1. Blood Pressure Regulation

Frank’s formula, BP regulation: \[ BP = CO \times TPR \]
\[ CO = HR \times SV \]

Baroreceptor reflex: rapid, moment-to-moment adjustments in BP

Renal system: responsible for long-term BP control
2. Definition of Human Hypertension (HT)

A sustained elevation of systolic and/or diastolic BP above an arbitrarily defined level (systolic >139 mmHg and/or diastolic >89 mmHg)

- secondary HT can be cured by surgical procedures (early diagnosis of cause)
- primary (essential) HT is a lifelong disease, needs longterm control & treatment

3. Classification of Hypertension (HT)

3.1. Based on severity

<table>
<thead>
<tr>
<th>systolic (mmHg)</th>
<th>diastolic (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 and &lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120 - 139 or 80 - 89</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>140 -159 or 90 - 99</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>&gt;160 or &gt;100</td>
</tr>
</tbody>
</table>

3.2. Based on pathogenesis

3.2.1. Secondary HTs (< 10%)

- neurogenic HT caused by brain damage
- cortisol overproduction: hypophysis or adrenal gland tumor
- aldosterone overproduction: adrenal gland tumor hyperplasia
- renal artery stenosis or occlusion
- adrenal medullary tumor: pheochromocytoma

3.2.2. Primary (essential) HTs (> 90%)

- primary cause(s) unknown, possibly multi-factorial defects
- genetics
- smoking
- caffeine
- stress
- salt intake
- alcohol
- obesity
- age
- others

4. Consequences of Sustained Hypertension

4.1. Histological changes, organ damage

- failure in blood supply, renal failure (fibrinoid necrosis)
- aneurysms (rupture of blood vessels)
- loss of microcirculation
- myocardial and/or cerebral infarction
- increased risk of stroke
- increased risk of heart failure
4.2. Public health consequences

Gains in Life Expectancy in Years for 35-Year-Old Individuals

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce cholesterol level:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To 200 mg/dl if 200–239 mg/dl</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>To 200 mg/dl if 240–299 mg/dl</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>To 200 mg/dl if ≥300 mg/dl</td>
<td>4.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Reduce number of cigarettes smoked:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>By 50%</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Eliminate smoking</td>
<td>2.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Reduce diastolic blood pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To 88 mm Hg if 90–94 mm Hg</td>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>To 88 mm Hg if 95–104 mm Hg</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>To 88 mm Hg if ≥105 mm Hg</td>
<td>5.3</td>
<td>5.7</td>
</tr>
<tr>
<td>Reduce weight:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>To ideal if &lt;30% over ideal</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>To ideal if ≥30% over ideal</td>
<td>1.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

5.1. Non-drug treatment

- salt intake (2.5g/d $\rightarrow$ 1 g/d)
- calorie intake, weight loss
- alcohol consumption
- physical activity
- stress factors
- smoking, caffeine intake

5.2. Drug treatment

1. **Diuretics**
2. Renin / A-II system (ACEI, ARBs)
3. **Calcium antagonists**
4. Beta-receptor antagonists
5. Alpha-antagonists
6. Inhibit NE release
7. Vasodilators
8. Central acting alpha2-agonists
9. Ganglionic blockers
10. Potassium-sparing diuretics

5.2.1. Diuretics (Frontline agents for hypertension)

$\downarrow$ BP by depletion body of Na\(^+\) and reducing blood volume (BV)

High clinical value as antihypertensive & combination therapy, inexpensive

**Mechanism of action**

Initial: $\downarrow$ body store Na\(^+\) $\rightarrow$ $\downarrow$ BV $\rightarrow$ $\downarrow$ CO $\rightarrow$ $\downarrow$BP ($\uparrow$TPR, reflex)

Chronic: CO unchg, $\downarrow$ TPR, $\downarrow$ NE $\rightarrow$ $\downarrow$[Ca\(^++\)], $\rightarrow$ $\downarrow$vascular tone

Direct vasodilating effect: probably by opening K\(^+\) channels

**Thiazides (1st of equals):**
- act on early distal tubule
  (eg. chlorothiazide)
- inhibit Na\(^+\) reabsorption

**Loop Diuretics:**
- act on loop of Henle
  (eg. furosemide)
- most potent

**Adverse effects**

- potassium depletion (hypokalemia): hazardous in persons taking digitalis
- magnesium depletion
- impair glucose tolerance (diabetes)
- increase serum lipids
- increase serum uric acid concentration (gout)
- photosensitivity

**Potassium Sparing Agents:**
- act on late distal tubule, weak action
  (eg. spironolactone)
- hyperkalemia
- used in combination therapy
- spironolactone (blocks action of aldosterone)
**ACETAZOLAMIDE**
- Carbonic anhydrase inhibitor which inhibits the reabsorption of \( \text{HCO}_3^- \) in the proximal convoluted tubule.
- Weak diuretic properties.

