Drugs Used In Treatment of Heart Failure

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Reference

Basic & Clinical Pharmacology

BG Katzung, SB Masters, AJ Trevor

McGraw Hill LANGE

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Heart Failure

- Occurs when cardiac output is inadequate to provide O_2 needed by the body.
- 5-yr mortality rate ~ 50%
- Most common cause is coronary artery disease, and hypertension.

Heart Failure

Types:

1. **Systolic failure: Reduced mechanical pumping, contractility and ejection fraction.**
2. **Diastolic failure: Stiffening and loss of adequate relaxation → reduction of filling and cardiac output. Ejection fraction may be normal, even though stroke volume is significantly reduced.**

Heart Failure

Factors involved:

1. Defects in excitation-contraction coupling machinery of the heart. This is believed to be the primary defect.
2. Baroreceptor reflex.
3. Sympathetic nervous system.
4. Kidney.
5. Renin-angiotensin-aldosterone system and other peptides.
6. Death of myocytes (apoptosis).

Heart Failure

- **Clinical research has shown that therapy directed at non-cardiac targets may be more valuable for the long-term treatment of HF than traditional positive inotropic agents (cardiac glycosides, digitalis). (Prolong survival and reduce mortality).**

Heart Failure

- **ACE inhibitors, ARBs, certain β blockers, aldosterone receptor antagonists, and combined hydralazine-nitrate therapy are the only agents in current use that prolong life in patients with chronic heart failure (both systolic and diastolic failure).**
- **Positive inotropic drugs are helpful mainly in acute systolic failure. Cardiac glycosides also reduce symptoms in chronic systolic heart failure.**

Pathophysiology of Heart Failure

- **Heart failure is a syndrome of different causes.**
- **It can involve the right ventricle, left ventricle or both.**
- **Cardiac output usually below normal.**
- **Systolic dysfunction associated with low cardiac output, low ejection fraction (< 45%; normal > 60%) is typical of acute failure (MI).**

Pathophysiology of Heart Failure

- **Diastolic dysfunction often occurs as a result of hypertrophy and stiffening of the myocardium. Cardiac output is low, but ejection fraction may be normal. This type of heart failure does not usually respond well to positive inotropes.**

Pathophysiology of Heart Failure

"High output" failure also occurs:

- **The demands are so great that even increased cardiac output is insufficient.**

1. **Hyperthyroidism**
2. **Anemia**
3. **Beriberi (vitamin B_1) deficiency**
4. **AV-shunts**

- **Responds poorly to drugs and should be treated by correcting the underlying cause.**

Pathophysiology of Heart Failure

Signs and symptoms of all Types of HF:

1. **Tachycardia.**
2. **Shortness of breath.**
3. **Decreased exercise tolerance.**
4. **Cardiomegally.**
5. **Peripheral and/or pulmonary edema**
6. **Rapid muscular fatigue**

Pathophysiology of Heart Failure

Compensatory Mechanism:

I. Neurohumoral (extrinsic) compensation:

1. The sympathetic nervous system:

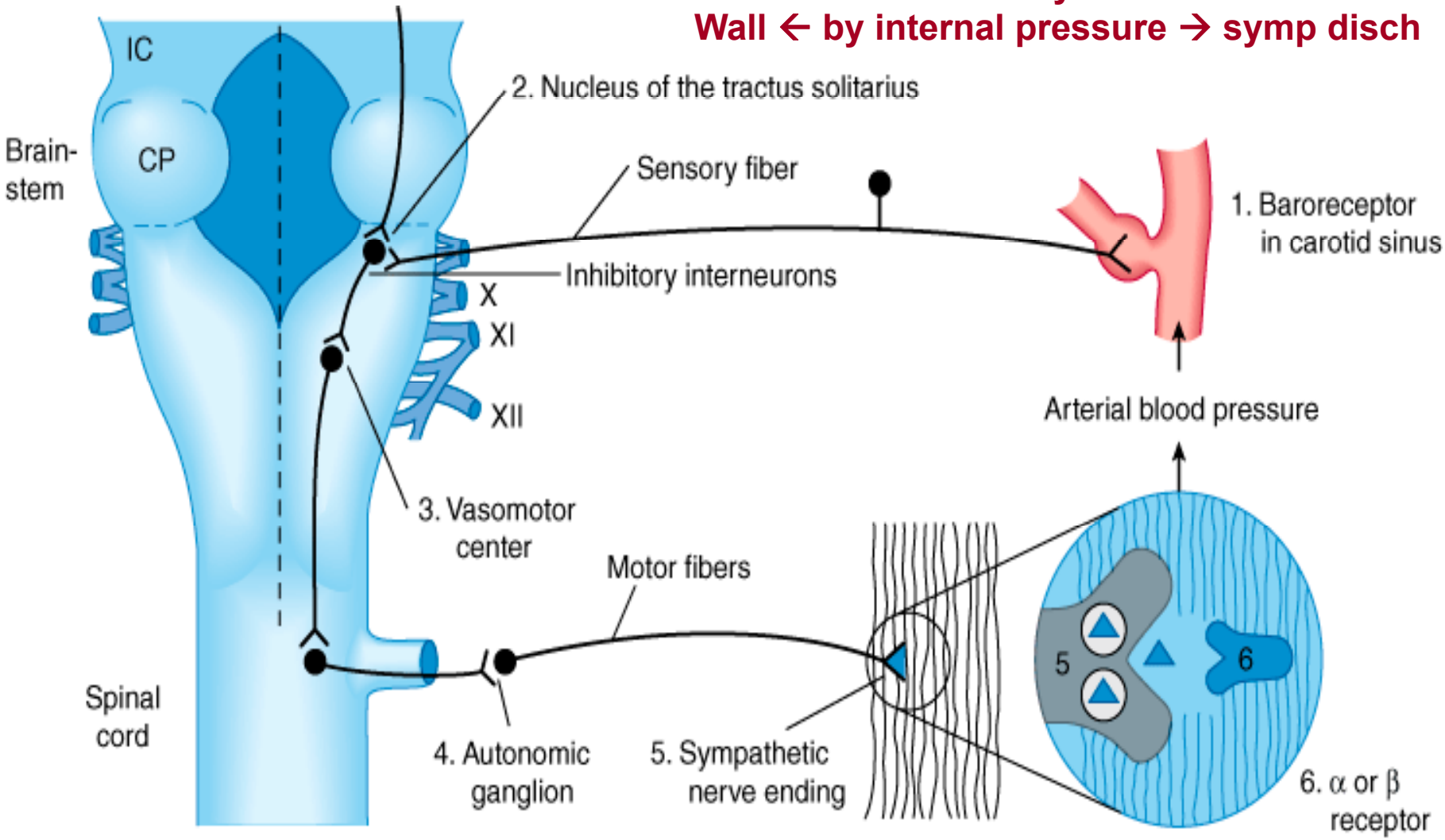
The baroreceptor reflex appears to be reset with a lower sensitivity to arterial pressure in patients with heart failure→ reduced sensory input to the vasomotor center even at normal pressure →

