Lecture #2
Hypertension

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Cardiovascular System & Its Diseases:

Hypertension

Overview

Part 1: What Do We Know?

Background  common CV disease
Diagnosis  elevated BP
Aetiology  essential or secondary

Part 2: How Do We Treat?

Normal Regulation Of Blood Pressure
Drug Therapy
Surgical Intervention
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What Do We Know?: Background

- Most Common Cardiovascular Disease
- Present In 24 % Total USA Population Source NHANES Survey
- Prevalence varies with Age, Race, Education, Diet and other factors
- Increases incidence of Renal Failure, Coronary Disease, Cardiac Failure & Stroke
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What Do We Know?: Diagnosis

- Repeated (usually 3 measurements), Elevated Blood Pressure Above Normal Levels (BP < 120/90 mm Hg)
- Often Asymptomatic until overt organ damage is imminent or has occurred
- Even Mild Hypertension (BP > 140/90 mm Hg) increases risks
- Blood Pressure is Age-Dependent
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What Do We Know?: Diagnosis

(Envelopes represent the Standard Deviation of the Mean)
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What Do We Know?: Aetiology

- **Essential Hypertension** (cause unknown though multifactorial, most common)

  Risks Factors include:

  - Hyperlipidemia
  - Diabetes
  - Genetic, Family History
  - Diet (high salt)
  - Stress

- **5 – 10% Identifiable Cause** (often secondary)

  *for example,*

  - Renal Artery Constriction
  - Coarctation of the Aorta (narrowing of aorta)
  - Phaeochromocytoma (tumor of adrenal glands)
  - Cushing’s Disease (hypercortisolism)
  - Primary Aldosteronism (elevated aldosterone)
Hypertension

**What Do We Know?:** Secondary Hypertension

**Hyperthyroidism:** endogenous (tumor) or drug-mimicking thyroid hormones elevate BP.

**Oral Contraceptives:** reversible elevation of BP. May be related to HT associated with pregnancy (eclampsia) attributed to oestrogen activation of renin-angiotensin-aldosterone system.

**Phaeochromocytoma:** due to circulating catecholamines liberated from tumors of chromaffin tissue (adrenal medulla). Uncommon though scientifically interesting. Treatment by surgical excision.

**Coarctation of aorta:** constriction of the aorta is congenital condition. Constriction site usually in the thoracic aorta beyond the arch. Site of coarctation is compensated by large network of collateral blood vessels. Treatment involves surgical reconstruction.
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How Do We Treat?: Normal Regulation Of Blood Pressure

4 Sites Of Regulation:

Blood Pressure:
Cardiac Output × Peripheral Vascular Resistance

** Hints At Possible Therapeutic Approaches **
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How Do We Treat?: Drug Therapy

Major Drug Groups:
- Diuretics
- Sympathoplegics (Sympatholytic)
- Vasodilators
- Angiotensin Antagonists
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How Do We Treat?: Diuretics

2 Main Actions:
Reduce Blood Volume
Affect Smooth Muscle Tone

2 Main Drug Classes:
Thiazides mild HT
Loop Diuretics severe HT
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How Do We Treat?: Diuretics

**Thiazides** (e.g. *hydrochlorothiazide*):
Mild/Moderate Hypertension
Block Na⁺/Cl⁻ symporter, ↑Ca²⁺ reabsorption
Orally Active
Toxicity: K⁺ depletion/Hypokalemia
(esp. patients with arrhythmias, infarcts etc)

**Loop Diuretics** (e.g. *furosemide*):
Moderate/Severe Hypertension
Block Na⁺/K⁺ / 2Cl⁻ symporter, ↑Ca²⁺ excretion
Oral & Intravenous
Toxicity: K⁺ depletion/Hypokalemia

