The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

INFILTRATIVE CARDIOMYOPATHY

Siti Elkana Nauli

For INTRO..

- Common secondary form of Restrictive Cardiomyopathy
- Infiltrative means something infiltrates the myocardium (ventricle and atrial), pericardium

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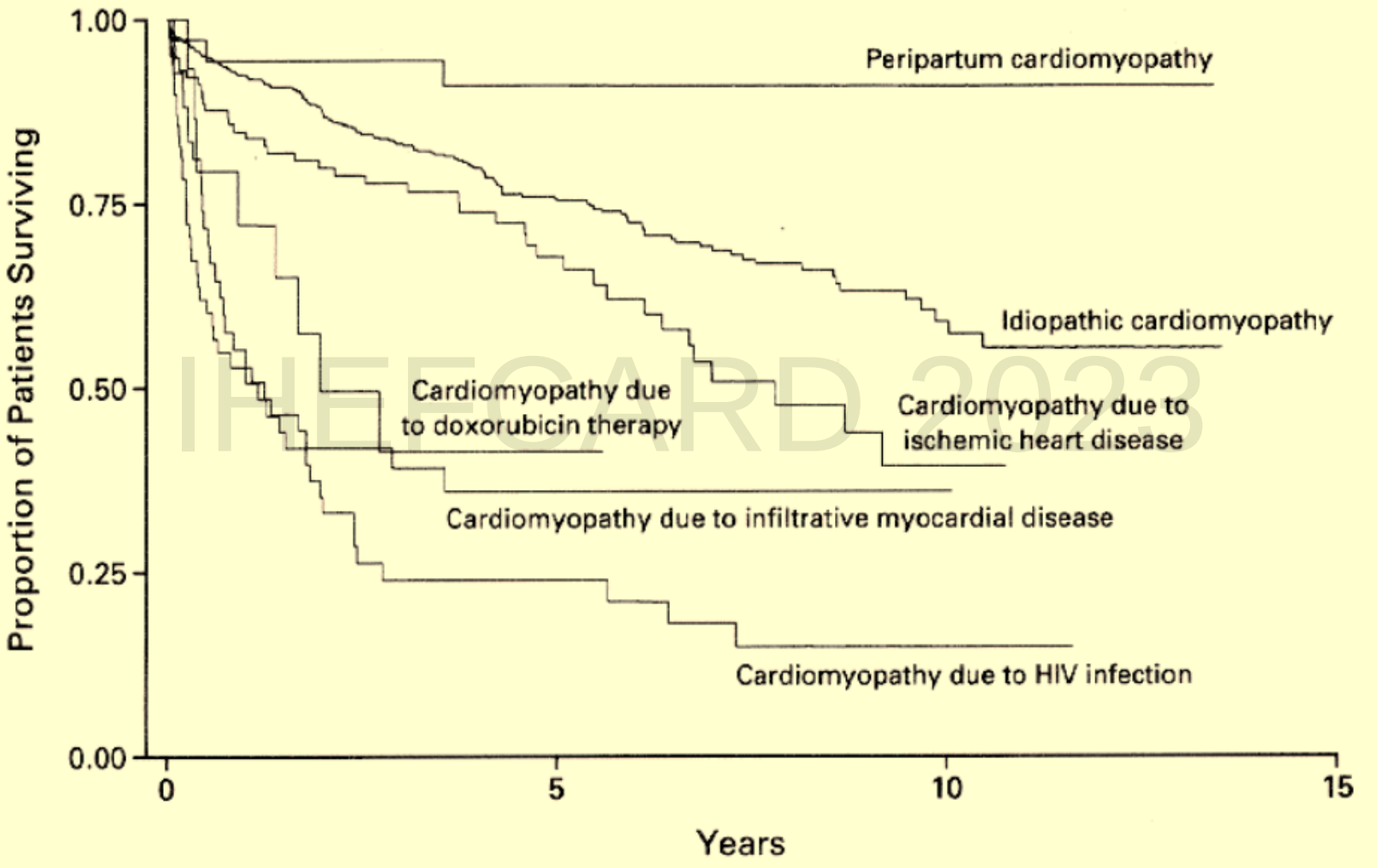
→ deposition of abnormal substances within the heart tissue

→ causes the ventricular walls to develop diastolic dysfunction

→ less commonly and more of a late presentation of the disease, systolic dysfunction

WHY IT IS IMPORTANT



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FelkeAr et al. NEJM 2000

SCOPE OF INFILTRATIVE CARDIOMYOPATHY

- Sarcoidosis
- Hemochromatosis
- Amyloidosis
- Scleroderma
- Carcinoid heart disease
- Glycogen storage diseases such as Fabry disease
- Radiation induced
- Metastatic malignancy

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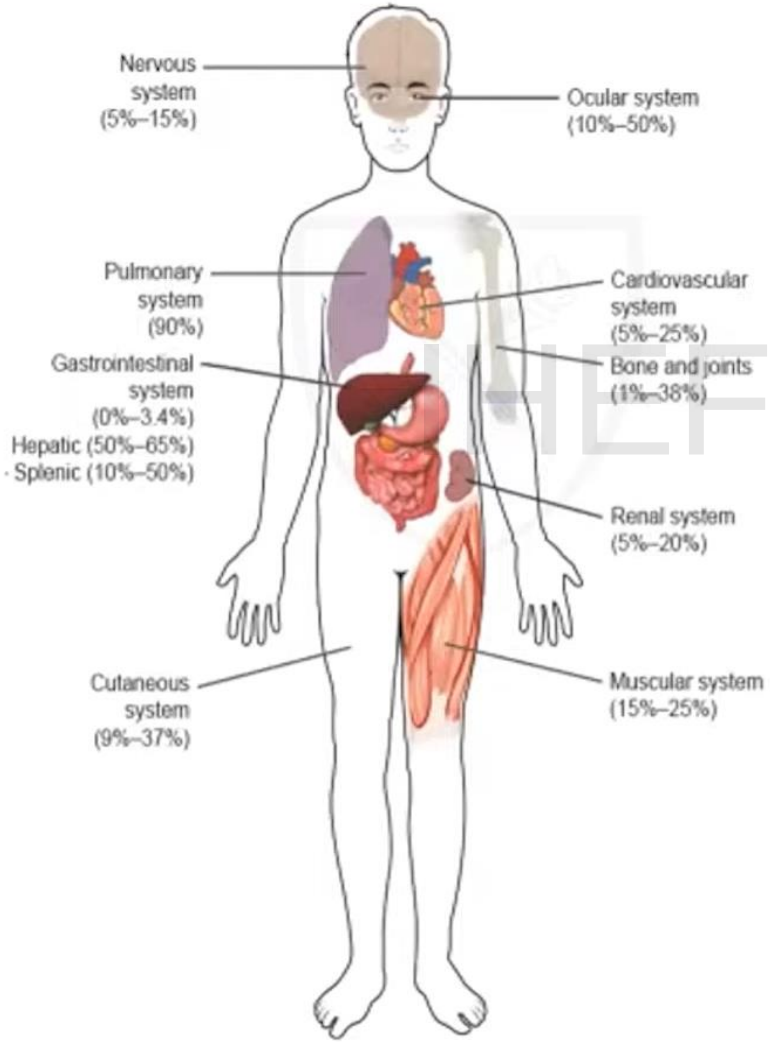
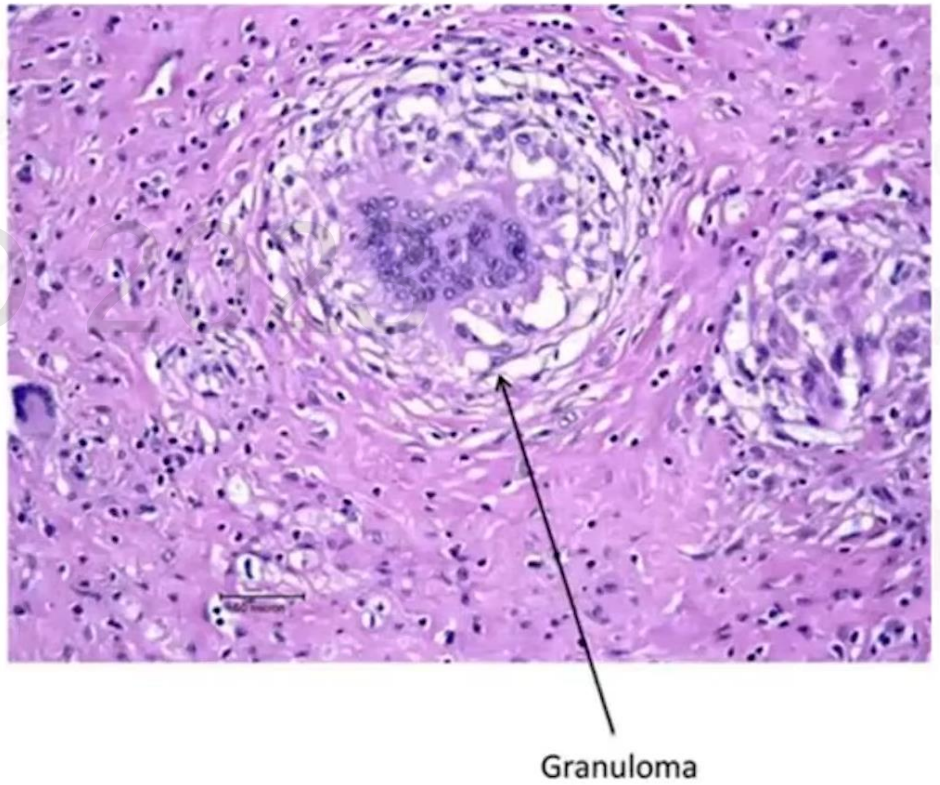
1 CARDIAC SARCOIDOSIS

