
UNIVERSITÀ
DEGLI STUDI
DI PADOVA

# CARDIOMIOPATIA IPERTROFICA

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## Hypertrophic cardiomyopathy

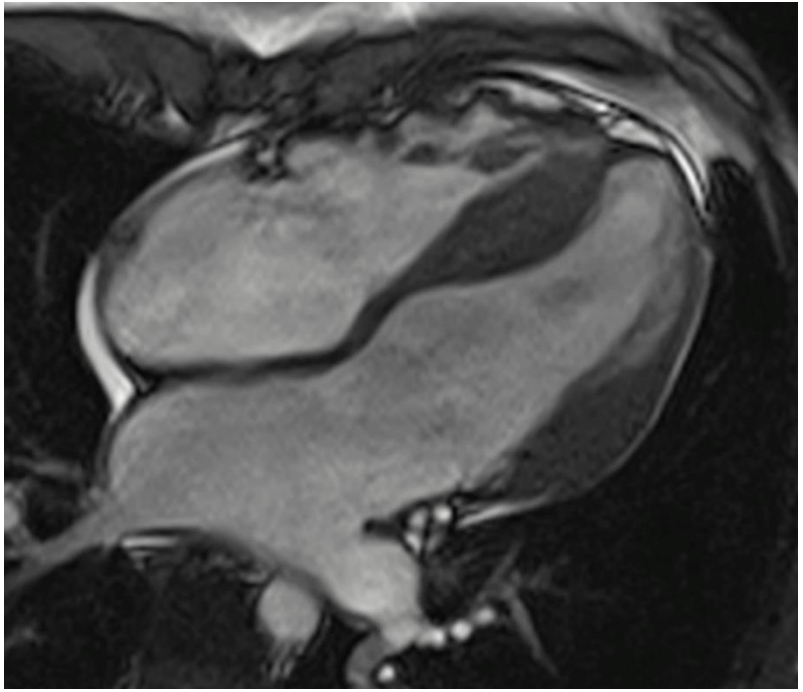
Wall thickness ≥ 15 mm (13 mm if familiar)

Most frequent cardiomyopathy (1:3-500)

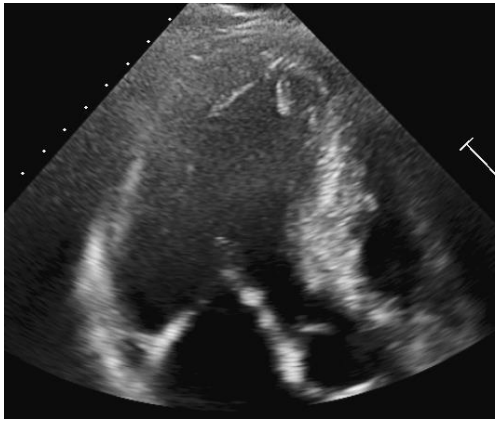
Underestimated

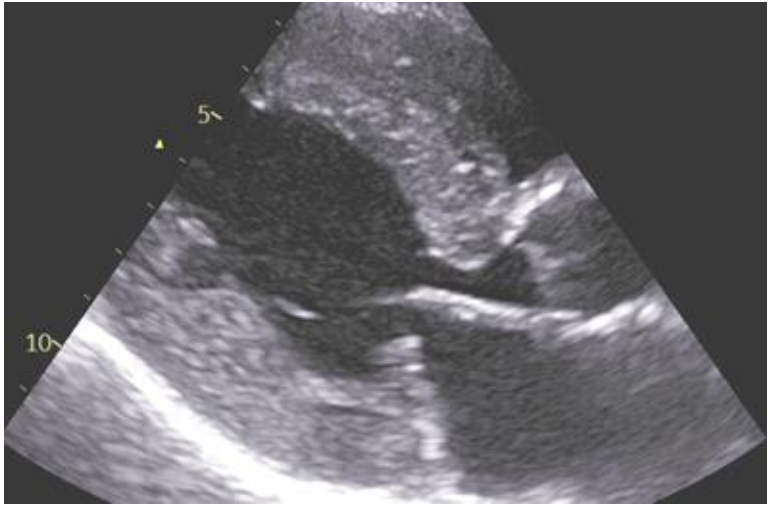
Frequently affects young people

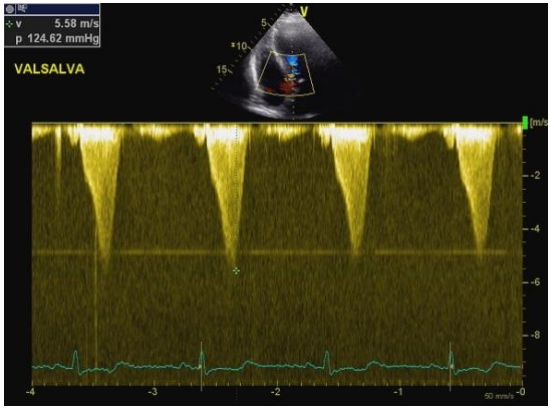
Common cause of SCD and HF



# HCM: Echo






- Availability
- Affordability
- Accessibility
- Portability

**HCM IS NOT ANYMORE A SUFFICIENT DIAGNOSIS**

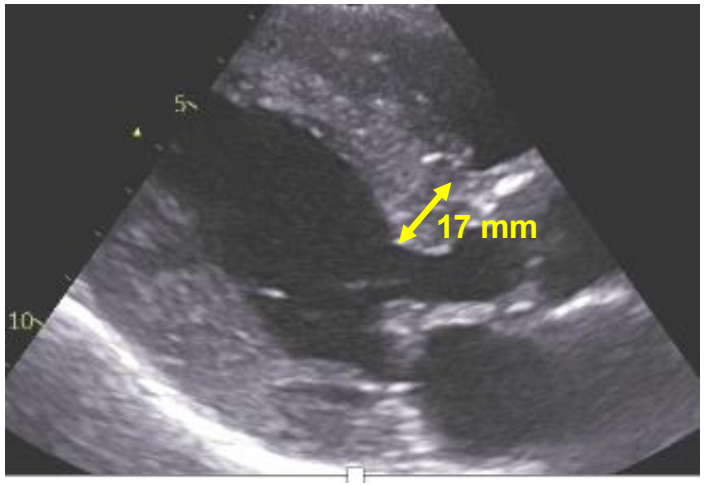
**WHY THIS HEART IS THICKENED?**

- LVOTO
  - Doppler
  - Valsalva
  - Exercise
- SAM
- GLS

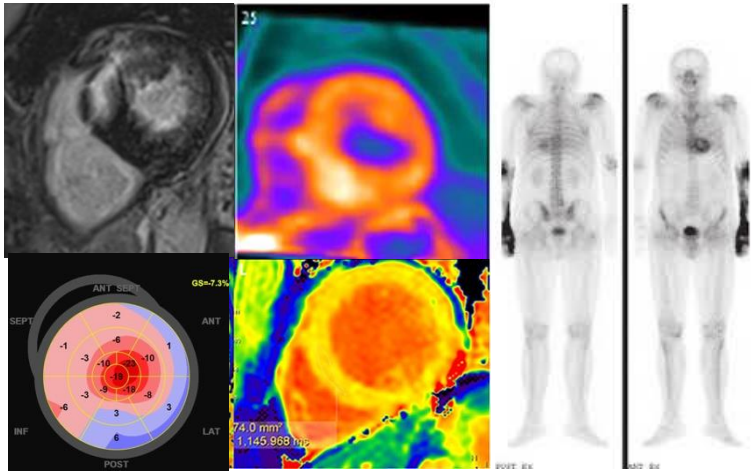
# Phenotype is the key

# HCM → CM with Hypertrophic Phenotype

## CHANGING DIAGNOSTIC APPROACH



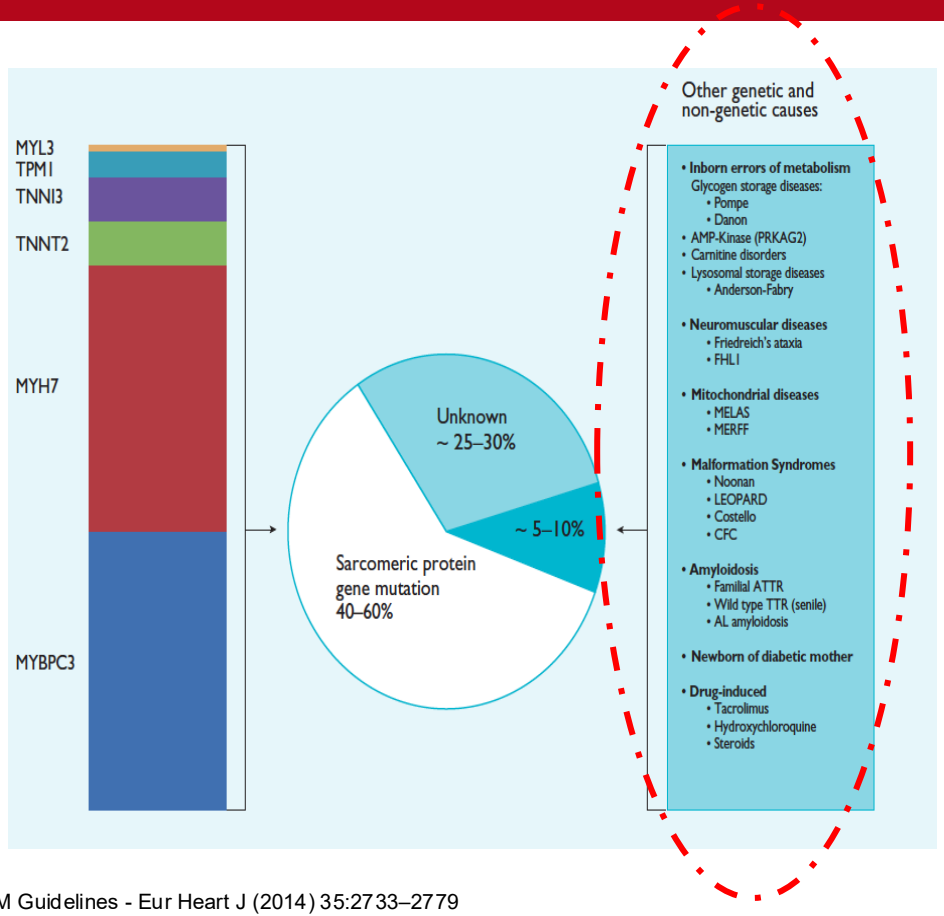

Structural/anatomic abnormality

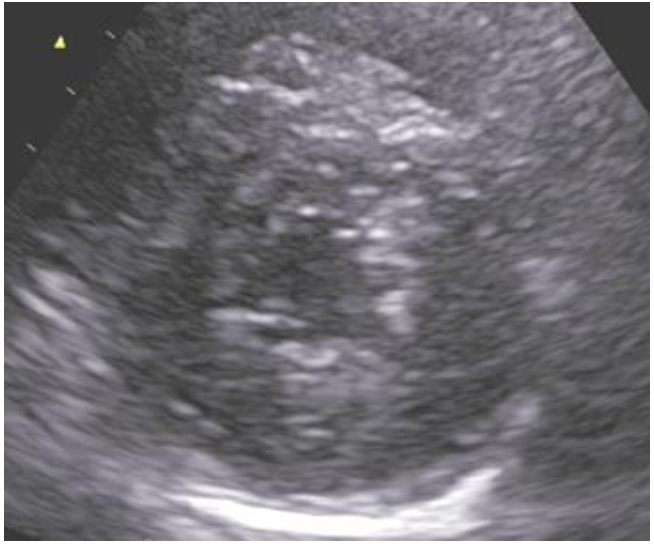


Pathobiological hypothesis
Etiologic diagnosis

**ETIOLOGIC DIAGNOSIS → SPECIFIC TREATMENT**

# HCM → CM with Hypertrophic Phenotype



ESC HCM Guidelines - Eur Heart J (2014) 35:2733–2779

# CMR in HCM: Guidelines

**Recommendations for cardiovascular magnetic resonance evaluation in hypertrophic cardiomyopathy**

| Recommendations | Class[a] | Level[b] | Ref.[c] |
|---|---|---|---|
| It is recommended that CMR studies be performed and interpreted by teams experienced in cardiac imaging and in the evaluation of heart muscle disease. | I | C | 148,149 |
| In the absence of contraindications, CMR with LGE is recommended in patients with suspected HCM who have inadequate echocardiographic windows, in order to confirm the diagnosis. | I | B | 126,127 |
| In the absence of contraindications, CMR with LGE should be considered in patients fulfilling diagnostic criteria for HCM, to assess cardiac anatomy, ventricular function, and the presence and extent of myocardial fibrosis. | IIa | B | 124,126,127,130 136,138–143 |
| CMR with LGE imaging should be considered in patients with suspected apical hypertrophy or aneurysm. | IIa | C | 127,129 |
| CMR with LGE imaging should be considered in patients with suspected cardiac amyloidosis. | IIa | C | 22,147 |
| CMR with LGE may be considered before septal alcohol ablation or myectomy, to assess the extent and distribution of hypertrophy and myocardial fibrosis. | IIb | C | 150,151 |

