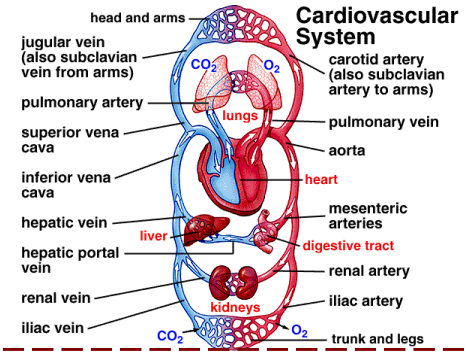
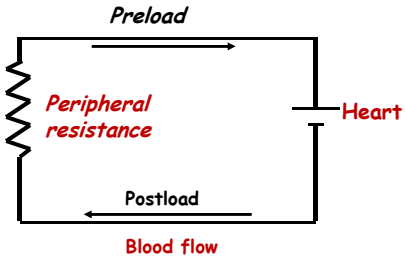
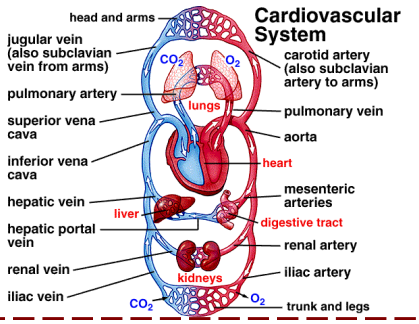
II. Cardiac glycosides

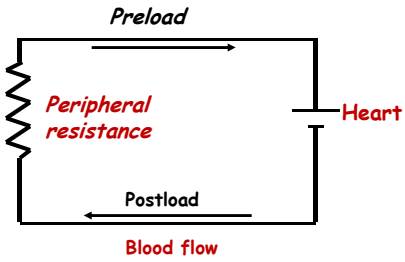
A. Review of congestive heart failure (CHF)





Case study (Foye's) "BD is a 67 year-old man who was admitted with a complaint of shortness of breath that has increased over the last few months. He also indicated that he has recently gained more than 12 pounds without changing his eating or exercise habits and that he often has trouble breathing when climbing stairs at home. Physical examination reveals that he has systemic edema, hepatomegaly, neck vein distension, weakness, fatigue, rales, and cyanosis"





Summary

Contractility of heart

The heart's ability to pump blood effectively to meet the needs

Cardiac output

Blood volume of heart

Systemic blood pressure

Renal blood flow

Edema (where?)

Renal failure?

How to treat it?

B. Classification of positive inotropic agents

a. Glycosidic inotropic drugs

b. Nonglycosidic inotropic drugs

- Phosphodiesterase III inhibitors
- β-adrenergic receptor agonists

C. Therapeutic effects of positive inotropic agents

Enhance cardiac contractility

Table 26.2. (Foye's Textbook) Effects of cardiac glycosides

	Atrium	Ventricle	AV Fiber	SA Node	Node
Contractility	↑	↑	—	—	—
Excitability	0	Variable	↑	—	—
Conductivity	↑	↑	↓	↓	—
Refractory period	↓	↓	↑	↑	—
Automaticity	—	—	↑	—	↓

AV, atrioventricular; SA, sinoatrial; ↑ increased action; ↓ decreased action; 0, no action; —, no data available.

D. Glycosidic positive ionotropic drugs

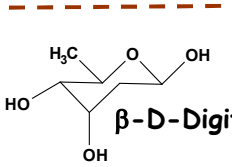
(a). General considerations

- Natural products
- Cardiac conductivity/contractility enhancement
- Decrease of refractory period
- Narrow safety margin
- Wide individual variation in dose required

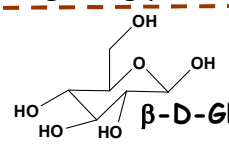
(b). Major structural features of the cardiac glycosides

