

Heart Failure in Children & Management



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What a normal heart do everyday:

- Consumes more energy than any other organ.
- It cycles about 6kg of ATP every day (20 to 30 times its own weight).
- It beats about 100,000 times
- Pumps approximately 10 tons of blood through the body.

(NEJM 356;11 www.nejm.org march 15, 2007 1141)

Definition of HF

- “the failure of cardiac function to maintain appropriate pulmonary and systemic circulation, with resulting secondary consequences”
- HF can also reflect abnormalities of vascular function, systemic and metabolic responses, and abnormalities of other organs such as the kidney.

Definition

Heart fails to meet the circulatory and metabolic needs of body.

Mechanism of Compensation

Heart Rate

- Neural and hormonal input

Contactility

- 2^o Catecholamines and autonomic input

Augmenting preload

- Constriction of venous capacitance vessels
- Renal preservation of intravascular volume

Pathophysiology

Reduced
myocardial
contractility



Heart
failure

Increase
haemodynamic
burden

HF/Cardiomyopathy (CM) - epidemiology

- 10% of tertiary care pediatric care setting patients develop symptomatic HF.
- 50% of them have CHD (70% preserved in infancy).
- CM in general occur in 8 per 100000 infant (HCM reported up to 1 in 500).
- Risk of death in 2 years in :
 - RCM is 50%
 - HCM is 12%
 - DCM is 14%
- A 5 – years risk for death or transplantation for around 50% for patients with dilated CM.

Systolic dysfunction

Diminished ventricular contractility > reduce SV > reduce CO

Causes

Anatomic stresses

- Eg: Coarctation of Aorta > increase afterload (end systolic wall stress)

Neurohormonal factors

- Increase systemic vascular resistance

Diastolic dysfunction

Decreased ventricular compliance > increase venous pressure (to maintain ventricular filling)

Causes

Anatomic obstruction

- Eg: Pulmonary venous obstruction > prevent ventricular filling

Reduce ventricular compliance

- In cardiomyopathy and transplant rejection

External constrain

- Pericardial effusion

Poor haemodynamic after Fontan procedure

- Increase pulmonary vascular resistance

Pathology (clinical level)

1 . High output HF

- Frequently seen in infants and young children.
- Occurs in various congenital lesions with increased pulmonary blood flow (eg. Large VSD/PDA/AP window and common art. Trunk).
- Ventricular systolic function is typically preserved or even hyperdynamic with an increased LV chamber dimension

High output HF

- Age of presentation is 2 weeks to 6 months (High PVR may delay the presentation.)
- FTT
- Sweating
- Pallor
- Tachypnea
- Hyperdynamic pulses
- Rales may be noted, frank pulmonary edema is infrequent.
- Gallop rhythm
- Hepatomegaly
- Peripheral edema is invariably absent except in the terminal phase.

2. Low output HF

- 1. Acute decompensation:
 - Like in obstruction of LV outflow (HLHS, critical AS, or severe coarctation of the aorta).
 - Decreased pulses
 - Pallor
 - Frank circulatory collapse between 2 and 14 days of life.
 - Tachypnea (either due to excessive pulmonary blood flow, elevated pulmonary venous pressure, or hypoxemia with acidosis) deferent from cyanotic CHD where they are blue but not tachypnic.

Low output HF

- 2. Less acute decompensation
 - Primary or acquired diseases of the myocardium (such as dilated CM or acute myocarditis) can mimic some features of the previous clinical appearance: in addition to:
 - Displaced or diffuse cardiac apex.
 - Gallop rhythm
 - Soft heart sounds
 - Murmur of mitral regurgitation(All indicate a dilated hypocontractile LV, rather than a primarily obstructed outflow tract).

Acute Heart Failure



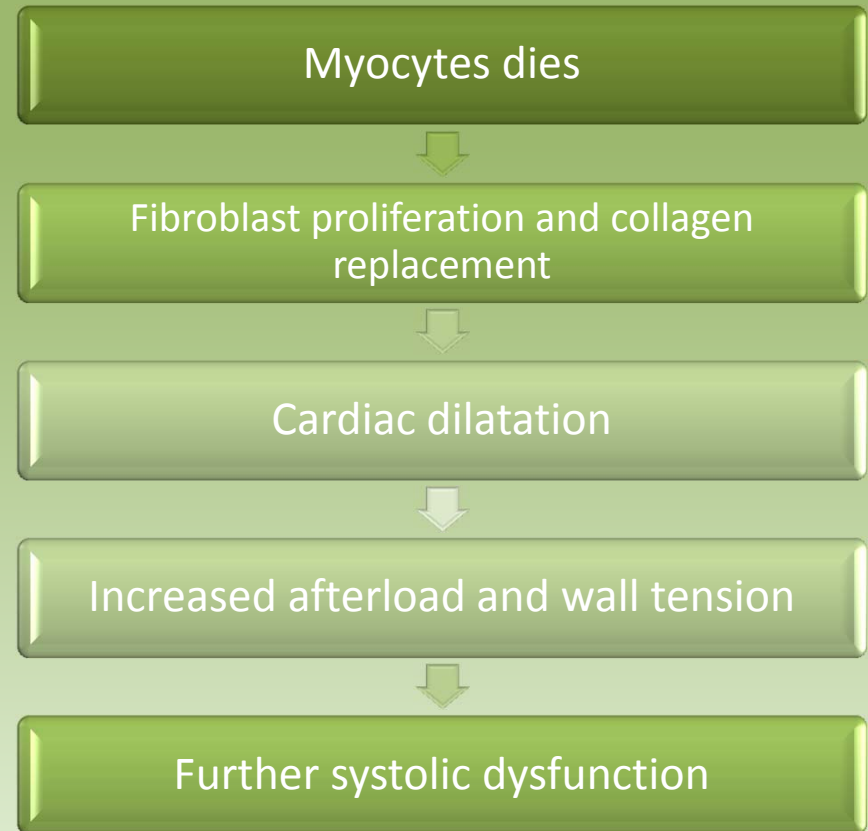
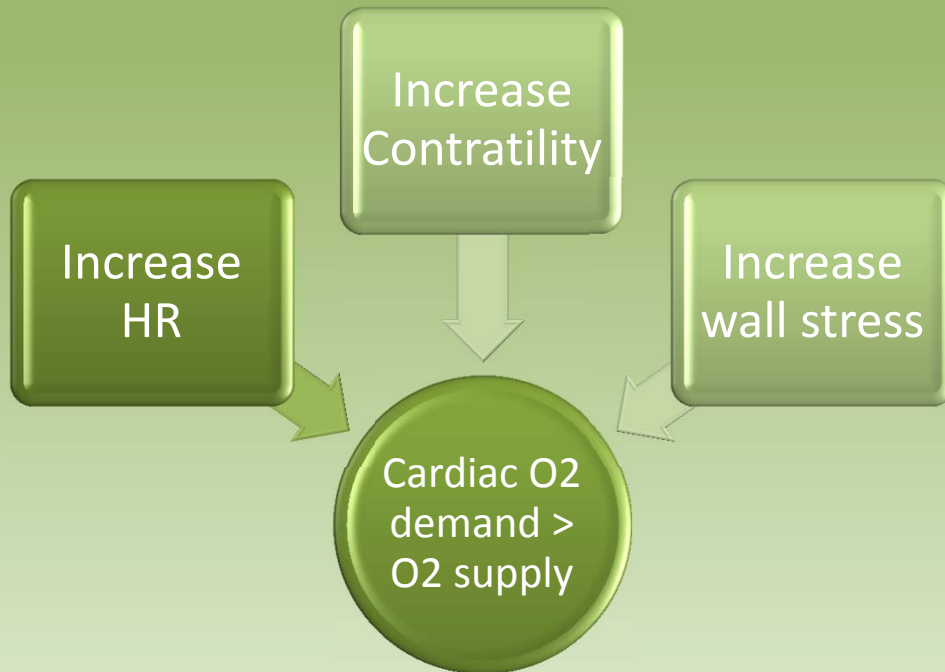
Chronic Heart Failure

Neurohormonal mechanism (SNS + RAAS -> direct cardiotoxicity + necrosis)

- Increase contractility
- Peripheral vasoC
- Salt + fluid retention

Cellular adaptation

- Energy starvation + loss of mitochondria
- Cytotoxic mechanism > necrosis
- Acceleration of apoptosis



Signs and Symptoms in INFANT

Left venous congestion

Tachypnoea (> 50)	Respiratory distress (retraction)
Grunting and difficulty with feeding	Diaphoresis during feeding (catecholamine surge)
Cardiomegaly and gallop rhythm	Tachycardia (> 160bpm)

Right venous congestion

Hepatosplenomegaly	JVP – not reliable 9 distance btwn RA to angle of jaw less than 8-10cm
Ascites / edema - less frequently	Most – FAILURE TO THRIVE
Lead to renal and hepatic failure	

In OLDER CHILD

Left venous congestion

Tachypnoea
(>30)

Respiratory
distress

Wheezing
(cardiac
asthma)

Right venous congestion

Hepatosplenomegaly

JVP distention

Edema / ascites /
pleural effusion

Clinical manifestation of poor CO

Fatigue / low
energy

Sweating

Pallor

Cool
extremities

Poor growth

Dizziness

Altered
consciousness

Syncope

Causes of CHF

Cardiac causes

Arrhythmia

- Complete heart block
- Supraventricular tachycardia
- Ventricular tachycardia
- Sinus dysfunction

Structural heart disease

Myocardial dysfunction (sys/dias)

- Systolic dysF – myocarditis, dilated cardiomyopathy, malnutrition, ischemia
- Diastolic dysF – hypertrophic cardiomyopathy, restrictive cardiomyopathy, pericardial tamponade

Non-cardiac causes

Increased preload (V overload)

- Structural heart disease (VSD, PDA, AR, MR)
- Anemia

Increased afterload

- Structural heart disease (AS, PS)
- HPT

Reduce O₂ carrying capacity (anemia)

High demand (sepsis)

Causes of CHF according to age gp

Fetus

- Anemia (Rh sensitive / fetal maternal transfusion)
- Arrhythmia- supraventricular tachycardia
- Myocardial dysF – myocarditis / cardiomyopathy
- Structural HD – rare (AV valve regurgitation)

