Good Morning

Drugs used in Congestive Heart Failure

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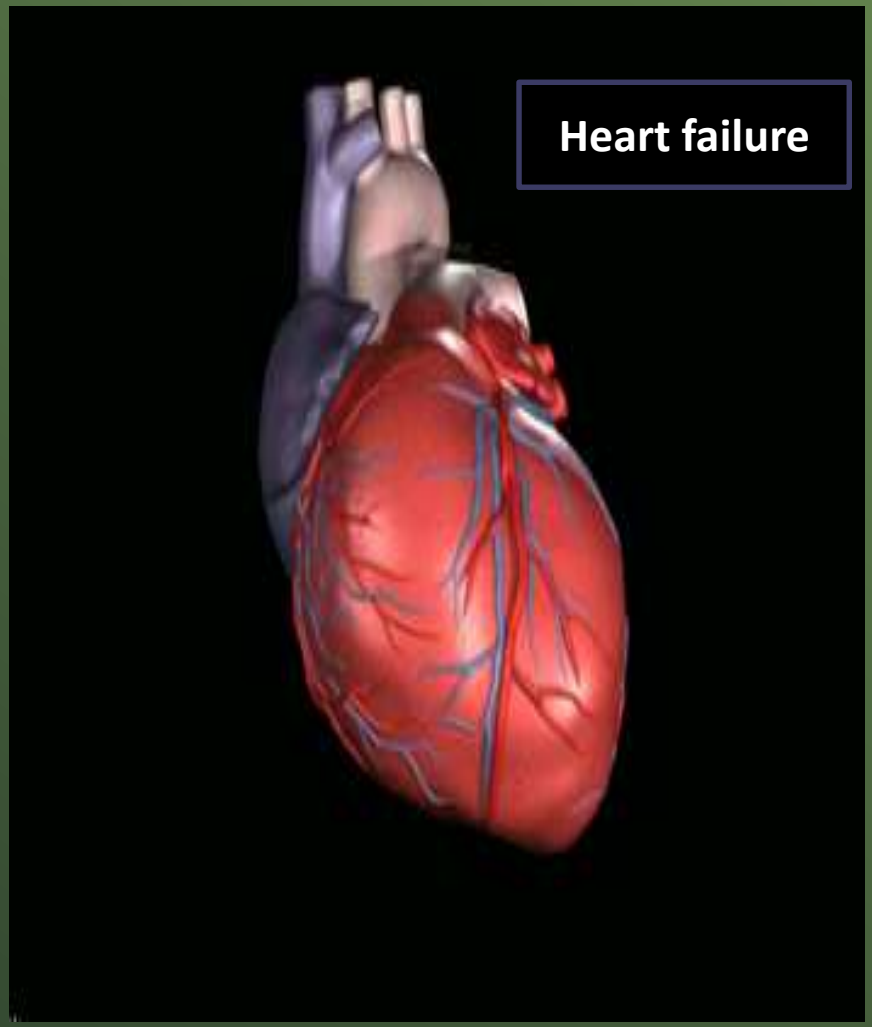
Introduction

Congestive heart failure (CHF), or heart failure, is a condition in which the heart is unable to pump sufficient blood to meet the metabolic demand of the body and also unable to receive it back because every time after a systole.

A normal heart pumps blood in a smooth and synchronized way.

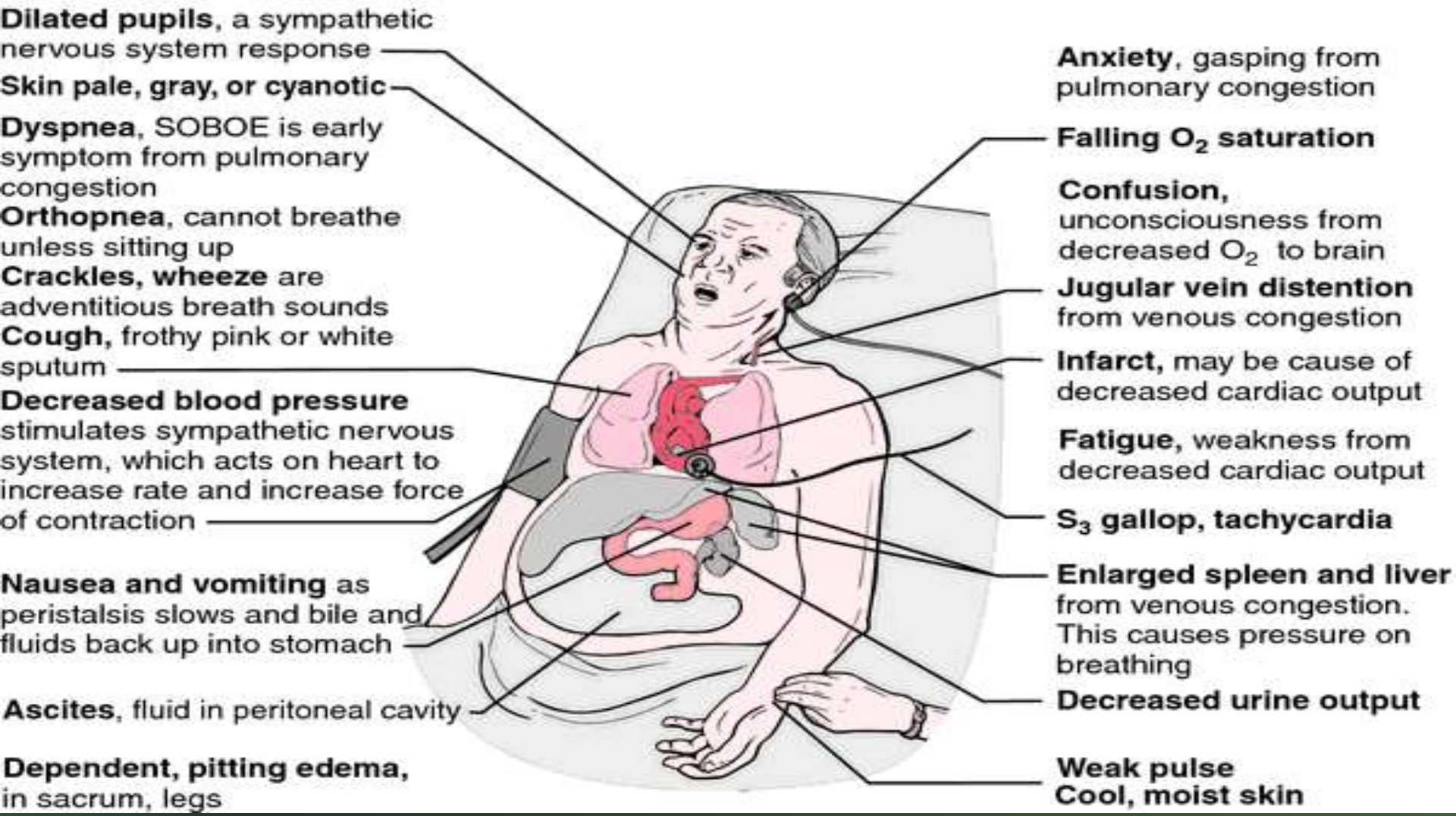


A heart failure heart has a reduced ability to pump blood.

