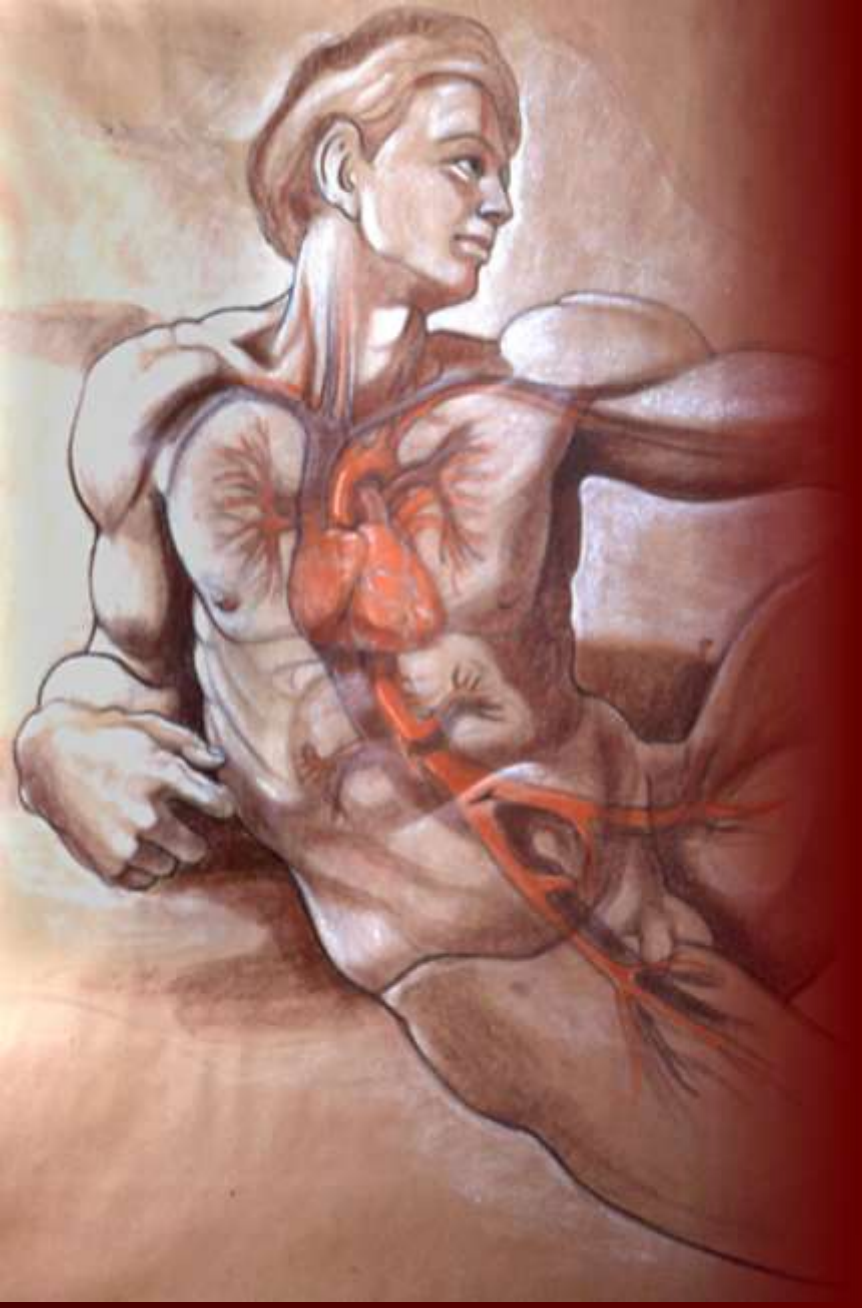

Cardiovascular Pathophysiology 2

Roman Benacka

Department of Pathophysiology

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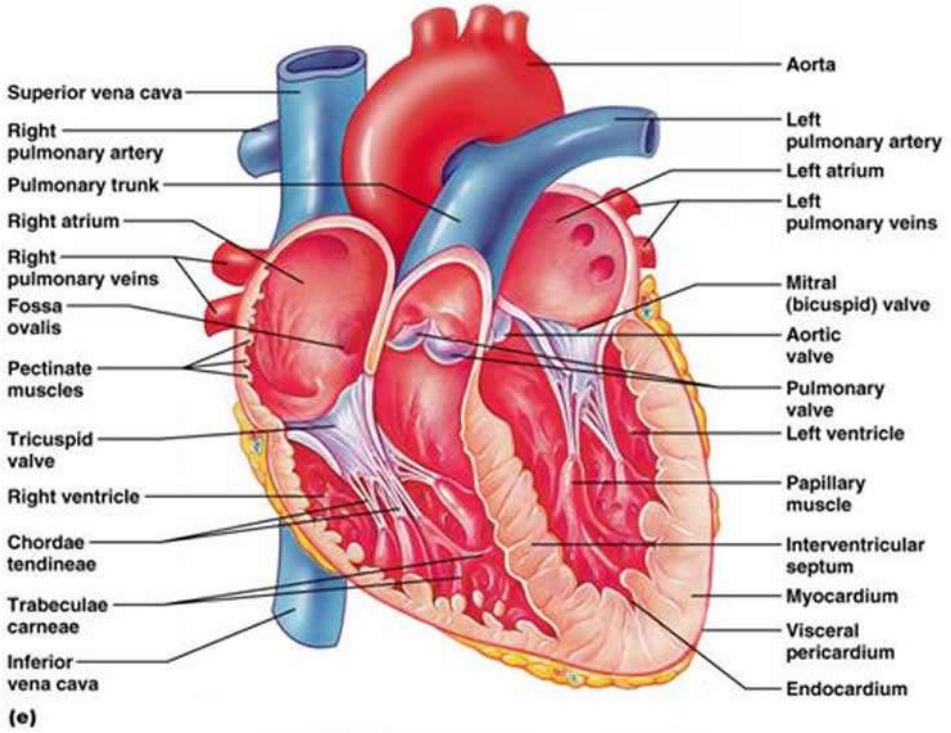
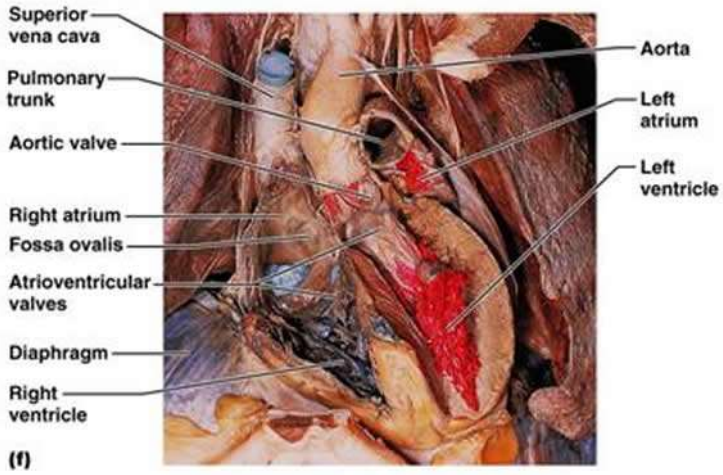
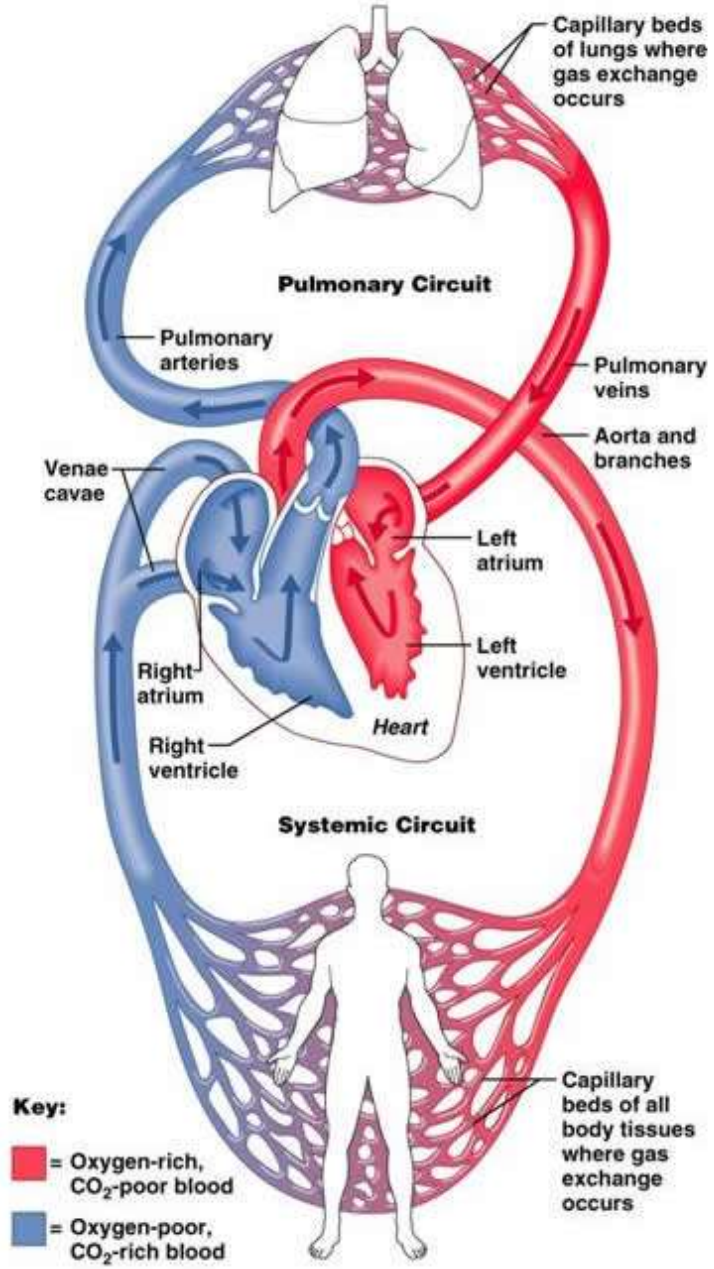
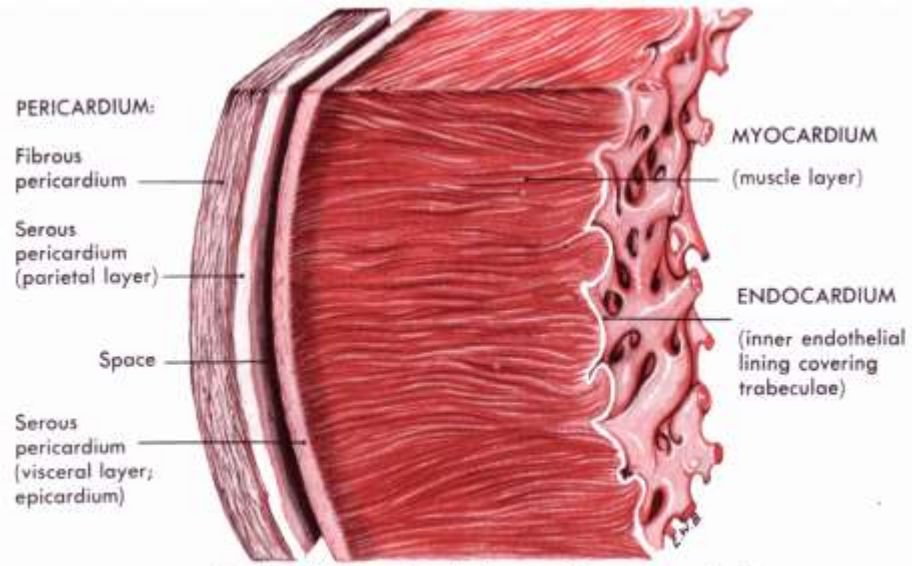
Heart pump