Neonate / infants

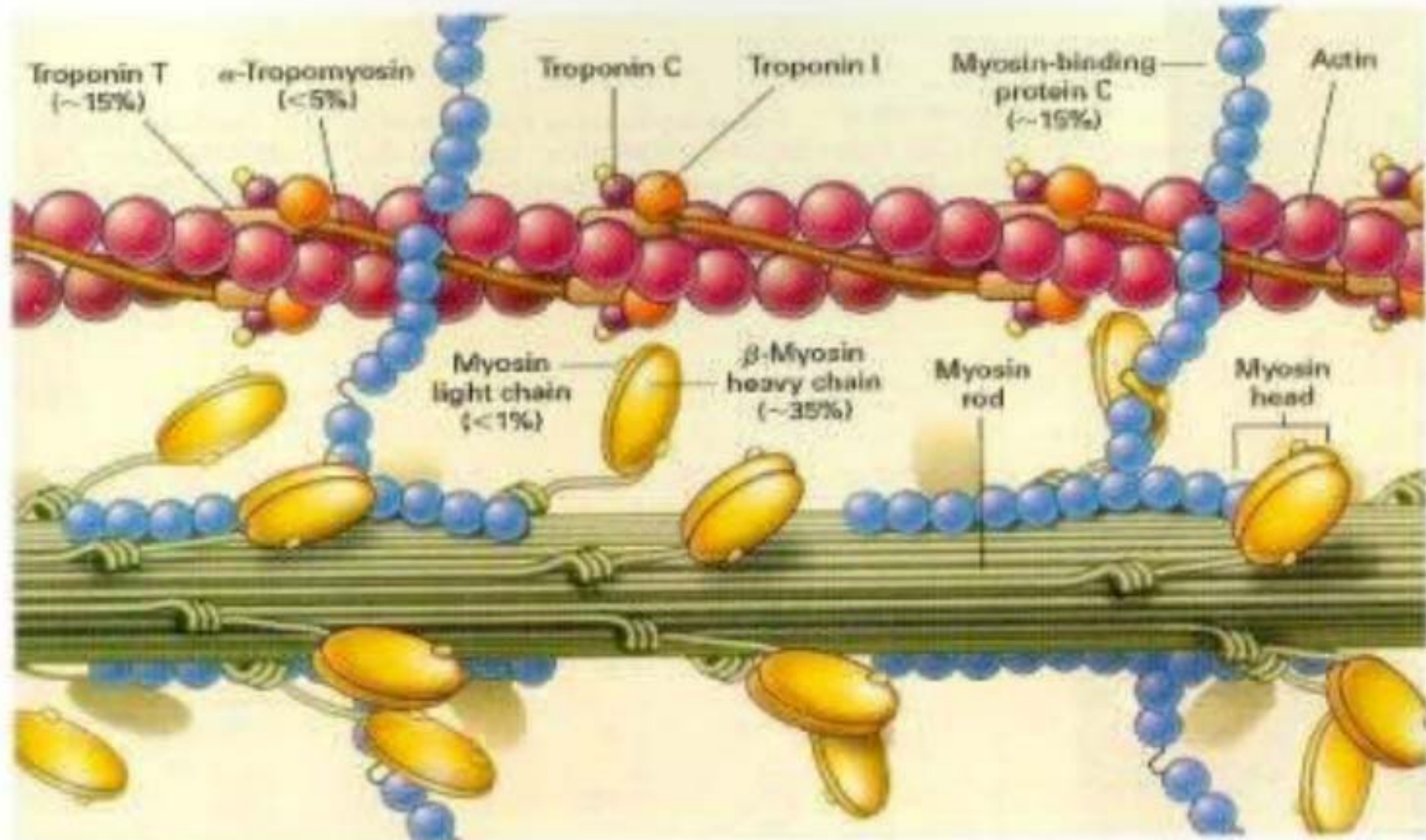
- Structural heart disease – thus depend on patency of the ductus arteriosus
- Myocardial disease- 1^o myopathic abnormalities / IEM
- Respiratory illness / anemia / infection

Older childs

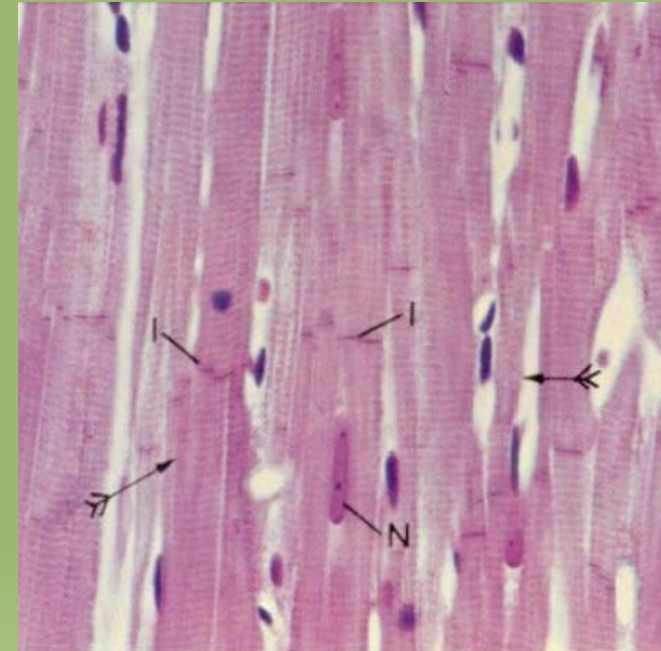
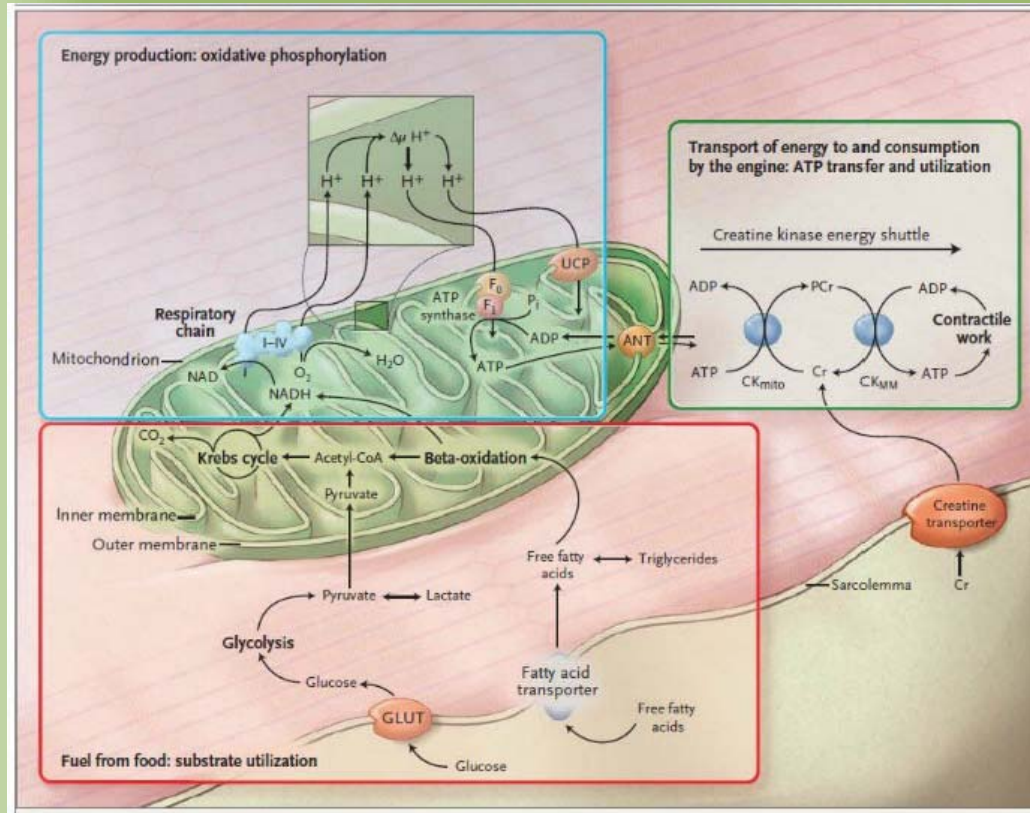
- Left sided obstruction disease – aortic stenosis / coarctation
- Myocardial dysf (myocarditis / cardiomyopathy)
- HPT / renal failure
- Rarely : arrhythmias / IHD

Adolescent

- Structural heart disease
- Chronic arrhythmia
- Acquired heart disease - cardiomyopathy