Classification of CHF

- **BY EJECTION FRACTION**
  - Reduced ejection fraction(<40-50%)- systolic heart failure
  - Preserved ejection fraction(>40-50%)- diastolic heart failure
- **BY TIME COURSE**
  - Chronic heart failure(CHF)
  - Acute heart failure (Cardiogenic Shock)
- **ANATOMICALLY**
  - Left sided- LHF
  - Right sided- RHF(CHF)
- **BY OUTPUT**
  - High output failure-Thyrotoxicosis, Paget's disease, Anemia, Pregnancy, A-V fistula
  - Low output failure

Sign & Symptoms



How Heart Failure Is Diagnosed

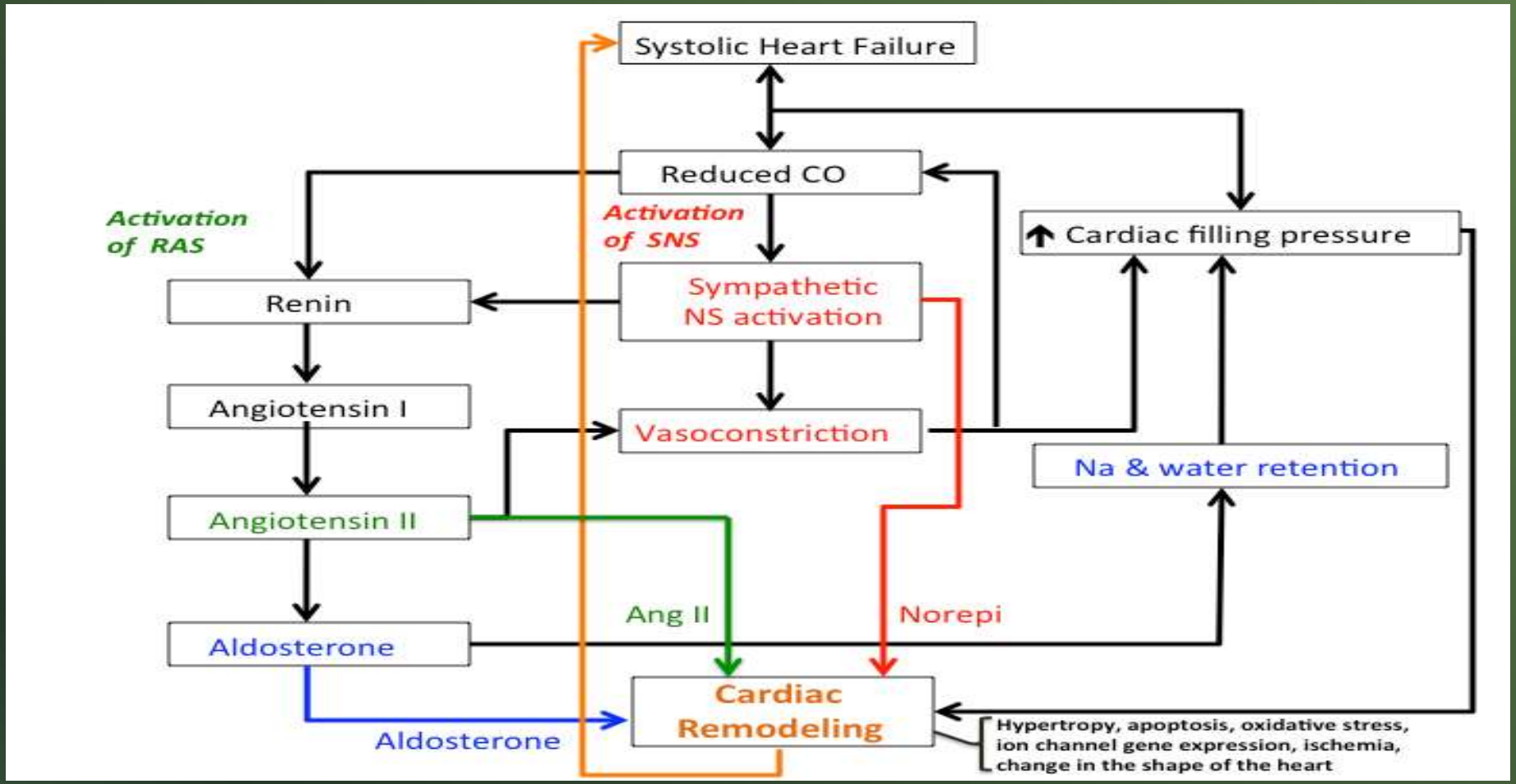
- Medical history is taken to reveal symptoms
- Physical exam is done
- Tests
  - Chest X-ray
  - Blood tests
  - Electrical tracing of heart (Electrocardiogram or "ECG")
  - Ultrasound of heart (Echocardiogram or "Echo")
  - X-ray of the inside of blood vessels (Angiogram)

Key Indicator for Diagnosing Heart Failure

Ejection Fraction (EF)

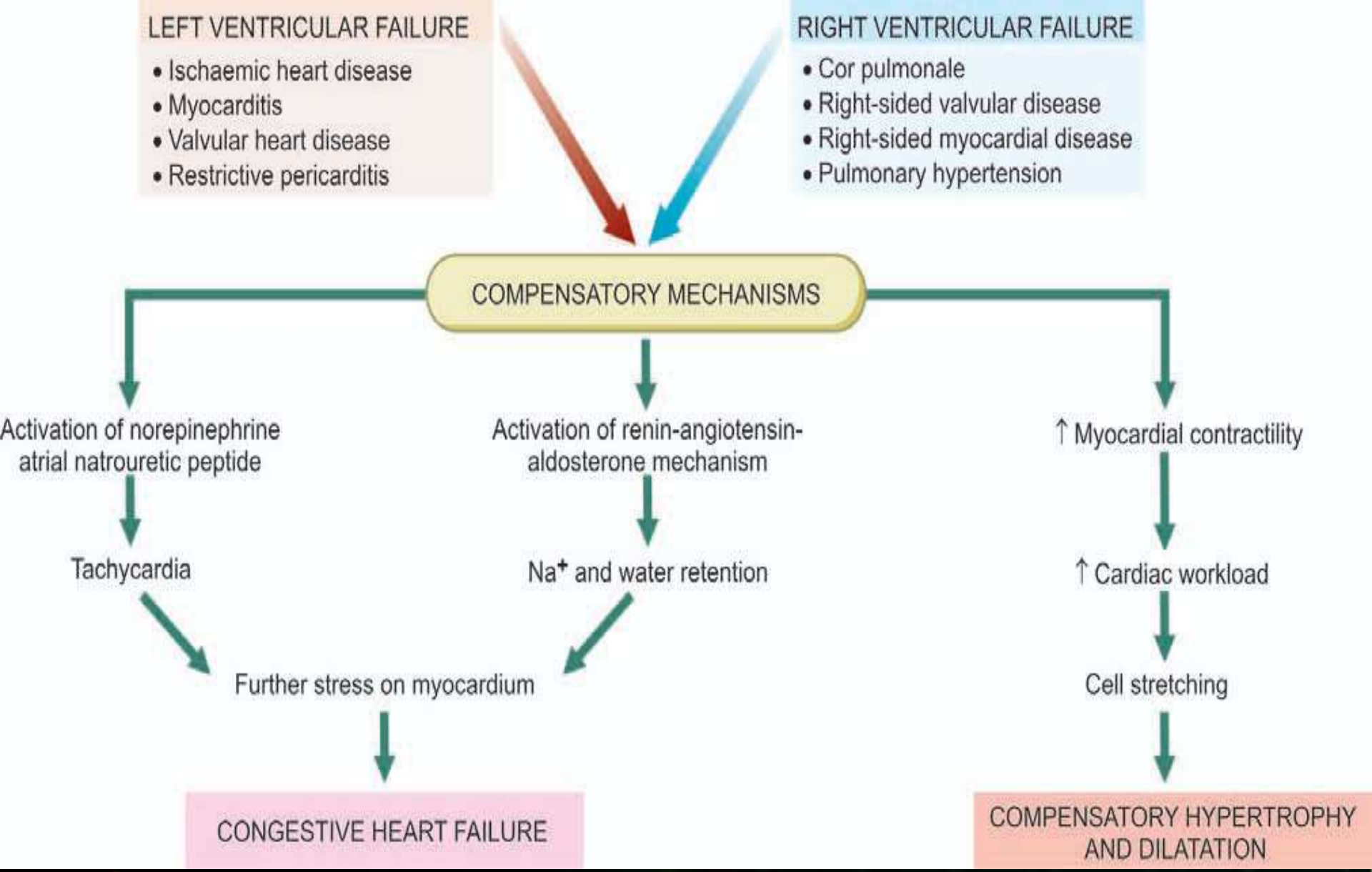
- Ejection Fraction (EF) is the percentage of blood that is pumped out of your heart during each beat