ESC 2014

## 6.3. Cardiovascular Magnetic Resonance Imaging

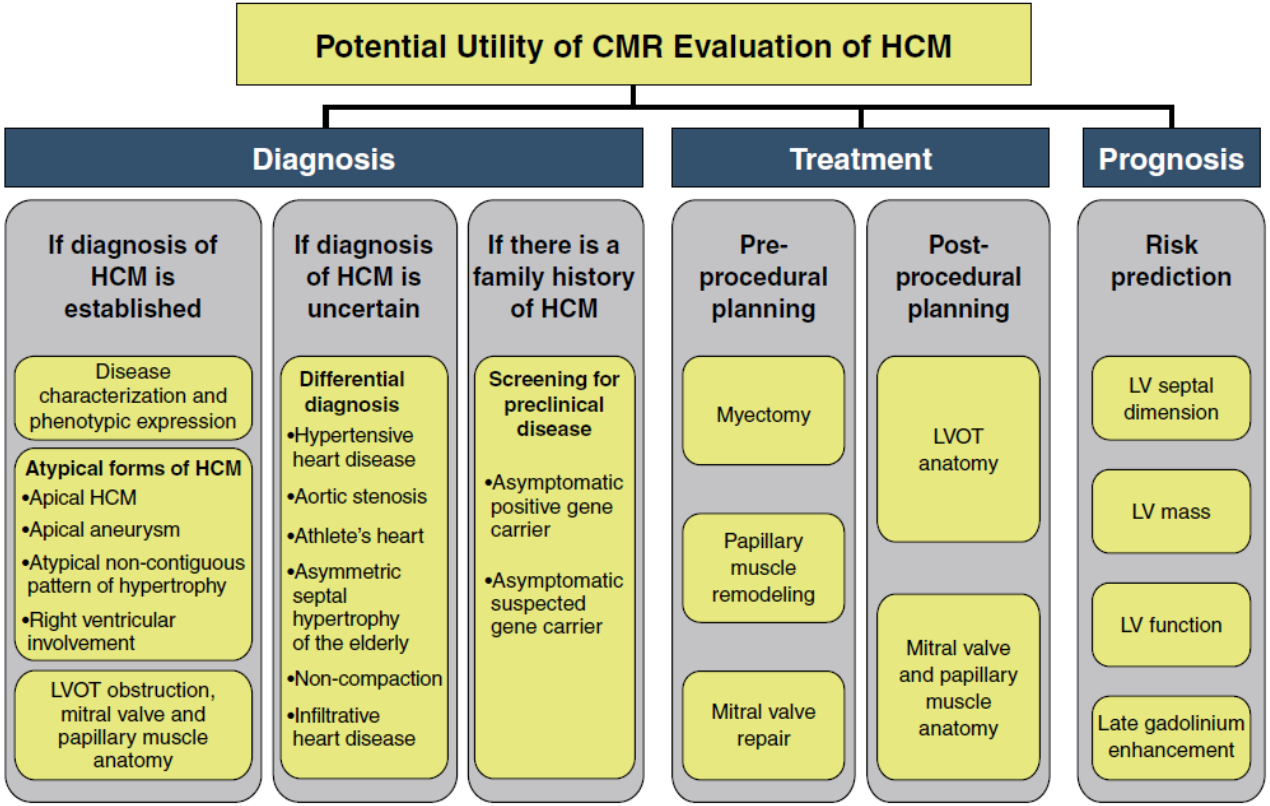
**Recommendations for CMR Imaging**

**Referenced studies that support the recommendations are summarized in Online Data Supplement 4.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. For patients suspected to have HCM in whom echocardiography is inconclusive, CMR imaging is indicated for diagnostic clarification.[1–7] |
| 1 | B-NR | 2. For patients with LVH in whom there is a suspicion of alternative diagnoses, including infiltrative or storage disease as well as athlete's heart, CMR imaging is useful[1–7] (Figure 1). |
| 1 | B-NR | 3. For patients with HCM who are not otherwise identified as high risk for SCD, or in whom a decision to proceed with ICD remains uncertain after clinical assessment that includes personal/family history, echocardiography, and ambulatory electrocardiographic monitoring, CMR imaging is beneficial to assess for maximum LV wall thickness, ejection fraction (EF), LV apical aneurysm, and extent of myocardial fibrosis with LGE.[1–15] |
| 1 | B-NR | 4. For patients with obstructive HCM in whom the anatomic mechanism of obstruction is inconclusive on echocardiography, CMR imaging is indicated to inform the selection and planning of SRT.[16–20] |

AHA 2020

# CMR in HCM




*To AY, JACC CVI 2011*

# Outline

Hypertrophic Cardiomyopathy

Athlete's heart

Arterial Hypertension and Aortic Stenosis

(Cardiac Amyloidosis)

Anderson-Fabry

Iron overload

Other rarity

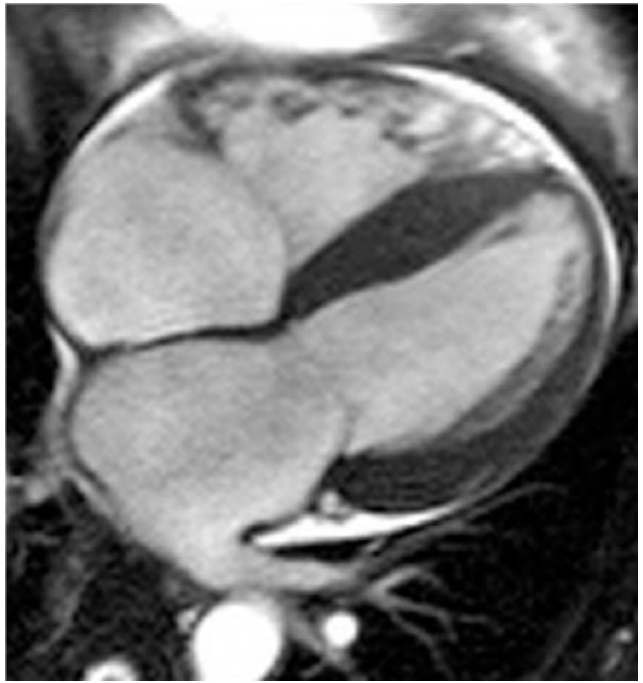
# HCM: Intro

Characterized by LVH

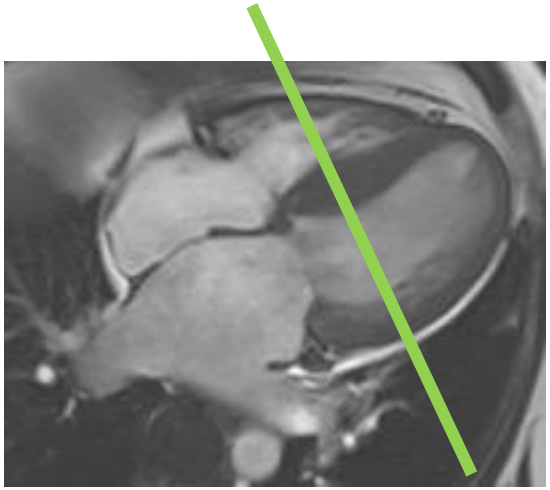
- LV outflow obstruction
- Mitral regurgitation
- Diastolic dysfunction
- Myocardial ischemia

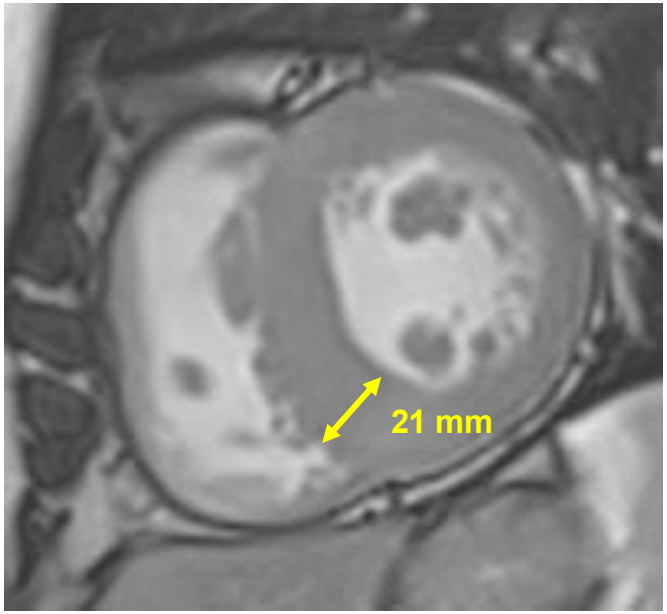
These structural and functional abnormalities produce a variety of symptoms, including:

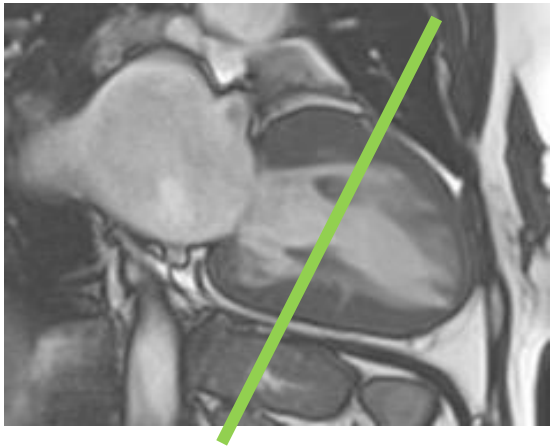
- Dyspnea
- Chest Pain
- Palpitation
- Presyncope/Syncope
- Fatigue



# Thickness estimation: general rules





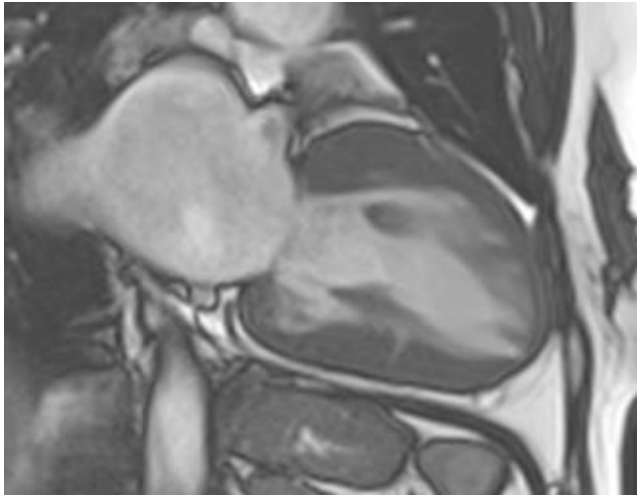



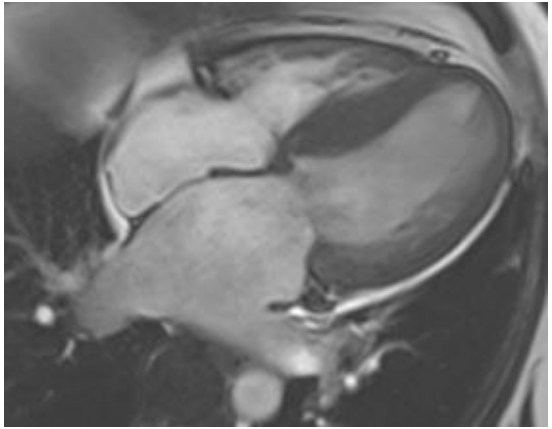
1. **Measure on SAX images**

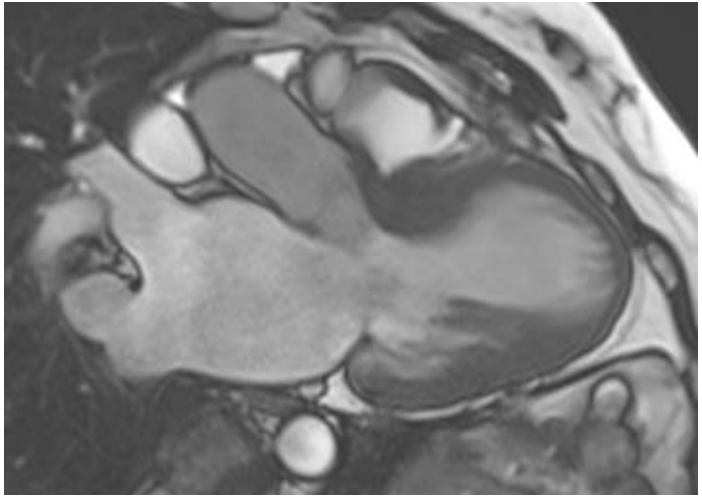
(SAX must be perpendicular to IVS and anterior wall)

2. **Assess multiple segments and describe in report**
3. **Careful with septo-marginal trabeculations**

# CMR in HCM: Long axis

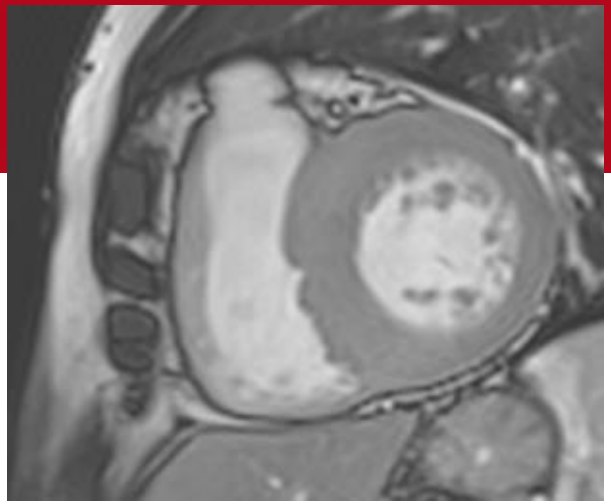


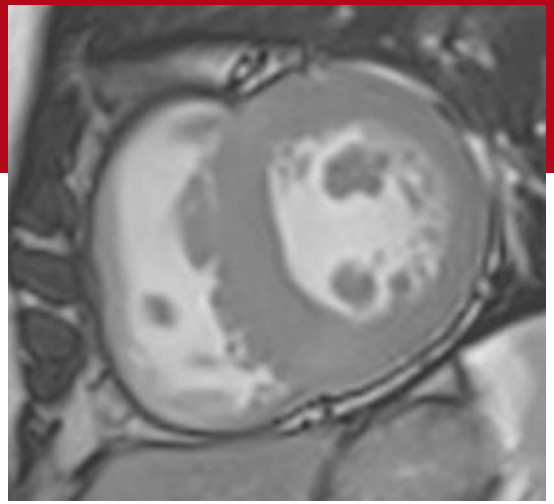


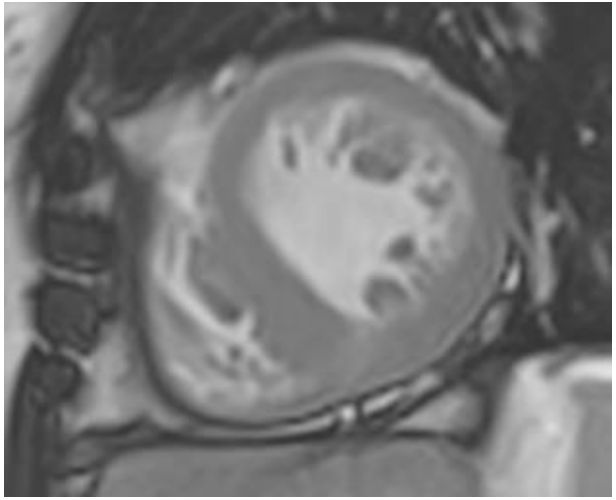


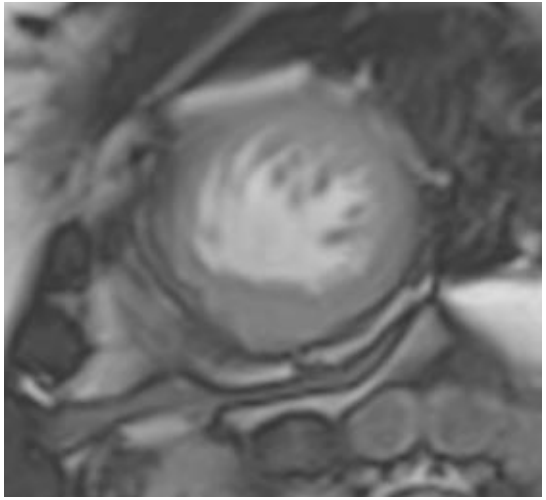
1. LVH (asymmetric)
2. Reduced cavity size
3. Crypts
4. RV and IAS hypertrophy
5. Papillary muscle abn
6. Apical aneurysm
7. LVOT Obstruction
8. SAM of LAM
9. Mitral valve abn and mitral regurgitation