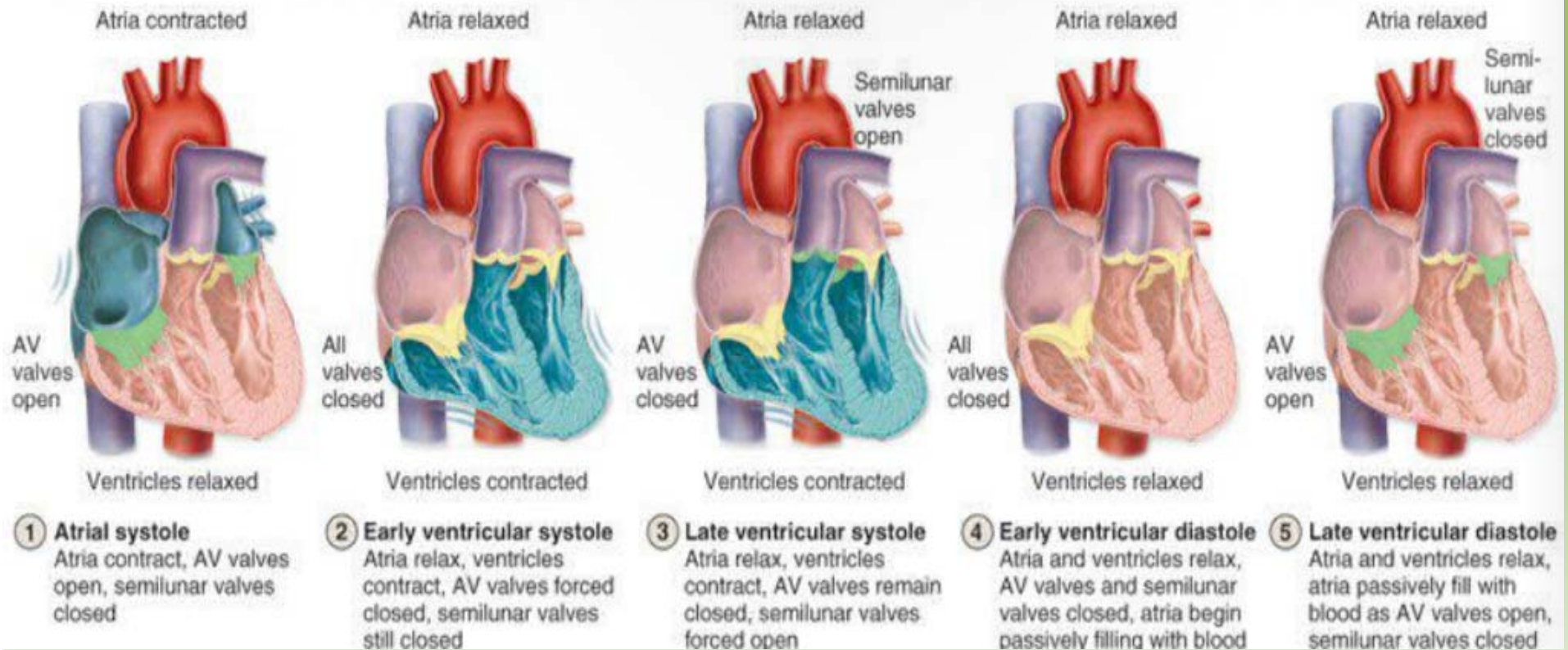


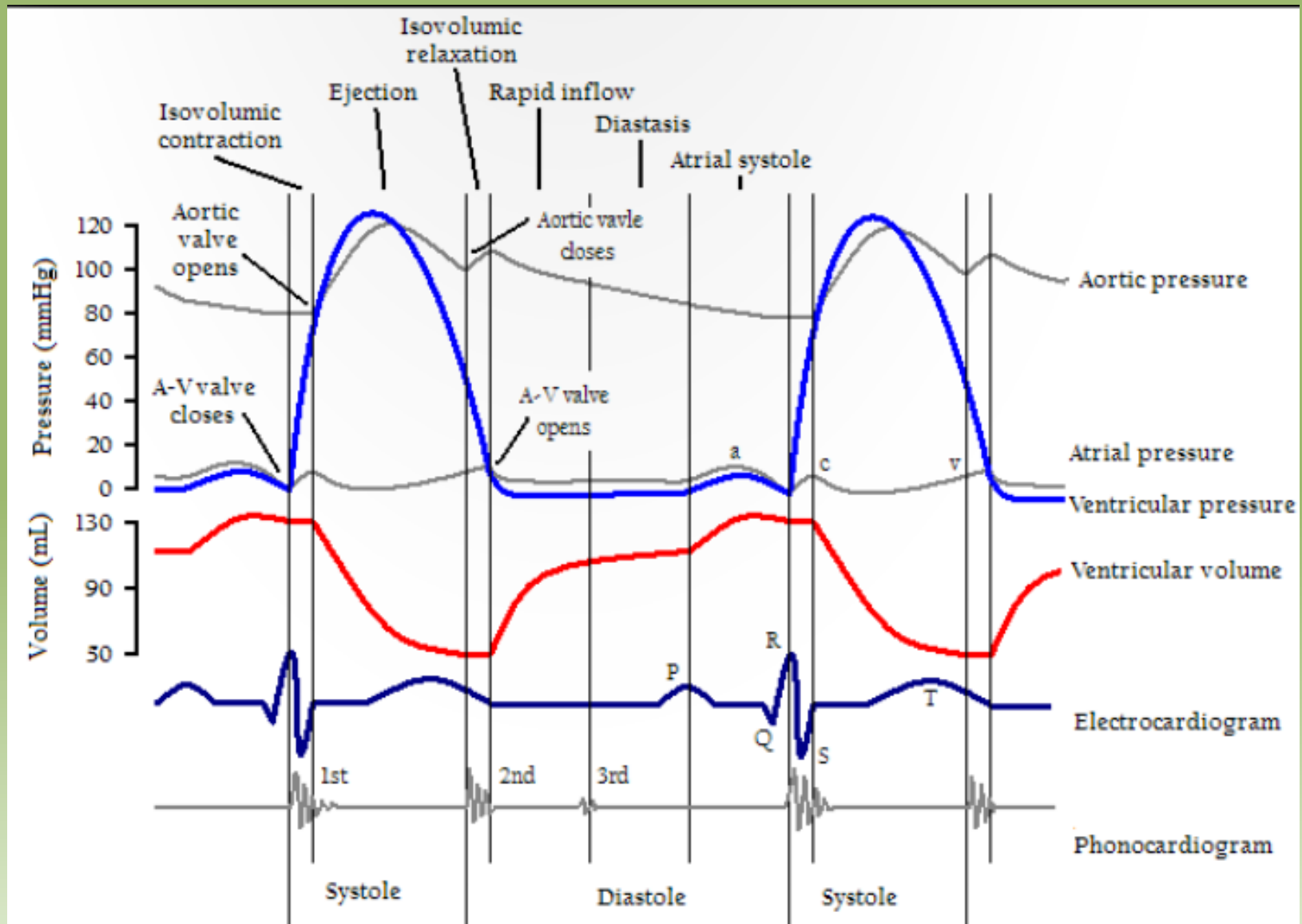
Histology & Cell level



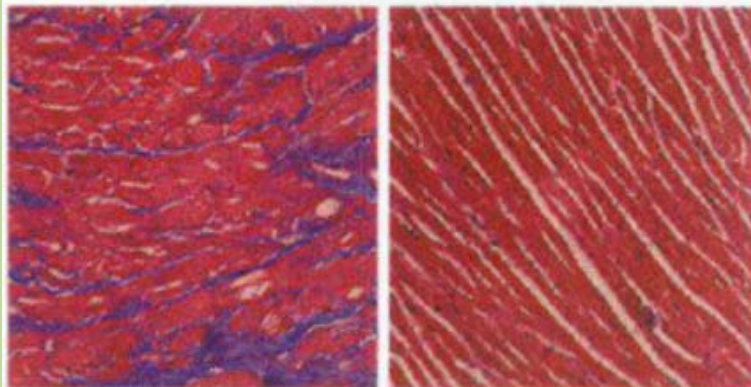
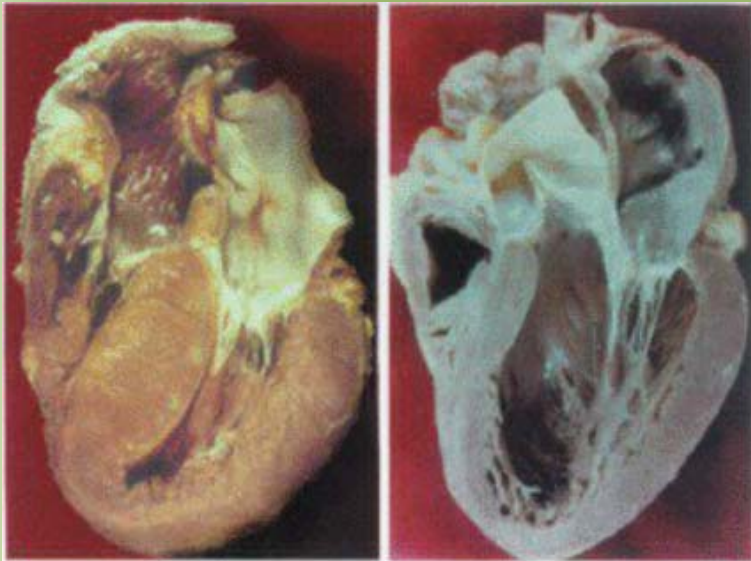
Cardiac Muscle, H&E (Med)
I = Intercalated discs
N = Nuclei
Arrows = Cross trabeculae

Structure \ Phase	Atrial systole	Early ventricular systole	Late ventricular systole	Early ventricular diastole	Late ventricular diastole	
	Atria	Contract	Relax		Relax	
Ventricles	Relax	Contract		Relax		
AV valves	Open	Closed			Open	
Semilunar valves	Closed		Open		Closed	



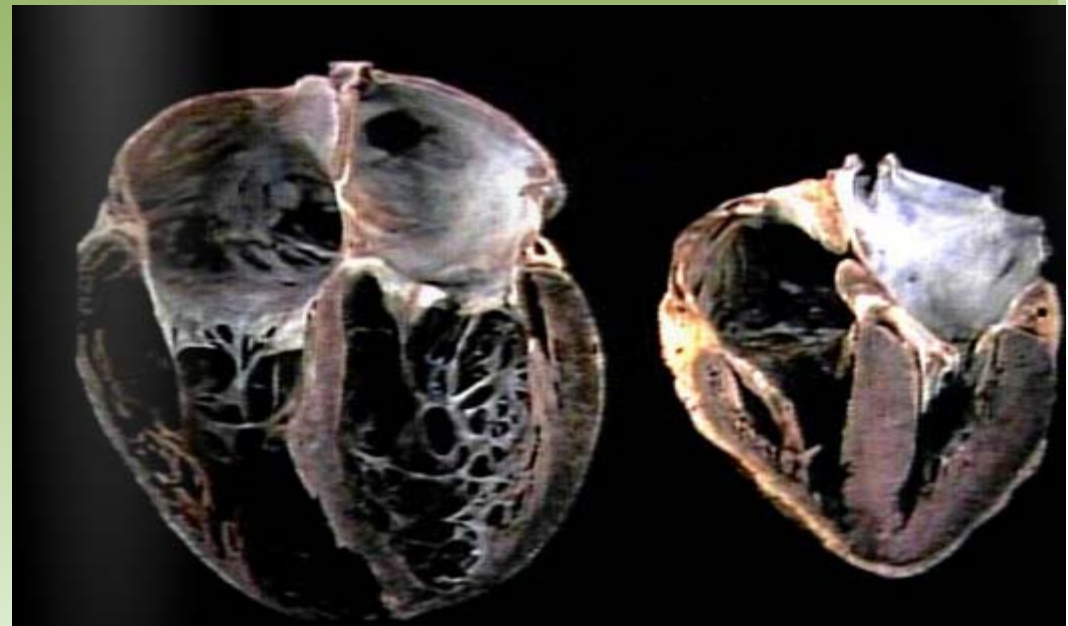
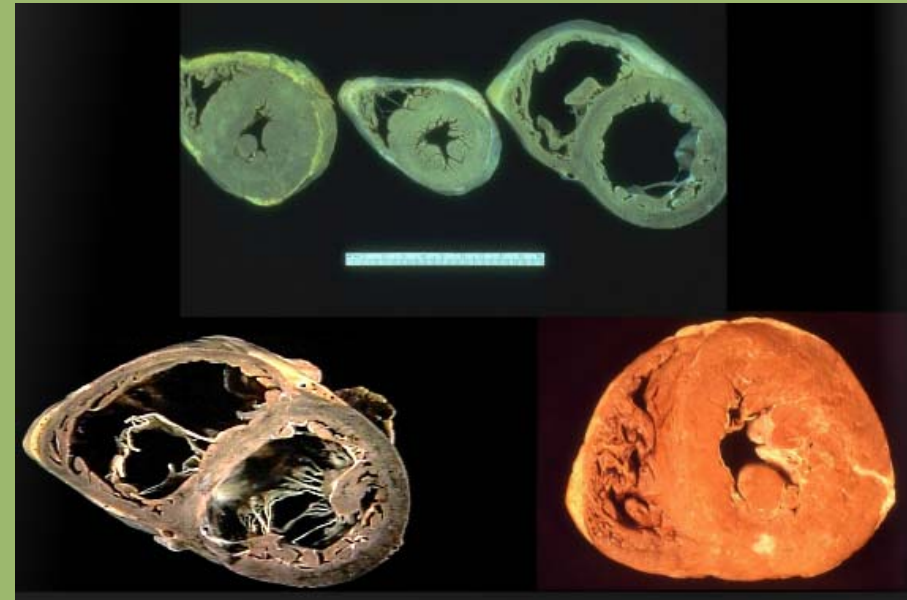


