HYPERTROPHIC CARDIOMYOPATHY

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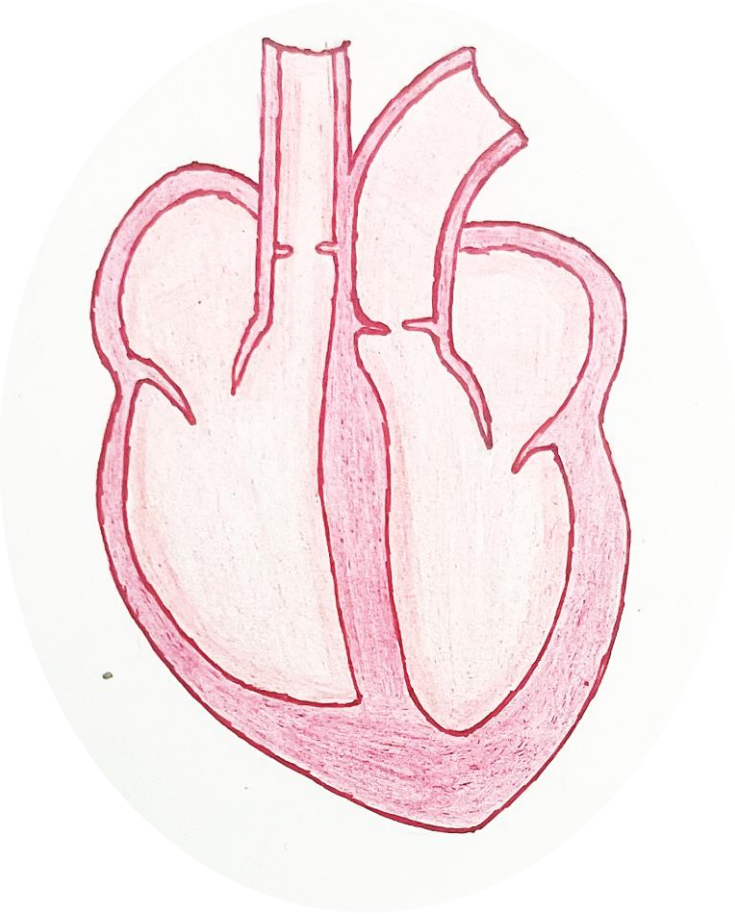
TIRUPATHI

CARDIOMYOPATHY

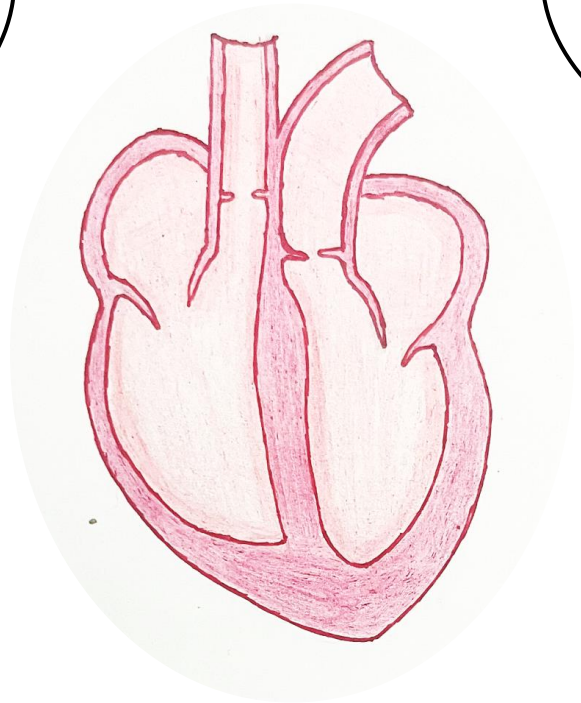
- Cardiomyopathies are a heterogeneous group of diseases, resulting from abnormality in myocardium associated with abnormalities in mechanical and/or electrical dysfunction that usually exhibit inappropriate ventricular hypertrophy or dilatation



CARDIOMYOPATHY

Secondary cardiomyopathy

Myocardial involvement as a component of a systemic or multiorgan disorder (e.g. hemochromatosis, amyloidosis)



