DRUGS FOR HEART FAILURE

[2012]

CHF usually occurs when the cardiac output is inadequate to meet the metabolic needs of the body.

In CHF, the ventricular dysfunction may be primarily systolic (i.e. inadequate force generation to eject blood normally as in ischemicc heart disease) or it is may be diastolic (inadequate relaxation to permit normal filling as a result of hypertrophy or stiffness of the myocardium).

CHF due to sytolic dysfunction usually respond to inotropic drug e.g. digoxin while CHF due to diastolic dysfunction does not respond optimaly to these drugs.

Rarely high output failure occurs whereby needs of the body are so great inspite of the↑C.O. this form of failure poorly responds to +ve inotropic drugs.

Treatment is by correcting the underlying cause.

the primary symptoms of all types of CHF include: tachycardia, decreased exrecise tolerance, SOB, peripheral and pulmonary edema, cardiomegaly.

The decreased execise tolerance and easy fatigability are due to ↓C.O. while other manifestations are due to compensatory mechnisms.

Physiology Of Cardiac Muscle Contraction:

Contraction of the cardiac muscle is due to movement of actin and myosin in cardiac sarcomers during systole resulting from the interaction of Ca^+ with actin troponin tropomyosin system.

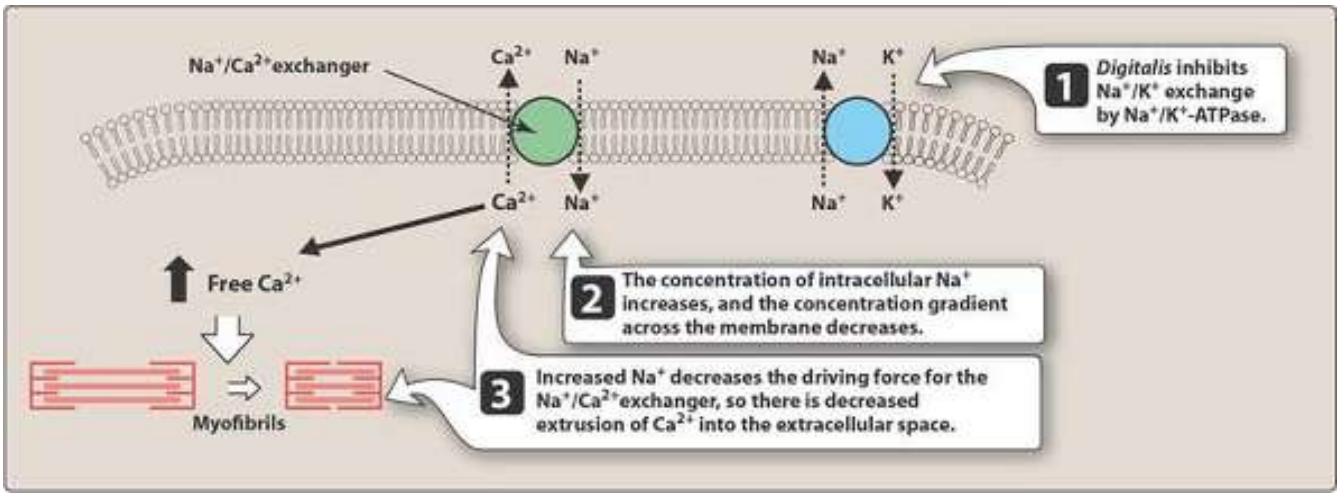
This activator Ca^+ comes from 2 sources:

1. From outside the cell, enter during plateau phase of action potential through voltage gated Ca^+ channels.
2. Release of Ca^+ from the sarcoplasmic reticulum which depend on the amount stored in the SR and the amount of trigger Ca^+ that enter the cell.

Therefore the contraction of cardiac muscle is directly related to the concentration of the free cystolic Ca^+.

Removal of Ca^{+}: Na-Ca exchanger: which exchange Ca with Na thus any change in the intracellular concentration of Na will affect the cellular levels of Ca^{+}.