* Indicates drug name should be remembered
## Diuretics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Pharmacology</th>
<th>Indication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td>Block Na+/Cl⁻ symporter (Distal convoluted tubule)</td>
<td>Mild – Moderate HT</td>
<td>* Hydrochlorothiazide</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>Block Na+/K+/2Cl⁻ symporter (Thick ascending loop)</td>
<td>Moderate-Severe HT</td>
<td>* Furosemide</td>
</tr>
</tbody>
</table>

* Indicates drug name should be remembered
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How Do We Treat?: Sympathoplegics

Main Action: Decrease Sympathetic Discharge or its effects on Cardiovascular System

Pharmacological Targets:

1. Centrally Acting Agents
2. Ganglion Blockers
3. Postganglionic Sympathetic Neuron Blocker
4. Adrenoceptor Blockers
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How Do We Treat?: Sympathoplegics

Centrally Acting Agents: $\alpha_2$-selective agonists

- **Drugs:**
  - Clonidine
  - Methyldopa (prodrug converted to methylnorepinephrine in CNS)

- **Indication:** Mild & Moderate Hypertension

- **Mechanism:** Sympathoplegic effect not known

- **Toxicity:** Minimal, sudden cessation causes severe HT
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How Do We Treat?: Sympathoplegics

Ganglion Blockers: nicotinic cholinoceptor antagonists

- **Drugs:** Trimethaphan (first agents developed for hypertension)

- **Indication:** Severe Hypertension (rapid onset)

- **Mechanism:** Blocks nAChR in autonomic ganglia

- **Toxicity:** Intolerable (orthostatic hypotension, blurred vision, constipation)
  Used rarely
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How Do We Treat?: Sympathoplegics

Postganglionic Sympathetic Neuron Blockers

- **Drugs:** * Reserpine, Guanethidine
- **Indication:** Rarely Used
- **Mechanism:** Reserpine blocks uptake; Guanethidine prevents neurotransmitter release
- **Toxicity:** Intolerable (depression, sexual dysfunction, orthostatic hypotension)
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How Do We Treat?: Sympathoplegics

Adrenoceptor Blockers: $\alpha_1$- and $\beta_1$-receptor antagonists

- **Drugs:**
  - *Prazosin* (Block $\alpha_1$-receptors)
  - *Propanolol* (Block $\beta_1$-receptors)

- **Indication:**
  - Mild Hypertension ($\alpha$ and $\beta$-blockers, important monotherapy)
  - Moderate-Severe HT ($\beta$-blocker, polypharmacy)

- **Mechanism:** Antagonism of $\alpha$- and $\beta$-receptors

- **Toxicity:**
  - Mild ($\alpha$-blocker; marked 1st dose hypotension & mild tachycardia)
  - Moderate ($\beta$-blocker; may cause asthma, bradycardia, heart failure)
## Sympathoplegic Drugs

<table>
<thead>
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<th>Drug Class</th>
<th>Pharmacology</th>
<th>Indication</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centrally Acting Agents</td>
<td>$\alpha_2$-selective agonists</td>
<td>Mild – Moderate HT</td>
<td>* Clonidine, Methylidopa</td>
</tr>
<tr>
<td>Ganglion Blockers</td>
<td>nAChR antagonists</td>
<td>Rarely used</td>
<td>Trimethaphan</td>
</tr>
<tr>
<td>Postganglionic Sympathetic Neuron Blockers</td>
<td>Block Neurotransmission</td>
<td>Rarely Used</td>
<td>* Reserpine, Guanethidine</td>
</tr>
<tr>
<td>Adrenoceptor Blockers</td>
<td>$\alpha_1$- and $\beta_1$-receptor antagonists</td>
<td>Mild (monotherapy) Moderate-Severe HT (polypharmacy)</td>
<td>* Prazosin, * Propanolol</td>
</tr>
</tbody>
</table>
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How Do We Treat?: Vasodilators

