Management of Hypertension

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What do you think is the cause of this patient's hypertension?

- 55 year old man with hypertension that you are treating has well controlled on his current medicines for several months
- He calls from Vale, CO saying his BP is markedly elevated
- What is/are the most likely causes?

Patient is known to have hypertension. Visiting Tucson and now has headache and hypertension (BP 180/100)

- Current medicines include
  - Amlodipine 5 mg AM
  - Losartan 100 mg PM
  - Clonidine 0.1 pm high BP
  - Direct Renin inhibitor
- You recommend that she?

James Edgar Paulkin, MD (1881-1951)

Did not tell Franklin Delano Roosevelt that he had hypertension for two reasons

He did not want Roosevelt to worry

Antihypertensive Medications were not marketed as yet

Hypertensive Treatments

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922</td>
<td>Strict low-salt diet</td>
</tr>
<tr>
<td>1925</td>
<td>Lumbar sympathectomy</td>
</tr>
<tr>
<td>1944</td>
<td>Kempner rice diet</td>
</tr>
<tr>
<td>1944</td>
<td>Reserpine</td>
</tr>
<tr>
<td>1950</td>
<td>Hexamethonium</td>
</tr>
<tr>
<td>1951</td>
<td>Hydralazine</td>
</tr>
<tr>
<td>1952</td>
<td>Carbonic anhydrase inhibitors</td>
</tr>
<tr>
<td>1955</td>
<td>α methyldopa</td>
</tr>
<tr>
<td>1957</td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>1959</td>
<td>Guanethidine</td>
</tr>
<tr>
<td>1959</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>1962</td>
<td>β-blockers</td>
</tr>
<tr>
<td>1964</td>
<td>Furosemide</td>
</tr>
<tr>
<td>1970</td>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td>1974</td>
<td>Sodium nitroprusside</td>
</tr>
<tr>
<td>1980</td>
<td>Angiotensin-converting enzyme inhibitors</td>
</tr>
<tr>
<td>1995</td>
<td>Angiotensin II receptor blockers</td>
</tr>
<tr>
<td>2007</td>
<td>Direct renin inhibitors</td>
</tr>
</tbody>
</table>

1940s-1960s
High blood pressure was
"Essential"
Should the BP be lowered?

"For aught we know, the hypertension might be a compensatory mechanism that should not be tampered with even were it certain that we could control it." Paul W. White, MD 1931

"May not the elevation of blood pressure be a Natural response to guarantee a more normal circulation to the heart, brain and kidneys" Dr. F Trice

The VA Cooperative Study, 1967

<table>
<thead>
<tr>
<th>Cohort</th>
<th>143 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>51 years</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Diastolic BP 115-129 mmHg</td>
</tr>
<tr>
<td>Design</td>
<td>Double blind: placebo control</td>
</tr>
<tr>
<td>Therapy</td>
<td>HCTZ, reserpine, hydralazine</td>
</tr>
<tr>
<td>Duration</td>
<td>1.5 years</td>
</tr>
<tr>
<td>BP change</td>
<td>-43/30 mmHg</td>
</tr>
</tbody>
</table>

HCTZ=hydrochlorothiazide

The VA Cooperative Study, 1967:
Assessable Morbid/Fatal Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=70</th>
<th>Active Rx* n=73</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated hypertension</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Coronary event</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Renal damage</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<0.001 active drug therapy vs placebo

The VA Cooperative Study, 1967:
Conclusions

- The actively treated group experienced a reduction in multiple hypertension-related endpoints
  - 21 morbid/fatal events on placebo
  - 1 morbid/fatal event on active therapy


The VA Cooperative Study, 1970

<table>
<thead>
<tr>
<th>Cohort</th>
<th>380 men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>50 years</td>
</tr>
<tr>
<td>Eligibility</td>
<td>Diastolic BP 90-114 mmHg</td>
</tr>
<tr>
<td>Design</td>
<td>Double blind: placebo control</td>
</tr>
<tr>
<td>Therapy</td>
<td>HCTZ, reserpine, hydralazine</td>
</tr>
<tr>
<td>Duration</td>
<td>5.5 years (mean=3.8 yrs)</td>
</tr>
<tr>
<td>BP change</td>
<td>Diastolic BP -19 mmHg</td>
</tr>
</tbody>
</table>