Pathophysiology of Heart Failure

→ **increased sympathetic and reduced parasympathetic outflow → tachycardia, increased cardiac contractility and increased vascular tone.**

- **Initially this is beneficial, it increases cardiac output and renal perfusion.**
- **After a short time, down regulation of β_1-adrenoceptor – G protein effecter system → reduced stimulatory effect.**

BRs are stimulated by stretch of the vessel Wall ← by internal pressure → symp disch



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Baroreceptor reflex arc

Pathophysiology of Heart Failure

2. Increased angiotensin II production:

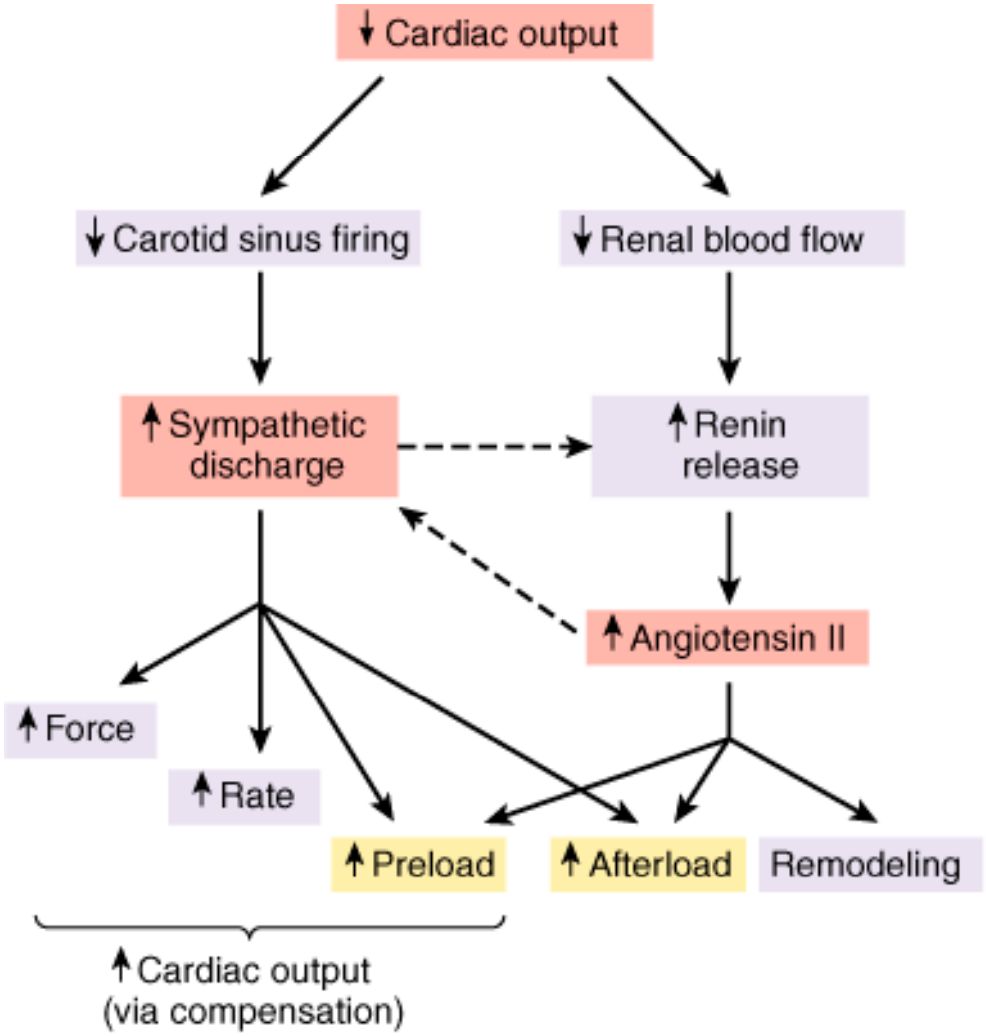
a. vasoconstriction and increased after load.

b. sodium and water retention and increased preload.

c. remodeling of both the heart and the vessels.

