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CARDIOVASCULAR SYSTEM

Cardiac Tonic – These are the drugs which stimulate the heart.
Eg. Cardiac Glycosides.

Cardiac Glycosides – It represents a family of compound which are derived from, foxglove plant (*digitalis purpurea*).

- William withrin Ist used it to treat dropsy which occur due to heart failure.
- Cardiac glycosides are compounds which consist of sugar part attached with non sugar part (steroid nucleus & lactone ring) with the help of O2 molecule.
  Lactone ring and cyclo pentane perhydro phenanthren ring are aglycone part where as sugar part is the glycone part.

	Source	**Plants**
(1)	Digoxin	D. lanata
(2)	Digitoxin	D. purpurea
(3)	Gitaxin	D. purpurea
(4)	Gilalin	D. purpurea
(5)	Strophanthin K	Strophanthus combe
(6)	Ouabain	S. gratus
(7)	Thevetin	Thevetia herefolia
(8)	Bufotoxin	Bufovulgaris

Structural Effect – Sugar part attached at C3 affect Pharmacokinetics (PK) properties of glycosides like water solubility, self penetrability duration of action etc.
Pharmacodynamics properties like cardiac activity depends on lactone ring and steroid nucleus.

Mode of Action (MOA) – In heart the process of membrane depolarization or repolarization is controlled by Na+, K+ and Ca++ ions. When action potential is generated Na+ enters inside the membrane along with Ca++ (Na+ - Ca++ exchanger) (3 Na+ - 2 Ca++). The higher Intracellular Ca++ conc. Results in efflux of K+, the reestablishment of action potential occur by reverse of Na+ - K+ exchange which require energy provided by an enzyme. Na+ K+ ATPas Cardiac. Glycosides inhibit this enzyme. Which lead to reduce Na+k+ exchange, intracellular Na+ and Ca++ conc. Which further result in ↑ in myocardial contraction or +ve ionotropic effect.

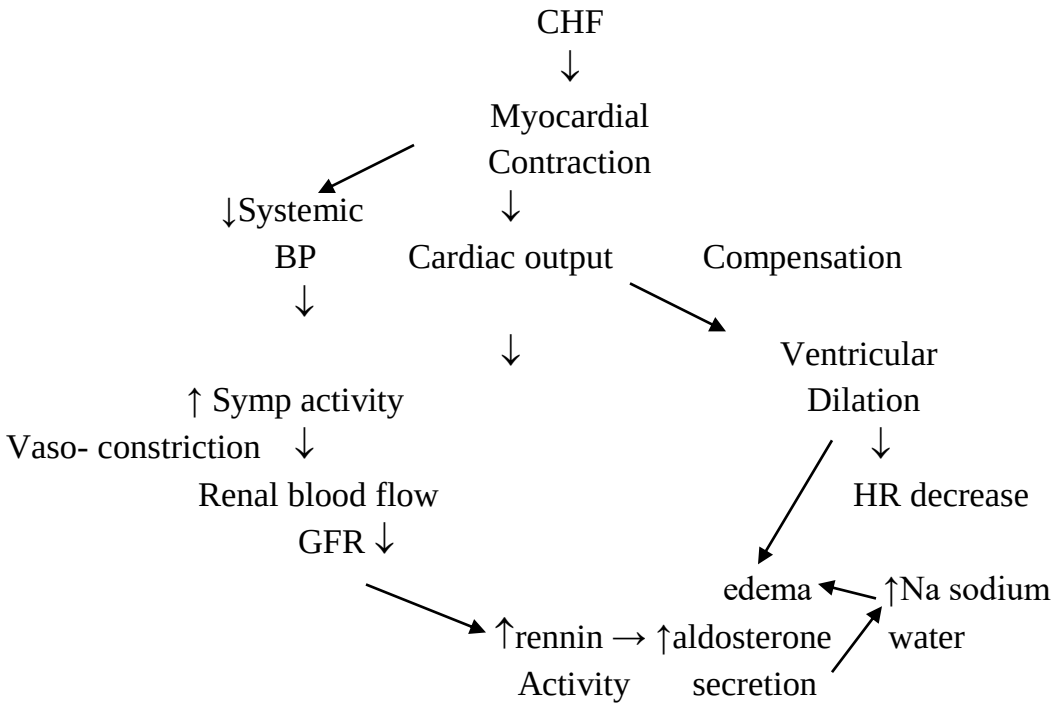
Pharmacological Effect –

(1) On Heart – Cardiac glycosides increase cardiac output myocardial contrac. in failing heart. In normal heart this increase very minimum.

