Definition and classification of the cardiomyopathies

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Historical Context

- WHO: 1980 classification

  "heart muscle diseases of unknown cause"
- WHO 1995 classification

  "diseases of myocardium associated with cardiac dysfunction"

How should we define cardiomyopathies?

BASED ON

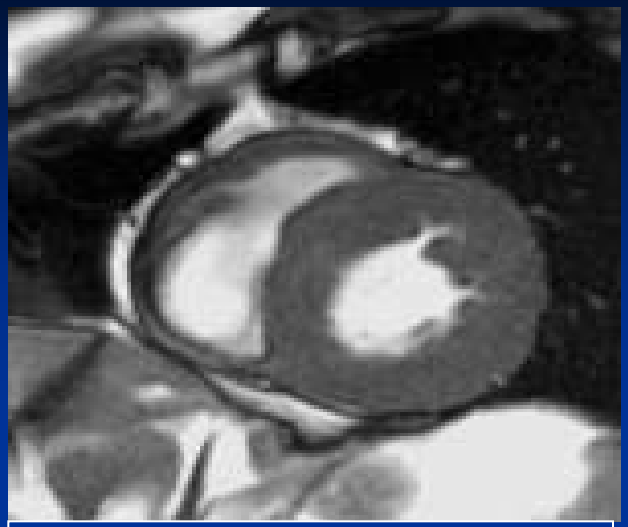
- origin?
- anatomy?
- physiology?
- biopsy histopathology?
- genetics?

Based on Origin

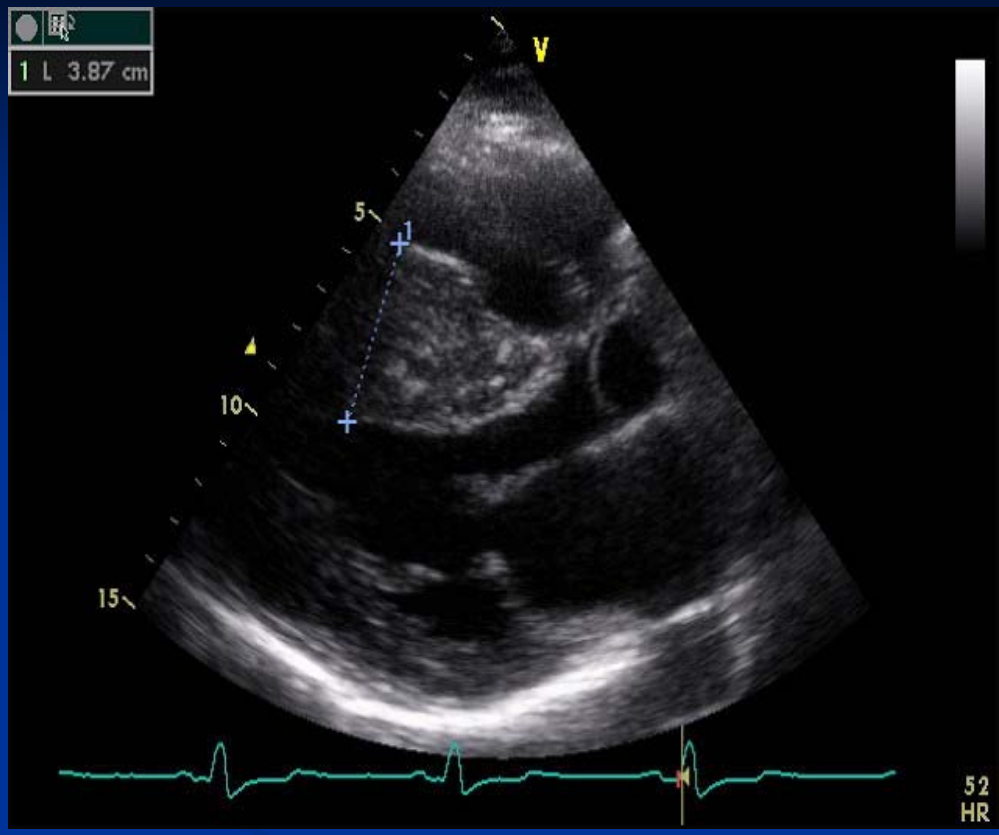
DILATED CARDIOMYOPATHY

- Idiopathic
- Familial/Genetic
- Viral
- Immune
- Alcoholic/Toxic

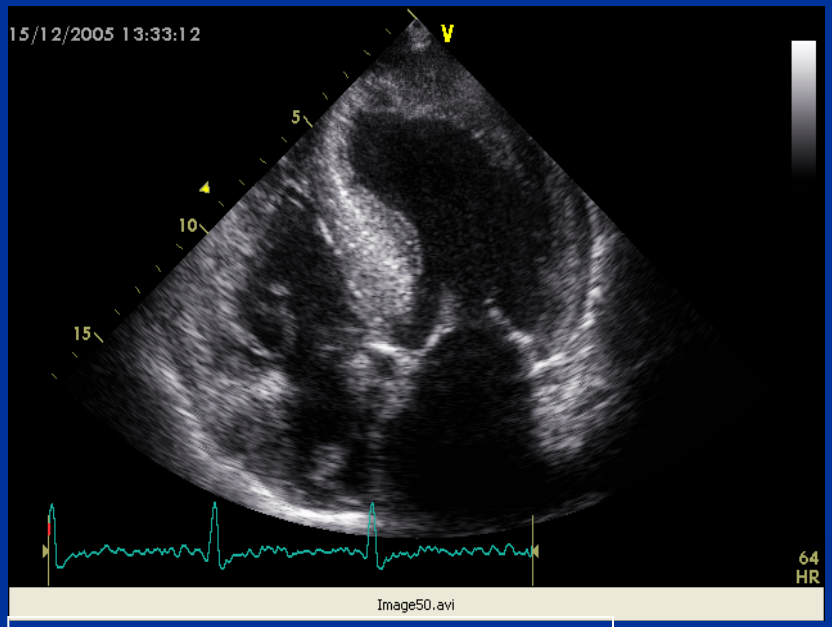
Based on Anatomy



Fabry

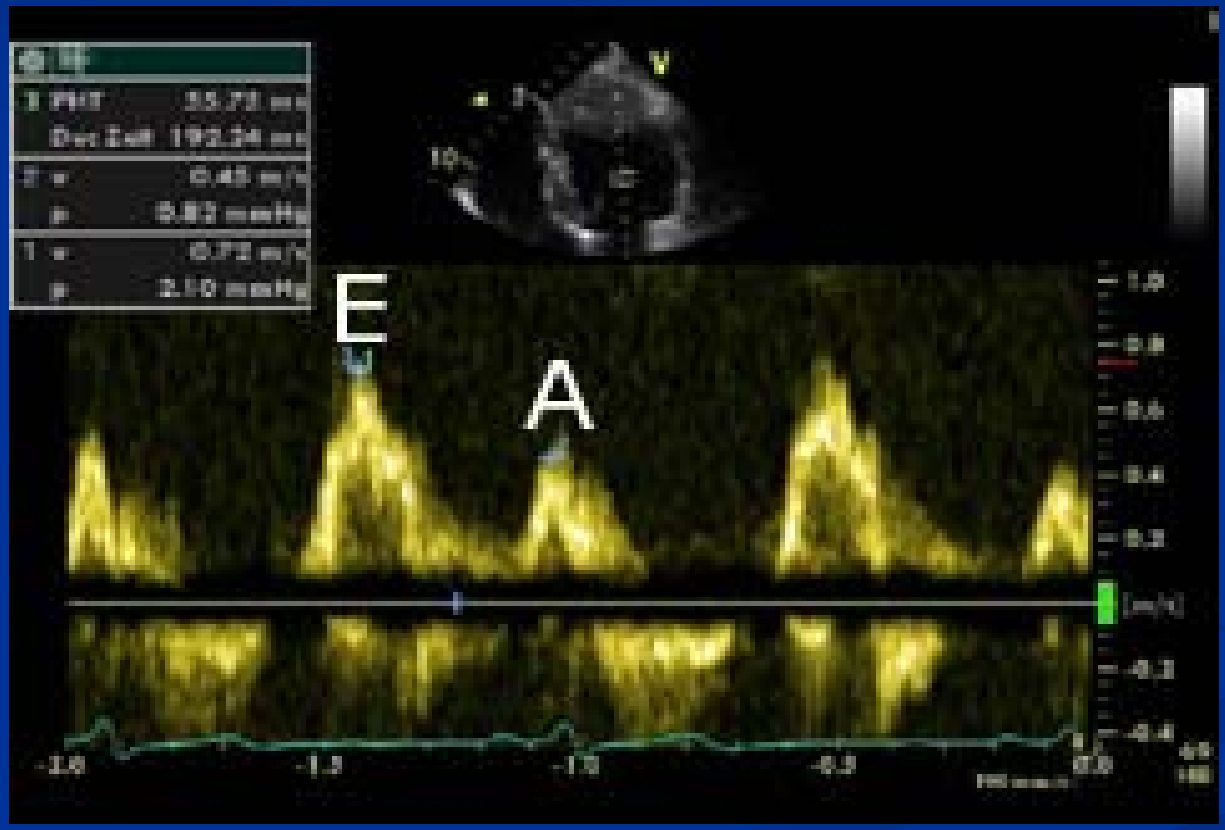


HCM

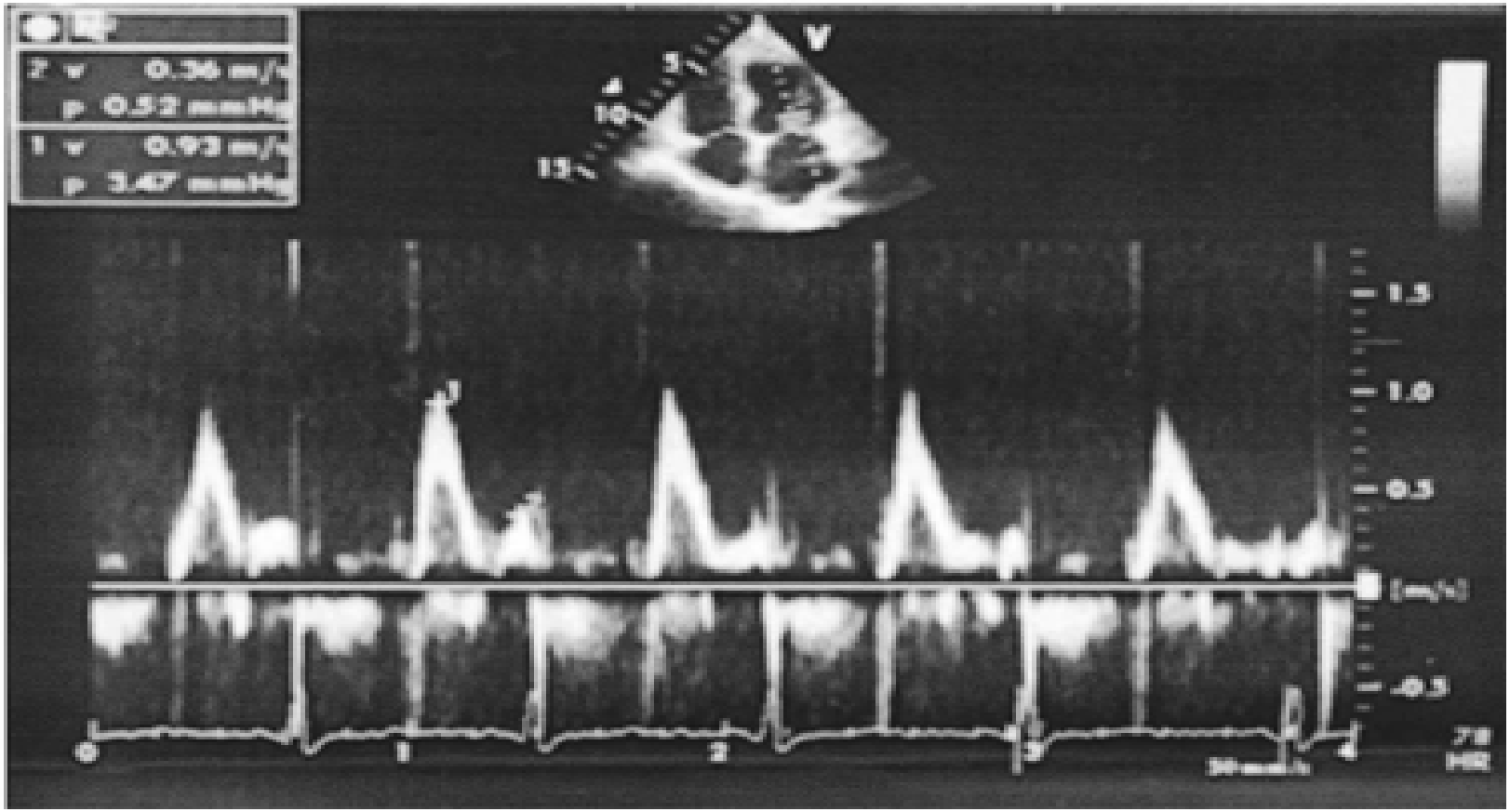


Cardiac amyloidodis

Based on physiology (Filling Pattern)