3. ANP, ADH, and endothelin production.

Pathophysiology of Heart Failure



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Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, sympathetic discharge facilitates renin release, and angiotensin II increases norepinephrine release by sympathetic nerve endings (*dashed arrows*).

Pathophysiology of Heart Failure

II. Intrinsic compensatory mechanisms:

1. **Myocardial hypertrophy** improves cardiac performance initially. Later on, it can lead to ischemia, impairment of diastolic filling and changes ventricular geometry.

Pathophysiology of Heart Failure

2. **Remodeling** is a term applied to dilation of the heart (other than passive stretch) and the slow structural changes that occur in stressed myocardium:

   a. Proliferation of connective tissue cells.

   b. Abnormal myocardial cells with some biochemical characteristics of fetal myocytes.. myocytes die at an accelerated rate through apoptosis, leaving the remaining myocytes subject to even greater stress.

Pathophysiology of Cardiac Performance

1. **Preload:**

- **Preloads > 20-25 mmHg (because of ↑ blood volume, ↑ venous tone) → pulmonary congestion.**
- **Reduced by salt restriction, diuretics & venodilators.**

2. **Afterload:**

- **The resistance against which the heart pumps.**

Pathophysiology of Cardiac Performance

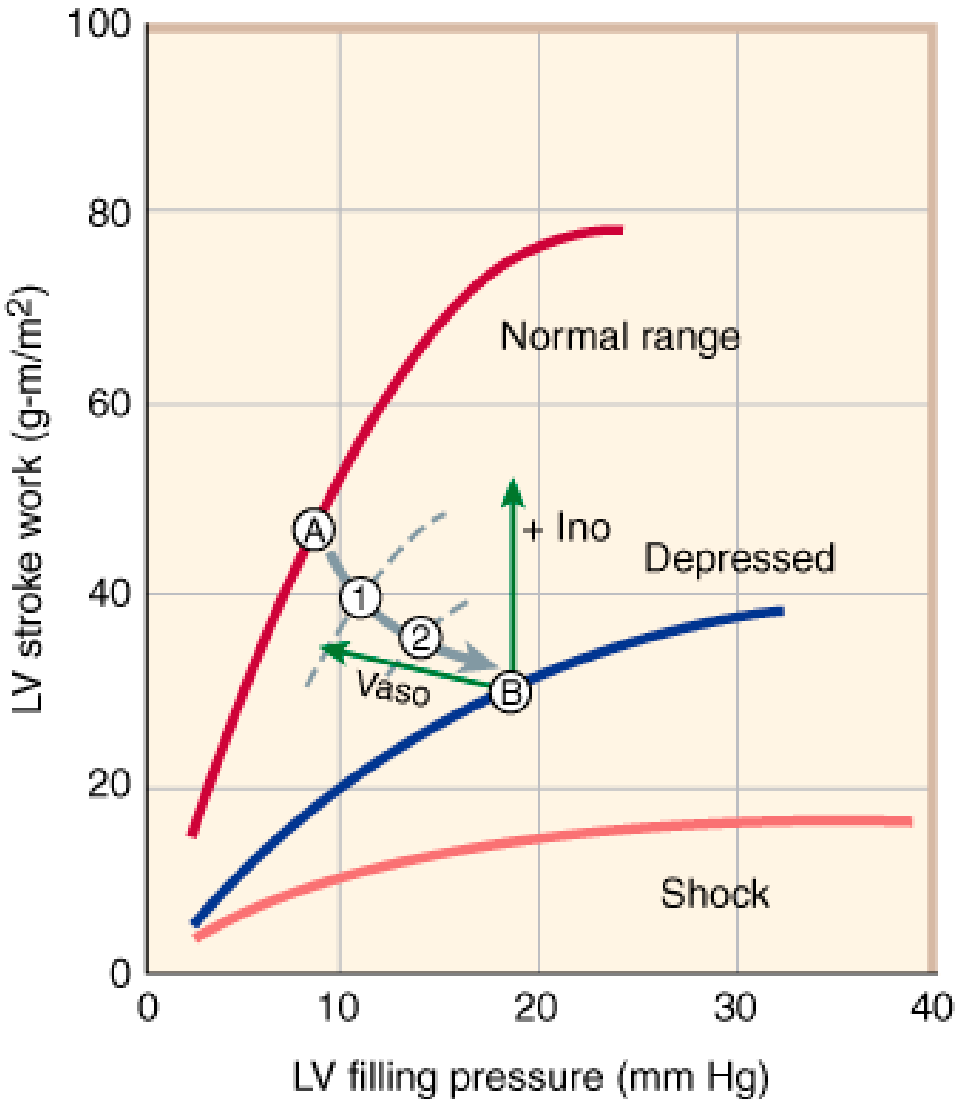
- It is represented by aortic impedance and systemic vascular resistance.
- In chronic failure, as cardiac output declines, systemic resistance increases as a result of sympathetic stimulation and activation of renin-angiotensin-aldosterone system & endothelin.
- Reduced by arterial dilators.

