BLOOD PRESSURE:
Systolic / Diastolic NORMAL: 120/80
- Systolic = measure of pressure as heart is beating
- Diastolic = measure of pressure while heart is at rest between beating

HYPERTENSION:
- Sustained elevation of arterial blood pressure above “normal”
  - Systolic ≥ 140 mm Hg
  - Diastolic ≥ 90 mm Hg

REDUCE HIGH BP TO SLOW PROGRESSIVE ORGAN DAMAGE:
- Brain: thrombosis
- Eyes: retinopathy
- Kidney: nephropathy, renal failure
- Heart: atherosclerosis, MI, CHF, hypertrophy

WAYS OF LOWERING BP:
- Reduce preload (diuretics)
- Reduce contractility & heart rate (beta blockers)
- Reduce TPR (vasodilators)

DETERMINANTS OF BLOOD PRESSURE: BP = CARDIAC OUTPUT X TOTAL PERIPHERAL RESISTANCE

DEFINITIONS:
- Cardiac output (CO): amount of blood pumped by each side of heart in one min
  - CO = heart rate x stroke volume
- Stroke volume: volume of blood pumped by each ventricle in one contraction

CONTRACTILITY AND CENTRAL NERVOUS SYSTEM:
- Stimulation of sympathetic nervous system → release of norepinephrine → increased heart rate and contractility
  - Innervates SA and AV node + cardiac muscle
- Stimulation of parasympathetic nervous system (vagus) → release of acetylcholine → decreased heart rate
  - Innervates SA and AV node only

ACETYLCHOLINE:
1. Decreases cAMP
2. Less sodium moving into SA node
3. Slower If current
4. Lower heart rate

NOREPINEPHRINE:
1. Norepinephrine binds to B1 adrenergic receptor in heart
2. B1 receptor activation increases cAMP
   a. Activates protein kinase
      i. Phosphorulates calcium channel on plasma membrane
      ii. More calcium enters
      iii. Releases calcium from SR
      iv. Calcium binds to troponin
      v. Actin slides over myosin
      vi. INCREASED CARDIAC CONTRACTION
   b. Activates HCN channel in SA node
      i. Important for entry of sodium (If) in pacemaker current
      ii. Increased sodium into SA node = increased heart rate

LIFESTYLE MODIFICATIONS:
- Lose weight – DASH diet (dietary approaches to stopping hypertension)
- Exercise (aerobic; 30 min/day)
- Control diabetes
DRUGS AFFECTING RAAS

DRUGS TO REDUCE RAAS ACTIVITY:
1. Inhibit renin release from JGC by blocking B1 receptors (propranolol, metoprolol)
2. Block ACE and therefore angiotensin II formation using ACE inhibitors
3. Block angiotensin II receptors
4. Inhibit renin activity with a direct renin inhibitor (Aliskiren)

RAAS AND EFFECTS OF ANGIOTENSIN II:

ACE INHIBITORS: - prils

ADVERSE REACTIONS:
- Dry/persistent/irritating cough (5-20%) → angioedema (<1%) = nose, throat, airway obstruction
  > May be due to elevation of bradykinin and/or prostaglandin buildup in URT (dilation of blood vessels → fluid build up)
- Hyperkalemia: can be worsened by concurrent use of K+ supplements or K+ sparing diuretics
  > Normally aldosterone promotes sodium reabsorption, making the lumen negative, allowing K secretion
  > When aldosterone is blocked, prevent sodium reabsorption and secretion of K = hyperkalemia
- Hypotension: after initial doses in patients on Na+ restricted diets or on diuretics (lowers BP VERY WELL)
  > Contraindicated during pregnancy: risk of fetal hypotension, fetal malformations, or death (NEED A II)

USES:
- Hypertension
  o Major effect is decrease in peripheral resistance (oppose vasoconstriction)
- Heart failure
  o Break vicious cycle (see Loop Diuretics notes)
- Left ventricular dysfunction
- Acute myocardial infarction
- Chronic kidney disease
ANGIOTENSIN RECEPTOR BLOCKERS: -artans

