Pharmacology

Drugs that Affect the Cardiovascular System
Topics

- Electrophysiology
- Vaughn-Williams classification
- Antihypertensives
- Hemostatic agents
Cardiac Function

• Dependent upon
  – Adequate amounts of ATP
  – Adequate amounts of Ca^{++}
  – Coordinated electrical stimulus
Adequate Amounts of ATP

• Needed to:
  – Maintain electrochemical gradients
  – Propagate action potentials
  – Power muscle contraction
Adequate Amounts of Calcium

- Calcium is ‘glue’ that links electrical and mechanical events.
Coordinated Electrical Stimulation

- Heart capable of automaticity
- Two types of myocardial tissue
  - Contractile
  - Conductive
- Impulses travel through ‘action potential superhighway’.
A.P. SuperHighway

- Sinoatrial node
- Atrioventricular node
- Bundle of His
- Bundle Branches
  - Fascicles
- Purkinje Network
Electrophysiology

- Two types of action potentials
  - Fast potentials
    - Found in contractile tissue
  - Slow potentials
    - Found in SA, AV node tissues
Fast Potential

Phase 1

Phase 2

Phase 3

Phase 4

controlled by Na$^+$ channels = "fast channels"

RMP -80 to 90 mV
Fast Potential

- Phase 0: Na\(^+\) influx “fast sodium channels”
- Phase 1: K\(^+\) efflux
- Phase 2: (Plateau) K\(^+\) efflux
  - AND Ca\(^{++}\) influx
- Phase 3: K\(^+\) efflux
- Phase 4: Resting Membrane Potential
Cardiac Conduction Cycle

![Diagram of Cardiac Conduction Cycle]

- TP: Threshold Membrane Potential
- RP: Resting Membrane Potential
- ECG complex
- QRS complex
- T wave
- ORS
Slow Potential

dependent upon Ca\textsuperscript{++} channels = “slow channels”
Slow Potential

- Self-depolarizing
  - Responsible for automaticity
- Phase 4 depolarization
  - ‘slow sodium-calcium channels’
  - ‘leaky’ to sodium
- Phase 3 repolarization
  - $\text{K}^+$ efflux
Cardiac Pacemaker Dominance

- Intrinsic firing rates:
  - SA = 60 – 100
  - AV = 45 – 60
  - Purkinje = 15 - 45
Cardiac Pacemakers

- SA is primary
  - Faster depolarization rate
    - Faster Ca$^{++}$ ‘leak’
- Others are ‘backups’
  - Graduated depolarization rate
    - Graduated Ca$^{++}$ leak rate
Potential Terms

effectively refractory period

relative refractory period

action potential duration

APD

ERP
Dysrhythmia Generation

- Abnormal genesis
  - Imbalance of ANS stimuli
  - Pathologic phase 4 depolarization
    - Ectopic foci
Dysrhythmia Generation

- Abnormal conduction
- Analogies:
  - One way valve
  - Buggies stuck in muddy roads
Reentrant Circuits
Warning!

- All antidysrhythmics have arrhythmogenic properties
- In other words, they all can CAUSE dysrhythmias too!
AHA Recommendation Classifications

- Describes weight of supporting evidence NOT mechanism
  - Class I
  - Class IIa
  - Class IIb
  - Indeterminant
  - Class III

- View AHA definitions
Vaughn-Williams Classification

- Class 1
  - Ia
  - Ib
  - Ic
- Class II
- Class III
- Class IV
- Misc

- Description of mechanism NOT evidence
Class I: Sodium Channel Blockers

- Decrease Na\(^+\) movement in phases 0 and 4
- Decreases rate of propagation (conduction) via tissue with fast potential (Purkinje)
  - Ignores those with slow potential (SA/AV)
- Indications: ventricular dysrhythmias
Class Ia Agents

- Slow conduction through ventricles
- Decrease repolarization rate
  - Widen QRS and QT intervals
    - *May promote Torsades des Pointes!*