Pathophysiology of Cardiac Performance

3. **Contractility:**

- **Intrinsic contractility is reduced in chronic heart failure (low output) → decreased velocity of muscle shortening and rate of intraventricular pressure development and stroke output.**
- **Heart is still capable of responding to positive inotropes.**

Left ventricular Function Curve



Relation of left ventricular (LV) performance to filling pressure in patients with acute myocardial infarction, an important cause of heart failure. The upper line indicates the range for normal, healthy individuals. At a given level of exercise, the heart operates at a stable point, eg, point A. In heart failure, function is shifted down and to the right, through points 1 and 2, finally reaching point B. A "pure" positive inotropic drug (+Ino) would move the operating point upward by increasing cardiac stroke work. A vasodilator (Vaso) would move the point leftward by reducing filling pressure. Successful therapy usually results in both effects.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th Edition: http://www.accessmedicine.com

Pathophysiology of Cardiac Performance

4. **Heart rate:**

- **Major determinant of cardiac output**
- **Increase as a compensatory mechanism to reduced cardiac output (β_1)**
- **First mechanism that comes into play to maintain cardiac output.**

Diuretics

- They reduce salt and water retention, edema, and symptoms.
- Reduce venous pressure and ventricular preload.
- Reduction of heart size → improve pump efficiency (major importance in systolic failure).

Loop diuretics (furosemide) are the drugs of choice in congestive heart failure.

Diuretics

Spironolactone (and eplerenone):

1. Is an aldosterone antagonist, prevents sodium and water retention.
2. Decreases morbidity and mortality in patients with severe heart failure.
3. Prevents myocardial and vascular fibrosis and barorecepyor dysfunction induced by aldosterone.

ACEIs and Angiotensin Receptor Blockers

1. Reduce resistance – afterload
2. Reduce sodium and water retention – preload
3. Reduce tissue angiotensin levels (or actions):

   A. Reduce sympathetic activity probably by reduction of angiotensin's presynaptic effects on norepinephrine release

ACEIs and Angiotensin Receptor Blockers

B. Reduce long-term remodeling of the heart and blood vessels → reduction of morbidity and mortality.

- **ACEIs (& ARBs), and diuretics are first line therapy for chronic heart failure**

Vasodilators

- **Vasodilators are effective in acute heart failure because they reduce preload (venodilation), and afterload (arteriolar dilation), or both.**
- **Long-term use of hydralazine and isosorbide dinitrate can also reduce damaging remodeling of the heart.**

β-Adrenoceptor Blockers

- **These drugs can precipitate acute cardiac decompensation – dangerous.**
- **Most patients with chronic heart failure respond favorably to certain β-blockers:**

  Carvedilol, Bisoprolol, Metoprolol, Nebivelol.
- **Reduce mortality in patients with severe and stable heart failure.**

β-Adrenoceptor Blockers

Suggested mechanisms:

1. Attenuation of the adverse effects of high concentrations of catecholamines (including apoptosis).
2. Up-regulation of β-receptors.
3. Reduction of excessive heart rate.
4. Reduction of remodeling through inhibition of the mitogenic activity of catecholamines.

β-Adrenoceptor Blockers

- **Must be administered very cautiously and at low doses.**
- **Several months of therapy may be required before improvement is noted in the form of slight elevation of ejection fraction, slower heart rate and reduction in symptoms.**

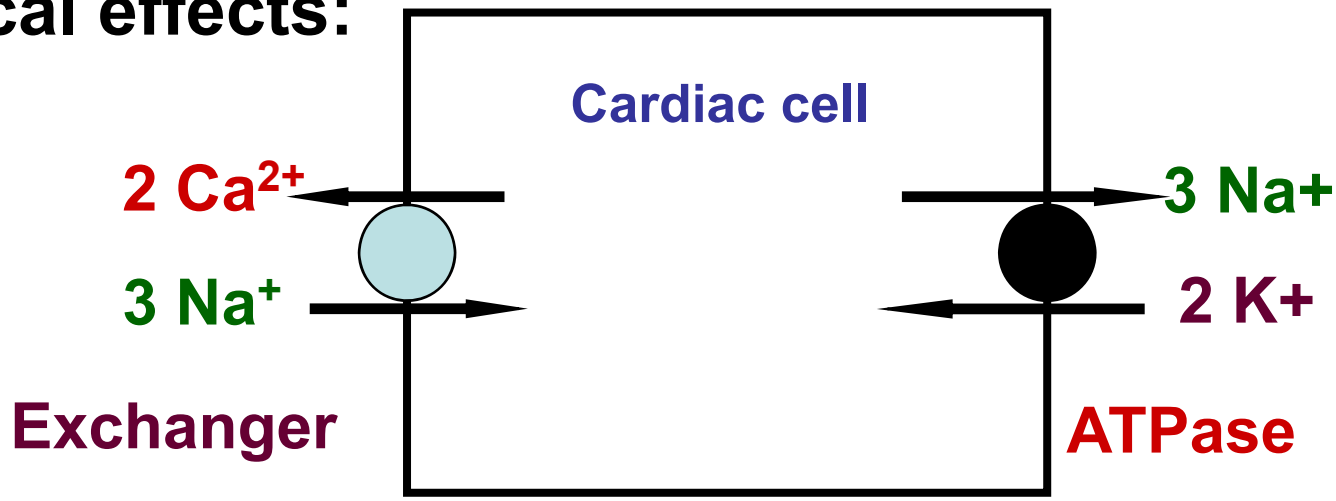
Cardiac Glycosides (Digitalis)

- Come from a plant – foxglove.
- Active ingredients: digoxin & digitoxin, which belong to the cardiac glycosides.
- Chemically composed of a steroid nucleus, linked to a lactone ring and a series of sugars.
- Not the first drug, and never the only drug used in treatment of heart failure.