Pathophysiology

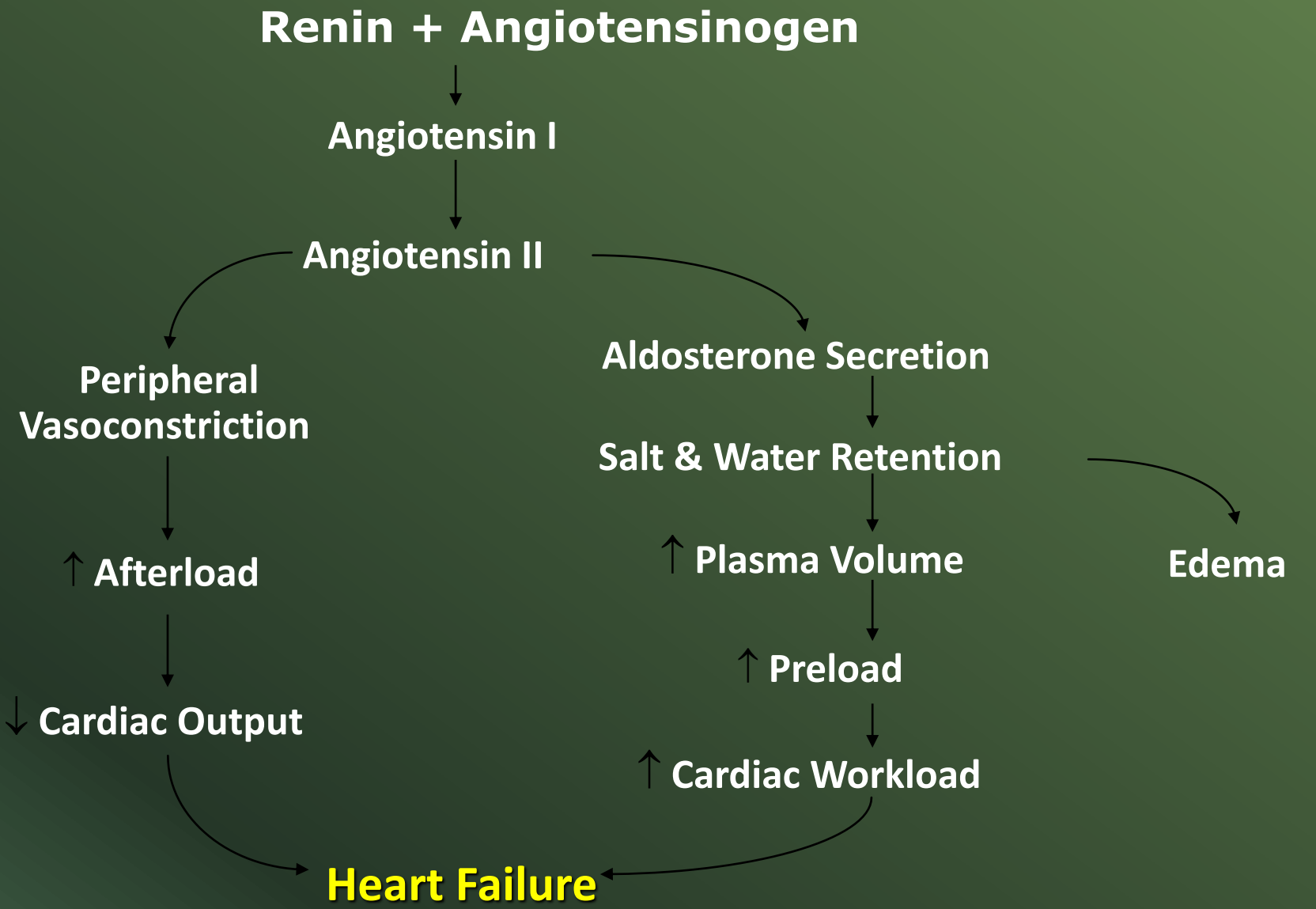


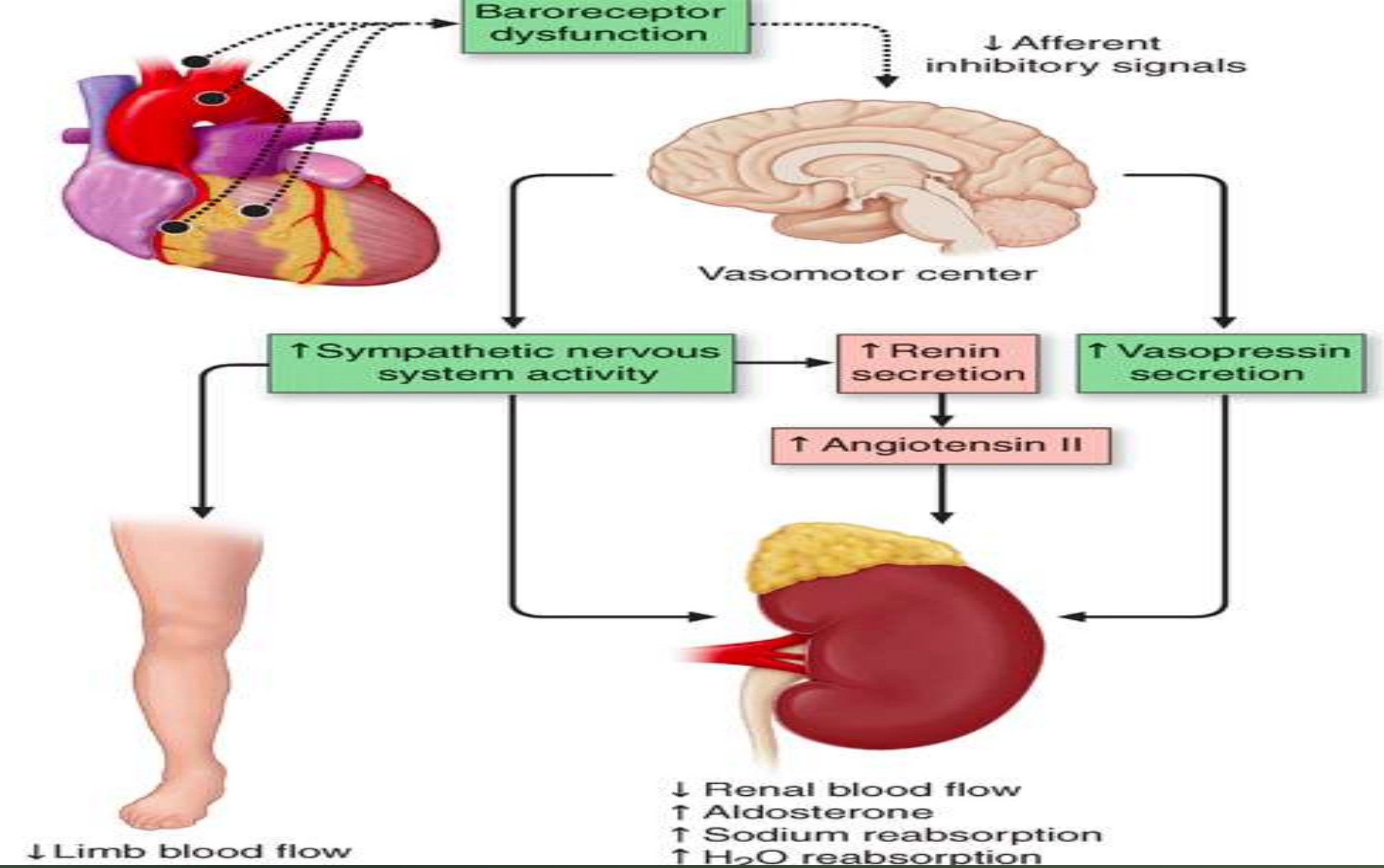
Compensatory Mechanisms

- Sympathetic nervous system stimulation
- Renin-angiotensin system activation
- Myocardial hypertrophy
- Altered cardiac Rhythm


LEFT VENTRICULAR FAILURE
• Ischaemic heart disease
• Myocarditis
• Valvular heart disease
• Restrictive pericarditis
RIGHT VENTRICULAR FAILURE
• Cor pulmonale
• Right-sided valvular disease
• Right-sided myocardial disease
• Pulmonary hypertension
COMPENSATORY MECHANISMS
Activation of norepinephrine atrial natrouretic peptide
Activation of renin-angiotensin-aldosterone mechanism
↑ Myocardial contractility
Tachycardia
Na+ and water retention
↑ Cardiac workload
Further stress on myocardium
Cell stretching
CONGESTIVE HEART FAILURE
COMPENSATORY HYPERTROPHY AND DILATATION

Renin-angiotensin system




Baroreceptor dysfunction
↓ Afferent inhibitory signals
Vasomotor center
↑ Sympathetic nervous system activity
↑ Renin secretion
↑ Vasopressin secretion
↑ Angiotensin II
↓ Limb blood flow
↓ Renal blood flow
↑ Aldosterone
↑ Sodium reabsorption
↑ H_2O reabsorption

Treatment strategies of CHF-GOAL

The therapeutic goal for CHF is to increase cardiac output, reduce preload and afterload and to increase myocardial contractility.

1) Inotropic agents that increase the strength of contraction of cardiac muscle
2) PDEI (phosphodiesterase inhibitors) agents that increase cAMP to induce systoles and vasodilatation
3) Calcium sensitizers extracellular fluid volume
4) β adrenergic agonist
5) β adrenergic antagonist
6) Vasodilators: Calcium channel blocker
7) Decreasing RAS activity: ACEI and AT1 antagonist
8) Diuretic agents

Classification of Drugs used in CHF

1. **Inotropic drugs:**

(a)Cardiac glycosides: Digoxin, Digitoxin, Ouabain

(b)Sympathomimetics: Dobutamine, Dopamine

(c) Phosphodiesterase III inhibitors: Amrinone

2. **Diuretics:**

(a)High ceiling diuretics: Furosemide, Bumetanide

(b)Thiazide like diuretics: Hydrochlorothiazide, Metolazone, Xipamide

3. **Aldosterone antagonist-**

Spironolactone, Eplerenone

Cont.

4. Inhibitors of Renin-Angiotensin system-

(a) ACE-inhibitors: Enalapril, Ramipril

