Antihypertensives

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Blood Pressure

- Blood pressure is the force that circulating blood exerts on walls of arteries.
- Two blood pressures are measured, systolic blood pressure and diastolic blood pressure.
- Systole occurs while the heart contracts. Diastole occurs while the heart rests between beats.

Blood pressure = Cardiac output x Peripheral vascular resistance (CO x PVR)
Antihypertensive Drugs

What is Hypertension:
A common, incurable, persistent, but usually asymptomatic disease whose treatment provides no obvious benefit.
Definition: Hypertension

Elevation of arterial blood pressure above 140/90 mm Hg
Introduction

- Thirty percent of people with high blood pressure don’t know they have it.
- Of all people with high blood pressure, 11 percent aren’t on therapy (special diet or drugs), 25 percent are on inadequate therapy, and 34 percent are on adequate therapy.
Average 14 readings: two per session, taken morning and evening for 7 days.
A classification of hypertension is based on the impact on risk.

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertensive</td>
<td>120-139</td>
<td>or 80-89</td>
</tr>
<tr>
<td><strong>Hypertensive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>or 90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥160</td>
<td>≥100</td>
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**Classification of Hypertension**
Primary (Essential) Hypertension

- 90% of cases have no specific cause
- High blood pressure associated with increased peripheral vascular resistance
- Multifactorial abnormalities
  - Genetics
  - Stress
  - Environment and diet (Smoking/High salt diet)
Clinical Presentation

- Most times asymptomatic (a ‘silent’ disease)
- Headache
  - Coincides with morning surge in BP
  - Circadian variation of blood pressure

BP variations

*Increased BP variability is associated with increased organ damage and cardiovascular morbidity.*

- “White Coat” or isolated office hypertension.
- Masked hypertension.
- Morning surge of BP.
- During Sleep: “Non dipping” and “extreme dipping”.

Mortality is Related to Blood Pressure

% of Expected Mortality

Systolic Blood Pressure

- 88-97
- 98-127
- 128-137
- 138-147
- 148-157
- 158-167
- 168-177
- 178-187
- >188

[Bar chart showing mortality rates for different systolic blood pressure ranges for men and women.]
Mortality is related to blood pressure

Benefits of Lowering BP

Antihypertensive therapy has been associated with:

- 35% to 40% mean reduction in stroke incidence.
- 20% to 25% reduction in myocardial infarction.
- More than 50% reduction in HF.
Currently, the prevalence of hypertension in the US age 35-45 years is as follows:

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>White Women</td>
<td>17%</td>
</tr>
<tr>
<td>White Men</td>
<td>26%</td>
</tr>
<tr>
<td>African American Women</td>
<td>37%</td>
</tr>
<tr>
<td>African American Men</td>
<td>44%</td>
</tr>
</tbody>
</table>
Uncomplicated to Complicated/Malignant Hypertension: End-Organ Damage

- Chronic hypertension alters blood vessel/cardiac muscle structure
  - Decreases blood vessel diameter
  - Diminishes distribution of oxygenated blood to tissue targets
  - Cardiac hypertrophy
  - High blood pressure ultimately leads to major end-organ damage i.e., heart attack, stroke, renal failure

- Need to diagnose and treat hypertension early

vascular hyperplasia  edema

papilledema
Treating Hypertension

**Lifestyle Modification:** Alterations in diet and exercise may reduce blood pressure in some patients.

**Drug Treatments:** There are many antihypertensive drugs, commonly used in combination therapy.

**Tailor treatment according diagnostic exam**
- Uncomplicated vs complicated disease
- Ethnicity
- Severity of hypertension
- Pregnancy
- Drug Interactions
- Patient compliance
Non-pharmacologic Treatment

Lifestyle Modifications:

- Weight reduction
- Diet rich in potassium and calcium and sodium reduction.
- Dietary Approaches to Stop Hypertension (DASH) eating plan (1600-mg sodium) has effects similar to single drug therapy.
- Physical activity.
Sites of action of antihypertensive drugs.
Sites of action of antihypertensive drugs.

