



# Childhood cardiomyopathies

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Centre de Référence Maladies Rares  
Malformations Cardiaques Congénitales Complexes-M3C  
Centre de Référence Maladies Rares  
Maladies Cardiaques Héréditaires- CARDIOGEN



European Reference Network  
for rare or low prevalence complex diseases

Network  
Respiratory Diseases (ERN-LUNG)



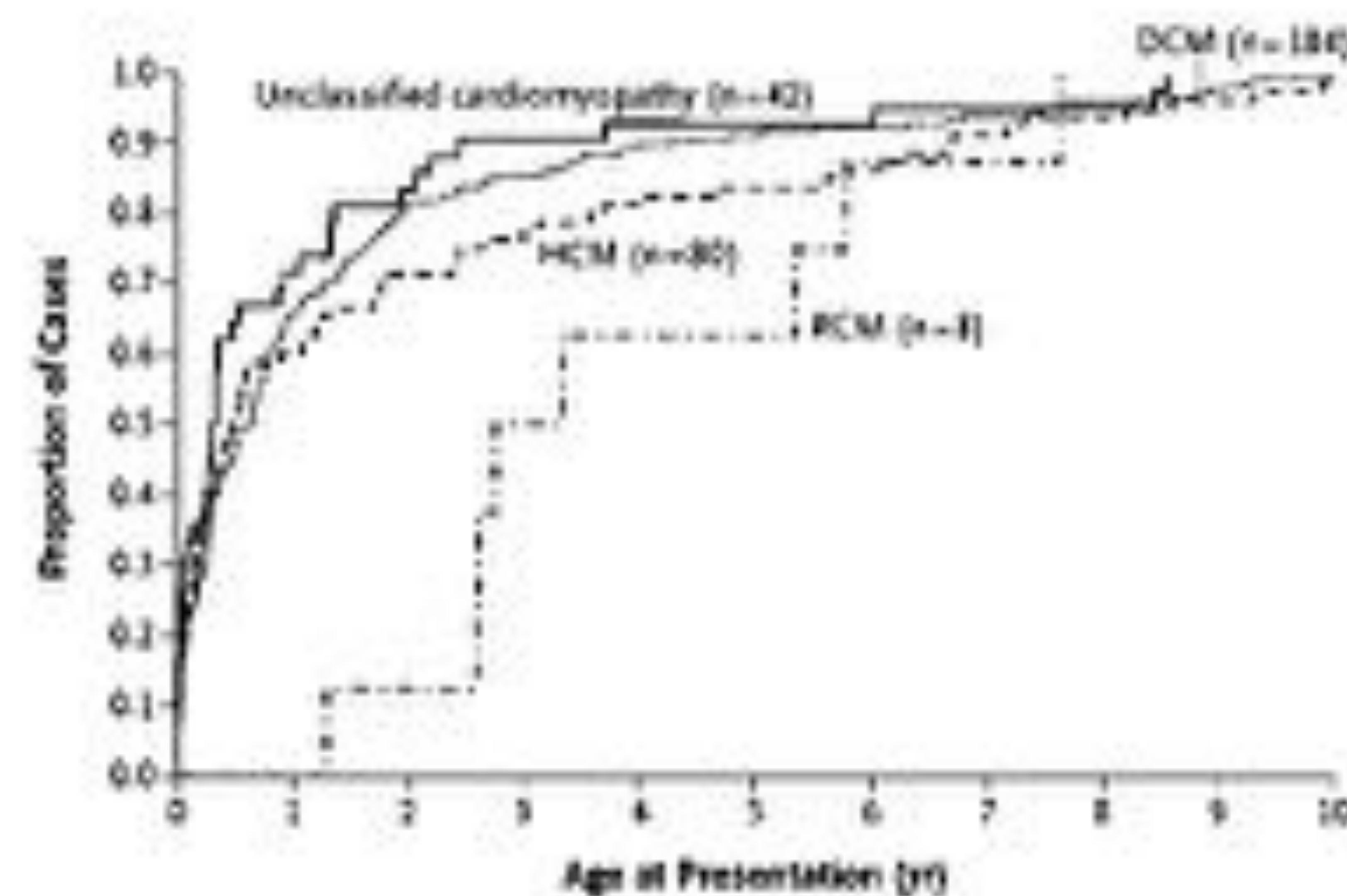
European Reference Network  
for rare or low prevalence complex diseases

Network  
Heart Diseases (ERN GUARD-HEART)

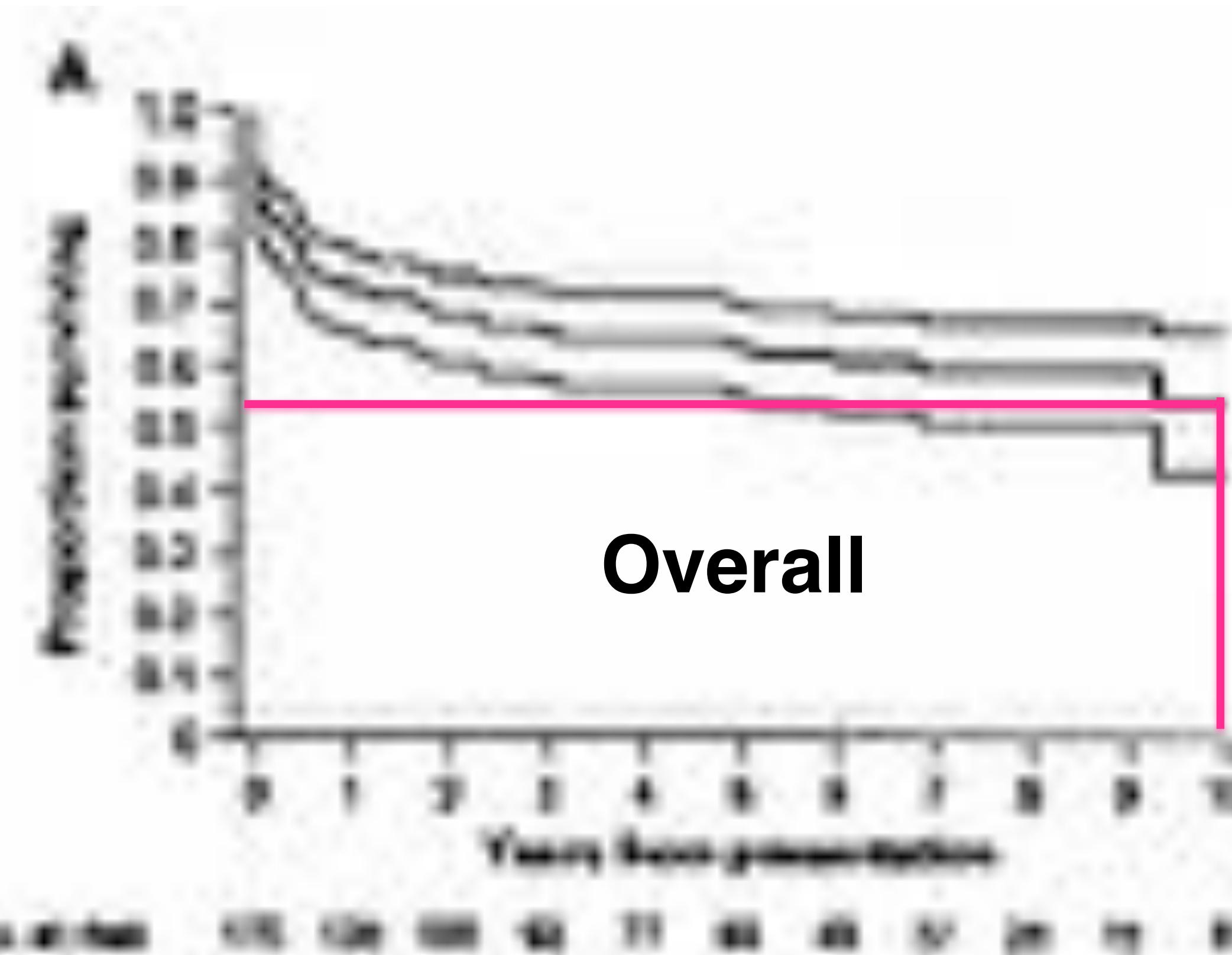
# Epidemiology

- Annual incidence of childhood cardiomyopathies : 1.13 per 100,000
- Incidence higher among children <1 year :  
8.34 vs. 0.70 per 100,000
- Categorized according to type :
  - Hypertrophic 42 %
  - Dilated 51%
  - Restrictive 2.5%
  - Non compaction 9.2%
- Sudden death as presenting symptom 3.5%

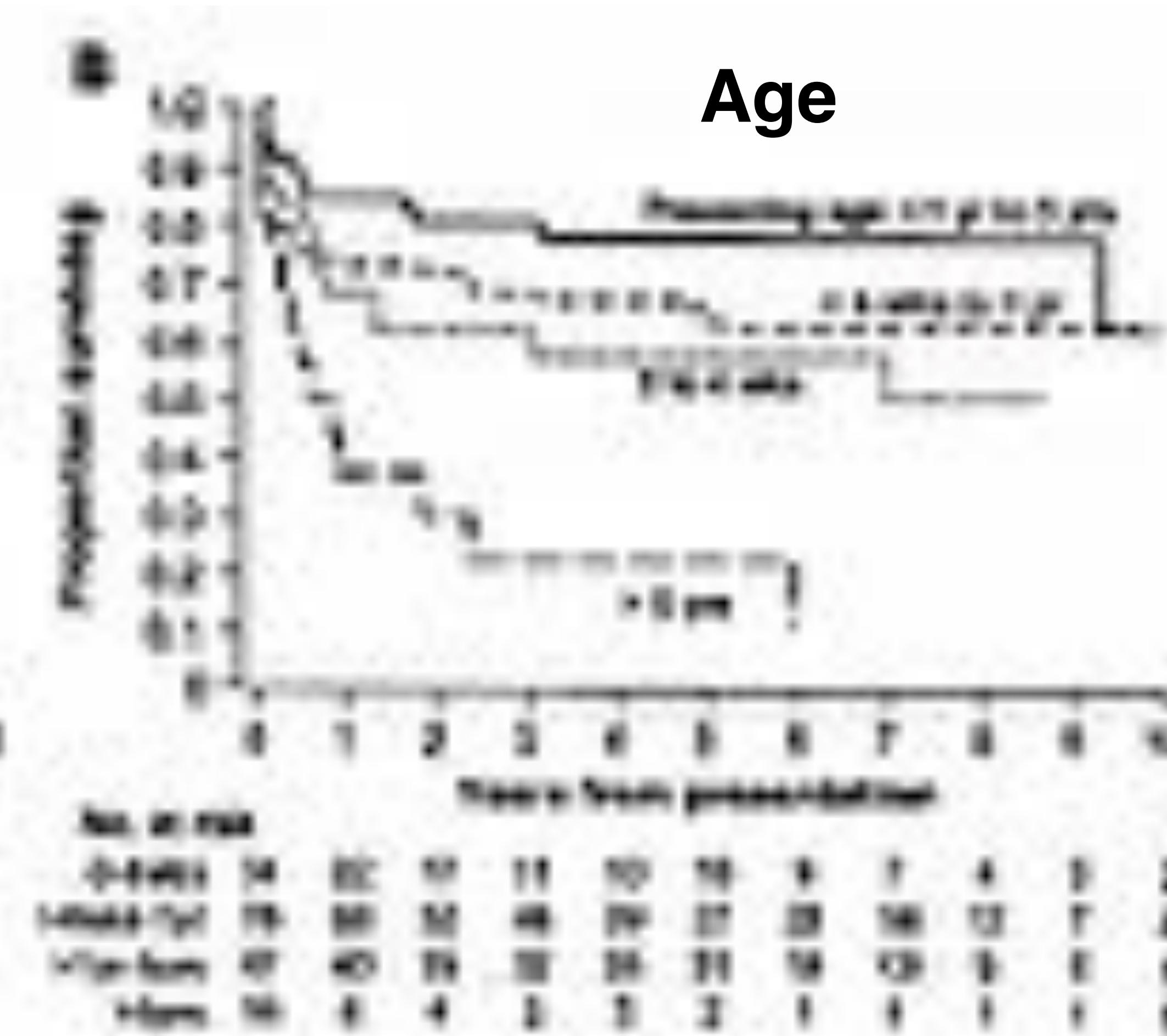
# Cumulative frequency distribution of age at presentation



# Survival to death or transplantation from time to presentation in pediatric cardiomyopathies



Overall

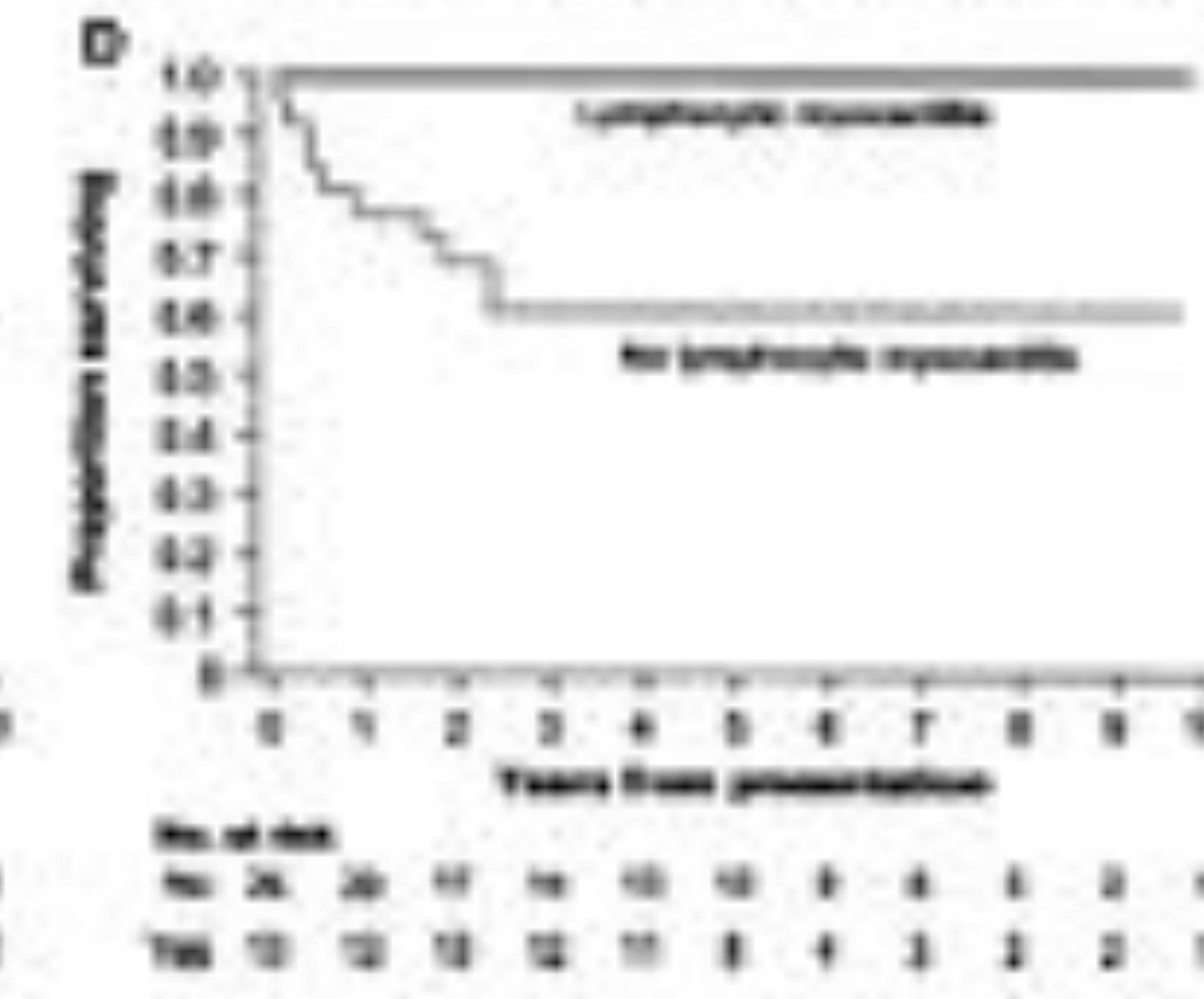
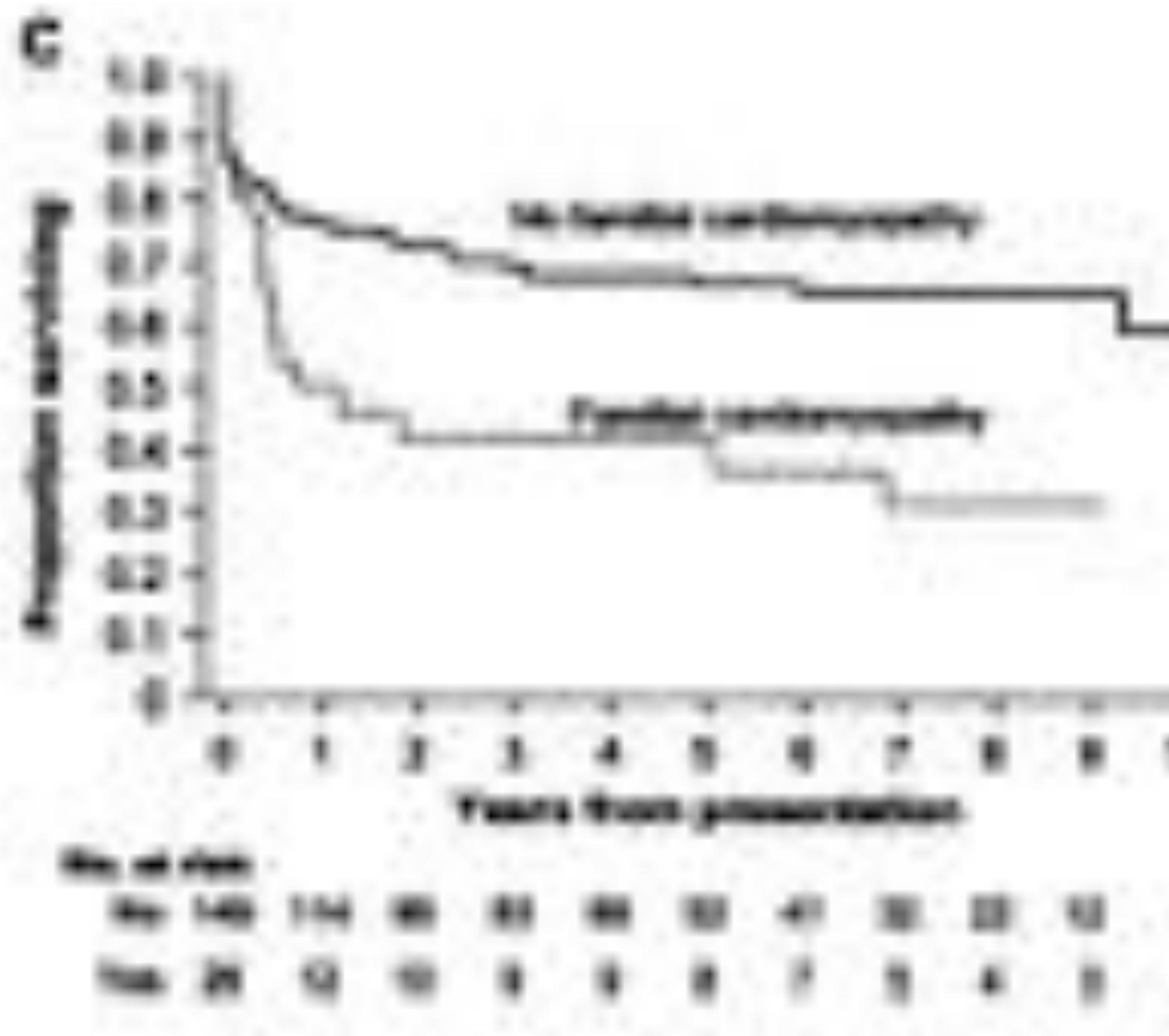


Age

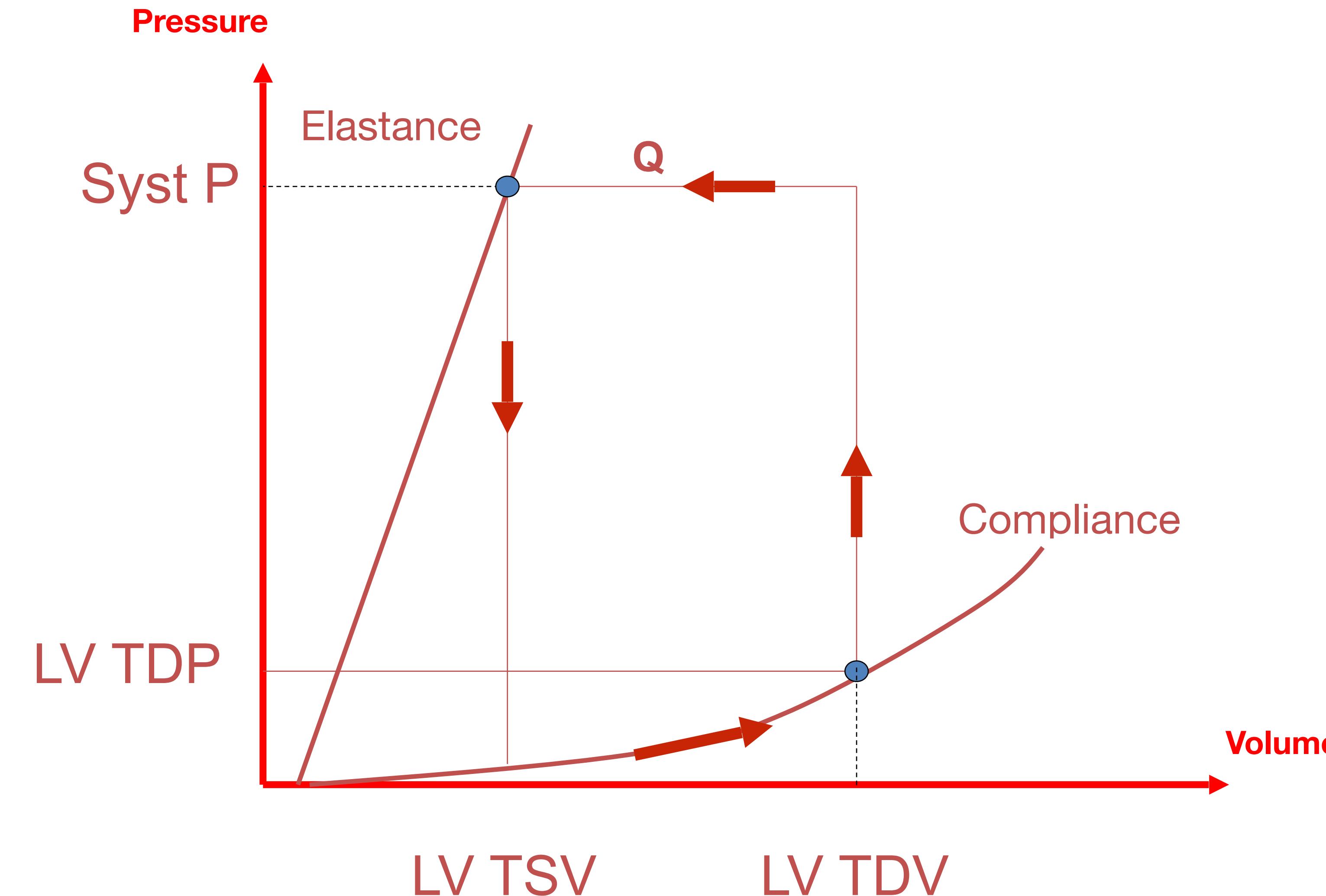
No. at risk

Time from presentation

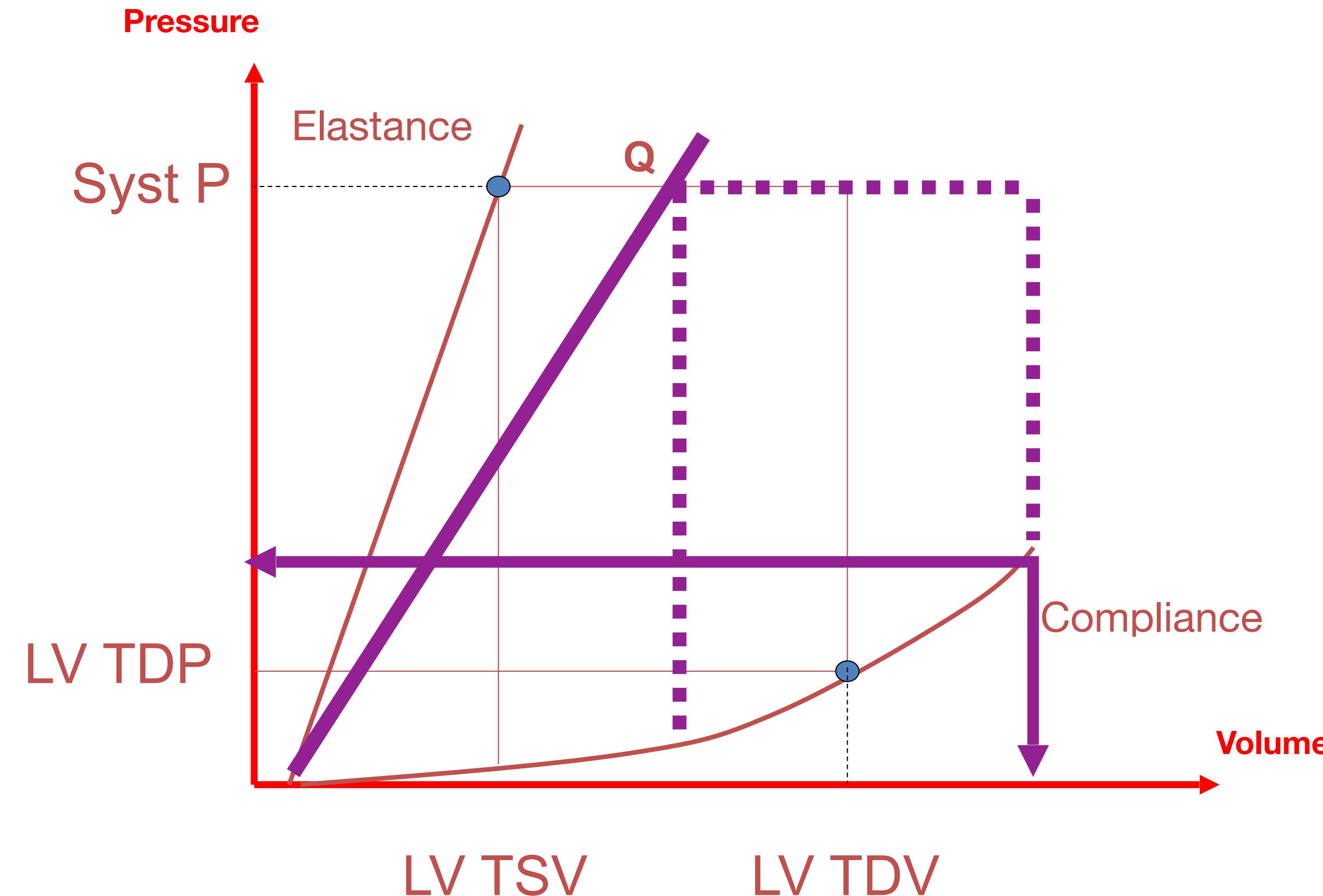
# Survival to death or transplantation from time to presentation in pediatric cardiomyopathies



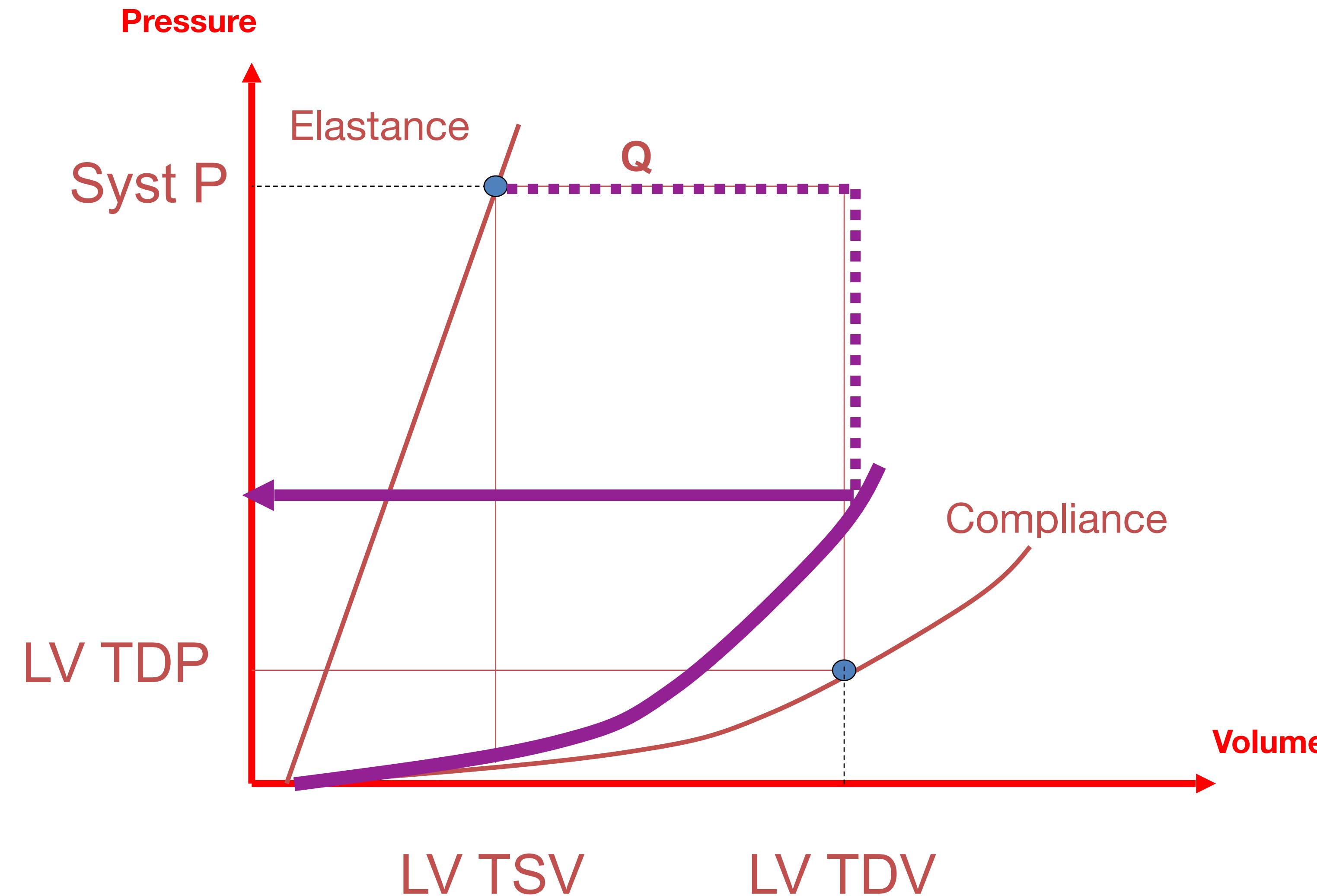
# Pressure-Volume loop



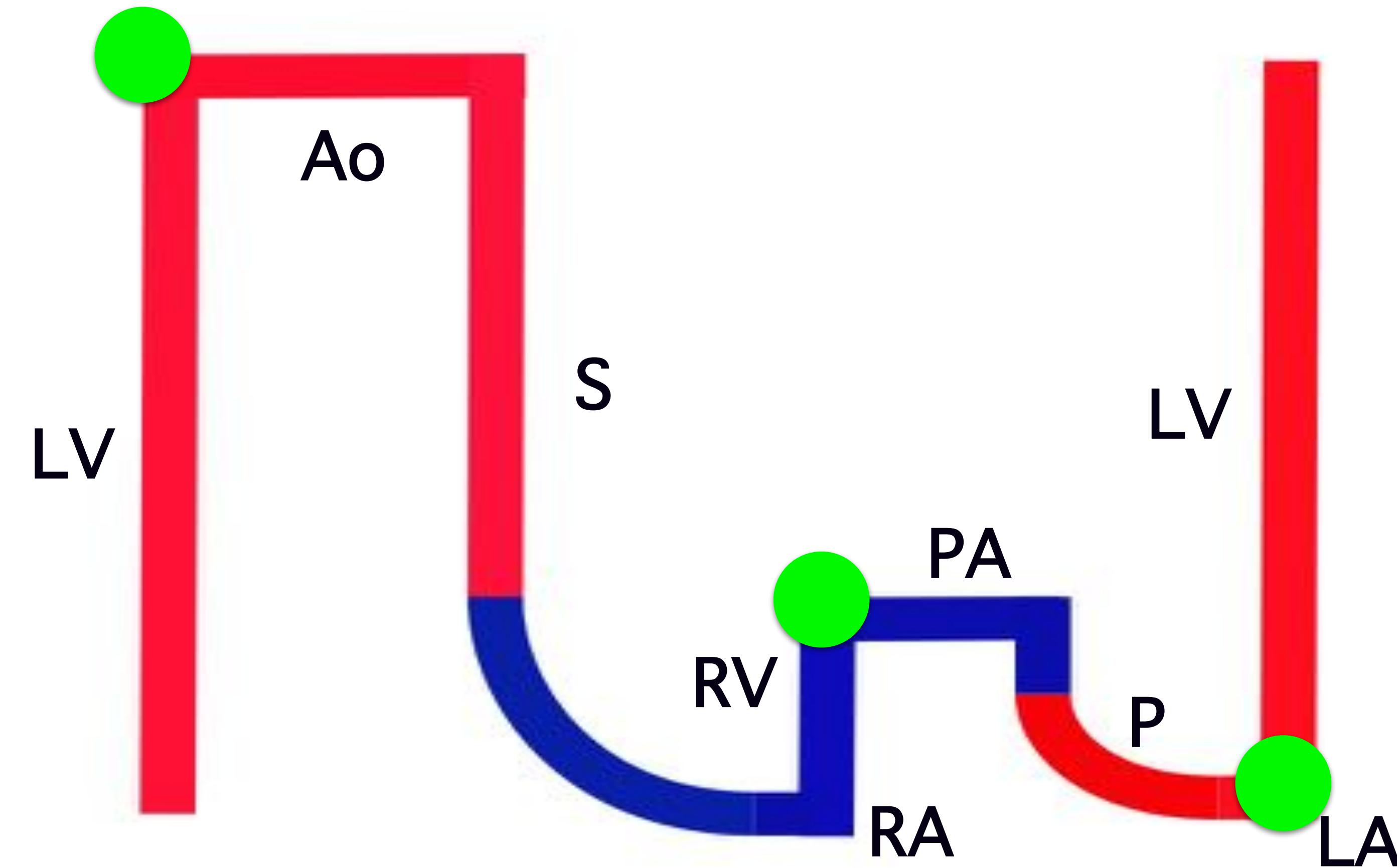
# Dilated cardiomyopathy with poor contractility

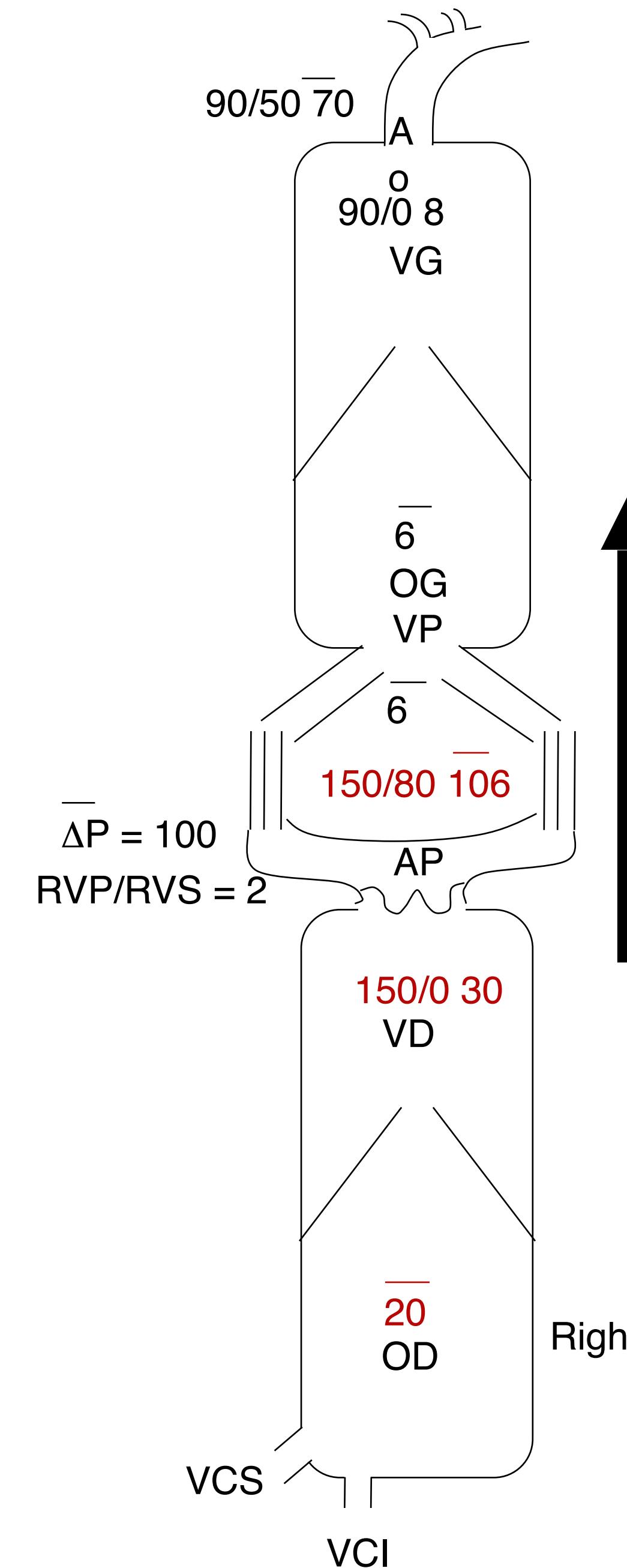
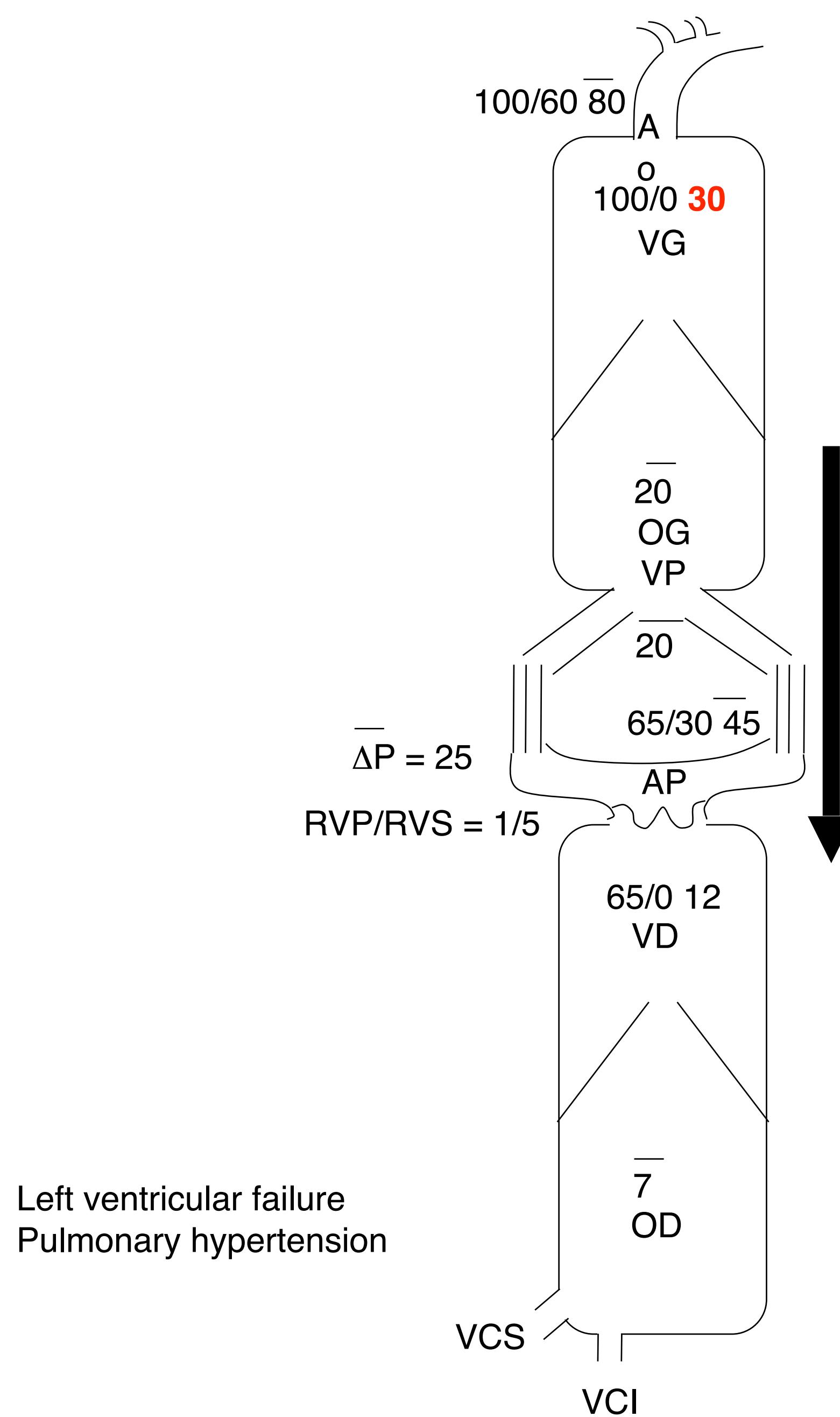


# Restrictive cardiomyopathy with poor compliance



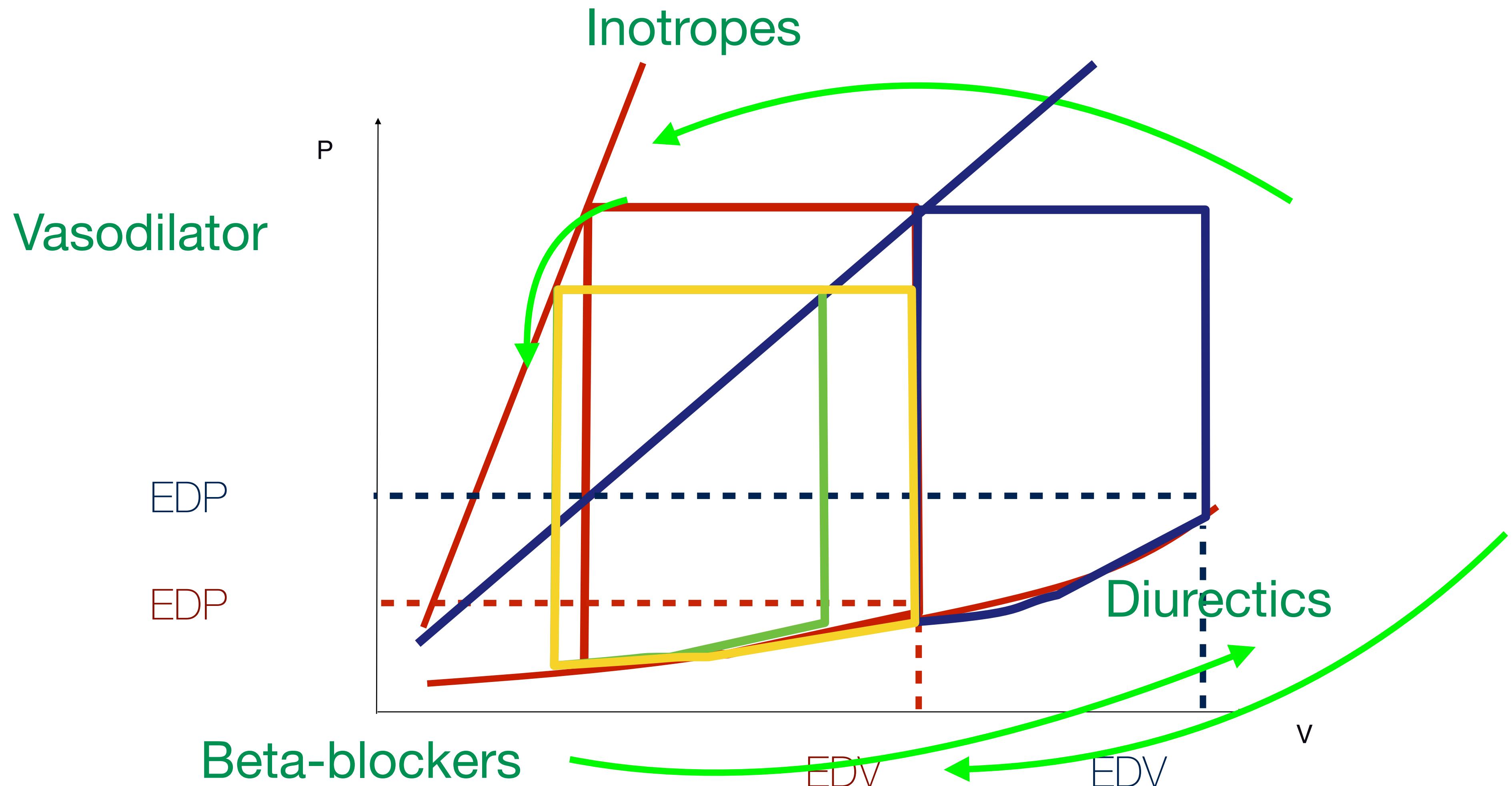
# Hemodynamic in normal heart - Bottlenecks