Superior vena cava
Right pulmonary artery
Pulmonary trunk
Right atrium
Right pulmonary veins
Fossa ovalis
Pectinate muscles
Tricuspid valve
Right ventricle
Chordae tendineae
Trabeculae carneae
Inferior vena cava
Aorta
Left pulmonary artery
Left atrium
Left pulmonary veins
Mitral (bicuspid) valve
Aortic valve
Pulmonary valve
Left ventricle
Papillary muscle
Interventricular septum
Myocardium
Visceral pericardium
Endocardium
(e)

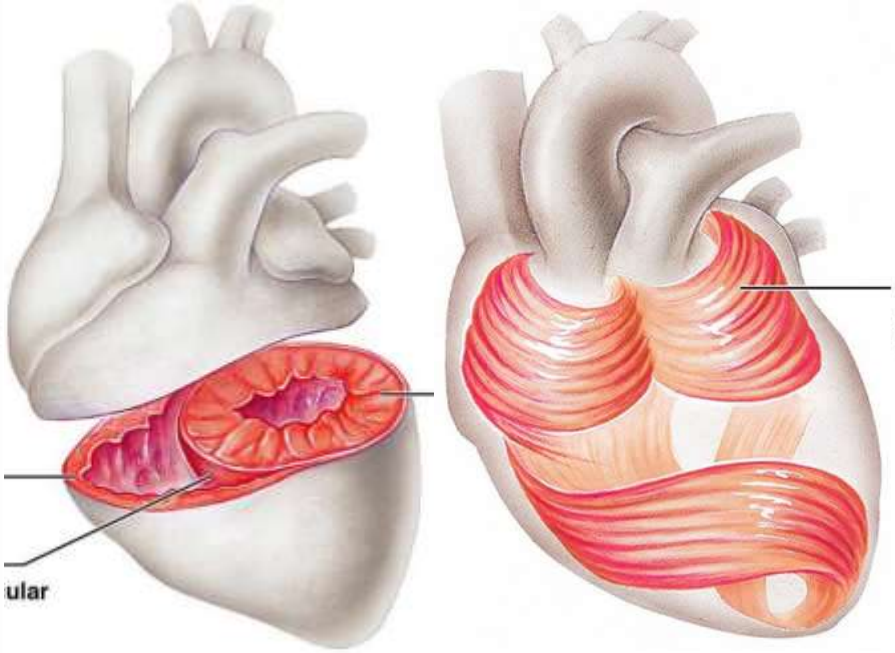

Superior vena cava
Pulmonary trunk
Aortic valve
Right atrium
Fossa ovalis
Atrioventricular valves
Diaphragm
Right ventricle
Aorta
Left atrium
Left ventricle
(f)

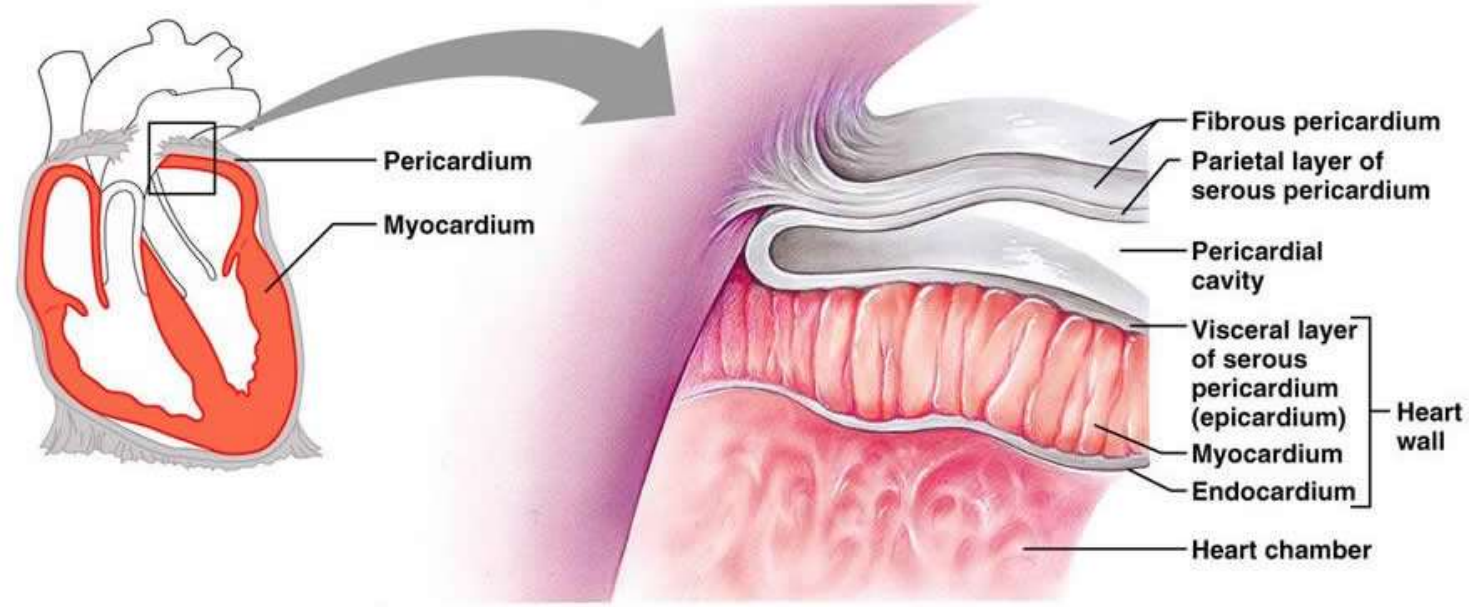

Capillary beds of lungs where gas exchange occurs
Pulmonary Circuit
Pulmonary arteries
Pulmonary veins
Aorta and branches
Venae cavae
Left atrium
Left ventricle
Right atrium
Heart
Right ventricle
Systemic Circuit
Capillary beds of all body tissues where gas exchange occurs
Key:
= Oxygen-rich, CO_2-poor blood
= Oxygen-poor, CO_2-rich blood

