www.clinicalculator.com/english/nephrology/cockroft
Modification of diet in renal disease (MDRD) = http://www.mdrd.com
Schwartz = http://www.kidney.org/professionals/kdoqi/gfr_calculatorPed.cfm

Table 4

STAGE	DESCRIPTION =Kidney damage with…	GFR (ml/min/1.73m2)
1	normal or increased GFR	> 90
2	mild decrease in GFR	60-89
3	moderate decrease in GFR	30-59
4	severe decrease in GFR	15-29
5	kidney failure	<15 or dialysis

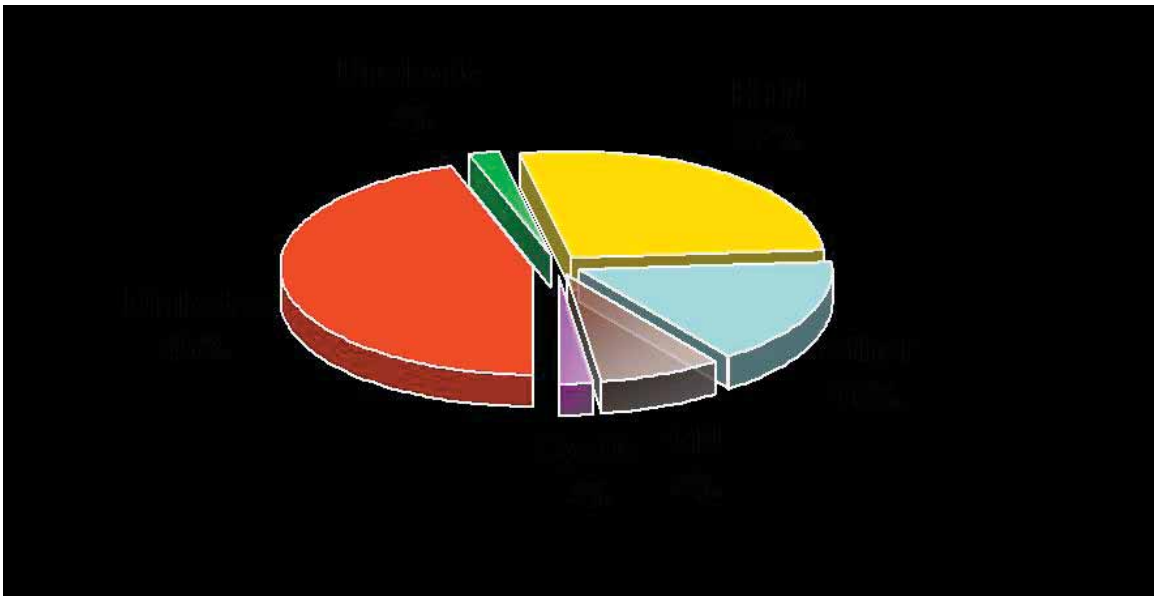

Figure 1: Causes of ESRD. USRDS 2008 Annual Data Report

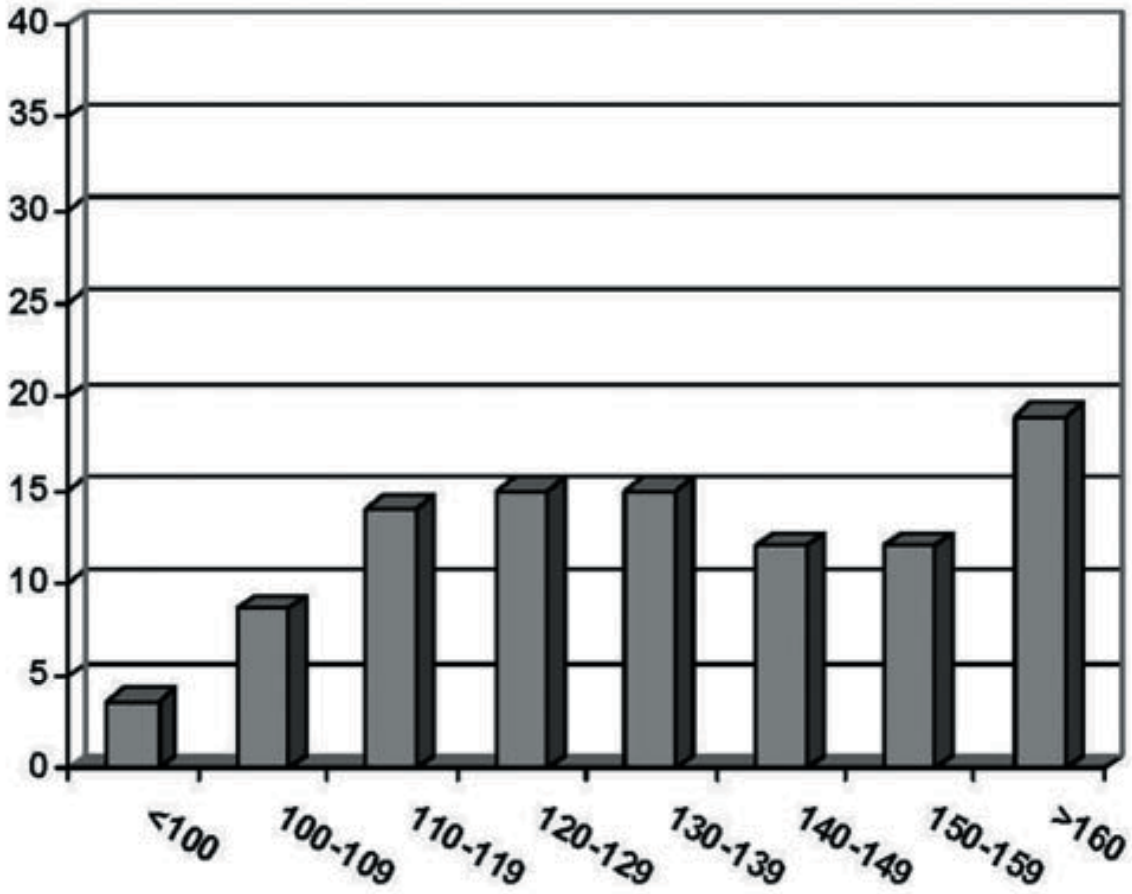

Figure 2:
Distribution of Systolic Blood Pressure (mmHg) among Adults with CKD in NHANES IV. Peralta et al. Hypertension 2005 ; 45 ; 1119-1124

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Special Populations: Elderly

Silas P Norman, MD

Learning Objectives:

1. To understand the prevalence of HTN in the elderly U.S. population.
2. To understand importance of screening for autonomic neuropathy in older individuals.
3. To understand the challenges to treatment of HTN in elderly individuals.

Pre-Test Questions:

1. Which of the following are special concerns for HTN treatment in the elderly?
    a. Tendency towards orthostatic blood pressures
    b. Risk for falling
    c. Costs of medications
    d. All of the above **(Correct answer)**
2. Which of the following is more likely in older versus younger individuals with HTN?
    a. Orthostatic hypotension
    b. Isolated systolic HTN
    c. Isolated diastolic HTN
    d. A and B **(Correct answer)**
    e. A and C
3. What is the goal blood pressure for older individuals with HTN?
    a. Higher than the goal for similar young people
    b. Lower than the goal for similar young people
    c. Age does not directly influence goal BP levels **(Correct answer)**

Hypertension can be a particular problem for elderly individuals. In addition to issues of diagnosis and follow up, treatment can be a particular challenge. As the population of the U.S. continues to age, the challenge of effectively managing blood pressure in this population will increase. Hypertension prevalence is clearly associated with increasing age. In individuals age sixty-five and over, up to 80% will have HTN.[1] Such prevalence is unmatched by any other medical condition. The elderly with HTN are also less likely to have HTN in isolation from other co-morbid conditions.[2] As a result, the overall cardiovascular risk experienced by older patients will often exceed the risk experienced by a similar group of younger candidates.[3, 4] The burden of HTN is not experienced by all elderly populations equally, with African-American and Hispanic groups disproportionately affected by HTN.[1]

In the management of HTN in the elderly, there are two distinct sets of challenges, one medical and the other financial. From the medical standpoint, the issues are an increased risk of autonomic dysfunction (AD) and co-morbid illnesses along with documented poor control relative to younger

individuals.[2, 5] The risk of AD increases with increasing age.[6, 7] Clinically, this is manifest as orthostatic blood pressures (SBP drops > 10 mmHg or DBP > 5 mmHg going from sitting to standing), which can complicate management. The effect of orthostatic BP drops is that individuals under treatment are at increased risk of symptomatic hypotension, increased medication side effects and a not insignificant increase in risk of falling. Appropriate management requires first that seated and standing measures of BP are done and second that recommendations for home monitoring specify standing BP's and third that the target BP goal is focused on control of the standing BP. For many patients this may translate into the need for larger doses of anti-hypertensive medications in the evening (when the person will be supine for several hours) compared to the morning doses.

Elderly patients are far more likely than younger individuals to have isolated systolic HTN (ISH).[8] Isolated systolic HTN may account for as much as 80% of the HTN seen in the elderly population. As a consequence, the particular choices of medication may need to be specialized. A practitioner must also keep in mind the relatively low control rates found in the elderly. Part of the issue is the relative unawareness many patients have about their diagnoses, with only about 50% of individuals aware they are hypertensive. Despite awareness of the high frequency of multiple cardiovascular co-morbidities in the elderly population, HTN is frequently uncontrolled. In fact, elderly patients are up to five times more likely to have uncontrolled blood pressure than their younger counterparts.[9] A major reason for the lack of SBP control in the elderly has to do with the magnitude of the SBP elevation that is often far above goal levels. Also, co-morbidities such as obesity, diabetes mellitus, CKD (both depressed GFR and albuminuria), and the presence of pressure-related target-organ injury are more common in elderly than non-elderly hypertensives. All of these conditions have been shown to confer resistance to the BP lowering effect to anti-hypertensive agents.

Co-morbid illnesses increase the difficulty of appropriately treating elderly individuals with HTN. A significant number of individuals will have DM, coronary heart disease (CHD), congestive heart failure (CHF) or be on chronic anticoagulation therapy. Each of these conditions requires sensitivity to the recommended medication classes for each disease. Elderly individuals may have physical limitations to home BP monitoring, such as poor vision or difficulty standing for prolonged periods of time. In addition, individuals may be particularly sensitive to the effects of BP lowering or not tolerate

side effects particularly well. A holistic and integrated approach to HTN management in this population is necessary for the best outcomes and should include coordination of management by what are often multiple care providers.

A non-medical, but real concern is the cost of medication.[10, 11] Elderly individuals are less likely to be working and more likely to be on fixed incomes than their younger counterparts. In addition, as elderly patients may have co-morbid medical conditions, their out of pocket medical costs may be substantial prior to starting anti-hypertensive therapy. The financial issue also impacts access to health care and BP monitoring which must be considered. In assessing elderly individuals, a provider needs to be comfortable with having frank and open discussions about the financial realities of care and design a treatment plan that minimizes the economic burden to the treated individual. Such an approach must involve aggressive and deliberate use of generic medications, minimize polypharmacy and encourage consistent feedback from the treated individual to ensure that the HTN treatment is not placing an undue burden on the individual.

Hypertension treatment is covered in a separate section of the book, but there are a few issues worth noting. The first is that several studies have demonstrated the effectiveness and utility of treating HTN in older and elderly individuals.[12-14] Cardiovascular events, most notable stroke and heart failure, can be reduced and treated individuals experience reduced morbidity and in many cases, reduced mortality. Secondly, the treatment goals for older and elderly individuals are no different from those in the general population. Specifically, using the JNC-7 recommendations as a guide, BP should be less than 140 mmHg over less than 90 mmHg in most individuals and less than 130 mmHg over less than 80 mmHg in individuals with DM or CKD. Third, an appreciation for cultural differences is necessary to achieve optimal results.[15] In regards to specific medications, the thiazide diuretics have shown great efficacy in the elderly population, as have ACE-I and calcium channel blockers.[13,16,17] Nevertheless, thiazide diuretics and calcium channel blockers will lower BP more as monotherapy than other antihypertensive drug classes; however, single drug therapy with any drug class is unlikely to control BP, especially SBP to below goal levels in most elderly antihypertensives. Thus, in most situations the practitioner will be using combination drug therapy, typically a diuretic or calcium channel blocker, in combination with a RAAS inhibitor in a slow, deliberate approach to BP lowering in the elder population.

Figures:
Figure 1. Graph showing prevalence of HTN with increasing age

Tables:
Table 1. Trials Involving Older Persons

Essential points check:

1. Hypertension is extremely common in older individuals.
2. Elderly individuals often have multiple co-morbid medical conditions in addition to HTN.
3. Orthostatic hypotension is a significant issue in the treatment of HTN in elderly individuals.
4. The goals for HTN treatment do not change with age.

Post-Test Questions:

1. Compared to young people the prevalence of HTN in the elderly is
    a. Increased **(Correct answer)**
    b. Decreased
    c. The same

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Table 1

Trials Involving Older Persons

HOT	Hypertension Optimal Treatment Study	Lancet 1998
HOPE	Heart Outcomes Prevention Evaluation Study	NEJM 2000
HYVET	Hypertension in the Very Elderly Trial	NEJM 2008
Syst-Eur	Systolic Hypertension in Europe Trial	Lancet 1997
SHEP	Systolic Hypertension in the Elderly Program	JAMA 1991

Figure 1: **Prevalence, Treatment and Control of HTN in US Adults, NHANES 2003-2004**

Table 1. Prevalence, Treatment, and Control of HTN in US Adults (NHANES 2003-2004)[a]

Characteristic (n, N)	Prevalence of HTN, % (Mean SBP/DBP mm Hg)	All Patients With HTN: Those Receiving Treatment for HTN, %	All Patients With HTN: Those Receiving Treatment for, and Controlled for, HTN, %
Total sample (4646, 192.4M)	31.4 (142/74)	68.5	52.9
Sex			
Men (2284, 94.2M)	32.2 (139/76)	67.2	56.5
Women (2362, 98.3M)	30.5 (145/73)	69.9	49.4
Age, range, y			
18-39 (1945, 79.5M)	8.8 (132/84)[b]	48.5[b]	74.0[b]
40-49 (706, 41.9M)	27.9 (136/84)	62.9	64.3
50-59 (529, 31.6M)	44.2 (138/79)	75.5	55.3
60-69 (665, 20.0M)	63.8 (141/74)	80.7	54.0
≥70 (801, 19.4M)	77.3 (148/68)	65.4	33.3
Race or ethnicity			
Black (990, 21.6M)	37.4 (142/78)[b]	69.8	50.5
Hispanic (1112, 21.6M)	21.3 (145/74)	63.5	45.9
Non-Hispanic white (2351, 139.3M)	32.3 (140/73)	68.8	55.2

Special Populations: Diabetes Mellitus

Silas P. Norman, M.D.

Learning Objectives:

1. To understand the prevalence of diabetes mellitus (DM) in the U.S. population.
2. To understand the high cardiovascular risk associated with HTN in individuals affected by DM.
3. To understand the importance of renin-angiotensin-aldosterone blockade in the treatment of HTN in individuals with DM.

Pre-Test Questions:

1. What is the leading cause of end-stage kidney disease (ESRD) in the U.S.?
    a. Diabetes mellitus **(correct answer)**
    b. Glomerulonephritis
    c. Hypertension
    d. Non-steroidal anti-inflammatory drugs
2. Which of the following are appropriate screening tests for individuals with DM?
    a. Urine microalbumin
    b. Ophthalmology examination
    c. Monofilament testing
    d. A and B**(correct answer)**
    e. A, B and C

Diabetes (DM) is the leading cause of end-stage kidney disease and a risk factor for cardiovascular death. Over twenty million Americans are affected by diabetes and the prevalence is increasing.[1] According to the Centers for Disease Control and Prevention (CDC-P) DM affects approximately 10% of the adult, non-institutionalized population (Figure 1).[2] The incidence of DM is associated with increasing age, obesity and African-American, Hispanic and Native American ethnicities (Figure 2). Perhaps the most significant change in the distribution of DM has been the increase in children, adolescents and young adults who are now developing diabetes.[3, 4] Diabetes is also a leading cause of and co-morbidity associated with HTN. Approximately 75% of individuals affected by DM will also have HTN at some point during their lifetimes.[5] The concomitant existence of DM and HTN in the

same individual is associated with a significant increase in cardiovascular (CV) death risk highlighting the importance of early, aggressive treatment.

The majority of individuals affected with DM are classified as having Type II diabetes mellitus (DM2.)[1] Type II diabetes, previously referred to as adult-onset diabetes is driven largely by increases in body weight. In the general population, this largely reflects an imbalance between energy intake and energy expenditure that favors the former. Currently one-third of the U.S. is overweight and an additional one-third is frankly obese, leading to a high background risk in the population.[6] The prevalence of obesity is rising and as a consequence the prevalence of DM2 is also increasing.[7] In addition, with the increasing age of the U.S. population there are a growing number of at risk individuals as well as a large number of individuals whom have years of accumulated DM morbidity and resultant CV disease outcomes. The African-American population has an increased risk of the development of DM.[2, 8] Combined with the high prevalence of HTN and risk for CKD, individuals are at extraordinarily high CV risk.[9] Similarly, Native Americans have long been known to have a very high frequency of DM and increased risks also for CKD. The Hispanic population is another demographic group at increased risk relative to non-Hispanic Whites, highlighting the challenges to treating HTN in the diabetic individual.
Individuals affected with DM have accelerated atherosclerosis associated with DM. The increased vascular disease in part is due to the abnormal binding of excess glucose residues with proteins, lipids and nucleic acids, the so called advanced glycation end products (AGE's).[10, 11] The eventual consequence of AGE covalently binding to amino acids is the micro- and macrovascular complications that are common in diabetes. Hypertension is one of those complications. In addition, DM affected patients often have a compounding issue which is the autonomic neuropathy (micro-vascular complication) that develops in DM. As a result, DM patients often have both HTN and significant orthostatic hypotension, which can complicate treatment.

Approximately 75% of persons with diabetes mellitus have hypertension (BP $\geq$ 130/80 mm Hg or taking BP medication) Treatment of HTN in individuals with DM is important to prevent multiple micro- and macro-vascular morbidities associated with DM. Poor BP control along with hyperglycemia) is a major cause of retinal bleeding in DM. Furthermore, the majority of the cardiovascular complications associated with DM are related to non-glycemic CVD risk factors. Thus, it is absolutely necessary to control non-

glycemic risk factdors such as hypertension to maximally reduce the adverse CVD-renal outcomes in DM.

Diabetes mellitus is a potent risk factor for CV disease[12-14] and currently ranks as the sixth leading cause of death in the U.S. In addition, DM is the leading cause of end-stage kidney disease.[15] Individuals with DM without coronary artery disease (CAD) have a risk for first myocardial infarction (MI) comparable to non-diabetics who have suffered a previous MI.[16] In addition, the risk of stroke in individuals with DM is 2-3 times the non-diabetic risk.[9] Each of these risks can be decreased by effective blood pressure control. The United Kingdom Prospective Diabetes Study (UKPDS) was pivotal in that it demonstrated that HTN control had the potential to provide more CV risk reduction than glucose control in some patients.[17-19] The importance of HTN control in diabetics has been reinforced by the findings of many other studies including the Hypertension Optimal Treatment (HOT)[20], Appropriate Blood Pressure Control in Diabetes (ABCD), Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET), the Heart Outcomes Prevention Evaluation (HOPE)[21, 22], the Reduction of End-points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL)[23, 24] and the Irbesartan in Diabetic Nephropathy Trial (IDNT)[25] studies, among others.

Treatment in DM should center on the common themes of HTN control for all patients; lifestyle modification[26], treating blood pressures to goal and the use of generic medications and daily dosing schedules to improve adherence. In addition, recognition of the overlapping CV risk factors helps to guide therapy. In addition to glucose control, management of obesity and dyslipidemia and recognition of other states for which specific medications or classes of medications are indicated (such as aspirin therapy) can help a provider to maximize outcomes. The DM patient with HTN should also have as the cornerstone of pharmacologic therapy a renin-angiotensin-aldosterone system (RAAS) blocker, typically an angiotensin converting enzyme inhibitor (ACE-I).[27] As discussed in the section on chronic kidney disease, the ACE-I and angiotensin receptor blockers appear to not simply decrease blood pressure, but also reduce proteinuria which is a marker for both kidney disease and CV risk. As DM individuals are at high CV risk, BP should be targeted to be consistently less than 130 over less than 80 mmHg.[28] In addition, as many diabetics have significant autonomic neuropathy with large changes in BP from sitting to standing. In this situation the standing BP rather than seated BP should be the target for daily control. Equally important is dosing medication to achieve 24-hour blood pressure control.

In candidates with significant orthostasis, this may mean preferentially dosing the bulk of anti-HTN medications in the evening so that nocturnal BP is controlled. Such dosing should utilize medications whose effects will only last 6-8 hours such that in the morning when the patient needs to stand, they will have an effective blood pressure to do so. Drug classes most likely to cause/contribute to orthostatic hypotension include alpha blockers, sympatholytic agents (e.g., clonidine) and diuretics (esp. when the patient has been overdiuresed).

Like all other patients, the DM patient needs close follow up and aggressive effort to make sure BP goals are achieved. During treatment, in addition to BP measures, attention should be paid to urinary microalbumin or proteinuria as well as the level of glucose control.[29] Diabetic patients with HTN are at very high risk of death and CV morbidity. With aggressive HTN intervention, a significant number of CV events, including incident ESRD can be prevented.Essential point's check:

1. Diabetes Mellitus is highly prevalent in the U.S.
2. Diabetes Mellitus is a potent risk factor for cardiovascular death.
3. Diabetes is the leading cause of end-stage kidney disease.
4. Anti-hypertensive therapy in patients with diabetes mellitus should involve blockade of the renin-angiotensin-aldosterone axis.
5. Appropriate treatment of HTN in patients with diabetes has been shown to reduce cardiovascular morbidity and mortality.

Post-Test Questions:

1. In patients with diabetes mellitus, identify the first line anti-hypertensive agent.
    a. Calcium channel blocker
    b. Beta blocker
    c. Angiotensin converting enzyme inhibitor**(correct answer)**
    d. Alpha blocker

2. In patients with diabetes mellitus Type II, in addition to anti-hypertensive therapy, which other activity is likely to improve outcomes?
    a. Glucose control

b. Weight loss

c. Weight gain

d. A and B**(correct answer)**

e. A and C

3. What is the goal blood pressure for individuals with diabetes mellitus?

a. < 140/ < 90 mmHg

b. < 150/ < 90 mmHg

c. < 130/ < 85 mmHg

d. < 130/ < 80 mmHg **(correct answer)**

Figures:

Figure 1. Prevalence of Diabetes by Age Category

Figure 2. Prevalence of Diabetes by Race/Ethnicity

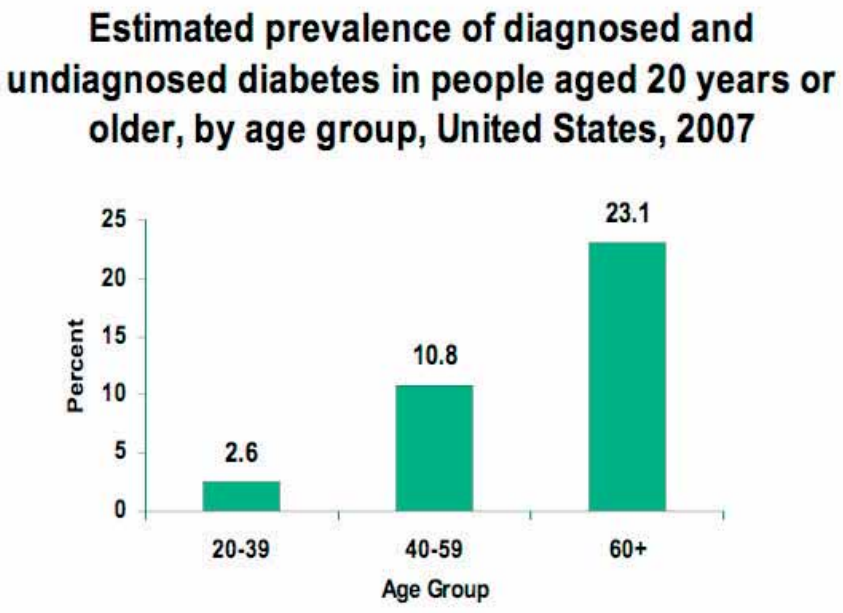

Figure 1.

CDC. National Diabetes Fact Sheet, 2007.
Source: 2003–2006 National Health and Nutrition Examination Survey estimates of total prevalence (both diagnosed and undiagnosed) were projected to year 2007

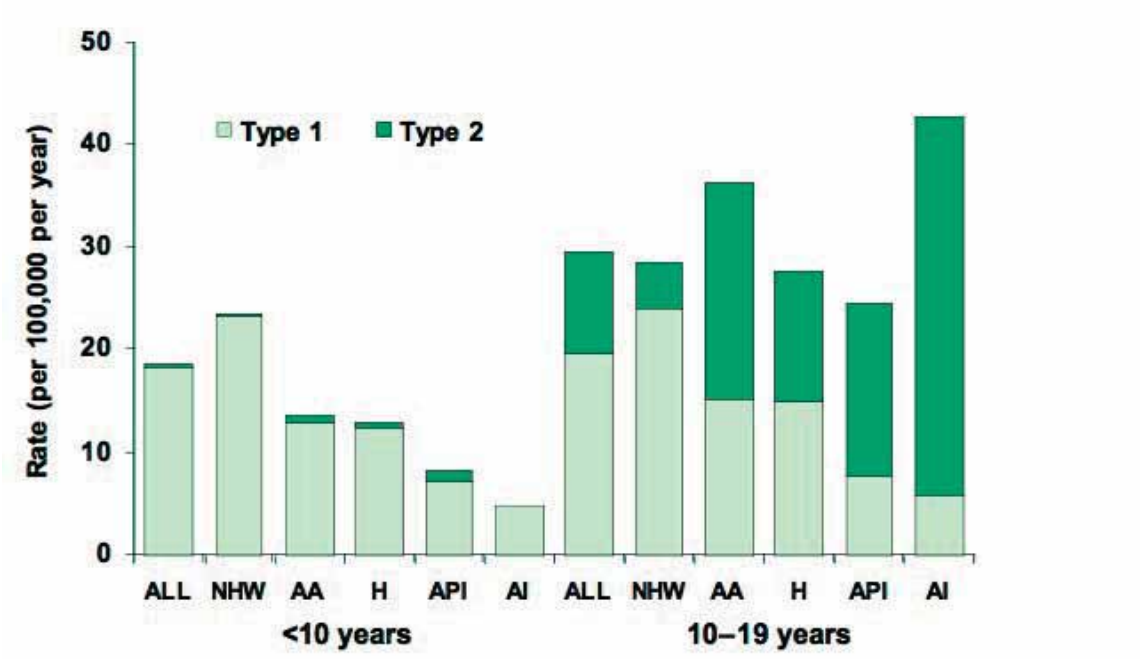

Figure 2.

CDC. National Diabetes Fact Sheet, 2007.
Source: SEARCH for Diabetes in Youth Study
NHW=Non-Hispanic whites; AA=African Americans; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians

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Special Populations: Obesity

Silas P Norman, MD

Learning Objectives:

1. **To understand the prevalence of** obesity in the U.S. population.
2. To understand the impact of obesity on the development of HTN.
3. To understand the challenges to treatment of HTN in overweight individuals.

Pre-Test Questions:

1. Which of the following are increased in obese individuals?
    a. The risk of hypertension
    b. The risk of diabetes mellitus
    c. The risk of metabolic syndrome
    d. All the above **(Correct answer)**
2. Which of the following should be part of the management of HTN in obese individuals?
    a. Increased aerobic activity **(Correct answer)**
    b. Increased average caloric intake
    c. Delaying pharmacological hypertension treatment until weight loss goals achieved
    d. All of the above
3. Which of the following groups are at increased risk for obesity?
    a. African Americans
    b. Hispanics
    c. Caucasians
    d. A and B **(Correct answer)**
    e. A and C

Obesity is an often unrecognized epidemic in the U.S. Currently and estimated two-thirds of the country is overweight (body mass index, BMI $\geq$ 25 kg/m2) and one-third is frankly obese (BMI $\geq$ 30 kg/m2).[1, 2] Increasingly, obese and morbidly obese weights have been found in the pediatric population resulting in an increasing risk for HTN, DM and future heart disease.[3] The risk for obesity is higher in the poor and also increases with age. Obesity is a particularly problematic problem in minority populations as the baseline risk for development of DM and CKD among other diseases is elevated at baseline and strongly influenced by weight gain.

Even before individuals are frankly obese, excessive body weight can have a negative physiological impact on intravascular volume, the relative distribution of intravascular volume between the peripheral and central vasculature, cardiac function, and vascular hemodynamics (Table 1). The development of excessive body weight and HTN are two components of the metabolic syndrome (Table 2). The metabolic syndrome has been linked to an increased risk of adverse CV outcomes and over 20% of the U.S. population meets the definition of the syndrome.[4, 5] Individuals with metabolic

syndrome may have additional quality of life limitations from their weight itself. The increased cardiovascular risk found in this population highlights the negative consequences of even small amounts of weight gain. Untreated, a number of individuals' metabolic syndrome or just frank obesity will progress to frank diabetes mellitus, develop hypertension, and increasingly manifest dyslipidemias such as high triglycerides and depressed HDL cholesterol. As such, when treating the obese, hypertensive population, the provider will need to focus on the overall cardiovascular health of the individual.

Obesity is not equally distributed across populations. African-Americans (AA), particularly women, have the highest prevalence of obesity of any racial group in the U.S.[6] Not surprisingly, AA, especially women, also have the highest prevalence of HTN in the U.S.[7] The consequence of disproportionate obesity in some populations is that CV morbidity and mortality is also not equally distributed among populations. The reasons for differences in overweight and obesity among AA (and Hispanics) compared to non-Hispanic whites has little to do with genetic differences and much to do with cultural and socio-economic differences.[8, 9] Also, African American women consume more calories and exercise less than their white counterparts beginning in their late teens.

A number of cultural norms can impact the development and progression of obesity. For example, AA and Hispanics have a number of traditional foods that we now appreciate as calorie-dense and carbohydrate rich that directly contribute to increased caloric intake and obesity. Such culturally-linked food preferences are introduced early, increasing the challenge for both patients and providers to modify intake.[10] In addition, foods that may pose substantial health risk are frequently targeted to minority populations.[11] The cultural norms that define beauty in cultures also clearly impact the likelihood willful caloric restriction, particularly in women.[12] Cultural differences in levels of exercise and physical activity also likely play a substantive role in obesity risk.[13] Modification is further complicated in individuals with limited financial resources. An awareness of cultural differences that may impact obesity and HTN is necessary to help individuals modify their bodyweights within the context of their daily experiences and expectations.

Socio-economic differences across populations play a significant role in the development of obesity and as a consequence, HTN. Among the poor in this country, obesity is disproportionately prevalent. As AA and Hispanics are disproportionately poor, we see excessive obesity in these groups.[9] Individuals with limited incomes are at dual disadvantages. First, they often cannot afford healthier

foods and turn out of necessity to calorie-rich but nutritionally poor foods. Second, the poor tend to have lower education levels and less access to medical care, further increasing the risk for obesity and HTN. In addition, such individuals may be less likely to have their HTN diagnosed and even after diagnosis, may be less able to afford the recommended treatments.

Obesity is particularly relevant because it adds to and exacerbates the co-morbidities often seen in individuals presenting for medical care. Obesity can not only contribute to HTN, DM and hyperlipidemia, but also makes such diseases harder to control. In the treatment of HTN in obese individuals, weight management needs to be a central focus of the overall treatment plan.[14] Weight loss can result decreases in BP similar to what can be realized with most medications. Not only has obesity been linked to an increased risk for developing hypertension, it is also a marker for pharmacological treatment resistance. In addition, aerobic activity done as part of weight loss can further decrease BP. For example, regular walking has been shown to attenuate weight gain associated with age.[15] Instruction on low sodium diets (such as the DASH diet) can also play a positive role in HTN management. As up to half of patients being treated report that their provider has not discussed their weight with them, it is incumbent on all providers to elevate weight control and weight reduction to the same status reserved for discussions of DM. HTN and other medical disease.

Patients should be reminded that becoming overweight or obese typically has taken years if not decades. As such, lifestyle modifications designed to promote weight loss will also take weeks to months before significant weight loss may be realized. At the same time, patients may feel symptomatically improved with modest weight loss. The promotion of lifestyle modifications should proceed in parallel with pharmacologic treatment. The first priority of HTN management is control of the blood pressure. Medications can always be withdrawn as patients make the lifestyle changes necessary to reduce their tendency towards HTN. Often, encouraging patients with the possibility of freedom from some of all of their anti-hypertensive medications if they adjust their diet and exercise regimens can be a potent inducement for action. Obesity is a significant but manageable contributor to HTN and CV disease overall and must be approached on multiple fronts simultaneously for maximum effect.

Figures:

1. Graph showing prevalence of obesity in the U.S., NHANES
2. Graphic showing risk of CVD associated with obesity

Tables:

1. Criteria for metabolic syndrome

Essential points check:

1. Obesity is extremely common in the U.S. and increases the risk of HTN.
2. Obesity is related to multiple other medical conditions that increase the risk for cardiovascular death.
3. Obesity disproportionately affects African-American and Hispanic individuals.
4. Weight loss should be a key part of the plan to control HTN in overweight individuals.

Post-Test Questions:

1. The highest prevalence of hypertension in the U.S. is found in
    a. Asian women
    b. Caucasian women
    c. African American women **(Correct answer)**
    d. Native American women
2. The Metabolic Syndrome consists of which of the following?
    a. Elevated blood pressure
    b. Elevated serum glucose
    c. Central obesity
    d. Dyslipidemia
    e. All of the above **(Correct answer)**
3. Which of the following have been shown to be effective in reducing obesity related hypertension?
    a. Weight loss
    b. Increased aerobic exercise
    c. Low sodium diets
    d. All of the above **(Correct answer)**

Figure 1:

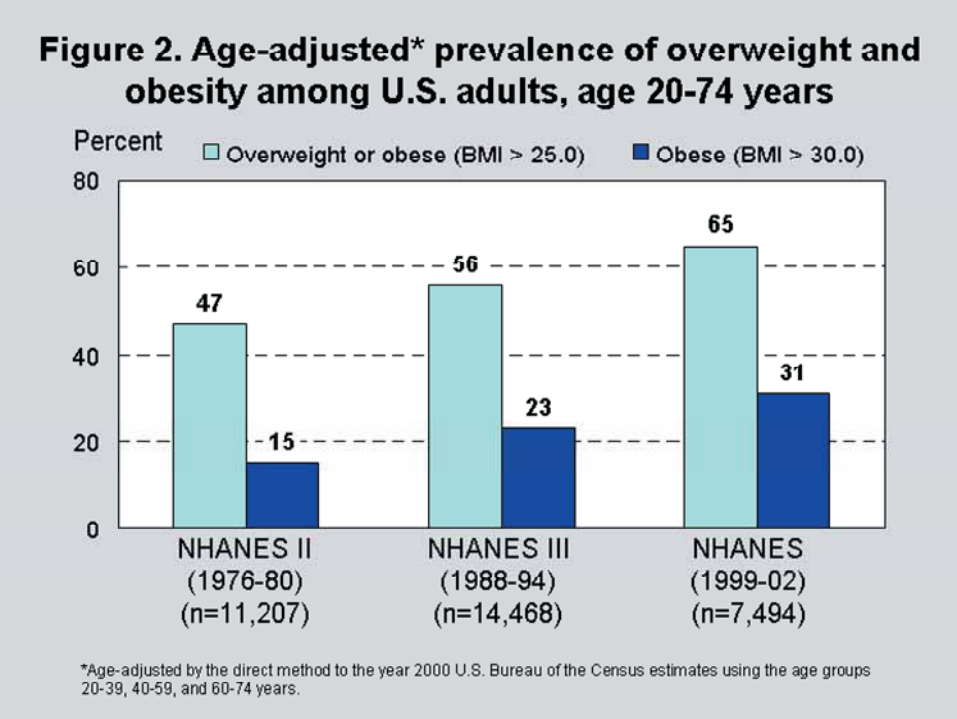

Table 1. Metabolic Syndrome [16]

Diagnosed by having 3 or more of the following:	
Central Obesity	**Value**
Waist circumference	Male > 40 inches, Female > 35 inches
Dyslipidemia	
Fasting tryglicerides	≥ 150 mg/dL
Fasting HDL-C	Male < 40mg/dL, Female < 50mg/dL
Elevated blood pressure	≥ 130/85 mmHg
Elevated fasting glucose	≥ 100 mg/dL

Figure 2:

Increased Risk for Disease with Increased Bodyweight

Increased Relative Risk of Obesity Related Diseases with Higher BMI				
Disease	BMI of 25 or less	BMI between 25 and 30	BMI between 30 and 35	BMI of 35 or more
Heart Disease	1.00	1.39	1.86	1.67
Diabetes (Type 2)	1.00	2.42	3.35	6.16
Hypertension	1.00	1.92	2.82	3.77
Stroke	1.00	1.53	1.59	1.75

Source: Centers for Disease Control. Third National Health and Nutrition Examination Survey. Analysis by The Lewin Group, 1999.

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Special Populations: African-Americans

Silas P Norman, MD

Learning Objectives:

1. To appreciate the prevalence of HTN in minority populations in the U.S.
2. To understand the differential impact of HTN on CV outcomes in minority populations.
3. To understand the challenges to treatment of HTN in minority populations.

Pre-Test Questions:

1. Which of the following groups have the highest prevalence of HTN?
    a. African Americans **(Correct answer)**
    b. Hispanics
    c. Caucasians
    d. Asians
2. African-Americans with HTN are at increased risk for which of the following?
    a. Myocardial infarction
    b. Stroke
    c. Chronic kidney disease
    d. All of the above **(Correct answer)**
3. What is the approximate prevalence of HTN among Hispanics in the U.S.?
    a. 70-75%
    b. 50-55%
    c. 25-30% **(Correct answer)**
    d. 10-15%

Introduction

African-Americans (AA) are disproportionately affected by HTN. In the U.S., over 40% of AA adults are affected by HTN. As a consequence, the CV morbidity and mortality in AA exceeds that seen in their white counterparts.[1] There are clear differences in the frequencies of end-organ complications such as stroke, myocardial infarctions and end-stage kidney disease. Though genetic factors have long been thought to underlie the excess HTN risk seen in this population, other factors such as greater burden of risk enhancing conditions such as obesity/physical inactivity, longer duration of hypertension, higher prevalence of risk enhancing co-morbidities such as diabetes and CKD, and once hypertension is treated, lower control rates all likely contribute to the excess risk of target-organ injury and adverse pressure-related clinical events associated with hypertension in African Americans relative to white populations.

Incidence and Prevalence

The overall incidence of HTN is very difficult to determine. In part, this difficulty stems from changes in the definition of HTN over time. In addition, although many individuals may start treatment for HTN, the assumption is that the HTN is not new, but long standing and newly discovered. Framingham data suggests an overall incidence rate that varies from 3.3% to 8.6% depending on age.[2] The specific incidence in the AA population is similarly unknown. What is known is that AA's appear to have a younger onset of HTN than their non-AA counterparts.[3] As such, the years at risk may be greater in AA than in other demographic groups. Prevalence, however, is easier to estimate. Data from the Centers for Disease Control and Prevention (CDC-P) shows in excess of 40% of AA's to have HTN, with prevalence increasing with increasing age.[4] Like other demographic groups, the overall prevalence of HTN in AA's appears to be increasing. One of the paradoxical consequences of the high prevalence of HTN in the AA community is that the experience of being hypertensive has been to a degree normalized, perhaps leading to an under appreciation for the consequences of untreated HTN. In understanding the high prevalence of HTN among AA, a number of predisposing factors must be considered.

Genetics

There is likely a genetic contribution to HTN in AA's, as in other demographic groups, however there is no substantive evidence that the genetic contribution to HTN in African Americans is greater than in whites. Numerous investigators have speculated the possibility that AA's may have an increased tendency towards sodium retention, a trait that may have been favorably selected during the passage from Africa to the Americas. Genes known to be associated with increased HTN risk have also been studied.[5] Such approaches have considered the so-called genetic bottleneck hypothesis. The hypothesis considers that the individuals brought to the Americas during the slave trade represent only a fraction of the overall genetic diversity of Africans, resulting in a population predisposed to HTN at a frequency not seen in Africans as a whole. Such theories remain speculations as they have not been validated. Additional investigations have focused on differences in sodium sensitivity, an intermediate BP phenotype linked to obesity, CKD, endothelial stiffness, impaired nitric oxide synthesis/metabolism and polymorphisms in the RAAS among other things. To date, outside of the known greater risk factors for hypertension – obesity and physical inactivity (especially in women) – the

premature onset of HTN and the larger overall HTN burden in the African American population remains unexplained.

Congenital explanations may also contribute to the excessive HTN seen in AA. African-Americans do have a higher risk for small for gestational age infants than other ethnic groups.[6] As renal glomerular development is complete at birth, small infants may have less renal mass and fewer glomeruli at delivery. Over time, there seems to be an increased predisposition to develop CKD, so it follows that HTN risk would be increased also.[7, 8] There are also interesting observations regarding preeclampsia, which suggests that reactivity to oxidative stress, may contribute to HTN. African-American women are known to have a higher risk of preeclampsia as well as HTN compared to their white counterparts. In addition, for all women affected with preeclampsia, there appears to be a higher risk in offspring of future preeclampsia and HTN. The overall impact of such predisposition is unclear, but may be a disease specific example of a generalized vascular hyper reactivity.

Culture and Environment

In the AA community, there is an increased incidence and prevalence of obesity, which is a known risk factor for the development of HTN.[9] Obesity has been increasingly diagnosed in the adolescent population and is more prevalent in AA children than any other racial/ethnic group except Hispanics. Increasing rates of obesity in the AA community undoubtedly contribute to the excess HTN seen in AA's. Dietary intake and low rates of exercise contribute to the excess obesity seen in AA's. Dietary intake is a critical contributor to both obesity and HTN. Foods that are calorie dense, nutritionally lacking and high in sodium are key instigators of HTN. In addition there is a stronger association between diet and the development of metabolic syndrome in AA than in whites and Hispanics.[10] These types of food are common in the AA community provided by fast food restaurants and convenience stores. Studies have established that the density of fast food establishments is higher in AA than any other communities.[11] Consideration of patient's ability to choose healthy foods must be put in the context of how and where the patient lives. African-Americans are exposed to food promotions with potentially adverse consequences more frequently than their white counterparts.[12] In addition, the availability of alcohol provides another source of empty calories that contribute to obesity. In the same vein, access to quality food is often limited. Analysis of the Multi-Ethnic Study of Atherosclerosis showed that AA's were more likely to live in neighborhoods with significantly less

access to healthy foods than their white counterparts.[13] Grocery stores are often difficult to find and access to fresh fruits and vegetables is difficult. There are a number of culturally traditional foods that clearly contribute to obesity. Fried foods with heavy sodium contents are staples for many individuals. Socieo-economic status is of course a significant part of the issue, but so it a lack of nutritional understanding and the difficulty of altering established eating patterns. Cultural significance of obesity as it relates to standards of beauty, particularly for females can be a strong contributor to obesity. Add to these circumstances the poverty that heavily overlaps with AA populations and a predisposition to obesity related to environment is easy to see.

The second contributor to obesity is lack of exercise, in particular, aerobic exercise. There are multiple important overlapping issues. One is the prevalence of television and video games, which have been shown to limit the physical activities of all Americans, particularly adolescents. Overall lack of financial resources may preclude joining health and fitness establishments. Concerns for physical safety limit the ability to walk around ones neighborhood or use local parks. Finally, physicians do not have diet and exercise discussions with their patients.[14] These effects combine to increase the risk for obesity and as a consequence, HTN.

Common constellations of diseases contribute to the excess HTN seen in AA's. African-American's have a disproportionate prevalence DM, in part due to obesity that also contributes to HTN. The majority (70 -80%) of all diabetics will have HTN at some point during their course of disease and some 15% of AA have DM. As AA have a high prevalence of obesity and DM, the high frequency of HTN is not surprising.

Barriers to Care

Much has been written about AA distrust in the U.S. health-care system. This mistrust may be manifested not just by avoidance of medical care, but also by more subtle behaviors that may undermine health. In particular, there is evidence that AA may doubt the need for and efficacy of medications. As a result, even AA seeking regular medical care may not have the high quality outcomes expected. For providers, a belief that HTN in AA is particularly hard to control may paradoxically lead to less effort on the part of providers to effect control, reinforcing the idea that HTN

in AA is poorly controlled. There are issues of health literacy that may impact AA patient beliefs and acceptance of medical disease and provides the foundation for effective management. Importantly, inadequate access to quality health care may also negatively impact hypertension control rates in the U.S.

Treatment

Effective treatment of HTN can reduce the incidence of CKD and overall cardiovascular events.[15-17] The International Society on Hypertension in Blacks (ISHIB) has articulated a step-wise, coherent approach to HTN management in the AA population.[18] The initial part of the treatment plan for HTN in AA and all ethnic groups is accurate measurement of height, weight and BP's and an appreciation for the inaccuracy of self-reporting.[19] In the treatment of AA patients with HTN, essentially a standard approach to management should be taken.[3] This includes accurate measurement of HTN, institution of initial drugs as indicated by level of BP and other co-morbid conditions that represent a compelling indication for specific classes of medication and regular follow up. There is evidence that thiazide type diuretics may be particularly useful first-line medications and similarly, long acting CCB's also have evidence based efficacy to support recommendations as first line therapy. There are recent studies that also highlight the benefits of combination anti-hypertensive therapies in this group and the fact that HTN in AA can in fact be controlled with common medications.

While patient race and ethnicity is important to consider in the overall care of each patient, most importantly, providers should recognize that generally all classes of medications work in all peoples.[20] Prescribers of medications should recognize that cost is an issue for many patients, so an attempt to consider the cheapest effective medications is important. The need for affordable medications is highlighted by the fact that the average patient may require 3-4 medications for control. In addition, adherence to therapy has been shown to be a function of dosing frequency, so once-daily medications should be used when possible. A core belief in both patients and providers that HTN can be effectively controlled in AA is necessary for the best outcomes. Asking patients to monitor blood pressures at home improves the accuracy of the BP measurements as well as engages the patient in the treatment plan.

As a part of the approach to managing HTN in AA, therapeutic lifestyle change (TLC) must play a central role. Aerobic exercise along with sodium restriction and diets high in fruits and vegetables clearly improve BP similar to anti-hypertensive monotherapy.[21] Therapeutic lifestyle change has been shown to decrease both pre-HTN as well as HTN.[22, 23] Educational efforts to improve diet have also clearly been shown to be effective.[24] Education directed specifically towards increasing intake of fruits and vegetables can be helpful by reducing the tendency towards obesity and reinforcing HTN control.[25, 26] Discussions between patients and providers to help identify both individual and family patterns of eating can help in formulating a more realistic care plan.[27] Aerobic exercise and weight-loss of as little as 5% of body mass can provide significant improvements in blood sugar control, lipids, obesity as well as HTN.[28, 29] As part of the treatment contract, explicit recommendations and expectations for exercise by the patient need to be made. In addition, frank discussions about patient perception about barriers to exercise such as availability of sidewalks and the risk of crime.[11] These recommendations should be evaluated, reinforced and updated at each clinic visit. With a comprehensive approach that emphasizes prevention and lifestyle modification along with appropriate use of medications, good HTN control can be achieved in the AA population.

Figures:

1. Graph showing prevalence of HTN in the U.S., stratified by gender and race (CDC-P)
2. Graphic showing HTN prevalence by age (Fields, LE. Hypertension, 2004; 44:398-404

Tables:

1. Major Cardiovascular Risk Factors in AA (Table 2 Management of High Blood Pressure in African Americans, Archives of Internal Medicine, 2003;163:525-541)
2. Therapeutic Lifestyle Changes (Table 5 of above article)
3. Treatment algorithm (page 532 of above article)

Essential points check:

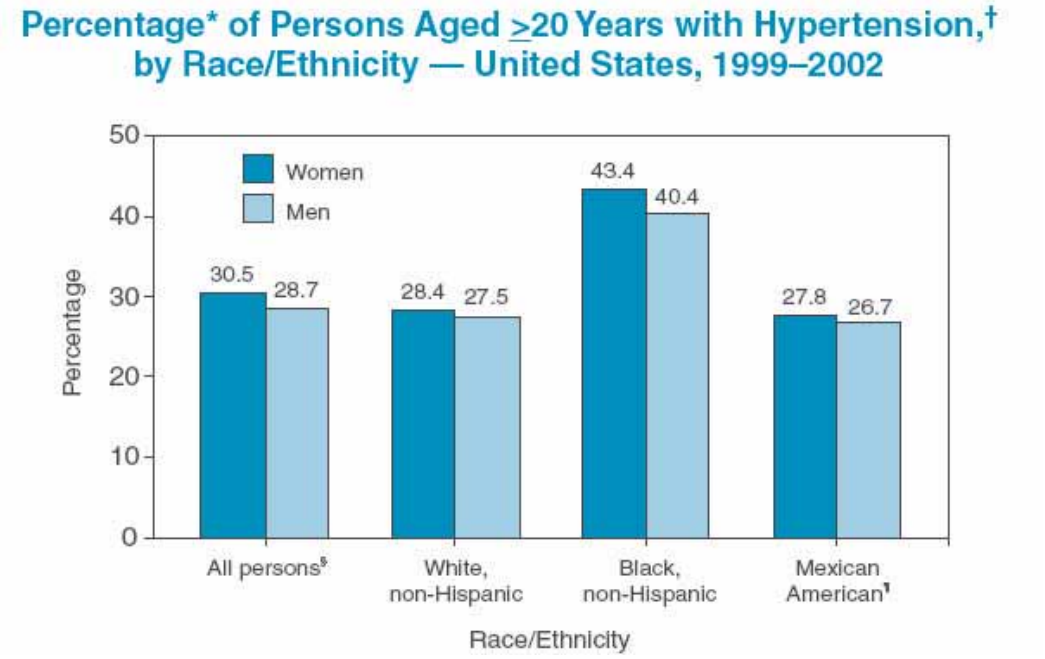
1. African-Americans have a disproportionate risk for the development of HTN.
2. African-American individuals have an earlier onset of HTN and may have a more rapid progression of CV disease than their non-Hispanic white counterparts.
3. Socieo-economic and environmental differences, not genetics, account for most of the differences in HTN outcomes seen in the AA population.