# CMR in HCM: short axis





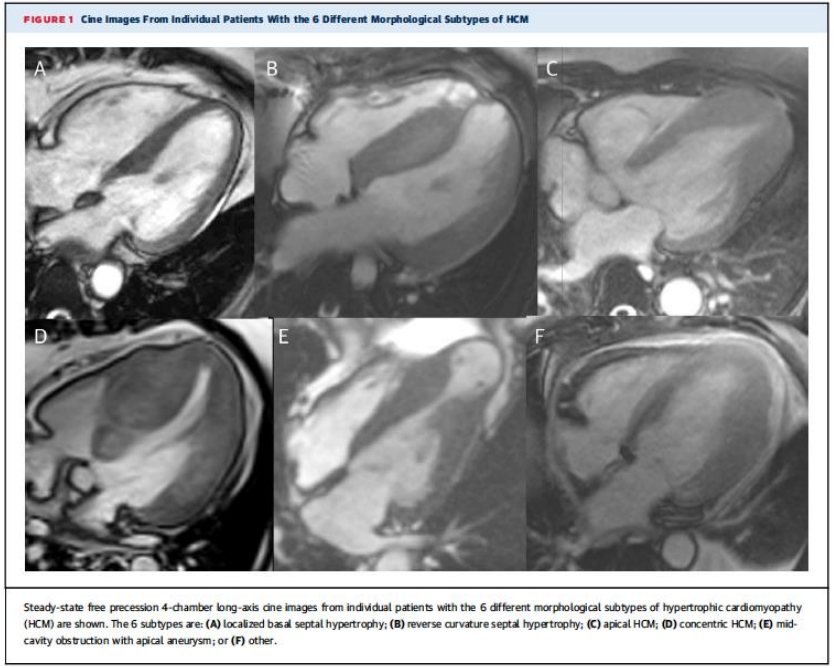




1. LVH subtypes
2. Asymmetry (>1.3-1.5)
3. RV hypertrophy (>7mm)
4. Papillary abnormalities

# HCM phenotypic heterogeneity

## HCMR project
## 2755 pts with HCM



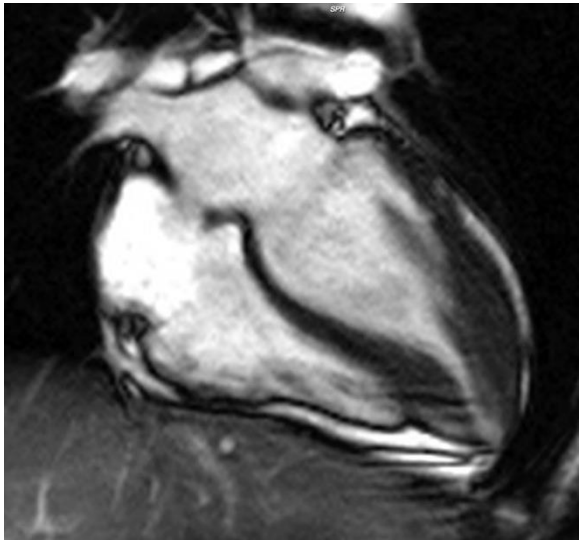

**6 different morphological subtypes of HCM:**

a) localized basal septal hypertrophy
b) reverse curvature septal hypertrophy
c) apical HCM
d) concentric HCM
e) Midcavity obstruction with apical aneurysm
f) other

Neubauer et al JACC 2019

## Apical HCM

- The normal left ventricular wall tapers towards the apex
- Apical HCM have wall thickness in the apex ≥15 mm and a ratio of maximal apical to basal posterior wall thickness ≥1.5 (*relative apical hypertrophy*)
- ECG lateral T-wave inversion and relative apical hypertrophy are core features.
- Additional features include a dilated left atrium, scarring, apical cavity obliteration and apical microaneurysms



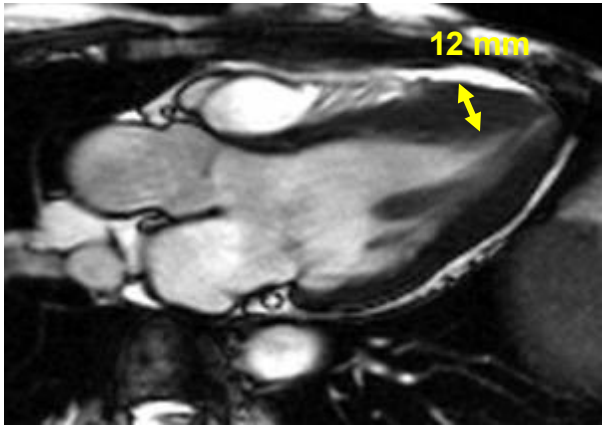
# Thickness estimation: apical HCM

1. Measure on the three **LAX images.**

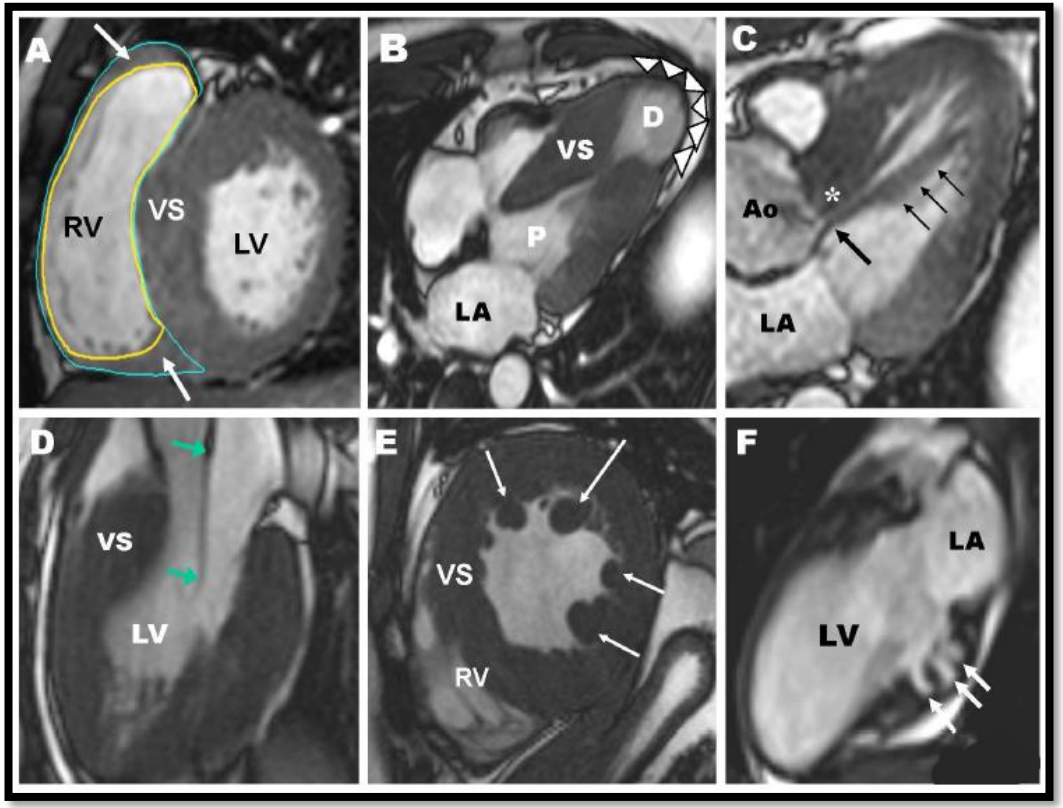
2. Choose images **not foreshortening** the ventricle, visualizing the true cardiac apex.

3. In choosing where to measure (septal, anterior, inferior or lateral), **consult the SAX** views in order to **avoid the base of papillary** muscles and **trabeculae**.

4. Measures must be **perpendicular** to the axis of the wall and at the point of maximal thickness



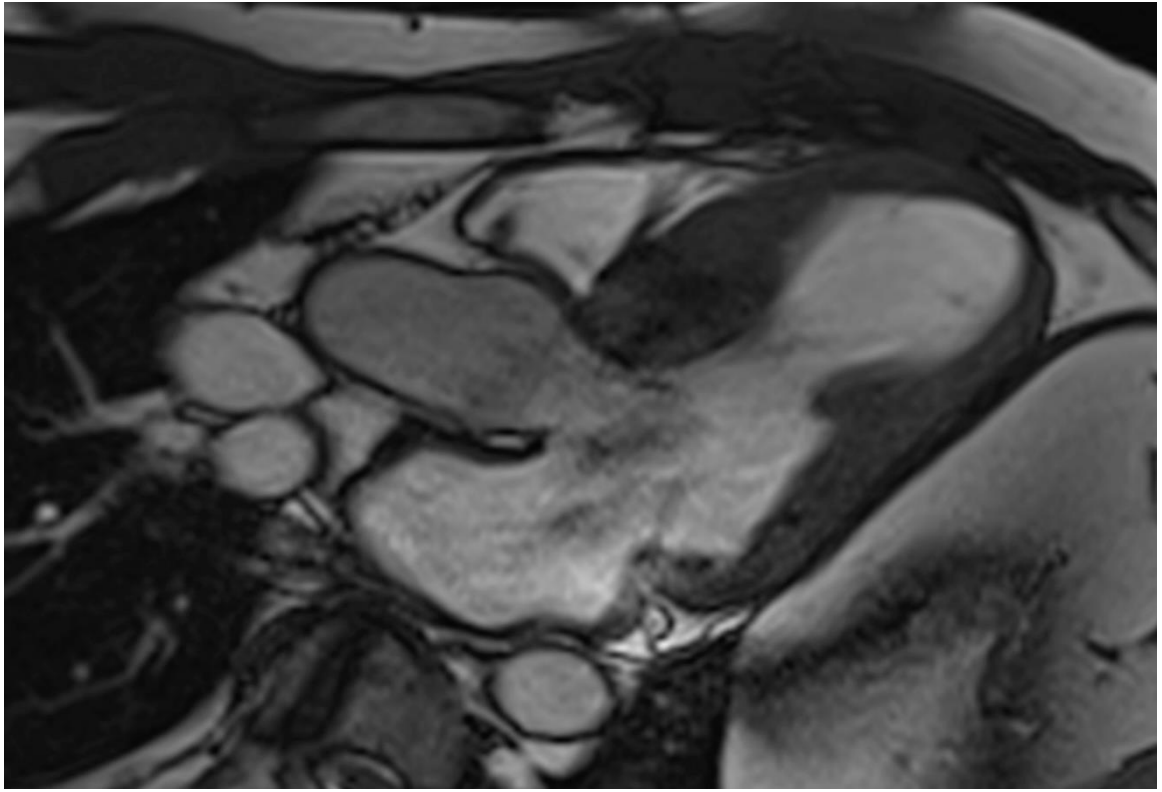
# CMR in HCM: typical signs

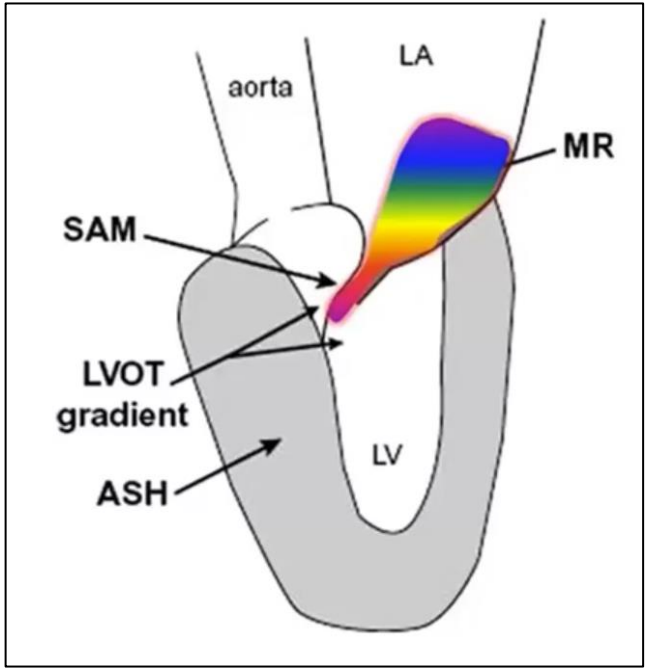



**Always describe in your reports!**

Maron MS, J Cardiovasc Magn Reson 2012

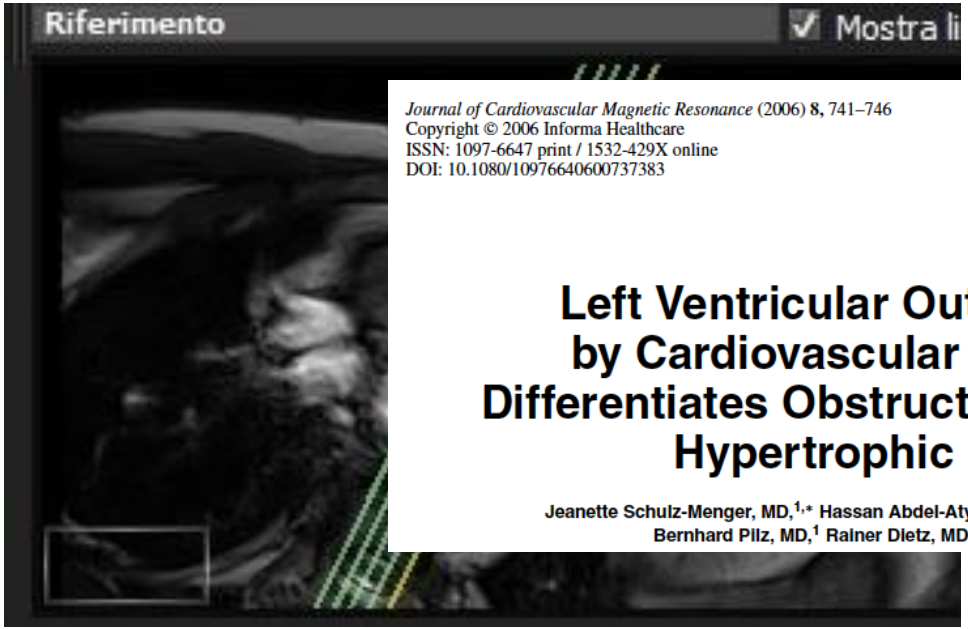
# SAM and MR






*Estimate with Flow CMR*

# LVOT Obstruction




*Journal of Cardiovascular Magnetic Resonance* (2006) **8**, 741–746
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DOI: 10.1080/10976640600737383