Based on physiology (restrictive pattern)

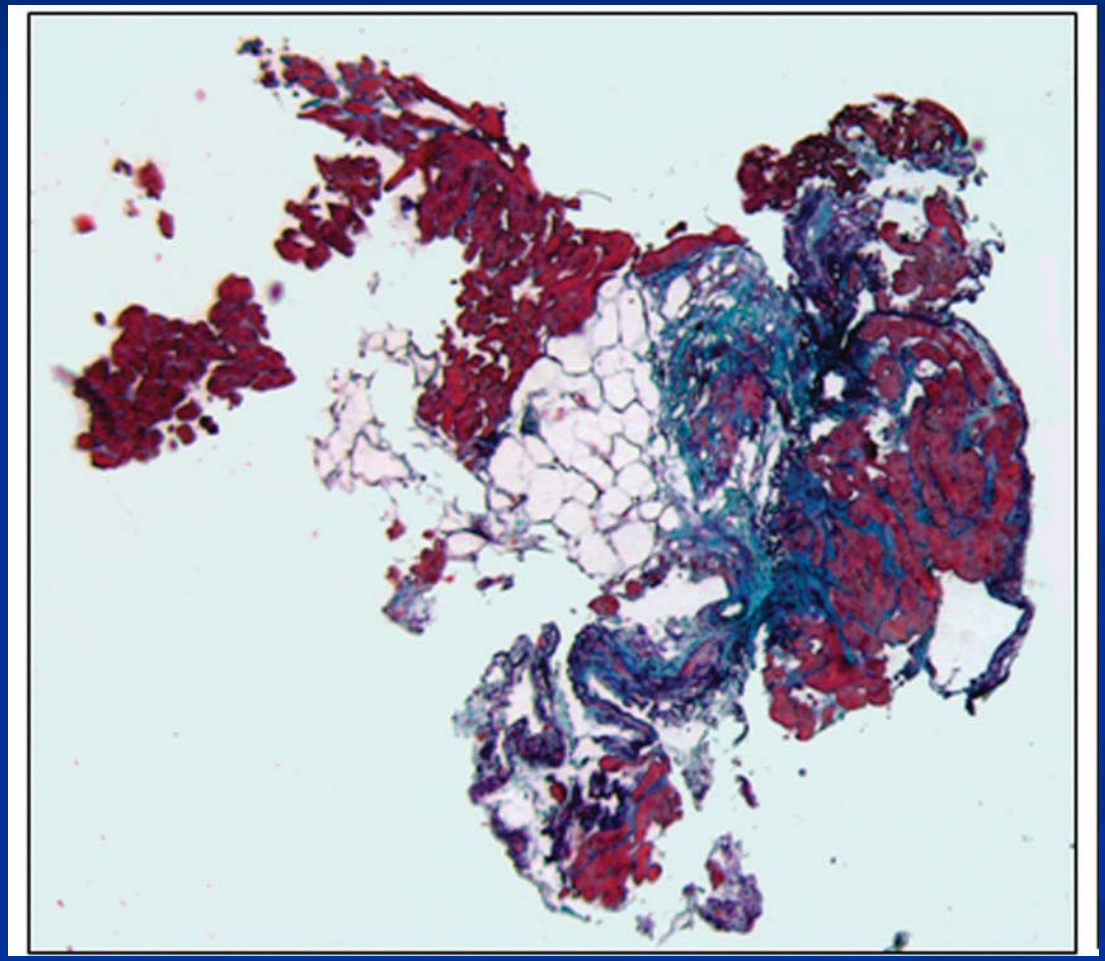


Based on physiology

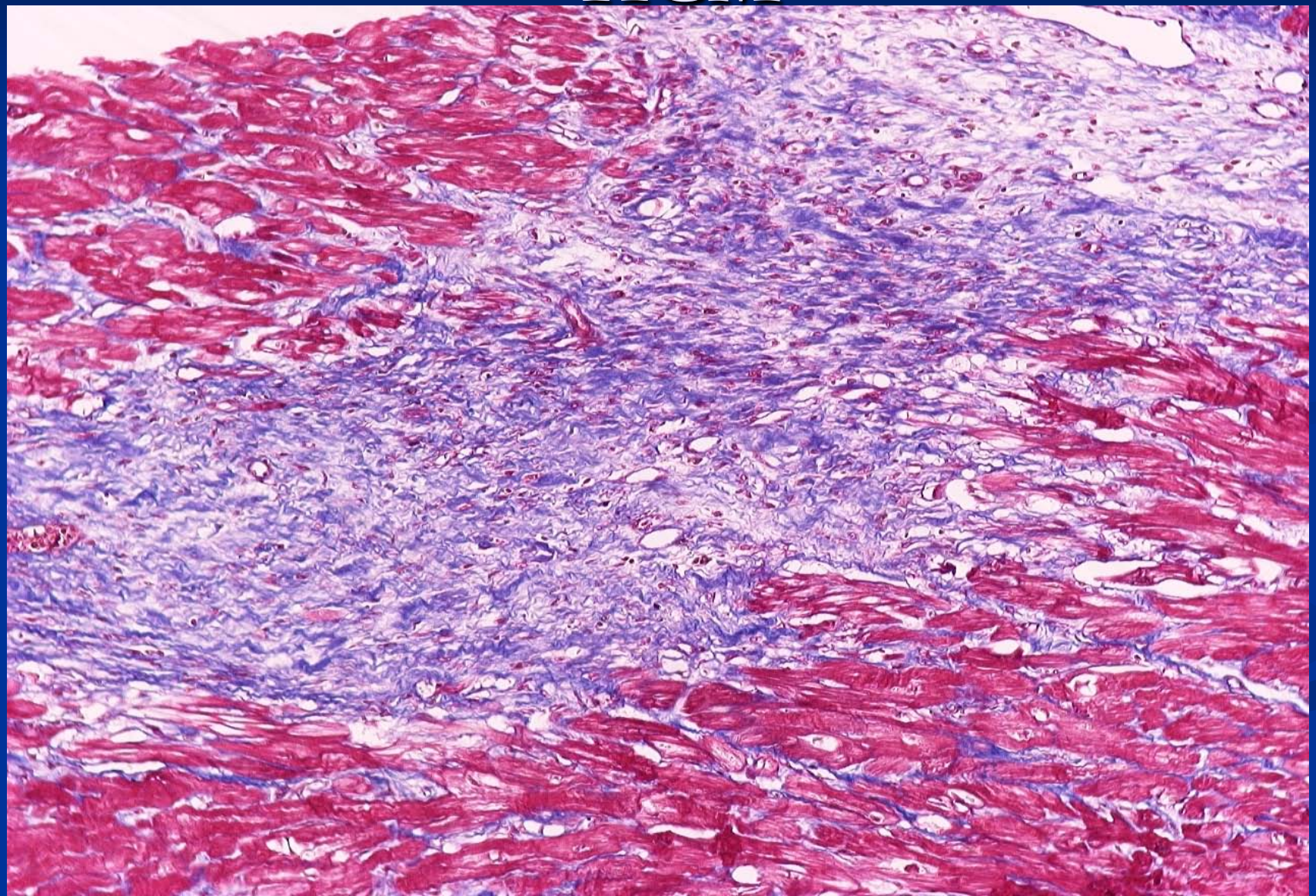
- Restrictive cardiomyopathy
- Hypertrophic-restrictive cardiomyopathy