Heart muscle

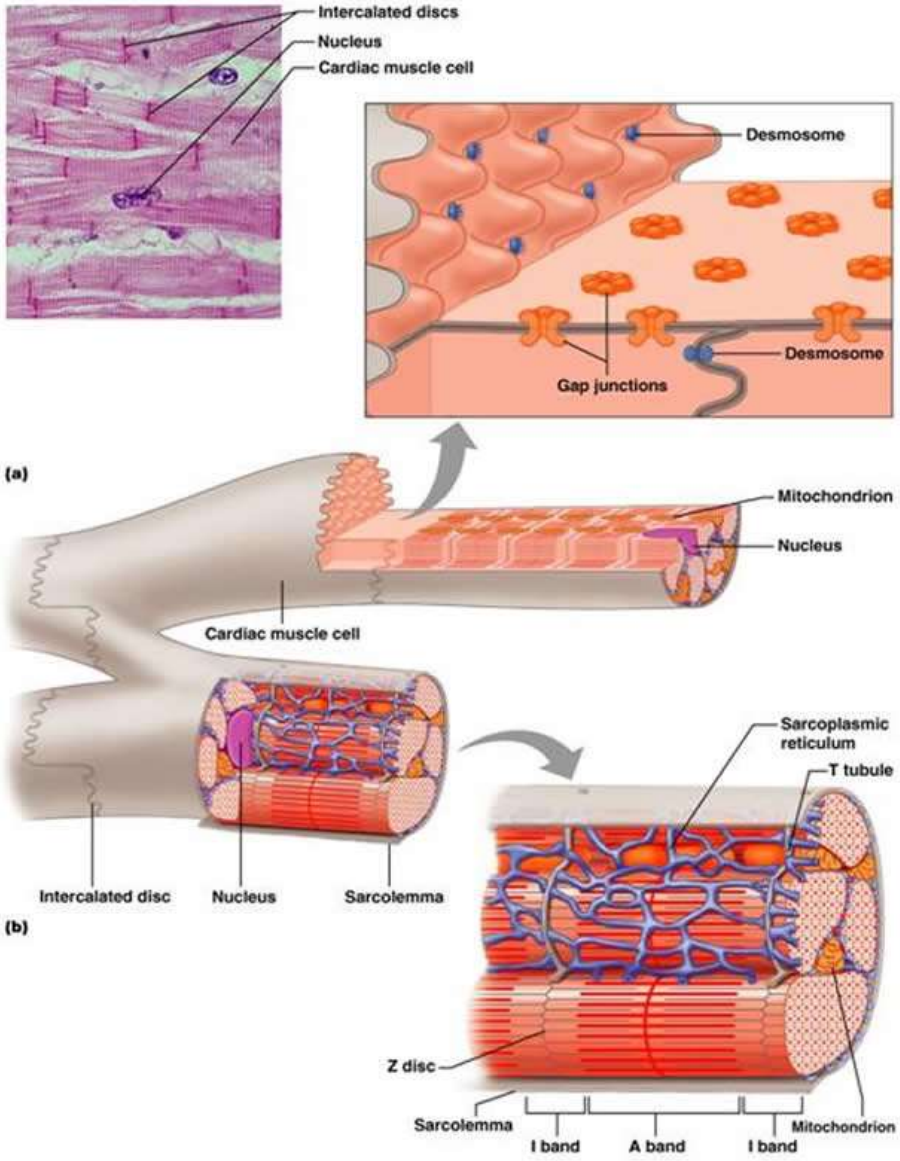


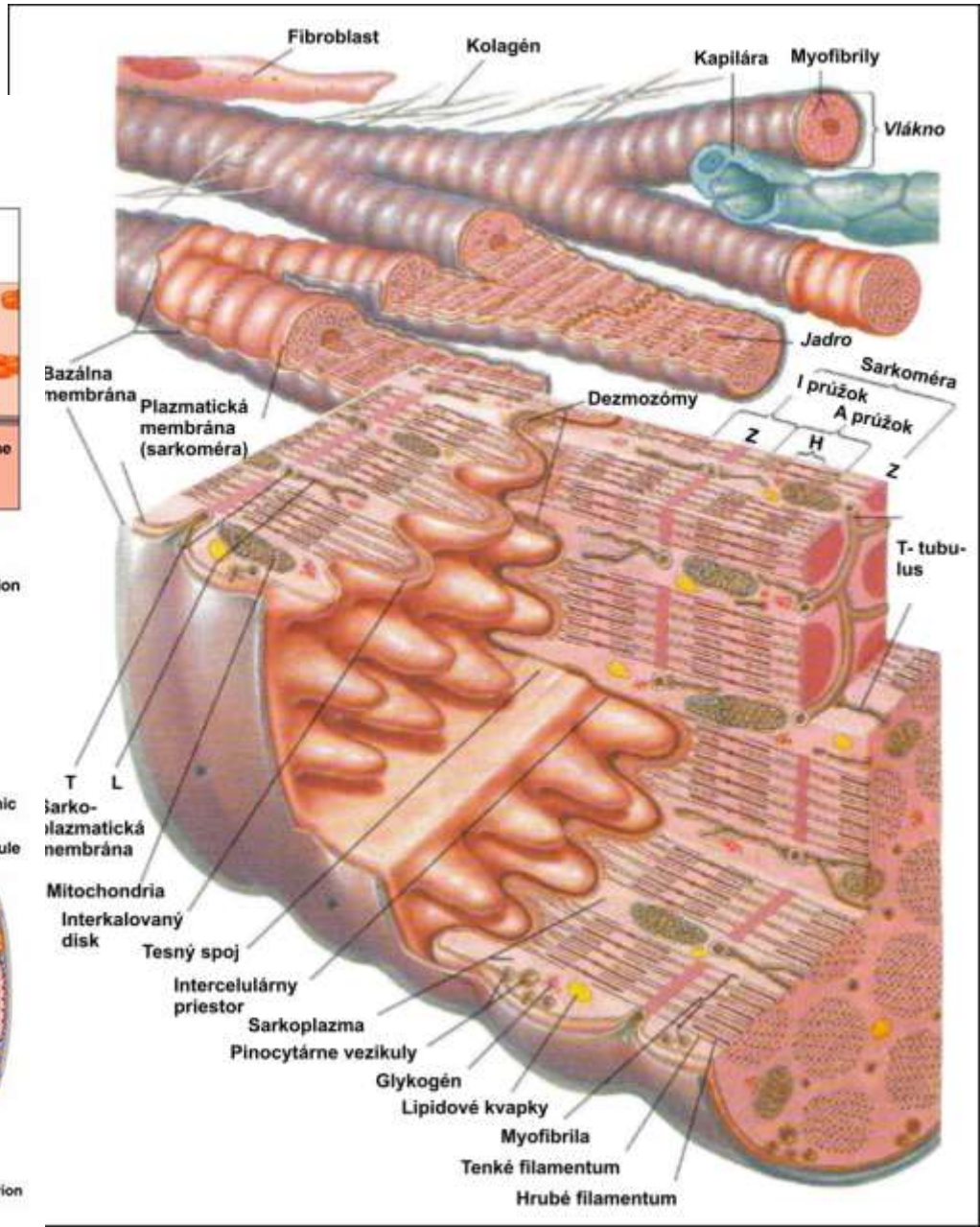
Section of the heart wall showing the components of the outer pericardium (heart sac), muscle layer (myocardium), and inner lining (endocardium).





Heart muscle





Cardiomyopathies - Description

- **Definition:** Heterogenous group of disorders characterized by progressive structural pathological alterations in heart muscle affecting its efficient pumping functionality in different ways. Reasons include hereditary, congenital or acquired conditions or their combination affecting heart musce itself but should exclude cardiac muscle remodellation due to adaptive or compensatory hemodynamic responses.
- **Types**:
  - **dilated** – dilation and systolic dysfunction of left chamber or left and right chambers
  - **hypertrophic** – asymmetric chamber hypertrophy (septum) wirth diastolic disfunction
  - **restrictive** – severe diastolic dysfunction due to increased muscle stiffnes
  - **arrhythmogenic dysplasia of right chamber** – progressive replacement of heart muscle with fat and connective tissue
- **Etiology::**
  - **secondary cardiomyopaties** – heart disorders; e.g. infective myocarditis, valvular disorders, degeberation, dystrrophy, non – cardiac conditions - toxic-metabolic (alcohol, cocaine, drugs), etc
  - **primary cardiomyopathies** - non-secondary, i.e. unfound underlying disorders → hereditary, congenital, unknown reason .

Cardiomyopathies – Etiology in general

Primary cardiomyopathies

- **Genetic**
  - Hypertrophic cardiomyopathy (HCM or HOCM)
  - Arrhythmogenic right ventricular cardiomyopathy (ARVC)
  - Isolated ventricular non-compaction
  - Mitochondrial cardiomyopathy
- **Mixed, e.g.**
  - Dilated cardiomyopathy (DCM)
  - Restrictive cardiomyopathy (RCM)
- **Acquired, e.g.**
  - Postpartum cardiomyopathy
  - Takotsubo cardiomyopathy
  - Loeffler endocarditis

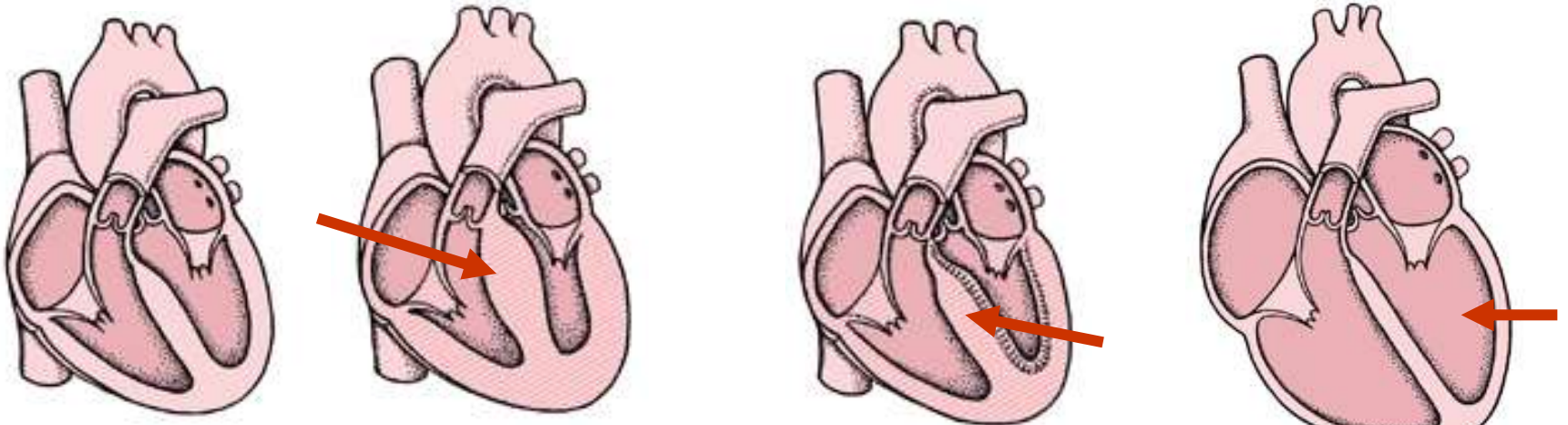
Secondary cardiomyopathies

- **Metabolic**
  - Amyloidosis, hemochromatosis
- **Inflammatory**
  - Chagas disease, coxackie, echo viruses
- **Endocrine**
  - Diabetic cardiomyopatia
  - Hypertyroidism, Acromegaly
- **Toxic**
  - Anticander chemotherapy, Alcohol
- **Neuromuscular**
  - Muscular dystrophy
- **Nutritional hypoxic**
  - Obesity
  - Ischemic cardiomyopathy

Cardiomyopathies - Comparison

	DILATED	RESTRICTIVE	HYPERTROPHIC
Ejection fraction (normal >55%)	Usually <30% when symptoms severe	25–50%	>60%
Left ventricular diastolic dimension (normal <55 mm)	≥60 mm	<60 mm (may be decreased)	Often decreased
Left ventricular wall thickness	Decreased	Normal or increased	Markedly increased
Atrial size	Increased	Increased; may be massive	Increased; related to abnormal
Valvular regurgitation	Related to annular dilation; mitral appears earlier, during decompensation; tricuspid regurgitation in late stages	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to valve-septum interaction; mitral regurgitation
Common first symptoms	Exertional intolerance	Exertional intolerance, fluid retention early	Exertional intolerance; may have chest pain
Congestive symptoms[a]	Left before right, except right prominent in young adults	Right often dominates	Left-sided congestion may develop late
Arrhythmia	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families; atrial fibrillation.	Ventricular uncommon except in sarcoidosis conduction block in sarcoidosis and amyloidosis; atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

Cardiomyopathies - Hemodynamic changes



Normal heart

Hypertrophic CM

Restrictive CM

Dilated CM

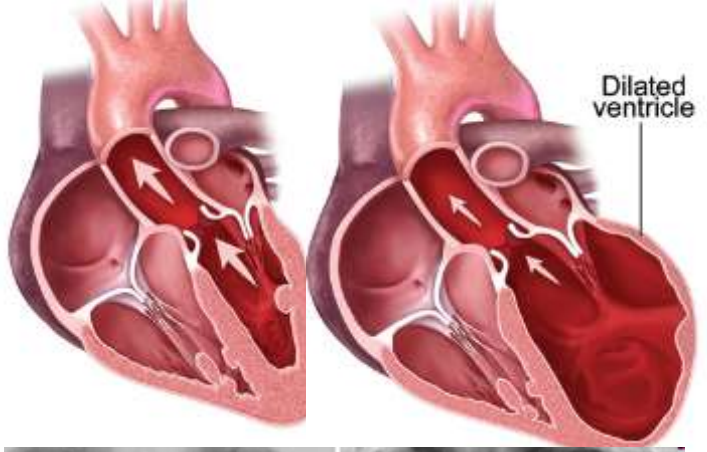
Hypertrophy → ↑ ejection pressure, but ↓ the relaxation & diastolic filling (diastolic failure).
Septal hypertrophy → subvalvular stenosis → narrowing an aortal outlet → ↑ resistance → ↑ ventricular hypertrophy (systolic failure)