- **Sites of action**
  - **CO** → **BP**
  - **SV** → **SVR**

- **Contractility**
  - β-blockers
  - CCB

- **Preload**
  - β-blockers
  - CCB

- **Venous tone**
  - α₁-blockers
  - Sodium nitroprusside
  - ACE inhibitors
  - AT₁ antagonists

- **Intravascular volume**
  - Na⁺/H₂O retention
  - Diuretics
  - ACE inhibitors
  - AT₁ antagonists

- **Direct innervation**
  - α₁-blockers
  - Central
  - α₂-agonists

- **Circulating regulators**
  - α₁-blockers
  - Central
  - α₂-agonists
  - ACE inhibitors
  - AT₁ antagonists

- **Local regulators**
  - Endothelin antagonists
  - Sodium nitroprusside
  - ACE inhibitors
  - AT₁ antagonists

- **CCB** Direct arterial vasodilators
Antihypertensive drugs may be divided into the following classes:

- **Diuretics**
- **Calcium channel blockers**
- **Beta blockers**
- **Angiotensin converting enzyme (ACE) inhibitors (ACEI)**
- **Angiotensin Receptor Blockers (ARBs)**
- **Central \( \beta \)-adrenergic receptor agonists**
- **Adrenergic neuron blocking agents**
- **Peripheral \( \alpha \)-adrenergic antagonists**
- **Vasodilators**
Ways of Lowering Blood Pressure

- Reduce plasma volume (diuretics)
- Reduce cardiac output (β-blockers, Ca\(^{2+}\) channel blockers)
- Reduce peripheral vascular resistance (vasodilators)

\[ \text{MAP} = \text{CO} \times \text{TPR} \]
Overview: Antihypertensives and sites of action

- Methyldopa
- Clonidine
- Reserpine
- Guanethidine
- Prazosin
- Propranol (β Blockers)
- Hydralazine
- Minoxidil
- SNP
- Diazoxide
- ACEI
- CCB’s
- ARB’s

Diuretics
Diuretics (‘Water Pills’)
History

- Diuretics discovered in the 1930s and used to treat antibacterial infections
- Patients noticed that the drugs made them urinate frequently
- In 1950s, William Schwartz and Karl Beyer implemented and refined their usage to treat patients with hypertension
Diuretics:
General Properties

- Reduce morbidity and mortality in patients with hypertension
- Often first-line antihypertensive therapy either alone or in combination
- Provide adequate treatment of BP control in patients with mild or moderate primary hypertension
- Most efficacious in “low renin” or volume-expanded forms of hypertension
- Very effective for treatment of hypertension in African Americans
Diuretics: Drawbacks

- Can adversely affect serum lipids and can reduce insulin sensitivity (watch out for diabetic patients!)
  - The effect on diabetes may occur in the long-term use of diuretics (i.e. years of treatment)
- Requires 2 weeks to become fully effective
- PVR may increase at first
Thiazide Diuretics - Effects on Kidney

Hydrochlorothiazide (Hydrodiuril) - Prototype
- Block Na⁺/Cl⁻ cotransporter
- Increase Na⁺/Cl⁻ excretion
- Increase K⁺ loss

Chlorthalidone (Hygroton)
- Thiazide-like
Diuretics

**Thiazide diuretics:**

Effective in mild and moderate HT with normal renal and heart function.

- Hydrochlorothiazide.
- Chlorthalidone: long acting.
- Bendrofluazide.
- Indapamide: vasodilating and lipid neutral. Also induces regression of LVH.
Thiazides

- Cause Na\(^+\) and water excretion
- Reduce blood volume and CO (PVR may increase)
- Chronically, PVR decreases, CO returns to normal
- Total peripheral resistance decreases due to a decrease in Na\(^+\) in vascular smooth muscle.
- Diuretics used to relieve sodium retention caused by vasodilators or sympathoplegic antihypertensives
Thiazides: additional considerations

- May develop resistance
- Use a more efficacious diuretic
  - Loop Diuretics
Loop/High Ceiling Diuretics