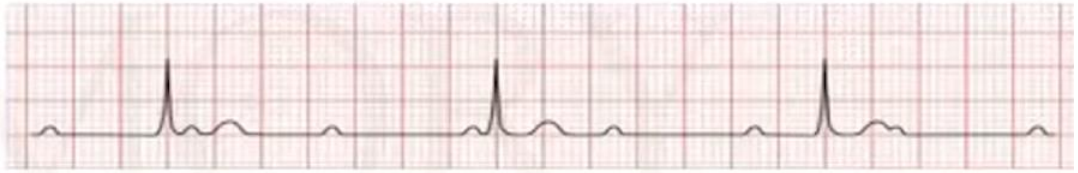


THIS IS NOT A SOLE DIAGNOSIS

- Inflammatory disease of unknown etiology
- Affects multiple systems
- 2-5% cardiac sarcoidosis, maybe as high as 20-30% on autopsy
- Japanese : 58%, cause of death in 85% cases
- Prognosis is poor, patients can deteriorate quickly

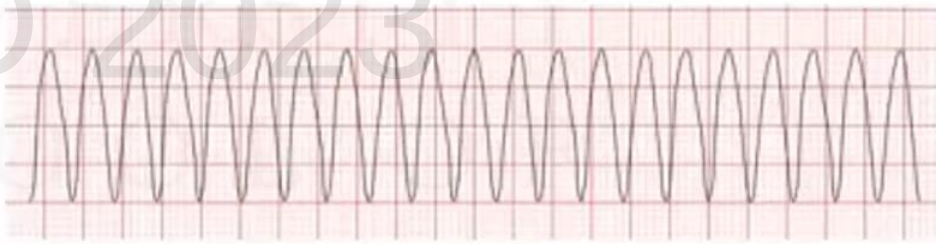


Cardiac Sarcoid: clinical features



Heart Block:

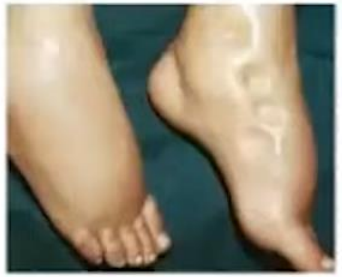
26–62% in AV block, 12–61% in bundle branch block, 28% CHB



Ventricular arrhythmias: 0–15% in SVT,

2–42% in VT, and 12–65% in sudden cardiac death

Congestive heart failure prevalence of 10–30%



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Initial Clinical Manifestation of Sarcoidosis	Reported Prevalence
Arrhythmias	
AV Block	26-62%
Bundle Branch Block	12-61%
Supraventricular Tachycardia	0-15%
Ventricular Tachycardia	2-42%
Sudden Cardiac Death	12-65%
Cardiomyopathy	
Congestive Heart Failure ▶ Left ventricular systolic failure ▶ Heart failure with preserved ejection fraction or restrictive disease ▶ Right ventricular failure secondary to pulmonary disease	10-30%
Pericardial	
▶ Pericardial effusion detected by echo (common) ▶ Pericarditis (rare)	20%

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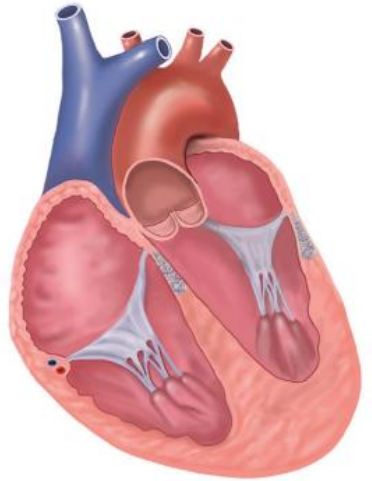
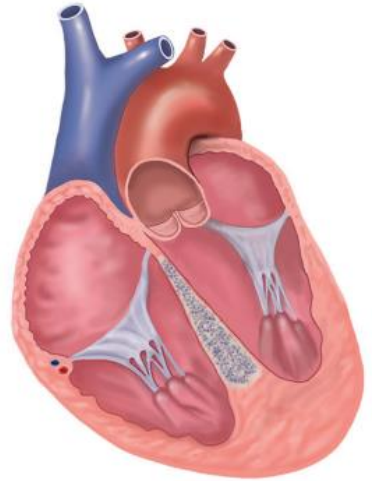
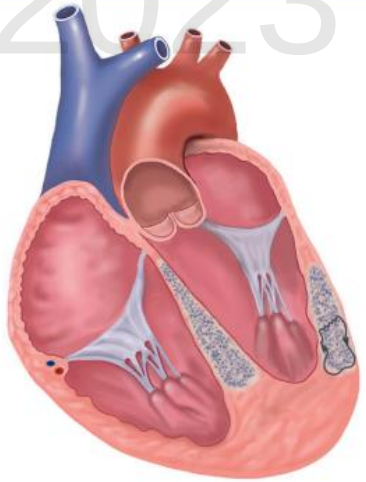


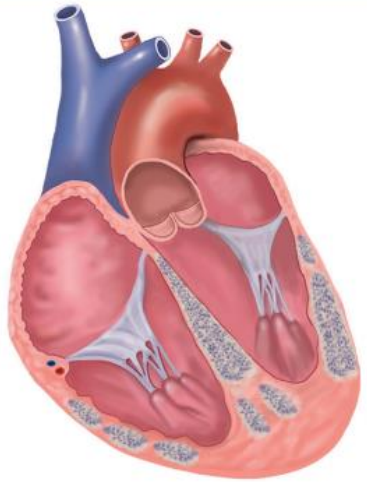
Small patches of basal involvement, usually clinically silent



Large area of septal involvement, often clinically manifest as heart block



Re-entrant circuit involving area of granuloma/fibrosis leading to VT



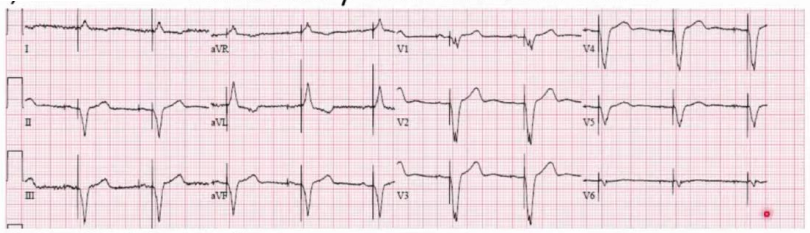
Extensive areas of LV and RV involvement, often clinically manifest as heart failure +/- heart block +/- VT

Birnie, D.H. et al. J Am Coll Cardiol. 2016;68(4):411-21.