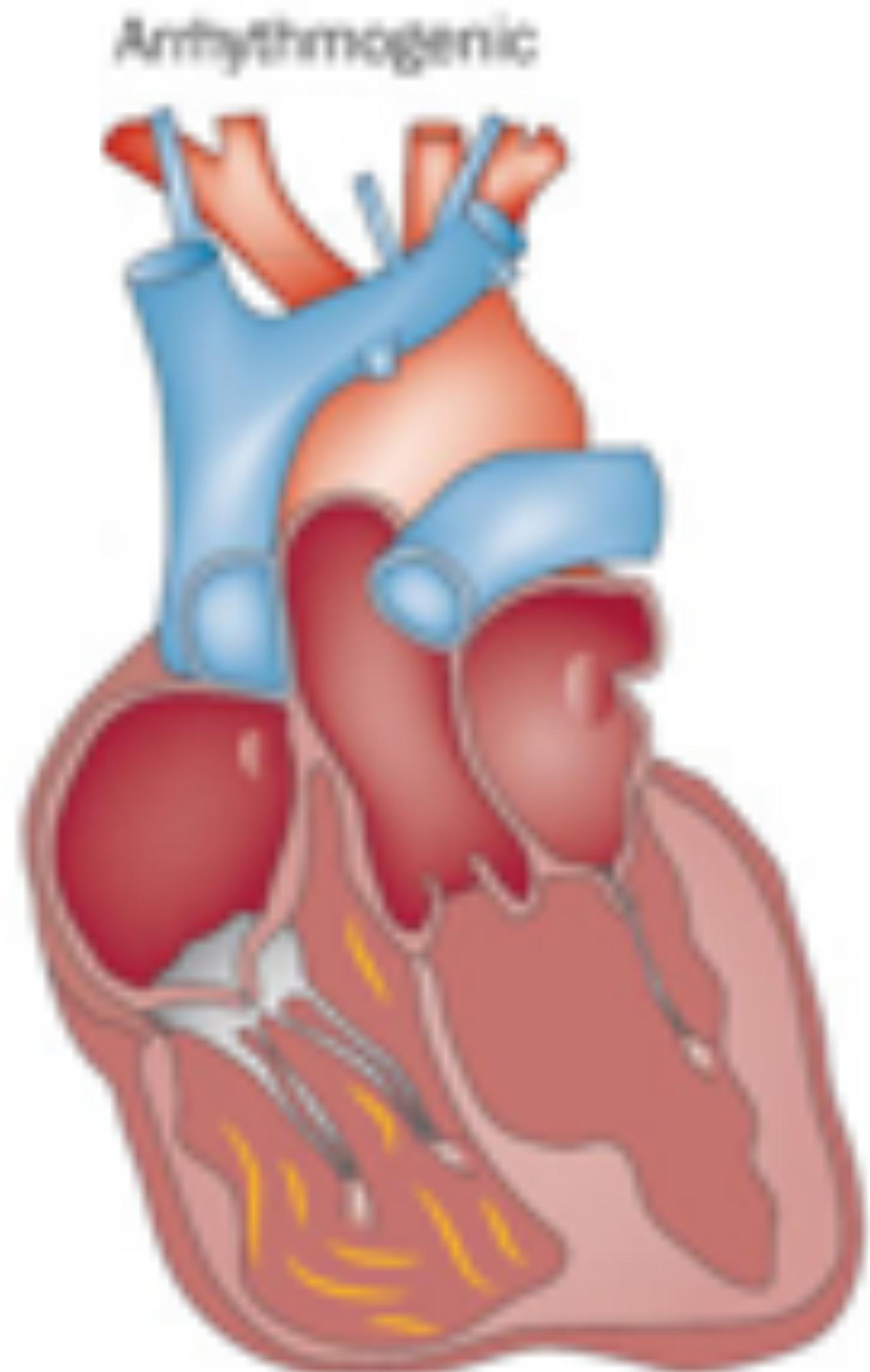
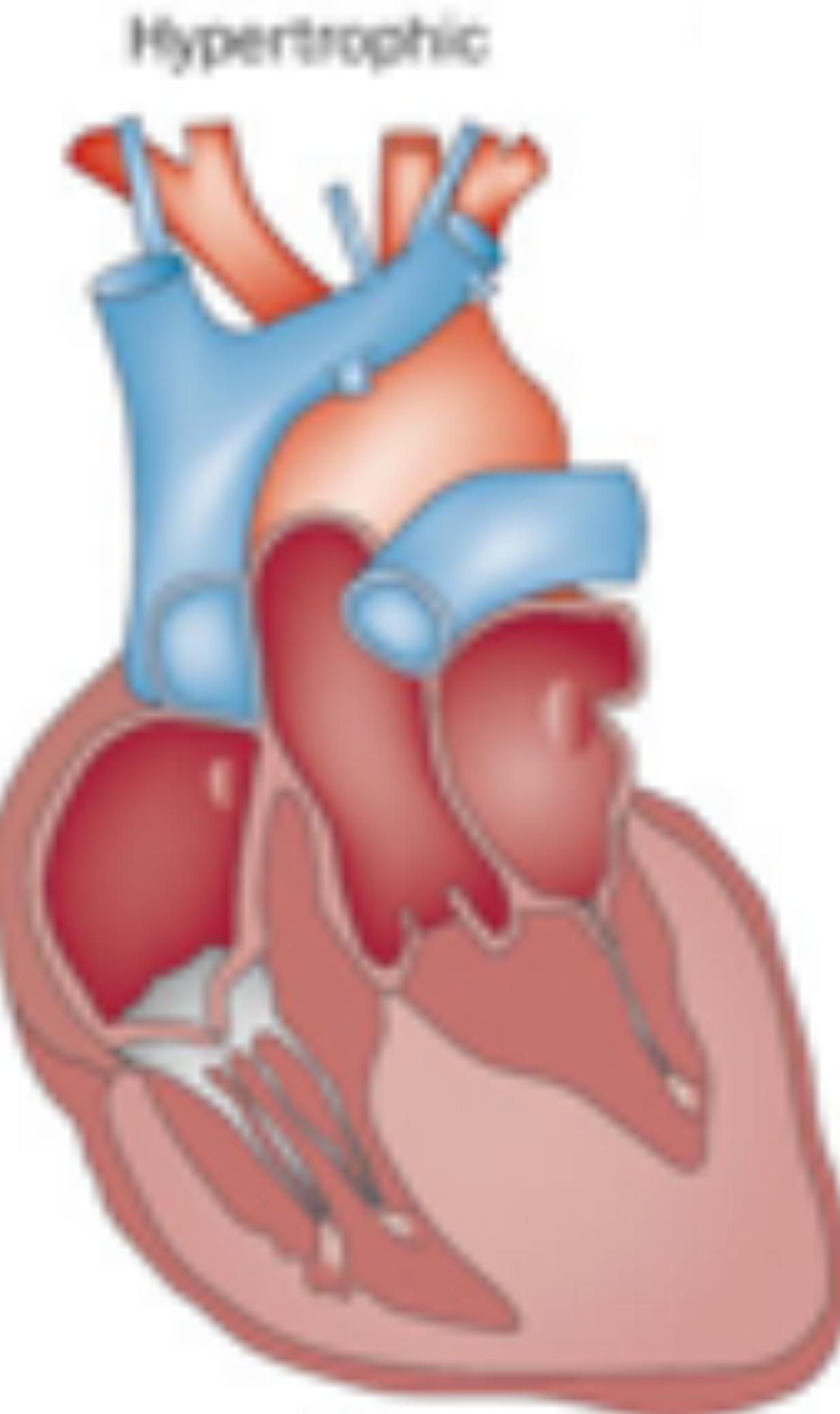
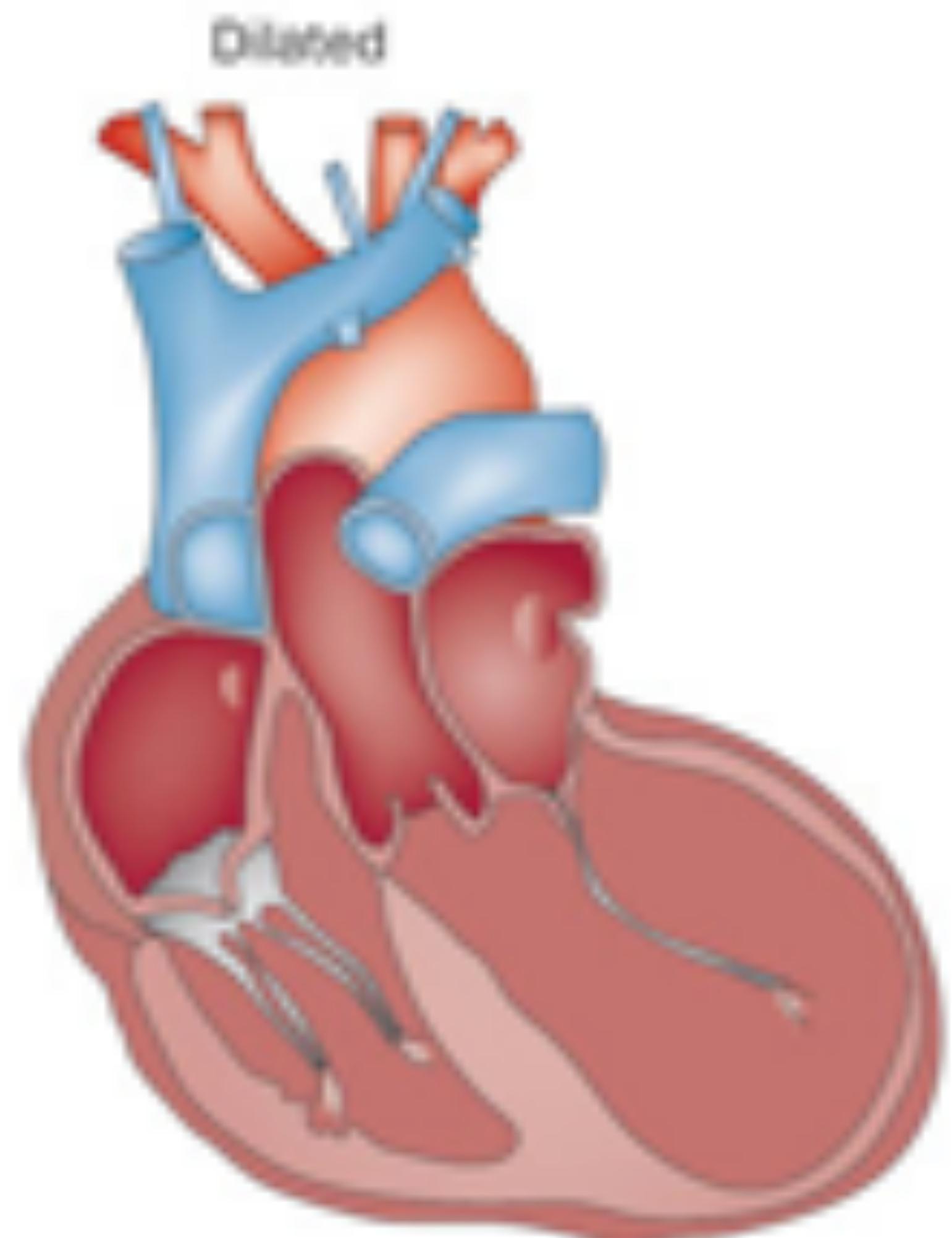
# Systolic dysfunction

## Low contractility/treatment

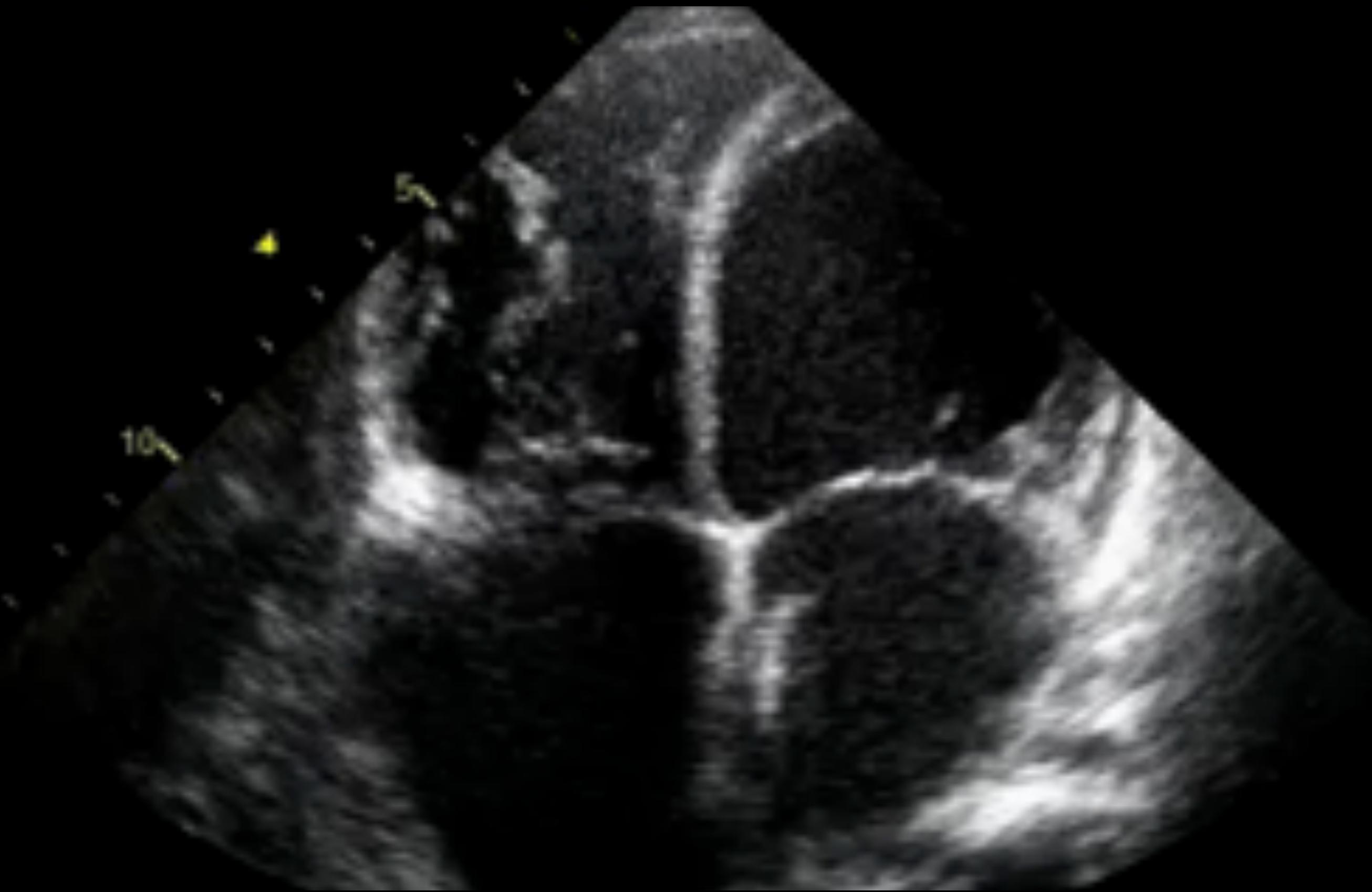
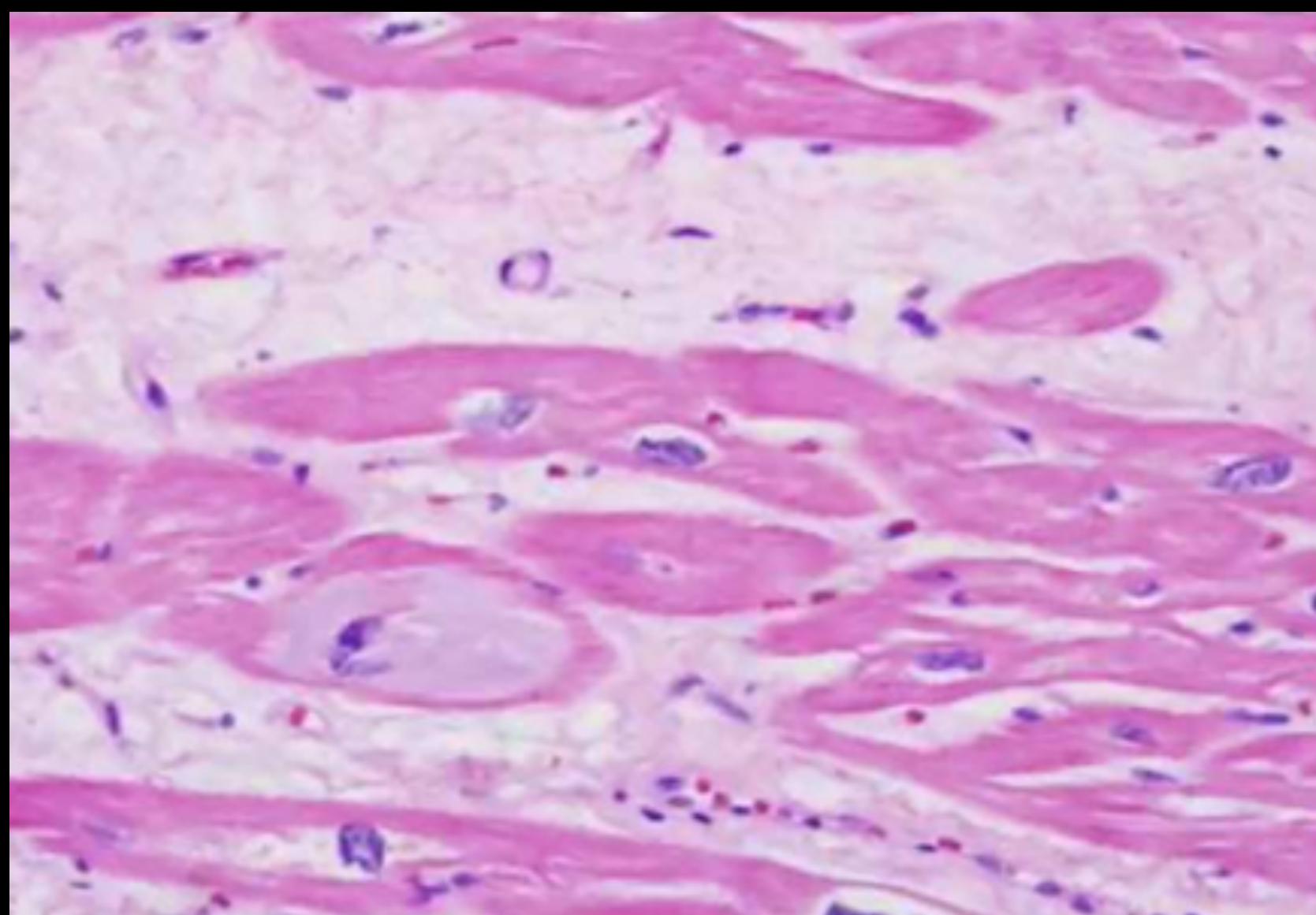
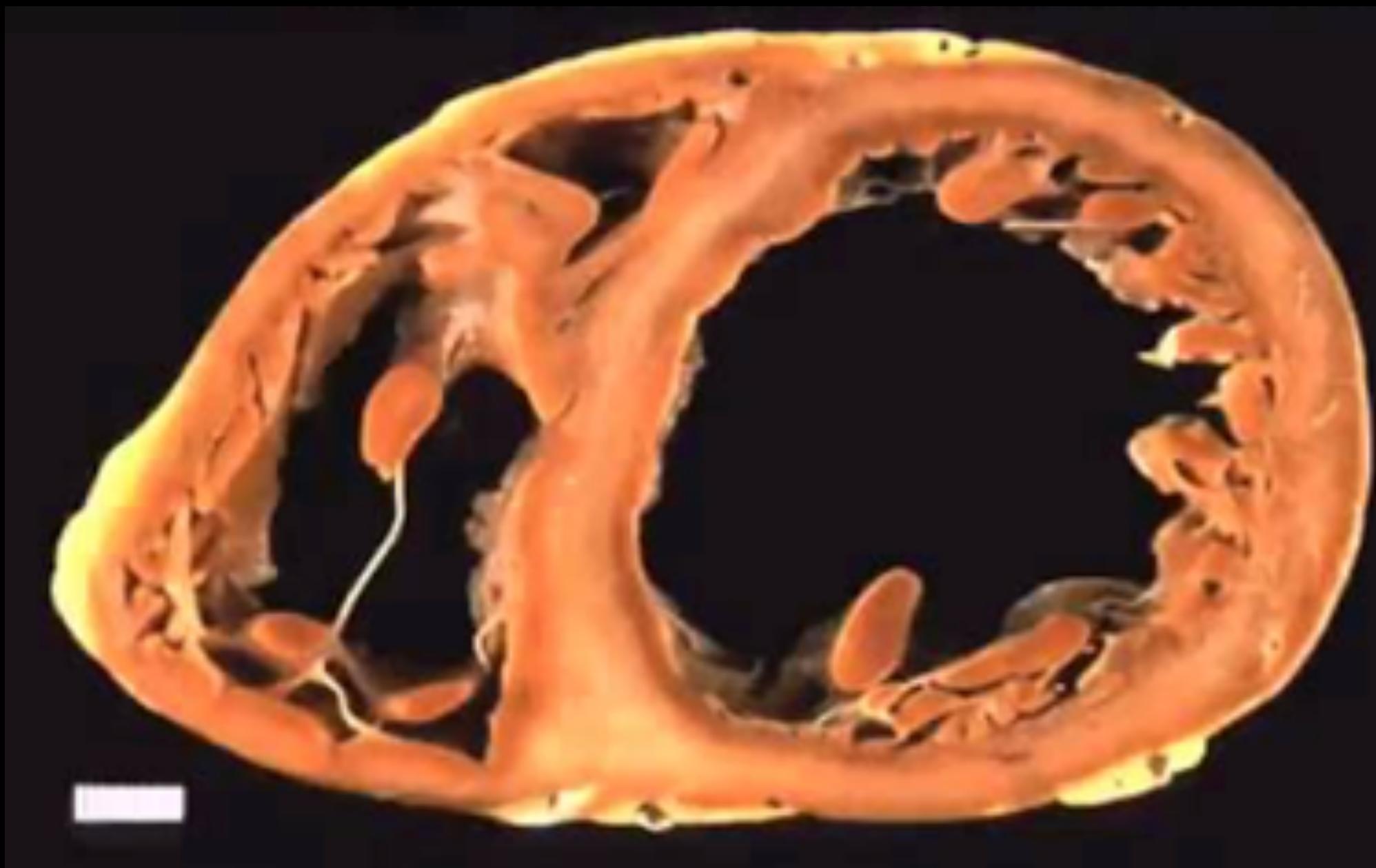


# Phenotypes of cardiomyopathies

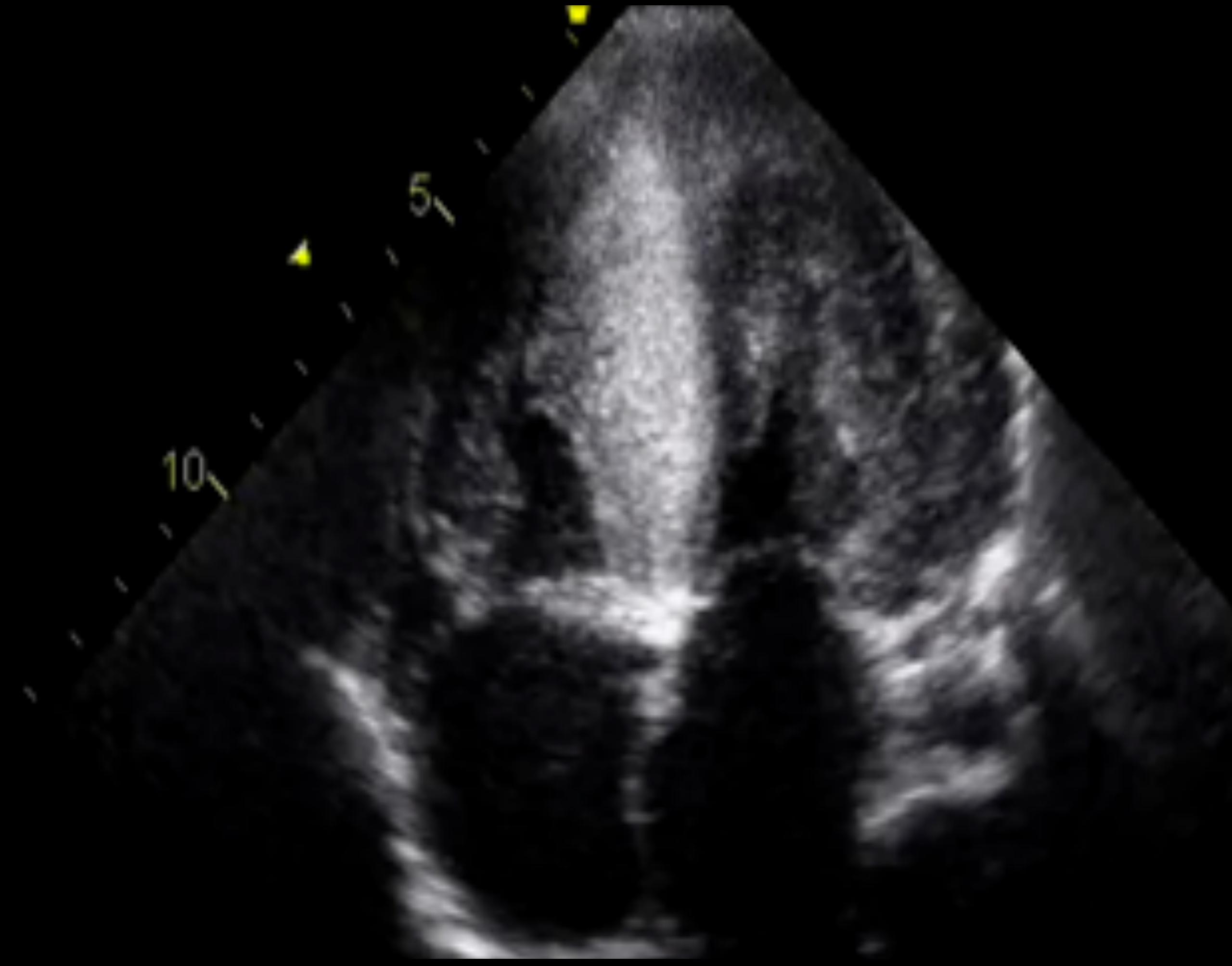
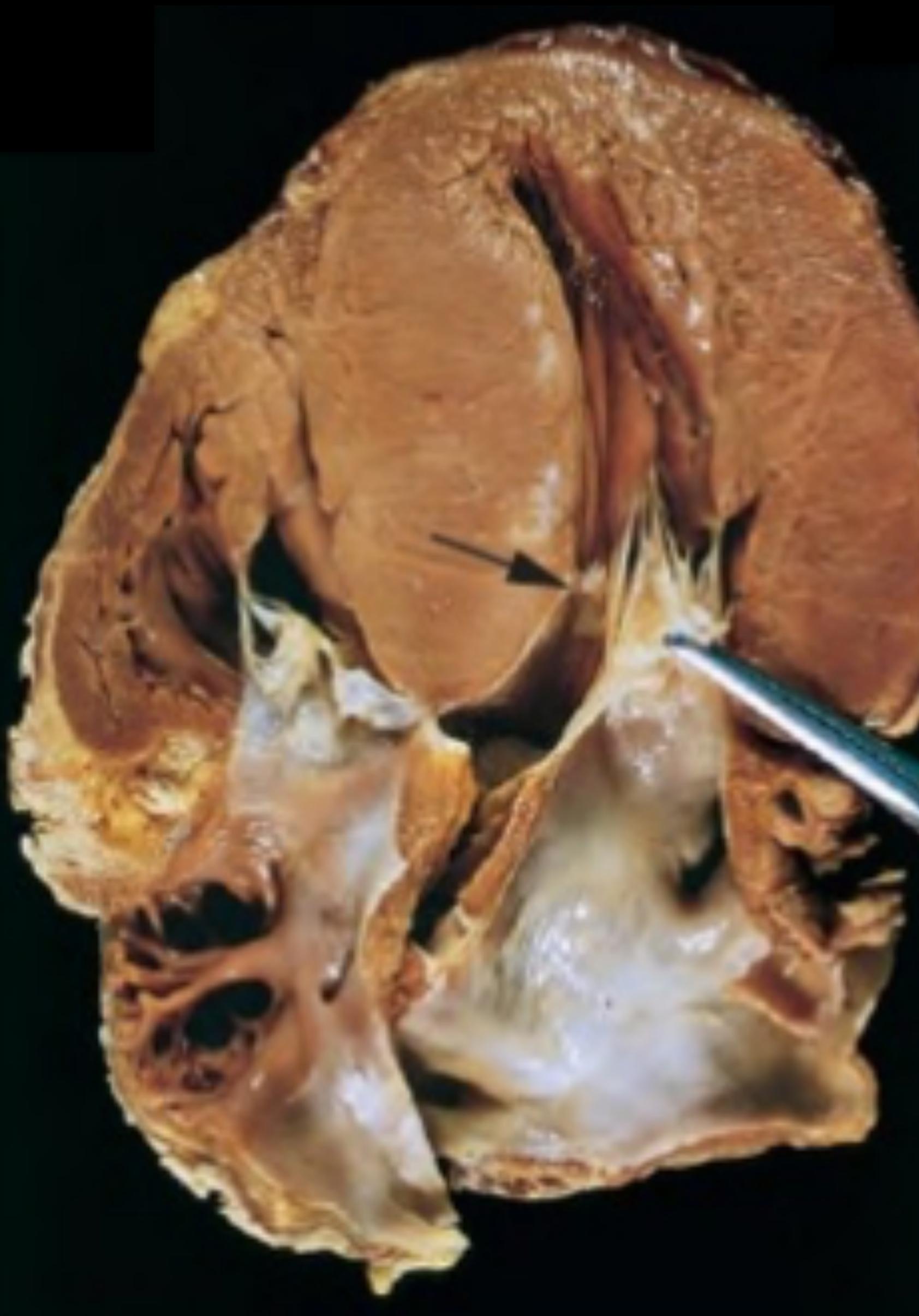
# Cardiac phenotypes



# Dilated cardiomyopathy



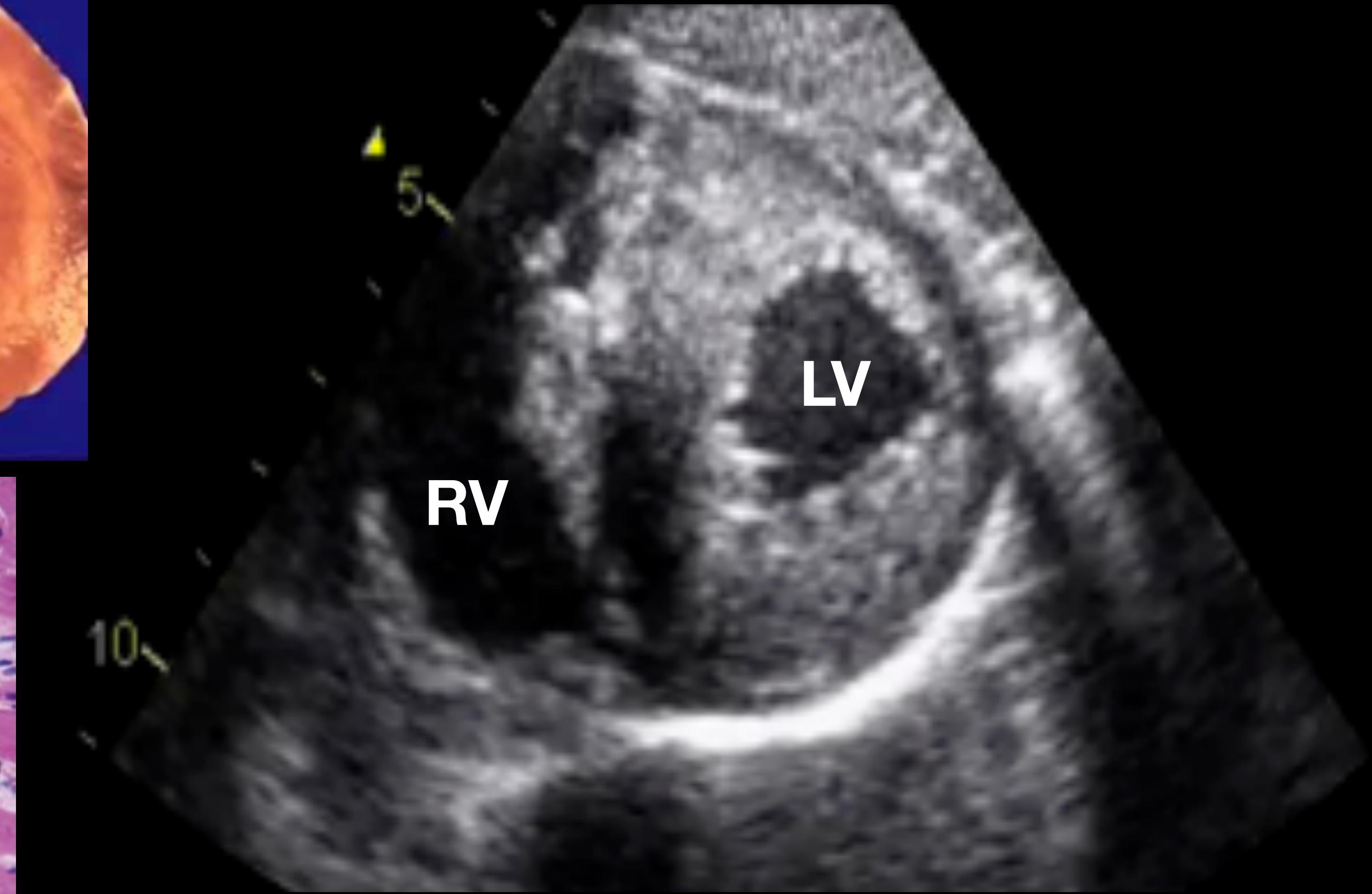
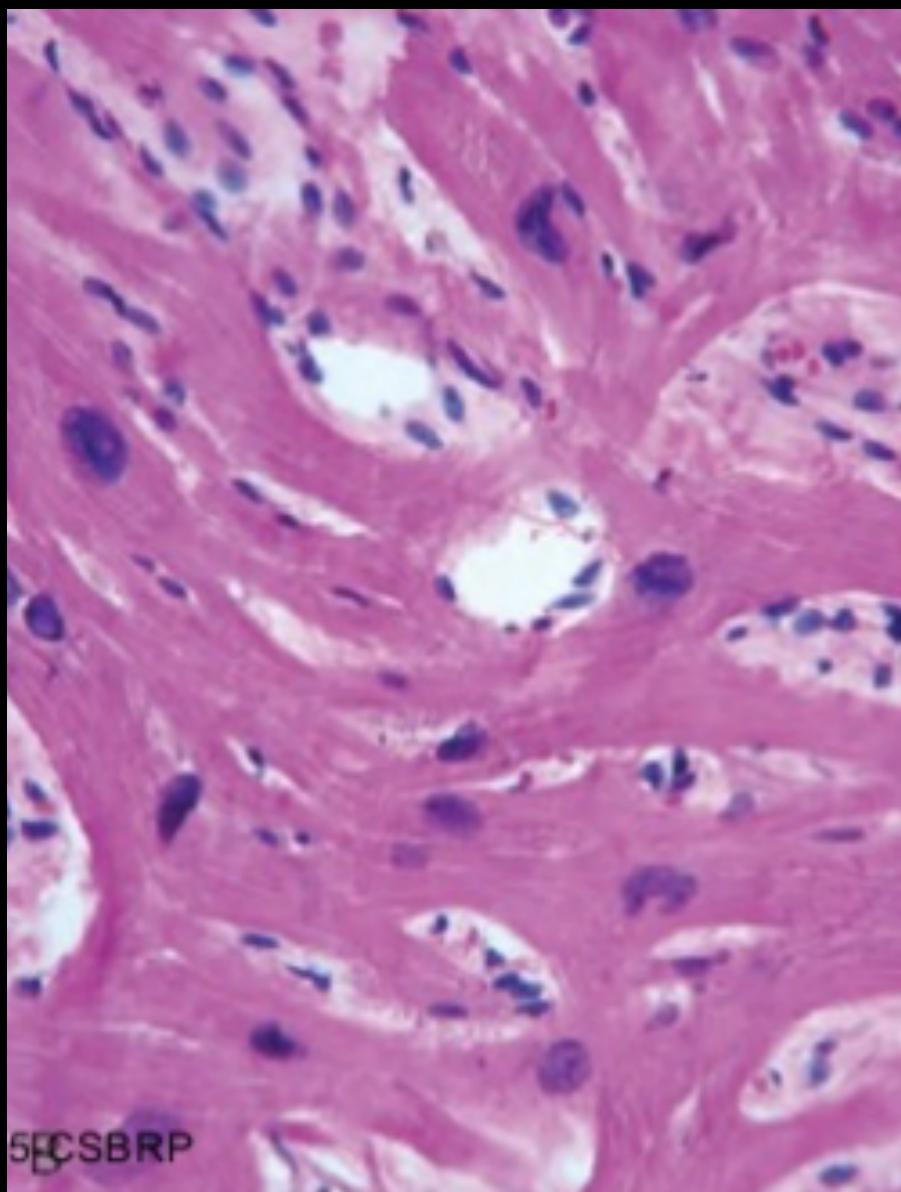
# Hypertrophic cardiomyopathy



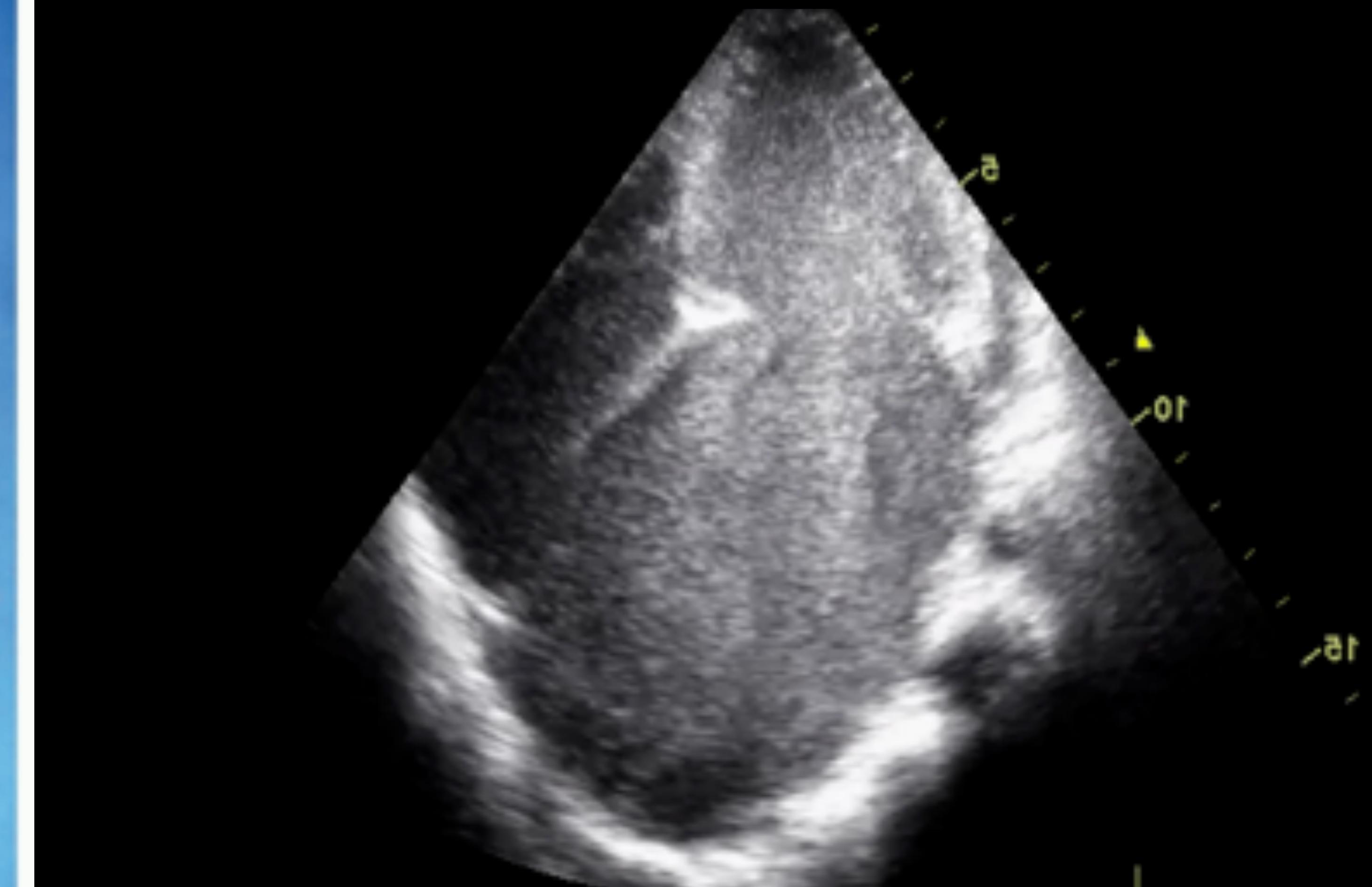
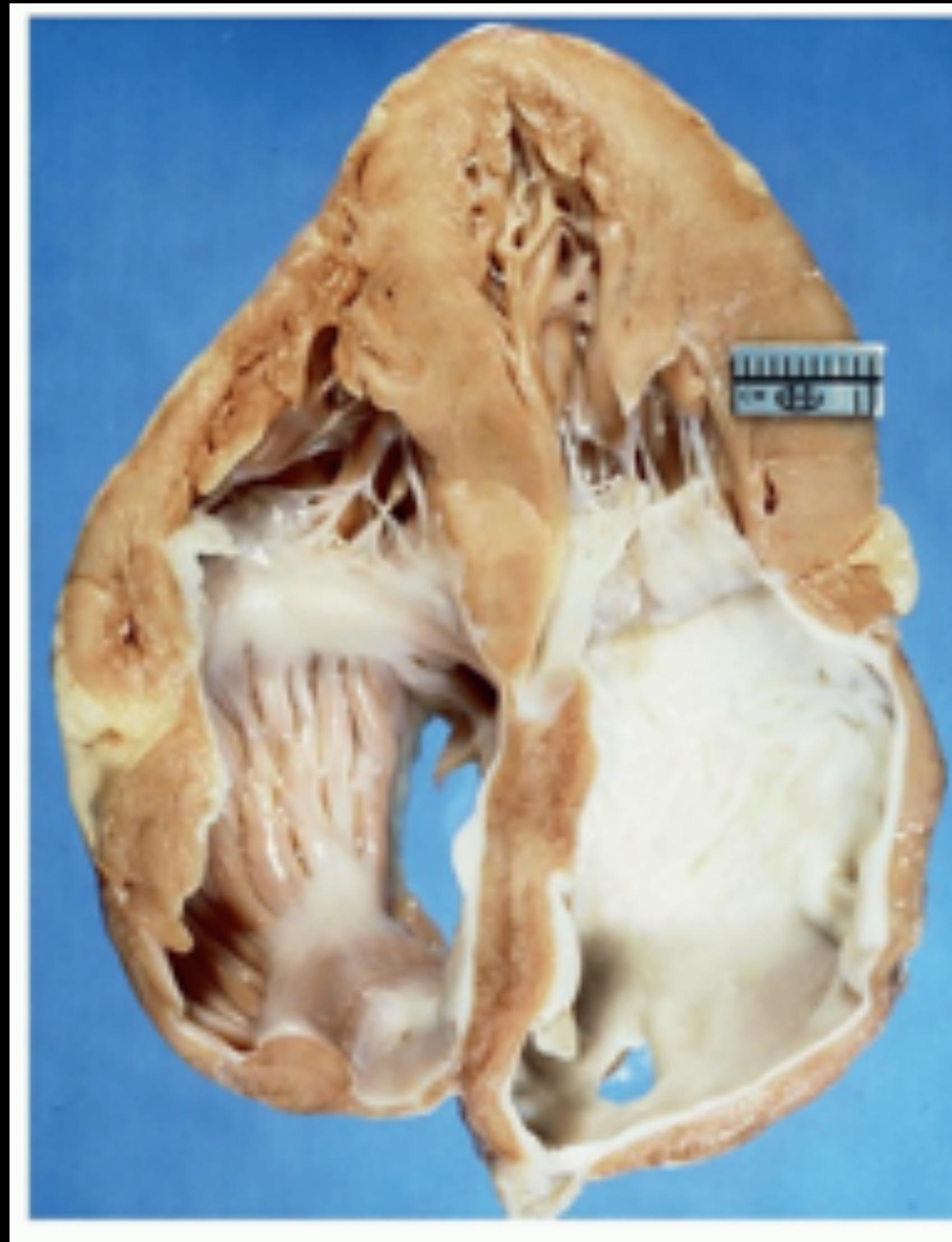
# Hypertrophic cardiomyopathy