  Restrictive filling pattern

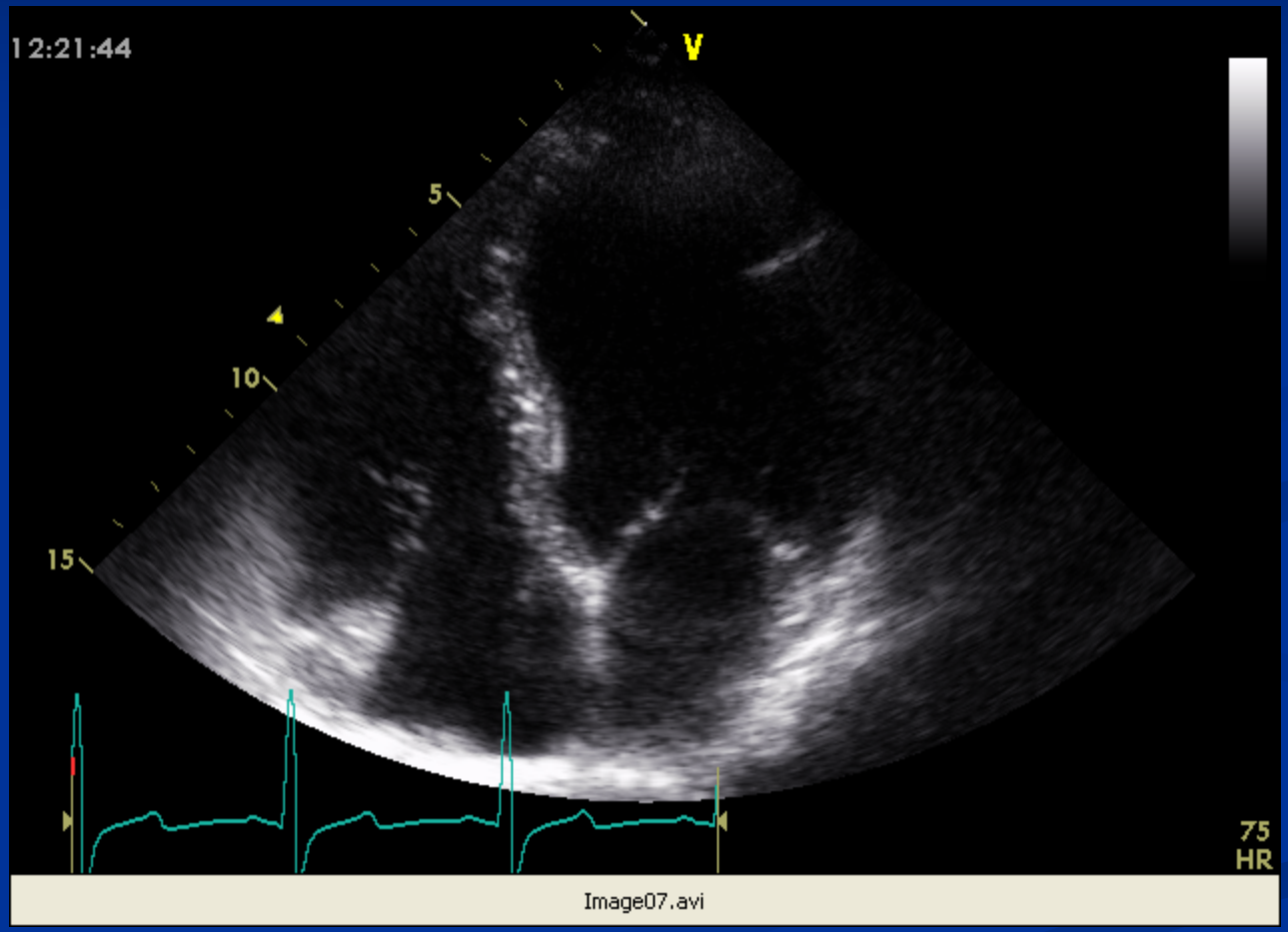
Based on biopsy histopathology ARVC



Based on biopsy histopathology HCM



DCM, male, 44-y-old



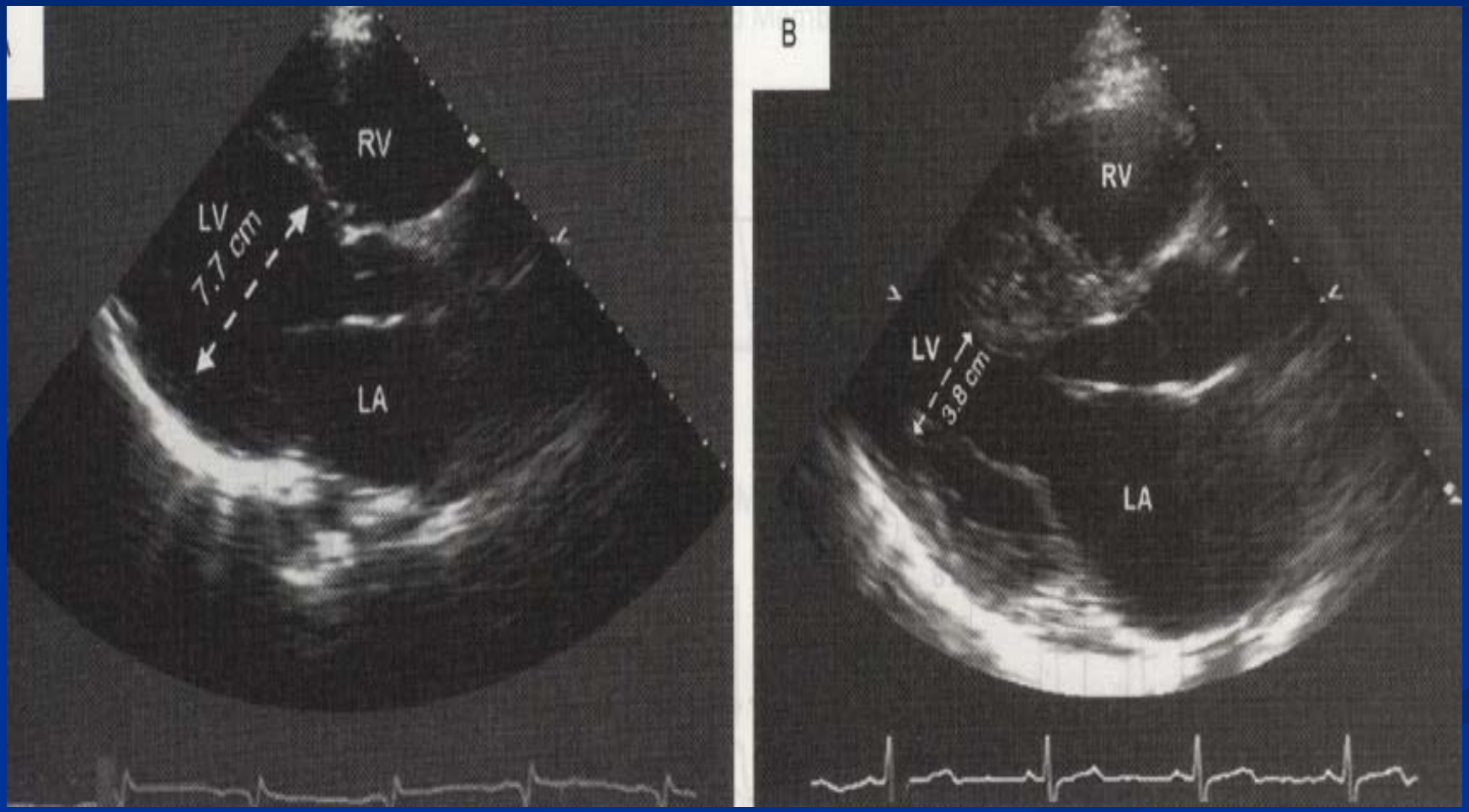
Light microscopy: Two myocardial samples with severe interstitial and endocardial fibrosis. Myocytes with irregular profiles, focal hypertrophia and myofibrillar lysis. No myocarditis; no extracellular accumulation; no endocardial thrombosis.
Ultrastructural findings on electron microscopic study: One myocardial sample from paraffin-embedded tissue processed for electron microscopy. Myocytes: myofibrillar lysis, mitochondrial cristolysis, lipid droplets, nuclei with irregular profiles. Interstitium: fibrosis with dense collagen bundles, absence of inflammatory cells. No extracellular accumulation.
Histology: Two myocardial showing findings similar to A, with sparse and focal inflammatory cells in one sample.
Ultrastructural findings on electron microscopic study: One myocardial sample showing findings similar to A, with more pronounced myofibrillar lysis. No amyloid.
Findings consistent with cardiomyopathy

Eloisa Arbustini

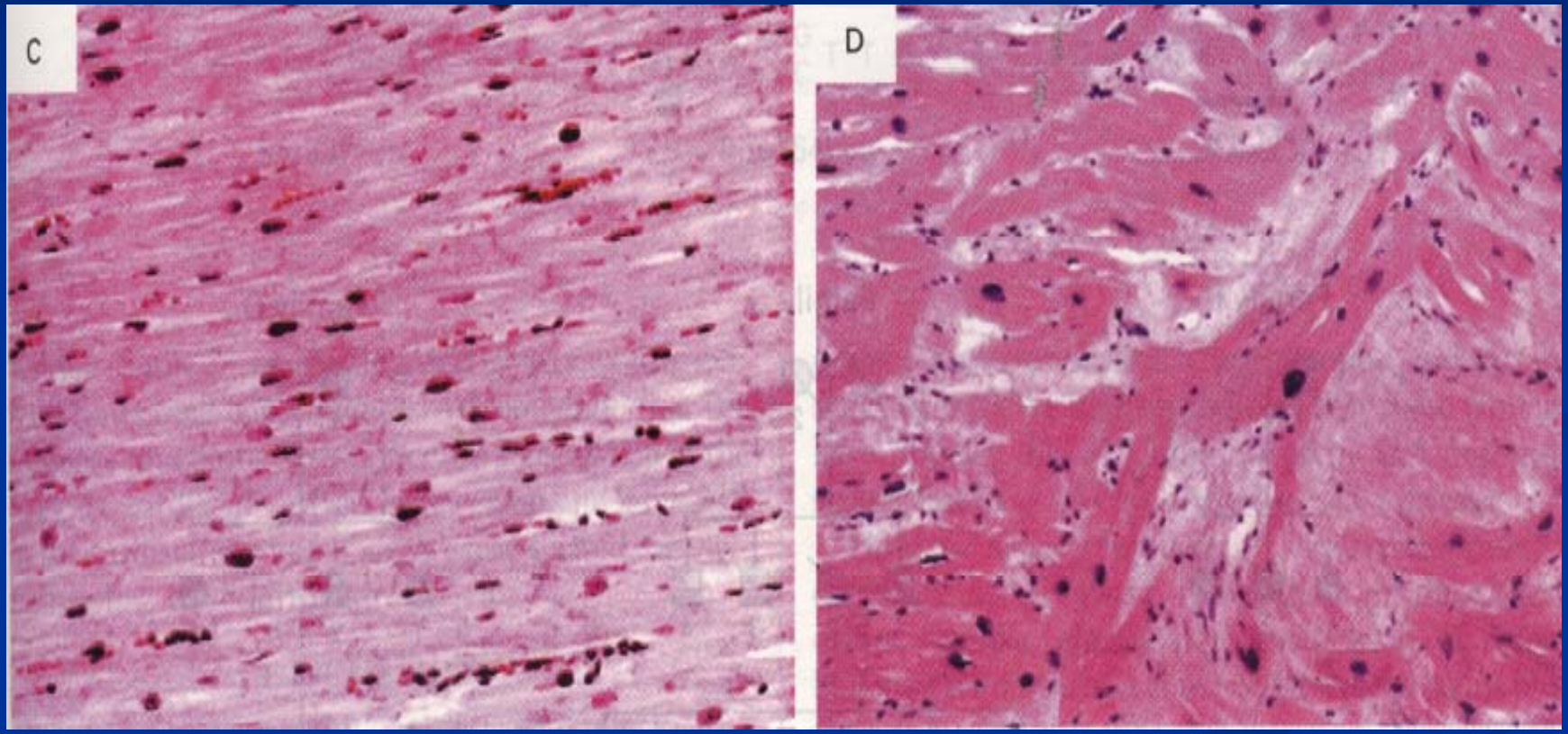
Classification Based Mainly on Molecular Genetics

B-myosin heavy chain gene mutations

DCM HCM



DCM HCM



Disease-causing mutations in the human beta-cardiac Myosin Heavy Chain gene

- 194 hypertrophic cardiomyopathy mutations
- 13 dilated cardiomyopathy mutations
- 7 other mutations
- 7 variants of uncertain effect
- 15 polymorphisms

Circulation. 2006;113:1807-1816

- **AHA Scientific Statement**
- **Contemporary Definitions and Classification of the Cardiomyopathies**
- **An American Heart Association Scientific Statement From the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention**
- Barry J. Maron, MD, Chair; Jeffrey A. Towbin, MD, FAHA; Gaetano Thiene, MD; Charles Antzelevitch, PhD, FAHA; Domenico Corrado, MD, PhD; Donna Arnett, PhD, FAHA; Arthur J. Moss, MD, FAHA; Christine E. Seidman, MD, FAHA; James B. Young, MD, FAHA

AHA: Definition of Cardiomyopathies

- *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with*
- *mechanical*
- *and/or electrical dysfunction*
- *that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation*
- *and are due to a variety of causes that frequently are genetic.*
- *Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure–related disability.*

New definition: basic characteristics

- mechanical dysfunction (diastolic or systolic dysfunction)
- electrical dysfunction (life-threatening arrhythmias)
- ion channelopathies (long-QT syndrome, Brugada syndrome)
- no histopathological abnormalities
- abnormalities at the molecular level in the cell membrane