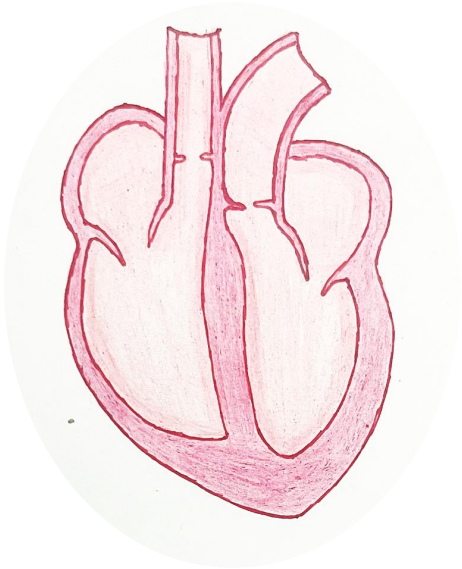
Primary cardiomyopathy

Primarily involving heart muscle

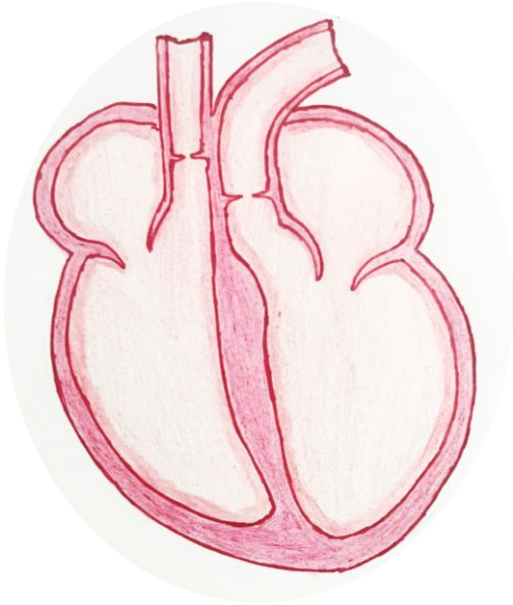
CARDIOMYOPATHY

- Types of cardiomyopathies are determined by clinical, functional and pathologic patterns

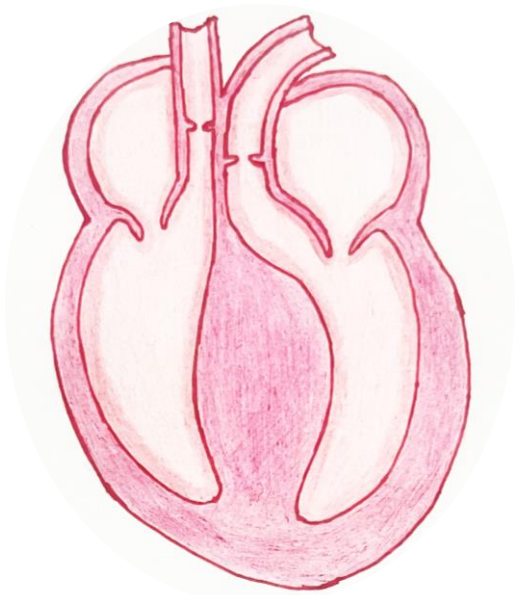
Normal heart



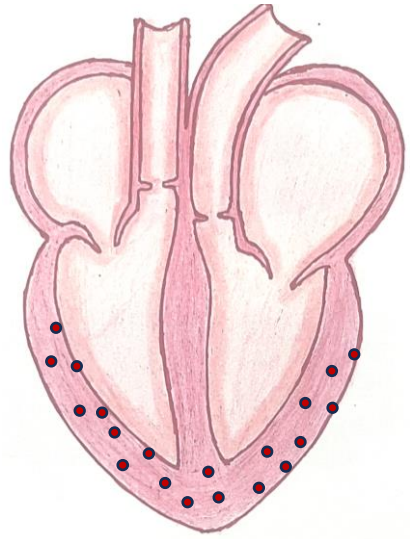
Dilated cardiomyopathy



Hypertrophic cardiomyopathy



Restrictive cardiomyopathy



Among the three major patterns, DCM is most common (90% of cases), and restrictive cardiomyopathy is the least frequent

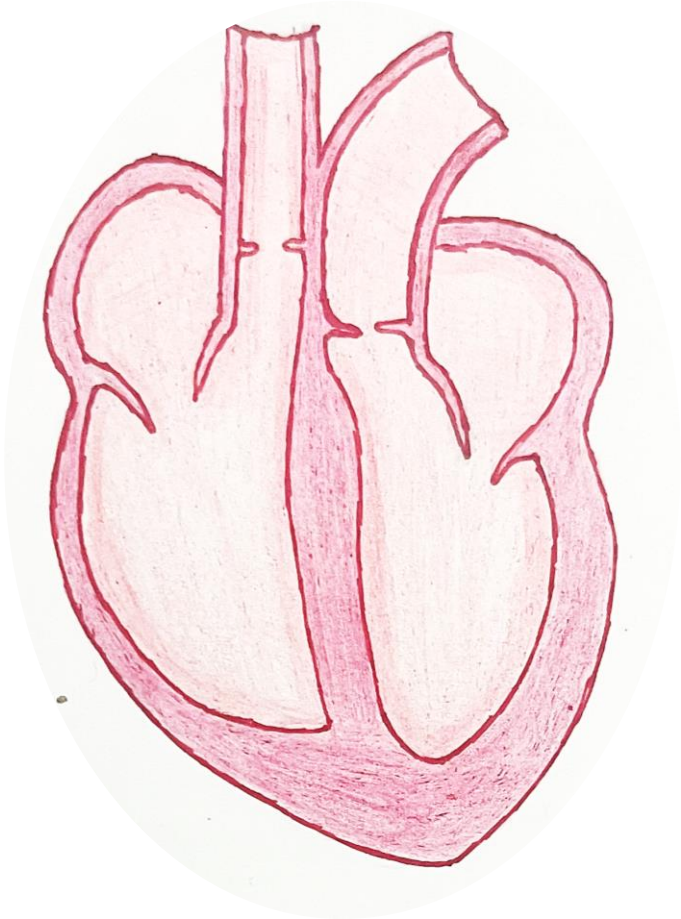
CARDIOMYOPATHY

Functional pattern	Left ventricular ejection fraction	Mechanism of heart failure	Causes of phenotype
Dilated	< 40%	Impairment of contractility (systolic dysfunction)	Genetic, alcohol, peripartum, myocarditis, hemochromatosis, chronic anemia, doxorubicin (Adriamycin), chagas disease, idiopathic
Hypertrophic	50 – 80%	Impairment of compliance (Diastolic dysfunction)	Genetic, Friedreich ataxia, storage diseases, infants of diabetic mother
Restrictive	45 – 90%	Impairment of compliance (Diastolic dysfunction)	Amyloidosis, radiation induced fibrosis idiopathic

