Cardiovascular System & Its Diseases

Lecture #4

Heart Failure & Cardiac Arrhythmias

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Congestive Heart Failure

Pathophysiology: What Is It?

"Chronic or acute state resulting from failure of the heart to meet oxygen demands of the body"

Underlying Problems:

Left Ventricular Dysfunction (original explanation)
(i.e. failure to pump / hemodynamic model, treat with positive inotropic agents)

Neuroendocrine Activation (now included)
(prevent or delay re-modeling)

Congestive Heart Failure

Pathophysiology: What Is It?

Progressive and highly lethal disease state that may follow:

- Uncontrolled Hypertension
- Diabetes
- Myocardial Infarction
- Valve Dysfunction
- Viral Myocarditis
- Other Conditions

Congestive Heart Failure

Pathophysiology: Classification

Clinical Congestive Heart Failure

(New York Heart Association)

Class I: Failure is associated with no limitations on ordinary activities and symptoms but are revealed during exercise.

Class II: Characterized by slight limitation on ordinary activity resulting in fatigue and palpitations

Class III: No symptoms at rest but fatigue etc with less than ordinary physical activity

Class IV: Associated with symptoms **even** at rest

Congestive Heart Failure

Pathophysiology: Disease Progression

Primary Effects (Hemodynamic Model):

- Reduced Cardiac Output
- Excessive Sympathetic Discharge
- Salt & Water Retention

Pharmacological Intervention Useful

Long-term Effects (Neuroendocrine Activation):

- Remodeling
- Cardiac Hypertrophy
- Cardiac Apoptosis

Reaching An Endpoint Stage

Congestive Heart Failure

Pathophysiology: Cardiac Output

Determined By Several Factors

Preload: (**Atrial Pressure)** Increased in heart failure due to increased blood volume and venous tone **Treated with salt restriction and diuretics**

Afterload: **(Vascular Resistance)** Increased due to reflex sympathetic outflow and renin-angiotensin system though elevated **afterload** may further reduce cardiac output **Reduction of arterial tone**

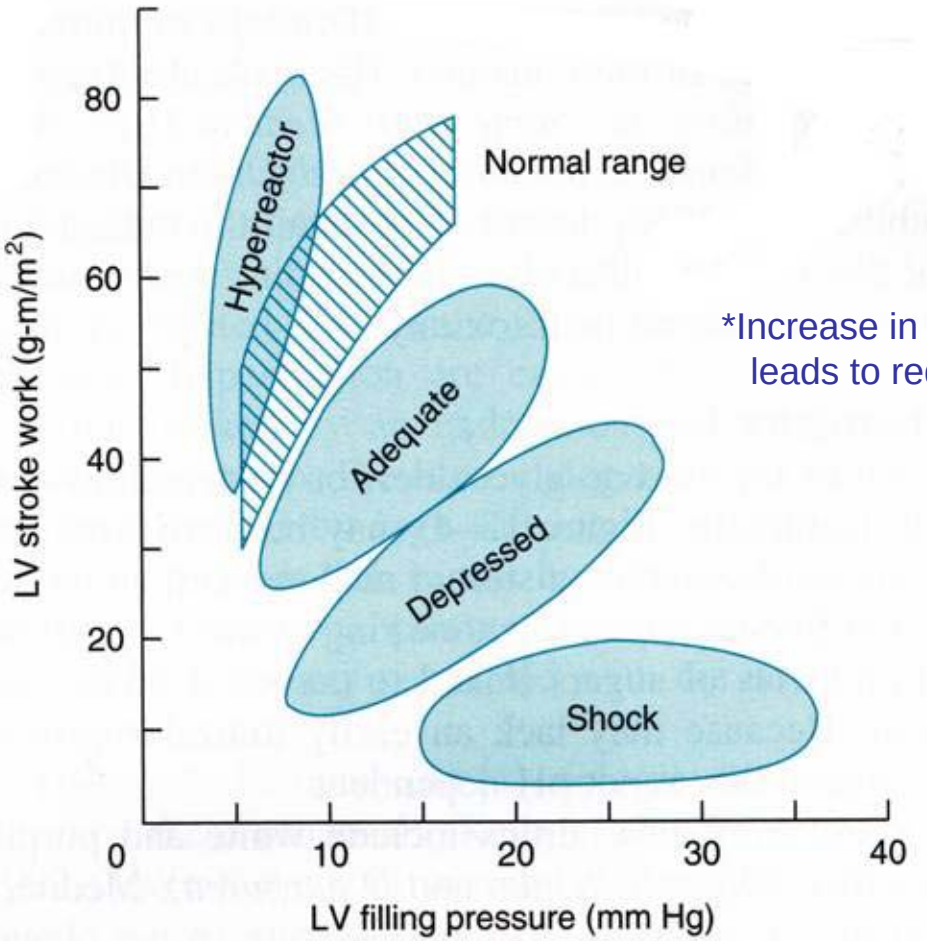
Contractility: Reduction in intrinsic contractility and therefore reduction in pump performance **Inotropic drugs to increase contractility**