PATHOLOGY AT CELLULAR LEVEL

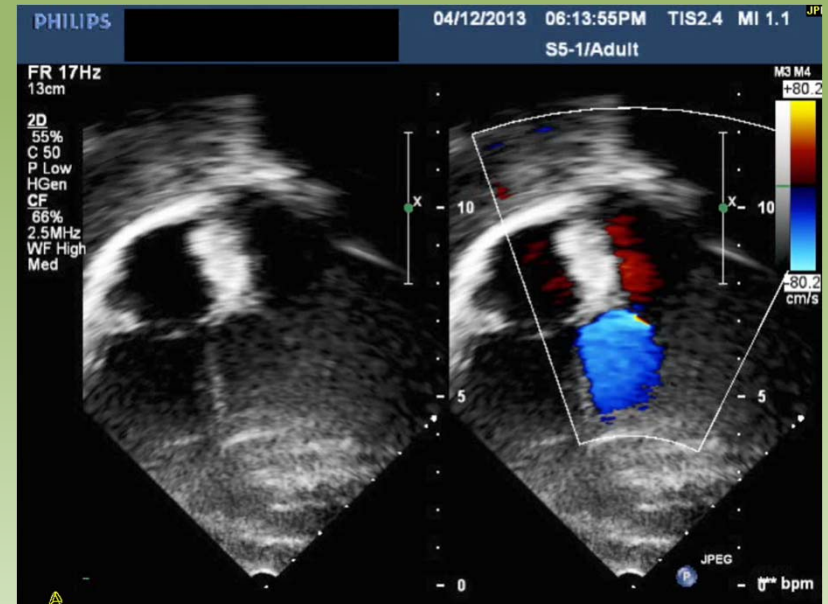
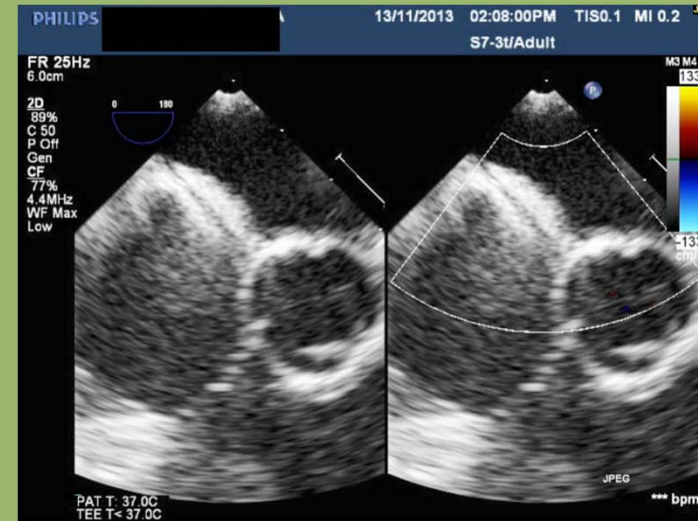
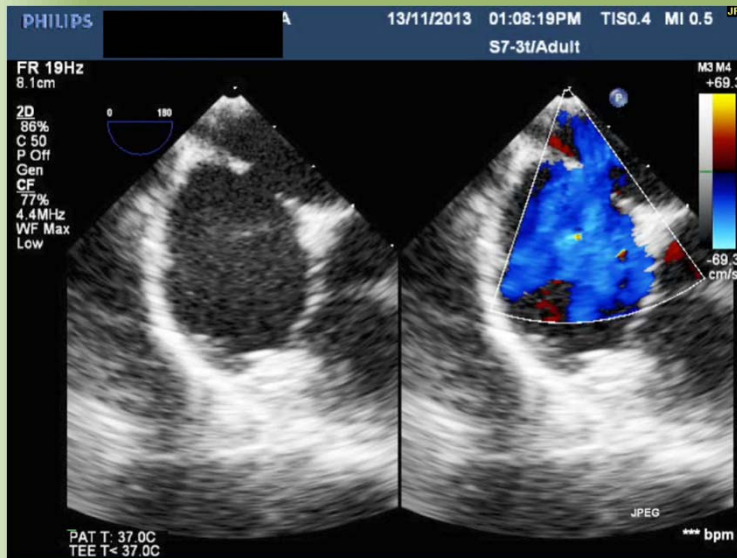


HCM

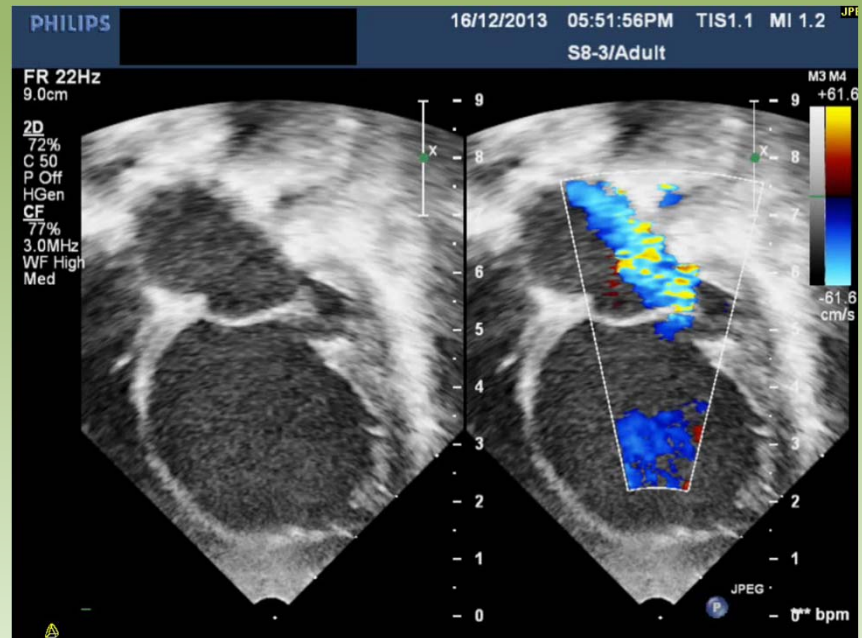
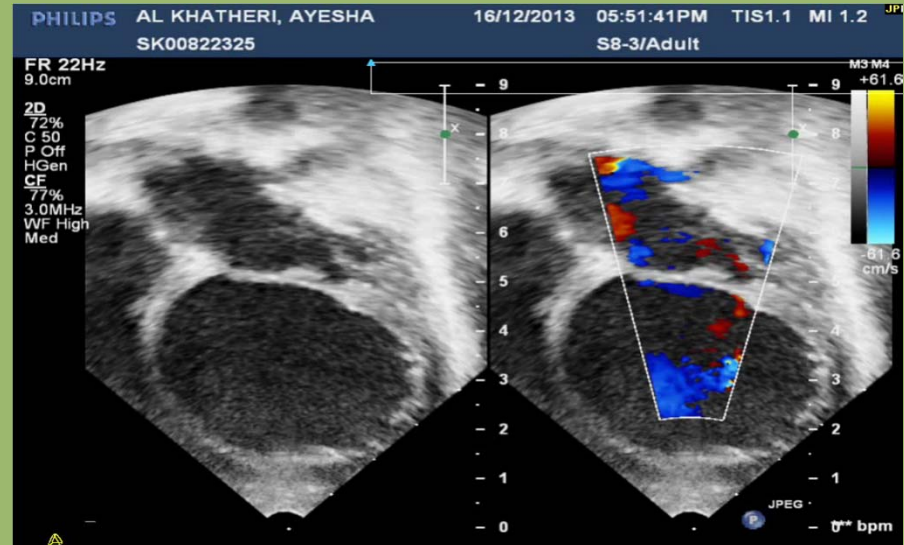
Normal



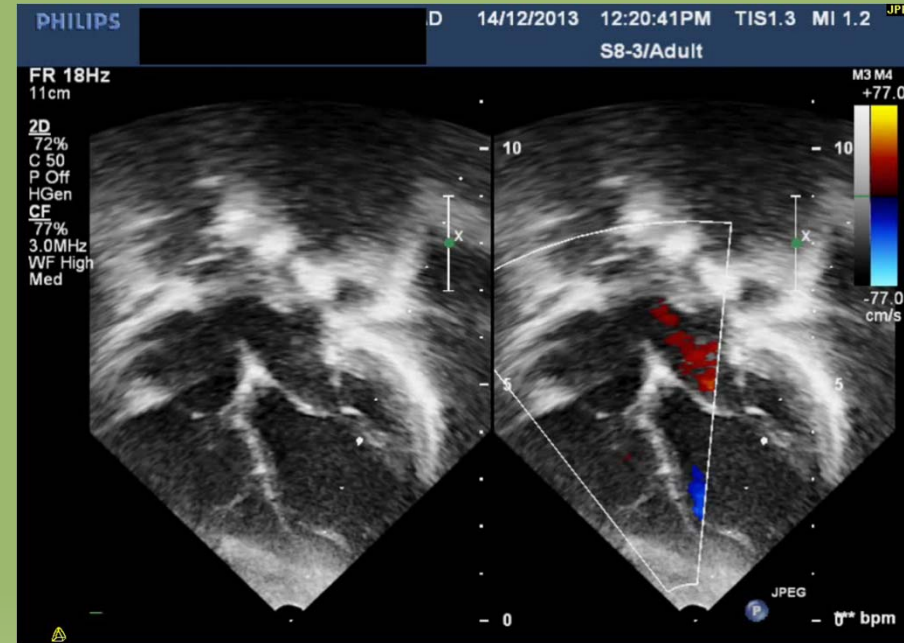
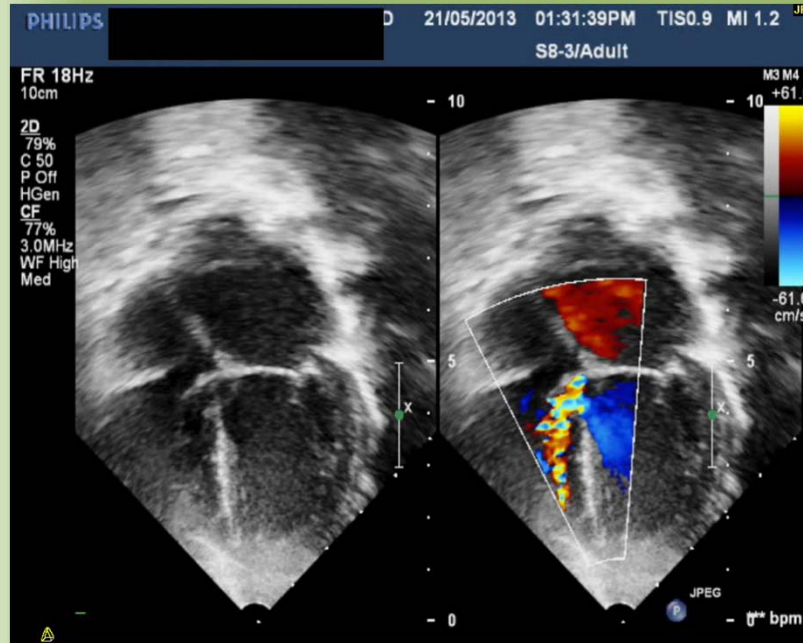
Atrial Septal Defect