Cardiac glycosides = sugar moiety + nonsugar (aglycone) moiety

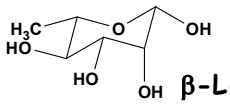
Sugars



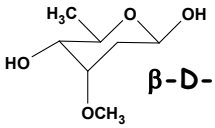
β-D-Digitoxose



β-D-Glucose



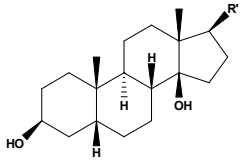
β-L-Rhamnose



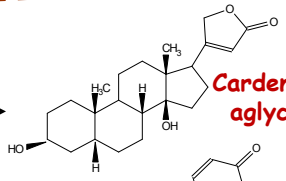
β-D-Cymarose

Aglycones

17-lactone

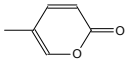


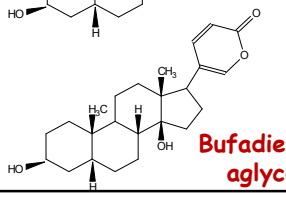
When R'=



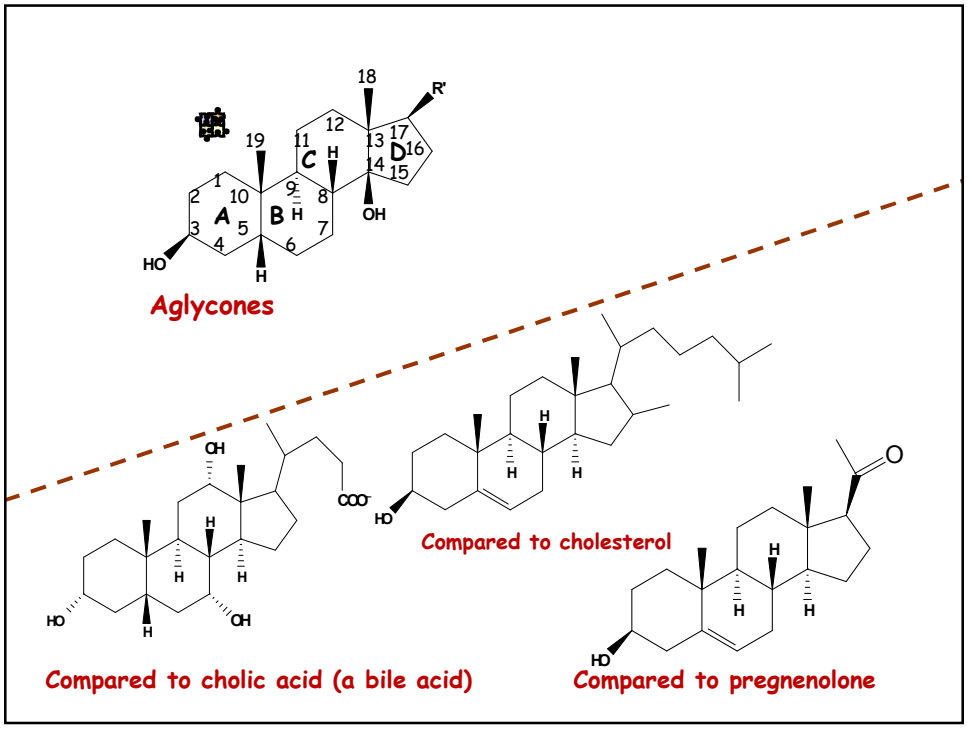
Cardenolide aglycone

When R'=





Bufadienolide aglycone

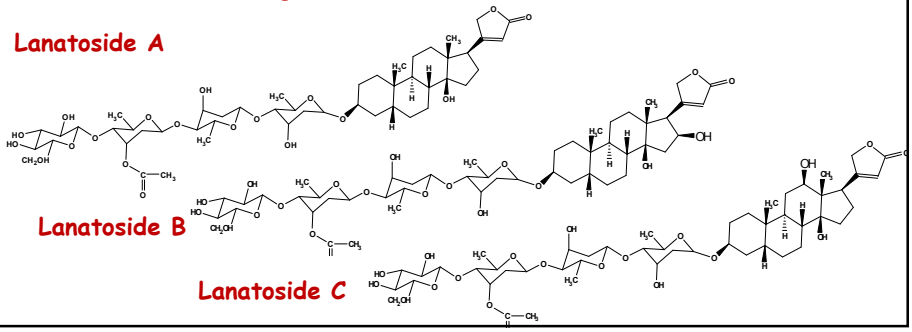


(c) Major cardiac glycosides

Glycosides extracted from the plant and *Digitalis lanata* (foxglove plant)