Heart Rate: Increases through sympathetic NS compensation

Congestive Heart Failure

Pathophysiology: Depression of Ventricular Performance

Ventricular Performance



Preload

*Increase in atrial pressure during HF leads to reduced **pump function***

Congestive Heart Failure

Pathophysiology: Compensatory Responses

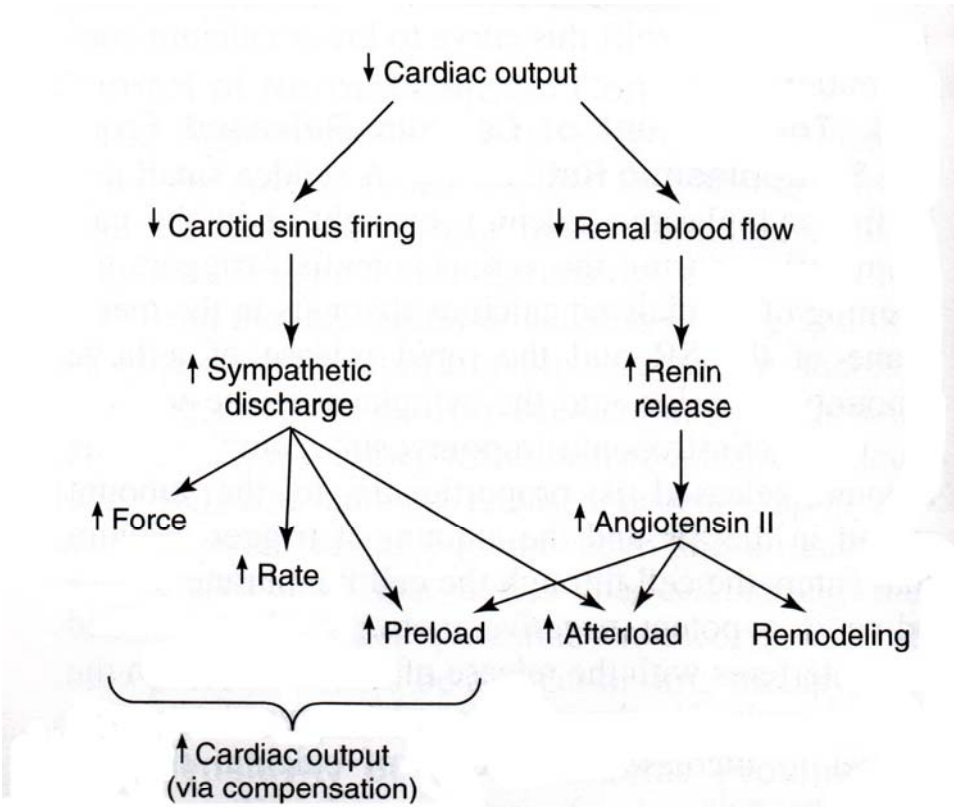


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

Congestive Heart Failure

THERAPEUTIC OVERVIEW

PROBLEM	Force of contraction ↓
	Ventricular dilatation
	Cardiac output ↓
	Total peripheral resistance ↑
	Venous pressure ↑
	Development of edema
	Tissue perfusion ↓
	Exercise tolerance ↓
GOAL	Reverse signs and symptoms of heart failure, improve quality of life
	Arrest ventricular remodeling
	Increase survival
NONDRUG THERAPY	Cardiac work reduction through rest and salt restriction
DRUG THERAPY	Diuretics
	Vasodilators
	ACE inhibitors
	Positive inotropic drugs:
	Cardiac glycosides
	Sympathomimetics
	Phosphodiesterase inhibitors
	β-Blockers

Congestive Heart Failure

Pharmacological Intervention: Overview of Drug Strategy

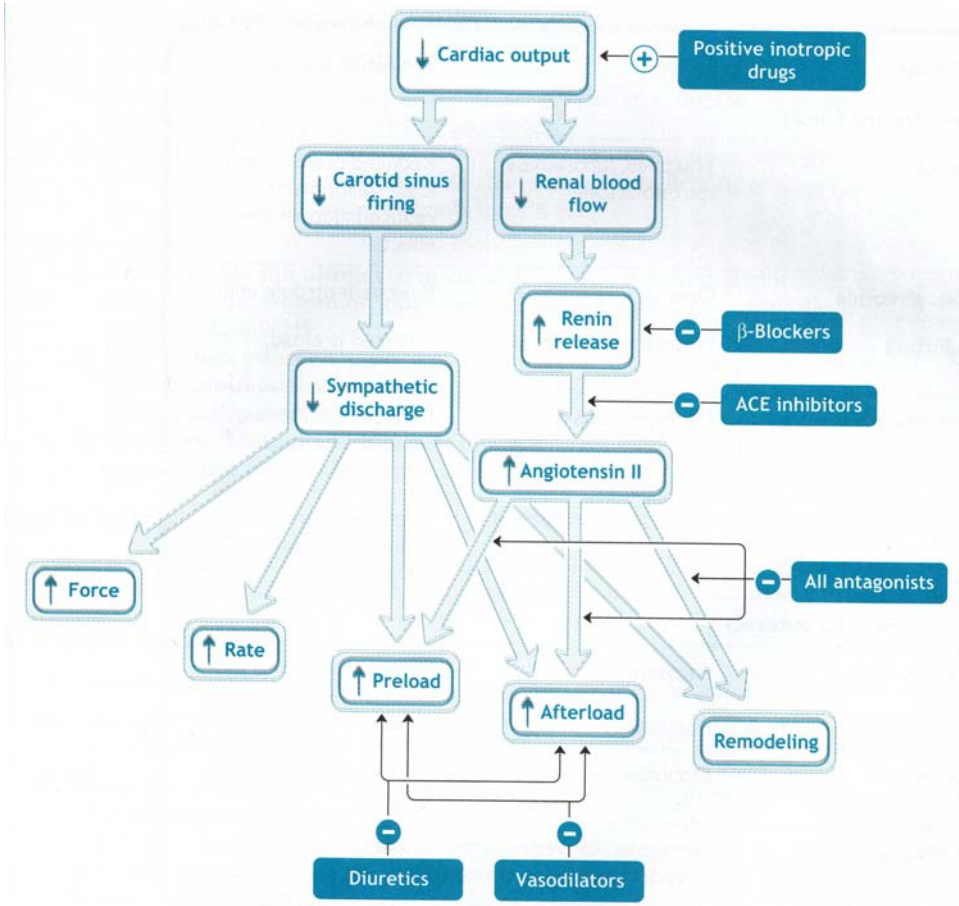


Figure 3–4. Pathophysiologic processes and drug targets in heart failure. Activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system initially compensates for diminished cardiac performance but thereafter accelerates the process of cardiac failure. Drugs that interfere with these compensatory responses are useful in therapy. β blockers probably have several additional sites of action.