(2) On Autonomic N.S. – Digoxin reduces sym. Over activity of heart & ↑ es vagal activity.

(3) *CNS* – At normal doses effect is minimum but toxic dose may stimulate CTZ resulting in vomiting & mental confusion.

(4) Kidneys – In CHF Congestive heart failure patient due to vasoconstriction renal blood flow ↑ es resulting in ↑se rennin activity, aldosterone secretion and retention of Na+ & water Cardiac glycosides by reducing sympathetic activity reduce rennin & aldosterone secretion along with natriuresis (creation of Na+) and reduce edema.



Pharmacodynamics –

Digitalis have long H. L. (40 hrs.) Narrow TI , low margin of safety. Special dosing regimen are required 4 these agents eliminated by liver & kidney.

Digitalization – It is the process of dosing with digitalis which may be slow or rapid with the objective of attaining a steady stage plasma drug conc. In cardiac patient.

It follows as –

(1) loading dose – it is the dose that is given to load the conc. of drug in bld required to achieve initial response.

(2) Maintenance Dose – It is the dose that is given to maintain conc. of drug in blood.

In Dogs – 0.01 – 0.02 mg/kg oral in 2 divided doses on Ist day.

0.01 – 0.02 mg/kg oral in 2 divided doses given daily for I/V → 0.01 – 0.02 mg/kg.

Drug Interaction –

(1) Quinidine compete with binding site and reduces renal clearance of digitalis.

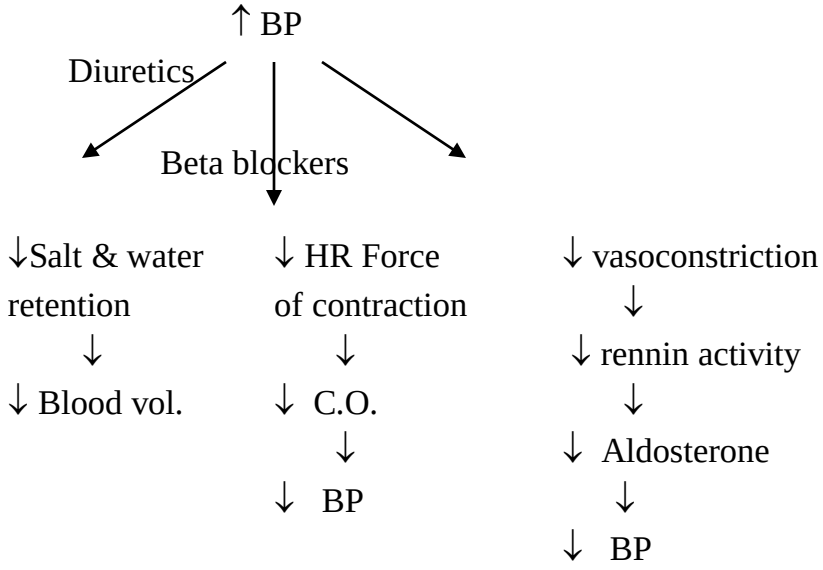
(2) NSAID and B blockers compete with K+ for Na+ K+ pump and ↑ es toxic effect of digitalis.

Therapeutic Use –

(1) CHF

(2) Cardiac arrhythmia (irregular heart beat)

Antihypertensive drug – there are the agents that lower the elevated BP in systemic hypertension.



Classification –

(1) β blockers – Atenolol, Propanolol, These drugs block β receptor of heart producing red in C.O. reduce HR and force of contraction. It also inhibit release of rennin together reducing B.P.

(2) Vasodilators – Ca channel blockers, ACE inhibitors.
These drugs relaxes vascular smooth muscles by red in vasoconstriction, rennin actively resulting in reduce systemic blood pressure.

(3) Spironolactone Thiazides etc. These drugs reduces EcF volume by red in salt & water relention all together reducing systemic B.P.

Antiarryhthmic drugs –

What causes arrhythmias?