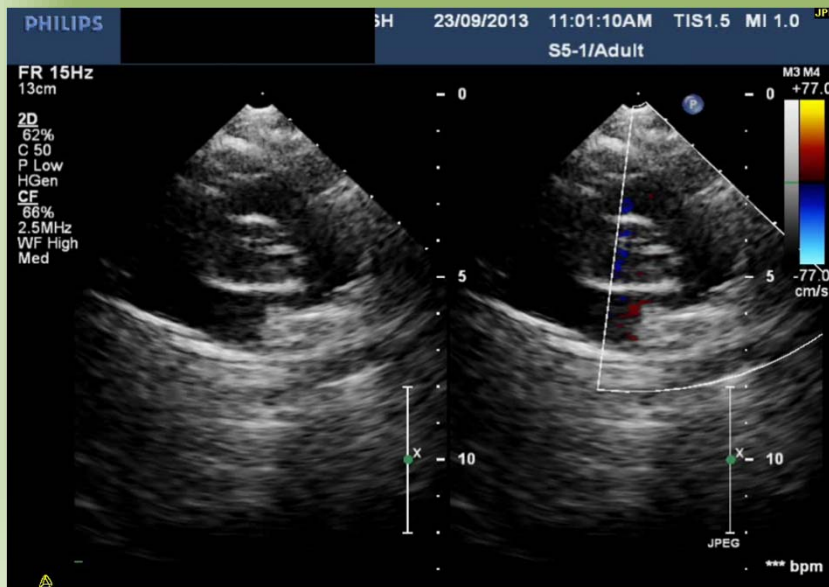
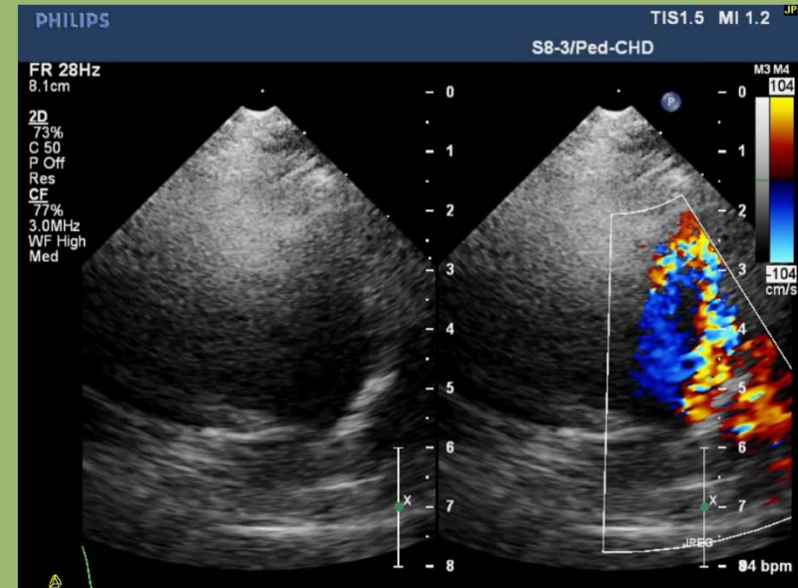
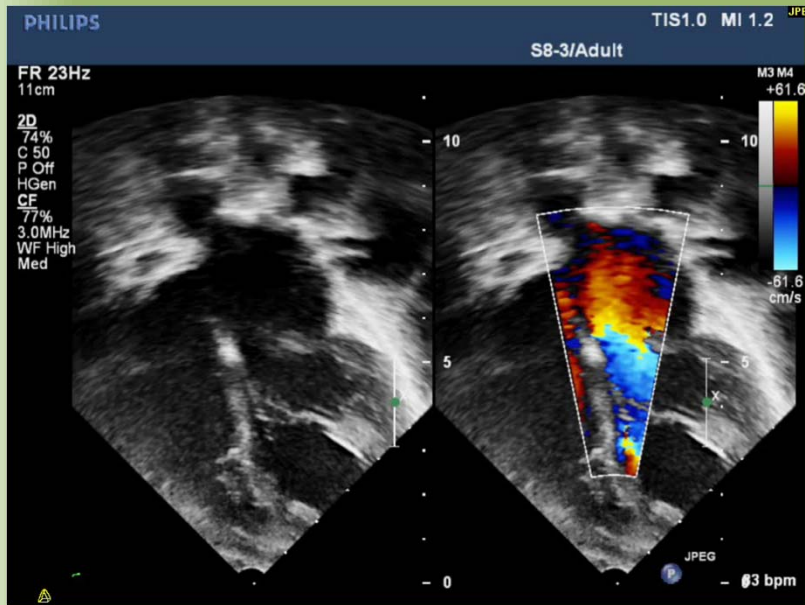
Dilated Cardiomyopathy



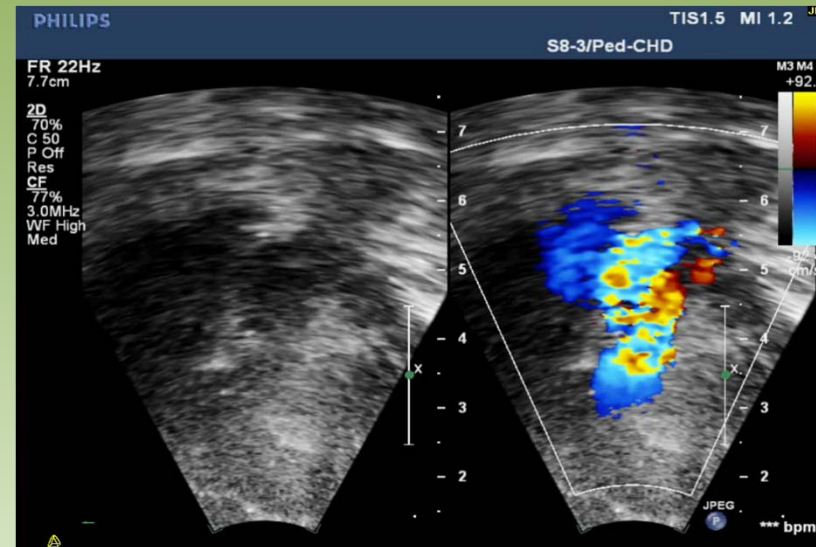
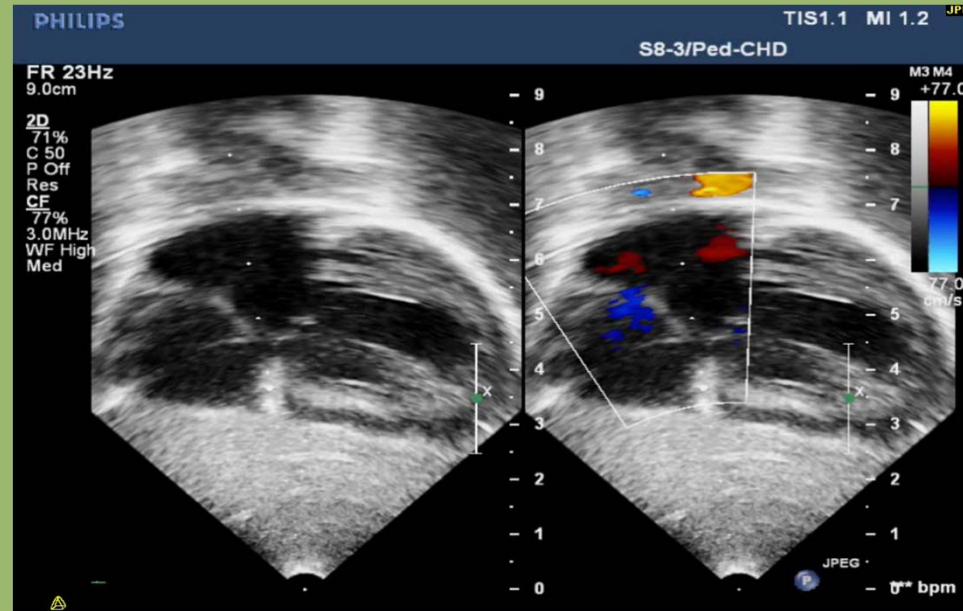
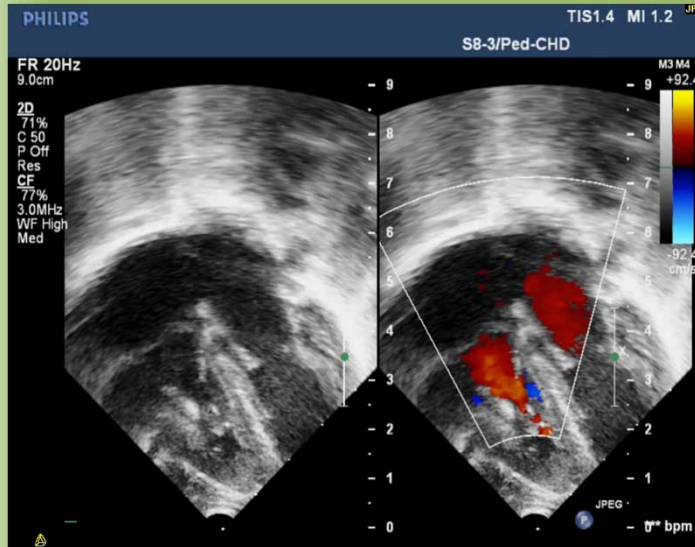
Ventricular Septal defect



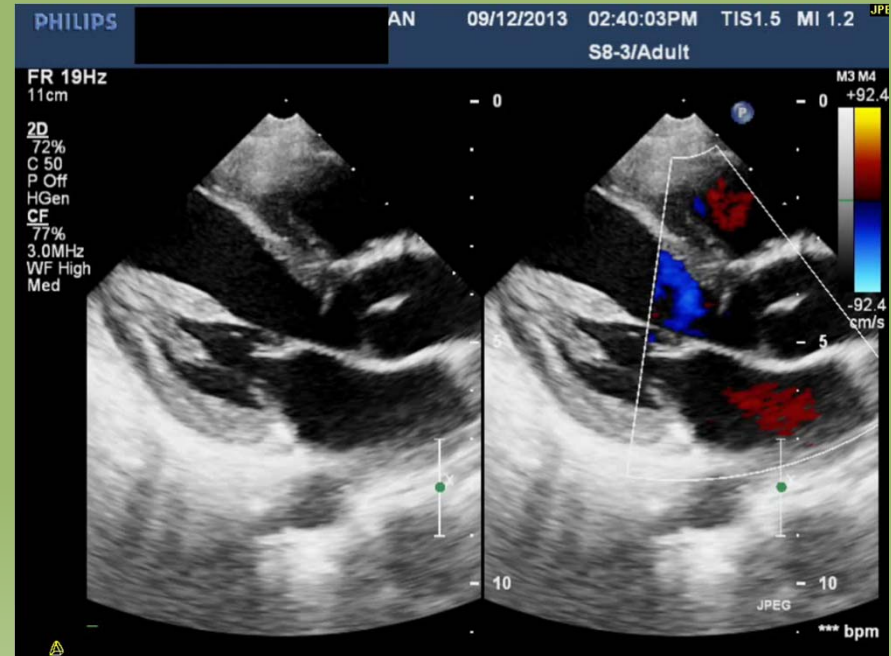
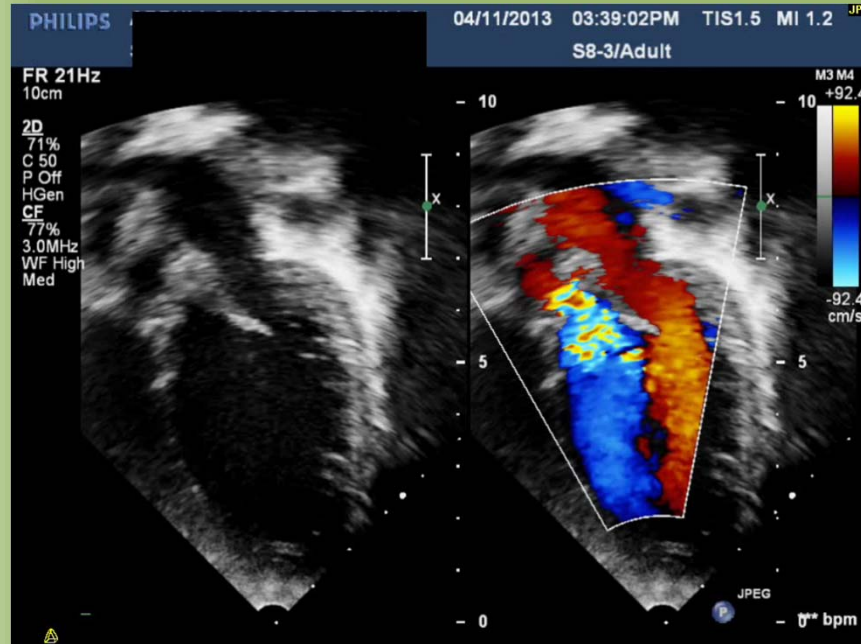
Patent Duct



Pulmonary Valve stenosis



Aortic Reg & Sub Aortic stenosis



Investigation

Hx + PE + BP (UL and LL)