The VA Cooperative Study, 1970:
Assessable Morbid/Fatal Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=194</th>
<th>Active Rx* n=186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerated hypertension</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Total coronary event</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Fatal coronary event</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Renal damage</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

*P<0.001 active drug therapy vs placebo
VA Cooperative Study Group. JAMA. 1970;213;1143-1152.
National High Blood Pressure Education Program

- The advertising firm had ordered 100,000 information packets, but after Ann Landers' column appeared, they received 300,000 requests for information about high blood pressure.

Mr. Jim Shields 2004

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**Hypertension:**

- One of the most important preventable causes of premature death America!

*Lancet 2002; 360; 1347*

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**Hypertension:**

- 62% of strokes and 49% of heart attacks are caused by high blood pressure!

*World Health Report 2002*
Hypertension:

A proven modifiable risk factor for:
- Death
- Stroke
- Atrial Fibrillation
- Myocardial infarction
- Heart Failure
- Dialysis
- Renal transplantation

JNC VI. Arch Intern Medicine 1997; 157: 2413

In clinical trials, antihypertensive therapy has been associated with reductions in:

- Myocardial Infarction: 20-25%
- Stroke: 35-40%
- Heart Failure: >50%

The JNC 7 Report. JAMA 2003; 289: 2560

Hypertension

The benefits of antihypertensive drug therapy have been confirmed by the largest number of clinical trials in all of medicine

Brit Medical J 2003; 236: 61
JAMA 2003; 290: 199

80 year old male

- BP 170/90
- Home BP 160-170/88-92 mmHg
- GFR 48
- No symptoms
- Should he be treated at this age?

Hypertension: A Paradox

- Easily diagnosed
- Simple, non-invasive, and accurate method of measuring BP available since 1905

JNC VI. Arch Intern Medicine 1997; 157: 2413
Hypertension:
- Yet only a little more than 1/3 (37%) of patients with hypertension have their blood pressure control to less than 140/90 mm Hg.
- This means that almost 2/3 of patients have hypertension that is difficult to manage or "refractory."

Etiology of Hypertension
- 93% of patients with hypertension have primary (essential) hypertension.
- Patients with primary hypertension are born with 1/2 the number of nephrons.

Glomerulus in Hypertension
- The presence of relatively few glomeruli leads to increased filtration by each glomerulus.
- Over time, this hyperfiltration may cause glomerular injury.

Hypertension Increases with AGE
- Normal BP at age 50, you have a 90% chance of having hypertension by age 90.

Refractory Hypertension
Resistant or Difficult to Control Hypertension
- BP of at least 140/90 mm Hg or at least 130/80 mm Hg in patients with diabetes, or renal disease (Creatinine of >1.5 mg/dL) . . . . despite adherence to treatment with full doses of at least 3 antihypertensive medications, including a diuretic.

JNC 7 JAMA 2003; 289: 2560
Home BP Monitoring Essential

- Study of nearly 5,000 patients
- 13% White Coat hypertension
- 9% Masked hypertension
- Home BP better determinant of outcome
- Taken much more often, and at various times of the day, not just office hours

*JAMA* 2004; 291: 1342

Lack of a nocturnal decline in BP (non-dipping) has been related to an increase in end-organ damage and cardiovascular events

- Verdecchia *et al.* Hypertension 1994; 24: 793-801
- Staessen *et al.* JAMA 1999; 282; 539-546
- Ohkubo *et al.* J Hypertens 2002; 20: 2183

I have all of my hypertensive patients buy BP unit for home monitoring

What Kind of Reports Do I Get?

Resistant or Difficult to Control Hypertension

Possible "White Coat"?