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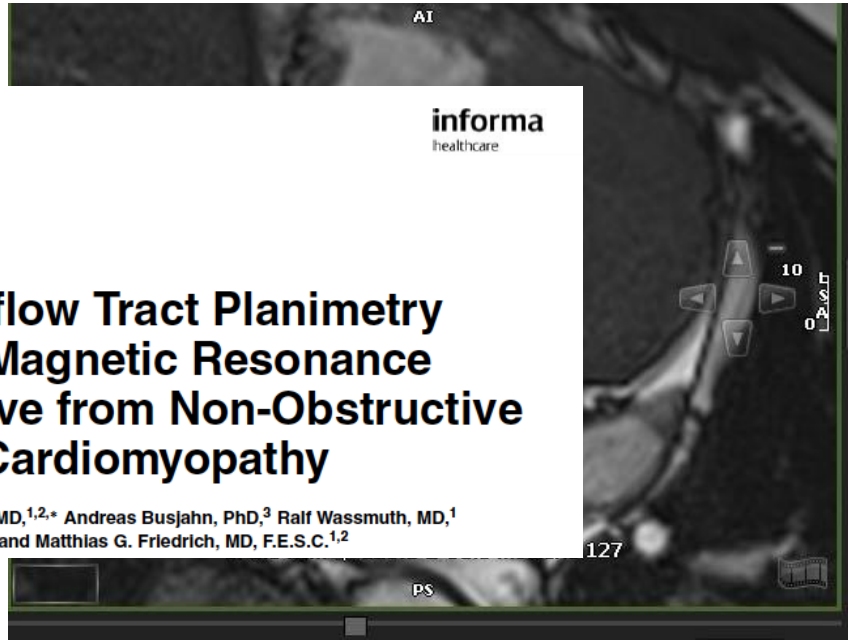
healthcare

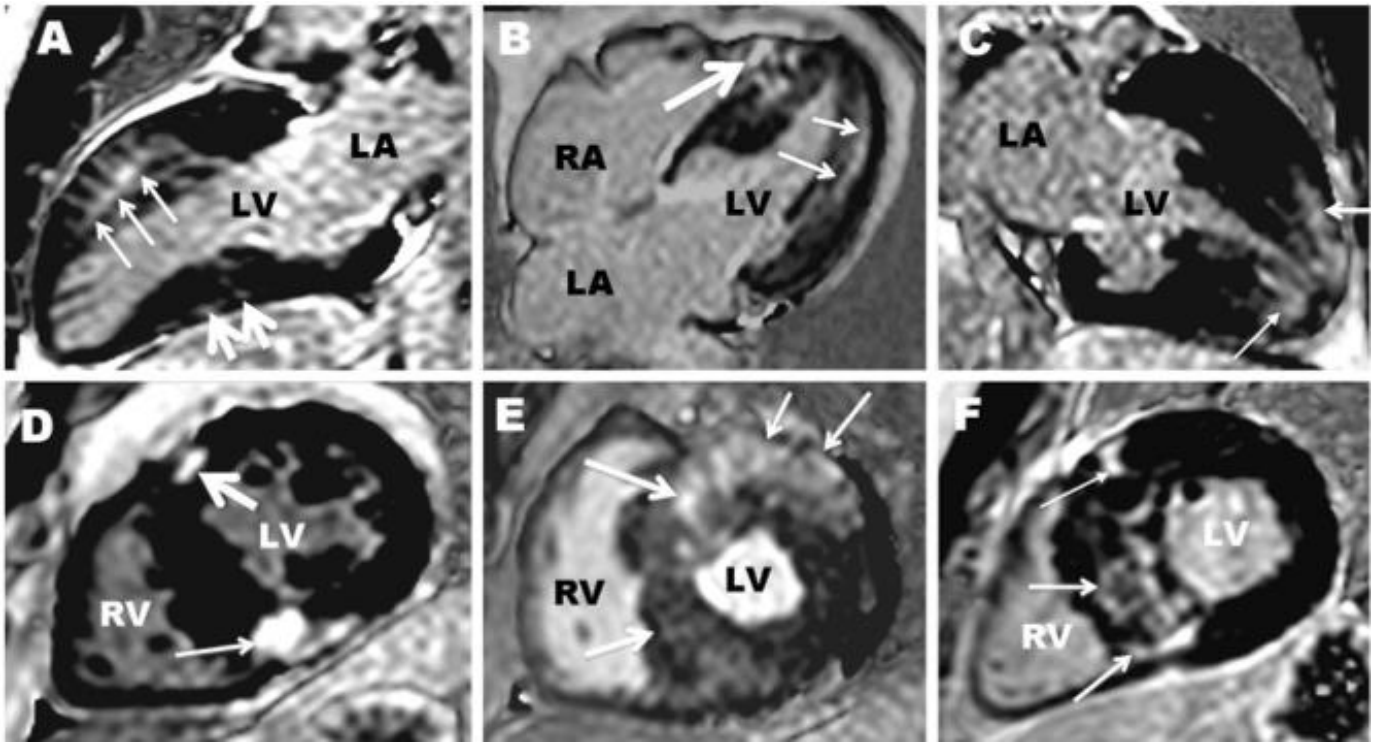
## Left Ventricular Outflow Tract Planimetry by Cardiovascular Magnetic Resonance Differentiates Obstructive from Non-Obstructive Hypertrophic Cardiomyopathy

Jeanette Schulz-Menger, MD,[1,*] Hassan Abdel-Aty, MD,[1,2,*] Andreas Busjahn, PhD,[3] Ralf Wassmuth, MD,[1] Bernhard Pilz, MD,[1] Rainer Dietz, MD,[1] and Matthias G. Friedrich, MD, F.E.S.C.[1,2]




**A cutoff value of 2.7 cm2 can differentiate HOCM from HNCM with a sensitivity and specificity of 100%**

# LGE in HCM

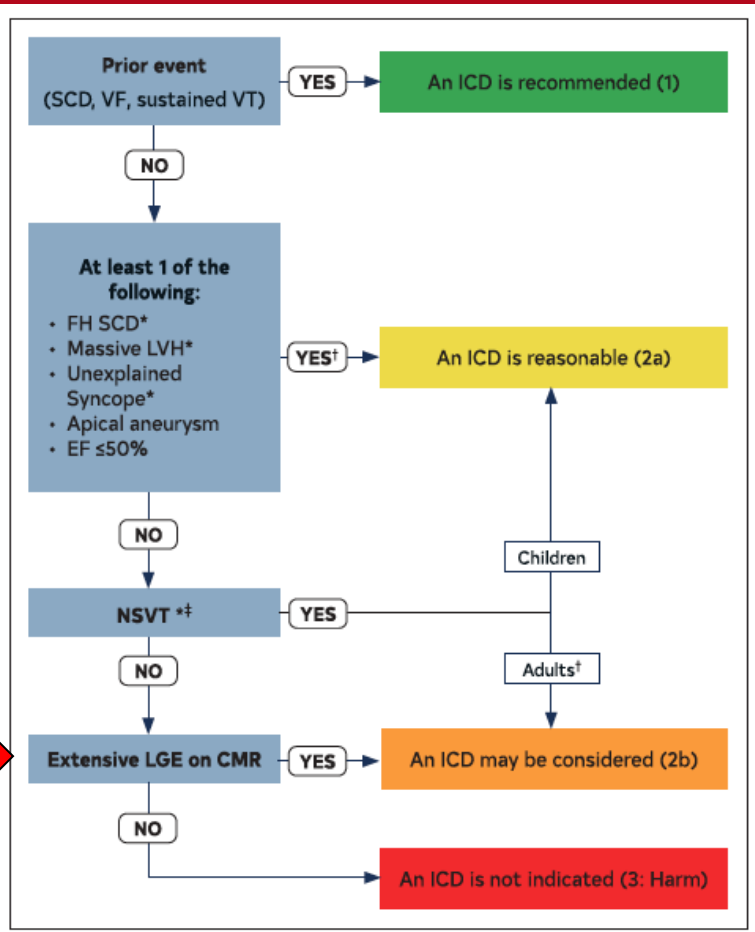



Maron MS, J Cardiovasc Magn Reson 2012

# LGE in HCM

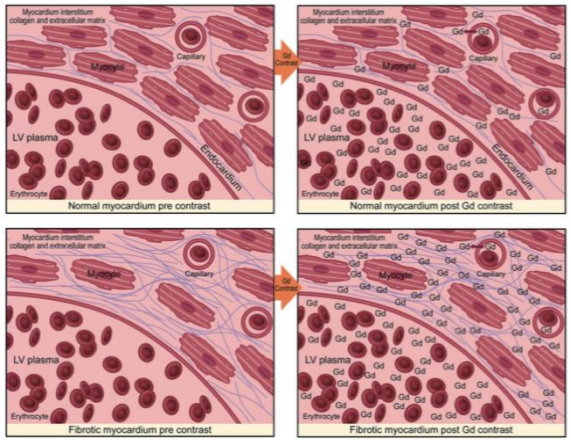
## Prognostic Value of Quantitative Contrast-Enhance Cardiovascular Magnetic Resonance for the Evaluati of Sudden Death Risk in Patients With Hypertrophic Cardiomyopathy

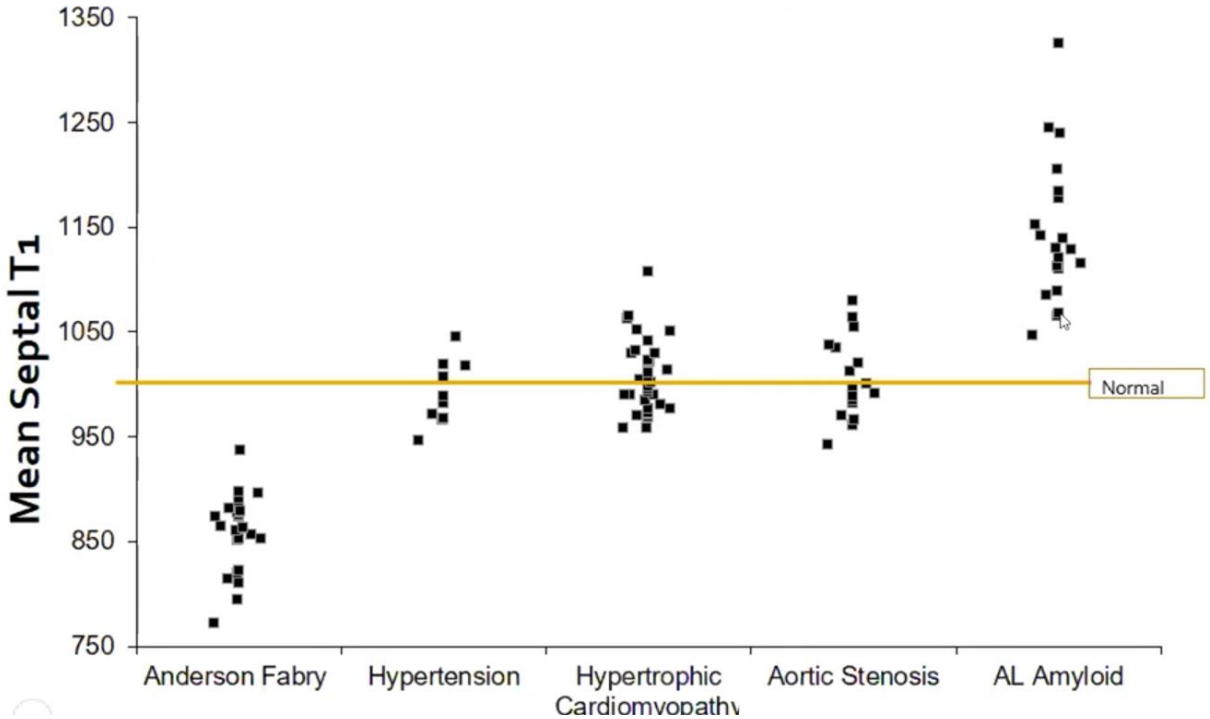
- 1293 pts (mean age 46 y)
- Follow up 3y
- SCD n=37
- Extent of LGE associated with an increased risk of SCD events
- Those with LGE>15% LV mass increased risk of SCD