Congestive Heart Failure

Pharmacological Intervention: Positive Inotropic Drugs

- Drugs: Cardiac Glycosides (e.g. Digoxin*) steroidal molecules from digitalis and other plants

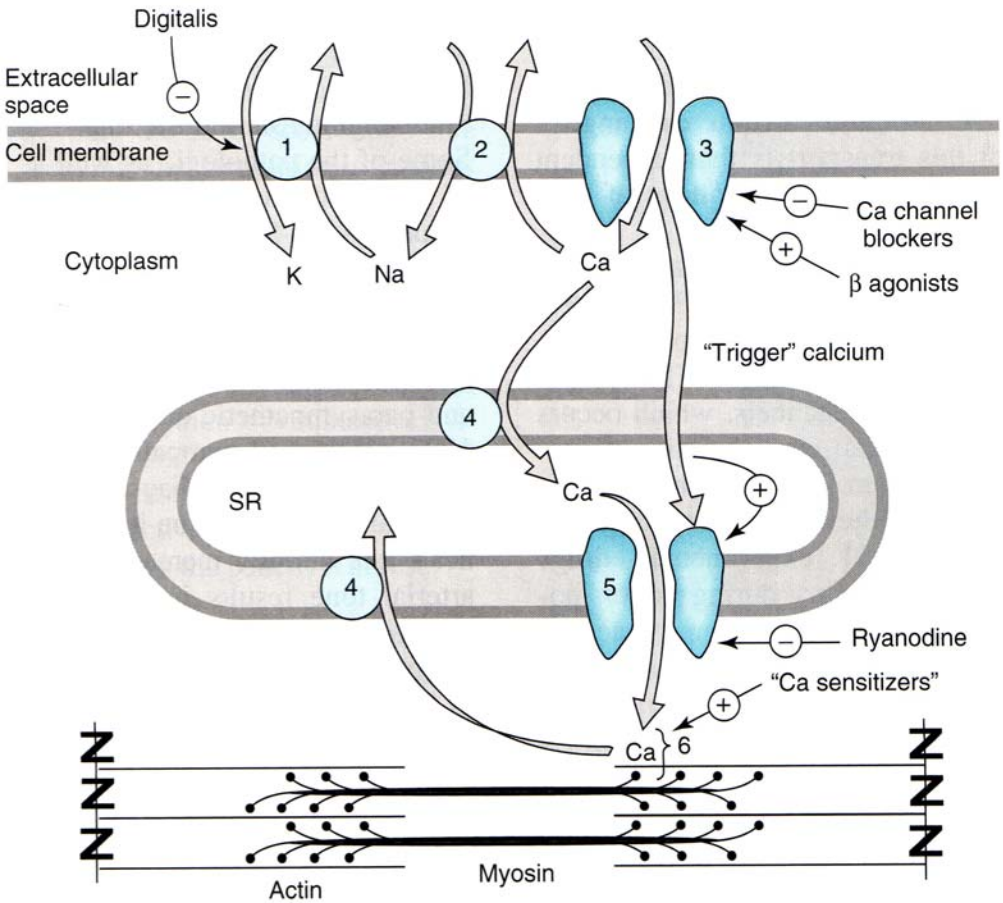
- Mechanism: Block Na^+ / K^+-ATPase positive inotropic effect
  Cardiac parasympathetic effect slow AV conduction, useful in atrial fibrillation

- Indications: Primarily for Heart Failure
  Atrial Fibrillation

- Side-effects: Very Toxic
  Cause Cardiac Arrhythmias
  GI upset
  Neuroendocrine effects rare