1. Uptake by SR, more than 99% of Ca^{+} is stored in the SR and mitochondria.

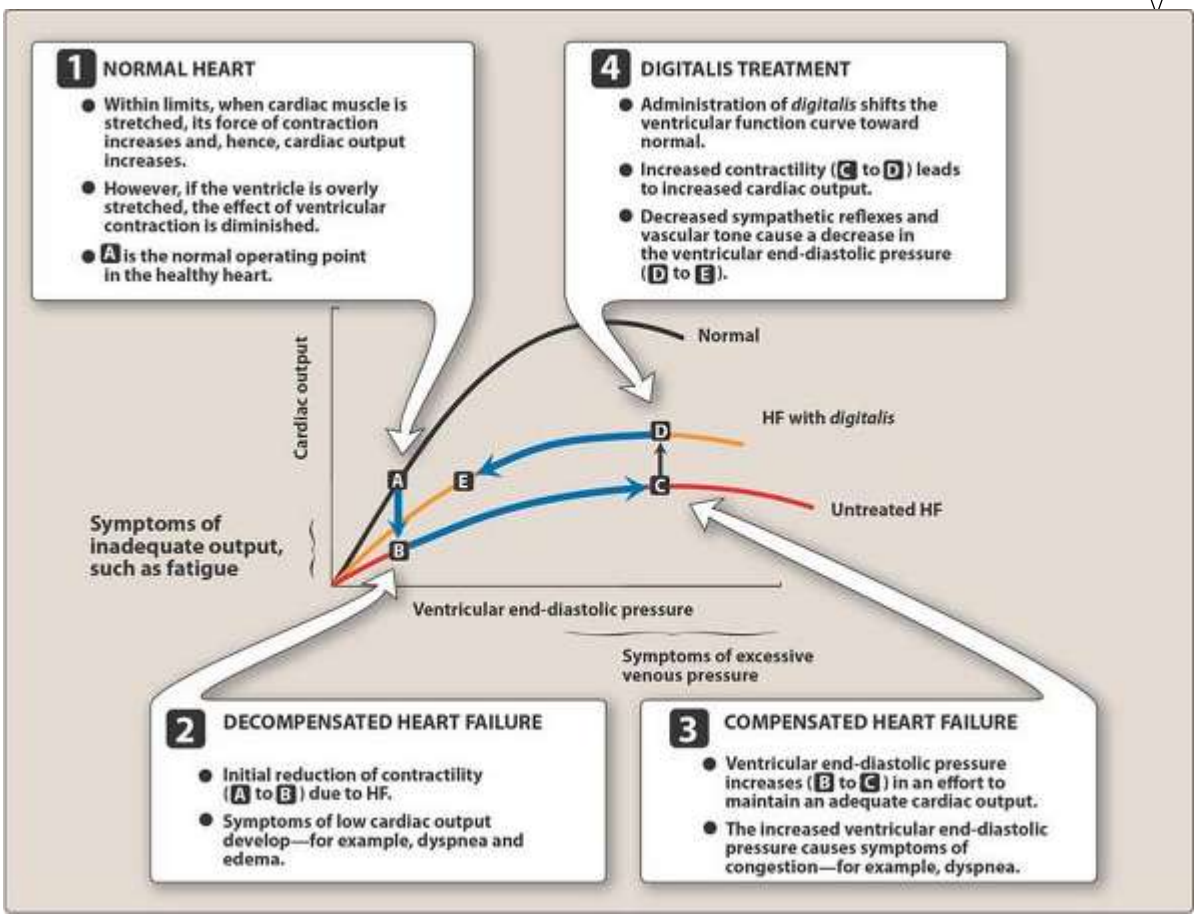


Pathophysiology of Cardiac Performance:

It's a function of 4 primary factors:

1. Preload: is the volume of the blood that fills the ventricles in diastole, when it is↑, it causes overfilling of the heart which ↑the work load.

- Starling law: within limits, the ventricular performance is related to the degree of myocardial stretching.
- When left ventricular performance (e.g. stroke volume or C.O.) is plotted as a function of L.V. filling pressure (preload), then the resulting curve is called L.V. function curve… therefore when preload is↑leads to↑ in ventricular stretching and will enhance the ventricular function.
- The limit is End Diastolic Pressure (EDP) of 15 mmHg when there is plateau of performance.
- On the other hand marked stretching causes marked deterioration of ventricular function and EDP of 20 mmHg or more results in pulmonary congestion.
- In HF, preload usually↑because of ↑in blood volume and venous tone.
- Reduction of preload is the goal of salt restriction and diuretic therapy.
- Vasodilators also reduce preload by redistributing the blood into peripheral veins away from the heart.