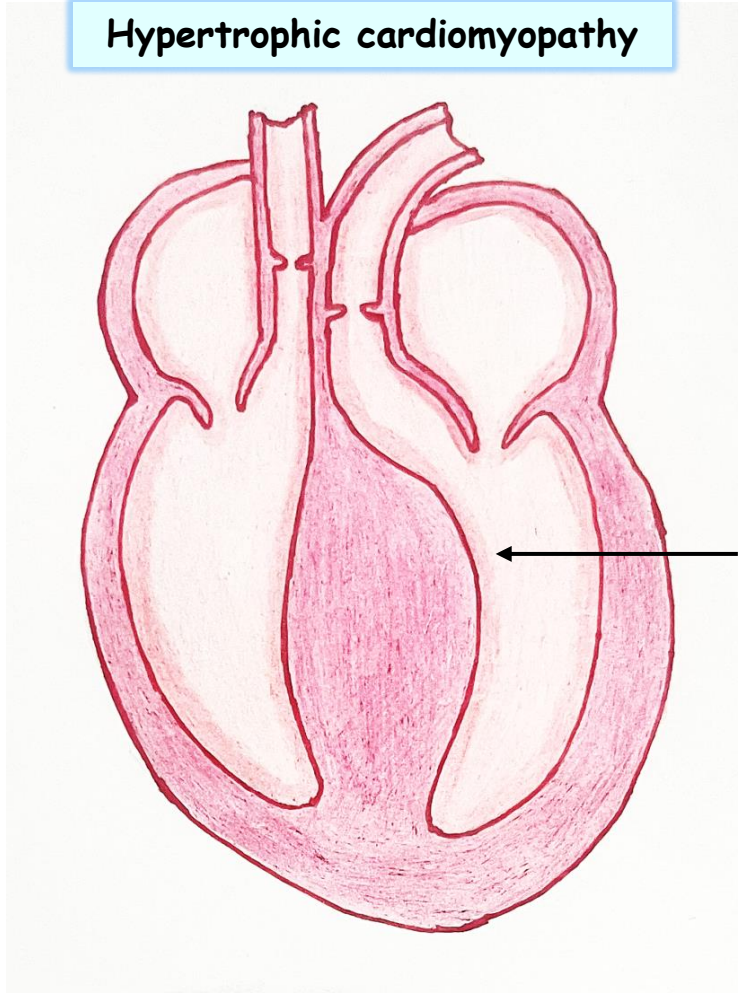
HYPERTROPHIC CARDIOMYOPATHY (HCM)

- Myocardial dysfunction due to asymmetric hypertrophy of interventricular septum and left ventricular wall