A frequent cause of arrhythmia is coronary artery disease because this condition results in myocardial ischemia or infarction. When cardiac cells lack oxygen, they become depolarized, which leads to altered impulse formation and/or altered impulse conduction. The former concerns changes in rhythm that are caused by changes in the automaticity (spontaneous activity) of pacemaker cells or by abnormal generation of action potentials at sites other than the SA node (termed ectopic foci). Altered impulse conduction is usually associated with complete or partial block of electrical conduction within the heart. Altered impulse conduction commonly results in reentry, which can lead to tachyarrhythmias. Changes in cardiac structure that accompany heart failure (e.g., dilated or hypertrophied cardiac chambers), can also precipitate arrhythmias. Finally, many different types of drugs (including antiarrhythmic drugs) as well as electrolyte disturbances (primarily K+ and Ca++) can precipitate arrhythmias.

What are the consequences of arrhythmias?

Arrhythmias can be either benign or more serious in nature depending on the hemodynamic consequence of the arrhythmia and the possibility of evolving into a lethal arrhythmia. Occasional premature ventricular complexes (PVCs), while annoying to a patient, are generally considered benign because they have little hemodynamic effect. Consequently, PVCs if not too frequent, are generally not treated. In contrast, ventricular tachycardia is a serious condition that can lead to heart failure, or evolve into ventricular fibrillation and cause death. (Arrhythmia – Irregular heart beat)

These are the agents or drug to prevent or treat irregularities of cardiac rhythum like alteration of impulse generation abnormal impulse conduction or both of them.

Classification – According to Vaughan, William & singh. These drugs classified it folloues into 4 main classes

Class 1
Class 2
Class 3
Class 4

Class 1 – This group contain Na channel blocker.

Class 1

↓

3 subclasses

↓

↓	↓	↓
Class 1 (a)	Class 1 (b)	Class 1 (c)
Quinidine	Lignocaine	Flecainide
Procainamide	phenytoin	Encainide
Disopyramide	Tocainide	Indicainide
Mexiletine		

Class 2 –
β blocker group – Propanolol, Atenolol, Sotalol etc.

Class 3 –
K+ channel blockers – Bretylium, Amiodarone, sotalol.

Class 4 – Ca++ channel blockers – Nifedipine, Verapamil, diltiazem.

Class 5 – Cardiac Glycosides.

Class 1 Drugs – These drugs interface with Na+ channels, also k/as membrane stabilizing agents because it decrease exciting properly of plasma membrane they bend to only open Na channels and less activity in resting stage of these channels.
Pharmacology – It lengthen action potential, repolarization, refractory period and suppress phase o.
Dose –
Quinidine – 20 mg/kg oral in dogs lignocaine 1- 2 mg/kg I/V ,,

Class 2 drugs – These drugs block β receptors thereby reducing symptom. Activity of heart. It reduces abnormal conduction of impulse through AV node.

Class 3 drugs – These drugs block K channels prolong duraleon of action potential & refractory period. They do not affect Na channel.
Dose –
Bretylium – 5-20 mg/kg IV in dogs.

Class 4 drugs – These drugs are slow Ca channel blockers, reduce contractibility of heart and abnormal impulse conduction through AV node.
Dose –
Verapamine – 1-5 mg/kg oral (Dogs) 3 times daily.

Cardiac glycosides – These drugs reduce conduction of abnormal impulses through, AV node & increse vagal activity of heart.

Vasodilators – These are the drugs that cause relaxation of blood vessels, thereby reduce myocardial work load, ↑ cardiac output, reduce BP and rate of fluid form
Classification –

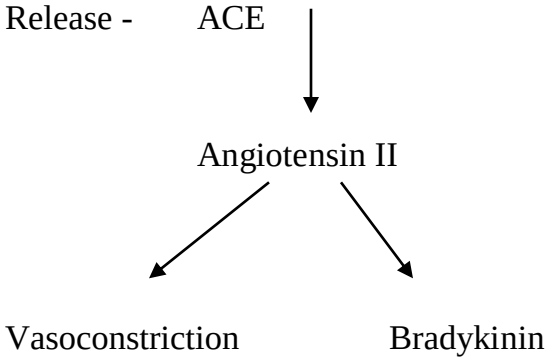
(1) Arterial vasodilators – Eg. Hydralazine, Diazoxide, Minoxidil
Ca channel blocker – verapaimil, Diltiazem, Nifedipine, Amlodipine.
K channel openers- Pinacidil, cromokalim.
(2) Venous Vasodilators – Organicnitrates
(3) Mixed Vasodilators – ACE inhibitors Captopril, ramipril
Angiotensin receptor antagonist – Losartan
Antiadrenergic drugs – Prazosin, doxazosin, phenstolamine.
(4) Miscellaneous drugs – Nicotinic acid, xanthirne, papeverime.