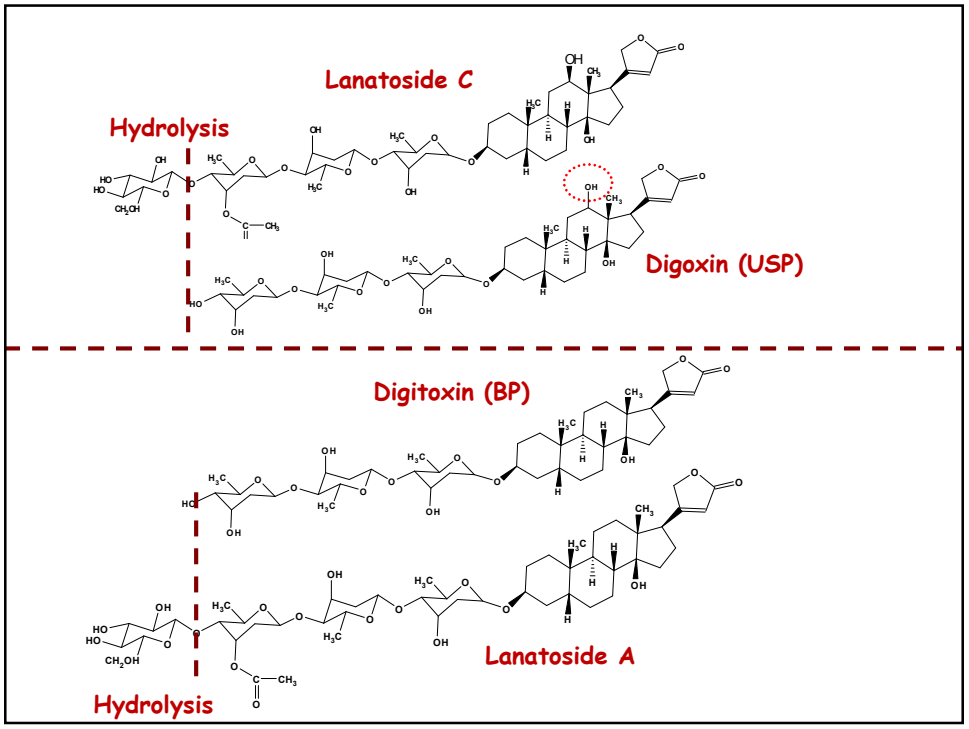
Natural Product	Glycoside	Aglycone	Sugar
 Digitalis lanata, foxglove (leaf)	Lanatoside A (digilanide A)	Digitoxigenin	Glucose-3-acetyldigitoxose-digitoxose-digitoxose
	Lanatoside B (digilanide B)	Gitoxigenin	
	Lanatoside C (digilanide C)	Digoxigenin	