Connective tissue cummulation + depositions → ↓ compliance, elasticity → ↓ end - diastolic relaxation & filling (diastolic failure).
Rigidity → ↓ contractilityt → ↑ ventricular volume cuymmulation (systolic failure)

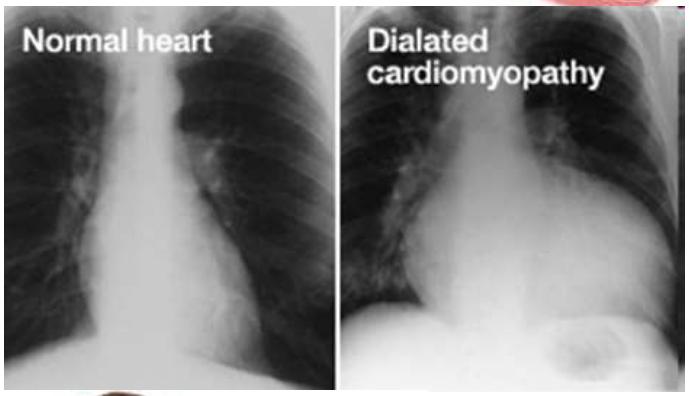
Defect → dilation → ↑ diastolic filling + ↓ contractility ejection) → ↓ Ejection force and volume

→ Congestive heart failure

1. DILATED CARDIOMYOPATHY (DCM)



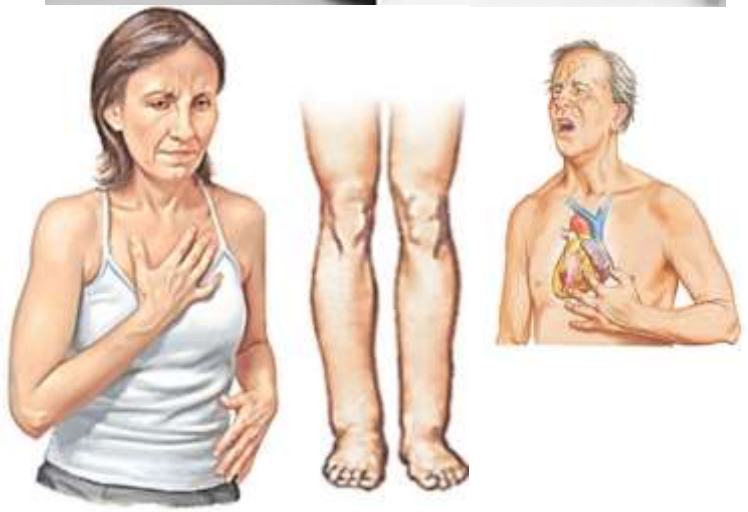
- **Alt.:** Congestive cardiomyopathy, Idiopathic cardiomyopathy
- **Def:** Progressive mostly irrevesible disorder leading to dilation of the heart cavities with systolic dysfunction
- ´**Path:** Frequently starts in LV than goes to RV then to atria. **Ventricles** have **thin wall** (event. **excentric hypertrophy**), **big cavity** relative insuficiency of valves; cardiomyocytes (hypertrophy or atrophy)
- **Occ:** the most common type, mostly in adults 20 – 60y; more common in black americans
- **Etio:** toxic - metabolic, infections, post-infarction (fibrosis), genetic forms **= 25–35%**
- **Clin**: **Heart failure and volume overload signs/sympt.**



- Early sy.: during exertion, sport, infection →

Fatigue, Dyspnea, arrhythmias, stenocardia; swelling of the ankles, feet, legs, abdomen and veins in the neck

- Late sy.: in rest, night → left heart failure; decompensation (lung edema) -> cough, short breath, paroxysmal nocturnal dyspnoea, ortopnoea, palpitations



Stenocardia, feeling tight on chest, dyspnoea after excercise. In the evening edemas on lower extremity.

Etiology of dilatated cardiomyopathy

Parasitosis: Chagas disease (Trypanosoma cruzi)common infection in Mid- and South Americ most common infectious cause of cardiomyopathy

Toxic cardiomyopathy (chemotherapeutics., Doxorubicin, cocain, heroine

Infection: acute virus based myocarditis – Coxackie B, enteroviruses)

Diabetic cardiomyopathy

Dilatated cardiomyopathy

Ischemic cardiomyopathy after myocardial infarction

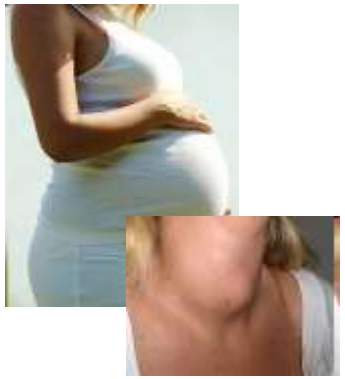
Alcoholic cardiomyopathy

Autoimmune mechanisms

Tachycardic cardiomyopathy = strctural-functional defects unmasked e.g. hyperthyreosis, excessive use of stimulants (coffein), uncontrolled tachyarrhythmias

Peripartum cardiomyopathy

several weeks or months after labor; reversible in 50% of cases

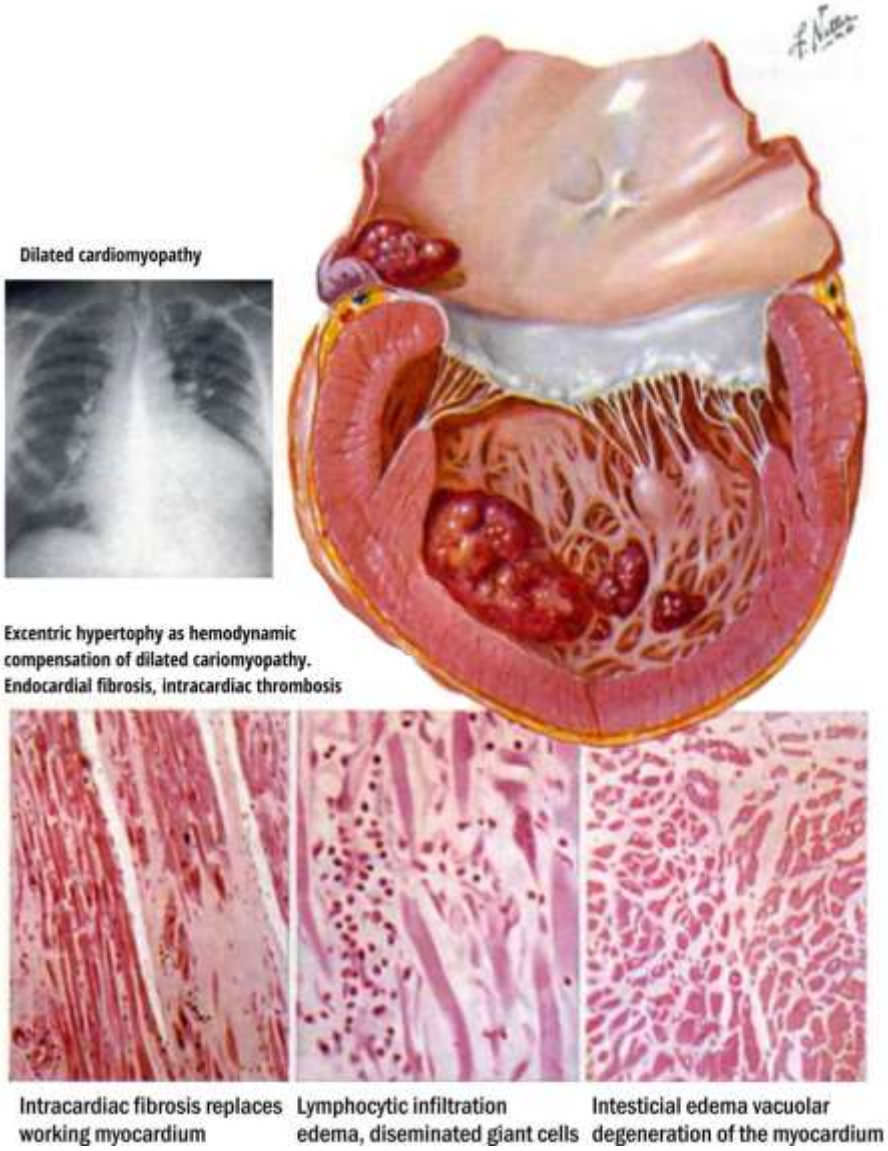


Familial dilated cardiomyopathy

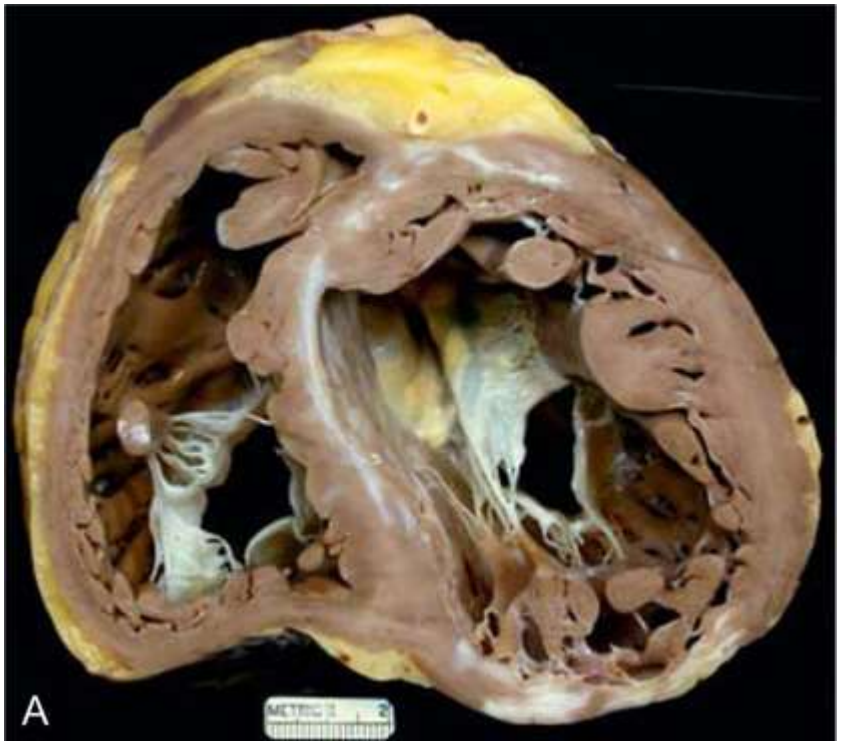
25–35% of patients genetically very heterogenous disease; subclinical manifestant forms: asymptomatic changes in heart muscle