**THIAZIDES**
- Inhibit reabsorption of \( \text{Na}^+ \) and \( \text{Cl}^- \) in distal tubule, resulting in retention of water.
- Most commonly used diuretics.

**BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID**
- Inhibit the \( \text{Na}^+\text{K}^+\text{Cl}^- \) co-transport in ascending loop of Henle, resulting in retention of \( \text{Na}^+ \), \( \text{Cl}^- \) and water in the tubule.
- These drugs are the most efficacious of the diuretics.

**SPIRONOLACTONE, AMILORIDE, TRIAMTERENE**
- *Spironolactone*, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of \( \text{Na}^+ \) and secretion of \( \text{K}^+ \).
- *Amiloride* and *trimterene* block \( \text{Na}^+ \) channels.
- These agents can prevent loss of \( \text{K}^+ \) that occurs with thiazide or loop diuretics.

---

**Fluctuation Throughout a Day**
(Case: Male, 35 years of age)

![Graph showing fluctuation in blood pressure throughout the day](image-url)
5.2.2. Drugs Acting on the Sympathetic Nervous System

This is a heterogeneous group of drugs according to their putative site(s) of action

- ↓ BP by ↓ TPR
- inhibit cardiac function (↓ CO)
- ↑ venous pooling in capacitance vessels

Centrally acting sympatholytic agents

Useful, but not frontline class

Clonidine
α-Methyldopa (analog of L-dopa - converted to α-methyl-NE)

Act on central α₂-receptors to reduce sympathetic outflow from vasopressor centers in the brainstem but allow these centers to retain or even increase their sensitivity to baroreceptor control.

- good clinical value as antihypertensives, useful but not frontline
- no metabolic side effects
- does not interfere with exercise/performance

- adverse effects: sedation, mental depression, lactation
withdrawal effect (can be very serious, esp. clonidine)

Ganglion-Blocking Agents

Earliest class of effective drugs used to treat hypertension, low clinical value

- competitively block ganglionic nicotinic receptors (SNS, PNS)
- clinical value as antihypertensive drug is very low.

Trimethaphan
- i.v. injection, rapid effect, short half life (precise titration)
- hypertensive crisis, controlled hypotension

Mecamylamine
- orally active

Serious adverse effects:

sympathoplegia: - excessive orthostatic hypotension
- sexual dysfunction

parasympathoplegia: - constipation, urinary retention
- glaucoma, blurred vision
- dry mouth
Adrenergic Neuron-Blocking Agents

Antihypertensive clinical value is low, effective but agents of last resort

Guanethedine, \textit{(Bretylium used as antidysrhythmic)}
- inhibits release of NE from nerve terminals
- gradual depletion of NE stores
- neuronal uptake (uptake 1) is essential for action
- tricyclic antidepressants, cocaine decrease effectiveness

Adverse effects:  
- marked postural hypotension
- diarrhea, impaired ejaculation

Reserpine

Antihypertensive clinical value is low, effective but agent of last resort

- inhibit uptake of NE into storage vesicle (also DA, 5-HT)
- leads to depletion of transmitter stores (peripheral & CNS action)

Adverse effects:  
- sedation, mental depression, Parkinsonisms
- increases gastric acid secretion
Adrenoceptor Antagonists

Antagonize effects of catecholamines at alpha and beta-adrenoceptors
High clinical value as antihypertensives (esp. β-antagonists)

Alpha-Adrenoceptor Antagonists

Drugs of choice in hypertensive crisis, not frontline for chronic hypertension, used for unique circumstances (ie. pheochromocytoma, benign prostrate hypertrophy). Low but constant use.