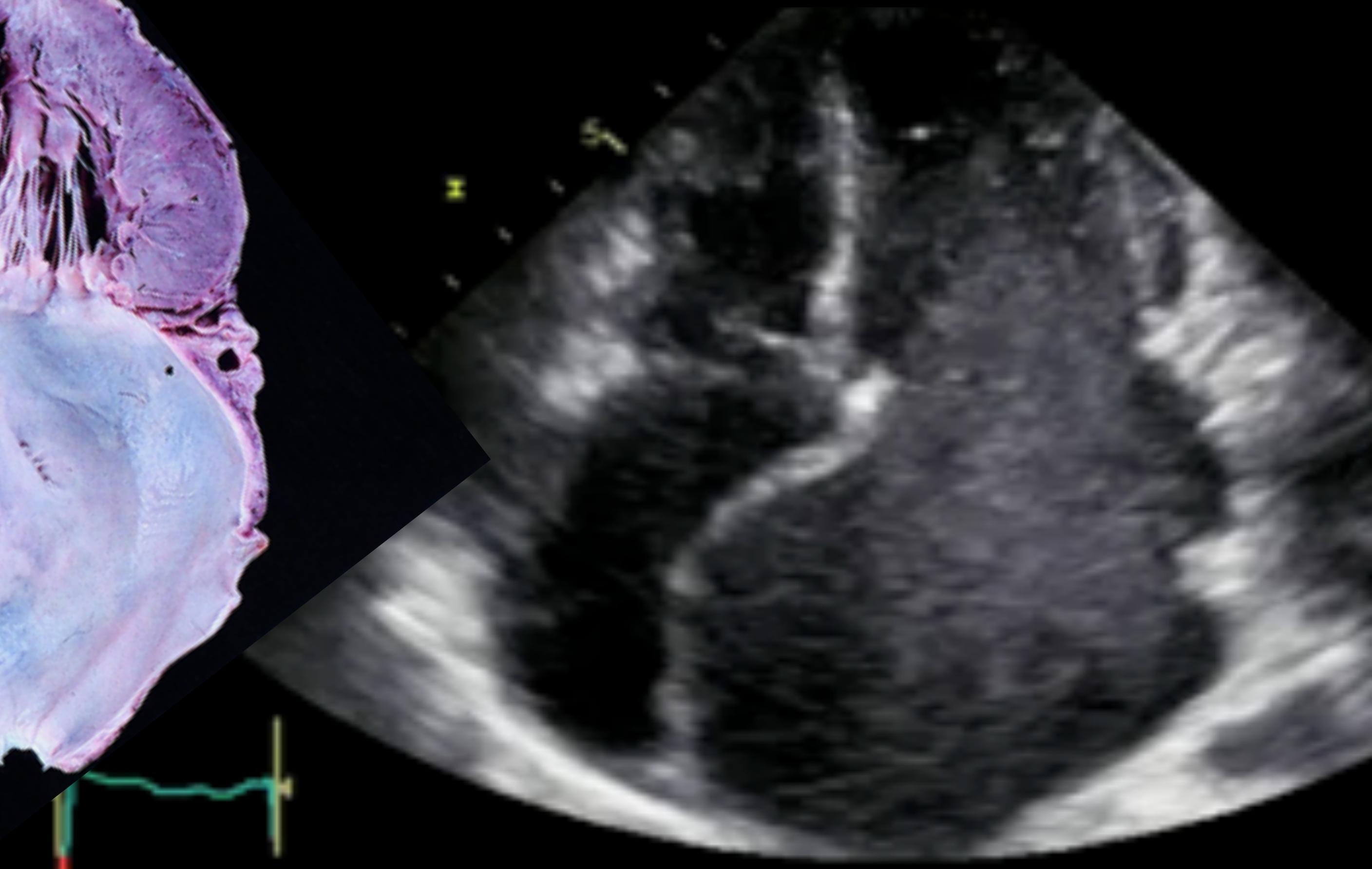
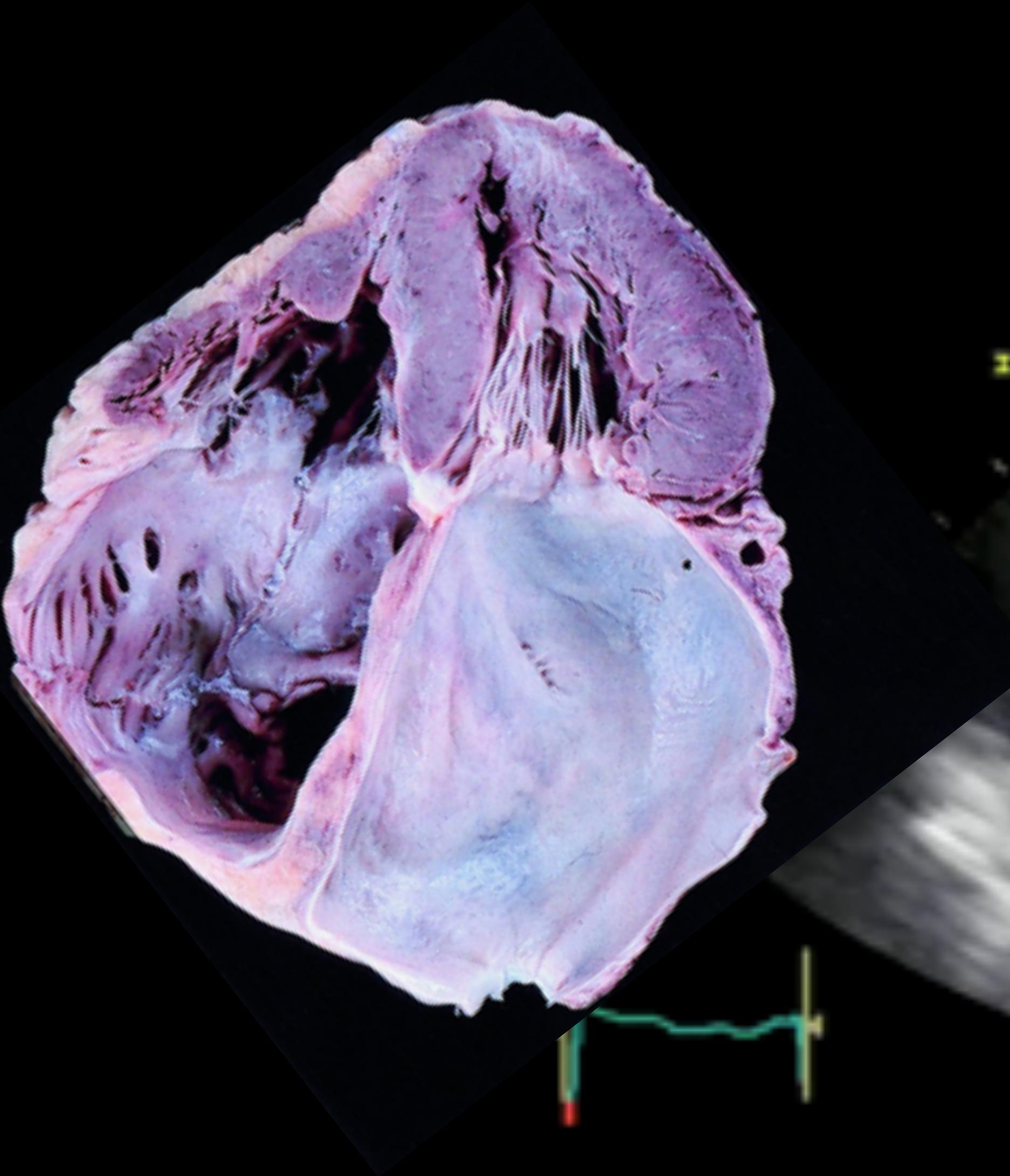
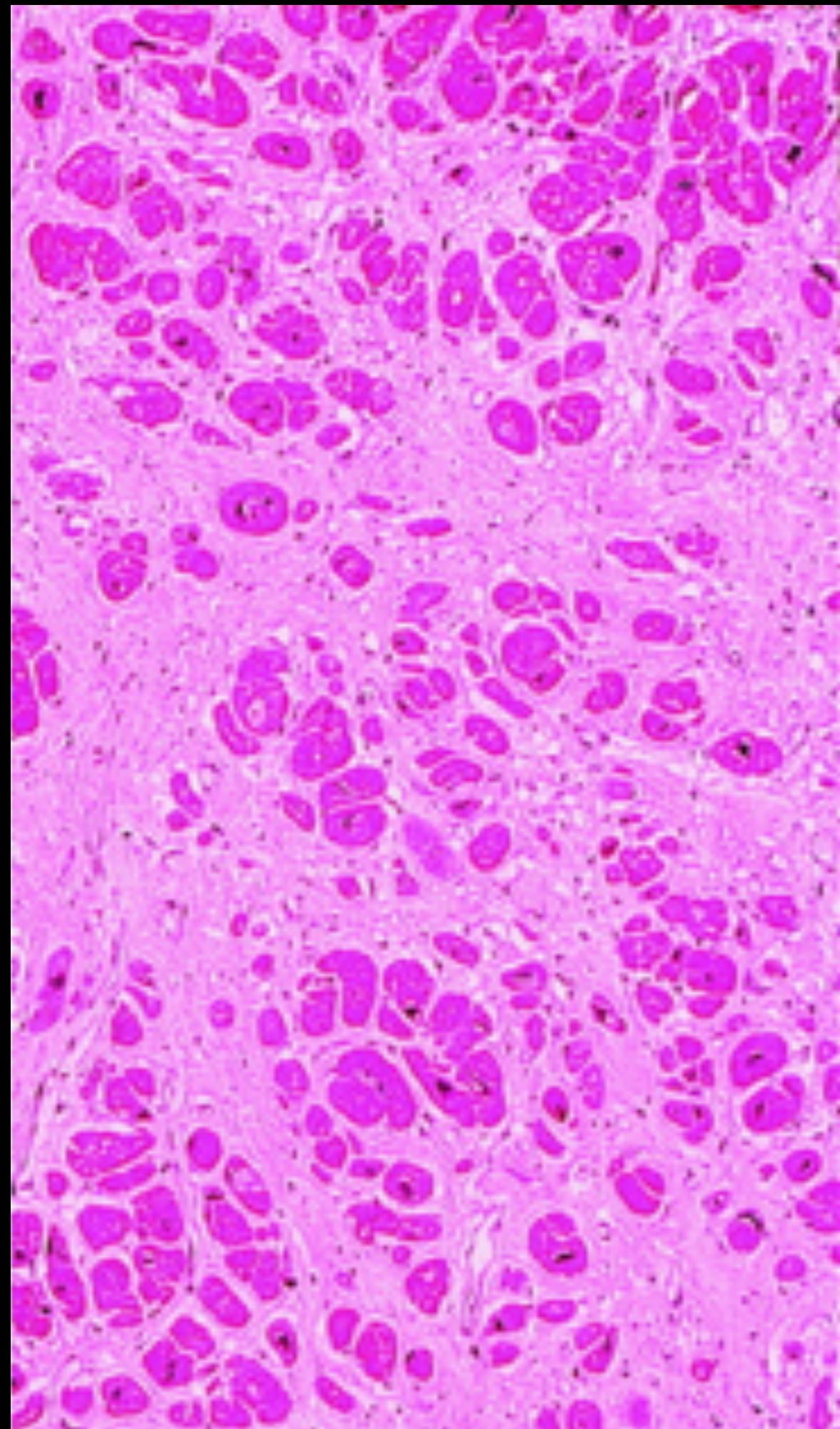
**Myofibrillar  
disarray**



# Restrictive cardiomyopathy

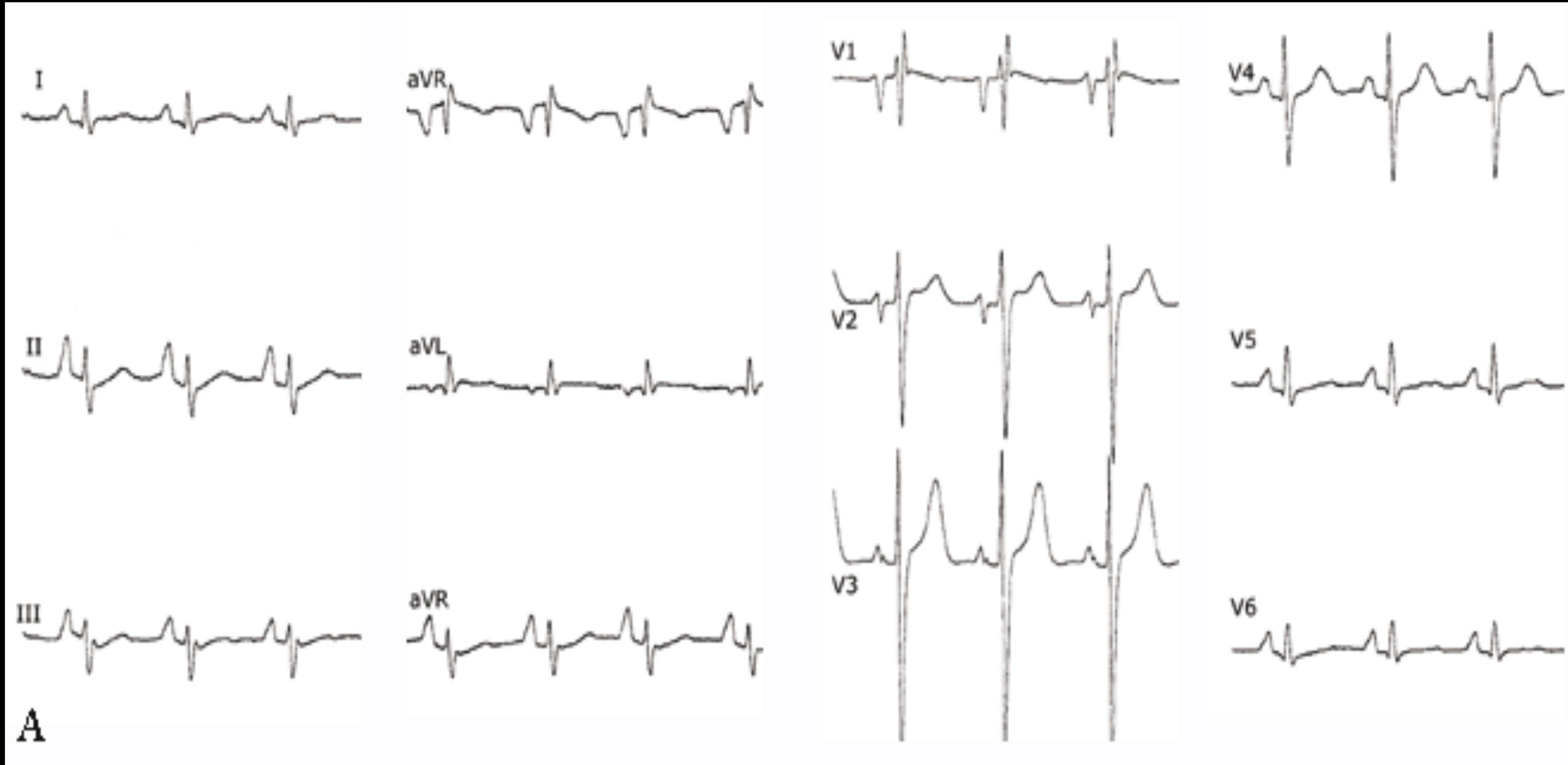


# Restrictive cardiomyopathy

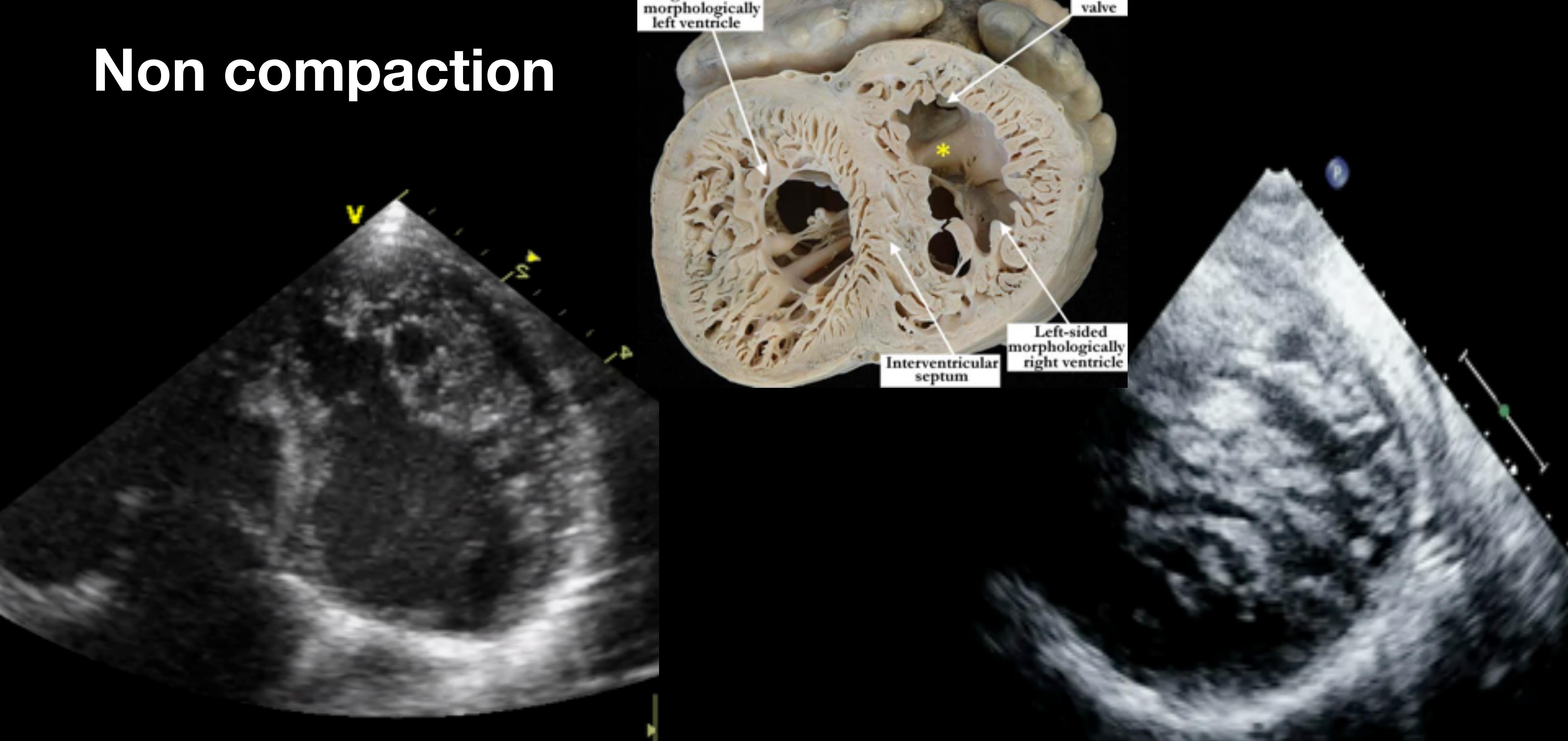


# Restrictive cardiomyopathy

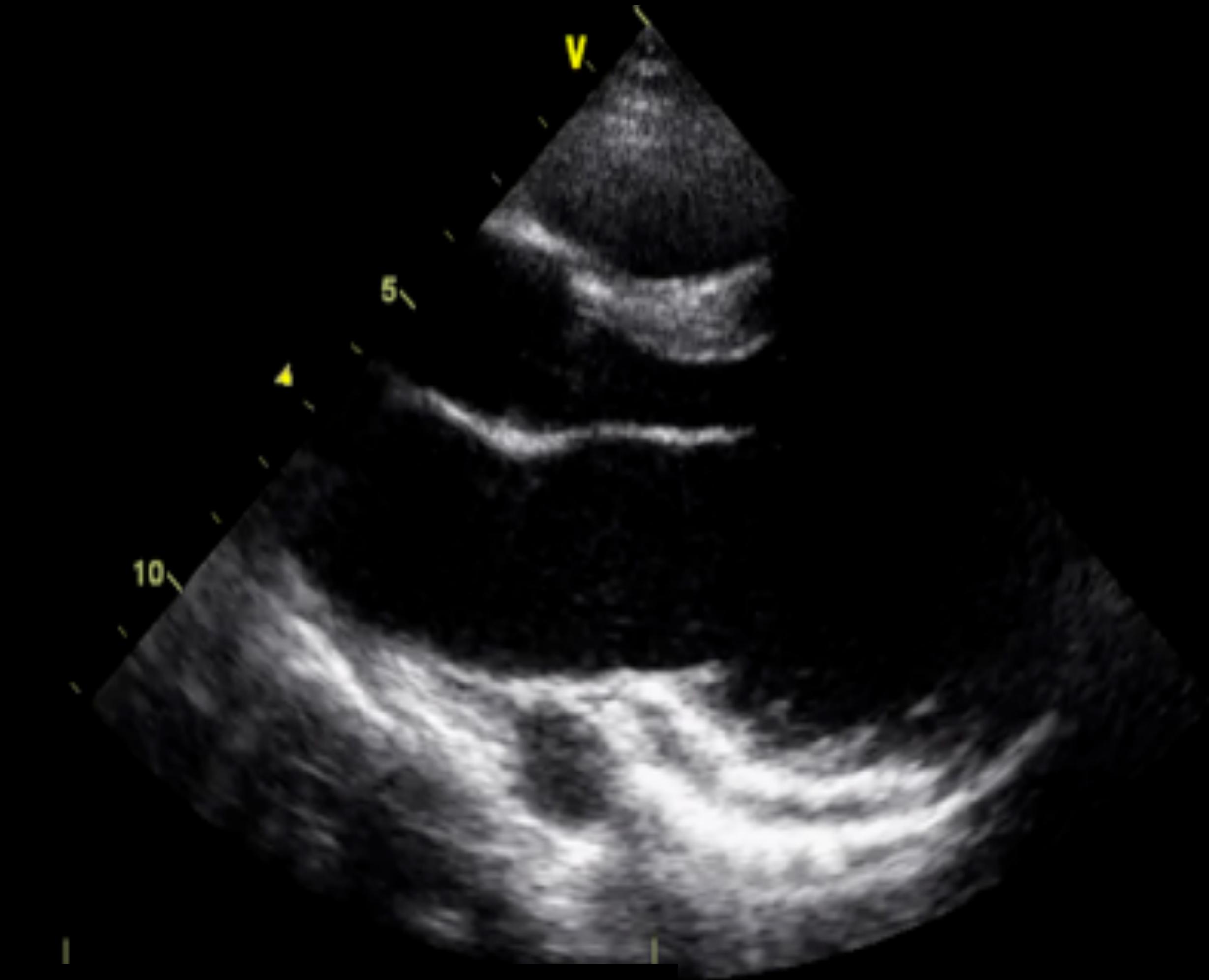
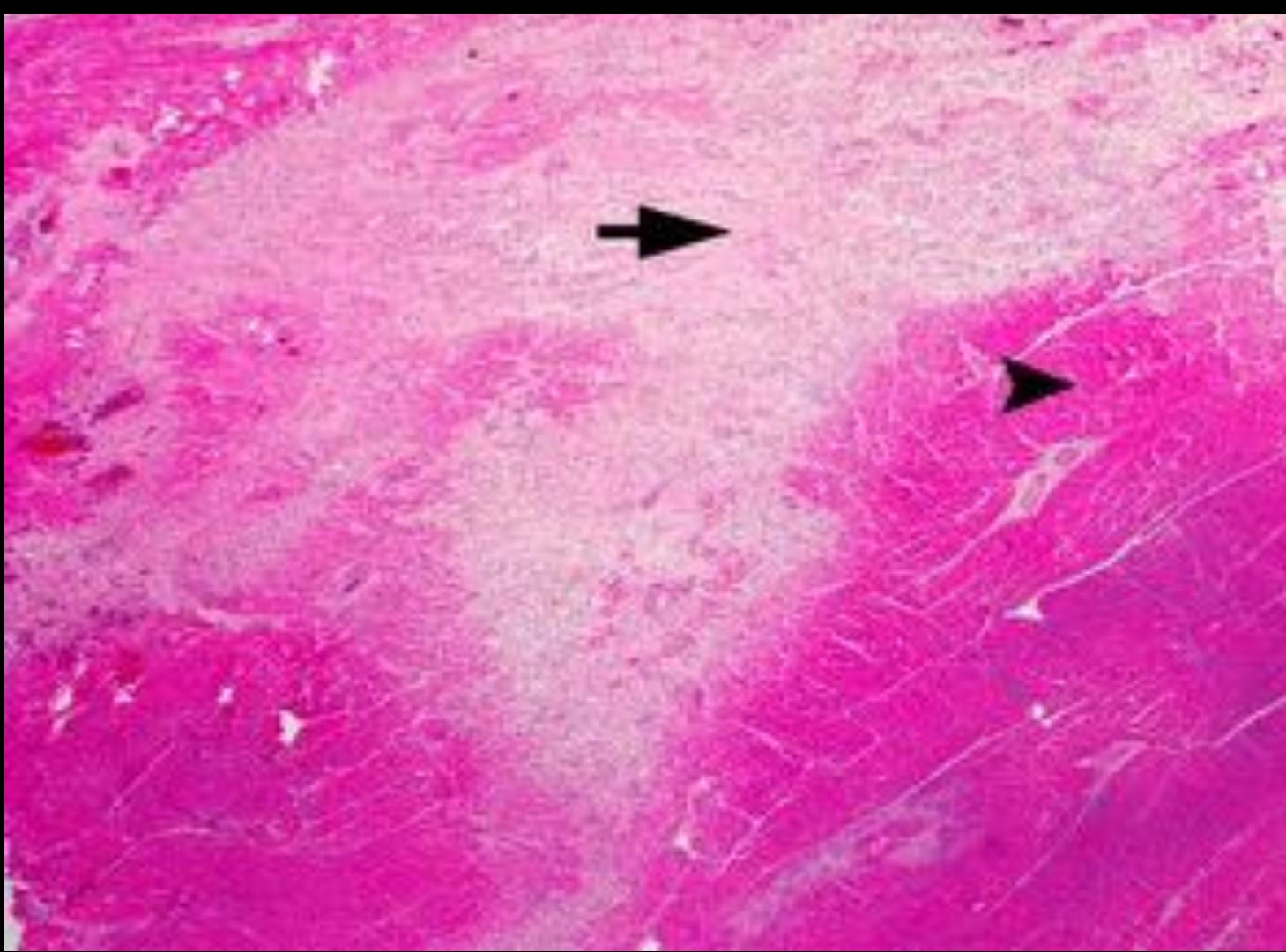
## ECG



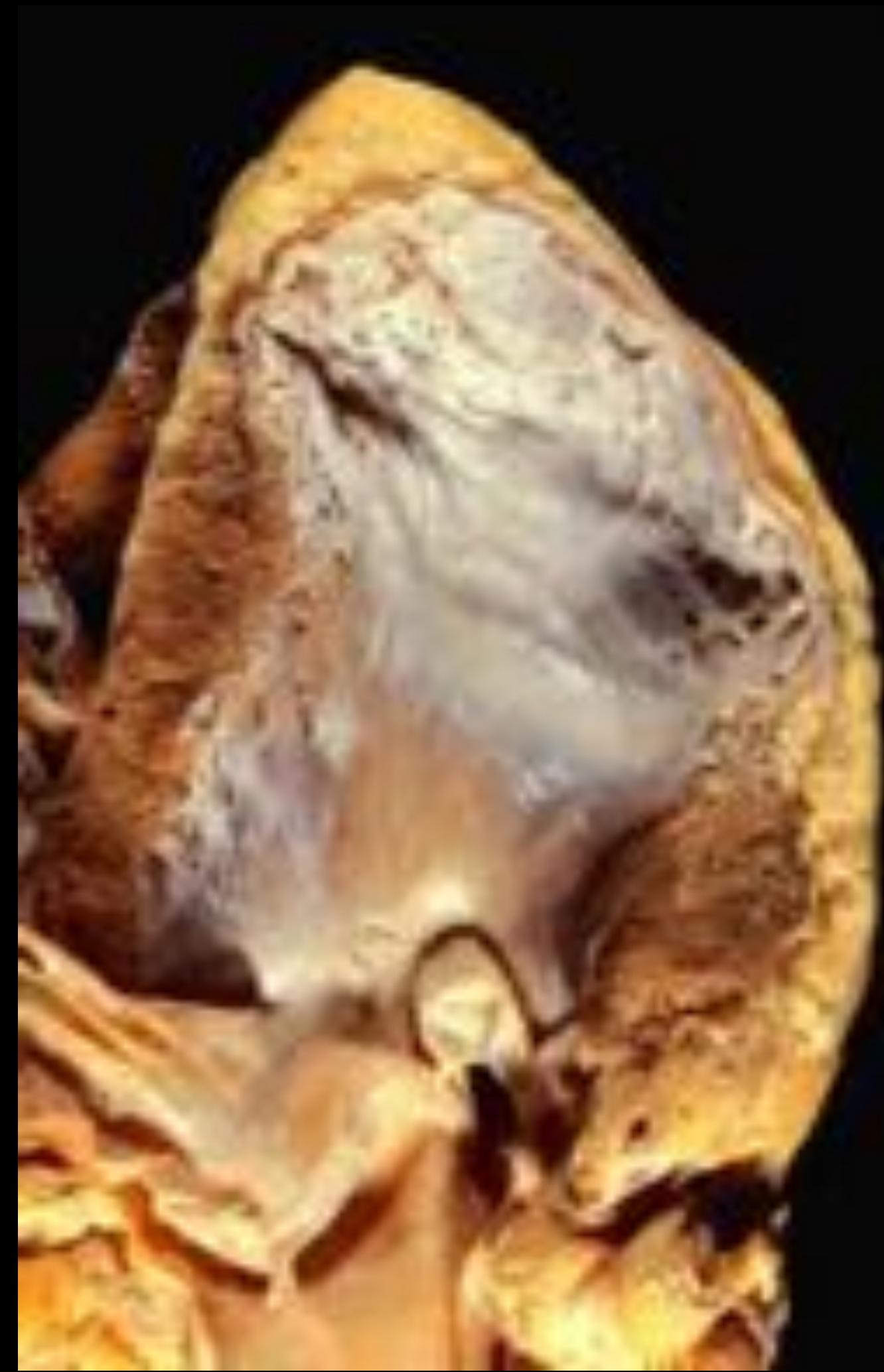
# Non compaction



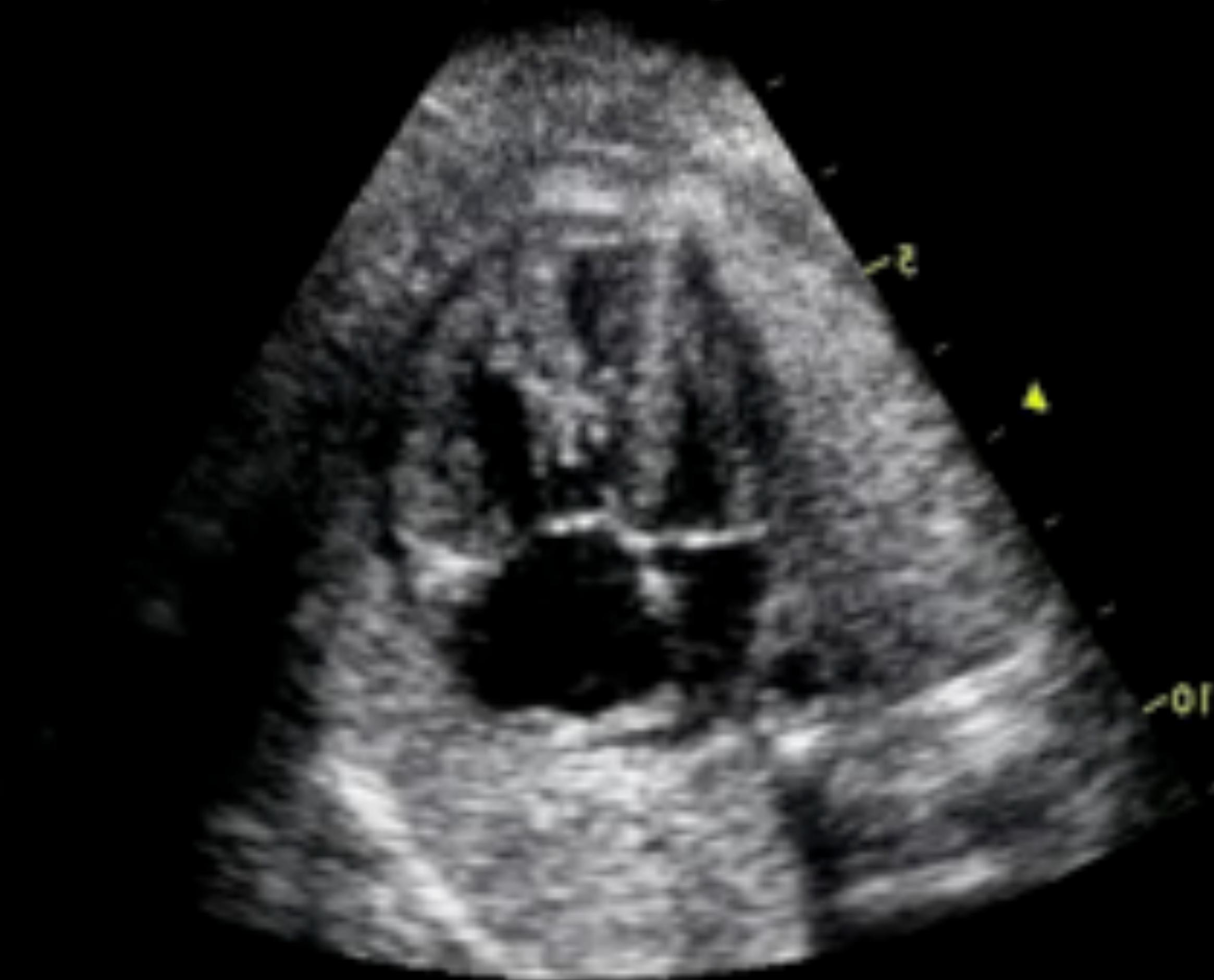
# Ischemic cardiomyopathy



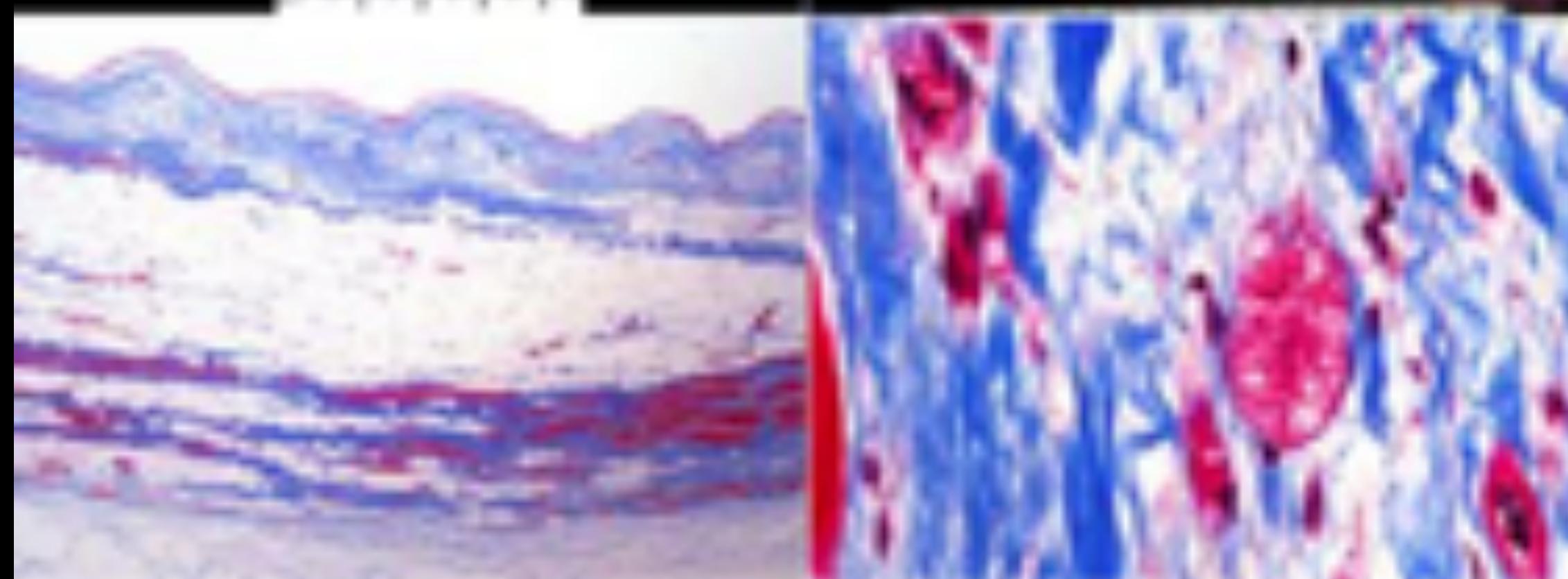
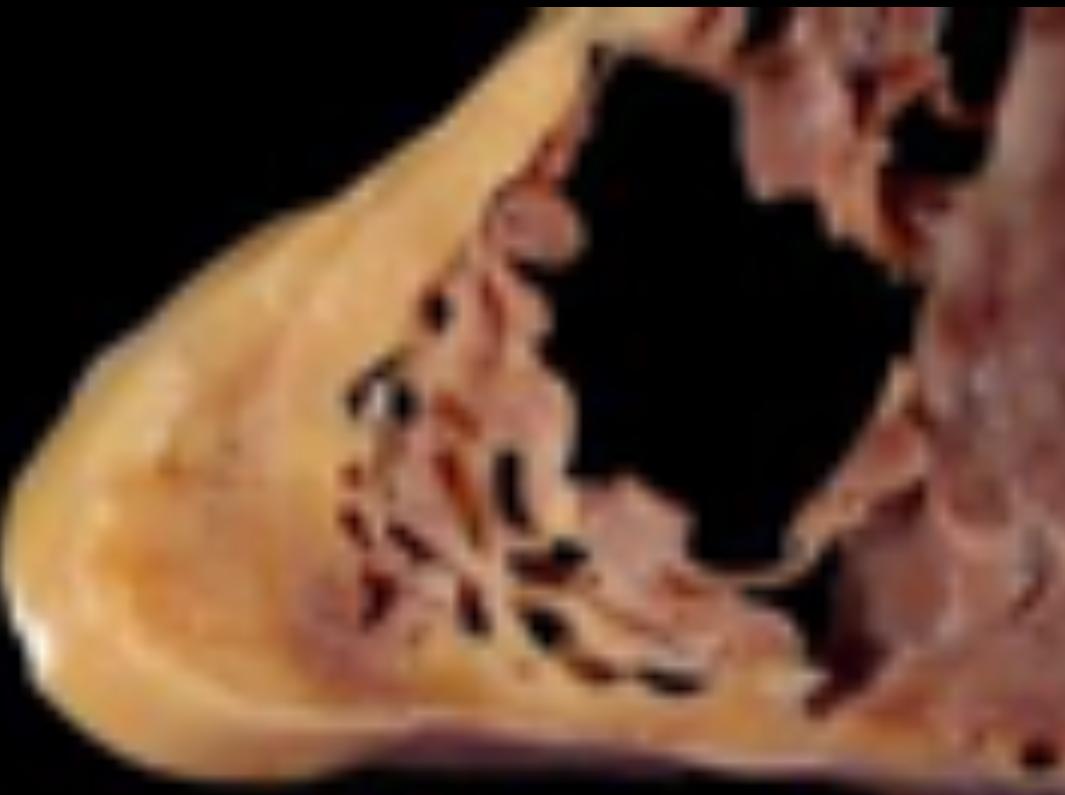
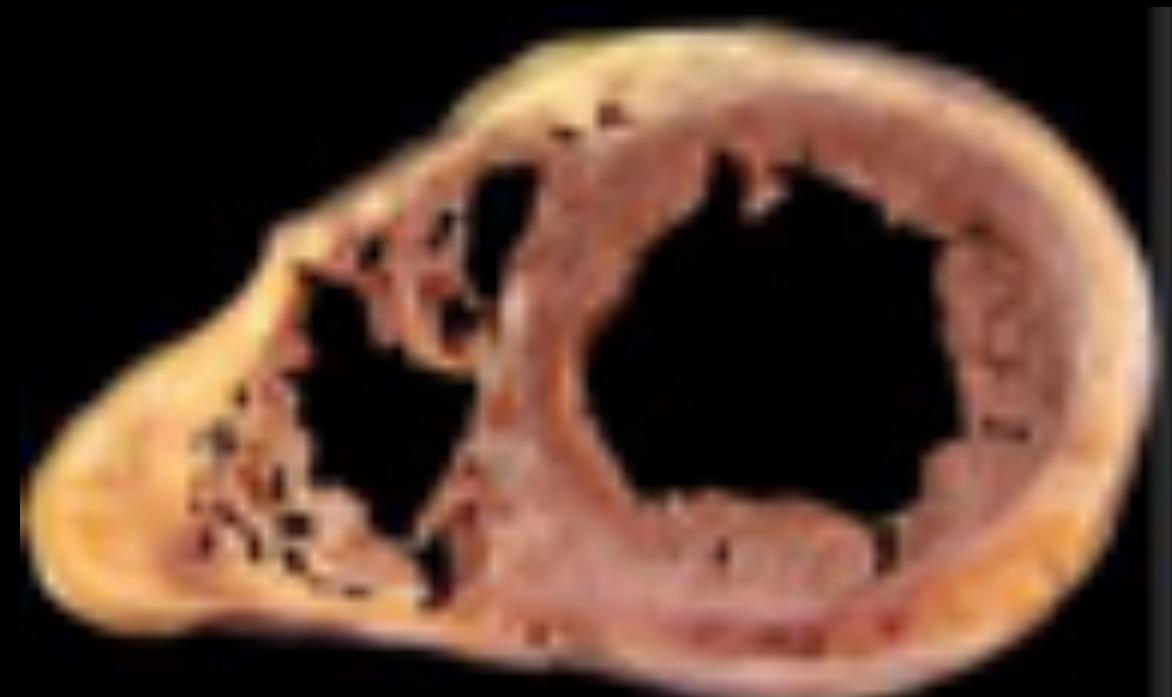
# Left ventricular aneurysm