Digitalis

Pharmacodynamics:

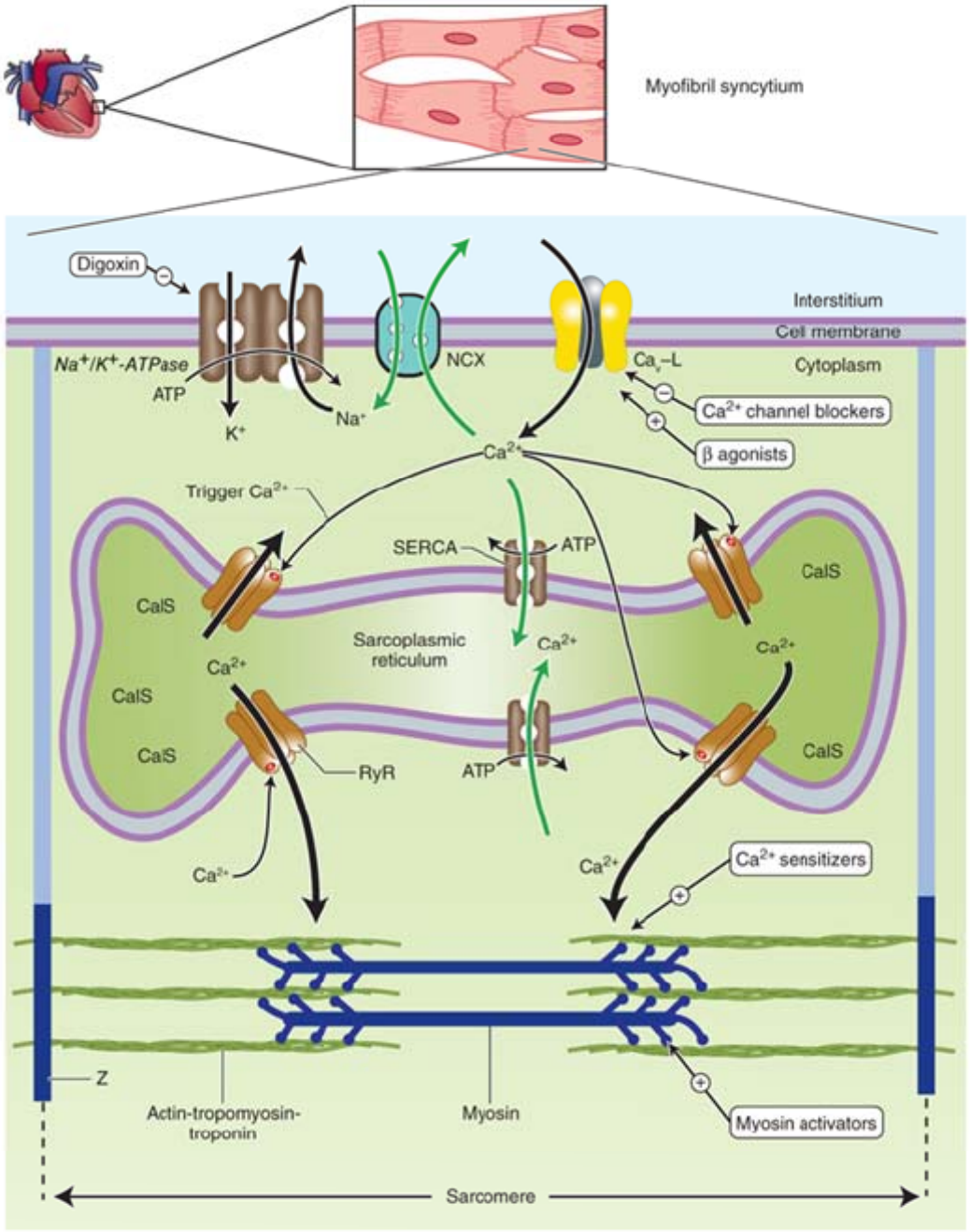
1. **Mechanical effects:**



Digitalis glycosides inhibit the Na^+, K^+-ATPase

Digitalis

- ***Additional functions of Na^+/K^+-ATPase have been postulated, involving apoptosis, cell growth, and differentiation, immunity, and carbohydrate metabolism.***



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

FIGURE 13–1

Schematic diagram of a cardiac muscle sarcomere, with sites of action of several drugs that alter contractility. Na^+/K^+-ATPase, the sodium pump, is the site of action of cardiac glycosides. NCX is the sodium-calcium exchanger. Ca_V-L is the voltage-gated, L-type calcium channel. SERCA (sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase) is a calcium transporter ATPase that pumps calcium into the sarcoplasmic reticulum. CalS is calcium bound to calsequestrin, a high-capacity Ca^{2+}-binding protein. RyR (ryanodine RyR2 receptor) is a calcium-activated calcium channel in the membrane of the SR that is triggered to release stored calcium. Z is the Z-line, which delimits the sarcomere. Calcium sensitizers act at the actin-troponin-tropomyosin complex where activator calcium brings about the contractile interaction of actin and myosin. Black arrows represent processes that initiate contraction or support basal tone. Green arrows represent processes that promote relaxation.