Post-Test Questions:

1. The excess HTN in African Americans and Hispanic populations may be related to which of the following?
    a. Obesity
    b. Limited access to health care
    c. Culturally related dietary intake
    d. All of the above **(Correct answer)**

2. Which of the following contribute to poor HTN control rates in African-Americans?
    a. Lack of belief among some patients of the need for medications
    b. Impression among providers that HTN in African Americans is particularly hard to treat
    c. Concerns for physical safety limiting aerobic activities
    d. All of the above **(Correct answer)**
3. Which of the following are part(s) of a comprehensive approach to treatment of HTN in minority populations?
    a. Accurate measurement of height weight and blood pressure
    b. Prompt initiation of initial pharmacological therapy
    c. Encouragement of therapeutic lifestyle change
    d. All of the above **(Correct answer)**

Figure 1:



HTN in the U.S., stratified by gender and race (CDC-P)

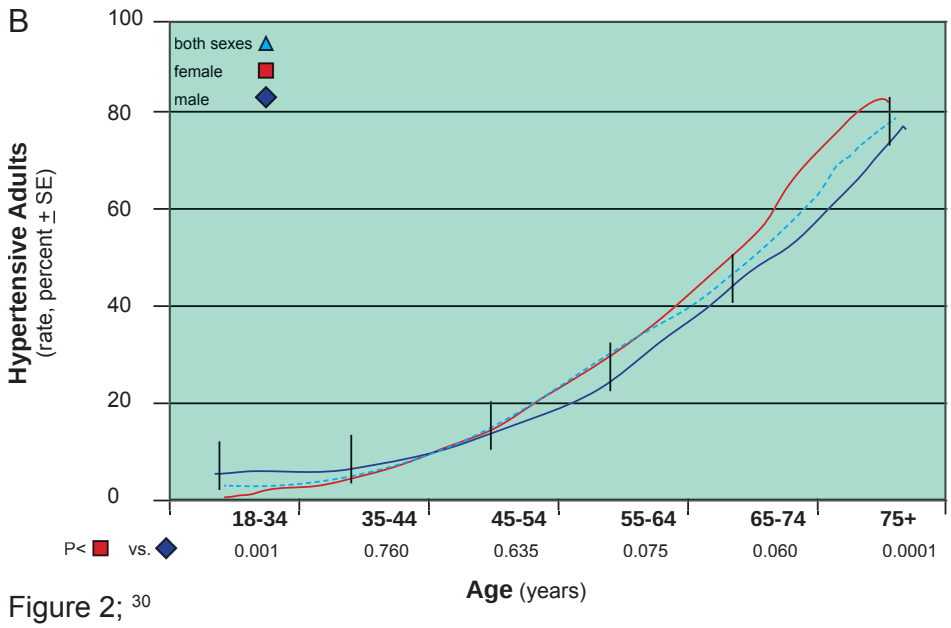


Figure 2; [30]

Table 2. Major Cardiovascular Risk Factors in African Americans

Behavioral markers that increase for development of high blood pressure[1,7]
- Smoking
- Obesity
- Inactivity
- Excessive alcohol intake
- High dietary intake of fat and sodium
- Low dietary intake of potassium

Clinical makers associated with high blood pressure[1,7,25]
- Low birth weight
- Family history of CD, diabetes, or premature heart disease
- High-normal blood pressure (130-139/85-89 mm Hg)
- Adult weight gain

Major risk factors for CHD[28,30,52]
- Smoking
- Elevated blood pressure (whether treated or untreated)
- Elevated serum total cholesterol or LDL-C levels
- Low serum HDL-C level
- Diabetes mellitus
- Advancing age
- Obesity
- Inactivity

Additional important risk factors for CD[1,32]
- History of cardiovascular event (MI, stroke, revascularization)
- Kidney disease
- Evidence of target-organ damage (proteinuria, LVH, heart failure, TIA, peripheral arterial disease, atherosclerosis, retinopathy)
- Male or postmenopausal woman
- Family history of CVD in women aged <65 y or men aged <55 y
- Central obesity
- Elevated blood glucose level
- Low socioeconomic status
- Elevated triglyceride levels
- Microalbuminuria

Abbreviates: CHD, coronary heart disease; CD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C; low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction; TIA, transient ischemic attack.

Table 1: [18]

Table 5. Therapeutic Lifestyle Changes

Medical Target	Realistic Personal Plan to Achieve Goal
Normal weight for height	Lose weight gradually by making permanent change in daily diet for the entire family.
	Set a reasonable weight loss goal (even 5-10 lb [2.2-4.5 kg] can make a difference).
	Eat fewer fast food and fried foods, and eat more fruits and vegetables.
Dietary goals:	Eat more grains, fresh fruits, and vegetables.
Low fat	Eat fewer overall fats and healthier fats, such as olive oil.
Low sodium	Eat fewer processed foods and fast foods.
High potassium	Read labels and pay attention to the sodium and fat content of foods.
Adequate calcium	Identify high-sodium foods (eg. potato chips or hot dogs) that can be comfortably omitted.
	Identify low-sodium, high-potassium snacks (eg. dried fruits, bananas, orange juice, raw vegetables).
	Do not salt foods when cooking; instead, taste foods first and add salt at the table if needed.
	Use vinegar or lemon juice instead of salt for seasoning.
	Do not season foods with smoked meats, such as bacon or ham hocks.
	Become more aware of food sources that are rich in calcium.
	If lactose intolerant, try lactose-free milk or yogurt, or drink calcium-fortified juices or soy milk.
Limit alcohol	Men: no more than 2 beers, 1 glass or wine, or 1 shot of whiskey (or hard liquor) per day.
	Women: no more than 1 beer or 1 glass of wine per day (a shot of whiskey exceeds these recommendations).
Physical fitness	Increase physical activity as part of the daily routine; eg, if currently sedentary, get off the bus 6 block from home, or walk in the evening with a spouse or friend.
	Gradually increase time spent at an enjoyable activity to 30-45 min at least 5 days a week.
No tobacco use	For nonsmokers, do not start.
	For current smokers, attempt smoking cessation, increase tolerance for failure, and be willing to continue the effort until success is achieved.
	Be aware that smokeless tobacco products (eg, chewing tobacco) also have associated risks.

Table 2: [18]

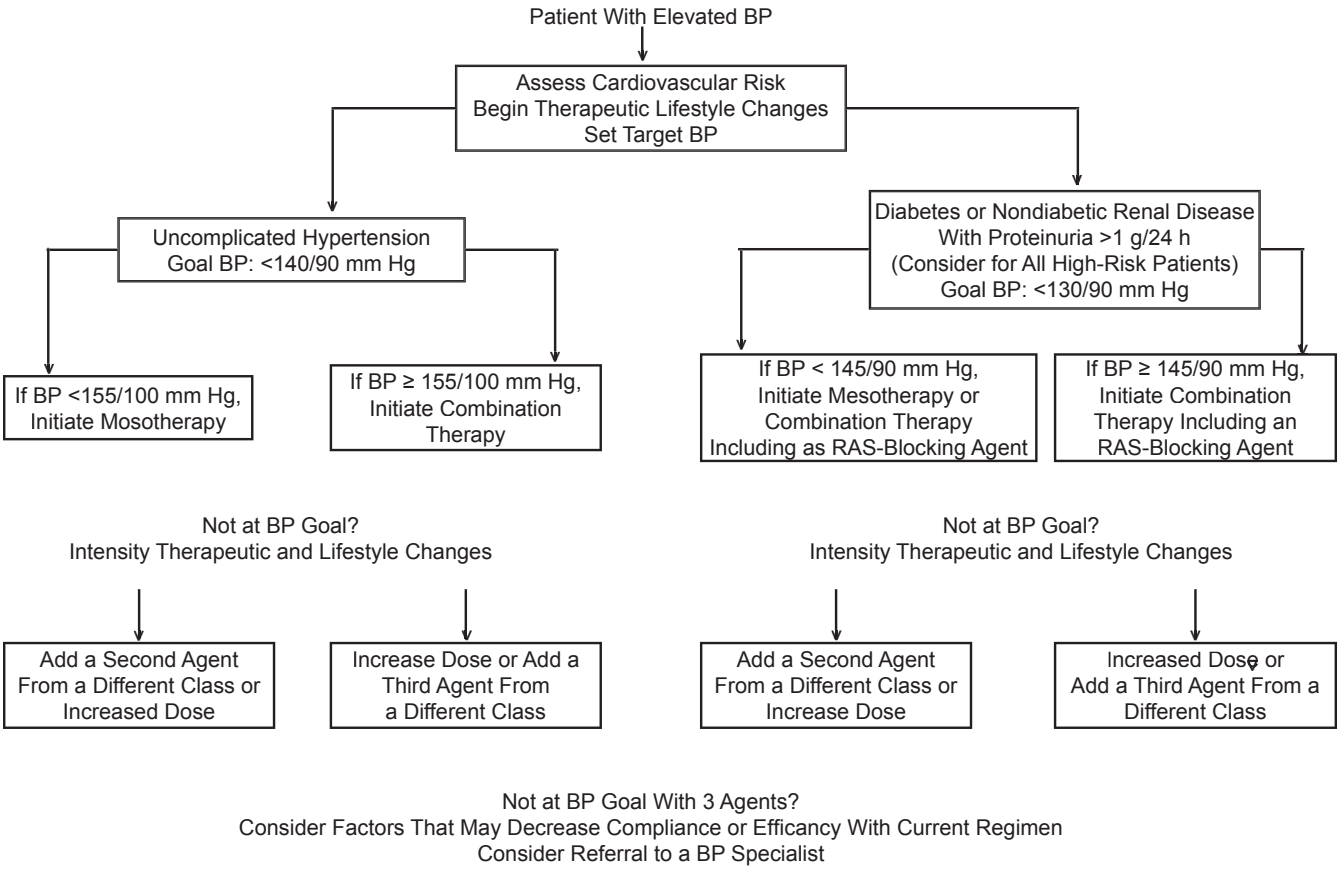


Table 3: [18]

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Special Populations: Hispanics

Silas P Norman, MD

Learning Objectives:

1. To understand the prevalence of HTN in the Hispanic population.
2. To understand the effect of Hispanic sub-populations on the estimation of HTN prevalence.

Pre-Test Questions:

1. What is the approximate prevalence of HTN among Hispanics in the U.S.?
    a. 70-75%
    b. 50-55%
    c. 25-30% **(Correct answer**)
    d. 10-15%
2. Hispanics in general represent a relatively elderly population?
    a. True
    b. False **(Correct answer)**

3. Blood pressure targets for Hispanic individuals with HTN should be
    a. Lower than JNC-7 recommendations
    b. Consistent with JNC-7 recommendations **(Correct answer)**
    c. Higher than JNC-7 recommendations

The discussion of HTN and HTN related morbidity in the Hispanic population is difficult for several reasons. First, there is a relative lack of data. Hispanic ethnicity has not been consistently captured and Hispanic sub-populations vary in prevalence significantly across the U.S. Secondly, although Hispanic individuals share a common ancestry, the HTN risk and self-reported prevalence among Hispanic sub-populations is significantly different.[1] Third, there is often co-mingling of Hispanic Americans with recent immigrants, which further confounds study results. Nevertheless, we can make some general statements about HTN in the Hispanic population.

Overall Hispanics appear to have a prevalence of HTN similar and sometimes lower than non-Hispanic Whites (NHW).[2, 3] The prevalence of HTN in Hispanics as estimated by the prevalence in Mexican Americans is approximately 27-28%. Also, the cardiovascular mortality attributable to HTN in Hispanics is consistent with that in the NHW population. Hispanics are the largest and fastest growing ethnic group in the U.S. and also the youngest. As a result, there is a large at-risk population that requires prevention and treatment services. There is a clear association between Hispanic acculturation and cardiovascular risk with primarily Spanish-speaking Hispanics likely to have higher BP than English-speaking Hispanics.[4]

There do not appear to be different biological mechanisms for HTN in Hispanics and NHW. Differences

appear to be related to access to care and adherence to anti-hypertensive mediations. The most striking example of a Hispanic sub-population with limited access to health care is the undocumented Hispanic population, which may number as many as 12 million. In addition, like many Americans, Hispanics also may be underinsured. Both young and elderly Hispanics appear less likely to take anti-hypertensive medications than both NHW and African-Americans.[5, 6] The reasons for this seem to relate primarily to education about HTN and access to treatment. Diet is a major contributor to HTN and dietary changes that are inconsistent with cultural norms may be difficult for some patients.[7] Interestingly, although there is clearly excess obesity among Hispanics,[8] which along with diet seem to contribute to an excess prevalence of DM, there appears to be a less than expected effect on the risk for HTN.

Treatment

There is little data to support the idea that Hispanics BP is any more difficult to control than in non-Hispanic Whites. Much of the challenge in treatment relates to improving awareness of and education about HTN. The goals and approach to HTN management in Hispanics is generally similar to other racial and ethnic groups. At the same time, attention of course needs to be paid to issues of culturally competent care and the need to recognize patients for whom a Spanish-speaking provider would be a particular asset. There should be recognition that there are a number of different Hispanic sub-populations, cultural norms and risk factors across the larger Hispanic population. Hispanic patients should have BP goals established consistent with JNC-7 recommendations and their other medical co-morbidities and therapeutic lifestyle change should be encouraged.

Figures:

Figure 1-2, figures 1 and 2 from the CDC MMWR Feb 24, 2006/55(07); 177-180
Essential points check:

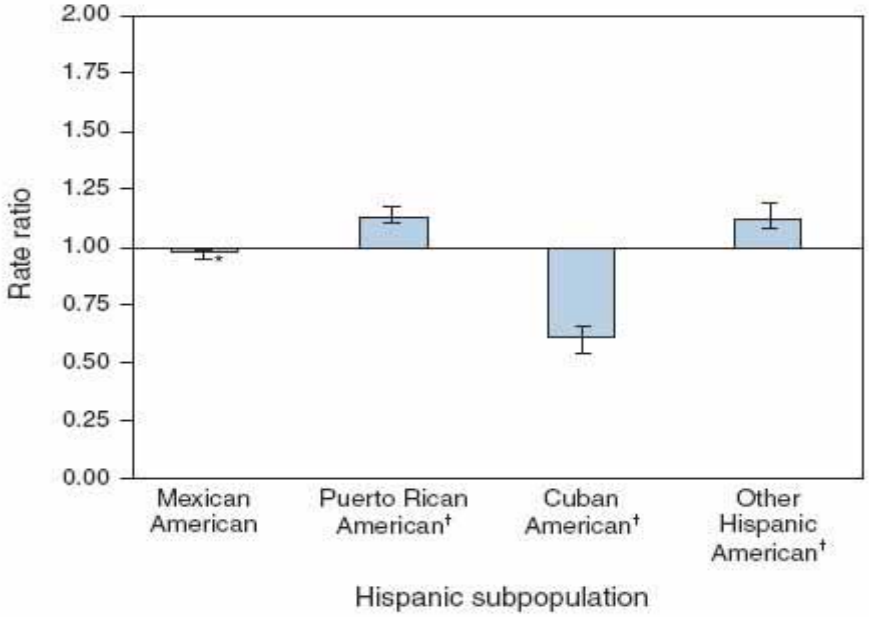
1. Hypertension prevalence in Hispanics is similar to that in NHW.
2. Improved HTN control in Hispanics requires efforts to improve awareness of HTN in the community.
3. The goals for HTN treatment are the same as in NHW.

Post-Test Questions:

1. The prevalence of HTN is very similar among Hispanic sub-populations in the U.S.
    a. True
    b. False **(Correct answer)**
    c.
2. Compared to non-Hispanic Whites, the risk for HTN in Hispanics can be related to which of the following?

a. Genetic differences
b. Adherence to anti-hypertensive medications
c. Access to health care
d. A and B
e. B and C **(Correct answer)**

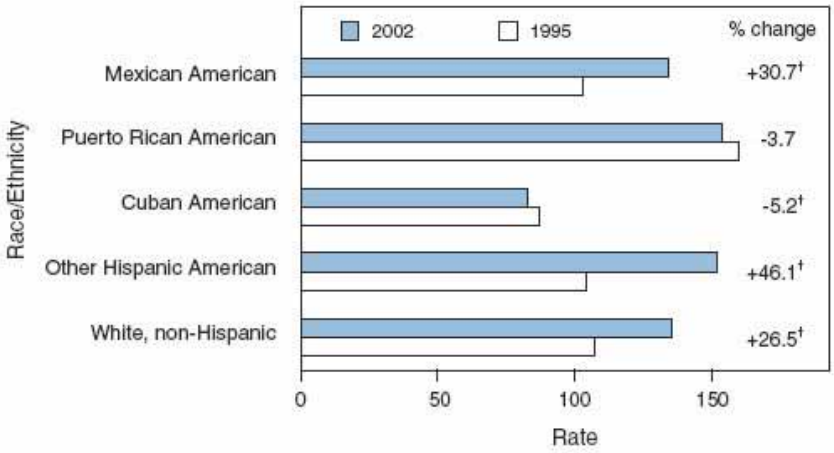
FIGURE 1. Rate ratios of age-standardized, hypertension-related mortality rates among adults aged ≥25 years, comparing selected Hispanic subpopulations to non-Hispanic whites — United States, 2002



* 95% confidence interval.
† p<0.01.

CDC MMWR Feb 24, 2006/55(07); 177-180

FIGURE 2. Age-standardized, hypertension-related mortality rates* and relative percentage changes among adults aged ≥25 years for non-Hispanic whites and selected Hispanic subpopulations — United States, 1995 and 2002



*Per 100,000 population.
†p<0.01.

CDC MMWR Feb 24, 2006/55(07); 177-180

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Obstructive Sleep Apnea

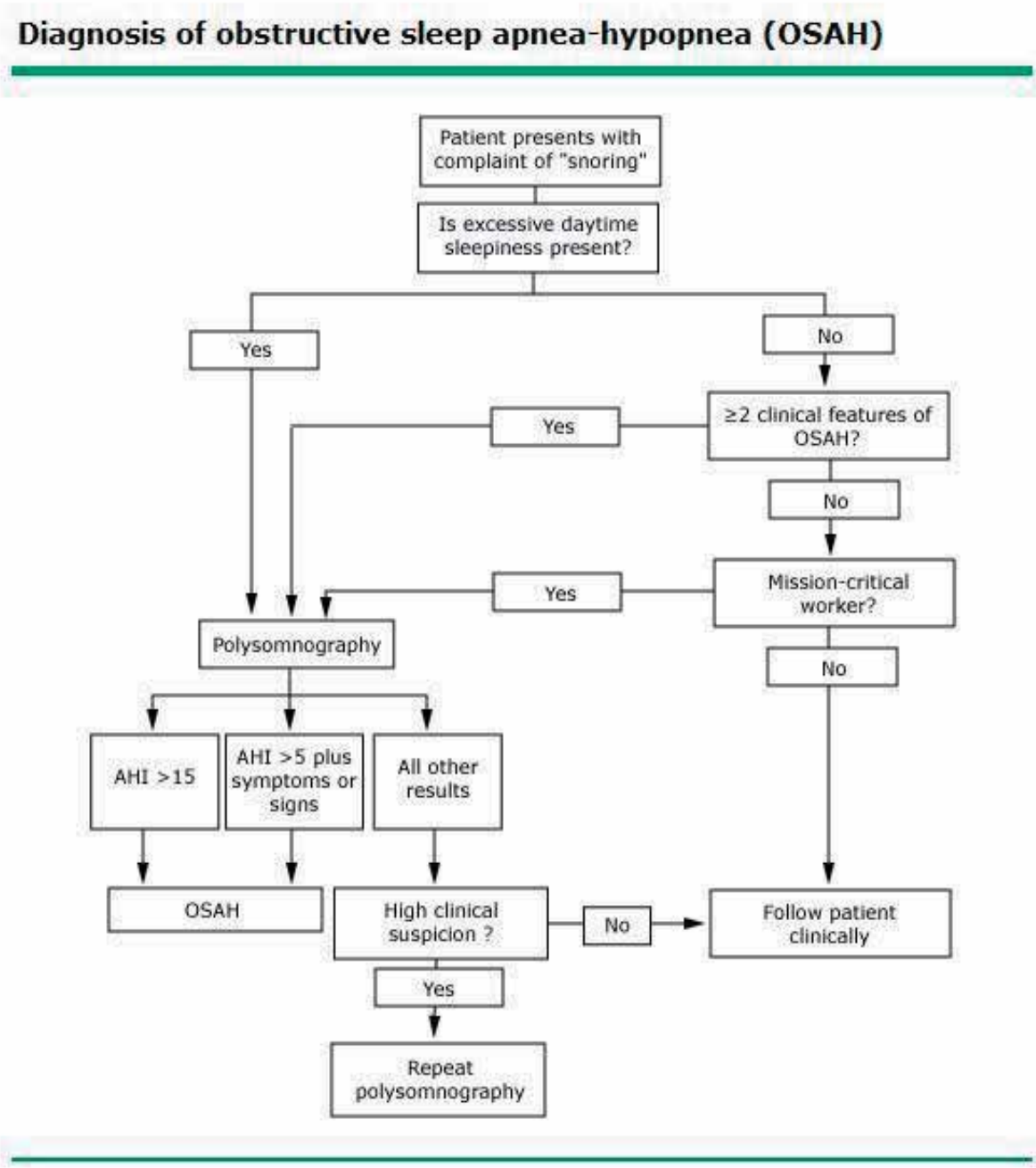
Susan Steigerwalt, MD

Obstructive sleep apnea (OSA) is a common cause of secondary HTN and is also an identified cause of non-dipping of the nocturnal BP as well as masked HTN (normal office BP with elevated ambulatory BP). At-risk hypertensives should be screened for obstructive sleep apnea, at least with a symptom questionnaire, as diagnosis and subsequent treatment of OSA with CPAP (continous positive pressure to avoid airway occlusion) may lower BP. In established uncontrolled hypertensives, treatment of OSA decreases blood pressure by on average 5/3 mmHg (23). In population studies, OSA has been associated with an increased risk for congestive heart failure, stroke, coronary artery disease, and sudden cardiac death. Stroke survivors have a 43-91% prevalence of OSA.[1]

Clinical clues to OSA include neck size greater than or equal to 17 inches, partner witnessed loud snoring, choking and/or gasping at night, and excessive daytime sleepiness. Two useful tools are the Epworth Sleepiness scale (downloadable from the internet) and the Berlin Sleep Questionnaire. If patient has a positive screening test for OSA, further evaluation with an overnight polysomnogram is indicated. Treatment is suboptimal, but CPAP is indicated for symptomatic relief of daytime sleepiness and has also been shown to improve hypertension control as well as to lower CVD risk.

The severity of sleep apnea can be characterized by apnea (complete cessation of airflow for 10 seconds)-hypopnea (reduction of airflow followed by arousal from sleep or a drop in oxyhemoglobin saturation) index (AHI). OSA is a collapse of the upper airway that results in activation of the sympathetic nervous system which arouses the patient from sleep. Multiple mechanisms appear to cause/contribute to OSA-related elevations in BP (fig1).

Figure 1;



Clinical presentation and diagnosis of obstructive sleep apnea in adults, Lewis R Kline, MD @ *UptoDate*

The prevalence of OSA in hypertensive populations ranges between 30 – 40%. OSA is more common in African Americans than whites, men than in women, and in obese compared to lean persons. Other groups at risk for OSA include those with a crowded posterior pharynx attributable to a small, recessed chins and/or severely enlarged tonsils. There is a familial clustering of OSA as non-obese patients may also have OSA. A comprehensive review of OSA was recently published.[2]

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Pheochromocytoma

Susan Steigerwalt, MD

Men and women are equally affected by pheochromocytoma. (Approximately 85 - 90% of these tumors are 90% found within adrenal glands) and other catecholamine secreting tumors (extra adrenal are known as catecholamine secreting paragangliomas) are extremely RARE occurring in (less than 0.2% of all hypertensives) causes of uncontrolled hypertension. Ninety eight percent of pheochromocytomas are intra-abdominal;the other 2% are located either in the intrathoracic > neck locations. The majority of extra-abdominal pheochromocytomas are located below the diaphragm. Approximately 10% of pheochromocytomas are malignant; extra-abdominal pheochromocytomas as well as very large tumors are more likely to be malignant. Roughly 10% of pheochromocytomas are familial. Familial tumors are more likely to be bilateral than unilateral.

The diagnosis of pheochromocytoma is akin to tying to find a needle in a haystack. Further complicating the diagnosis of pheochromocytoma is the fact that individuals with pheochromocytoma may not be persistently hypertensive. The classic symptom triad in persons with pheochromocytoma is paroxysmal hypertension (85 – 95%), headache (90%), and generalized sweating (60 - 70%). Orthostatic hypotension is commonly encountered. Other symptoms may occur such as palpitations, panic disorder, psychiatric disturbances, weight loss, and cardiomyopathy. Factors triggering the aforementioned symptoms can also help identify those with pheochromocytoma. Accordingly, precipitation of this symptom cluster by anesthesia, exercise, urination, defecation, bending over, pregnancy or palpation of the abdomen, the ingestion of tyramine containing foods, or use of monoamine oxidase inhibitors, should heighten ones suspicion regarding the presence of pheochromocytoma. A list of differential causes mimicking pheochromocytoma is shown in table 1. Clinical presentation includes discovery in the work up of an incidental adrenal mass, suggestive history in a symptomatic patient, or family history in the case of familial disease pregnant patients who have hypertension of unknown etiology or duration should be tested for pheochromocytoma.

Table 1

Differential diagnosis of pheochromocytoma and type spells

Endocrine
Pheochromocytoma
"Hyperandrenergic spells"
Thyrotoxicosis
Primary hypogonadism (menopausal syndrome)
Medullary thyroid carcinoma
Pancreatic tumors (eg, insulinoma)
Hypoglycemia
Carbohydrate intolerance
Cardiovascular
Labile essential hypertension
Cardiovascular deconditioning
Pulmonary edema
Syncope
Orthostatic hypotension
Paroxysmal cardiac arrhythmia
Angina
Renovascular disease
Psychologic
Anxiety and panic attacks
Somatization disorder
Hyperventilation
Factitious (eg, drugs, valsalva)
Pharmacologic
Withdrawal of andernergic-inhibitor
MAO-inhibitor RX + decongestant
Sympathomimetic ingestion
Illegal drug ingestion (cocaine, PCP, LSD)
Chlorpropamide-alcohol flush
Vancomycin ("red man syndrome")
Neurologic
Postural orthostatic tachycardia syndrome (POTS)
Autonomic neuropathy
Migraine headache
Diencephalic epilepsy (autonomic seizures)
Stroke
Cerebrovascular insufficiency
Other
Unexplained flushing spells
Mast cell disease
Carcinoid syndrome
Recurrent idiopathic anaphylaxis

Reproduced with permission from: Young, WF Jr. Pheochromocytoma and primary aldosteronism. Cancer Treat Res 1997; 89:239. Copyright © 1997 Springer Science and Business Media.

ANY patient, who develops paroxysmal hypertension with anesthesia induction or during a procedure, or with use of MAO inhibitors or consumption of tyramine containing foods, should have formal testing for pheochromocytoma. Pheochromocytoma should also be looked for when a patient presents with recurrent hyperadrenergic spells (non exertional palpitations, diaphoresis, headache, tremor or pallor), resistant hypertension, and onset of hypertension at age less than 20, and history of gastric stromal tumor or pulmonary chondromas.

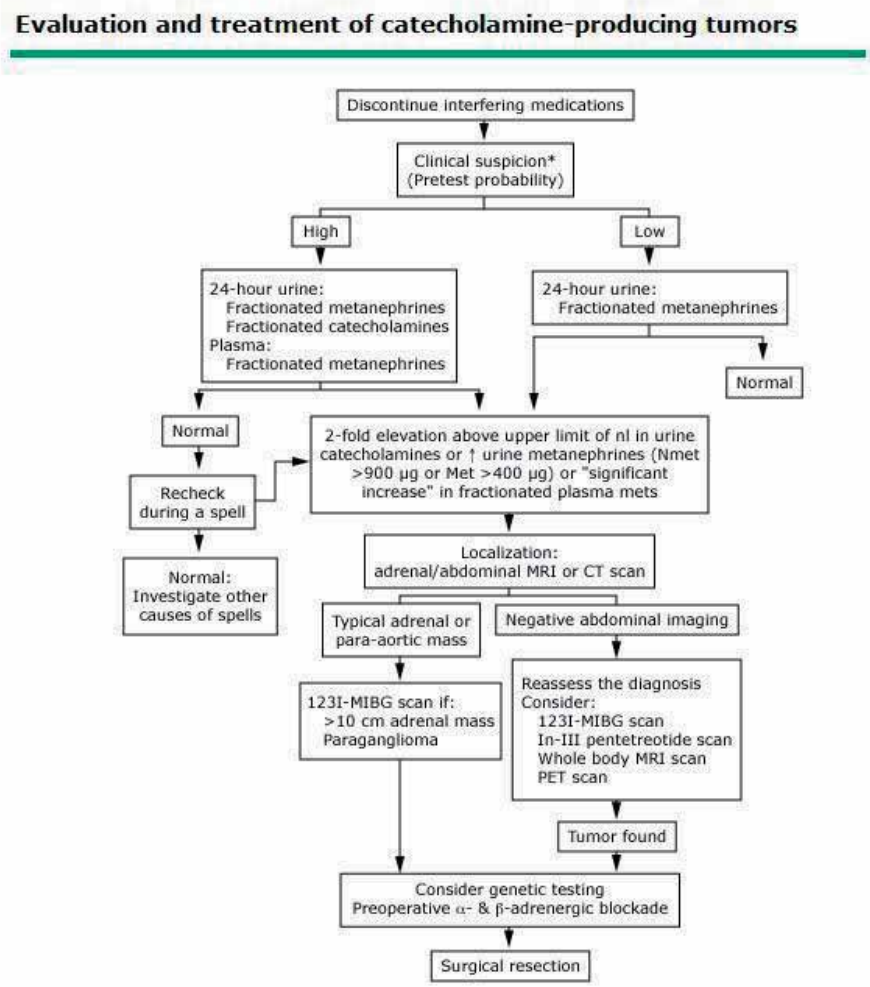
Familial Pheochromocytoma associated MEN2 , or von Hippel-Lindau disease is frequently asymptomatic and normotensive. Also, Remember, a patient with cutaeneous neurofibromas associated with NF1 and hypertension is much more likely 1-5%) to have a pheochromocytoma as the cause of their hypertension.

Diagnostic testing: Urinary and plasma fractionated metanephrines and catecholamines are the preferred tests. They should be performed by high pressure liquid chromatography (HPLC) to avoid problems with “interfering substances”- medications such as labetolol do not need to be stopped when using HPLC. 24 hour urines, while cumbersome, have a sensitivity and specificity of 98%. It is critical to measure creatinine to verify adequacy of the collection (10-15 mg/kg body weight in women; 15-25 mg/kg in men). An alternative, reserved mainly for patient where the index of suspicion is high, or those unable or unwilling to collect a 24 hour urine, is plasma fractionated metanephrines: the predictive value of a negative test is excellent; however the specificity is poor , particularly in patients over 60 years of age(too many false positive tests). It is important to remember that congestive heart failure, panic attacks, obstructive sleep apnea, MI and stroke are associated with increased catecholamines, but rarely the 10x normal seen with pheochromocytoma. The excellent review (figure 1) by Young and Kaplan gives greater detail on testing. Radiologic localization of the tumor follows biochemical confirmation. CT or MRI of the chest, abdomen and pelvis is usually the first test. MIBG scintography can detect tumors missed by CT or MRI. Plasma and urinary catecholamines have been utilized in the diagnosis of pheochromocytoma. However, there are problems with these tests. They may be falsely positive because of non-specific stimulation of the patient during test measurement, because of decreased renal catecholamine clearance in persons with low glomerular filtration rates, and/or because of labetolol metabolites resulting in falsely elevated urinary norepinephrine/epinephrine metabolites [1] Catecholamine measures may also be falsely negative when tumors are only episodically secretory. Some tumors are also biochemically silent.

Measurement of plasma free metanephrines is the preferred diagnostic test. Metanephrines are catecholamine metabolites and are much less likely to be falsely negative than measurement of catecholamine's when tumors are episodically secretory. In addition, non-specific stimulation of patients during blood draws will not falsely elevate metanephrines. An important compared the sensitivity and specificity at the upper reference limits of commonly used diagnostic tests, including plasma metanephrines using receiver operating curves [2]. Sensitivity and specificity was highest for plasma free metanephrines indicating that this test was best for both exclusion of pheochromocytoma as well as for its confirmation.

Most pheochromocytomas are > 2 cm in size are easily localized by CT or MRI scanning. MRI scanning is, however, more sensitive than CT.

Figure 1:



See text for details.
VMA: vanillylmandelic acid; CT: computed tomography; MRI: magnetic resonance imaging; 123I-MIBG: 123I-meta-iodobenzylguanidine.
* Clinical suspicion is triggered by paroxysmal symptoms (especially hypertension); hypertension that is intermittent, unusually labile, or resistant to treatment; family history of pheochromocytoma or associated conditions; or an incidentally discovered adrenal mass.

Modified and reprinted with permission from Young, WF Jr. Pheochromocytoma: 1926-1993. In: Trends in Endocrinology and Metabolism, vol 4, Elsevier Science, Inc 1993. p 122.

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Suggested reading:

UptoDate Version 17.3 Clinical Presentation and Diagnosis of Pheochromocytoma William F Young MD

Norman Kaplan, MD

Polycystic Ovary Syndrome (PCOS)

Susan Steigerwalt, MD

Objectives:

- Understand/ Describe the prevalence of PCOS
- Understand/Explain the pathophysiology of hypertension in PCO
- Understand/List the Cardiovascular risk factors associated with PCO/ post test questions

Polycystic Ovary Syndrome [PCOS] (characterized by elevated free testosterone and insulin resistance) should be considered in all young women presenting with hypertension with irregular menses (oligomenorrhea-less than 9 menstrual periods /year), particularly those with primary infertility. PCOS occurs in 7 % of women in industrialized countries. It is, however, more common in African Americans, Hispanics and obese women (28%in one study).

Forty three percent of women with PCOS have metabolic syndrome; 50%in the US are obese, most commonly centripetal, with preferential location in the visceral fat depot. Accordingly, PCOS is an increasing problem in the U.S. PCOS is also under-diagnosed, and because of its associated features presents an excellent opportunity to prevent future disease.

A majority of women with PCOS have sleep disordered breathing, even those who were not obese.[1] This relationship appears to correlate directly with insulin levels and presence of impaired glucose tolerance, independent of BMI, although average BMI in a recent study was 31.[2] Ninety two percent of women in one study had a high risk of OSA based on Epworth sleepiness scale or the PSQI.[3]

Ambulatory blood pressure monitoring may be needed to diagnose hypertension in many women with PCOS. Interestingly, in one study 62% of obese and 2% of lean PCOS women had a lack of nocturnal fall in BP. In non-obese Taiwanese PCOS patients, higher androgen levels correlated with HTN while pharmacological blockade of the renin angiotensin system lowered both BP and androgens.[4]

The mechanism of hypertension in PCOS is likely multifactoral: increased adrenergic drive, depressed adiponectin, insulin resistance, inflammation, OSA, and activation of the renin angiotensin system as manifested by elevations in plasma renin activity (PRa)and prorenin levels.. There is also an association between raised endothelin (ET)-1 levels (a potent vasoconstrictor) and androgens in

PCOS, independent of BMI that decrease with metformin treatment. [5] The pathophysiology of PCOS has been elegantly reviewed. [3]

PCOS has not been specifically linked to adverse cardiovascular outcomes, per se. Nevertheless, women with PCOS manifest several high risk markers for future cardiovascular disease including: 1) an atherogenic lipid profile, 2) elevated c-reactive protein, 3) leucocytosis, 4) levels, 5) increased endothelin, 6) raised insulin levels, 7) left ventricular hypertrophy, 8) diastolic dysfunction, 9) increased coronary calcification and endothelial dysfunction, and 10) elevated plasminogen activator inhibitor (PA-I) levels.

In summary, PCOS is common and under-diagnosed; once diagnosed, the patient **must** be screened for hyperlipidemia, obstructive sleep apnea and masked hypertension preferably with 24 hour ambulatory blood pressure monitoring. Additional features of PCOS such as infertility and increased risk of endometrial cancer must be co-managed with the patients' gynecologist. Treatment consists of weight loss, exercise and insulin sensitizing agents such as metformin, which may also restore fertility, and comprehensive CVD risk factor management including control of BP.

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Primary Aldosteronism

Susan Steigerwalt, MD

Definition
Prevalence
Clinical Features
Diagnosis
Types of Pathology
Evaluation and Therapy

Pre test questions:

1) What are the characteristics of hypertensive patients who should be screened for primary aldosteronism (PA)?

2) What are the mechanisms for high BP in PA?

3) What is the recommended screening test for PA? What is the role for confirmatory testing?

Primary aldosteronism (PA) is a syndrome resulting from the autonomous hyper secretion of aldosterone that is non suppressible by sodium loading. Aldosterone (aldo) is produced by a solitary adenoma or hyperplasia, or a combination of the two. The excess aldosterone results in cardiovascular hypertrophy and fibrosis as well as proteinuria most prominently when there is high dietary consumption of sodium. Other metabolic perturbations in the setting of high circulating aldosterone levels include an increase in plasminogen activator inhibitor 1 (PAI-1) associated with increased thrombosis and hypertension that may be, though not invariably, accompanied by hypokalemia, metabolic alkalosis, mild hypernatremia and glucose intolerance. Patient with PA have higher cardiovascular morbidity and mortality than age and sex-matched patients with primary hypertension. Thus, it is important to diagnose when it is present as there are specific treatments such as use of thiazide diuretics to control the aldosterone-induced volume expansion and aldosterone antagonists (spironolactone and epleronone) to specifically antagonize elevated circulating aldosterone levels and also the removal of solitary adrenal glands when hypersecretion of aldosterone can be localized to one adrenal gland.

Primary aldosteronism occurs in about 20% of patients with resistant hypertension (BP above goal despite therapeutic doses of three antihypertensive medications, including a diuretic or controlled BP on at least 4 BP lowering medications) and up to 10% of unselected hypertensive populations.

Clinical Features: This is usually found in individuals age 30-50; however familial forms may present in childhood and it may be found in elderly patients with resistant or paroxysmal hypertension Based on recently published guidelines by the Endocrine Society[1], the following hypertensives have been recommended for PA case-finding (screening): 1) stage 2 HTN, 2) resistant HTN, 3) HTN and spontaneous hypokalemia, 4) HTN with adrenal incidentaloma, or 5) HTN plus a family history of premature onset HTN or CVA < 40 years.

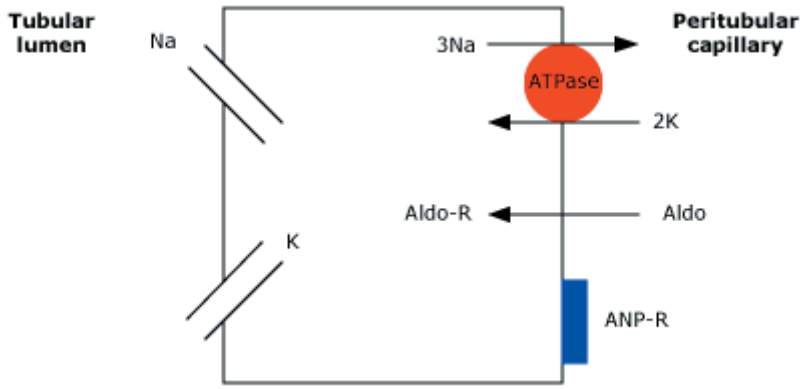
Although severe hypokalemia (K<3.0 meq/l) was described in Conn's original description of PA at the University of Michigan in 1955, only about 1/3 of patients reported within the last 10 years have hypokalemia, defined as K< 3.5 meq/l. When hypokalemia is present, it is associated with muscle weakness; polyuria from a loss of renal concentrating ability; renal cysts; impaired insulin secretion and glucose intolerance. Hypokalemia may also accelerate vascular injury. In diuretic-treated patients hypokalemia is even less specific (more false positivies). Thus, in diuretic-treated individuals severe hypokalemia (K < 3.0 meq/l) should raise suspicion of the presence of PA. Modest hypernatremia (143-148 meq/l) and sodium chloride resistant metabolic alkalosis also occur, in conjunction with volume expansion. Hypomagnesemia may also be present. Hypomagnesemia can make replacement of potassium difficult since hypomagnesemia causes renal potassium wasting. Thus, both magnesium and potassium may need measurement and replacement. Also, circulating serum magnesium levels do not accurately reflect the presence of total body magnesium depletion given that magnesium is primarily an intracellular cation

Renal and Vascular Effects of Aldosterone

Aldosterone increases sodium reabsorbtion in exchange for potassium in the collecting duct via activation of the Mineralocorticoid receptor. Aldosterone also stimulates an increase in number of and activity of sodium (ENAC) channels in the distal tubule on the luminal side of the membrane (figure 1) to cause volume expansion, but also may interact with the alpha-2 subunit of the sodium-potassium ATPase to increase myogenic tone and increase BP via a oubain-like substance in the blood (so called endogenous inhibitor of sodium-potassium atpase pump).[2,3] Aldosterone also causes endothelial dysfunction and decreases in baroreceptor sensitivity, both of which enhances vascular reactivity and contributes to elevations in BP. Proteinuria is increased in PA, particularly in the setting of high sodium

intake. [4]

Figure 1;
Ion transport in collecting tubule cell



Schematic representation of sodium and potassium transport in the sodium reabsorbing cells in the collecting tubules. The entry of filtered Na into the cells is mediated by selective sodium channels in the apical (luminal) membrane; the energy for this process is provided by the favorable electrochemical gradient for Na (cell interior electronegative and low cell Na concentration). Reabsorbed Na is pumped out of the cell by the Na-K-ATPase pump in the basolateral (peritubular) membrane. The reabsorption of cationic Na makes the lumen electronegative, thereby creating a favorable gradient for the secretion of K into the lumen via K channels in the apical membrane. Aldosterone, after combining with the cytosolic mineralocorticoid receptor (Aldo-R), leads to enhanced Na reabsorption and potassium secretion by increasing both the number of open Na channels and the number of Na-K-ATPase pumps. Atrial natriuretic peptide, on the other hand, acts primarily in the inner medullary collecting duct by combining with its basolateral membrane receptor (ANP-R) and activating guanylate cyclase. ANP inhibits sodium reabsorption by closing the Na channels. The potassium-sparing diuretics act by closing Na channels, amiloride and triamterene directly and spironolactone by competing with aldosterone. Used with permission from Dr. Raymond Townsend @ *Uptodate*

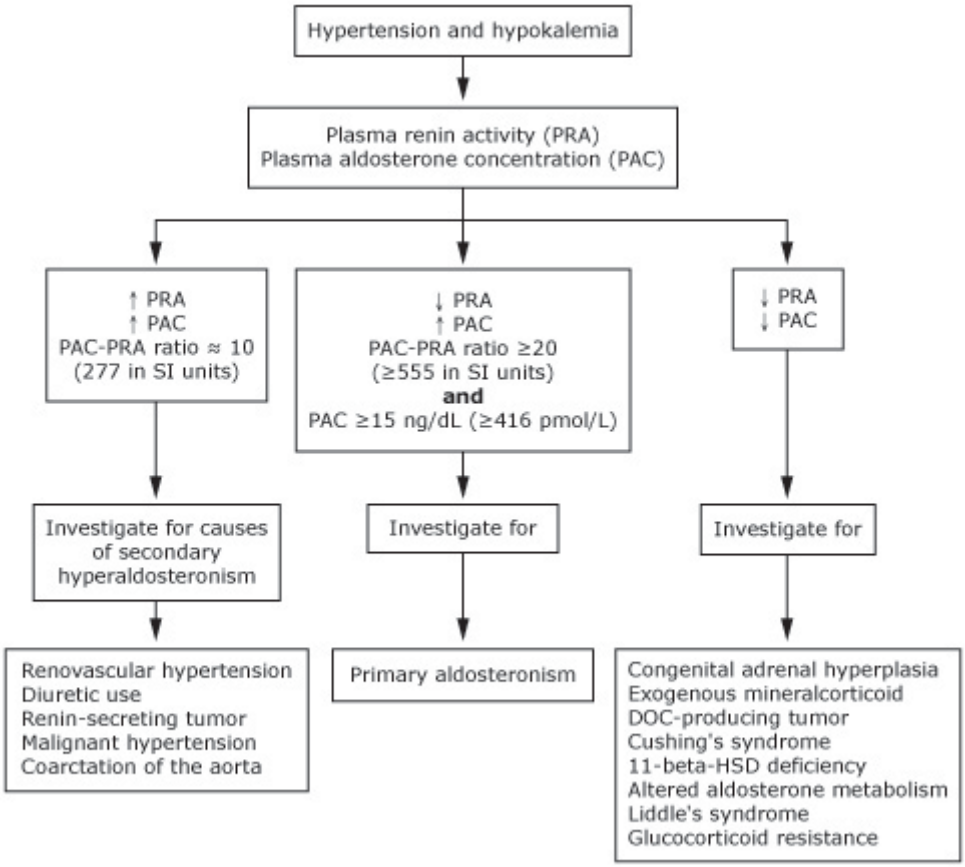
Diagnosis and Evaluation

Recent guidelines published by the Endocrine Society in 2008 detail the evaluation of PA. (Figure 2) The first test is the plasma aldosterone /renin ratio (ARR), preferably performed the morning. This screening test has both false positives and false negatives. Although many antihypertensives can affect levels of renin and aldo, only two render the test uninterpretable. **The test must be performed in patients who have not taken either an aldosterone antagonist or a renin inhibitor within the past 4-6 weeks**. A positive screen consists of an aldosterone level > 14 ng /dl (416 pmol/l), with a PRA less than 1 ng /ml/hr (12.8 pm/l in SI units); nevertheless, a not inconsequential proportion of patients with PA will not have circulating aldosterone levels > 14 ng/dl. PRA is now being performed in some laboratories as a direct renin concentration or DRC, which requires conversion. Knowing local values

and assays is key to interpretation of results! The ARR is considered positive when it is at least > 20; the higher the ARR over 20, the greater the probability of Primary Aldosteronism. There are few false positives when the ARR exceeds 40.

Figure 2:

PAC/PRA ratio in hypertension and hypokalemia [5]



Use of the plasma aldosterone concentration (PAC)-to-plasma renin activity (PRA) ratio to differentiate among different causes of hypertension and hypokalemia. Adapted from: Young, WF Jr, Hogan, MJ, Renin-independent hypermineralocorticoidism. Trends Endocrinol Metab 1994; 5:97.

Confirmatory Testing

Confirmatory testing is based on the principle that volume loading, either intravascularly or orally, does not suppress the circulating plasma aldosterone level. The recently published Endocrine Society Guidelines suggest one of four suppression tests. . However, the most practical test for most practitioners to administer due to logistics and issues with payment for services will be an oral sodium

loading with 200 mmoles (4.6 grams) per day over 3 days; provide adequate potassium replacement prior to doing this test to ensure normal serum potassium levels (hypokalemia can artificially depress serum aldosterone levels even in during H “autonomous” aldosterone secretion). PA is unlikely to be present if the urinary aldosterone is < 10 ug/24 h but is very likely if urinary aldosterone secretion is > 12 ug/24 h (> 14 ug/d if Cleveland Clinic assay is used) in the urine collected between days 3 and 4 of oral sodium loading. These urinary aldosterone cut-points do not necessarily apply to patients with CKD because in this condition urinary aldosterone levels may be lower even in the presence of PA. Any patient with severe uncontrolled hypertension or heart failure might be placed at risk by volume loading. Switching to drugs with minimal impact on the RAAS system during testing such as alpha blockers, CCBs and hydralizine during can be used to control BP. Patient safety comes first!

Once the diagnosis of PA has been established, subtype classification using a thin section (3mm) adrenal CT scan is recommended. Following CT imaging, adrenal venous sampling (AVS) is critical to lateralizing production of aldosterone in a patient who is a surgical candidate. This generally includes those individuals less than 60 years of age, and those with severe hypertension or electrolyte abnormalities, as well as medically non-compliant patients who will not take their pills. If unilateral over-secretion is documented, adrenalectomy will remove the source of aldosterone and improve blood pressure (though often not cure). AVS is an operator-dependent procedure, with the right adrenal gland vein being more difficult to cannulate. Arguably, the major reason to image the adrenal glands once excessive and non-suppressible aldosterone has been established is to ensure that a large aldosterone- producing adrenal carcinoma is not missed; CT imaging is also helpful prior to AVS for localization of the more difficult to cannulate right adrenal vein. Though it may be of interest to the curious physician, once elevated, non-suppressible aldosterone secretion has been confirmed the presence or absence of an adrenal adenoma/hyperplasia will not significantly change management. Accordingly, if no adenoma or hyperplasia is found, adrenal gland is anatomically normal but unilateral hypersecretion can be confirmed, assuming the patient is a reasonable surgical candidate; laparoscopic adrenalectormy will still be indicated.

Testing for Familial forms of Primary Aldosteronism-

Family history is very important. The key historical information is premature onset of HTN and/or

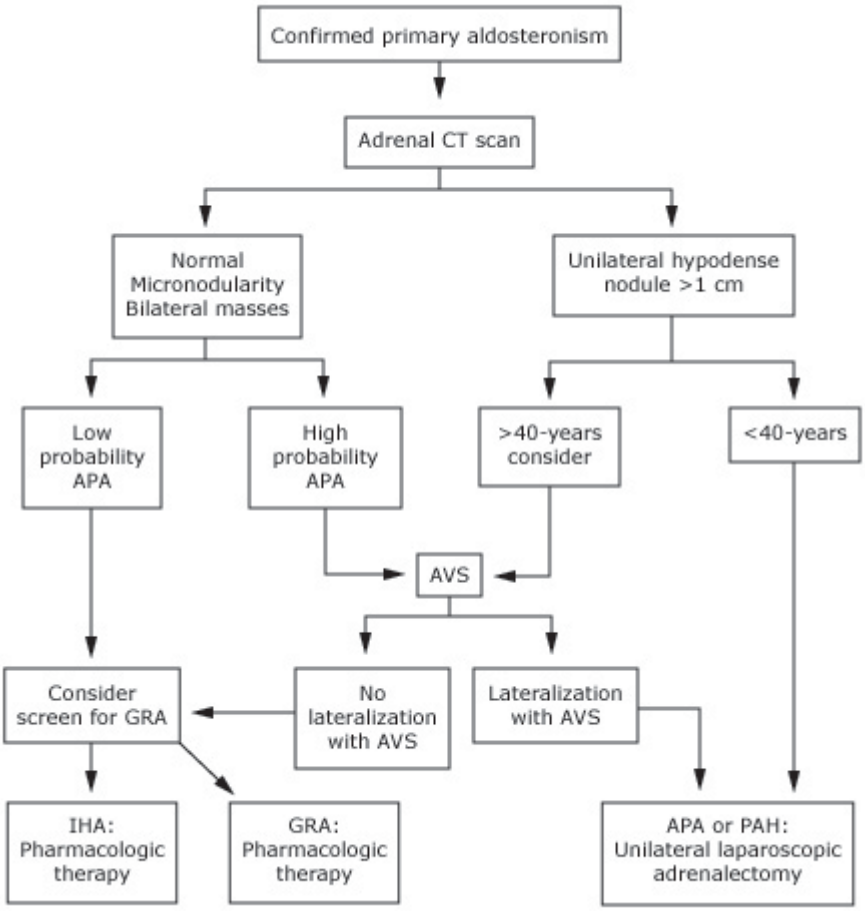
CVA (especially hemmorhagic) prior to 40 years of age. Two major syndromes are glucocorticoid remedial aldosternism (GRA) (detailed below) and autosomal dominant in which patients and/or family members present with early onset of hypertension and hemorrhagic stroke. GRA represents a chimera of the aldosterone synthase gene and 11-beta hydroxylase resulting in ACTH dependent aldosterone production that is always “on”. Aldosterone is aberrantly produced in the zona fasculata instead of the zona glomerulosa. GRA is diagnosed by genetic testing available from the laboratory of Dr. Richard Lifton at Yale University. Treatment is with low dose dexamethasone in the hands of an expert in management of this disease.

The Second Familial form of GRA is also autosomal dominant. However, this form of GRA is not ACTH dependent and therefore GRA mutation testing is negative. The adrenal anatomic abnormalities are variable and include both adenoma and hyperplasia.

Treatment

Unilateral laparoscopic adrenalectomy should be offered for surgical candidates with unilateral hypersecretion of aldosterone irrespective of whether an adrenal adenoma or hyperplasia or a normal gland is detected on CT imaging (Figure 3). Cure of hypertension occurs in only about 50% of individuals. Patients older than 60 or with >5 years duration of hypertension have poorer results in regards to hypertension cure.

Figure 3; Endocrine Society



See text for details.
APA: aldosterone-producing adenoma; AVS: adrenal venous sampling; CT: computed tomography; GRA: glucocorticoid-remediable aldosteronism; IHA: idiopathic hyperaldosteronism; PAH: primary adrenal hyperplasia. Copyright 2008, The Endocrine Society

Medical management with aldosterone antagonists is indicated prior to surgery as well as over the long-term for those not undergoing surgery. Spironolactone, which has been available for over 40 years, has the side effects of breast tenderness/gynecomastia and sexual dysfunction, particularly with doses of more than 50 mg/d. Recent studies have suggested that in patients with adrenal hyperplasia, doses of 25-50 mg, combined with other medications such as CCBs and chlothalidone, may control BP with fewer side effects. Higher doses may, however, be required in patients with adrenal adenomas. Chlorthalidone, a thiazide-like diuretic, will also be an important drug in the therapeutic armamentarium because of the high likelihood of plasma volume expansion despite the well established kaliuretic effect of thiazide diuretics. Other antihypertensive agents such as calcium antagonists may be needed to

control BP in addition to aldosterone antagonists and thiazide diuretics.