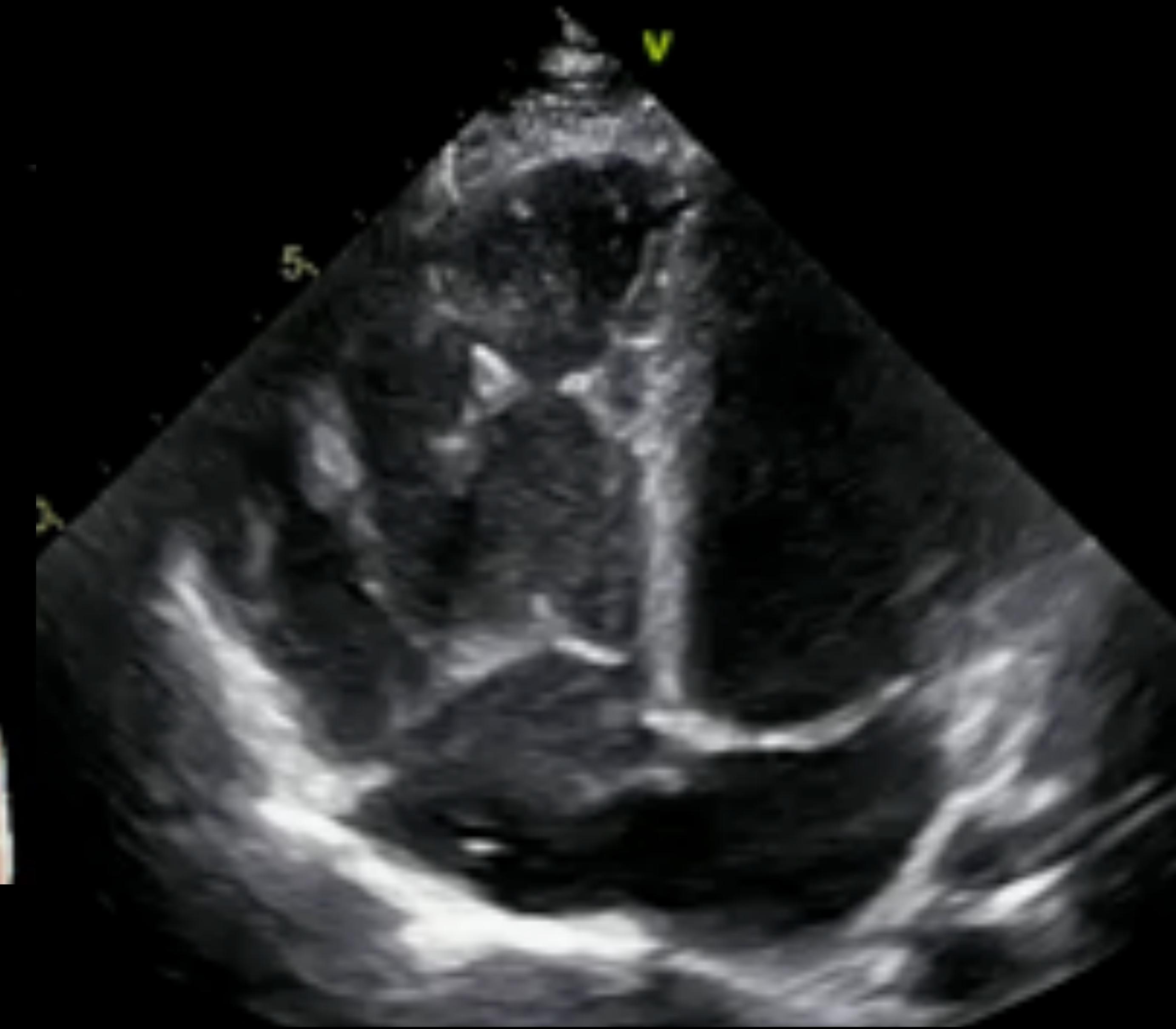
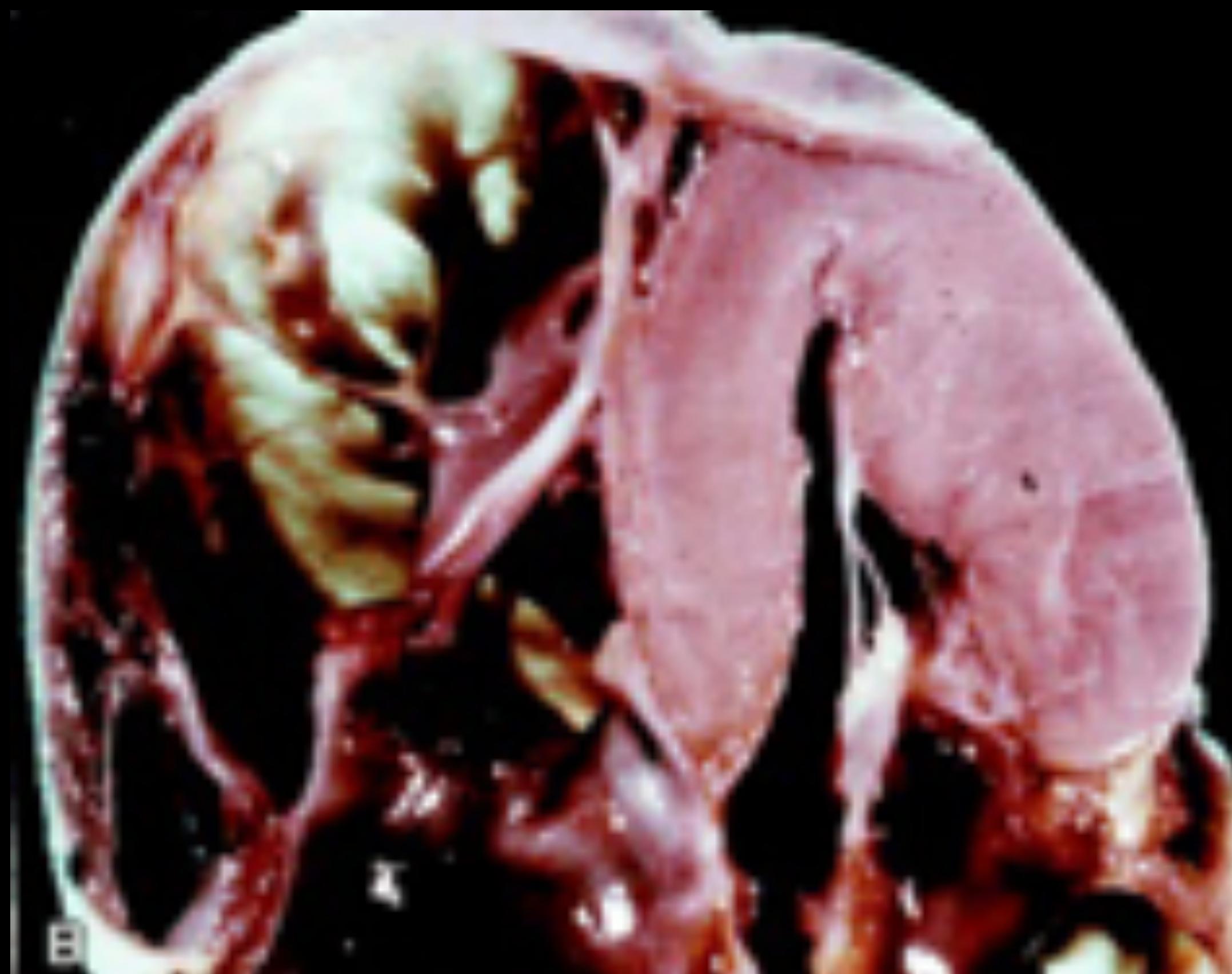
# Right ventricular cardiomyopathies



A.R.V.D



A.R.V.D



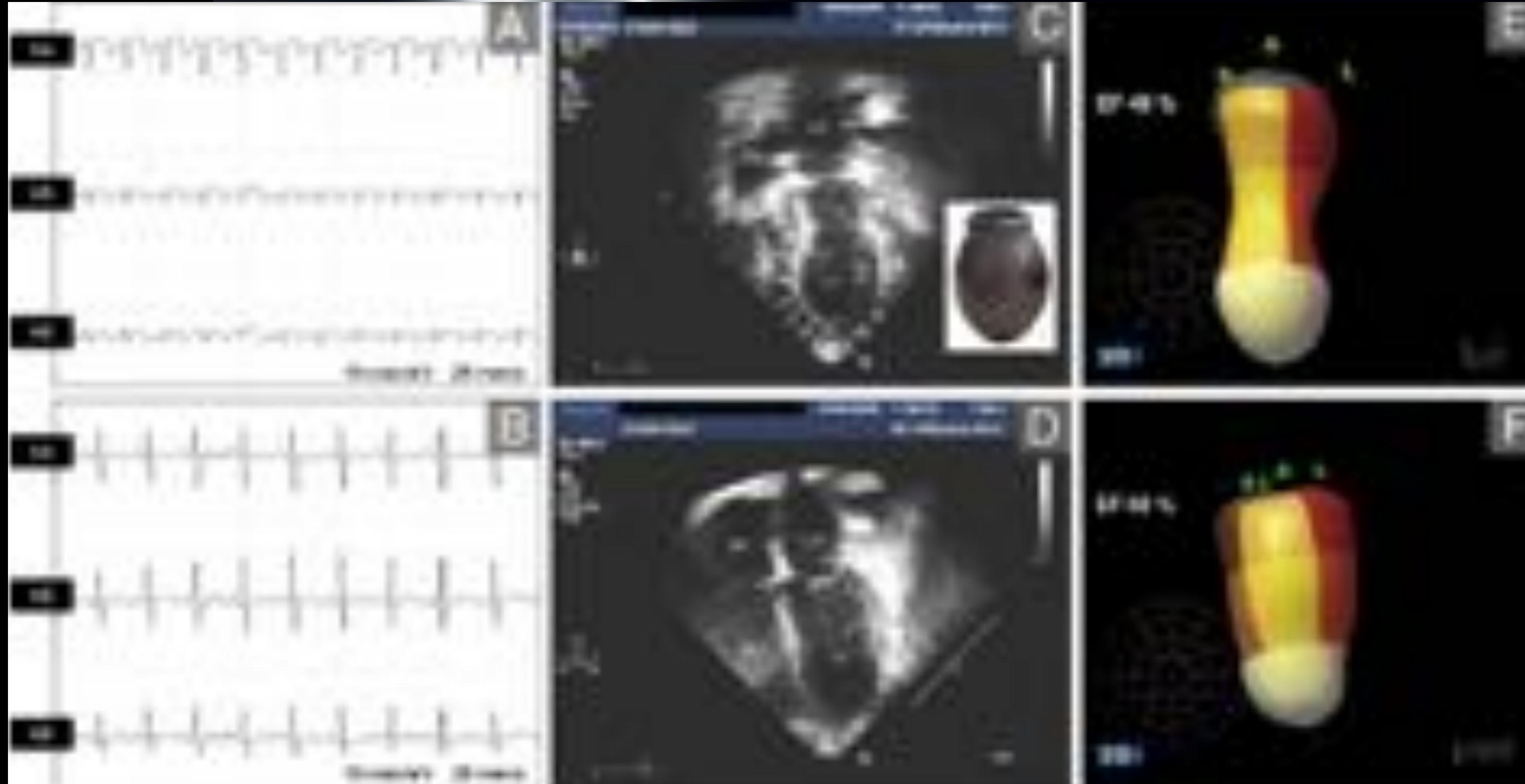
# Difficulties in phenotyping

- Unusual phenotypes
  - Dilated with hypertrophic walls and restrictive physiology
- Changing phenotype
  - From hypertrophic to dilated
- Uncertain phenotype
  - Penetrance increasing with age

# **Cardiomyopathies are rarely familial and a known cause of ventricular dilatation and/or hypertrophy should be extensively searched**

- Tako-tsubo
- Volume and pressure overload
- Myocardial ischemia
- Sustained arrhythmias
- Infective myocarditis
- Toxic
- Neuromuscular disorders
- Syndromic cardiomyopathies
- Metabolic diseases

# Purely environmental cardiomyopathy ?

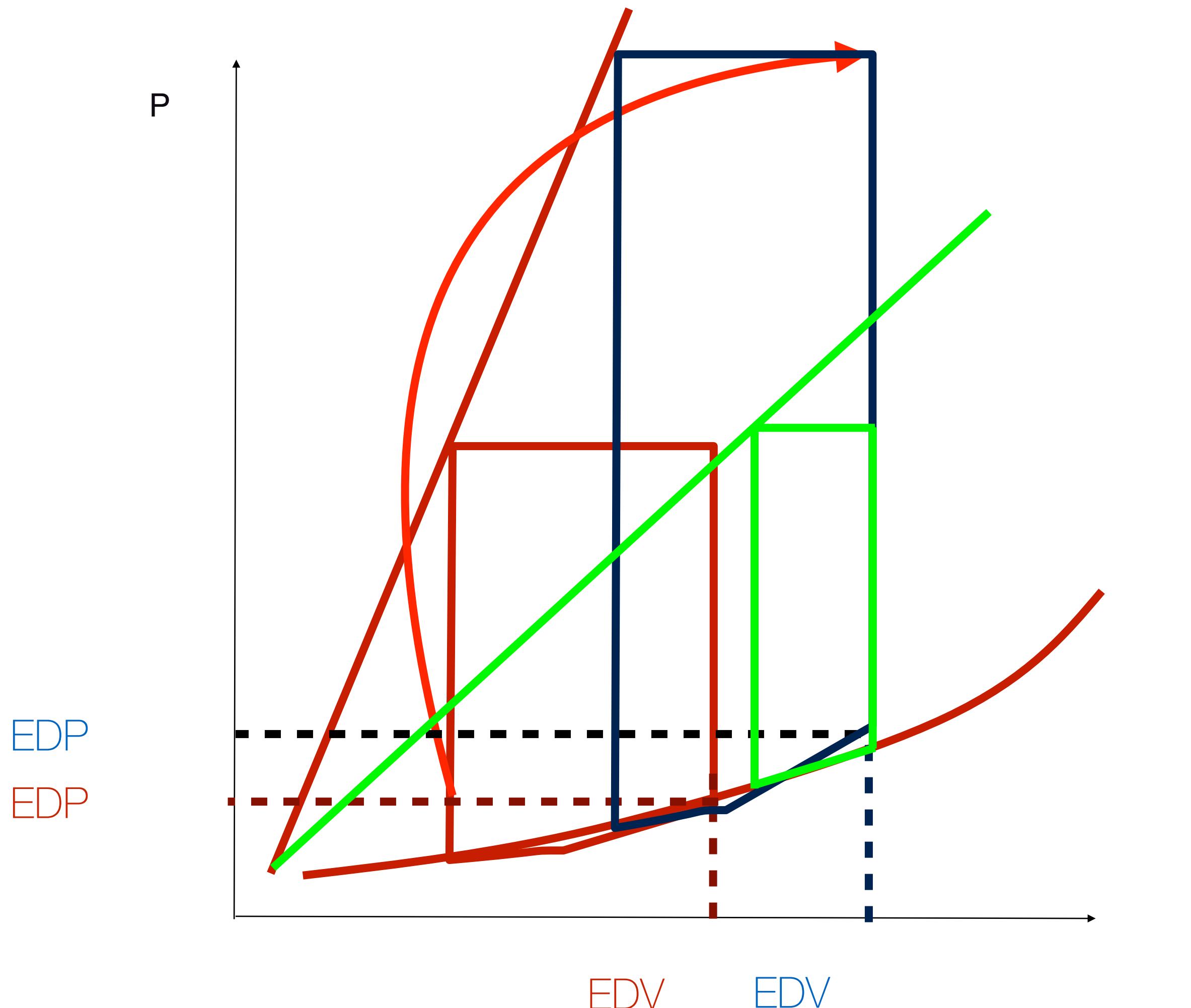


Takotsubo

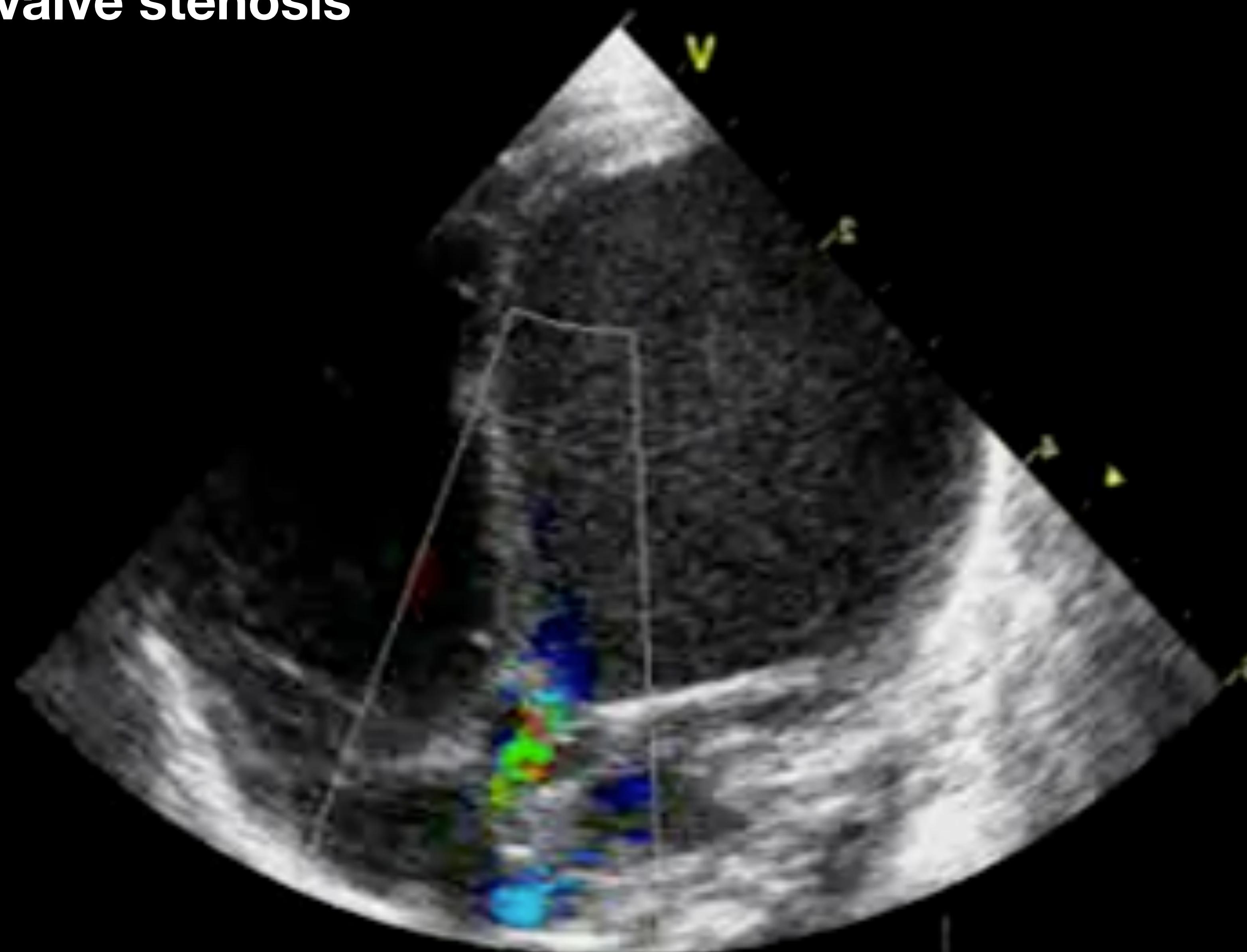
Schoof F et al. J Am Coll Cardiol. 2010 Jan 19;55(3):e5.  
Bajolle F et al. Cong Heart Dis 2009;4:387-90

# Heart failure due to increased afterload

## Normal contractility and compliance

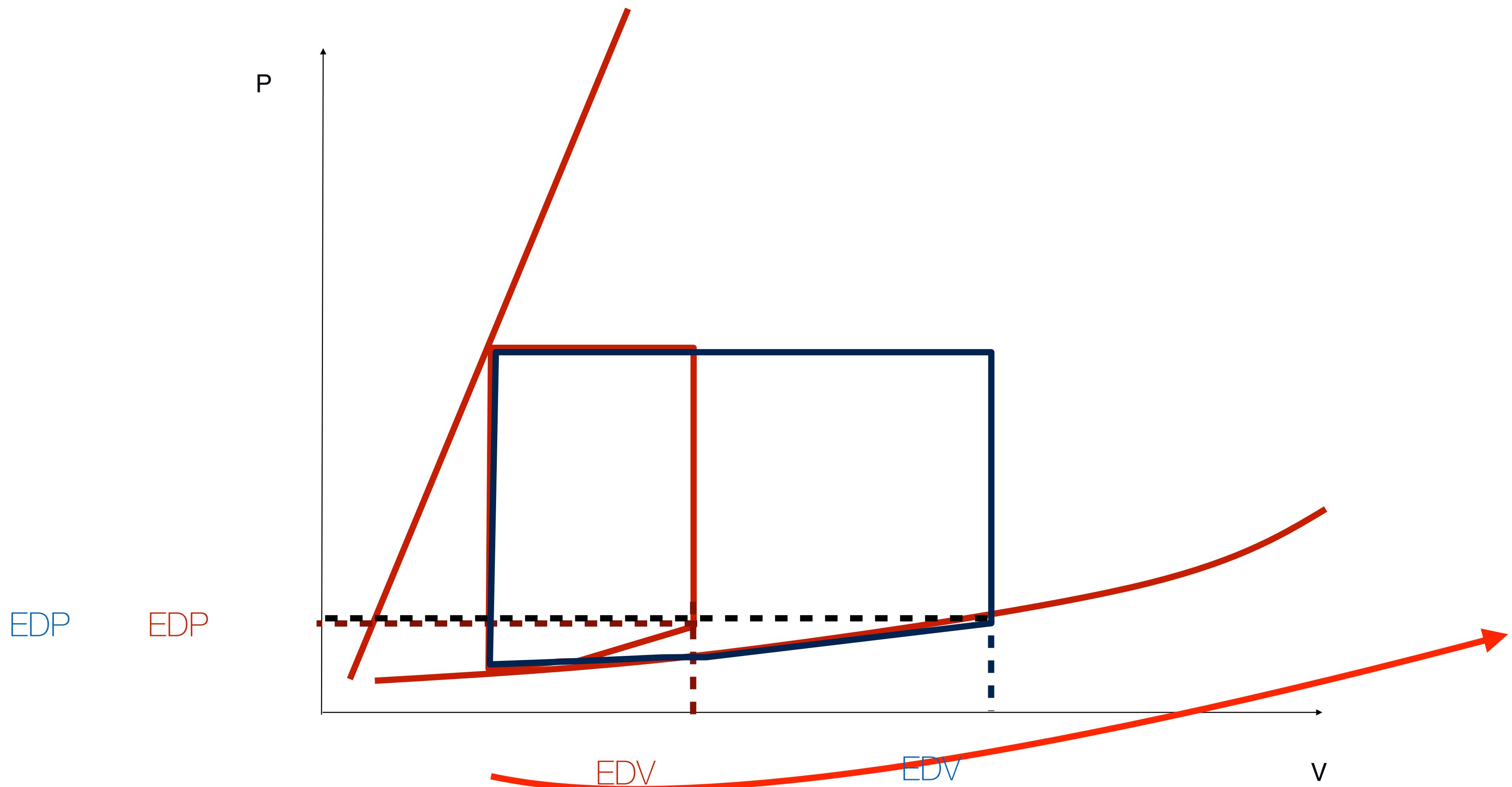


# Critical aortic valve stenosis

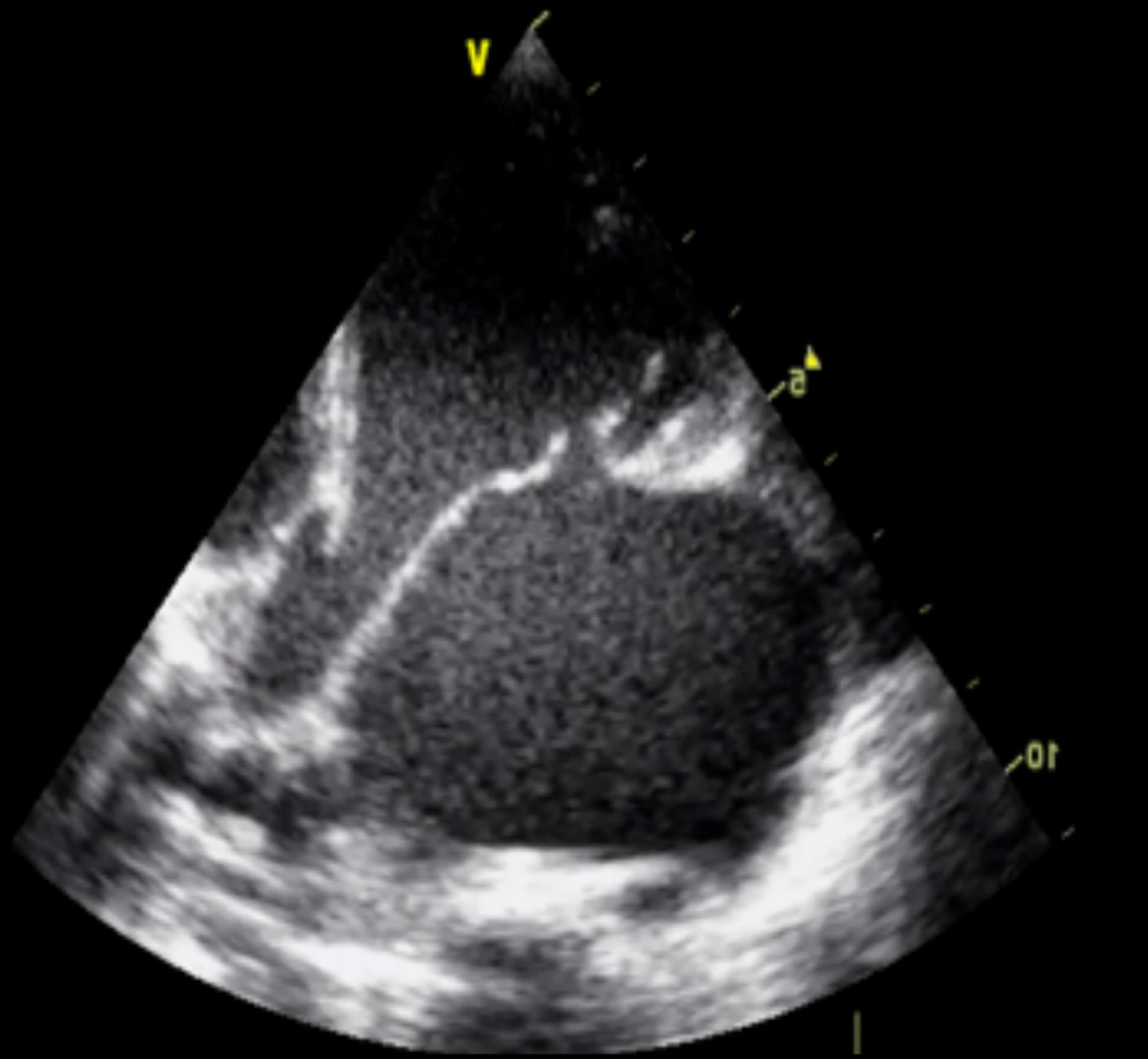


# Heart failure due to increased preload

## Normal contractility and compliance



# Severe mitral valve regurgitation

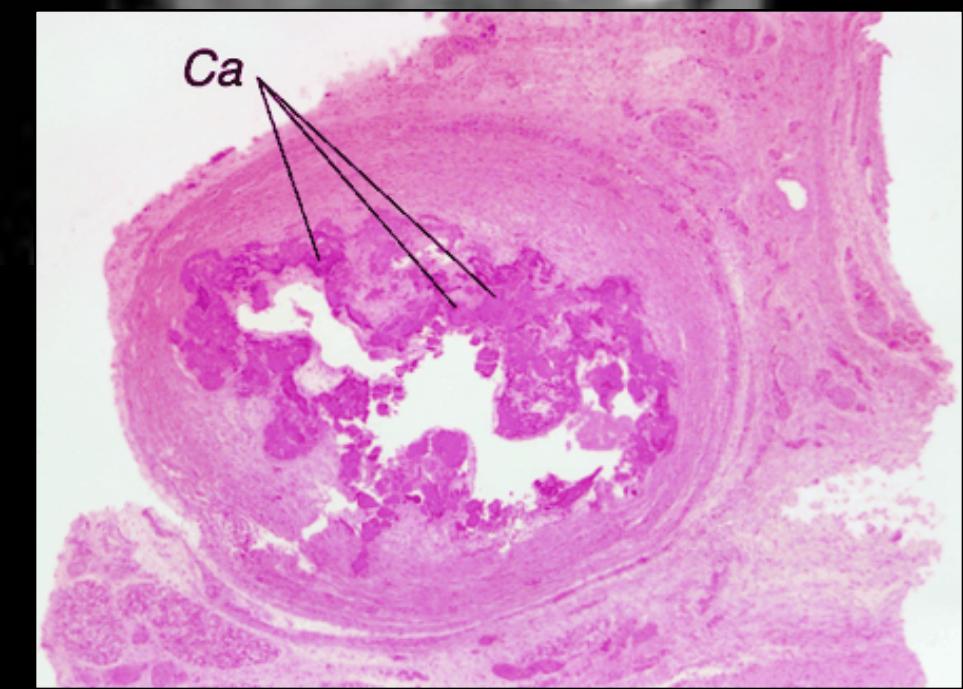
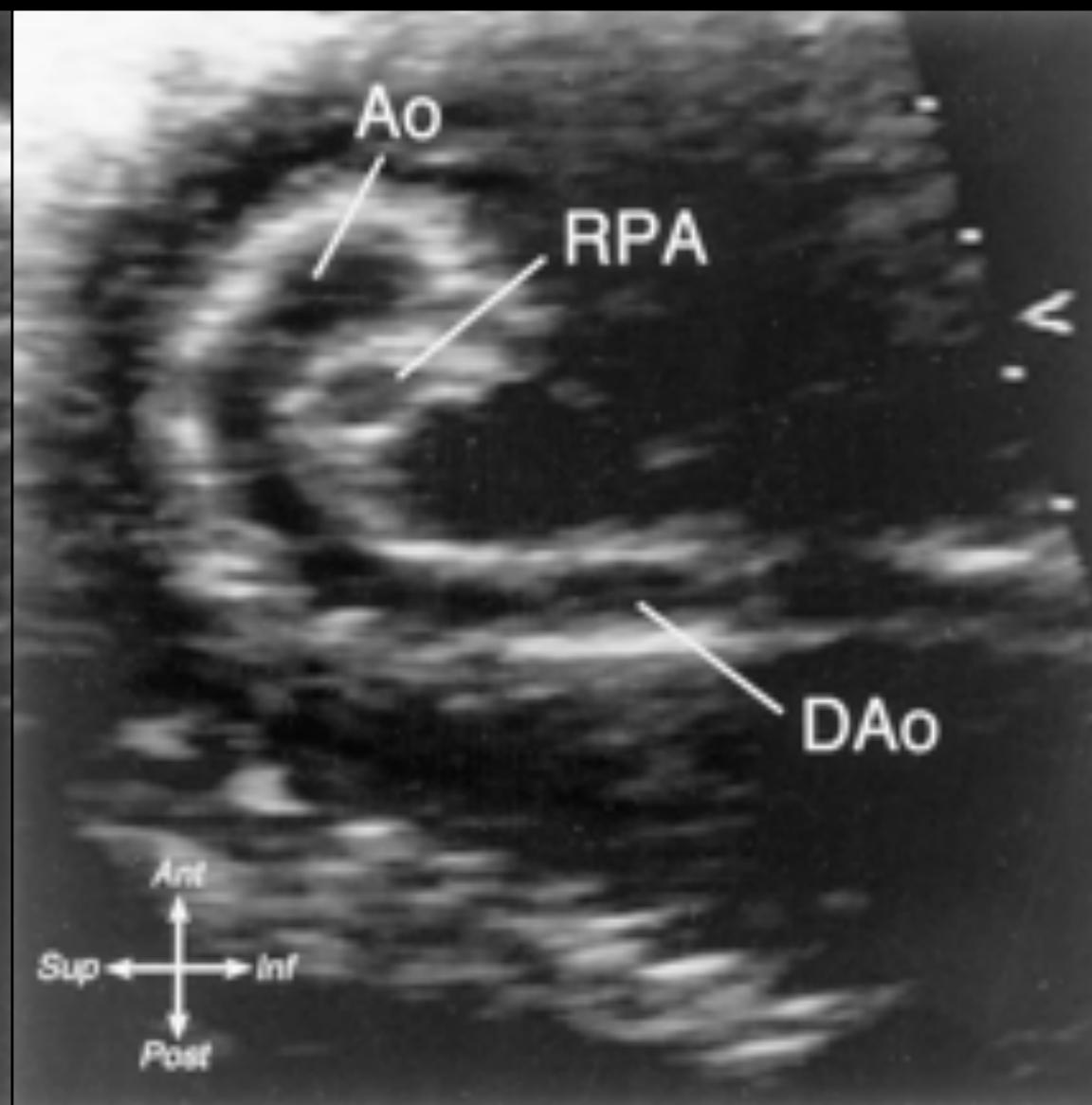


# Ischemic cardiomyopathies



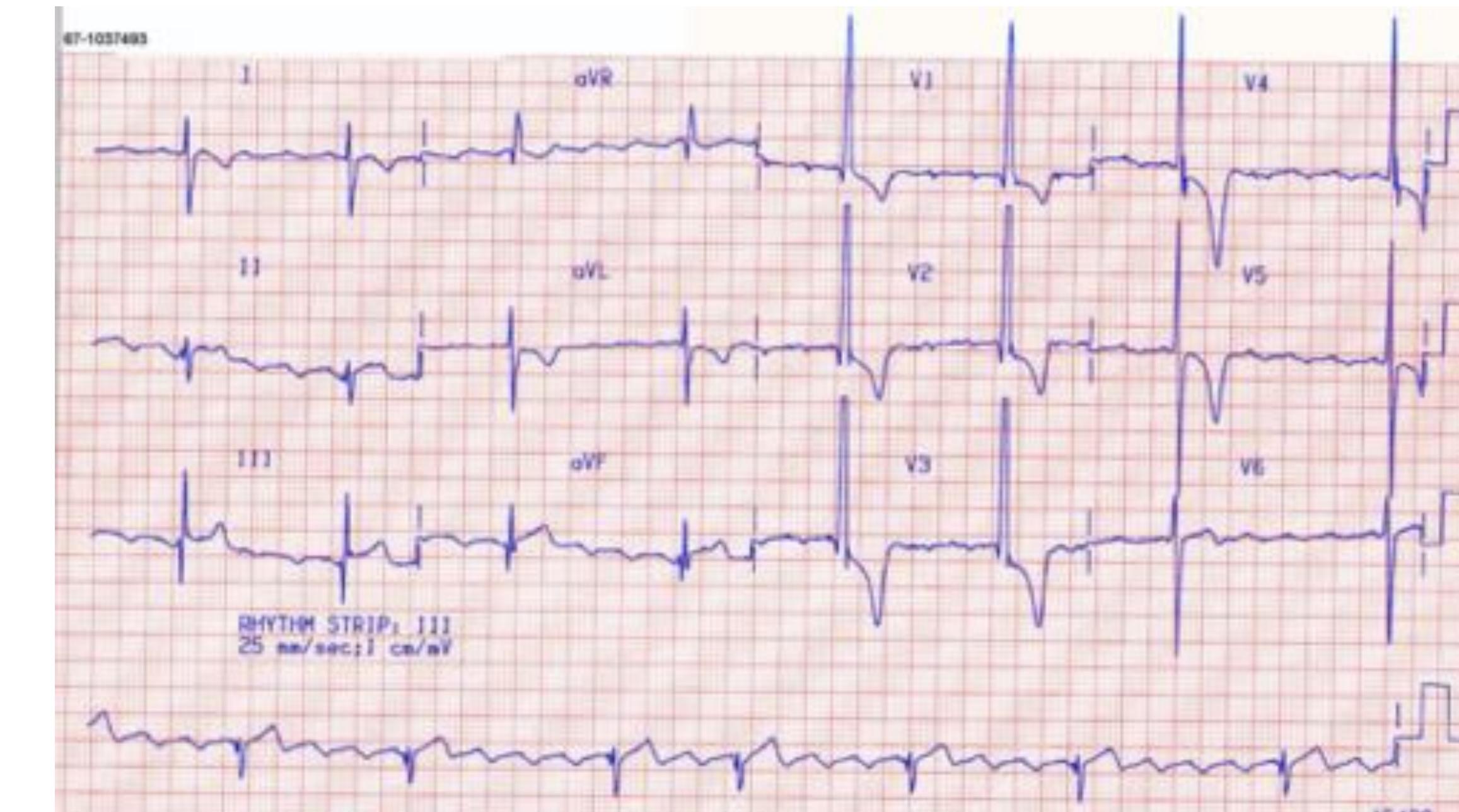
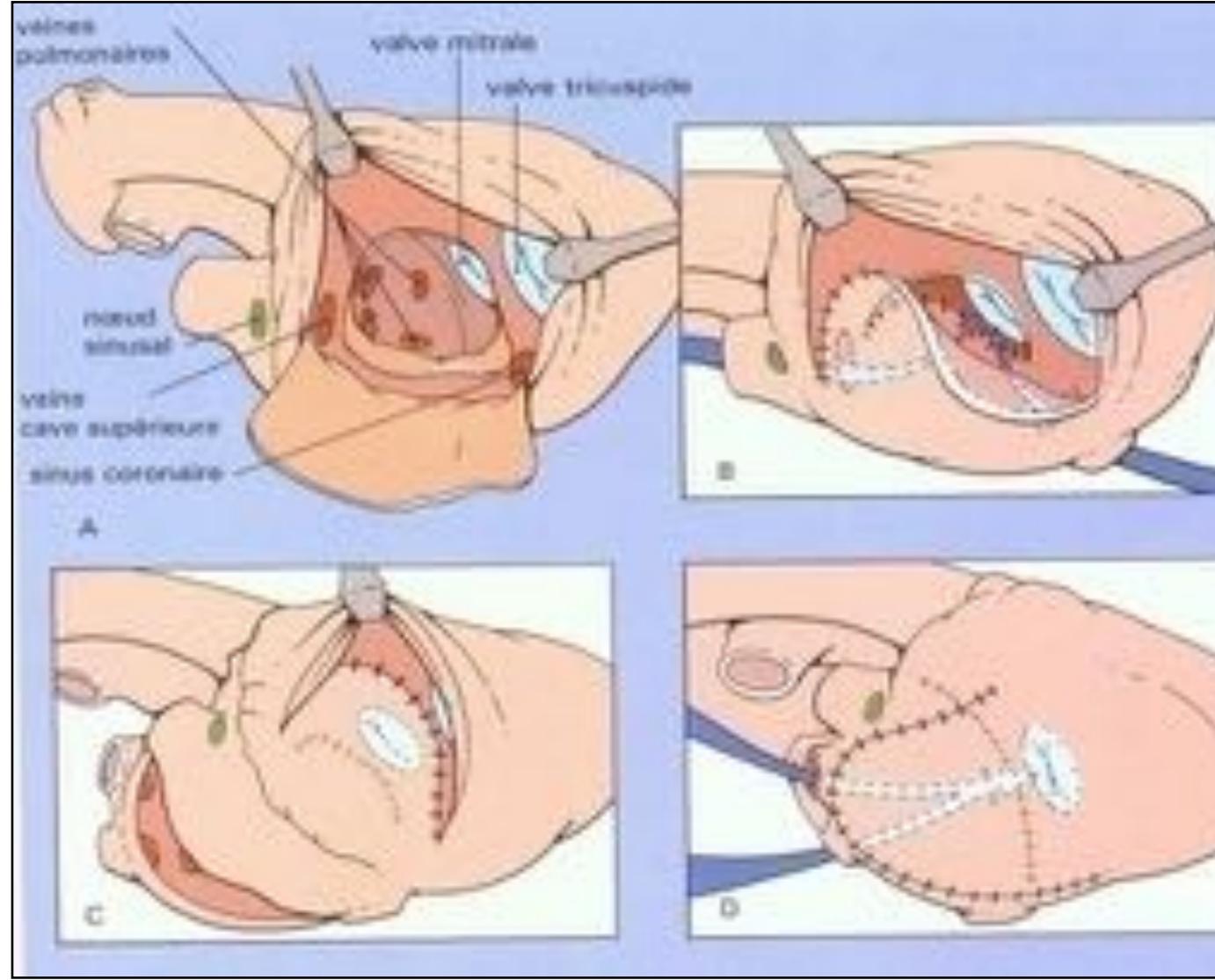
ALCAPA-Main stem atresia  
Post-operative  
TGA  
Kawasaki disease  
Hypercholesterolemia  
GACI

GACI



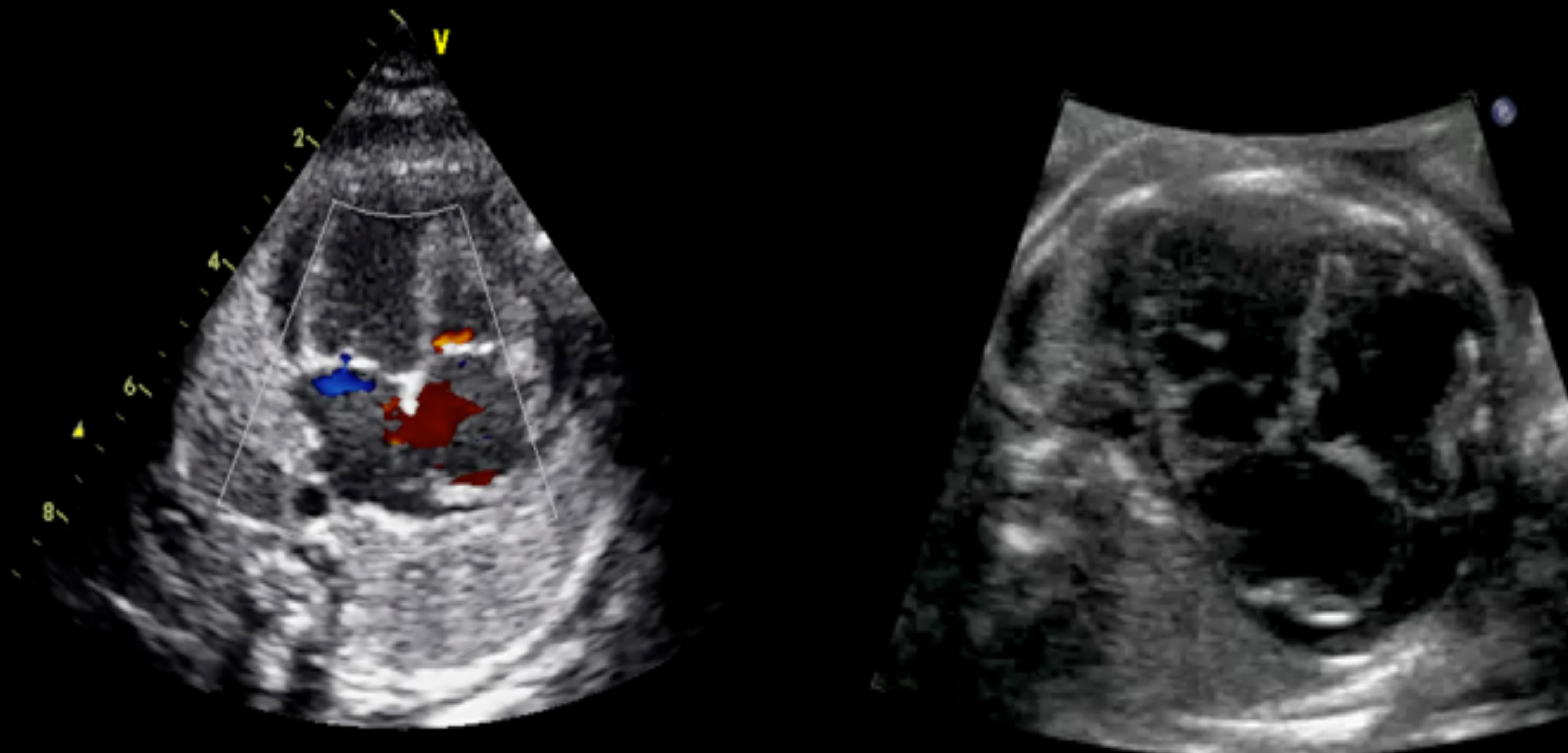
# Arrhythmic cardiomyopathy

- Supraventricular tachycardia of the newborn
- Booby-traps
  - Atrial arrhythmias after atrial correction of TGA
  - Arrhythmias after TCPC



# Arrhythmic cardiomyopathy fetal

*JT/AVB*



# Aetiology of dilated cardiomyopathies

(continued)

## Drugs

Antineoplastic drugs Anthracyclines; antimetabolites; alkylating agents; Taxol; hypomethylating agent; monoclonal antibodies; tyrosine kinase inhibitors; immunomodulating agents  
Psychiatric drugs Clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants.

## Infection

Viral (including HIV), bacterial (including Lyme disease), mycobacterial, fungal, parasitic (Chagas disease)

DCM caused by infectious myocarditis.