- Act at the TAL which has high absorptive capacity (Na+)
- Block the Na⁺/K⁺/Cl⁻ cotransporter
- Increase Na⁺ excretion

**Furosemide (Lasix)**
**Ethacrynic Acid (Edecrin)**
Loop Diuretics: Indications

- Hypertension where short acting diuretic is indicated
  - **Rapid onset of Action**
    - IV 5 minutes
    - Oral 1-2 hours
    - **Duration 4-6 hours**

- Useful in patients refractory to less potent diuretics (heart failure, renal insufficiency, nephrotic syndrome)

- Edema (furosemide-pulmonary edema)
General Diuretics: Side effects

- \(K^+\) depletion (\(K^+\) supplements)
- \(Mg^{2+}\) depletion
- Avoid in patients with arrhythmias, acute MI
- Impaired glucose tolerance
- Increased serum lipid levels
- Increased uric acid/gout
Loop Diuretics and Potassium Loss

- Hypokalemia is a problem
- Signs and symptoms of hypokalemia:
  - muscle weakness
  - drowsiness
  - cardiac arrhythmia
- Managed with $K^+$ supplementation ($K^+$ salts or foods rich in $K^+$) and restricted $Na^+$ intake
- Use of $K^+$ sparing diuretics
Potassium Sparing Diuretics
The Na+ channel inhibitors

- Block Na\(^+\) channel in the late distal tubule
- Prevent the Na gradient that drives K\(^+\) secretion in the tubular lumen (Na\(^+\)/K\(^+\) ATPase)
- Useful in combination with loop diuretics

- Prototype: Amiloride (Midamor)
Potassium Sparing Diuretics: The Aldosterone Antagonist

- Block aldosterone binding to its receptor
- Decrease synthesis of $\text{Na}^+ / K^+$ ATPase and $\text{Na}^+$ channel
- Thereby increases $\text{Na}^+$ excretion
- Increase $\text{K}^+$ absorption
Aldosterone Receptor Antagonists

Spironolactone (Aldactone)
- Late distal tubule and collecting duct
- Decrease $\text{Na}^+$ reabsorption
- Decrease $\text{K}^+$ secretion
Potassium Sparing Diuretics: Indications

- Useful in patients taking digitalis

- Enhance Na\(^+\) excretion in combination with other diuretics
Diuretics and Kidney Disease

Efficacy of diuretics may be compromised during kidney failure

- Diuretics act to modulate electrolyte balance via effects on transporters/channels within the kidney
- Thus, the efficacy of diuretics to modulate transporter/channel function within a damaged kidney will likely be diminished
- May not effectively resolve hypertension under these conditions
Calcium Channel Blockers
‘CCBs’
Calcium Channel Blockers

- Block $\text{Ca}^{2+}$ in cardiac/smooth muscle
- Dilate peripheral arterioles
- Reduce peripheral vascular resistance
Calcium Channel Blockers
(Dihydropyridine Class)

Amlodipine (Norvasc) and Nifedipine (Adalat)

- Block Calcium in vascular smooth muscle (vasodilate)
- Decrease PVR
- No effect on AV node conduction
- Useful in angina
Calcium Channel Blockers
(Nondihydropyridines)

Verapamil (Isoptin)
- Direct negative inotropic and chronotropic action (cardiodepressive)
- May cause heart failure in patients with borderline cardiac reserve (Do not use in patients with LV dysfunction)

Diltiazem (Cardizem)
- Decreases AV conduction and heart rate
- Weaker negative inotrope then verapamil
Calcium Channel Blockers: Side Effects

- Hypotension
- Cardiac depression (Diltiazam, verapamil)
- Tachycardia (Nifedipine)
- Headache
- Flushing
- Edema (Nifedipine)
- Constipation
Calcium Channel Blockers: Drug Interactions

- Use of either verapamil or diltiazem (nondihydropyridines) in combination with β-blocker could cause marked bradycardia and cardiac conduction blockade