(b) Angiotensin (AT receptor) antagonists: Losartan

5. Vasodilators-

(a) Venodilators: Glyceryl trinitrate

(b) Arteriolar dilator: Hydralazine

(c) Arteriolar + Venodilator: Sod. Nitroprusside

6. β-Adrenergic blockers:

Metoprolol, Bisoprolol, Carvedilol

7. Others-

(a) Metabolic cardioprotectives: Trimetazidine

(b) Calcium sensitizers: Levosimendan

(c) Levocarnitine

(1) Inotropic drugs
(a)Cardiac Glycosides

If a sugar molecule is joined together with a non sugar molecule by a ether linkage it is called a glycoside.

Sugar + Non-sugar → Glycoside

Digitoxose + Steroidal Lactone → Cardiac Glycoside

1 to 4 sugar

Aglycon (genin)

Source

Leaves of Digitalis lanata provide two – DIGOXIN and DIGITOXIN, while leaves of Digitalis Purpurea (Fox glove) are the major source of digitoxin.

Seeds of Strophanthus gratus provide two Active glycoside – STROPHANTHUS-G and OUABAIN, While seeds of strophanthus kombe yield primarily STROPHANTHIN-K.

History


William Withering

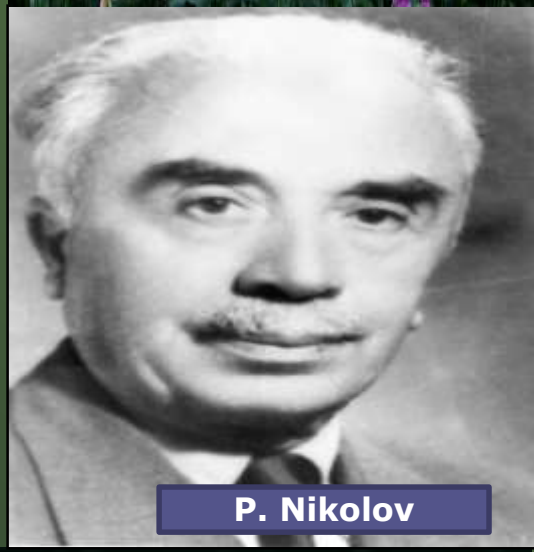
The man credited with the introduction of Digitalis into the practice of medicine was Scottish doctor William Withering. Withering was born in Wellington, Shropshire, England in 1741.

The ***Digitalis*** or foxglove genus contains a number of Cardioactive glycosides, the first of which, known as Digitalin, was identified in the mid-eighteen hundreds by the French scientists Theodore and Homolle Ouevenne. Then in 1875 Oswald Schmiedeberg (1838-1921) identified foxglove as a major source of the potent chemical named digitoxin.

Cont.

Another important chemical was isolated from (Digitalis lanata) woolly foxglove in 1930 by the English chemist Sydney Smith.

The first experiments were carried out by Professor P. Nikolov (1894–1990) on Digitalis lanata.



P. Nikolov

Digoxin

- A cardiac glycoside extracted from foxglove leaves (*Digitalis* sps.) is the most important Inotropic agent.
- Increase the contractile force.
- Particularly indicated in patients with atrial fibrillation.
- **MOA-** Inhibits the Na^+/K^+-ATPase, which is responsible for Na^+/K^+ exchange across the muscle cell membrane →increased $[Na^+]_{in}$→ increased $[Ca^{2+}]_{in}$→ increased force of myocardial contraction.