## Auto-immune diseases

Giant-cell myocarditis (GCM) Multinucleated giant cell;

Inflammatory DCM DCM caused by biopsy-proven, non-infectious myocarditis

Polymyositis/dermatomyositis; Churg–Strauss syndrome; Wegener's granulomatosis; systemic lupus erythematosus, sarcoidosis

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The vocabulary problem  
*Matriochka*



# Infectious cardiomyopathies

Viral myocarditis

Lyme disease

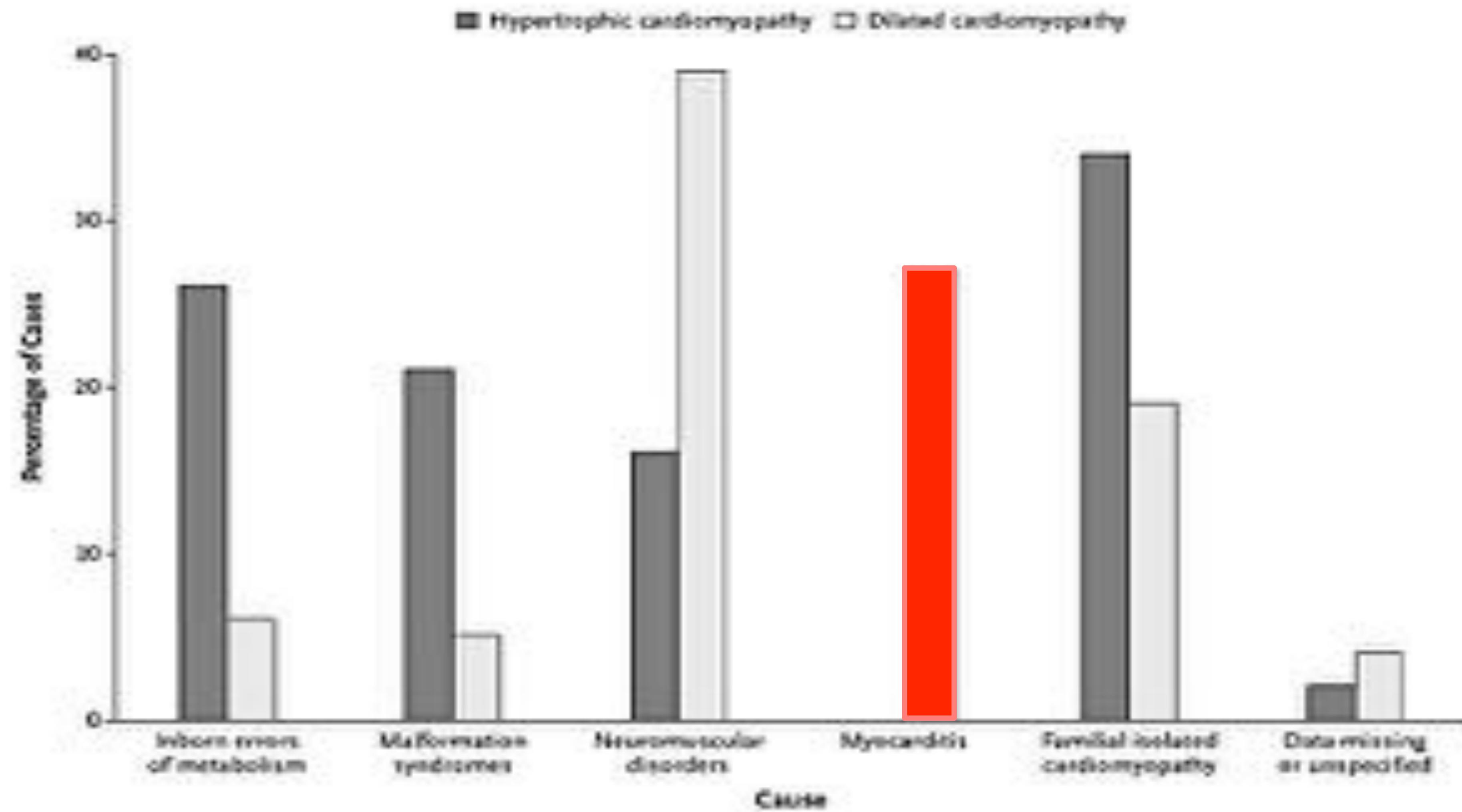
Chagas disease

HIV

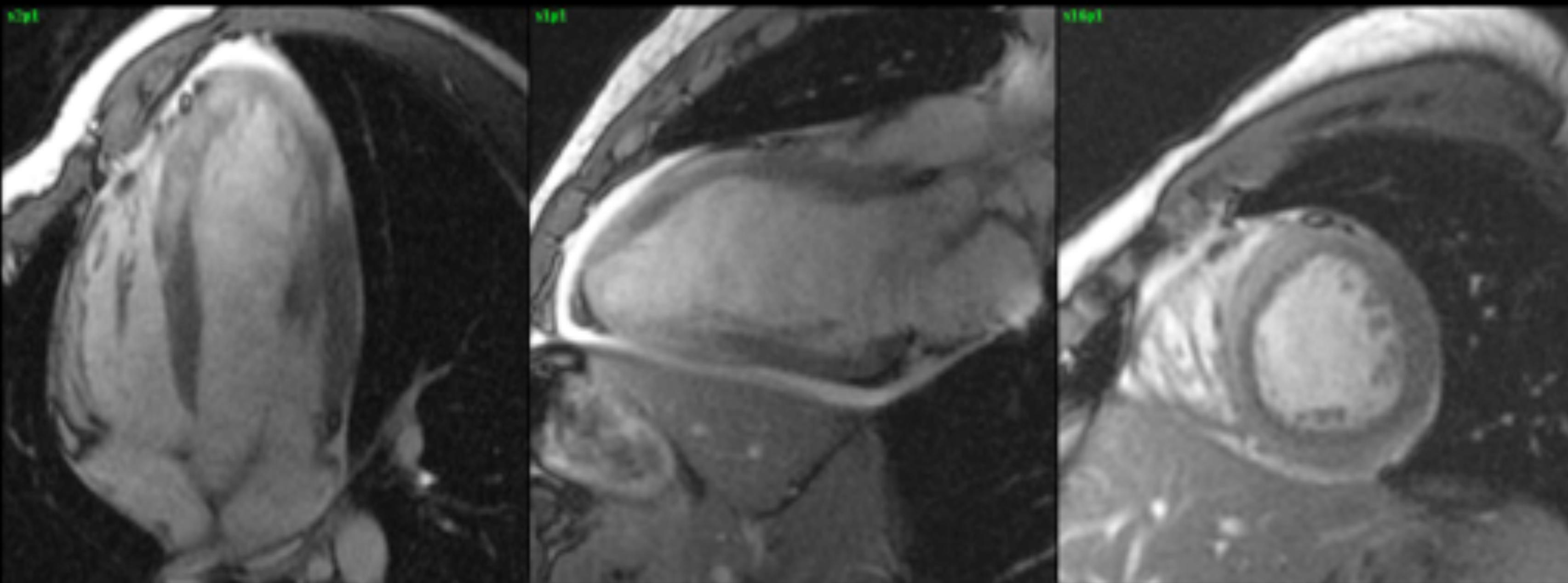
Toxoplasmosis

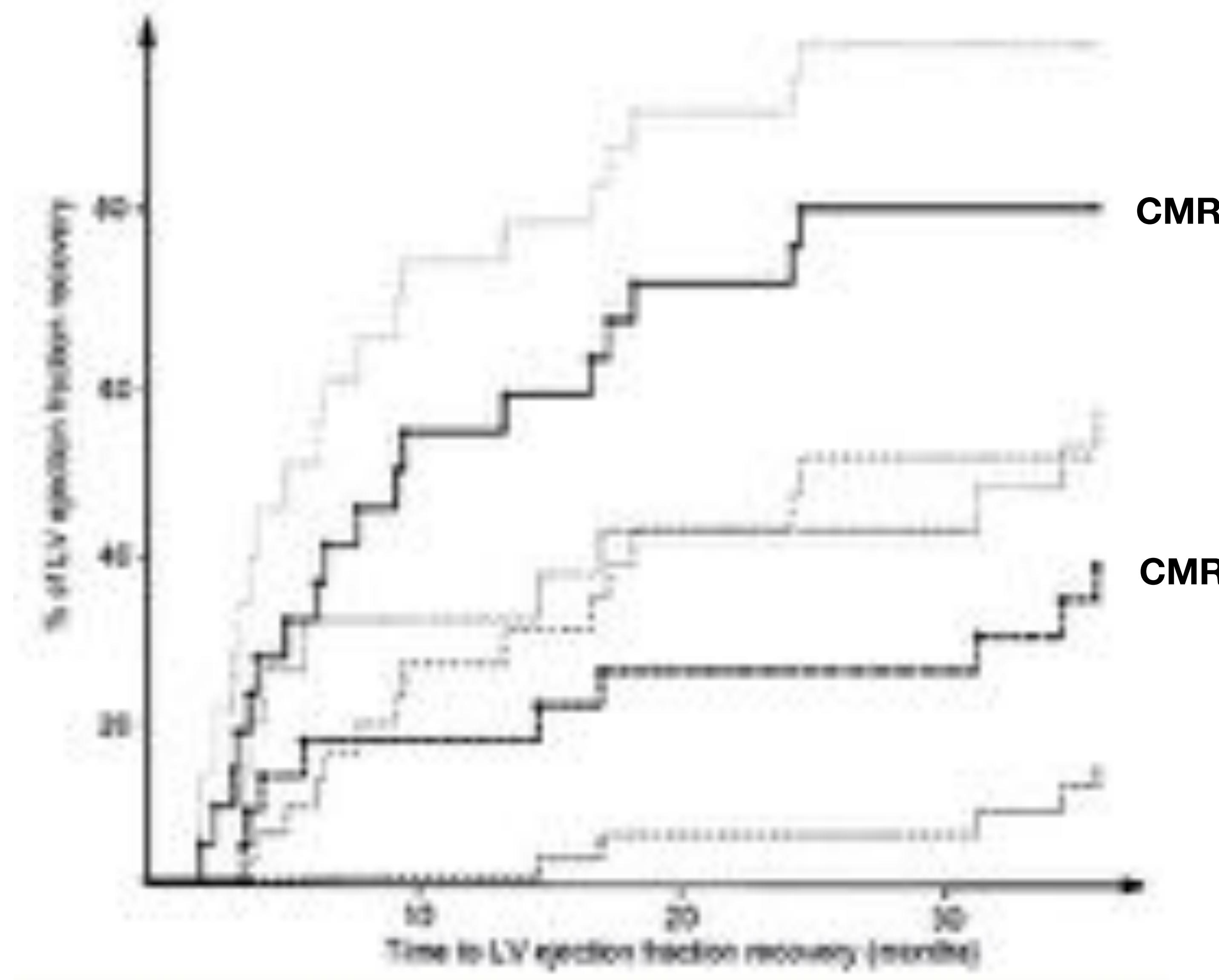
Rheumatic

# Myocarditis in children



# Myocarditis

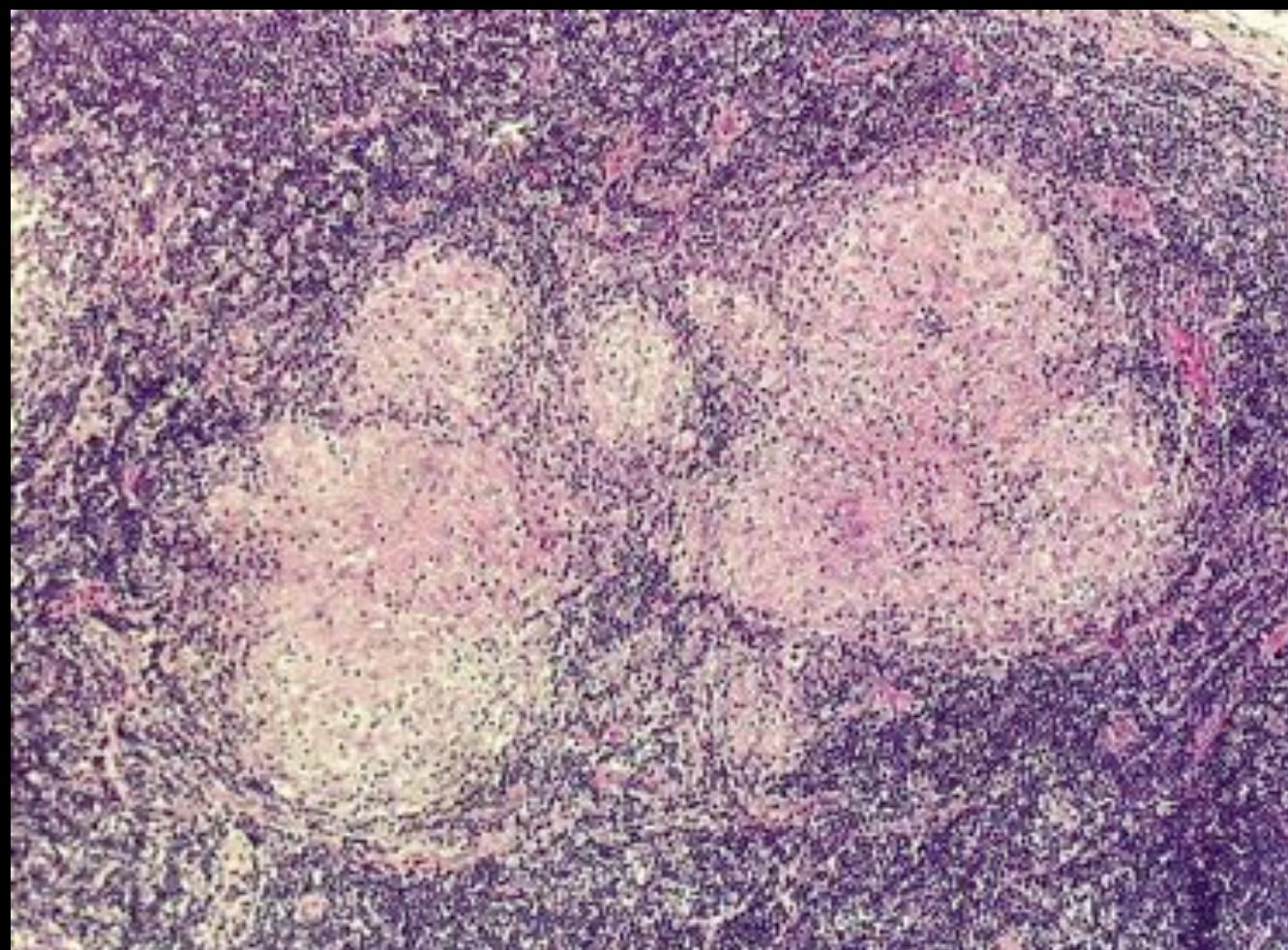




**Time to recovery of left ventricular function in CMR-positive group (full line) and in the CMR-negative group (dotted line) with 95% CI (grey dotted lines).**

# Pediatric vasculitis and myocardial involvement

*Takayasu*



Multifactorial  
Systemic hypertension  
Ischemia  
Inflammation

Ebesberger U et al. Images in Cardiology 2013  
Mavrogeni S et al. Int J Cardiol 2011;148:223-4

# Myocardial involvement/myocarditis in childhood vasculitis

*Systemic onset  
Juvenile Idiopathic  
Arthritis  
Still's disease*



*Kawasaki disease*



*MIS-CA*



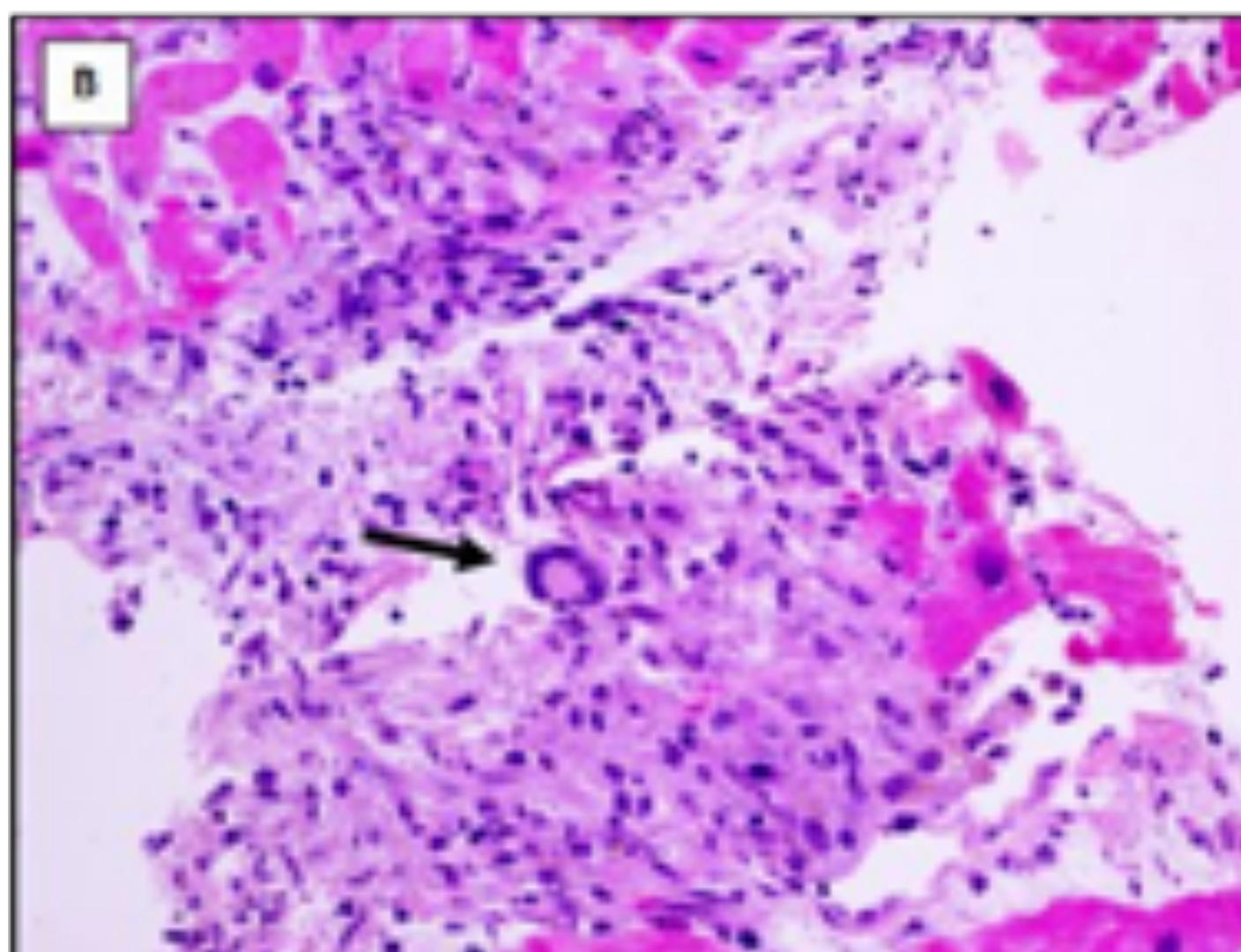
Bindstadt BA et al. Pediatrics 2005;116:e89-e93

Mondal R et al. Indian Heart J 2013;80:67-9

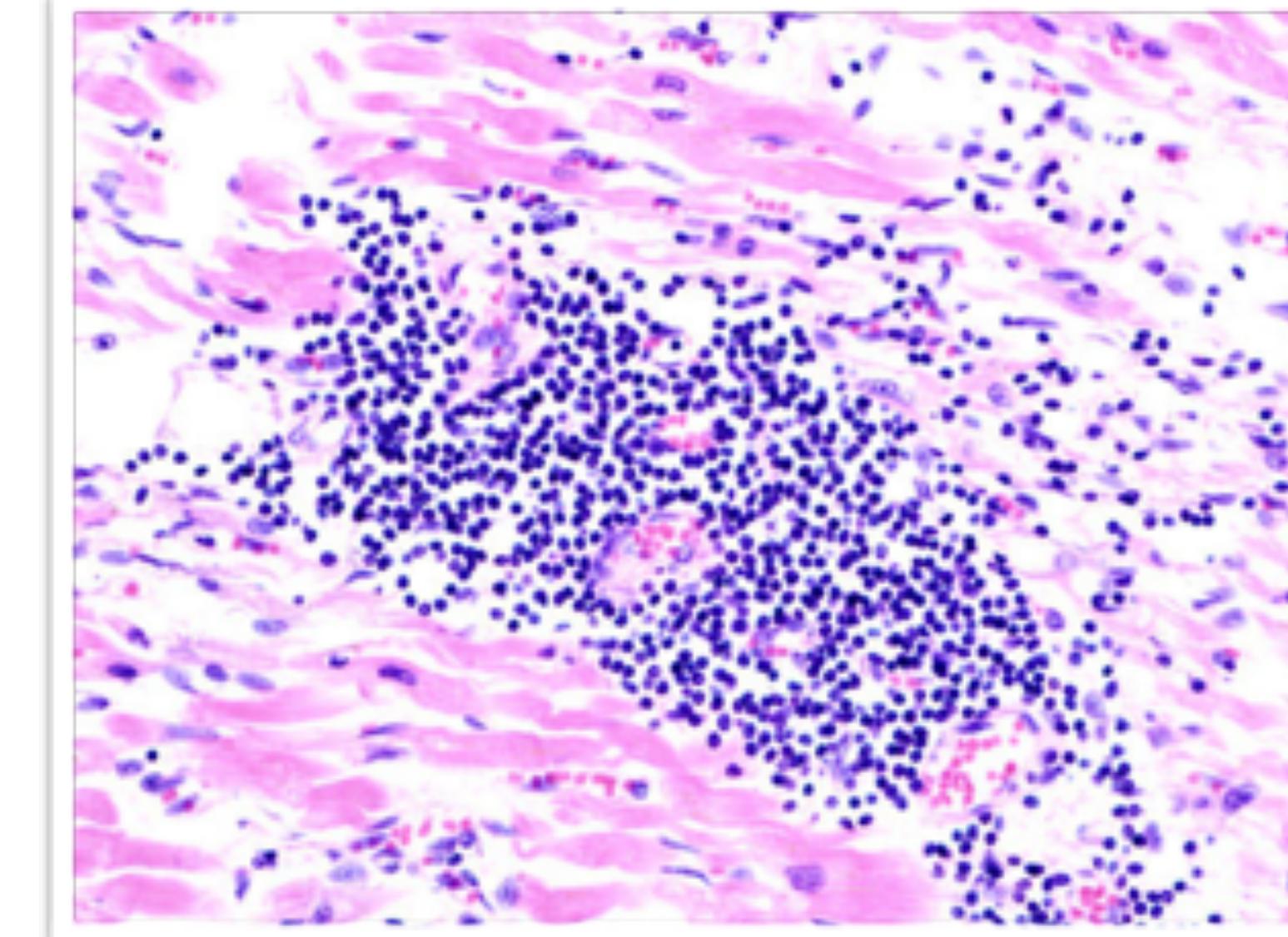
Harada M et al. Histopathology 2012;61:1156-67

Belhadjer Z et al. Circulation 2020

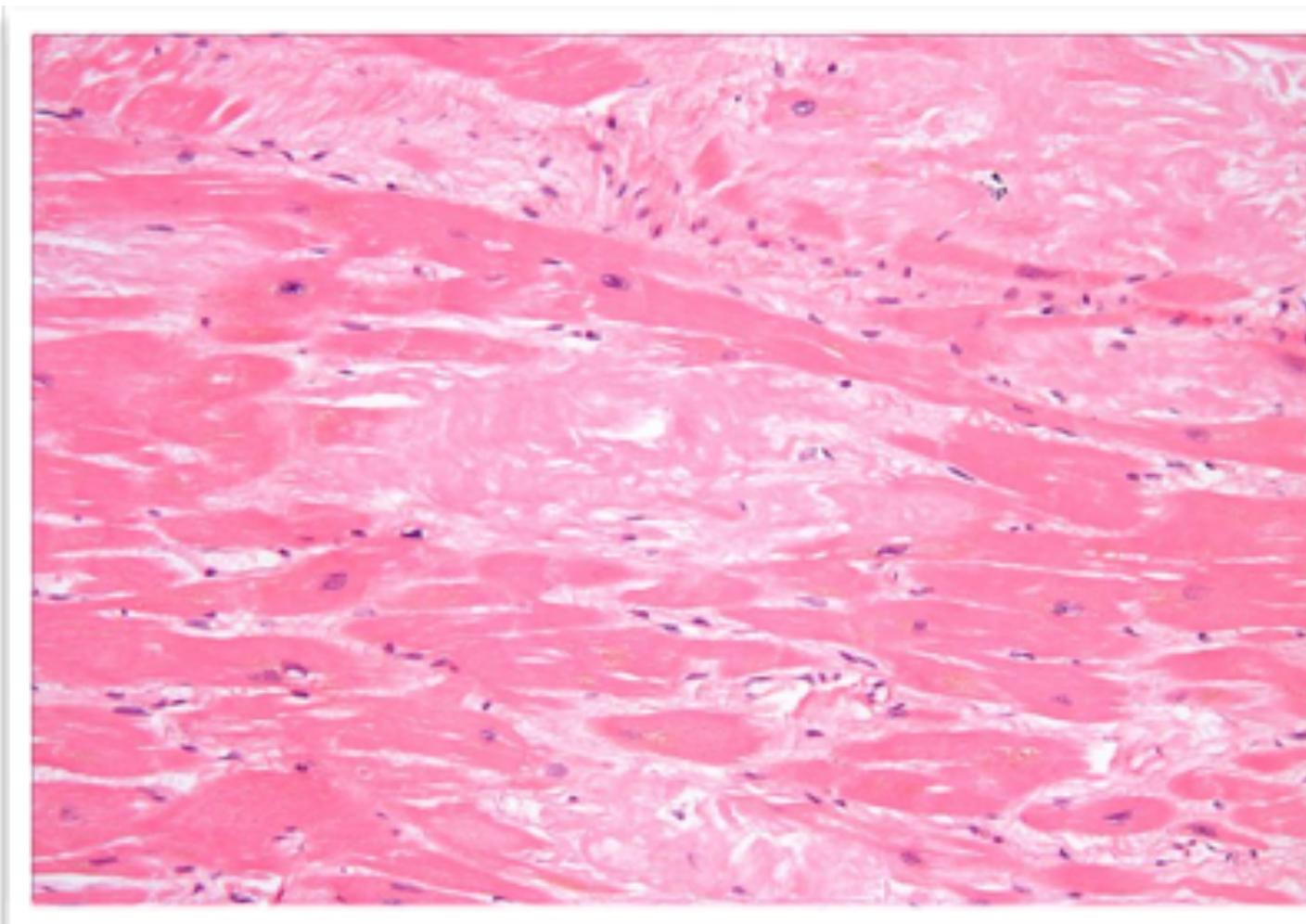
# Auto-inflammation, immunodeficiency and metabolic disorders



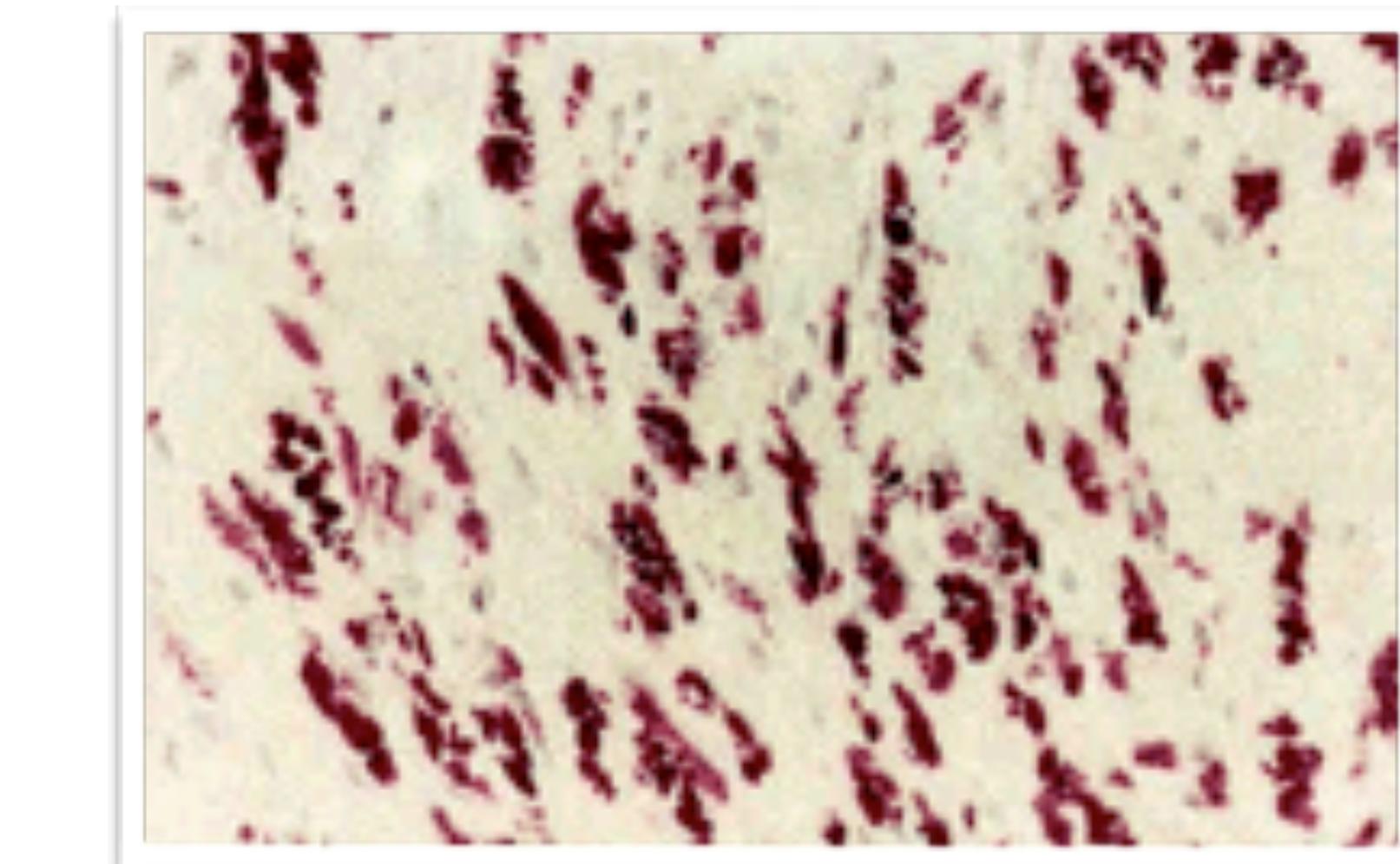
Giant cell myocarditis



Viral myocarditis



Amyloidosis



Amylopectinosis in Glycogenosis type IV-Andersen's disease

# Toxic

- Anthracyclines
- Radiations

# Neuromuscular disorders

- Dystrophinopathies
  - Duchenne de Boulogne
  - Becker
- Emery-Dreyfus
- Laminopathies
- Steinert
- Friedreich

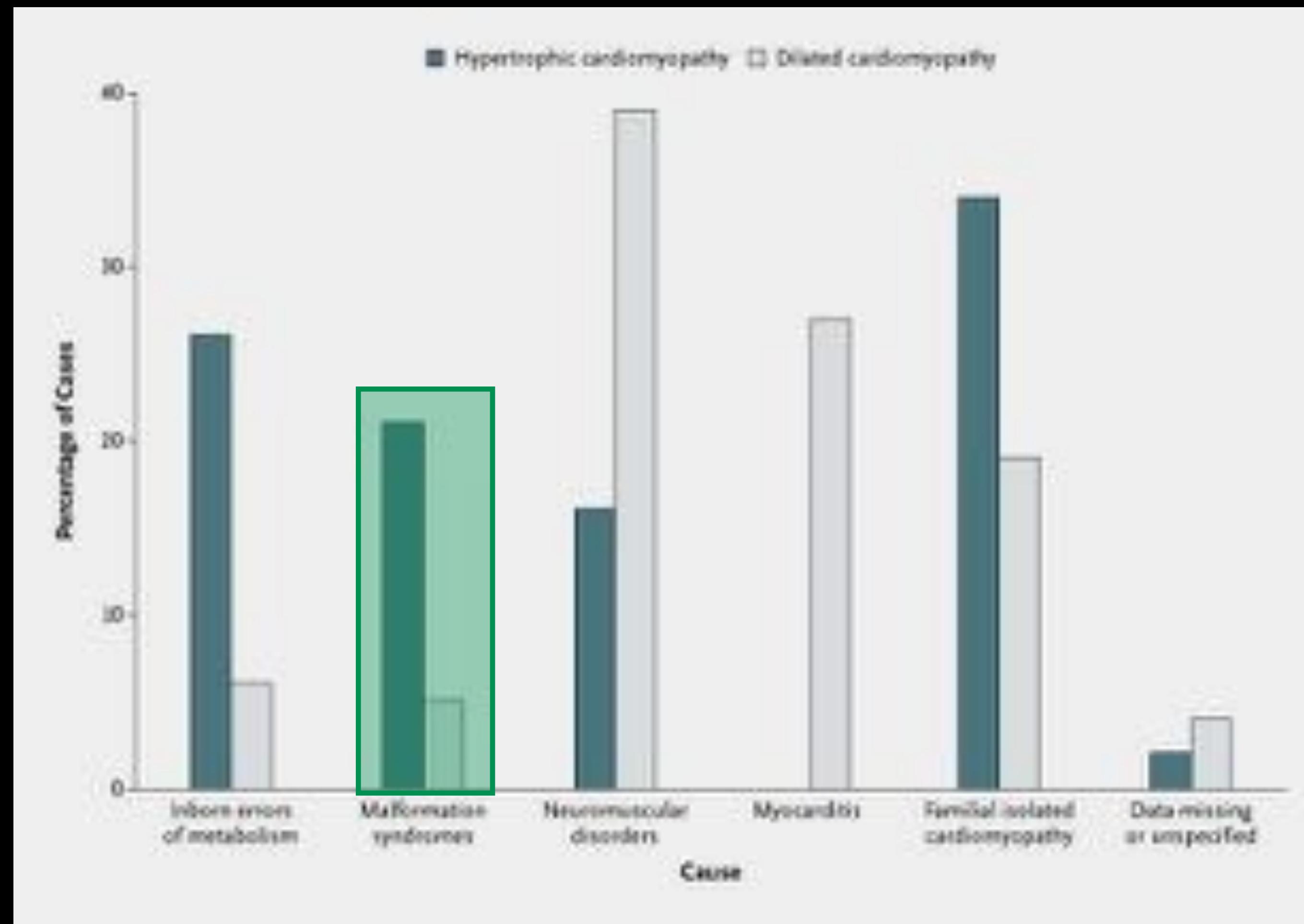


**First stop !**

# What have you done ?

- Clinical examination
- Medical history
- ECG
- Echocardiography
- Troponine
- MRI

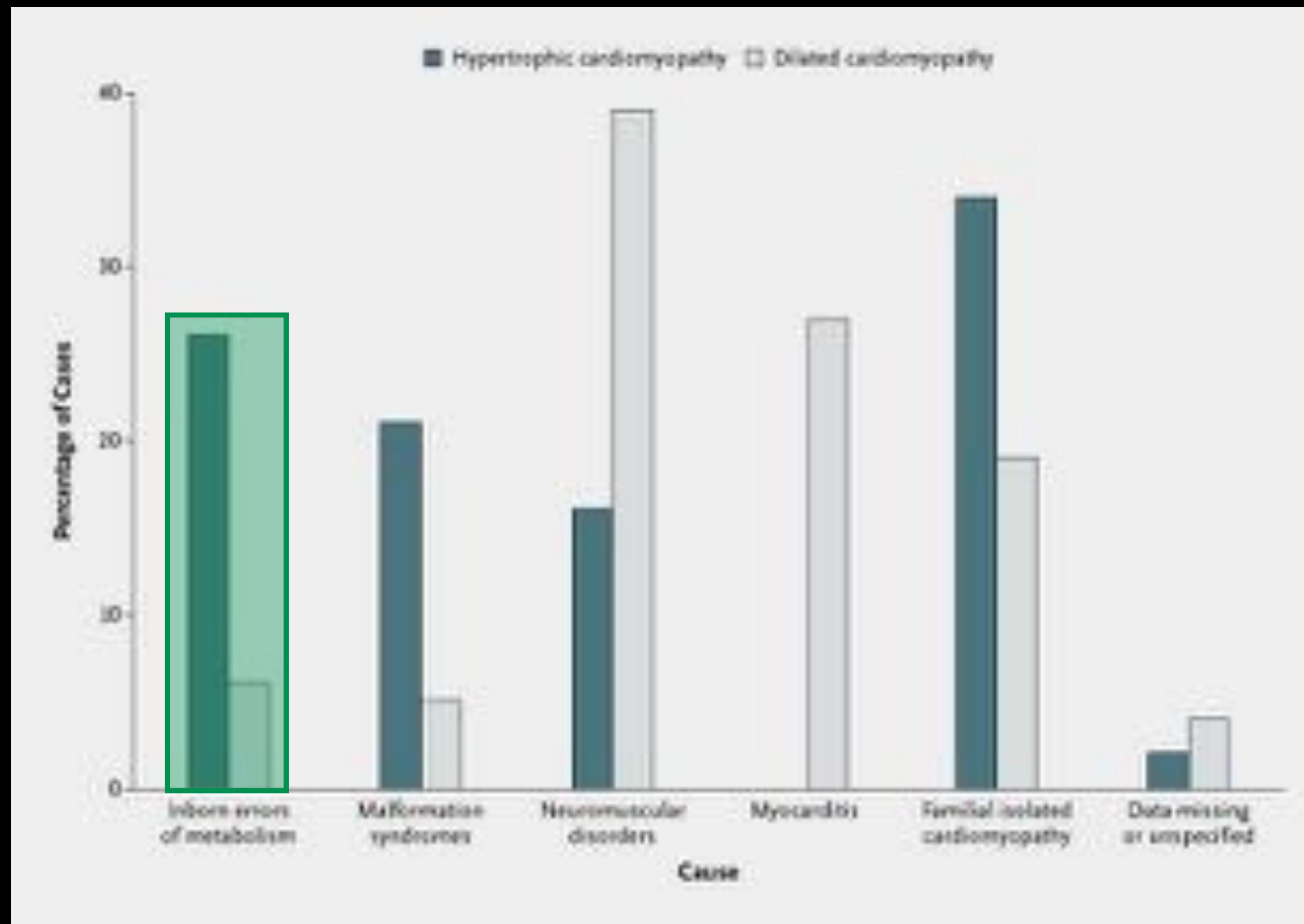
# Malformation syndromes and cardiomyopathies





**RASopathies**

# Inborn errors of metabolism and cardiomyopathies



# Cardiac involvement in IEM

- Cardiomyopathies
  - Storage diseases
  - Systolic dysfunction in energetic defects & intoxications
  - Phenotypic variability and atypical evolution of RC defects
- Arrhythmias
  - Triggered and automatic activities in intoxications
  - Facilitated conduction and accessory pathways in glycogenoses
  - Atypical AV blocks
- Valvular thickening in mucopolysaccharidoses
- Pericardial effusion in glycosylation defects
- Congenital heart defects<sup>1</sup>?

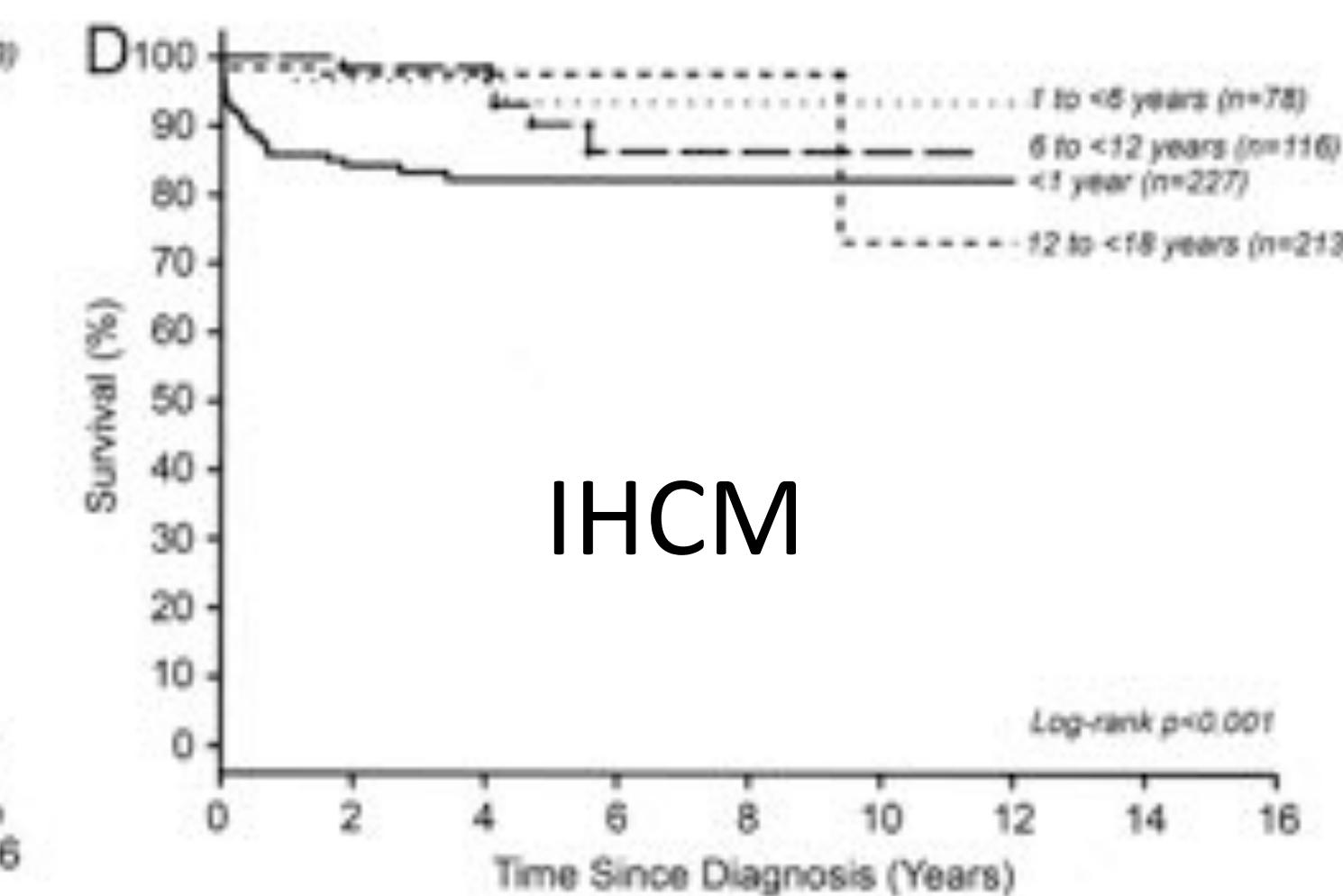
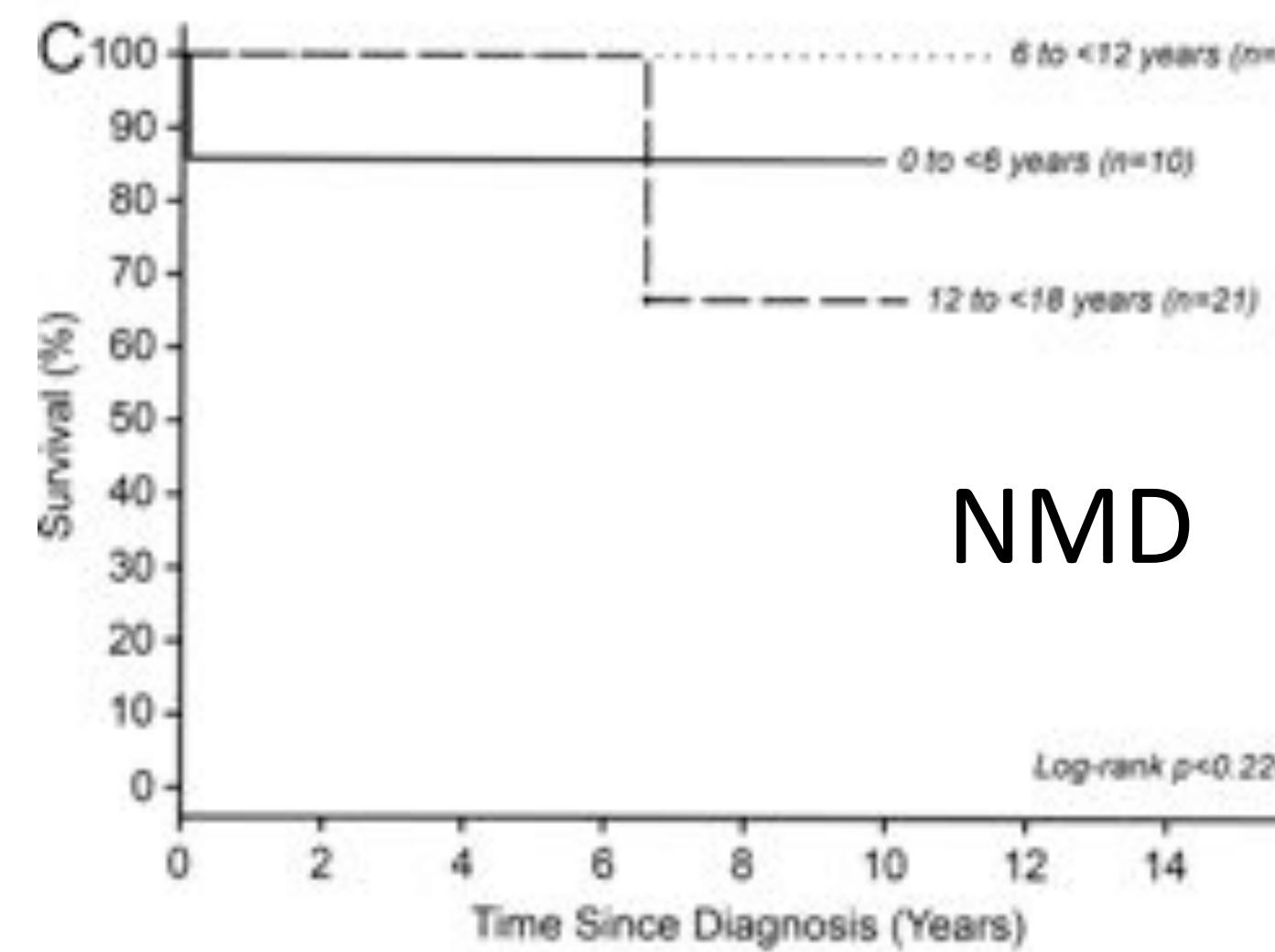
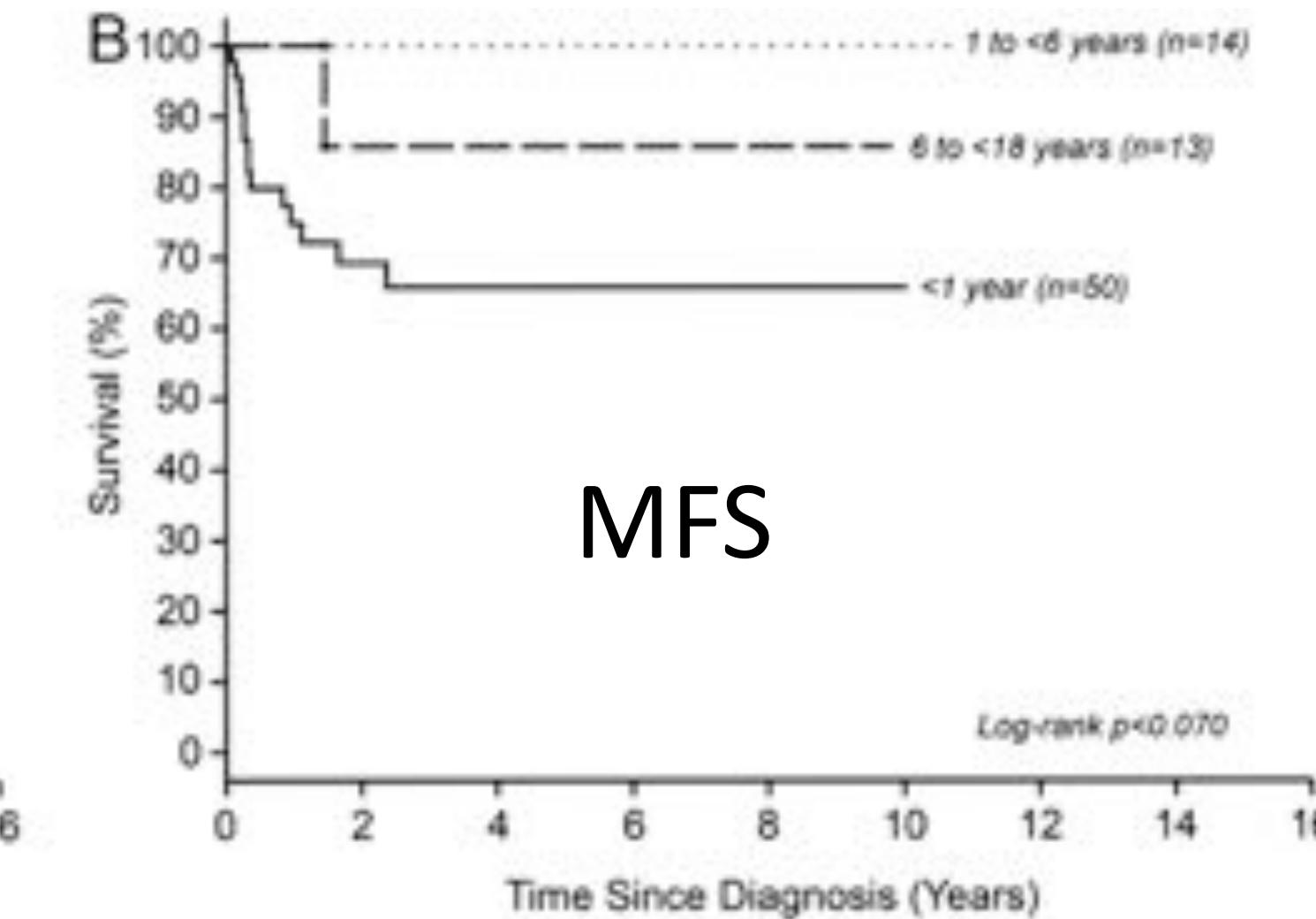
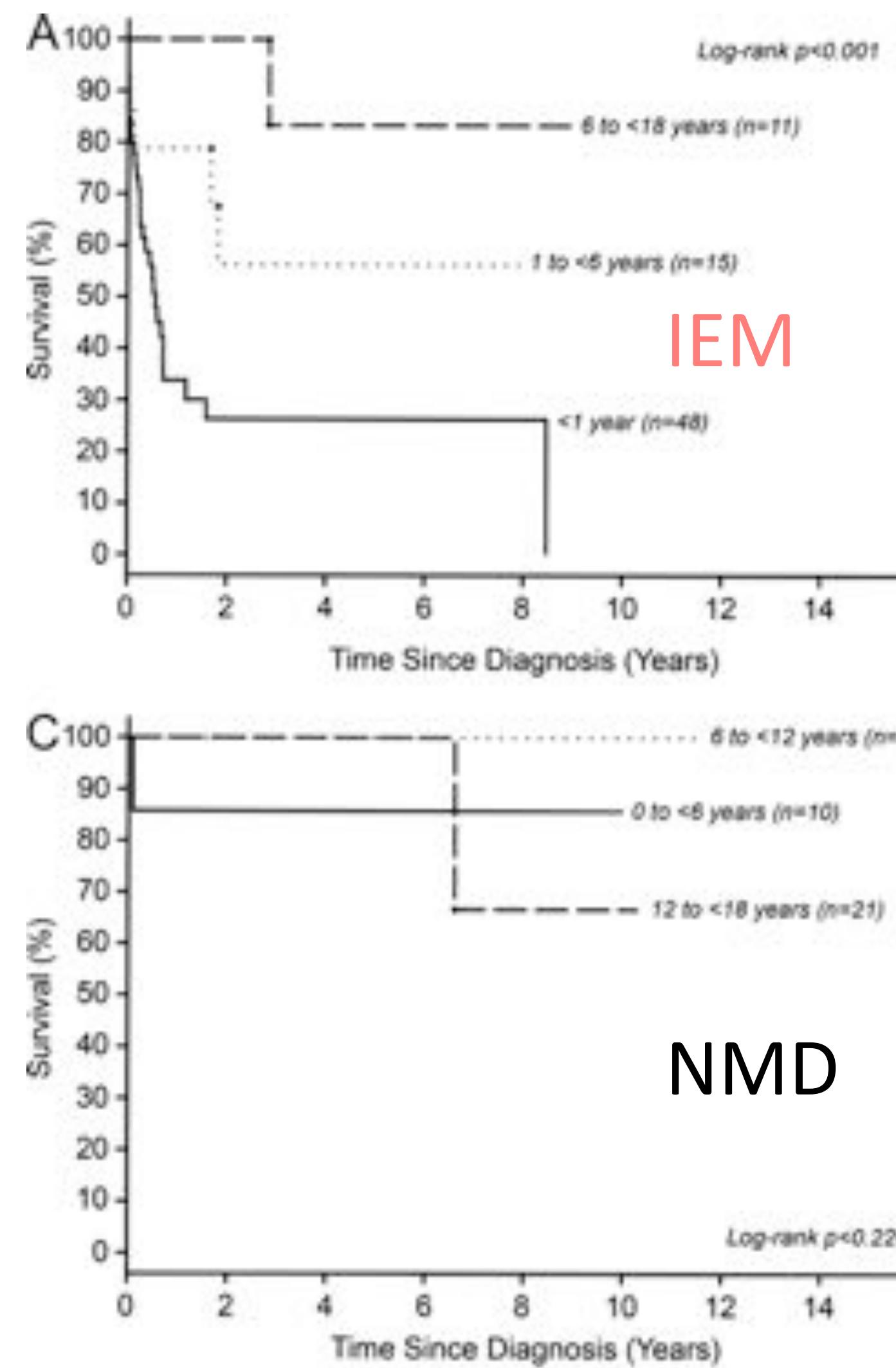
1-Romano S. et al. J Med Genet 2009.