2. Afterload: is the systemic vascular resistance against the heart must pump the blood, this is frequently ↑ in CHF which leads to ↓ C.O.

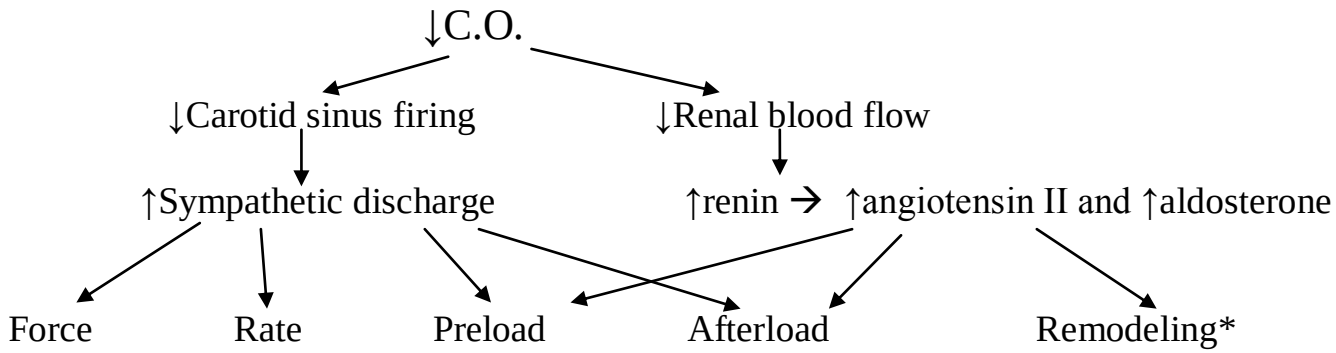
   This sets the stage for the use of the drugs that ↓ or reduce arterial tone in CHF.

3. Contractility: in patients with chronic low output failure, there is reduction in the intrinsic contractility of myocardium resulting in reduction of pump performance; here comes the role of +ve inotropic drug.

4. Heart rate: which is the major determinant of C.O. (i.e., C.O. = S.V. x Ht. rate). The heart rate ↑ as the S.V. ↓, this is the 1st compensatory mechanism to maintain the C.O.

Compensatory Mechanisms in CHF:

1. Neuro-hormonal reflex involves:
   a. The sympathetic nervous system
   b. The renin-angiotensin-aldosterone system



*remodeling: change the shape (geometry) of the ventricles

These compensatory mechanisms↑ the work of the heart and can further contribute to the decline in the cardiac function.

2. Myocardial hypertrophy: is the most important intrinsic compensatory mechanism, the ↑in myocardial mass helps to maintain cardiac performance in the phase of pressure or volume overload. However, after initial beneficial effect, hypertrophy can lead to ischemic changes, impairment of diastolic filling and alteration in ventricular geometry (remodeling) due to proliferation of abnormal myocardial cells and C.T. which die at the accelerated rate leaving the remaining myocardial cells subject to even greater overload.

Drugs used to treat CHF

1. Diuretics: loop diuretics and thiazides AND SPIRONOLACTONE.
2. Vasodilators:
   a. ACE inhibitors (arteries and veins and angiotensin receptor blockers
   b. Hydralazine
   c. Minoxidil } Arteries
   d. Isosorbide → mainly veins
   e. Brain natriuretic peptide(BNP) Nesiritide
   f. Endothelin antagonists Bosentan ,tezosentan
3. Cardiac inotropic agents
   a. Cardiac glycosides (digoxin, digitoxin)

b. β-adrenergic agonist (dobutamine, dopamine)
c. Phospho diesterase inhibitors (amrinone, milrinone)

4. Beta-blockers: most patients with chronic stable heart failure respond favorably to certain β-blockers (carvedilol, metoprolol) inspite of the fact that these drugs can ppt. acute decompensation of cardiac function.

Remodeling: the term applied to dilation (other than that due to passive stretch) and slow structural changes that occur in the stressed myocardium.

