CARDIOVASCULAR PHARMACOLOGY

1. Antihypertensive agents
2. Vasodilators & treatment of angina
3. Drugs used in heart failure
4. Drugs used in arrhythmias

Only need to know drugs discussed in class

OBJECTIVES

At the end of this section you should be able to:

1. Describe the basic physiology/pathophysiology of the cardiovascular system
2. Name major groups of cardiovascular drugs & give examples for each group
3. Describe the mechanisms of action of major groups of cardiovascular drugs
4. List major toxicities of cardiovascular drugs

ANTIHYPERTENSIVES

1. Hypertension
2. Normal regulation of blood pressure
3. Drugs:
   - Sympatholytics
   - Vasodilators
   - ACE Inhibitors
   - Diuretics

HYPERTENSION

- Most common cardiovascular disease
  - 15% of North Americans require treatment
- Causes known in 10 – 15% of cases
  - genetic factors, environmental factors, psychological stress, diet
- If left untreated:
  - Damage to blood vessels, renal failure, coronary disease, stroke.
- Treatment:
  - Slows blood vessel damage & decreases morbidity & mortality

NORMAL REGULATION OF BLOOD PRESSURE

BP = CO X PVR

Anatomy of BP control:
- Aterioles (resistance)
- Venules (capacitance)
- Heart (rate/cardiac output)
- Kidney (volume)
NORMAL REGULATION OF BLOOD PRESSURE

BARORECEPTORS
Moment to moment regulation of blood pressure
Baroreceptors in carotid artery & aorta monitor stretch of blood vessels
↑ stretch → baroreceptor stimulation
→ ↓ SNS activity
↓ stretch → ↓ baroreceptor activity
→ ↑ SNS activity

RENIN-ANGIOTENSIN-ALDOSTERONE
Kidney controls long-term blood pressure by controlling blood volume
↓ BP → ↑ renin → ↑ angiotensin II
angiotensin II → constriction of vessels
→ ↑ aldosterone
(↑ aldosterone → ↑ Na+ retention & ↑ blood volume)

DECREASED ARTERIAL PRESSURE

Renin (kidney)
Renin substrate (angiotensinogen)
Angiotensin I
ACE (lungs)
Aldosterone secretion
↓ Renal salt & water retention
Angiotensin II
Vasoconstriction
INCREASED ARTERIAL PRESSURE

ANTIHYPERTENSIVE THERAPY
Goal is to decrease BP thereby preventing organ damage
- Interfere with mechanisms that regulate BP
- Balance between toxicity of treatment & risk of not treating
- Monotherapy or combined therapy

CENTRALLY ACTING SYMPATHOLYTICS
Clonidine
- in CNS adrenergic neurons regulate ANS
- increased adrenergic activity → ↑ SNS & ↓ PSNS
- α₂ receptors on adrenergic nerve terminals in CNS
clonidine = α₂ agonist (↓ cAMP ∴ inhibitory)
: clonidine → ↓ NE in CNS → ↓ SNS & ↑ PSNS activity
= ↓ CO & PVR
Clonidine toxicity (due to CNS effects)
= sedation & impaired concentration
**PERIPHERALLY ACTING SYMPATHOLYTICS**

Reserpine:
- Blocks uptake of NE into synaptic vesicles
- Less NE available for release
- ↓ CO and PVR
- Low doses used for mild to moderate hypertension
- Enters CNS: affects NE, dopamine and serotonin uptake in brain
- CNS toxicities: sedation, depression, Parkinson-like symptoms

**VASODILATORS**

Beta blockers:
- Non-selective (eg. propranolol) used frequently, toxicities associated with β₁ blockade (asthma)
- Selective β₁ (eg. metoprolol)
- Effect on BP: block of β₁ in heart → ↓ CO
- Block of β₁ in juxta-glomerular region of kidney → ↓ renin release → ↓ PVR

Alpha blockers:
- Selective α₁ (eg. prazosin)
  - Block α₁ receptors in arterioles and venules
  - Salt and water retention occurs → often administered with diuretics or beta blockers
  - Toxicity rare: dizziness, headache

**VASODILATORS**

Oral Vasodilators: (eg. Minoxidil)
- Potent drug used in severe hypertension
- Opens K⁺ channels & stabilizes membrane at resting potential → contraction less likely & relaxes smooth muscle
- Toxicity: tachycardia, palpitations, angina, sweating, headache, edema

**VASODILATORS**

Parenteral Vasodilator: (given IV for hypertensive emergencies, short-acting)
- Sodium nitroprusside: dilates arterial and venous vessels
  - ↑ cGMP in smooth muscles → relaxation
- Toxicities: hypotension, cyanide accumulation
Calcium channel blockers: (eg. verapamil) can be used for long-term and emergency treatment. Inhibit \( \text{Ca}^{2+} \) influx into arterial smooth muscle cells \( \rightarrow \) dilation. Toxicities: severe cardiac depression.

\[ \text{ACE} = \text{Angiotensin Converting Enzyme} \]

ACE converts angiotensin I to angiotensin II. Angiotensin II is one of the most potent vasoconstrictors known. It triggers secretion of aldosterone (from adrenal gland) and ADH (from pituitary gland). ACE inactivates bradykinin.