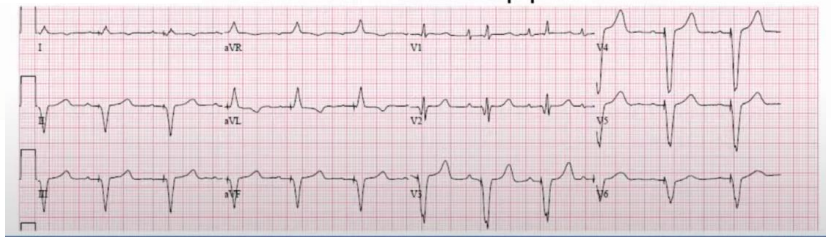
Heart Block

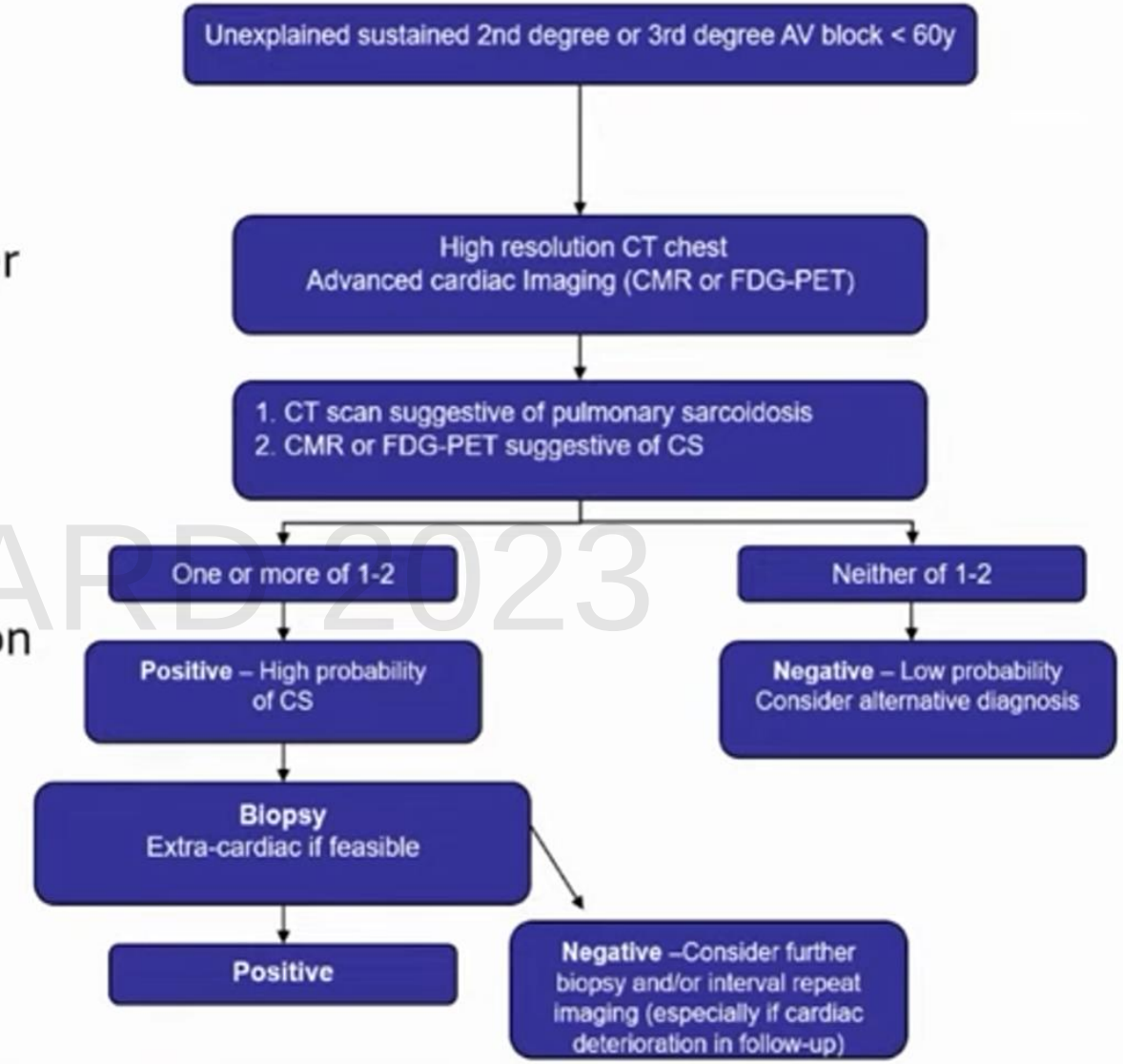
- Unexplained Heart Block Should Trigger Isolated Sarcoidosis Screening*
- Can be Unpredictable (or Predictable)
  - Proximal HPS Inflammation (Quick)
  - Progressive HPS Fibrosis (Very Slow)
- Responsive to Early Immunosuppression

Pulmonary Sarcoidosis Flare



After Immunosuppression





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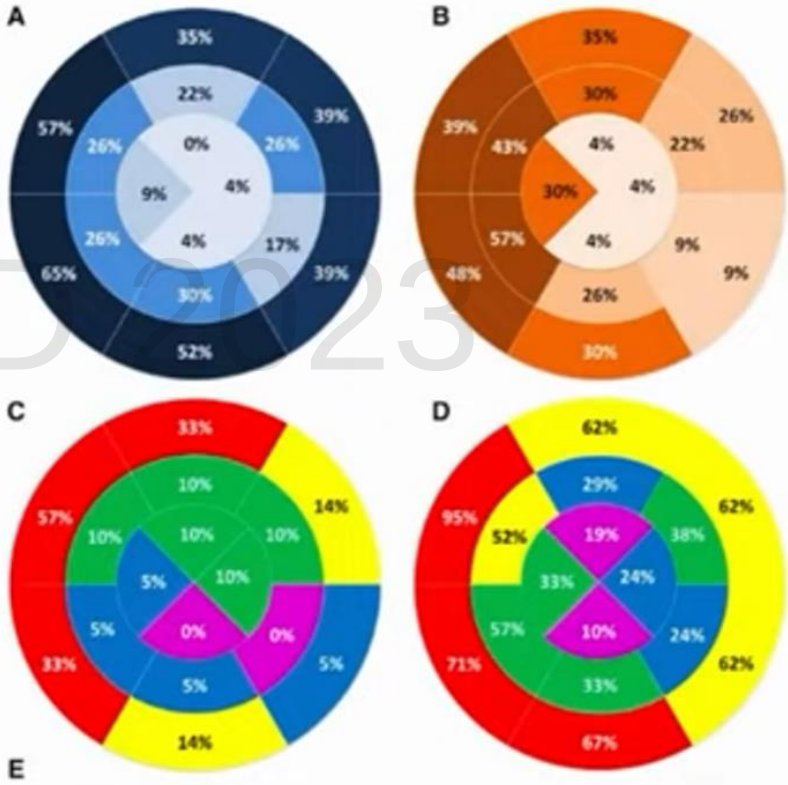
Scar Patterns in Cardiac Sarcoidosis

- Old Teaching
  - Sarcoidosis preferentially affects the septum and conduction system
- New Teaching
  - Sarcoidosis can go anywhere
  - Septum (~90%)
  - Non-Septum (~90%)
  - RV or LV (100%)
  - Endo, Epi, Mid-Myo (100%)



Muser, Marchlinski, et al. Circulation AEP 2016

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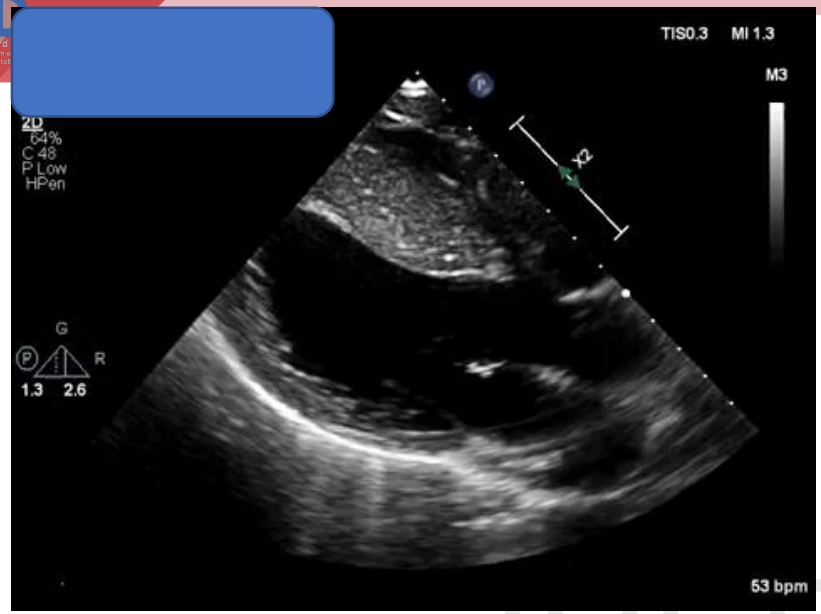