Chan RH, Circulation 2014

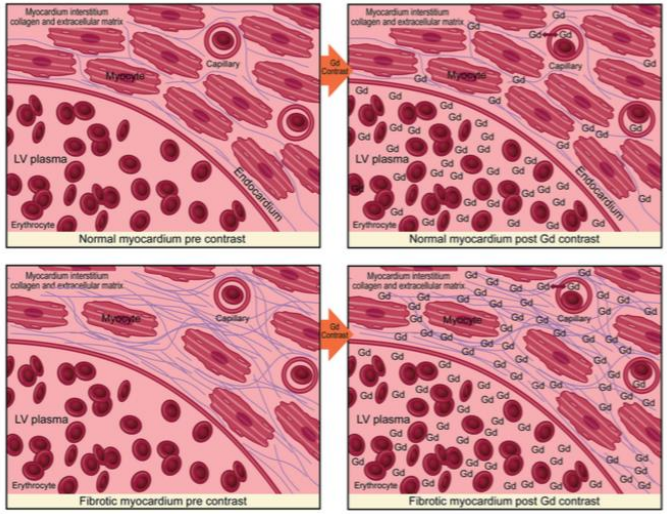
# Native T1

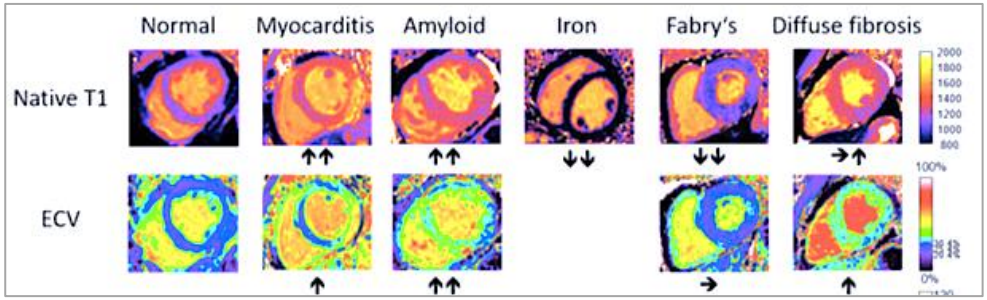


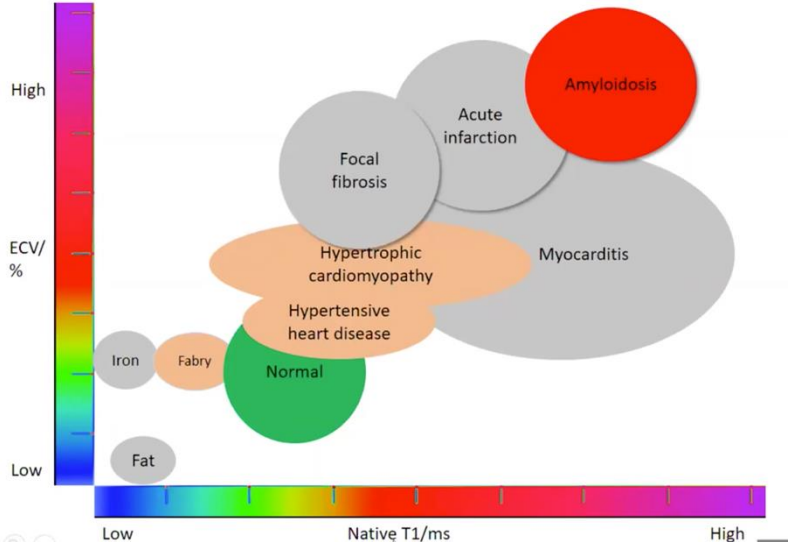




Sado D et al., Circa Cardiovasc Imaging 2013

# ECV


Myocardium interstitium collagen and extracellular matrix
Myocyte
Capillary
LV plasma
Endocardium
Erythrocyte
Gd
Gd contrast
Normal myocardium pre contrast
Normal myocardium post Gd contrast
Fibrotic myocardium pre contrast
Fibrotic myocardium post Gd contrast


Normal
Myocarditis
Amyloid
Iron
Fabry's
Diffuse fibrosis
Native T1
ECV
2000
1800
1600
1400
1200
1000
800
100%
0%


High
ECV/ %
Low
Amyloidosis
Acute infarction
Focal fibrosis
Hypertrophic cardiomyopathy
Myocarditis
Hypertensive heart disease
Iron
Fabry
Normal
Fat
Low
Native T1/ms
High

# Outline

- Hypertrophic Cardiomyopathy
- Athlete's heart
- Arterial Hypertension and Aortic Stenosis
- Cardiac Amyloidosis
- **Anderson-Fabry**
- Iron overload

# Anderson-Fabry Disease

## Key Points

1. **General**
   - Multi-system lysosomal storage disease
   - Inherited, X-linked (men > women)
2. **Disease pathophysiology:**
   - Caused by GLA variants causing deficient α-Gal A activity leading to an accumulation of (Gb3) in affected tissues, including the heart, kidneys, vasculature, and peripheral nervous system
3. **Concentric LVH**
   - Relatively late disease manifestation (3rd decade in men, 4th decade in women)
   - Patterns of hypertrophy often indistinguishable from HCM
   - LVH associated with progressive myocardial fibrosis

- RARE: The reported incidence, between 1 in 40,000 and 1 in 117,000.
  A recent reanalysis of 5,491 patients with a clinical diagnosis of LVH and/or HCM screened for Fabry reported a prevalence of GLA pathogenic genetic variants of 0.93% in males and 0.90% in females.
  (Doheny D et al J Med Genet 2018)

- More than 1,000 GLA variants (P, LP, VUS, B, LB)

# Anderson-Fabry Disease

Typical CMR features include :

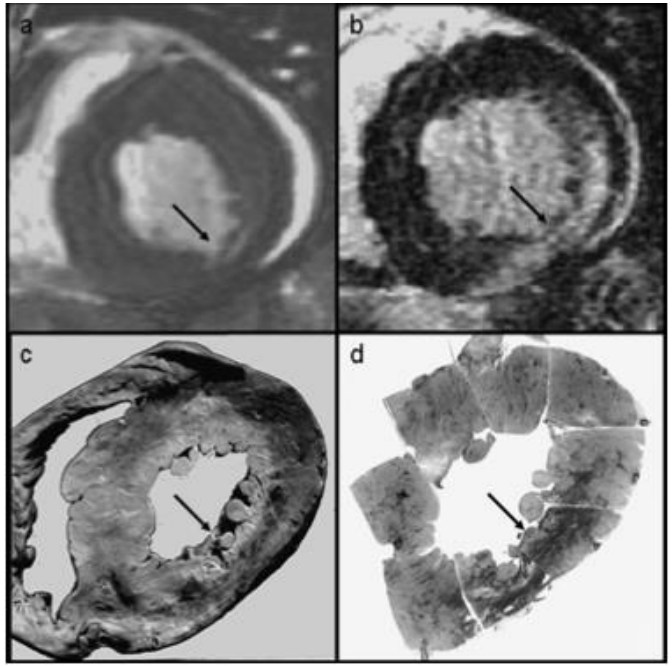
1. Concentric increase in LV mass (great contribution of the papillary muscle)

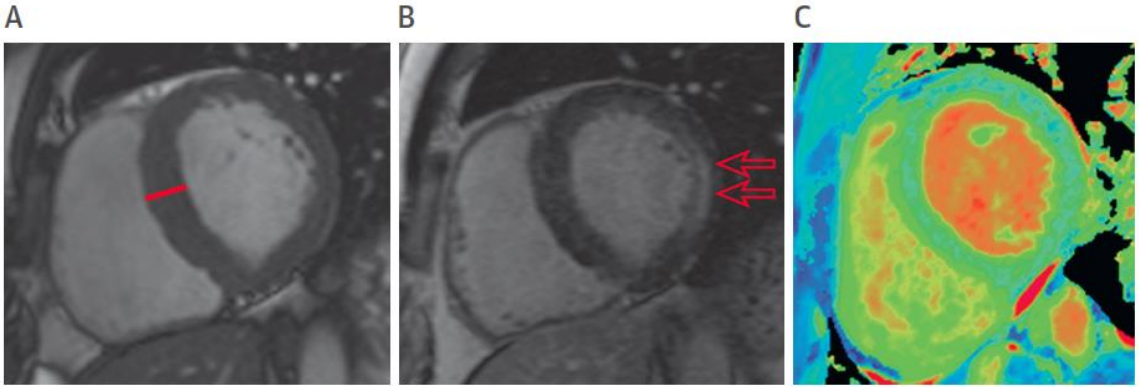
2. Late gadolinium enhancement (LGE), initially in the basal or mid inferolateral wall, midwall or subepicardial pattern (present in 50% of cases, !males)

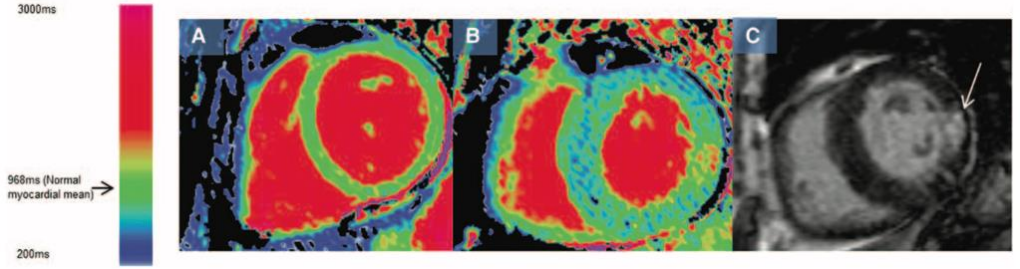
3. Low native T1, likely reflecting glycosphingolipid myocardial storage and occurring before the development of significant LVH

4. ECV normal or low (intracellular deposition, DD with amyloid!)

# Anderson-Fabry Disease

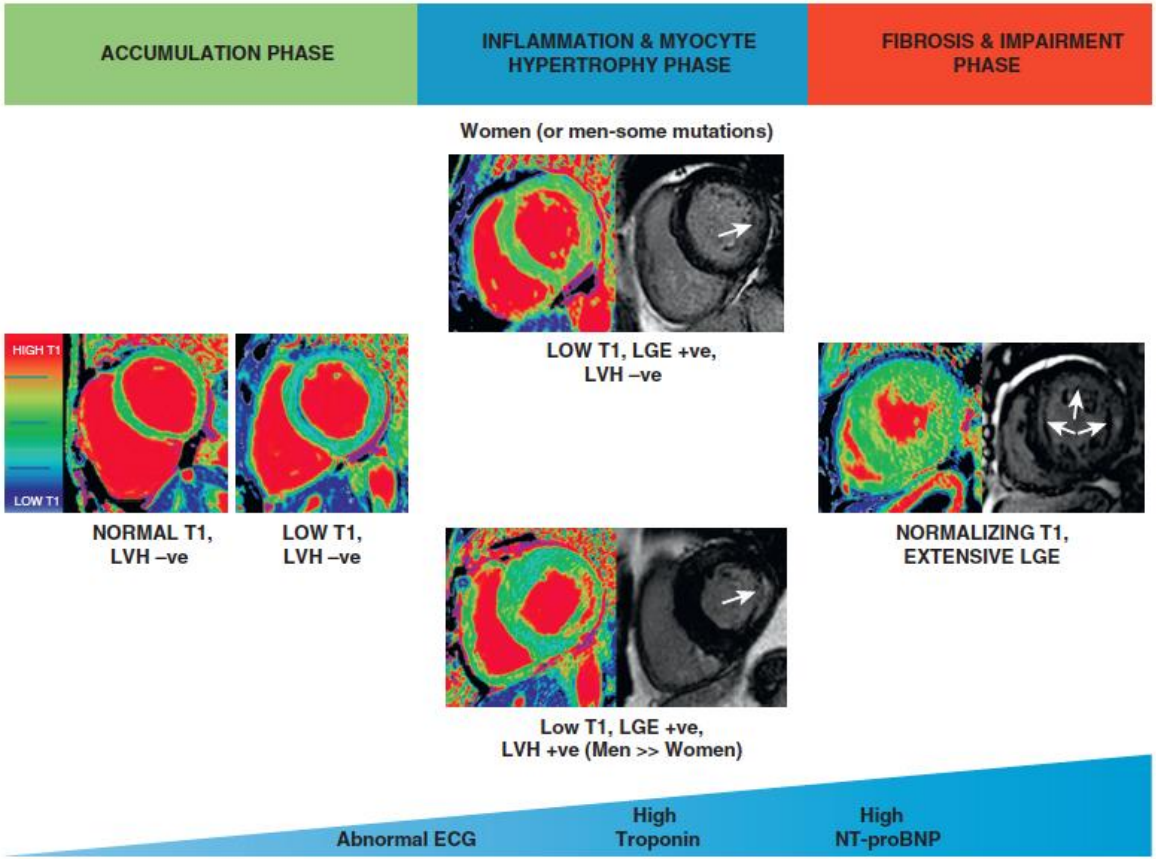



Moon J. J Cardiovasc Magn Reson 2006
Sado DM, Circ CVI 2013
Perry JACC CVI 2019

# Anderson-Fabry Disease




- The pathology in AFD hearts can progress with time.
- T1 values decreased with increasing age (males and females)
- Men show a more rapid decrease in T1 with age, but have increase after LVH.
- Women had a less rapid decrease in T1 and after LVH demonstrate stabilization of T1 values

Sphingolipid deposition is followed by **inflammation, hypertrophy, and fibrosis**. Therefore, T1 relaxation times may be normal (pseudonormalization of T1 times) in areas with both sphingolipid deposition and fibrosis

Nordin JACC CVI 2019

# Outline

- Hypertrophic Cardiomyopathy
- Athlete's heart
- Arterial Hypertension and Aortic Stenosis
- Cardiac Amyloidosis
- Anderson-Fabry
- **Iron overload**

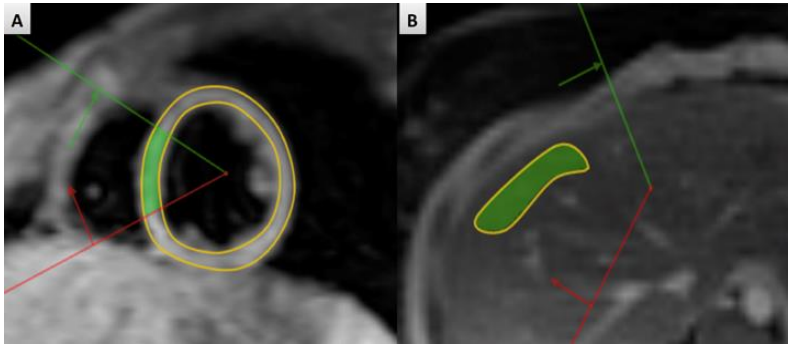
# Iron overload

## Key Points

1. **Iron overload cardiomyopathy**
   - Potentially reversible cause of heart failure under effective therapy
   - **Dilated phenotype –** majority of patients, impaired systolic function
   - **Restrictive phenotype -** non-dilated ventricles, preserved systolic function, diastolic dysfunction, enlarged atria
2. **Risk of developing heart failure**
   - T2* > 20 ms: low
   - T2* 10-20 ms: intermediate
   - T2* <10 ms: high