- Verapamil and diltiazem may add to the inhibitory effects of digoxin on AV conduction

- Amlodipine: combination with ACE inhibitor reduced CV events in hypertensive patients (ASCOT trial study)
CCB Indications

- Useful in low renin hypertension
  - Low renin hypertension is usually more common in African American and elderly patients

- Useful in controlling BP and cardiovascular events in patients with isolated systolic hypertension, particularly the elderly
Beta-Adrenergic Receptor Blockers

®-Adrenoceptor Antagonists

‘®Blockers’
Cardiac effects:

- Increase cardiac output
  - Increase heart rate
  - Increase heart contractility
History

- Raymond Ahlquist (MCG) in 1948 was searching for a drug to relieve menstrual cramps and coincidentally found epinephrine stimulated heart rate through a distinct set of receptors (®) in the heart.

- By 1964, a research chemist, Sir James Black, having read these published observations developed ®-blockers.
Mechanism of Action: Effect on the cardiac myocyte

The endogenous pathway

- Beta-AR are coupled to Gs-proteins
- Gs-proteins activate adenylyl cyclase to form cAMP
- Increased cAMP activates PK-A
- PK-A phosphorylates L-type calcium channels and MLC-K,
  1. Increase inotropy (contractility).
  2. Gs-protein activation also increases heart rate (chronotropy)

A Beta blocker will block this pathway to decrease inotropy and chronotropy
Mechanism of Action: Effect on the blood vessel

The endogenous pathway
- Beta-AR are again coupled to $G_s$-proteins
- However, in contrast to heart, increased cAMP inhibits MLC-K in VSMC

1. A modest effect (relative to other vasoactive autacoids) causing blood vessel relaxation

- A Beta blocker will also block $b_1$-AR in the kidney which will decrease renin production, and decrease vessel tone
Propranolol (Inderal): Mechanisms of Action

- Nonselective, competitive antagonist of \( \beta_1 \) and \( \beta_2 \) adrenergic receptors (block binding of NE)
- Cardioprotective
  - Decreases heart rate
  - Decreases contractile force
  - Decreases cardiac output
  - Delays AV node conduction
  - Neutralize reflex tachycardia induced by vasodilators
- Reduces central sympathetic nervous system output
- Small vasoconstrictive effect (Increase PVR)
- Reduces renin release (\( \beta_1 \)) (effective in patients with high renin activity as is common in younger patients having hypertension)
Propranolol: Side-effects

- Hypotension, AV block, severe bradycardia (negative chronotrope), possibly HF
  - Careful consideration in patients with conduction problems/bradycardia
- Bronchial constriction/spasm
  - Do not use in asthmatic patients
- Acute withdrawal syndrome (receptor supersensitivity) in patients, predisposing to myocardial ischemia
- Increase triglyceride levels and decrease HDL levels
- Induce glucose intolerance
  - Careful usage in diabetic and obese patients
- Lipid soluble, cross BBB-Nightmares/depression
Propranolol:
Contraindications

- Bronchial asthma
- Peripheral vascular disease
- AV (heart) block
Other ™ blockers

**Atenolol (Tenormin)**
- ⊂ 1 selective antagonist
- Administered once daily
- Less lipid soluble than other ™ antagonists

**Metoprolol (Lopressor)**
- Selective inhibitor to 1
- Useful in asthmatic patients

**Nadolol (Corgard)**
- Non-selective ™ antagonist
- Administered once daily
Blockers: Indications

- Mild and moderate hypertensives
- Useful in patients receiving vasodilators to prevent sympathetic reflex tachycardia
- Also useful in controlling BP in patients with underlying heart disease (congestive HF, ischemia, MI)
Angiotensin Converting Enzyme Inhibitors
‘ACE Inhibitors’
Workers in the banana plantations of Brazil were known to collapse after being bitten by a specific viper.

A Brazilian biochemist Maricio Rocho e Silva purified the venom extracts and sent his post-doc with extracts to study their effects in the lab of Sir John Vane (London).