Phenoxybenzamine (non-competitive α1-receptor blocker)
- reflex tachycardia effect, postural hypotension
- therapeutic value in pheochromocytoma treatment (acute & chronic)

Prazosin (selective α1-receptor blocker)
- selective alpha1-receptor blocker in arterioles and venules (dilates both resistance and capacitance vessels)
- does not produce reflex tachycardia
- used to treat Benign prostrate hypertrophy (DOC)

Phentolamine (non-selective α-receptor blocker)
- reflex tachycardia effect (always given together with beta-blocker)
- diagnostic and therapeutic value in pheochromocytoma

Adverse effects:  
- salt and fluid retention
- beneficiary effect on plasma lipids
- postural hypotension (all agents)

Beta-Adrenoceptor Antagonists

- High clinical value as antihypertensive agents, frontline class

Multiple mechanisms of action:
- central effect: inhibition of central sympathetic tone
  BUT: beta-blockers (like Nadolol, Sotalolol don't cross CNS)
- inhibition of renin secretion: beta1-receptors mediate renin release
  BUT: beta-blockers ↓ BP when plasma renin activity low
  beta-blockers (like Pindolol) don't ↓ plasma renin activity
- effect on cardiac beta1-receptors: ↓ HR → ↓ CO → ↓ BP
  BUT: with continued treatment CO unchg, ↓ TPR → ↓ BP

Features of beta-adrenoceptor antagonists (end in –olol, if –alol have unique feature
- Selective vs non-selective (A to M, beta1-selective)
- Partial agonist activity (ISA)
- Membrane stabilizing action (LA-action)
- Lipid solubility (least important feature)
Propranolol:  - non-selective $\beta$-receptor blocker
- no partial agonist action (no ISA)
- membrane stabilizing action

Adverse effects:  
- ↓ myocardial reserve (blockade of cardiac $\beta_1$-ARs)
- asthma (blockade of bronchial $\beta_2$-ARs)
- peripheral vascular insufficiency
- diabetes (blockade of hepatic $\beta_2$-ARs)
- ↑ plasma TG and ↓ HDL
- CNS: nightmares, mental depression, insomnia
- withdrawal syndrome (supersensitivity of beta-receptors)

Labetalol, Carvedilol  
- alpha and beta-receptor blocker
- beta/alpha = 3:1
  HR unchg, CO unchg, ↓ TPR $\rightarrow$ ↓ BP

Uses:  - pheochromocytoma (acute & chronic), CHF, hypertensive crisis (iv)
5.2.3. Vasodilators

- useful but not frontline, usually given with beta-blockers or diuretics
- relax smooth muscle of arterioles → ↓ TPR.
- high clinical value (in combinations and hypertensive emergencies)

Hydralazine

- EDRF / Nitric oxide / cGMP involvement
- dilate arterioles but not veins
- ↓ TPR → reflex tachycardia
- bioavailability: 25% (slow and rapid acetylators)

Adverse effects:
- direct vasodilation
- reflectory sympathetic activation
  - headache, nausea, palpitations
  - sweating, flushing, ↑ HR can provoke angina
- lupus reaction (mainly in slow acetylators)

Minoxidil (Rogaine)

- opens K⁺-channels in smooth muscle membranes
- stabilization of membrane at its resting potential, contraction less likely.
- dilates arterioles but not veins

Adverse effects:
- reflex sympathetic stimulation (use with with β-blocker)
- fluid retention (combo-therapy, diuretics)
- hypertrichosis (topical application as Rogaine)
Sodium Nitroprusside
- used for acute emergency hypertension and congestive heart failure
- used i.v., (cyanide toxicity via oral administration)
- activation of guanylyl cyclase (direct and/or via release of NO)
- intracellular $\uparrow$ cGMP $\rightarrow$ relaxation of vascular smooth muscle
- dilates both arterial ($\downarrow$ TPR) and venous vessels
- venous return to the heart is decreased, reflex tachycardia

Adverse effects:
- cyanide liberation $\rightarrow$ cyanide toxicity
- thiocyanate elimination by the kidney (high dose, long duration of the infusion, insufficient amount of sulfur donor, defect in cyanide metabolism)
- metabolic acidosis, arrhythmias, severe hypotension
- methemoglobinemia

Diazoxide
- use for acute emergency hypertension
- opens K⁺-channels - stabilizes membrane potential
- dilates arteriolar vessels $\downarrow$ TPR $\rightarrow$ reflex $\uparrow$ HR $\rightarrow$ $\uparrow$ CO
- inhibits insulin release (via opening K⁺-channels on beta cell membrane)
- similar structure as thiazide diuretics but no diuretic effect
5.2.4. Calcium Channel Blockers

- important, frontline class of agents
- inhibition of calcium influx into cardiac and arterial smooth muscle cells
- dilate arterioles $\rightarrow$ ↓TPR $\rightarrow$ ↓BP (less verapamil, more nifedipine)
- negative inotropic action on heart (more verapamil, less nifedipine)
- can cause constipation, nausea, flushing, dizziness
- can cause gingival hyperplasia (nifedipine)
- contraindicated in CHF