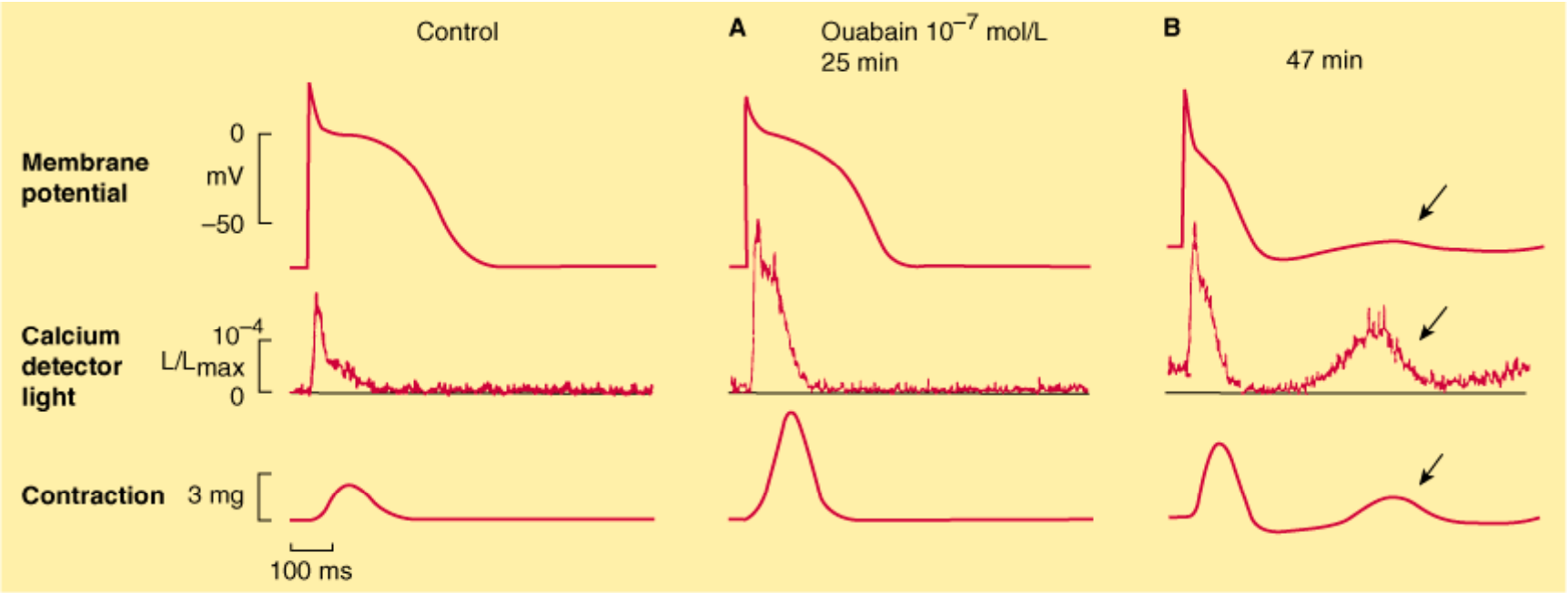
(Ryanodine is a potent negative inotropic plant alkaloid that interferes with the release of calcium through cardiac SR channels.)

Digitalis

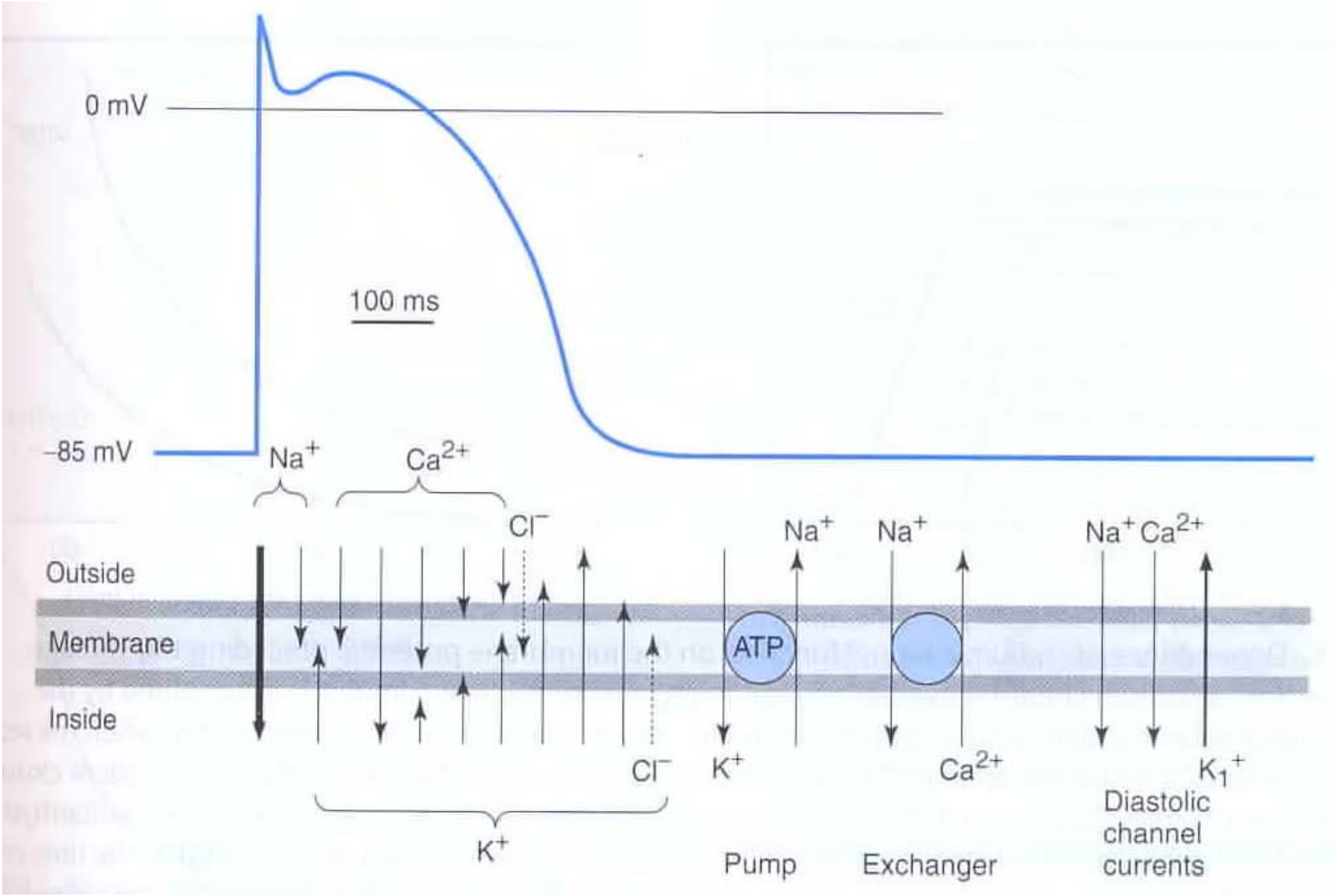
- **Inhibition of Na^+, K^+-ATPase increases intracellular Na^+ → reduction in calcium expulsion from the cell through**