Lanatoside A



Lanatoside B

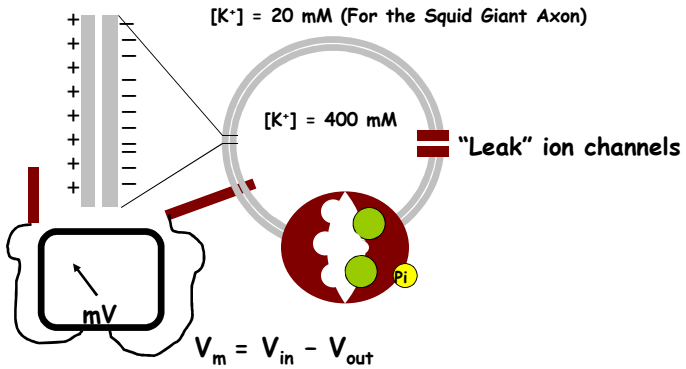
Lanatoside C



(d). Mechanism of action of cardiac glycosides

Inhibition of Na^+/K^+-ATPase pump-Side effect related

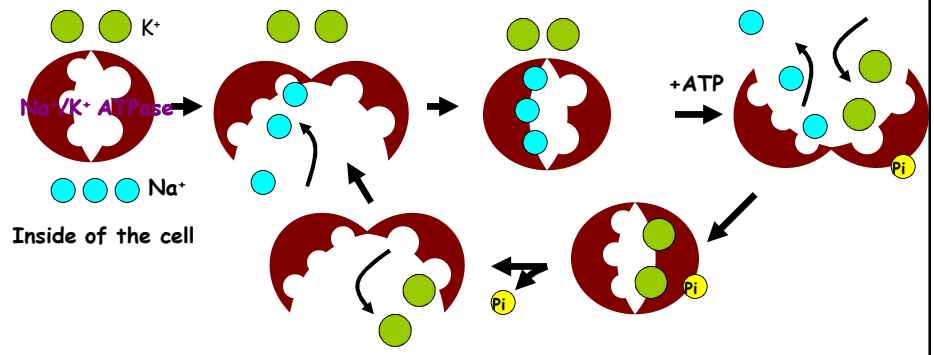
The movement of cations across the membrane results in non-zero membrane potential, because of there are "leak" ion channels on the cell membrane.



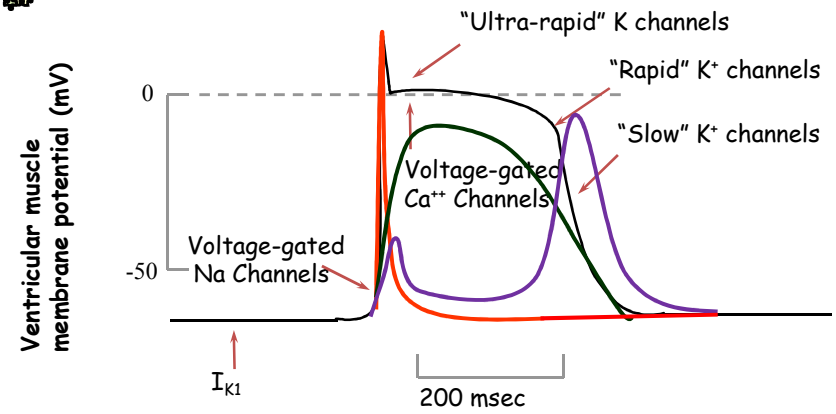
Na⁺-K⁺-ATPase is a(n)_____
a. Ion channel?
b. Receptor?
c. Enzyme?
d. All of the above?

Na+-K+ ATPase

The passive fluxes of Na+ and K+ through non-gated ion channels are balanced by active pumping by Na+-K+ ATPase (primarily)



Ion channels and membrane potential on the myocardiac membrane

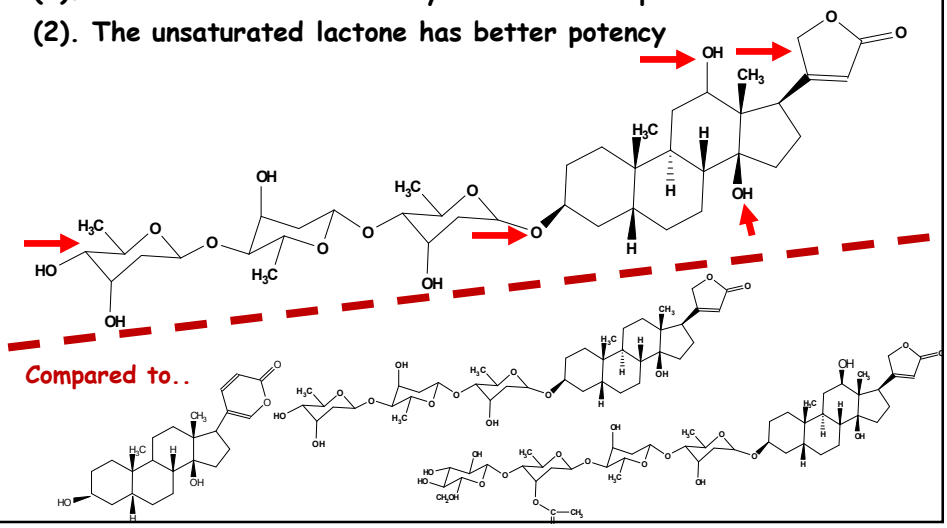


Na++ and Ca++ channels are responsible for the depolarization. K+ channels are responsible for the repolarization