Cont.

- **Positive inotropic effect**
  (without increasing of oxygen consumption)
- **Positive batmotropic effect**
- **Negative chronotropic effect**
- **Negative dromotropic effect**

Extracardiac effect:

- **Blood Vessels-** Has direct vasoconstrictor effect, there is no prominent effect on BP as it is secondary to the improvement in circulation.

Cont.

- **Kidney-** Diuresis occurs due to improvement in renal perfusion, which brings about a shift of oedematous fluid into circulation.

- **GIT-** The effect include anorexia, diarrhea, nausea and vomiting (stimulation of CTZ)

- **CNS Effect-** These include disorientation, hallucination (in elderly), visual disturbance and aberrations of colour perception.

Pharmacokinetic profile of three typical cardiac glycosides

Parameters	DIGITOXIN	DIGOXIN	OUABAIN
Oral absorption	95% - 100%	75%-90%	0 (nil)
Administration	Oral	Oral	I.V.
aVd (L/Kg)	0.6	6-7	18
Protein binding	90	30	0 (nil)
Plasma half life	6-7 days	38-40 hr	18-20 hr
Onset of action	2 hr	½ hr	Very rapid (given I.V.)
Duration of action	Very long	Intermediate	Short
Metabolised (%)	80 (liver)	20 (liver)	0
Excretion	Mainly bile, also urine	Urine (unchanged)	Urine (unchanged)
Doses a) Digitalising dose	1.0 mg in 24 hr or 0.4 mg every 12 hr for total 3 doses orally	0.5-0.75 mg 8 hrly for total 3 doses orally	0.2-0.5 mg I.V. In cases of acute heart failure
b) Maintenance dose	0.1 mg single dose per day	0.25-0.5 mg per day	

Therapeutic uses

1) **Congestive heart failure-** Drug of choice for "low out put HF" due to HT, IHD or arrhythmias.
2) **Paroxysmal supraventricular tachycardia-** it's a arrhythmia due to reentry phenomenon taking place at SA or AV node. They frequently respond to digitalis favorably, because of reflux vagal activation which slow the conduction of impulses.
3) **Atrial Flutter and Atrial Fibrillation-** As it decreases conduction velocity and increases ERP of AV node.
4) **Dilated Heart-**As it is helpful in restoring cardiac compensation.

Side effects

Extracardiac Side effects

- **GIT-** Anorexia, nausea, vomiting, diarrhoea and abdominal cramps.
- **CNS-** Headache, fatigue, neuralgia, blurred vision, loss of colour perception**.**
- **Endocrinal-** Gyanecomastia in males (very rare)

Management of extracardiac side effects requires no more than reducing the dose of digoxin.

Cont.

Cardiac side effects and Management of toxicity:

Include bradycardia, partial or complete heart block, atrial or ventricular extrasystoles, coupled beats, ventricular fibrillation and fatal cardiac arrhythmias.

- If severe intoxication- administration of digitalis antibodies, e.g., Digibond Fab fragments (Digitalis immune Fab.)
- These antibodies are raised against digoxin. These also recognize digitoxin and Ouabain

Contraindications:

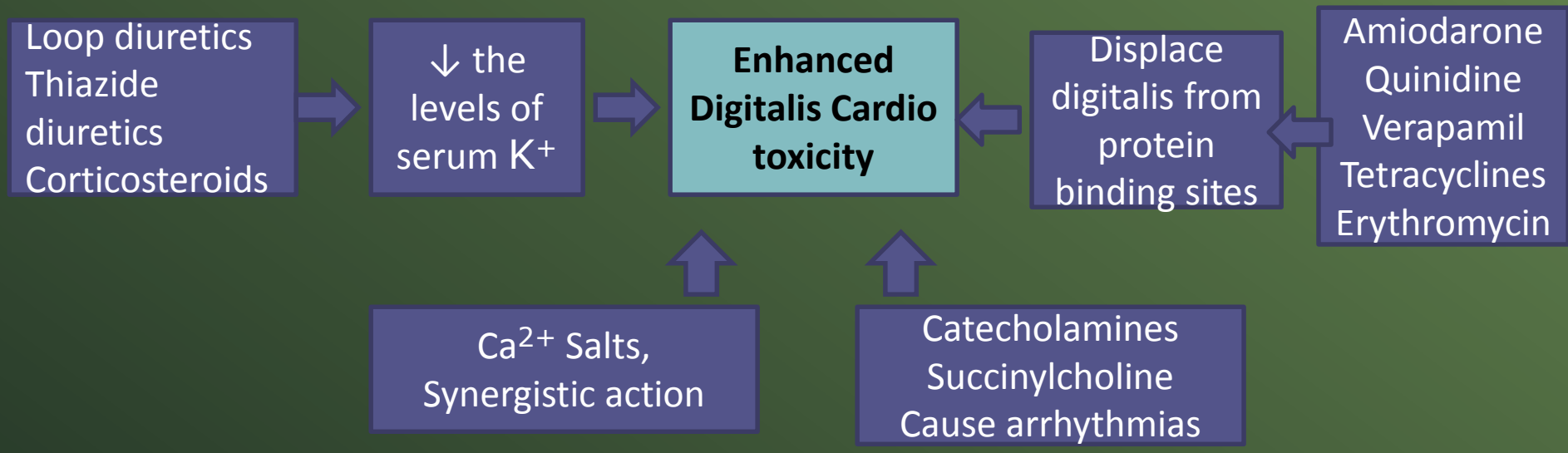
Patients with-

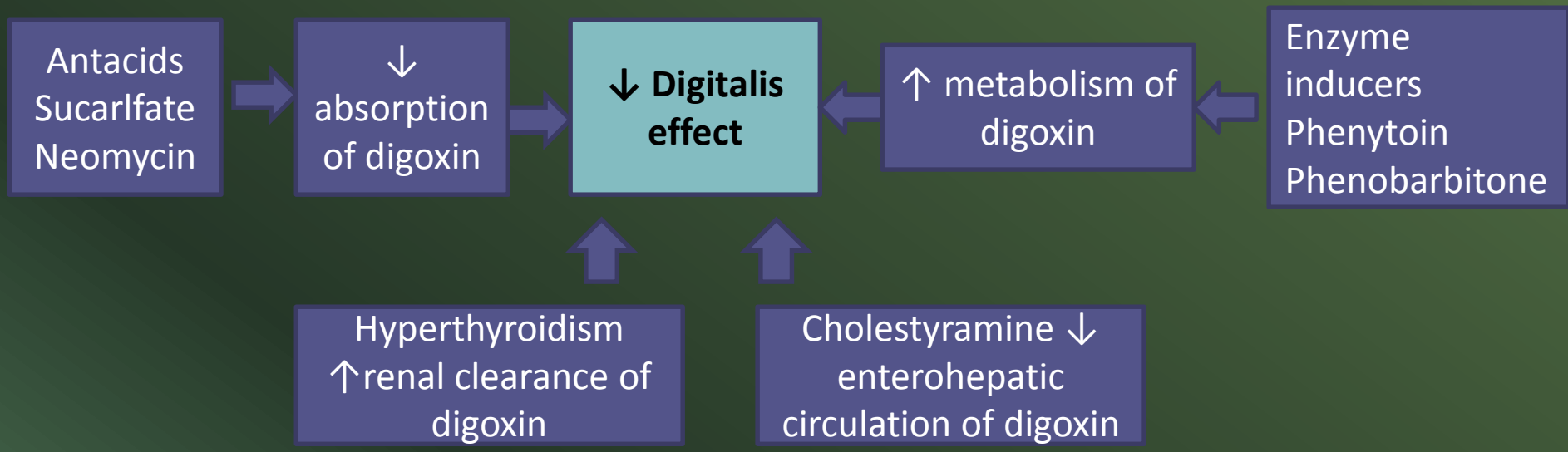
- Hypokalemia
- renal impairment
- MI- When HF is accompanied with atrial flutter & fibrillation
- Hypothyroidism
- Myocarditis or grossly damaged myocardium
- Hypomagnesemia
- Hypercalcemia and
- Pulmonary disease
- Ventricular fibrillation

- Patient must be advised not to take nonprescription cough or cold medications, antacids, laxatives, or antidiarrheals without consulting the physician.