Epleronone, is also a mineralocorticoid receptor antagonist that has much more specific for the mineralocorticoid receptor (less testosterone antagonism and progesterone agonism), meaning less breast tenderness/gynecomastia and sexual dysfunction. It has a smaller evidence base, and is less potent than spironolactone on a mg per mg basis.

Amiloride, a sodium channel (ENAC) blocker, is also used in patients unable to tolerate spironolactone or afford epleronone. No long term target organ outcome data are available. In patients with CKD Stage 4 AA are contraindicated due to the risk of hyperkalemia. In eligible patients, the Endocrine Society Guidelines[1] recommends laparoscopic adrenalectomy as the definitive treatment of choice due to lifelong medication side effects and adherence to therapy.

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Suggested reading:

Kaplan, Norman: Clinical Hypertension Lippincott Williams and Wilkes 2009: p 339-358

Renal Artery Stenosis

Robert D. Safian, MD, FACC, FAHA, FSCAI, FSVM

INTRODUCTION

Renal artery stenosis (RAS) is caused by a heterogenous group of diseases with different pathophysiology, clinical manifestations, treatment approaches, and outcomes. The two most common forms of RAS are fibromuscular dysplasia (FMD) and atherosclerosis (ARAS), whereas inflammatory disease of the arterial circulation and congenital abnormalities are far less common. Traditionally, renovascular syndromes have been broadly classified into two categories: Renovascular hypertension and ischemic nephropathy. These categories are potentially misleading since they imply a causal relationship between RAS, hypertension, and renal dysfunction. Although causal relationships are evident in experimental models of RAS, they are more difficult to prove in human diseases. Furthermore, a causal relationship suggests that revascularization of RAS should favorably impact BP and renal function, yet available clinical data have failed to demonstrate unequivocal benefits of renal revascularization.

Despite a lack of consensus regarding the appropriateness of revascularization for RAS, the number of percutaneous renal artery interventions performed in Medicare beneficiaries between 1996 and 2000 increased from 7,660 to 18,520.[1] The base of evidence supporting renal revascularization is limited by heterogeneous causes of hypertension and renal dysfunction, insufficient understanding of the relationship between renal ischemia and nephropathy, inconsistent techniques for revascularization, ambiguous terminology and endpoints to assess clinical benefit, and the lack of large-scale randomized trials. These limitations are recognized by numerous medical specialties [2,3] and by third party payors, and were partly responsible for recent considerations by the Centers for Medicare and Medicaid Services to deny reimbursement coverage for renal artery stenting. It is important to place RAS in appropriate perspective, particularly with regard to the identification of renal ischemia and nephropathy. This perspective should incorporate understanding of the epidemiology, clinical markers, and diagnosis of RAS; establish a relationship between RAS and important disease states; distinguish renal ischemia and nephropathy; use optimal revascularization techniques; and avoid renal injury (Table 1). The goals of therapy are to arrest atherosclerosis, control hypertension, preserve renal function, and prevent injury to vital organs.

EPIDEMIOLOGY OF RAS

Fibromuscular dysplasia. FMD is an uncommon disease of unknown etiology, typically occurs in young females < 30 years of age, and often affects the renal, carotid, and femoral arteries. FMD should be considered in young patients if severe hypertension is not associated with obesity, oral contraceptives, or known renal parenchymal disease. Unilateral or bilateral renal FMD may cause renovascular hypertension, but renal failure/ischemic nephropathy is unusual. The most common form of renal FMD is medial fibroplasia, characterized by a beaded appearance of the artery in which the beads are larger than the vessel (Figure 1). Renovascular hypertension due to FMD is readily cured by balloon angioplasty.[4,5] Renal FMD is characterized by progressive stenosis and occlusion, so patients should have regular follow-up.

Atherosclerotic renal artery stenosis. ARAS is a common clinical entity, affecting 7% of patients over age 65 with no known racial predilection, 30% of patients with coronary artery disease, and 60 % of patients with hypertension, coronary or peripheral artery disease, and renal insufficiency.[6,7] Unlike FMD, ARAS is not a common cause of renovascular hypertension but is commonly associated with renal dysfunction.[8] The expectation post-renal stenting, however, should not be cure of hypertension given that many patients with critical renal artery stenosis had pre-existing essential hypertension. Accordingly, a more realistic expectation is to reduce the intensity of antihypertensive drug treatment needed to control BP. Ischemic nephropathy is an important cause of chronic kidney disease and is the most common cause of end-stage renal failure in elderly patients without diabetes, representing the primary etiology of end-stage renal disease in 5-16% of patients initiating dialysis each year.[9-13] Ischemic nephropathy leads to progressive renal dysfunction and renal atrophy in 25 % of patients, despite aggressive antihypertensive therapy [2,9,14,15] Renal artery stenting has supplanted angioplasty for ARAS[6], due to better lumen enlargement and less restenosis (Figure 2).[16-21]

CLINICAL MANIFESTATIONS OF RAS

Screening for RAS. There are no guidelines for routine screening for RAS. In some patients, the diagnosis of RAS is made incidentally during angiographic evaluation of lower extremity arterial diseases, while in others a high index of suspicion is required, based on American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Table 2, Section 1).

Hypertension Manifestations. Hypertension manifestations include onset of severe hypertension at age < 30 (FMD) or at age >55 (ARAS), and resistant, accelerated or malignant hypertension.[8,22]

Renal manifestations. Renal ischemia may present as acute renal failure, with rise in serum creatinine (Scr) within 14 days of initiation of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). While considered a marker for bilateral RAS, this observation is neither sensitive nor specific for RAS,[23] since ACEI-induced renal failure is potentiated by sodium depletion and pre-existing nephropathy;[24] also, some patients with "critical" [>60% luminal occlusion] bilateral renal artery stenosis experience no rise in creatinine when treated with RAS blockade. It should, however, be noted that in patients with reduced nephron mass/reduced kidney function experience a fall in BP, even when no RAS blocker is used, the creatinine may rise because renal autoregulation of glomerluar pressure is significantly dependent on systemic arterial pressure. Thus, even when RAS blockade is utilized in patients with critical bilateral RAS and the creatinine rises, a significant portion of the rise in creatinine is plausibly attributable to the drop in systemic BP rather than the glomerular micro-circulatory effects of pharmacological interruption of the local RAS system. Other renal manifestations are subtle or insidious, including unexplained chronic renal failure, small kidney, and asymmetry in renal dimensions.[25,26] Patients with RAS and abnormal perfusion by renal scintigraphy or other objective measurements should be considered to have renal ischemia (Table 3).

Cardiovascular manifestations. Cardiovascular manifestations usually occur in the setting of malignant hypertension. The classic manifestation is "flash" pulmonary edema not explained by coronary artery or valvular disease, especially if left ventricular function is normal.[27,28] Flash pulmonary edema is most often associated with critical bilateral RAS, a volume-dependent form of hypertension. Other cardiovascular manifestations include severe hypertension associated with acute coronary syndromes, acute aortic syndromes, stroke, transient cerebral ischemia, intracranial hemorrhage, encephalopathy, and papilledema [22] (Table 3). The mere presence of angina, congestive heart failure, coronary artery disease, and peripheral artery disease are not strong indications for evaluation of RAS in the absence of other considerations mentioned above.

ASSESSMENT OF RAS AND ITS CLINICAL SIGNIFICANCE

Establish the diagnosis of RAS. If clinical manifestations suggest RAS, the contemporary approach is to use renal duplex ultrasound (RDU), magnetic resonance angiography (MRA), or computerized tomography angiography (CTA) to identify RAS[6,8,20]. "Drive-by" angiography and assessment of the renal arterial system are not recommended (Table 2, Section 2)[6]. Accordingly, it is critical to consider

the clinical history and patient characteristics, not just the renal artery anatomy, when deciding to pursue the diagnosis of critical renal artery stenosis.

Invasive angiography is recommended to confirm the diagnosis of RAS (Table 4); determine the etiology (Figure 1); identify dual, accessory or aberrant renal arteries (Figure 3); identify diseases of the abdominal aorta (Figure 4); and evaluate the nephrogram (Figure 5). The nephrogram is frequently overlooked, but provides extremely important information regarding blood flow, renal dimensions, and neovascularity. Angiographic patterns suggestive of nephropathy include intrarenal arteriolar narrowing, pruning of the distal vessels, and loss of cortical blood flow [29-31]. In most cases, abdominal aortography with digital subtraction provides superb images of the abdominal aorta and renal circulation (Figure 4). Since 30 % of patients have dual, accessory, or aberrant renal arteries (Figure 3), selective angiography alone may preclude complete assessment of the renal arteries.

Establish a relationship between RAS and vital organ dysfunction. Once “anatomic” RAS is recognized, it is important to establish a relationship between RAS and vital organ injury (Table 3). Hypertension per se (especially well-controlled hypertension), in the absence of renal or cardiovascular dysfunction, is not an indication for ARAS revascularization. Clinical manifestations of renal injury are similar for vascular and nonvascular causes (Table 3). When RAS and non-vascular etiologies co-exist, it may be difficult to establish RAS as the cause of renal dysfunction.

The renal artery, the kidney, and renal function. In simplistic terms, the kidney is a filter with inflow (renal arteries), outflow (renal veins), and a reservoir (renal pelvis, ureters, and bladder) (Figure 6). In the context of renal vascular diseases, filter function (renal function) is influenced by inflow to the filter (renal artery perfusion) and the integrity of the filter (nephropathy). Filter dysfunction may be due to inflow impairment (RAS and renal ischemia), filter impairment (nephropathy), or both. The essential feature is the filter (kidney); patients with nephropathy may not improve after renal artery revascularization, depending on the extent of baseline nephropathy before revascularization and the degree of renal injury after revascularization. The relationship between renal ischemia and nephropathy is central to understanding published studies and ongoing trials of RAS, and failure to do so is the most important source of ambiguity about the benefits of renal revascularization.

Clinical evaluation of nephropathy. The complete evaluation of patients with ARAS and vital organ injury must include a baseline assessment of nephropathy (Table 5) and renal ischemia (Table 6). The clinical evaluation for nephropathy includes Scr, urinalysis, renal duplex ultrasound (ultrasound

to assess renal dimensions and duplex to assess renal resistive index [RRI]), and selective renal arteriography in some patients (to assess cortical blood flow and intrarenal arteriolar patterns). Individually, none of these parameters is an absolute predictor of outcome, and over-reliance on any single test may exclude patients who might benefit from revascularization.[32-34] In any given patient, certain measures may indicate greater degrees of nephropathy than others, but advanced nephropathy is characterized by proteinuria > 1 gram/24 hr, renal length < 10 cm, and RRI >0.8, compared to others with less nephropathy.

Scr is the most common measure of renal function, but is limited for assessing the extent of dysfunction or for distinguishing nephropathy from renal ischemia. Scr is insensitive to glomerular filtration rate (GFR) until 50-75 % of renal mass has been lost (Figure 7). Stated in another way, a patient who loses 50 % of renal mass (as might occur after nephrectomy or with unilateral renal artery occlusion) should have a normal Scr; Scr $\geq$ 2 mg/dL in a patient with unilateral ARAS is generally indicative of significant nephropathy.[35] Selective renal arteriography and renal biopsy can be used to assess nephropathy. Although a biopsy can reliably confirm nephropathy, it is impractical and uncommonly used. Arteriographic findings provide useful information that complements the noninvasive evaluation (Table 4, Figure 5).

Clinical evaluation of renal ischemia. Several noninvasive and invasive methods have utility for estimating renal blood flow, assessing the hemodynamic significance of RAS, and identifying renal ischemia (Table 6).[36,37] Nuclear scintigraphy with Technetium-labeled pentetic acid (^{99M}Tc-DTPA) is reliable for measuring fractional renal blood flow[36-39] and when used in conjunction with ^{125}I-Iothalamate, allows accurate measurement of total- and single kidney-GFR. In patients with unilateral RAS, hypoperfusion of the stenotic kidney is reasonable evidence for renal ischemia[36]; patients with normal renal blood flow may have RAS, but not ischemia.

The invasive evaluation of renal ischemia is based on hemodynamic assessment of RAS rather than renal artery perfusion per se (Table 6). Stenosis severity is determined by visual estimates or quantitative angiography using a single angiographic projection may be inaccurate due to plaque eccentricity and vessel foreshortening, and has poor correlation with hemodynamic significance.[40] Translesional pressure gradients (TLG) can be measured with small catheters or special pressure wires, and TLG > 20 mmHg is considered hemodynamically significant.[20] Fractional flow reserve (FFR) can determine the hemodynamic significance of RAS[40,41], and FFR < 0.80 may predict a favorable BP

response to revascularization.[42] Intravascular ultrasound (IVUS) is extremely useful for assessing vessel dimensions and stenosis severity in FMD patients, and when used with TLG provides a useful assessment of ischemia and improvement after angioplasty. IVUS may also be used to guide stenting for ambiguous ARAS.[43] Renal frame counts (RFC) and renal blush scores (RBS) are used to assess the hemodynamic significance of RAS[44], but high RFC and low RBS may be observed with nephropathy without RAS.[30,31]

TREATMENT AND RENAL ARTERY REVASCULATIZATION

Medical management. All patients with atherosclerosis, including those with RAS, should be managed with appropriate CVD risk factor modification to limit atherosclerosis, including regular exercise, dietary modification, and smoking cessation. In diabetic patients, strict control of blood sugar is recommended to limit microvascular disease. Since many patients with RAS have hypertension, current guidelines recommend achieving BP <140/80 mmHg for nondiabetics and <130/80 mmHg for persons with diabetes and/or CKD, in accordance with JNC guidelines. Angiotension converting enzyme inhibitors (ACEI) or angiotension receptor blockers (ARB) are recommended as first line treatment for all patients with unilateral or bilateral RAS, regardless of baseline renal function. However, renal function and serum potassium should be checked within 2 weeks of initiating therapy, and at periodic intervals thereafter, to monitor patients for rising Scr and hyperkalemia. Patients with bilateral RAS may be especially sensitive to volume depletion, so diuretics should be used with caution and limited to patients with overt manifestations of volume overload. Nevertheless, bilateral critical renal artery stenosis is a volume dependent form of hypertension and judicious use of diuretics will often be needed for controlling intravascular volume expansion, an important factor in the control of BP. There are no special cautions about the use of beta blockers or calcium antagonists in any patients with RAS, and these agents are important adjuncts to antihypertensive therapy.

Technique of renal artery revascularization. For FMD patients, balloon angioplasty is the intervention of choice, and stenting is only used for bail-out indications. Procedural success approaches 100 %, and restenosis occurs in < 10 % within 10 years.[45-48] Renal angioplasty is better in discrete lesions in major renal arteries, and worse in diffuse FMD in small segmental, arcuate, and interlobar vessels. Since renal arteriography is not reliable for assessment of FMD stenosis severity or vessel dimensions, we recommend the pressure wire and IVUS to assess TLG, vessel dimensions, and

stenosis severity. Patients with non-obstructive FMD (no TLG, no stenosis by IVUS) should be treated conservatively.

In patients with ARAS, stenting is recommended to eliminate elastic recoil, minimize dissection, and maximize lumen enlargement.[49-51] Most studies report procedural success rates of 95-100 %, residual diameter stenosis < 10 %, restenosis rates of 10-15 % within 1 year, and major complications in < 2 % (20, 50-53).[20,21,50-52]

There are a number of important technical and procedural considerations (Table 7), to avoid renal artery injury, kidney injury, and atheroembolization. Selective renal arteriography should be guided by abdominal aortography; the catheter-in-catheter or no-touch techniques should be utilized to minimize contact with the aortic wall and injury to the renal ostium during guiding catheter engagement[53](Figure 8). The nephrotoxic effects of radiographic contrast are minimized by maintaining adequate hydration, limiting contrast volume, and using digital subtraction angiography. Renal embolization during revascularization appears to be fairly common[54,55] and one small randomized study suggested potential benefit of a combination of distal embolic protection and intravenous abciximab.[56] Since 14 % of patients have early renal bifurcations (Figure 3), complete renal “protection” may not be possible. Most devices are not designed for the renal circulation and may add procedural time and complexity, so the long-term value of renal embolic protection has not been established.

Is mild improvement in blood pressure clinically relevant? Among conventional risk factors, hypertension has the strongest association with stroke, kidney disease, and congestive heart failure; is the most important modifiable risk factor in reducing cardiovascular morbidity, mortality, and disability; is easy to recognize; and has been proven to increase survival when treated in accordance with simple guidelines.[57] Even small decrements in systolic (10 mmHg) and diastolic (3-6 mmHg) BP are associated with 30-40 % reduction in risk.[58,59] Therefore, therapies which offer even small absolute improvements in BP are worthy of consideration, because they may translate into large clinical benefits and risk reduction.

ARAS and hypertension outcomes. There are 3 published randomized trials comparing angioplasty to medical therapy in a total of 210 hypertensive patients with ARAS ![60-62] In one trial, angioplasty produced significant reduction in BP and medication requirements at three months, whereas medical therapy did not.[60] Since, 44% of medical patients crossed-over to angioplasty at 3 months, the intention-to-treat analysis revealed no difference in BP or medication requirements at 1-year. In another

trial, angioplasty resulted in significant reduction in BP and antihypertensive medications in patients with bilateral ARAS.[61] In a third, 28 % of medical patients crossed over to angioplasty. A contemporary review of 2 randomized trials, 8 comparative studies, and 34 cohort studies concluded that angioplasty leads to greater reduction of BP than medical therapy, particularly in patients with bilateral RAS.[63]

Several prospective studies and meta analysis documented reduction in BP after renal stenting [16,51,64-72] In the only prospective randomized trial of angioplasty versus stenting in 85 patients,[19] revascularization resulted in significant reduction of systolic (19 mmHg) and diastolic (12 mmHg) BP. There may be a relationship between renin-angiotensin activation and renal production of brain natriuretic peptide (BNP), and BNP may predict the hypertension response to renal stenting.[73,74] After ARAS revascularization, hypertension cure (normal BP no medication) is observed in < 10 % of patients, regardless of revascularization techniques.

RAS and malignant hypertension. The augmented renin and angiotensin II levels in some patients with stenosis of a solitary kidney or that may occasionally occur in patients with bilateral ARAS may promote acute volume loading and vasoconstriction, flash pulmonary edema, and other manifestations of malignant hypertension.[6,75-79] Prevention of recurrent pulmonary edema is a Class I recommendation for renal revascularization[6], based on several small studies.[77,79,80,27]

Failure of renal revascularization to cure hypertension. The explanations for why renal revascularization does not cure hypertension are somewhat speculative (Table 8). There is a persistent misperception that ARAS patients have renovascular hypertension, and contemporary reviews continue to use this terminology.[2,20] While the experimental Goldblatt models are compelling demonstrations of renin-angiotensin activation due to RAS[81], the mechanisms of hypertension in humans with and without RAS are far more complex, and include sympathetic and cerebral nervous system activation, vasoactive oxygen species, abnormalities in endothelial dependent relaxation, and ischemic and hypertensive intra-renal injury.[82-86] Patients with ARAS do not have renovascular hypertension, as evidenced by similarities in the extent of renin activation compared to hypertensive patients without RAS[87,88] and the low cure rate of hypertension after successful revascularization. Although lumen enlargement after balloon angioplasty for ARAS is clearly suboptimal, observational studies do not suggest different cure rates after renal artery bypass or stenting.[89-100] The most likely explanations are that patients with ARAS have essential hypertension, many do not have renal ischemia, and unrecognized hypertensive nephropathy leads to self-perpetuating hypertension.

ARAS, ischemic nephropathy, and improvement in renal function after revascularization. ARAS patients with renal dysfunction may have varying degrees of nephropathy and renal ischemia. Some studies showed improvement or stabilization of Scr after stenting in 22-68 % of patients[16,63], in contrast to a consistent deterioration after medical therapy alone.[60,63] Several studies documented improvement in Scr and in the slope of reciprocal Scr after stenting, compatible with beneficial effects of revascularization on renal function (104-106).[101-103] In a contemporary prospective study, patients with documented severe ARAS were treated with aggressive anti-hypertensive therapy and risk factor modification according to current guidelines. Renal artery stenting was recommended for increasing Scr, decline in nuclear GFR, or malignant hypertension. Despite aggressive medical therapy for 21 months, there was a 7% increase in Scr, a 15% decline in GFR, and 39% of patients developed worsening stenotic-kidney GFR. In contrast, renal stenting resulted in 13-19 % improvement in total- and single-kidney GFR[36], similar to other studies.[38,39] Nevertheless 25-30 % have deterioration in renal function despite revascularization. The key observation in prior studies of ischemic nephropathy is the crucial importance of baseline renal function[71,104-108]: Baseline Scr > 1.5 mg/dL is the single strongest predictor of late death[66] look at, and the risk of renal failure rises 3-fold for each increment of 1.0 mg/dL in baseline Scr.[88-90]

Failure of renal revascularization to improve renal function. The explanations for failure to improve or stabilize renal function after revascularization are multifactorial (Table 8), including revascularization of patients without renal ischemia, insensitivity of the Scr to changes in GFR when < 50 % of renal mass is revascularized (e.g. unilateral ARAS) (Figure 7), failure to identify baseline nephropathy, and procedure-induced nephropathy.

The causes of procedure-induced nephropathy after revascularization include acute tubular necrosis, contrast nephropathy, and renal embolization (Table 9). Acute tubular necrosis is usually due to acute blood loss, and is characterized by progressive rise in Scr, oliguria, and increased fractional sodium excretion. Contrast nephropathy is characterized by rising Scr 2-4 days after exposure, oliguria or normal urine output, and normal urinary sodium concentration. Distal embolization may not be recognized until the Scr rises days or weeks after discharge. Urinalysis and sodium excretion may be normal, although urine eosinophils may be present. The treatment for all three conditions includes correction of underlying volume depletion and maintenance of adequate hydration.

ARAS and cardiovascular outcomes. Four-year survival rates are 57% and 89% for patients with and

without ARAS,[109] and mortality rates are higher with more severe ARAS and with bilateral ARAS.[6],[109] The risk of cardiovascular events at 6 years is 50%, which exceeds the risk attributable to hypertension alone (2,14,113-116,122). [2,14,110-114] Although ARAS adds incremental risk to cardiovascular morbidity and mortality, there are no data that renal revascularization improves cardiovascular outcomes. The Cardiovascular Outcomes in Renal Atherosclerotic Lesions trial (CORAL) is actively randomizing 1080 patients with documented hypertension and taking ≥ 2 antihhpertensive drugs plus hemodynamically significant unilateral or bilateral stenosis or renal dysfunction as defined by an estimated GFR < 60 ml/min/1.73 m2, to optimal medical therapy or to optimal medical therapy plus renal artery stenting.[115] The primary end-point is a composite of cardiovascular or renal death, stroke, myocardial infarction, hospitalization for heart failure, doubling of Scr, or need for renal replacement therapy.

RECOMMENDATIONS

New classification for RAS, renal ischemia, and nephropathy. We recommend the following classification to allow identification of patients with and without nephropathy, and with and without renal ischemia (Figure 9, Table 10):

Type 1: Normal kidneys (no nephropathy)

Type 2: Nephropathy (parenchymal disease)

Type A: No renal ischemia (hemodynamically insignificant RAS)

Type B: Renal ischemia (hemodynamically significant RAS)

This classification offers a reasonable framework for evaluation of patients with RAS, and allows identification of patients with normal (Type 1) and abnormal (Type 2) kidneys, and with normal (Type A) and abnormal (Type B) renal perfusion. The goal of the classification and the associated clinical evaluation is to supplement existing guidelines, to provide more consistent terminology, and to offer a framework for evaluating renal ischemia and nephropathy.

Patient selection for revascularization (Figure 10). The general approach to patient selection for revascularization involves evaluating patients with appropriate manifestations (Table 2, Section 1) and performing an imaging study to confirm the diagnosis (Table 2, Section 2). Those who have vital organ injury (Table 3) should have an evaluation of baseline nephropathy (Table 5) and renal ischemia (Table 6), prior to revascularization. The best candidates for revascularization are those with vital organ injury, renal ischemia, and no nephropathy (Table 10, Figure 9). Renal stenting should be performed with

the goals of minimizing injury to the renal artery and kidney (Table 7, Figure 8). All patients should be evaluated for post-procedural nephropathy (Table 9), and should have regular follow-up. Nevertheless, the benefits of revascularization have not been definitively proven, thus the need for a large, randomized, adequately powered clinical trial such as CORAL.

Approach to hypertensive patients without vital organ injury. For asymptomatic patients < 30 years old with controlled or resistant hypertension, CTA is reasonable to diagnose FMD. Recommendations for revascularization are influenced by patient age, FMD location and distribution, hemodynamic significance of stenosis, and tolerance of antihypertensive medication. In the majority, angioplasty is appropriate to control (and likely cure) hypertension.

In older patients with new or refractory hypertension, imaging studies are reasonable to detect ARAS, but revascularization is controversial in the absence of renal ischemia or cardiovascular injury. These patients should first undergo a thorough evaluation for occult nephropathy (Table 5) and renal ischemia using nuclear renal blood flow or invasive assessment (Table 6). For patients with no nephropathy and normal renal blood flow (Type 1A), we would intensify the antihypertensive regimen and follow patients clinically for the development of vital organ injury. For patients with unilateral or bilateral ARAS, no nephropathy, and abnormal perfusion we would “reclassify” such patients as having renal ischemia (Type 1B).

Approach to hypertensive patients with vital organ injury. Hypertensive patients with manifestations of vital organ injury (Table 3) should undergo an imaging study to detect RAS. Patients with renal FMD should undergo renal angioplasty, if possible. Patients with ARAS should undergo clinical evaluation to identify nephropathy (Table 5) and renal ischemia (Table 6). The best candidates for revascularization are those with minimal or no nephropathy and renal ischemia (Type 1B). The worst candidates are those with advanced nephropathy (Type 2), especially if renal ischemia is absent (Type 2A). If performed, renal revascularization should include the technical considerations to minimize renal injury (Table 7).

Approach to renal FMD. Since 25 % of patients with renal FMD have carotid FMD, carotid duplex ultrasound is recommended if renal FMD is identified. In addition, patients with carotid FMD may have berry aneurysms of the circle of Willis, so intracranial MRA or CTA is advisable, too. Decisions about revascularization of renal FMD are simpler than ARAS, because of the high (> 80 %) cure rate and durability (90 % patency at 10 years) after angioplasty. Since hypertensive FMD patients

generally have renovascular hypertension, ACEI and ARB are usually effective. Patients who do not respond or develop vital organ injury should be considered for revascularization. Clinical follow up is recommended; uncontrolled hypertension or new vital organ injury should prompt repeat invasive evaluation.

Approach to unilateral ARAS. In patients with controlled-hypertension and no vital organ injury, we recommend assessment for nephropathy (Table 5) and renal ischemia (Table 6), before considering revascularization. If these studies demonstrate normal kidneys and no renal ischemia (Type 1A), we recommend antihypertensive therapy (including ACEI or ARB), smoking cessation, exercise, weight reduction, optimal management of hyperglycemia and hypercholesterolemia, and aspirin.

If studies demonstrate normal kidneys and renal ischemia (Type 1B), we consider this a manifestation of "unilateral" vital organ injury, and such patients could be considered for renal stenting. The physician may be confronted by a more challenging decision in patients with serum creatinine > 2 mg/dL and unilateral ARAS. In these patients, nephropathy is highly likely (Type 2), and preservation of renal function is less likely after revascularization. If such patients develop cardiovascular injury, renal revascularization may be reasonable if renal ischemia is present (Type 2B), although renal function may not improve; recommendations in these patients should be individualized.

Approach to bilateral ARAS or ARAS of a solitary kidney. Patients with bilateral ARAS or ARAS of a solitary kidney may have global severe renal ischemia, and are more prone to pulmonary edema than those with unilateral RAS. When a diagnosis of bilateral ARAS is made, the nature of the clinical evaluation is similar to the one described for unilateral ARAS, and includes a thorough assessment for nephropathy (Table 5) and renal ischemia (Table 6). The presence of advanced nephropathy (Type 2) is a predictor of poor recovery of renal function after revascularization, particularly if renal ischemia is absent (Type 2A). Although there may be benefit for preventing recurrent pulmonary edema if renal ischemia is suggested by noninvasive or invasive evaluation (Type 2B), renal function may not improve.

Patients with severe bilateral ARAS, minimal or no nephropathy, renal ischemia (Type 1B), and cardiovascular injury are ideal candidates for renal revascularization. Evidence for nephropathy may be missed if Scr is the only measure of renal function. Such patients should be considered for revascularization if nuclear GFR is < 60 cc/min/1.73 m2, even in the absence of cardiac or cerebral dysfunction, before the development of more advanced renal dysfunction. Nuclear blood flow studies and/or invasive assessment of ischemia are useful in patients with bilateral ARAS to identify the more

hemodynamically impaired renal artery, and to serve as a baseline for follow-up.

Approach to patients with end-stage renal disease (ESRD). Patients who are initiated on dialysis may have a combination of renal ischemia and ischemic nephropathy.[13] In the absence of diabetes or other confirmed nephropathy, it is reasonable to perform an imaging study to diagnose ARAS in patients who have been on dialysis for less than 1 year (Table 2, Section 1).[6] Patients with unilateral stenosis or occlusion are unlikely to benefit, but patients with bilateral ARAS or occlusion may separate from dialysis after renal revascularization (Figure 11).[116] The diagnosis of ARAS can be established noninvasively, but concerns about nephrogenic systemic fibrosis have attenuated the enthusiasm for gadolinium-enhanced MRA.[117] Conventional arteriography may be the best technique to assess morphologic suitability for stenting, and requires 10-fold less iodinated contrast than CTA.

Followup of patients with RAS. There are no specific guidelines for following patients with RAS. Our approach to all RAS patients (with or without revascularization) includes semi-annual assessment of blood pressure, Scr, and vital organ injury (Table 3). For ARAS patients, we recommend annual or bi-annual evaluation of nuclear GFR and split renal blood flow. After stenting for ARAS, we recommend repeat nuclear blood flow studies at 3 months after revascularization, once early effects of contrast and medication requirements have stabilized and annual follow up thereafter. Initial improvement in stented-kidney GFR followed by deterioration is highly suggestive of stent restenosis. Other imaging studies, particularly RDU and CTA, are potentially useful for assessment of stenosis severity, and when combined with nuclear blood flow studies can provide a nice assessment of renal perfusion and restenosis.

Novel biomarkers of kidney disease. Scr is not ideal for the diagnosis of acute renal injury[118], and assessment of contrast nephropathy and atheroembolization may improve if there are better biomarkers to assess renal injury. Cystatin C is a novel biomarker that may identify patients with subtle reduction in GFR indicative of early renal disease.[119] Neutrophil gelatinase-associated lipocalcin (NGAL) is a host-defense protein which may allow earlier detection of acute injury from contrast or other causes[118,114], and may correlate with clinically important outcomes, such as death, ICU admission, and dialysis.

CONCLUSIONS

Despite publication of the 2005 ACC/AHA guidelines, there is persistent controversy about renal artery revascularization. This controversy stems from imprecise understanding of renal vascular syndromes and their relationship to hypertension and renal dysfunction, and is compounded by failures to differentiate renal ischemia from nephropathy, resulting in confusing and conflicting data about outcomes.

Renal FMD represents the "purest" form of human renovascular disease, is commonly associated with renovascular hypertension, and is rarely associated with nephropathy. Revascularization by balloon angioplasty is associated with high cure rates of hypertension and sustained clinical benefit in the majority of patients.

In contrast, ARAS is a disease of the elderly with a high incidence of generalized atherosclerosis, multiple risk factors for coronary and peripheral arterial disease, and a strong association with many diseases known to cause nephropathy. It may be difficult to determine a causal relationship between ARAS and renal and cardiovascular dysfunction, and to differentiate the extent of renal dysfunction due to ischemia and nephropathy. These distinctions are important since the outcomes after revascularization are most dependent on the extent and reversibility of baseline renal function (which is most strongly related to nephropathy) and the degree of renal ischemia.

The 2005 ACC/AHA guidelines provide a nice template for clinical indications for evaluation of RAS, screening tests to evaluate RAS, indications for renal revascularization, recommendations for pharmacological management, and recommendations for the type of renal revascularization. It is also important to differentiate renal ischemia from nephropathy, avoid renal injury, assess nephropathy after revascularization, delineate the causes of failure of renal revascularization, and follow patients with RAS. We propose the following terminology for patients with renal vascular diseases (Table 11):

 # 1: The term "renovascular hypertension" should be reserved specifically for patients with renin-dependent hypertension, in whom revascularization is expected to cure hypertension. For practical purposes, this is true for many patients with FMD, but not with ARAS.

 # 2: Hypertension in patients with ARAS may be classified as "controlled, resistant, accelerated, or malignant", depending on the clinical circumstances. Patients with ARAS and hypertension should not

be classified as having “renovascular hypertension”, since there is no compelling evidence that ARAS causes hypertension, and cure of hypertension after revascularization is rare.

 # 3: The term “renal ischemia” should be reserved for patients with RAS and abnormal renal perfusion (unilateral or bilateral).

 # 4: The term “renal artery stenosis” should be used for patients with “anatomic” stenosis, but has no implications regarding renal ischemia.

#5: The term “nephropathy” should be reserved for patients with renal parenchymal disease. “Ischemic nephropathy” should be reserved for patients with renal parenchymal disease associated with longstanding atherosclerosis and intra-renal arteriolar disease. Other forms of nephropathy may be based on the presence of known diseases, such as diabetes (diabetic nephropathy), hypertension (hypertensive nephropathy), interstitial diseases (interstitial nephropathy), or may be acquired as a complication of revascularization (acute tubular necrosis, contrast nephropathy, and renal embolization).

Medical therapies, particularly antihypertensive drug therapy and therapies to limit atherosclerosis, are the primary therapies for all patients with RAS. The optimal use of renal artery revascularization is poorly defined. Contemporary decisions about renal revascularization must include an assessment of the severity and functional significance of RAS (renal ischemia), the condition of the kidneys (nephropathy), and the association between RAS and vital organ injury. The benefits and risks of renal revascularization will be improved by careful patient selection. Better results will be achieved in patients with vital organ injury, renal ischemia, and no nephropathy. Appropriately designed randomized clinical trails are essential to define the role of renal revascularization. Such trials must incorporate assessment of renal ischemia and nephropathy, since these factors have the strongest influence on outcome.

FIGURE LEGENDS

Figure 1. The most common types of renal artery stenosis (RAS). Left, fibromuscular dysplasia (FMD), characterized by a beaded appearance of the mid or distal renal artery in which the beads are larger than the vessel (medial fibroplasia). Right, atherosclerotic renal artery stenosis (ARAS), characterized by stenosis of the ostium and proximal renal artery.

Figure 2. Endovascular revascularization of ARAS. Left, baseline image before intervention (same as Figure 1, right panel). Middle, suboptimal angiographic result after balloon angioplasty, characterized by significant residual stenosis, elastic recoil, and dissection (arrow). Right, final result after stent placement demonstrates optimal lumen enlargement.

Figure 3. Schematic representation of common configurations of renal arterial origins from the abdominal aorta. A, single renal artery occurs in 55 % of population. B, Single renal artery with early bifurcation occurs in 14 % of population. C, dual arterial circulation in which two major renal arteries supply a single kidney, occurs in 8 % of population. D, single major renal artery and one or more smaller accessory renal arteries, occur in 7 % of population. Other configurations (not shown) occur in 16 %, including aberrant origins of the renal arteries from other visceral vessels, iliac arteries, and aortic bifurcation. (Modified from Uflacker R. Atlas of Vascular Anatomy.2nd edition. Philadelphia, PA: Lippincott, Williams, and Wilkins, 2007:609.

Figure 4. Conventional abdominal aortogram using digital subtraction angiography (AP projection) demonstrating early (left), mid (middle), and late (right) phases of the contrast injection. Aortography is used to identify the configuration of the renal arterial origin (see Figure 3) as well as associated

disease of the abdominal aorta and visceral circulation.

Figure 5. Arteriographic patterns of progressive nephropathy. A, normal kidney (renal resistive index [RRI] 0.6) with normal cortical blood flow and intrarenal arteriolar circulation. B, mild hypertensive nephropathy (RRI 0.7) with mild diffuse intrarenal arteriolar narrowing and preserved cortical flood flow. C, advanced hypertension and ischemic nephropathy (RRI 0.8), with diminished cortical blood flow, vascular pruning (arrows), and diffuse intrarenal arteriolar narrowing. D, end-stage kidney due to hypertensive nephropathy (RRI 0.9). with no cortical blood flow and extensive intrarenal arteriolar disease.

Figure 6. Schematic representation of the kidney as a filter. Overall filter function is influenced by inflow to the filter (RAS and renal ischemia), integrity of the filter (nephropathy), outflow from the filter (renal vein obstruction), and disorders of collection (obstructive uropathy).

Figure 7. Relationship between glomerular filtration rate (GFR) and serum creatinine concentration. Loss of 50 % of GFR is not associated with measurable elevation of serum creatinine. When > 75 % of GFR is lost, there is a strong relationship between GFR and serum creatinine. (Modified from reference 35)

Figure 8. Schematic illustrations of invasive techniques to avoid renal artery injury and atheroembolization during renal artery stenting. Left, catheter-in-catheter technique employs a tapered 4 or 5 French soft-tip diagnostic catheter loaded inside a 6 or 7 French guiding catheter. After engaging the renal artery with the diagnostic catheter, the 0.014 inch angioplasty wire is advanced across the stenosis and positioned distally. The guiding catheter is advanced over the diagnostic catheter, and once positioned the diagnostic catheter is removed. Right, the no-touch technique utilizes a 0.035-inch J wire inside the guiding catheter, to lift the tip off the aortic wall. With the 0.035-inch wire in place, the guiding catheter is aligned with the renal artery, and a 0.014-inch guidewire is used to cross the stenosis. The 0.035”-inch guidewire is removed, and the guiding catheter is advanced over the 0.014-inch wire to engage the renal artery.

Figure 9. Schematic illustration of disorders of nephropathy (Type 1 or 2) and renal ischemia (Type A or B). Type 1A=normal kidneys, no renal ischemia: In the presence of unilateral or bilateral atherosclerotic renal artery stenosis (ARAS), serum creatinine (Scr), total glomerular filtration rate (GFR), and single-kidney GFR (SK-GFR) are normal, and renal perfusion is symmetric. Type 1B=normal kidneys, renal ischemia: In the presence of renal ischemia and unilateral ARAS, Scr is

normal, but total GFR and stenotic kidney GFR are depressed, and renal blood flow is asymmetric. With bilateral RAS, Scr is normal, but total-and SK-GFR are depressed. Renal blood flow may be symmetric (shown here) or asymmetric. Type 2A=nephropathy, no renal ischemia: In the presence of unilateral or bilateral ARAS, Scr, total GFR, and SK-GFR are abnormal, and renal perfusion is symmetric. Type 2 B=nephropathy, renal ischemia: In the presence of unilateral ARAS, Scr, total GFR, and SK-GFR are abnormal, and renal perfusion is asymmetric. With bilateral ARAS, Scr, total GFR, and SK-GFR are abnormal, and renal blood flow may be symmetric (shown here) or asymmetric. Invasive assessment of renal ischemia may be useful, and complements the nuclear blood flow evaluation (see Table 6), particularly when nephropathy is present.

Figure 10. Algorithm for the evaluation, treatment, and followup of patients with renal artery stenosis.

Figure 11. Renal arteriographic findings in a 72 year old man with end-stage renal failure on dialysis for 7 months. Left and right panels demonstrate chronic total occlusion of the right and left renal arteries, respectively (top), high grade residual stenosis and dissection after balloon angioplasty (middle, arrows), and widely patent renal arteries after stenting (bottom). He remained off dialysis for 7 years following revascularization with a stable serum creatinine of 1.5-1.7 mg/dL, but died after a large stroke due to cardiac embolization from atrial fibrillation.

Table 1. Contemporary evaluation of renal vascular diseases.

Causes of Renal Artery Stenosis (RAS)

- Fibromuscular dysplasia (FMD)
- Atherosclerotic renal artery stenosis (ARAS)
- Inflammatory diseases and vasculitis
- Congenital abnormalities

Clinical manifestations of RAS (see Table 2, Section 1).

- Hypertension: Resistant, accelerated, and malignant
- Renal: Acute and chronic renal failure
- Cardiovascular: Acute cardiac, aortic and cerebral injury

Diagnosis of RAS (See Table 2, Section 2).

- Rely on imaging techniques (RDU, MRA, CTA)
- Invasive angiography in select patients (Table 4)
- Avoid assessment of renin activity

Assess relationship between RAS and vital-organs

- Renal, cardiac, and cerebral injury (Table 3)
- Distinguish renal ischemia from nephropathy (Table 5, Table 6)

Avoid renal injury during revascularization (Table 7)

Arrange appropriate follow-up

Abbreviations: RDU=renal duplex ultrasound, MRA= magnetic resonance angiography, CTA=computerized tomography angiography

Table 2. ACC/AHA guidelines for renal arterial disease (6)

	Level of Evidence	Class
1. Clinical indications for evaluation for RAS		
HYPERTENSION MANIFESTATIONS		
Hypertension onset age < 30 (FMD)	B	I
Hypertension onset age > 55 (ARAS)	B	I
Resistant hypertension	C	I
Accelerated hypertension	C	I
Malignant hypertension	C	I
RENAL MANIFESTATIONS		
Acute renal failure after ACEI/ARB	B	I
Unexplained small kidney	B	I
Asymmetry in renal dimensions > 1.5 cm	B	I
Unexplained Chronic renal failure	B	II A
New Dialysis	B	II A
CARDIOVASCULAR MANIFESTATIONS		
Unexplained pulmonary edema	B	I
Multivessel CAD alone	B	II B
PAD alone	B	II B
Unexplained CHF	C	II B
Refractory angina	C	II B

2. Screening tests for RAS

RDU, MRA, CTA	B	I
Contrast angiography for ambiguous noninvasive	B	I
tests	C	I I I
Captopril renal scintigraphy	B	I I I
Selective renal vein sampling	B	I I I
Plasma renin activity	B	I I I
Captopril stimulated renin secretion		

3. Indications for revascularization*

Asymptomatic bilateral ARAS	C	I I B
Asymptomatic solitary ARAS	C	I I B
Asymptomatic unilateral ARAS	C	I I B
RAS and Class I indications for RAS evaluation	B	I I A
RAS and intolerance to medication	B	I I A
Bilateral ARAS and progressive renal dysfunction	B	I I A
Solitary ARAS and progressive renal dysfunction	B	I I A
Unilateral ARAS and chronic renal dysfunction	C	I I B
ARAS and unexplained pulmonary edema	B	I
ARAS and unexplained recurrent CHF	B	I
ARAS and unstable angina	B	I I A

4. Recommendations for pharmacological treatment		
ACEI or ARB for RAS and hypertension	A	I
Calcium channel blockers for RAS and	A	I
hypertension	A	I
B-blockers for RAS and hypertension		
5. Type of renal artery revascularization		
Renal stent for ARAS patients who meet criteria	B	I
Angioplasty for FMD, with bailout stenting	B	I

*Assumes hemodynamically significant ARAS (See Table 4A)

Abbreviations: ACC/AHA=American College of Cardiology/American Heart Association, RAS=renal artery stenosis, FMD=fibromuscular dysplasia, ARAS=atherosclerotic renal artery stenosis, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, CAD=coronary artery disease, PAD=peripheral arterial disease, CHF=congestive heart failure, RDU=renal duplex ultrasound, MRA=magnetic resonance angiography, CTA=computerized tomography angiography.

Class I – conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.

Class II – Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa – Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb – Usefulness/efficacy is less well established by evidence/opinion.

Class III – Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful / effective and in some cases may be harmful.

Level of Evidence A – Data derived from multiple randomized clinical trials or meta-analyses.

Level of Evidence B – Data derived from a single randomized trial or nonrandomized studies.Level of Evidence C – Only consensus opinion of experts, case studies, or standard-of-care.**Table 3.**

Manifestations of vital organ injury

Renal ischemia

- Acute renal failure
- Chronic renal failure
- Unilateral small kidney
- Renal hypoperfusion

Cardiovascular injury

- Hypertension and unexplained pulmonary edema
- Hypertensive crisis and acute coronary syndrome
- Hypertensive crisis and acute aortic syndrome

Cerebrovascular injury

- Transient ischemic attack
- Stroke
- Intracranial hemorrhage
- Papilledema
- Encephalopathy

Table 4. Goals of invasive angiography for RAS

Confirm the diagnosis and etiology of RAS (see Figure 1)

Identify dual, accessory, or aberrant renal arteries (see Figure 3).

Identify aneurysmal and occlusive diseases of the aorta and visceral circulation (see Figure 4)

Evaluate the nephrogram (see Figure 5).

- Patterns of intra-renal arteriolar disease
- Adequacy of cortical blood flow
- Renal dimensions
- Neovascularity

Abbreviations: RAS=renal artery stenosis

Table 5. Clinical evaluation of renal parenchymal disease (nephropathy)

Factor	Comment
Serum creatinine	Easy to measure and inexpensive. Relatively insensitive to degree of renal dysfunction (see Figure 7), and not reliable for differentiating nephropathy from renal ischemia.
Proteinuria	Easy to measure and inexpensive. Proteinuria ≥ 1 gram/24 hour is a good indication of nephropathy, but lesser degrees of proteinuria are less reliable.
Renal dimensions	Renal length 10 – 12 cm is generally favorable. Renal length ≤ 6 cm indicates irreversible renal injury (atrophic kidney).
Renal resistive index (RRI)	RRI < 0.7 is a good measure of reversibility. Although RRI > 0.8 indicates parenchymal disease, it should not be used as the sole indicator of irreversible renal dysfunction.
Renal arteriogram	Preservation of cortical blood flow and absence of intra-renal arteriolar disease are indicators of reversible renal dysfunction. Poor cortical blood flow and severe diffuse intra-renal arteriolar disease are markers of advanced nephropathy (see Figure 5).
Renal Biopsy	Reliable for histologic confirmation of nephropathy, but not practical for most patients

Table 6. Clinical evaluation of renal artery perfusion and renal ischemia

Noninvasive assessment of renal blood flow
^{125}I-Iothalamate GFR (Total GFR)
^{99M}Tc-DTPA (Split renal function and single-kidney GFR)
Invasive assessment of significance of RAS
Percent diameter stenosis by visual estimates or quantitative angiography
Translesional pressure gradient (TLG)
Fractional flow reserve (FFR)
Intravascular ultrasound (IVUS)
Renal frame counts (RFC)
Renal blush score (RBS)

Abbreviations: GFR= glomerular filtration rate, RAS=renal artery stenosis, ^{99M}Tc-DTPA= technetium-labeled pentetic acid.

Table 7. Technical considerations to avoid renal injury during renal stenting

Avoid injury to renal artery ostium
Minimize catheter manipulation
No-touch technique (Figure 8)
Catheter-in-catheter technique (Figure 8)
Minimize contrast nephropathy
Hydration
Limit contrast volume
Prevent distal embolization
Distal embolic protection devices (?)
Glycoprotein IIb / IIIa inhibitors (?)

Table 8. Causes of failure of renal revascularization

Failure to improve / cure hypertension

- Stenosis is not hemodynamically significant (no renal ischemia)
- Hypertension is “essential,” not “renovascular”
- Renal parenchymal disease and self-perpetuating hypertension
- Intra-renal vascular disease
- Suboptimal revascularization result

Failure to improve / stabilize renal function

- Stenosis is not hemodynamically significant (no renal ischemia)
- Inability to detect improvement using serum creatinine
- Pre-existing renal parenchymal disease
- Contrast nephropathy
- Renal embolization
- Acute tubular necrosis

Table 9. Assessment of worsening renal function (nephropathy) after renal revascularization

	Acute Tubular Necrosis	Contrast Nephropathy	Distal Embolization
Clinical Features	Hypotension and blood loss	None	None
Creatinine	Steady and progressive rise	Rises within 2-4 days of procedure; peak at 7 days	Steady and progressive rise; may occur days or weeks after intervention
Urinalysis	Normal	Normal	Normal; Microhematuria is uncommon; eosinophils may be present
Urine sodium	Increased	Normal	Normal
Urine output	Oliguria	Normal or oliguria	Normal
Treatment	Correct cause, hydration	Hydration	Hydration
Diuretics	Avoid	Avoid	Avoid

Table 10. Classification of RAS, renal perfusion and renal parenchymal disease

Type	I A	I B	II A	II B
Perfusion	NL* No	Renal ischemia No	NL* Yes	Renal ischemia Yes
Scr **Proteinuria**	NL No	URAS – NL BRAS – NL or ↑ No	NL or ↑ May be present	NL or ↑ May be present
RRI	< 0.7	< 0.7	> 0.8	> 0.8
Arteriolar narrowing	None	None or mild	Yes	Yes
Arteriolar pruning	None	None	Yes	Yes
Cortical blood flow	NL	NL	↓	↓
Biopsy	NL	NL	Abnormal	Abnormal
Nuclear GFR	NL	URAS: NL BRAS: NL or ↓	↓	URAS: ↓ BRAS: ↓
DTPA Split Function	URAS: SYM BRAS: SYM	URAS: ASYM BRAS: SYM or ASYM	URAS: SYM BRAS: SYM	URAS: ASYM BRAS: SYM or ASYM
TLG	None	≥ 20 mmHg	None	≥ 20 mmHg
FFR	NL	< 0.8	NL	< 0.8

*These patients have "anatomic" RAS, but no renal ischemia (normal perfusion)

Abbreviations: Scr=serum creatinine, RRI=renal resistive index, GFR= glomerular filtration rate, DTPA=^{99M}-Tc-labeled pentetic acid, TLG=translesional pressure gradient, FFR=fractional flow reserve, URAS=unilateral renal artery stenosis, BRAS=bilateral renal artery stenosis, NL=normal, ↑=increased, ↓=decreased, SYM=symmetric, ASYM=asymmetric.

Table 11. New terminology for renal vascular diseases

HYPERTENSION

Renovascular Hypertension: Renin-dependent hypertension, typical of young patients with FMD; characterized by high likelihood of cure of hypertension after revascularization.

Essential Hypertension: Typical form of hypertension in the elderly, associated with manifestations of atherosclerosis; causal relationship between ARAS and hypertension is absent.

Controlled hypertension: Blood pressure controlled with ≤ 2 medications according to current guidelines.

Refractory hypertension: Blood pressure exceeds current guidelines despite ≥ 3 medications.

Accelerated hypertension: Previously controlled hypertension becomes progressively uncontrolled, exceeds current guidelines, and remains poorly controlled despite multiple additional medications.

Malignant hypertension: Uncontrolled hypertension associated with acute renal or cardiovascular injury.

RENAL ARTERY STENOSIS (NO ISCHEMIA)

Unilateral RAS: Anatomic unilateral RAS without objective renal ischemia

Bilateral RAS: Anatomic bilateral RAS without objective renal ischemia

RENAL ISCHEMIA

Unilateral RAS: Objective renal ischemia in the distribution of the stenotic renal artery

Bilateral RAS: Objective renal ischemia in one or both renal arteries.

NEPHROPATHY (PARENCHYMAL DISEASE)

Ischemic nephropathy: Renal parenchymal disease due to long-standing intra-renal arteriolar disease associated with generalized atherosclerosis.

Diabetic Nephropathy: Renal parenchymal disease due to long-standing diabetes.

Hypertensive Nephropathy: Renal parenchymal disease due to long-standing hypertension, intra-renal arteriolar disease, and self perpetuating hypertension

Other Nephropathies: Renal parenchymal diseases associated with other known glomerular or interstitial renal diseases.

