ANTIHYPERTENSIVE AGENTS AND VASODILATORS

Lecture 5
Hypertension

- Blood pressure
  - \( BP = CO \times PVR \)
    - Interaction between autonomic nervous system, cardiovascular system and renal system
  - Normal: \( \leq 110/70 \)
  - Prehypertension: \( <130/90 \)
  - Hypertension: \( \geq 130/90 \)
  - Taken in 3 different office visits
Hypertension

- Etiology of HPN
  - Primary or essential = no specific cause
    - Genetic risk
  - Secondary
    - Hyperthyroidism
    - Pheochromocytoma
    - Renal disease
    - Diabetes
    - Obesity and dyslipidemia
Hypertension

- Hypertensive urgency
  - BP $\geq 180/110$

- Hypertensive emergency
  - Hypertensive urgency with end organ damage
  - Ex. Hypertensive encephalopathy, angina, stroke, etc.

- Goal
  - Decrease blood pressure to 130-140/90
  - Do not decrease more than 20% of MAP every hour
    - Proper brain perfusion
Hypertension

- Treatment
  - Pharmacologic
    - Dependent on level of BP, presence of end-organ damage and presence of co-morbidities
    - Single/Mono-therapy vs combination therapy
  - Non-pharmacologic
    - Diet and exercise
    - Salt restriction
    - Control co-morbidities (ex. DM)
    - Avoid other substances which may increase BP
      - Ex. cold remedies, caffeine, smoking, alcohol, contraceptives
    - Patient education
Introduction to antihypertensive agents

- 4 general mechanisms:
  1. Decrease blood volume
     - Decrease sodium = Diuretics
  2. Sympathoplegic agents (sympatholytic)
     - By vasodilation, cardiac function, venous pooling
     - 4 groups
  3. Decrease PVR
     - Direct vasodilators
     - 4 groups
  4. Inhibit RAAS
     - Block production or action of angiotensin → PVR by vasodilation and decrease aldosterone effect
Diuretics

- Review of the renal system and urine formation
- RAAS system
  - RAAS system through the juxtaglomerular apparatus
  - Renin: increases aldosterone secretion via production of angiotensin.
  - Angiotensin: increases aldosterone, anti-diuretic hormone, blood pressure and thirst.
  - Aldosterone: increases active reabsorption of Na+ and secretion of K+ by the distal tubules
Diuretics

- Increase urine volume = depletes blood volume
- Basic MOA
  - Inhibits NaCl transporter = down reabsorption in the renal tubules = down water reabsorption
    - Ex. furosemide (loop of Henle), hydrochlorthiazide (DCT)
  - Aldosterone antagonism
    - Inhibits Na reabsorption from the DCT and collecting tubule
    - Ex. spironolactone
  - Osmotic diuretic
    - Increase osmolarity of urine = down water reabsorption
    - Ex. mannitol = only thru IV infusion
- Effect
  - Can decrease BP by 10-15mmHg
Diuretics

- Side effects
  - Hyponatremia
  - Hypokalemia
    - Except for spironolactone (potassium sparing diuretic)
  - Increases uric acid reabsorption
    - May precipitate gout
  - May increase blood lipid levels
Sympathoplegic agents

- Drugs that act on the CNS
- Drugs that act on autonomic ganglia
- Drugs that reduce release of norepinephrine
- Drugs that block postsynaptic adrenoreceptors
Centrally acting sympathoplegics

- **Basic MOA:** reduce sympathetic outflow from the brainstem → vasodilation

- **Methyldopa**
  - Converted to α-methyldopamine and α-methylnorepinephrine
    - Replaces norepinephrine in the vesicles of the axon
    - A false sympathetic transmitter
    - Stimulates central alpha receptors = vasodilation
    - Safe for pregnant patients

- **Side effect**
  - Sedation and lactation
Centrally acting sympathoplegics

- **Clonidine**
  - Stimulates central alpha receptors and arterial alpha receptors
  - Produces a brief rise in blood pressure followed by a more prolonged hypotension by inhibiting sympathetic stimulation from the medulla
  - Reduces heart rate and promotes vasodilation