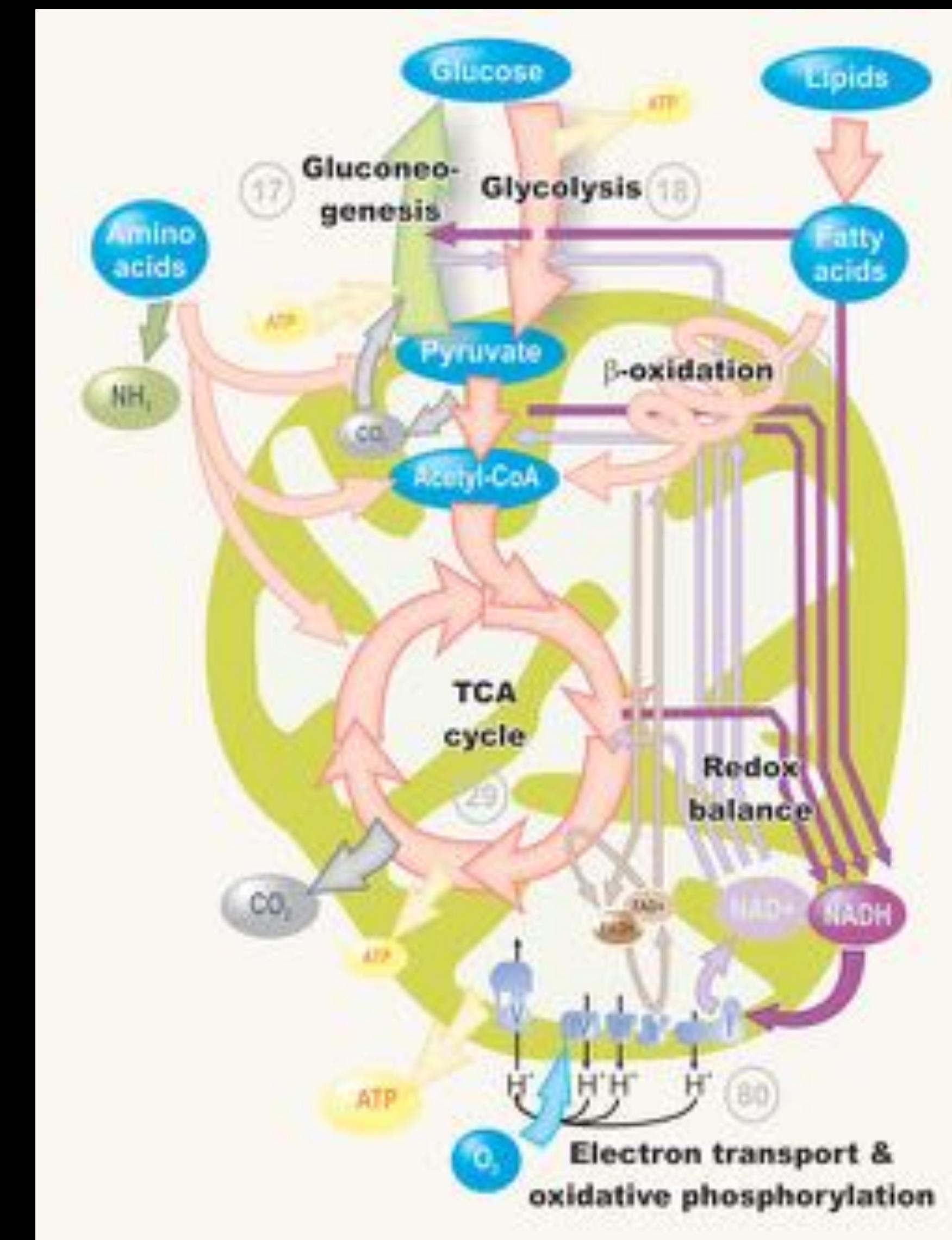
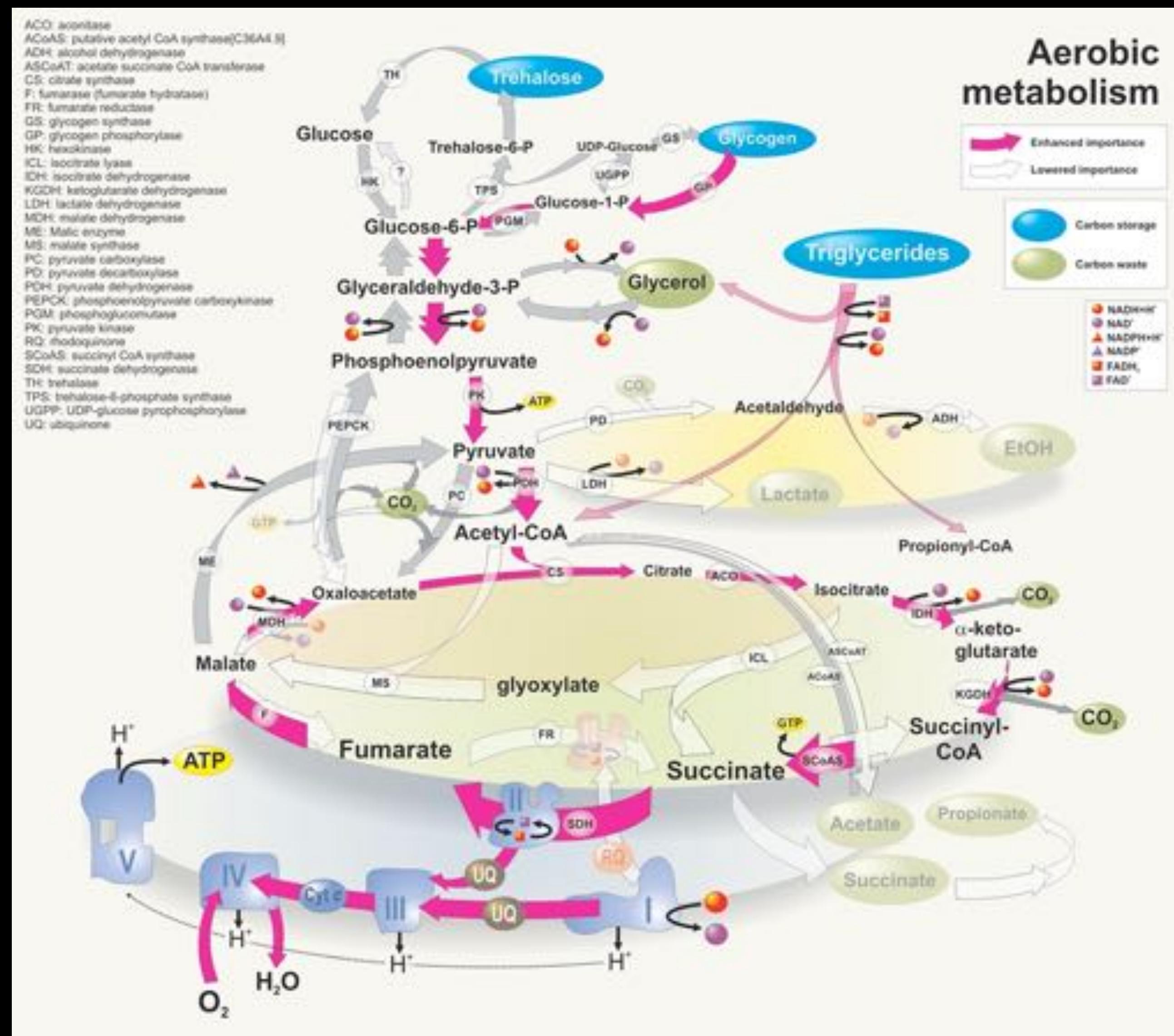
Conotruncal heart defects in three patients with congenital disorder of glycosylation type Ia (CDG Ia)

# **When should you think of metabolic cardiomyopathy ?**

- Family history of sudden death or unexplained death in infancy
- Multisystemic disease
- Changing phenotype
- Severe hemodynamic compromise with mild alteration of LV function
- Atypical anomalies of ECG : left bundle branch bloc, AVB, ventricular tachycardia

# Survival rates according to cause of HCM





# Cardiac metabolism for pediatric cardiologists

Substrate accumulation (non toxic):  
storage diseases

Lysosomal : HCM, valves  
Peroxisomal  
Reticulum: glycosylation

Substrate

Metabolism

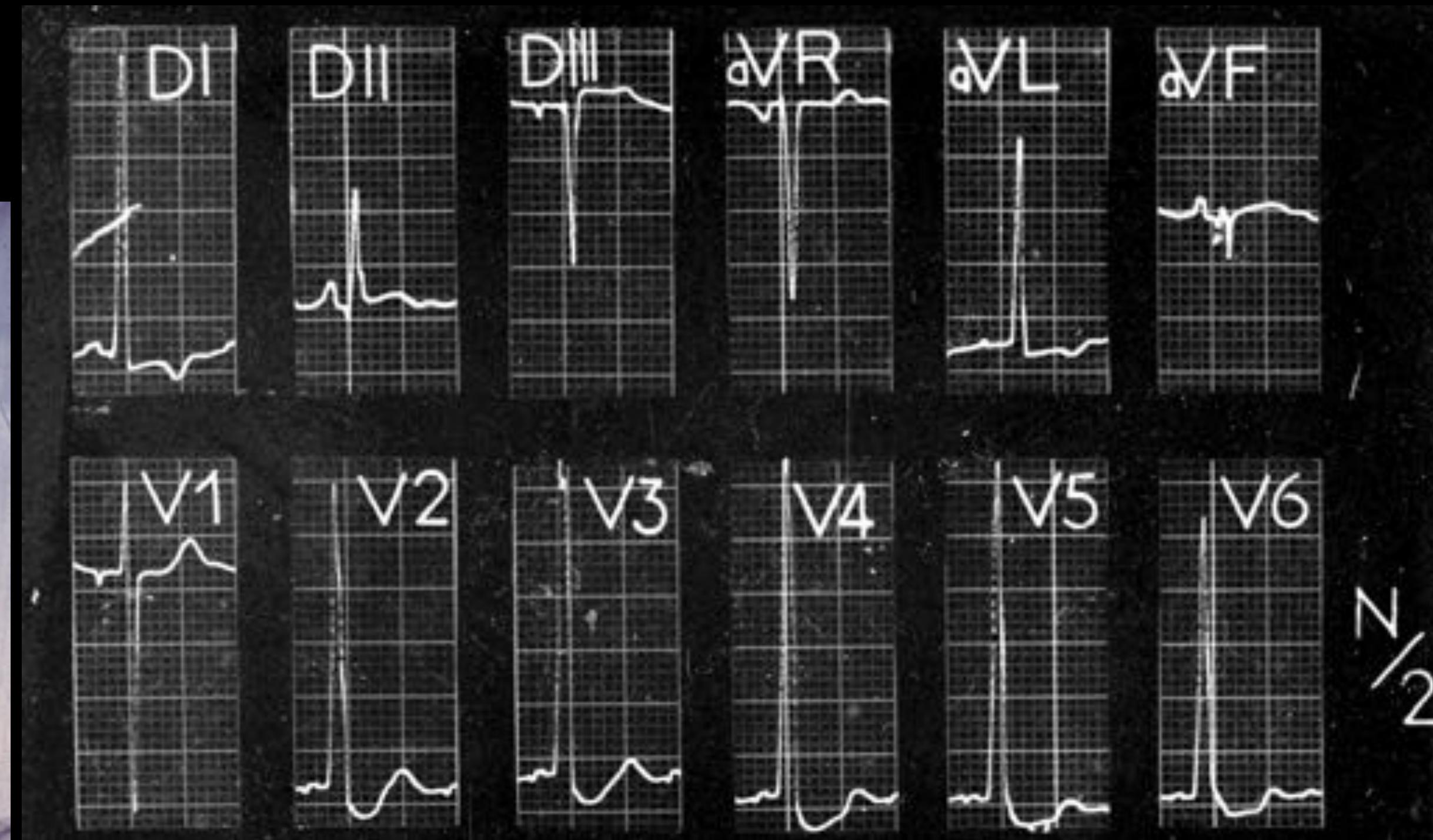
Product

Organic aciduria

Fatty-acid oxydation  
Respiratory chain  
Krebs cycle  
Glycogenoses

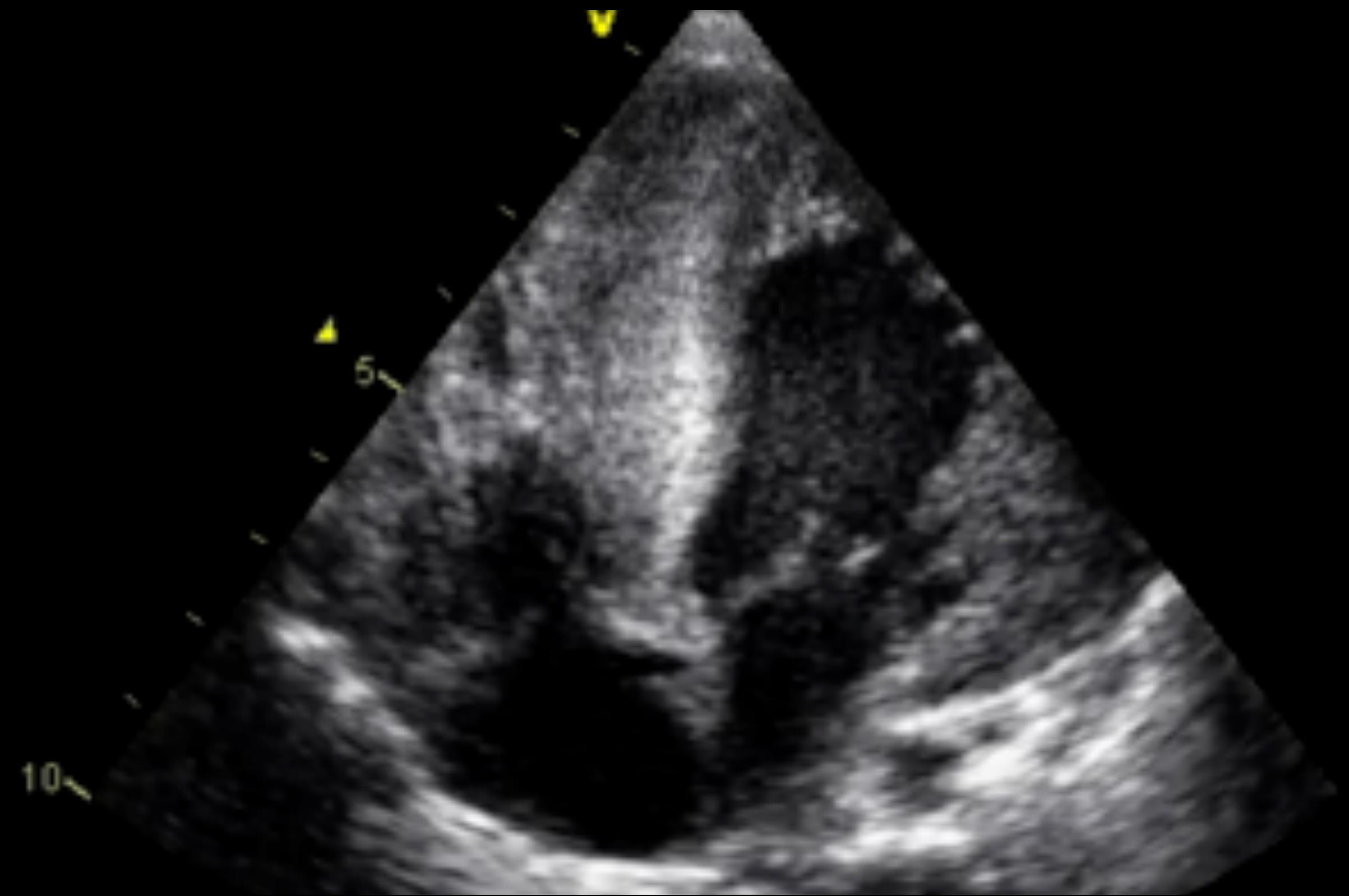
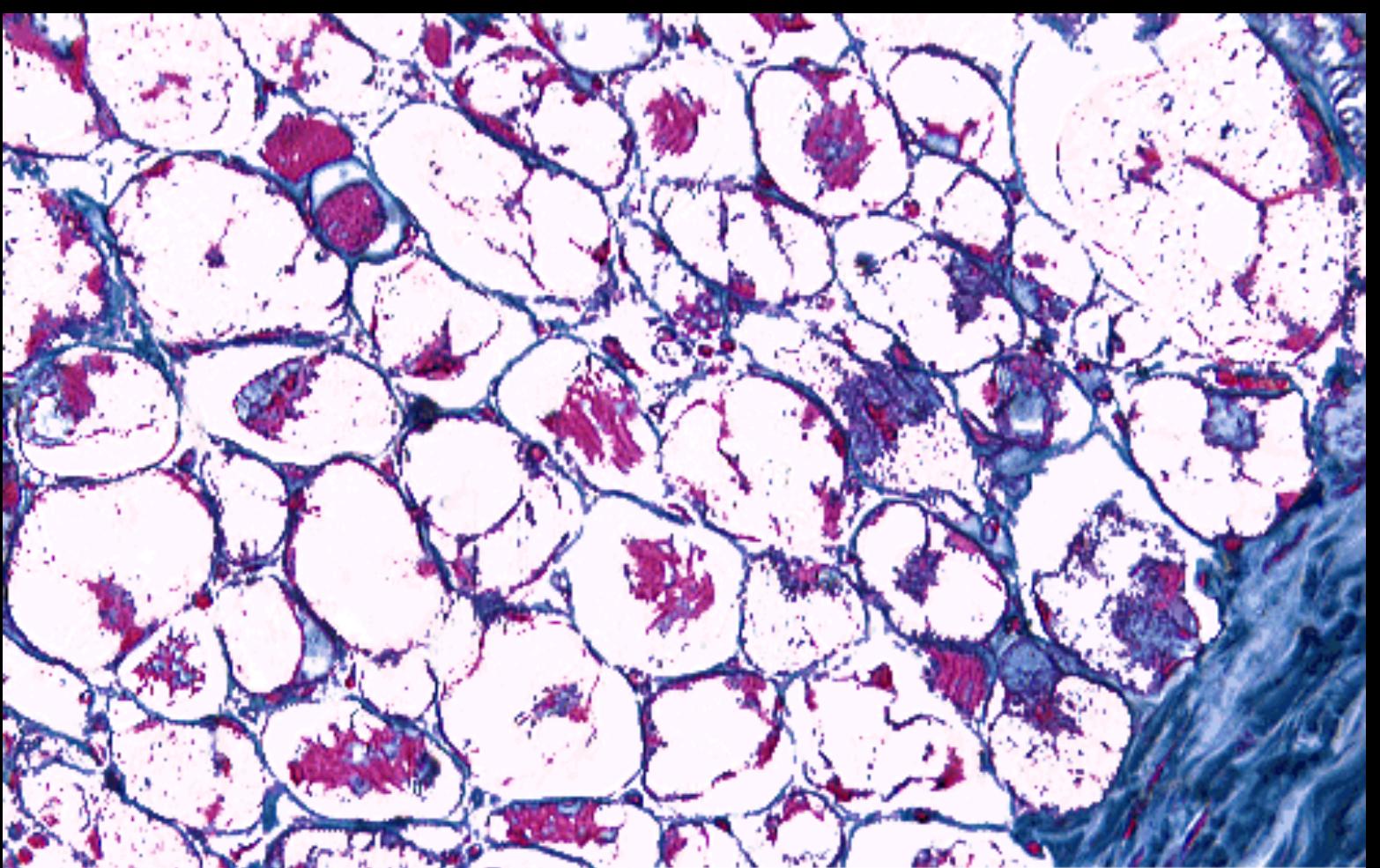
Substrate accumulation (toxic):  
intoxication diseases

Product decrease or absent :  
energetic defects

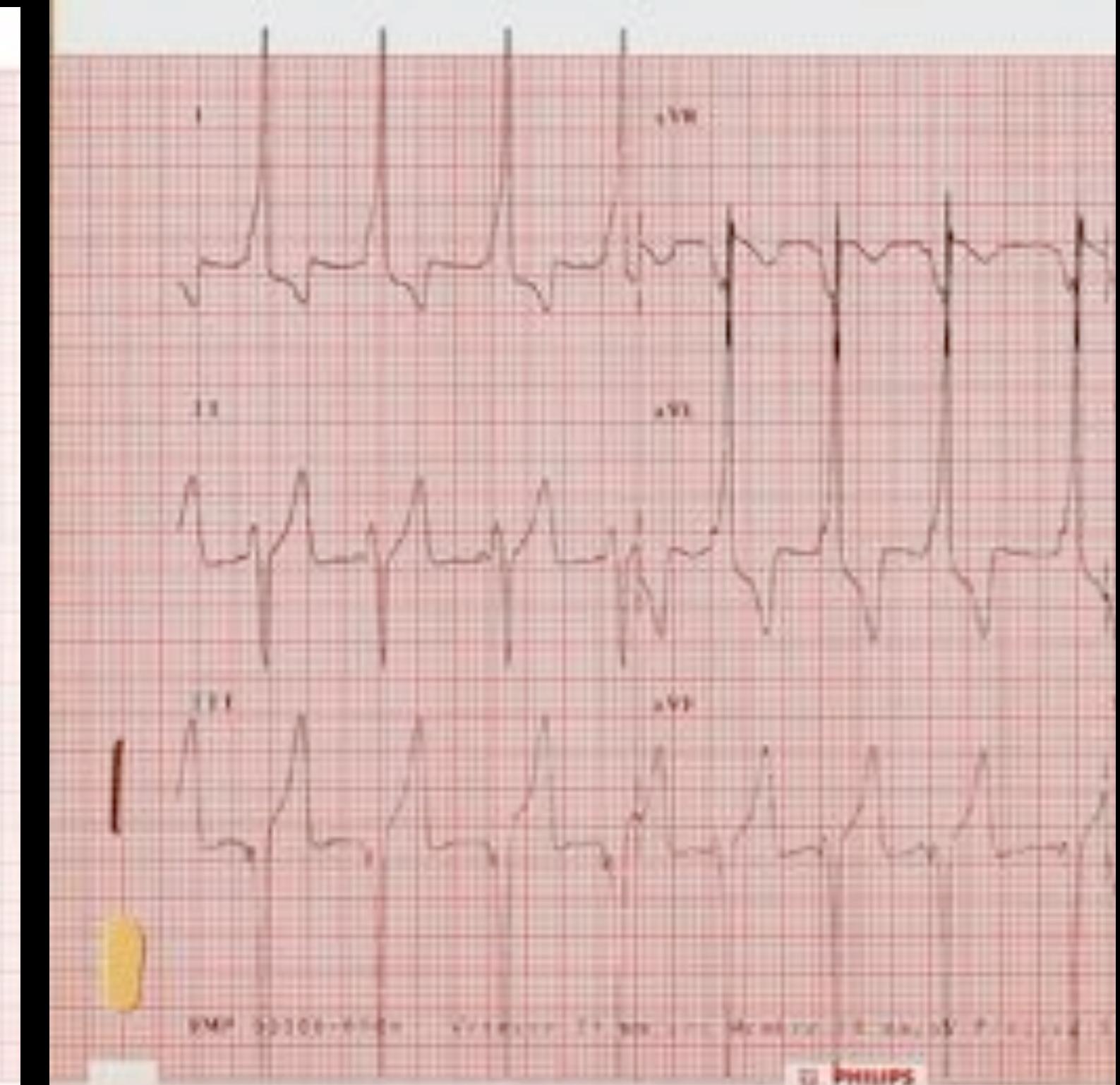
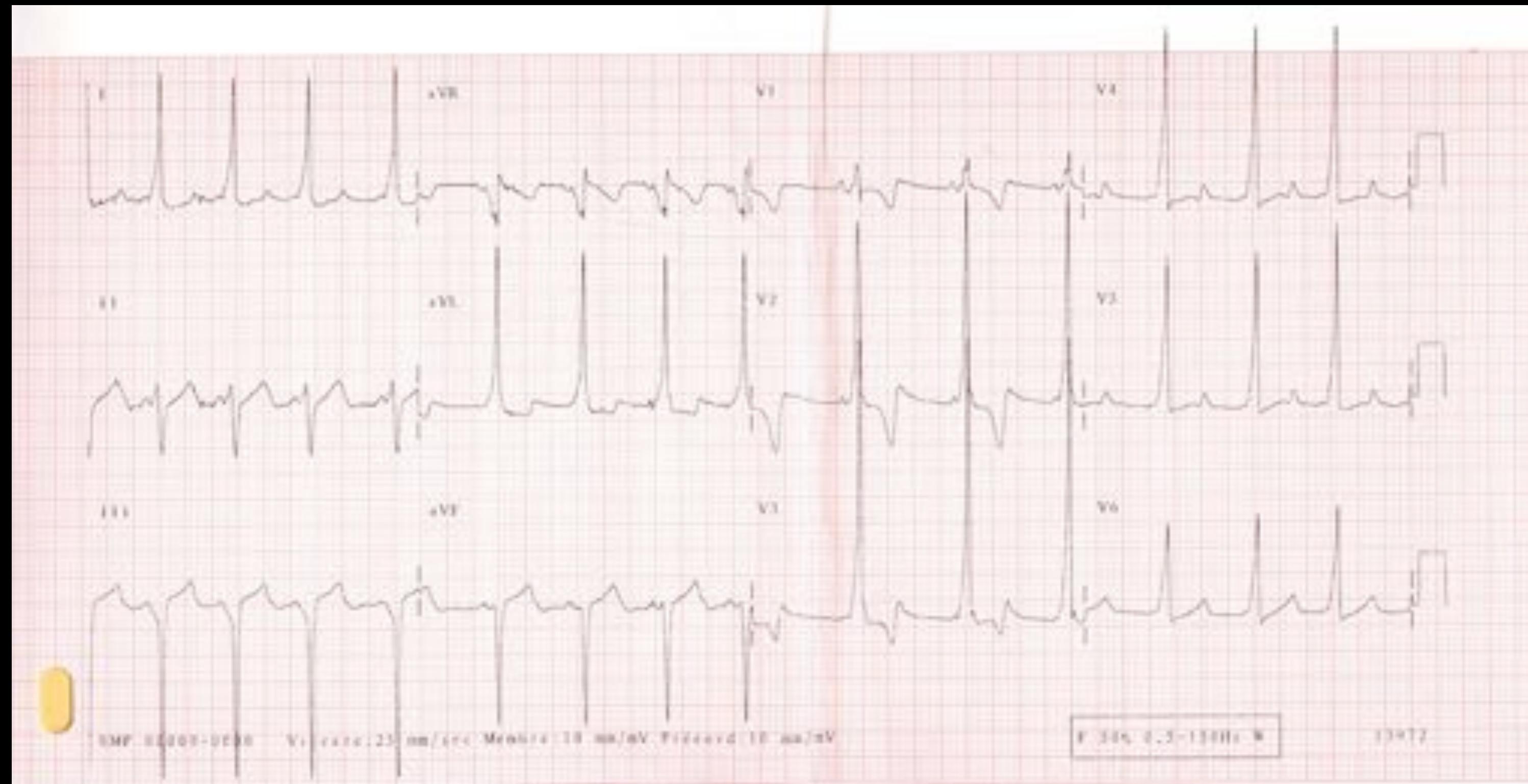


Pompe's disease

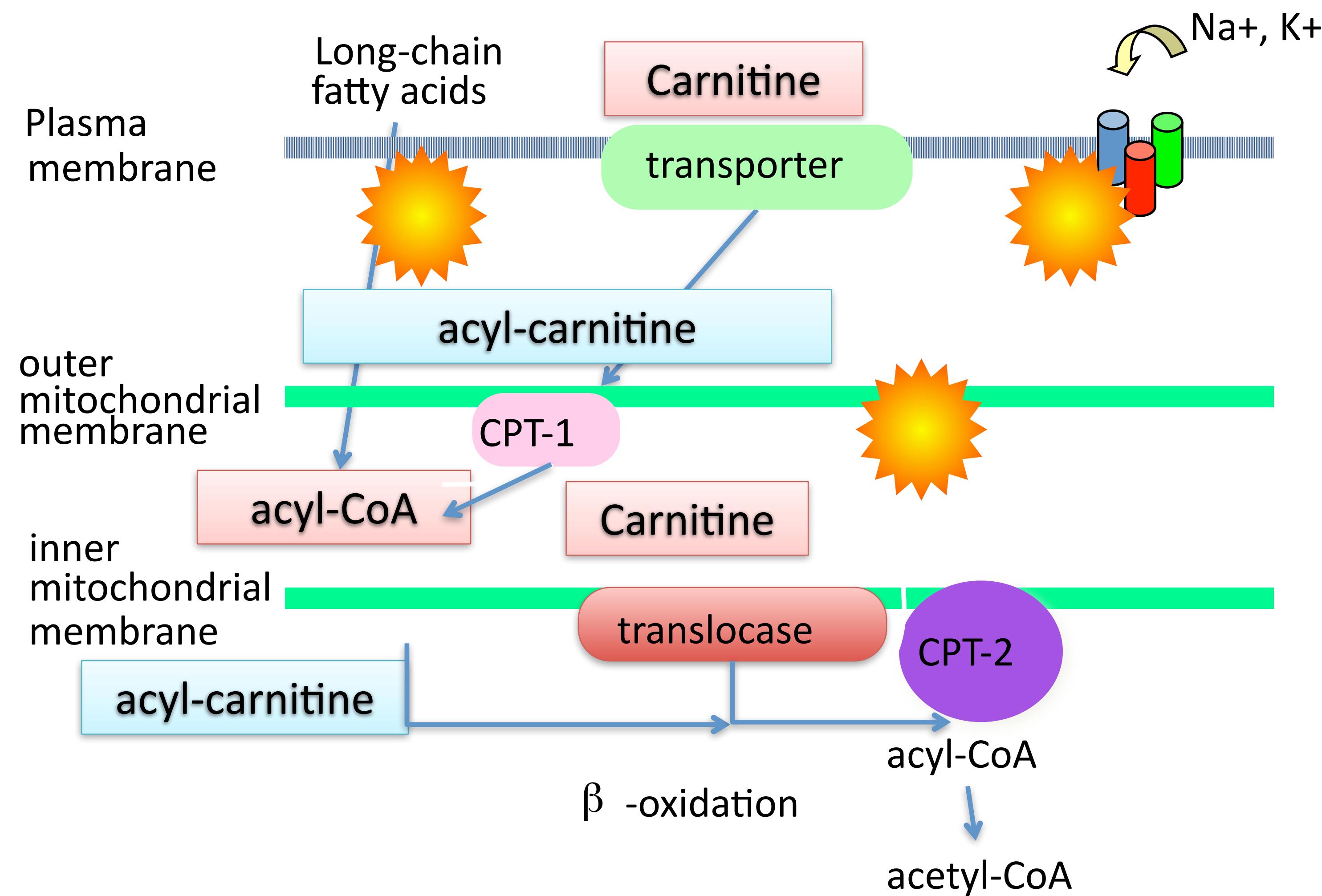
# Pompe's disease



# PRKAG2



# Fatty acid oxidation



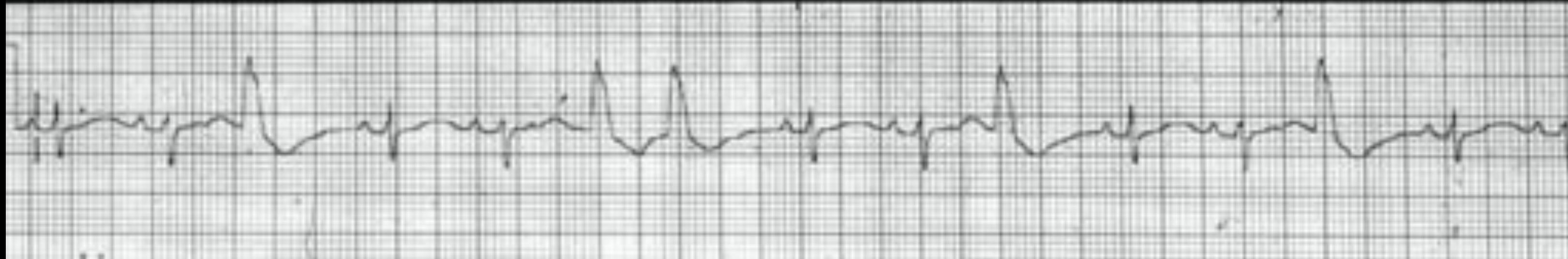
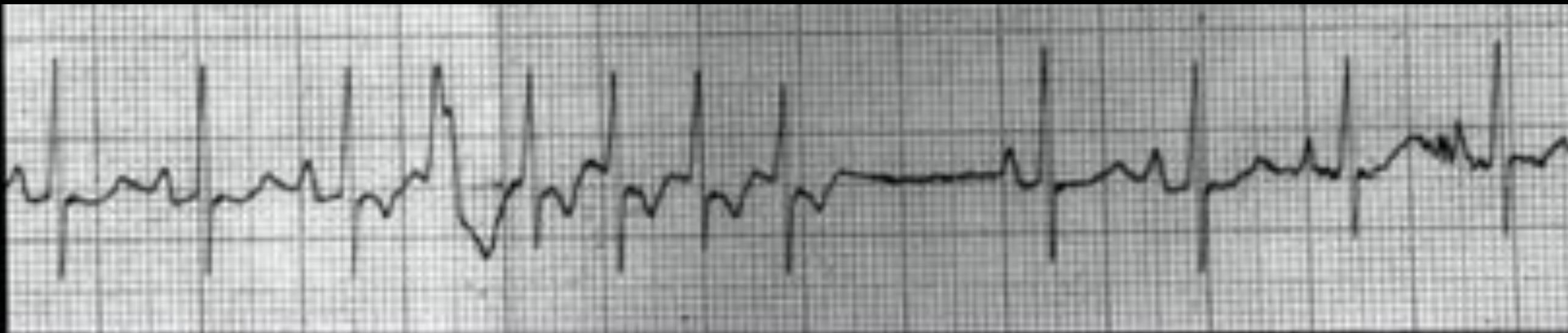
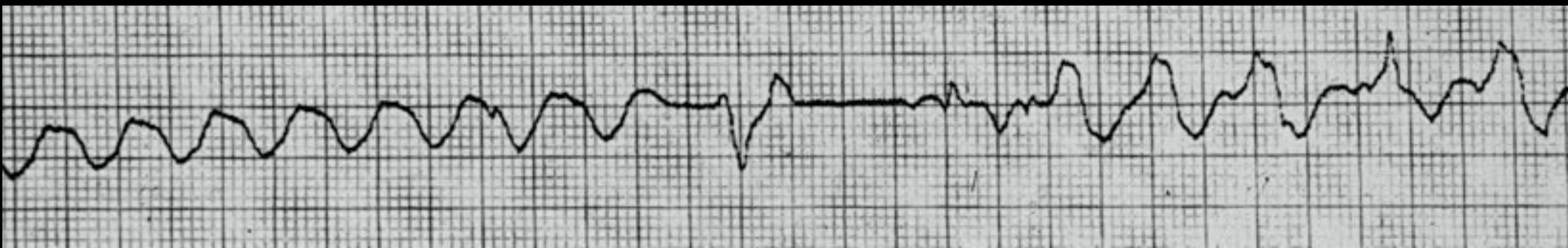
# Presenting symptoms of FAO disorders

Neonatal neurological distress	23%
Hypoglycemia Hypoketotic	46%
Reye 's syndrome	30%
<b>Arrhythmias</b>	<b>14%</b>
<b>Cardiomyopathies</b>	<b>12%</b>
<b>Sudden death</b>	<b>7%</b>
<b>Near-miss</b>	<b>7%</b>
Myolysis, myoglobinuria	6%
Muscular weakness	2%
Hepatomegaly	2%
Cholestasis	1%