Procedure Related Nephropathy: Acquired parenchymal injury (transient or permanent) that may be related to acute tubular necrosis, radiographic contrast, renal embolization, or other causes.

Abbreviations: FMD=fibromuscular dysplasia, RAS=renal artery stenosis, ARAS=atherosclerotic renal artery stenosis

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Public Health Approaches to Hypertension Control

Kevin Piggott, MD, MPH and Velma Theisen RN, MSN

Essential Points

1. Public health interventions include population-based initiatives and strategies targeting higher risk groups.

2. Prevention of high BP includes a healthy lifestyle with a focus on maintaining a healthy weight, reducing excess dietary sodium, adequate intake of fruits, vegetables, and potassium as well as on regular physical activity and avoidance of excessive alcohol intake.

3. Public health provides leadership for incorporation and application of evidence-based guidelines including screening recommendations, clinical diagnosis and management, along with policy changes to increase control of high BP.

4. Public health supports general population awareness initiatives including media campaigns, educational material targeted for populations at higher risk and partnership with other organizations such as during National High Blood Pressure month or other national campaigns.

5. Public health monitors and reports epidemiological data, supports national risk factors surveys, and identifies gaps and opportunities for reducing the burden of high BP in Michigan.

Objectives:

1. To describe the burden and impact of uncontrolled high blood pressure in Michigan.
2. To identify key primary prevention interventions for controlling high BP.
3. To provide resources and references for public health interventions to improve high BP control.

Pre/post Test questions:

1. The prevalence of high BP increases with
   a. Advancing age
   b. African American populations
   c. Increasing overweight
   d. All of the above

2. Prehypertension is a classification introduced in the last national guidelines (JNC VII) and refers to
   a. Readings between 130-139/85-89
   b. “White coat hypertension”
   c. Readings between 120-139/80-89
   d. Readings at 140/90

3. The role of public health in controlling hypertension is
   a. Describing and reporting the burden
   b. Developing population-based and targeted strategies to reduce the burden
   c. Assuring implementation of appropriate health measures

d. All of the above
e. None of the above

4. The National Institutes of Health provides periodic updates to national hypertension guidelines for health professionals and the latest report is
   a. 2006 Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure
   b. Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation and Treatment of High Blood Pressure
   c. Trends in Prevalence, Awareness, Treatment and Control of Hypertension in the United States
   d. None of the above

5. Policy changes improving control of hypertension might include
   a. Regulating the amount of sodium added to foods
   b. Enhancing third-party coverage of prescriptions for treating hypertension
   c. Supporting pay-for-performance initiatives that target hypertension control
   d. All of the above

Public Health measures that promote prevention and enhance control of hypertension are effective means to reduce leading causes of death such as stroke, kidney disease and heart disease. The core functions of public health, - assessment, policy development and assurance - are described in this chapter to identify public health approaches to hypertension control. Public health approaches focus on population-wide strategies with an emphasis on prevention, early detection and quality assurance. The traditional medical focus tends to be downstream where the focus is on diagnosis and treatment of individuals This is substantiated by estimates that the U.S. spends 95% of the trillions of healthcare dollars on direct medical services and only 5% on public health approaches. Yet, medical services as a determinant of health accounts for only 10-15% of all preventable mortality. Social circumstances, behavioral choices and environmental conditions are determinants that account for 55-60% while genetics accounts for about 30%.[1] The following sections will review hypertension from the public health perspective of health assessment, policy development and assurance.

Health Assessment:

The public health burden of hypertension in the U.S. is substantial. It is estimated that over 70 million adults, 18 yrs and older, have hypertension for a prevalence of 29 to 31%.[2,3] It is the most common primary diagnosis in the outpatient setting with 35 million visits in 2002 [4]and represents $69.4 billion dollars in direct and indirect healthcare expenditures in 2008.[5] Additionally, an estimated 31% of adults have prehypertension with the prevalence being greater amongst men (40%) than women (23%).[6] In the U.S., BP increases with age and a majority of adults have hypertension by the sixth decade of life. By the seventh to eighth decade hypertension is present in ≥ 70% of this population.[7] Blood pressure has a continuous positive relationship to cardiovascular risk and begins at BP levels even below the pre-hypertensive range. In fact CVD mortality doubles every 20/10 mm Hg above 115/75 mm Hg. Hypertension is also a significant risk factor for cerebrovascular disease, chronic kidney disease and peripheral vascular disease. Hypertension in the U.S. accounts for 49 percent of episodes of heart failure as well as 35 percent of myocardial infarctions and strokes.[8] Considering that heart disease is the leading cause of death and cerebrovascular disease is the third leading cause; hypertension has a significant impact on mortality in the U.S.[9] The Behavioral Risk Factor Survey (BRFS), a telephone survey conducted by the Michigan Department of Community Health (MDCH) has

monitored hypertension screening and control for over a decade.[10] Previous BRFS results showed that 95 % of the respondents have had their BP measured and the latest Michigan BRFS reported 29% having ever been told by a physician they had high BP. Of those who had been told they had high BP, 79.4% reported taking blood pressure medication. The BRFS also monitors and reports other behavioral risk factors such as weight, fruit and vegetable intake, physical activity and cigarette smoking. A summary of selected risk factors from the 2007 BRFS results compared to the U.S. average is shown below:

	Overweight	Less Than 5 Fruits Vegetables/Day	No Leisure Physical Inactivity	Cigarette Smoking
Michigan	64.6 %	78.7%	20.9%	21.1%
U.S.	63%	75.7%	23%	19.7%

In 2006 the BRFS reported only 4.8% of Michiganians were practicing four key healthy lifestyles - a healthy weight, eating 5 fruits and vegetables per day, engaging in regular physical activity and not smoking.[10] Evidence from studies show that these healthy lifestyles are efficacious in preventing and controlling essential hypertension. The following information describes the role of these behaviors in hypertension.

The established modifiable risk factors for hypertension described in The Seventh Report of the Joint National Committee are as follows; 1) excess body weight, 2) excess dietary sodium intake, 3) inadequate intake of fruits, vegetables, and potassium, 4) physical inactivity, and 5) excess alcohol intake.[11] Family history of hypertension and African American ancestry are risk factors for hypertension and although not modifiable they can be identified and monitored. Identification of those who meet the criteria for prehypertension is also important to focus the public, patients, and physicians on the importance of this BP range. JNC VII makes it clear that prehypertension is not a disease category. Rather, its purpose is to be an alert to promote intervention by the adoption of healthy lifestyles in hopes of preventing or delaying the development of hypertension.

Excess body weight increases hypertension and is an increasing problem in the U.S. According to NHANES data, obesity (defined as a BMI ≥ 30 kg/m^2) has increased from 22.9% in 1988-1994 to 32.2% in 2003-2004 time periods.[12,13] Overweight and obesity combined (defined as a BMI ≥ 25 kg/m^2) has increased from 55.9% in NHANES 1988-1994 to 66.3% in NHANES 2003-2004. In the Framingham Heart Study, a 5% weight gain over 4 years was associated with a 20 – 30% increased odds of hypertension.[14] A BMI of 25.0-29.9 is associated with a 2.4 times relative ten year risk of developing hypertension among men and 3.8 times and 4.2 times relative ten year risk for a BMI of 30-34.9 and ≥ 35 respectively.[15] A 4.5 kg (10 pounds) weight loss can reduce BP and/or prevent hypertension in a large proportion of overweight persons with an anticipated 5 – 20 mmHg systolic blood pressure reduction per 10 kg (22 pounds) loss.[11] Ideally, maintaining a healthy weight throughout one's lifetime is preferred.

Consuming a diet less than 2,300 mg of sodium per day (about 1 teaspoon of salt) is currently recommended for most Americans; except individuals with hypertension, blacks and middle-aged and older adults who should consume less than 1,500 mg.[16] The average American diet contains 3,375 mg per day.[17] Decades of research support a causal relationship between dietary sodium intake and elevated BP.[18] Multiple meta-analyses of randomized controlled studies have found significant reductions in BP associated with a reduction in sodium intake.[18] A reduction of 100 mmol/day of sodium intake resulted in a 0.75 – 3.57 mm Hg decrease in SBP and a 0.1 – 1.66 reduction in DBP. Importantly, lowering sodium intake by just 44 mmol/L demonstrated a 38% reduction in the incidence

of hypertension.[19] Furthermore, there appears to be a graded response in BP to lower sodium consumption.[20]

Further dietary approaches include eating a diet high in fruits, vegetables and low fat dairy products but low in saturated and total fat.[11] This is the foundation of the recommended Dietary Approaches to Stop Hypertension (DASH) eating plan. This plan is high in potassium from the fruits and vegetables as well as high in calcium from low-fat dairy products. Meats are limited. Implementing such a diet is believed to lower systolic blood pressure by 8 – 14 mm Hg.[11,20] A combination of DASH diet and sodium reduction has effects on blood pressure equivalent to single drug therapy.[20]

In persons who are physically inactive, the risk for developing hypertension is 30-50% greater than for those physically fit.[18] Increasing aerobic exercise has been shown to reduce BP in both hypertensives and non-hypertensives. This inverse relationship has been noted at all ages, in both genders, and in racial subgroups. It is independent of body weight. As a result, exercising for at least 30 minutes per day the majority of the days of the week is recommended. In doing so, it may be reasonably anticipated to reduce SBP by 4 – 9 mm Hg.[11]

Excess alcohol intake is associated with elevated BP.[21-23] In the ARIC study, it was found that drinking alcohol in amounts greater than 210 g per week (3 alcoholic beverages) was associated with a greater risk of developing hypertension in normotensive persons after 6 years of follow-up. The risk was greatest in African American men.[24] Reduced alcohol consumption in normotensive men has been shown in a meta-analysis to reduce SBP by almost 4 mm Hg and diastolic by approximately 2 mm Hg.[24] It is therefore recommended that men have no more than 2 alcoholic beverages per day and for women, no more than one.

The classification of prehypertension (BP of 120-139/80-89) was introduced in JNC VII essentially replacing the prior category of “high normal” (BP of130-139/85-89) and a range that had been considered “normal” (BP of 120-129/80-84). The significance of this classification is to highlight the importance of the increased cardiovascular risk associated with this range of BP’s and to initiate appropriate lifestyle changes to prevent or delay the development of hypertension. Progression to hypertension from “normal” and “high normal” BP’s during a median of 10.9 years of follow-up was 37.3% and 58.1% respectively.[25] Prehypertension is associated with an increased risk of left ventricular hypertrophy, coronary artery disease, myocardial infarction, and renal arteriosclerosis.[26] It is also associated with an increased cardiovascular and all-cause mortality.[27] Utilizing the lifestyle measures of reduced sodium intake, DASH eating plan, physical activity, maintaining a healthy weight or losing weight if overweight or obese and limiting alcohol consumption can be effective to lower prehypertensive BPs but the impact on outcomes is largely unknown.[28] Pharmacotherapy for uncomplicated prehypertension is not currently recommended.[28,26,11] The PREMIER clinical trial [29] showed that a behavioral program of weight loss, sodium reduction, increased physical activity, limited alcohol intake and the behavioral program with the DASH eating plan can reduce systolic and diastolic BP. Furthermore, both interventions were superior to advice alone.

Implementation of healthy lifestyle changes in the current healthcare system is challenging. The identification of hypertension risk factors is a preventive service and the United States Preventive Services Task Force (USPSTF) does recommend screening for high BP in adults. However, Yarnall et.al. have shown that 7.4 hours per day is needed for the provision of preventive services alone in the current model of healthcare delivery.[30] When hypertension is identified, receiving recommended care occurs only 64.7% of the time and when counseling or education is a recommended service, it is received only 18.3 % of the time.[31] There are movements to reform the current acute care model, such as the patient centered medical home, which may improve the ability to provide these services The complexities of our healthcare system that preclude the delivery of recommended services are beyond the scope of this chapter, but they need to be addressed and not ignored. Likewise, it is important to take seriously what is important to patients and incorporate their preferences in clinical decision making.[32]

Policy Development: Public health professionals contribute to policy development by supporting legislation, or working with organizations to change their internal policies. One well-known public health effort is smoke-free initiatives. Increasing of taxes, supporting local regulations, encouraging smoke-free worksite policies, encouraging coverage of smoking cessation treatment, and smoke-free legislation for public places are a few of the examples. Similar initiatives either are being done or could be done in hypertension. Some examples are as follows:

1) Supporting improvements in coverage of prescriptions for hypertension control. Working with employer groups and insurers to recognize the importance of eliminating barriers, both cost and convenience to enhance adherence to antihypertensive treatment.
2) Policies encouraging adequate physical activity in the schools, encouraging healthy choices in school lunch programs, and supporting community design that encourages physical activity, all are important strategies to prevent obesity and therefore reduce future hypertension.
3) Policies that encourage restaurants and food manufacturers to label healthy food choices, the ingredients on products provide information to consumers so they can make healthy food decisions.
4) Working with food producers to limit added salt in food products.
5) Encouraging farm markets and increasing fresh foods at locations such as convenience stores where there are limited choices in many poorer communities.

Assurance: Public health initiatives have been implemented to increase the utilization of evidence-based clinical guidelines for hypertension.
Examples include the following:

1) Working with the Michigan Quality Improvement Consortium (MQIC), MDCH representatives and staff have provided input to MQIC to support the assurance that physicians will follow the latest hypertension guidelines. The MQIC guidelines are disseminated statewide and are used by health organizations in pay for performance and other practice performance evaluations.
2) Another role includes disseminating training material, supporting educational resources, screening forms and other material to provide guidance for appropriate community hypertension services.
3) Public health supports services for high-risk, underserved populations. Free or low-cost clinics provide the screening and treatment needed for these populations.
4) Public health programs focus on media and public education campaigns to inform the population about the importance of periodic screening, high BP control, appropriate treatment goals and treatment modalities. Providing services to the medically underserved is a critical component of public health. Collaboration with partners like the National High Blood Pressure Education Program and/or the American Heart Association, public health staff annually plan a range of educational or media events during National High Blood Pressure Month.
5) Special MDCH projects have been funded: grants to health plans to enhance the tracking and process improvement activities for members diagnosed with high BP to increase control rates, a self-instructional BP measurement quality improvement program has been developed and disseminated to health professionals statewide, projects in worksites have focused on increasing access to hypertension services.
   MDCH projects have incorporated and trained public health staff in the latest clinical guidelines such as the Maternal and Child Infant Program's nursing interventions for

pregnant women with hypertension and the WISEWOMAN program that screens and counsel's low-income middle-age women primarily through local health departments for high BP and other cardiovascular risks.

The above examples are a few of the efforts that public health has made to contribute to the detection, treatment and control of hypertension in Michigan. The role of public health differs from traditional clinical settings because public health considers population-based approaches. The role of assessment, policy leadership and assurance are supportive of clinical medicine and complement the effort to prevent and control hypertension in our population.

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Hypertension Is Not Asymptomatic

John M. Flack, MD, MPH

Hypertension has long been dubbed the “silent killer”. As with virtually any myth, there is typically at least a grain of truth inside the myth. Accordingly, some patients with hypertension do not have any recognizable symptoms. However, many other patients do experience symptoms, although few of the symptoms are specific to the hypertensive condition.

A significant reason why many hypertension trials report that antihypertensive drugs that lower blood pressure (BP) are tolerated equivalent to placebo has to do with how BP-related symptoms are ascertained. In most pharmacological hypertension clinical trials the reported side effects/symptoms are only ascertained when the patient volunteers that they are experiencing something unusual. However, in other trials where side effects/symptoms were ascertained at each visit, by staff blinded typically blinded to treatment status, using a sensitive side effect instrument, a different reality emerges.[1,2,3] That is, there are several lines of evidence that hypertension does cause symptoms. First, is that pharmacological treatment that lowers BP results in fewer BP-related symptoms than placebo[1] in this study[2] and others[4,5], quality of life was also better in participants taking antihypertensive medications than placebo. Second, is that the burden of BP-related symptoms is greater at higher than lower levels of BP.[3] Finally, though this evidence is a bit more indirect, several trials have reported greater persistence on antihypertensive drug treatment than placebo[6], an observation consistent with the occurrence of fewer side effects during active antihypertensive treatment.

What complaints fall under the heading of pressure-related symptoms? Weakness, fatigue, sleep disturbance, nervousness, headache, and chest pain have all been linked to higher BP levels and, in turn, when BP levels fall, the intensity of these symptoms declines in parallel. Obviously none of these complaints either individually or even in aggregate are specific enough to diagnose hypertension by. On the other hand, when you are treating patients with hypertension it is very reasonable to query patients regarding these symptoms and to note the change in their intensity as the BP falls during treatment. There is one caveat though based on years of clinical experience that is important. Some patients feel worse before they feel better during pharmacological BP lowering. Thus, warning the patient that they may transiently feel worse before they feel better is an important strategy in preventing abrupt discontinuation of prescribed medications that are responsible for the fall in BP. In the patients

mind they will have no problem identifying that the onset of feeling bad was preceded by the new medication(s) you put them on. Transiently feeling "bad" typically lasts a few days to a week or slightly longer. However, when it occurs, it is almost always an easily misinterpreted sign of success.

It is important to realize that not every patient has symptoms. I have cared for patients with systolic BP levels in excess of 200 mm Hg and highly focused and probing history taking could not elicit any complaints, either general or specific, that might be construed as pressure-related. On the other hand, there are countless other patients with much more modest BP elevations who have many or all of the aforementioned pressure-related symptoms. Many of these individuals also report resolution of these symptoms with the fall in BP that occurs during the intensification of antihypertensive drug therapy. However, the existence of pressure-related symptoms in no way discounts the existence of drug- or antihypertensive drug class-specific symptoms.

The relevance of recognizing that BP elevations are related to and appear to cause symptoms should be self-evident. When drug-treated patients with poorly controlled BP are complaining of not feeling well they are most often, in my experience, complaining of pressure-related side effects. Other patients perceive that they are experiencing drug-related side effects whenever their antihypertensive drug regimen is changed; much of the time they are actually experiencing transient symptomatology related to the fall in their BP. Thus, if you are constantly changing their antihypertensive medications to try and find medications that won't cause side effects you are embarking on a fruitless journey. The only drugs not likely to be perceived as causing side effects in these patients are drugs that don't effectively lower BP. Often times the most appropriate therapeutic decision to make when patients complain of drug-related symptoms, that are in reality pressure-related symptoms, is to intensify treatment and warn them about transient symptoms that may occur when the BP falls rather than switching antihypertensive medications in the misguided attempt to find the drug that does not cause symptoms.

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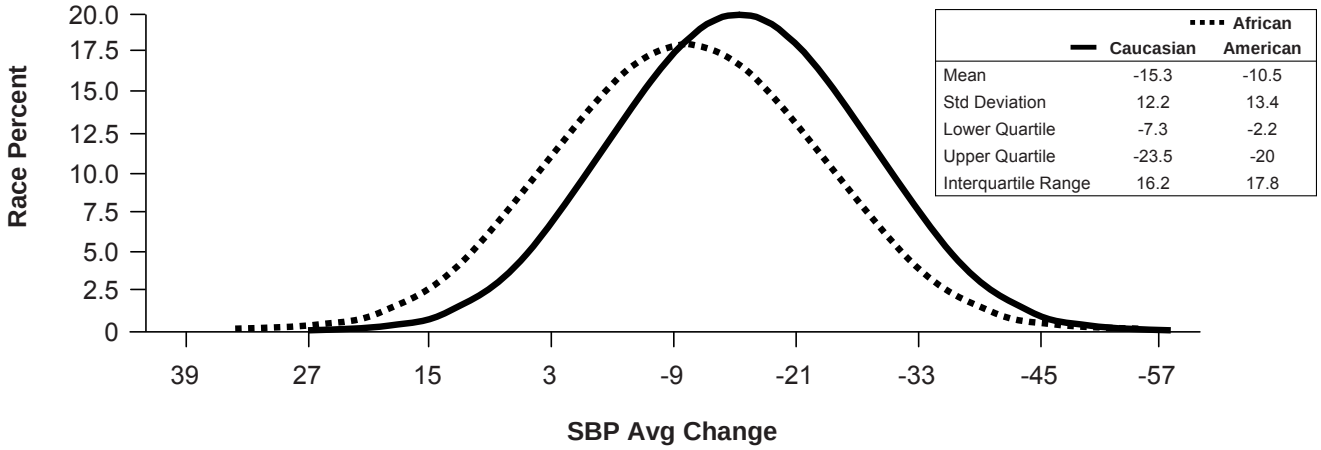
Role of Race in the Selection of Antihypertensive Drug Therapy

John M. Flack, M.D., M.P.H.

Race has long been a primary consideration when selecting antihypertensive drug therapy. Numerous studies have shown that the average BP lowering response of African American hypertensives as a *group* has been less than that of white hypertensives to antihypertensive drugs that exert their primary mechanism of action on the renin angiotensin system (ACE inhibitors, ARB's, Beta Blockers, Direct Renin Inhibitors). Some hypertension experts have also touted the notion that diuretics and calcium antagonists lower BP more effectively in African American than white hypertensives. However, the BP response data suggesting differential BP responses for racial groups has been less consistent for diuretics and calcium antagonists than for RAS blockers. Nevertheless, the question arises as to the relevance of extrapolating group BP response data to all *individuals* of any racial group when making anti-hypertensive drug selections. Indeed, when the avoidance of ACE inhibitors in African Americans with HTN has been promulgated it has been mis-labeled *individualization* of therapy.

As we march steadily toward the era of personalized medicine the utilization of immutable racial/ethnic identity as inflexible guide to the prescription of antihypertensive drugs for individuals of any race is an outdated concept. A number of characteristics that vary at the *individual* level have been shown to influence the response to antihypertensive drug therapy. For example, characteristics that attenuate BP responsiveness to anti-hypertensive drug therapy includes obesity, the presence of pressure-related target-organ injury (e.g., LVH), albuminuria, depressed kidney function, and diabetes.[1,2] These traits do, however, tend to occur and cluster more in African Americans than whites and likely explain some of the aforementioned racial differences in BP response. Nevertheless, as Flack and Sehgal[3] have pointed out, the variability in BP response to an antihypertensive drug class is much greater *within* a racial group than *between* them. Moreover, the BP response distributions to monotherapy with a single anti-hypertensive drugs mostly overlaps between racial groups. This means that very little of the BP response distribution to monotherapy with a single anti-hypertensive drug is unique to any race. And, counter-intuitively, some African American hypertensives actually respond better to monotherapy with a RAS blocker than some whites. This makes the blanket extrapolation of racial group BP responses to monotherapy to a single antihypertensive agent an exercise in inaccuracy.

Figure 1. Blood Pressure Response to Quinapril (1-3 Follow-up Visits)[4]



Mokwe E et al., Hypertension June 2004

There are other reasons to eschew the generalization of racial patterns in BP response to single antihypertensive agents. One important one is that antihypertensive monotherapy in any racial group is not terribly important because the vast majority of hypertensive patients of any race/ethnicity will need combination antihypertensive drug therapy to achieve and maintain their BP below target levels. Thus, even if one racial group, on average, tends to respond more robustly to a given antihypertensive drug class, the majority of *individuals* of that group will be left with BP levels above their target levels. Moreover, there are no racial/ethnic BP response differences to RAS blockers when these agents are combined with either a diuretic or a calcium antagonist. In addition, an increasingly diverse population within the confines of the United States does not neatly fit the African American: white paradigm that has dominated the debate in the hypertension literature over the last several decades regarding the impact of race/ethnicity on pharmacological BP responses.

How is the practitioner to use race/ethnicity in their evaluation and treatment of hypertension? Ideally, race/ethnicity should not be the sole criterion upon which drug therapy selections are based for

individuals of any race or ethnicity. Once patients have been thoroughly evaluated and the appropriate BP target selected and communicated to the patient, the practitioner should select therapy based on the compelling indications for specific treatments that are present. A highly important decision is to determine whether the patient needs initial treatment with one or two anti-hypertensive agents – a decision that is significantly dependent upon how far above goal BP the patient is. In patients close to their goal BP, say less than 10/5 mm Hg above goal, it is not unreasonable to *favor* diuretics and calcium antagonists in African Americans given the greater likelihood of lowering BP below target levels with a single antihypertensive agent. However, the most important aspect of antihypertensive drug therapy, irrespective of the individual drug(s) chosen for an individual of any race/ethnicity, is to follow the patient close enough (titrate drugs ~ every 4 – 6 weeks) to ensure that goal BP levels are achieved and maintained over the long-term. Clearly, informed drug choices are important. And, in this regard, the most important decisions will related to the optimal use of antihypertensive drug combinations. The concern about the race/ethnicity of an individual patient and its importance to successful antihypertensive drug therapy has been grossly overemphasized similar to the misplaced focus on antihypertensive monotherapy instead of on combination drug therapy. The inordinate concern about race has led to the under-utilization of therapies with compelling indications in individual African American patients because of the misplaced concern regarding the lack of BP lowering efficacy of monotherapy with the drug class (e.g. ACE inihibitors in CKD). In such situations, the drug with the compelling indication will virtually always be used with other antihypertensive agents if goal BP is to be attained.

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Older Patients Need Elevated Systolic Blood Pressure to Perfuse Their Stiff Vessels

John Flack, MD, MPH

It is absolutely true that as we age our arterial vasculature becomes less pliable and compliant. Vessel stiffening, while linked to the aging process, does not mean that elevated systolic pressures are need to adequately perfuse vital organs such as the brain in older persons. Numerous pharmacological treatment trials in older persons have established the benefits of treating isolated systolic hypertension - the prototype hypertension phenotype for stiff arterial blood vessels. The old adage that a normal SBP is “100 plus your age” has been repeatedly disproven as having any merit.

It is, however, true that rapid reductions in BP in persons with stiff arterial blood vessels can precipitate acute target-organ ischemia. Thus, the goal for BP lowering in persons with stiff arterial vessels is to gradually lower BP over many weeks to months toward goal levels. How does the clinician know which patient has stiff arterial blood vessels? Well, for one, a reasonably crude indicator is advancing age. The diastolic BP begins to fall while the systolic BP continues to rise around the middle of the 6th decade of life. Generally speaking, the wider the pulse pressure the stiffer the arterial blood vessels. Persons with diabetes manifest premature aging of the vasculature and will therefore prematurely show the wide pulse pressure hypertension phenotype. Older persons with stiff arterial vessels are also more prone to orthostatic drops in their BP, in part because of reduced sensitivity of the baroreceptors. Accordingly, the BP in older persons should always be checked in the seated and standing position. If BP falls upon standing then the standing BP should be used as the target. Eliminate or reduce the doses of antihypertensive drugs known to cause/contribute to orthostatic hypotension - alpha blockers, central adrenergic inhibitors, and diuretics.

The myth regarding stiff BP needing high arterial BP to perfuse them has, unfortunately, been a cover for those who believe that they are harming older persons by pharmacologically lowering the BP. The clinical evidence strongly proves just the opposite. Nevertheless, it does not hurt to start with lower drug doses and titrate a bit less frequently in an effort to more gradually lower BP in older persons with stiff vessels.

Initial Evaluation of the Hypertensive Patient

B. Diaczok, MD and A. Badshah, MD

Purpose

Evaluation of hypertensive patients has multiple objectives:[1,2,3]

a. To assess lifestyle and identify other cardiovascular risk factors and/or coexisting disorders that may affect prognosis and guide treatment
b. To determine the duration of elevated BP, treatment history including compliance, and possible pressure-related symptoms (e.g., nervousness, headache, sleep disturbance)
c. To identify possible causes of high BP
d. To assess the presence or absence of target organ damage and clinical cardiovascular disease

Patient Evaluation

Evaluation of patient consists of:

e. Medical History
   i. Hypertension history – date of onset, usual BP level, treatment history, compliance, etc.
   ii. Target organ damage
   iii. Identifiable causes of hypertension
   iv. Cardiovascular risk factors
f. Physical examination
g. "Routine" laboratory tests and other diagnostic testing

History

Medical history should include any previous diagnosis, treatment and complications of hypertension.[4,5] The patient with new onset hypertension should be assessed for their adherence to appropriate diet and lifestyles as well as to exposures that might have contributed/caused the BP elevation.[6,7] Patient should be screened for identifiable causes of hypertension, if indicated.[8,9] All non-BP cardiovascular risk factors also should be identified.[9]

Major Risk CVD Risk Factors	Lifestyle	Emerging Risk Factors	Coronary Heart Disease Risk Equivalent
-LDL cholesterol	-Sedentary life style	-CRP	-Diabetes
-Low HDL	-Obesity	-Lp(a)	-Abdominal Aortic Aneurysm
-Smoking	-Atherogenic, diet	-Subclinical Atherosclerosis	-Peripheral Vascular Disease
-Age		-Calcium score	-Symptomatic Carotid Disease
-Family history		-microalbuminuria	
		-CKD	

HDL:	Less than 40mg/dl is considered low
Age:	Males over 45 and females over 55 years old.
Current smoker:	Smoking one or more cigarettes in the past month. (The amount of cigarettes smoked correlate with increased risk).
Family history:	Premature atherosclerosis in a first degree relatives—son, daughter, brother,

sister, mother and father. A family history of coronary events is premature if occurring in females less than 65 or males less than 55 years of age.

Central weight gain: Waist circumference of 40 inches or greater in a male and 36 inches or greater in a female.

Evaluation for Target-organ Damage

Heart
- Left Ventricular Hypertrophy
- Heart Failure
- Angina
- Prior myocardial infarction
- Prior coronary revascularization

Brain
- Stroke
- Transient Ischemic Attack
- Dementia

CKD

Peripheral Artery Disease

Retinopathy

Hypertensive Heart Disease (HHD), Left Ventricular Hypertrophy (LVH) and Congestive Heart Failure (CHF)

Hypertensive heart disease represents the accumulation of a lifetime of long-term functional and structural adaptations to the increased BP load.[10] Left ventricular hypertrophy (LVH), an increase in left ventricular (LV) wall thickness and mass, is associated directly with the level of BP, age, and body size. Elevated SBP and body size are major contributors to increased left ventricular mass/LVH.[11]

The prevalence of LVH is difficult to assess and depends on the method and criteria used. Echocardiography is more sensitive than ECG, but is also more expensive and labor intensive. LVH prevalence among hypertensive patients ranges from 20 to 60%.[10,11] As with other forms of target organ damage, LVH is more prevalent in African Americans and older patients. LVH is an independent risk factor for stroke, myocardial infarction, sudden death and heart failure.[10]

Heart failure is the final phase of hypertensive heart disease and involves the progression from hypertension to diastolic dysfunction with preserved systolic function and ultimately to ventricular dilatation and systolic cardiac dysfunction/failure.[2,3]

Angina, myocardial infarction, prior coronary revascularization

Obtain a history of prior revasularization(s) and/or other vascular procedures, myocardial infarction, chest pain typical for angina, type and outcomes of stress testing, and peripheral vascular disease.[12]

Stroke, TIA and Dementia

The risk of ischemic stroke, hemorrhagic stroke, and dementia all increase at higher levels BP.[2] Patients should be screened for a past history, symptoms or signs of stroke. Vascular bruits should be noted. If clinically suspected, a mini-mental exam should be performed to screen for dementia. Successful treatment of BP lowers the risk of subsequent strokes and slows progression of dementia.[5]

Chronic Kidney Disease

The kidney is both a target as well as the cause/contributor to hypertension.[13] Evaluation of kidney function in hypertensive patient has several purposes. First, to ascertain the level of kidney function which is a key determinant in the JNC 7 risk stratification scheme and also to define the nature and activity of nephropathy.[1]

The diagnosis of renal disease can be made by multiple diagnostic tests including the urinanalysis and calculation of an estimated glomerular filtration rate (GFR) utilizing the MDRD equation utilizing the serum creatinine. Utilizing serum creatinine without estimating GFR may underestimate the presence of renal insufficiency, especially in women.[13]

Chronic kidney disease is defined as GFR < 60ml/min/1.73m^2 or the presence of albuninuria (>300mg/d or 200mg/g creatinine [spot urine albumin:crea ratio]).[9] The urinary albumin:creatinine ratio is easily determined on random, spot urine collections and is typically all that is need to quantify urinary protein excretion; it is rarely necessary to order timed 24 hour urine collections. On the other hand, some practitioners will utilize the urine protein:crea ratio at higher levels of urinary protein excretion.[9]

The risk for CVD rises dramatically at incrementally lower levels of kidney function. CKD is an independent risk factor for CVD and, persons with CKD manifest a high prevalence of hypertension. CVD risk also exhibits a continuous relationship with albuminuria which is at least in part a reflection of higher BP levels at higher levels of albuminuria.[10]

Peripheral artery disease (PAD)

Patients should be screened for a past history of peripheral vascular disease, previous revascularization or signs and symptoms of PAD. Peripheral pulses should be palpated and auscultation of carotids, abdomen and femoral artery performed to determine the presence of bruits.[10,14,15] In patient with signs or symptoms of PAD critical stenosis of one or both renal arteries should be suspected especially in the setting of resistant hypertension as well as in those with hypertension plus depressed kidney function.[1,2] The optimal treatment (medical therapy versus medical therapy plus angioplasty/stenting)for critical renal artery stenosis has yet to be determined.[10]

Retinopathy

Hypertensive retinopathy is a condition characterized by a spectrum of retinal vascular signs in people with elevated BP.[16] Numerous studies confirm the strong association between the presence of signs of hypertensive retinopathy and elevated BP.[5] Opthalmologic evaluation is considered standard practice in evaluating hypertensive patients and is supported by previous and current JNC reports.[1]

Hypertensive retinopathy was first described by Dr. Marcus Gunn in the late 19th century. In 1939 Keith Wagener and Barker showed that these signs were predictive of death in hypertensive patients. Their report classified hypertensive retinopathy into four groups of increasing severity.[16]

Though opthalmoloscopic evaluation is a central part of the initial and ongoing medical examination of hypertensive patients, direct opthaomoscopic examination is highly unreliable with high variability in observed findings both within a single observer over time as well as between observers at a given point in time.[4,5] Nevertheless, the noted high variability does not negate performing careful opthalmoscopic evaluations during the initial evaluation of the the hypertensive patient as well as periodically during their ongoing care.

On the basis of photographic studies, hypertensive retinopathy is common in people over 40 years of age, even in those without a history of hypertension; this is likely

because pressure-related retinopathy occurs at incrementally higher BP levels within the so-called normal range, not just when BP crosses an arbitrary threshold of normalcy.[1] Prevalence rates utilizing photography ranged from 2 to 15 percent for various signs of retinopathy compared to 1 to 2 percents in studies utilizing direct opthalmoscopy. A higher prevalence of retinopathy has been reported amongst African Americans than among whites, a difference that can be plausibly attributed to their higher incidence, prevalence, and severity of hypertension as well as their greater coexistence of diabetes.[1]

The presence of retinal changes in normotensive patients may be a marker of a pre-hypertensive state.[4] There is a clear association of hypertensive retinopathy with stroke. The ARIC (Atherosclerosis Risk In Community), a multisite cohort study, showed that signs of hypertensive retinopathy of photographs was associated with a risk of newly diagnosed stroke that was 2 - 4 times higher than in patients without retinal findings, even the analyses were controlled for hypertension, smoking and lipid levels. The association of hypertensive retinopathy with coronary heart disease has, however, been less robust.[3]

Classification of Hypertensive Retinopathy [16]

Grade of Retinopathy	Retinal Signs	Systemic Associations
None	No detectable signs	None
Mild	Generalized arteriolar narrowing narrowing, arteriovenous nickingclinical opacity ("copper wiring") of coronary heart arteriolar wall, or a combination of these signs	Modest association with risk of stroke, subclinicalstroke, disease and death
Malignant	Signs of moderate retinopathy Plus swelling of the optic disk,	-Strong association with death

Identification of Secondary Causes of Hypertension

There are multiple causes of secondary HTN.[8] Listed below are some of the more common etiologies. Please note that the historical and clinical findings suggestive of secondary HTN are neither sensitive nor specific, yet they do significantly inform clinical judgment regarding the likelihood of a given type of secondary HTN and therefore the need to pursue this diagnosis.

Historical and Clinical Findings Suggestive of Secondary Hypertension [1,7,8,10]

Resistant HTN
HTN and unprovoked hyopkalemia or severe (<3.0 meq/l) diuretic-induced hypokalemia (primary aldosteronism)
Snoring and/or large neck size [> 18 inches in men] (sleep apnea)
Onset of hypertension prior to puberty
Abrupt rise in BP over a previously stable lower level
Onset prior to age 30 with no obesity or family history of hypertension
HTN in a vasculopath (unilateral or bilateral critical renal artery stenosis)
Acute elevation of creatinine after initiation of ACE or ARB (bilateral critical renal artery stenosis)
Flash pulmonary edema (bilateral critical renal artery stenosis)
Azotemia (bilateral critical renal artery stenosis causing ischemic nephropathy)

Premature stroke and/or family history (before 40 years of age), especially hemmorhagic (suspicious for glucocorticoid remedial aldosteronism [GRA])

Causes of Secondary or Resistant Hypertension [1, 7,8,10]
Critical unilateral or bilateral renal artery stenosis
Renal parenchymal disease
Coarctation of the aorta
Cushing's syndrome and glucocorticoid excess states
Drug induced and dietary causes
Primary aldosteronism
Hyperthyroidism
Hypothyroidism
Hyperparathyroidism
Obstructive uropathy
Pheochromocytoma
Sleep apnea/sleep disordered breathing

Renovascular Hypertension and CKD

Renal artery stenosis and renovascular hypertension should be suspected in a number of circumstances including: Onset of hypertension before age 30, especially in the absence of family history of hypertension; onset of hypertension after age 55; an abdominal bruit, especially if a diastolic component is present; malignant/accelerated hypertension; hypertension that had been easy to control but is now resistant; recurrent flash pulmonary edema; renal failure of uncertain etiology, especially in the absence of proteinuria or abnormal urinary sediment; acute renal failure after the use of either an ACE or ARB – this is, however, controversial as not all experts concur that ACE's or ARB's are important causes renal dysfunction/failure in patients with critical bilateral renal artery stenosis.[4,8]

Diagnosis of renal artery stenosis may be suggested by renal artery duplex doppler ultrasound (in patients without significant abdominal girth); critical stenosis of one or both renal arteries can be confirmed by one of several imaging studies such as magnetic resonance angiography (MRA) of the renal artery, or CT renal angiography or the gold standard, renal artery angiography.[8,10] In patients with depressed kidney function in whom you wish to avoid the possibility of contrast-induced nephropathy, carbon dioxide angiography can provide an anatomic assessment of the presence/absence of renal artery obstruction – albeit with lesser quality images than renal arteriography.[8,10]

The most common paranchymal kidney diseases associated with hypertension are chronic glomerulonephritis, polycystic kidney disease and hypertensive nephrosclerosis.[10]

Coarctation of the aorta

Coarctation of the aorta accounts for 5 to 10% of congenital cardiac lesions with boys being affected 1.3 to 2 times the rate of girls.[15] Most cases are sporadic, however, there are some reports of concordance in monozygotic twins. Coarctation of the aorta is observed in 10 to 35% of patients with Turner's syndrome but infrequently occurs in Down's syndrome.[15]

Obstruction usually occurs distal to the left subclavian artery resulting in equal arms pressures but diminished pulses in the legs. Coarctation rarely occurs before the take off of the left subclavian artery which, if it occurs, results in unequal arm BP and

pulses (lower in the left arm).[4]

Cardiac manifestations associated with coarctation include ventricular septal defect (17%), aortic valvular stenosis (6 – 13%), and hypoplastic left ventricle (9%).[5] Extracardiac manifestations include berry aneurysms (3 – 5%) and hemangiomas.[15]

Patients with coarctation of the aorta usually present in childhood with respiratory distress and signs of congestive heart failure. Magnetic resonance imaging is sensitive in locating and assessing the extent of the coarctation.[15]

Cushing's syndrome and cortisol excess

Cushing syndrome presents with a cluster of findings commonly seen in primary care clinics—obesity, hypertension and depression.[17] Clues suggesting cortisol excess include truncal weight distribution, thinning of the skin with easy bruising and violaceous/pigmented abdominal striae, poor wound healing, glucose intolerance, moon facies, buffalo hump, and increased hirsutism in females. [4,5,17]

Drug Induced and dietary causes

Medication exposures may result in hypertension or resistance to treatment. Physicians should screen for prescription, over the counter and herbal medications known to raise BP.[18] Dietary history should assess the sodium intake and alcohol use.[4,5] Below is a table of common drug and dietary culprits:

Prescription	Over the counter	Herbal	Illicit drugs
NSAIDS	Sudaphed	Diet pills	Cocaine
Effexor	Diet pills	Bitter orange	Amphetamines
Oral contraceptives		Ma Huang	
Erythopoetin		Ephedra	
Cyclosporin			
Tacrolimus			
Diet pills			
Adderal			
Concerta			

Dietary Causes

Excessive salt intake
Rapid weight gain
Alcohol
Licorice (naturally flavored)

Hyperaldosteronism

Primary aldosteronism (PA) occurs in approximately 10% of hypertensive patients.[18] Historical estimates have been much lower, however, broader screening of hypertensive patients have been the source of these newer estimates. PA prevalence rates of 15 – 20% have been observed amongst those with resistant HTN.[10,18] Patients with resistant hypertension, unprovoked hypokalemia, or excessive diuretic-induced hypokalemia (<3.0 meq/l) should be screened; the AM plasma aldosterone:renin ratio is the most helpful screening test. It should, however, be noted, that the majority of patients with proven PA will NOT manifest hypokalemia. Other symptoms that may be present and are attributable to hypokalemia include weakness, muscle cramps, fatigue and paresthesias. Nocturia and polyuria are most likely attributable to hypokalemia-induced renal concentrating defects. Peripheral edema is, however, rare despite persistently elevated and non-suppressible (with saline) aldosterone levels.[1-3,18]

Thyroid disease

Thyroid disease is estimated to affect as many as 9 to 15% of adult females and a smaller percentage of male patients.[6] Screening includes looking for signs and symptoms and obtaining a TSH. Epidemiologic studies of community-based populations suggest that BP elevations occur in persons with hypo- and hyper-functioning of the thyroid gland.[1,3,6]

Hyperthyroidism results in decreased systemic vascular resistance increased cardiac output and decreased arterial compliance. This combination of hemodynamic effects results in preferential elevation of the SBP. Treatment of hyperthyroidism and the use of B-blockers usually reverse this BP elevation.[6,9]

Hypothyroidism results in endothelial dysfunction and impaired vascular smooth muscle relaxation leading to increased systemic vascular resistance and elevated DBP. Hypothyroidism is also a known cause of isolated diastolic hypertension, the least common hypertension phenotype. Approximately 30% of hypothyroid patient have elevated diastolic BP. Administration of thyroid hormone replacement therapy usually lowers BP.[3,6]

Hyperparathyroidism[8,18]

The prevalence of hypertension in increased in primary hyperparathyroidism. Patients may be asymptomatic with hypertension being their initial manifestation. Surgical treatment of hyperparathyroidism, however, does not always improve BP control.

Obstructive Uropathy[1,3,19]

The prevalence of hypertension among patients with ureteral occlusion varies according to whether the renal obstruction is unilateral or bilateral.
Bilateral ureteral obstruction results in BP elevation in approximately three quarters of affected patients. Unilateral ureteral obstruction results in hypertension in ~ 20 to 30% patients. Relief of acute obstruction
typically leads to resolution of the BP elevation.

Pheochromocytoma

Pheochromocytoma should be suspected in patients with labile hypertension or paroxysms of hypertension accompanied by headache, palpitations, pallor and truncal sweating[4,7] Pallor is more common than sweating. Some patients present with anxiety, nervousness or panic attacks. However, many patients with pheochromocytoma do not have sustained BP elevations.[1,7,10]

The prevalence of pheochromocytoma is less than 0.5% of patient with hypertension. Surgical removal of the tumor results in hypertension cure in up to 90% of patients.[7] Determination of the serum metanephrine level is the screening test of choice.[10]

Obstructive Sleep Apnea-Hypopnea syndrome

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is characterized by repetitive episodes of airflow reduction due to pharyngeal narrowing, leading to acute gas exchange abnormalities and sleep fragmentation resulting in neurobehavioral and cardiovascular consequences.[20]

Nearly 40% of outpatients in a survey of urban primary care practices reported clinical characteristics of obesity, hypertension, snoring sleepiness, and tiredness

suggestive of OSAHS.[20] The prevalence of sleep apnea in hypertensive populations ranges between 30 – 40%. Men are 2 to 3 times more likely to be affected than women.[21]

Population-based studies have associated OSAHS with cardiovascular disease, stroke and hypertension. In the Sleep Heart Health Study, 6,424 patients were longitudinally studied with in-home polysomnography.[20] In the highest quartile of apnea-hypopnea frequency (>11/hr) the adjusted odds of self reported cardiovascular disease was 1.42 (95% confidence interval, 1.13 – 1.78).[22] The strongest links were to congestive heart failure and stroke.[21]

Strong evidence for an association of OSAHS and hypertension comes from the Wisconsin Sleep Cohort Study. Subjects underwent serial in-laboratory polysomnography. A dose-dependent like between apnea-hypopnea frequency at baseline and the development of hypertension was identified. For a baseline apnea-hypopnea frequency of 15/hr the odds ratio for hypertension at 4 years was 2.89 (confidence interval, 1.46 – 5.64).[23]

Intermittent hypoxia, negative intrathoracic pressure variations and arousal characteristics of apneas and hypopneas lead to acute increases in BP and the termination of disordered breathing events, evolving into sustained hypertension via chronically heightened sympathetic nervous system activity and arterial baroreceptor dysfunction.[21]

History should focus on breathing disturbances during sleep, unsatisfactory sleep quality, daytime dysfunction, and OSAHS risk factors. A collateral history should be obtained from the patient's bed partner. Reports of habitual, socially disruptive snoring and witnessed apneas terminated by snorts or gasps increase diagnostic accuracy. Sleepiness, per se, however, lacks diagnostic sensitivity and specificity.[20,21]

Physical examination focuses on craniofacial and soft tissue conditions associates with increased upper airway resistance, such as retrognathia, deviated nasal septum, low-lying soft palate, enlarged uvula, and base of tongue. Obesity and neck circumference over 43cm (17.5inches) correlates with an increased likelihood of OSAHS.[20]

Treatment of OSAHS may, though not invariably, result in improvement of hypertension. However, treatment of sleep apnea does lower cardiovascular risk.[22]

Physical Examination [1,4-10,20,21]

General appearance

Vital signs

- A Retinopathy
- B Neck/chest
- C Cardiac
  - i. Inspection of precordium
  - ii. Palpation of PMI
  - iii. First sound
  - iv. S 3 Gallop
  - v. S 4 Gallop
  - vi. Murmurs
- D Abdomen
  - vii. Renal bruits
  - viii. Bladder distention

E Circulation
G Neurologic

General appearance

Inspection begins when the patient first enters the clinic. Observe the patient's behavior and gait for signs of neurologic deficits. Observe respiratory pattern for signs of dyspnea on exertion. Determine the patient body habitus. Central weight gain (apple shape) correlates with metabolic risk factors for cardiovascular disease.

Waist measurement

Patient should be wearing gown and non-restrictive briefs or underwear. The measurement should not be made over clothing. The patient should stand erect with the abdomen relaxed, the arms at the sides and feet together. The measurer faces the subject and places an inelastic tape around the subject in a horizontal plane at the level of the natural waist. The measurement should be taken at the end of a normal expiration without the tape compressing the skin. Record to the nearest 0.1cm.

Respiration

Respiration affects the level of BP, with SBP falling during inspiration. The basis for this effect is twofold. First, during inspiration, intrathoracic pressure falls, the lungs expand, and pulmonary venous capacitance increases. This results in increased venous return to the right ventricle and diminished blood flow to the left ventricle. The decreased left ventricular preload contributes to the lowered SBP. Second, changes in intrathoracic pressure are directly transmitted to the intrathoracic aorta. The degree of fall in systemic BP is proportional to the fall in intrathoracic pressure. During the normal respiratory cycle SBP falls between 5 to 10 mm/Hg from the end of expiration to the end of inspiration. In asthma, however, this drop is larger and may exceed 10mm/Hg. The excessive drop in systolic BP during the respiratory cycle is known as the pulsus paradoxus. Pulsus paradoxus has also been observed in pericardial tamponade.

Pulse

Manual determination of pulse rate is integral to BP evaluation. Pulse rate, rhythm and pulse contour are evaluated. Tachycardia or bradycardia may reflect intrinsic cardiac disease, medical illness or reaction to medication. Similarly, rhythm reflects cardiac arrythmias. The brachial pulse should be compared to the apical impulse (palpated or auscultated). Not all cardiac contractions are transmitted to the periphery – this is particularly true in special situations such as atrial fibrillation. Premature ventricular contractions (PVC) result in uncoordinated ventricular contraction and diminished stroke volume. Thus, only assessing the presence of peripheral pulses may underestimate the true heart rate.

Similarly, patients with pulsus alternans, alternating weak and strong ventricular contractions result in only half of the cardiac contractions being effective. This discrepancy of peripheral and apical rate is known as pulse deficit. Pulsus bisferiens, a double peak in the pulse, is difficult to palpate, but may manifest as a "split" Korotkoff sound.

Palpate pulses in both arms and one leg. Coarctation of the aorta usually presents with equal radial but diminished femoral pulses. Rarely (<5%) of patients with coarctation of the aorta will present with unequal radial pulses.

Blood Pressure

In addition to the level of BP, the pulse pressure (difference between SBP and DBP)

may shed light on underlying medical conditions. Accordingly, a wide pulse pressure may be a consequence of a hyperdynamic left ventricle from fever, anxiety, anemia or thyrotoxicosis. Other causes of a wide pulse pressure include aortic insufficiency. Poorly compliant arterial vasculature, such as occurs with ageing and/or diabetes mellitus, also cause wide pulse pressure. Conversely, a narrow pulse pressure may occur in the as a consequence of a poorly contractive left ventricle or cardiac tamponade.

Neck

The neck exam should focus on the thyroid and vascular pulsations. Visible and palpable pulsations around the clavicular heads may indicate aneurysmal dilatation of the aortic arch. As the ascending aorta and arch increase in diameter due to hypertensive atherosclerotic disease, the arch is displaced cephalad bringing the innominate, subclarian and carotid arteries origins near the thoracic outlet.

Venous pulsations reflect right atrial pressures. Visible venous pulsations in the neck can occur with right ventricular heart failure, pulmonary hypertension and/or tricuspid valve disease.

Cardiac examination

Cardiac exam consists of inspection, palpation, and auscultation. First, inspect and palpate the precordium to locate the PMI. In healthy individuals the PMI is located in the 5th left intercostals space, mid-clavicular line. The location of the PMI reflects cardiac size. Downward or lateral displacement indicates cardiac enlargement. The size and quality of PMI reflect cardiac contractility. Increased contractility due to fever, hyperthyroidism or anemia results in a hyperdynamic precordium. Normal contractility results in a quarter sized tapping impulse. Impaired cardiac contractility results in an enlarged poorly palpable and sustained (heave) PMI.

First Heart Sound

The first heart sound is very important in the auscultation of the heart. A diminished S1 may be due to mitral regurgitation, diminished ejection fraction or increased diastolic filling time. An accentuated S1 may be due to fever, anemia, or a hyperdynamic left ventricle.

During auscultation the first heart sound may sound split. Physiologic splitting of S1 ranges from 20 to 30 milliseconds and is not detectable by human ears. This double sound is due to either an accentuated splitting of S1, an ejection click or S4 gallop. True, wide splitting of S1 is the result of a right bundle branch block.

An ejection click is the result forceful opening of the aortic valve and is always followed by the murmur of aortic sclerosis or stenosis. Left ventricular contractility should be preserved to generate sufficient force to generate an ejection click.

The third reason for a “split” first heart sound is a S4 gallop, reflecting a stiff, non-compliant left ventricle of early hypertensive heart disease.