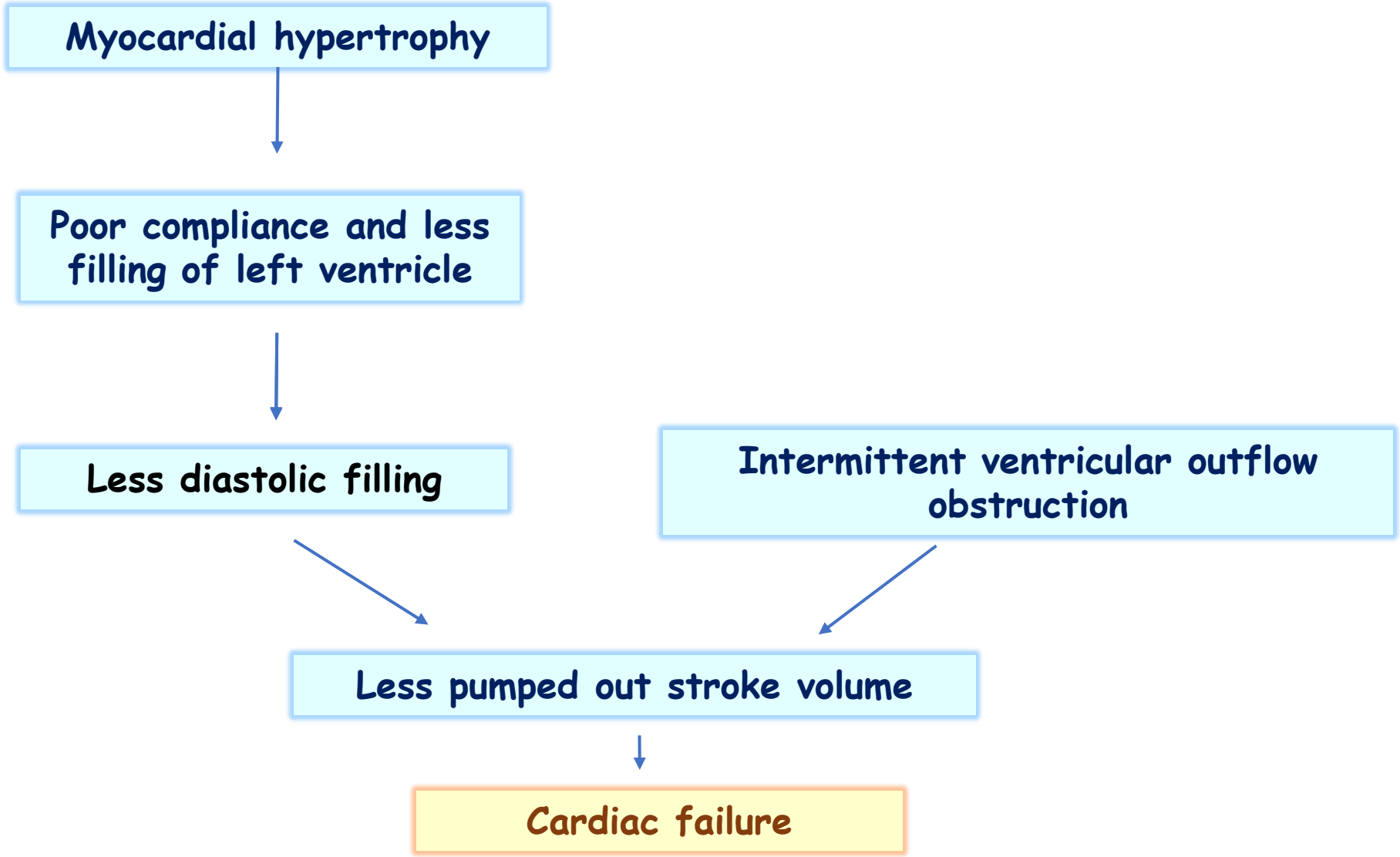
Normal heart



Hypertrophic cardiomyopathy



HYPERTROPHIC CARDIOMYOPATHY (HCM)



HCM causes primarily diastolic dysfunction, systolic function is usually preserved

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Pathogenesis

CAUSES

Genetic causes

- Beta-myosin heavy chain
- Myosin binding protein C
- Troponin I and Troponin T
- Tropomyosin Alpha 1 chain

Storage diseases

- Gauchers disease
- Pompe disease
- Anderson-Fabry disease

} Lysosomal storage disorders

Mutations in mitochondrial gene related disorders

- Fredreich's ataxia (degenerative disorder which damages spinal cord and peripheral nerves)
- MELAS (Mitochondrial myopathy, encephalopathy, Lactic acidosis and stroke like episodes)

Malformation syndromes

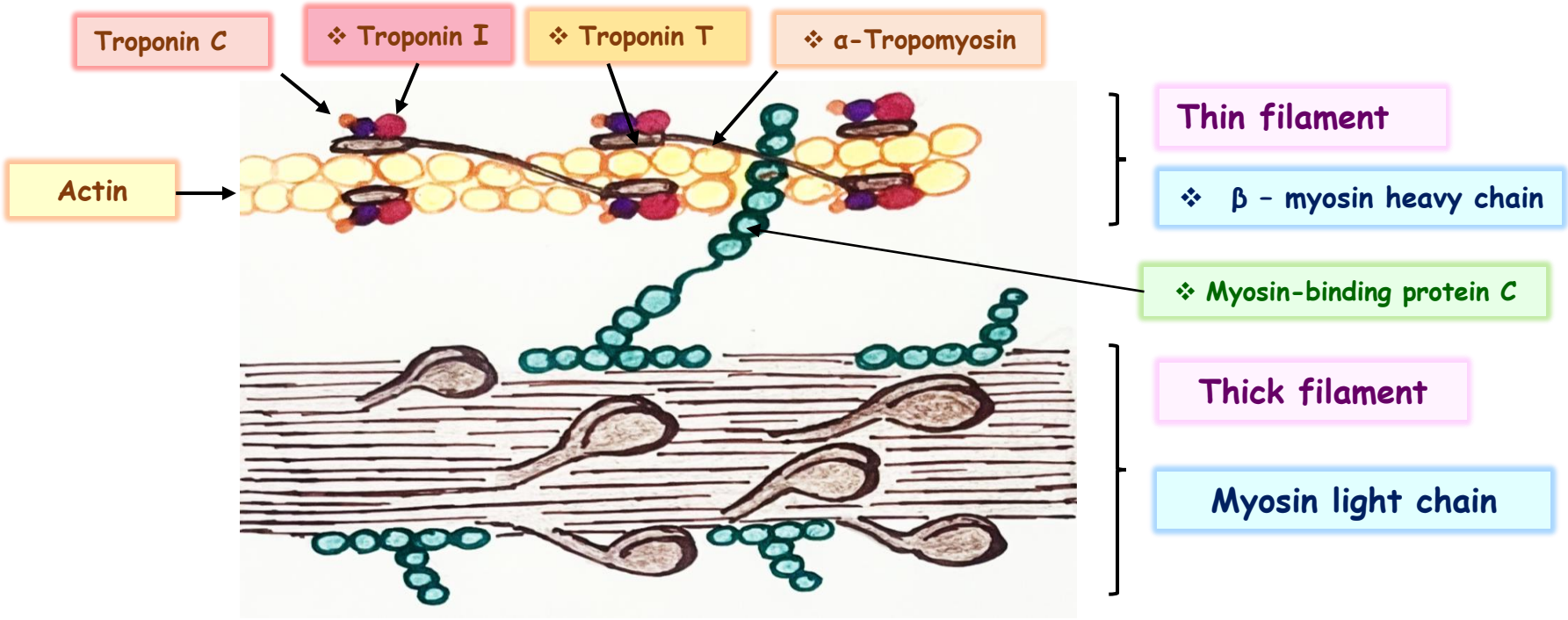
- LEOPARD (Lentigines, ECG abnormalities, Ocular hypertelorism, Pulmonary stenosis, Abnormal genitalia, Retarded growth, Deafness)
- NOONAN – heterogenous phenotypic manifestation with wide set eyes, low set ears, short stature and pulmonic stenosis
- COSTELLO SYNDROME – mutation in HRAS gene affecting heart, muscles, bones, skin, brain, spinal cord