FBC and Hb concentration

- Anemia / infection

BNP

- Distinguished CHF from primary respiratory process
- >100 pg/mL (in adult and children)
- Normal slightly high in neonates

Serum electrolyte

- Dilution hypoNa⁺ / hypoNa^{+2⁰} to water retention
- Elevated K⁺ due to renal compromise / tissue destruction
- Elevated lactate and depleted serum bicarb due to tissue hypoxia
- Increase BUN and creatinine due to reduces renal blood flow

ECG

- Structural abnormalities
- Coronary artery disease
- Complete AV block
- Arrhythmia

Echo

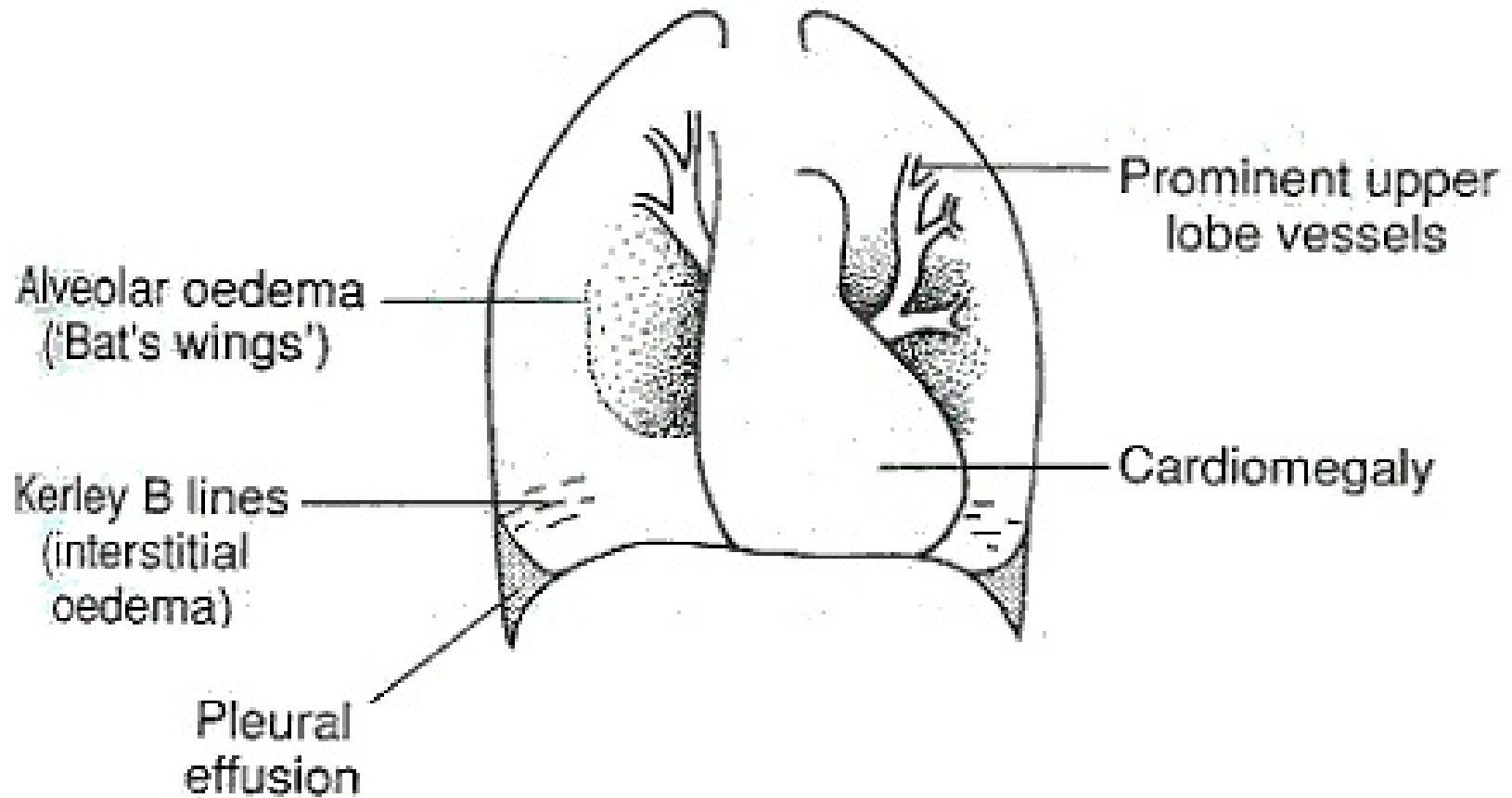
- Indicated in child with unexplained CHF
- Assess cardiac function – anatomic lesion
- Not diagnostic
- Usage of sedative in child with CHF will result in cardiac decompensation

Chest xray of CHF



Cardiac silhouette is enlarged

Exception of CHF with normal chest xray in **RESTRICTIVE CARDIOMYOPATHY**, venous obstruction (**TAPVR**) , **DIASTOLIC DYSFUNCTION**)



The CXR in left ventricular failure

Remember A B C D E

Inpatient management Outpatient management

Afterload reduction

- Nitroglycerin (GTN) –dilate veins > reduce right and left atrial pressure > reduce BP and improve coronary blood flow

Enhance contractility

- Dopamine- natural catecholamine > b adrenergic agonist > increase contractility + improve renal perfusion
- Dobutamine- syntetic catecholamines > increase contractility and peripheral vasoC (not improve renal perfussion)

Mechanical circulatory support

- Extracorporeal membrane oxygenation
- Ventricular assist devices

Afterload reducing agents

- ACE inhibitor (captopril, enalapril) >decrease vascular resistance > improve CO

Beta blocker

- Carvedilol, metaprolol >antagonize sympathetic activation

Diuretics

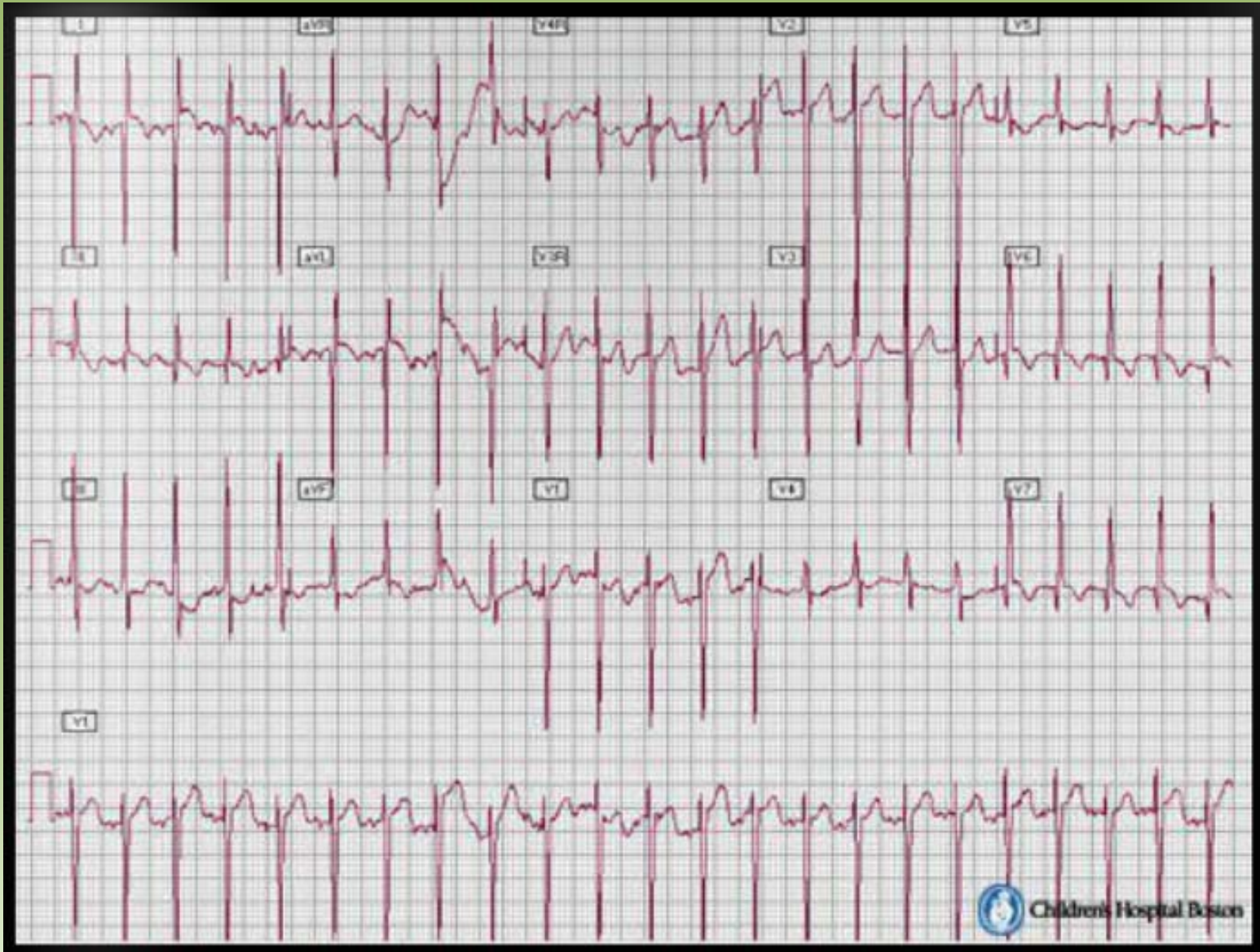
- Maintain euvolemic state
- Furosemide- loop diuretics > removes K+, 2Cl-, Na+
- Thiazides- distal tubular diuretic
- Spironolactone - cardiac glycoside > + inotropic effect and decrease vascular resistance