  Na^+, Ca^{2+}-exchanger → increase in intracellular Ca^{2+} → Increased cardiac contractility.

  [↑Na^+, ↑Ca^{2+}, ↓K^+ inside cardiac cells]



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, Lmax) and is roughly proportional 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*).


0 mV
100 ms
-85 mV
Na+
Ca2+
Cl−
Na+
Na+
Na+ Ca2+
Outside
Membrane
Inside
ATP
Cl−
K+
Ca2+
K1+
K+
Pump
Exchanger
Diastolic channel currents

Digitalis

2. **Electrical effects:**

A. Direct actions:

- **An early, brief prolongation of action potential (AP) followed by shortening (especially the plateau).**
- **Shortening of AP duration is probably due to increased K^+ conductance that is caused by increased intracellular Ca^{2+}.**

Digitalis

→ → **Shortening of atrial and ventricular refractoriness.**

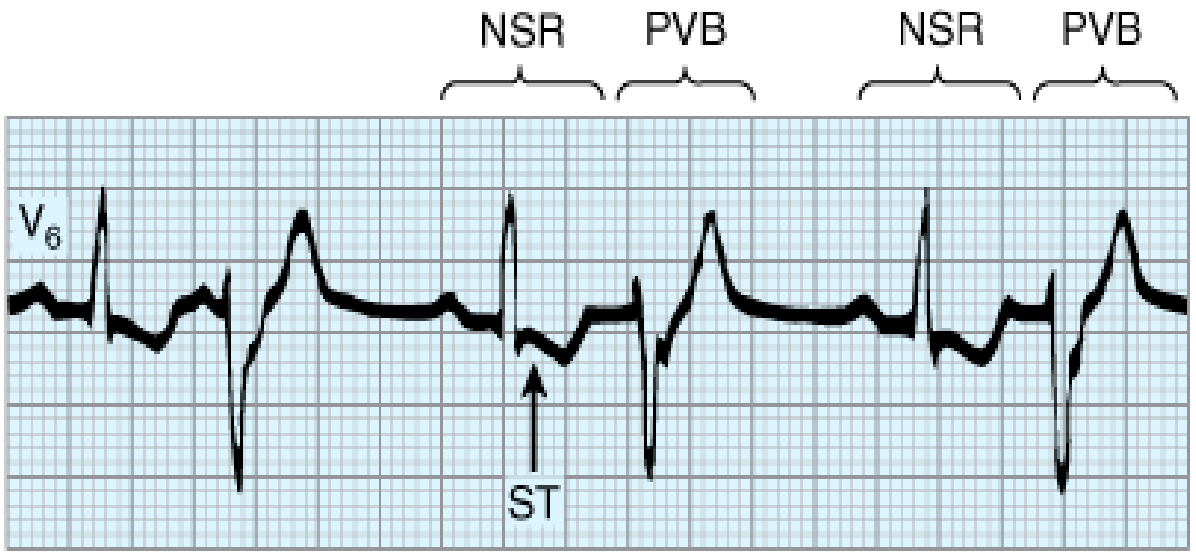
- **At higher concentrations, resting membrane potential is reduced (less negative) as a result of inhibition of the sodium pump and reduced intracellular K^+.**

Digitalis

- As toxicity progresses, oscillatory depolarizing after potentials (delayed after-depolarizations, DADs) following normal action potentials start to appear.
- These are associated with overloading of the intracellular calcium stores and oscillations in the free intracellular calcium ion concentration.

Digitalis

- **When afterpotentials reach threshold, they elicit action potentials (premature depolarizations, ectopic “beats”) that are coupled to the preceding normal action potentials. → → bigeminy, sustained tachycardia and ventricular fibrillation, which could be fatal.**



Electrocardiographic record showing digitalis-induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats and are the electrocardiographic manifestations of depolarizations evoked by delayed oscillatory afterpotentials

TABLE 13–2 **Effects of digoxin on electrical properties of cardiac tissues.**

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, ↓ QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

Digitalis

B. Autonomic actions:

1. **At low dose therapeutic doses, cardioselective parasympathomimetic effects predominate – blocked by atropine.**

- **It involves: sensitization of baroreceptors, central vagal stimulation, and facilitation of muscarinic transmission at cardiac muscle cells.**

Digitalis

- These effects occur more on atrial and AV nodal function than Purkinje or ventricular function. (cholinergic innervation is much more in the atria).