By 1970, the lab of Sir John Vane found the effect was on ACE, ultimately leading to the development of ACE inhibitors.
Renin-Angiotensin-Aldosterone System (RAAS)

ACE Inhibitors
Inhibit conversion of inactive angiotensin I to angiotensin II which:
  • reduces vessel tone
  • reduces Na+ retention via aldosterone
  • blocks degradation of bradykinin, a vasodilator

  • Very useful in diabetic patients
    • Slows progression of renal disease

Thus RAAS pathway has multiple effects via discrete pathways which are important in blood pressure control, but which act to increase blood pressure
Enalapril
- Excretion is primarily renal – dose should be reduced in patients with renal insufficiency

Ramipril
- Peak plasma concentration within 1 hour
- $t_{1/2} – 2-4$ hrs

Lisinopril
- Slowly absorbed; plasma $t_{1/2} – 12$ hrs; administered once daily

Captopril
- Sulfhydryl containing moiety causes some taste changes
ACEI: Side-effects

- Severe hypotension in hypovolemic patients
- Hyperkalemia
- Angioedema (0.1-0.5%)
  - rapid swelling of nose, throat, mouth, larynx, lips, or tongue
  - may relate to inhibitory effect bradykinin catalysis
  - Greater risk in African Americans
- Cough (10-20%)
- Skin rash (10%)
- Taste alterations (6%)
ACE inhibitors: Contraindications

- **ACE Inhibitor**
  - Can cause hyperkalemia
  - Hyperkalemia can be exacerbated with potassium sparing diuretic

- Some studies indicate that ACEI are not effective in lowering BP in the African American population

- Pregnancy – ACEI suppresses cell proliferation which will impair embryonic development; should not be administered in second or third trimester
Angiotensin I Receptor Blockers (ARB’s)

**Losartan (Cozaar)**
- Decreases TPR
- Inhibits Aldosterone release
- Block Na⁺ reabsorption
Blocking AT$_1$ receptor is antihypertensive

AT1 Prototype antagonist = Losartan

- Vasoconstriction
- Cell Growth and Proliferation
- Aldosterone release
- Central Sympathetic activation
- Sodium and water retention

- Vasodilation
- Restrains cell growth and proliferation
- Mediates NO and PGI$_2$ release in kidney
- Renal sodium excretion
- Dilates afferent renal arteriole
Losartan:

Side Effects

- Angioedema
  - Subcutaneous swelling of eyes and lips
- Not to be administered during pregnancy (first trimester)
  - AT receptors important in embryonic renal development
- Dizziness
ACEI versus ARB

- Use ACEI and ARB in hypertensive patients with heart failure, renal disease, and diabetes.
- ACEI costs $0.11/cap vs. $0.48-0.90/cap for ARB.
- Use ACEI as first choice vs. ARB, unless patients cannot tolerate ACEI (angioedema), then use ARB.
Peripheral $\beta_1$ Adrenergic Receptor Blockers
‘Peripheral $\beta_1$ Blockers’
Prazosin (Minipres): Mechanism of Action

- Blocks $\alpha_1$-AR on resistance vessels from binding NE released from nerve terminals
- Decreases vascular tone (vasodilates)
- Thereby decreases PVR and BP
Prazosin:
Side effects

- Postural dizziness (14%)
- Headaches (8%)
- Drowsiness (8%)
- ‘first dose phenomenon’
  - Syncopal reaction-orthostatic hypotension (upon standing)
  - After first dose, tolerance to this reaction
Other selective \( \beta \)-adrenergic receptor blockers

Doxazosin and Terazosin

- longer \( t_{1/2} \) than prazosin
- used for treatment of benign prostate hypertrophy
Recent Recommendations on \( \alpha \)-blockers

- \( \alpha \)-blockers are less effective than diuretics in preventing cardiovascular events, mainly heart failure (ALLHAT clinical study)
- NIH recommends NOT to use \( \alpha \)-blocker as the first drug of choice in hypertension (it is safe, just not effective in preventing heart failure)
- A reasonable addition, to facilitate blood pressure control
‘Adrenergic Neuron-Blocking Agents’
‘Sympatholytics’
Adrenergic Neuron-Blocking Agents