*PDQ:*
- procainamide (Pronestyl®)
- disopyramide (Norpace®)
- qunidine
- (Quinidex®)
Class Ib Agents

- Slow conduction through ventricles
- Increase rate of repolarization
- Reduce automaticity
  - Effective for ectopic foci
- May have other uses

LTMD:
- lidocaine (Xylocaine®)
- tocainide (Tonocard®)
- mexiletine (Mexitil®)
- phenytoin (Dilantin®)
Class Ic Agents

- Slow conduction through ventricles, atria & conduction system
- Decrease repolarization rate
- Decrease contractility
- Rare last chance drug

- flecainide (Tambocor®)
- propafenone (Rythmol®)
Class II: Beta Blockers

- Beta₁ receptors in heart attached to Ca²⁺ channels
  - Gradual Ca²⁺ influx responsible for automaticity
- Beta₁ blockade decreases Ca²⁺ influx
  - Effects similar to Class IV (Ca²⁺ channel blockers)
- Limited # approved for tachycardias
Class II: Beta Blockers

- propranolol (Inderal®)
- acebutolol (Sectral®)
- esmolol (Brevibloc®)
Class III: Potassium Channel Blockers

- Decreases $K^+$ efflux during repolarization
- Prolongs repolarization
- Extends effective refractory period
- Prototype: bretyllium tosylate (Bretylol®)
  - Initial norepi discharge may cause temporary hypertension/tachycardia
  - Subsequent norepi depletion may cause hypotension
Class IV: Calcium Channel Blockers

- Similar effect as β blockers
- Decrease SA/AV automaticity
- Decrease AV conductivity
- Useful in breaking reentrant circuit
- Prime side effect: hypotension & bradycardia

- verapamil (Calan®)
- diltiazem (Cardizem®)

- Note: nifedipine doesn’t work on heart
Misc. Agents

- adenosine (Adenocard®)
  - Decreases Ca\(^{++}\) influx & increases K\(^{+}\) efflux via 2\(^{nd}\) messenger pathway
    - Hyperpolarization of membrane
    - Decreased conduction velocity via slow potentials
    - No effect on fast potentials

- Profound side effects possible (but short-lived)
Misc. Agents

- Cardiac Glycocides
- **digoxin (Lanoxin®)**
  - Inhibits NaKATP pump
  - Increases intracellular Ca^{++}
    - via Na^{+}-Ca^{++} exchange pump
  - Increases contractility
  - Decreases AV conduction velocity
Pharmacology

Antihypertensives
Antihypertensive Classes

- diuretics
- beta blockers
- angiotensin-converting enzyme (ACE) inhibitors
- calcium channel blockers
- vasodilators
Blood Pressure = CO \times PVR

- Cardiac Output = SV \times HR
- PVR = Afterload
**BP = CO x PVR**

**Cardiac Factors**
- Heart rate
- Contractility
  1. Beta Blockers
  2. CCB’s
  3. C.A. Adrenergics

**Circulating Volume**
- Salt
- Aldosterone
  1. ACEi’s
  2. Diuretics

**Key:**
- CCB = calcium channel blockers
- CA Adrenergics = central-acting adrenergics
- ACEi’s = angiotensin-converting enzyme inhibitors
BP = CO \times PVR

Hormones
1. vasodilators
2. ACEI’s
3. CCB’s

Peripheral Sympathetic
Receptors
alpha
beta
1. alpha blockers
2. beta blockers

Central Nervous System
1. CA Adrenergics

Local Acting
1. Peripheral-Acting Adrenergics
Alpha_1 Blockers

Stimulate alpha_1 receptors -> hypertension
Block alpha_1 receptors -> hypotension

- doxazosin (Cardura®)
- prazosin (Minipress®)
- terazosin (Hytrin®)
Central Acting Adrenergics

• Stimulate alpha$_2$ receptors
  – inhibit alpha$_1$ stimulation
    • hypotension