## Tips & Tricks

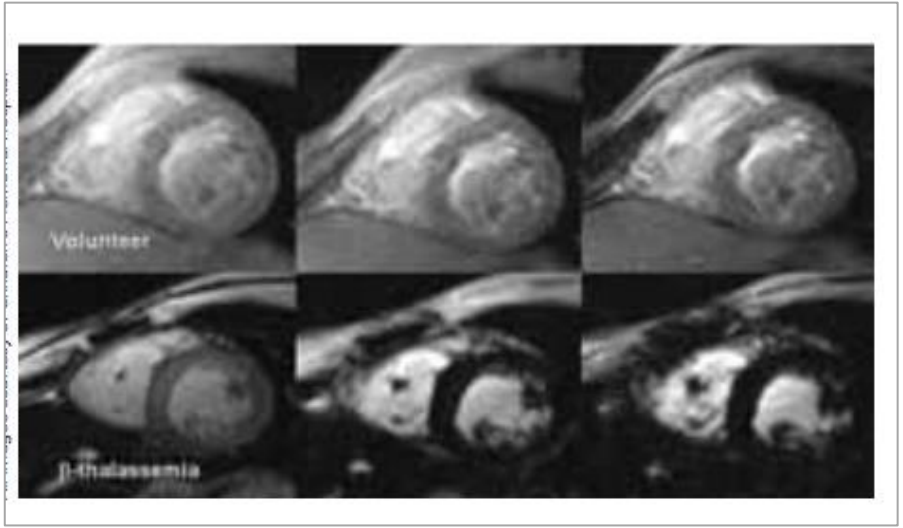
1. Assess T2* values in the septum (fewer artefacts) as iron deposition is similar in all LV segments
2. High correlation of T2* values and native T1 values (T2*↓, native T1↓)

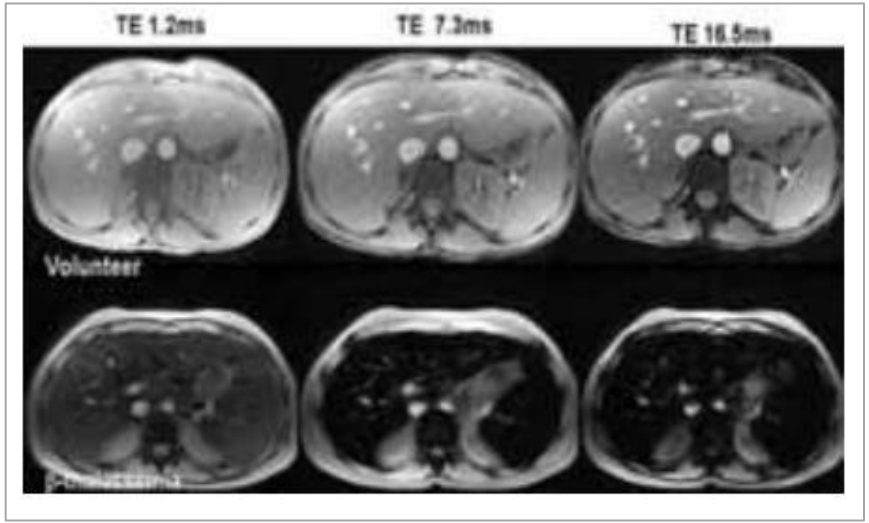



T2* contours: ROIs are placed in the ventricular septum (A) and the liver (B).

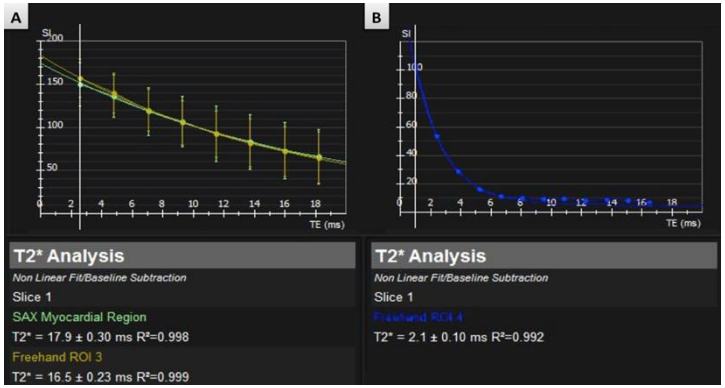
# Iron overload

- Only non-invasive method to assess myocardial iron loading
- Iron has paramagnetic properties → shortens T2



# Iron overload




T2* calculation: Graphs of the relaxation of T2* values over time to compute T2* values of myocardium (A) and liver (B).
T2* of the ventricular septum was 16.5ms consistent with mild myocardial iron overload and intermediate risk of developing heart failure, T2* of liver was 2.1ms consistent with severe iron overload of the liver.

| Myocardial T2*(ms) | Myocardial R2* (Hz) | Dry weight (MIC) (mg/g) | Hepatic T2* (ms) | Hepatic R2* (Hz) | Dry weight (LIC) (mg/g) | Classification |
|---|---|---|---|---|---|---|
| ≥20 | ≤ 50 | ≤ 1.16 | ≥15.4 | ≤ 65 | ≤ 2 | **None** |
| 14-20 | 50 – 71 | 1.16 – 1.8 | 4.5-15.4 | 65 - 224 | 2-7 | **Mild** |
| 10-14 | 71 – 100 | 1.8 – 2.7 | 2.1 – 4.5 | 224 - 475 | 7-15 | **Moderate** |
| ≤10 | ≥ 100 | ≥ 2.7 | ≤2.1 | ≥ 475 | ≥ 15 | **Severe** |

Liver Iron Content (LIC); Myocardial Iron Content (MIC).

EACVI CMR Pocket Guide

# Scan Protocol for HCMs (not amyloidosis)

- Trufi sagittale, coronale e assiale
- Cine 3 LAX
- Pacchetto Cine SAX
- Cine bulbo aortico ed LVOT per origine delle coronarie e planimetria LVOT
- T1 mapping 1-2 SAX (medio ± basale) + 4 CH
- T2* in 3 SAX se sospetto clinico siderosi

*MDC*

- Perfusione in 3 SAX (basale medio apicale)
- Flussi Aorta e Polmonare

*attesa 8-10 minuti, poi*

- TI SCOUT in SAX medio o 4 CH
- LGE in 3 LAX e pacchetto SAX
- Dopo 15 minuti, T1 mapping post contrasto (SAX medio+ 4CH)
- (opzionale, solo se sospetta trombosi endocavitaria) LGE con TI lungo

# Outline

Hypertrophic Cardiomyopathy

Athlete's heart

Arterial Hypertension and Aortic Stenosis

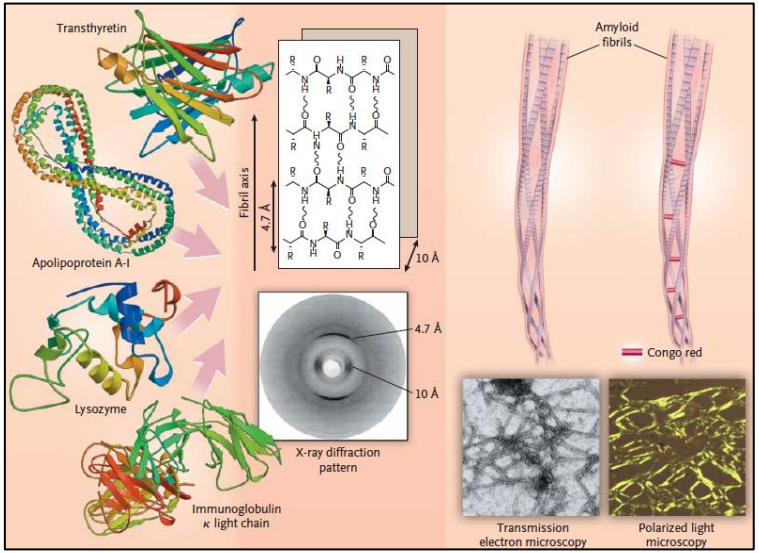
**Cardiac Amyloidosis**

Anderson-Fabry

Iron overload

# BACKGROUND

- The systemic amyloidosis are a group of diseases characterized by the deposition of amyloid, a material formed from misfolding of proteins
- Hereditary or acquired
- Deposition can occur in one or more organs including heart, nerves, kidney, eyes, liver, causing function impairment.



# BACKGROUND

Table 1 | **Some human diseases associated with protein misfolding and amyloid aggregation***

| Disease | Aggregating protein or peptide | Polypeptide length (number of residues) | Structure of protein or peptide |
|---|---|---|---|
| ***Neurodegenerative diseases*** | | | |
| Alzheimer's disease | Amyloid-β peptide | 37–43 | Intrinsically disordered |
| Spongiform encephalopathies | Prion protein or its fragments | 230 | Intrinsically disordered and α-helical |
| Parkinson's disease | α-synuclein | 140 | Intrinsically disordered |
| Amyotrophic lateral sclerosis | Superoxide dismutase 1 | 153 | β-sheet and Ig-like |
| Huntington's disease | Huntingtin fragments | Variable | Mostly intrinsically disordered |
| Familial amyloidotic polyneuropathy | Transthyretin mutants | 127 | β-sheet |
| Non-neuropathic systemic amyloidosis | | | |
| Amyloid light chain (AL) amyloidosis | Immunoglobulin (Ig) light chains or its fragments | ~90 | β-sheet and Ig-like |
| Senile systemic amyloidosis | Wild-type transthyretin | 127 | β-sheet |
| Haemodialysis-related amyloidosis | $\beta_2$-microglobulin | 99 | β-sheet and Ig-like |
| Lysozyme amyloidosis | Lysozyme mutants | 130 | α-helical and β-sheet |
| ***Non-neuropathic localized amyloidosis*** | | | |
| Apolipoprotein A1 (Apo A-1) amyloidosis | Apo A-1 fragments | 80–93 | Intrinsically disordered |
| Type II diabetes | Amylin | 37 | Intrinsically disordered |
| Injection-localized amyloidosis | Insulin | 21 and 30 | α-helical and insulin-like |

*A selection of diseases associated with extracellular amyloid deposits or intracellular inclusions with amyloid-like characteristics. See REF. 5 for a more comprehensive list of the approximately 50 human protein misfolding diseases and their associated proteins.

**Table 2** | Clinical manifestations of some systemic amyloidoses according to the major site of involvement*

| Site of involvement | Form of amyloidosis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AL | AA | ATTR | SSA | AApoI‡ | AApoII | ALys | AFib§ | $A\beta_2M$ |
| Kidney‖ | ++ | +++ | + | - | ++ | ++ | +++ | +++ | - |
| Heart‖ | +++ | + | +++ | +++ | ++ | + | (+) | + | (+) |
| Peripheral nervous system | ++ | | +++ | +¶ | + | | | | |
| Autonomic nervous system | ++ | ++ | +++ | – | – | – | – | – | – |
| Liver | ++ | ++ | – | – | ++ | – | ++ | + | (+) |
| Spleen | + | ++ | – | – | ++ | – | + | + | (+) |
| Skin | (+) | – | – | – | – | – | – | – | – |
| Gastrointestinal tract | ++ | + | – | – | – | – | ++ | – | – |
| Muscoloskeletal system | ++ | – | (+)# | – | – | – | – | – | +++ |
| Thyroid | + | + | – | – | – | – | – | – | (+) |
| Adrenal glands | + | + | – | – | – | – | – | – | (+) |
| Eyes | – | – | ++ | – | – | – | – | – | – |
| Testis | (+) | – | – | – | ++ | – | – | – | – |
| Tongue | +++ | (+) | – | – | – | – | – | – | – |
| Factor X deficiency | + | – | – | – | – | – | – | – | – |

*Clinically, it is difficult to distinguish AL, AA, familial (ATTR, AApoI, AApoII, ALys, AFib) and senile systemic amyloidosis from each other because of overlapping clinical presentations and a lack of an informative family history in many patients with hereditary amyloidosis. ‡In AApoI amyloidosis, mild renal failure usually develops in the absence of urinary protein loss and can remain stable for years. §AFib amyloidosis manifests with proteinuria that can rapidly progress to nephrotic range; uniquely among the hereditary amyloidoses, it has been reported in children. ‖The kidney and heart are frequent sites of amyloid deposition. ¶Mainly carpal tunnel syndrome. #Charcot arthropathy. Abbreviations: +++ very common; ++ common; + rare; (+) very rare; –, does not occur.

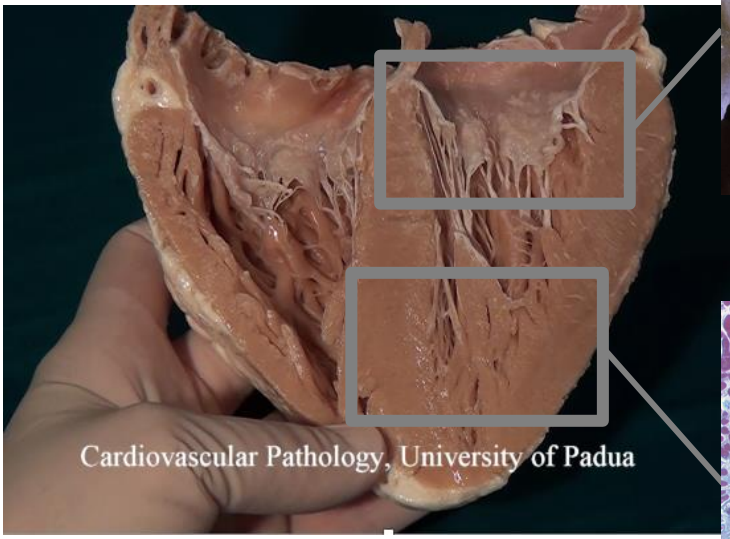
*Knowles TP. Nat Rev Mol Cel Biol. 2014*
*Perfetto F. Nat Rev Rheumatol. 2010*

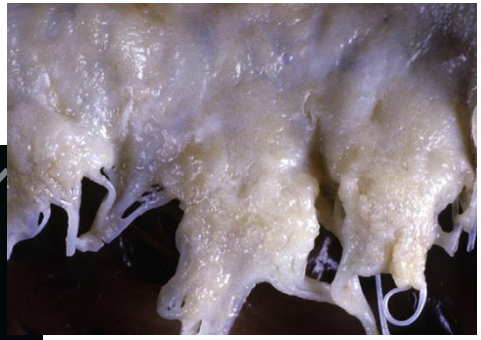
# BACKGROUND

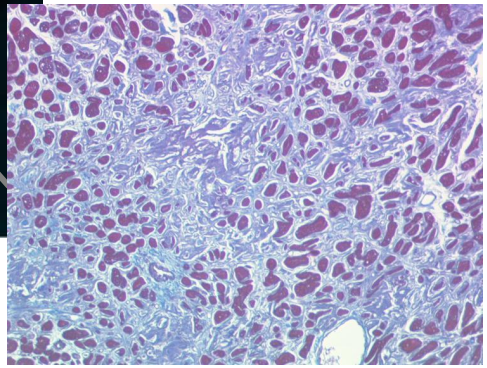
- The 2 commonest forms of amyloidosis are transthyretin amyloidosis (ATTR), derived from wild-type or mutant transthyretin, and light-chain (AL) amyloidosis.