S4 Gallop

The S4 gallop is the result of the left atrium contracting and pumping blood into a stiff, non-compliant left ventricle. The gallop is heard best at the apex (over the area of the PMI) with the bell of the stethoscope. The S4 precedes the S1 and may be misinterpreted as a “split” S1. The S4 gallop correlates with the presence of an inverted or bi-phasic p wave (enlarged left atrium) on ECG. Patient with first degree heart block may have an audibly increased interval between S4 and S1.

An S4 gallop is not considered a normal finding and is a result of left atrial

contraction into a stiff, non-compliant left ventricle typically due to pressure-overload hypertrophy (hypertensive heart disease. Ventricular ischemia can also contribute to or cause ventricular stiffening.

S3 Gallop

The S3 gallop is the result of rapid ventricular filling in early diastole. The gallop may be misinterpreted as a split S2. The S3 represents volume overload and is usually is indicative of heart failure. However, an S3 gallop may be heard in children as well as in volume expanded states such as pregnancy; in these latter two situations the S3 gallop does not indicative a failing left ventricular and is a normal variant.

Murmurs

Cardiac murmurs may shed light on the diagnosis of hypertensive heart disease. Early in the disease the ventricle develops constrictive hypertrophy with hyperdynamic ventricular contraction. The aortic valve may calcify and develop sclerosis. This combination results in an ejection click with an aortic sclerosis murmur. During late hypertensive heart disease, the left ventricle dilates. This dilatation expands the mitral valve annulus and may result in a murmur of mitral regurgitation.

Abdominal exam

Inspect the abdomen (and chest) for scars suggesting coronary bypass surgery. Look for any pulsations suggesting aortic aneurysm. Auscultate the epigastric area for bruits. Percuss the epigastric area for signs of distended urinary bladder. Palpate the abdomen for pulsatile masses suggesting aneurysmal dilatation or an ectatic aorta. Patients with polyscystic kidneys may also present with palpable abdominal masses.

Circulation

Evaluate arterial pulses to determine the presence of atherosclerotic vascular disease and coarctation of the aorta. Auscultate the carotid as well as other major arteries (e.g., femoral) for bruits. If no bruits are present, gently palpate each carotid independently for delayed upstroke suggestive of aortic stenosis, or collapsing downstroke suggestive of aortic insufficiency. The radial pulses should always be equal. Diminished femoral impulses with intact radial pulses suggests coarctation of the aorta. The posterior tibial artery should always be present. However, the dorsalis pedis impulse is absent as a normal variant in 10 to 15% of the population.

Neurologic

Evaluate the patient's mental status for signs of dementia. If clinically warranted the practitioner should perform a formal mental status assessment. Inspect cranial nerves, sensation, strength, reflexes, cerebellar function, station and gait. Cerebellar dsymetria may be the only physical finding that leads one to suspect heavy consumption alcohol.

Tests

Medical tests are obtained for risk stratification purposes, to identify target organ damage, to screen for and identify common secondary causes of hypertension, to identify all other non-BP forms of CVD, and to help monitor therapy. [2,9,24] An exhaustive evaluation for secondary causes is not warranted in all or even most hypertensive

patients.[8] However, the history and physical are important for determining who needs evaluation and for what secondary causes.

The ECG is obtained to identify target organ damage, conduction defects and rhythm disturbances. Inspect the ECG for signs of myocardial infarction, first degree heart block, left ventricular hypertrophy and bundle branch blocks.[11]

Calcium, potassium, other electrolytes and BUN and creatinine are obtained to evaluate renal function and electrolyte disturbances suggestive of secondary hypertension.[3,8,9] Patients with EGFR < 60 ml/min/1.73 m2 are considered to have CKD. A random urinary albumin:crea ratio should be obtained in ALL hypertensive patients, not just those with diabetes. Levels > 200 mg/g represent CKD even if the EGFR is not depressed.[9,10,13]

Fasting blood glucose is obtained to screen for diabetes; a recent expert panel has endorsed measuring a random hemoglobin A1C as a screen for diabetes with values ≥ 6.5 as being diagnostic of diabetes. The prevalence of type 2 diabetes and pre-diabetes are increased in hypertensive patients. [9,10,12]

Fasting lipid profile (total cholesterol, HDL, triglycerides and LDL) are obtained and used in calculation of the Framingham Risk Score to estimate the patient's 10 year risk of coronary artery disease.[25,26]

Urinalysis is obtained to look for active urine sediment. Urinary concentrating ability, an early casualty in chronic kidney disease, can be inferred from the specific gravity. [2]

Hemoglobin and hematocrit should be obtained. Low hemoglobin may be attributable to chronic kidney disease. Conversely, elevations may indicate signs of chronic hypoxia, renal cell carcinoma or Gaisbock's syndrome. [1-3,12]

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Lifestyle modifications and blood pressure

Joel Topf, M.D.

Objectives:

1. To appreciate the importance of lifestyle intervention in hypertension management.
2. To understand the major lifestyle modifications that has the most effect on blood pressure.

Pre-Test

1. Which of the following electrolytes has the most impact on blood pressure?
    a. Sodium (correct answer)
    b. Calcium
    c. Magnesium
    d. Phosphorus
2. Which of the following lifestyle modifications can improve blood pressure?
    a. Weight loss
    b. Weight gain
    c. Aerobic exercise
    d. A and C (correct answer)
    e. B and C

Introduction

While the bulk of clinical research on hypertension involves drug therapy there is a robust core of literature exploring non-pharmacological methods to control BP. Life-style changes in diet and exercise along with weight loss can lower BP and some interventions have been shown to reduce CV and overall mortality. The life-style modifications that are best studied include:

- Low sodium diet
- DASH Diet
- Decreased alcohol intake
- Weight loss
- Increased physical activity

JNC-7 suggests lifestyle modifications for all individuals to prevent hypertension. They also specifically suggest lifestyle modification for patients with pre-hypertension (120-139/80-89 mmHg). Patients without diabetes or kidney disease and pre-hypertension can be given a trial of lifestyle modifications for 6-12 months before initiating drug therapy. Lifestyle modifications are also recommended to be used concurrent with drug therapy in all stages of hypertension.

Reduction of Sodium

The centrality of sodium intake to BP has repeatedly been shown in epidemiologic studies which tie daily sodium ingestion to the prevalence of hypertension and to the risk of hypertension associated with increasing age. Hypertension is rare in populations with sodium intake of less than 50 mmol (1.2 grams) daily. The landmark Intersalt Study looked at 24-hour urine collections from various locations around the world and from individuals of various ages. They found a 100 mmol increase in sodium intake was associated with average 3 mm Hg higher systolic BP. The association was stronger in people aged 40-59 compared to younger peers with an average of 6/3 mmHg higher BP per 100 mmol of sodium higher sodium intake.[1]

More important for this discussion, reductions in sodium intake by individuals results in reductions in BP. A meta-analysis of 20 trials of hypertensive patients that looked at sodium reduction for at least 6 months revealed that a reduction of 78 mmol (1.8 g) of sodium a day resulted in 5/2.6 mmHg improvement in BP.

These data along with the mechanistic data showing an etiologic role for sodium in hypertension

and evidence that anti-hypertensive medications have increased effectiveness when paired with sodium restriction have resulted in national and international clinical guidelines calling for sodium restriction:

- JNC 7 recommends a sodium intake of 100 mmol (2.3 g) per day
- 2007 European Society of Hypertension recommends reducing sodium intake to less than 85 mmol (2 g) per day
- American Diabetes Association recommends sodium restriction as part of lifestyle modification which can be attempted in cases of mild hypertension prior to drug therapy or in conjunction with drug therapy for more severe hypertension
- K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease recommends dietary intake of less than 2.4 g (100 mmol/d) of sodium for most patients with CKD and high blood pressure

The most compelling data for salt restriction concerns reduction in cardiovascular disease and mortality. Cook et al. looked at long term follow-up following two randomized controlled trials of sodium restriction in patients aged 30-54 with pre-hypertension. Patients in the intervention group were provided repeated counseling on identification of low sodium foods, and taught to monitor and reduce sodium intake. After 18 months, participants had reduced daily sodium intake by 44 mmol (1 g). The BP lowering effect of this intervention was initially modest with a reduction of 1.7/0.8 mm/Hg in the first trial and 1.2/0.7 mm/Hg in the second.

The follow-up 10-15 yrs later showed that patients originally enrolled in the low-sodium group continued to demonstrate salt conscious behaviors, however no follow-up measurement of sodium intake was attempted. The interesting finding was that patients randomized to the low salt diet had a 25% (RR 0.75, 0.57-0.99) reduction in cardiovascular events and a non-significant 20% reduction in mortality (RR 0.80, 0.51-1.26, p=0.34). These are dramatic health benefits from modest reductions in sodium intake.[2]

DASH diet

Reduced sodium intake is well known and often advised but there are other dietary strategies to reduce BP. These include:

- Low fat diet
- High calcium intake

- High potassium intake
- High magnesium intake
- Vegetarian diet
- High fiber diet

Studies that focused on a simple strategy of supplementing one of these nutrients (fiber, calcium potassium etc.) have generally been disappointing. The DASH (Dietary Approaches to Stop Hypertension) diet attempted to combine multiple dietary strategies by testing a whole diet strategy rather than an individual nutrient strategy.

The DASH Trial [3] used a diet rich in fruits and vegetables to provide increased fiber and potassium along with other trace minerals. Low-fat dairy products provided increased calcium while keeping the diet low in saturated and total fat. Trial participants randomized to the DASH diet were provided meals containing 4-5 servings of fruit, 4-5 servings of vegetables, 2-3 servings of low fat dairy and <25% of calories from fat. The diet was not sodium restricted and subjects ingested 3 g (130 mmol) of sodium a day. Subjects ate breakfast and dinner at the research site and were given lunches and week-end meals to take home.

The results were dramatic:

- Decreased BP of 5.5/3.0 mmHg
- Decreased in hypertensives 11.4/5.5 mmHg
- Maximal BP response occurred after only 2 weeks

A follow-up trial examined if adding sodium restriction on top of the DASH diet would provide additional benefit. Patients were randomized to either a control diet or the DASH diet that involved three different levels of sodium intake (150, 100, and 50 mmol/day). Sodium restriction lowered the BP in both diets but was more potent in patients on the control diet. Sodium restriction did not further enhance the BP lowering effect of the DASH diet. When subjects on the DASH diet reduced sodium intake from 150 to 100 mmol/d their BP fell only 1.3/0.6 mmHg while going from 100 to 50 mmol/d decreased the BP by 1.7/1.0. People with pre-existing hypertension were more sensitive to decreases in dietary sodium. Patients on the control diet had a more robust response to decreases in dietary sodium: 150 to 100 mmol/d decreased the BP 2.1/1.1; going from 100 to 50 mmol/d decreased the BP 4.6/2.4.[4] These two landmark DASH trials proved the effectiveness of the DASH diet in a highly controlled experimental design (a feeding study) where the subjects received dietician-prepared meals.

When subjects are given instruction and guidance but are required to prepare their own food the results are less impressive. This was shown in the PREMIER Trial in which patients were randomized to one of three arms: one control, and two experimental groups.[5] In the first experimental group, patients had 18 face-to-face meetings to review weight loss and strategies to reduce sodium and alcohol consumption. The same recommendations were given to the second intervention group with additional counseling on adopting the DASH diet.

Counseling resulted in significant weight loss of 5 kg in both experimental groups versus loss of 1 kg in the control group. There was no difference in physical activity, but physical fitness did improve. There was no reduction in alcohol or sodium intake. Investigators found good separation in the potassium intake with the greatest increase in potassium in the DASH group as would be expected. Both of the experimental groups had greater reductions in BP than the control group. Forty percent of the patients randomized to the established risk factor counseling and 48% of the patients in the established risk factor counseling plus DASH were able to lower their BP below 120/80 mmHg. The difference was not statistically significant. There was no improvement in BP control with the addition of the DASH diet over counseling patients on established risk factors.

The lack of benefit of the DASH diet illustrates that multiple lifestyle interventions cannot be assumed to be additive and that experimental data on the effectiveness of an intervention may not translate to real world advantages when people need to implement complex dietary advice on their own.

Moderation of alcohol

Reducing alcohol intake can lower BP and reduce the likelihood of developing hypertension. Despite the salutary effect on BP modest alcohol intake is associated with reduced CV and all-cause mortality. The discrepancy between elevations in BP and subsequent reductions in mortality serves as a stark reminder that intermediate end-points may not describe the full impact of a risk factor. All advice must be individualized to patients, and some patients with a personal or family history of alcoholism will need particularly careful counseling, but overall it seems imprudent to recommend abstinence to all patients given the repeatedly demonstrated association with decreased mortality and CV mortality with modest alcohol consumption.

In a prospective study of alcohol intake, over nine years, in nearly half a million patients, drinking at least one drink a day was associated with a 30-40% lower CV mortality. Patient who drank

more than 4 drinks a day had 3 to 7 times the rate of death from cirrhosis, alcoholism, head and neck cancer and liver cancer compared to people who abstained. However, the reduction in CV death overwhelmed the increase in alcohol related deaths and total mortality, even at 4 drinks a day, was less than that seen in people who abstained from alcohol. The cardio-protective effect of alcohol was more apparent in older patients and patients with higher cardiovascular risk.[6]

The cardio-protection from alcohol extends to people with preexisting hypertension. In the Physicians Health Study of 14,000 hypertensive men, without prior stroke, myocardial infarction or cancer, investigators found a 28% lower mortality in both weekly and daily drinkers despite the fact that the highest systolic and diastolic blood pressures and rates of tobacco use were found in the daily drinkers. Alcohol provided the most protection to patients with higher BP and advanced age.[7]

Despite the paradoxical relationship between alcohol consumption and mortality there is compelling data showing alcohol's association with the development of hypertension and the ability to worsen pre-existing hypertension.

Sesso, et. al. looked at 42,000 normotensive participants in the Women's Health Study and Physicians Health Study and found a steady increase in the risk of developing hypertension in men with increasing alcohol intake. In women there was a J-curve with decreased risk of hypertension with modest alcohol intake but increasing risk of hypertension with alcohol intake over 2 drinks per day.[8]

In a meta-analysis of 14 randomized controlled trials of reduced alcohol consumption, investigators found an average decease in BP of 3.3/2 mmHg associated with alcohol reduction. The effect was robust and was detected even when the analysis was restricted to only: high quality, long-term studies including either hypertensive or normotensive participants.[9] It is prudent for men with hypertension to consume two or fewer alcoholic drinks per day and women 1 or fewer. Despite the impressive epidemiological data presented above regarding lower morbidity and mortality at higher alcohol intakes, these studies were not rot randomized studies. Thus, the recommendations for limited intake of alcohol in men and women with hypertension.

Weight loss

Numerous studies have demonstrated reductions in BP with weight loss. In a meta-analysis of 25 studies Neter, et al found a drop in BP of 1.1/0.9 mm Hg for every kg of weight lost.[10] A second meta-analysis looked at the change in BP related to weight loss over time and found that the peak effect on BP comes soon after the weight loss and the effect attenuates over time. Aucott et al

interestingly found only a 6.0/4.6 decrease in BP with a 10 kg loss of body weight, at two years of follow-up, half of what would be expected from the Neter study. An important observation was that the BP improvement was reduced if the weight loss was surgical in nature. [11]

Aerobic exercise

Aerobic exercise has been shown to lower BP by an average of 3/2 mmHg. The effect attenuates when you look at studies of longer duration and in studies with less stringent verification of adherence.[12] In a study on the dose effect of exercise, greater hypotensive effect was found with 61-90 minutes compared to 30-60 minutes a week. More than 90 minutes was not more effective than 61-90 minutes. While minutes/week did influence SBP, the diastolic pressure was not affected and the frequency of exercise did not alter the BP effect.[13] In a separate study by the same team, increased age attenuated the BP effects of exercise but gender did not.[14]

Summary

Lifestyle modification provides an effective prevention in pre-hypertensives and is an adjunct to therapy in established hypertensives. The findings of multiple investigators demonstrate that a variety of modifications including dietary, exercise, sodium restriction and fish oil can have positive effects on patients.[15] Even alcohol, with mixed outcomes can be adjusted to minimize BP and maximize cardiovascular benefits. Lifestyle modification has a definite role to play in the control of BP and should be included as part of the individualized management plan for every patient.

Post-Test

1. Which of the following are parts of the D.A.S.H. diet?
    a. Low fat diet
    b. High calcium intake
    c. Low potassium intake
    d. A and B (**correct answer**)
    e. A, B, and C

2. After how many minutes of weekly exercise are the maximum effects of aerobic exercise experienced?
    a. 0
    b. 0-30
    c. 31-60
    d. 61-90 (**correct answer**)
    e. Greater than 90 minutes

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Goals for Treatment of Hypertension

Khaled Ismail, MD

Goals and Objectives:

- Know the BP goals set forth by the JNC 7 guidelines.
- Understand the benefits of antihypertensive therapy.
- Be familiar with some of the data supporting currently recommended therapeutic goals for the treatment of hypertension.

Pretest:

1. A 57-year-old male with a history of coronary artery disease, hypertension, diabetes, and hyperlipidemia presents to your office for routine follow up. His most recent serum creatinine was 0.9 mg/dL and microalbuminuria was less than 20 mcg/mg. His BP is 155/100 and pulse is 72 beats per minute. He takes metoprolol 25 mg twice daily and lisinopril 20 mg once daily. What is the next best step in his management?

a. See him back in 3 months and recheck his BP
b. Reassure him that his hypertension is controlled and follow up in 1 year.
c. Uptitrate his lisinopril, his metoprolol, or both until BP is < 140/90.
d. Add a thiazide diuretic. (**correct answer**)

The principle goals of antihypertensive therapy are the reduction in cardiovascular morbidity and mortality, reduction in the incidence of end-stage renal disease, and slowing the progression of chronic kidney disease (CKD). **The recommended blood pressure (BP) goal for antihypertensive therapy as outlined by JNC 7 is <140/90 mmHg for most individuals**. The MRFIT study [1] was a cohort of 347,978 men ages 35 to 57 years that were screened for risk factors that contribute to cardiovascular disease. An increase in mortality was found for every 10 mmHg increase in systolic blood pressure (SBP) between 120 mmHg to 200 mmHg. The mortality risk was increased significantly at SBP of greater than 139 mm Hg. The MRFIT data is corroborated by the observations made in prospective, placebo-controlled trials such as the Systolic Hypertension in the Elderly Program [2] and Systolic Hypertension in Europe [3] trials. Importantly, multiple studies demonstrate that the excess cardiovascular risk is abrogated by effective antihypertensive therapy. (Figure 1)

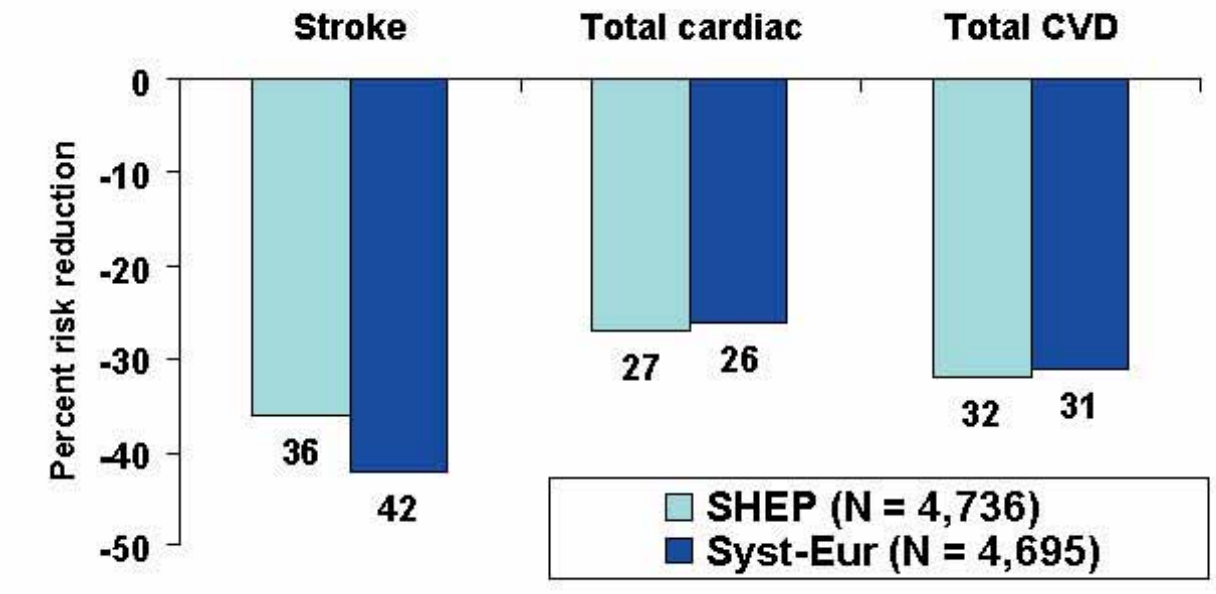
The BP goal in patients with diabetes or CKD is based upon data from multiple studies including the modification of diet in renal disease (MDRD) study. Chronic kidney disease is currently defined as an estimated glomerular filtration rate of less than 60mL/min per 1.73m2 body surface area or the presence of albuminuria of greater than 300 mg/d or a urinary albumin:crea ratio in excess of 200 mcg/mg. In the MDRD study, it was found that participants with CKD who were treated to a lower goal had slower progression of renal disease, progression to ESRD, and less proteinuria. This effect was most pronounced in patients with greater than 1 gram of daily proteinuria. On the basis of the accumulated data, the BP goal recommended by JNC 7 for patients with diabetes or CKD is a BP of less than 130/80 mmHg.

The issue of whether or not there exists a “J-curve” phenomenon has been long disputed. A “J-curve” is an inflection point in the BP vs. mortality curve below which mortality and morbidity rise. It is argued that diastolic blood pressure (DBP) below a certain level may compromise coronary perfusion pressure and lead to increased cardiovascular risk as is seen in some observational studies.[4] There are, however, data from the SHEP Pilot study showing that DBP < 70 mm Hg in older persons with

isolated systolic hypertension have a significantly higher prevalence of carotid (and presumably coronary) atherosclerosis. Moreover, the greatest benefit of treatment was seen in the very persons with underlying atherosclerotic disease. There is little doubt based on observational studies that a Jcurve does indeed exist. However, there is virtually no uncofounded evidence that the J curve is attributable to pharmacological BP lowering. This issue will come into consideration most often when treating older persons with isolated systolic hypertension. These individuals typically have wide pulse pressures (very stiff, atherosclerosis laden) vessels. Gradual reductions in BP make eminent sense when treating these high-risk, older individuals. The safe lower limit of BP is therefore at the discretion of the treating physician and should be individualized to each patient. Nevertheless, as a practical matter, there are far more patients with uncontrolled BPs than those with excessively controlled BPs. Therefore the overall efforts should be directed towards improved BP lowering in the majority of patients. On the other hand, this does not preclude a bit of extra caution when lowering markedly elevated and highly risky SBP levels in typically older patients with very low DBPs.

Knowledge of BP goals is essential for optimal patient care. Education of patients and patient families about BP goals and the consequences of uncontrolled BP can facilitate a team approach to reducing HTN and HTN associated morbidities. An appreciation for the importance of truly achieving goal BPs and a willingness to increase therapy regularly until a patient is unequivocally on target is necessary for maximum patient benefits. With targeted goals and optimized control, many of the adverse consequences of uncontrolled HTN can be avoided. The main aim is to consistently maintain BP below goal levels. This will require more than a single antihypertensive agent in the vast majority of hypertensive patients. Another important issue is to avoid therapeutic inertia. That is, observing BP levels above goal and not changing and/or intensifying antihypertensive drug therapy.

Figure 1. Reductions in Stroke, Cardiovascular events and cardiovascular death (CVD) with antihypertensive therapy from the SHEP and Syst-Eur trials.



Key Points:

1.) The recommended JNC 7 goal for BP in most individuals is <140/90 mmHg.

2.) The recommended JNC 7 BP goal for those with diabetes or CKD is <130/80 mmHg

3.) Whether or not a "J-curve" phenomenon exists is controversial and lower limits of safe BP control should be individualized to each patient, and

4.) The majority of hypertensive patients will require more than one antihypertensive agent to attain and persistently maintain Bp levels below goal levels

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Compelling Indications for Specific Antihypertensive Medication Classes

Khaled Ismail, MD

Learning Objectives:

1. Learn the various coexisting conditions for which specific classes of antihypertensive drugs are indicated.
2. Understand the evidence supporting the use of different antihypertensive drug classes in patients with these comorbidities.

Pretest:

1. A 38 year-old male with a history of type 2 diabetes presents to your office for a routine checkup. His BP is 155/95 mmHg and his last hemoglobin A1C was 8.9%. His BP on a previous visit 6 weeks ago was 150/90 mmHg. He currently takes only insulin. Which medication is the best choice for initial antihypertensive therapy?

a. hydrochlorothiazide 25mg
b. losartan 50 mg/d plus chlorthalidone 25 mg/d (**correct answer)**
c. metoprolol 25 mg bid
d. amlodipine 5 mg/d
e. clonidine 0.1mg bid

The JNC 7 guidelines published in 2003 identified several "compelling indications" for prescribing certain antihypertensive medication classes.[1] These indications include congestive heart failure (CHF), a history myocardial infarction or stroke, chronic kidney disease, diabetes and an overall elevated risk for coronary artery disease.

Large, randomized controlled trials (RCT) have shown survival benefits independent of BP control when treating HF (specifically systolic dysfunction) when beta blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are administered. The investigators found a 31% relative risk reduction in all-cause mortality at one year in patients with American Heart Association class 4 heart failure patients treated with enalapril.[2] The ARB valsartan was found to reduce hospitalization due to CHF in patients with class 2 or greater heart failure.[3] Beta-blockers such as extended-release metoprolol have been shown in RCT to significantly reduce mortality.[4,5] The administration of the aldosterone antagonist, spironolactone to patients with classes 3 and 4 heart failure has also been associated with a 30% reduction in mortality.[6] Following myocardial infarction, beta-blockers, ACE inhibitors and aldosterone antagonists have each been associated with significant reductions in mortality (23%, 19%, and 15% respectively).[5,7,8] Thus, in hypertensive patients with systolic heart failure, it is imperative that these drug classes be preferentially used in the prescribed antihypertensive regimens.

Numerous prospective studies in animals and humans have shown the renoprotective effects of RAS antagonists in patients with CKD. Thus, these agents are definitely indicated in patients with diabetic and non-diabetic nephropathy.[9,10] It is a mistake, however, to believe that BP control, in most instances, will be obtained without additional antihypertensive agents – most notably diuretics and/or calcium antagonists.

Diabetic patients should be treated with RAS antagonists – either an ACE inhibitor or an ARB.

RAS antagonists slow CKD progression, profoundly reduce proteinuria and, at least in some though not all studies, appear to provide protection against cardiovascular events that is not directly linked to BP reductions. For example, the RENAAL trial was an RCT that randomized 1513 patients with diabetes and nephropathy to losartan or placebo.[10] The investigators found a 16% relative risk reduction in the primary composite endpoint of doubling of the serum creatinine, end-stage renal disease or death.

Angiotensin converting enzyme inhibitors and ARB are the drugs of choice in recurrent stroke prevention. In RCT, the use of ACE inhibitors or ARB has resulted in 30-50% relative risk reductions in the risk of recurrent stroke.[11-13] Nevertheless, these agents will very likely be utilized along with other antihypertensive drug classes to obtain and persistently maintain BP control.

For hypertensive patients with any of the co-morbid conditions for which specific drugs are indicated, BP control to goal is, however, an absolute necessity to confer maximal target-organ protection while preventing undesirable CVD-renal events. Familiarity with the compelling indications for anti-hypertensive medications allows a provider to provide optimal care and to reduce preventable morbidity and mortality.

Table 6. Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

High-Risk Conditions With Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	β-Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist	
Heart failure	•	•	•	•		•	ACC/AHA Heart Failure Guideline,[40] MERIT-HF,[41] COPERNICUS,[42] CIBIS,[43] SOLVD,[44] AIRE,[45] TRACE,[46] ValHEFT,[47] RALES[48]
Post–myocardial infarction		•	•			•	ACC/AHA Post-MI Guideline,[49] BHAT,[50] SAVE,[51] Capricorn,[52] EPHESUS[53]
High coronary disease risk	•	•	•		•		ALLHAT,[33] HOPE,[34] ANBP2,[36] LIFE,[32] CONVINCE[31]
Diabetes	•	•	•	•	•		NKF-ADA Guideline,[21,22] UKPDS,[54] ALLHAT[33]
Chronic kidney disease			•	•			NKF Guideline,[22] Captopril Trial,[55] RENAAL,[56] IDNT,[57] REIN,[58] AASK[59]
Recurrent stroke prevention	•		•				PROGRESS[35]

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; AIRE, Acute Infarction Ramipril Efficacy; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin-receptor blocker; BHAT, β-Blocker Heart Attack Trial; CCB, calcium channel blocker; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation–American Diabetes Association; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non–Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial.

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.

†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs.

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Key Points:

1.) Certain drug classes offer improved cardiovascular and renal morbidity and mortality beyond simple BP control in patients with specific co-morbidities; some drugs with compelling indications, however, do not necessarily confer any special benefit to patients with a given co-morbidity but have rather been proven safe to use in high-risk patients with a given co-morbidity (e.g., diuretics in heart failure)

2.) ACE inhibitors, beta-blockers and aldosterone antagonists are the drugs of choice in patients with congestive heart failure with systolic dysfunction.

3.) Beta-blockers, ACE inhibitors, and aldosterone antagonists are the drugs of choice post myocardial infarction.

4.) ACE inhibitors and ARB are the drugs of choice in patients with diabetes or CKD.

5.) ACE inhibitors and ARBs are the drugs of choice in patients with previous stroke.

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Overview of Major Anti-Hypertensive Classes

William Repaskey, M.D.

Diuretics

While there are no fewer than eight distinct antihypertensive drug classes, diuretics remain a major cornerstone of antihypertensive therapy. There are multiple reasons for this including the fact that they are inexpensive, have a proven track record of effectiveness since their development in the 1950s, and diuretics enhance the effectiveness of all other antihypertensive drug classes. Numerous studies over many years have demonstrated their equal if not superior effect in preventing the cardiovascular complications of hypertension. Most recently, the landmark ALLHAT study which involved 40,000 hypertensive individuals showed that diuretics appear to prevent cardiovascular complications associated with hypertension as effectively as ACE inhibitors or calcium-channel blockers.[1] On the basis of these types of studies that authors of the JNCVII national guidelines recommend that thiazides be used as initial therapy for the treatment of uncomplicated hypertension in most patients. Thiazides can be used either alone or combined with other classes of antihypertensive drugs with demonstrated benefit (e.g., ACE inhibitors, angiotensin II receptor antagonists, beta blockers, and calcium-channel blockers).[2] Of note, the ALLHAT trial did show that the majority of patients will require treatment with 2 or more agents to accomplish adequate blood pressure control [3], so the typical approach to therapy in a standard patient will employ a diuretic in combination with another agent. Diuretics effectively lower BP in all population sub-groups and, as monotherapy, they lower BP on average as or more effectively than other antihypertensive drug classes.

Pharmacology/Mechanism of Action

The clinically utilized diuretics are divided into 3 distinct subclasses based on their chemical structure, target of activity, mechanism of action within the renal tubule, pharmacologic effect and side effect profile. These subclasses include the thiazides, loop diuretics, and the potassium sparing and aldosterone antagonist diuretics. All diuretics fundamentally promote excretion of sodium, chloride and water from the body. Diuresis contracts the extracellular fluid volume and as a consequence, decreases cardiac output. There is an initial, transient hypotensive effect, though homeostatic mechanisms, including activation of the renin-angiotensin activating system, later return extracellular volume to pre-

treatment levels – albeit though at a lower BP. The hypotensive effect of thiazides is also, in part, likely secondary to direct arterial vasodilation.

Thiazide diuretics inhibit sodium reabsorption from the luminal side of epithelial cells in the distal tubule by blocking the Na+/Cl- transporter. They are effective in placebo-adjusted lowering BP by 10–15 mm Hg in most patients, and often provide adequate treatment for mild or moderate essential hypertension in patients with normal renal function; thiazides are, however, ineffective in lowering BP when used at normal doses when the estimated glomerular filtration rates is less than ~ 45 ml/min/1.73 m^2. Hydrochlorothiazide is the prototypical example of this diuretic subclass. The thiazides are also useful in mild heart failure and because they decrease urinary calcium excretion, these agents can be useful in the prevention of nephrolithiasis. Chlorthaoidone, a thiazide-like diuretic, lowers BP and remains an effective diuretic agent with EGFR's as low as the mid to low 30's. Chlorthalidone also has a much longer duration of action than HCTZ. Metolazone is another thiazide-like diuretic that works well even in patients with markedly reduced kidney function. Metolazone is also used in combination with furosemide to accomplish even more robust diuresis than would be possible with either agent alone.

The loop diuretics selectively inhibit NaCl reabsorption in the thick ascending limb of the loop of Henle. Because of the large NaCl absorptive capacity of the thick ascending limb (and the limited tubular capacity to reabsorb sodium distal to this site) these are the most potent diuretic agents available. Because they require more frequent dosing and tend to have a more prominent side effect profile, they are not used routinely as anti-hypertensives unless the patient has depressed kidney function. They are commonly used for hypertension in patients with renal impairment, typically once the GFR is less than 40 ml/min/1.73m^2. Furosemide (Lasix) is the prototypical agent in this class.

The potassium sparing diuretics directly block the epithelial sodium channel in the distal convoluted tubule thereby blocking sodium reabsorption. The aldosterone antagonists are also potassium sparing and block the action of aldosterone in the collecting duct thereby increasing sodium and water excretion and decreasing potassium and hydrogen ion excretion. The potassium sparing diuretics are generally used adjunctively with the thiazide diuretics while the aldosterone antagonists are used in excess aldosterone states such as heart failure and to prevent and treat ascites in patients with liver disease; nevertheless, aldosteronae antagonists are very potent antihypyertensive agents as evidenced by their substantive BP lowering when used alone or in combination with other

antihypertensive agents in resistant hypertension. An added benefit of these agents when used with a thiazide or loop diuretic is that they will reduce the likelihood of hypokalemia. Amiloride is the prototypical potassium sparing agent and spironolactone is the prototypical aldosterone antagonist. Potassium–sparing diuretics, however, should be avoided in individuals with depressed kidney function (EGFR < 50 ml/min/1.73 m^2). The risk of hyperkalemia further increases when using these agents concurrently with other RAS blockers such as ACE inhibitors, ARB's, and DRI's.

Toxicity/Adverse Effects

All the diuretics will cause urinary frequency and varying types and degrees of electrolyte and metabolic disturbances. Of particular importance thiazides can cause hyponatremia (especially in older patients) and dose-related hypokalemia, which can precipitate cardiac dysrhythmias. Additionally, since diuretics contract the extracellular fluid volume they can occasionally cause volume depletion and therefore result in pre-renal azotemia. . These electrolyte and volume effects can be associated with perceived symptoms such as lassitude, thirst, muscle cramps and weakness. Because of their effect on uric acid, both thiazide and loop diuretics may induce gout attacks in susceptible individuals. Both thiazide and loop diuretics also cause magnesium wasting which, in turn, can contribute to the kaliuretic properties. Spironolactone is a weak antagonist of androgen receptors and can cause breast tenderness and gynecomastia (men) and menstrual irregularities (women). It can also cause significant hyperkalemia. Thiazides can worsen glucose tolerance, especially when they cause hypokalemia; however, this adverse metabolic effect can be largely prevented by combining these agents with RAS blockers or other potassium-sparing diuretics.

Dosing

It is worth noting that based on the results of the ALLHAT trial many authorities have come to recommend chlorthalidone as the preferred diuretic in the treatment of hypertension, instead of hydrochlorothiazide. Other studies have shown greater BP lowering, especially at night with chlorthalidone compared to HCTZ. Chlorthalidone also has a longer duration of action than HCTZ and therefore should confer greater protection against rises in BP in the setting of intermittent non-compliance with prescribed anti-hypertensive drug therapy. Another potential advantage of chlorthalidone over HCTZ is that it will induce a diuresis and lower BP at more depressed levels of kidney function than HCTZ. .

Preparations and Dosage:
Oral antihypertensive drugs*

Thiazide diuretics
chlorothiazide (Diuril) 125–500 mg QD/BID
chlorthalidone (generic) 12.5–25 mg QD
hydrochlorothiazide (Microzide, HydroDIURIL) 12.5–50 mg QD
polythiazide (Renese) 2–4 mg QD
indapamide (Lozol) 1.25–2.5 mg QD
metolazone (Mykrox) 0.5–1.0 mg QD
metolazone (Zaroxolyn) 2.5–5 mg QD

Loop diuretics

bumetanide (Bumex) 0.5–2 mg BID
furosemide (Lasix) 20–80 mg BID
torsemide (Demadex) 2.5–10 mg BID
Potassium-sparing diuretics
amiloride (Midamor) 5–10 mg QD/BID
triamterene (Dyrenium) 50–100 mg QD/BID

Aldosterone receptor blockers
eplerenone (Inspra) 50–100 mg QD
spironolactone (Aldactone) 25–50 mg QD

Beta Blockers

It has been known since the 1940s that bilateral excision of the thoracic sympathetic chain results in lowering BP. The discovery of the importance of the adrenergic nervous system in the control and regulation of BP ultimately led to the development of the beta adrenergic blockers, as well as the alpha blockers and central adrenergic inhibitors. Sir James W. Black successfully developed the first clinically utilized beta blocker, propranolol, in the late 1950s, an accomplishment for which he was later awarded the Nobel Prize in Medicine. The overall BP lowering effect and reductions in CVD has, however, been less than observed with diuretics. Authorities recommend, based on the completed clinical trials to date, that beta blockers are appropriate as initial monotherapy in patients with a specific indication, namely, post-myocardial infarction/ischemic heart disease and systolic heart failure, where they appear to have particular benefit.

Pharmacology/Mechanism of Action

The beta blockers lower BP by decreasing both heart rate and cardiac contractility via their action on the beta 1 receptors of the sinoatrial node and the myocardium and thus lower cardiac output;

and also by effecting blockade of the beta receptors at the juxtaglomerular complex which reduces renin secretion and diminishes activation of the renin angiotensin system. Beta blockers are sub-classified based on whether they are cardioselective (beta 1-specific) or nonselective (beta 1 and beta 2) receptor blockers; whether they possess intrinsic sympathomimetic activity (ISA); or by whether they are lipid-soluble. They are all, however, similarly effective regarding their BP lowering efficacy; however, these various qualities tend to predict their toxicities.

Toxicity/Adverse Effects

Lipid solubility determines whether the particular agent will penetrate the blood-brain barrier and thereby potentially affect CNS function. Lipid-soluble beta blockers will thus cause more central nervous system disturbances, including nightmares and confusion (e.g. propranolol). Fatigue and sexual dysfunction can occur and will tend to limit use in young, active patients; however, these latter two side effects may also be related to the reduction in cardiac output that occurs during beta blocker therapy. Agents with intrinsic sympathomimetic activity (ISA) produce less resting bradycardia than do those without ISA (e.g. acebutolol, pindolol) and can be useful when bradycardia is a limiting side effect. Additional notable adverse effects sometimes observed include heart block, cold extremities and exacerbation of Raynaud's phenomenon. Because their use can result in unopposed alpha receptor activation by intrinsic or extrinsic sympathomimetics, it is held that patients experiencing a cocaine overdose must not be treated with beta blockers as this would cause crescendo hypertension and a reduction in coronary blood flow. A beta blocker overdose is treated with glucagon and, in refractory cases, with cardiac pacing. Traditionally, beta blockers were thought to be relatively contraindicated in patients with obstructive lung disease with concern that antagonism at the bronchial beta 2 receptor would provoke bronchospasm. Of note, a 2005 Cochrane database systematic review of trials comparing cardioselective (*1-adrenergic receptor-specific) *-blockers with placebo found no adverse respiratory effects and concluded that beta blockers need not be withheld in COPD patients who have a valid indication for *-blocker therapy, such as CAD or heart failure.[4] More recently, concerns have been raised regarding the adverse effect of beta blockers on glucose tolerance. A 2007 study appeared to show that the risk of developing diabetes and glucose intolerance was significantly greater with diuretics and beta blockers compared to ACE inhibitors and ARBs.[5] Beta blockers can mask symptoms (tachycardia but not sweating) associated with hypoglycemia and also delay the metabolic recovery from hypoglycemia.

Preparations and Dosages:

The Oral Beta Blockers

Atenolol (Tenormin) 25–100 mg PO QD
Betaxolol (Kerlone) 5–20 mg PO QD
Bisoprolol (Zebeta) 2.5–10 mg PO QD
Metoprolol (Lopressor) 50–100 mg PO QD/BID
Metoprolol extended release (Toprol XL) 50–100 mg PO QD
Nadolol (Corgard) 40–120 mg PO QD
Nebivolol (Bystolic) QD
Propranolol (Inderal) 40–160 mg PO BID
Propranolol long-acting (Inderal LA) 60–180 mg PO QD
Timolol (Blocadren) 20–40 mg PO BID

Beta Blockers with Intrinsic Sympathomimetic Activity
Acebutolol (Sectral) 200–800 mg PO BID
Penbutolol (Levatol) 10–40 mg PO QD
Pindolol (generic) 10–40 mg PO BID

Calcium Antagonists

Calcium channel blockers (CCBs) were first developed in the 1960s and brought into routine clinical practice in the 1980s. They are widely used for the treatment of hypertension, angina, and cardiac arrhythmias. Numerous studies conducted since the 1980s, including the VA Cooperative Study[6], the Treatment Of Mild Hypertension Study (TOMHS)[7], and the German HANE[8] study have demonstrated the CCBs to be equivalent or superior in controlling BP than other agents, including diuretics, ACE inhibitors and beta blockers . Furthermore, a recent meta-analysis of more than 150,000 patients in 29 trials comparing different categories of antihypertensive drugs found that CCB-based therapy was superior to placebo in preventing stroke and coronary heart disease, though inferior to diuretic, blocker therapy and ACE inhibitor therapy in preventing heart failure.[9] Such findings are consistent with the findings of the ALLHAT trial that found amlodipine to be as effective as the compared diuretic (chlorthalidone) in preventing all CVD outcomes except for heart failure.[10] The CCBs are effective and generally well tolerated, and their long duration of action and favorable adverse effect profile make them widely prescribed antihypertensive agents. They seem to be effective as initial therapy or monotherapy for BP treatment and combine very effectively with RAS blockers for lowering BP and reducing CVD. Calcium antagonists are therefore very important antihypertensive drugs in the treatment of hypertension. Calcium antagonists, unlike many other antihypertensive agents, maintain their BP lowering efficacy in high or ad-lib dietary sodium environments and also experience minimal

attenuation of their BP lowering effectiveness when used with non-steroidal anti-inflammatory drugs.

Pharmacology/Mechanism of Action:

The calcium channel blockers are varied in structural morphology but all function by blocking the transmembrane flow of calcium ions through voltage-derived channels (L-type channels) in vascular and non-vascular smooth muscle. Blockade of these channels prevents calcium influx which is required for smooth muscle contraction and cardiac myocyte contraction. This results in smooth muscle relaxation decreased peripheral vascular resistance, dilation of coronary arteries, and a decrease in myocardial contractility. The agents are further sub classified into the dihydropyridine and non-dihydropyridine classes based on their chemical structure. The dihydropyridine class (members identified with the suffix "-dipine") are relatively more selective for vascular smooth muscle and are probably a bit more potent BP lowering agents than non-DHP calcium antagonists. The non-dihydropyridine CCBs are, in contrast, more selective for the myocardium and cardiac conduction system and less active in vasculature smooth muscle. They are comprised of the phenylalkylamine subclass, including verapamil, and the benzothiazepine subclass, which includes diltiazem. Of the two medications, verapamil is more selective for the myocardium and is effective in the treatment of arrhythmias and for angina by reducing myocardial oxygen demand. Diltiazem is intermediate in its myocardial/vascular smooth muscle specificity and causes a hypotensive effect without provoking as much reflex cardiac stimulation as the dihydropyridines.

Toxicity/Adverse Effects:

The DHP calcium channel blockers can cause flushing, headache, lower extremity edema and reflex tachycardia with dependent edema being the most common dose-related side effect. The reflex sympathetic response is less common with the longer acting dihydropyridines (e.g. amlodipine). The non-dihydropyridines can cause bradycardia, impaired electrical conduction (e.g., atrioventricular nodal block), and depressed contractility, so patients with conduction defects or systolic dysfunction should not be given these medications. The more cardioselective CCBs can interact dangerously with beta blockers since both classes of drugs have overlapping effects of decreasing cardiac contractility and impeding cardiac conduction. Concomitant administration of these drugs can cause advanced heart block and greatly impaired inotropic function of the heart. Thus, non-DHP CCB's should not be used with beta blockers; however, DHP CCB's can be safely used with beta blockers. All CCB's can depress sino-atrial node firing in patients with sick sinus syndrome so no CCB should be used in

patients with tachy-brady syndrome without a functdioning ventricular pacemaker. The dose-dependent peripheral edema that occurs mostly with DHP CCB's is most effectively treated/prevented with either simultaneous use of an ACE or an ARB; this form of edema is probably more diuretic sensitive than previously thought.

Preparations and Dosages:
CCBs—nondihydropyridines
diltiazem extended release (Cardizem CD, 180–420 1Dilacor XR, Tiazac†)
diltiazem extended release (Cardizem LA) 120–540 1
verapamil immediate release (Calan, Isoptin†) 80–320 2
verapamil long acting (Calan SR, Isoptin SR†) 120–480 1–2
verapamil (Coer, Covera HS, Verelan PM) 120–360 1

CCBs—dihydropyridines
amlodipine (Norvasc) 2.5–10 1
felodipine (Plendil) 2.5–20 1
isradipine (Dynacirc CR) 2.5–10 2
nicardipine sustained release (Cardene SR) 60–120 2
nifedipine long-acting (Adalat CC, Procardia XL) 30–60 1
nisoldipine (Sular) 10–40 1

ACE INHIBITORS

The development of the ACE inhibitors began in 1898 with the discovery of the renin-angiotensin system. Investigators discovered that a kidney extract that they called renin was able to induce hypertension in rabbits. These findings stimulated further investigations that ultimately resulted in the discovery of angiotensin II, an oligopeptide with myriad hypertensive effects on the cardiovascular and renal systems. In the 1950s the angiotensin converting enzyme (ACE) was discovered in plasma and it was later shown to be the key enzyme that converts angiotensin I, a biologically inactive peptide derived from angiotensinogen by the enzymatic action of renin, to angiotensin II. In the 1970s Sir John Vane discovered that the profound hypotensive effects caused by exposure to the venom from a Brazilian viper (bothrops jararaca) were attributable to the ability of the venom to block the function of ACE. Investigators at Squibb pharmaceuticals later utilized this information to develop the first ACE inhibitor, captopril. Since then, the ACE inhibitors have become a critical tool in the treatment of cardiovascular and renal disease, including hypertension.

Numerous studies regarding the effectiveness and safety of the ACE inhibitors in the treatment of hypertension have been conducted over many years since captopril was first put into clinical use in 1981. Recently, investigators conducted a meta-analysis of 92 trials with a total of 12,954 participants

(mean age, 54 years). Overall, ACE inhibitors were found to have a modest collective effect in reducing BP. The mean reduction in SBP ranged between 6 mm Hg and 9 mm Hg, and the mean reduction in DBP was 4-5 mm Hg.[11] It was notable that all the ACE inhibitors studied were homogeneous in their efficacy and that lower doses were generally as effective in reducing BP as the manufacturer's maximum recommended doses. This observation can be most readily explained by the fact that ACE inhibitors have relatively flat-dose-response curves.

ACE inhibitors are notable for a low incidence of side effects and ease of dosing. For this reason they are very popular antihypertensive agents in clinical practice, though, as noted under the diuretic section above, national guidelines continue to endorse the use of thiazide diuretics as first line agents for the treatment of uncomplicated hypertension. They have traditionally been perceived to be more effective in Caucasians and younger patients, though more recent data suggests they are effective in African American patients, as well, with perhaps higher dosing. Race, however, should never be sole criterion upon which an ACE inhibitor or any other antihypertensive agent is either chosen or avoided.[12]

The ACE inhibitors have pleiotropic effects on the renal and cardiovascular systems making them ideal antihypertensive agents for specific medical populations. There is some evidence that they have a beneficial effect on glucose metabolism (improve glucose tolerance without affecting fasting glucose levels) and appear to delay the onset of type 2 diabetes. These agents reduce preload and afterload, down-regulate sympathetic activity by blocking the facilitating effects of angiotensin II on sympathetic nerves, and promote renal excretion of sodium and water by blocking the effects of angiotensin II in the proximal tubule and by antagonizing angiotensin II-mediated aldosterone secretion. ACE inhibitors also inhibit cardiac and vascular remodeling associated with chronic hypertension and heart failure. All of these qualities make ACE inhibitors excellent antihypertensives for the treatment of patients with heart failure and following myocardial infarction for which they have been shown to reduce mortality in multiple clinical trials. Finally, there is abundant evidence from many clinical trials demonstrating that the ACE inhibitors are effective in reducing proteinuria and decreasing the rate of decline in kidney function in patients with chronic kidney disease. While strict control of BP appears to be the most important in regards to preservation of kidney function, it also appears that the ACE inhibitors have a beneficial effect on renal function – especially amongst those individuals with

significant proteinuria.

Pharmacology/Mechanism of Action

The renin-angiotensin-aldosterone axis begins with the hepatic production of angiotensinogen, a 452 amino acid alpha 2 globulin. In response to perceived hypotension or decreased delivery of sodium and chloride at the level of the juxtaglomerular apparatus, the kidney secretes renin, a peptide hormone that converts angiotensinogen to angiotensin I. Angiotensin I is biologically inactive. Angiotensin converting enzyme (ACE) or kinninase II is found widely throughout the body and occurs in three main isoforms. The enzyme is found in particularly high concentrations in the pulmonary capillary endothelium where it catalyzes the final enzymatic step in the lysis of angiotensin I to produce angiotensin II; inhibitor of ACE/kinninase II also raise bradykinin levels which, in turn, augment nitric oxide (NO) levels. While the multiple enzymatic steps of the renin-angiotensin-aldosterone axis each represent a potential target for an antihypertensive agent to act upon, the ACE inhibitors block this step thus decreasing the amount of circulating angiotensin II. This effectively abrogates the myriad effects of angiotensin II on the kidney and cardiovascular system, including vasoconstriction, stimulation of aldosterone release, promotion of renal sodium reabsorption, vasopressin secretion and increased cardiac contractility and all these effects cause a decrease in BP.

Toxicity

ACE inhibitors are very well tolerated and have a low incidence of side effects. The most common, annoying side effect of ACE inhibitors is a dry cough appearing in 10-30% of patients. The effect is related to the elevation in bradykinin, an enzymatic product of high molecular weight kininogen and a potent vasodilator. Angiotensin converting enzyme normally enzymatically degrades bradykinin but in the presence of the ACE inhibitors this process is impeded. Hypotension can also be a problem, especially in heart failure patients. Angioedema (life-threatening airway swelling and obstruction; 0.1-0.2% of patients) and hyperkalemia (occurs because aldosterone formation is reduced) are also adverse effects of ACE inhibition. The incidence of angioedema is 2 to 4-times higher in African Americans compared to Caucasians; however, the absolute rates of angioedema are low in both races. ACE inhibitors are contraindicated in pregnancy as they are associated with a variety of birth defects. Additionally, patients with bilateral renal artery stenosis may experience renal failure if ACE inhibitors are administered because a decrease in circulating angiotensin II alters efferent and afferent

glomerular capillary flow and thus decreases glomerular filtration. Generally this is not a perceptible a problem with unilateral renal artery stenosis because the unaffected kidney can usually maintain sufficient filtration after ACE inhibition; however, with bilateral renal artery stenosis this effect cannot be compensated for. A rise in the serum creatinine often occurs in hypertensive patients with depressed glomerular filtration rates, a situation where antagonism of the renin angiotensin system is indicated when BP is lowered with or without ACE inhibitor containing regimens The rise in creatinine reflects a decline in the global GFR because of preferential dilation of efferent compared to the afferent arteriole (an ACE inhibitor effect) and also because of the drop in systemic BP; in the setting of depressed kidney function the kidney is simply not able to efficiently autoregulate glomerular pressure. Older patients, those taking diuretics, and individuals with the highest baseline serum creatinine levels tend to have the most marked rises in creatinine when ACE inhibitors are used in antihypertensive regimens in the setting of depressed kidney function. Practitioners should become concerned when the rise in creatinine exceeds a 30% rise from baseline levels. The serum creatinine may stay above baseline levels, come back to baseline levels or even fall below baseline levels over the long-term after the initial rise in serum creatinine.