- Deplete norepinephrine from presynaptic, postganglionic sympathetic nerve terminals

- Inhibit release of norepinephrine in response to sympathetic nerve stimulation

- Reduce cardiac output and total peripheral resistance
Guanethidine (Ismelin): Mechanism of action

- Guanethidine enters peripheral nerve terminals via the same transporter as NE.
- Depletes NE stores in vesicles.
- False neurotransmitter.

\[ G = \text{guanethidine} \]
\[ \text{NE} = \text{norepinephrine} \]
Guanethidine: Pharmacokinetics

- Effective orally (takes 72 hrs to reach maximum effect)
- Plasma $t_{1/2}$ – approximately 5 days
- Guanethidine is indicated only for moderate to severe hypertension
Reserpine (Serpasil): Mechanism of Action

- Blocks transport of dopamine into storage granules in nerve terminals
- Depletes stores of catecholamines and serotonin in CNS and PNS
- Decreases sympathetic tone, total peripheral resistance and cardiac output
Reserpine: Pharmacokinetics

- Absorbed from GI tract (2-6 wks to achieve maximal effect)
- Plasma $t_{1/2}$ – 11.5-16 days
- Largely hepatic metabolism
Guanethidine and Reserpine: Side Effects

- Orthostatic hypotension (Guanethidine)
- Depression
- Nasal Congestion
- Bradycardia
- Impotence (Guanethidine)
- Diarrhea (Guanethidine)
- Salt and water retention
Guanethidine and Reserpine: Drug Interactions

- Drugs that alter function of the amine pump can block uptake to site of action: tricyclic antidepressants, monoamine oxidase inhibitors, ephedrine, amphetamines, phenothiazines

- After chronic use of guanethidine, the above agents could cause hypertension due to development of receptor supersensitivity
Rarely indicated

- The a adrenergic blocking agents are not frequently prescribed because of their adverse effects
- Can be a last resort in refractory (unmanageable) hypertension
- Reserpine is cost-effective
Central $\alpha_2$-Adrenergic Receptor Agonists
Centrally Acting Sympathoplegic Drugs
‘Central $\alpha_2$ Agonists’
Central $\alpha_2$-Adrenergic Agonists

- **Methyldopa** and **clonidine** cross BBB to stimulate $\alpha_2$ receptors in vasomotor center in brainstem
- Inhibit sympathetic and increase parasympathetic outflow to periphery
- Decrease BP
- At high concentrations, increase BP by stimulating peripheral $\alpha_2$ receptors

**Vasomotor center**

**VN**=ventral nucleus

**RVLM**=rostral ventrolateral medulla
Central \( \beta_2 \)-AR Agonists: Mechanism of Action

- Heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor function are reduced.

- Vascular smooth muscle: \( \beta_2 \) adrenergic receptors located on vascular smooth muscle open \( \text{Ca}^{2+} \) channels and cause vasoconstriction. Not evident clinically unless given intravenously.
Central $\alpha_2$-AR Agonists

- **Clonidine, (guanabenz and guanfacine):** Direct acting $\alpha_2$ adrenergic receptor agonists.

- **$\beta$-methyldopa:** Prodrug taken up by central adrenergic neurons and converted to the $\alpha_2$ adrenergic receptor agonist $\beta$-methylnorepinephrine.
Clonidine (Catapres): Pharmacokinetics

- Oral plasma $t_{1/2}$ – 12-16 hrs
- Transdermal administration of clonidine by patch (replaced once per week) useful in patients unable to take oral medication
Clonidine: Side Effects

- **Dry mouth (44%)**
- **Drowsiness (50%)**
- **Dizziness (15%)**
- Clonidine can cause sodium retention, but may be used at low doses w/o addition of diuretic
Tricyclic antidepressants can reverse the antihypertensive effects of clonidine.
Methyldopa (Aldomet): Side Effects