Case Scenario

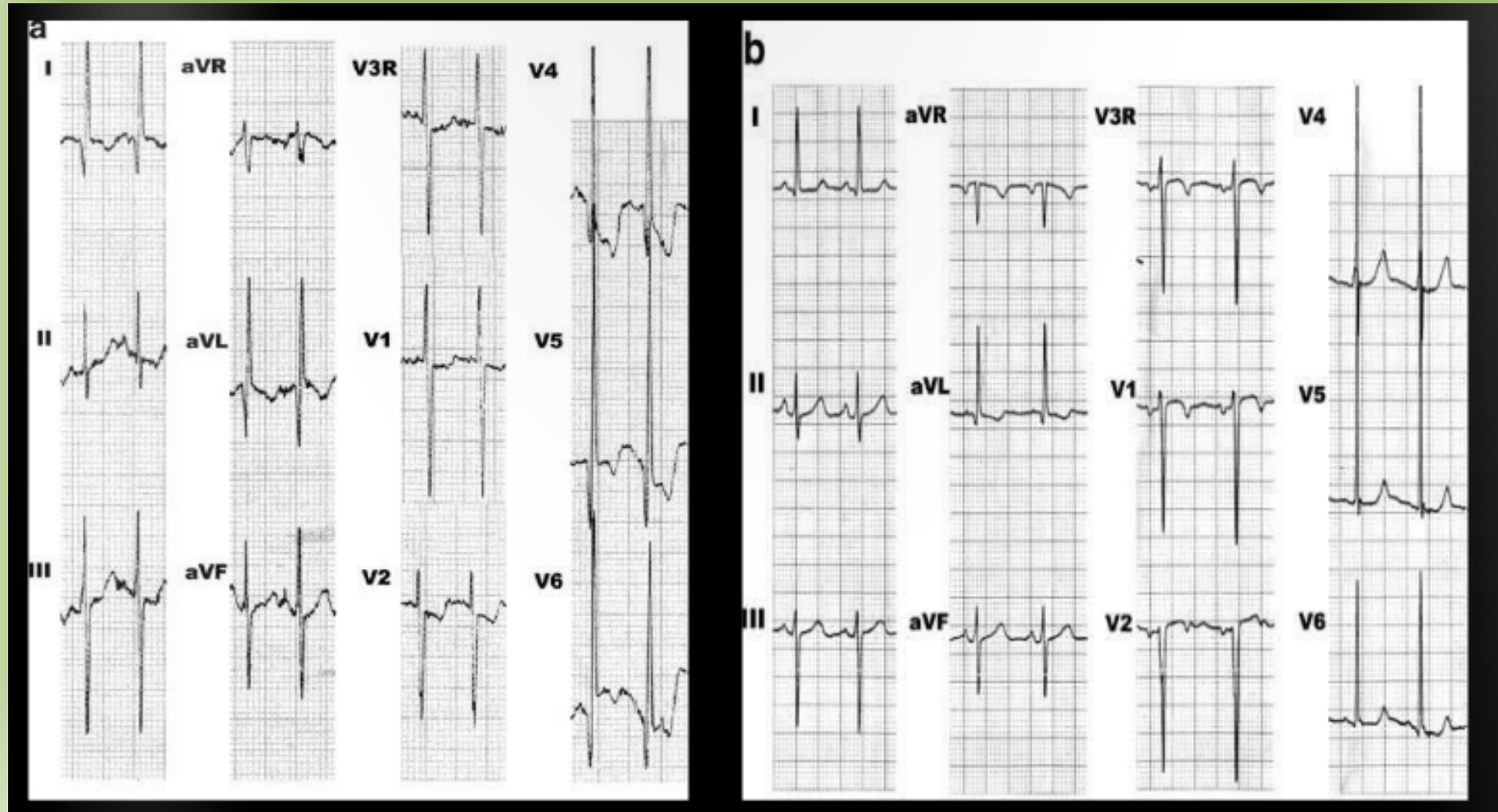
- 3 months old boy with FTT, SOB, fatigability and sweating during feeding.
- On exam
 - Weak pulses , large liver, congested chest, tachycardia with gallop rhythm, long systolic murmur at the apex.
 - X – ray -> cardiomegaly.
 - ECG

ALCAPA

- Bland – white – garland syndrome
- Presents between 2 and 6 months of age.
- Dilated LV, mitral regurgitation
- Fairly typical ECG pattern of an anterior infarct
- qs wave in I and aVL, with ST segment elevation and T wave inversion in lateral leads (LV strain).
- Timely recognition allows corrective reimplantation with excellent long-term results.



Resolved post op





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Pharmacology of CHF

Introduction

- Review focusing on new and emerging therapies for heart failure.
- Many of these have no data to support use in children.
- The latest advances are being developed in adults and a sound judgment and experience are required to apply these medications in treating paediatric heart failure.

Heart Failure in Children

- Represents a complex interrelationshipsip between neurohormonal and hemodynamic mechanisms.
- Widely heterogenous aetiology.
- Current strategies focus on manipulation of neurohormonal pathways.

Digoxin

- Today, the most common indications for digoxin are [atrial fibrillation](#) and [atrial flutter](#) with rapid ventricular response,
- ↓ High ventricular rate leads to insufficient diastolic filling time.
- By slowing down the conduction in the AV node and increasing its refractory period, digoxin can reduce the ventricular rate.
- The arrhythmia itself is not affected, but the pumping function of the heart improves owing to improved filling.

Digoxin

- The use of digoxin in heart problems during sinus rhythm was once standard, but is now controversial. In theory, the increased force of contraction should lead to improved pumping function of the heart, but its effect on prognosis is disputable, and other effective treatments are now available.
- Digoxin also strengthens the force of your heartbeat, which is why it is useful in heart failure. Heart failure is a condition where your heart does not work as well as it should.
- Digoxin is no longer the first choice for congestive heart failure, but can still be useful in patients who remain symptomatic despite proper diuretic and ACE inhibitor treatment.

Beta-Blockers

- Prevent Ventricular remodelling and fibrosis.
- Also have anti arrhythmic,
- Negative chronotropic (slow HR)
- positive lusiotropic (myocytes relaxation)and coronary vasodilatation effects.
- Carvedilol has beta 1, beta 2 and alpha blocking properties and free radical scavenging abilities.

Carvedilol

- Neurohormonal indices improve with Carvedilol (reduced catecholamines, reduced activation of Renin Angiotensin system).
- Dizziness, lethargy, hypotension and headache may limit use (in up to 50%). The dosing and titration scheme is important.
- Pharmacokinetic studies in progress.

Nebivolol

- Highly selective beta 1 blocker with unique endothelial relaxation and vasodilating effects through endothelial nitric oxide generation.
- Shown to improve LVEF in elderly, reduce LVEDP and improve effort tolerance.
- Not licensed for use, no paediatric dosing.

Natriuretic peptides

- B type natriuretic peptide (BNP) secreted from Ventricular myocardium in response to increased filling pressures.
- BNP acts on RAA (renin – angio-aldosterone) system, adrenergic system and Arginine-Vasopressin system.
- Endogenous BNP levels elevated in children with heart failure to induce Vasodilatation and diuresis (reduce afterload and preload)

Nesiritide

- Recombinant form of BNP. IV administration produces vasodilatation and diuresis.
- Shown to be beneficial in adults with acute decompensated CCF.
- In a study of 30 paediatric patients a bolus of 1mcg/kg followed by infusion of .005 to .02mcg/kg/min resulted in significant reduction in fluid balance and lower RA pressure. (arrhythmia, hypotension).

Calcium sensitizing agents

- Act by prolonging effects of calcium on myocardium.
- Do not affect Calcium levels hence lesser arrhythmias from Calcium overload.
- Levosimendan- Inodilatory drug with +ve chronotropic, inotropic and vasodilatory effects without increase in myocardial O₂ consumption.

Levosimendan

- Allows for longer half life and more effective utilisation of Calcium in myocardium.
- Half life of 80 hrs after an infusion period of 24 hours.
- In adults with CCF, shown to improve cardiac output, lower Pulm Cap wedge pressure and improve symptoms. Several clinical trials.
- Continuous infusion 0.1 to 0.4 mcg/kg/min increased cardiac output (39%) and stroke volume (28%) and lowered Pulm, Coronary and peripheral vasc resistance.

Levosimendan

- LIDO study- Levosimendan better choice than Dobutamine in low output Cardiac failure.
- REVIVE study- Shorter ICU stay, greater BNP reduction in study group (Adults with CCF requiring IV diuretics) compared to Placebo.
- Similar pharmacokinetics in children as in adults with CCF (shorter $\frac{1}{2}$ life in 6-12 month olds).

Levosimendan

- Paediatric case reports of improvement in PVR, LV function and cardiac index (infant post MI).
- PVR reduced to 3.6 from 9.2 Wood units after 24 hr infusion in 16 yr old listed for heart-lung transplant.
- Promising but further data and experience necessary.

The Renin-angiotensin-aldosterone Cascade

Reduced blood volume (ECV) or pressure decrease NaCl delivery to macula densa
Increased sympathetic tone or reduced [NaCl] in macula densa release renin

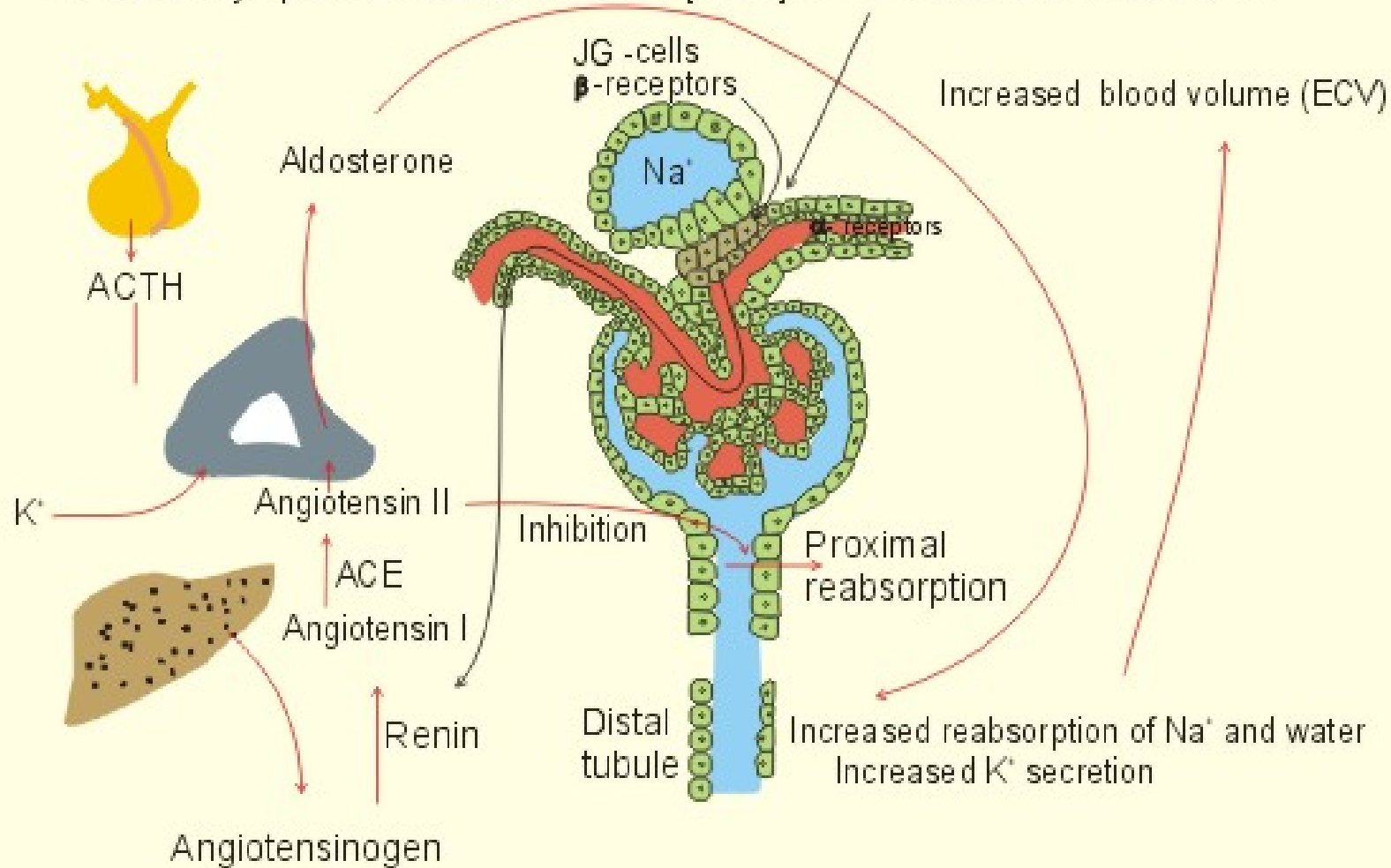


Fig. 24-5

Angiotensin Receptor Blockers

- Block the Angiotensin 1 (AT1) receptor preventing the binding of Angiotensin II a potent vasoconstrictor.
- AT1 receptor blockade also prevents activation of latter steps of the RAA cascade, inhibits release of Aldosterone and norepinephrine.
- The AT2 receptor may be activated by these drugs resulting in peripheral vasodilatation and tissue repair.