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Pathogenesis -Genetic causes

- Autosomal dominant pattern of inheritance
- HCM is most commonly caused by mutations in any one of several genes that encode sarcomeric proteins
- Mutations causing HCM are found most missense mutations commonly in the genes encoding

  β- heavy chain myosin, Myosin-binding protein C , Cardiac Troponin I, Troponin T, α-tropomyosin



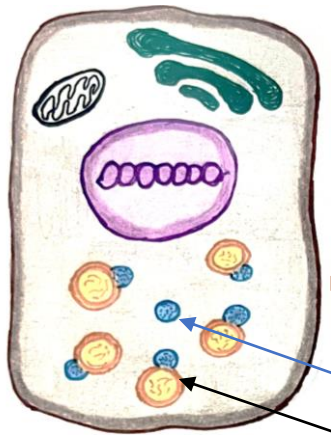
HYPERTROPHIC CARDIOMYOPATHY (HCM)

Pathogenesis

- Precise mechanism by which these mutations cause HCM is unclear
- Evidence suggests that it arises from defective energy transfer from its source of generation (mitochondria) to its site of use (sarcomeres)
- In contrast, DCM is mostly associated with abnormalities of cytoskeletal proteins
- Mutations in certain genes can give rise to either HCM or DCM, depending on the site and nature of the mutation

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Pathogenesis – Storage disorder