Preparations and Dosages:

benazepril (Lotensin†) 10–40 mg PO daily
captopril (Capoten†) 25–100 mg PO BID
enalapril (Vasotec†) 5–40 mg PO daily
fosinopril (Monopril) 10–40 mg PO daily
lisinopril (Prinivil, Zestril†) 10–40 mg PO daily
moexipril (Univasc) 7.5–30 mg PO daily
perindopril (Aceon) 4–8 mg PO daily
quinapril (Accupril) 10–80 mg PO daily
ramipril (Altace) 2.5–20 mg PO daily
trandolapril (Mavik) 1-4 mg PO daily

ANGIOTENSIN RECEPTOR–BLOCKING AGENTS

The angiotensin receptor blockers (ARBs) are effective in the treatment of hypertension and they are well tolerated. Arguably, ARB's are the best tolerated anti-hypertensive drug class today. The BP lowering efficacy of ARBs appears to be comparable to the ACE inhibitors. Recently a Cochrane review evaluated 46 randomized controlled trials examining 9 ARBs, and found that the overall efficacy in reducing systolic and diastolic blood pressure was -8 mm Hg and -5 mm Hg, which was similar to

the effect found by the ACE inhibitors. The peak effect of ARBs was also similar, with an average BP reduction of approximately 12/7 mm Hg. All the ARBs studied were essentially equivalent in effectiveness. Much like ACE the inhibitors, ARBs were as effective at lower doses as they were at the manufacturer's highest recommended doses. Again, similar to the ACE inhibitors, this observation reflects the relatively flat dose-response curve of the ARBs.

Pharmacology/Mechanism of Action:

Once it was determined in the 1930s that renin was not the direct cause of increased BP in experimental animals but rather an enzyme that led to the production of the culprit agent, angiotensin II, efforts were made to identify agents that could block the actions of angiotensin II at its receptor. Angiotensin II exerts its pharmacologic effect at the AT1 receptor which is a G protein-linked transmembrane protein found mainly in the heart, adrenal glands, brain, liver and kidneys where it effects vasoconstriction, aldosterone release, renal sodium reabsorption and vasopressin secretion. Angiotensin I Type 2 (AT2) receptors are highly expressed in the developing fetus but they decline rapidly after birth. In the adult, AT2 receptors are present only at low levels and are mostly found in the heart, adrenal glands, uterus, ovaries, kidneys and brain.[13] The AT3 and AT4 receptors have been described but there function not yet elucidated.

Initial pharmacologic success at the AT1 receptor was accomplished with saralasin, a modified form of the angiotensin II peptide that was developed in the early 1970s. Saralasin was not clinically useful however, because it was poorly bioavailable, had a short duration of action, and acted as a partial agonist at the receptor.[14] Nevertheless, studies with saralasin confirmed the importance of angiotensin II in the control of BP and, after many years of laboriously screening candidate compounds and performing function testing, researchers at Merck Pharmaceuticals developed the first angiotensin receptor blocker, losartan. Losartan was introduced into clinical use in 1995 and there are today 9 separately marketed ARBs available.[11]

The ARBs have no effect on bradykinin metabolism and are therefore more selective blockers of angiotensin effects than ACE inhibitors. ARBs block activation of the AT_1 receptor by its agonist angiotensin II. They also have the potential for more complete inhibition of angiotensin action compared with ACE inhibitors because enzymes other than ACE are capable of generating angiotensin II via non-ACE pathways. Angiotensin receptor blockers provide benefits similar to those of ACE inhibitors in patients with heart failure and chronic kidney disease.

Similar to the ACE inhibitors the ARBs effect vasodilation, down regulate sympathetic adrenergic activity, promote renal excretion of sodium and water, block aldosterone secretion and inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure, and myocardial infarction.

Toxicity/Side Effects:

Side effects with ARBs are rare and they are tolerated better than the ACE inhibitors. Because they do not increase bradykinin levels, they do not cause dry cough or the angioedema that are associated with ACE inhibitors. Like ACE inhibitors, ARBs are contraindicated in pregnancy. Also, as with ACE inhibitors, they are contraindicated in the setting of bilateral renal artery stenosis in which case they can cause acute renal failure due to disruption of juxtaglomerular control of afferent and efferent arteriolar blood flow. The rise in creatinine during antihypertensive drug therapy previously described with ACE inhibitors can also occur with ARBs. ARBs also can cause hyperkalemia, though they may be a bit less likely to do so than ACE inhibitors.

Preparations and Dosages:

Angiotensin II antagonists
candesartan (Atacand) 8–32 mg PO daily
eprosartan (Teveten) 400–800 mg PO daily/BID
irbesartan (Avapro) 150–300 mg PO daily
losartan (Cozaar) 25–100 mg PO QD/BID
olmesartan (Benicar) 20–40 mg PO daily
telmisartan (Micardis) 20–80 mg PO daily
valsartan (Diovan) 80–320 mg PO QD/BID

Alpha Blockers

Abbott Labs developed the first alpha blocker, terazosin, in 1987, marketed as a once daily formulation for the treatment of hypertension. There are now at least 6 alpha blockers available commercially. While they are as effective as other agents in reducing diastolic and systolic blood pressure, evidence has accumulated since 1987 that the alpha blockers may be associated with greater cardiovascular morbidity and mortality when used as monotherapy in the treatment of hypertension. Most recently and most persuasively, the ALLHAT trial demonstrated conclusively that alpha blocker use was associated with a 25% higher relative risk of developing combined cardiovascular disease outcomes that was associated with an ~ 3 mm Hg lesser SBP lowering compared to the reference drug group, Chlorthalidone.[10] Risks included a two-fold difference in CHF

and nominally statistically significant higher risks of stroke, angina, and coronary revascularization. The ALLHAT findings prompted termination of the doxazosin arm of the trial 2 years earlier than scheduled and has led national guideline writers and other authorities to recommend that the alpha blockers not be used as primary monotherapy for the treatment of hypertension.[10] Nonetheless, they remain useful when combined with other agents to accomplish satisfactory BP control and they are especially useful in older men with benign prostate hyperplasia in whom they are effective in reducing lower urinary tract symptoms. Additionally, the non-selective alpha-antagonists, including phenoxybenzamine and phentolamine, remain useful in hypertensive emergencies caused by pheochromocytoma. Used in conjunction with beta-blockade to blunt reflex tachycardia these medications help to control BP until the tumor can be surgically removed.

Pharmacology/Mechanism of Action:

The alpha blockers block noradrenaline-mediated vasoconstriction by binding to alpha-adrenoceptors located on the vascular smooth muscle. They operate as competitive antagonists to the binding of norepinephrine that is released by sympathetic nerves synapsing on smooth muscle. Alpha blockers are competitive antagonists with the exception of phenoxybenzamine, an irreversible, non-competitive antagonist at the receptor.

Vascular smooth muscle has two primary types of alpha-adrenoceptors: alpha1 (α1) and alpha2 (α2). In contrast, only α2-adrenoceptors are found on the sympathetic nerve terminals. Smooth muscle α1 and α2-adrenoceptors are linked to a g-protein, which activates smooth muscle contraction through the IP3 signal transduction pathway. Prejunctional α2-adrenoceptors located on the sympathetic nerve terminals serve as a negative feedback mechanism for norepinephrine release.

Toxicity/Side Effects:

The most common side effects are related directly to alpha-adrenoceptor blockade and include dizziness, orthostatic hypotension, nasal congestion headache, fluid retention and reflex tachycardia (especially with non-selective alpha-blockers due to blockade of α2-prejunctional adrenoceptors which enhances release of norepinephrine).

Direct Vasodilators

There are 2 major direct vasodilators in clinical use today, minoxidil and hydralazine. They each have distinct mechanisms of action and are effective in lowering BP typically as adjunctive therapies. Accordingly, because of side effects and other considerations neither are considered first line in the treatment of uncomplicated hypertension.

Hydralazine, along with methyldopa, is a preferred agent for the treatment of hypertension during pregnancy (e.g., for preeclampsia) and as an adjunct antihypertensive in other hypertensive populations. Long-term, high-dose (> 300 mg/day) hydralazine is not used as a primary drug for treating hypertension because it elicits a reflex cardiovascular sympathetic increase in heart rate and cardiac output, and the resulting myocardial oxygen demand can provoke angina pectoris or myocardial infarction.

Minoxidil is more potent than hydralazine but has more adverse effects, including sodium and water retention and hypertrichosis. It is used primarily to reduce BP in patients who have been poorly controlled on various multi-drug regimens. Because it tends to increase pulse rate and trigger salt and water retention, minoxidil is typically administered with both a potent diuretic and a β blocker (or non-DHP CCB). Minoxidil is often a therapy of last resort in patients with chronic kidney disease (CKD) who have been unresponsive to other antihypertensive medications. In patients with established CKD, minoxidil can stabilize GFR, if not improve renal function, when BP is properly controlled. Occasionally, the edema with minoxidil can be of sufficient severity to require combination therapy with a loop diuretic and metolazone.

Pharmacology:

Hydralazine's mechanism of action has not been comprehensively detailed but appears to have multiple, direct effects on vascular smooth muscle. Hydralazine's effects are highly specific for arterial vessels and causes smooth muscle hyperpolarization likely by opening K+-channels. It also may inhibit IP3-induced release of calcium from the smooth muscle sarcoplasmic reticulum, which calcium would otherwise combine with calmodulin to activate myosin light chain kinase, which induces contraction. Finally, hydralazine stimulates the formation of nitric oxide by the vascular endothelium, leading to cGMP-mediated vasodilation.

Minoxidil is a representative agent of the potassium-channel openers that activate ATP-

sensitive K+-channels in vascular smooth muscle. Opening these channels hyperpolarizes the smooth muscle, which closes voltage-gated calcium channels and decreases intracellular calcium. With less calcium available to combine with calmodulin, there is less activation of myosin light chain kinase and phosphorylation of myosin light chains leading to vessel relaxation and vasodilation. Because small arteries and arterioles normally have a high degree of smooth muscle tone, minoxidil is particularly effective in dilating these resistance vessels, decreasing systemic vascular resistance, and lowering arterial pressure. There can be a dramatic drop in arterial pressure leading to reflex cardiac stimulation (baroreceptor-mediated tachycardia).[15]

Toxicity/Adverse Effects:

Common side-effects of hydralazine include diarrhea, reflex tachycardia, headache, anorexia, nausea, vomiting, depression and palpitations. Additionally, hydralazine has been associated with a drug-induced lupus syndrome, which resolves when the drug is stopped.

Minoxidil causes sodium and water retention, possibly new or worsening pleural and pericardial effusions, aggravation of myocardial ischemia and/or left ventricular hypertrophy, flushing and reflex tachycardia, and T wave changes on EKG. Additionally, hypertrichosis, a side effect first noticed in patients when minoxidil was introduced in the early 1980s, has been considered a favorable effect by some making topical minoxidil now one of the top treatments available for male pattern baldness. This side effect limits the acceptance of minoxidil in female patients.[16]

Preparations and Doses:

Hydralazine (Apresoline) 25–100 mg PO BID
Minoxidil (Loniten) 2.5–80 mg PO BI

Central Adrenergic Inhibitors

Like the direct vasodilators, the central adrenergic inhibitors are useful adjuncts in the treatment of hypertension but are not considered first line agents because of their CNS effects, in particular. They tend to be useful and effective in hypertensive patients with renal disease because they do not compromise renal function.

This class of drugs includes clonidine, guanabenz, guanfacine, and α-methyldopa. Of these, clonidine is the most commonly used and has particular utility in that it can be applied transdermally

once per week as a patch; thus, it may be useful for non-adherent patients (e.g., those with dementia). Alpha-methyldopa is, as mentioned above, along with hydralazine, one of two preferred agents for the treatment of hypertension in pregnancy due to lack of demonstrated harmful effects on the developing fetus.

Pharmacology:

Clonidine, guanabenz and guanfacine are structurally related compounds and have similar antihypertensive profiles. These agents stimulate α2-adrenergic receptors in the brain stem and reduce sympathetic outflow to the peripheral vasculature, thus lowering systemic arterial resistance and heart rate. Because they have a central action, they are more likely than other anti-hypertensives to produce drowsiness, lethargy, and depression.[17]

Alpha methyldopa is a structural analog of dopa and functions as a pro-drug. After administration, α-methyldopa is converted to α-methynorepinephrine, which then serves as the α2-adrenoceptor agonist in the medulla to decrease sympathetic outflow.

Reserpine is an old, centrally acting drug that depletes synaptic stores of noradrenaline and other catecholamines. The long duration of action is a desirable characteristic in anti-hypertensive agents. Low doses of reserpine can be used very effectively to lower BP with a low-risk of depression seen at higher doses. Nasal stuffiness is the most commonly encountered side effect.

Toxicity/Adverse Effects:

Side effects of the centrally acting alpha 2 adrenoceptor agonists include sedation, dry mouth, bradycardia, orthostatic hypotension, and impotence. Constipation, nausea and gastric upset are also associated with the sympatholytic effects of these drugs. Fluid retention and edema is also a problem with chronic therapy; therefore, they are typically administered concurrently with a diuretic. Of particular note, sudden discontinuation of clonidine can lead to rebound crescendo hypertension, which results from excessive sympathetic activity. The tendency towards significant rebound of hypertension quality makes the oral formulation of clonidine less appealing for routine use, though, as noted, the transdermal formulation does have its advantages in certain patient populations. These agents should not be used with concurrent beta blockade.

Preparations and Dosages:

clonidine (Catapres†) 0.1–0.8 mg PO BID
clonidine patch (Catapres-TTS) 0.1–0.3 mg TD weekly
methyldopa (Aldomet†) 250–1,000 mg PO BID
reserpine (generic) 0.1–0.25 mg PO daily
guanfacine (Tenex†) 0.5–2 mg PO daily

In summary, there are a number of drug classes for clinicians to choose from to treat patients. Which class or classes of medications are used depends on what compelling indications the patient has for a specific class and which side effects are likely to be well tolerated and also, quite importantly, which drug classes work most effectively with each other. There has been a progressive appearance of new drug classes over the last sixty years and we are likely to continue to see additional medications added to the anti-hypertensive regimen as drug development continues.

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Principles of Combination Therapy

Kiran Saraiya DO and Jason Biederman DO, FACOI, FASN

Learning Objectives

- Combination therapy with two or more antihypertensive medications increases efficacy and reduces adverse outcomes.
- When reductions in systolic blood pressure of greater than 20 mm Hg or diastolic pressure of greater than 10 mm Hg are necessary to achieve goal, combination therapy is usually necessary and should be considered at the initial evaluation.
- Blood pressure lowering medication combinations most likely to result in additive or synergistic blood pressure reductions based upon their pharmacological profiles are reviewed in this section.

Pre-test question:

Which of the following statements regarding combination anti-hypertensive therapy is true?

a. Combination therapy is more effective but will result in greater side effects.
b. Combination therapy is more effective and will result in fewer side effects. **(Correct)**
c. Combination therapy is rarely necessary to achieve target blood pressure recommendations
d. All combinations of two antihypertensive agents will result in additive or synergistic decreases in blood pressure.

Multiple clinical trials including the Systolic Hypertension in the Elderly Program (SHEP), Hypertension Optimal Treatment (HOT) study, United Kingdom Prospective Diabetes Study (UKPDS), Modification of Diet in Renal Disease (MDRD) study, African American Study of Kidney Disease and Hypertension (AASK), and Appropriate Blood Control in Diabetes (ABCD) trial have demonstrated a need for multiple drug therapy (often more than three agents) to achieve blood pressure targets in the majority of patients. Materson et al. showed that only 50% of patients respond to single drug therapy, regardless of the agent used.[1] However, the majority of patients who “respond” to single drug anti-hypertensive drug therapy remain above goal BP levels. A meta-analysis of 354 randomized control trials demonstrated that low dose combination therapy was more efficacious than monotherapy (see Table 1). The usual maximum (standard) doses of most agents afford only an additional 20% of blood pressure reduction compared to a half standard dose because many antihypertensive agents (e.g., RAAS blockers) have flat dose-response curves. At the same time, maximum doses of medications may be associated with significantly more side effects. As a consequence, the addition of two medications at half maximum dose tends to be more effective than the maximum dose of one agent

with less side effects.[2]

Two drug antihypertensive drug therapy combinations that lower BP most effectively are listed in Table 2. As an example, combinations of renal angiotensin aldosterone system (RAAS) blockers with either calcium channel blockers or diuretics represent highly effective BP lowering combinations. Response rates of greater than 80% have been demonstrated in some studies. Such a combination may be very useful in African American patients in particular who are less likely to respond to RAAS blockade alone. Diuretics used alone can induce volume contraction, resulting in increased activity of the RAAS, sodium and water retention, which may offset the diuretic benefits. Addition of RAAS blockade further improves HTN control and maintains diuretic benefits. In addition, RAAS blockade markedly attenuates the metabolic derangements associated with diuretic mono-therapy including hypokalemia, hypomagnesemia, and hypercholesterolemia.[3] RAAS blockade results in venodilation and, in the setting of ad lib dietary sodium intake, will result in enhanced renal sodium absorption which limits their antihypertensive effectiveness; diuretics effectively counteract the tendency of these agents to induce salt and water reabsorption and thereby significantly augment the BP lowering efficacy of RAAS blockers.

Calcium channel antagonists (CCB), particularly DCCB, activate the SNS and RAAS, providing the rationale for combination therapy of CCB and RAAS blockade. Calcium channel blockers additionally have natriuretic effects and the resulting negative sodium balance further increases RAAS activity. Combination therapy ameliorates CCB induced peripheral edema along with other dose related side effects such as headache and constipation.[3] The combination of a calcium channel blocker and a RAAS blocker lowers BP to a similar degree as the combination of a diuretic and RAAS blocker. In the Accomplish trial [4], the CCB plus ACE inhibitor combination more effectively prevented cardiovascular events than the diuretic plus ACE inhibitor.

Beta blockade results in alpha-adrenergic reflex vasoconstriction that is a result of un-opposed alpha adrenergic receptor stimulation. The addition of a direct vasodilator or a dihydropyridine calcium channel antagonist (DCCB) is complementary and can result in improved HTN control and decrease side effects. The DCCB (and direct vasodilators) mayactivate the sympathetic nervous system (as well as RAAS) providing further rationale for combination therapy with beta-blockers. Of note, combinations of non-dihydropyridine calcium channel blockers and beta-blockers should be avoided in most instances as both classes of medication have negative chronotropic and inotropic effects.[3] In

general, the response to beta-blocker monotherapy in African American and older patients is modest, and therefore the combinations of beta blockers with either diuretics or dihydropyridine calcium channel blockers can be particularly useful in this population. Dose dependent side effects of beta blockade such as lethargy and insomnia occur less frequently with combination therapy.[3]

Some antihypertensive drug combinations cannot be recommended as some combinations may result in an unacceptable side effect profile while conferring minimal incremental BP lowering. For example combinations of beta-blockers and centrally acting agents may add significantly to lethargy. And, though commonly utilized in clinical practice, this combination should be avoided given the modest incremental BP reduction afforded when two drug classes working on the sympathetic nervous system are combined. Furthermore, this combination of antihypertensive drugs may also result in significant bradycardia. Additionally, calcium channel blockers and vasodilators are less likely to be effective when used together than other combinations and may exacerbate peripheral edema.[5] The combination of an ACE inhibitor and an ARB can be useful in patients with proteinuria. However, this combination provides little incremental BP lowering over the use of either monotherapy, is associated with an increased risk of renal dysfunction and hypotensive symptoms, and cannot be recommended for routine use. Nephrologists and Hypertension specialists may occasionally opt for this combination. However, they will do so with clear vigilance for hyperkalemia, adverse symptoms, and worsening kidney function.

Used effectively, combination therapy can improve adherence by minimizing side effects and reducing pill burden. Utilizing half-maximum doses of individual agents in combination with additional agents can provide the most effective treatment for patients and should be utilized whenever more than one medication is needed. Thoughtful use of combination therapy can help to decrease HTN associated morbidity and mortality through improved HTN control.

Table 1:

Table 3 Efficacy: effects of two different drugs on blood pressure separately and in combination (summary results from 119 randomised placebo controlled comparisons; adapted from Law et al[7])

	Average (SE) fall in blood pressure (mm Hg) (treated minus placebo)	
Treatment	**Systolic**	**Diastolic**
Observed		
"First" drug alone	7.0 (0.4)	4.1 (0.3)
"Second "drug alone	8.1 (0.3)	4.6 (0.3)
Both drugs together	14.6 (0.5)	8.6 (0.4)
Expected		
Sum of first and second drugs alone	15.1	8.7
Difference between observed and expected (95% CI)	–0.5 (–1.4 to 0.4)	–0.1 (–1.0 to 0.8)

Table 4 Efficacy: blood pressure lowering effects of drugs when used at half standard dose separately and in combination

	Blood pressure reduction* (95% CI)		
	One drug	**Two drugs**	**Three drugs**
Systolic blood pressure (mm Hg)	6.7 (6.1 to 7.2)	13.3 (12.4 to 14.1)	19.9 (18.5 to 21.3)
Diastolic blood pressure (mm Hg)	3.7 (3.1 to 4.3)	7.3 (6.2 to 8.3)	10.7 (9.1 to 12.4)

*Reductions in blood pressure adjusted to a usual pretreatment blood pressure of 150/90 mm Hg, the average blood pressure in people aged 50-69 years who have a stroke or ischaemic heart disease event.[7]

(Law et al., 2003

Table 2:

Table 6. Meaningful combinations of antihypertensive agents based on pharmacological properties additive or synergistic BP reduction[a]

- Agents that inhibit the renin-angiotensin-aldosterone system (ACE inhibitors, ARB, SARA[b]) WITH agents that affect sodium balance (diuretics)
- Agents that inhibit sympathetic nervous system (β-blockers, α/β-blockers, central α_2-agonists) WITH agents that directly vasodilate (hydralazine, minoxidil, nitrates).
- Agents that inhibit sympathetic nervous system (β-blockers, α/β-blockers, central α_2-agonists) WITH agents that affect sodium balance (diuretics)
- Agents that block calcium channels WITH agents that inhibit the renin-angiotensin-aldosterone system (ACE inhibitors, ARB, SARA[b])
- Agents that block calcium channels WITH agents that inhibit sympathetic nervous system (β-blockers, α/β-blockers, central α_2-agonists)

Combinations with little to no blood pressure lowering potentiation

- Agents that inhibit the renin-angiotensin-aldosterone system (ACE inhibitors, ARB, SARA[b]) WITH agents that inhibit sympathetic nervous system (β-blockers, α/β-blockers, central α_2-agonists)[c,d]
- Agents that block calcium channels WITH agents that directly vasodilate (hydralazine, minoxidil, nitrates).

Source: JNC: *JNC 7: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* NHLBI, Bethesda, MD, 2004.

[a]Also, if dosed appropriately, combining within classes such as a β-blocker with clonidine or an ACE inhibitor with an ARB is acceptable.

[b]SARA-selective aldosterone receptor antagonist.

[c]ALLHAT: ACE inhibitor arm regimen averaged 4 to 5 mmHg higher SBP in African-American subgroup over 6 yr compared to other arms of trial.

[d]Use of a β-blocker added to an RAS blocker will potentiate BP reduction if resting pulse rate is $\geq$76 beats per minute.

(JNC VII, 2004)

Post-test questions

Which of the following blood pressure combinations would be anticipated to be least effective?

a. An acei plus a ccb
b. An acei plus a diuretic
c. An acei plus a beta blocker **(Correct)**
d. A beta blocker plus a vasodilator

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Adherence

Crystal Martin, MD and Michael Misuraca, MD

Learning objectives:

1.) To understand the various ways to assess medication adherence.

2.) To understand the factors that reduce adherence to antihypertensive therapy.

3.) To understand strategies to improve adherence to prescribed therapies.

Pretest question:

Which of the following is true regarding patient adherence?

1) Pill counts at office visits are an accurate measure of medication adherence.

2) Once daily drug therapy does not improve adherence.

3) Most patients are compliant with their medications.

4) Medication costs and co-pays >$10 affect patient adherence. (Correct answer)

Hypertension affects an estimated 72 million adults in the U.S. (American Heart Association) The National Health and Nutrition Examination Surveys (NHANES) have demonstrated improvements in hypertension treatment rates from 1999 to 2004, but without similar improvements in the prevalence of HTN control.[1] Poor medical adherence may explain much of the unacceptably low rates of blood pressure control and clearly contributes to the increased risk of stroke, coronary heart disease, congestive heart failure, and renal failure seen in the hypertensive population.[2-4]

Adherence may be defined as the extent to which a patient's behavior coincides with medical or health advice.[5] Data from medication adherence studies indicate that between 20-60% of patients fail to follow prescriptions.[6-8] Direct measures of medication adherence, such as electronic medication monitoring, direct observation, or serum and urine drug concentration measurements are expensive and burdensome for routine clinical use. In clinical practice, indirect measures to determining adherence such as patient questionnaires, unstructured conversation, daily diaries, pill counts; rates of prescription refills, and assessing clinical response are practical but may be less reliable.[9,10]

Table 1: [9]

Table 2. Major Predictors of Poor Adherence to Medication, According to Studies of Predictors.	
Predictor	**Study**
Presence of psychological problems, particularly depression	van Servellen et al.,[51] Ammassari et al.,[52] Stilley et al.[53]
Presence of cognitive impairment	Stilley et al.,[53] Okuno et al.[54]
Treatment of asymptomatic disease	Sewitch et al.,[55]
Inadequate follow-up or discharge planning	Sewitch et al.,[55] Lacro et al.[56]
Side effects of medication	van Servellen et al.[51]
Patient's lack of belief in benefit of treatment	Okuno et al.,[54] Lacro et al.[56]
Patient's lack of insight into the illness	Lacro et al.,[56] Perkins[57]
Poor provider–patient relationship	Okuno et al.,[54] Lacro et al.[56]
Presence of barriers to care or medications	van Servellen et al.,[51] Perkins[57]
Missed appointments	van Servellen et al.,[51] Farley et al.[58]
Complexity of treatment	Ammassari et al.[52]
Cost of medication, copayment, or both	Balkrishnan,[59] Ellis et al.[60]

Identifying indicators of poor adherence allow physicians to initiate appropriate interventions to improve adherence. Table 1 above lists major predictors associated with poor adherence. Interventions that successfully improve adherence include patient education, drug information, minimizing number and frequency of pills per day, identifying daily reminders or medication aids, i.e. pillbox or bubble packs, and more frequent clinic visits or clinic staff contact. In a scientific review of published randomized controlled trials (RCT) of interventions to assist patient adherence, approximately 50% of the interventions tested were associated with statistically significant increases in adherence and 17 of 39 interventions tested were associated with significantly improved treatment outcomes.[5] Complex interventional programs integrating multiple methods were the most effective for long-term treatment.

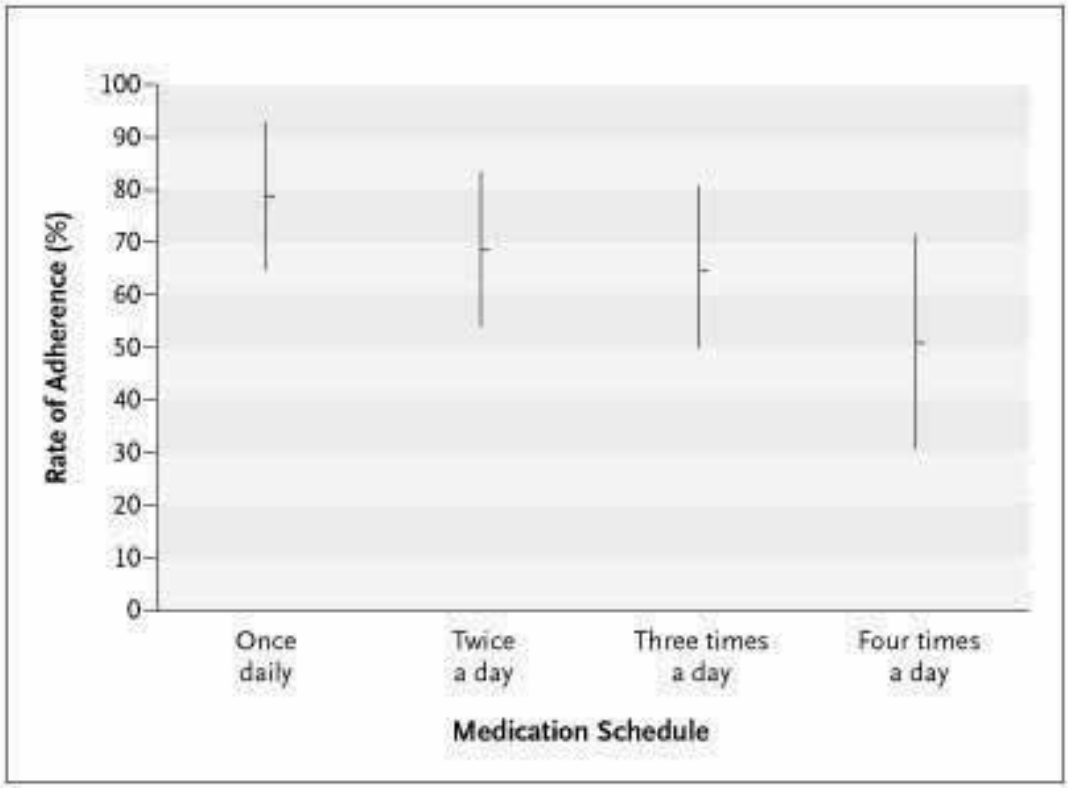
Maintaining effective patient-provider communication, addressing adherence with understanding and empathy, improving provider availability, and including the patient and family in health related decision-making, helps to build patient's trust and willingness to participate in their care. Patient trust in their physician has been found to an important factor in predicting subsequent adherence.[11] Self-monitoring of blood pressure should be encouraged as a mechanism to monitor a patient's adherence, to provide positive reinforcement and to improve hypertension control. Multidisciplinary teams including counselors, nurse practitioners, and pharmacists have also been effective in helping improve medication adherence and HTN outcomes, as well as lowering the overall cost of care. A

recently published RCT investigated the effectiveness of ward-based pharmacist interventions in reducing morbidity and hospital care among older patients. Investigators demonstrated a 16% reduction in all hospital visits and a 47% reduction in visits to the emergency department in the pharmacist intervention group.[12] A similar study in an inner city ambulatory care clinic found greater overall "taking adherence"(78.8% vs. 67.9%), "scheduling adherence"(53.1% vs. 47.2%), and "refill adherence"(109% vs. 105%) respectively in the pharmacist intervention group compared to a control group assigned to usual care.[6] The effects of the intervention dissipated in the post intervention period, highlighting the importance of continuous engagement of patients in efforts to control HTN.

The responsibility for adherence is shared among the patient, provider and the health care system. When prescribing medications, providers need to consider not only pharmacologic efficacy but also simple dosing regimens and inexpensive drugs. Limits on health insurance drug benefits, expensive co-pays, and lack of drug coverage have a negative impact on patient adherence and contribute to adverse outcomes. Comparisons of outcomes in Medicare+Choice patients with capped benefits of $1000 versus unlimited drug benefits demonstrated fewer office visits (RR 0.97) higher rates of ER visits (RR 1.09), higher non-elective hospitalizations (RR 1.13), and increased death (RR 1.22) in patients with capped benefits.[8] Furthermore, a retrospective cohort study of first-fill adherence for patients with HTN found a co-pay of less than $10 was associated with greater patient adherence than co-pays greater than $10 (87% vs. 72% respectively, $p< 0.001$). Referral to assistance programs, access to reliable supply systems, and encouraging non-pharmaceutical therapy (low salt diet, exercise, weight loss) can help ease the cost burden and improve adherence to prescribed therapy.

A large pill burden has been shown to be a major factor contributing to poor patient adherence. Several Cochrane systematic reviews have recently evaluated the evidence for specific interventions to improve adherence to antihypertensive or lipid-lowering drugs.[13,14] The review of interventions to promote antihypertensive drug adherence included 38 studies of 58 different interventions and concluded that strong evidence supports the value of reducing the number of daily doses.[13] Pill burden reduction can be achieved not only by limiting the total number of antihypertensive drugs but also by favoring usage of once-daily formulations over twice-daily and three times daily formulations. Keeping care simple by using once-daily drugs and using the fewest drugs needed to achieve blood pressure goal is central to improving patient adherence. The use of combination agents is a good strategy to reduce pill burden. However, many combination medications are relatively new and newer agents tend

to be more costly and sometimes unavailable through many prescription drug plans. The following graph from Osterberg and Blaschke illustrates the inverse relationship between dosing frequency and adherence rate.[9]



Post-test question:

In summary, medication non-adherence is a complex and common phenomenon. Improving patient adherence requires recognition of the multiple overlapping factors that contribute to non-adherence, including but not limited to patient understanding, dosing frequency and the costs of medication. Addressing these issues often requires the consistent efforts of a multidisciplinary team. Integrated approaches that also directly involve the patient have been shown to significantly improve HTN control and reduce adverse HTN outcomes.

Post-test question:

35y/o male w/ h/o hypertension diagnosed 2 years ago presents to your clinic for a routine physical exam. He missed his last 2 appointments and admits to missing his medications up to 3-4 times per week. He is presently taking Clonidine 0.1mg BID. His blood pressure is 160/100 and HR 85. His physical exam is unremarkable. What is your next step?

1) Inform him that his noncompliance will cause a heart attack or stroke and he should take his medication as prescribed.

2) Increase to Clonidine 0.2mg q8hrs.

3) Stop Clonidine and initiate single pill combination therapy with a CCB and ACEi once daily, have him return in 1-2 weeks for blood pressure check and give him a prescription for a home blood pressure machine for self monitoring. (Correct answer)

4) Add a beta-blocker, metoprolol 25mg BID and have him return in 6 months.

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Hypertension Treatment in Special Situations

Hani AlSharif, Ankur Sandhu, and Mark D Faber

Orthostatic Hypotension

Pretest question:

Which ONE of the following patients meets the definition of orthostatic hypotension?

A. 16 mm Hg decrease in systolic blood pressure first observed after standing 5 minutes
B. 16 mm Hg decrease in diastolic blood pressure after standing 5 minutes
C. 10 mm Hg decrease in systolic blood pressure after standing 2 minutes
D. 10 mm Hg decrease in diastolic blood pressure after standing 2 minutes(**correct)**

Which ONE of the following statements about orthostatic hypotension is correct?

A. It is a rare disorder in healthy home dwelling ambulatory adults, occurring in less than 5% of such patients.
B. It is not associated with increased mortality if diabetic patients are excluded.
C. Symptoms may improve if the head of the bed is elevated 5 degrees during sleep
D. Sympathomimetic amines improve symptoms of orthostatic hypotension without worsening supine hypertension. **(correct)**

Definition:

Orthostatic hypotension (OH) is defined as the persistent and consistent occurrence upon assuming an upright posture (within 3 minutes) of

1. A 20 mm Hg or more decrease in systolic pressure, and/or
2. A 10 mm Hg or more decrease in diastolic pressure.

Prevalence and Significance:

A recent Scandinavian study of home dwelling ambulatory patients older than 75 years found an incidence of OH of 34%.[1] Although many patients are asymptomatic, OH is an important cause of morbidity and mortality, especially in the elderly. Patients can develop symptoms of cerebral hypoperfusion, such as tachycardia, dizziness, sweating or syncope. The most obvious risk of

orthostatic hypotension, especially in elderly patients, is the risk of serious injury due to falling due to syncope or near-syncope, with resulting hip fracture or head injury. The severe supine hypertension that frequently accompanies OH is also a potential source of morbidity. All elderly patients and all patients at increased risk of OH including those with diabetes mellitus and those with neurologic diseases should be screened for orthostatic decreases in BP. Ambulatory 24 hour BP monitoring may be helping in detecting or monitoring the supine hypertension associated with this syndrome.

Shibao [2] reported that hospitalizations in patients with OH numbered 233 per 100,000 in patients over 75 years old, with a median length of hospital stay of three days, and an in-hospital mortality rate of 0.9%. Equally discomforting is the observation of increased mortality in patients with OH. Middle aged patients with OH in the Atherosclerosis Risk in Communities Study experienced a hazard ratio of death of 2.0 (95% CI 1.6-2.7) [3] even after adjustment for known cardiovascular risk factors or after excluding those dying with the first 2 years of follow-up and those with known cancer, diabetes, CHD, hypertension and CVA. Elderly patients with OH also have increased mortality.[4]

Pathophysiology and Etiology

The physiology of the baroreflex is complex (figure 1). Baroreceptors are stretch sensitive receptors located in the adventitia of blood vessels. The major function of the baroreflex appears to be short term regulation of BP and buffering of minute to minute blood pressure fluctuations. The term “receptor” is a misnomer as BRs work by relaying afferent signals to the brainstem, not by receptor mediated signaling. The most sensitive BRs are located in the aortic arch and sinuses of the left and right carotid arteries, but other receptors are situated in the inferior vena cava and heart. The innervation of the carotid sinus and aortic arch BRs are through the glossopharyngeal nerve (CN IX) and the vagus nerve (CN X) respectively. Increases in BP result in stretching of blood vessel walls and generation of action potentials within BRs. This effect is enhanced with higher elevations in BP. Generated action potentials travel to the nucleus of the solitary tract located in the medulla. Here, glutaminergic excitatory fibers activate the caudal venterolateral medulla which in turn sends inhibitory GABAnergic signals to the rostral venterolateral medulla (RVML). This inhibition results in parasympathetic stimulation with a resultant reduction in heart rate and a drop in peripheral resistance and thus lowering blood pressure. Conversely, a reduction in BP as seen in low output states, results in decreased baroreceptor firing and inhibits parasympathetic vagal response, which activates the RVML causing sympathetic activation (increased cardiac output, systemic venous return and total peripheral resistance) and an increase in

BP.

It is important to note that labile hypertension (sometimes to the extent of episodic hypotension), not orthostatic hypotension, is the most common presentation of BR failure. The key difference appears to be absence of splanchnic vascular tone in patients with OH, resulting in large amounts of blood pooling in the abdomen. The causes of OH can be categorized as drug induced, primary or secondary neurogenic disorders, and non-neurogenic disorders.[5] All result in dysfunction of the afferent (arterial and venous) and/or efferent limbs of the baroreceptor reflex. The baroreceptor reflex circuit contains both vasoconstrictive (adrenergic) and vasodepressor (parasympathethic) elements. Common causes of baroreflex dysfunction include:

1. Volume depletion
2. Drugs (including diuretics, alpha-adrenoreceptor antagonists, antihypertensive medications, tricyclic antidepressants, dopamine agonists)
3. Neuropathies (peripheral neuropathy from diabetes or amyloidosis)
4. Neurological disorders (Parkinson's, Lewy body disease, multiple system atrophy, postural orthostatic tachycardia syndrome)
5. Adrenal insufficiency
6. Idiopathic orthostatic hypotension

Diagnosis and Workup

A detailed history of current medical conditions is essential:

1- Past Medical history (diabetes, heart failure, HIV Parkinson's etc)
2- Review of systems (presence of diarrhea, fever, vomiting, headaches)
3- Medications (antihypertensive, anticholinergic, antidepressants)
4- Family History (Hereditary sensory autonomic neuropathy)
5- Social History (alcohol, recreational drugs)

Laboratory Workup

Laboratory tests are guided by the history and acuity of the disease course, and may include fasting blood sugar, HIV, RPR, tests of the hypothalamic-pituitary-adrenal axis, and autoimmune

markers (RF, Anti SS-A or SS-B)

Imaging and Other tests

The following tests may be indicated as directed by clinical suspicion:

1- EKG/Telemetry
2- CT head or brain MRI
3- Tilt table testing
4- Nerve conduction studies or EMG
5- Bladder ultrasound
6- Lumbar puncture

Management and Treatment

Nonpharmacological treatments include:

1- Treatment of underlying etiology if possible (e.g., improved glycemic control in diabetic neuropathy)
2- Correction of volume depletion
3- Physical maneuvers (e.g., slow assumption of upright posture after sleep, avoiding isometric exercise, tensing of lower body muscles)
4- Compression stockings
5- Deliberate volume expansion with increased water intake or saline infusion
6- Elevating the head of bed on blocks (15 cm or approximately 5 degrees) to prevent nocturnal baroreceptor deactivation.[6,7]

Pharmacological treatments can be used for symptomatic relief. Much of the treatment is anecdotal and the reader is referred to recent reviews [5,8,9] for details. It is unknown whether or not symptomatic treatment reduces the morbidity and mortality associated with orthostatic hypotension. Before adding medications for the treatment of orthostatic hypotension, medications known to cause or exacerbate the syndrome should be discontinued or decreased if possible. Antihypertensive medications should be adjusted to maintain a normal standing BP. It is understood that this frequently results in considerable elevation of supine or seated blood pressures

1- Fludrocortisone : a mineralocorticoid that helps retain sodium and water, thereby partially compensating for vascular tone that inappropriately high for normal intravascular volumes

2- Midodrine : an α-adrenergic agonist that causes vasoconstriction and increases peripheral vascular resistance. This medication is particularly effective in patients with noradrenergic denervation, and should probably be avoided in the evening to avoid further worsening of supine hypertension. Other alpha-adrenergic agonists that have been used include ephedrine, pseudoephedrine, and phenylephrine.

3- Yohimbine, a centrally and peripherally acting α-2 adrenoceptor antagonist, increases sympathetic nervous system efferent output by antagonizing central or presynaptic a2-adrenoreceptors. Side effects of yohimbine include anxiety, tremor, palpitations, diarrhea and supine hypertension

4- Clonidine, predominantly a presynaptic α-2 adrenoceptor agonist, has a sympatholytic effect in normal individuals by decreasing catecholamine release. Clonidine has lesser affinity for postsynaptic α-1 adrenoceptors, but this effect can normally be seen only at high doses (> 1 mg per day). However, in patients with neurogenic OH and markedly diminished central efferent sympathetic activity, the postsynaptic affects may predominate. The drug needs to be used with caution since it can exacerbate hypotension in some patients.

5- Droxidopa (L-*threo*-3,4-dihydroxyphenlyserine or L-DOPS) has been reported to improve OH. It has been suggested that droxidopa may be less likely to exacerbate supine hypertension than standard pressor drugs such as midodrine. The drug appears to replete postganglionic adrenergic axons, thereby restoring physiologic control of supine BP. It also seems to improve OH even where there is a severe loss of postganglionic fibers (as in pure autonomic failure) thereby suggesting an extraneuronal mode of action as well.

6- Non-selective beta blockers, such as propranolol, result in unopposed stimulation of peripheral α-1 receptors.

7- Desmopressin, a vasopressor that helps constrict peripheral vessels and may increase cerebral and coronary blood flow

8- Pyridostigmine, a cholinesterase inhibitor that increases ganglionic trafficking in proportional response to orthostatic stress

9- SSRI antidepressants

Key Points

- OH is present in up to 1/3 of ambulatory patients > 75 years old, and is associated with increased rates of hospitalization and mortality
- Orthostatic BP should be measured in all elderly patients, and patients with disease such as diabetes mellitus, spinal cord injury, and Parkinsons disease who have an increased risk of OH
- Commonly used medications associated with OH include diuretics, alpha-antagonists used for prostatism, antihypertensive medications, and non-SSRI antidepressants
- Combinations of non-pharmacologic and pharmacologic strategies are required to minimize both symptoms of orthostatic hypotension and exacerbation of supine hypertension.

Figure 1: [8]

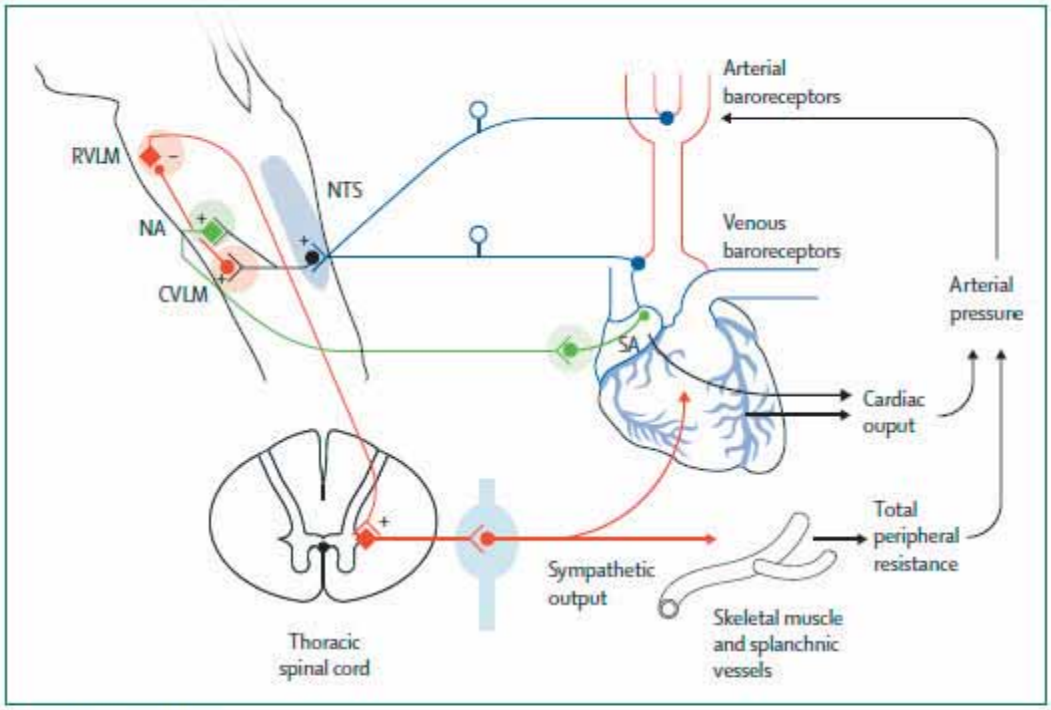

***Figure 1:* Baroreflexes**
Baroreceptor afferents (dark blue) synapse at the nucleus of the tractus solitarius (NTS). The vagal baroreflex pathway (green) runs from the NTS to the nucleus ambiguus (NA) and sends efferents to the sinoatrial node (SA). The adrenergic baroreflex pathway (red) runs from the NTS to the caudal ventrolateral medulla (CVLM), and from there to the rostral ventrolateral medulla (RVLM). The adrenergic pathway continues with sympathetic efferents from the RVLM to the interomediolateral thoracic spinal cord, and from there to autonomic ganglia and to the heart, arterioles, and venules.

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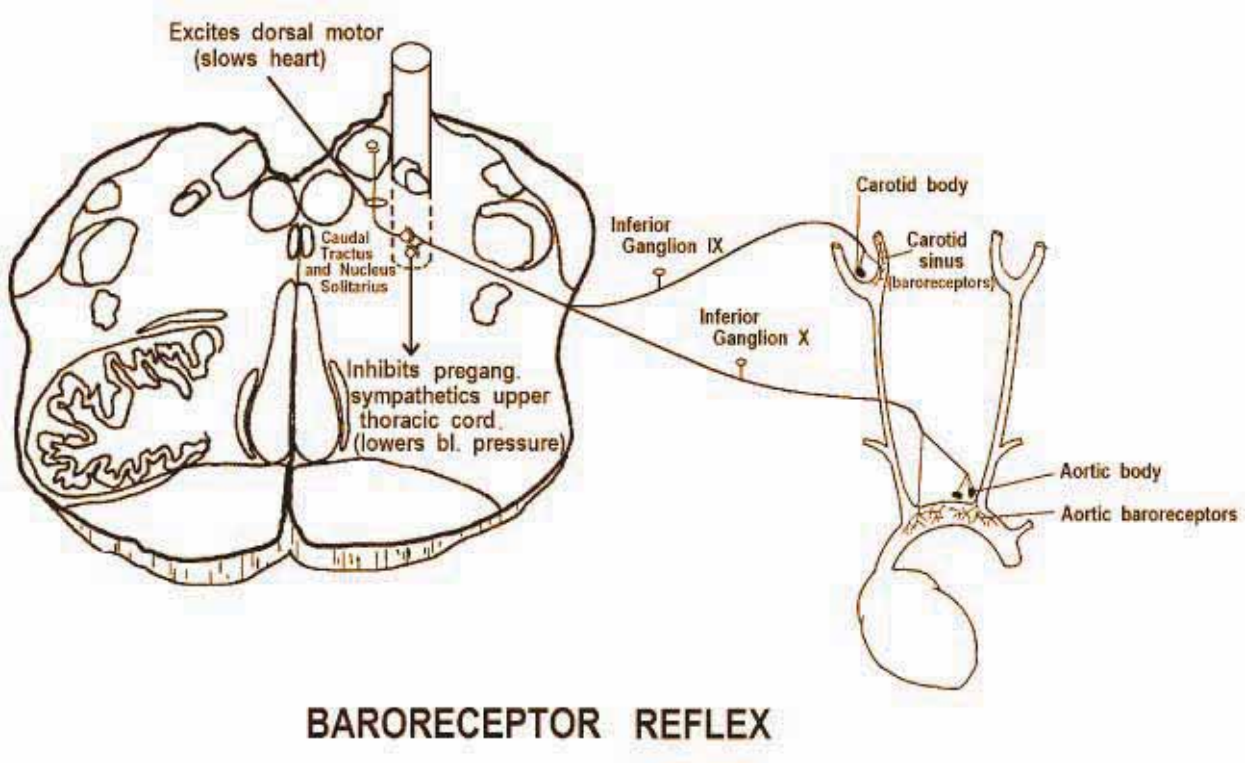
Baroreceptor Dysfunction

Ankur Sandhu, MD

The arterial baroreflex is primarily involved in tight regulation of short-term BP control. Dysfunction of the baroreceptor (BR) reflex plays an under-recognized but crucial role in the pathogenesis of hypertension. BRs are stretch sensitive receptors located in the adventitia of blood vessels. The term "receptor" is a misnomer as BRs work by relaying afferent signals to the brainstem, not by receptor mediated signaling. The most sensitive BRs are located in the aortic arch and sinuses of the left and right carotid arteries, but other receptors are situated in the inferior vena cava and heart. The innervation of the carotid sinus and aortic arch BRs are through the glossopharyngeal nerve (CN IX) and the vagus nerve (CN X) respectively. Increases in BP result in stretching of blood vessel walls and generation of action potentials within BRs. This effect is enhanced with higher elevations in BP. Generated action potentials travel to the nucleus of the solitary tract located in the medulla. Here, glutaminergic excitatory fibers activate the caudal venterolateral medulla which in turn sends inhibitory GABAergic signals to the rostral venterolateral medulla (RVML). This inhibition results in parasympathetic stimulation with a resultant reduction in heart rate and a drop in peripheral resistance and thus lowering BP. Conversely, a reduction in BP as seen in low output states, results in decreased baroreceptor firing and parasympathetic vagal response, which activates the RVML causing sympathetic activation (increased cardiac output, systemic venous return and total peripheral resistance) and an increase in BP.



www.neuroanatomy.wisc.edu/.../Images/11B.jpg

The baroreceptor reflex plays an important role in buffering acute changes in BP, whereas longer long term control is maintained through neurohumoral mechanisms. It is important to note that the baroreceptor set point is not fixed; for instance in hypotension the set point will be lowered, in some instances the BRs response can be silent. The contrary is true of established hypertension, where the baroreflex is set at a higher threshold and a reduced gain. The reduction in gain is thought to be a consequence of reduced BRs sensitivity. This finding is also noted in congestive cardiac failure.[1-3]

BARORECEPTOR DYSFUNCTION (BD)

There have been many animal studies, namely in dogs, where temporary denervation of baroreceptors resulted in severe volatile BP readings. BD is a syndrome. Most case reports describing BD are in the setting of carotid endartectomies and carotid artery anomalies, although it can arise through any disruption in the baroreceptor pathway (e.g., neck trauma or irradiation, carotid tumor resection, lesions in the nucleus tractus solitarii, CN IX and X). [3,4,5] It can masquerade clinically as a pheochromocytoma because of its associated volatile hypertension (often exceeding SBP≥ 200), possible stigmata of hypertensive emergency, orthostatic tachycardia, palpitations and emotional

lability. The wide fluctuations in BP have been linked to a large catecholamine surge. In rare instances, vagal predominance (labeled “vagotonia”) may occur, characterized by hypotension, bradycardia and in severe cases asystole. In 1985 Fagius and Walsh performed temporary anesthetic blocks of CN IX and X in human subjects they reported severe hypertension, tachycardia with increased sympathetic activity. As mentioned previously BD mimics pheochromocytoma and this must be ruled out in this setting.[4-7]

TREATMENT

In keeping with its under-recognized and under-reported nature, the literature addressing treatment of BD is sparse, consisting mostly of observational case reports. In the acute setting, hypertensive crisis has been managed by IV labetalol, nitroprusside or phentolamine. In less acute settings centrally acting α adrenoreceptor blockade with clonidine or phenoxybenzamine has been advocated.[6,7]

CONCLUSION

The baroreceptor reflex is vital in ameliorating acute changes in blood pressure. BD results in unexplained labile hypertension, tachycardia, and palpitations that can mimic pheochromocytoma. This syndrome is under-recognized and under-reported, with limited data looking at long term sequelae. [5-7]

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Resistant hypertension

Ziad Arabi, MD

Learning objectives:

1-To recognize resistant hypertension and to differentiate it from psuedoresistasnce;

2-To review the factors that might contribute to BP resistance including life style factors, suboptimal therapy, drugs related and secondary causes of HTN; and

3- To review nonpharmacological and pharmacological treatments including the proper use of diuretics and medications combinations.