DILATED CARDIOMYOPATHY (DCM)

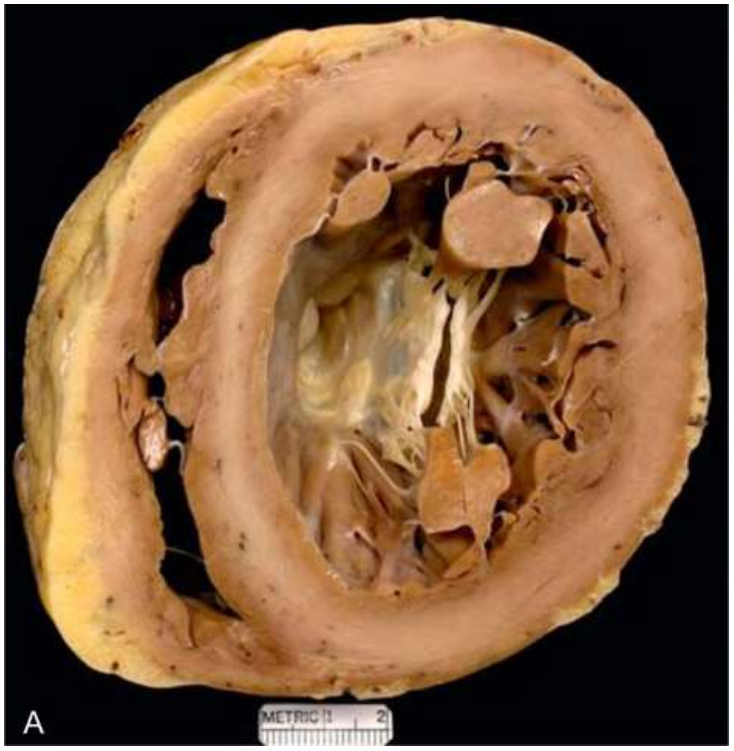
- **Ptg:** Heart chambers dilate → heart muscle doesn't contract normally → **low ejection fraction** blood cummulation in lungs → intestitial edema → ortopnoe, dyspnoe **(systolic left heart failure);**
- heart valve problems → valvular insufficiency,
- **arrhythmias** ventricular tachyarrhytmia / bradyarrhythmia
- weak evacuation blood stasis → **thrombosis**;
- **Lab:** Complete blood count, metabolic panel, Thyroid function tests, Cardiac biomarkers, B-type natriuretic peptide assay, Chest radiography, Echocardiography Cardiac magnetic resonance imaging (MRI), Electrocardiography (ECG)
- **Th:** ACE inhibitors → LV dysfunction, Diuretics → volume overload, b-blockers → Digoxin →inotrope, LV failure, Warfarin → trombolytic (atrial fibrilation)



DILATED CARDIOMYOPATHY (DCM)



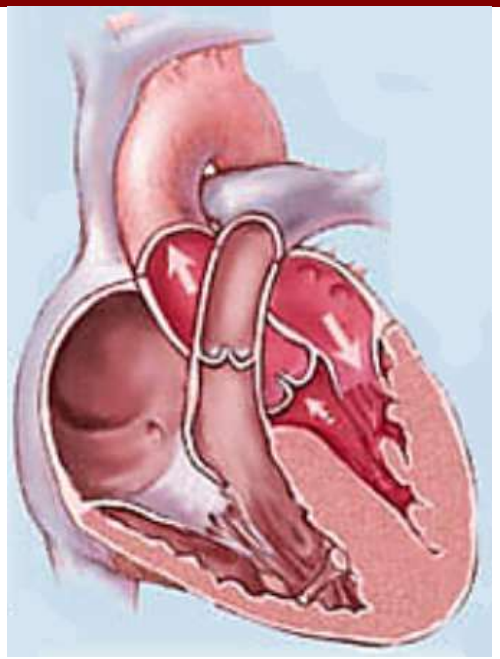
Case 1: Ischemic cardiomyopathy. The heart in a 48-year-old man who had had at least 2 acute myocardial infarcts in the past. posteriorly and the other anteriorly. The left ventricular ejection fraction was about 5%. (a) View of the heart showing both tricuspid and mitral valves. Both ventricles are greatly dilated.



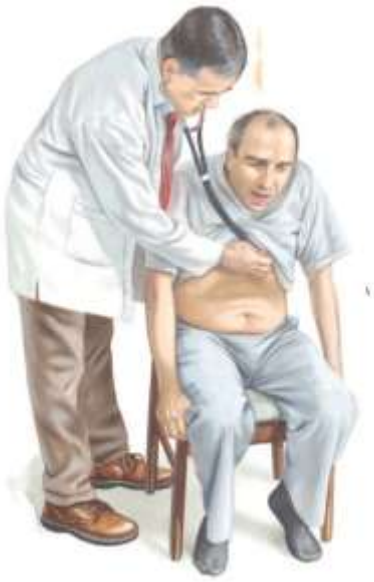
Case 2. Idiopathic dilated cardiomyopathy. 61-year-old woman with chronic heart failure since age 51 years on medical therapy until age 59 years, when the heart failure worsened considerably and an implantable cardiac defibrillator was inserted. She never had chest pain. Earlier in life she had had several children. No foci of fibrosis or necrosis.

Roberts, W. et al.: Morphologic Features of the Recipient Heart in Patients Having Cardiac Transplantation ... . Medicine. 93. 211-235, 2014. 10.1097/MD.0000000000000038.

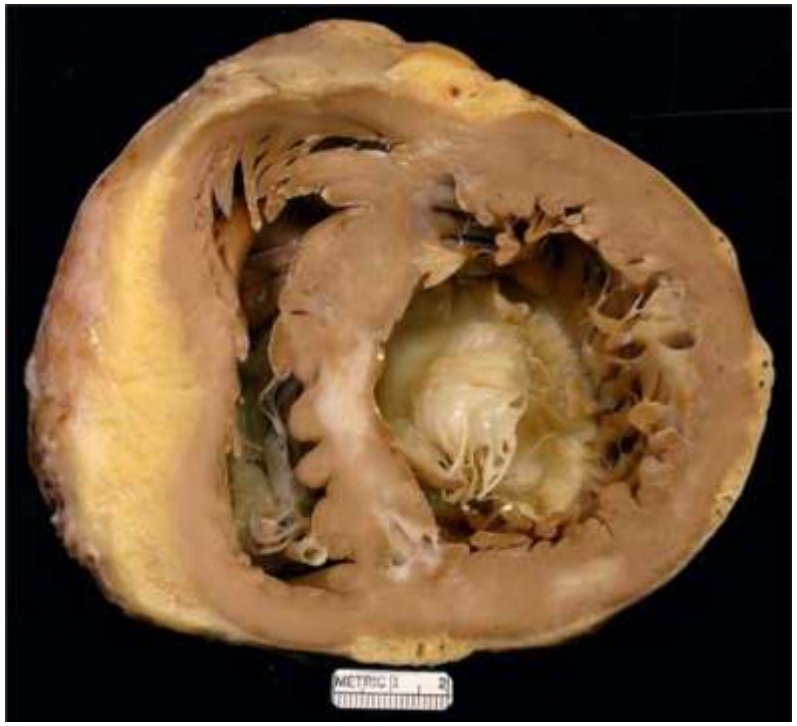
2. HYPERTROFIC CARDIOMYOPATHY (HCM)



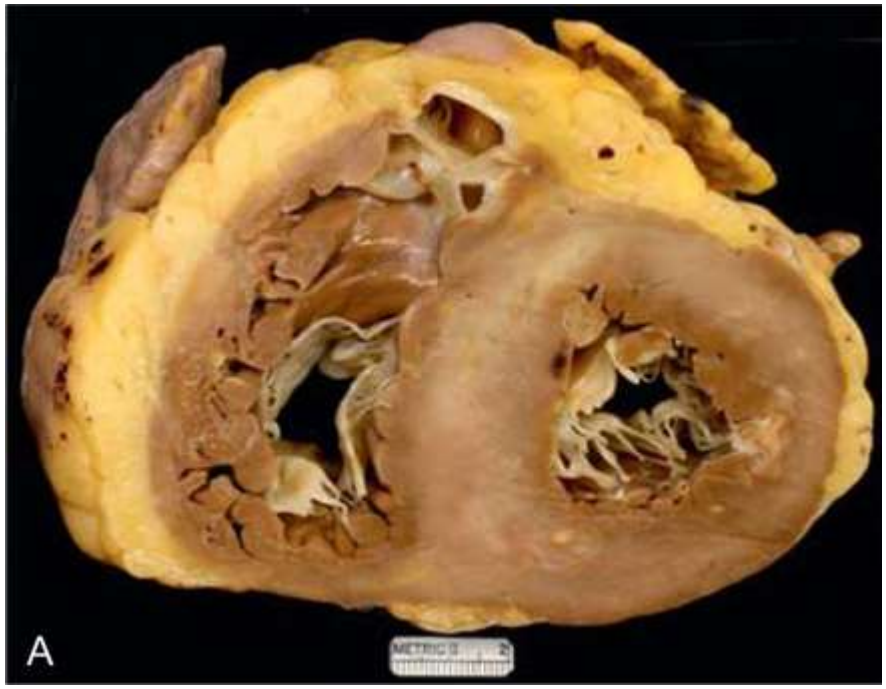
- **Def:** **progressive disease,** often apears in childhood, or in adulthood; sudden cardiac death from maligant arrhytmia (trigger is extreme physical activity); non-compensatory (no hemodynamic reason) **hypertrophy of myocard** (mainly septum) resulting into **subvalvul obstruction (about 1/3 of patients with systolic dyafunction)** and weak diastolic relaxation, filling (**diastolic dysfunction**), lower contractility;
- **Etio: 50-60% cases genetic;** AD – trait, sarcomeric proteins, in 45% mutations in genes for heavy β myosine, 35% cardiac myosine binding protein C; insertions / deletion polymorphisms in gene for ACE ;
- **Path: concentric hypertrophy**; small ventricular diameter; simialr picture as in metabolic accumulates (Fabry dis., glycogensis, amyloidosis…); dezorganisation of muscle fibres (disarray), hypertrohy of cardiomyocytes, interstitial fibrosis
- **Clin.:** dyspnoea, tiredness, **diastolic heart failure,** pulmonary vein congestion; myocardial ischemia (capillary pressure in systole, decrease of myocardart filling in diastole); arrhythmias