Considering (c) in cardiac inotropic agents, they ↑cAMP by inhibiting phosphodiesterase iso enzyme III which in turn ↑Ca^{+} entry during the A.P., they also have significant vasodilatory effect, they are used for acute heart failure, their toxicity prevents long term use which includes B.M. toxicity, liver toxicity and also cardiac arrhythmia.

Cardiac Glycosides:

All the commonly used cardiac glycosides of which digoxin is considered as the prototype, combine a steroid nucleus with unsaturated 5 mem. lactone ring and a series of sugars linked to the C3 of the nucleus. For the effect on the heart, we need the steroid nucleus and the lactone ring. The sugar series differ from each other and affect the pharmacokinetics of the drug.

Source: fox glove digitalis lanata and D.purpurea, squill (med. sea onion), strophanthus gratus and other tropical and temperate zone plants, Certain toads have cardiac glycosides in their skin glands.

D.purpurea	D.lanata	S.gratus
Digoxin	Digoxin	Ouabain
Digitoxin	Lanatocide	Strophanthline
	Deslanoside	

- The most important property of cardiac glycoside is their +ve inotropic effect (i.e. increase the force of myocardial contraction ↑ and C.O. at a reduced metabolic cost).

Pharmacological Effect on Heart Contractility:

- Mechanical effects: ↑ in the force of contraction by ↑ in both the velocity of myocardial contraction and the max. force that is developed.
- ↑ in cardiac contractility leads to the following:

1. ↑ in C.O. to resemble that of normal heart.
2. ↓ EDP or volume thus ↑ the efficacy of contraction and therefore ejection fraction is increased.
3. The resulting improvement in the circulation will lead to ↓ sympathetic activity and ↓ peripheral resistance.
4. ↓ in heart rate because of these effects by ↑ in vagal tone.
5. Improvement in renal blood flow
6. O_2 demand will be ultimately ↓.

Note: there is ↑ renal blood flow because of improved circulation.

Mechanism of Action:

Cardiac glycosides combine reversibly with the Na^+-K^+ ATPase of the cardiac cell memb., resulting in inhibition of pump activity and this causes ↑ in Na^+ conc. inside the cell which favors the transport of Ca^+ into cell via Na^+-Ca^+ exchanger and thus ↑ intracellular Ca^+ resulting in an ↑ in the systolic force of contraction.

Electrical Effects:

In the intact subject it is a mixture of direct and indirect actions (due to ↑ in the vagal tone). In the lower portion of the dose range parasymp. effects dominate (mainly on the atria). As the dose increases , more of the symp. effects come into play:

Direct Effect	Atrial	AV node	Vent. And purkinjie fibers
ERP	↑	↑	↓
Conduction velocity	↓	↓	→
Automaticity	↑	↑	↑

Indirect Effect	Atrial	AV node	Vent. And purkinjie fibers
ERP	↓	↑	→
Conduction velocity	↑	↓	→
Adverse effects	extra systole	AV block	PVC and Bigmeny
Arrhythmia	Tachycardia	AV nodal tachycardia	VT and VF
ECG changes	→	PR interval is ↑	T and ST is depressed QT ↓

ERP: effective refractive period
VT: ventricular Tachycardia
VF= ventricular fibrillation
PVC: premature ventricular count
Bigmeny: one normal and one ectopic beat

Therapeutic Uses:

1. Cardiac failure by the direct action on ↑contractility, they are of great value in the treatment of severe left ventricular systolic failure after initiation of diuretics and ACE inhibitors, only if the patient has AF well it becomes 1st choice.
2. Atrial fibrillation: by the vagal effect on the AV node reducing conduction velocity, thus it is slowing the ventricular rate (i.e. digoxin does not revert the atrial fibrillation to the normal sinus rhythm).
3. Atrial flutter: by the vagal action on the AV node to reduce the rate and also by shortening the refractory period of the atrial muscle to convert flutter to fibrillation in which the ventricular rate is more readily controlled.
4. Paroxysmal Atrial Tachycardia (PAT) by the vagal effect frequently respond to digoxin, adenosine, and Ca^{+} channels blockers are the best now.

Contraindications:

Cardiac temponade, constrictive pericarditis, high output CHF, Hypertrophic Obstructive Cardiac Myopathy (HOCM), wolf-parkinson- white syndrome.