2. At toxic levels, sympathetic outflow is increased which sensitizes the myocardium and exaggerates all the toxic effects of the drug.

Digitalis

- ***The most common cardiac manifestations of digitalis toxicity include atrioventricular junctional rhythm, premature ventricular depolarizations, bigeminal rhythm, ventricular tachycardia, and second-degree atrio-ventricular blockade.***
- ***It is claimed that digitalis can cause virtually any arrhythmia.***

Digitalis

3. **Effects on other organs:**

- **They affect all excitable tissue**

A. **GIT: most common site of toxicity outside the heart, both directly and through the CNS (CRT-Z) → anorexia, nausea, vomiting, diarrhea, abdominal discomfort.**

Digitalis

B. CNS effects include vagal and chemoreceptor trigger zone stimulation: disorientation, hallucination and visual disturbances (including color perception), agitation & convulsions.

C. Gynecomastia: in men, rare (steroid structure).

Digitalis

Interaction with Electrolytes:

A. K^+:

1. **They inhibit each other's binding to Na^+, K^+- ATPase. Therefore, hyperkalemia reduces the action of digitalis, while hypokalemia facilitates action → toxicity.**
2. **Abnormal cardiac automaticity is inhibited by hyperkalemia. Moderately increased serum K^+ reduces the toxic effects of digitalis.**

Digitalis

B. Ca^{2+}:

It facilitates toxic actions by accelerating overloading of intracellular Ca^{2+} → abnormal automaticity .

- **Hypercalcemia increases the risk of digitalis-induced arrhythmias.**

C. Mg^{2+}:

Effect is opposite to that of calcium.

- **Hypomagnesemia increases digitalis toxicity.**

Digitalis

Pharmacokinetics:

- Digoxin is 2/3rds excreted unchanged by the kidney (Its CL ~ CLcr).
- Digitoxin is metabolized in the liver, secreted in gut as metabolites (digoxin is one), undergoes enterohepatic recirculation (long t½).
- 10% of individuals harber enteric bacteria capable of inactivating digoxin → reduced bioavailability. Antibiotics produce sharp increase in BA and toxicity of digoxin in these individuals.

	Digoxin	Digitoxin
Lipid solubility	Medium	High
Bioavailibility	65-80%	> 95%
Half-life (hours)	36-40	168
Plasma protein binding(%)	20-40	>90
% metabolized	< 40	> 80
Vd (L/Kg)	6.3	0.6

Digitalis

Therapeutic Uses:

1. **Heart failure:**

- **Most helpful in patients with dilated hearts.**
- **Usually given after ACEIs.**
- **~ 50% of patients respond.**
- **Better results are obtained if patients have atrial fibrillation in addition to heart failure.**

Digitalis

2. **Atrial fibrillation: to reduce ventricular rate (parasympathetic effect).**

- **Therapeutic range 0.8-2 ng/mL (~1). Toxicity appears above 1.5 ng/mL (low therapeutic index). AF may require higher concentrations.**
- **Do NOT Improve Mortality.**

Digitalis

Interactions:

1. **Hypokalemia.**
2. **Hypercalcemia.**
3. **Hypomagnesemia.**
4. **Antibiotics.**

- **All increase toxicity. Is that right?**

Digitalis

5. Quinidine displaces digoxin from tissue binding sites and decreases its clearance → enhances toxicity.
6. Agents which release catecholamines sensitize the myocardium to digitalis-induced arrhythmias

Digitalis

Contraindications:

- **Avoid in arrhythmia associated with Wolff-Parkinson-White syndrome because it increases the probability of conduction through the alternative rapidly conducting AV pathway, especially that associated with atrial fibrillation.**

Digitalis

Management of digitalis toxicity:

- **Stop digitalis administration.**
- **ECG monitoring.**
- **Measure serum levels.**
- **Measure electrolytes and correct electrolyte imbalance.**
- **Antiarrhythmic drugs: lidocaine or phenytoin.**
- **Digitalis antibodies (digoxin-induced fab).**

Digitalis

- **<u>Notice:</u> Digitalis- induced arrhythmias, except ventricular fibrillation, are made worse by electrical cardioversion.**

- **Cardiac glycosides have an extremely narrow therapeutic index and may not decrease mortality in chronic heart failure.**

Other Positive Inotropes

- **Safer (than digitalis) positive inotropic agents are required.**

1. **Bipyridines: Milrinone**
2. **β_1-Adrenoceptor agonists: Dobutamine**

Milrinone

- **Inhibits phosphodiesterase isozyme 3 which results in an increase in cAMP and increase in contractility and vasodilation.**
- **Increase myocardial contractility by increasing inward calcium flux in the heart during the action potential.**
- **May also affect sarcoplasmic reticulum calcium movement.**

Milrinone

- **Elimination half-life of 3–6 hours, 10-40% excreted in urine.**
- **Toxicity includes nausea and vomiting; arrhythmias.**
- **Used only intravenously and only for acute heart failure or severe exacerbation of chronic heart failure.**

Dobutamine

- Selective β_1-Adrenergic agonist.
- Increases cardiac output with a decrease in ventricular filling pressure.
- More inotropic than chronotropic action.
- May produce tachycardia and increased O_2 requirement →angina and arrhythmias.

Dobutamine

- **Tachyphylaxis (tolerance) occurs, and thus, intermittent infusion may benefit some patients with chronic heart failure.**
- **Dopamine (D >> β >> α) may be used in acute heart failure when there is a need to increase blood pressure.**