- **Side effects**
  - Highly lipid soluble = easily enters the brain
  - Sedation and dry mouth (↓salivation)
Ganglion blocking agents

- Blocks ganglions of both sympathetic and parasympathetic nerves
  - Too many side effects
  - Not used anymore
**Inhibit Norepinephrine release**

- **MOA:** Inhibit release of NE from the axon
- **Guanethidin**
  - Significant anti-sympathetic effect
  - Inhibits release of NE as well as replaces NE in the vesicles = depleting NE stores
  - Polar chemical = does not enter the CNS
- **Side effects**
  - Hypotension, diarrhea, impaired ejaculation or retrograde ejaculation
Inhibit Norepinephrine release

- **Reserpine**
  - Decreases norepinephrine production by inhibiting VMAT (vesicular membrane associated transporter)
  - Decreases sympathetic activity

- **Side effects**
  - Affects brain and peripheral nerves
  - Sedation, lassitude, nightmares and mental depression
Adrenoceptor Antagonists

- Alpha and beta blockers
- α1 blockers (-zosin)
  - Prazosin, terazosin, doxazosin
  - Dilates arterioles and venules
  - Concomitant salt and water retention
  - Also useful for men with urinary bladder obstruction such as BPH
    - Relaxes prostate muscle
- Side effect
  - 1st dose phenomenon = sudden drop in BP after the 1st dose
    - 1st dose should be a small dose, succeeding doses may be increased.
<table>
<thead>
<tr>
<th>Type</th>
<th>Tissue location</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>α1</td>
<td>Most vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Pupillary dilator muscle</td>
<td>Contraction (dilates pupil)</td>
</tr>
<tr>
<td></td>
<td>Pilomotor smooth muscle</td>
<td>Erects hair</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>↑ inotropy</td>
</tr>
<tr>
<td>α2</td>
<td>Post synaptic CNS neurons</td>
<td>Probably multiple (↓ BP)</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>Aggregation</td>
</tr>
<tr>
<td></td>
<td>Adrenergic and cholinergic nerve terminals</td>
<td>Inhibits transmitter release</td>
</tr>
<tr>
<td></td>
<td>Some vascular smooth muscle</td>
<td>Contraction</td>
</tr>
<tr>
<td></td>
<td>Fat cells</td>
<td>Inhibits lipolysis</td>
</tr>
</tbody>
</table>
Adrenoceptor Antagonists = Opposite effect

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<thead>
<tr>
<th>Type</th>
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<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>β1</td>
<td>Heart, juxtaglomerular cells</td>
<td>↑chronotropy and inotropy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑renin release</td>
</tr>
<tr>
<td>β2</td>
<td>Respiratory, uterine and vascular smooth muscle</td>
<td>Smooth muscle relaxation</td>
</tr>
<tr>
<td></td>
<td>Skeletal muscle</td>
<td>↑Potassium uptake</td>
</tr>
<tr>
<td></td>
<td>Human liver</td>
<td>Activates glycogenolysis</td>
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<tr>
<td>β3</td>
<td>Fat cells</td>
<td>lipolysis</td>
</tr>
<tr>
<td>D1</td>
<td>Smooth muscle</td>
<td>Dilates renal blood vessels</td>
</tr>
<tr>
<td>D2</td>
<td>Nerve endings</td>
<td>Modulates transmitter release</td>
</tr>
</tbody>
</table>
Adrenoceptor Antagonists

- β blockers
- Propanolol
  - Non-selective beta blocker
  - Decreases HR
  - Inhibits stimulation renin production
  - Decreased sympathetic activity
  - → decreased BP
- Side effect
  - Bradycardia
  - Asthma (promote bronchoconstriction)
  - Diabetes (inc. blood glucose)
Adrenoceptor Antagonists