(e). Structure, activity and pharmaceutical properties

(1). All structures indicated by arrows are dispensable

(2). The unsaturated lactone has better potency



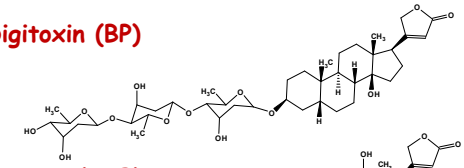
Compared to..

(3). Effect of glycoside structure on partition coefficient

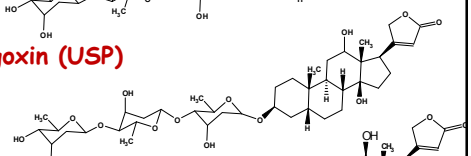
Drugs	Partition coefficient (CHCl3/16% aq.MeOH)	Dosage form
Digitaxin (BP)	96.5	Tablets, injection
Digoxin(USP and BP)	81.5	Tablets, elixir, pediatric
Lanatoside C (BP)	16.2	Tablets

- More lipid solubility
  - Faster absorption
  - Longer duration
- Partition coefficients
  - Lipid solubility

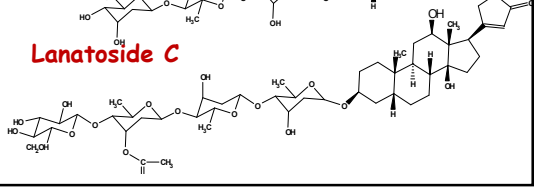
Digitoxin (BP)



Digoxin (USP)



Lanatoside C



Summary and comparison

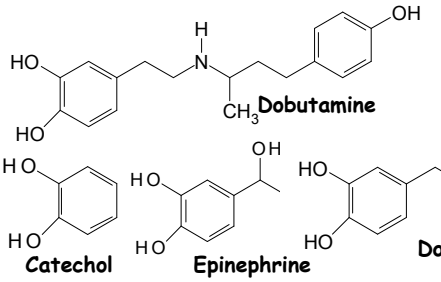
	Digoxin(USP and BP)	Digitaxin (BP)
Gastrointestinal absorption	70-85%	95-100%
Average half life	1-2 days	5-7 days
Protein binding	25-30%	90-95%
Enterohepatic cycling	5%	25%
Excretion	Kidneys; largely unchanged	Hepatic metabolism
Therapeutic plasma level	0.5-2.5 ng/ml	20-35 ng/ml
Digitalizing dose (mg)	Oral:0.75-1.5; IV: 0.5-1.0	Oral:0.8-1.2; IV: 0.8-1.2
Maintenance dose (mg)	0.125-0.5	0.05-0.2

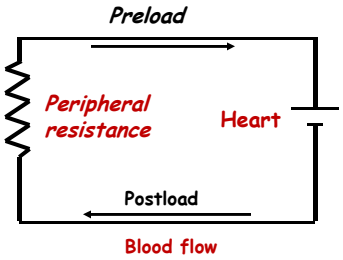
(f). Drug-drug interactions of cardiac glycosides

- Quinidine
  Compete P-gp efflux pumps with cardiac glycosides
- Thiazide interaction
  Hypokalotion-low [K+]
  Na-K transport

E. Nonglycosidic positive ionotropic drugs

1. β-adrenergic receptor agonists (catecholamine)





Adrenergic receptor subtype	Cardiac effects
α_1	Smooth muscle contraction
α_2	Smooth muscle constriction and neurotransmitter inhibition
β_1	Heart muscle contraction
β_2	Smooth muscle relaxation
β_3	Enhance lipolysis

E. Nonglycosidic positive ionotropic drugs

2. Phosphodiesterase III inhibitors

"Bipyridine"-Inamrinone and milrinone