Saudubray J Inher Metab Dis 1999;22:488-502

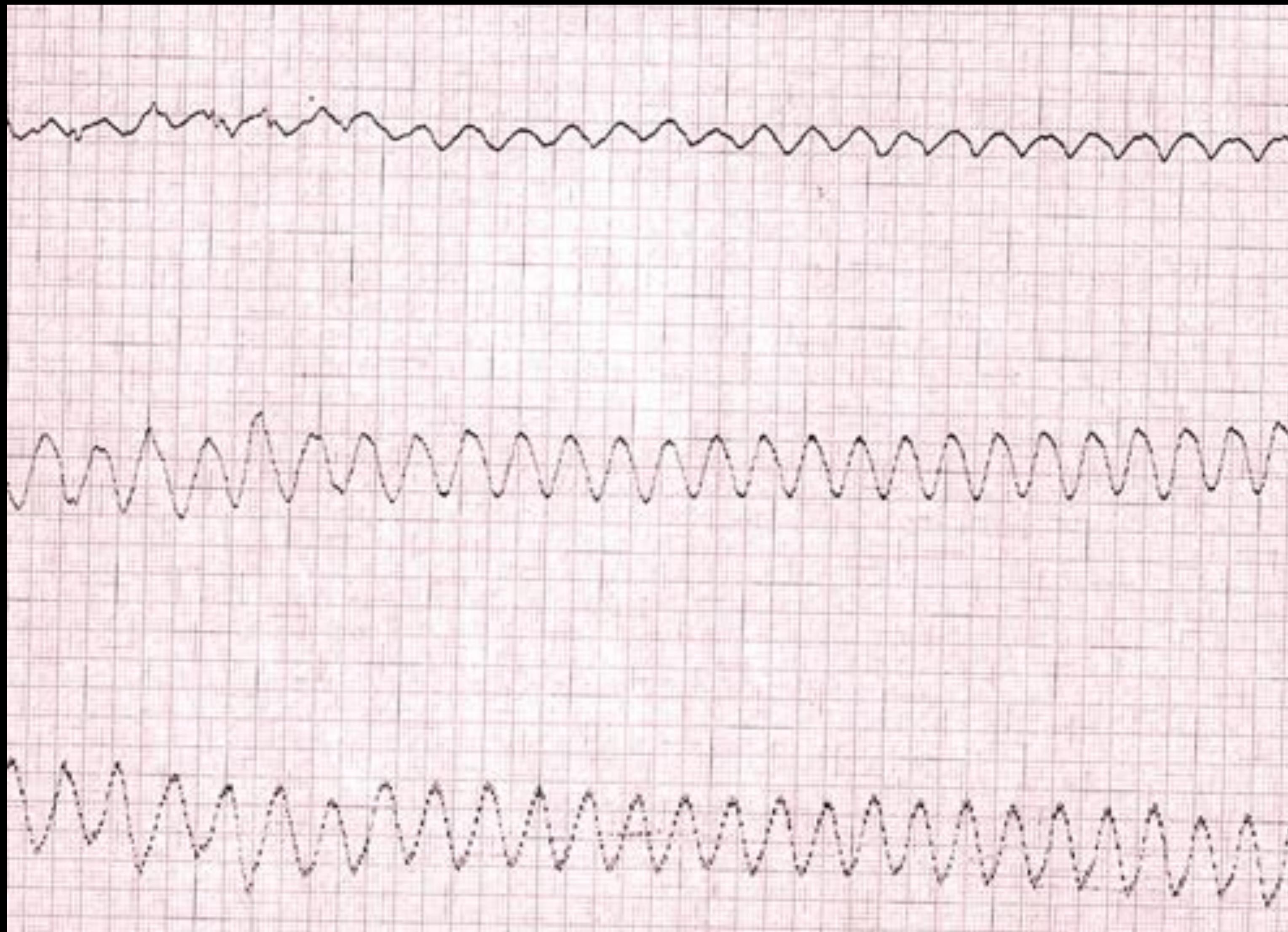
# Fatty acid oxidation

## *Neonatal ECG*



# Fatty acid oxidation

## *Neonatal ECG*

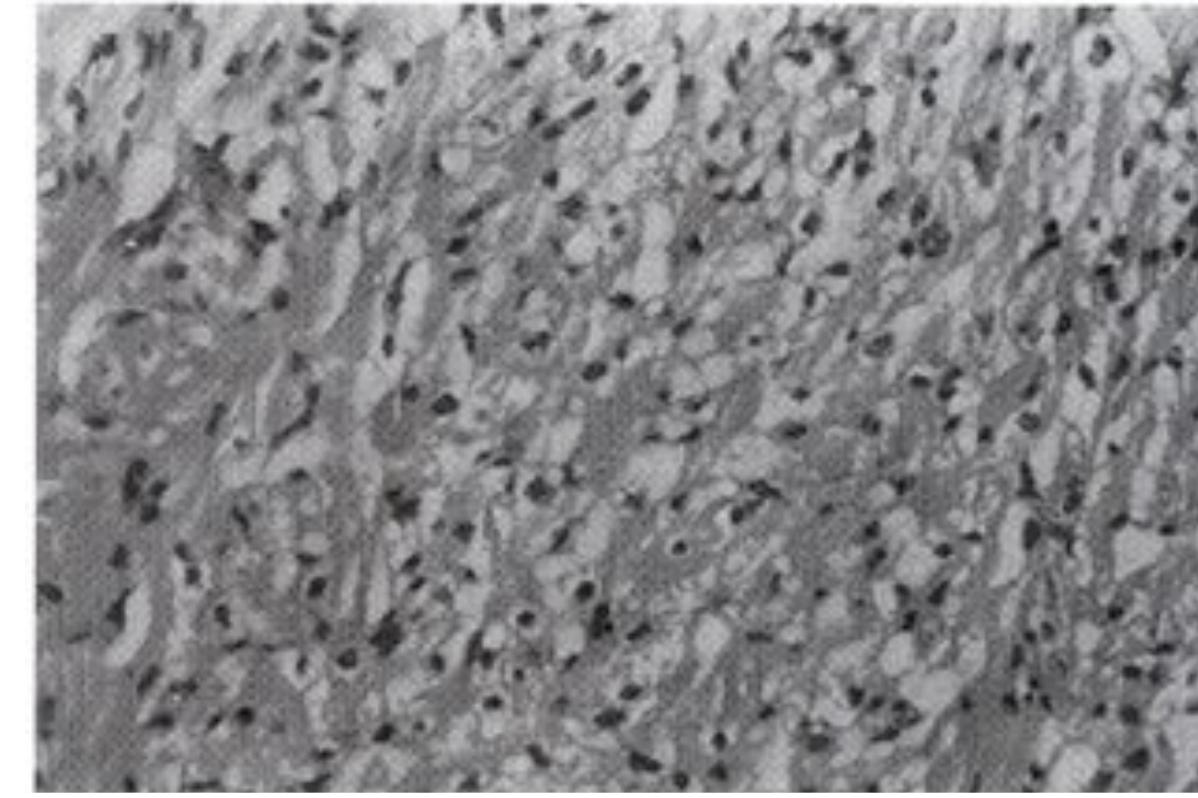




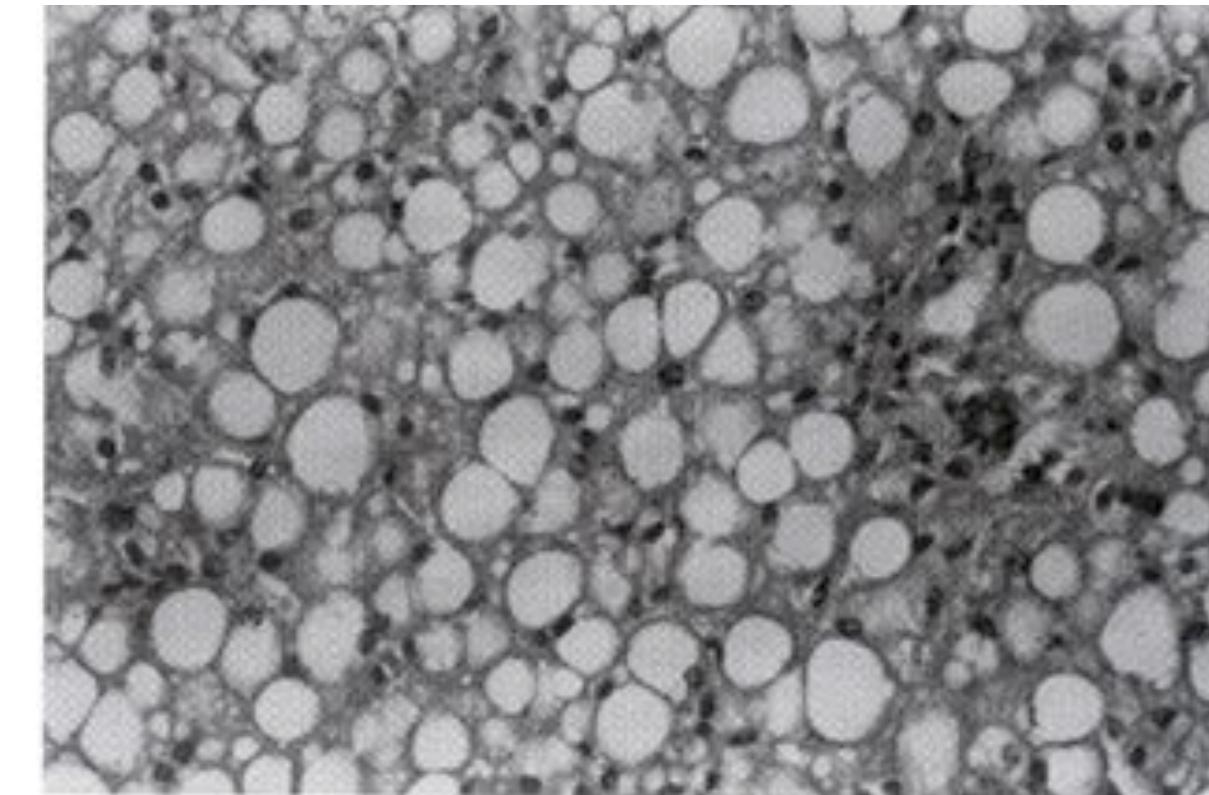
**Carnitine deficiency**

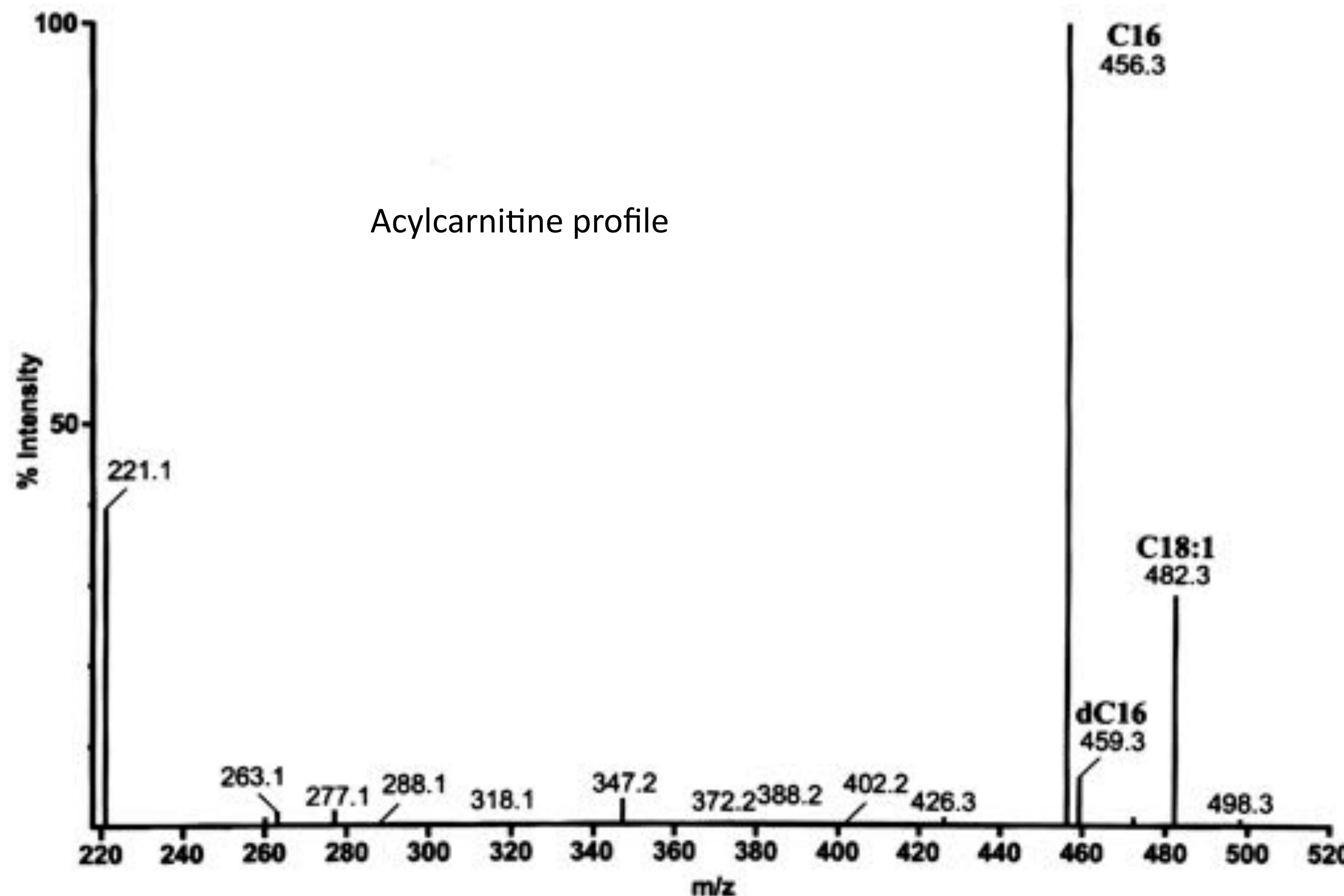
# How to diagnose FAO disorders ?

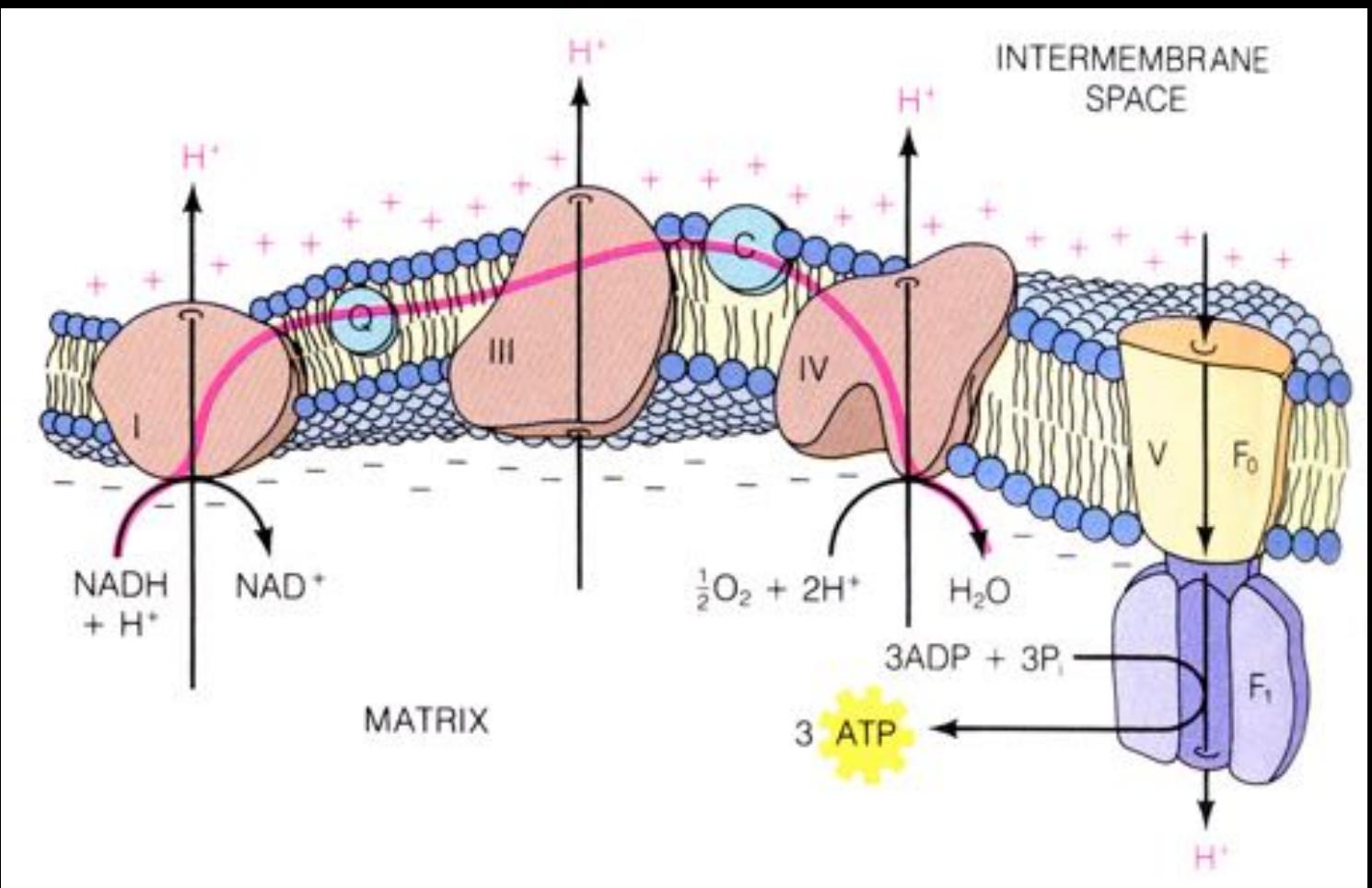
- Acidosis, hypoglycemia, hypoketosis
- Carnitine (total and free)
- Organic acids
- Acylcarnitine profile
- FAO by lymphocytes or fibroblasts
- Specific enzymes studies
- Molecular diagnosis



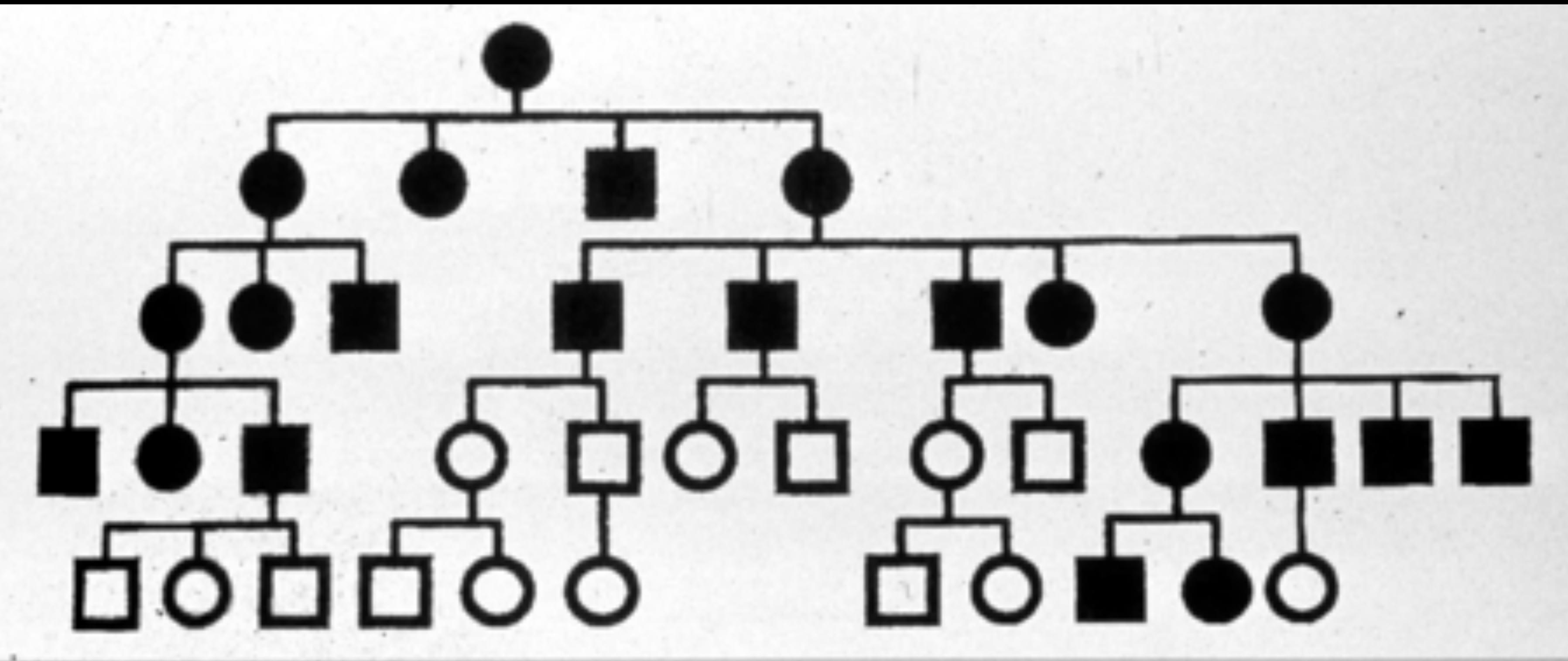
Muscle biopsy





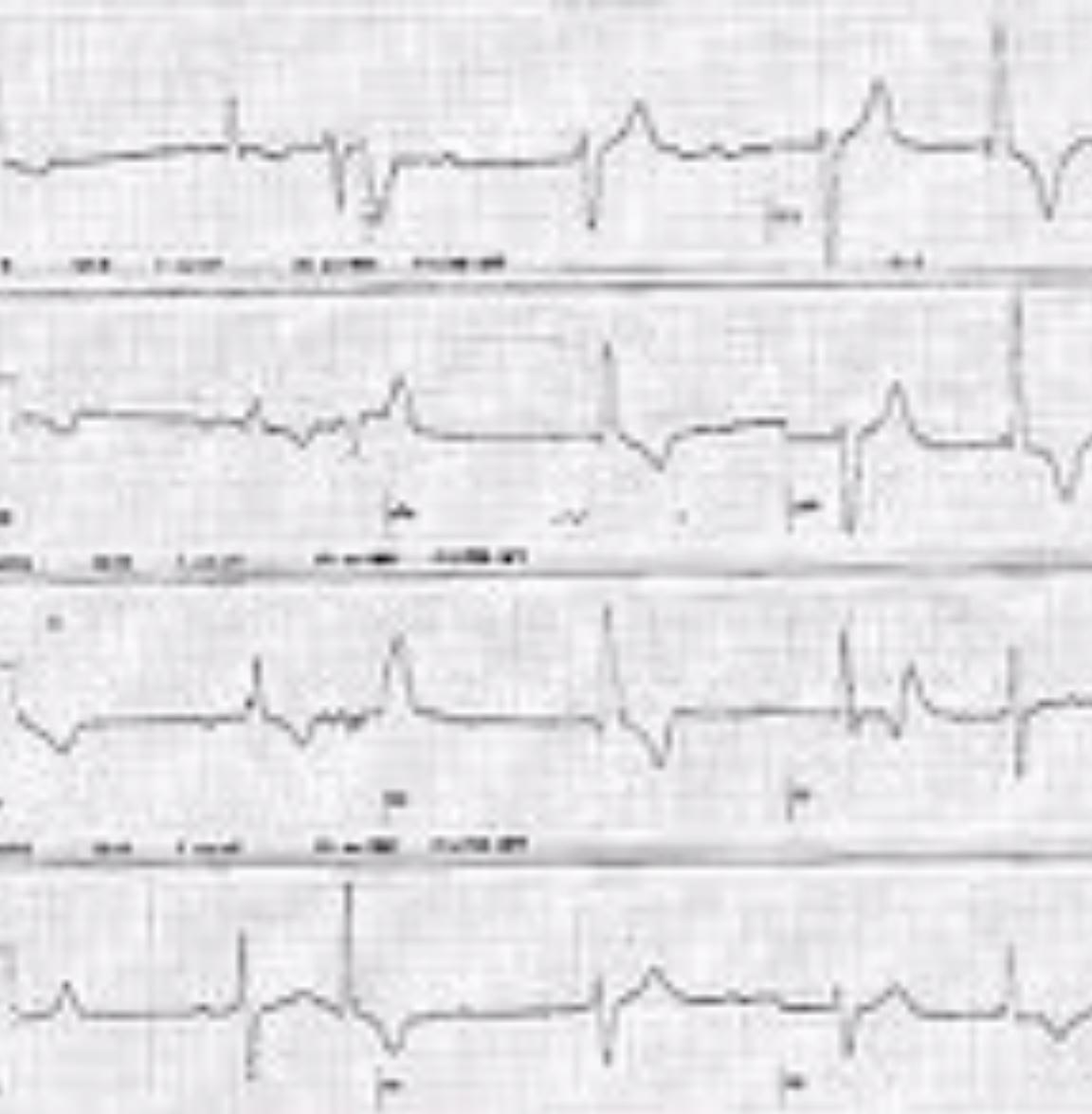
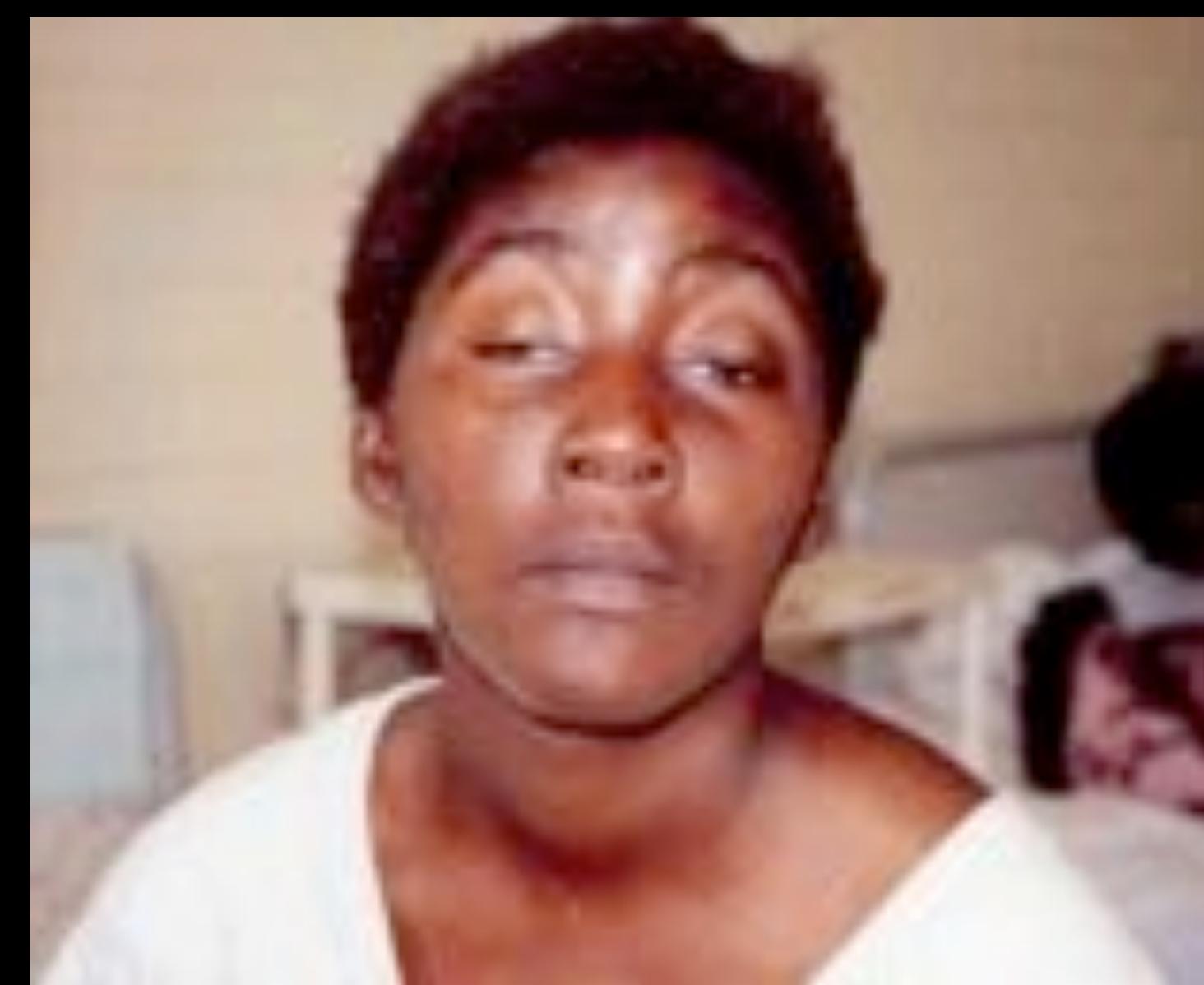


## Mitochondrial disease

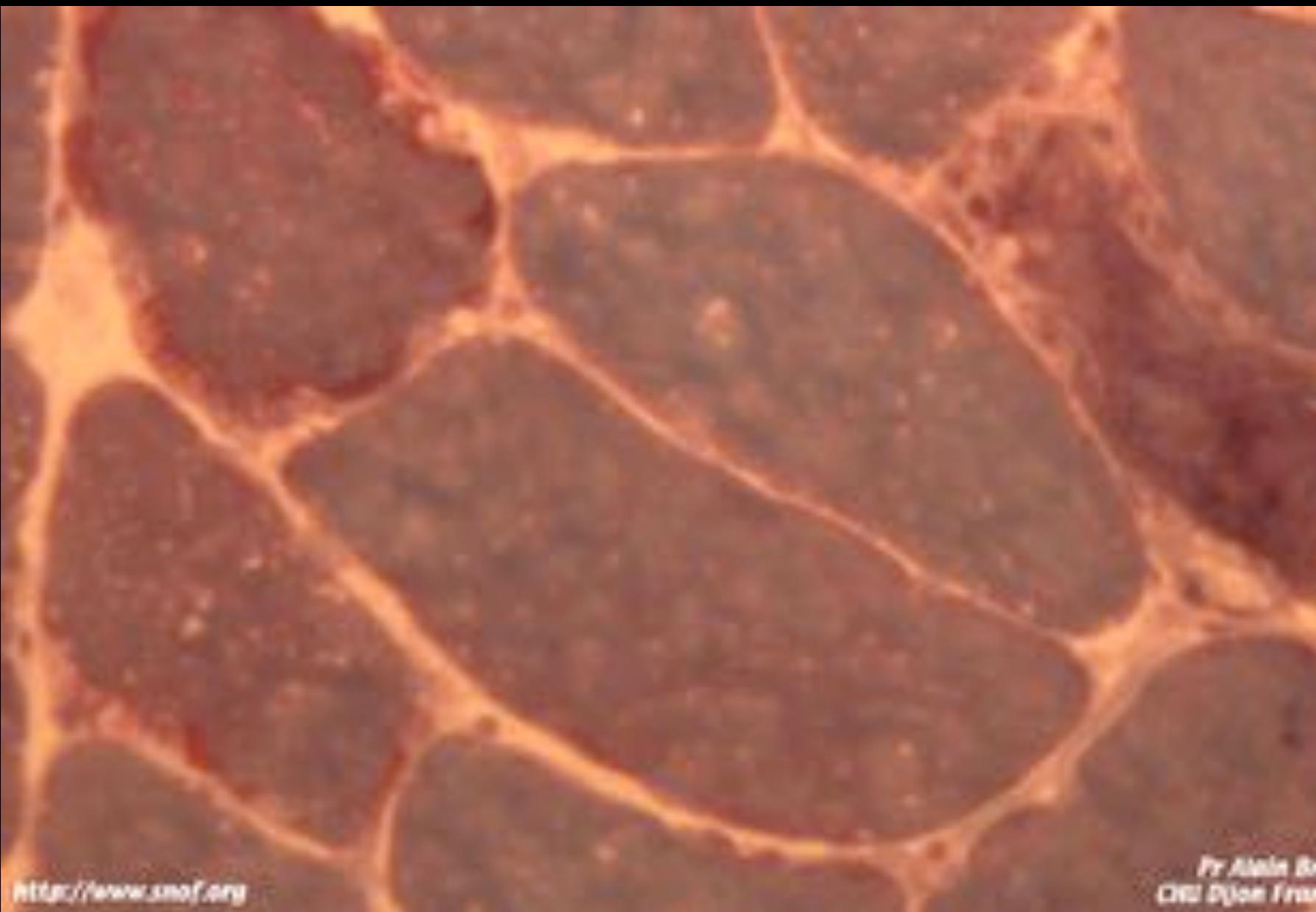


# Presenting symptoms of OXPHOS disorders

- Highly variable
- Generalized disease or isolated cardiomyopathy
- Biology rarely helpful
- Prenatal diagnosis almost impossible
  - Genetic heterogeneity
  - Secondary OXPHOS defects
  - Amniocytes might express the OXPHOS defect or not



Kearns-Sayre Syndrome



<http://www.usuf.org>

Pr Alain Brun  
CHU Dijon France



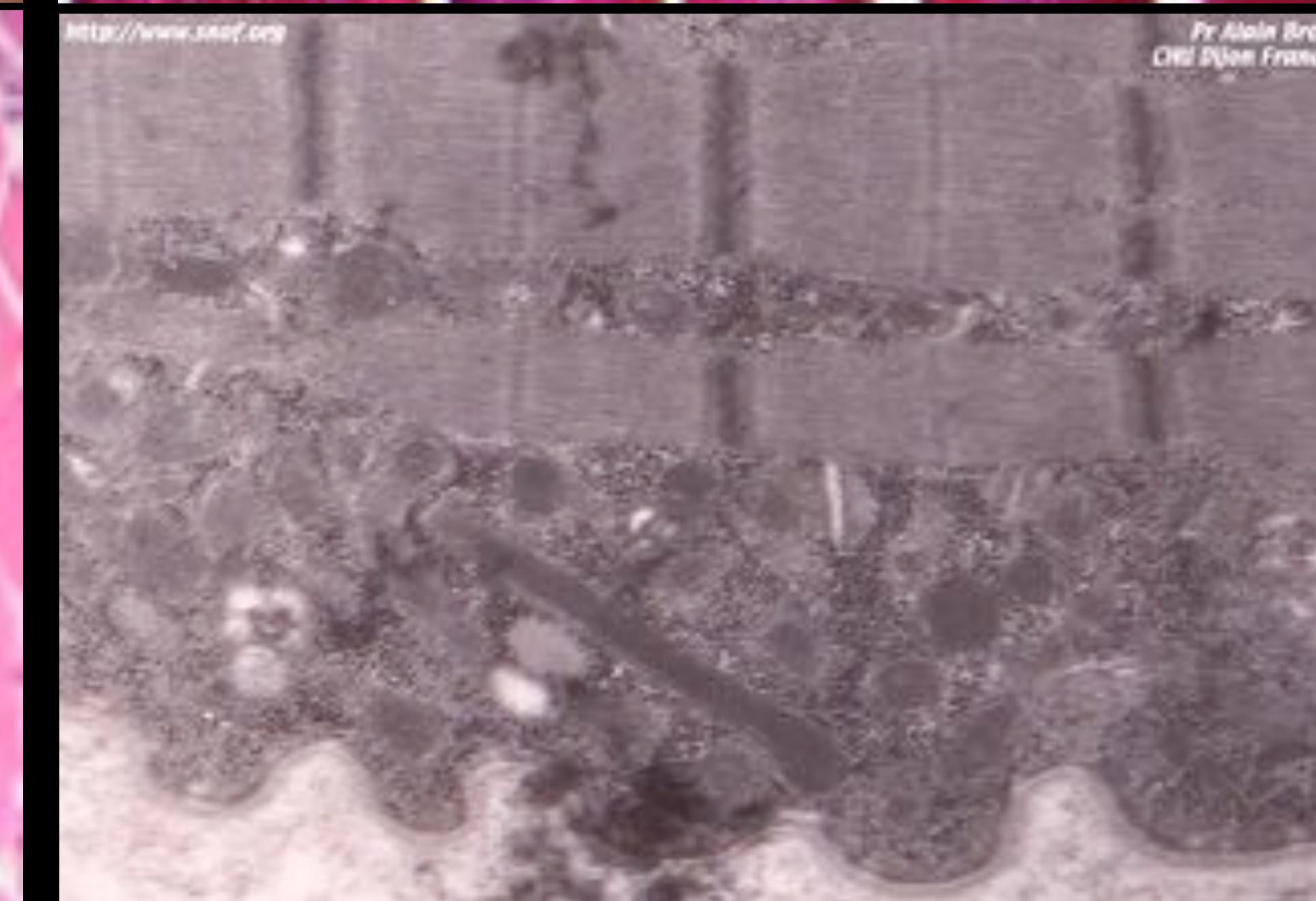
Ragged-fibers in Kearns-Sayre syndrome 20X Masson's Trichrome

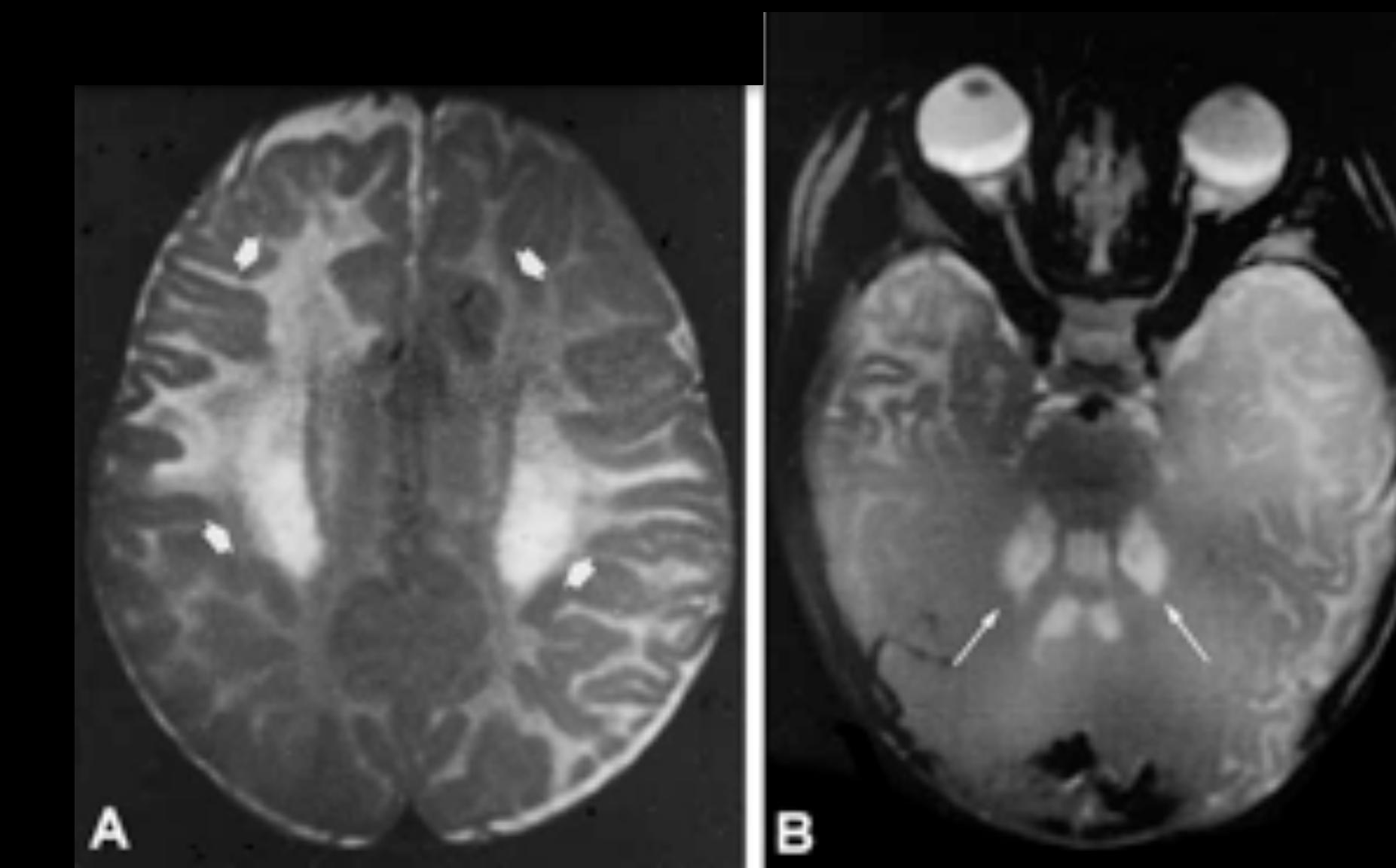
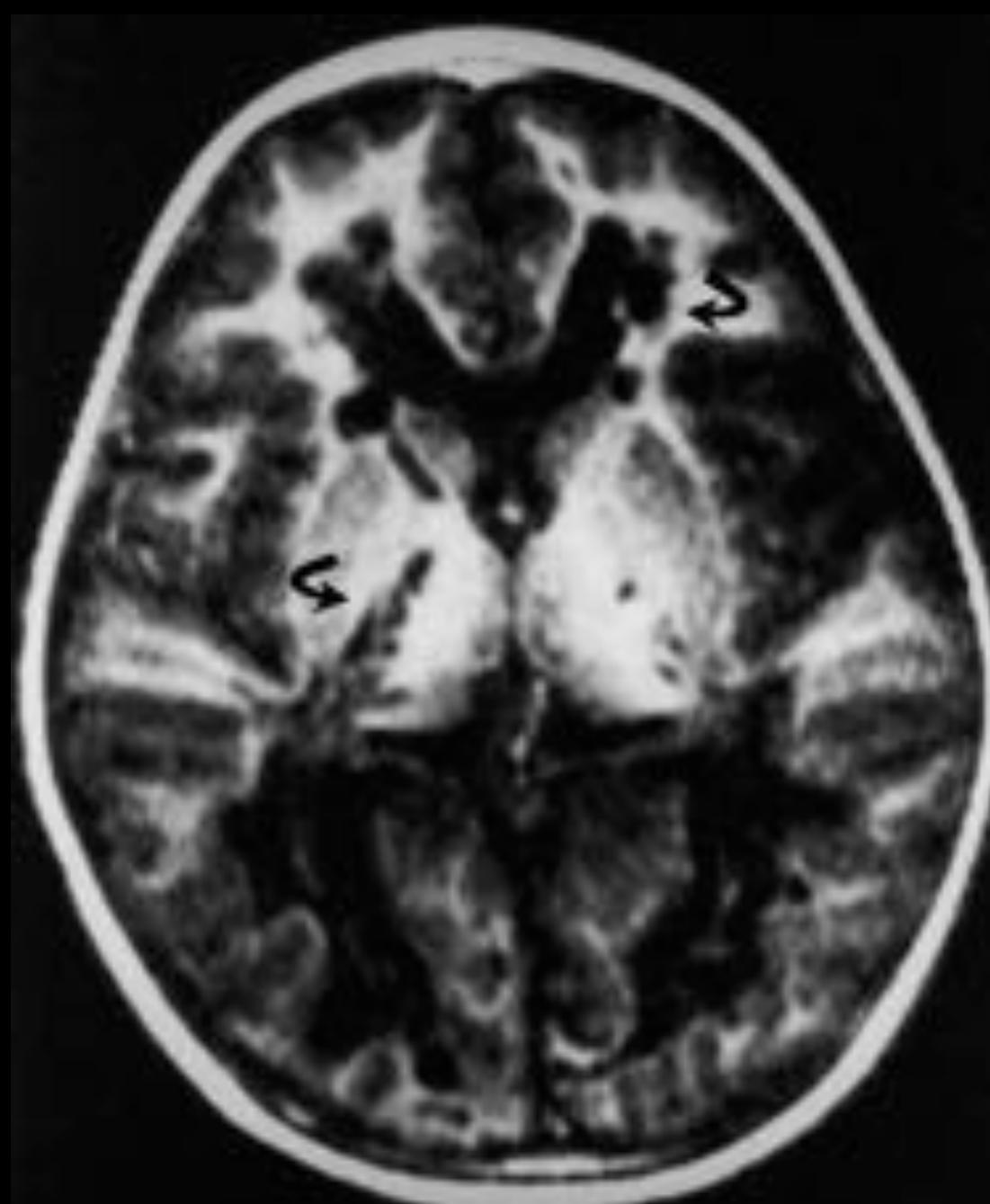
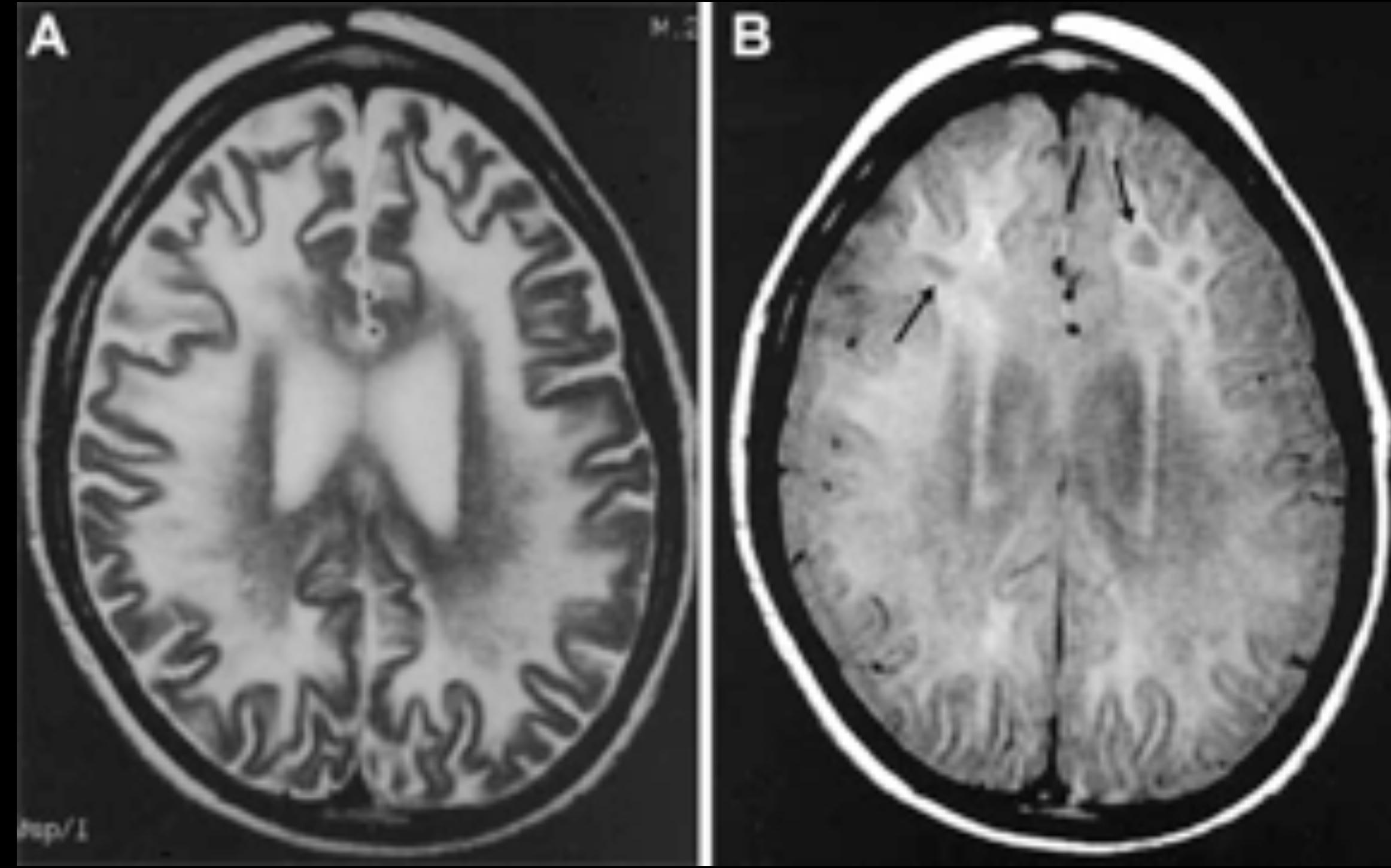
<http://www.usuf.org>