- **β blockers**

- **Metoprolol and atenolol**
  - Selective β1 antagonist = ↓HR
  - Extensively metabolized by liver enzymes (Cyt P450)
  - Better for asthmatic and diabetic patients

- **Other beta1 blockers**
  - Nadolol, carteolol, pindolol, acebutolol, labetalol, carvedilol, esmolol.
## Direct Vasodilators

<table>
<thead>
<tr>
<th><strong>Mechanism</strong></th>
<th><strong>Examples</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Release of nitric oxide from endothelium</td>
<td>Nitroprusside, hryalazine, nitrates</td>
</tr>
<tr>
<td>Reduction of calcium influx</td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>Hyperpolarization of smooth muscle membrane through opening of potassium channels</td>
<td>Minoxidil, diazoxide</td>
</tr>
<tr>
<td>Activation of dopamine receptors</td>
<td>Fenoldopam</td>
</tr>
</tbody>
</table>
Vascular smooth muscle cell

**Ca^{2+} channel blockers**

**Ca^{2+}**

**Calmodulin**

**Ca^{2+} - Calmodulin complex**

**MLCK**

**Myosin-LC kinase (MLCK)**

**Myosin-LC**

**Myosin-LC-PO_{4}**

**Actin**

**Contraction**

**Relaxation**

**ATP**

**cAMP**

**MLCK(PO_{4})_{2}**

**cGMP**

**β_{2} agonists**
1. **Stimulus**: This is the initial trigger that causes the depolarization phase.

2. **Depolarization**: The membrane potential decreases from rest potential towards +30 mV due to the opening of sodium channels.

3. **Repolarization**: The membrane potential returns to the resting state due to the opening of potassium channels and sodium pumps.

4. **Hyperpolarization**: The membrane potential further decreases beyond the resting state.

5. **Rest potential**: The membrane potential stabilizes at a negative value, typically around -90 mV.

6. **Active sodium and potassium pumps**: These pumps restore the sodium and potassium gradients across the membrane.
### Direct Vasodilators

<table>
<thead>
<tr>
<th>Arteriodilators</th>
<th>Venodilators</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td></td>
<td>Nitrates</td>
</tr>
<tr>
<td>Minoxidil</td>
<td></td>
<td>Na nitroprusside</td>
</tr>
<tr>
<td>Diazoxide</td>
<td></td>
<td>ACEI and ARB</td>
</tr>
<tr>
<td>Fenoldopam</td>
<td></td>
<td>Centrally acting</td>
</tr>
<tr>
<td>CCB’s</td>
<td></td>
<td>alpha1 blockers</td>
</tr>
</tbody>
</table>

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Direct Vasodilators

- **Sodium nitroprusside**
  - **MOA:** release of NO to endothelium
    - By activation of guanylyl cyclase → vessel relaxation
  - Only parenterally administered (no oral preparation)
  - Used for hypertensive emergencies
    - Rapidly lowers blood pressure within minutes
    - Effects disappear rapidly as well.
  - **Side effects**
    - Metabolized to cyanide, which is then metabolized to thiocyanate (less toxic form)
      - Cyanide poisoning (metabolic acidosis, arrhythmias, hypotension)
      - Take hydroxycobalamin (Vit B12) to combine with cyanide to create an inert compound (cyanocobalamin)
Direct Vasodilators

- **Hydralazine**
  - Arteriodilator
  - **MOA:** release of nitric oxide
  - For initial therapy of severe hypertension
- **Side effects**
  - Tachyphylaxis = cannot be used over long periods
  - Headache, nausea, anorexia
  - Lupus like syndrome = arthralgia, myalgia, skin rash, fever
    - Disappears after discontinuation of drug
Direct Vasodilators

- Nitrates or nitrites
  - Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, nitric oxide
  - Vasodilator (both arteries and veins)
    - Relaxes all smooth muscles (no effect on cardiac or skeletal muscles)
  - MOA: releases nitric oxide in endothelium which relaxes blood vessels
  - Rapidly metabolized by the liver into inactive substances
    - Preferred route is sublingual, which bypasses the liver
    - Except isosorbide mononitrate (good for oral route)
Direct Vasodilators