HYPERTROPHIC CARDIOMYOPATHY (DCM)

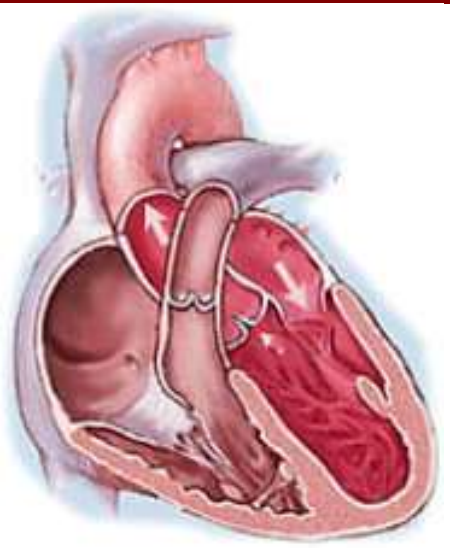


Case 1. Hypertrophic cardiomyopathy. *41-year-old man; hypertrophic cardiomyopathy was diagno-sed at 6 y.. At age 26 years, atrial fibrillation appeared and during the next 15 years he was cardioverted 98 times. He eventually developed complete heart block, and a pacemaker was inserted. At age 30 years, an intracardiac defibrillator was implanted.*

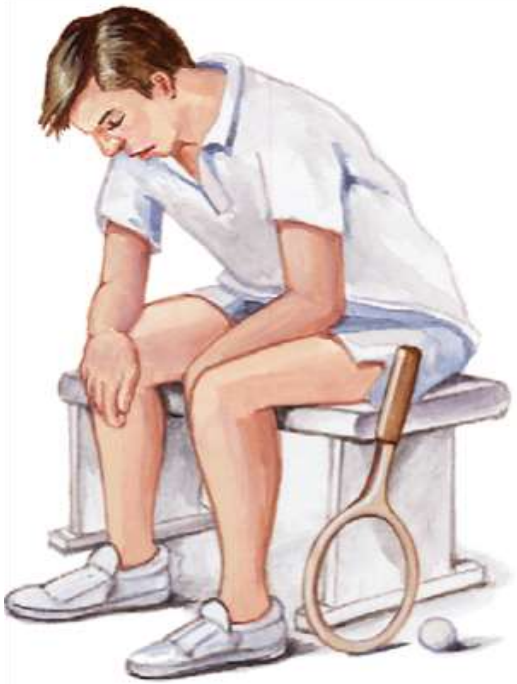


Case 2. Hypertrophic cardiomyopathy. *68-year-old obese man with obstructive sleep apnea, and chronic renal disease, stage 3. was diagnosed with hypertrophic CM years earlier.with recurrent episodes of ventricular tachycardia, atrial fibrillation and other atrial arrhythmias. implantable cardiac defibrillator.*

3. RESTRICTIVE CARDIOMYOPATHY (RCM)



- **Def:** walls are rigid due to infiltration; diastolic stretching (and blood filling) of chambers is restricted (reduced compliance) → ↓ EDV (end diastolic volume) of either or both ventricles; systolic function and wall thickness are normal
- **Occ:** least common CM; 5% of all primary heart muscle diseases
- **Class: 1. Extramyocardial ECM (non cardial dis.) → a) non-infiltratíve, b) infiltrative** (e.g. amyloidosis, sarcoidosis, hemochromatosis,…); **2. Myocardial ECM**

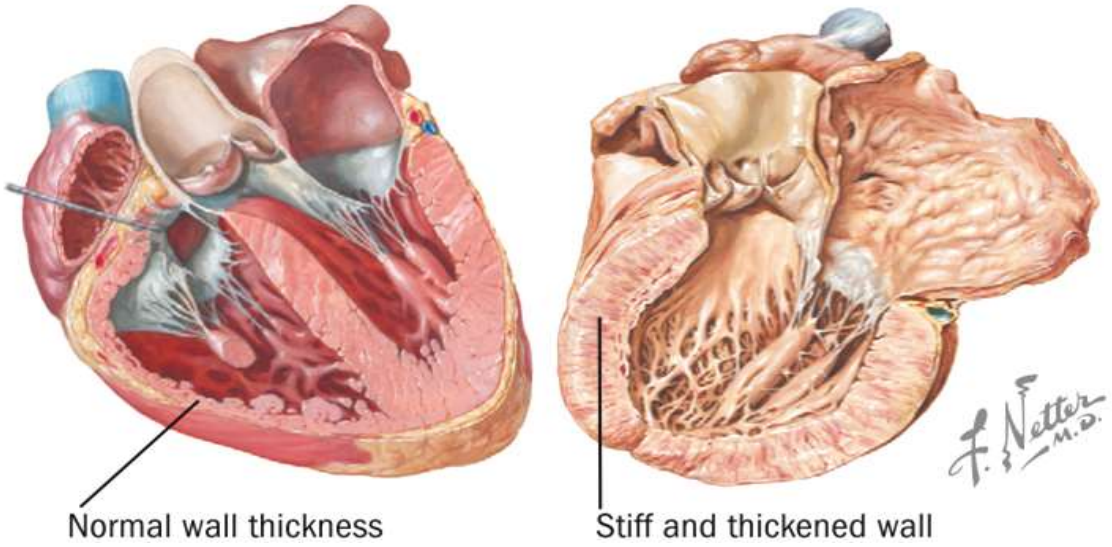


- **Etio:**

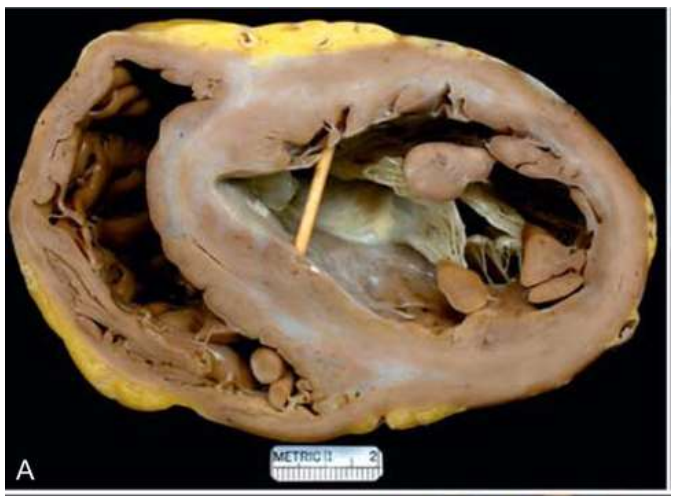
  a) idiopathic (not other category, unindentified, ? hereditary) **;** **b) primary** (cardiac dis.), e.g. endomyocardial fibroelastosis , Löffler's endocarditis, **c) secondary** (systemic dis.) – infiltrative (amyloidosis, hemochromatosis, sarcoidosis); interstitial fibrosis (post radiation therapy)
- **Sy:** a) **tiredness, failting** (orthostatic hypotension) = frequent sy., b) **right heart failure signs** (swelling of lower extrem.) = among first, c) **heavy breathing (dyspnoe),** palpitations, precardiac pain (angina - like)

RESTRICTIVE CARDIOMYOPATHY

- **Ptg: atrias are extremly dilated** + **thrombi** are often formed; **thickening of chambers** and valves (infiltration);
- **Dif.dg:** restriction due to constrictive pericarditis.

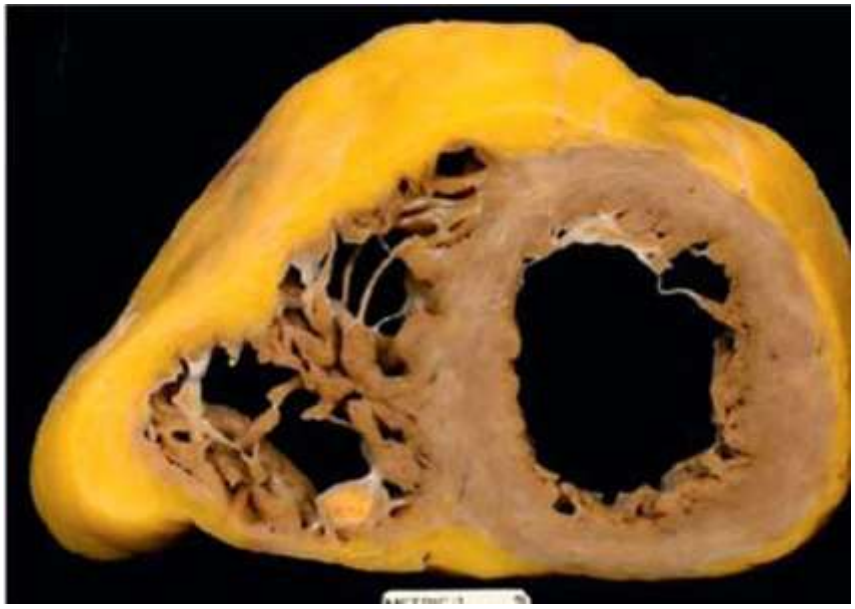


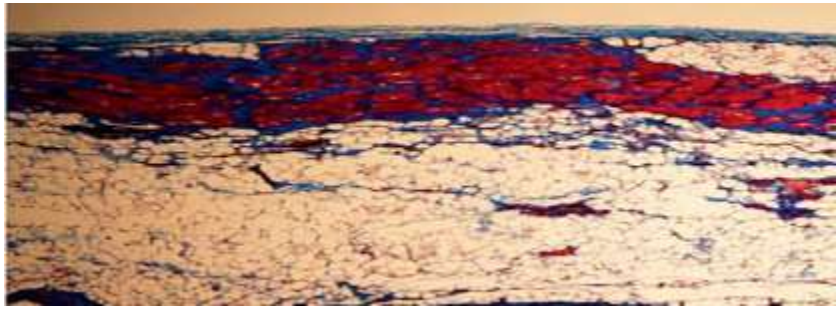
Case 1: Restrictive cardiomyopathy. *Cardiac sarcoidosis.52-year-old woman who had developed heart failure beginning at age 48 years (severe global left ventricular hypokinesis, ejection fraction of 10%) normal coronary arteries, implantable cardiac defibrillator/pacemaker*