Entities excuded from the new definition

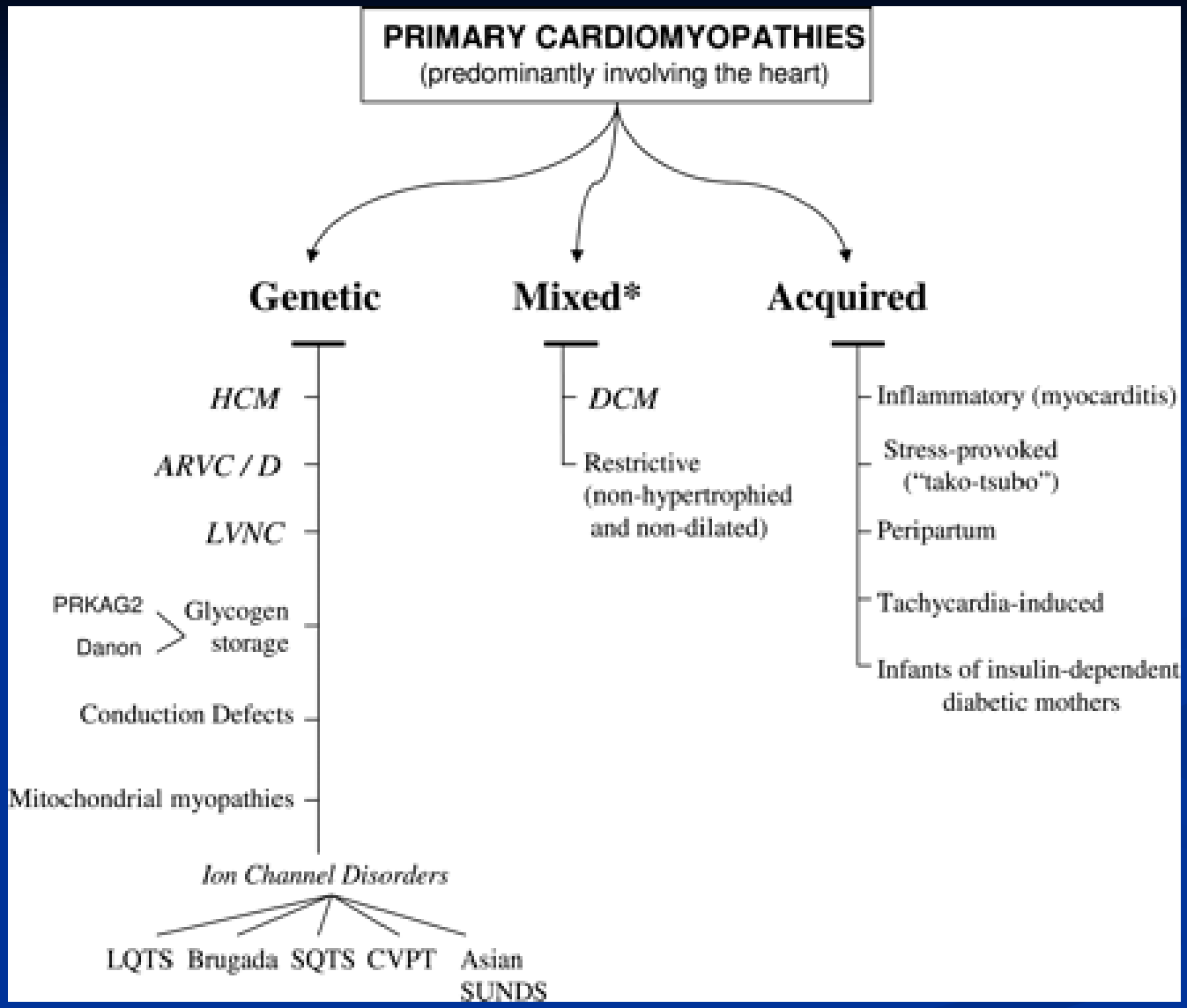
pathological myocardial processes and dysfunction that are a direct consequence of

- valvular heart disease
- systemic hypertension
- congenital heart disease
- atherosclerotic coronary artery (ischemic cardiomyopathy)
- metastatic and primary intracavitary or intramyocardial cardiac tumors
- diseases affecting endocardium with little or no myocardial involvement
- hypertensive HCM.

AHA: Classification of Cardiomyopathies

Primary cardiomyopathies

- solely or predominantly confined to heart muscle genetic, nongenetic, acquired
- *Secondary* cardiomyopathies
- pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders
- old definition: "specific cardiomyopathies" or "specific heart muscle diseases"


PRIMARY CARDIOMYOPATHIES
(predominantly involving the heart)
Genetic
Mixed*
Acquired
HCM
ARVC / D
LVNC
PRKAG2
Danon
Glycogen storage
Conduction Defects
Mitochondrial myopathies
Ion Channel Disorders
LQTS
Brugada
SQTS
CVPT
Asian SUNDS
DCM
Restrictive (non-hypertrophied and non-dilated)
Inflammatory (myocarditis)
Stress-provoked ("tako-tsubo")
Peripartum
Tachycardia-induced
Infants of insulin-dependent diabetic mothers

Hypertrophic Cardiomyopathy

Definition: Myocardial hypertrophy in the absence of any other cause capable to produce the magnitude of hypertrophy present

Incidence: 0.2% (1/500)

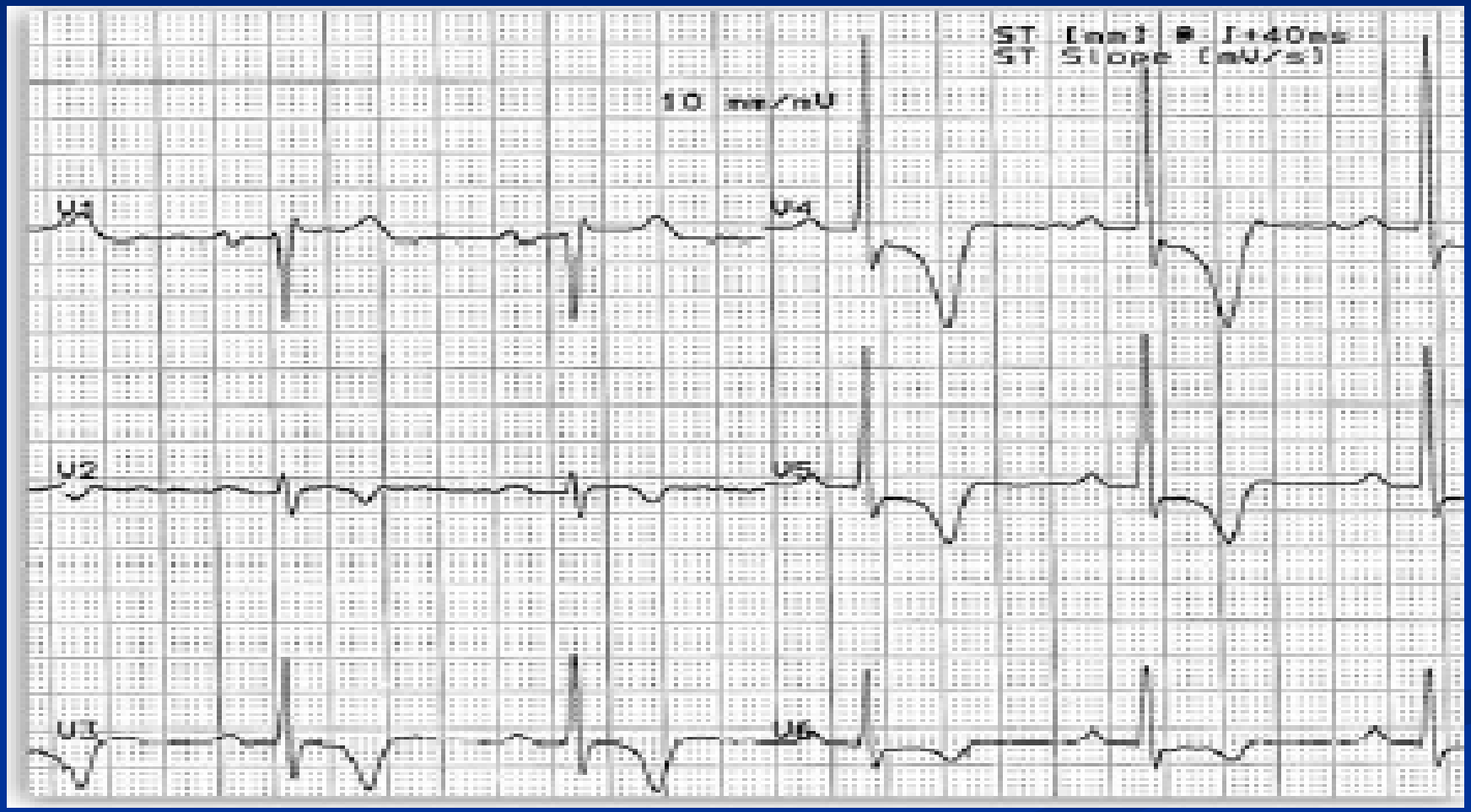
HYPERTROPHIC CARDIOMYOPATHY diagnosis

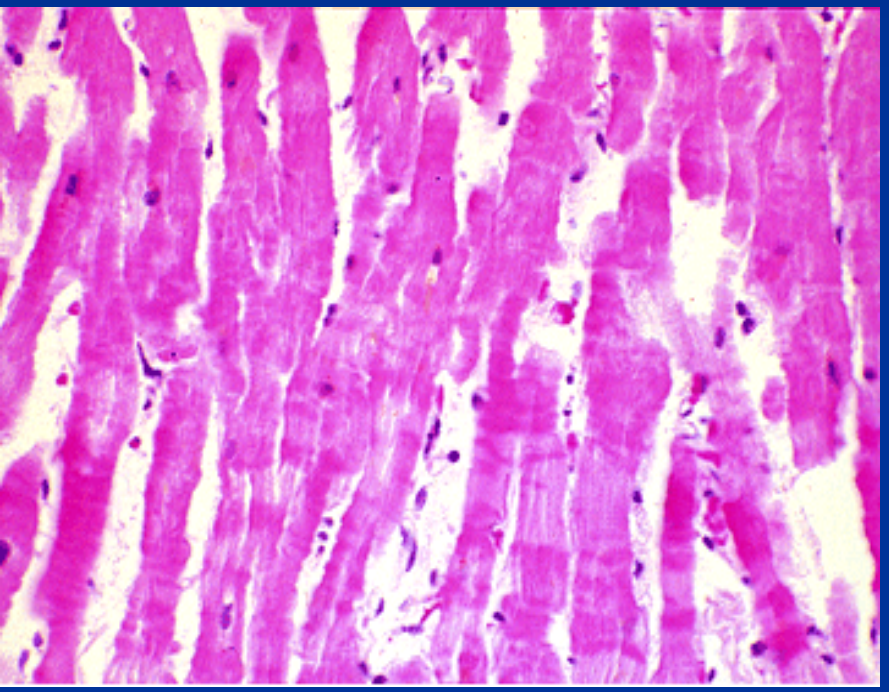
1. Echo: maximal wall thickness>14mm

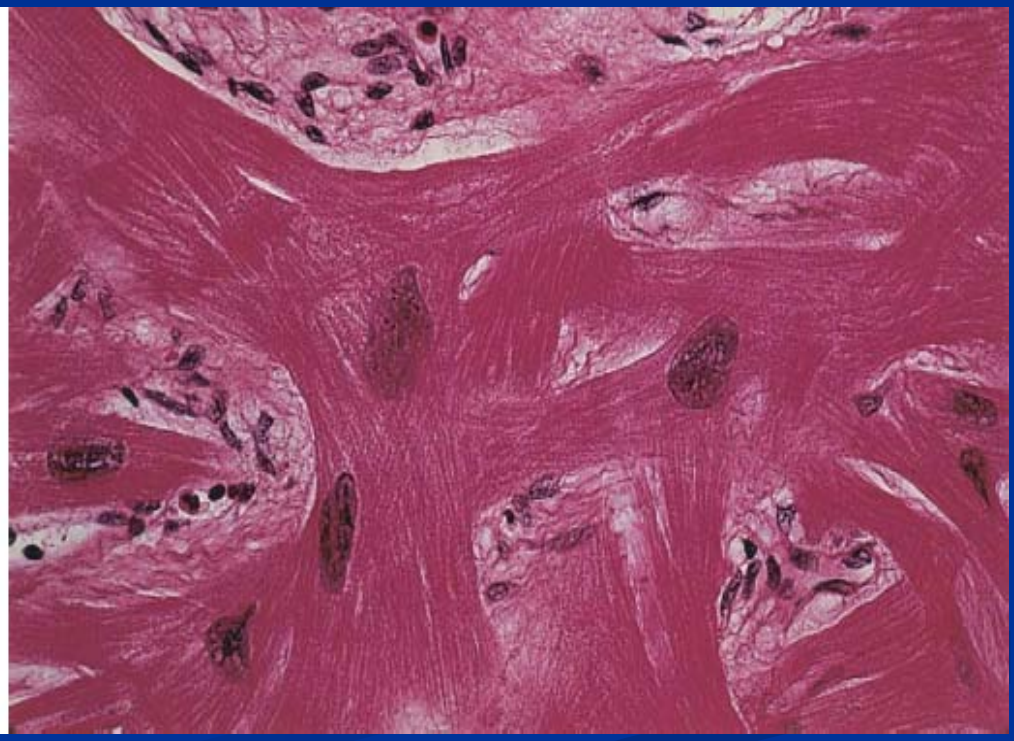
2. Maximal wall thickness=14 or 13 mm
   ECG changes compatible with HCM
   Positive family history