- Nitrates or nitrites
  - Effect
    - Rapid onset of action and short duration
    - Decreases preload (venodilation)
      - Not good for normal hearts
      - Good for heart failure and heart overload
    - Dilates coronary blood vessels = increase flow
    - Slight decrease in platelet aggregation
    - Decreases afterload (arteriodilation)
Direct Vasodilators

- Nitrates or nitrites
  - Side effects
    - Tolerance = cannot be used over several days
    - Reflex sympathetic response
    - Headache = dilation of cerebral arteries = throbbing or pulsating headache
Direct Vasodilators

- Calcium Channel Blockers (CCB)
  - 2 groups
  - Dihydropyridines
    - -dipine
  - Non-dihydropyridines
    - Verapamil
    - Diltiazem
  - MOA: inhibits calcium influx into vascular smooth muscles, thus decreasing muscle contractility of the blood vessels
  - Vasodilator: Arteries > veins
Direct Vasodilators

- Calcium Channel Blockers (CCB)
  - Dihydropyridines
    - Amlodipine, nifedipine, nicardipine, felodipine
    - Blocks calcium channels in blood vessels = vasodilation
  - Side effects
    - Headache
    - Reflex tachycardia
Direct Vasodilators

- Calcium Channel Blockers (CCB)
  - Non-dihydropyridines
    - Verapamil
      - Modest vasodilation
      - Blocks cardiac contractility and significant SA and AV node conduction
        - Decreases HR = $\downarrow$ workload of heart
    - Diltiazem
      - Modest vasodilation
      - Blocks cardiac contractility and moderate SA and AV node conduction
        - Decreases HR = $\downarrow$ workload of heart
Direct Vasodilators

- **Minoxidil**
  - **MOA:** hyperpolarization of smooth muscle (K channels)
  - **Arteriodilator**
  - **Side effect**
    - Hypertrichosis = used as a topical agent
Direct Vasodilators

- Diazoxide
  - MOA: hyperpolarization of resting membrane potential by opening K channels
  - Arteriodilator
- Side effect
  - Excessive hypotension
  - Inhibits insulin release
Direct Vasodilators

- Fenoldopam
  - MOA: dopamine1 (D1) receptor agonist
  - Arteriodylilorator
  - Side effect
    - Increases intraocular pressure (not good for glaucoma patients)
Angiotensin blockers

- Review of the renal system and urine formation
- RAAS system
  - RAAS system through the juxtaglomerular apparatus
  - Aldosterone: increases active reabsorption of Na+ and secretion of K+ by the distal tubules
  - Renin: increases aldosterone secretion via production of angiotensin.
  - Angiotensin: increases aldosterone, anti-diuretic hormone, blood pressure and thirst.
    - Angiotensin II = vasoconstrictor
Angiotensin blockers

- RAAS system
  - Renin is released from the kidneys (JG-App)
  - Renin acts upon angiotensinogen to form Angiotensin I
  - Angiotensin I is converted to Angiotensin II by ACE (Angiotensin converting enzyme) in the lungs
  - Angiotensin II is converted to Antiogensin III in the adrenal gland
    - Angiotensin II and III stimulate aldosterone release → sodium and water reabsorption
Angiotensin blockers

- ACE inhibitors
  - -pril
- ARB’s (Antiogensin receptor blockers)
  - -sartan
- Aldosterone antagonists (diuretic)
- Renin antagonist
  - aliskiren
Angiotensin blockers

- **ACE inhibitors**
  - Captopril, enalapril, perindopril, quinapril, etc.
  - Inhibits conversion of angiotensin I to angiotensin II
    - Prevents vasoconstriction and aldosterone secretion
  - Prevents inactivation of bradykinin
    - Stimulates release of NO → vasodilation
  - No reflex sympathetic activation → good for patients with heart failure
  - Diminishes proteinuria and stabilizes renal function
    - Especially good for patients with kidney problems or diabetes
Angiotensin blockers