- Both frequently involve the heart, producing an infiltrative cardiomyopathy with left ventricular hypertrophy and restrictive pathophysiology.

# BACKGROUND

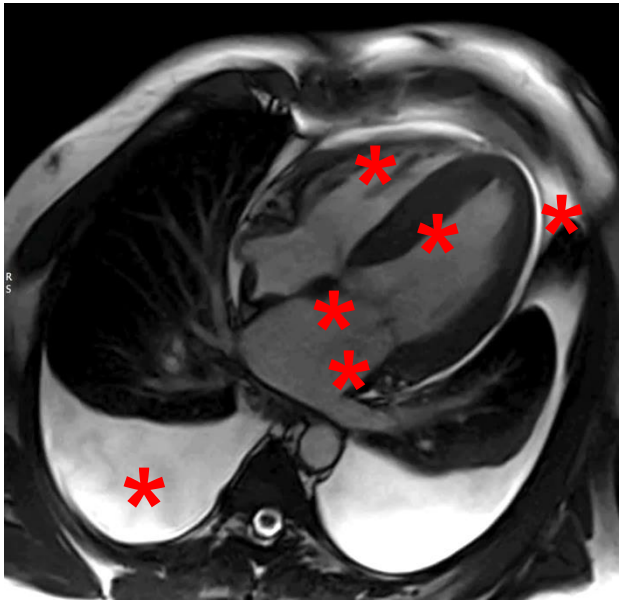




- Amyloid deposits may be identified within the myocardial interstitium, vasculature, valves, or parietal pericardium
- Tends to involve the subendocardial and midmural regions, more than the subepicardial region.
- Is typically nonuniform and patchy
- These locations of deposition are not type specific and can occur in any form of cardiac amyloidosis

# IMAGING FEATURES

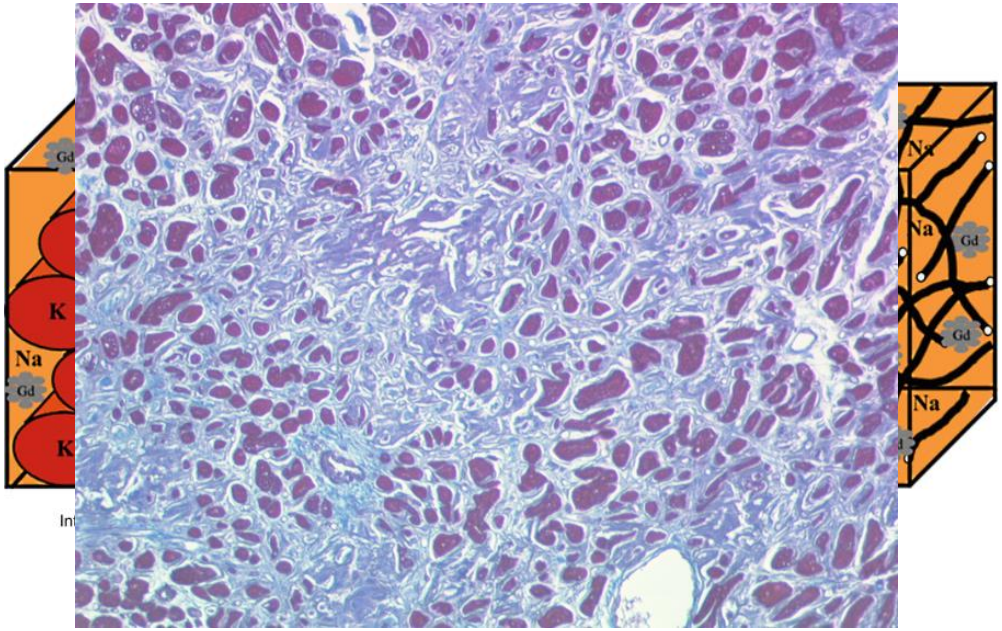


1. Increased LV wall thickness and LV mass on SSFP cine
2. Look at the RV
3. Look at the IAS and atria
4. SVi (better than EF)
5. Pleura and pericardium

# Gad-based CMR

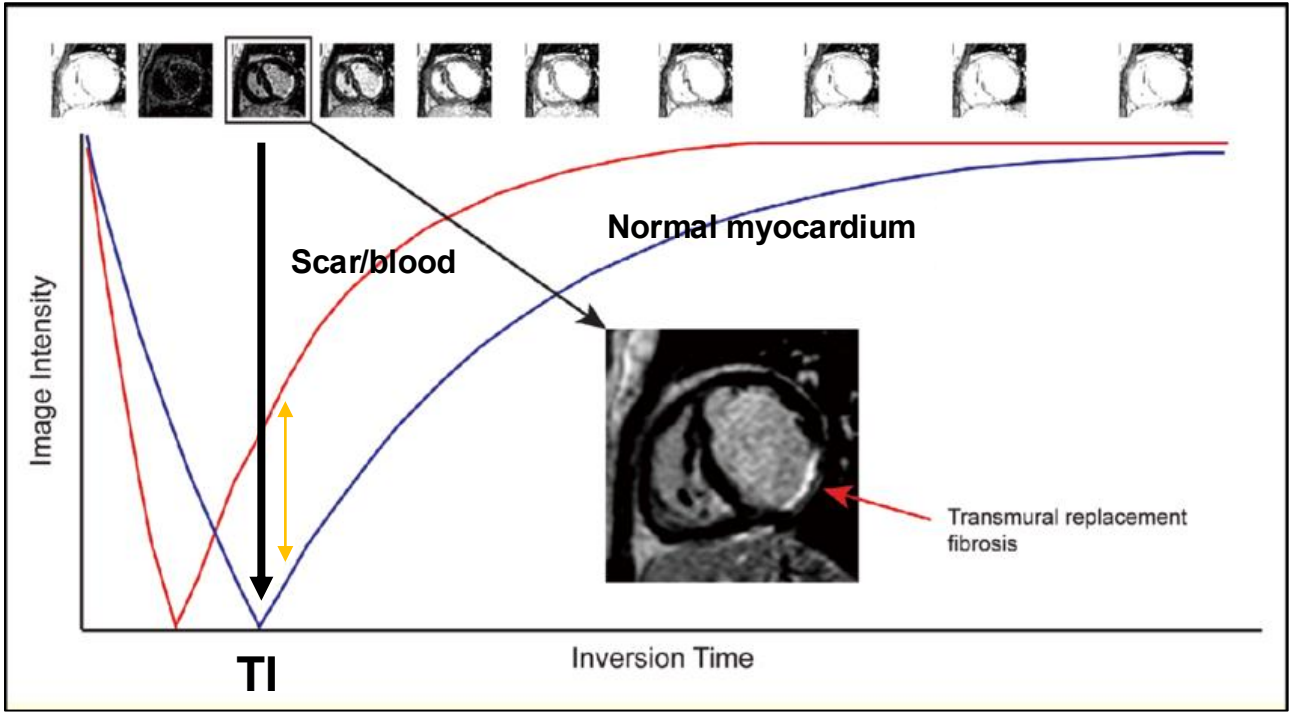
Criteria for diagnosis
of cardiac amyloid

- Abnormal gadolinium kinetics
- LGE
- Extracellular Volume




*Mahrholdt H, Eur Heart J 2002*

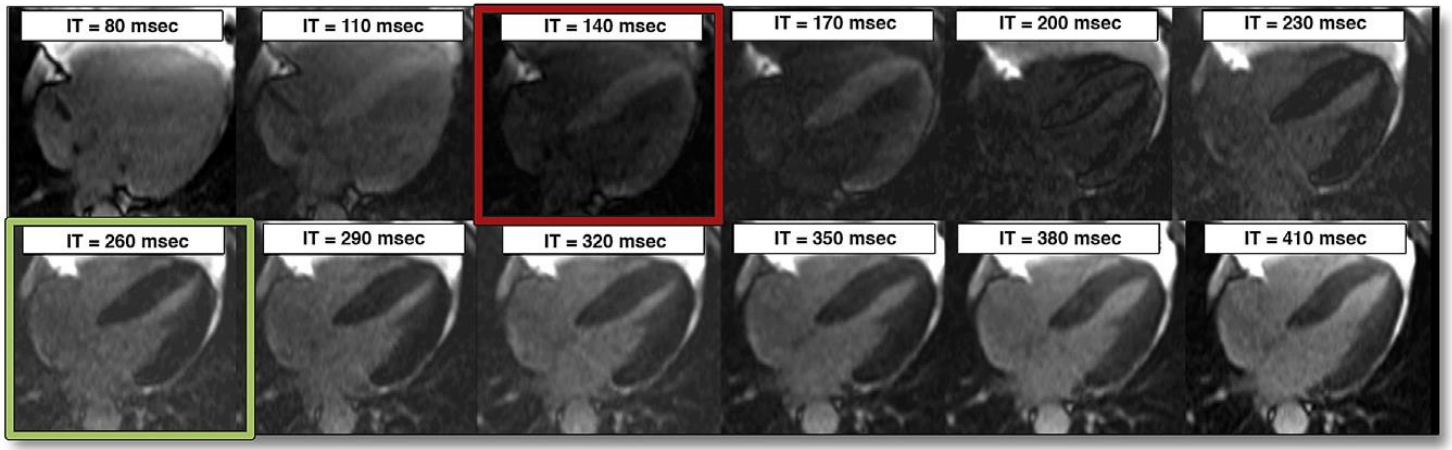
# TI SCOUT E INVERSION RECOVERY TECHNIQUE