3. No hypertrophy
   Positive family history and abnormal ECG

4. Gross ECG abnormalities


ST [mm] @ J+40ms
ST Slope [mV/s]
10 mm/mV
V4
V2
V1
V6





Hypertrophic Cardiomyopathy

- firstly described by Teare in 1958
- incidence of familial form: 60-70% with autosomal dominant pattern of inheritance
- Remaining cases: sporadic
- Variable penetrance:

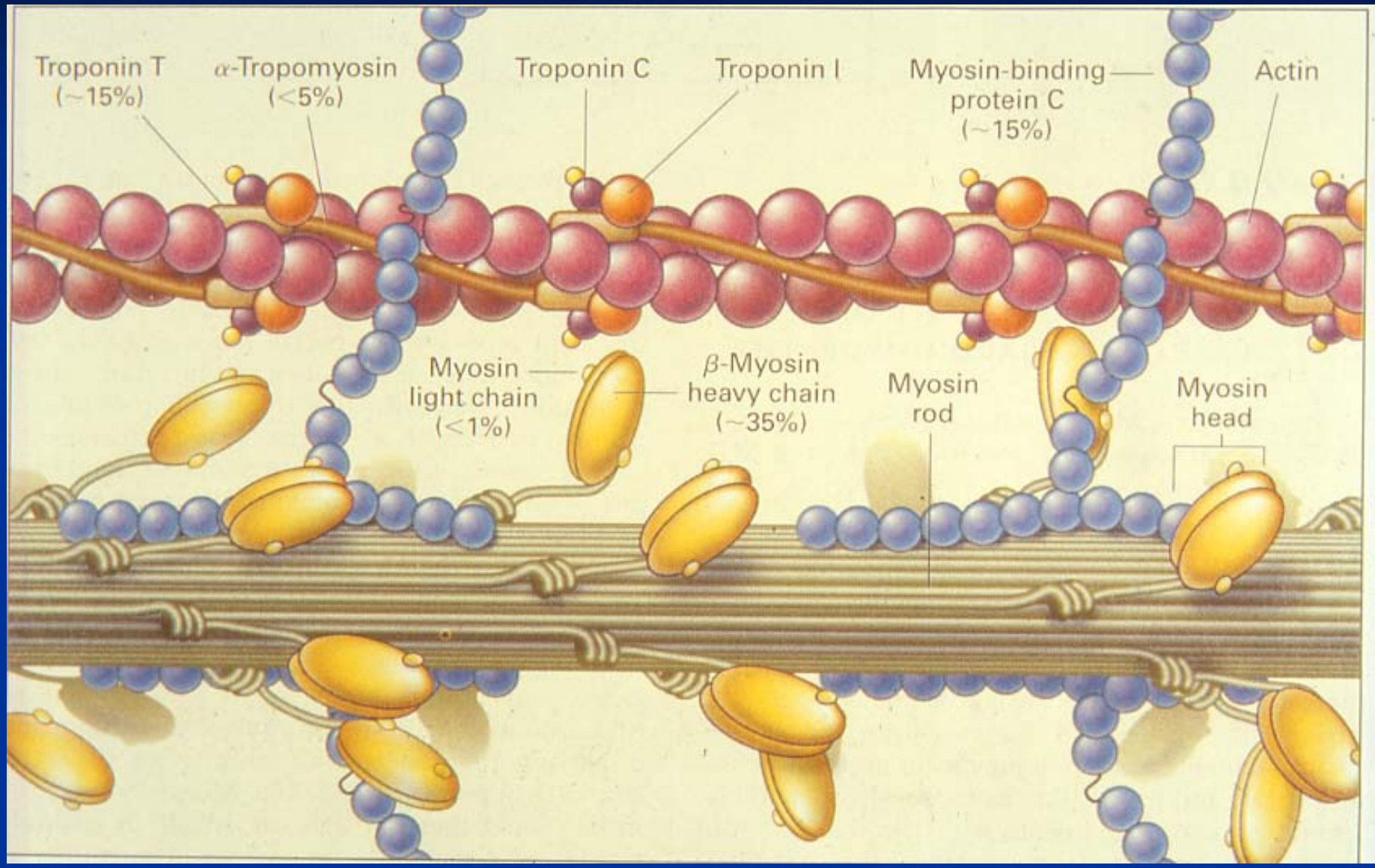
  phenotype positive/ genotype positive

Familial Hypertrophic Cardiomyopathy

Disease of sarcomere characterized by mutations in the genes coding for contractile and regulatory proteins of contraction (H. Watkins)-1990

>500 HCM-causing gene mutations

(Sarcomere protein gene mutation data base available at:http://www.cardiogenomics.med.harvard.edu)


Troponin T
(~15%)
α-Tropomyosin
(<5%)
Troponin C
Troponin I
Myosin-binding
protein C
(~15%)
Actin
Myosin
light chain
(<1%)
β-Myosin
heavy chain
(~35%)
Myosin
rod
Myosin
head

Genes Responsible for Human Hypertrophic Cardiomyopathy

Gene	# Mutations	Incidence
b-myosin heavy chain	194	30-50%
myosin binding protein C	149	30-50%
cardiac-troponin T	31	4%
cardiac-troponin I	27	4%
a-tropomyosin	11	5%
essential myosin light chain	10	1%
regulatory myosin light chain	5	1%
cardiac- actin	7	1%

Non-Sarcomeric Genes Responsible for Human Hypertrophic Cardiomyopathy

- **gene for muscle LIM protein (MLP)**
- The genes encoding the gamma-2 regulatory subunit of adenosine monophosphate-activated protein kinase (PRKAG2)
- the gene encoding lysosome-associated membrane protein 2 (LAMP2)
- **The gene for titin**
- **The gene for the protein titin-cap (T-cap/telethonin)**

Gene Mutation Forms in Familial Hypertrophic Cardiomyopathy

- Missense (δυσυνθετικές)
- Deletions (ελλείψεις)
- Insertions (προσθήκες)
- Truncated (ακρωτηριαστικές)

B-Myosin Heavy Chain Gene

Codon

AATCGTATGC{**TAC**}TGTGCATAATCG…

exon

22.000 bp
A: Adenine
T:Thymine
C:Cytocine
G:Guanine

B-Myosin Heavy Chain Gene

EXON 23

codon **403**

↓

AATGCA**TGC**TTGAGTCTGAC:MHC gene

↓

…… Arg……b-MHC protein

B-Myosin Heavy Chain Gene

EXON 23

codon **403**

AATGCA**TGC**TTGAGTCTGAC:MHC gene

..... T**A**C.....mutant gene

……Gln ……b-MHC protein

Arg403Gln

B-Myosin Heavy Chain Gene

EXON 23

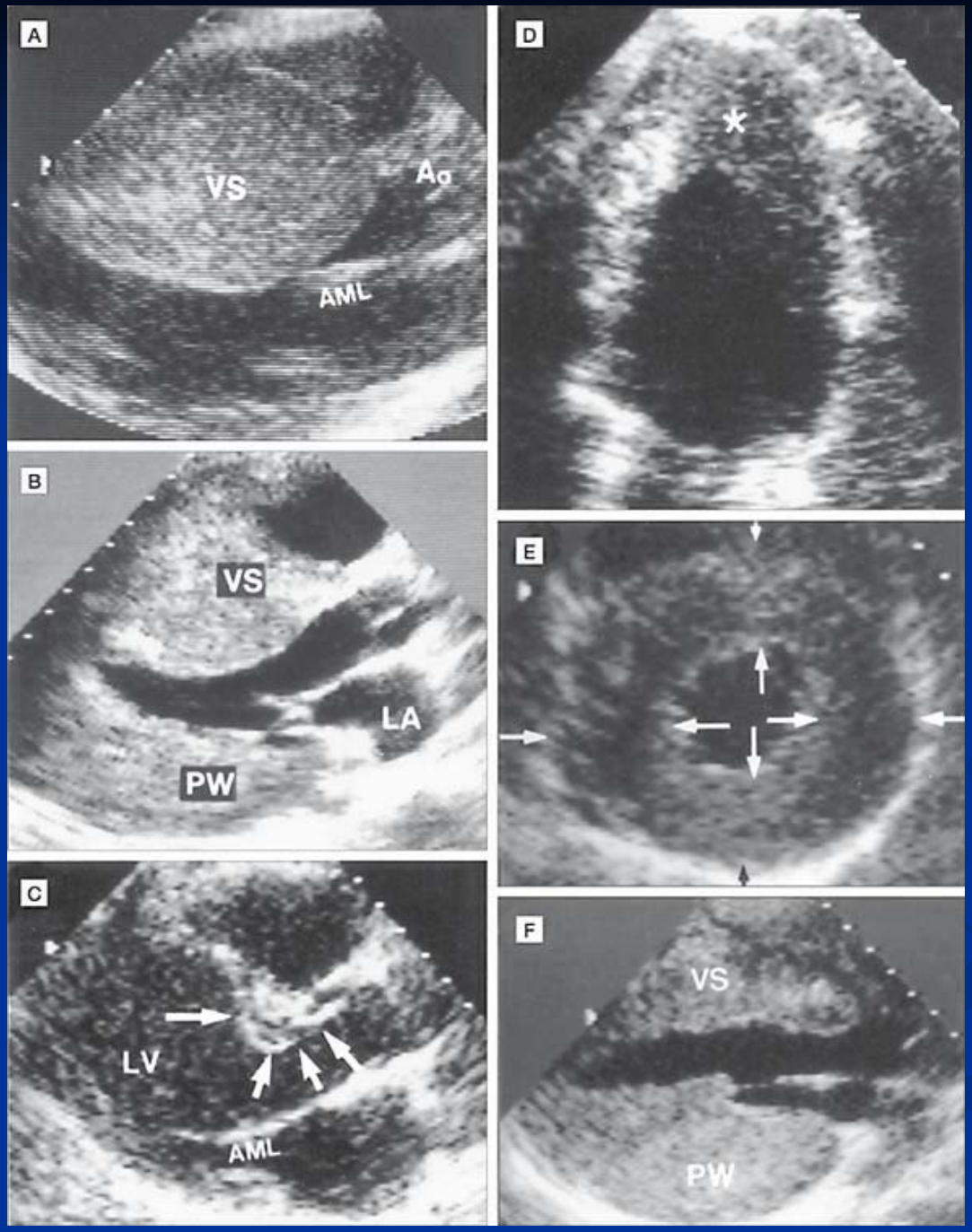
codon **403**

AATGCA**TGC**TTGAGTCTGAC: b-MHC gene

..... T**A**C.....mutant gene

…… Gln ……b-MHC protein

Arg403Gln


A
VS
Ao
AML
B
VS
LA
PW
C
LV
AML
D
*
E
F
VS
PW

Healthy Carriers in HCM

- Up to 30% of genetically affected adults, are not identified by conventional criteria (Healthy Carriers)
- The majority of them will develop some form of HCM before the age of 50 years