- Pregnancy

Drug Interactions





(B) Sympathomimetics

They improve cardiac performance through positive inotropic effect and lead to an increase in intracellular cAMP which results in the activation of protein kinase. Slow Ca^{2+} channels are then phosphorylated by protein kinase which increases Ca^{2+} flow into the myocardial cell causing increased force of contraction of heart muscles.

Dobutamine

- The most commonly used inotropic agent other than digitalis. On heart, dobutamine has more selective inotropic than chronotropic effect without any significant change in peripheral resistance and BP.
- Its half life is about 2 min and therefore must be given by I.V. (5-10 μg/kg/min.)
- It ↑ CO, therefore urinary output, and stroke volume with affecting HR, TPR or BP.
- Tolerance may develop on repeated use.
- As it ↑ BP it should be avoided in patients with history of HT.

Dopamine

- When given by I.V. infusion in low dose (2-5 µg/kg/min.) acts on D1 receptor in kidney and causes dilatation of renal blood vessels resulting in an increase in GFR, renal blood flow and urinary output.
- In therapeutic doses (5-10 µg/kg/min.), also stimulate β1 receptors resulting in an increase in CO but the TPR is unchanged.
- In high doses (above 10 µg/kg/min.) it then activates α1 receptors also, which causes vasoconstriction with an increase in TPR and pulmonary pressure.
- Adverse effects include nausea, vomiting, tachycardia, ectopic beat, HT in high dose.

(C) Phosphodiesterase III inhibitors

- Amrinone and Milrinone are the two phosphodiesterase inhibitors. They inhibiting the enzyme phosphodiesterase, increase the stay cAMP with in the myocardial cell ⇨ as a result sustained rise of Ca^{2+} concentration in these cells occurs ⇨ rise of cardiac contractility.

- Both are also called "Inodilators" because they increase cardiac contractility and at the same time produce vasodilatation.

Cont.

- Thrombocytopenia is the most prominent and dose related side effects, but is mostly transient and asymptomatic.
- Nausea, diarrhoea, abdominal pain, liver damage, fever are the other side effects.

Dose-

- **Amrinone**: 0.5 mg/kg bolus inj. Followed by 5-10 µg/kg/min. IV infusion (Max. 10 mg/kg in 24 hr.)
- **Milrinone:** 50 µg/kg IV bolus followed by 0.4 – 1.0 µg/kg/min. infusion.

Diuretics

They generally cause natriuresis and water removal ⇒ this leads to removal of fluid from the body ⇒ leading to reduction of volume of blood + other ECF components (= reduction of overload) reduction of ⇒

- Pulmonary congestion (dyspnea) +
- Peripheral congestion (peripheral edema) +
- Preload

Cont.

-High ceiling diuretics- (FUROSEMIDE, BUMETANIDE)

High ceiling diuretics act principally on the ascending limb loop of Henle. They are high potency diuretics and are effective even when there is renal insufficiency. IV furosemide promptly increases systemic venous capacitance and produces rapid symptomatic relief in acute left ventricular failure.

Adverse effects- Acute fluid loss, hypotension, Hypokalemia, Hypomagnesimia, Hyperuricemia, Ototoxicity

Dose- Furosemide (LASIX): 20-80 mg, tab. orally

Cont.

-Thiazide diuretics- (Hydrochlorothiazide)

Act principally on the early distal tubule of the nephron and are of moderate potency. Thiazide diuretics become inefficient in presence of renal insufficiency.

Thiazide however cannot be used where the GFR is < 50 ml/min.

AEs- Hypokalemia, Metabolic defects, Volume depletion, Hypersensitivity reaction.

Dose- Hydrochlorothiazide (Esidrex) 25-100 mg/day

-Aldosterone antagonist-
(Spironolactone, Eplerenone)

These enhances Diuresis by promoting Na+ and Water excretion (While retaining K+) and prevents Myocardial as well as vascular fibrosis which is responsible for pathological remodeling of the heart.

AEs: Hyperkalemia is a major risk during the therapy and require serum K+ monitoring. Gynaecomastia may occur in male patients, after long term use.

Dose: - 25-50 mg OD orally

Inhibitors of Renin-Angiotensin system
-ACE inhibitor-

These drugs not only block the conversion of Ang-I to Ang-II but also prevent the breakdown of bradykinin to vasodilatation. They also decrease aldosterone secretion and hence reduce salt and water retention, so CO improves.

They also cause natriuresis and most imp. They Prolong the survival by preventing pathological remodeling of the heart and blood vessels.

Cont.

Most commonly used ACEIs

- **Enalpril** (2.5 mg BD and worked up to 10 mg BD)
- Lisinopril (2.5 - 5 mg OD, worked up to 20 mg OD)
- Ramipril (2.5 mg OD, worked up to 10 mg OD)

AEs- Hypotension after first dose, dry cough, angioneurotic oedema, foetal hypotension with a risk of foetal malformation if administer during II or III trimester of pregnancy, hyperkalemia.

DIs- Non systemic antacid reduce the BA of ACEIs, NSAIDs may impair the hypotensive effects of ACEIs by blocking bradykinin-mediated vasodilatation etc.

Angiotensin (AT1 receptor) antagonists

-Losartan-

ARAs stimulate renin release and increases circulating Ang II levels, resultant increased amount of Ang II would now stimulate AT2 receptor which are lying unblocked causes vasodilatation.

Dose- 25-50 mg OD

AEs-

- Cause foetal toxicity
- Precipitate renal failure in patients with bilateral renal artery stenosis.
- Hyperkalemia in patients with renal failure
- First dose hypotension in rare cases may occur

Vasodilators

These agents reduce pulmonary congestion and increase cardiac out put by reducing preload and/or after load. They also prevent remodeling of the heart.

The nitrate receptors presents on smooth muscle. The nitrate receptors possess –SH groups which reduce nitrates to nitrite and nitric oxide (NO). The NO itself gets converted to an intermidiate- reactive nitorsothiol which activates intracellular guanylate cyclase (GC) to convert GTP to cGMP results in vascular smooth muscle relaxation.

Cont.

Venodilators

-Nitorglycerine –

In patients of HF with dyspnoea, venodilators like or long-acting nitrates are preferred because these may reduce the filling pressure and ultimately the pulmonary congestion.

Dose-

Route	Dose (mg)	Onset (min)	Duration (hrs)
Sublingual	0.5	2-5	0.25-0.5
Oral	5-15	20-30	4-8
Ointment (2%)	-	15-30	3-8
Transdermal	5-10 mg/24hr	30-40	Max. 24 hr

Cont.