**Difference is due to Gad retention/T1 recovery**

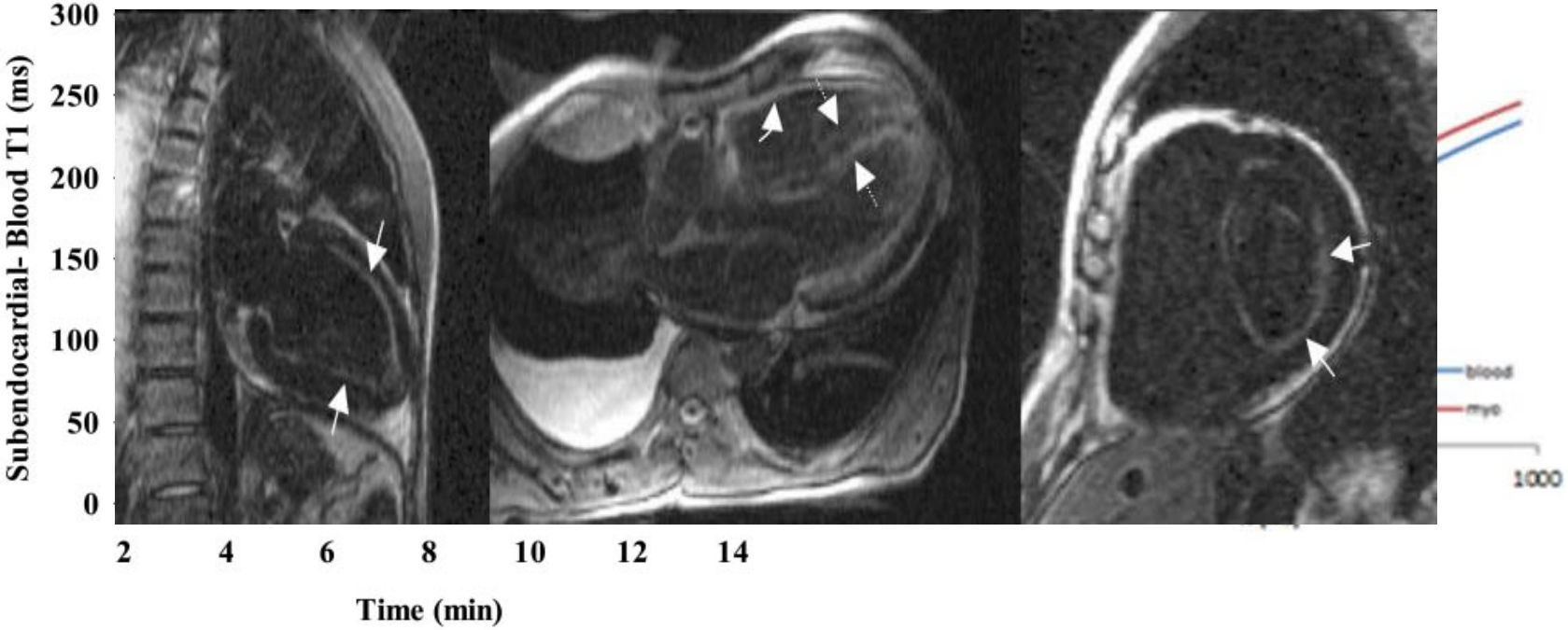
# Normal gadolinium kinetics

**Blood pool reaches the null point prior the normal myocardium**




*White J et al. JACC CVI 2014*

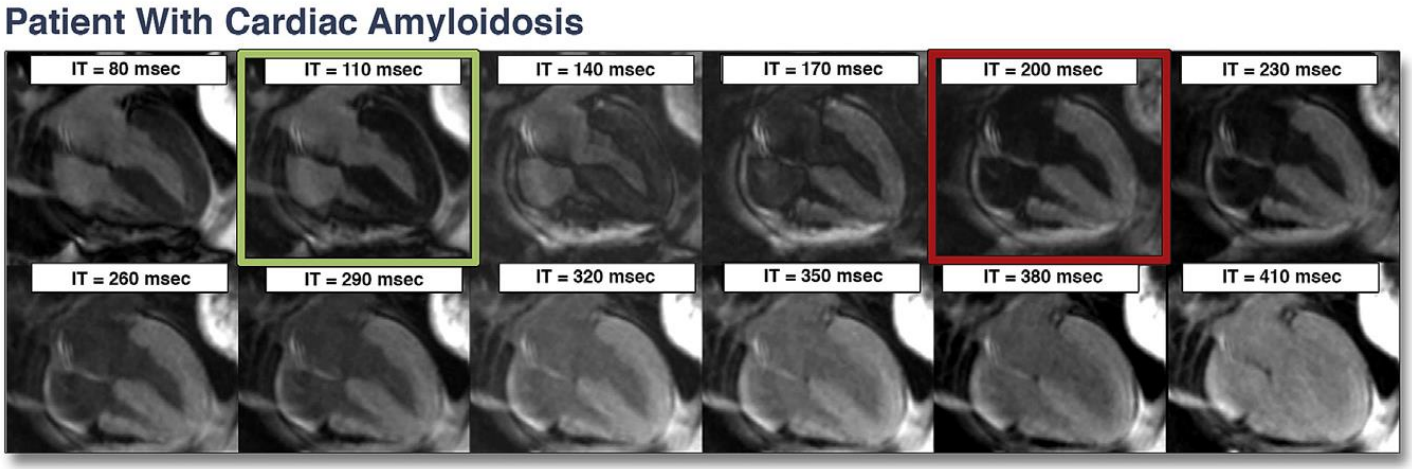
# Abnormal gadolinium kinetics




*Modified from Maceira et al. Circulation 2005 and Fontana M, Circulation 2015*

# Abnormal gadolinium kinetics

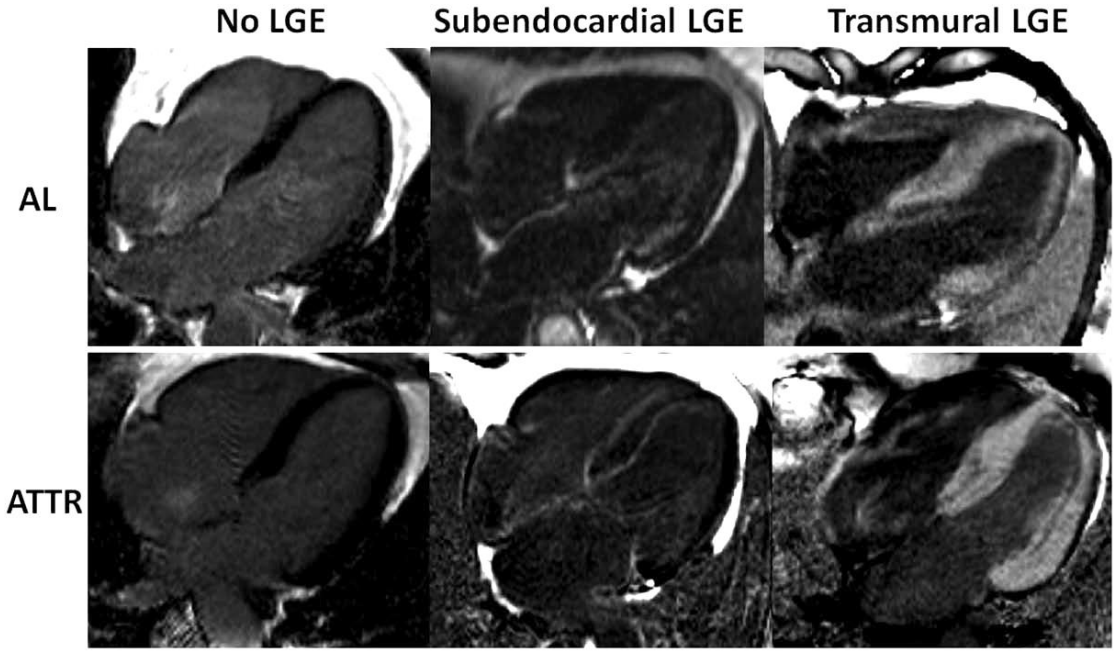
## Amyloidotic myocardium reaches the null point prior/= the blood pool




*White J et al. JACC CVI 2014*

# LGE in cardiac amyloidosis

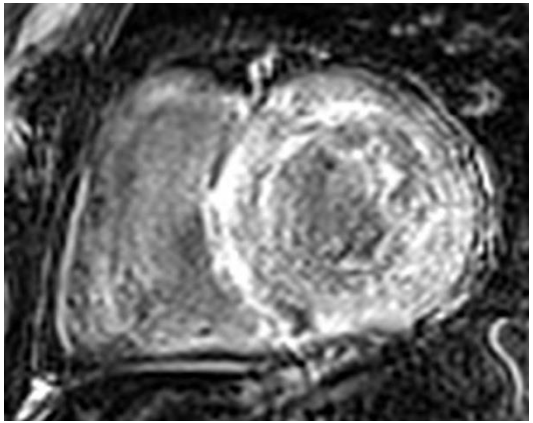
- A typical LGE pattern has a diagnostic sensitivity of 85% to 90%
- Specificity about 90-92%, but possible verification bias

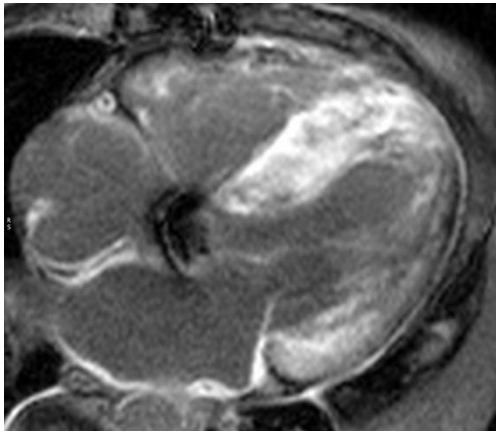


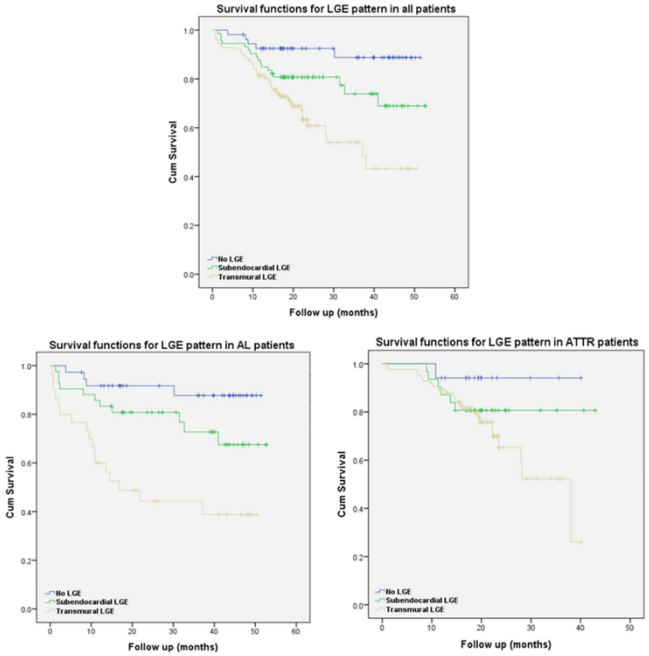

*Zhao et al. BMC Cardiovascular Disorders 2016*

*Fontana M al, Circulation 2015*

# LGE in cardiac amyloidosis








*Fontana M al, Circulation 2015*

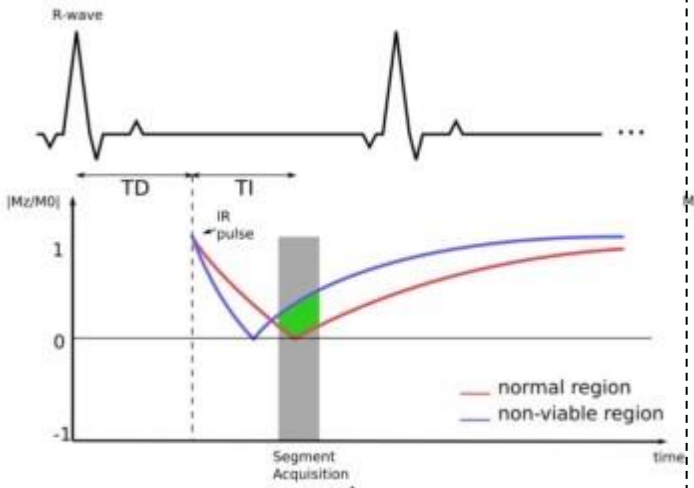
# LGE in cardiac amyloidosis

**Practical recommendations**

- Use PSIR technique
- Protein-bound contrast agents (Gd-BOPTA) should be avoided
- Perform LGE imaging earlier and complete quickly

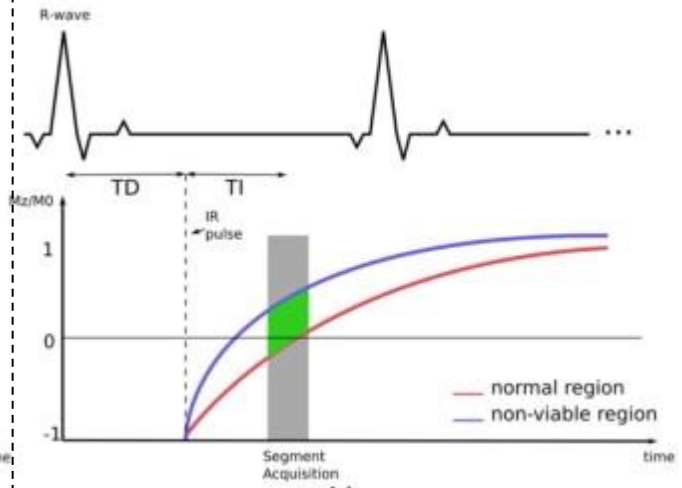
# MAG and PSIR

## MAG



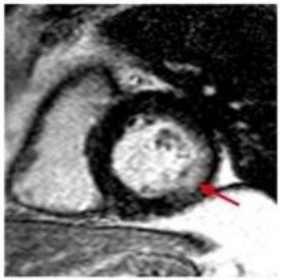

a)

## PSIR

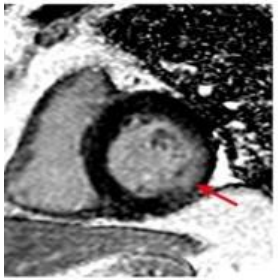



b)

**Magnitude-only inversion recovery (MAG-IR)**



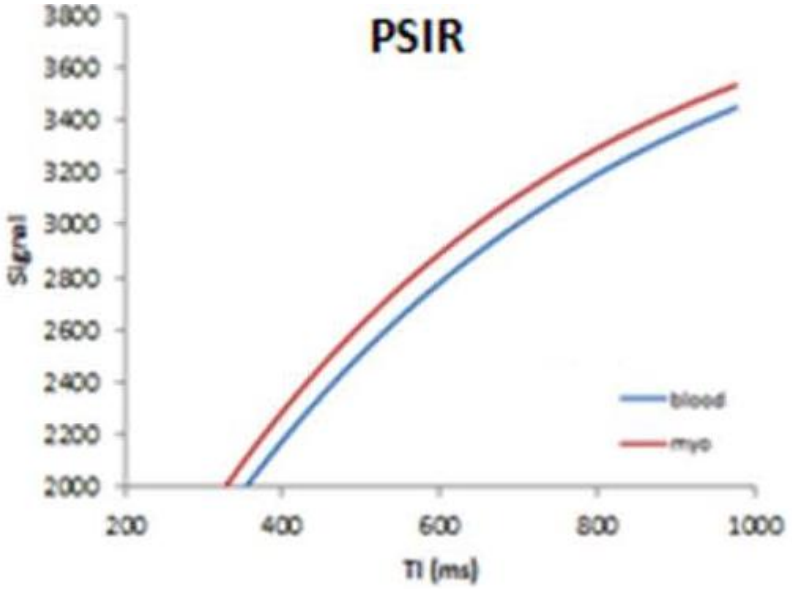
c)

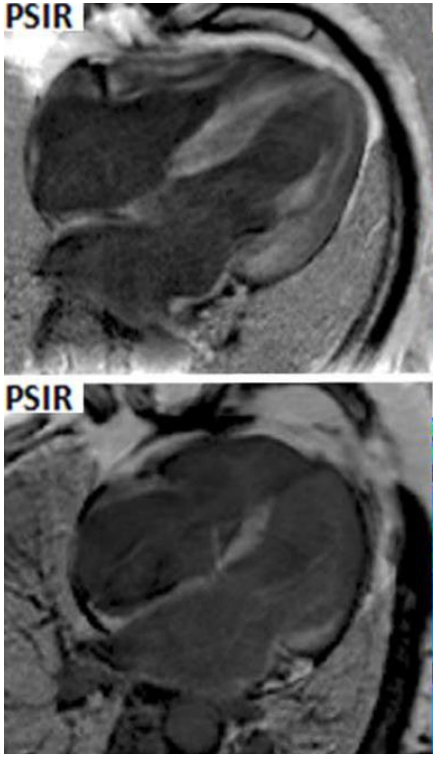


d)

**Phase-sensitive inversion recovery reconstruction (PSIR)**

# PSIR




*Fontana M al, Circulation 2015*

# CMR protocol

- Trufi sagittale, coronale e assiale
- Cine 3 LAX
- Pacchetto Cine SAX
- T1 mapping 1-2 SAX (medio ± basale) + 4 CH

*MDC*

- Perfusione in 3 SAX (basale medio apicale)
- Flussi Aorta e Polmonare

*attesa 3-4 minuti, poi*

- TI SCOUT in SAX medio o 4 CH
- LGE in 3 LAX e pacchetto SAX
- Dopo 13 minuti, T1 mapping post contrasto (SAX medio+ 4CH)


UNIVERSITÀ
DEGLI STUDI
DI PADOVA

# GRAZIE PER L'ATTENZIONE

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