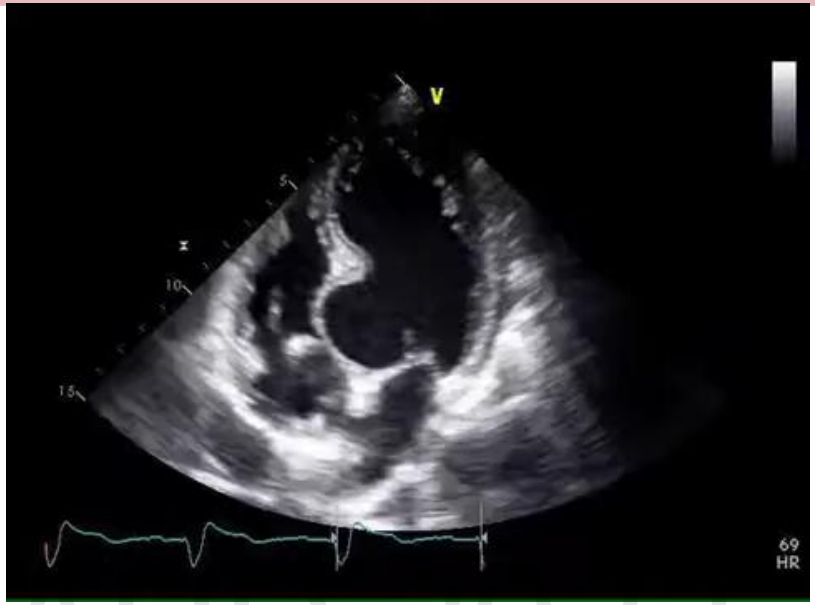

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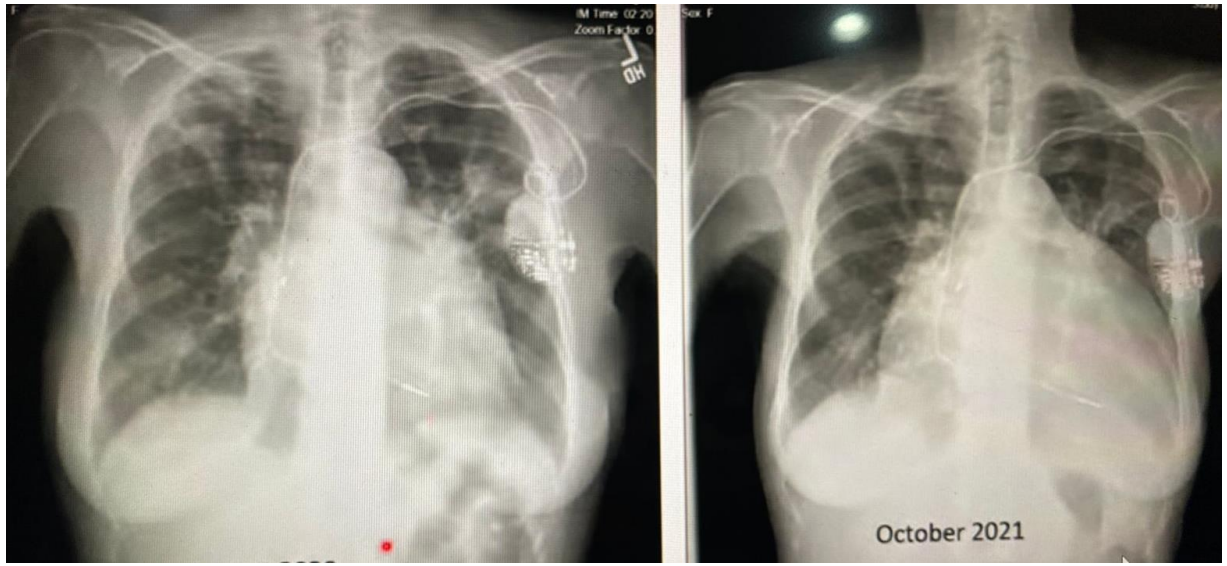
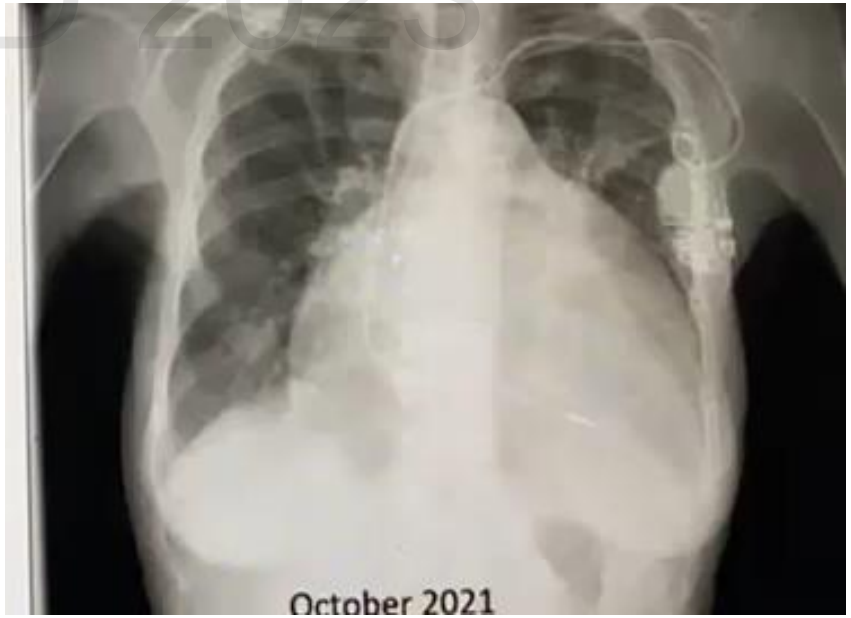
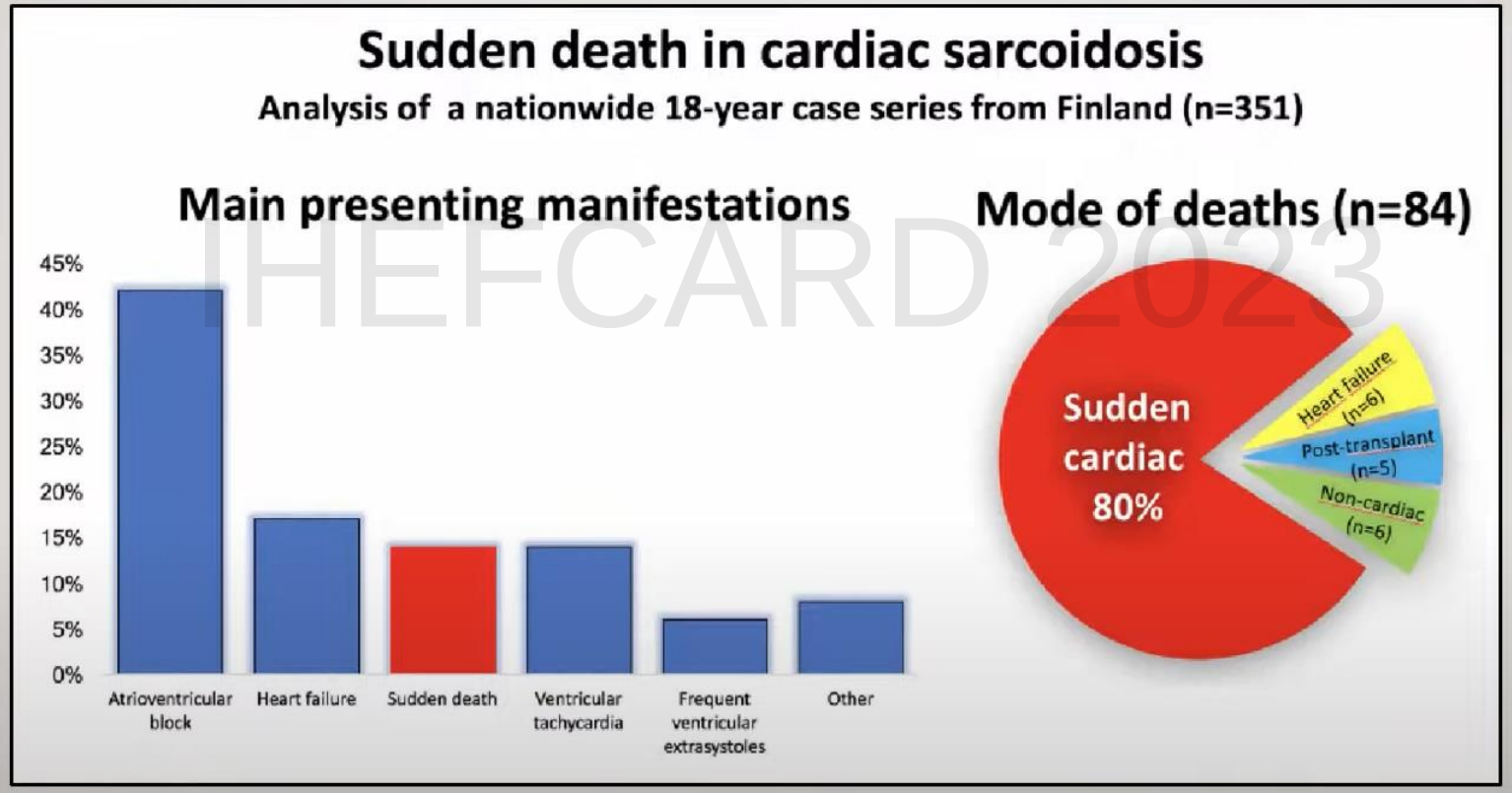




SUDDEN DEATH IN CARDIAC SARCOIDOSIS



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HRS Criteria for the Diagnosis of CS

1. **Histological diagnosis from myocardial tissue**
   CS is diagnosed in the presence of noncaseating granuloma on histological examination of myocardial tissue with no alternative cause identified (including negative organismal stains if applicable)
2. **Clinical diagnosis from invasive and noninvasive studies:**
   It is probable* that there is CS if:
   a) There is a histological diagnosis of extra-cardiac sarcoidosis; and
   b) 1 or more of following is present:
      - Steroid ± immunosuppressant responsive cardiomyopathy or heart block
      - Unexplained reduced LVEF (<40%)
      - Unexplained sustained (spontaneous or induced) VT
      - Mobitz type II second- or third-degree heart block
      - Patchy uptake on and/or late gadolinium enhancement on CMR (in a pattern consistent with CS) and/or positive gallium uptake (in a pattern consistent with CS); and
   c) Other causes for the cardiac manifestation(s) have been reasonably excluded.