HCM pathophysiology

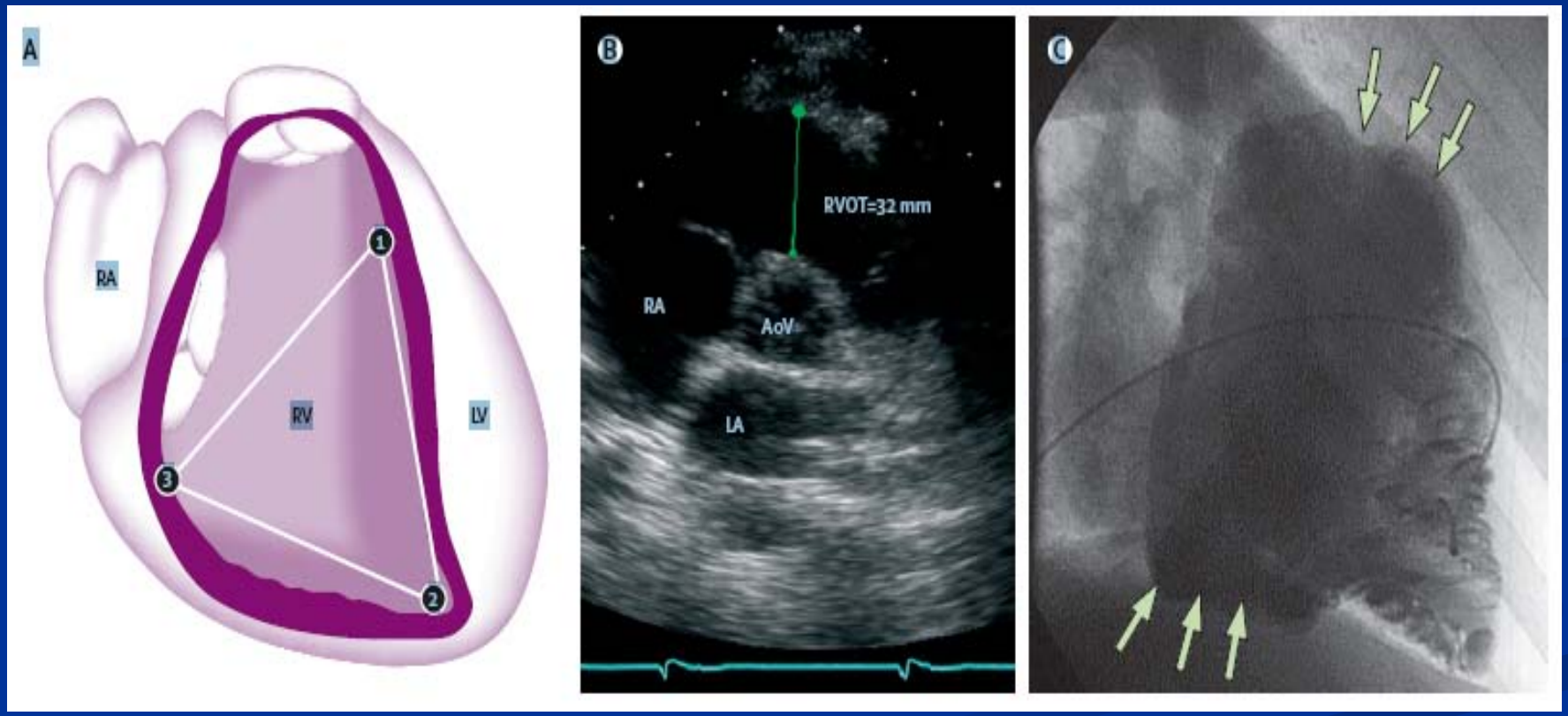
	Clinical assessment
Sarcomeric protein defect	None
↓	
↓ Myofibrilar shortening	Doppler, TVI
↓	
Disarray	ECG
↓	
Hypertrophy	Echo

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

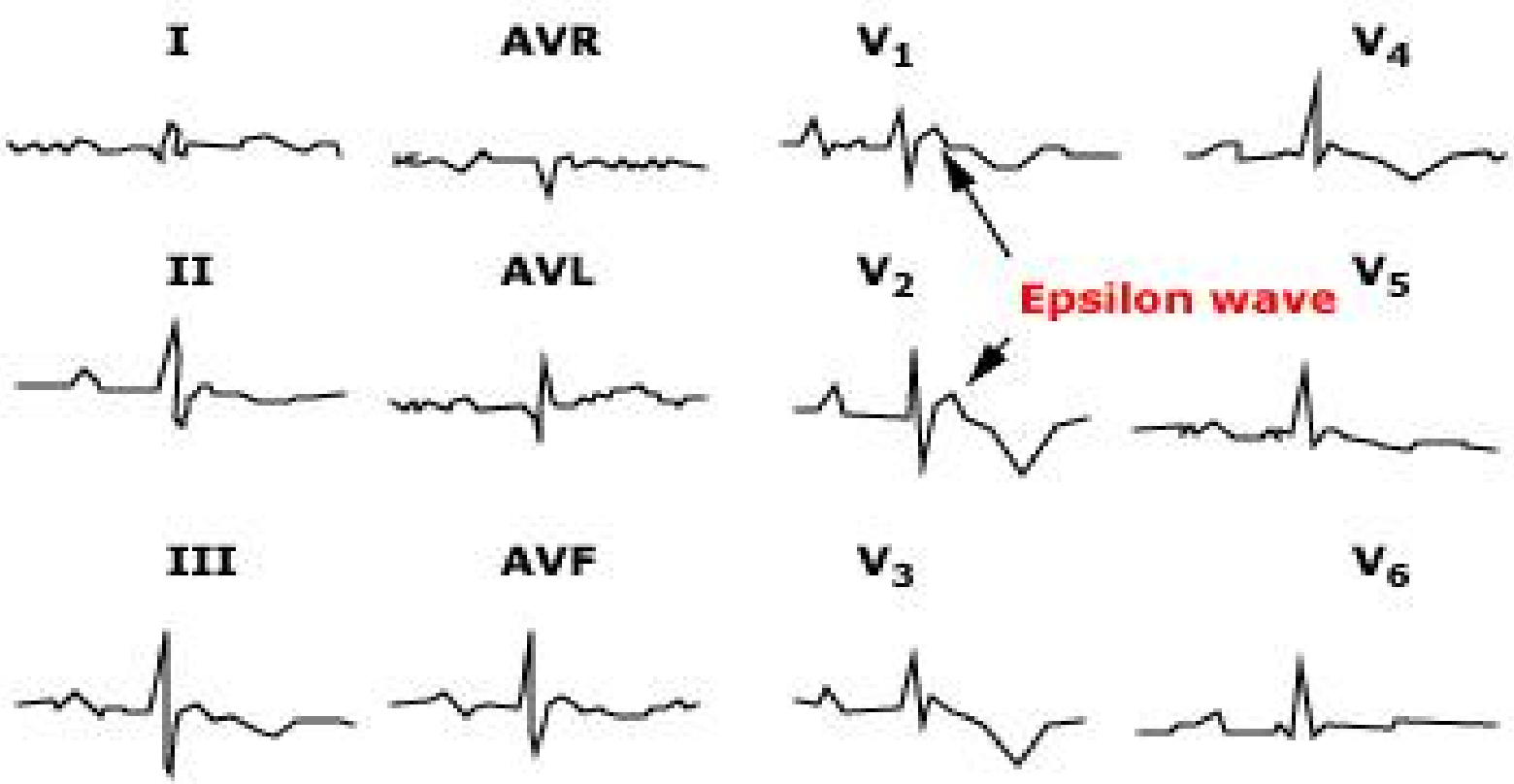
- 1:5000
- involves predominantly the right ventricle with progressive loss of myocytes and fibrofatty tissue replacement

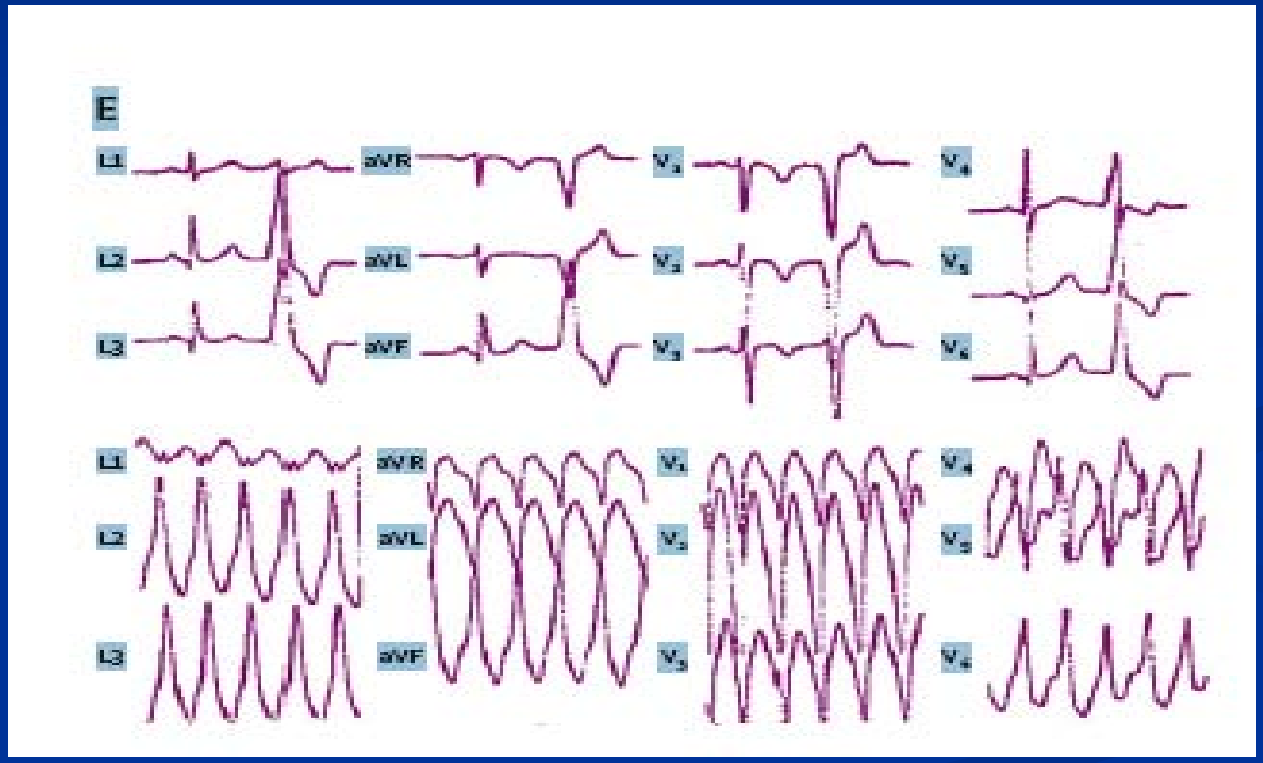
Pathogenesis

- The replacement of the right ventricular myocardium by fibrofatty tissue is progressive (epicardium or midmyocardium and then transmural)
- Progression then leads to wall thinning and aneurysms, typically located at the inferior, apical, and infundibular walls (so-called triangle of dysplasia), the hallmark of ARVC


A
RA
RV
LV
1
2
3
B
RVOT=32 mm
RA
AoV
LA
C

ECG IN ARVC




E
L1
aVR
V1
V4
L2
aVL
V2
V5
L3
aVF
V3
V6
L1
aVR
V1
V4
L2
aVL
V2
V5
L3
aVF
V3
V6

Dilated Cardiomyopathy

Increased ventricular chamber size with reduced contractility in the absence of CAD, valvulopathy, pericardial disease.