ANGIOTENSIN II RECEPTORS:
- Two main receptor types: AT₁ & AT₂
- Most known actions of AT II are mediated by AT₁ receptors
  - AT₁ receptors predominant in vascular smooth muscle

ARbs MOA:
- Competitive inhibitors of angiotensin type 1 receptors
- Primary action is to decrease total peripheral resistance
- Has no effect on bradykinin metabolism = less likely/no cough

ADVERSE EFFECTS:
- Hypotension
- Potential to cause hyperkalemia
- Contraindicated in pregnancy

DIRECT RENIN INHIBITORS: Aliskiren

CONTROL OF RENIN SECRETION:
- Competitively blocks proteolytic activity of renin, preventing processing of angiotensinogen to angiotensin I
- Reduces angiotensin II and aldosterone levels
- Combination may attenuate long-term use of ACE or ARB induced compensatory rise in renin
- Similar hemodynamic actions as ACE inhibitors and ARBs
- Contraindicated in pregnancy

OVERVIEW OF DRUGS TO REDUCE RAAS ACTIVITY:
- Aliskiren can block renin release from jGA with beta blockers
- ACE-Inhibitors can block renin release through other enzymes than ACE
- Aliskiren primarily acts on the renin-angiotensin system
- Vasoconstriction, cell growth, and sodium/water retention are attenuated
- ARBs block AT₁ receptors to show downstream effects
- Angiotensinogen can be converted to Ang I and Ang II through different pathways
- Negative feedback loop involves renin and ACE
- Bradykinin buildup in smooth muscle causes vasodilation, which can lead to cough or angioedema
Hypertensive Drugs

**ADRENORECEPTORS:**
- B2 blocker can prevent release of norepinephrine
- A2 stimulator can increase inhibition of norepinephrine

**DISTRIBUTION OF ADRENORECEPTORS:**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Sympathetic Effect</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Tone of blood vessel is mixture of α1 and β2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Because α1 predominates, blood vessels are always slightly constricted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constriction (α1)</td>
<td></td>
<td>α1 receptor activation increases IP3 → release of calcium → contraction</td>
</tr>
<tr>
<td>Dilation (β2)</td>
<td></td>
<td>β2 receptor stimulation forms cAMP which (IN VASCULAR SMOOTH MUSCLE) inhibits MLCK → myosin cannot be phosphorylated → prevents contraction = vasodilation</td>
</tr>
<tr>
<td>Heart</td>
<td>Increased contractility (β1)</td>
<td>β1 stimulation increases cAMP which (IN THE HEART) increases PKA → allows extracellular calcium to enter → greater release of calcium from SR → increases overall amount of calcium = increase FORCE of contraction</td>
</tr>
<tr>
<td>Tachycardia (β1)</td>
<td></td>
<td>Increased cAMP also stimulates HCN channel in SA node → sodium enters through faster → sodium current increases → INCREASED HEART RATE</td>
</tr>
<tr>
<td>Bronchi</td>
<td>Relaxation (β2)</td>
<td>REMEMBER THIS IN ASTHMATIC PATIENTS WHEN USING BETA BLOCKERS</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Renin release (β1)</td>
<td>β1 stimulation at juxtaglomerular cells releases renin</td>
</tr>
</tbody>
</table>

**BETA BLOCKERS MECHANISM OF DECREASING BP:**

<table>
<thead>
<tr>
<th>B-Adrenoceptor blockers</th>
<th>Activation of β1, α1 receptors on heart</th>
<th>Decrease in blood pressure</th>
</tr>
</thead>
</table>

**BETA BLOCKER TYPES:**
- Non-selective: block both B1 (heart, JGC) and B2 (bronchi)
  - Propranolol
- Relatively selective B1 at lower doses
  - Metoprolol
  - Blocks both B1 and B2 at higher doses
- Mixed: α1, B blocking
  - Labetalol
- Mixed: B blocking and partial agonist
  - Pindolol