Japanese Circulation Society for the Diagnosis of CS (2017)

1. **Histological diagnosis group (those with positive myocardial biopsy findings)**
2. **Clinical diagnosis group (those without a positive myocardial biopsy)**
   Granulomas are found in organs other than the heart, and clinical findings are strongly suggestive of cardiac involvement; or clinical findings are strongly suggestive of pulmonary or ophthalmic sarcoidosis and at least 2 of the 5 characteristic laboratory† and clinical findings of sarcoidosis are strongly suggestive of CS

Clinical findings that strongly suggest the presence of cardiac involvement.

1. 2 or more of the 5 major criteria are satisfied.
2. 1 of the 5 major criteria and 2 or more of the 3 minor criteria are satisfied.

1. **Major criteria**
   a) High-grade atrioventricular block or fatal ventricular arrhythmia (i.e., VT or VF)
   b) Basal thinning of the ventricular septum or abnormal ventricular wall anatomy (ventricular aneurysm, thinning of the middle or upper ventricular septum, regional ventricular wall thickening)
   c) Left ventricular contractile dysfunction (left ventricular ejection fraction <50%)
   d) Abnormalities of ^{67}Ga citrate scintigraphy or ^{18}F-FDG PET
   e) Gadolinium-enhanced CMR with delayed contrast enhancement of the heart
2. **Minor criteria**
   f) Abnormal ECG findings: ventricular arrhythmias (NSVT, multifocal PVCs), bundle branch block, axis deviation, or abnormal Q waves
   g) Perfusion defects on myocardial perfusion scintigraphy (SPECT)
   h) Endomyocardial biopsy: monocyte infiltration and myocardial fibrosis

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Trivieri et al. JACC VOL. 76, NO. 16, 2020

Treatment

Should we treat? →

- **Survival benefit:**
- 5 year survival of 75% in patients who were treated early vs 10% in untreated patients
- **Reduction in AV block and arrythmias**
- Twenty-seven of 57 (47.4%) patients treated with corticosteroids had improvements in AV conduction.
- 16 patients were not treated with corticosteroids and none of them improved.

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Who warrants treatment? →

- **Mobitz II or 3rd degree heat block and evidence of myocardial inflammation**
- **Frequent ventricular ectopy and nonsutained ventricular arrhythmias and evidence of myocardial inflammation**
- **LV dysfunction and evidence of inflammation**

How do we treat? →

- **Steroids**
- **Other immunosuppressive agents.**

TREATMENT

- Corticosteroid treatment
  - Still controversy about clinical efficacy and initial dose dan duration.
  - May halt the progression of cardiac disease and improve survival
  - Does not seem to reduce the incidence of VA
- Antiarrhythmic agents
  - Antiarrhytmic and BB often needed in sarcoid heart disease treatment although no prospective studies evaluate the use
  - BB might actually increase the risk of heart block
  - Amiodaron could exacerbate restrictive lung disease in sarcoidosis
- Pacemakers and ICD
  - May often become necessary if the conduction system is extensively involved
  - VT due to re-entry and has different inducibility between the active and inactive phase of sarcoid heart disease in an EP study
- Cardiac transplantation in younger pts with severe end stage irreversible cardiac failure or resistant VT.
- Sarcoid can attack transplanted heart
- GDMT is a must

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2 HEMOCHROMATOSIS

- PRIMARY and SECONDARY
- PRIMARY : mutation of genes controlling iron absorption → increases iron absorption out of control → autosomal recessive pattern
- SECONDARY : multiple blood transfusions from blood disorders

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CLINICAL MANIFESTATIONS

- Usually occur in 40-50s in men and in women after menopause
- Fatigue, skin hyperpigmentation, arthritis of hands (2nd and 3rd metacarpal phalangeal joints, joint stiffness
- 43% fibromyalgia
- Classical trial : cirrhosis, diabetes mellitus, bronze skin colour
- Siderophilic bacteria/virus : Yersinia enterolitica (foodborne), Vibrio vulnivicus (seafoods), Listeria monocutogenes, Salmonella enterica, Aspergillus fumigatus, Hep B and C

- Organ damages :
  - ✓ Liver : hepatomegaly, fibrosis/cirrhosis, hepatocellular cancer (30% with cirrhosis)
  - ✓ Excessive alcohol drinking and viral hepatitis aggravate liver injury
  - ✓ Heart : HF, cardiomyopathy, arrhythmia, rarely SCD
  - ✓ Endocrine : pancreas (T2DM, Hypopituitarism, hypogonadism, hypothyroidism, adrenal insuff
  - ✓ Brain : cognitive dysfunction, rarely Parkinson disease, amyotrophic lateral sclerosis
  - ✓ Joints : arthritis of the hands, knees, shoulders
  - ✓ Skin : hyperpigmentation. Bronze skin

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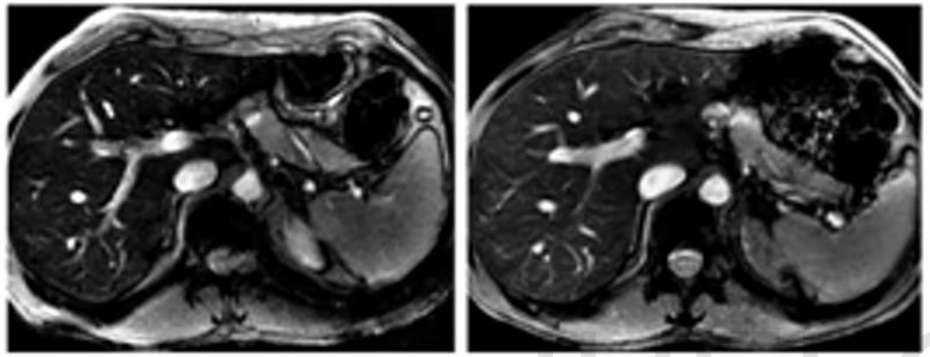
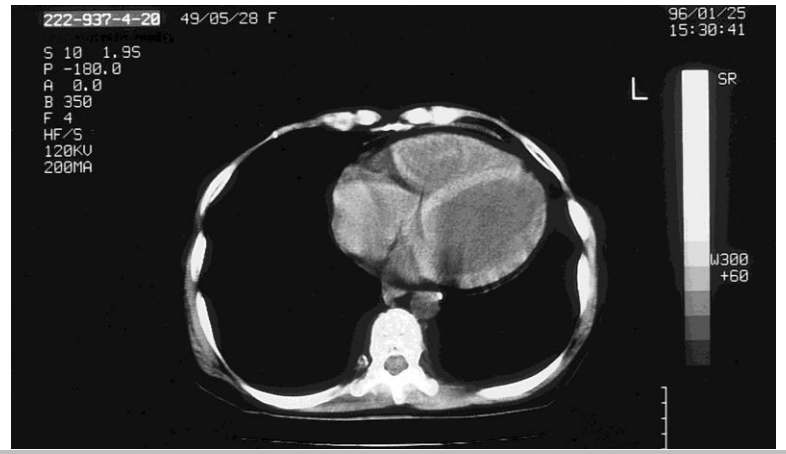
Diagnosis



Hemocromatosis MRI **1 yr after phlebotomies**
(Low signal density in T2 weighted image)
-Educational images by RSNA



Test for serum ferritin and transferrin saturation

- **High serum ferritin*** (>300 ng/ml in men or >200 ng/ml in women)
  and
- **High transferrin saturation*** (> 45%)
- *American Asso. Study of Liver Disease 2011
- If the transferrin saturation is normal, iron overload is unlikely.