Hydralazine – It cause smooth muscle hyperpolarization by opening of k channels & inhibit release of Ca from SER reducing contraction. It also stimulate nitric oxide formation resulting in vasodilatation.
Use – Hypertension & CHF
Dose – Dog – 0.5 – 2 mg/kg oral.

Ca channel blockers – These drugs bind to L- type Ca channel found on cardiac cells SA node and AV node and vascular smooth muscle. There by blocking entry of Ca++ into the cell resulting in vasodilatation, negative ionotropic effect and reduce conduction velocity.
Use – Hypertension
Dog – 0.05 – 0.25 mg/kg oral.
K channel Openers – These drugs open ATP sensitive K channels in vascular smooth muscle cause hyper polarization which closes Ca channels resulting in vasodilation effect.

Venous Vasodilators –
Organic nitrates – These drugs react with enzyme. Which reduce to No or nitrosothiol which is then reduce to No this No activate guanyl cyclase to form c GMP increse in its concentration. Produce vasodilation effect. ↑ cGMP inhibit Ca entry into the cells and produce vasodilatation effect.
Use – (1) Glyceryl trinitratc is used in acute laminitis in horse.
(2) As 2% ointment in carpinna in dogs.

ACE Inhibitors –
Renin – Angiotensin I



These drugs inhibit formation of angiotensin II by inhibiting the action of ACE thereby producing vasodilatory effect.
It also block break down of bradykinin thus contributing to vasodilatory effect.

Angiotensin receptor blocker – these drug act as an antagonist for AT1 and AT2 receptors present on blood vessels and heart there inhibiting smooth muscle contraction and producing vasodilatation.
Use – Hypertension.

Antiadrenergic drugs – These drugs act as an antagonist of X receptors (X receptors produce vasoconstriction) thereby blocking binding of nor epinephrine to these receptors resulting in vasodilatation effect.

Miscellaneous Drugs –

(1) xanthine – Phosphodiesterase

Exception – inhibitor

↓

CAMP catalyze

↓

↑ CAMP → relaxation

These agent inhibit phosphodiesterase enzyme. Which catalyze CAMP, reduction in enz. Causes ↑ accumulation of CAMP. In smooth muscles it cause relaxation. bcez CAMP inhibit myosin light chain kinase with produce relaxation effect.

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CARDIAC GLYCOSIDES

It represents a family of compounds that are derived from fox clove plant (digitalis pupurea). William witherting used this plant to treat oedema due to failure.

Name and sources of cardiac glycosides.

Plant	source	Sugar	Aglycon part
1. Digitalis lanata	1. Digoxin 2. Digitoxin 3. Gitoxin	Digitoxose	1. Digoxigenin 2. Digitoxigenin 3. Gitoxigenin
2. Digitalis purpurea	1. Digitoxin 2. Gitoxin 3. Gitalin	Digitoxose	1. Digitoxigenin 2. Gitoxigenin 3. Gitoxigenin hydrate
3. Strophanthus kombe	Strophanthin K	Glucose and Cymarose	Strophanthidine
4.strophanthus gratus	Ouabain (strophanthan G)	Ramanose	Ouabagenin
5.Urginia martima	Proscillaridine A	-	-
6. Thebetia nerifolia	Thebetin	-	-

Glycosides –

Compounds linked by an oxygen atom to a sugar molecule are known as glycoside. It is synthesised from plant carbohydrate by hydrolysis. It consists of sugar and nonsugar parts, basic steroid nucleus also known as cyclopentanoperhydrophenantherane..... ring has sugar molecule attached to 3^{rd} carbon and hydroxyl molecule attached to 14^{th} carbon.

Structure – activity relationship.

1. Sugar part attached at 3^{rd} carbon influence water solubility, cell penetration, duration of action and other pharmacokinetic properties. It also helps in fixation of compounds on cardiac cells.
2. Cardio activity of the molecule depends on the aglycon part. Lactone ring at 17^{th} carbon is essential for pharmacological action. Saturation of this ring reduces cardiotonic effect. it also plays important role in receptor binding.