**ADVERSE EFFECTS OF BETA BLOCKERS:**
- Expose asthmatics to increased risk of bronchoconstriction
- Bradycardia (use this property in treatment of arrhythmias)
- Rebound hypertension on sudden discontinuation (due to receptor supersensitivity) = GRADUAL DECREASE
- Masking sympathetic discharge seen with hypoglycemia, cold extremities
  - Hypoglycemia causes catecholamine release to break down glucagon into glucose → increase HEART RATE → diabetic patients know they are becoming hypoglycemic
  - BETA BLOCKERS mask increased heart rate = unaware of impending hypoglycemia
  - Lose opposing dilation/relaxation of B2 in blood vessels = a2 constriction is more = cold extremities
**ALPHA BLOCKERS:**

**USES:**
- Not as clinically useful as B-blockers
- Selective α1 blockers most useful: prazosin, terazosin, doxazosin
  - Non-selective α receptor would block α1 postsynaptically (= vasodilation) BUT ALSO block α2 presynaptically (BLOCKING inhibition of release of norepinephrine)
  - Blocking α1 receptor prevents formation of IP3 which prevents calcium release from SR = VASODILATION

**ADVERSE EFFECTS OF α1 BLOCKERS:**
- Dilate veins, reduce venous return
  - α1 receptors on veins can also be blocked = relaxed and dilated
  - Veins are capacitance vessels = blood can pool in veins → less blood going to heart = less preload = less cardiac contraction = less blood supply to brain
- First dose postural hypotension (50% of pts within 90 mins after administration)
  - Start with low doses, patient reclining

**VASODILATORS:**

**ARTERIOLAR:** decrease lumen diameter → reduce peripheral resistance → decrease blood pressure

**CALCIUM CHANNEL BLOCKERS (CCB):**

**CLASSES OF Ca2+ CHANNEL BLOCKERS:**
- Primary action on arterioles: 
  - dihydropyridines (Nifedipine, Amlodipine, Felodipine, Nimodipine)
- Primary action on heart muscle: verapamil
- Primary action on conducting tissue: diltiazem

**L-TYPE Ca2+ CHANNELS:**
- Contractile cells (atria, ventricle)
- Calcium current formed in SA node
  - CCBs block opening of L-type calcium channel → block formation of calcium current → action potential not formed in SA node
- Vascular smooth muscle contraction
  - CCBs block calcium entry through L-type calcium channel = prevents activation of MLCK = prevents phosphorylation of myosin = NO CONTRACTION = RELAXATION

**MINOXIDIL:**
- MOA: opens K+ channels in vascular smooth muscle → hypopolarization → decrease calcium entry through L-type Ca2+ channel
- Major side effects:
  - Hypertrichosis (abnormal, excessive hair growth)
    - Rogaine (topical)

**HYDRAZINE:**
- Mechanism (unclear): opens K+ channels (EDHF) → generates NO → increase in cGMP → stimulates cGMP dependent protein kinase → K+ leaves cell → hypopolarization = decrease amount of Ca2+ moving into cell
  - cGMP dependent protein kinase also stores calcium in SR so it is unavailable for contraction
  - OVERALL: smooth muscle relaxation

**COMPENSATION:**
- Because blood pressure drops, baroreceptors stop firing, and sympathetic discharge causes renin release = INCREASED BLOOD PRESSURE
- Therefore minoxidil and hydralazine NEED TO BE GIVEN WITH DIURETICS & BETA BLOCKERS

**ARTERIOLAR AND VENULAR:** Nitroprusside
- Smooth muscle relaxation in arteries → lumen diameter opens → reduced peripheral resistance → decrease BP
- Smooth muscle relaxation in veins → reduce amount of blood → reduce cardiac output → decrease BP

**DISCUSSED IN FUTURE LECTURES**
CENTRAL NERVOUS SYSTEM:

**CLONIDINE:**
- Stimulates α2 receptors in the brain → decrease release of norepinephrine → decrease BP
- May also suppress renin release

**METHYLDOPA:**

- Methyldopa activates presynaptic α2 receptors to decrease NE release → reduce blood pressure
- Also displaces norepinephrine from presynaptic terminals (secondary action)
- Activates presynaptic α2 receptors in brainstem, decreasing NA release