4. ARRHYTHMOGENIC DYSPLASIA OF RIGHT CHAMBER

- **Def:** non-ischemic genetically based type of cardiomyopathy with fibro- fatty or fatty infiltration and replacement of the right ventricular myocardium associated with RV arrhythmias (premature ventricular beats, ventricular tachycardia, ventricular fibrillation VF.
- **Epi:** may manifest in children; most common first signs in young adults (males mainly); 30–50% familial
- **Clin**: (80%) syncope dyspnea excercise related (cause of sudden cardiac death in athletes) ; (20%) palpitations; right ventricular outflow tract (RVOT) tachycardia (monomorphic ventricular tachycardia).
- **Etio:** usually AD - inherited disease (variable expression) linked with mutations of protein components of desposomes in intercalated disks of cardiomyocytes; linked with diffuse palmoplantar keratoderma, and woolly hair (AR - Naxos disease)





Case 1: *26-year-old man developed symptoms of heart failure at age 12 years, followed later by ventricular arrhythmias and bundle branch block. left ventricular ejection fraction fell to 15%. dilatation of both ventricles. ventricular wall in the right ventricular of adipose tissue, fibrous tissue, and a few myocardial cells*

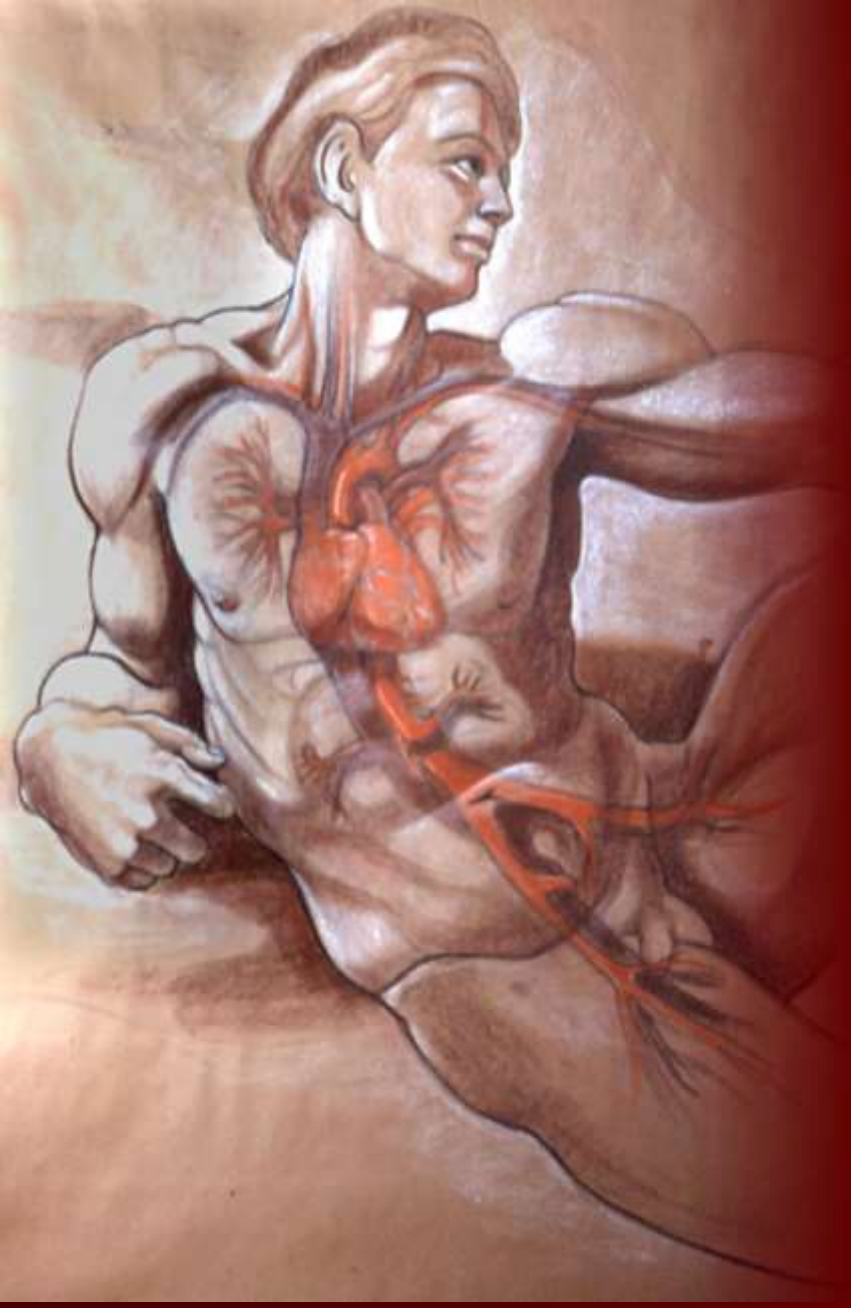
ARRHYTHMOGENIC DYSPLASIA OF RIGHT CHAMBER

- **Pat:** starts subepicardially leading to transmural defect (possibly aneurysmal dilatation of the RV in 50%) in the diaphragmatic, apical, and infundibular regions. Residual myocardium in RV (trabeculae) hypertrophied. LV involved in 50–60% (late in disease,poor prognosis).

Two patterns:

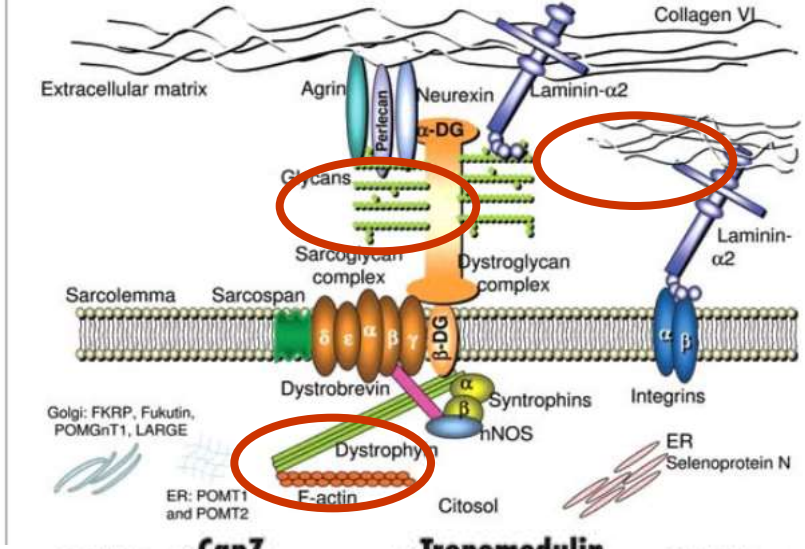
A. Fatty infiltration: fatty tissue without wall thinning.
B. B Fibro-fatty infiltration: patchy myocarditis is involved in up to 2/3 of cases, with inflammatory infiltrates (mostly T cells)

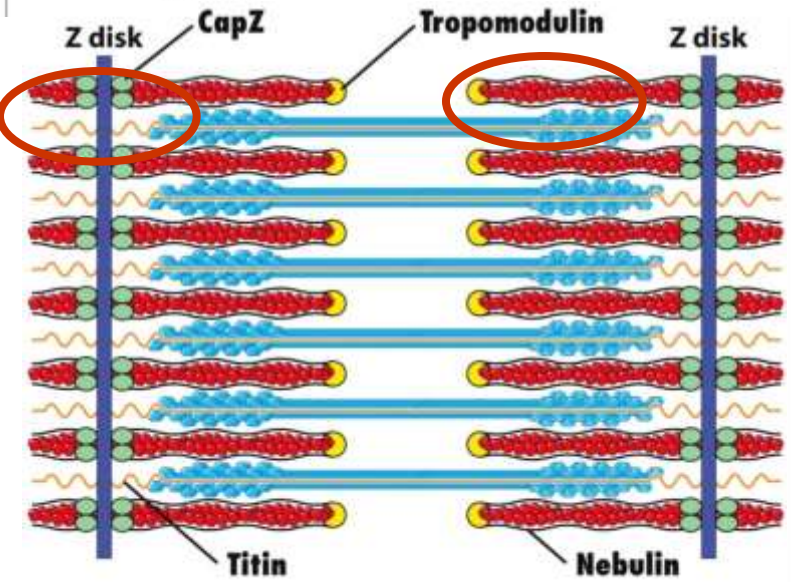
- Ptg: abnormal aggeregation of desmin (intermediate filament protein linked to the desmosomes) & associated proteins; various mutations in the desmin (DES) gene (penetrance 20–35%)