Congestive Heart Failure

Pharmacological Intervention: Positive Inotropic Drugs



Digoxin block of Na^+/K^+ ATPase

↓

Less expulsion of cytosolic Ca^{2+} by Na^+/Ca^{2+} exchanger

↓

Increased elevation cytosolic Ca^{2+} from sarcoplasmic reticulum

↓

Increased Contractility

Congestive Heart Failure

Pharmacological Intervention: Positive Inotropic Drugs

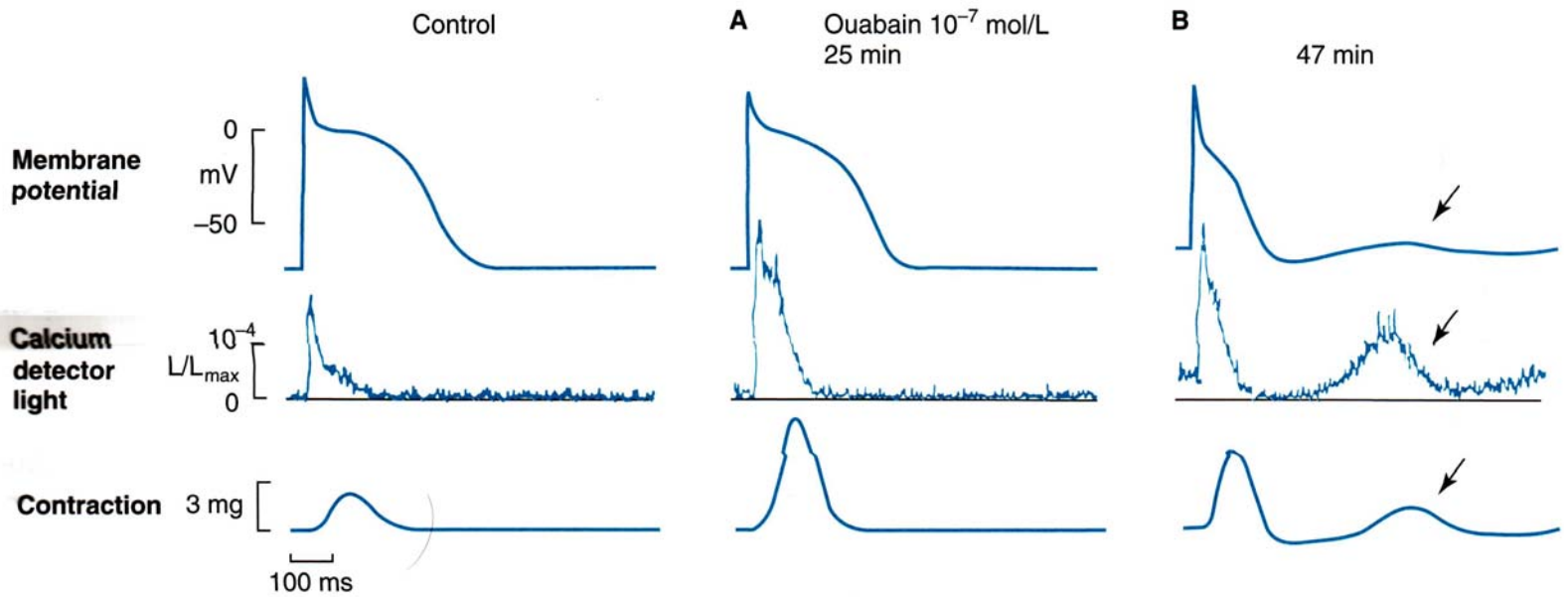


Figure 13–5. Effects of a cardiac glycoside, ouabain, on isolated cardiac tissue. The top tracing shows action potentials evoked during the control period, early in the "therapeutic" phase, and later, when toxicity is present. The middle tracing shows the light (L) emitted by the calcium-detecting protein aequorin (relative to the maximum possible, L_{max}) and is roughly proportionate to the free intracellular calcium concentration. The bottom tracing records the tension elicited by the action potentials. The early phase of ouabain action *(A)* shows a slight shortening of action potential and a marked increase in free intracellular calcium concentration and contractile tension. The toxic phase *(B)* is associated with depolarization of the resting potential, a marked shortening of the action potential, and the appearance of an oscillatory depolarization, calcium increment, and contraction *(arrows)*. (Unpublished data kindly provided by P Hess and H Gil Wier.)

Congestive Heart Failure

Pharmacological Intervention: Diuretics

- Drugs: Diuretics (e.g. Furosemide)
- Mechanism: Lower blood volume
- Indications: Useful in almost all Heart Failure patients
  - Loop diuretics — Furosemide, acute pulmonary edema & severe, chronic heart failure
  - Thiazides — Hydrochorothiazide, Mild chronic failure
  - Spironolactone — Aldosterone antagonist
- Side-effects: Hypokalemia

Congestive Heart Failure

Pharmacological Intervention: Angiotensin Antagonists

- Drugs: ACE inhibitors (e.g. Captopril) & Receptor Antagonists (e.g. Losartan)

- Mechanism: Reduce Angiotensin II synthesis ACE inhibitors
  Block AT1-type receptors Angiotensin receptor inhbitors

- Indications: First line agents (with diuretics) in Heart Failure
  AT1-type antagonists used if ACE inhibitors are not tolerated

- Side-effects: Renal Damage ACE inhibitors
  Contraindicated in Pregnancy AT1 antagonists

Congestive Heart Failure

Pharmacological Intervention: Other Drugs

- β-Blockers: **Metoprolol**, prolong life in chronic heart failure
  - Mechanism unknown may involve reduced renin secretion
- β-Agonists: **Dobutamide**, β1 selective for severe heart failure
  - Increases cardiac force, reduces afterload result of increasing cardiac output
- Phosphodiesterase Inhibitors: **Theophylline**, acute decompensation in HF
  - Increases cAMP levels in cardiac and vascular tissue
- Vasodilators: **Nitroglycerin**, acute decompensation in Heart Failure
  - Reduce afterload (increasing ejection fraction) and preload (reduce myocardial O_2 requirement)

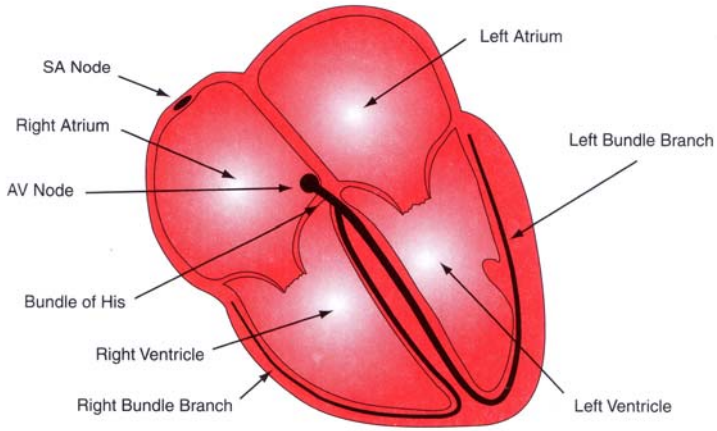
Congestive Heart Failure

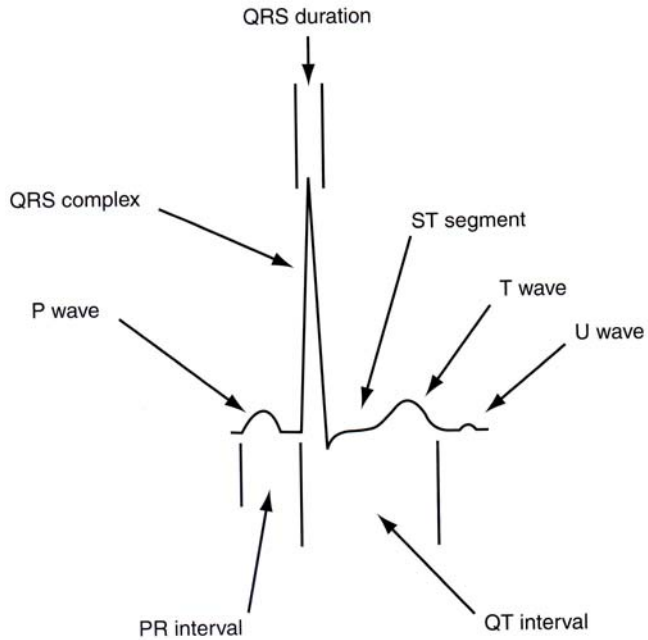
Pharmacological Intervention: Summary of Drug Strategy