Prevalence:40/100.000 persons

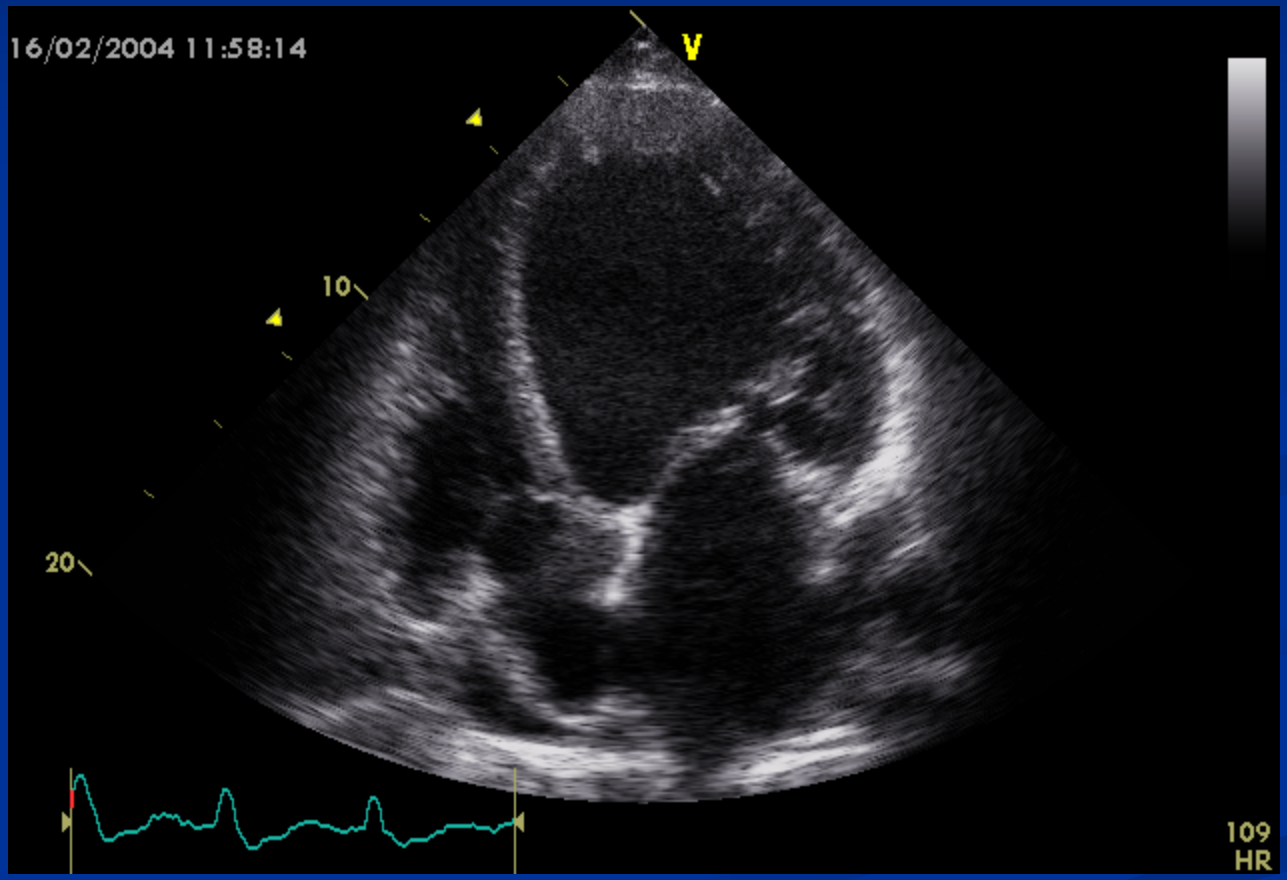
Natural history: • heart failure

• leading cause of heart transplantation

• high rate of SCD

• high mortality rate: 50% 5 years after initial diagnosis

ECHO



DILATED CARDIOMYOPATHY

- Idiopathic
- Familial/Genetic
- Viral
- Immune
- Alcoholic/Toxic

Familial Dilated Cardiomyopathy (FDC)

- Incidence: 50% (familial history)
- Patterns of inheritance: autosomal dominant

autosomal recessive

X-linked

matrilineal
(mitochondrial DC)

The phenotype can be characterized

- by an isolated cardiac dysfunction (isolated DCM)
- or include conduction defects (atrioventricular block or sinus node dysfunction)
- and/or skeletal muscular disorders

Genetic causes of DCM

Sarcomere

ß-Myosin heavy chain (*MYH7*)

Troponin T (*TNNT2*)

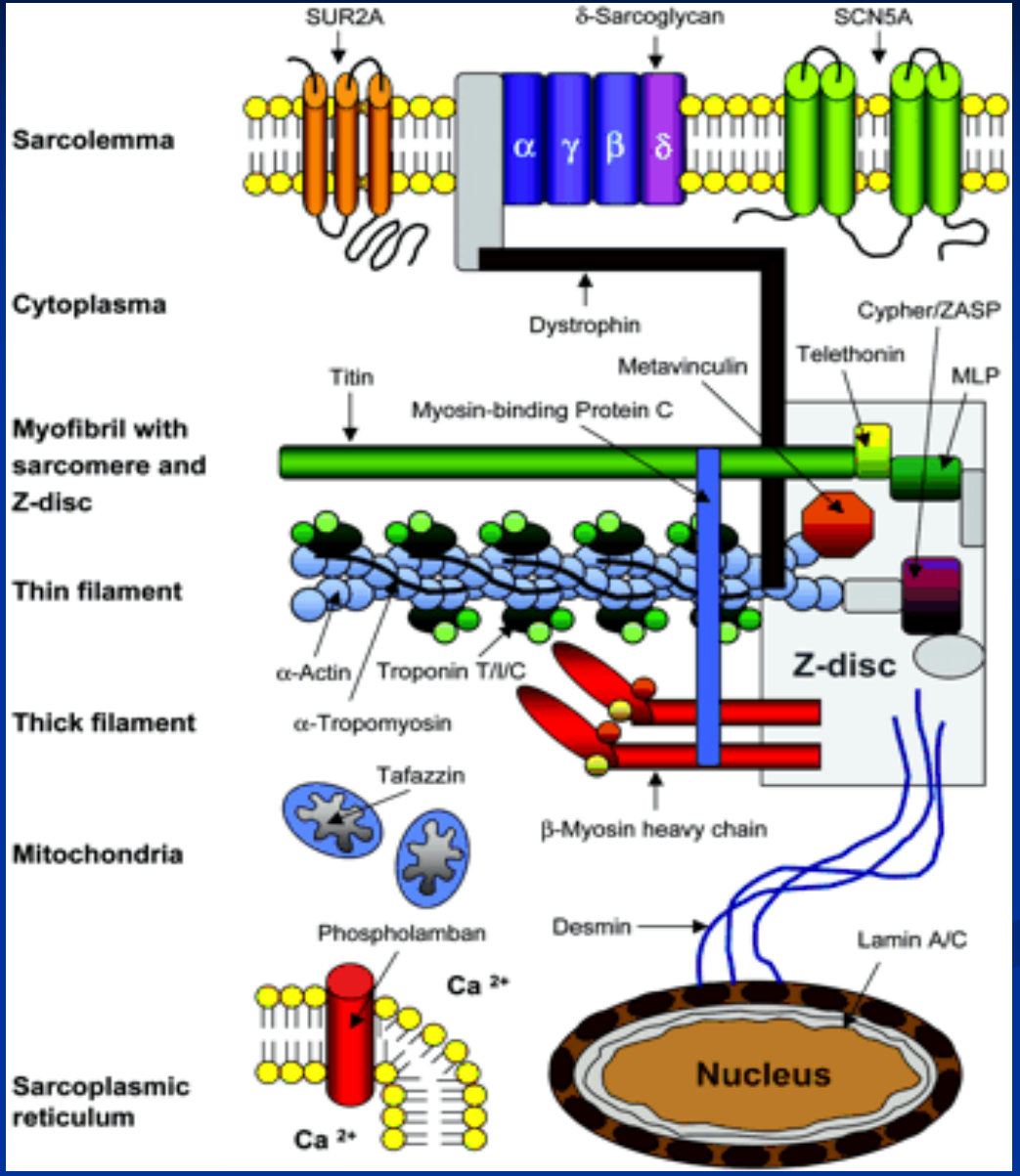
Troponin I (*TNNI3*)

Troponin C (*TNNC1*)

Cardiac -actin (*ACTC*)

Tropomyosin (*TPM1*)

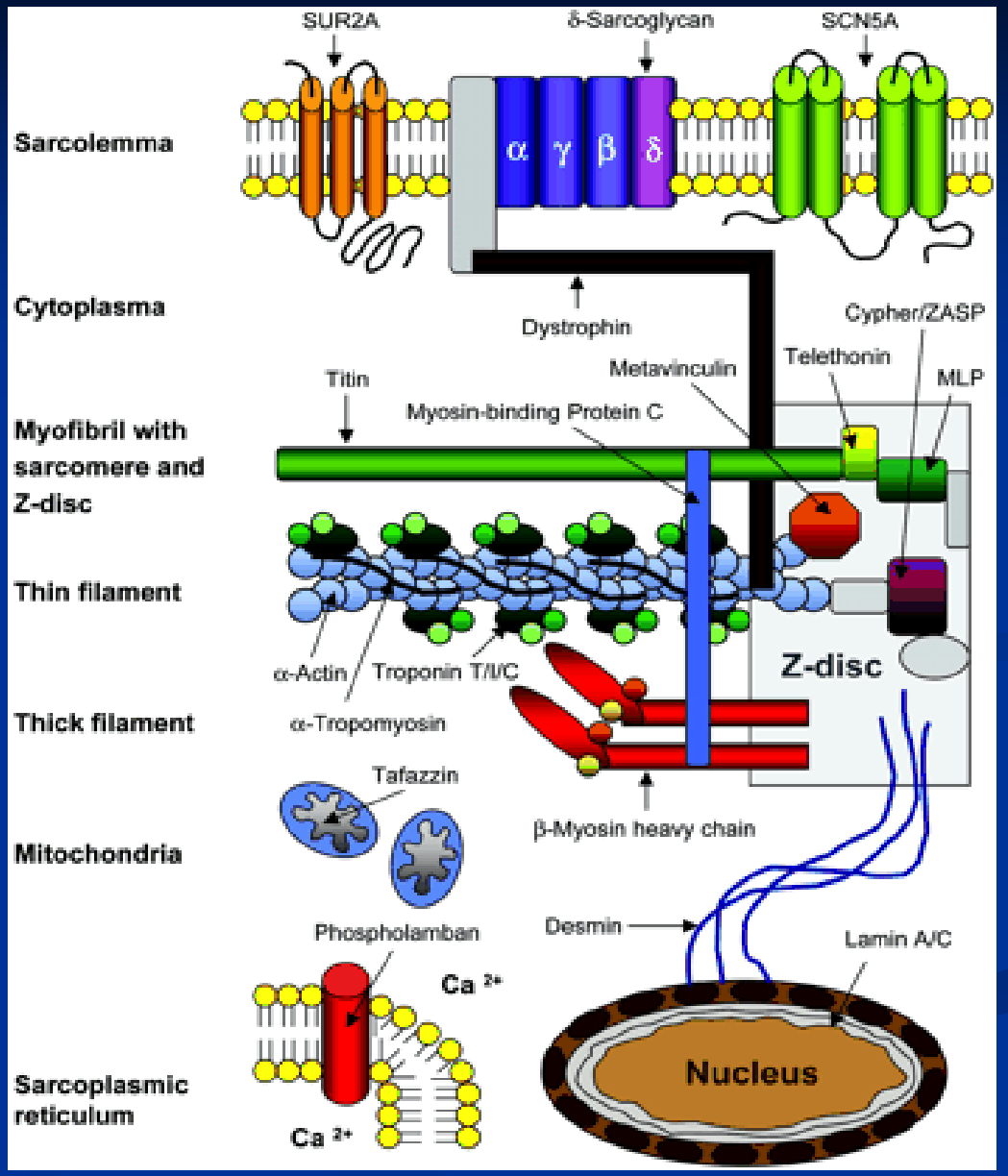
Myosin-binding protein C (*MYBPC3*)



Genetic causes of DCM

Sarcomere and Z-disc associated proteins

- Titin (TTN)
- Titin-cap/telethonin (TEL)
- Muscle LIM protein (CRP3)
- Metavinculin (VCL)
- Cypher/ZASP (LDB3)