Test for HFE mutation
(C282Y/C282Y or C282Y/H63D)

(+) → **Hereditary hemochromatosis**

(-) → **Hereditary hemochromatosis with a different genotype** (HJV,HAMP, HFR2, or SLC40A1) or **acquired iron overload**

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TREATMENT

- PHLEBOTOMY
  - ✓Prevent organ dysfunction and improve organ function
  - ✓Not necessary in pts without iron overload
  - ✓Some HFE mutation do not develop iron overload, but the ferritin level may be high due to infection, inflammation, alcohol, hepatitis → MRI
- IRON CHELATION
  - ✓Start if serum ferritin >1000 ng/ml
  - ✓Limited use in pts who can not tolerate phlebotomy

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3 What is Amyloid

- A disorder of misfolded protein
- Misfolded protein deposit in organs and tissues
- AMYLOID TYPE (Cardiac involvement)
  - AL : cardiac biopsy + in all (variable clinical significance)
  - ATTR (familial) : varies with mutation, spectrum from neuropathy to cardiomyopathy
  - SSA (senile=wild type) : isolated cardiac + carpal tunnel

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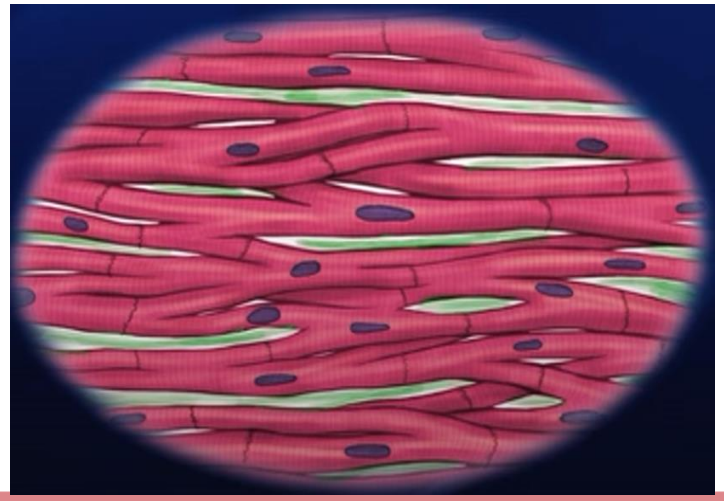
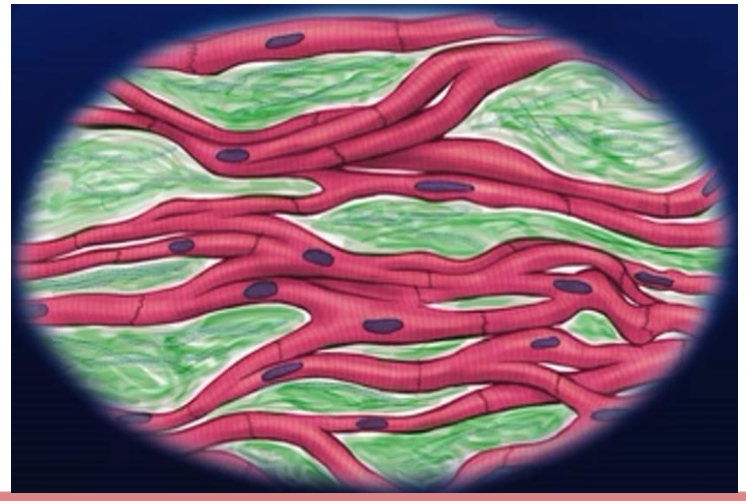
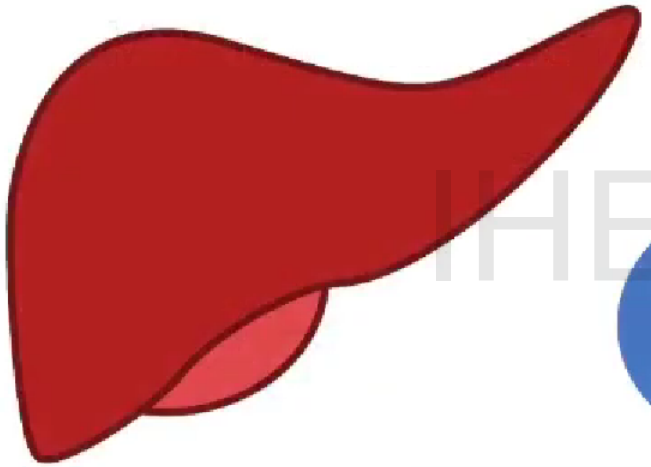
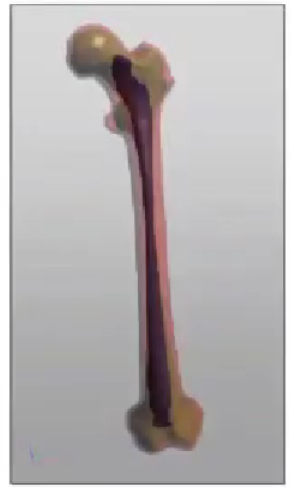




Amyloid



- Amyloid
  - ATTR
    - Wild Type
      - Senile
    - Genetic
      - Mutant
  - Light Chain (AL)



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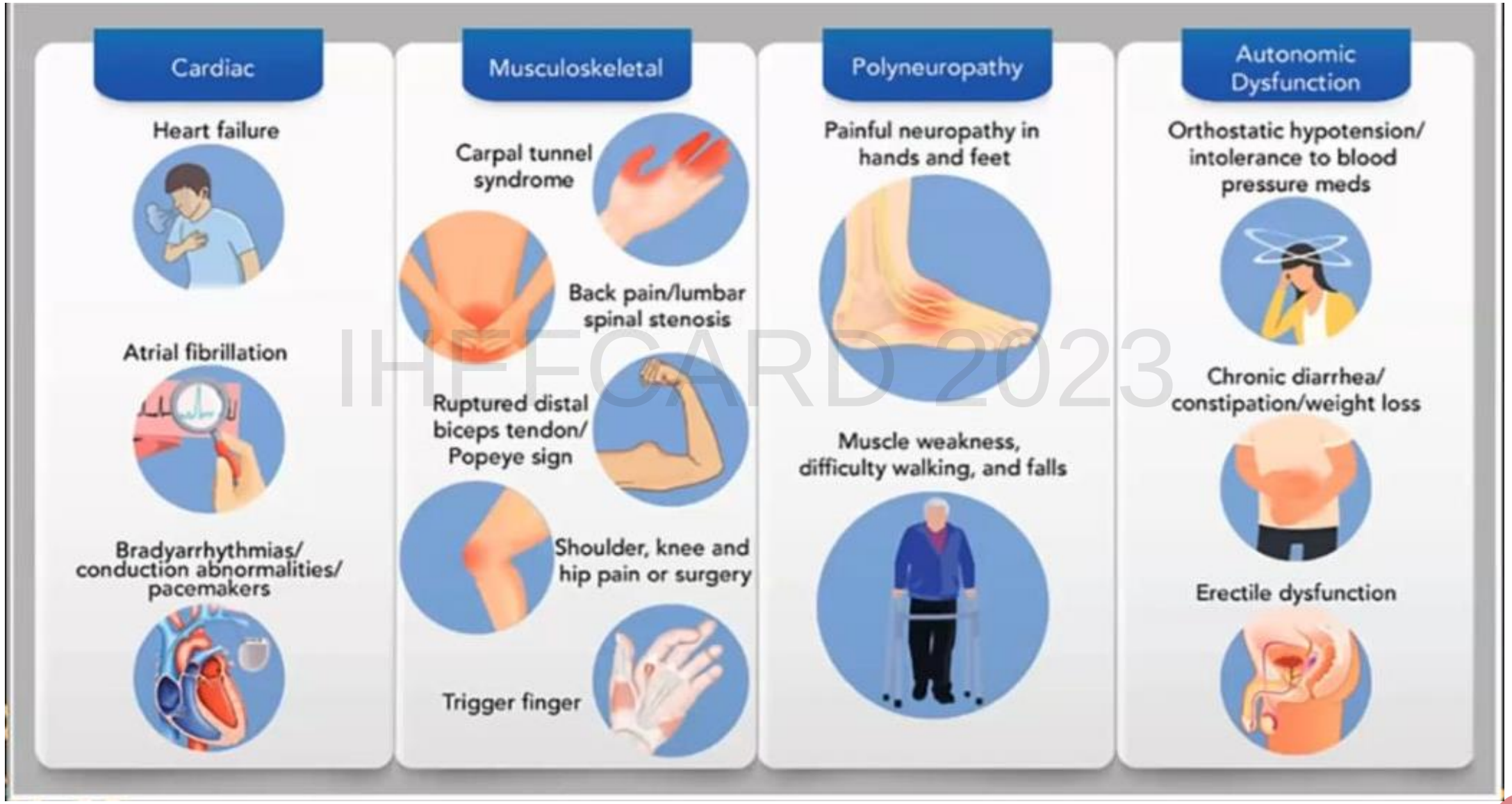