Pr Alain Brun  
CHU Dijon France



Appearance of 'ragged-fibers'  
in Kearns-Sayre syndrome HK  
10X

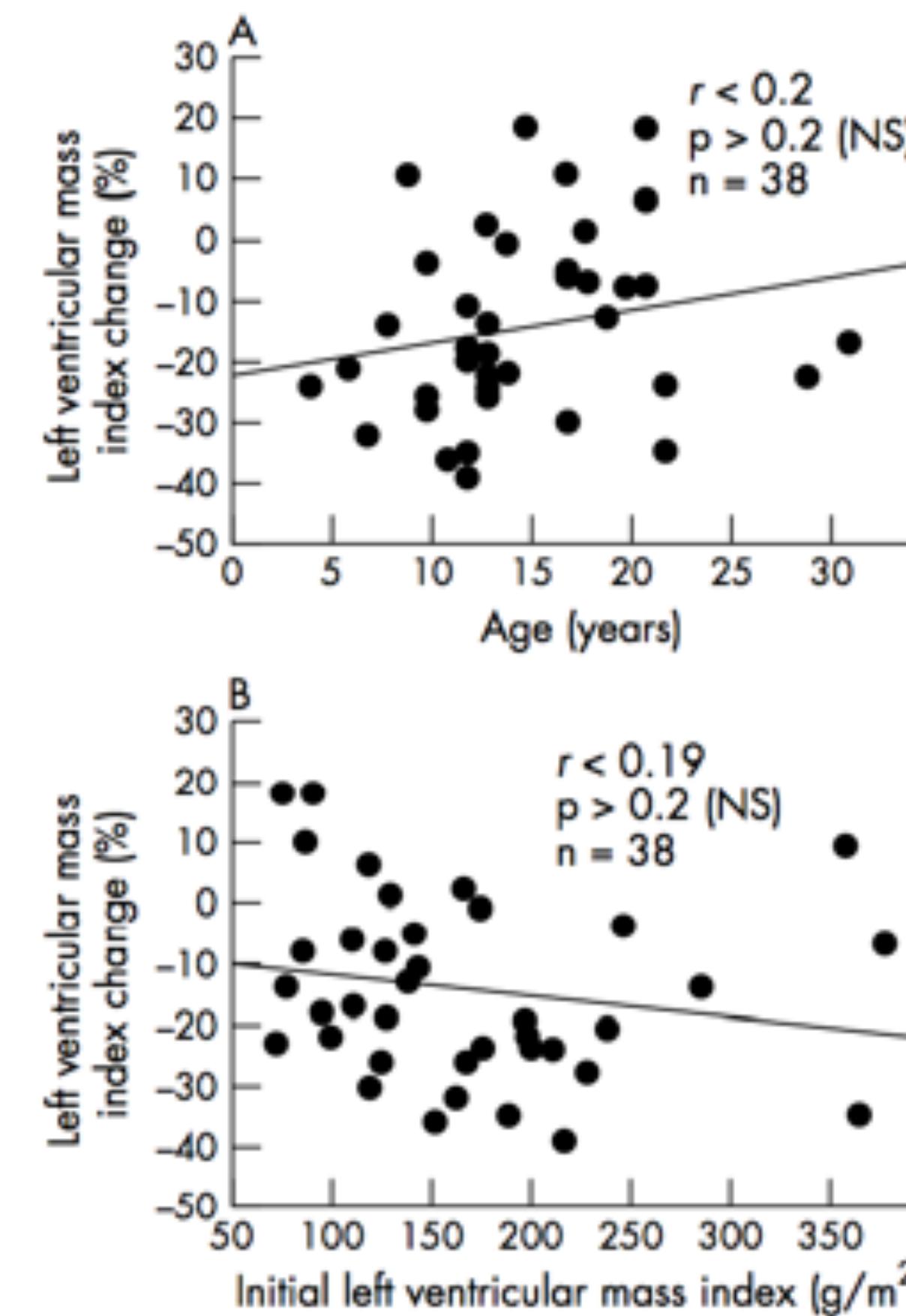
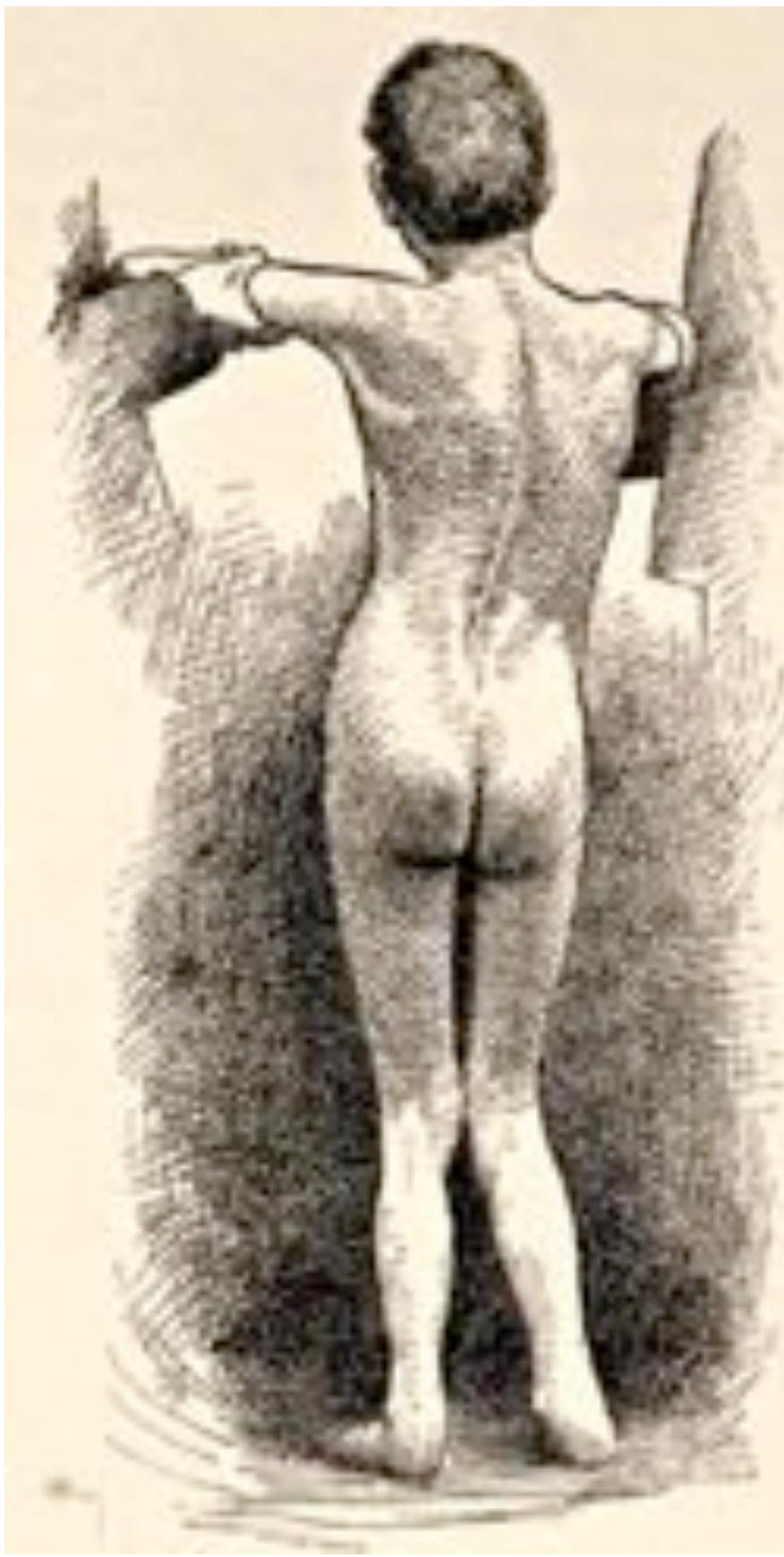




# Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia

A O Hause, Y Aggoun, D Bonnet, D Sidi, A Munnich, A Rötig, P Rustin

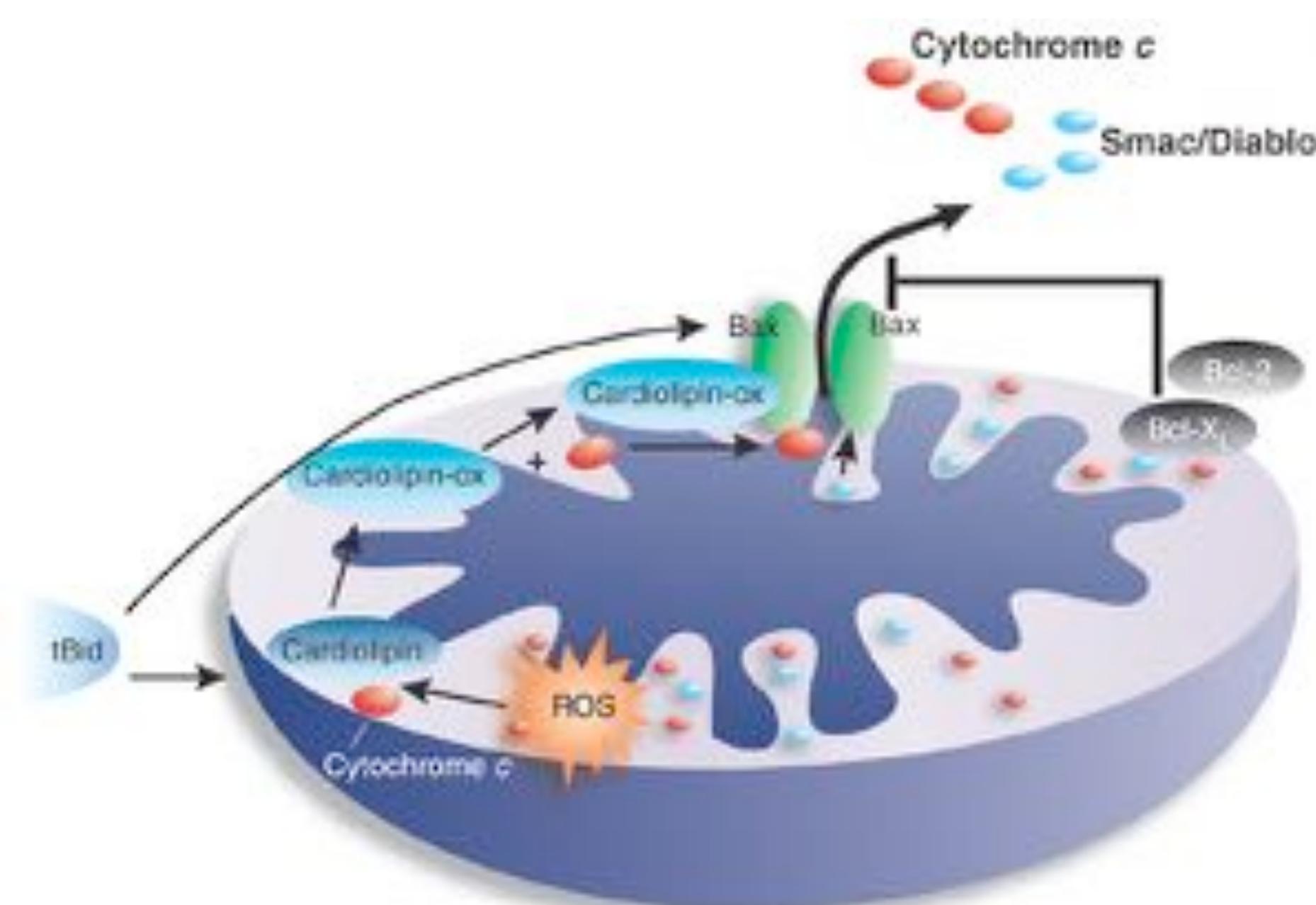
Heart 2002;87:346–349



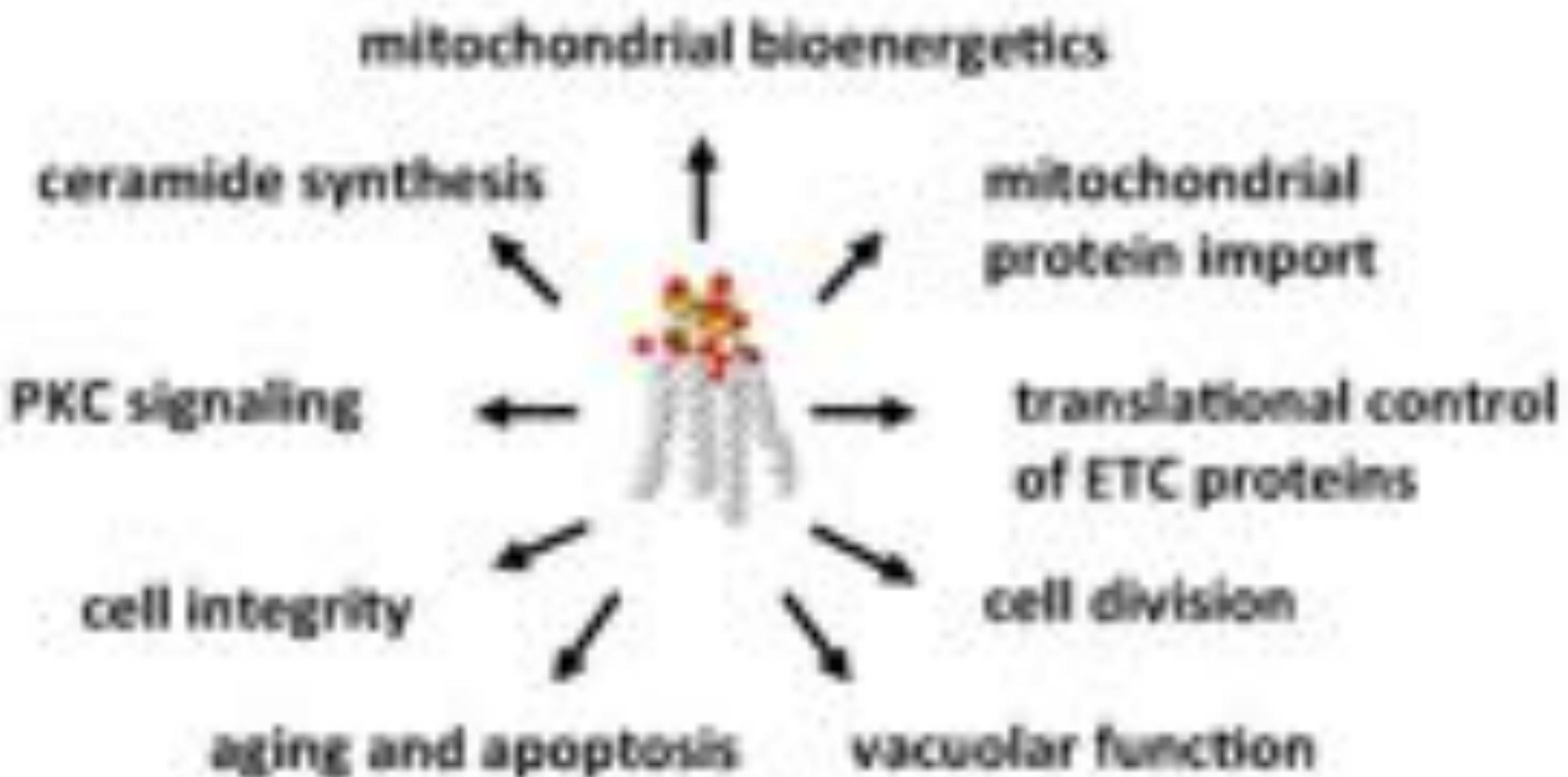
Kearney M, Orrell RW, Fahey M, Pandolfo M. Antioxidants and other pharmacological treatments for Friedreich ataxia. Cochrane Database Syst Rev. 2012 Apr 18;4:CD007791.

# Barth syndrome

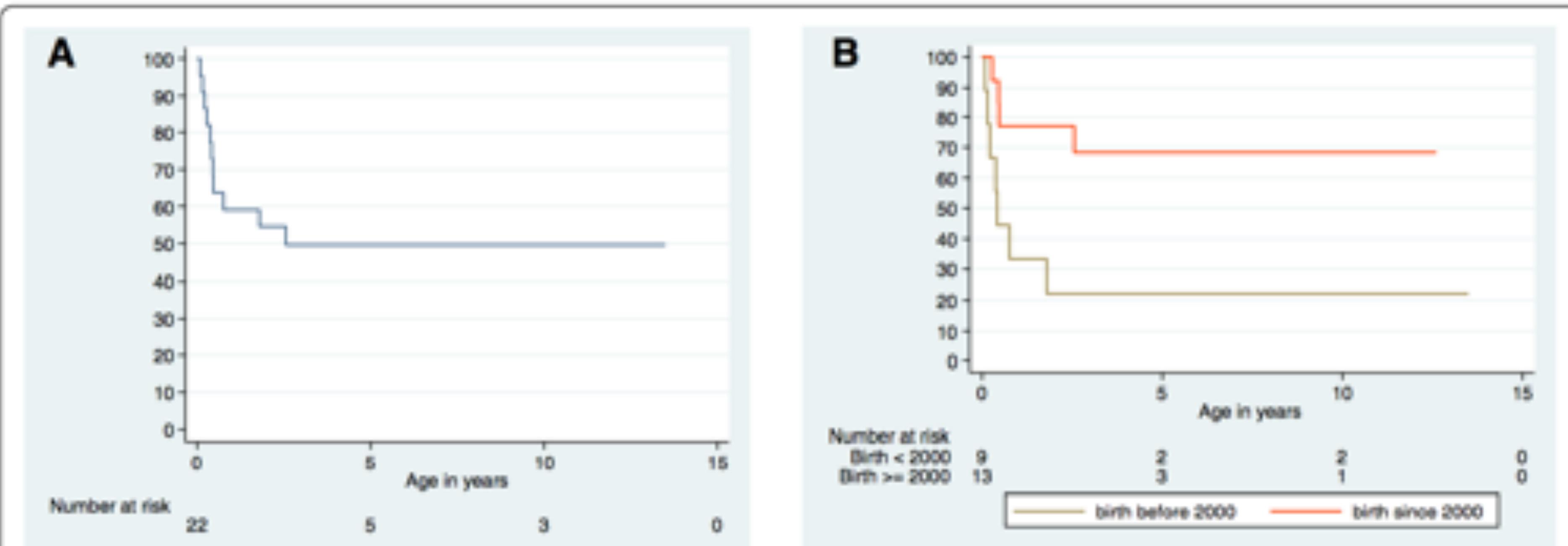
- DCM or non compaction
- Neutropenia (variable)
- Screening in boys
- Genetic counseling
- Issue uncertain



## Functions of cardiolipin Modifiers of Barth syndrome?

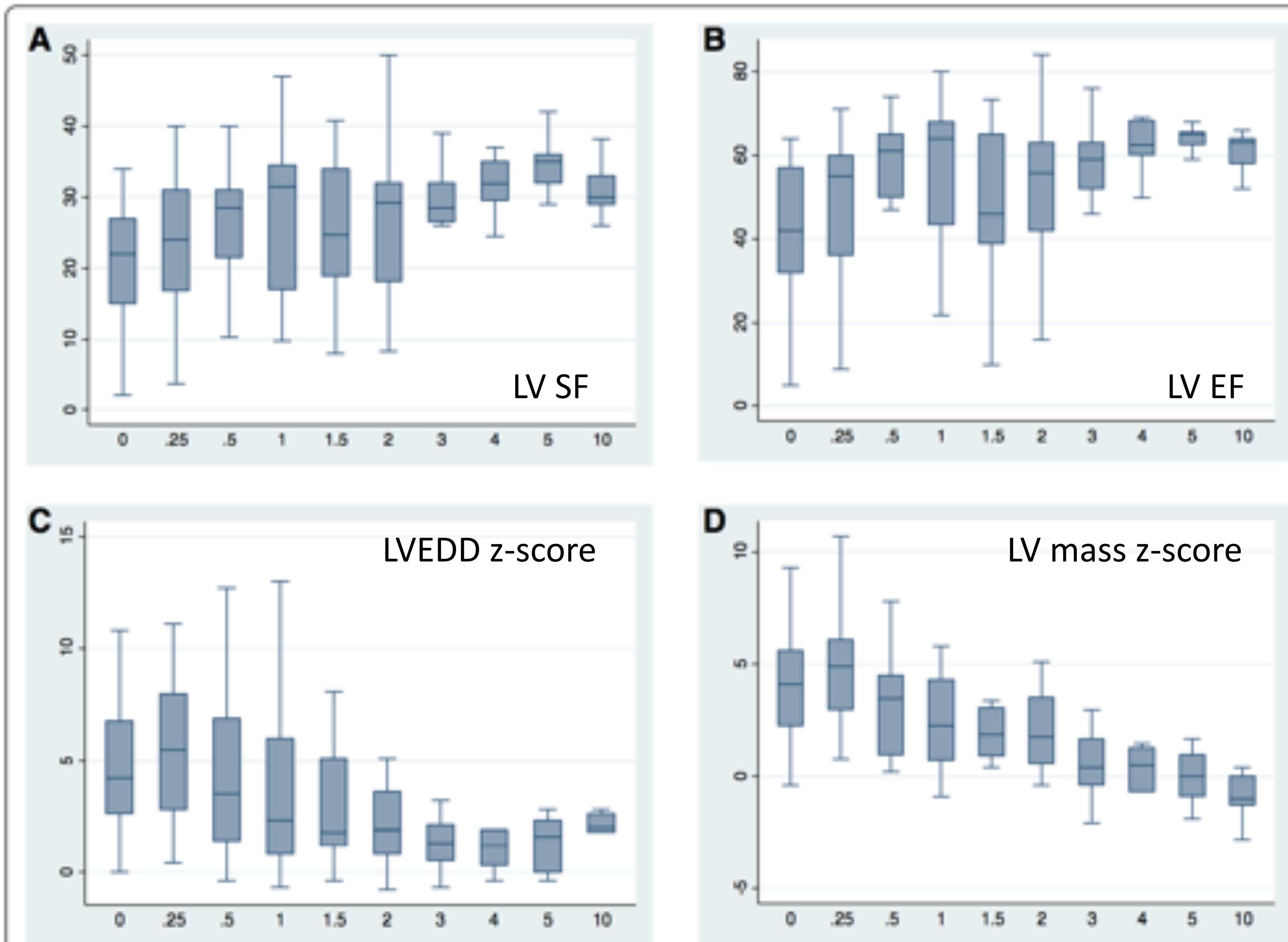


# Barth syndrome



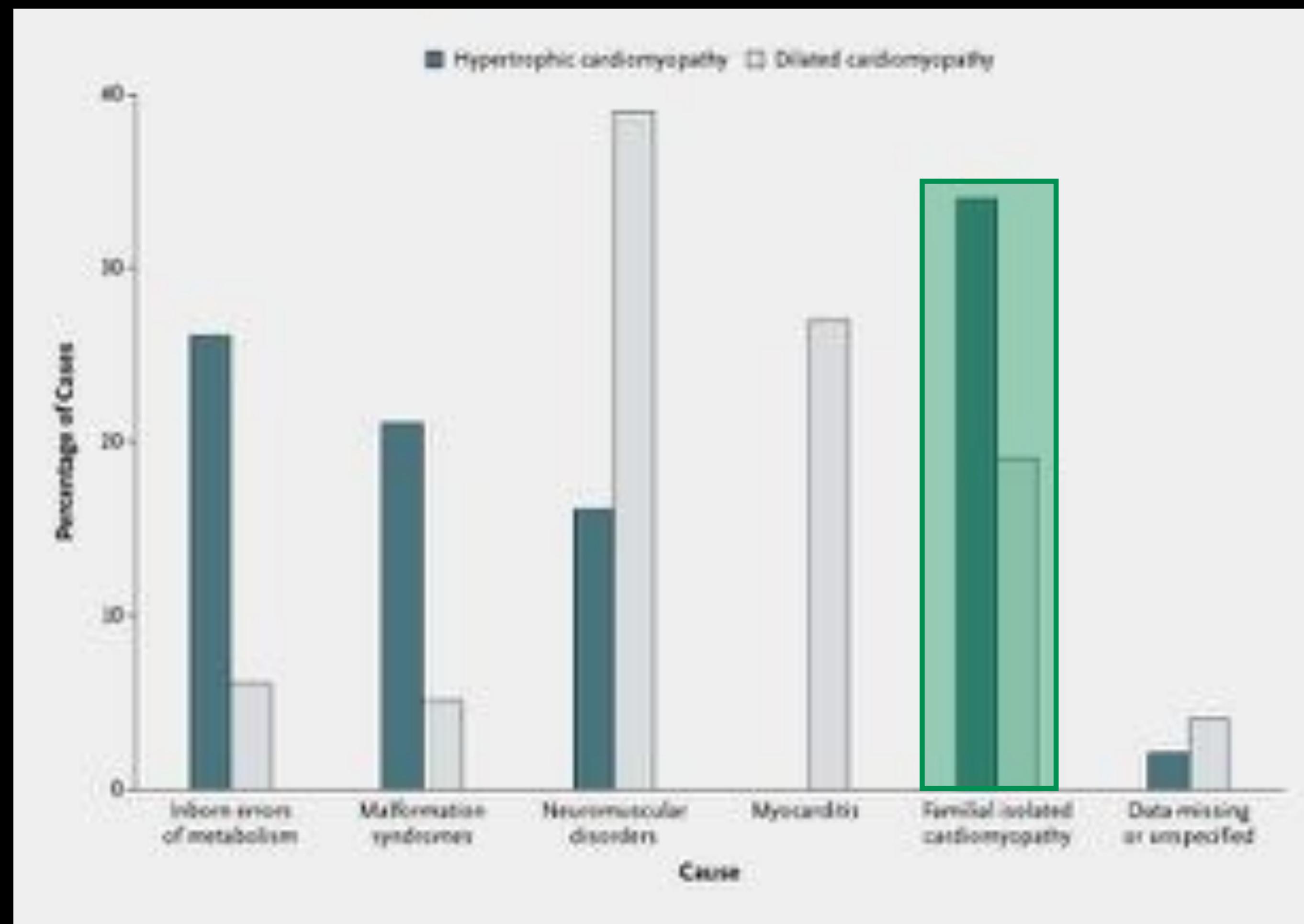
**Figure 4** Overall survival and survival according to birth year of the French Barth syndrome cohort. **A)** Kaplan-Meier plot and 95% confidence intervals showing the overall survival of the French Barth syndrome cohort. Time is expressed in years since birth. **B)** Kaplan-Meier plot showing the survival of the French Barth syndrome cohort according to birth year (before and in or after 2000). Even though the total number of patients is quite limited, the difference in survival is both important (survival at 5 years: 22% for patients born before 2000 and 70% for patients born in or after 2000) and statistically significant ( $p = 0.009$ ). This suggests that recent progress in the management of heart dysfunction may improve the survival of patients with BTHS.

# Barth syndrome

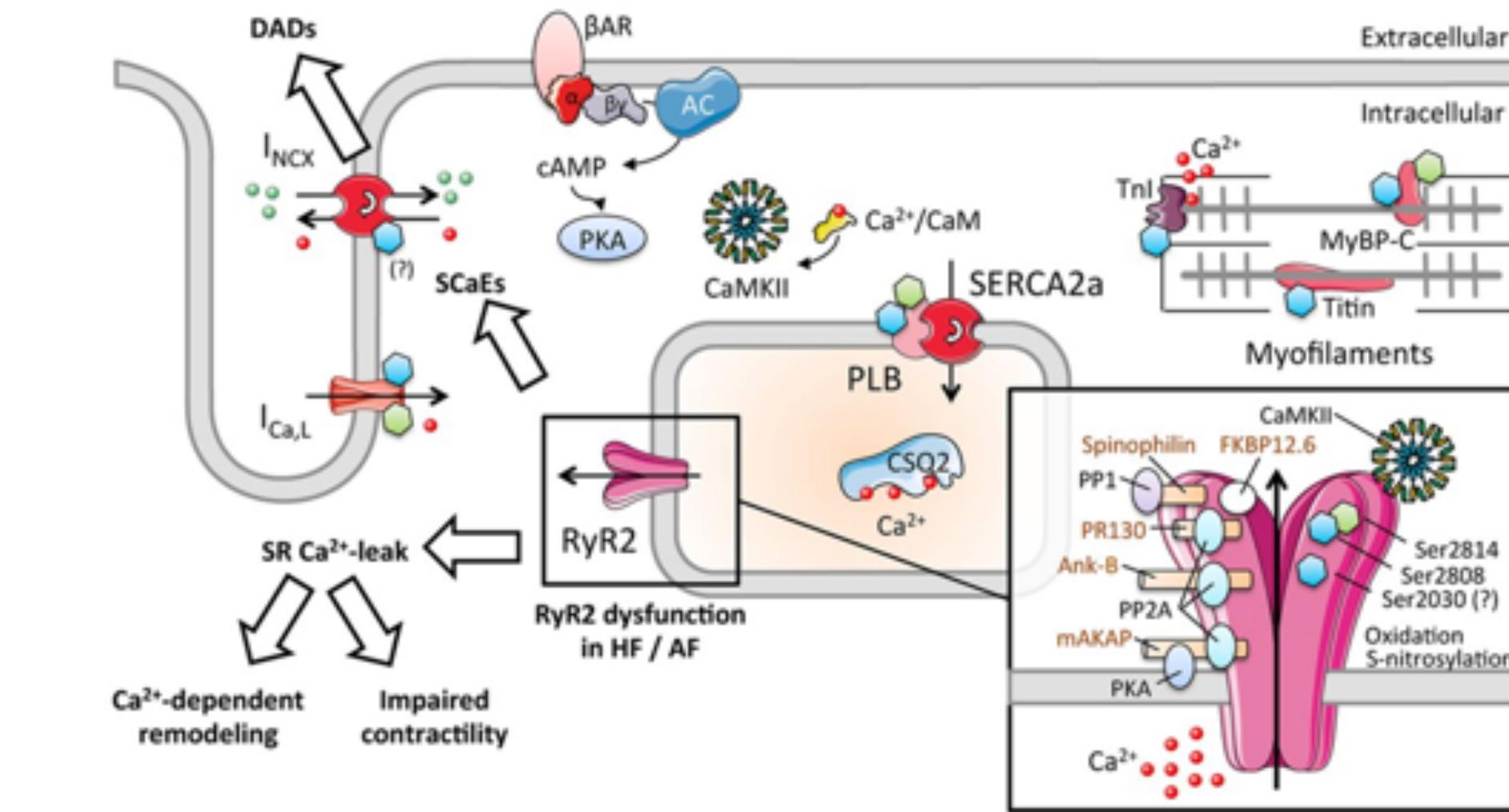
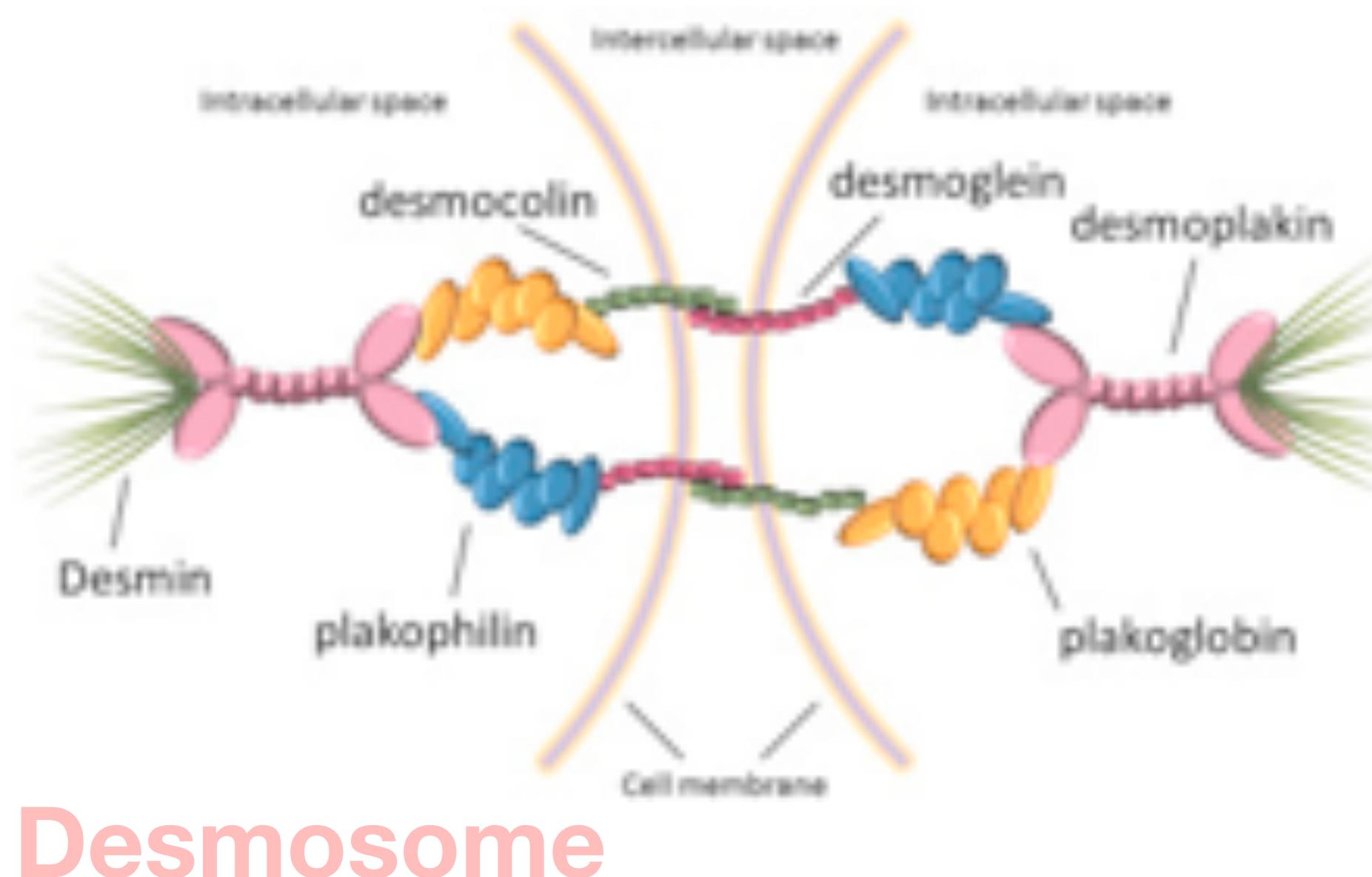
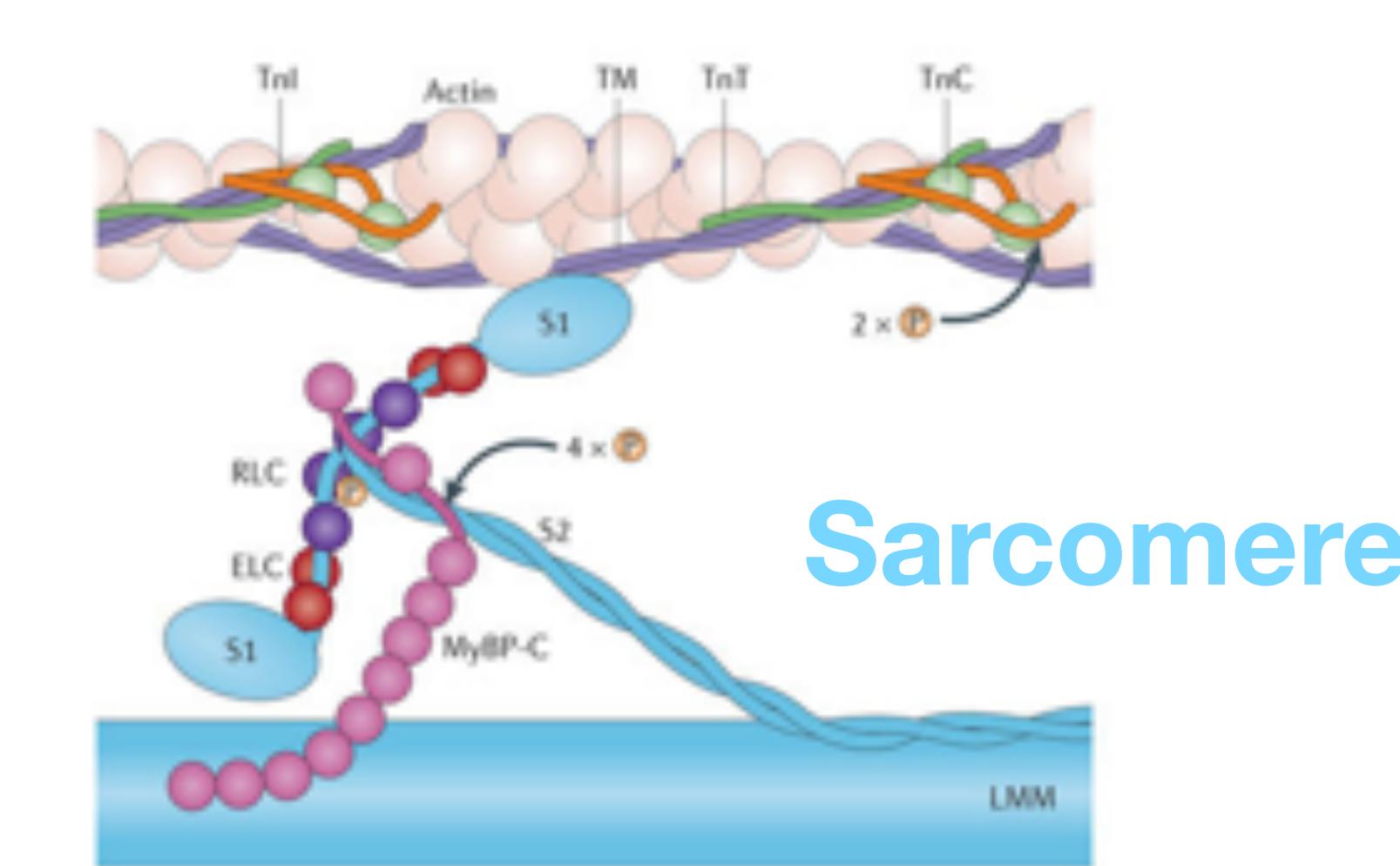
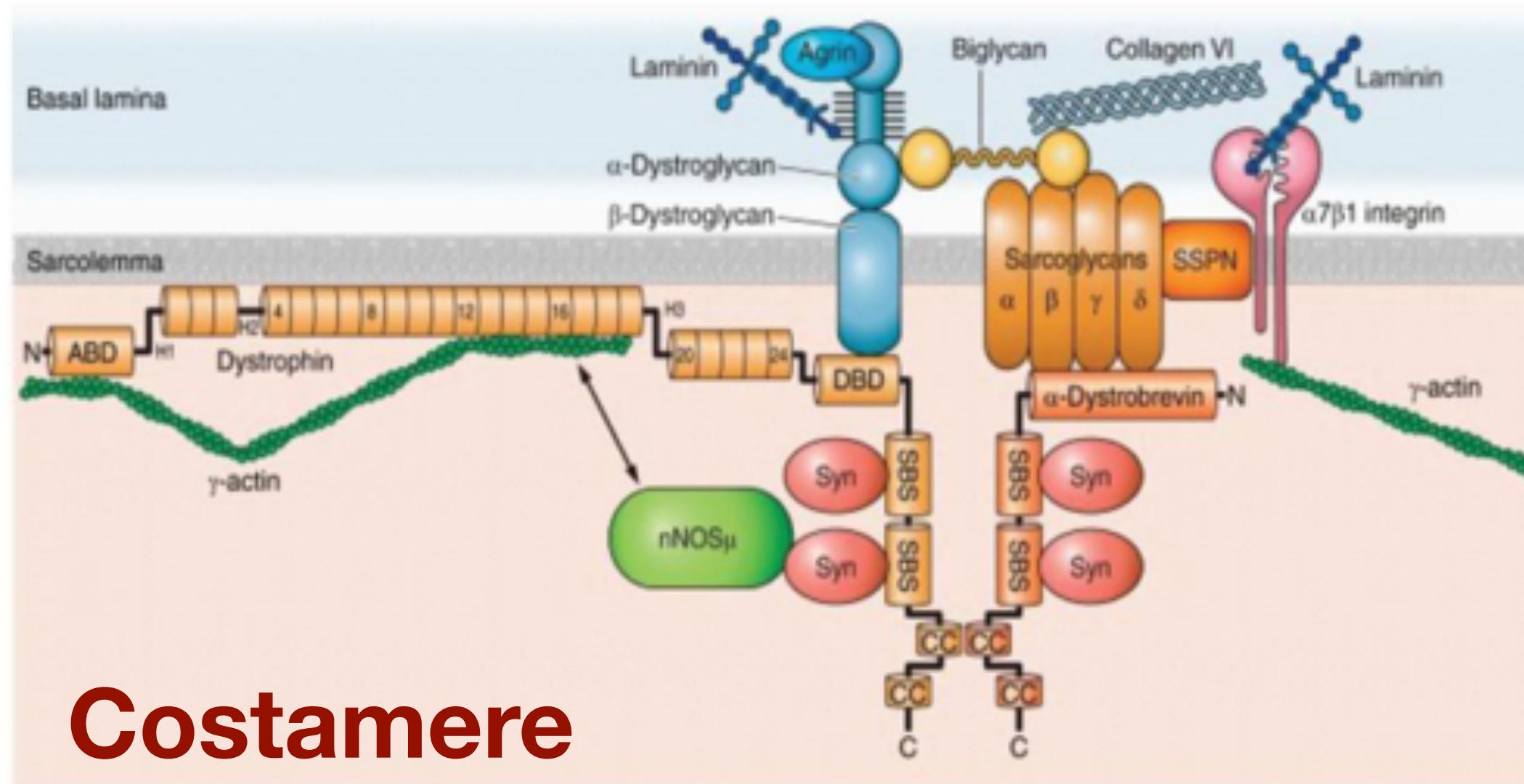


**Figure 2** Box plots showing the distribution of cardiology parameters as determined by ultrasound according to age. Age is shown for the following categories: 0, birth to age 3 months; 0.25, between 3 months and 6 months; 0.5, between 6 months and 1 year; 1, between 1 and 1.5 years; 1.5, between 1.5 and 2 years; 2, between 2 and 3 years; 3, between 3 and 4 years; 4, between 4 and 5 years; 5, between 5 and 10 years; 10, >10 years old. The heart indicators are as follows: **A)** shortening fraction (SF), reported as %; **B)** ejection fraction (EF), reported as %; **C)** z-score of the left ventricular end diastolic diameter (LVEDD); **D)** z-score of the left ventricular mass (LV mass).

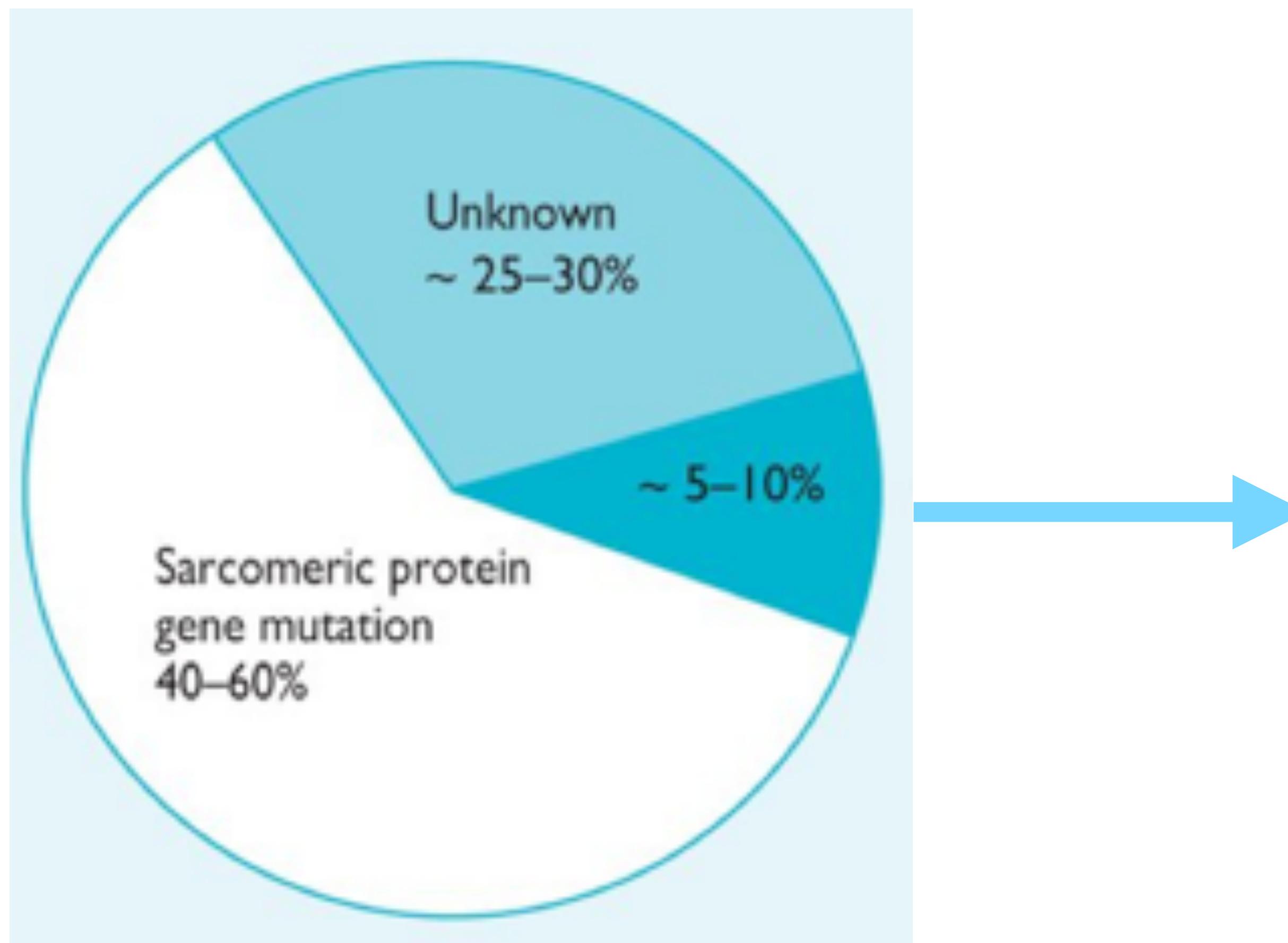
# Familial isolated cardiomyopathies



# Cardiomyopathy genes in pediatric inflammatory cardiomyopathy



# Genetic screening for HCM in adults



- Inborn errors of metabolism
  - Glycogen storage diseases:
    - Pompe
    - Danon
  - AMP-Kinase (PRKAG2)
  - Carnitine disorders
  - Lysosomal storage diseases
    - Anderson-Fabry
- Neuromuscular diseases
  - Friedreich's ataxia
  - RHLI
- Mitochondrial diseases
  - MELAS
  - MERFF
- Malformation Syndromes
  - Noonan
  - LEOPARD
  - Costello
  - CFC
- Amyloidosis
  - Familial ATTR
  - Wild type TTR (senile)
  - AL amyloidosis

# Familial screening

- First degree relatives
- ECG
- Echocardiography
- Genetic testing according to local practice and legal recommandations for presymptomatic screening

# **Summary of clinical evaluation and etiology search for cardiomyopathies**

- Medical history personal and familial
- Cardiac examination
- ECG + Echocardiography
- MRI + troponin
- Genetic clinic for syndromes
- Metabolic screening
  - Glucose, ketone bodies, lactates,
  - Chromato organic acids, acylcarnitines, carnitine T+F
  - and that's it!



TATOO