AEs- Throbbing headache, flushing of face, palpitations, dizziness, Tolerance develop rapidly if used orally in sustained release form, or transdermally or by I.V. infusion without drug free interval.

DIs- Sildenafil and other vasodilator potentiate the hypotensive action of nitrates (Inhibit the metabolizing enzymes PDE-IV and potentiate further release of cGMP), sudden death occures.

Cont.

Arteriolar dilator
-Hydralazine-

Vasodilatation due to hydralazine is partly endothelium dependent and may involve generation of nitric oxide and stimulation of cGMP, increase in intracellular levels of cGMP are associated with vascular smooth muscle relaxation.

Hydralazine (25-50 mg BD orally) and is generally not employed BY I.V. route because the onset of action is hardly different than that of oral

AEs- Headache, tachycardia, nausea, nasal congestion, and anginal attack (due to tachycardia), prolong use in High doses it causes reversible disseminated lupus erythematosus like syndrome

Cont.

Arteriolar + Venodilator

(Sod. Nitroprusside)

Sod. Nitroprusside activates guanylyl cyclase either directly or through release of nitric oxide. This results in an increase in the intracellular levels of cGMP which provides vascular smooth muscle relaxation.

Patients having severe chronic failure benefitted by combination of arteriolar + venodilator, And useful in patients in whom ACEIs are contraindicated or are not tolerated.

Cont.

Dose-It is powerful parenterally administered vasodilator, the onset effect is rapid (30 sec.) after I.V. infusion (0.3 µg/kg/min, slowly raised to 0.5 µg/kg/min) and disappear within 10 min after discontinuation.

AEs- Other than headache, nausea and vomiting Which quickly dissipate after the infusion is stopped.

β-Adrenergic blockers:

Metoprolol, Bisoprolol, Carvedilol

As a general rule β- blockers are contraindicated in CHF. Because HF patients have a decreased CO since CO is equal to stroke volume (SV) multiplied by heart rate (HR), an increase HR would be necessary to maintain an adequate CO in the presence of decreased SV as observed in HF. As a result, a decrease in HR and cardiac contractility produced by β- blockers would be expected to produce acute cardiac decompensation, in patients with HF.

Cont.

β- blockers like Metoprolol, Bisoprolol, carvedilol, improve ventricular function and prolong the survival in HF patients.

Doses-

Metoprolol- 50-100 mg OD orally

Bisoprolol- 2.5-10 mg OD orally

Carvedilol- 6.25 mg BD orally, increased to 12.5 mg BD

Cont.

AEs-

- Bronchoconstriction
- Sudden withdrawal of β- blockers is very dangerous most imp. Cause seems to be up regulation of β- adrenoceptors due to use of β- blockers.
- Person who use insulin or oral antidiabetic tab. Are susceptible to develop hypoglyemia.
- Occasionally can produce some CNS symptoms like depression and sleep disturbance.
- Rash, urticaria rarely.
- Can mask some symptoms of hyperthyroidism.

Absolute CIs- Severe bradycradia, pre existance gross block in the conducting system and overt left ventricular failure, Asthma, COPD, Depression, Active peripheral vascular disease.

Other drugs

Metabolic cardioprotectives: Trimetazidine

It prevents the degradation of membrane unsaturated fatty acids by lipid peroxidation and thus reduce myocardial O2 demand. It also inhibit the superoxide cytotoxicity to protect the myocardium from the harm full effect. but can cause *parkinsonism*.

Dose- 20-60 mg OD tab. and cap.

Calcium sensitizers
-Levosimendan-

It increases sensitivity of troponin in the Heart to calcium. This results in increased myocardial contractility. It is infused i.v. for short treatment of severe heart failure.

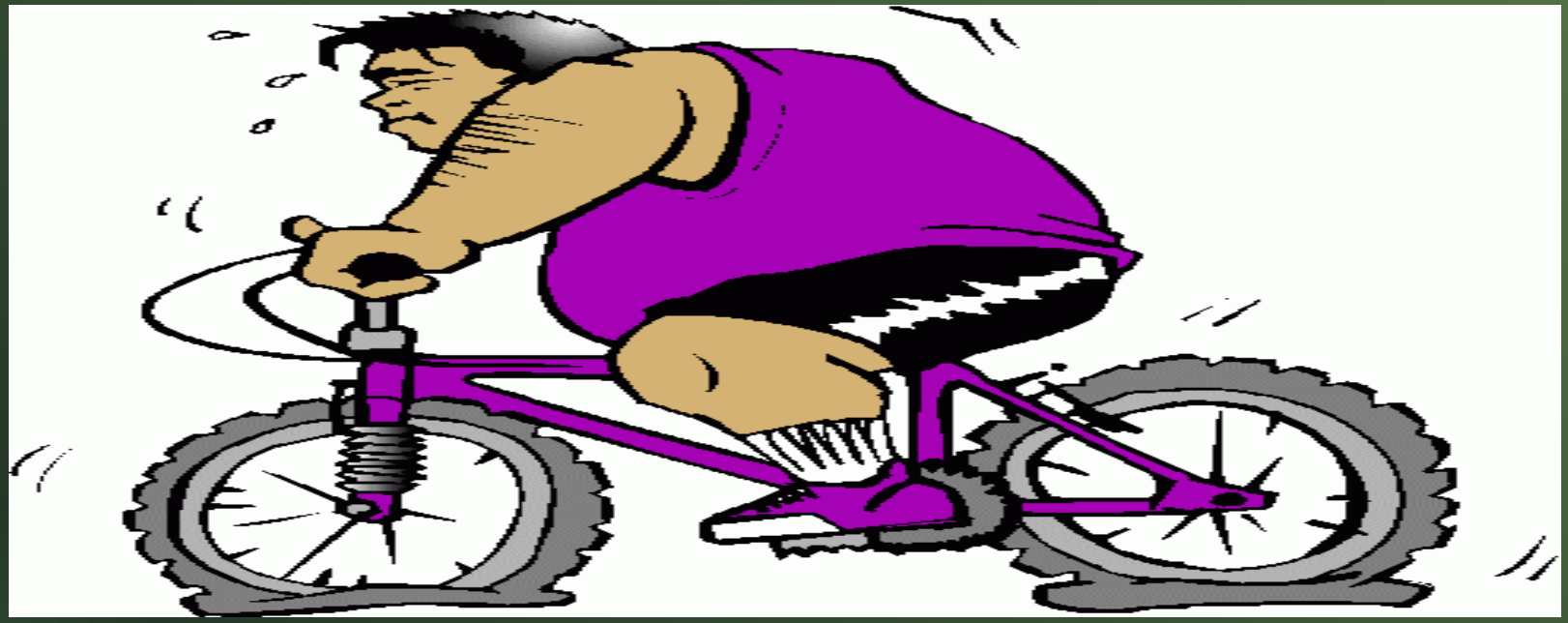
Levocarnitine

It is a N-containing amino acid in muscle, which has antioxidant activity. It is indicated in cardiomyopathy and muscle dystrophy caused by carnitine deficiency.

Preparations containing **Coenzyme Q_{10}** (a part of the mitochondrial redox system), stimulate ATP synthesis and improve myocardial contractility in CHF.