Drug Group	Drugs	Beneficial Effects
Chronic failure (oral)		
Diuretics	Thiazides, furosemide, spironolactone	Reduced preload, afterload; spironolactone, reduced aldosterone effects
Cardiac glycoside	Digoxin	Positive inotropic effect
Vasodilators	Hydralazine, isosorbide dinitrate	Reduced preload, afterload
Angiotensin antagonists	Captopril, losartan	Reduced remodeling, preload, afterload, apoptosis
β blockers	Carvedilol, metoprolol	Reduced afterload, reduced remodeling, apoptosis
Acute failure (parenteral)		
Diuretics	Furosemide	Reduced pulmonary vascular pressures, preload
β_1 Agonists	Dobutamine	Increased cardiac force, output
Vasodilators	Nitroprusside, nitroglycerin	Reduced preload, afterload

Cardiac Arrhythmias

Back To Basics: Cardiac Electrophysiology





SA Node:
Small collection of cells that initiate atrial systole

AV Node:
1. Provides delay in impulse transmission
2. Protects ventricles from atrial fibrillation

Bundle of His:
1. Divides R and L bundles
2. Provides orderly depolarization of ventricles

P wave:
atrial Systole

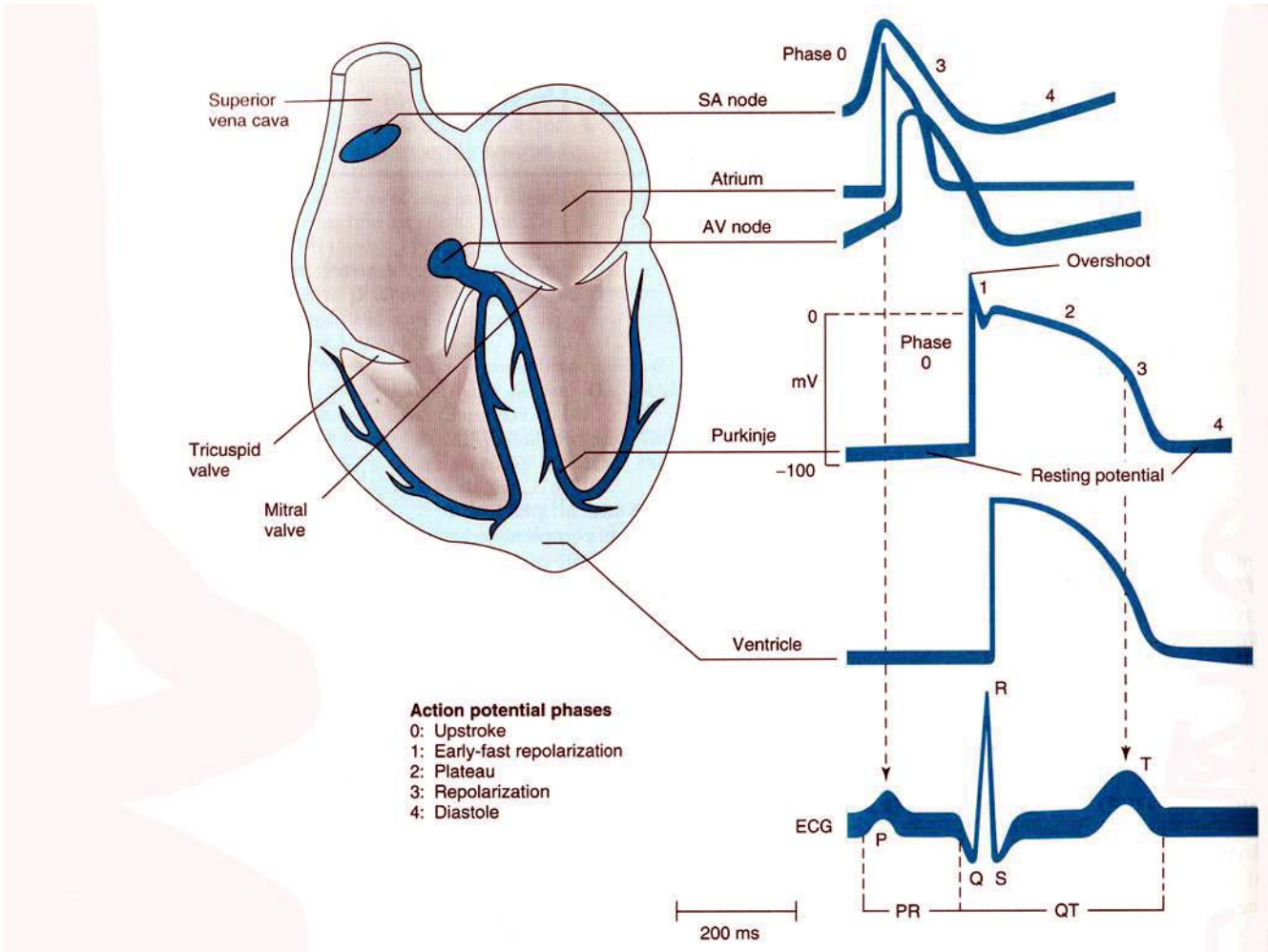
QRS complex:
Ventricular systole

PR interval:
delay at AV node

T wave:
ventricular repolarization

Cardiac Arrhythmias

Back To Basics: Cardiac Electrophysiology



Cardiac Arrhythmias

Back To Basics: Molecular Components of Action Potential

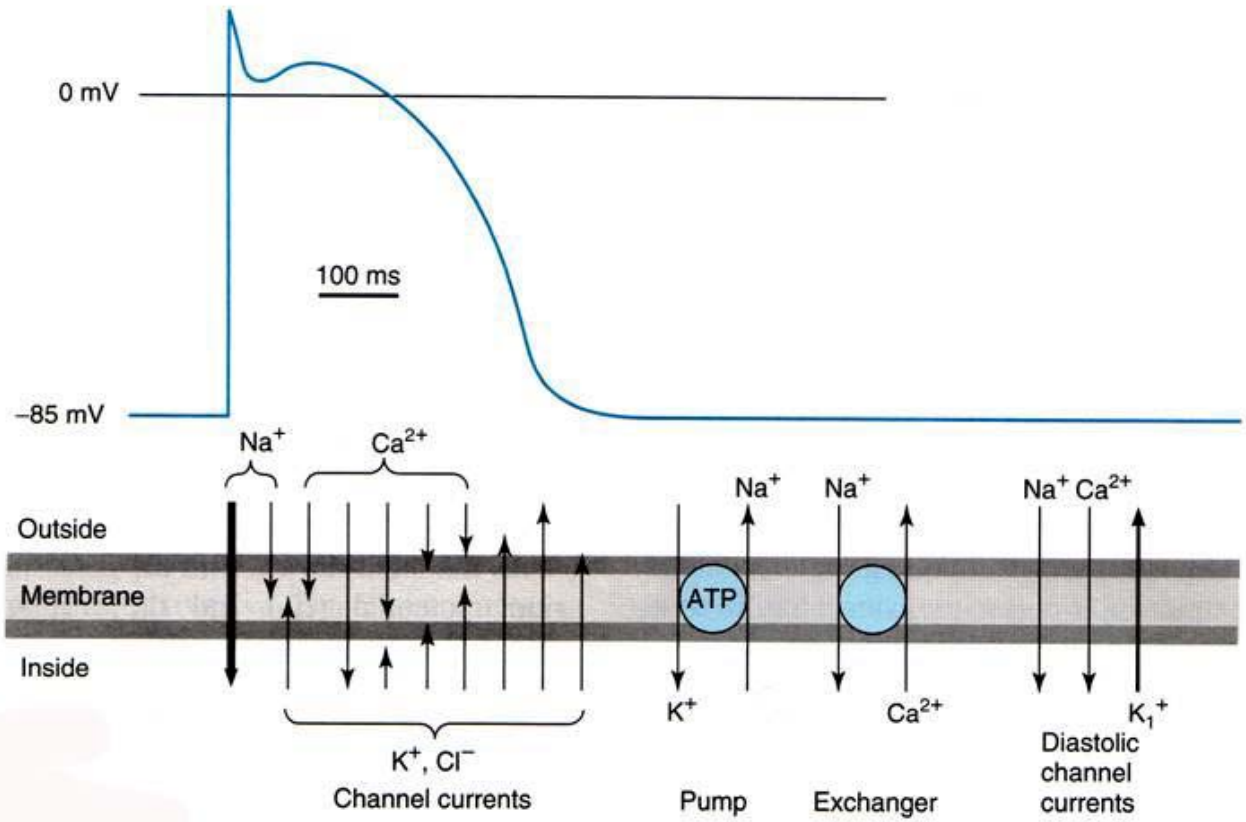
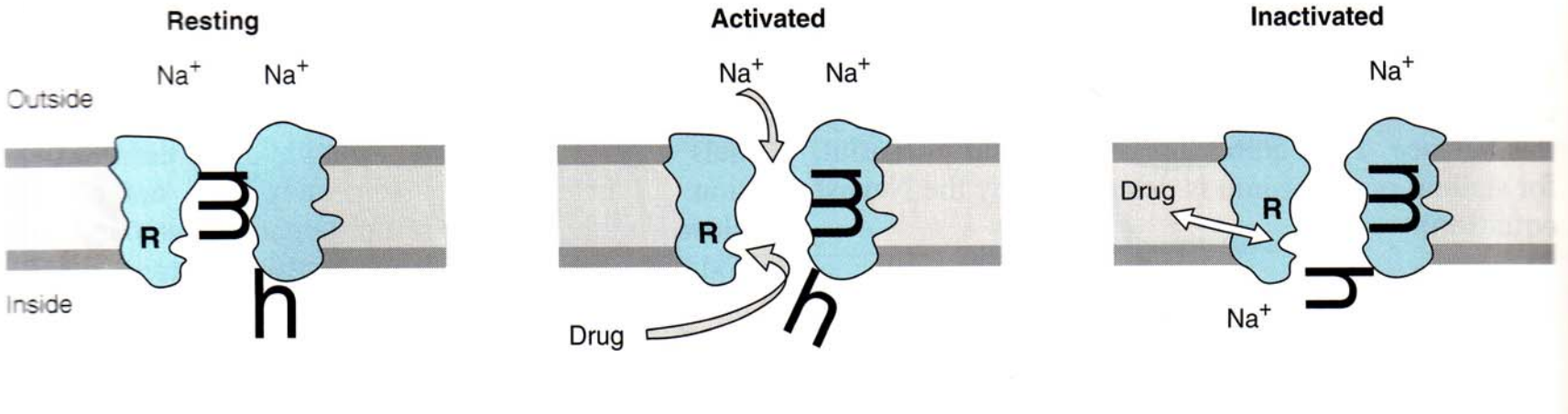


Figure 14–3. Schematic diagram of the ion permeability changes and transport processes that occur during an action potential and the diastolic period following it. The size and weight of the arrows indicate approximate magnitudes of the ion channel currents. Multiple subtypes of potassium and calcium currents, with different sensitivities to blocking drugs, have been identified.

Cardiac Arrhythmias

Back To Basics: Ion Channels Adopt Different Conformational States



Similar functional behavior is also found with K^+ and Ca^{2+} channels

Cardiac Arrhythmias

Pathophysiology: Aetiology

- **Two main causes:**
  - (i) Abnormal Pacemaker Activity
  - (ii) Cardiac Conduction
  - (iii) Or Both