• clonidine (Catapress®)
• methyldopa (Aldomet®)
Peripheral Acting Adrenergics

- reserpine (Serpalan®)
- inhibits the release of NE
- diminishes NE stores
- leads to hypotension
- Prominent side effect of depression
  - also diminishes seratonin
Adrenergic Side Effects

- **Common**
  - dry mouth, drowsiness, sedation & constipation
  - orthostatic hypotension
- **Less common**
  - headache, sleep disturbances, nausea, rash & palpitations
Angiotensin I

ACE

Angiotensin II

1. potent vasoconstrictor
   - increases BP
2. stimulates Aldosterone
   - Na⁺ & H₂O reabsorption

RAAS

Angiotensin I

ACE

Angiotensin II

ACE Inhibitors
Renin-Angiotensin Aldosterone System

- Angiotensin II = vasoconstrictor
- Constricts blood vessels & increases BP
- Increases SVR or afterload
- ACE-I blocks these effects decreasing SVR & afterload
ACE Inhibitors

- Aldosterone secreted from adrenal glands cause sodium & water reabsorption
- Increase blood volume
- Increase preload
- ACE-I blocks this and decreases preload
Angiotensin Converting Enzyme Inhibitors

- captopril (Capoten®)
- enalapril (Vasotec®)
- lisinopril (Prinivil® & Zestril®)
- quinapril (Accupril®)
- ramipril (Altace®)
- benazepril (Lotensin®)
- fosinopril (Monopril®)
Calcium Channel Blockers

- Used for:
  - Angina
  - Tachycardias
  - Hypertension
CCB Site of Action

diltiazem & verapamil

nifedipine (and other dihydropyridines)
CCB Action

- diltiazem & verapamil
  - decrease automaticity & conduction in SA & AV nodes
  - decrease myocardial contractility
  - decreased smooth muscle tone
  - decreased PVR

- nifedipine
  - decreased smooth muscle tone
  - decreased PVR
Side Effects of CCBs

- Cardiovascular
  - hypotension, palpitations & tachycardia
- Gastrointestinal
  - constipation & nausea
- Other
  - rash, flushing & peripheral edema
Calcium Channel Blockers

- diltiazem (Cardizem®)
- verapamil (Calan®, Isoptin®)
- nifedipine (Procardia®, Adalat®)
Diuretic Site of Action

- Proximal tubule
- Loop of Henle
- Distal tubule
- Collecting duct
Mechanism

- Water follows Na⁺
- 20-25% of all Na⁺ is reabsorbed into the bloodstream in the loop of Henle
- 5-10% in distal tubule & 3% in collecting ducts
- If it cannot be absorbed it is excreted with the urine
- ↓ Blood volume = ↓ preload!
Side Effects of Diuretics

- electrolyte losses [Na$^+$ & K$^+$]
- fluid losses [dehydration]
- myalgia
- N/V/D
- dizziness
- hyperglycemia
Diuretics

- Thiazides:
  - chlorothiazide (Diuril®) & hydrochlorothiazide (HCTZ®, HydroDIURIL®)
- Loop Diuretics
  - furosemide (Lasix®), bumetanide (Bumex®)
- Potassium Sparing Diuretics
  - spironolactone (Aldactone®)
Mechanism of Vasodilators

- Directly relaxes arteriole smooth muscle
- Decrease SVR = decrease afterload
Side Effects of Vasodilators

- hydralazine (Apresoline®)
  - Reflex tachycardia
- sodium nitroprusside (Nipride®)
  - Cyanide toxicity in renal failure
  - CNS toxicity = agitation, hallucinations, etc.
Vasodilators

- diazoxide [Hyperstat®]
- hydralazine [Apresoline®]
- minoxidil [Loniten®]
- sodium Nitroprusside [Nipride®]
Pharmacology

Drugs Affecting Hemostasis
Hemostasis

- Reproduce figure 11-9, page 359 Sherwood
Platelet Adhesion
Coagulation Cascade

• Reproduce following components of cascade:
  – Prothrombin -> thrombin
    • Fibrinogen -> fibrin
  – Plasminogen -> plasmin
Platelet Inhibitors