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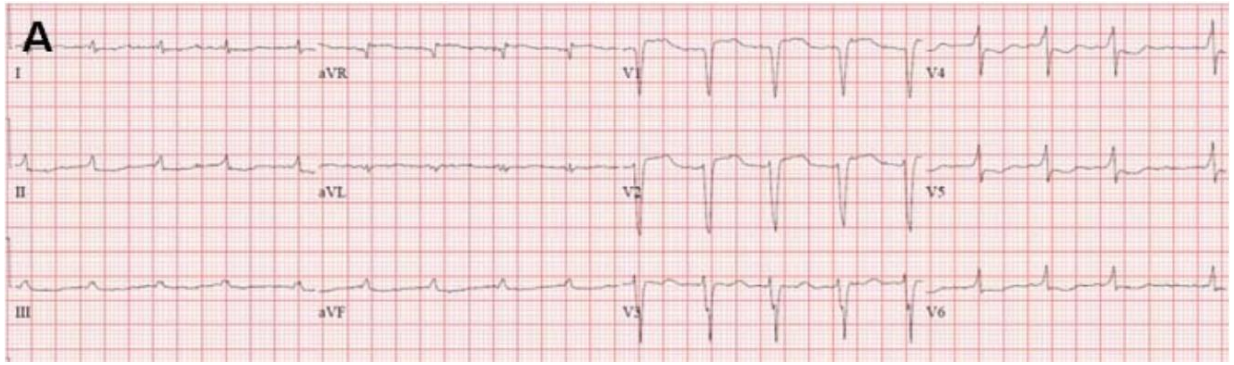
- PRESENTATION : Vague, common symptoms
  - Dyspneu, fatigue, chest pain
  - AF, syncope, stroke, conduction disease
  - Overt heart failure
    - Unexplained weight loss
    - Peripheral or autonomic neuropathy
    - Nephrotic syndrome
    - Unexplained hepatomegaly

Delayed Diagnosis
A major factor in poor prognosis



ECG in Cardiac Amyloid

ECG	AL (n=127)	TTR-Senile (177)	TTR-Fam (82)
Low voltage	45%	10%	4%
Pseudo-infarct	47	24	14
AF	10	34	10
LVH	16	3	10

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Red Flags - Cardiac

- Heart failure (preserved EF) HFpEF
- Unexplained increased wall thickness on echo >12 mm
- Low voltage on EKG (56%)
- Aortic Stenosis, 16% of TAVR evaluations, thickened of valves
- New normalization of BP
- Atrial fibrillation
- Intolerance to HF meds

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Red Flags for Cardiac Amyloidosis

Echocardiography:
- Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm
- Thickening of right ventricle free wall, valves

Intolerance to beta-blockers or ACE inhibitors

Low normal blood pressure in patients with a previous history of hypertension

History of bilateral carpal tunnel syndrome, often requiring surgery

AL	ATTR
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of *hypertrophic cardio*myopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

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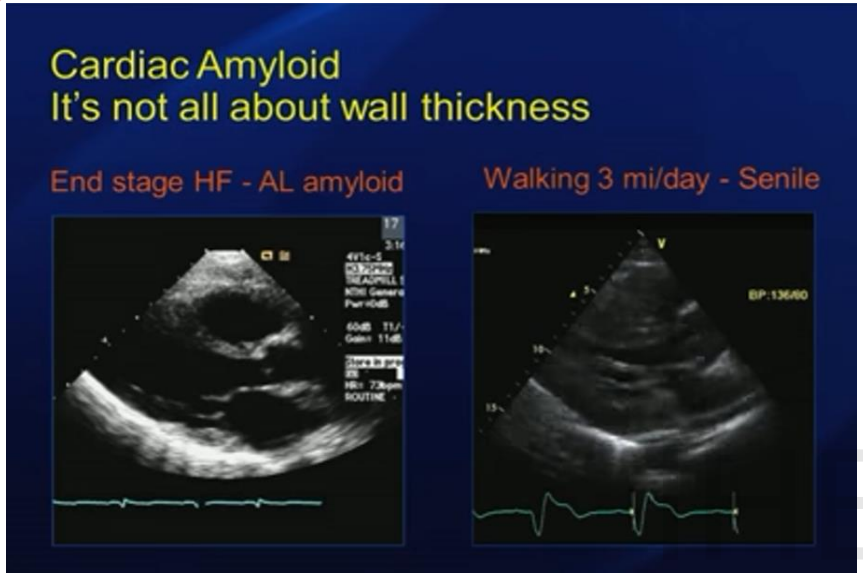
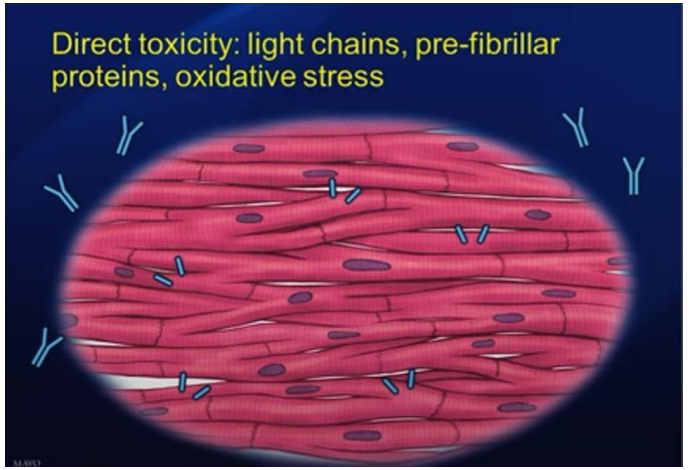
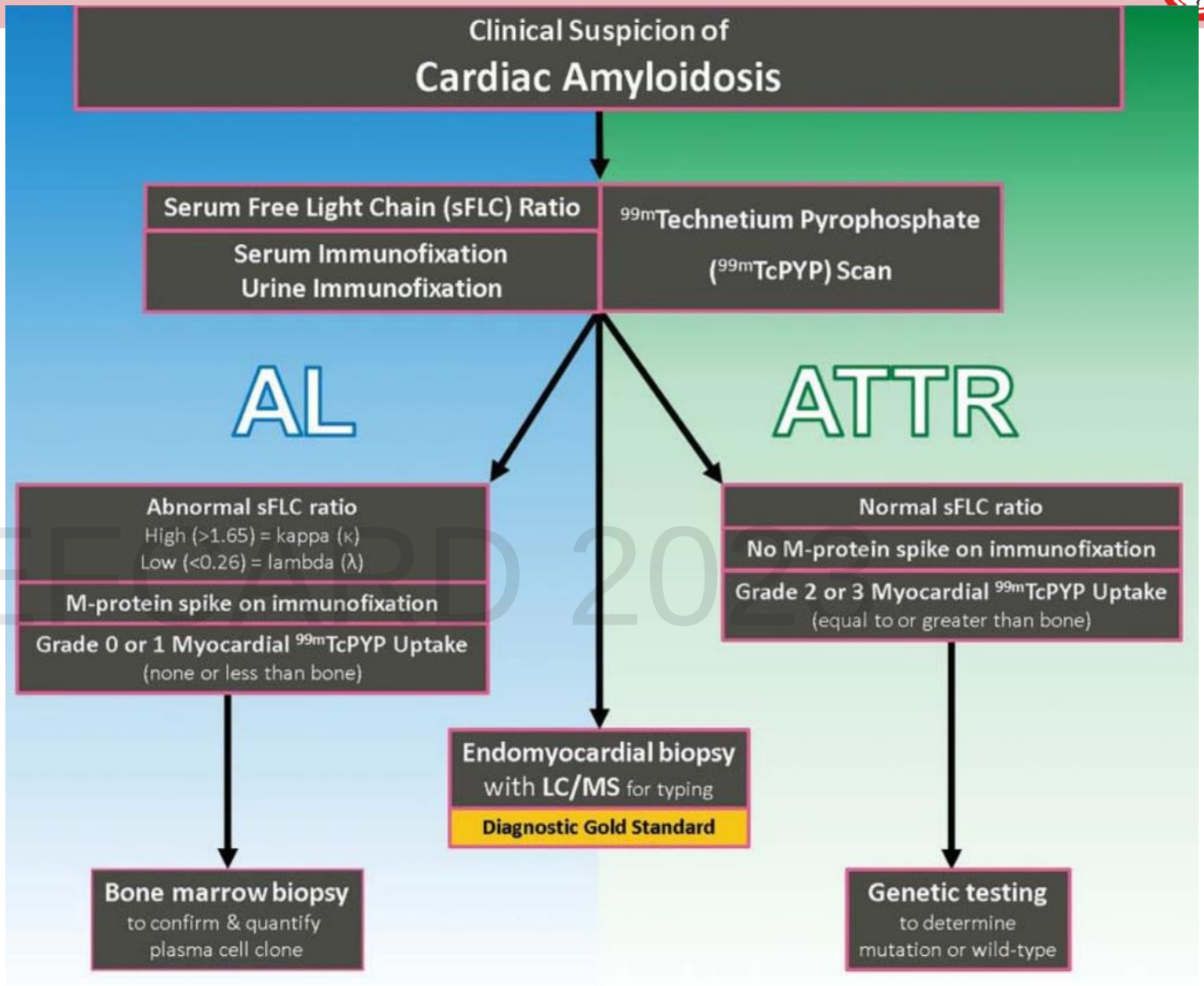
Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. Cleve Clin J Med. 2017