Pretest: JJ is a 58 year old African American female with history of HTN, DM, hyperlipidemia, and osteoarthritis. Her last BP readings in the clinic over the last 6 months were 175/94, 184/78 and 192/105 mm Hg. Her estimated glomerular filtration rate is 40 ml/min/1.73 m^2. Medications include atenolol 50 mg BID, lisinoprol 40 mg daily, amlodipine 5 mg daily, simvistatin 40 mg at bed time and ibuprofen 400 mg TID PRN for knee pain. Her physical exam and labs are otherwise unremarkable.

The best first step to improve her BP control would be: A) to increase amlodipine to 10 mg daily, B) change lisinopril to 20 mg BID, C) increase atenolol to 10 mg BID, D) - add clonidine 0.1 mg BID and titrate up as needed, or E) - add Furosemide 20 mg BID. (**Correct answer**)

Definition: Resistant hypertension (RH) is defined as persistently elevated BP despite adherence to a regimen of three optimally dosed antihypertensive agents of different classes including a diuretic or controlled BP on 4 or more antihypertensive medications. Optimal dosing is reasonably considered to be at least half of the FDA approved maximal dose of an antihypertensive agent given the known relatively flat BP dose-response curve for most drugs

Blood Pressure Goals: The BP goal according to JNC 7 for most hypertensive patients is < 140/90 mm Hg. However, in individuals with CKD (DGFR < 60 ml/min/1.73 m^2 or spot albumin:crea ratio > 200) or DM, the BP goal is < 130/80 mm Hg.

Prevalence: The exact prevalence of RH is unknown yet.[1] However, it is estimated that RH is relatively common affecting 10 to 15% of the patients with HTN [2] and.[3]

ETIOLOGY

Resistant HTN in most of the cases is mutifactorial.[4] Causes can be divided as patient-related causes (life style factors, adherence), physician-related (suboptimal therapy), medication-related and disease-related (or secondary HTN). It is also very important to rule out psuedoresistance. Pseudoresistance can result from poor BP technique, poor medication adherence, white-coat effect**,** or pseudohypertension (Osler phenomena):

Lifestyle Factors

1- **Obesity** is a common feature of patients with resistant hypertension and more than 40 percent of patients with resistant hypertension are obese.[5] Accordingly, obesity is known to be associated with resistance to pharmacological BP lowering.

2- **Excessive dietary salt intake** has been specifically documented as being common in patients with resistant hypertension.[2] The frequency of salt sensitivity is increased among patients who are at least 60 years of age, patients who are African American or obese, and patients with renal impairment.[6] Approximately 75 – 80% of dietary sodium intake can be linked to the consumption of high sodium foods (e.g., processed meats, canned goods).

3- **Heavy alcohol intake** is associated with treatment-resistant hypertension.[7] On the other hand, alcohol reduction is associated with a significant reduction in systolic and diastolic blood pressures of -3.31 mm Hg and -2.04 mm Hg, respectively.[8] Alcohol consumption should be kept to 2 or fewer drinks per day in men and no more than 1 drink per day in women.

Physician Related Factors (Suboptimal therapy)

Suboptimal therapy was the single most common (and most correctable) cause of resistant hypertension. The major causes of inadequate medical treatment were lack of administration of enough effective drugs and failure to prevent volume expansion with adequate diuretic therapy.[9] It is important to ensure the diuretic therapy is appropriate to the level of kidney function. For example, hydrochlorothiazide is ineffective when the estimated glomerular filtration rate is < 45 ml/min.1.73 m^2, at least when dosed conventionally. Chlorthalidone, a thiazide-like diuretic, effectively lowers BP down to estimated glomerular filtration rates in the low to mid 30's. It is not uncommon for patients with poorly

controlled BP to have been victimized by “therapeutic inertia”. That is, to have repeated clinic visits with elevated BP levels noted, but with no intensification of therapy being undertaken. Also, utilization of ineffective drug combinations – beta blockers plus RAAS blockers, beta blockers and clonidine, or ACE inhibitors and ARBs – contributes to poor BP control.

Drug -related factors

A variety of medications and substances can raise the BP and, contribute to treatment resistance.[10] Examples include nonsteroidal anti-inflammatory drugs (NSAIDs), Selective COX-2 inhibitors, sympathomimetic drugs, oral contraceptives, and some herbal preparations.[11] While the use of these agents is fairly common, their effects are highly individualized and these agents account for only less than 2 percent of cases of resistant hypertension.[9]

Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors, impair the excretion of sodium, cause volume retention, and also inhibit the production of local renal vasodilatory prostaglandins. The therapeutic action of angiotensin-converting–enzyme (ACE) inhibitors and loop diuretics (but not calcium-channel blockers) depends on the availability of these prostaglandins.[12] At equally effective doses for osteoarthritis management, the ability on NSAID and COX2 inhibitors to destabilize hypertension control is not universally equal among all agents used [12] and.[13] The effect of acetaminophen on BP medications seems almost inert when compared to piroxicam and Ibuprofen.[14] Sulindac is one NSAID that has not been shown to affect renal prostaglandin synthesis and raise BP.

Disease related factors (or secondary hypertension)

Secondary causes of HTN accounts of less than 5 percent of all HTN causes[15] and up to 10 percent of cases of RH.[16] Blood pressure elevations are often more challenging to treat until the underlying secondary cause is identified and treated. Secondary causes of HTN are addressed separately under the Chapter of Secondary Hypertension.

1- **Renal Parenchymal Disease**: Only less than 15% of the patients with CKD who are followed in nephrology clinics achieve blood pressure control (of <130/80 mm Hg) despite of the use on average of 3 different antihypertensive agents.[17] Chronic kidney disease has been linked to resistance to the BP lowering effect of antihypertensive agents.

2- **Critical Renal Artery Stenosis or Renovascular Hypertension:** Should be suspected

especially in elderly smokers who have evidence of diffuse atherosclerotic vascular disease, an abdominal bruit, hypokalemia, a recent increase in the severity of hypertension, or an acute decline in renal function shortly after institution of therapy with an ACE inhibitor.[18] Bilateral renal artery stenosis should be suspected in patients with a history of "flash" pulmonary edema, especially if systolic heart function is preserved.[2] More than 90% of renal artery stenosis are atherosclerotic in origin; Less than 10% of renal lesions are fibromuscular in etiology developing most commonly in women, <50 years of age.[19] However, it must be noted that it remains controversial as to how important renal artery stenosis is to BP elevations in a causal sense.

3- **Primary Aldosteronism:** Older studies estimated that 6% of hypertensive patients have primary hyperaldosteronism.[20] More contemporary estimates are that ~10% of all hypertensives have primary aldosteronism while ~ 20% of individuals with resistant hypertension are affected. The prevalence is even higher (10- 20%) among patient with among patient with RH [21] and.[22] In addition, patients with resistant hypertension as a group have higher plasma aldosterone levels and lower plasma renin activities than normotensive controls or those with controlled hypertension.[23] Consideration of primary aldosteronism should not be limited to hypokalemic patients, since more than 50 percent of patients with this disorder are not hypokalemic [21]and.[24]

4- **Obstructive Sleep Apnea :**Obstructive sleep apnea is very common in patients with RH with prevalence reached up to 83 % at one university hypertension clinic.[25] Treatment of sleep apnea with continuous positive airway pressure (CPAP) likely improves blood pressure control.[26]

5- **Pheochromocytoma** and **Cushing's syndrome** are rare but important causes of secondary HTN and they are addressed separately.

Treatment Recommendations

Nonpharmacological Recommendations

Patients should routinely be encouraged to reduce their intake of sodium, lose weight (if appropriate), engage in moderate exercise, and reduce their intake of alcohol. Reductions in dietary sodium intake have been shown to have a prompt and profound BP lowering effect in persons with resistant hypertension.

Treatment of Secondary Causes of Hypertension

When renal artery stenosis, obstructive sleep apnea, primary aldosteronism, pheochromocytoma, or Cushing's disease is suspected or confirmed, treatment will be specific for that particular disorder.

Pharmacological Treatment

The best approach to treat RH has not been directly evaluated in randomized trials and the choice of treatment regimen is based largely on physiological principles and clinical experience. Because volume overload is common among such patients, the most important therapeutic maneuver is generally to add or increase diuretic therapy.[23] It is important to ensure that the diuretic is appropriate to the level of kidney function. Also, sometimes utilization of more than one diuretic will be necessary in complex, multi-drug regimens. Another important therapeutic maneuver is to titrate BP medication up to ideal doses and, or to use effective combinations of BP medications [27] and.[2] The medication regimen should be examined closely for ineffective antihypertensive drug combinations.

Withdrawal of Interfering Medications particularly NSAIDs and Cox II inhibitors if possible.[2] Therefore, if analgesics are necessary, sulindac or acetaminophen or even mild narcotic pain medications may be preferable to most NSAIDs in subjects with resistant hypertension.

Diuretic Therapy as explained above is very essential to overcome the inappropriate volume expansion seen in RH and it is in fact essential aspect of the definition of resistant HTN.

Thiazide diuretics:

While Hydrochlorothiazide is widely used and effective in treating HTN in patients with normal renal function; Chlorthalidone is the recommended and the most effective thiazide diuretic for resistant HTN.[2] The extremely long half-life of 40 to 60 hours for chlorthalidone differentiates it from HCTZ, which has a much shorter half-life from 3.2 to 13.1 hours.[28] However chlorthalidone might be associated with excessive degrees of hypokalemia and requires more monitoring[28]; however, this is of much less concern when chlorthalidone is used together with RAAS blockers given that the latter reduces the incidence of hypokalemia by two-thirds to three quarters. Chlorthalidone also, in contrast to hydrochlorothiazide, is available only in few fixed-dose combinations and generally requires separate dosing.[2] Metolazone, a long-acting thiazide-like diuretic, is highly effective in persons with depressed kidney function

Loop diuretics

In patients with underlying CKD, loop diuretics should be strongly considered. Short-acting loop diuretics, such as furosemide or bumetanide must be given two or three times per day.[29] Longer-acting diuretics such as torsemide may be given once a day.[18]

Mineralocorticoid Receptor Antagonists

Spironolactone [30] and amiloride [31] are safe and effective in treating RH. Interestingly, the BP reduction with use of spironolactone is quite impressive and is not limited to patients with hyperaldosteronism.[32] Hyperkalemia is uncommon with either agent[33], however, it still needs to be monitored especially in high risk patients.[2] Patients with diabetes mellitus are particularly prone to hyperkalemia given that ~ one-third have hyporeninemic hypoaldosteronism (type IV renal tubular acidosis). Breast discomfort occurs in ~6% of patients treated with spironololactone.[34]

Dosing

Patients who take at least one of their hypertensive agents at bedtime had better nocturnal and 24-hour mean BP control.[35]. http://circ.ahajournals.org/cgi/content/full/117/25/e510 - R138-189141#R138-189141Twice-daily dosing of BP medications might be considered to minimize side effects associated with the peak effects of too many antihypertensive medications being taken at the same time.

Combination Therapy

Beyond studies of 2-drug combinations, there is little data assessing the efficacy and safety of specific combinations of 3 or more drugs.[2] A generally useful strategy is to combine agents from various classes, each of which has one or more of the following effects: a reduction in volume overload

Here are several examples of medication combinations that might be useful to overcome BP resistance:
1-Combined alpha- and beta-blockers (Labetalol and Carvedilol) may improve BP control.
2-Centrally acting agents (for example, clonidine) are effective antihypertensive agents but have a higher incidence of adverse effects.
3-Dual diuretic therapy (such aldosterone antagonist plus a thiazide or loop diuretic).[36]

4-Direct vasodilators (e.g.minoxidil) may be necessary in some cases – typically in men (causes fine vellus hair growth and is thus usually avoided in women). The use of minoxidil will necessitate concomitant beta-blockerade or the use of nonDHP calcium channel blockers to slow the pulse rate down and loop diuretics such as furosemide to counterbalance the minoxidil-induced fluid retention. .

5-Dual calcium-channel blockers (a dihydropyridine, such as amlodipine, plus a nonDHP calcium antagonist such as verapamil.[37]

Summary and Recommendations

White coat HTN and therapeutic noncompliance should be considered in persons suspected of having resistant HTN. Resistant HTN is typically multi factorial. Obesity and excessive alcohol and salt might exacerbate HTN resistance. Suboptimal dosing, the use of too few drugs, and inadequate use of diuretics are the most common causes of RH in primary care. Secondary causes (including exogenous substances) must also be considered.

Post test

RR is 48 year old man with history of uncontrolled HTN and a myocardial infarction ~ 6 months ago. His BP readings at his last three clinic visits were 179/95, 164/89 and 183/72 mm Hg while his pulse ranged from s 87 to 96 beats/min. His weight has been stable at 207 lbs. BUN and creatinine were 25 and 1.5, respectively. He continues to smoke but he does not exercise. His medication list includes metoprolol 25 mg BID, HCTZ 25 mg daily, and lisinopril 10 mg daily. He states that he has been compliant with medication for the last three months.

Which one of the following choices represents the best approach to improve his BP control: 1) intensify life style modification, including smoking cessation and weight loss, 2) noncompliance is very likely and no medication adjustment is needed at this time, 3) screen for pheochromocytoma, 4) increase lisinopril to 20 mg/d, or 5) increase metoprolol to 50 mg BID and add amlodipine 5 mg/d. **(Correct answer)**

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HYPERTENSIVE URGENCY AND EMERGENCY

Ankur Sandhu, MD and Mark Faber, MD

CASE

A 49 year old woman is brought to the emergency department by a relative with a one day history of headache, blurred vision and confusion. She has been out of her anti-hypertensive medications for one week. Her past medical history is significant for stage 3 CKD due to hypertensive nephrosclerosis, and abuse of crack cocaine and marijuana. Blood pressure is noted to be 220/130mmHg. Physical examination reveals a confused patient, with papilledema, elevated JVP, and bibasilar crackles. Neurological exam revealed normal power in all 4 limbs, bilateral clonus, and equivocal Babinski signs. Serum values are significant for K^+ 3.4mEq/L, BUN 30 mg/dL, creatinine 3.5 mg/dl (baseline 1.7 mg/dL), BNP 1400 pg/ml, and initial cardiac troponin 1.8ng/mL. Urine toxicology analysis is positive for canabinnoids. ECG reveals left ventricular hypertrophy by voltage criteria with T wave inversions in lateral leads. A chest X-ray reveals bilateral pulmonary edema with cardiomegaly. Computed tomography of the head without contrast reveals low attenuation suggestive of ischemia/ ischemic edema in the cortex and subcortical white matter of the parieto-occipital lobes. The patient was admitted to the cardiac intensive care unit treated with intravenous nitroprusside and intravenous furosemide 80mg Q 12 hours. Her BP decreased to 196/100 mm Hg over the first three hours. During the next 12 hours there was progressive improvement in neurological status and resolution of pulmonary edema. She was switched to oral antihypertensive medications and transferred to a general practice unit.

EPIDEMIOLOGY AND ETIOLOGY

Approximately 1-2% of the 72 million U.S. patients with hypertension can be expected to experience a hypertensive emergency. Despite the widespread availability of effective antihypertensive medications, hypertensive urgency or emergency (defined in the following section) still accounts for up to 25% of emergency room visits.[1] As this case illustrates, > 90% of patients with hypertensive emergencies have been previously diagnosed with essential hypertension and have received prescriptions for antihypertensive medication [2] but inadequate BP control [3], medication non-adherence[4], and drug abuse [5] are major risk factors. Despite widespread agreement that the vast majority of hypertensive emergencies are caused by severe essential hypertension, it remains standard practice to evaluate patients for causes of secondary hypertension if it has been done previously at some point following control of their BP.

DEFINITIONS

The management of extreme elevations in BP has been hampered historically by the use of overlapping, and loosely defined terminology. The JNC 7 complete report [6] retains the term "hypertensive crisis" which is further divided into categories of "hypertensive emergency" and "hypertensive urgency." Hypertensive emergency is defined as "severe elevation in BP that *is typically* > 180/120 and complicated by evidence of new or progressive target organ dysfunction (TOD)," such as the complications listed in Table 1. Thus, our case study is an example of a hypertensive

emergency by virtue of the associated encephalopathy, congestive heart failure, and papilledema. It is important to note however that the rate of BP change also influences the degree of TOD and clinical symptoms associated with a given BP elevation. To an extent, the arteriolar hypertrophy induced by chronic hypertension protects target organs from abrupt increases in transmitted pressure during acute increases in BP. In contrast, far smaller elevations of BP can result in true hypertensive emergencies in the setting of *de novo* hypertension, such as that seen during preeclampsia or acute drug toxicity. Hypertensive emergencies require therapy that immediately lowers BP but not to normal, as detailed in Therapy section below. The reader is also referred to several recent reviews on the subject [7-11]

TABLE 1
Target Organ Damage associated with hypertensive emergencies

TARGET ORGAN	SIGNS/SYMPTOMS
BRAIN	Intracerebral hemorrhage, posterior reversible leukoencephalopathy, seizures, confusion, TIA, cerebral infarction
HEART	Pulmonary edema, acute myocardial infarction, acute coronary syndrome/ unstable angina pectoris
BLOOD VESSELS	Aortic dilatation, acute aortic dissection, microangiopathic hemolytic anemia
KIDNEY	Acute renal failure (acute kidney injury), hematuria, proteinuria
RETINA	Papilledema, hemorrhages, retinal edema, visual disturbances
UTERUS	Eclampsia

In the absence of identifiable new or worsening pressure-related TOD, BP ≥ 220/120 is classified and a “hypertensive urgency.” In contradistinction to its name however, BP in this situation should be reduced over 24-48 hours. There is no evidence that the benefits of rapid BP lowering outweigh the risks in the absence of acute TOD. Despite the absence of acute TOD non-life threatening symptoms such as anxiety, headache, palpitations, or mild dyspnea may be present.

The older term, “malignant hypertension” is synonymous with severe elevations in BP associated with encephalopathy and papilledema or acute renal failure. This term has been abandoned by clinical hypertension experts as misleading and imprecise (as has “accelerated hypertension”) but remains in use in the ICD9 CM classification of diseases. Its use is best limited to that context.

PATHOPHYSIOLOGY

The underlying mechanisms of essential hypertension remain largely speculative. The events that explain the transition from hypertensive urgency to emergency, and the corresponding initiation of acute TOD, are even less well understood. There is general agreement that in a subset of patients the abrupt and/or severe elevation of BP or the neuroendocrine milieu associated with it leads to vasoconstriction and endothelial injury. This in turn activates multiple proinflammatory and procoagulant pathways, which in turn further aggravate the endothelial injury, increased peripheral resistance, hypertension, and adverse neuroendocrine milieu. Ultimately, fibrinoid necrosis of arterioles and tissue ischemia result in the clinical manifestions of TOD. Maladaptive imbalances in the renin-angiotensin-aldosterone (RAA) axis, catecholamines, interleukins, vasopressin, endothelin, and nitric oxide are some of the implicated mechanisms. Pressure induced natriuresis and volume depletion is thought to be another common pathogenetic factor. Thus, rather than using diuretics as in chronic hypertension, the treatment of hypertensive emergencies frequently entails the use of intravenous saline except in case of decompensated congestive heart failure and pulmonary edema.

TREATMENT

Hypertensive Urgency

The risks of rapidly lowering the BP in patient with hypertensive urgency, given the absence of acute TOD, are generally agreed to outweigh the benefits. Therefore, following confirmation that TOD is in fact not present and that acute secondary causes have been addressed (Table 2) the goal is to gradually reduce blood pressure to “safer” levels (≤ 160/95) over 24 to 48 hours with usual doses of common oral antihypertensive medications In the emergency room, therapy is often started with relatively short acting and quicker acting drugs such as clonidine, captopril, labetolol, or nicardipine to facilitate discharge after several hours of observation, but the patient should be switched to longer acting drugs more suitable for chronic therapy. Despite the common practice of using intravenous drugs to treat hypertensive urgency, there is rarely a compelling reason to do so. In patients with chronic kidney disease the risks of starting an ACE inhibitor or ARB acutely need to be carefully considered if the patient’s likelihood of obtaining follow-up care appears to be low. Regardless, prior to discharge the ER should ascertain that the patient is asymptomatic, and that provision for short term follow-up has been made. Increasingly, the ER must also work with a social worker or discharge planner to obtain a short term supply of medication for the patient as well, with referral to appropriate resources for medication dispensing as well as medical care. Symptomatic patients, those failing to show any improvement in BP despite initial therapy, those with extreme elevations of blood pressure, and those very unlikely to obtain follow up care should be considered for at least 23 hour admission. Careful discharge instructions, with advice to return if symptoms worsen, are also essential. Multiple adjustments of medications and dosages are likely to be needed over weeks to months.

Table 2. Evaluation of Patient with Hypertensive Urgency and Emergency

ETIOLOGIES	EXAMINATION/ STUDY	COMPLICATIONS	EXAMINATION /STUDY
Medication non-adherence	Hx, pill counts	Encephalopathy	Hx, PE, CT if indicated
Pain	Hx, PE	Cardiac	Hx, PE, EKG; CXR, CT if indicated
Amphetamine, cocaine, PCP abuse	Hx, PE, drug screen	Vasculopathy	Hx, PE, CBC, platelets; CXR, CT if indicated
Alcohol withdrawal	Hx, PE, ? drug screen	Renal failure, proteinuria	Hx, PE, lytes 7, urinalysis
Drug interaction/ effect (e.g., sympathomimetic ± MAO inhibitor, TCA + MAO inhibitor)	Hx, PE	Retinopathy	Fundoscopy, vision testing
Bladder outlet obstruction	Hx, PE, ultrasound if indicated	Eclampsia	Hx, PE, (see section on eclampsia)
Volume overload (especially in setting of CKD)	Hx, PE		
Preeclampsia	Hx, PE, U/A, lytes 7, uric acid		

Hx = history PE=physical exam U/A= urinalysis U/S=ultrasound CXR=chest X-ray

Hypertensive Emergency

The specific treatment of hypertensive emergencies remains largely opinion-based. In a meta-analysis examining 15 randomized control trials (869 patients) conducted through August 2007, the Cochrane Collaboration[12] concluded that current trials have been unable to prove that in hypertensive emergencies either 1) antihypertensive medications reduce morbidity or mortality in hypertensive emergencies compared to placebo or than 2) any one particular first line antihypertensive medication reduces morbidity or mortality more than any other medication. There has been considerable debate and no real consensus over medication use in patients presenting with hypertensive emergency. Only two

trials included a placebo arm. Seven drug classes were identified: nitrates (9 trials), ACE inhibitors (7 trials), Calcium channel blockers (6 trials), alpha-1- adrenergic antagonists (4 trials), diuretics (3 trials), direct vasodilators (2 trials) and dopamine agonists (1 trial). Table 3 lists the drugs primarily used for the management of hypertensive emergencies. Hypertensive emergencies are treated initially with intravenous medications while hypertensive urgencies are almost always treated with oral medications.

Table 3—*Dosage of Commonly Used Parenteral Antihypertensive Medications*
Clevidipine 2 mg/hour, titrate as needed by doubling every 3 minutes to maximum dose 32 mg/hour[13a]
Enalaprilat 1.25 mg over 5 min every 4 to 6 h, titrate by 1.25-mg increments at 12- to 24-h intervals to maximum of 5 mg q6h
Esmolol 500 µg/kg loading dose over 1 min, infusion at 25 to 50 µg/kg/min, increased by 25 µg/kg/min every 10 to 20 min to maximum of 300 µ/kg/min
Fenoldopam 0.1 µg/kg/min initial dose, 0.05 to 0.1 µg/kg/min increments to maximum of 1.6 µg/kg/min
Labetalol 20-mg initial bolus, 20- to 80-mg repeat boluses or start infusion at 2 mg/min with maximum 24-h dose of 300 mg
Nicardipine 5 mg/h, increase at 2.5 mg/h increments every 5 min to maximum of 15 mg/h
Nitroglycerin 5 µg/min, titrated by 5 µg/min every 5 to 10 min to maximum of 60µg/min
Nitroprusside 0.5 µg/kg/min, increase to maximum of 2 µg/kg/min to avoid toxicity
Phentolamine 1- to 5-mg boluses, maximum 15-mg dose

General treatment principles in this setting have been established – immediate lowering of BP to levels that halt additional hypertensive TOD without inducing new TOD due to ischemia. JNC-7 [6] suggests that BP be lowered no more than 25% within the first hour, and then to 160/100-110 within 2-6 hours. An alternative and more cautious set of BP goals would be to lower BP ~ 10% in the first few hours and then by no more than 25% during the first 24 hours. As detailed below, other recommendations exist for particular situations. The need for immediate but controlled decreases in BP usually indicates the need for monitoring in a critical care setting with an arterial BP monitor, and continuously infused intravenous medications.

NEUROLOGICAL EMERGENCIES

Acute Ischemic Stroke

Patients presenting with an acute stroke frequently demonstrate severe elevations of BP due to multiple underlying mechanisms including preexisting hypertension, Cushing's reflex, and activation of multiple pathways including the RAA axis, cortisol, and catecholamines. While extreme elevation of BP is a risk factor for poor outcome due to cerebral edema and intracranial hemorrhage, there is also concern that acute lowering of BP will result in extension of infarction size because of loss of cerebral autoregulation in the watershed area around the infarct (ischemic penumbra) and pressure-dependent cerebral blood flow in this area during the acute phase. Recommendations for therapy must be considered expert opinion (level C evidence) based due to the poor quality and conflicting nature of published evidence. The Cochrane Collaboration analyzed the studies available as of July 2007 that assessed the effect of deliberately altering BP within one week following an acute stroke, and the effect of different vasoactive drugs in that setting.[13] Their review included 12 trials with a total of 1153 patients receiving medications that included angiotensin converting enzyme inhibitors, angiotension II receptor blockers, beta blockers, and calcium channel blockers among others. There was no demonstrable overall morbidity or mortality effect. No distinction was made between ischemic and hemorrhagic stroke. In most instances, acute BP lowering with intravenous antihypertensive mediations need not be considered unless BP exceeds 220 mm Hg systolic and/or 120 mm Hg diastolic. However, emergent IV antihypertensive medication(s) will be warranted even at BP levels below the aforementioned BP thresholds in the presence of concomitant new or worsening target-organ injury (e.g., pulmonary edema, heart failure).

The least controversy exists in patients considered eligible for thrombolytic therapy. According to recent American Heart Association/ American Stroke Association Stroke Council guidelines[14], BP should be reduced to <180/110 using drugs such as intravenous labetolol or nicardipine to reduce the risk of intracranial bleeding prior to administration of rtPA. During or after administration of thrombolytic therapy goal blood pressure is 180/105. Nitroprusside and enalaprilat are considered secondary choices. Patient who require nitroprusside for BP control prior to thrombolytic therapy are ineligible for treatment with rtPA. The use of anti-hypertensive agents in ischemic stroke in the absence of thrombolytic therapy has a far weaker rationale and a less favorable benefit to risk ratio. The risk of ischemia is considered highest in the first 24 hours. The guidelines for ischemic stroke[14] therefore caution against treating BP within the first 24 hours unless the BP exceeds 220/120 mm Hg, in which case it is considered reasonable (but not of proven benefit) to lower the BP 15-25% during the first 24 hours. Easily titratable, short acting drugs should be used initially that can be rapidly reversed if excessive decreases in BP or neurologic deterioration occur. After the first 24 hours, the patient's chronic antihypertensive medications can generally be resumed.

Hemorrhagic Stroke

In hemorrhagic stroke, the need to maintain cerebral perfusion is balanced by the concern that uncontrolled hypertension has the potential to resultant in expansion of the intracerebral hemorrhage. Separate AHA guidelines have been published on hemorrhagic stroke that include BP management [15]. Systolic blood pressure (SBP) > 200 mm Hg or mean arterial blood pressure (MAP) > 150 mm Hg is considered an indication for aggressive BP lowering using continuous intravenous infusion therapy, preferably with an arterial line BP monitoring. SBP > 180 mm Hg (MAP >130 mm Hg) is considered

an indication for careful and modest additional lowering to SBP 160/90 mm Hg (MAP 110 mm Hg). However, if there is suspicion of increased intracranial pressure, simultaneous intracranial pressure monitoring may be required to maintain cerebral perfusion pressure 60 - 80 mm Hg.

Subarachnoid Hemorrhage (SAH)

The management of BP in patients with subarachnoid hemorrhage can be divided into 2 distinct phases. Prior to definitive therapy of the bleeding source, immediate blood BP control (MAP < 100 mm Hg or SBP < 160 mm Hg) is considered a key aspect of preventing additional bleeding. Following surgical clipping or occlusion by endovascular coils of the ruptured aneurysm, cerebral vasospasm (which occurs in approximately 30% of patients following SAH) becomes the primary threat to the patient's recovery. Traditional management during the period of risk for vasospasm (approximately 3 weeks) consists of 21 days of nimodipine plus "triple H" therapy (hypertension, hypervolemia, and hemodilution) as needed.[16]

Hypertensive Encephalopathy

Hyperperfusion of the cerebral cortex during hypertensive emergencies can lead to headache, nausea, vomiting, and visual disturbances. In more severe cases seizures, confusion or decreased level of consciousness may result. The underlying pathology is a spectrum consisting of cerebral edema, posterior reversible leukoencephalopathy, small hemorrhages, and fibrinoid necrosis and fibrin thrombi with microinfarctions. Symptoms typically develop over 24 – 48 hours, and start to resolve within 12 hours of controlling the BP. Although a CT of the head is usually indicated initially to rule out intracerebral hemorrhage, other etiologies must be ruled out if there is no improvement noted with 12 hours. MRI is more sensitive than CT for detecting ischemic changes and the posterior leukoencephalopathy, brain stem pathology, and microhemorrhages. The latter are seen on gradient echo pulse sequences.

CARDIAC EMERGENCIES

Acute Coronary Events

Increased left ventricular afterload and wall tension increases myocardial oxygen consumption, while LVH may reduce oxygen supply by compressing coronary artery lumina and increasing microcirculatory and epicardial coronary wall thickness. Even in the absence of obstructing epidcardial lesions, vascular remodeling in the micro-circulation leads to impaired endothelial vasodilatory reserve which can significantly limit increases in myocardial blood flow and thus result in myocardial ischemia when oxygen demands increase. Pressure related endothelial injury can also occur in the coronary arteries. This can result in angina pectoris or myocardial infarction. While controlling BP with any medication quickly reduces oxygen demand, nitroglycerin is the preferred agent because of its preload reduction and coronary vasodilation. As in other situations of myocardial ischemia, beta-blockers are also useful for their negative inotropic and chronotropic effects which further decrease oxygen utilization. Beta- blocking agents commonly used in parenteral form are esmolol and labetolol. The combination of decreased myocardial oxygen demand and increased afterload can lead to acute congestive heart failure and pulmonary edema. In this case, intravenous furosemide, in addition to intravenous nitroglycerine, is indicated while beta-blockers should be avoided.

Acute Aortic Dissection

A parenteral beta blocker (either labetolol or esmolol) should be used initially in this setting to reduce heart rate and cardiac contractility, thereby reducing the shear mechanical forces imposed on the aortic walls and limiting further dissection. This is combined with the use of intravenous nitroprusside. The beta blocker reduces the reflex tachycardia that may otherwise occur with the use of a potent vasodilator. An aggressive reduction in BP (< 100- 120 systolic) needs to occur within 30 minutes.

HYPERADRENERGIC STATES

Hypertensive emergencies can arise from states of catecholamine excess, such as pheochromocytoma, interactions between monoamine oxidase inhibitors and sympathomimetic drugs, or cocaine use. In this situation, beta blockers can worsen the hypertension because of unopposed alpha adrenergic stimulation and peripheral vasoconstriction. Therefore, the use of a ganglion blocking agent such as intravenous phentolamine (or in less urgent situations oral phenoxybenzamine) must precede the use of a pure beta blocker. Alternatively, the combined alpha and beta adrenergic blocker labetalol is safe and effective. Rebound hypertension following sudden discontinuation of high dose clonidine (> 1.2 mg/day) is also a state of catecholamine excess. Although it also responds quickly to combined alpha and beta adrenergic blockade, resumption of clonidine is another simple alternative.

ACUTE KIDNEY INJURY (AKI)

In addition to papilledema, acute renal failure/ AKI were the earliest described TOD caused by severely elevated BP ("malignant hypertension"). The endothelial damage and arteriolar fibrinoid necrosis mirrors that seen in the heart, brain, and other organs. The syndrome is recognized by the combination of acutely decreased GFR, proteinuria, anemia, thrombocytopenia, and presence of schistocytes and other red cell fragments. It can be confused with hemolytic uremic syndrome or TTP, although the thrombocytopenia is generally less severe than in these other thrombotic microangiopathies while the BP elevation is usually more severe. Treatment principles are the same as in other types of TOD – rapid reduction of BP to levels that stop further vascular damage while maintaining perfusion of organs that generally have impaired autoregulation. Nitroprusside is commonly used although the dose and duration of use must be monitored and to avoid cyanide or thiacyanate toxicity. The simultaneous infusion of thiosulate can reduce but not eliminate the threat of this toxicity. Some advocate the use of the dopamine-1 receptor antagonist fenoldopam mesylate in this setting, not only to avoid toxicity but because it may increase renal blood flow and sodium excretion.

PREECLAMPSIA AND ECLAMPSIA

The treatment of pre-eclampsia and eclampsia is governed by the need to protect the health of both the mother and fetus. The role of medical management, discussed in a later section of this chapter, is only a temporizing measure until the fetus can be safely delivered. The choice of drugs is dictated both by efficacy and avoidance of fetal toxicity or harm. Drugs accepted as safe in this setting primarily include labetolol, nifedipine, nicardipine, and hydralazine.[17] Magnesium sulfate, generally indicated when a diagnosis of eclampsia or severe pre-eclampsia is entertained, is used primarily for prophylaxis against seizures, not management of hypertension *per se*.

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CONCLUSIONS:

The mortality and morbidity associated with hypertensive emergency and urgency is considerable in untreated patients. At the same time, there is potential for serious adverse effects of treatment and specific recommendations remain opinion based at this time. There are no definitive studies establishing the ideal levels or rates of blood pressure lowering. In hypertensive emergencies, a compromise must be reached between preventing additional target organ damage while maintaining perfusion. In each case choice of anti-hypertensive medications needs to be individualized.

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TREATMENT OF HYPERTENSION IN PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)

Mark D Faber, MD

Pretest Questions:

1. Which ONE of the following statements about the use of ACE inhibitors (ACEI) or ARBs in patients with stage 3 CKD (GFR 30-59 ml/min/1.73 m^2) is MOST correct?
    a. A 20% increase in serum creatinine indicates the likely presence of bilateral renal artery stenosis and is a contraindication to continued use of the drug until after renal artery revascularization.
    b. The use of an ACEI or ARB in patients with proteinuric stage 3 CKD can be expected on average to decrease proteinuria by 35%. **(correct answer)**
    c. There is evidence from multiple controlled trials that the use of an ACEI with an ARB in patients with proteinuric stage 3 CKD reduces the rate of GFR loss more than the use of either drug alone.
    d. The antiproteinuric effects of ACEI or ARB therapy are reduced by the concurrent use of a diuretic
2. Which ONE of the following statements concerning the treatment of hypertension in patients with diabetes mellitus is MOST correct?
    a. In the absence of specific contraindications, antihypertensive medication is indicated in all diabetic patients once the blood pressure reaches ≥ 140/90.
    b. Type 2 diabetic patients without nephropathy treated with captopril demonstrated fewer microvascular and macrovascular complications than patients treated with atenolol, despite equivalent levels of blood pressure. **(correct answer)**
    c. The recommended blood pressure goal for adult patients with diabetes mellitus is 135/85.
    d. The reductions in proteinuria and risk of end stage renal disease associated with the use of ACEI in diabetic patients with decreased GFR can be completely explained by concomitant reductions in blood pressure.

Overview

Hypertension is present in over 80% of patients with CKD. Multiple factors contribute to this high prevalence, including: ECF volume expansion; activation of the of renin-angiotensin-aldosterone system (RAAS); sympathetic nervous system overactivity; impaired nitric oxide synthesis and release; and decreased vascular compliance related to mineral bone disease. The treatment of hypertension in patients with chronic kidney disease reflects the general principles of hypertension management (i.e., inclusion of non-pharmacologic approaches and selecting drug regimens that are as safe, well-tolerated, convenient, and cost-effective as possible). However, the presence of low GFR or other manifestations of kidney disease introduces several additional concerns and considerations:

1. There is a need to select target blood pressures (widely agreed to be ≤ 130/80) and therapies most likely to preserve residual renal function. In addition to glomerular hypertension and hypertrophy, proteinuria itself is considered to be a mediator of progressive renal damage (as well as being an adverse prognostic factor). Thus, reduction of proteinuria is acknowledged as another important, if only a partial surrogate, target of antihypertensive therapy. RAAS inhibitors

[ACE inhibitors (ACEIs), angiotensin 2 receptor blockers (ARBs), direct aldosterone antagonists (spironolactone, epleronone), and most recently direct renin inhibitors (aliskiren) are the primary medications fulfilling these criteria. Non-dihyropyridine calcium channel blockers (NDHP CCBs) reduce proteinuria though they have not been shown in prospective studies to provide the renal protection observed with ACE inhibitors and ARBs. DHPCCBs preferentially dilate the efferent glomerular arteriole and therefore can raise intraglomerular pressure – alikely explanation for their inconsistent ability to lower proteinuria when used as monotherapy. However, when used in conjunction with proven renoprotective RAAS blockade, these agents do not attenuate the renoprotection of the RAAS blocker.

2. The ability of the kidney to maintain electrolyte and acid-base homeostasis is decreased, resulting in an increased risk of treatment-related complications such as hyperkalemia and metabolic acidosis when using RAAS inhibitors. In most patients with even advanced CKD, hyperkalemia can be managed through dietary potassium restriction, and the use of furosemide (or other potent diuretics used alone or in combination) and supplemental sodium bicarbonate. Occasionally, the chronic use of low dose (2.5 – 5 g with meals) sodium polystyrene resin (Kayexalate®) may be required.
3. In patients with certain etiologies of chronic kidney disease (e.g., renal artery stenosis or chronic CHF) the maintenance of GFR there is dependent on angiotensin II, resulting in disproportionate decreases in GFR during RAAS inhibitor therapy. In patients with late stage 4 or stage 5 CKD, any preventable further decrease in GFR may be unacceptable because it may accelerate the need for renal replacement therapy. Even patients with less severely decreased GFR are already on the steep portion of the GFR v. serum creatinine plot, thereby demonstrating larger increases in serum creatinine for a given further decrease in GFR than patients with normal GFR. This frequently results in discontinuation of ACEIs, ARBs, and diuretics in patients with CKD by physicians uncomfortable with any measurable elevation of serum creatinine or potassium above normal. Nevertheless, this clinical decision must be balanced against prospective clinical trial data showing a less steep decline in GFR over time with RAAS blockade in patients with advanced CKD. Furthermore, in patients with advanced CKD, the predicable rise in creatinine that occurs with either BP reductions and/or RAAS blockade will be exaggerated relative to the actual loss of kidney function. In general, increases in serum creatinine of up to 30% are considered acceptable. Larger increases in serum creatinine should prompt a search for volume depletion, or possibly a search for bilateral renal artery stenosis.
4. The efficacy of some medications (e.g., thiazide diuretics) is decreased in patients with moderately or severely decreased GFR. Other medications (e.g., loop diuretics) remain effective but requiring proportionately higher dosing as GFR decreases. Thiazide diuretics are ineffective below an estimated GFR < ~ 45 ml/min/1.73 m^2; however, chlorthlidone, a thiazide-like diuretic, remains effective at lower estimated GFR's down to ~ the mid to low 30's. Yet other medications (e.g.,

NDHP CCBs) may have decreased clearance in advanced stages of CKD and increased potential for dose-related side effects.

Diabetes Mellitus without Nephropathy

Intensive BP management (achieving a BP of ≤ 130/80) is an established means of lowering the risks of both macrovascular and microvascular disease in diabetic patients, on a par with intensive glycemic control.[1] A significant percentage of patients will require at least 3 medications to reach this target. Initiation of antihypertensive medication is recommended in all diabetics whose BP exceeds 140/90. Less certain is whether or not specific antihypertensive medications (specifically, RAAS inhibitors) lower risk more effectively than others drug classes in diabetic patients without evidence of kidney disease. The results of two large, widely reported trials suggest that the level of BP control, rather than the specific drugs used, determine the degree of risk reduction in this circumstance. The first of these studies was the UKPDS trial[2] of newly diagnosed diabetic patients with hypertension followed for a median of 8.4 years. Average achieved blood pressures in the both the "strict" (144/82) and "usual" (154/87) BP control groups were higher than current recommendations. The strict control group was further subdivided into initial treatment with either atenolol or captopril. Neither of these drugs was used in the higher BP group. 29% of the tight control group required 3 drugs to lower BP below the target range of 150/85. While there was a decreased risk of both macrovascular and microvascular complications (including albuminuria) in the strict control group, there were no significant differences between the captopril and atenolol arms.[3] The absence of a specific cardiovascular benefit to ACE inhibition in hypertensive patients without nephropathy was confirmed in the ALLHAT trial.[4] 33,357 hypertensive patients with increased risk of coronary heart disease (of whom 36% were diabetic) were studied. Coronary heart deaths and non-fatal MI (the primary outcome) were equivalent in the lisinopril, chlorthalidone or amlodipine groups. This was true overall and for the diabetic subgroup. There were no differences either in the risks of end stage renal disease or in the slope of GFR change according to treatment assignment.

Diabetes with Nephropathy

The earliest stage of diabetic nephropathy is defined as persistent dipstick-positive ("overt") proteinuria, which corresponds with the daily urinary excretion of approximately 300 mg albumin. Virtually all diabetic patients with serious kidney disease originate from this within subgroup. ACEIs and ARBs typically reduce albuminuria in patients with kidney disease by 35-45%. The effect is maximized

by sodium restriction or the use of diuretics. Stricter BP control is also associated with reduction in proteinuria, which independently correlates with improved renal outcomes and mortality rates[5]. Multiple studies have now shown additional decreases in proteinuria of similar magnitude in patients with diabetic nephropathy when a second RAAS inhibitor is added to an ACEI or ARB. Combinations of an ACEI and ARB[6] or addition of spironolactone[7-10] or epleronone[11] in patients already taking an ACEI or ARB, were studied. Safety concerns in patients with decreased GFR include an initial decrease in GFR of 5-10 ml/min that correlates with the magnitude of proteinuria reduction and plateaus early during treatment. Of particular concern is an increase in the need for acute dialysis and a trend towards higher mortality that did not reach statistical significance in patients treated with an ACEI and ARB in the ONTARGET trial[12]. Many but not all studies of dual or triple RAAS inhibition report an increased risk of hyperkalemia as well. NDHP CCBs result in similar decreases in albuminuria, while most other antihypertensive drugs have little to no effect on proteinuria.

The estimated lifetime risk of ESRD in patients with diabetes mellitus was approximately 16% prior to the widespread adoption of strict glycemic and BP control[13]. Doubling of serum creatinine occurred almost 78% of type I diabetics with overt proteinuria and a baseline serum creatinine ≥ 1.5 mg/dl who were randomized to receive antihypertensive medications other than ACE inhibitors or calcium channel blockers over a 4 year period. By comparison, in the group randomized to captopril, doubling of creatinine was observed in less than 36% of patients[14]. This benefit persisted after adjustment for the slightly lower BP maintained in the captopril group, and was not observed in patients with a baseline creatinine < 1.5 mg/dL (whose rate of creatinine was < 10% regardless of treatment). Target blood pressures in this 1993 study (< 140/90, or < 160 systolic and at least 10 mm Hg < baseline SBP) were higher than currently recommended targets, but probably reflective of blood pressures still commonly observed in clinical practice.

Non-Diabetic Chronic Kidney Disease

The management of hypertension in patients with non-diabetic CKD closely parallels that of CKD in patients with diabetes, as outlined above. Strict control of BP (≤ 130/80) reduces progression of CKD (loss of GFR) in a broad variety of non-diabetic kidney diseases as well as in diabetic nephropathy and is recommended by JNC-7[1] for patients with CKD. In contrast, the specific benefits of RAAS inhibition are limited to proteinuric (i.e., glomerular) diseases. This is largely expected in that 1) diabetes itself,

the prototypic disease in which RAAS inhibition has shown to be beneficial, is a glomerular disease; and 2) experimental models of kidney disease detailing the mechanisms underlying renal protection from RAAS inhibition almost all relate to it glomerular effects (including reduction of glomerular capillary pressure, reduction of mesangial albumin trafficking, direct improvement of glomerular permselectivity to albumin, reduction of glomerular hypertrophy, and inhibition of mesangial growth factors such as TGF-β and PDGF). The remainder of this section will refer only to non-diabetic CKD with proteinuria.

As in the case of diabetic nephropathy, ACEIs and ARBs generally reduce proteinuria by 35 to 45%.[15] Studies differ on whether supramaximal doses of ACEIs or ARBs (doses larger than those producing the greatest decreases in BP) result in further reductions in proteinuria.[16,17] Similarly, NDHP CCBs[18] possess significant anti-proteinuric effects in non-diabetic proteinuric CKD. The clinical relevance remains speculative in both cases; neither dual RAAS inhibition nor NDHP CCBs have been proven to preserve GFR. However, in light of multiple studies demonstrating an association between reduction in proteinuria and protection from GFR loss [19,20], it is generally considered worthwhile to reduce albuminuria to less than 500 – 1000 mg/day when possible.

The MDRD study[21] excluded patients with diabetes and contained a relatively high percentage of patients with autosomal dominant polycystic kidney disease (ADPKD). Although almost half of the patients studied received an ACEI, that decision was made by the patients' treating physicians prior to enrollment and the results were not analyzed or stratified according to treatment or not with an ACEI. Patients in the group randomized to a "usual" MAP < 107 mm Hg (approximately 140/90) lost residual GFR more quickly than those randomized to a "low" MAP of < 92 mm Hg (approximately 125/75). The former group actually achieved a MAP of 96 mm Hg (approximately 130/80). Interestingly, the benefit of lower BP in these patients was limited to patient with moderate (1-2.9 g/day) or especially severe (≥ 3 g/day) proteinuria, suggesting to some that a BP of <125/75 should be attempted in CKD patients with proteinuria (> 1 g/day).

The unique benefits of ACEIs in non-diabetic, proteinuric CKD patients were convincingly shown in the Ramipril Efficacy in Nephropathy[22] (REIN) study and in the African American Study of Kidney Disease[23] (AASK). In the REIN study both the ramipril and placebo groups were titrated to the same BP (DBP < 90 mm Hg). Patients excreting > 3 grams of protein daily randomized to ramipril showed slower rates of GFR loss (0.53 v. 0.88 ml/min per month). Apparent benefits persisted or increased for at least

44 months[24], and were also seen in patients with 1.5 – 3 g/day or proteinuria[25]. Patients in the AASK trial randomized to ramipril showed a 22% reduction in the combined endpoint of a 50% decrease in GFR, ESRD or death compared to those receiving amlodipine or metoprolol. Given the difficulties discussed above with the use of RAAS inhibition in patients with advanced stages of CKD, the question of which GFR or creatinine is "late" to show benefit is important. It is interesting to note that in the REIN study benefits were noted across the entire spectrum of GFR studied (11-101 ml/min/1.73 m2)[26]. Similarly, a Chinese study[27] demonstrated a reduction from 60% to 41% in the risk of serum creatinine doubling, ESRD, or death in patients with a serum creatinine between 3.1 and 5.0 mg/dL treated with benazepril versus placebo. However, it should be noted that participants were prescreened for the ability to tolerate an ACEI, and the intention to treat analysis may not be applicable to a general population of CKD patients.

End Stage Renal Disease

The prevalence of hypertension in chronic dialysis patients varies widely with the treatment modality, setting, and prescription. 86 % of patients on typical short (3-4 hours) 3 times per week were found to require antihypertensive medications[28], whereas <10% of patients in a well known nocturnal (8 hours, 3 times per week) dialysis unit in Tassin France[29,30] were reported to need BP lowering medications. The experience in daily home hemodialysis patients (especially nocturnal patients as opposed to short daily dialysis) is similar. The reported prevalence of hypertension in peritoneal dialysis is intermediate between those 2 extremes. Unfortunately, there are no controlled trials in dialysis patients reporting long term outcomes on which to base BP treatment recommendations. Epidemiologic studies are counterintuitive, and few believe they should be taken at face value. A large national database of prevalent US hemodialysis patients showed sharp increases in mortality for patients with systolic blood pressures < 140 mm Hg predialysis or < 120 mm Hg postdialysis[31]. The lowest associated mortality was in far higher blood pressures. Further complexity is introduced by differences between in-center and home (interdialytic) BP measurements [32,33] and the adverse association with cardiovascular morbidity and mortality of elevated pulse pressure[34] and absence of nocturnal "dipping[35]."

Opinion-based recommendations about BP management in dialysis patients have been issued.[36,37] Few would argue against the efficacy[38] or desirability of establishing "euvolemia" to minimize the need for antihypertensive medications, although some would define it somewhat as precisely the weight at which blood pressure is controlled without medications while others would merely define it as the absence of

peripheral edema and pulmonary congestion. In reality, true euvolemia is difficult to maintain in patients who are not on either nocturnal or daily dialysis. Antihypertensive medications will likely be needed in those cases. Guidelines have suggested aiming for predialysis blood pressures of <140/90 and post dialysis blood pressures of <130/80, the "reverse epidemiology" noted above notwithstanding. ACEIs and ARBs are favored because of their favorable cardiovascular risk factors in the non-dialysis population, although no comparative studies are available in dialysis patients. A recent meta-analysis[39] and systemic review reported favorable effects on cardiovascular and all-cause mortality in dialysis patients on various antihypertensive medications producing an average decrease in BP of 4-5/2-3 mm Hg.