- Like Clonidine, causes sedation, dry mouth, sodium retention, and dizziness

- With prolonged use, hemolytic anemia is a rare side effect
Clonidine and Methyldopa: 
**Drug interactions**

- Tricyclic antidepressants may prevent the antihypertensive effect
- Barbiturates may reduce the efficacy of through induction of hepatic microsomal enzymes
- Monoamine oxidase inhibitors when coadministered may produce hypertension and CNS stimulation
Indications

- Methyldopa is a first choice for hypertension during pregnancy

- Clonidine is useful in the diagnosis of pheochromocytoma (adrenal tumor) in hypertensive patients; it will reduce NE to lower than 500 pg/mL in tumor-free patients
Vasodilators
Vasodilators: Mechanism of Action

• Relax Vascular smooth muscle cells
• Vasodilate Arterioles
• Decrease PVR
• Decrease Blood Pressure

Smooth Muscle cell

Hydralazine
Minoxidil

Ca\(^{2+}\)
K\(^{+}\)

contract

Contractile elements
Hydralazine (Apresoline): 
Mechanism of Action

- Direct vasodilatory action on arterioles altering smooth muscle cell Ca$^{2+}$ by hyperpolarizing cell
- Decreases total peripheral resistance
- Sympathetic activity (Reflex responses)
  - Increased heart rate
  - Increased heart contractility
  - Increased plasma renin activity
Hydralazine: Pharmacokinetics

- Plasma $t_{1/2} = 1$ hr, but antihypertensive action of 12 hrs possibly due to storage in arterial wall
Hydralazine: Side-effects

- Reflex tachycardia
  - Can precipitate MI in elderly patients or patients with coronary artery disease
  - Reflex response can be blocked by addition of propranolol

- Sodium and water retention – can be prevented by addition of a diuretic

- Headache, Nausea, Dizziness

- Lupus syndrome
Minoxidil (Loniten) :
Mechanism of Action

- Activates ATP-sensitive K+ channels to cause hyperpolarization and smooth muscle cell relaxation
- Arteriolar vasodilation
- Decrease in total peripheral resistance
Minoxidil: Pharmacokinetics

- Plasma $t_{1/2}$ - 4 hrs, but hypotensive effect for 12-24 hrs
- Must be metabolized by the liver to form the active metabolite, minoxidil N-O sulfate
Minoxidil: Side effects

- Similar to hydralazine
- Hypertrichosis – accentuated hair growth

- **Minoxidil** is reserved for treatment of severe hypertension and must be given with a diuretic and a sympatholytic agent (usually a β-adrenergic receptor antagonist).
Indications

- Severe, resistant hypertension
Vasodilators in Treatment of Hypertensive Crisis
Vasodilators: Mechanism of Action

- Relax Vascular smooth muscle cells
- Vasodilate Arterioles
- Decrease PVR
- Decrease Blood Pressure

Vasodilators:
- Hydralazine
- Minoxidil
- Labetolol
- Carvedilol

Smooth Muscle cell

Hydralazine

Minoxidil

NE

\[ \text{contract} \quad \text{relax} \]

\[ \text{Ca}^{2+} \quad \text{K}^+ \]

SNP

\[ \text{NO} \]
Sodium Nitroprusside (SNP, Nipride): Mechanism of Action

- Liberates nitric oxide which dilates vascular smooth muscle
- Thereby, decreases total peripheral resistance
SNP: Pharmacokinetics

- Given by I.V. infusion
- Is light sensitive and unstable in aqueous solution
- Antihypertensive effect ceases upon stopping infusion
- Metabolized to sodium thiocyanate – slowly cleared by kidneys
- Toxic accumulation of cyanide can lead to lactic acidosis
SNP:
Side-effects

- Rebound hypertension
- Tolerance
Diazoxide (Hyperstat): Mechanism of Action

- Dilates arterial smooth muscle through activation of $K_{\text{ATP}}$ channels
- Little or no effect on venous smooth muscle
- Decreases total peripheral resistance
Diazoxide: Pharmacokinetics