Normal cell with autophagolysosome

Lysosomal enzyme deficicency

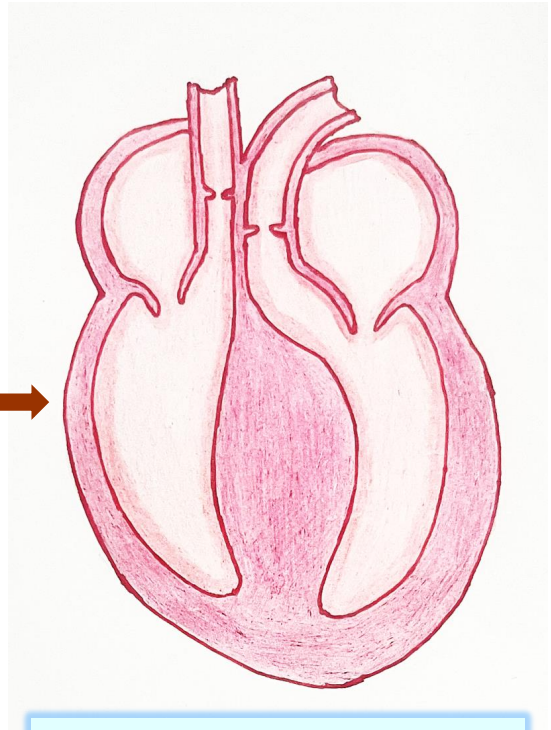
Lysosome

Autophagolysosome

Autophagosome

Accumulation of substrate in the cell

Cells size increases



Hypertrophic cardiomyopathy

Electrical conduction defect

Bi atrial enlargement

Papillary muscle hypertrophy

Myocardiocyte degeneration

Interstitial fibrosis

Restrictive cardiomyopathy

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Pathogenesis

Mutations in mitochondrial gene related disorders

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Mitochondrial dysfunction

↓

Oxidative stress

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Myocyte dysfunction

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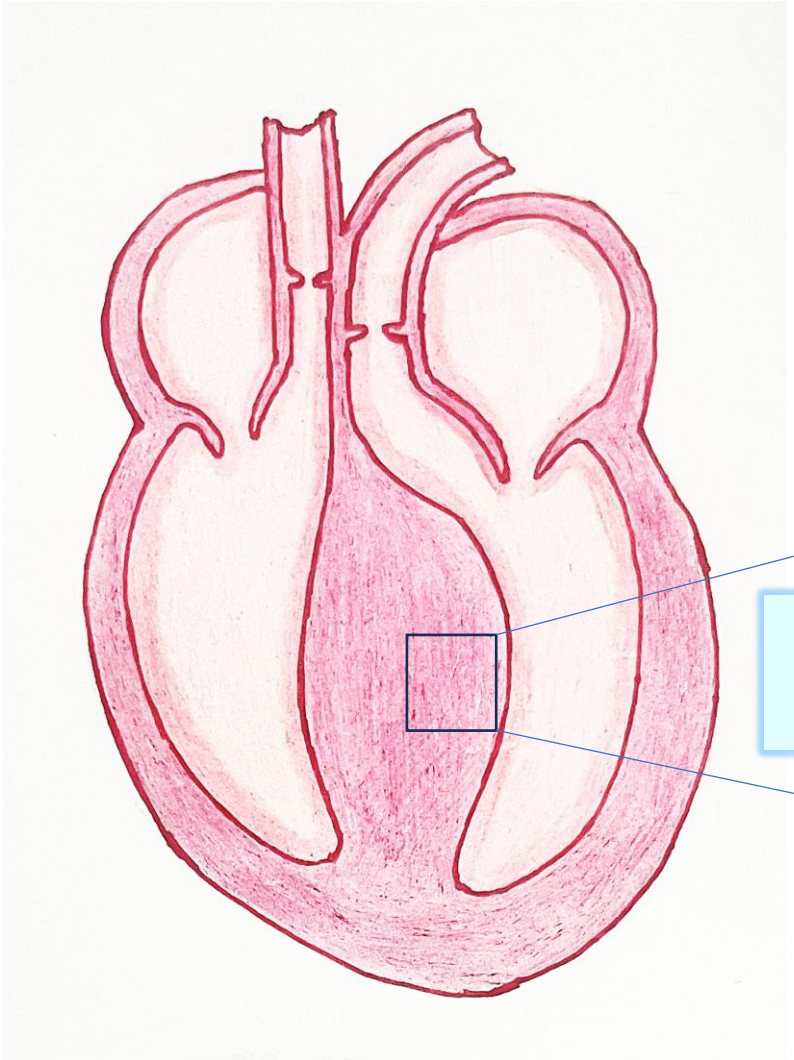
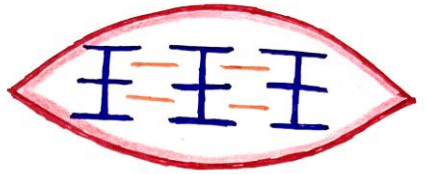
HYPERTROPHIC CARDIOMYOPATHY

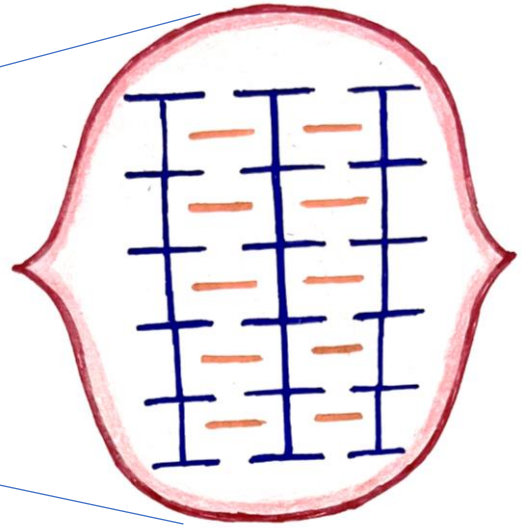
HYPERTROPHIC CARDIOMYOPATHY (HCM)