Main Action: Vasodilatation of arterioles by different mechanisms

<table>
<thead>
<tr>
<th>Mechanism of Vasodilation</th>
<th>Drug Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Release of nitric oxide</td>
<td>Hydralazine, *nitroprusside</td>
</tr>
<tr>
<td>Opening of K⁺ channels And hyperpolarization</td>
<td>Minoxidil sulfate, *diazoxide</td>
</tr>
<tr>
<td>Block of L-type Ca²⁺ channels</td>
<td>*Verapamil, *Diltiazem, *Nifedipine</td>
</tr>
</tbody>
</table>

Entire Drug Class: Part of Polypharmacy for Severe Hypertension

Ca²⁺ Channel Blockers: Monotherapy for Mild to Moderate Hypertension
How Do We Treat?: Nitrovasodilators

- **Drugs:** Hydralazine
  * Nitroprusside

- **Indication:** Severe HT (Polypharmacy)
  Hypertensive Emergency (nitroprusside)

- **Mechanism:** Activate soluble Guanylate Cyclase relaxing vascular smooth muscle

- **Toxicity:** Excessive hypotension & tachycardia (nitroprusside)
  Moderate tachycardia (hydralazine)
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**How Do We Treat?:** $K^+$ Channel Opener/Agonist

- **Drugs:** Minoxidil sulfate, *Diazoxide*
- **Indication:** Severe HT (polypharmacy)
- **Hypertensive Emergency** *(Diazoxide)*
- **Mechanism:** Hyperpolarize the cell, causing relaxation
- **Toxicity:** Severe tachycardia *(Minoxidil)*
  Mild tachycardia *(Diazoxide)*
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How Do We Treat?: \(\text{Ca}^{2+}\) Channel Blockers

3 classes of \(\text{Ca}^{2+}\) channel:

L-, T- and N-type families

L-type are mainly targeted for treatment of Hypertension
3 main classes of blockers

Vasoselective:
Dihydropyridines (e.g. * Nifedipine)

Cardiac & Vascular Acting:
Phenylalkylamines (e.g. * Verapamil)
Benzothiazines (e.g. * Diltiazem)

FIGURE 18-3 Chemical structures of calcium antagonists.
Each Drug Has A Distinct Allosteric Binding Site

![Diagram showing allosteric interactions between nifedipine, verapamil, and diltiazem binding sites](image)

**FIGURE 18-5**  Allosteric interactions occur among the nifedipine (NIF), verapamil (VER), and diltiazem (DTZ) binding sites of the voltage-dependent Ca$^{2+}$ channels. All three binding sites are located on the same subunit.
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**How Do We Treat?:** \( \text{Ca}^{2+} \) Channel Blockers

- **Drugs:** *Verapamil, Diltiazem, Nifedipine*

- **Indication:** Mild-Moderate HT (monotherapy)  
  Severe HT (polypharmacy)

- **Mechanism:** Voltage- & frequency-dependent block

- **Toxicity:** Most side-effects are due to excessive vasodilatation or cardiodepression
<table>
<thead>
<tr>
<th>DRUG</th>
<th>Problems</th>
<th>Major</th>
<th>Moderate</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VERAPAMIL</strong></td>
<td>Problems in 8% to 10% of patients</td>
<td>Cardiodepression</td>
<td>Hypotension</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AV node block</td>
<td>Constipation</td>
</tr>
<tr>
<td><strong>NIFEDIPINE</strong></td>
<td>Problems in 17% to 20% of patients</td>
<td>Hypotension</td>
<td>Headache</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DILTIAZEM</strong></td>
<td>Problems in 2% to 5% of patients</td>
<td>Hypotension</td>
<td>Peripheral edema</td>
<td>AV node block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiodepression</td>
</tr>
</tbody>
</table>
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**How Do We Treat?: Angiotensin Antagonists**

Two classes of Drugs:

1. ACE inhibitors (e.g. * captopril)
2. Angiotensin Receptor Inhibitor (AT$_1$-type) (e.g. * losartan)

(substitute when ACE inhibitors are not tolerated)
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How Do We Treat?: Angiotensin Antagonists