Angiotensin Receptor Blockers

- Clinical trials in humans have shown ARB's promote reversal of LV hypertrophy similar to ACE inhibitors.
- Recent trials (CHARM and VALIANT) have shown that ARB's with or without ACE inhibitors improve morbidity and mortality in adult patients with heart failure.
- Little literature regarding use of ARB's in children.

Endothelin Receptor Antagonists

- Endothelin 1 is a potent endothelial cell derived venous and arterial vasoconstrictor peptide.
- It acts on Endothelin A receptor (vasoconstriction, platelet aggregation) and Endothelin B receptor (smooth muscle relaxation through Nitric oxide and prostacycline release).

Endothelin Receptor Antagonists

- Dual antagonism (Bosentan) more beneficial than selective antagonism.
- Bosentan used in treatment of Pulmonary Hypertension.
- Has shown vasodilatory activity in patients with CCF but hepatotoxicity is a problem.
- Tezosentan- being studied in the VERITAS trial.

Aldosterone Antagonists

- Eplerenone- Selective Aldosterone receptor antagonist.
- Similar potency and mineralocorticoid effects as Spironolactone but fewer endocrine disturbances (lower affinity for androgen receptors).
- 100% bioavailable orally, peak level in 1-2 hrs, Cytochrome P 450 metabolised.

Eplerenone

- In combination with enalapril, shown to be most effective in reducing LVH in patients with hypertension and LVH.
- Pharmacokinetics in children have been studied, adult dose 50mg od.

Neural Endopeptidase inhibitors

- Inhibit the breakdown of ANP thus increasing natriuresis and vasodilatation (ANP decreases activation of RAA cascade).
- Candoxatril- NEP inhibitor known to increase plasma endothelin and natriuretic peptide levels in patients with CCF.
- May provide similar benefits as ACE inhibitors but most of the data from mild CCF.

Vasopressin Antagonists

- Arginine Vasopressin is a neurohypophyseal peptide hormone involved in a number of physiological activities related to heart failure.
- Vasoconstriction via V1a receptors, water and sodium retention via V2 receptors.
- Vasopressin antagonists act by blocking the V1a and V2 receptors.

Tolvaptan

- Oral V2 receptor antagonist studied in adults with CCF. Decreased edema and normal serum Sodium.
- EVEREST trial is comparing Tolvaptan 30mg od versus placebo in adults with CCF. Prelim results- reduced body weight without inducing renal dysfunction or hyponatremia.
- Paediatric use may follow after pharmacokinetic studies.

Future Trends

- Only a matter of time before many of the new pharmacological agents are used in treating CCF in children.
- Pharmacogenomics- Search for genetic polymorphisms that can influence drug therapy will have significant impact on treatment of heart failure.

Pharmacogenomics

- African Americans do not respond as well as other ethnic groups to ACE inhibitors, with fewer reductions in morbidity and mortality.
- This may be due to genetic polymorphism in genes encoding ACE, Angiotensinogen and Angiotensin II receptors.
- Multiple genetic polymorphisms are likely to be used to deduce response to medications.
- Beta blockers and digoxin may also be affected by G.Polymorphisms.



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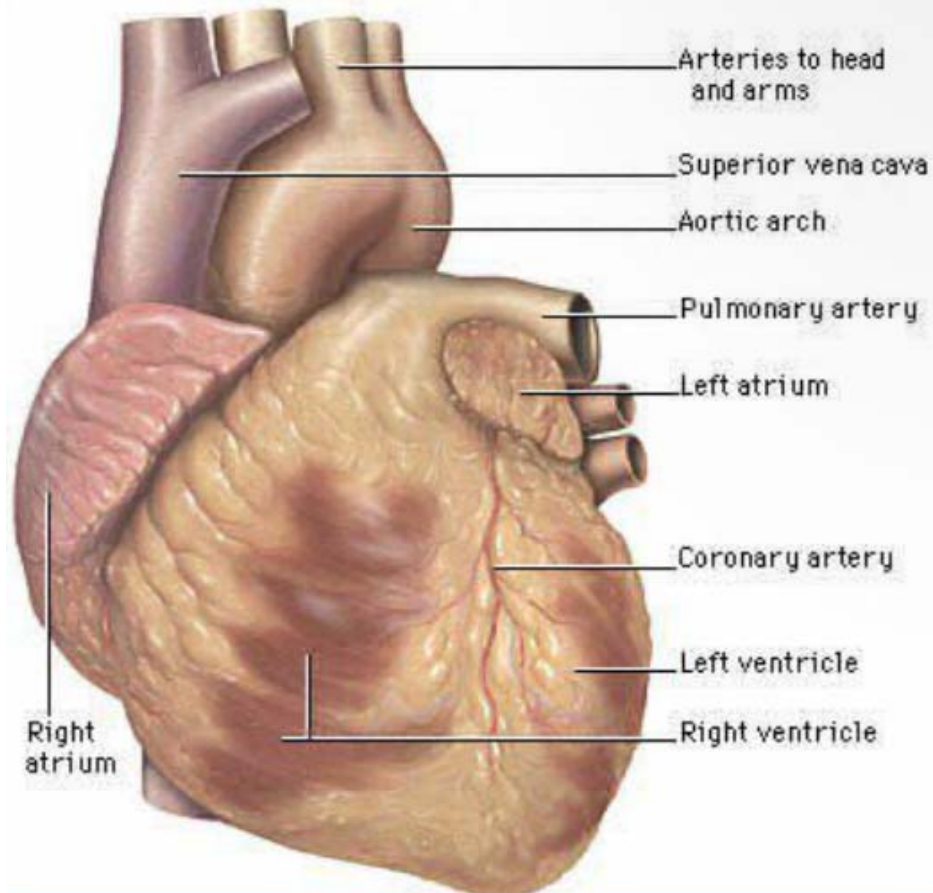
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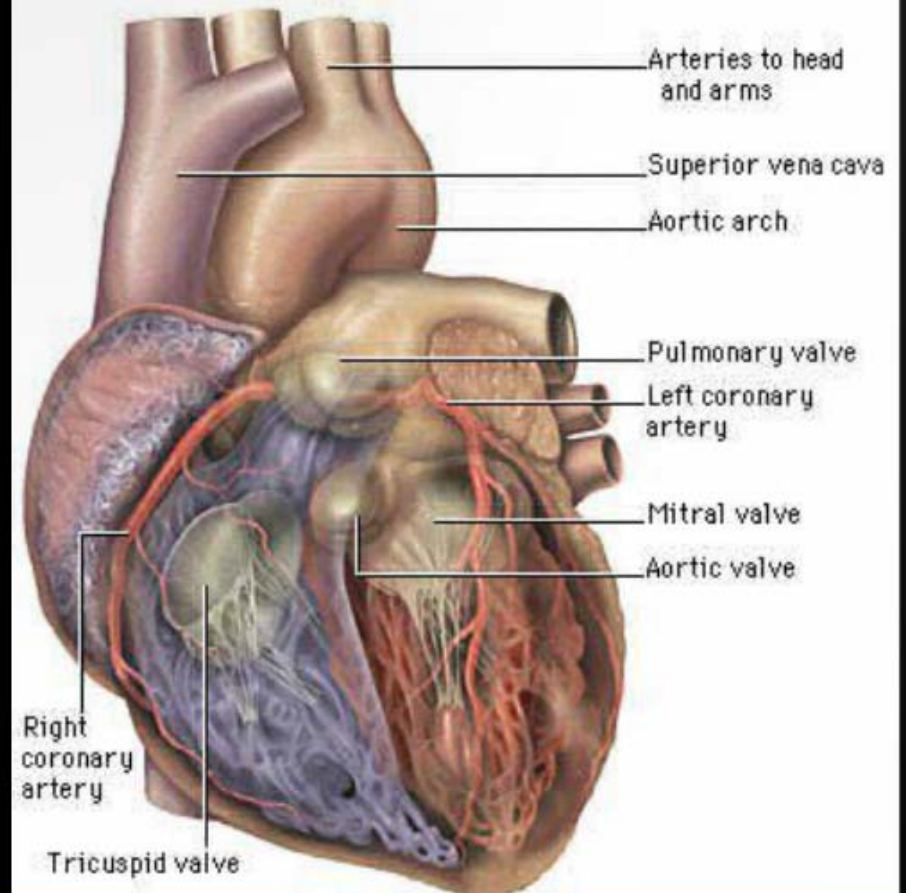
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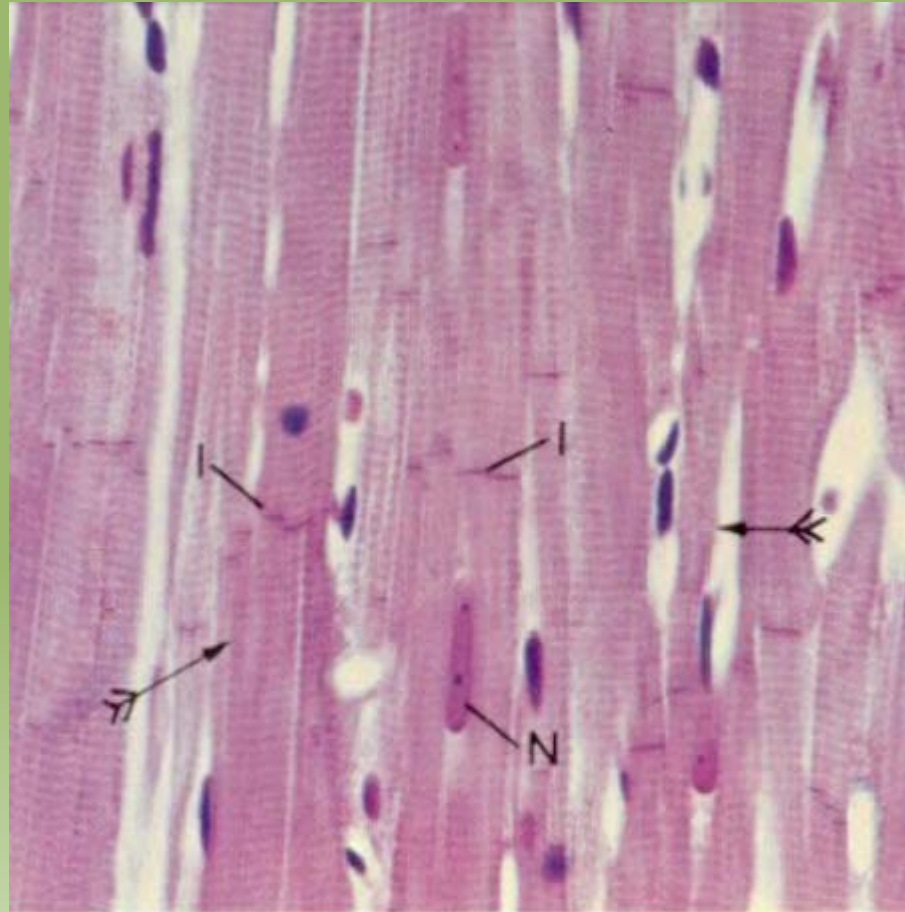
Exterior structures of the heart



Interior structures of the heart



HISTOLOGY



Cardiac Muscle, H&E (Med)

I = Intercalated discs

N = Nuclei

Arrows = Cross trabeculae



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