Non Pharmacological

- **Activity-**
  - Routine modest exercise for class I-III
  - For euvolemic patients- regular isotonic exercise such as walking or riding a stationary-bicycle ergometer



- **Diet-**
  - Restriction of sodium (2-3 g daily) is recommended in all patients, Extra < 2g reduction in moderate to severe cases.
  - Fluid restriction (<2 L/day) if hyponatremia (<130 meq/L)
  - Caloric supplementation- with advanced HF and unintentional weight loss or muscle wasting (cardiac cachexia)
  - Reduce or eliminate alcohol and caffeine
  - Quit Smoking

Three things for preventing heart diseases are – Eat less fried food, less butter and ghee. Second, exercise daily for around 45 minutes. And third, reduce stress in life

Surgical measures

- Cardiac Resynchronization
- Implantable Cardiac Defibrillators
- Intraaortic balloon counter pulsation
- Percutaneous and surgically implanted LV assist devices
- Biventricular Pacing
- Cardiac transplantation

Novel agents in HF

- Newer Inotropes-
  - Cardiac myosin activators- Omecamtive mecarbil
  - Na/K-ATPase inhibitors- Istaroxime
  - Ryanodine receptor stabilizers- JTV-519(K 201),S107,S44121
  - SERCA2a activators- MYDICAR
- Vasodilators- Relaxin
- Neuregulins-
  - recombinant human NRG-1β2

- Novel RAAS blockers-
  - Direct renin inhibitors- Oral Aliskiren,IV Remikiren, IV Enalkiren
  - Angiotensin receptor & neprilysin inhibitors- LCZ696, AHU377 ,Candoxatril, Ecadotril
  - Aldosterone blockers-
    - Non steroidal minrelocorticoid receptor antagonist- PF3882845,BR-4628
    - Aldosterone synthase inhibitors- FAD286, LCI699
- Dual ACE/NEP Inhibition – Vasopeptidase Inhibitors
  - Omapatrilat, sampatrilat, fasidotrilat, MDL 100240, Z13752A, BMS 189921 and mixanpril
- Dual NEP & ECE(endothelin converting enz.) inhibitors
  - GGS34043, GGS34226, GGS26303, SLV306

- Triple enzyme inhibitors of ECE/NEP/ACE
  - GGS26670
- Dual dopamine D2-α2 agonist
  - Nolomirol
- Dopamine β-Hydroxylase inhibitor
  - Nepicastat
- Adenosine A1 receptor antagonists
  - BG9719,BG9928
- Carnitine palmitoyl transferase-1(CPT-1) inhibitors
  - Etoxomir, Oxenicine
- Matrix Metalloproteinase (MMP) Inhibitors
  - Batimastat, ilomastat, marimastat and prinomastat
- Immune modulator
  - CelacadeTM

Cardiac Myosin Activators

(Omecamtive Mecarbil)

They accelerate transition of actin-myosin complex from a weakly bound to strongly bound configuration

↓

↑ myosin head interaction with actin

↓ nonproductive ATP hydrolysis

↓

↑duration of systole→↑stroke vol -→improvement in myocardial systolic function in absence of arrythmogenesis & ↑ O2 consumption.

- Currently under phase 2 trial.

Istaroxime

MOA-

- Inhibition of sodium/potassium adenosine triphosphatase (Na+/K+ ATPase).

- Drug is under phase 2 trial.

Vasodilators - Serelaxin

- **Recombinant human relaxin- 2**
- Relaxin- circulating peptide found in pregnant women
- Regulates systemic vasodilation
- Improves dyspnea significantly
- Dose 30 µg/kg/day infusion
- Currently under phase 3 trial.

SERCA 2a activators

- Improved systolic and diastolic functions, improved ventricular metabolic reserve, and reducing the likelihood of ventricular arrhythmias during ischemia-induced Ca^{2+} overload
- Currently under phase 3 trial.

Ryanodine receptor stabilizers (JTV519)

- preserve left ventricular systolic and diastolic function
- prevents left ventricular remodeling

Neuregulins

- Recombinant human NRG-1β2 infusion improve cardiac structure and function by 90 days
- Increase in cardiac output as well as vasodilator effect
- Currently under phase 3 trial.

Novel blockers of the renin–angiotensin aldosterone system

Direct renin inhibitors

- **Oral Aliskiren,IV Remikiren, IV Enalkiren**
- Reduce increased plasma renin activity directly independent of plasma levels of BNP, background effect of beta blockers & ACEI.
- MOA- inhibit conversion of Angiotensinogen to angiotensin-I
- Drawback- hyperkalemia, hypotension

Angiotensin receptor and neprilysin inhibitors

(Candoxatril, Ecadotril)

- Atrial natriuretic peptide, B, C and exogenous D-type, possess differing degrees of hemodynamic, neurohormonal, renal and cardiac effects

Novel approaches to aldosterone blockade

Non-steroidal mineralocorticoid receptor antagonists

- PF3882845 -greater blood pressure reduction and renal protection
- BR-4628 -dihydropyridine (DHP) structure

Aldosterone synthase inhibitors

- There is induction of aldosterone synthase (CYP11β2) or angiotensin II in the failing ventricle
- FAD286 - improved cardiac hemodynamic parameters, preventing progressive LV remodeling
- LCI699 - reduction in blood pressure

Triple Enzyme Inhibitors of ECE/NEP/ACE

- **GGS 26670**
- Improved LV function and reduced LV collagen accumulation better than either ACE alone or ECE-NEP inhibition

Dual Dopamine D2- Adrenoceptor agonist

- **Nolomirole**
- Inhibits catecholamine release from sympathetic nerve endings and also inhibits the release of TNF from cardiac tissue
- Significantly reduces hypertrophy and attenuates signs and symptoms

Dopamine-Hydroxylase Inhibitor

- DBH catalyses the conversion of dopamine (DA) to norepinephrine (NE) in sympathetic nerves
- Nepicastat- reduce norepinephrine synthesis.
- Phase 2

Adenosine A1 receptor antagonists

- BG 9928, BG 9719
- Protects renal function and exerts additive natriuretic effects without excessive potassium loss

Carnitine Palmitoyl Transferase-1 (CPT-1) Inhibitors

- CPT-1 helps in metabolism of fatty acid which is a source of energy production in heart
- Etoxomir, Oxfenicine
- dilation, prevents ventricular remodeling.

Matrix Metalloproteinase (MMP) Inhibitors

- Enhanced expression of MMP triggers signaling cascade of cardiac remodeling
- Batimastat, ilomastat, marimastat and prinomastat, PG-53072
- Prevent ventricular dysfunction and delay heart failure progression

Immune modulator

- **CelacadeTM**
- Prevents chronic inflammation and apoptotic cell death by activating physiological immune system's IL -10 mediated anti-inflammatory process.

- Improve quality of life in patients of NYHA class III or IV heart failure.
- Reduce the risk of death and hospitalization due to chronic heart failure

Can CHF prevented

CHF can't always be prevented, but there are many things can do to help.

Try preventing CHF by practising good heart health. This will also guard against heart attack, stroke, and coronary artery disease. Tips to follow include:

- Control high blood pressure
- Eat a healthy diet
- Exercise
- Control blood sugar levels (especially if you have diabetes)
- Maintain good blood cholesterol levels
- Quit smoking

Conclusion

Heart failure has reached epidemic proportions. Early identification of the risk factors and initiation of appropriate therapy at early stages prevents development of heart failure. Clinical diagnosis and diagnostic imaging, echocardiogram in particular identifies patients with heart failure. The optimum utilization of the available drugs, general measures and surgical procedures appropriate to the condition improves the outcome of these patients.


Thank you