- Yes

- Self or Ambulatory BP Monitoring
- Elderly? Oiler Maneuver

Osler maneuver to assess "pseudohypertension"

A positive result is reflected by the continued palpability of the radial artery (not the radial pulse) while the brachial artery is occluded with a blood-pressure cuff

*NEJM* 2006; 355:1934

Resistant or Difficult to Control Hypertension

Possible "White Coat"?

- Yes

- Self or Ambulatory BP Monitoring
- Elderly? Oiler Maneuver

Patient adherence?

- No

- Address concerns, educational issues

Takes time to educate the patient

Necessary that we do so
Not because they do not have insurance!
- 92% of adults with untreated or unsuccessfully treated high blood pressure have medical insurance

August New England Journal of Medicine 2001

Interfering or Exogenous Substances
- Sympathomimetic drugs (e.g. ephedra, phenylephrine, cocaine, and amphetamines)
- Herbal supplements (e.g. ginseng and yohimbine)
- Anabolic steroids
- Appetite suppressants
- Erythropoietin


Interfering or Exogenous Substances
- NSAIDs and COX inhibitors raise both systolic and diastolic BP by impairing excretion of sodium and inhibiting the production of local renal vasodilative prostaglandins
- Renal vasodilative prostaglandins are necessary for the therapeutic actions of ACE-I


Interfering or Exogenous Substances
- Excessive alcohol use (more than three or four drinks a day)
  - Xin et al. Hypertension 2001; 38: 1112
- High altitude
- High sodium intake (urinary sodium >150 mmols/day)
- Salt sensitivity increases with age (>60 yrs), in Blacks, and renal impairment
  - Weinberger MH. Hypertension 1996; 27: 481

What do you think is the cause of this patient’s hypertension?
- 55 year old man with hypertension that you are treating has well controlled on his current medicines for several months
- He calls from Vale, CO saying his BP is markedly elevated
- What is/are the most likely causes?
Resistant or Difficult to Control Hypertension

- Obese or Metabolic Syndrome?
  - Yes
  - Diet and Aerobic exercise
    - Consider Leptin band
  - No

- Possible secondary causes of hypertension?
  - Yes
  - Dx and Rx: Renal parenchymal or renovascular diseases
    - Adrenal disease
    - Thyroid disease
    - Cushing's syndrome
    - Phaeochromocytoma
    - Aortic coaractation
    - Sleep apnea
  - No

Etiology of Hypertension

- Primary (Essential) 93%
- Secondary 7%

Secondary Causes of Hypertension

- Chronic renal parenchymal disease
  - Usually resulting from diabetic nephropathy or hypertensive nephrosclerosis, may be the most common secondary cause of hypertension—hypertension begets hypertension
- In patients with low GFR, Rx with ACE-I, ARB or both plus loop diuretic
  - Furosemide etc. must be given two or three times a day
- Add beta blocker and/or non-dihydropyridine calcium channel blocker


Secondary Causes of Hypertension

- In renovascular hypertension caused by atherosclerotic renal artery stenosis, the blood pressure often remains high even after interventions (balloon and/or stents)
- In contrast to hypertension caused by less common fibromuscular dysplasia—the most common cause of secondary hypertension in younger women responds to renal artery stenting


Secondary Hypertension

- Intervention for secondary hypertension
  - Hyperaldosteronism
    - Surgery for adenoma
    - Aldosterone-antagonist (spironolactone) therapy for hyperplasia
- Surgery for pheochromocytoma
- CPAP or BiPAP for sleep apnea

Pepperell et al. Lancet 2002; 359: 204

Resistant or Difficult to Control Hypertension

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    - Thyroid disease
    - Cushing's syndrome
    - Phaeochromocytoma
    - Aortic coaractation
    - Sleep apnea
  - No

Optimize and intensify pharmacologic therapy
Refactory Physician

Studies have reported that medication was not increased (adding or increasing dose) in more than 50% of patients with poorly controlled hypertension despite repeated office visits