- Administered I.V.
- Onset of action within 2 min.
- Duration of action – 6-24 hrs
Diazoxide:
Side-effects

- Tachycardia
- Angina
Labetalol (Normodyne) and Carvedilol (Coreg): Mechanism of Action

- Mixture of $\beta_1$ and non-selective $\beta$-adrenergic receptor antagonist
  - Block adrenergic receptors in blood vessels and heart
  - Labetalol 1:3 selectivity $\beta_1$AR: $\beta$AR
  - Carvedilol 1:10 selectivity $\beta_1$AR: $\beta$AR
- Decrease total peripheral resistance w/o reflex tachycardia
Labetalol & Carvedilol: Pharmacokinetics

- Administered orally or i.v. (for hypertensive crisis)
- Useful in pheochromocytoma (Labetalol)
- Plasma $t_{1/2} = 2$ hrs (p.o.) and 5 hrs (i.v.)
Compensatory Responses to vasodilators can be managed with diuretics and \( \text{blockers} \)
Generalized hierarchy of antihypertensive medication

Thiazide

- Least expensive and very effective first line therapy for mild to moderate hypertension
- Also useful in volume overload associated with congestive HF
- Under age 55, may consider giving ACE/ARB

Low

Risk of new-onset diabetes

B-blocker

- Additional BP control

High

ACE Inhibitor

ARB (if coughing)

CCB

• Least expensive and very effective first line therapy for mild to moderate hypertension
• Also useful in volume overload associated with congestive HF
• Under age 55, may consider giving ACE/ARB

ACE

Other (β blockers Central acting Agents)
Step 1.

- High renin <55 years old, caucasion
  - ACEI ‘A’ OR β-blocker* ‘B’

- Low renin >55 years old or AA
  - CCB ‘C’ OR Diuretic ‘D’

Step 2.

- A OR \( R \) + C OR D

Step 3.

- A OR \( R \) + C + D

Step 4.

Resistant Hypertension

Add: either \( \beta \)-blocker or spironolactone or other diuretic

Adapted from Williams et al., J. Hum. Hyp., 2004.
Future Considerations

- Calcium Channel Blocker/ACE combination is better than β-Blocker/Thiazide at reducing CV events (Dahlof et al., Lancet, 2005)
- Multi-drug approach to managing hypertension (Polypills; statin, β-Blocker, diuretic, ACEI, aspirin, folic acid)
- Implantable mechanical baroreceptors? European trials ongoing
Conclusion

- **Diuretics, ACEI, CCB’s, and β-Blockers** are most commonly used antihypertensives.
- **With relatively few side effects and at low cost, these agents provide effective blood pressure control.**
- **Combination strategies** are useful in managing hypertension while also giving long term cardiovascular benefits.
Appendix

- **Pregnancy**
  - If taken before pregnancy, most antihypertensives can be continued except ACE inhibitors and angiotensin II receptor blockers.
  - Methyldopa is most widely used when hypertension is detected during pregnancy.
  - Beta-blockers are not recommended early in pregnancy.

- **African Americans**
  - Diuretics have been demonstrated to decrease morbidity and mortality, and hence should be first choice.
  - Ca++ blockers and alpha/beta blockers are effective.
  - Patients may not respond well to monotherapy with beta-blockers or ACE inhibitors.

- **Elderly**
  - Smaller doses, slower incremental increases in dosing, and simple regimens should be used.
  - Close monitoring for side effects (i.e., deficits in cognition after methyldopa; postural hypotension after prazosin) is appropriate.

- **Diabetes mellitus**
  - ACE inhibitors, alpha-antagonists, and calcium antagonists can be effective, and have few adverse effects on carbohydrate metabolism.

- **Hyperlipidemic**
  - Low dose diuretics have little effect on cholesterol and triglycerides.
  - Alpha-blockers decrease LDL/HDL ratio. Calcium-channel blockers, ACE inhibitors, angiotensin II receptor blockers have little effect on lipid profile.

- **Obstructive airway disease**
  - Avoid beta-blockers.