Mechanism of action –

Digitalis compounds are potent inhibitory of cellular Na – K ATPase, this ion transport system moves sodium ion out of the cell and brings potassium ions into the cell. Thus maintain the concentration gradient required across the cell membrane. Loss of these ions gradient leads to cellular depolarisation and negative membrane potential. When this Na – K ATPase is inhibited intracellular sodium ions concentration increase competes with calcium through this exchange mechanism leading to an increase in intracellular calcium concentration. This result in excessive intracellular calcium ions, in the heart increase intracellular calcium cause more calcium to be released by sarcoplasmic reticulum. More calcium available to bind to troponin C resulting in increase myocardial contraction.

The parasympathomimatic action of digitalis decrease heart rate and conduction velocity of impulse from AV node showing negative chromotrophy and dromotrophy.

Pharmacological effect –

1. Cardiac output –

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Digitalis produce increase in contraction in both normal and failing heart. Cardiac output in case of normal heart increase slightly or even decreases after treatment, where as in failing heart digitalis increases contraction, work capacity of ventricles, reduce residual ventricular volume, size of heart with overall increase in cardiac output.

2. Cardiac energy metabolism –

In normal heart with normal ventricular volume when digitalis is given, contraction increase with increase in myocardial oxygen demand. In failing heart digitalis cause bradycardia so, there is reduction in cardiac metabolism, myocardial oxygen demand along with reduction in heart size.

3. Effect on ANS –

In congestive heart failure there is compensatory sympathetic over activity. Digitalis reduce sympathetic over activity and increase vegal activity.

4. Effect on kidneys –

In failing heart there is excessive rennin production which causes hypervolumia and oedema. Digitalis increases cardiac contraction, improve cardiac output, more blood is pumped in the arterial side of kidney resulting in increase glomerular filtration rate and diurese.

Pharmacokinetics –

Cardiac glycosides have long half life (40 – 160 hours) therefore special dosing pattern is required. It also has narrow margin of safety and low therapeutic index. Higher dose may result in toxicity.

Digitalization –

It is the process of dosing with digitalis, which may be slow or rapid with the objective of attaining a steady state of plasma concentration of drug in cardiac patient.

Loading dose –

It is the dose that is given to load the concentration of drug in blood or necessary to achieve initial response.

Maintenance dose –

Dose that is given to maintain the concentration of drug in the blood.

Dose –

Digitalis in horse	33 – 36 mg /kg IM
Digitoxin in cattle	0.031 mg /kg IV
Digoxin in cattle	0.008 mg /kg IV
For dogs	0.01 – 0.02 mg /kg oral in two divided doses on first day.
	0.01 – 0.02 mg /kg oral in two divided dosses daily.
	0.01 – 0.02 mg /kg IV. Half the dose is given IV later 1/4th is given IV and then the remainder dose is given.

Therapeutic use –

1. Congestive heart failure –

Cardiac output is insufficient to supply oxygen need of the body resulting in heart failure. Digitalis compounds when used along with diuretics and vasodilators or alone improves cardiac output, ejection fraction, pulmonary congestion and oedema.

Due to vegal stimulation they reduce vasoconstriction and sympathetic adrenergic activity resulting in diuretic effect on kidneys.

2. Arterial fibrillation and flutter –

This condition leads to rapid ventricular rate which impair ventricular filling and reduce cardiac output.

Digitalis compounds reduce ventricular rate. It also activate vegal efferent nerve which reduce conduction of impulses from AV node resulting in reduced number of impulses to the ventricles and fall of ventricular rate.

It also decrease refractory period within the AV node.

Drug interaction –

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Those drugs which reduces potassium level competes with cardiac glycosides for Na – k ATPase binding site.
e.g quinidine.
Other drugs for CHF –
1). Phosphodiestrase inhibitors.
e.g milrinone, enoximone
these drugs inhibit phosphodiestrase enzyme , increase intra cellular level of cAMP resulting in more myocardial contraction.
2). Vasodilators –
e.g hydralazine, nitrates, β – antagonists.
3). ACE inhibitors –
E.g captopril, remipril etc.
4). Angiotensin – ii receptor antagonist.
e.g losartan
5). Endothelin receptor antagonist.
e.g Bosentan
6). Aquaretics. (ADH receptor antagonist)
E.g tolvaptan.
7). Prostacyclin analogue.
e.g Epoprostinole and treprostimil.