Nifedipine: - mainly arteriole vasodilation, little direct cardiac effect
- may cause reflex tachycardia, flushing, peripheral edema

Verapamil: - some cardiac slowing, constipation
- caution in digitalized patients (↑digoxin levels)

Diltiazem: - actions on cardiac & vascular beds

<table>
<thead>
<tr>
<th></th>
<th>Diltiazem</th>
<th>Verapamil</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Myocardial contractility</td>
<td>↓</td>
<td>↓↓</td>
<td>↓ or ↑ (reflex)</td>
</tr>
<tr>
<td>Nodal conduction</td>
<td>↓</td>
<td>↓↓</td>
<td>↑ (reflex)</td>
</tr>
<tr>
<td>Peripheral vasodilation</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Primary and secondary effects of vasodilator therapy in essential hypertension and the manner by which diuretic and beta-adrenergic blocker therapy can overcome the undesirable secondary effects. (From Koch-Weser J. Vasodilator drugs in the treatment of hypertension. Arch Intern Med 1974;133:1017–1027, copyright 1974, American Medical Association.)
5.2.5. Angiotensin-Converting Enzyme Inhibitors (ACEI) / Receptor Blockers (ARB)

- important, frontline class of agents, first among equals in diabetes
- inhibit action or production of angiotensin II
- Ag II is a potent vasoconstrictor peptide
- decrease aldosterone production

Angiotensin-Converting Enzyme (ACE) Inhibitors

- ACE is a peptidyl dipeptidase:
  - converts Ag I → active AgII (major effect)
  - degrades bradykinin (a potent vasodilator)
  - orally active
  - for i.v. use, hypertensive emergency
  - long-acting agents

Captopril:    - orally active
Enalapril:    - for i.v. use, hypertensive emergency
Benazepril, Fosinopril, Ramipril:    - long-acting agents

↓ TPR,  CO unchg,  HR unchg
- no reflex ↑ HR, probably due to resetting (↓) of baroreceptor reflex sensitivity
- improves intrarenal hemodynamics
- reverses cardiac hypertrophy
- need to take before or after meals

Adverse effects:
- severe hypotension in hypovolemic patients, bilateral renal a. stenosis
- hyperkalemia
- dry cough, skin rushes, glossitis
- altered sense of taste (loss of zinc)
- contraindicated 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester of pregnancy (tetrogenic)
- drug interactions with potassium-sparing diuretics, NSAIDs

Angiotensin Receptor Blockers (ARBs)  Losarton, Saralazin

- competitive inhibitor of AgII at its receptors, use increasing
- actions similar to ACEI but not associated with dry cough (no bradykinin effect)
- slight weak agonist activity (depends on circulating AgII level)
- used for chronic HT and diagnostic value (AgII dependency of HT)
6. Treatment of Hypertension

6.1. General considerations

- secondary HT can be cured by surgical procedures (early diagnosis of cause)
- primary (essential) HT is a lifelong disease, needs longterm control & treatment
- HT often insidious, causes no symptoms
- conversely treatment can produce even serious adverse effects
- patients compliance is very important
- treat the patient and not 'just' their BP (quality of life)

6.2. Treatment strategy

Initial step:  - nonpharmacological
sodium intake, weight loss, physical activity, alcohol, stress,
- overview of medication, other risk factors

IF NOT ENOUGH OR INITIALLY HIGHER STAGE OF HT -

Drug therapy:  - continue or start with drug therapy (Thiazide 1st choice)
- choose the proper medication?
- β-blockers efficacy may decrease as age increases.
- β-blockers are less effective in smokers.
- Blacks respond less to beta-blockers and ACE inhibitors
- β-blockers and ACE inhibitors better in ↑ plasma renin level.
- use long-lasting drugs (compliance)

Start with monotherapy:  - if necessary add second, third etc drug
(from different class)

<table>
<thead>
<tr>
<th>High Risk Condition</th>
<th>Recommended Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thiazide</td>
</tr>
<tr>
<td>Heart failure</td>
<td>X</td>
</tr>
<tr>
<td>Post MI</td>
<td></td>
</tr>
<tr>
<td>CAD Risk</td>
<td>X</td>
</tr>
<tr>
<td>Diabetes</td>
<td>X</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td></td>
</tr>
<tr>
<td>Stroke Prevention</td>
<td>X</td>
</tr>
</tbody>
</table>

7.0 Hypertension treatment summary

NOTE: Beta-blockers can be used with caution in the treatment of congestive heart failure. Contraindication include: bronchospasm, significant bradycardia, unstable heart failure and depression.

8.0 References