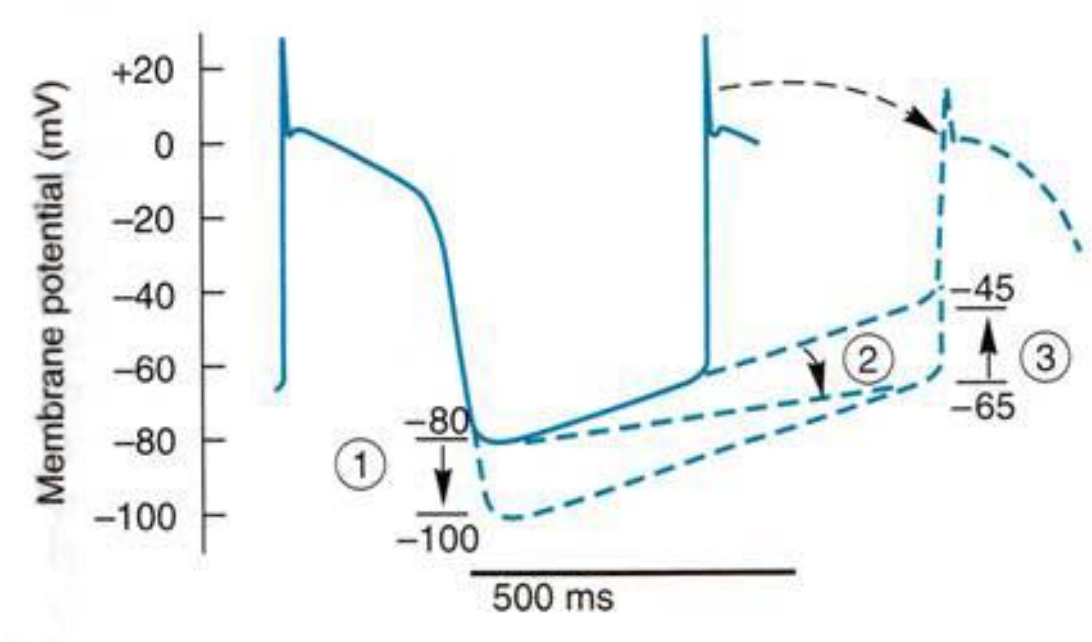
- **Risk Factors:**

  Ischemia, Hypoxia, Acidosis/Alkalosis, Electrolyte Abnormalities
  Excessive Catecholamine Exposure, Autonomic Influences,
  Drug Toxicity (e.g. antiarrhythmic drugs), Scarred/Diseased Tissue

- **Treatment:**
  - (i) Electrical Devices pacemakers, defibrillators
  - (ii) Electrical ablation of abnormal pathways
  - (iii) Drug Treatment

Cardiac Arrhythmias

Pathophysiology: Impulse Formation



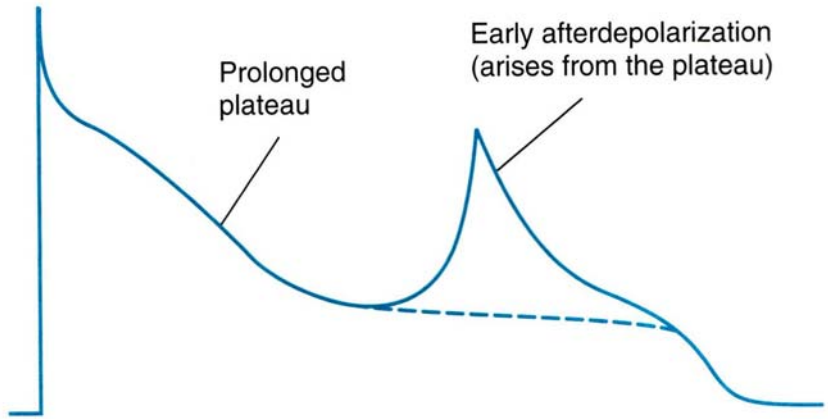
3 Ways Of Slowing Normal Pacemaker Activity

1. More Negative Diastolic Potential (e.g. open K+ channels)
2. Reduction Of Diastolic Depolarization (e.g. block Na+ or Ca2+ channels)
3. More Positive Threshold Potential (e.g. shift voltage sensitivity)

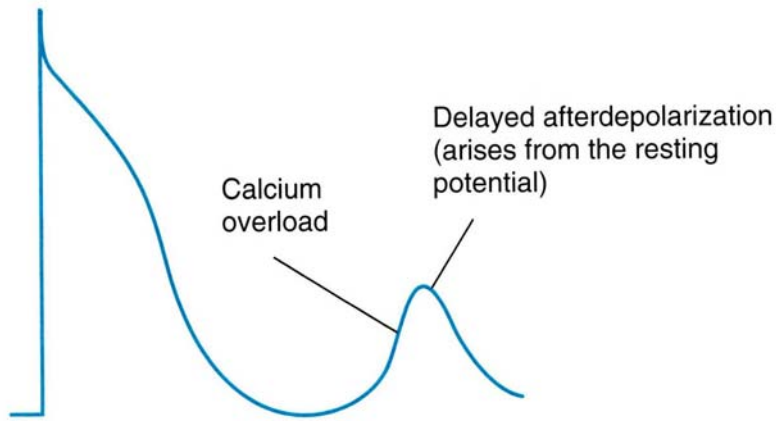
Cardiac Arrhythmias

Pathophysiology: Abnormal Pacemaker Activity

Early Afterdepolarization
(Often occur at slow heart rate)

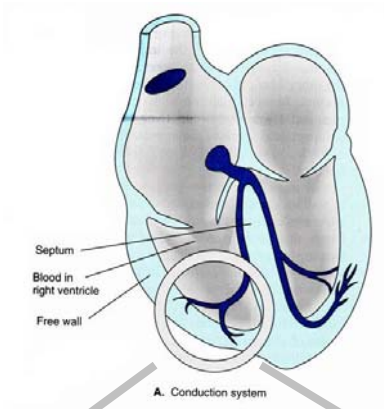


Delayed Afterdepolarization
(occur at fast heart rates)

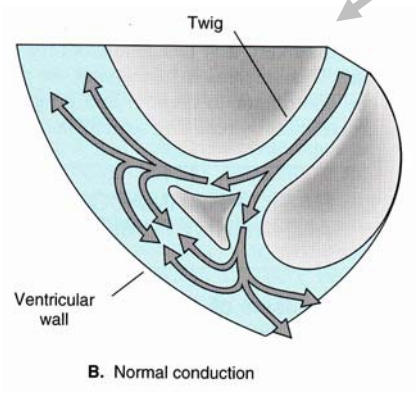


Cardiac Arrhythmias

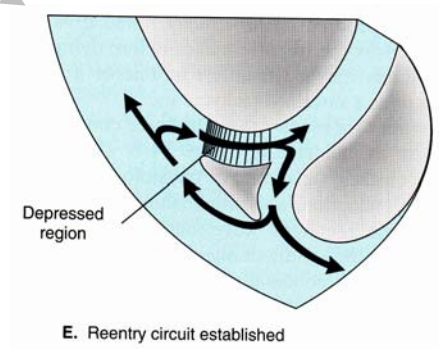
Pathophysiology: Disturbance Of Cardiac Conduction