- ACE inhibitors
  - Side effects
    - Hyperkalemia (potassium sparing effect)
      - Possible drug interactions with diuretics
    - Dry cough (due to accumulation of bradykinin)
    - Angioedema
    - Contraindicated during pregnancy
Angiotensin blockers

- Angiotensin receptor blockers (ARB)
  - Losartan, valsartan, candesartan, telmisartan
  - Similar effect with ACE inhibitors
    - Except no accumulation of bradykinin = less cough side effect
    - Decreased proteinuria and improved renal function
    - No sympathetic reflex response to vasodilation
  - Contraindicated in pregnancy
Angina pectoris

- Chest pain from myocardial ischemia
  - Due to lack of blood flow to heart muscles
  - Blockage of coronary arteries (CAD or coronary artery disease)
    - 2 types
    - Stable angina
      - Classic angina (effort angina) = atheromatous obstruction of coronaries, manifesting during effort or exercise
    - Unstable angina
Angina pectoris

- **Unstable angina or acute coronary syndrome**
  - When episodes of angina occur at rest, or when there is an increase in severity, frequency and duration of chest pain in patients with previously stable stable angina
  - Progressive blockage of the coronaries due to platelet plug or other occlusive thrombi

- **Special type of angina**
  - Prinzmetal angina (vasospastic angina) = transient spasm of localized portions of the coronaries (also due to atheromatous obstruction)
  - May be stable or unstable
Angina pectoris

- **Coronary blood flow**
  - Due to perfusion pressure (aortic diastolic pressure) and duration of diastole
    - Blood flows to coronary arteries only during diastole
  - Inversely proportional to coronary vascular resistance
Angina pectoris

- Treatment
  - Decrease oxygen demand (decrease workload of heart)
    - Increase contractility
    - Decrease heart rate = beta blockers
    - Decrease blood pressure or peripheral vascular resistance
  - Increase delivery (increase coronary blood flow)
    - Dilate vessels and prolong diastolic time
      - Vasodilators and beta blockers
    - Remove blockage or atherosclerosis
      - Anti hyperlipidemics, anti-platelets
## Angina pectoris

**Treatment**

- **Nitrates**

<table>
<thead>
<tr>
<th>Effect of Nitrates</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential benefits</td>
<td></td>
</tr>
<tr>
<td>↓ ventricular volume</td>
<td>↓ Myocardial O2 requirement</td>
</tr>
<tr>
<td>↓ arterial pressure</td>
<td></td>
</tr>
<tr>
<td>↓ ejection time</td>
<td></td>
</tr>
<tr>
<td>vasodilation of coronary arteries</td>
<td>Relief of coronary artery spasm</td>
</tr>
<tr>
<td>↑ collateral flow</td>
<td>↑ Perfusion to ischemic myocardium</td>
</tr>
<tr>
<td>↓ LV diastolic pressure</td>
<td>↑ Subendocardial perfusion</td>
</tr>
</tbody>
</table>
## Angina pectoris

<table>
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<th>Effect of Nitrates</th>
<th>Result</th>
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<tbody>
<tr>
<td>Potential deleterious effects</td>
<td></td>
</tr>
<tr>
<td>Reflex tachycardia</td>
<td>✆ Myocardial O2 demand</td>
</tr>
<tr>
<td>Reflex in contractility</td>
<td></td>
</tr>
<tr>
<td>➖ diastolic perfusion time due to tachycardia</td>
<td>➖ Coronary perfusion</td>
</tr>
</tbody>
</table>
Erectile dysfunction

- Due to atherosclerosis of vascular bed in penis
- Promote vasodilation to increase blood flow to penis and erectile tissue
- Deadly interaction with nitrates
  - Severe hypotension
  - 6 hour interval between nitrates and sildenafil