Presynaptic (AT₁) - ↑ NE release - Activates AT receptors \( \rightarrow \) ↑ DAG & IP₃

Smooth muscle (AT₁) - IP₃ \( \rightarrow \) ↑ \( \text{Ca}^{2+} \) release (endoplasmic reticulum)

Modified from www.colorado.edu/epob

Inhibits bradykinin and activates aldosterone and ADH.

Bradykinin = vasodilator - bradykinin \( \rightarrow \) ↑ prostaglandins (PGs) PGs bind to PG receptors \( \rightarrow \) ↑ cAMP \( \rightarrow \) vasodilation

Aldosterone - ↑ Na⁺ reabsorption in distal tubule and collecting duct (H₂O follows)

ADH = antidiuretic hormone (vasopressin) increases permeability of collecting tubule in kidney \( \rightarrow \) ↑ H₂O reabsorption
**ACE INHIBITORS**

- Angiotensinogen → Renin → Angiotensin I → Angiotensin II → Bradykinin → Inactive Peptide
- NE release → Aldosterone → Vasoconstriction → ADH → \( \uparrow \) Na⁺ Resorption → \( \uparrow \) K⁺ Excretion → \( \uparrow \) H₂O Resorption
- Vasoconstriction
- Blood Pressure

**ANGIOTENSIN INHIBITORS**

- ACE Inhibitors
  - Captopril: rapid oral absorption, \( t_{1/2} = 2 \) h, excreted by kidney
  - Enalapril: prodrug, metabolized to active drug (first-pass through liver)
    - \( - \) like captopril except \( t_{1/2} = 11 \) h

- \( \text{AT}_1 \) Antagonists
  - Losartan: Effectiveness similar to ACE inhibitors, parent drug and metabolite active with combined \( t_{1/2} = 8 - 10 \) h

**DIURETICS**

Decrease BP by depleting body Na⁺ (H₂O follows)

- Mild-moderate hypertension: can use diuretics alone (eg. Thiazides)
- Severe hypertension: more powerful diuretic (eg. Furosemide) in combination with a sympatholytic & vasodilator
- Diuretics enhance efficacy of ACE inhibitors

**DIURETICS**

**Diuretics**

- Thiazides
  - Inhibit NaCl transport in distal convoluted tubule
  - Absorbed well orally
  - Inexpensive and effective
  - Toxicities: hyperkalemia (potassium depletion) hazardous for patients with arrhythmias, acute myocardial infarction or taking digitalis; gout (precipitated by enhanced uric acid reabsorption); hyponatremia (dehydration)

- Loop diuretics (eg. Furosemide)
  - Inhibits cotransporter of Na⁺, K⁺ and Cl⁻ in loop of Henle (NaCl reabsorption inhibited)
  - Rapid and short acting
  - Used mainly for severe hypertension and pulmonary edema
  - Toxicities: same as thiazides; can also cause dose-dependent ototoxicity (hearing loss)
Mechanism: furosemide inhibits the Na\(^+\)/K\(^+\)/2Cl\(^-\) transporter, increasing Na\(^+\), K\(^+\), Cl\(^-\) & water loss, reducing blood volume & BP.

- Na\(^+\) restriction (low salt diet)
- weight reduction
- monotherapy (most cases):
  - sympatholytics or ACE inhibitor or Ca\(^{2+}\) channel blocker
  - thiazide diuretic - useful in mild to moderate hypertension
  - α\(_1\) blocker and other vasodilators not used initially

**Figure 15-4.** Ion transport pathways across the luminal membrane:

- Na\(^+\)
- K\(^+\)
- Cl\(^-\)
- ATP
- Na\(^+\) ATPase
- Mg\(^2+\), Ca\(^{2+}\)

**Clinical Management of Hypertension**

- Most patients do well on single drug

Compared to combination (“stepped”) care monotherapy is:
- simple
- better compliance
- relatively low incidence of toxicity

- used in severe hypertension or if one drug cannot control hypertension
- drugs added in stepwise fashion until optimal BP achieved

First: lifestyle changes (i.e. decrease salt and weight loss), then:
1. Diuretics
2. Sympatholytics
3. Vasodilators
4. ACE inhibitors

Add one at a time as needed

**Clinical Management of Hypertension**

Problems with combination “stepped” therapy:
- Lack of patient compliance because:
  - multiple medications to take
  - disease is asymptomatic
  - drugs are expensive
  - side-effects are common

Fixed-dose combinations available:
- advantage – increased compliance
- disadvantage – cannot titrate individual drug dosages