Normal Conduction



Region Of Re-entry



Re-entry is a common disturbance of conduction

Cardiac Arrhythmias

Pharmacological Intervention: Summary Of Drug Types

Antiarrhythmic Drugs are divided into five groups:

Class I: **Na^+ channel blockers** (e.g. Quinidine)

Class II: **β-Blockers** (e.g. Propanolol)

Class III: **I_{Kr} channel blockers** (e.g. Sotalol)

Class IV: **L-type Ca^{2+} channel blockers** (e.g. Verapamil)

Class V: **Miscellaneous** including adenosine, K^+ and Mg^{2+} ions

*** Anti-arrhythmic drugs have a **very low therapeutic index** and can provoke arrhthymias and heart failure. Recent trial showed that prophylactically treated patients had **2.5 fold increase in mortality** than placebo patients ***

Cardiac Arrhythmias

Pharmacological Intervention: Mechanism of Action

Class I: **Na^+ channel blockers**

IA: slow intraventricular conduction (increase QRS) & increase ventricular AP (increase QT)

IB: selective for abnormal tissue

IC: slow intraventricular conduction only

Class II: **β-Blockers** (e.g. Propanolol)

Slow AV conduction and prolong PR interval

Class III: **I_{Kr} channel blockers** (e.g. Sotalol)

Prolong ventricular AP therefore prolong PR interval

Class IV: **L-type Ca^{2+} channel blockers** (e.g. Verapamil)

Slow AV conduction & prolongs PR interval

Class V: **Miscellaneous** including adenosine, K^+ and Mg^{2+} ions

Congestive Heart Failure

Case Study

Francoise Laplante is a 63 year old bank executive who complains of difficulty sleeping and difficulty climbing stairs because of easy fatigue and shortness of breath.

She is not sleeping well. Her personal history reveals that she has smoked 15 cigarettes per day since she was a teenager and she has one or 2 glasses of wine per day. Her family history is unremarkable save for type II diabetes and obesity in her mother and one sister. Her past history includes essential hypertension and an anterior wall myocardial infarction at age 59.

Identify the Risk Factors of Cardiovascular Disease?

Congestive Heart Failure

Case Study

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Risk Factors:

Smoking, Older Age, Diabetes, Family History, Hypertension & Myocardial infarction

Congestive Heart Failure

Case Study

Current medication includes metoprolol 50 mg twice daily and hydrochlorothiazide 25 mg daily, metformin 1000 mg twice daily and insulin 20 units at bed time.

Physical exam reveals a tired looking woman with BP 140/80 mm Hg, P 60 beats/min and regular and respiratory rate 22/minute. Jugular venous pressure is elevated and there are crackles heard at both lung bases plus ankle edema. Echocardiography shows no valve disease, enlarged dilated left ventricle and a decreased ejection fraction.

Identify the drugs being used?

What do the symptoms indicate?

Congestive Heart Failure

Case Study

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Drugs being used:

Metoprolol (β-blocker); Hydrochlorothiazide (diuretic)
Metformin (oral hypoglycemic); Insulin

What do the symptoms indicate:

Venous distension, edema of lungs & ankles indicate volume overload

Heart Failure Patient!

Congestive Heart Failure

Case Study

The patient is started on captopril 5 mg twice daily and furosemide 40 mg daily and the hydrochlorothiazide is discontinued. One week later she reports that she is moderately improved and able to sleep at night. Her ankle swelling is improved.

Identify the drugs being used?

Why was hydrochlorothiazide stopped?

Congestive Heart Failure

Case Study

The patient is started on captopril 5 mg twice daily and furosemide 40 mg daily and the hydrochlorothiazide is discontinued. One week later she reports that she is moderately improved and able to sleep at night. Her ankle swelling is improved.

Identify the drugs being used:
Captopril (ACE inhibitor), furosemide (loop diuretic)

Cessation of hydrochlorothiazide:
Ineffective

Congestive Heart Failure

Case Study

She does very well for the next 18 months but once again develops shortness of breath with minimal exertion and is found to have developed atrial fibrillation, basilar lung crackles and ankle edema.

Her treatment is altered to include digoxin and larger doses of furosemide. Small doses of diltiazem are later added to improve heart rate control and improved blood pressure control.

Identify the drugs being used?

What do the symptoms indicate?

Congestive Heart Failure

Case Study

She does very well for the next 18 months but once again develops shortness of breath with minimal exertion and is found to have developed atrial fibrillation, basilar lung crackles and ankle edema.

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Identify the Drugs:
Digoxin (improves contractility) & Diltiazem (Ca channel blocker)

What do the symptoms indicate:
Further deterioration of Heart Failure

Overview of Lecture Series

1. Cardiovascular System

Bits 'N' Pieces
Blood, Heart, Blood-Vessels

Keeping It Under Control
Heart Rate, Blood Pressure

When Things Go Wrong
Hypertension, Heart Failure, Arrhythmias

2. Hypertension

Aetiology Diagnosis

Treatment
Sympathoplegic Drugs, Diuretics, Vasodilators, Angiotensin Antagonists

3. Myocardial Ischemia

Aetiology Diagnosis

Treatment
Symptomatic: Nitrites, Calcium Channel Blockers, β-Blockers

Prophylactic: Lipid lowering, Anti-coagulant, Anti-platelet drugs

4. Heart Failure & Cardiac Arrhythmias

Aetiology Diagnosis

Treatment
Heart Failure: Nitrites, Calcium Channel Blockers, Diuretics, Angiotensin Antagonists, β-Blockers, b-Receptor Agonist, Cardiac Glycosides

Arrhythmias: Channel Blockers (Groups I – IV), Miscellaneous