Myocardium is thick, heavy and hypercontractile



Normal Sarcomere

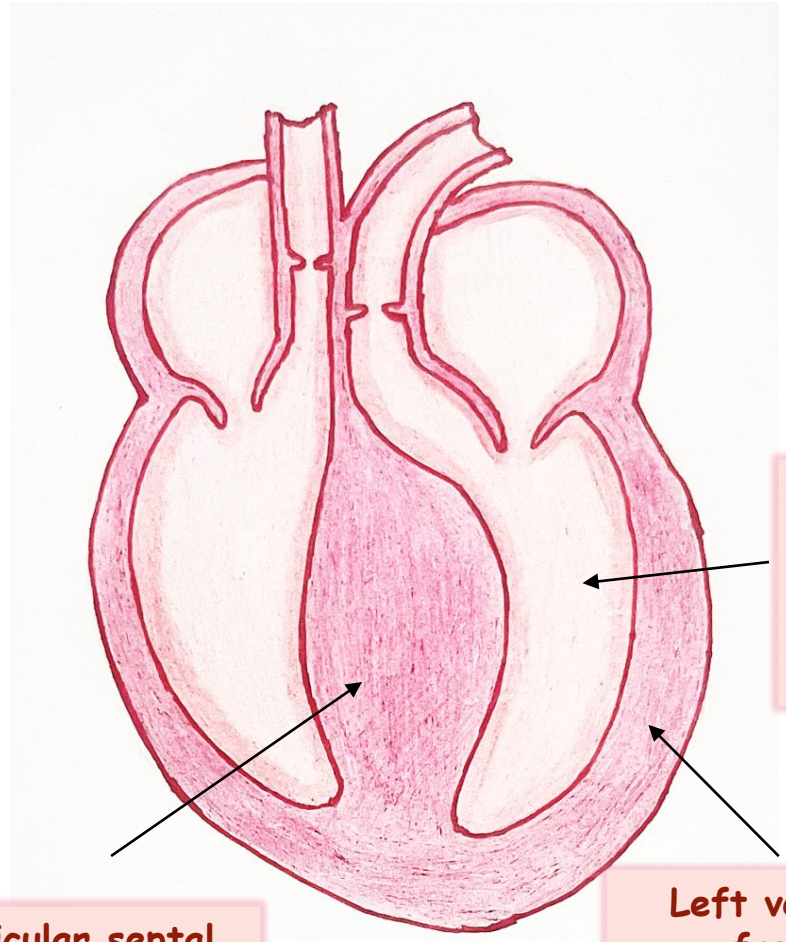


Sarcomeres arranged parallely and causes increased thickness

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Morphology

- Massive myocardial hypertrophy, usually without ventricular dilation
- Classic pattern involves disproportionate thickening of the ventricular septum relative to the left ventricle free wall, termed asymmetric septal hypertrophy
- On longitudinal sectioning, the normally round-to-ovoid left ventricular cavity may be compressed into a "banana-like" configuration by bulging of the ventricular septum into the lumen

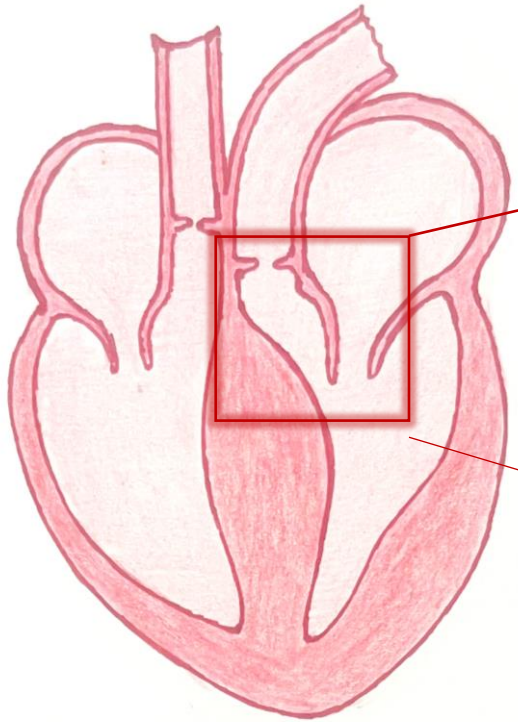


HYPERTROPHIC CARDIOMYOPATHY (HCM)

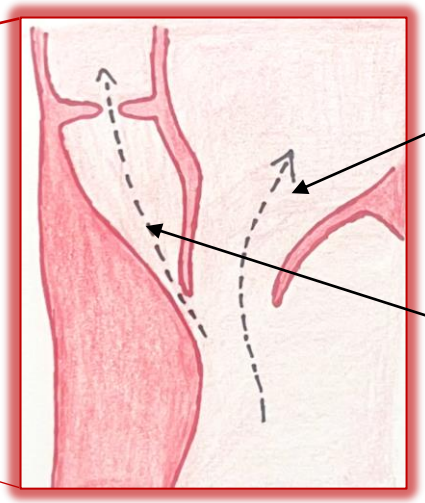
Morphology

- Although marked hypertrophy can involve the entire septum, it is usually most prominent in the subaortic region

- Left ventricular outflow tract often exhibits a fibrous endocardial plaque and thickening of the anterior mitral leaflet due to contact with septum



Thickening more prominent in subaortic region



Regurgitation into left atrium

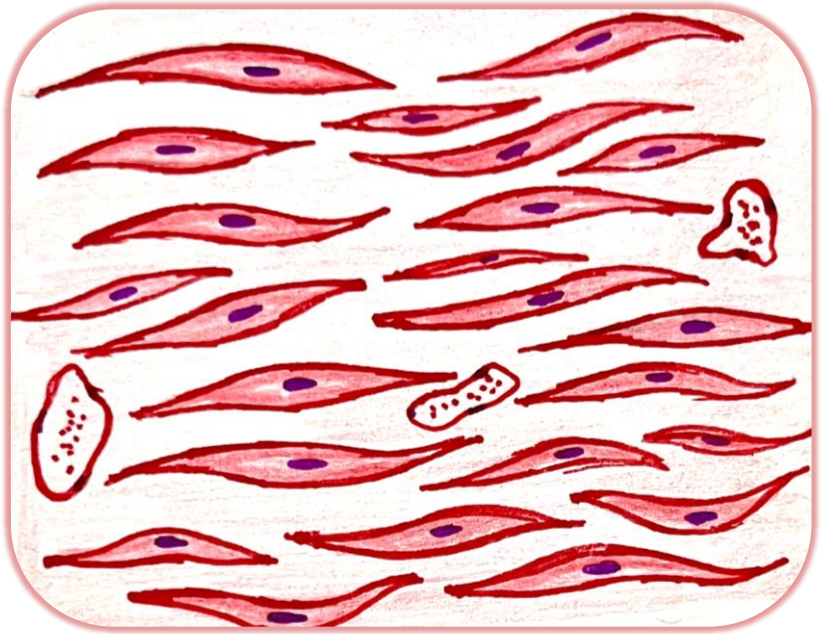
Obstruction to outflow and blood flow through small opening