Key Learning Points

- Intensive blood pressure management (achieving a BP of ≤ 130/80) is an established means of lowering the risks of both macrovascular and microvascular disease in diabetic patients, on a par with intensive glycemic control. A significant percentage of patients will require at least 3 medications to reach this target.
- Initiation of antihypertensive medication is recommended in all diabetics whose BP exceeds 130/80. ACEIs and ARBs are recommended for patients with proteinuria or decreased GFR, but diuretics, beta blockers, and calcium channel blockers are considered acceptable initial alternatives for diabetic patients without nephropathy
- The specific renal benefits (decreased progression of underlying renal disease and risk of ESRD) of ACEIs, ARBs, and other RAAS inhibitors are largely limited to patients with proteinuria. However, their use is still generally indicated because of their cardiovascular protection. Renal protection has been demonstrated in patients with stages 3, 4, and 5 CKD.
- The degrees of proteinuria reduction and reduction in annual GFR loss correlate with each other in multiple studies. As a result, general recommendations are to titrate antihypertensive medications to reduce proteinuria to ≤ 500 – 1000 mg daily. This can be facilitated by the use of maximal doses of a single RAAS inhibitor, and concurrent sodium restriction or use of diuretics. Although dual or triple RAAS inhibition results in additive reductions in proteinuria, it has not been shown to correlate with improved preservation of renal function. In addition, safety concerns have been raised about increased risks of acute kidney injury and hyperkalemia.

- Hypertension in dialysis patients is related to volume expansion in the vast majority of patients. Hypertension is rare in patients on extended dialysis regimens (8 hours per day, 3 or more days per week).

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Hypertension in Pregnancy

Radihka Thalla, MD and Mark D Faber, MD

Learning Objectives:

1) Define and classify hypertension disorders in pregnancy
2) List the risk factors for hypertension disorders in pregnancy
3) Review of management of hypertensive disorders in pregnancy

Pretest Questions

1. Which ONE of the following antihypertensive medications or medication classes is considered to be absolutely contraindicated for use during pregnancy?
    a. thiazide diuretics
    b. nifedipine
    c. atenolol
    d. hydralazine
    e. ACE inhibitors **(correct answer)**

2. Which ONE of the following statements regarding gestational hypertension is correct?
    a. Gestational hypertension can be diagnosed any time after the first trimester of pregnancy
    b. Gestational hypertension is defined as a blood pressure > 130/80
    c. Patients diagnosed with gestational hypertension whose blood pressure remains elevated12 week post-partum, in the absence of preeclampsia, probably had undiagnosed chronic hypertension **(correct answer)**
    d. Gestational hypertension should be routinely treated with antihypertensive medications

Hypertensive disorders, which represent the most common medical complication of pregnancy, affect 8 to 10% of all pregnancies in the United States. They remain a leading cause of both maternal and fetal morbidity and mortality. The risk for adverse events is largest in cases of pre-eclampsia, but gestational hypertension is also associated with increased maternal and fetal morbidity and mortality. The main risks to the mother are placental abruption, accelerated hypertension leading to hospitalization, and target organ damage, such as cerebral vascular catastrophe.[1] Fetal risks include growth restriction, and prematurity because of worsening of maternal disease necessitating early delivery. In the long term, hypertension in pregnancy has been linked to subsequent chronic hypertension and cardiovascular disease in women.[2]

Normal pregnancy is characterized by increases in cardiac output (~35 – 50%) and blood volume (~50%), reductions in peripheral vascular resistance (~25%) and decreased blood pressure. These changes begin to take place during the first 5 to 8 weeks of pregnancy and reach their peak late in the second trimester. Blood pressure achieves a nadir by mid-trimester as it falls ~ 10 mm Hg, and then returns to pre-pregnancy levels at term. Systolic blood pressure (SBP) is less affected than diastolic blood pressure (DBP) because of the increased cardiac output that offsets the vasodilatation.

DEFINITION AND CLASSIFICATION

Hypertension in pregnancy is defined as a SBP of 140 mm Hg and/or a DBP of 90 mm Hg or higher on at least two separate occasions at least six hours apart, after 20th week of gestation. In the outpatient setting, BP should be measured in the seated position, after a period of rest in a quiet environment. For hospitalized patients, the lateral recumbent position eliminates the effect of compression of the inferior vena cava by the enlarged uterus that impairs venous return and causes a decline in BP. Other important aspects of obtaining a reproducible and accurate BP are the use of an appropriate-sized cuff (1.5 times the upper arm circumference) and avoidance of tobacco or caffeine for at least 30 minutes preceding the reading. (Of course, the use of tobacco during pregnancy should be strongly discouraged altogether). White-coat hypertension occurs in up to 29% of women with no history of preexisting hypertension. A noninvasive 24-hour BP monitor can distinguish white-coat hypertension from true hypertension in the pregnant patient.

Classification of the Hypertensive Disorders of Pregnancy

The most important consideration in the classification of diseases in which BP rises abnormally is differentiation of hypertensive disorders that antedate pregnancy from potentially more serious disease arising from pregnancy itself. Four major categories (or classification designations) of the hypertensive disorders in pregnancy have been designated both by the National High Blood Pressure Education Program and American College of Obstetricians and Gynecologists guideline committees[1,3]: (1) chronic hypertension, (2) preeclampsia, defined as pregnancy-induced hypertension associated with proteinuria, (3) preeclampsia superimposed on chronic hypertension, and (4) gestational hypertension. Any of these may lead to maternal and perinatal complications

Chronic Hypertension

Chronic hypertension is defined as BP of 140/90 mm Hg or higher that either predates pregnancy or develops before 20 weeks gestation and persists > 6 weeks post-delivery. If hypertension was documented before conception, the diagnosis of chronic hypertension in pregnancy is straightforward. This condition complicates approximately 3% of pregnancies. Higher rates may be seen in any pregnancy; however, it preferentially occurs in older, obese, and African-American women. Chronic hypertension in pregnancy is classified as either mild or severe, with severe defined by diastolic readings of 110 mm Hg or higher.

Gestational Hypertension

Gestational hypertension is the most frequent cause of hypertension during pregnancy and is seen in 6% of pregnancies. It is defined as *de novo* hypertension after mid-pregnancy in the absence of systemic features of proteinuria. If preeclampsia is not present at the time of delivery, and BP returns to normal by 12 weeks postpartum, a diagnosis of “transient hypertension of pregnancy” can be made. Occasionally, women with apparent gestational hypertension remain hypertensive after delivery. These women most likely have pre-existing chronic hypertension, which was masked in early pregnancy by physiological vasodilation. In general, BP ≥140/90 mm Hg that persists beyond 6 – 12 weeks postpartum is indicative of chronic hypertension.

Preeclampsia

Preeclampsia is a pregnancy-specific syndrome that develops after 20 weeks gestation and is characterized by increased BP (≥ 140/90 mm Hg), proteinuria (> 300 mg/d), and edema in a woman who was normotensive before 20 weeks. This syndrome, which occurs in 2% to 3% of pregnancies, accounts for more than 50% of all the hypertensive disorders of pregnancy and is a major cause of fetal

and maternal morbidity and mortality. A severe and dangerous variant of preeclampsia is the HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome, which occurs in 1 of 1,000 pregnancies.

Preeclampsia Superimposed on Chronic Hypertension

The incidence of preeclampsia in women with chronic hypertension is about 15% to 25%, compared with 5% of pregnancies in women without preexisting hypertension. A diagnosis of superimposed preeclampsia is made when *de novo* proteinuria develops in the latter half of pregnancy or when the hypertension accelerates greatly in the last trimester. The rise in BP is SBP > 30 mm Hg or DBP > 15 mm Hg plus proteinuria and/or edema. The recurrence rate in subsequent pregnancies is high.

Risk Factors

Risk factors for preeclampsia have been studied extensively as preeclampsia is the hypertensive disorder of pregnancy most commonly associated with severe complications.

Risk Factors
Nullipara
First baby before the age of 20 or after 35
Hypertension before pregnancy
Having multiple births
African descent
Family History of pregnancy induced hypertension
Chronic kidney disease, diabetes mellitus
Obesity (BMI > 30)

1. *Race or ethnicity*: The risk associated with race or ethnicity is uncertain. Black women have higher rates of preeclampsia complicating their pregnancies compared to other racial groups, mainly because they have a greater prevalence of underlying chronic hypertension and greater obesity. A recent prospective study[4], identified a significantly increased risk of preeclampsia and decreased risk of gestational hypertension among Hispanic women relative to non-Hispanic Caucasians.

2. *Primigravid pregnancy and history of preeclampsia during previous pregnancies*: Although the underlying causative factors are not completely delineated, hypertension in preeclampsia is clearly a consequence of a generalized arterial vasoconstriction. Primigravidas have increased risk for preeclampsia. However, women with a history of preeclampsia have an increased risk during subsequent pregnancies. Other risk factors include extremes of reproductive age, obesity, family history of preeclampsia, chronic hypertension, diabetes mellitus, the presence of trophoblastic disease, multiple gestations, mother's own low birth weight, prematurity, and young age, connective tissue disease, and kideny disease.
3. *Stress and socioeconomic status*: Although traditionally considered risk factors, a recent prospective community-based cohort study[5] did not show any association of work stress, anxiety, depression or pregnancy-related anxiety early in pregnancy to the development of gestational hypertension or pre-eclampsia later in pregnancy. A recent study suggested that SSRI exposure during late pregnancy may identify women who are at an increased risk for gestational hypertension and preeclampsia.[6] A few studies that examined the association

between adult socioeconomic position and pregnancy induced hypertension have found contradictory results.

4. *BMI and maternal weight gain*: There are few modifiable risk factors for pregnancy-related hypertensive disorders, but body mass index (BMI) and maternal weight gain may be important factors. A recent prospective cohort study [7]found that preconception BMI> 30 was a risk factor for preeclampsia (OR 3.3) and severe transient hypertension (OR 8.8 in Caucasian women and 4.9 in Black women). High gestational weight gain was also a risk factor or, alternatively, was associated with risk factors for pregnancy induced hypertension [8] and preeclampsia.[9]

There is no single effective screening test that predicts preeclampsia.

Management

Evaluation and counseling of women with chronic hypertension should begin before conception and should include screening for target organ damage (including baseline measurement of renal function and proteinuria), and evaluation for secondary causes of hypertension. It is essential before conception that the patient's antihypertensive medications be reviewed and that those drugs harmful to the developing fetus (angiotensin-converting enzyme [ACE] inhibitors, angiotensin II receptor blockers) be discontinued and replaced with medications considered safe for use during pregnancy (methyldopa, labetalol).

It has to be recognized from the outset that the selection of a particular drugs to treat hypertension during pregnancy is all opinion based except for the avoidance of a small number of drugs known to be harmful to the fetus (e.g., ACEIs and ARBs as noted above). Only a few antihypertensive medications are recognized as being safe for use in pregnancy. No antihypertensive medication has specifically been proven safe for use during the first trimester It is exceeding difficult for ethical reasons to conduct randomized controlled trials during pregnancy. A recent Cochrane review[10] was only able to conclude "Until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects. Exceptions are diazoxide, ketanserin, nimodipine and magnesium sulphate, which are probably best avoided." The reader is also referred to recent comprehensive reviews on the management of hypertensive disorders during pregnancy [11-13]

Gestational vasodilation frequently allows the discontinuation of most or all antihypertensive medications early in pregnancy, although some may need to be restarted closer to delivery. Although bed rest is recommended for women with hypertension and preeclampsia, there is no evidence to show that it improves outcomes of pregnancy.

There is no evidence from controlled trials that antihypertensive drugs improve maternal or fetal outcome in mild to moderate hypertension (BP< 160/110), whether pregnancy-induced or chronic. Not surprisingly, guidelines vary as to recommended thresholds for initiating antihypertensive medications. The most recent US guidelines advise treatment at ≥ 160/105 [3]. Severe hypertension (≥ 160/110 requires prompt treatment to reduce the risk of maternal intracerebral hemorrhage or death. It is important that the obstetrical service or obstetrician be involved in women with a gestational age beyond 24 weeks to assist in antihypertensive management decisions that may affect the fetal status, as well as decide if or when emergent delivery is indicated.

Degree of Hypertension	Management
Mild	Rest, No medication
Moderate	Single agent therapy
Severe	Combination of Multiple agents

Pharmacologic Therapy:

Drugs for Gestational or Chronic Hypertension in Pregnancy

DRUG	DOSE	POTENTIAL SIDE EFFECTS
Methyldopa	0.5 to 3.0 g/d in 2 divided doses	orthostatic hypotension ,hepatitis and hemolytic anemia
Beta blockers		decrease uteroplacental blood flow; risk of growth restriction when started in first or second trimester (atenolol);
Labetalol	200 to 1200 mg/d in 2 to 3 divided doses	fetal growth restriction
Hydralazine	50 to 300 mg/d in 2 to 4 divided doses	neonatal thrombocytopenia
Nifedipine	30 to 120 mg/d of a slow-release preparation	
Diuretics Hydrochlorothiazide: Furosemide	 12.5 to 25.0 mg/d 40 to 80 mg daily	volume contraction and electrolyte disorders
ACE inhibitors and ARBs	Contraindicated	cardiac defects, fetopathy, oligohydramnios, growth restriction, renal agenesis and neonatal anuric renal failure

Methydopa is the most commonly used oral antihypertensive agent in pregnancy. It is a centrally acting α-2 receptor agonist, is usually well tolerated by pregnant women with a broad safety margin. Treatment with methyldopa has been reported to prevent subsequent progression to severe hypertension in pregnancy and does not seem to have adverse effects on uteroplacental or fetal hemodynamics or on fetal well being.[14] Children born to hypertensive women who received methyldopa treatment during pregnancy were followed from birth until age of 7 1/2 years. The frequency of problems with health, physical or mental handicap, sight, hearing, and behaviour was the same in children of treated and untreated women.[15] Methyldopa has also been shown recently to ameliorate the abnormal vascular stiffness characteristic of hypertensive disorders during pregnancy.[16] Methydopa-induced hepatitis and hemolytic anemia are rare side effects with short term treatment.

β-blockers are also widely used in pregnancy. None of the β-blockers have been associated with teratogenicity. A well designed prospective study from Glasgow reported that babies born to

women treated with atenolol in early pregnancy had significantly lower birth weights than those in the placebo group.[17] The adverse effect of atenolol was more pronounced in women receiving the drug earlier in their pregnancy, and continuing the drug for a longer duration.[18] The time of initiation of β-blocker therapy is an important consideration in intrauterine growth retardation. Beta blockers should generally be avoided before the third trimester unless BP cannot be sufficiently controlled by other antihypertensive agents such as methyldopa or hydralazine. Labetalol, a combined α- and β-blocker has gained wide acceptance in pregnancy and has been shown to be more effective than methydopa in the treatment of pregnancy-induced hypertension.[19]

Calcium channel blockers have been used to treat chronic hypertension, mild preeclampsia presenting late in gestation, and urgent hypertension associated with preeclampsia. Dihydropyridine calcium channel blockers are potent vasodilators that have been used successfully in pregnant patients with acute hypertension refractory to hydralazine and labetalol. Extended release nifedipine has been most widely used in pregnancy. In a recent prospective, multicenter, observational study suggests that utilization of calcium channel blockers during the first trimester of pregnancy does not represent a major teratogenic risk.[20] Administration of short-acting nifedipine is not recommended as it is reported to be associated with maternal hypotension and fetal distress.[21]

Hydralazine, is the first-line parenteral drug used in hypertensive emergencies. It can also be administered orally to control chronic hypertension. Hydralazine has been used in all trimesters of pregnancy, and data have not shown an association with teratogenicity, although neonatal thrombocytopenia and lupus have been reported. Because of its known side effects such as palpitations, headache, and dizziness when the drug is used alone, it is usually administered in combination with methyldopa or a beta blocker especially in patients who have failed monotherapy. The drug appears to be both safe and efficacious. Although hydralazine has not been reported to have any significant adverse effects on the fetus with chronic treatment, long-term follow-up studies are lacking. This drug is currently being recommended for use as a second-line agent.

Diuretic use in pregnancy remains controversial. Diuretics are commonly prescribed in essential hypertension before conception and are used during pregnancy for treating hypertension and cardiac disease. The current NHBPEP and JNC reports do not discourage continuation of diuretic therapy in patients who were on therapy before pregnancy.[3] However, diuretics should always be discontinued if the patient develops superimposed preeclampsia to prevent further volume contraction. If diuretics are indicated, they are safe and efficacious agents that can markedly potentiate the response to other antihypertensive agents and are not contraindicated in pregnancy except in settings in which uteroplacental perfusion is already reduced (preeclampsia and intrauterine growth restriction).

ACE inhibitors and angiotensin II receptor blockers are uniformly contraindicated in pregnancy and should be discontinued before conception. First-trimester exposure to ACE-I has been associated with a greater incidence of malformations of the cardiovascular and central nervous systems. ACE inhibitors also associate with fetal growth restriction, oligohydramnios, neonatal renal failure, and neonatal death. Other RAS system drugs, such as the newly released direct rennin inhibitors, should also be avoided during pregnancy.

Management of Preeclampsia:

When the diagnosis is preeclampsia, the gestational age, as well as the level of BP, influences the use of antihypertensive therapy. When antihypertensive therapy is used in women with preeclampsia, fetal monitoring is helpful to recognize any signs of fetal distress that might be attributable to reduced placental perfusion. The only cure for preeclampsia is delivery. Intravenous

hydralazine, a direct vasodilator, has traditionally been considered the drug of choice for treating severe hypertensive emergencies in pregnancy. Hydralazine acts directly on the uteroplacental vasculature to reverse vasospasm, and has a long history of success in gestation with acceptable immediate maternal side effects (tachycardia, headache, ventricular arrhythmias) and a low incidence of short- or long-term fetal effects (rarely, thrombocytopenia). There have been no studies showing that hydralazine causes congenital defects. Parenteral labetalol, an alpha–beta-adrenergic blocker, is rapidly replacing hydralazine as the most commonly used antihypertensive in the treatment of severe preeclampsia.

Conclusion:

Currently, there is little evidence to support the concept that BP control in pregnant women with chronic hypertension will prevent the subsequent occurrence of preeclampsia. As BP falls in early pregnancy, decreasing or even discontinuing medication and monitoring is often possible in women with mild or moderate hypertension. Acceptable agents include methyldopa, labetalol, and nifedipine in standard doses. Atenolol use should probably be avoided early in pregnancy. ACE-inhibitors and ARBs should be avoided in all trimesters.

Key Learning Points:

- Hypertension in pregnancy is defined as SBP of 140 mm Hg and/or DBP of 90 mm Hg or higher on at least two separate occasions at least six hours apart, after 20th week of gestation.

- Hypertensive disorders of pregnancy are categorized as chronic hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension

- Preeclampsia is a pregnancy-specific syndrome that develops in the latter half of pregnancy and is characterized by increased BP (≥ 140/90 mm Hg), proteinuria (> 300 mg/d), and edema in a woman who was normotensive before 20 weeks. This syndrome, which occurs in 2% to 3% of pregnancies.

- There is no evidence from controlled trials that antihypertensive drugs improve maternal or fetal outcome in mild to moderate hypertension (BP< 160/110), whether pregnancy-induced or chronic. The most recent US guidelines advise treatment at ≥ 160/105 to reduce the risk of maternal intracerebral hemorrhage or death.

- Hydralazine, alpha methyldopa, long acting nifedipine, and labetalol are used commonly to treat hypertensive disorders during pregnancy. The use of beta blockers other than labetalol and diuretics is more controversial. Inhibitors of the renin-angiotension-aldosterone axis (e.g., ACE inhibitors, ARBs, direct rennin inhibitors) are contraindicated at all stages of pregnancy.

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Diastolic Blood Pressure J-Curve

John M. Flack, M.D., M.P.H.

Controversy regarding BP management has arisen in persons with low DBP but elevated SBP because of the association of low DBP, in some epidemiological datasets, with an increased risk of CHD. The concern for the DBP J-curve has persisted even though there are no un-confounded data from randomized clinical trials of hypertension treatment confirming the presence of a treatment-induced J-curve. The Systolic Hypertension in the Elderly Program (SHEP) lowered DBP to an average level of ~68 mm Hg (versus 72 mm Hg in the placebo group) in older persons with isolated systolic HTN using a chlorthalidone-based antihypertensive drug treatment regimen with no evidence of a treatment-induced J-curve)[1] Also, in a smaller SHEP sub-study it was confirmed over 4 years average follow-up that fatal and non-fatal CHD was incrementally greater in those with greater evidence of atherosclerotic vascular disease; rates were 10.9% (no atherosclerosis), 29.8% (sub-clinical atherosclerosis), and 58.3% (clinical evidence of atherosclerosis).[2] In this same sub-study, CVD risk reduction with chlorthalidone-based antihypertensive drug therapy was greatest amongst individuals with the greatest evidence of atherosclerosis prior to treatment.

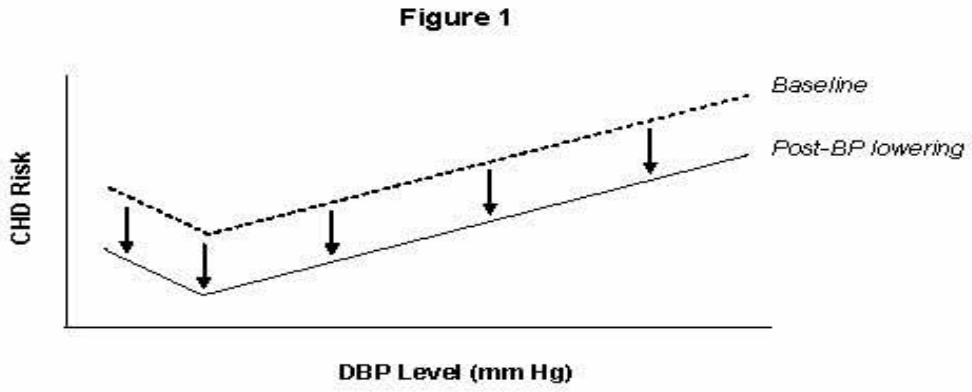
It is important to understand the known correlates of low DBP as these correlates likely explain the increased risk of CHD in persons with low DBP. It should be noted that this concern is mostly in older persons with HTN who are at much greater risk for low DBP than younger persons. Diastolic blood pressure levels in the population begin to trend lower in the mid sixth decade while SBP levels continue to rise with advancing age. Accordingly, many patients with very low DBP manifest striking concurrent elevations of SBP.

Low DBP (<75 mm Hg) has been linked to a much greater burden of large vessel atherosclerosis in older patients with isolated systolic HTN.[3] It is also known that wide pulse pressure isolated systolic HTN is attributable to the age-related stiffening of arterial elastic vasculature (aorta). During systolic ejection of blood from the heart energy is stored in the elastic aorta and during diastole this stored energy is released. This allows for continuous blood flow during the cardiac cycle while also augmenting BP during diastole. Reflected waves from the peripheral arterial tree help maintain DBP and therefore coronary perfusion pressure; virtually all coronary blood flow is during diastole. Two things happen when the arterial vascular tree stiffens and is less compliant. First, the energy storage in the elastic aorta is much less. Accordingly, SBP rises significantly because the stiff aorta is no longer

able to dissipate the pressure rise that occurs during energy storage and release in a more compliant (and youthful) aorta. Second, the reflection of the peripheral arterial waves moves earlier in the cardiac cycle. Thus, instead of these reflected waves appearing during diastole and augmenting coronary perfusion pressure, they arrive earlier and contribute to the prominent rise in SBP as well as to lower BP during diastole. The above represent the pathophysiological underpinnings of wide pulse pressure HTN that is the predominant HTN phenotype in older persons.

However, it must be remembered that SBP is the major determinant of myocardial wall stress and therefore oxygen requirements. In the coronary circulation when oxygen demands increase, coronary blood flow must increase because oxygen extraction cannot increase to meet the heightened demands. In patients with obstructive coronary heart disease, the concerns regarding the J-curve and worsening coronary perfusion pressure by further lowering BP should cause the practitioner to ensure that BP lowering occurs non-precipitously or gradually. When lowering BP in persons with wide pulse pressure HTN (and low DBP), SBP reductions are much greater than DBP reductions. Thus, despite lower DBP and lesser coronary perfusion pressure during diastole, the demands for increased blood flow will fall precipitously as SBP is lowered. The practitioner should not avoid pharmacological BP lowering in persons with low DBP and SBP elevations. However, BP lowering in person with this phenotype should be done cautiously. It is likely that pharmacological BP lowering actually lowers CHD risk at every DBP level but does not change the shape of the relationship of BP with CHD (Figure 1). The fear of antihypertensive drug therapy in patients with low DBP but elevated SBP levels is, to a degree, an extrapolation of epidemiologic observations into the domain of therapeutic relevance. Accordingly, a highly plausible explanation of the J-curve is that it does indeed exist and low DBP reflects the presence of underlying vascular pathology (stiffening, reduced compliance, increased atherosclerotic burden) that is primary culprit in the increased CHD risk. However, though pharmacological BP lowering lowers CHD risk, predominantly through SBP reductions, the overall shape of the relationship between DBP and CHD is not changed – just shifted downward.

Figure 1



This figure depicts the putative relationship between DBP across a broad range of BP levels from low to high. It is likely that pharmacological BP lowering lowers CHD risk at every DBP level without changing the overall J-shape of the DBP-CHD relationship in patients with isolated systolic hypertension.

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Use of Dihydropyridine Calcium Antagonist in Chronic Kidney Disease

John M. Flack, MD, MPH

There has been substantial concern in the literature regarding the use of dihydropyridine (DHP) calcium antagonists in patients with CKD, especially proteinuric kidney disease. The reason for this concern has been studies showing that DHP calcium antagonists do not reliably reduce proteinuria, or in some instances may increase proteinuria over and above baseline, when used as monotherapy. Some, though not all, studies show that renin angiotensin system (RAS)-based antihypertensive drug therapy preserves kidney function better than non-RAS containing antihypertensive drug regimens.[1,2] In both the African American Study of Kidney Disease (AASK) [2] and the Irbesartan Diabetes Nephropathy Trial (IDNT)[1] DHP calcium antagonist-based antihypertensive drug therapy was a less effect active comparator against RAS-based antihypertensive therapy for the preservation of kidney function. There are physiologically plausible reasons for this observation.

The renal microcirculation auto-regulates glomerular flow and pressure largely by constriction of the afferent arteriole when BP rises and dilation of the afferent arteriole when BP falls. DHP calcium antagonists interfere with micro-circulatory autoregulation of glomerular flow and pressure by preferentially dilating the afferent arteriole. Thus, when systemic pressure is not reduced to low levels, there will be greater transmission of potentially injurous systemic arterial pressure into the glomerulus.

Nevertheless, the practitioner must *interpret* these studies as well as understand how well they inform routing clinical practice. There are very few situations where RAS blockade will not be included in the treatment regimen of patients with CKD given that virtually every authoritative hypertension guideline recommends RAS blockade as preferred therapy in these patients. Given the proven treatment resistance to pharmacological BP lowering in CKD, especially proteinuric CKD, the vast majority of them will require multi-drug therapy – often times more than three drugs. The RENAAL study provided insight into the how the combination of DHP calcium antagonists and RAS blockade (with the ARB losartan) worked in patients with diabetic nephropathy; there was no diminution of the renoprotective effect of losartan when used simultaneously with DHP calcium antagonists.[3] Also, there are other likely more important reasons for choosing a DHP than a non-DHP calcium antagonist in persons with CKD than their effects as monotherapy on proteinuria. For example, in a patient also taking/requiring beta blockade, a commonly used antihypertensive drug class, the use of a DHP

calcium antagonist would be much safer and more logical than using a non-DHP calcium antagonist.

Thus, the combined use of a DHP calcium antagonist with a RAS blocker that preferentially dilates the glomerular efferent arteriole appears to result in no diminution of the reno-protective effect of RAS blockers, at least in diabetic nephropathy. It would be a rare clinical scenario when it would not be possible to use RAS blockade concurrently with a DHP calcium antagonist – the latter drug class often needed for its potent BP lowering effect. Accordingly, for all intents and purposes the concern about using DHP calcium antagonists in patients with CKD is a non-issue as long as RAS blockade is prescribed concurrently.

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Mark Britton, MD

Case 1
A hypertensive patient taking multiple antihypertensive medications with poor BP control without an appropriate diuretic prescribed.
Mrs. KT is a 56-year old white female who present with a difficult to control BP. Her BP has ranged between 150 to 170 mmHg systolic and 94 to 104 mmHg diastolic.
PMH: Hypertension and hyperlipidemia.
Medications: amlodipine 10mg daily, atentolol 50mg daily, quinapril 20mg daily and simvastatin 20mg daily.
Physical Exam: BP is 174/98 mmHg without orthostatic change, heart rate of 84 beats/min, temperature 97.6°F and RR of 12. Cardiac exam is normal except for an S4 gallop, lungs are clear and extremities have trace edema.
Laboratory Studies: sodium of 138 mEq/L, potassium of 4.8 mEq/L, chloride of 100 mEq /L, bicarbonate of 24 mEq/L, BUN of 16 mg/dl and Cr of 1.8 mg/dl (estimated GFR in the low 30's).

What is the next appropriate strategy in controlling Mrs. KT BP? Why?

Impression: Mrs. KT's BP is persistently elevated despite multiple antihypertensives. However, she does not have resistant HTN because she is not taking a diuretic. There are multiple reasons to suspect that she would benefit from a diuretic: 1) likely consumption of a high sodium diet; 2) reduced renal natriuretic capacity given her depressed kidney function, and 3) multiple non-diuretic antihypertensives, especially the beta blocker and ACE inhibitor, which clearly benefit from being utilized with a diuretic to enhance their BP lowering effect. Her condition is highly suggestive of volume expansion for which she could benefit from a diuretic. A good rule of thumb is that when taking more than two non-diuretic anti-hypertensives that at least one of them should be a diuretic. Ideally the diuretic should be matched to the level of kidney function. Accordingly, a traditional thiazide diuretic like HCTZ is unlikely to be effective in this lady given it loses its effectiveness around an EGFR of 45[1]. Even chlorthalidone which works down to a GFR in the low to mid 30's would be a gamble. Either metolazone, a long-acting thiazide-like diuretic, or furosemide would be good options. If furosemide is chosen, it must be dosed at least BID; furosemide is too short acting to be utilized once daily as it is, unfortunately, often prescribed.

Plan: Start the patient on a metolazone 2.5 – 5.0 mg/d and monitor her BP response

Case 2
A well controlled hypertensive patient with refractory hypokalemia despite replacement.
Ms. JC is a 60-year old female who present with low potassium levels. Her BP was uncontrolled until two months when she was started on hydrochlorothiazide 25mg daily. Subsequently it was noted that her potassium levels has been 3.2 mEq /L. She has been maintained on potassium chloride 40 mEq daily for the past one month.
PMH: Hypertension
Medications: Hydrochlorothiazide 25mg daily amlodipine 10mg daily and potassium chloride 40 mEq daily.
Physical Exam: BP of 117/74 mmHg, Heart rate of 76 beats/mm, temperature of 98.2°F and RR of 16. Heart exam revealed a normal S1 and S2, lungs are clear and the remainder of his physical exam is normal.
Laboratory studies: showed sodium of 136 mEq/L, potassium of 3.0 mEq/L, chloride of 100 meq/L, bicarbonate of 22 mEq /L, BUN of 21 mg/dl, Cr of 1.0 mg/dl and glucose of 98 mg/dl.

What is the most likely cause of this patient potassium being low? What are the steps that can be taken to prevent and treat the hypokalemia?

Impression: This is a patient with well control BP while taking a thiazide diuretics and a dihydropyridine calcium antagonist. Hypokalemia refractory to potassium supplement is associated with depletion of magnesium stores. The combination of hypokalemia and magnesium depletion is usually seen in individuals receiving thiazide or loop diuretic treatment.[2] It has been suggested that potassium wasting is due to Na-K-ATPase impairment cause by magnesium deficiency.[3] Thus, a reasonable strategy would be to empirically administer magnesium replacement therapy given that her kidney function is normal. Measurement of serum levels can be misleading, especially if normal, because magnesium is primarily an intracellular ion and circulating levels are not necessarily indicative of magnesium depletion. Interestingly, some hypertensive patients will experience sleep disturbance. Magnesium is a reasonably effective sleep aid.

Plan: Begin magnesium and potassium supplements together. Recheck potassium and magnesium levels after a few weeks.

Case 3
A hypertensive patient with diabetes who is taking a diuretic and the steps that can be taken to minimize or prevent diuretic induced hyperglycemia.

Mr. AV was started on hydrochlorothiazide for his HTN diagnosed three months ago; at the time of diagnosis his BP was 156/98 mm Hg. He has been taking glipizide for diabetes for the past 10 years which was well controlled until recently. He was recently discharged from the ED after experiencing an episode of elevated blood glucose (250 mg/dl). His BP at that time was 138/90 mmHg.

PMH: Hypertension and diabetes mellitus
Medications: Hydrochlorothiazide 25mg daily and glipizide 10 mg daily
Physical Exam: BP of 136/92 mmHg, heart rate of 76 beat/mm, temperature 98°F and RR 16. Cardiac exam is normal S1 and S2, Lungs are clear and extremities have no edema or cyanosis.
Fasting CBG today is 140

What is the most likely reason for the elevation of Mr. AV glucose level? What is the best step to take to minimize or prevent diuretic-induced hyperglycemia?

Impression: Mr. AV's BP has responded fairly well to the diuretic. However, his physician is not practicing evidence-based medicine. The initial anti-hypertensive drug that should have been prescribed was either an ACE inhibitor or an ARB. Nevertheless, because his BP was 26/18 mm hg above baseline when anti-hypertensive therapy was initiated, it was highly unlikely that BP control to < 130/80 mm hg would be obtained. Accordingly, he should have been placed on two drug therapy initially with one of the agents being either an ACE or an ARB; the other agent should have been either a diuretic or a calcium antagonist. Hypokalemia during diuretic therapy has been significantly linked to the development of hyperglycemia. A nice advantage of ACE or ARB therapy concurrent with a diuretic is that these agents substantially reduce the likelihood of diuretic-induced hypokalemia and have also been shown, not surprisingly, to minimize thiazide-induced elevations in serum glucose levels.

Plan: Start candesartan 4mg daily and continue hydrochlorothiazide.

Case 4

Hypertensive patient with CKD with poorly controlled BP control experiencing a significant elevation in creatinine when BP is lowered below his goal BP.

Mr. Bk is a 56-year old male who present with uncontrolled HTN two weeks ago 136/84 mmHg and an EGFR of 30ml/min/1.73m^2. He has taken losartan 50mg daily, metolazone 5mg daily and diltiazem SR 240mg twice daily for the last one year. The patient was subsequently started on furosemide 20mg once daily because he developed bilateral leg swelling. Mr. BK presents to clinic today, without complaints; his EGFR is now 20.

PMH: Hypertension, CKD and CVA.
Medications: Losartan 50 mg daily, metolazone 5 mg daily, diltiazem SR 240 mg bid and furosemide 20 mg qd.
Physical Exam: BP of 118/70 mmHg (no orthostatic change), heart rate of 92 beats /min, temperature 97.2^{o}F and RR 20. Heart: regular rhythm and an S4 gallop, Lungs: clear, Extremities: no edema, skin temp is normal.

What is most likely cause of the patient's reduced kidney function? What should be the appropriate step in the management at this time?

Impression: Mr. BK was not at goal initially requiring additional antihypertensive medications. The deterioration in his kidney function is most likely due to his drop in BP. It is also certainly possible that over-diuresis is playing a role in the deterioration of his kidney function. In the setting of reduced renal mass the relationship between systemic BP and renal glomerular is no longer sigmoidal but becomes quasi-linear. Thus, declines in BP may result in rises in creatinine, at least over the short-term because renal autoregulation of glomerular pressure is impaired. Plasma volume contraction will aggravate this condition.

Plan: Evaluate the patient for over-diuresis. In the absence of a new orthostatic BP change or a significant rise in serum HCO3 (indicative of a contraction alkalosis), you might consider ordering a BNP (brain natriuretic peptide) level. If even modestly elevated intravascular volume depletion is unlikely. A normal BP level will not be nearly as helpful. I would very likely simply follow this patient and recheck the serum creatinine over the next couple of weeks.

Case 5

A hypertensive patient who is being treated with multiple antihypertensive drugs who has significant orthostatic hypotension.

PC is a 68-year old male who present with a complaint of light-headedness especially when he stands. His other symptoms include change in vision, weakness and headaches. Four weeks ago his doxazosin was increased from 4mg qhs to 8mg qhs for better BP control.

PMH: Hypertension, BPH and diabetes.
Medications: Chlorthalidone 25mg daily, telmisartan 40mg daily, doxazosin 8mg qhs, and metformin 500mg twice daily.

Physical Exam: BP sitting 120/74 mmHg and standing 100/60 mmHg. Pulse: 68 and regular (pulse rate does not change with standing) HEENT: Arteriovenous nicking but no other fundoscopic changes; Heart: RRR, normal S1 and S2; Lungs: grossly clear. Extremities: no edema.

What are the risk factor(s) in this patient for orthostatic hypotension? What is the most likely cause of his orthostatic hypotension?

Impression: This is a 68-year old male with multiple risk factor(s) for orthostatic hypotension – Age, diabetes, diuretics and taking both a diuretic and an alpha antagonist for control of BP. Orthostatic hypotension is defined as a drop in systolic blood pressure of > 20 mmHg which can be associated with symptoms. Nevertheless, practitioners should pay attention to orthostatic declines in BP that are even less in magnitude than a 20 mm Hg decline. His doxazosin was recently increased with a subsequent development of his symptoms for orthostatic hypotension. However, the lack of rise in his pulse on standing as his BP falls is consistent with autonomic neuropathy, a likely consequence of his diabetes.
Plan: He should also be evaluated carefully for over-diuresis. And, even if over-diuresis is not detected, an empiric reduction in the diuretic dose is a meritorious consideration. Another consideration would be to switch him from chlorthalidone to HCTZ without a change in the daily dose; this would also effectively reduce his diuretic dose. It is likely that several factors have conspired to contribute to his orthostatic hypotension. Without question his dose of doxazosin should be reduced. If all of these changes do not eliminate his orthostatic BP decline, you must use his standing – not seated – BP as the guide to your therapeutic intensity.

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Case 6

A hypertensive patient with truly resistant hypertension (is taking a diuretic appropriate to the level of kidney function) to illustrate several atypical strategies for lowering blood pressure (BP) – use of dual diuretic therapy, use of dihydropyridine and rate-limiting calcium antagonists simultaneously, etc.

RH is an obese (body mass index of 40 kg/m^2) 32 year old lady with a BP of 168/88 mm Hg seated and 166/88 mm Hg standing, and pulse rate of 92 beats/minute. She currently c/o daily frontal headaches which are described as a "band across her forehead" that is relieved after taking extra-strength Tylenol. The pain typically abates some about an hour after she takes her antihypertensive medications. She takes all of her medications everyday. She denies any shortness of breath (SOB), chest pain (CP), or dizziness; however she does have occasional palpitations which occur suddenly. An echocardiogram was done recently because of her h/o palpitations; she was noted to have hyperdynamic cardiac function (ejection fraction of 75%). A comprehensive work-up for secondary hypertension was negative (renal angiogram, serum metanephrines, and aldosterone:renin ratio).

PMH: Hypertension for 5 years, chronic kidney disease (CKD), estimated glomerular filtration rate [EGFR] = 58 ml/min/1.73m^2), total hysterectomy last year.

Medications: chlorthalidone 25 mg qd, spironolactone 25 mg qd, amlodipine 10 mg qd, and lisinopril 40 mg bid.

Physical Exam: HEENT: arteriovenous nicking, silver wiring; Neck: normal, no bruits noted; Lungs: clear; Heart: RRR, +S4 gallop; Abdomen: obese and otherwise negative; Extremities: +2 dorsalis pedis pulses, no edema noted.

- ✓ **What is Ms. RH's Joint National Committee 7 (JNC) goal BP? Why?**
- ✓ **What medication addition/deletion/modification would you suggest? Why?**

Impression: This is a young hypertensive obese lady of child-bearing age with resistant hypertension; given that her BP is above goal while taking 4 antihypertensive agents, including dual diuretic use that is appropriate to her level of kidney function. Her goal BP is <130/80 mm Hg, given her h/o CKD with an EGFR of 58 ml/min/1.73m^2. The addition of a rate-limiting calcium channel blocker would provide better BP control, a reduction in heart rate, as well as an attenuation of her hyperdynamic cardiac function. Dual calcium channel blockade would be a very reasonable therapeutic option. The dihydropyridine, phenylalkylamine (verapamil), and benzothiazepine (diltiazem) calcium channels are distinct, though allosterically linked, as they are both acting through the L and T channels, inhibiting calcium ions entry at the alpha 1 subunit.[1] Dihydropyridines act more specifically on vascular smooth muscle than myocardium, while the phenylalkylamines act more specifically on myocardium than peripheral vessels. The combination of amlodipine and verapamil has been utilized in combination for the treatment of hypertension;this combination potently lowers BP and has been well tolerated.[2]
Plan: Begin verapamil SR 180 mg bid, and reevaluate BP in 3-4 weeks. Order baseline lab work today, and refer pt to the dietitian for a low-sodium (<2-gram) dietary regimen.

Case 7

A hypertensive patient with CKD and heavy proteinuria – what are the available strategies, other than

simply using renin angiotensin system (RAS) blockade, to minimize urinary protein excretion?

RK is a 58 year old gentleman with hypertension and heavy proteinuria with a main complaint of "difficult to control blood pressure". He states he has had high BP for approximately 20 years and states that it has never been consistently below 140/90 mm Hg. He currently complains of frequent, frontal, tension-type headaches which come and go throughout the day. The headaches are throbbing in nature and are only relieved with non-steroidal anti-inflammatory drugs. He denies any other complaints of SOB, CP, or dizziness. Mr. RK adds salt to an unrestricted diet and has a BMI of 33 kg/m^2. BP today is 158/90 mm Hg seated and156/90 mm Hg standing with a pulse rate of 68 beats/minute. A comprehensive workup for secondary hypertension was negative (renal angiogram, serum metanephrines, thyroid levels, and aldosterone:renin ratio).

PMH: Hypertension, headaches, proteinuria (spot urine albumin:creatinine ratio 3,250 mcg/mg) with preserved renal function (EGFR = 98 ml/min/1.73m^2)

Medications: amlodipine 10 mg qd, chlorthalidone 25 mg qam, lisinopril 40 mg bid, telmisartan 80 mg qd, and verapamil SR 240 mg bid.

Physical Exam: HEENT: arteriovenous nicking, silver wiring; Neck: normal, no bruits noted; Lungs: clear; Heart: RRR, +S4 gallop; Abdomen: obese and otherwise negative; Extremities: +2 dorsalis pedis pulses, trace edema bilaterally noted.

- ✓ **What is Mr. RK's Joint National Committee 7 (JNC) goal BP? Why?**
- ✓ **What are the multiple strategies, other than simply using renin angiotensin system (RAS) blockade, to minimize urinary protein excretion?**

Impression: This is a gentleman with resistant hypertension with a JNC goal BP of <130/80 mm Hg given his h/o heavy proteinuria. He is currently on 5 antihypertensive agents, all of which have been prescribed at their maximum doses; he is currently on dual-RAS blockage to minimize the magnitude of urinary protein excretion. Dual blockade with an angiotensin converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) has been reported to be superior to single agent RAS blockade both in reducing proteinuria and in slowing the progression of renal disease.[3,4] Recently, not only angiotension II but also aldosterone has been recognized as an important mediator of RAS-related target organ injury.[5] According to a recent 1-year randomized study by Furumatsu and colleagues[6], they discovered that triple blockade of the renin angiotensin aldosterone system (RAAS) with spironolactone administered in conjunction with an ACE-I and ARB, had a significantly beneficial effect on proteinuria than dual blockage in patients with non-diabetic nephropathy. However, triple blockade of the RAS system should be avoided in persons with EGFR <50-55 ml/min/1.73m^2. Weight loss, sodium restriction, and better BP control all are linked to reduction in urinary protein excretion and all should be implemented. Also, even though he has normal kidney function, he should be closely monitored for hyperkalemia. Strategies to minimize the likelihood of hyperkalemia with dual or triple RAS blockade include: 1) use 50 mg/d of chlorthalidone, or 2) consider the use of metolazone instead of chlorthalidone; both options will increase urinary potassium wastage.

Plan: With close monitoring of Mr. RK's potassium upon follow-up, we will begin eplerenone 25 mg q am (aldosterone antagonist). Eplerenone rather than spironlactone was used because this agent is less likely than spironolactone to cause breast tenderness or gynecomastia in men. He was advised to return to clinic within 3-4 weeks to reevaluate lab work as well as to monitor the BP response to. Serum potassium should be periodically monitored whenever taking RAS blockers; the use of dual and triple RAS blockade requires heightened surveillance of serum potassium levels at least 3-4 times per

year. Sodium restriction and weight loss will likely also contribute to BP lowering, and referral will be provided to follow-up with a dietitian for a low-sodium (<2-gram) dietary regimen.

Case 8

A hypertensive patient with CKD, and proper use of diuretics appropriate to level of renal function.

LN is a 67 year old lady with uncontrolled hypertension and symptoms of fatigue and difficulty falling asleep. She denies any chest pain, headaches, or lightheadedness. She is also complaining of frequent SOB with moderate exertion, such as when climbing two flights of stairs. Her BP is 170/94 mm Hg seated and 168/90 mm Hg standing with a pulse rate of 62 beats/minute. A recent echocardiogram showed left ventricular hypertrophy and normal systolic function (ejection fraction of 55%). A comprehensive workup for secondary hypertension was negative (renal angiogram, serum metanephrines, thyroid levels, and aldosterone:renin ratio).

PMH: Stroke, hypertension, mixed hyperlipidemia, and CKD (EGFR=32 ml/min/1.73m^2)

Medications: verapamil 240 mg qd, doxazosin 4 mg qhs, metoprolol 50 mg bid, aspirin 325 mg qd, atorvastatin 20 mg qhs

Physical Exam: HEENT: arteriovenous nicking, silver wiring; Neck: normal, no bruits noted; Lungs: clear; Heart: RRR, +S4 gallop; Abdomen: obese, and otherwise negative; Extremities: +2 dorsalis pedis pulses, +1 edema.

- ✓ **What is the most obvious problem(s) with her current regimen?**
- ✓ **Is there a compelling indication for any class (es) of antihypertensive agents given her chronic renal insufficiency?**
- ✓ **What types of diuretics would you utilize for adequate diuresis/volume control given her depressed renal function?**

Impression: This patient has uncontrolled, though not resistant, hypertension, and according to the JNC 7 goal BP is <130/80 mm Hg given her h/o CKD. The absence of a diuretic and the combined use of verapamil and a beta blocker are the most obvious problems wither her current regimen. Inclusion of a diuretic in the antihypertensive regimen will be the best option to enhance her BP lowering because diuretics are clearly needed to blunt fluid retention that can be induced by many anti-hypertensive drugs. Also, given her depressed kidney function, she has very limited renal sodium excretory capacity. The diuretic should be appropriate to her level of depressed kidney function. There is no absolute indication for a beta blocker (systolic heart failure, post-MI) thus the beta blocker is expendable in this regimen.

There is, however, a compelling indication for the use of renin-angiotensin system blocker, either an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), for preservation of kidney function. Additionally, the antihypertensive regimen should always include a diuretic appropriate to the level of kidney function when taking more than two non-diuretic hypertensive agents. The diuretics that will be consistently effective at depressed EGFR's of < 45 ml/min/1.73m^2 include loop diuretics (e.g., furosemide, torsemide) however they are short-acting and dosed bid. Metolazone (zaroxolyn) may also be utilized, which is also effective even when kidney function is not depressed and is a long-acting diuretic dosed qd. Chlorthalidone (thiazide-like diuretic) is very long-acting (t1/2

~70 hours) will function down to a EGFR in the mid 30's ml/min/1.73m^2. As with all thiazide diuretics, dosing is once daily.

Plan: Taper off the beta blocker over the next few weeks as there is no absolute medical indication for the use of a beta blocker. Begin lisinopril 20 mg qd (indicated because EGFR <60 ml/min/1.73m^2), and metolazone 5 mg qam, and continue her other medications. Advised pt to return to clinic within 2-3 weeks and reevaluate electrolytes, bun, and creatinine as well as to monitor her BP. Given the high probability that her BP will fall significantly with the addition of the diuretic, and her long-standing poorly controlled BP, she should definitely be advised that she might experience transient fatigue, lethargy, and/or reduced energy in concert with the fall in BP. Warning patients about these symptoms is beneficial because if they are not warned, and they indeed experience these symptoms, they may stop the effective antihypertensive medications prescribed and revert back to their old regimen.

Case 9

Ms. LN returns 2 weeks after addition of an ACE-I and diuretic, and lab results reveal a reduction in EGFR. What may be the cause of the reduction in renal function, and how would you handle?

Upon Ms. LN's return to clinic her BP was noted to be 142/80 mm Hg seated and 142/80 mm Hg standing with a pulse rate of 62 beats/minute. Routine lab work revealed an increased creatinine level by 20% from baseline of 1.6 to 2.0, and EGFR fell from 38 ml/min/1.73m^2 to < 29 ml/min/1.73m^2.

- ✓ **How would you proceed?**

We would continue the patient on her current regimen; however continue monitoring her renal function at follow-up visits. The reduction in EGFR is very likely attributable to an inability to quickly autoregulate her glomerular filtration rate. A more significant reduction in renal function (creatinine rise > 30%) would lead us to reduce the dose of the ACE-I or, possibly, discontinue the ACE-I. In this scenario, evaluation for bilateral renal artery stenosis, which is a contraindication to the use of ACE-I or ARB's, should be undertaken. Furthermore, we must keep in mind that the rise in creatinine is likely secondary to the significant drop in her BP and/or overdiuresis (due to the diuretic). Lisinopril may also be contributing to the rise in creatinine. In the setting of reduced nephron mass/reduced kidney function, the local intra-renal RAS system is activated. This results in efferent > afferent glomerular arteriolar dilation. When indicated RAS blockade is initiated, this may result in a global reduction in GFR that is detectable with a rise in creatinine. This is partly how RAS blockers protect the kidney. Over the long-term the creatinine may stay above baseline, return to baseline, or sometimes even fall below baseline levels. A marked drop in BP in patients with CKD, even without the use of RAS blockade, is commonly followed by a rise, a least transiently, in the serum creatinine level because of impaired renal autoregulation that has become more dependent on systemic pressure levels to maintain glomerular filtration, at least over the short-term.

Case 10

Ms. LN returns 4 weeks after addition of an ACE-I and diuretic, and is symptomatic. What may be causing these symptoms, and how would you handle?

Ms. LN is complaining of fatigue and generalized weakness. She denies any headaches or lightheadedness. Currently her BP is 130/78 mm Hg seated and 126/76 mm Hg standing with a pulse rate of 64 beats/minute.

- ✓ **What may be causing these new symptoms?**

Elevated BP can cause symptoms, such as headaches, sleep disturbances, which remain as long as the BP is elevated. Reductions in BP, especially rapid ones, but also even more modest and slower reductions may also result in symptoms such as fatigue and overall weakness. Nevertheless, these symptoms are almost always transient, as the symptoms due to the drop in BP wear off as the body adjusts to the lower BP measurements. Symptoms related to the drop in BP should be described to the patient during the visit where antihypertensive medications are either initiated or intensified to prevent the patient from discontinuing their antihypertensive agents because they "feel bad". These symptoms will resolve in due time, typically over a few days to 1-2 weeks if not sooner.

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National Kidney Foundation of Michigan
1169 Oak Valley Drive
Ann Arbor, Michigan 48108
Phone (734) 222-9800
(800) 482-1455 (In-state)
Fax (734) 222-9801
www.nkfm.org

Michigan Department of Community Health
Cardiovascular Health, Nutrition and
Physical Activity Section
109 W. Michigan Ave.
P.O. Box 30195
Lansing, Michigan 48909
Phone (517) 335-8374
Fax (517) 335-8593
www.michigan.gov/cvh