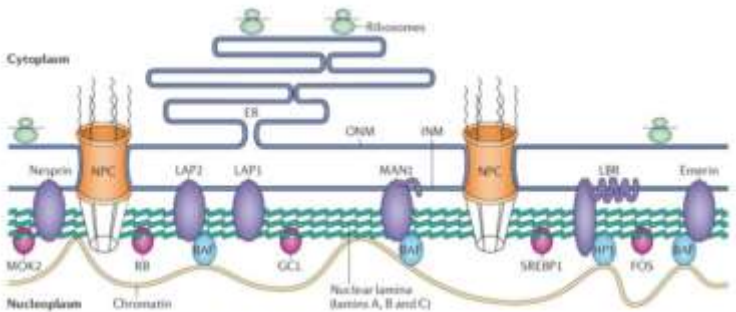


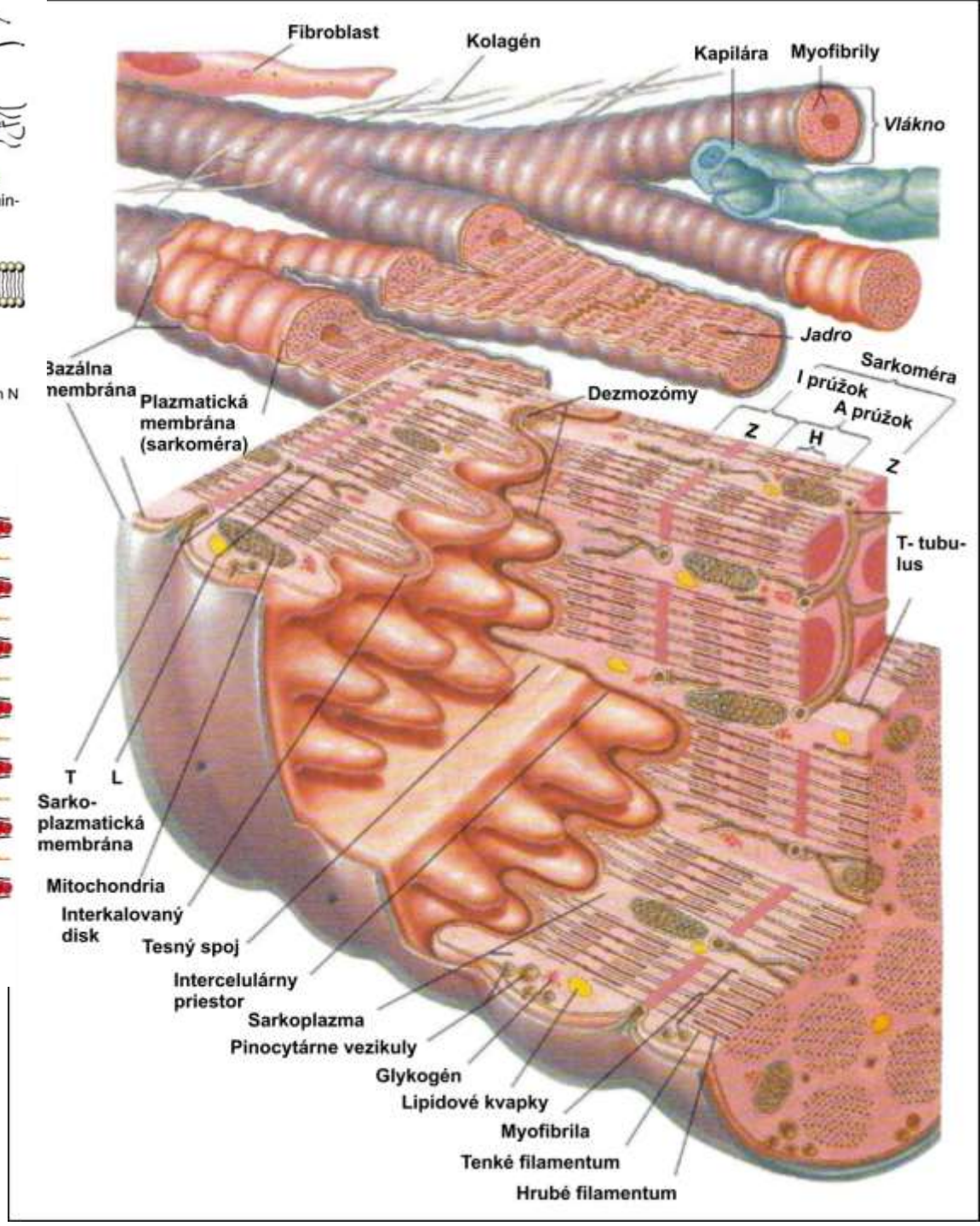
ADVANCED PATHOPHYSIOLOGY

Hereditary forms of cardiomyopathies


Collagen VI
Extracellular matrix
Agrin
Perlecan
Neurexin
Laminin-α2
α-DG
Glycans
Sarcoglycan complex
Dystroglycan complex
Laminin-α2
Sarcolemma
Sarcospan
β-DG
Dystrobrevin
Syntrophins
nNOS
Integrins
Golgi: FKRP, Fukutin, POMGnT1, LARGE
Dystrophin
ER
Selenoprotein N
ER: POMT1 and POMT2
F-actin
Citosol


Z disk
CapZ
Tropomodulin
Z disk
Titin
Nebulin


Cytoplasm
Ribosomes
ER
ONM
INM
Nesprin
NPC
LAP2
LAP1
MAN1
NPC
LBR
Emerin
MOK2
RB
BAF
GCL
BAF
SREBP1
HP1
FOS
BAF
Nucleoplasm
Chromatin
Nuclear lamina (lamins A, B and C)


Fibroblast
Kolagén
Kapilára
Myofibrily
Vlákno
Jadro
Sarkoméra
I prúžok
A prúžok
Z
H
Z
Bazálna membrána
Plazmatická membrána (sarkoméra)
Dezmozómy
T- tubulus
T
L
Sarko-plazmatická membrána
Mitochondria
Interkalovaný disk
Tesný spoj
Intercelulárny priestor
Sarkoplazma
Pinocytárne vezikuly
Glykogén
Lipidové kvapky
Myofibrila
Tenké filamentum
Hrubé filamentum

Familial dilated cardiomyopathy (CMD) – Examples

Type	Locus	Gene	Protein
CMD1A	1q21	LMNA	Lamin A
CMD1B	9q13	TMOD1	Tropomodulin-1
CMD1C	10q22-23	LDB3	PDZ domain-containing protein Z-BAND cypher
CMD1D	1q32	TNNT2	Troponin T type 2 (cardial)
CMD1E	3p	SCN5A	Sodiun channel
CMD1G	2q31	TTN	Titinin in sarcomere
CMD1I	2q35	DES	Desmin in sarcomeres
CMD1J	6q23-q24	EYA4	eyes absent (EYA) protein. transcriptional activator
CMD1L	5q33	SGCD	Delta-sarcoglycan
CMD1M	11p15.1	CSRP3	Cysteine and glycine-rich protein – myogenic regulatory factor
CMD1N	17q12	TCAP	Telethonin

Type	Locus	Gene	Protein
CMD1O	12p12.1	ABCC9	Receptor sulfonylurea 2 (SUR2)
CMD1P	6q22.1	PLN	Fosfolamban
CMD1R	15q14	ACTC	alpha Actin, cardiac muscle 1
CMD1S	14q12	MYH7	Myosine 7
CMD1T	12q22	TMPO	Thymopoietin
CMD1U	14q24.3	PSEN1	Presenilin-1
CMD1V	1q31-q42	PSEN2	Presenilin-2
CMD1W	10q22-q23	VCL	Vinculin
CMD1X	9q31	FCMD	Fukutin
CMD1Y	15q22.1	TPM1	Tropomyosin alpha-1 chain
CMD1Z	3p21.3-p14.3	TNNC1	Troponin C, slow skeletal and cardiac muscles
CMD1AA	1q42-q43	ACTN2	alfa-actinin 2 actin-binding protein
CMD2A	19q13.4	TNNI3	Troponin I
CMD3A	Xq28	TAZ	Tafazzin
CMD3B	Xp21.2	DMD	Dystrophin

Genetically heterogenous group of diseases

Mutations can be found in **contractile system proteins** (e.g. actin, tropomyosin, troponin C, myosin), **adaptors + sarcomere elements** (titin,desmin,), **sarcomere –to- membrane-to extracelullar attachment system** (sarcoglycam, dystrophin, presenilin,vinculin, actinin), enzymes (tafazzin) etc.

Familial hypertrophic cardiomyopathy (CMH) - Examples

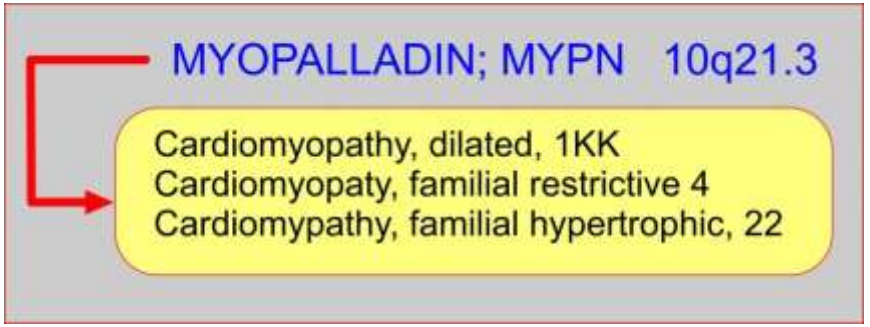
Forms	Gene	Locus	Encoded protein
CMH1	MYH7	14q12	Myosin heavy chain 7; beta subunite (MHC-β)
CMH2	TNNT2	1q32	Troponin T (type 2)
CMH3	TPM1	15q22.1	Tropomyosin 1 (alpha)
CMH4	MYBPC3	11p11.2	Myosin binding proteín C
CMH5	?	?	
CMH6	PRKAG2	7q36	AMP-activated PK (subunite gamma -2)
CMH7	**TNNI3**	**19q13.4**	**Troponin I, cardiac**
CMH8	MYL3	3p	Myosin light chain 3
CMH9	TTN	2q24.3	Titin
CMH10	MYL2	12q23-q24	Myosin regulatory light chain 2
CMH11	ACTC1	15q14	Cardiac alpha – actin 1
CMH12	CSRP3	11p15.1	Cysteine / glycine-rich protein 3

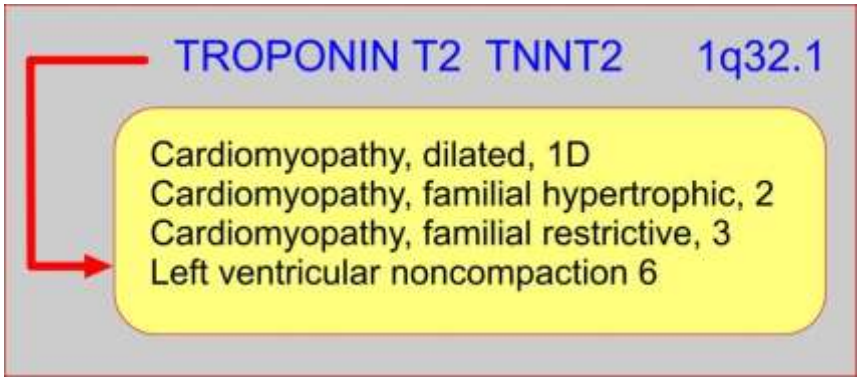
Mutated proteins are mostly **parts of sarcomeric contractile apparatus** (myosin, actin, troponine, tropomyosine, titin) . Mutations of troponin cause 50% mortality of HCM before 40 y.

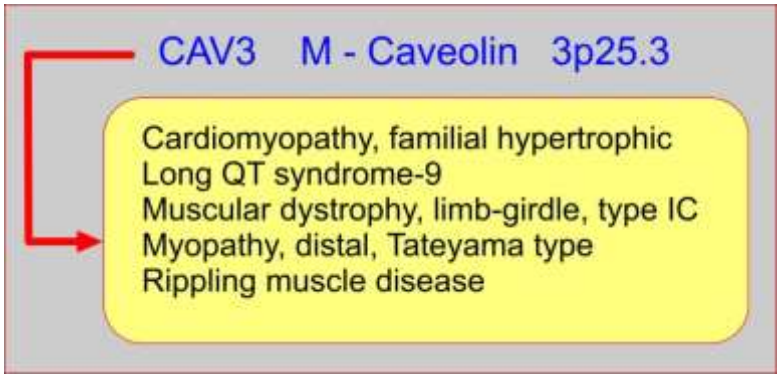
Allelic heterogenity in cardiomyopathies - Examples

Familial restrictive cardiomyopathy (CMH) Examples

Type	Locus	Gene	Protein
RCM1	19q13	TNNI3	Troponin I type 3 (cardial)
RCM2	10q23	DES 3	Desmin in sarcomeres
RCM3	1q32	TNNT2	Troponin T type 2 (cardial)
RCM4	10q21	MYPN	Troponin T type 2 (cardial)







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