Kinetics:

Because digitalis is frequently prescribed on long term therapy and because of the low margin of safety of the drug (lethal dose is only 5-10 times the minimum effective dose).
The drugs also have a long $t_{1/2}$, so they require a careful attention to their pharmacokinetics.

Drug	GI absorb.	Ptn. Binding	$t_{1/2}$ PMR	serum conc. ng/ml
Digoxin	≈ 75%	<30%	36 hr./kidney	0.5-2.5 / toxic>2
Digitoxin	90-100%	97%	5-7 days/liver	10-35 / toxic>35

*PMR: principle metabolic route

Administration and Dosage:

- You should not exceed the safety therapeutic range, the slow approach of digitalization is the safest method.
- If a more rapid effect is needed, then you can give a loading dose divided into 3-4 doses over 24 hours then followed by maintenance dose.
- Slow digitalization or maintenance doses of digoxin is 0.125-0.5 mg while loading dose is 0.5-0.75 mg every 8 hrs (3 daily) then followed by maintenance dose.
- Digoxin can be used I.V. but it's dangerous.

Factors predisposing to digoxin toxicity:

1. *Electrolyte disturbance*:
    a. *Hypokalemia*: may be produced by diuretics, steroids, vomiting and diarrhea.
- It can precipitate serious arrhythmia and this can be prevented by supplying K^+ or the use of K^+ sparing diuretics.
    b. *Hypercalcemia and hypomagnesemia*: also predispose to digoxin toxicity.
2. *Drugs:* quinidine and verapamil by displacement digoxin from binding site. quinidine also competes with digoxin for renal excretion, other drugs may↑ digoxin concentration and↑potential for toxicity include: Amiodarone, tetracycline, erythromycin, and other drugs that cause hypokalemia.
3. Hypothyroidism, hypoxia, renal failure, myocarditis are also predisposing factors for dig. toxicity.

Adverse Effects:

When the serum concentration is above therapeutic range then signs of digoxin toxicity will appear and these are:

1. Anorexia → earliest sign.
2. Nausea, vomiting, diarrhea (nausea and vomiting due to stimulation of CTZ).
3. Headache, malaise, fatigue, neuralgia, confusion, agitation, and even convulsions.
4. Vision change: include change in color perception, yellow vision → xanthopsia, hollows on dark objects.
5. Gynecomastia (rare) because it contains steroid nucleus
6. Cardiac toxicity

a. PVC: premature ventricular contraction: bigeminy, VT, VF.
b. AV dissociation and block → complete heart block.
c. PAT and non-paroxysmal often with AV block.
d. SA block and sinus arrhythmia.
e. Digoxin can virtually cause every variety of arrhythmia.

Delayed after depolarization are responsible for most types of dig. arrhythmias.(occurring during phase 4 due to entry of calcium)

Principles of Rx of digitalis toxicity:

1. Cardiac glycosides and K^+ depleting drugs are discontinued.
2. KCl is administered orally or by slow I.V. infusion if hypokalemia is present (unless there is AV block), Mg^+ deficiency may accompany hypokalemia and Mg^+ replacement may be necessary.
3. Cholestyramine binds to cardiac glycoside and has been used to fasten their elimination.
4. A digoxin specific Ab fragment (FAB) from immunized sheep is non-immunogenic and it is available for Rx of life threatening toxicity.
5. Rx of digoxin induced cardiac arrhythmias
    a. Atropine to control sinus bradycardia.
    b. Lidocaine (the best) for VT also procainamide can be used.
    c. Propranolol can be used for ventricular and supra ventricular tachycardia unless there is AV block.
    d. Phenytoin can be given for ventricular and atrial arrhythmia.
    e. Electrical conversion is often hazardous in the treatment of digoxin induced arrhythmia because it can ppt. VF. Only used when there is VF.

Acute heart failure treatment in short:

1. Oxygen supply and rest.
2. Morphine.
3. Diuretics mainly fursemide (I.V.).
4. Nitrates.
5. B-agonist → Dobutamine may be used.
6. Digoxin but ↑risk of arrhythmia due to hypoxia.
7. Sometimes the patient may have an element of bronchospasm and we may give aminophylline.