Donnelly JP, Hanna M.. Cleve Clin J Med. 2017



Consider gene sequencing:
ATTRZ / *TTR* Gene,
Full Gene Analysis, Varies

Consider gene sequencing, as appropriate:
- APO1Z / Apolipoprotein A-I (*APOA1*) Gene, Full Gene Analysis, Varies
- APO2Z / Apolipoprotein A-II (*APOA2*) Gene, Full Gene Analysis, Varies
- GSNZ / Gelsolin (*GSN*) Gene, Full Gene Analysis, Varies
- LYZZ / Lysozyme (*LYZ*) Gene, Full Gene Analysis, Varies
- FGAZ / Fibrinogen Alpha-Chain (*FGA*) Gene, Full Gene Analysis, Varies

Management of cardiac amyloidosis

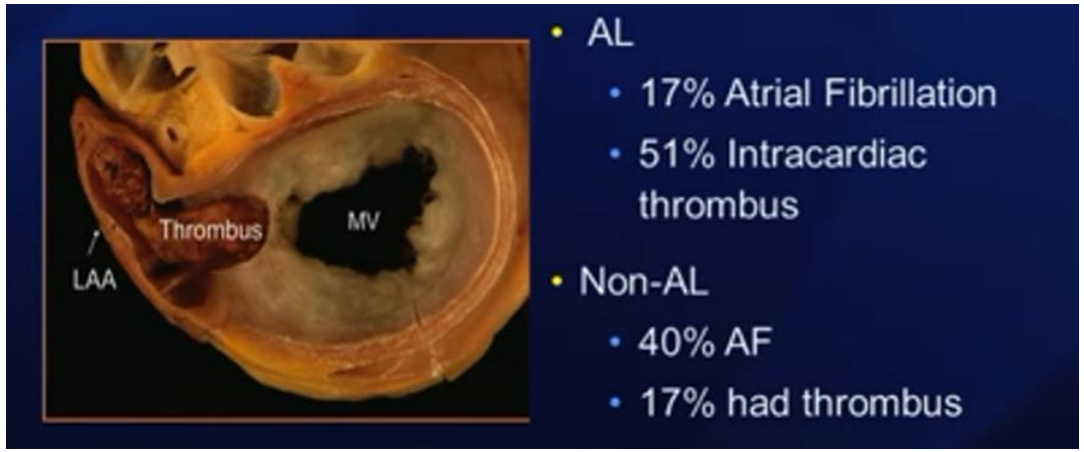
Heart failure

- ARNI/ACE inhibitor/ARB, BB may worsen restrictive physiology
- MRA and SGLT2i may be considered
- Loop + thiazide diuretic agents
- Heart transplant in select advanced patients
- Palliative care

Anticoagulation indicated in AF regardless of CHA_2DS_2-VASc score

Arrhythmias

- Atrial fibrillation: rate/rhythm + anticoagulation
- PPM for heart block
- ICD for VT/aborted SCD
- CRT if PPM-dependent?



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- Supportive care
- Diuretics
- Pleurx catheter
- Patient and family education
- AF – challenging – accept higher heart rate due to restrictive hemodynamics
- Digoxin may be preferable to beta/calcium channel blocker – low dose, level 0.5-0.8 ng/ml

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ATTRwt-CM

Tafamidis

- *Complex authorization process for tafamidis with potentially high copayments*
- *Avoid prescribing to patients who are too well (preclinical) or too sick (NYHA class IV) to benefit*

ATTRv-CM

Cardiomyopathy

Tafamidis

Neuropathy

TTR silencer therapy in collaboration with neurologist

AL-CM

Plasma-cell-directed in collaboration with hematologist (see Figure 12)

TAKE HOME for US.....

CONDITION	EPIDEMIOLOGY	PATHOLOGY	ECG	ECHOCARDIOGRAM	CMR	TREATMENT
Cardiac amyloidosis	6th or 7th decade acquired (AL, SSA) or inherited (ATTR)	Extracellular amyloid fibrils	Low-voltage QRS; pseudoinfarction; AV block	LV and RV hypertrophy; granular speckled myocardium; restricted basal longitudinal strain	Global LGE (Also consider radionuclide scanning)	AL: chemotherapy (CyBordD); TTR: diflunisal/tafamidis; ± heart-liver transplant
Cardiac Sarcoidosis	3rd or 4th decade; African Americans, northern Europeans, Japanese; female>male	Noncaseating granulomas surrounded by fibrosis	High-grade AV block	Septal thinning/ thickening; noncoronary segmental wall motion abnormalities	Pathy LGE, predominantly LV free wall and basal septum (Also consider FDG-PET)	Corticosteroids, PPM/ICD; ± cardiac transplant
Hemochromatosis/IOC	4th or 5th decade; inherited (*primary, HFE* mutation) or acquired (secondary)	Intracellular iron	Nonspecific repolarization abnormalities	Diastolic disease ± global systolic dysfunction	Shortened T2* time	Phlebotomy; chelation
Fabry Disease	2nd through 5th decade X1 linked error of glycosphingolipid metabolism	Perinuclear vacuoles and myocardial fibrosis	Increased voltage QRS	Concentric LV hypertrophy	LGE of the basal segments of the anterolateral and inferolateral walls	Enzyme replacement
Danon Disease	2nd or 3rd decade; inherited (LAMP2 deficiency)	Myocyte hypertrophy with vacuolization	Increased voltage QRS; short PR with delta wave	Massive LV hypertrophy with possible outflow tract obstruction	Sunbendocardial LGE sparing the septum	Supportive
Friedreich's Ataxia	2nd and 3rd decade; inherited (*frataxin* mutation)	Nonspecific myocyte hypertrophy and fibrosis	Nonspecific repolarization abnormalities	Increased septal thickness	Not used	Supportive

Abbreviations: CMR, cardiac magnetic resonance; ECG, electrocardiography; IOC, iron overload cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricle; RV, right ventricle.

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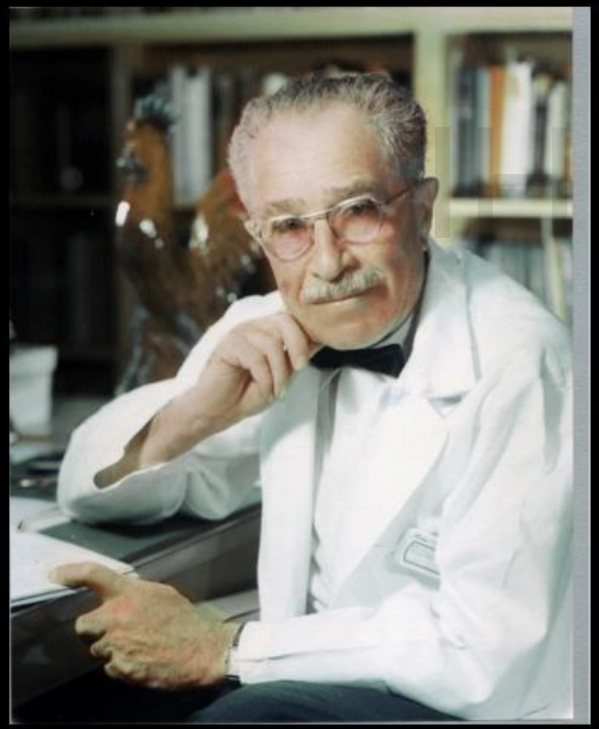
Altered Phenotypes in the Failing Heart



"The failing heart is not simply an enlarged version of the normal heart"

Louis N. Katz, 1966

Changes in:

- Architectural Phenotype
- Cellular Phenotype
- Molecular Phenotype

BECAUSE HEART FAILURE DOES MATTER

THANK YOU