Crescendo- decrescendo murmur

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Microscopy

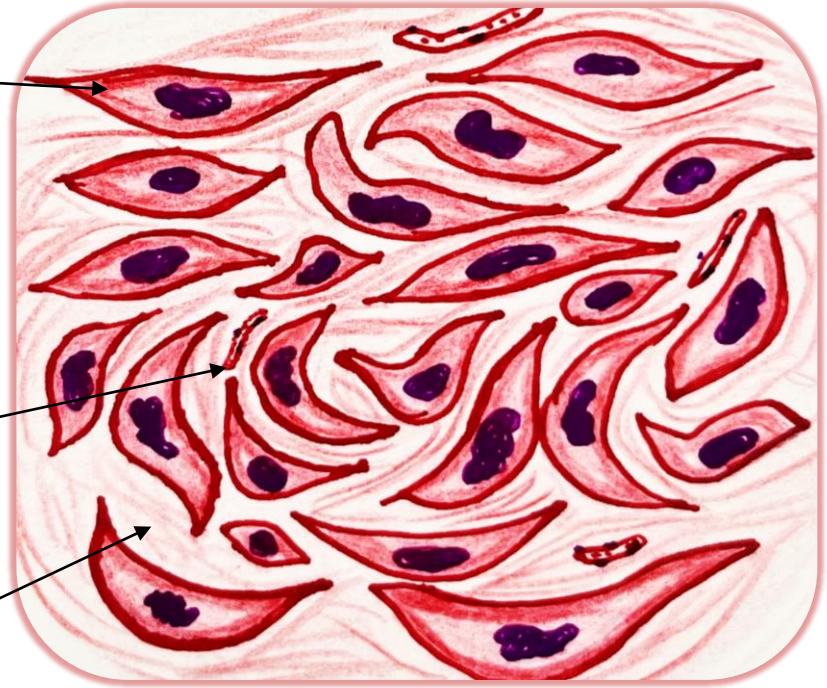
NORMAL MYOCYTE



Normal myocyte diametre is approximately 15 µm

- Massive myocyte hypertrophy
- Haphazard disarray of bundles of myocytes(myofiber disarray)
- Fibrotic narrowing of small intramural arteries
- Interstitial and replacement fibrosis

HYPERTROPHIC CARDIOMYOPATHY



Transverse myocyte diameter frequently greater than 40 µm

HYPERTROPHIC CARDIOMYOPATHY (HCM)

CLINICAL FEATURES

HYPERTROPHIED CARDIAC MUSCLE

- **Impaired diastolic filling**
- **Obstruction to left ventricular outflow**
  - Thickened ventricular region in subaortic region and anterior mitral leaflet moves toward the ventricular septum during systole
- **Myocardial ischemia**
  - Due to increased thickness of myocardium and fibrotic narrowing of intramuscular arteries

Impaired diastolic filling + **Obstruction to left ventricular outflow** → **Reduced stroke volume**

Obstruction to left ventricular outflow → **Increased pulmonary venous pressure** → **Exertional dyspnea**

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Clinical Features

Major clinical problems in HCM are

- Atrial fibrillation
- Mural thrombus formation leading to embolization and possible stroke
- Intractable cardiac failure
- Ventricular arrhythmias
- Sudden death (common cause of sudden, otherwise unexplained death in young athletes)

Treatment – either by Implantable cardioverter defibrillators or by surgical reduction of mass

SUMMARY

HYPERTROPHIC CARDIOMYOPATHY (HCM)

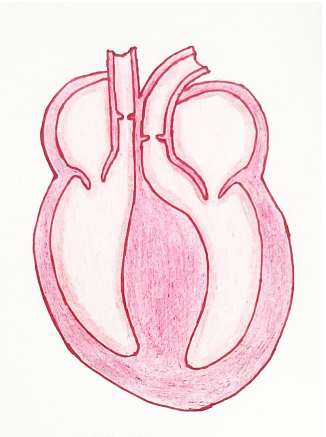
Definition: Myocardial dysfunction due to Asymmetric hypertrophy of interventricular septum and left ventricular wall

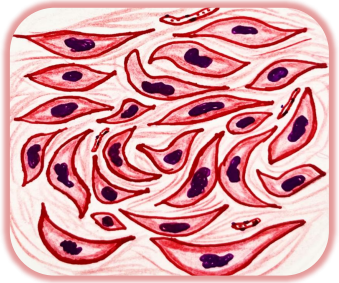
Etiology

- Genetic- mutations in genes encoding sarcomeric proteins
- Lysosomal Storage disorders, FD, PD, GD
- Mitochondrial gene mutation disorders, FA, MELAS
- Malformation syndromes, Leopard, Noonan, Costella

Morphology

- Asymmetric hypertrophy of interventricular septum and left ventricular wall
- Hypertrophied myocytes
- Disarray of muscle bundles
- Interstitial fibrosis





Clinical features

- Reduced stroke volume
- Increased pulmonary pressure leading to exertional dyspnea
- Myocardial ischemia

- Atrial fibrillation
- Ventricular arrhythmias
- Mural thrombus
- Cardiac failure
- Sudden death


Thank
you