- **Drugs:** * Captopril, * Losartan
- **Indication:** Mild-Moderate HT (monotherapy)
- **Mechanism:** ACE inhibitors; Competitive block of AT₁-receptor
- **Toxicity:** Cough, Severe Renal damage in Fetus (ACE inhibitors)
  Similar effects but milder (AT1-receptor antagonists)
ACE Inhibitors also prevent breakdown of Bradykinin
Table 15-1  Physiological Responses to Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Plasma Volume</th>
<th>CO</th>
<th>Heart Rate</th>
<th>TPR</th>
<th>Plasma Renin Activity</th>
<th>Sympathetic Nervous System Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>↔</td>
<td>↓</td>
<td>↔</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>β-blockers</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Centrally acting sympatholytics</td>
<td>↑ ↔</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
</tr>
<tr>
<td>Peripherally acting sympatholytics</td>
<td>↑ ↔</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>↑ ↔</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Orally active vasodilators</td>
<td>↑ ↔</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

↑ Increase; ↓ decrease; ↔ no change.
Major Drug Groups:

**Diuretics**
- Thiazides
- Loop Diuretics

**Sympathoplegics**
- Centrally Acting Agents
- Ganglion Blockers
- Postganglionic Sympathetic Neuron Blocker
- Adrenoceptor Blockers (α and β)

**Vasodilators**
- Nitrovasodilators
- K⁺ channel openers/agonists
- Ca²⁺ Channel Blockers

**Angiotensin Antagonists**
- ACE inhibitors
- Competitive block of AT1-receptor
**FIGURE 15-2**  Summary of sites and mechanisms by which antihypertensive drugs bring about a reduction in blood pressure. CO, Cardiac output; TPR, total peripheral resistance.
Pharmacological Management Of Hypertension

Patients with **Primary** or **Essential Hypertension** are initially given **monotherapy** (single drug treatment), usually a β-blocker, calcium channel blocker or **ACE inhibitor**

- Therapy is escalated to **Polypharmacy** (multiple drugs) if monotherapy is unsuccessful
Drugs are chosen from different groups to maximize efficacy and minimize toxicity (e.g. diuretic + sympathoplegic + vasodilator)

Emergency or Malignant Hypertension is associated with risk of imminent stroke

- Patients are hospitalized and treated with parenteral vasodilator, β-blocker and loop diuretic
LET'S PLAY DOCTOR
A 35-year-old African-American man with no significant past medical history presents to the outpatient clinic for a follow-up examination. One month earlier he was noted to have a blood pressure of 150/80 mm Hg on a routine health maintenance examination.

He has no complaints, takes no medications, and does not smoke or use alcohol or other drugs. His family history is significant for a father with high blood pressure. His blood pressure on this visit is 150/90 mm Hg.

What’s the likely diagnosis and why?

**Essential Hypertension**

Reasons; 95 % of all HT cases, Race, Family History
Hypertension

Case Study

What could happen to this patient if he does not receive treatment?

Multiple Possibilities

Heart: hypertrophy; myocardial infarction; heart failure

Brain: stroke

Kidney: renal failure; chronic kidney disease

Vasculature: peripheral vascular disease

Eye: retinopathy
Hypertension

Case Study

What is the most appropriate treatment for this patient?

- Assess BP for a third time in one month

- If elevated, suggest lifestyle change (exercise, diet etc)

- If unsuccessful, use diuretics (cheap & effective)
If the patient develops diabetes would you continue with diuretics?

-Use ACE inhibitors which are renoprotective
Cardiovascular System And Its Diseases

What Have We Learned?

AKA: What do I need to know for the Exam?

1. Regulation of Blood Pressure

2. Types of Hypertension: secondary and essential

3. Treatment: Most cases require drugs but occasional surgical intervention