- Inhibit the aggregation of platelets
- Indicated in progressing MI, TIA/CVA
- Side Effects: uncontrolled bleeding
- No effect on existing thrombi
Aspirin

- Inhibits COX
  - Arachidonic acid (COX) -> TXA2 (↓ aggregation)
GP IIB/IIIA Inhibitors

Diagram showing the interaction between GP IIb/IIIa receptors and fibrinogen, with GP IIb/IIIA Inhibitors blocking the interaction.
GP IIB/IIIA Inhibitors

- abciximab (ReoPro®)
- eptifibatide (Integrilin®)
- tirofiban (Aggrastat®)
Anticoagulants

- Interrupt clotting cascade at various points
  - No effect on platelets
- Heparin & LMW Heparin (Lovenox®)
- warfarin (Coumadin®)
Heparin

- Endogenous
  - Released from mast cells/basophils
- Binds with *antithrombin III*
- Antithrombin III binds with and inactivates excess thrombin to regionalize clotting activity.
  - Most thrombin (80-95%) captured in fibrin mesh.
- Antithrombin-heparin complex 1000X as effective as antithrombin III alone
Heparin

- Measured in Units, not milligrams
- Indications:
  - MI, PE, DVT, ischemic CVA
- Antidote for heparin OD: protamine.
  - MOA: heparin is strongly negatively charged. Protamine is strongly positively charged.
warfarin (Coumadin®)

- Factors II, VII, IX and X all vitamin K dependent enzymes
- Warfarin competes with vitamin K in the synthesis of these enzymes.
- Depletes the reserves of clotting factors.
- Delayed onset (~12 hours) due to existing factors
Thrombolytics

- Directly break up clots
  - Promote natural thrombolysis
- Enhance activation of plasminogen
- ‘Time is Muscle’

- streptokinase (Streptase®)
- alteplase (tPA®, Activase®)
- anistreplase (Eminase®)
- reteplase (Retevase®)
- tenecteplase (TNKase®)
Occlusion Mechanism
tPA Mechanism
Cholesterol Metabolism

• Cholesterol important component in membranes and as hormone precursor
• Synthesized in liver
  – Hydroxymethylglutaryl coenzyme A reductase
  – \((HMG \text{ CoA reductase})\) dependant
• Stored in tissues for latter use
• Insoluble in plasma (a type of lipid)
  – Must have transport mechanism
Lipoproteins

- Lipids are surrounded by protein coat to ‘hide’ hydrophobic fatty core.
- Lipoproteins described by density
  - VLDL, LDL, IDL, HDL, VHDL
- LDL contain most cholesterol in body
  - Transport cholesterol from liver to tissues for use (“Bad”)
- HDL move cholesterol back to liver
  - “Good” b/c remove cholesterol from circulation
Why We Fear Cholesterol

- Risk of CAD linked to LDL levels
- LDLs are deposited under endothelial surface and oxidized where they:
  - Attracts monocytes -> macrophages
  - Macrophages engulf oxidized LDL
    - Vacuolation into ‘foam cells’
  - Foam cells protrude against intimal lining
    - Eventually a tough cap is formed
  - Vascular diameter & blood flow decreased
Why We Fear Cholesterol

- Plaque cap can rupture
- Collagen exposed
- Clotting cascade activated
- Platelet adhesion
- Thrombus formation
- Embolus formation possible
- Occlusion causes ischemia
Lipid Deposition
Thrombus Formation
Platelet Adhesion
Occlusion Causes Infarction

- Thrombus
- Collateral Flow
Antihyperlipidemic Agents

- **Goal:** Decrease LDL
  - Inhibition of LDL synthesis
  - Increase LDL receptors in liver
- **Target:** < 200 mg/dl
- *Statins* are HMG CoA reductase inhibitors

- lovastatin (Mevacor®)
- pravastatin (Pravachol®)
- simvastatin (Zocor®)
- atorvastatin (Lipitor®)
Thank You!

- To Temple College EMS Professions for permission to use their materials