Treatment of Resistant or Refractory Hypertension

- The most important therapeutic maneuver is generally to add or increase diuretic therapy
- More than 60% of patients with resistant hypertension may have a response to this approach


Diuretic Therapy Enhances the Development of Diabetes

- Studies show that the risk of developing diabetes is about 3 times higher in hypertensive patients treated with diuretics

Pipeine, C and Cooper-DeHoff JACC2004; 44: 509

Diuretics increase the risk of diabetes

Pipeine, C and Cooper-DeHoff JACC2004; 44: 509

Percent reduction of new diabetes in randomized clinical trials by treatment group. The comparator groups contained predominantly either older BBs and/or thiazide diuretics

Pipeine, C and Cooper-DeHoff JACC2004; 44: 509
Hypertension

- Initial Drug for Hypertension
- Without Specific Risks

- Any discussion of single-drug therapy for initial drug therapy for hypertension without specific risks is moot
- Combination therapy is essentially unavoidable in the vast majority of patients -- for physiologic reasons
- Any drug that lowers BP is counteracted by a degree of renal salt and water retention because salt and water excretion is dependent on glomerular perfusion pressure

Hypertension

- 1950s: "Essential"
- 1960s: Diastolic BP most important "number"
- 1970s: "Normal systolic BP was 100 + age"
- 1990s: Systolic BP most important
- 2000s: Pulse pressure of increasing importance

Effect of Systolic BP and Diastolic BP on CHD Mortality: MRFIT Screened (N=316,099)*

- CHD Death Rate per 10,000 person-Years
- 100+ 140-159
- 90-99 120-139
- 80-89 70-74
- 75-79 <70
- Diastolic BP (mm Hg)
- Systolic BP (mm Hg)


Wide pulse pressure

(≥ 60 mm Hg)

Marker for "stiff" arterial system

Blood Pressure and Age

INVEST

Role of Diastolic BP

- 22,576 patients with CAD and hypertension
- JNC VI guidelines followed
- 70% BP controlled
- Mean BP was 119/84 mm Hg
- No difference in stroke
- MI were related to diastolic BP

INVEST
Role of Diastolic BP

- Diastolic BP >110 mm Hg = 12%
- Diastolic BP 90-110 mm Hg = 6%
- Diastolic BP 70-90 mm Hg = 3%
- Diastolic BP 60-70 mm Hg = 6%
- Diastolic BP <60 mm Hg = 12%

Messerli et al. Ann Internal Medicine 2006; 144:884

The J-Curve Between Blood Pressure and Coronary Artery Disease or Essential Hypertension

Exactly How Essential?
Franz H. Messerli, MD, Ganesh V. Panjrath, MD
New York, New York, and Baltimore, Maryland

Journal of the American College of Cardiology
2009;54:1827-1834

Wide pulse pressure is caused by stiff arteries

What causes stiff arteries?

Messerli and Panjrath, JACC 2009;54:1827

Aortic Stiffness Decreased

- Aerobic exercise
- N-3 fatty acids
- Estrogens
- Low salt diet
- Atorvastatin
- ACE-I/ARBs
- Calcium channel blockers
- Sildenafil
- AGE product breakers (control of diabetes etc.)

Antihypertensive Medications

- Diuretics: hydrochlorothiazide HCTZ, chlorothalidone 12.5, 25
- EDAC (ethacrynic acid) 25 mg
- ACE I: ramipril (Altace) 2.5 to 10 mg hs
- Enalapril 5-40 mg hs
- ARB: losartan (Cozaar) 25-100 mg hs
- Olmesartan (veluetan) 160-320
- Ramipril Blocker
- Tekturna (aliskiren) 150-300 day

BB: Toprol XL, (metoprolol succinate)
(metoprolol tartrate) BID
Carvedilol 6.25-25 BID
Vasodilator Minoxidil 2.5, 10 once daily
(hydralazine) 50-100 TID
Central Catapress TTX or clonidine transdermal 0.1-0.3