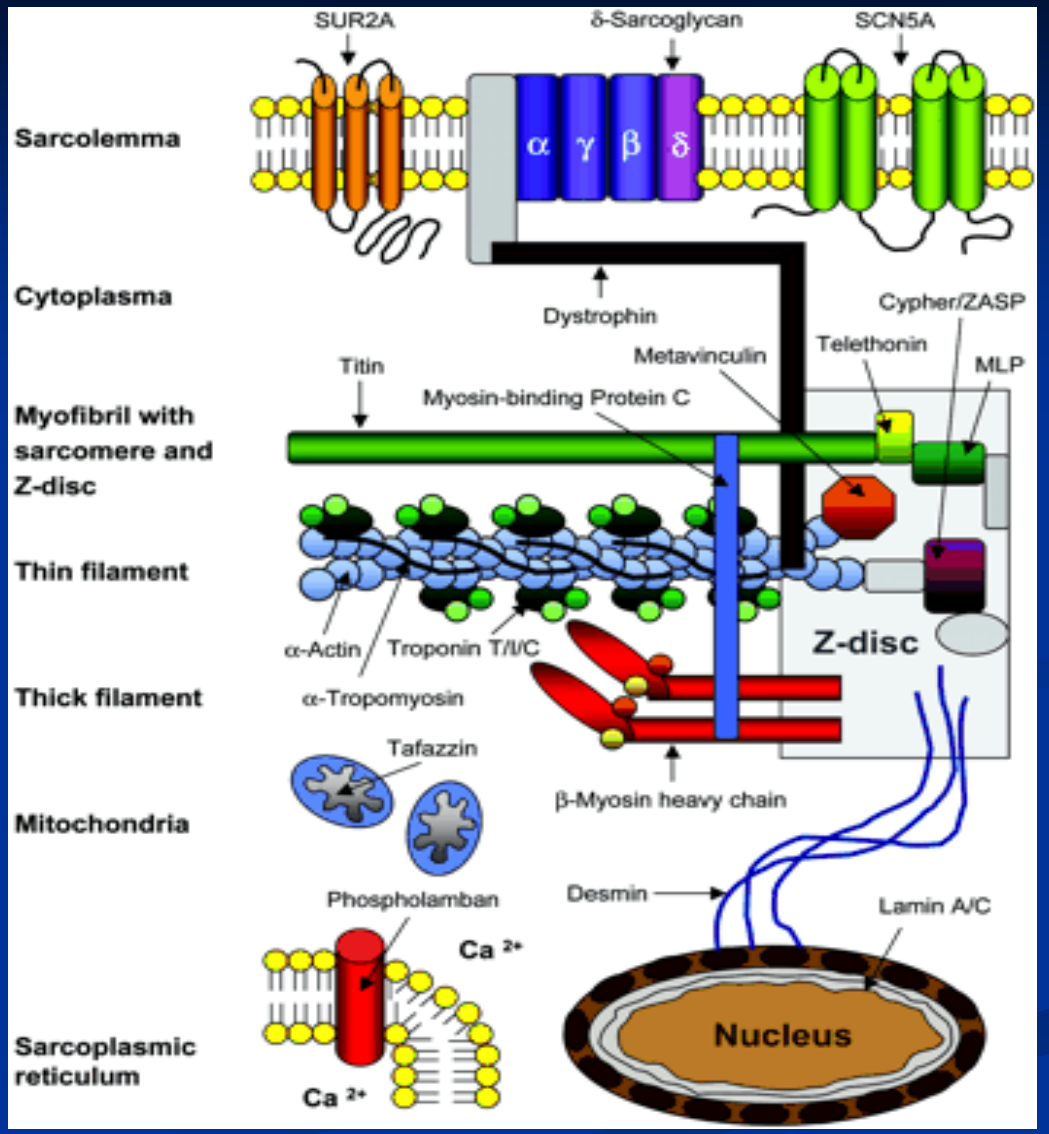
Genetic causes of DCM

Cytoskeleton

- Dystrophin *(DMD)*
- Sarcoglycan*(SGCD)*
- Intermediate filaments

  Desmin *(DES)*

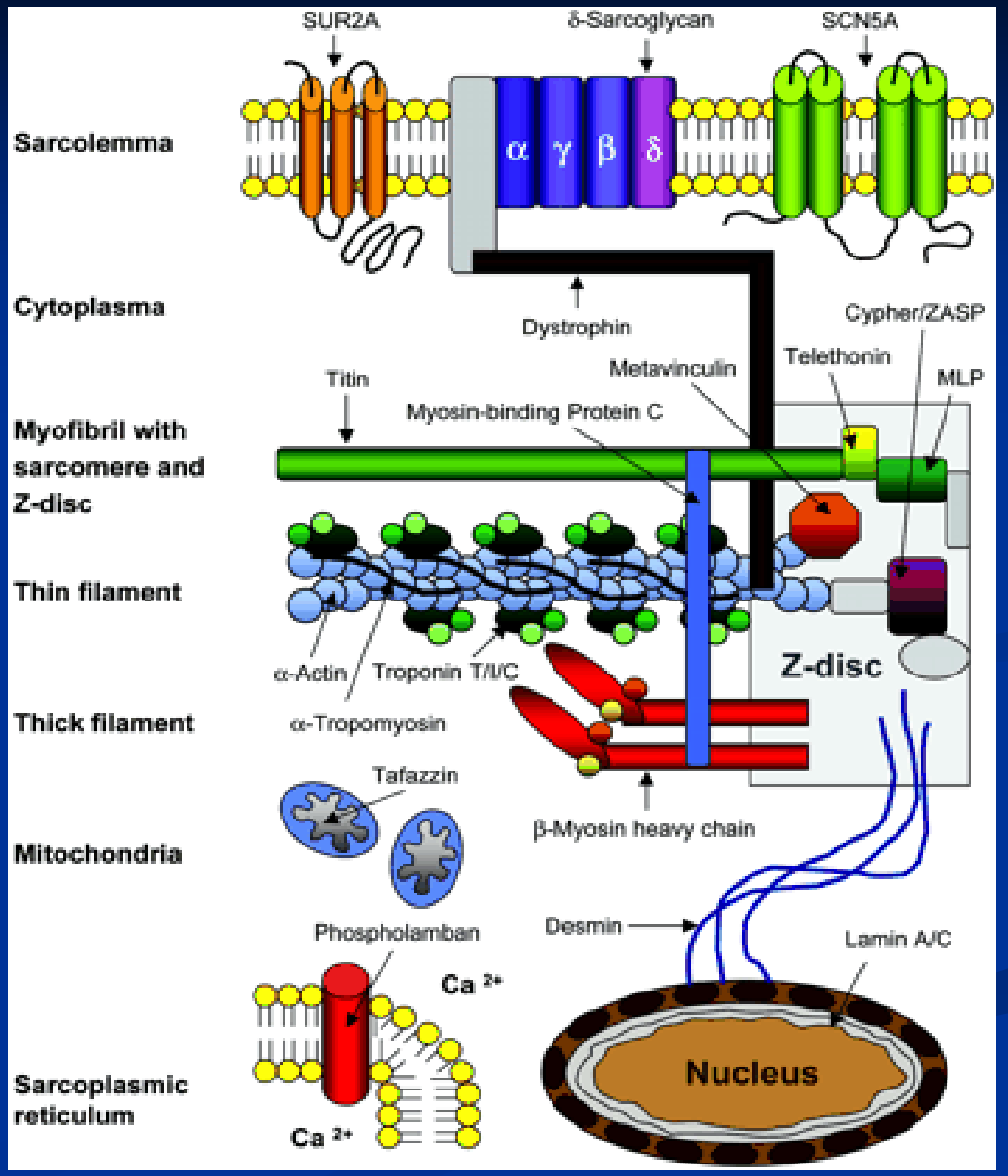
  Lamin A/C *(LMNA)*



Genetic causes of DCM

Channel and channel-associated proteins

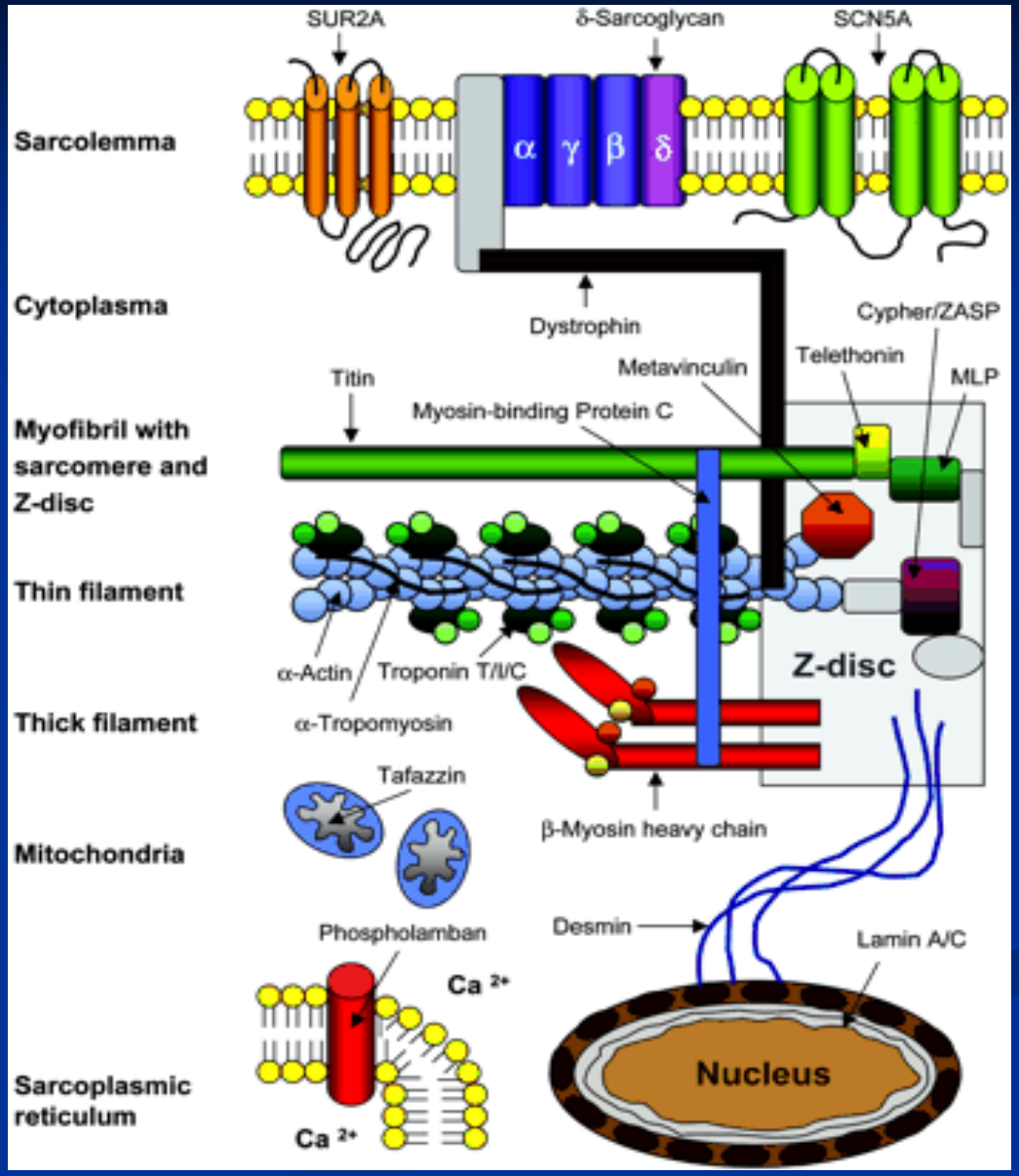
- Cardiac sodium channel (SCN5A)
- ATP-sensitive potassium channel (SUR2A/ABCC9)
- Phospholamban (PLN)



Genetic causes of DCM

Mitochondria

- Tafazzin (*G4.5*)



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