

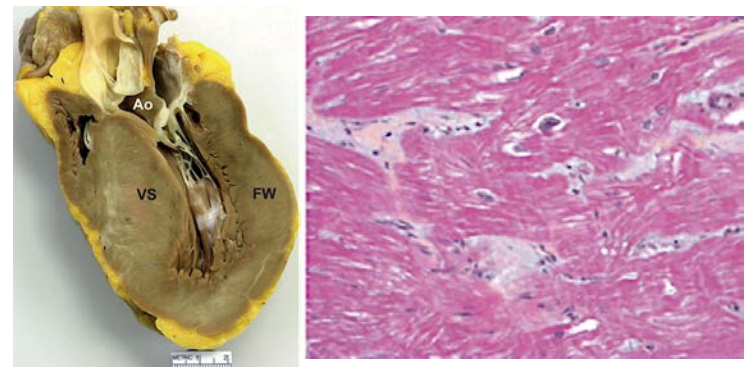
# ***How NOT to miss Hypertrophic Cardiomyopathy?***

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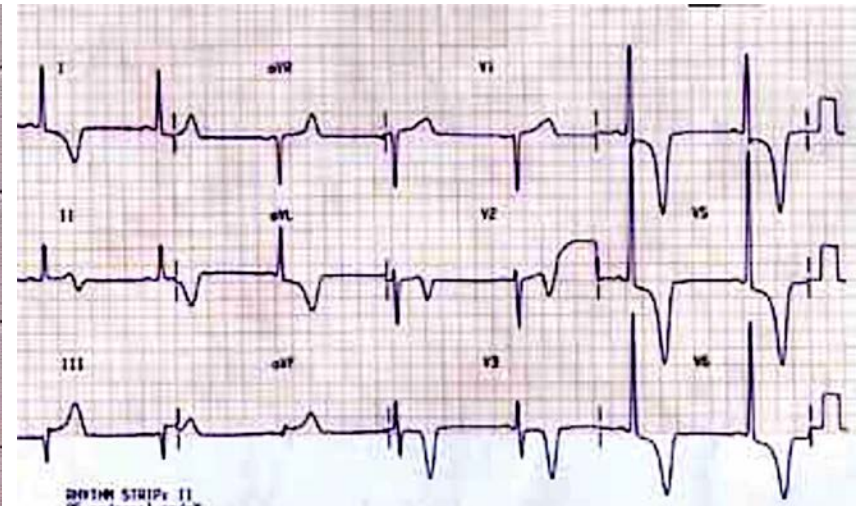
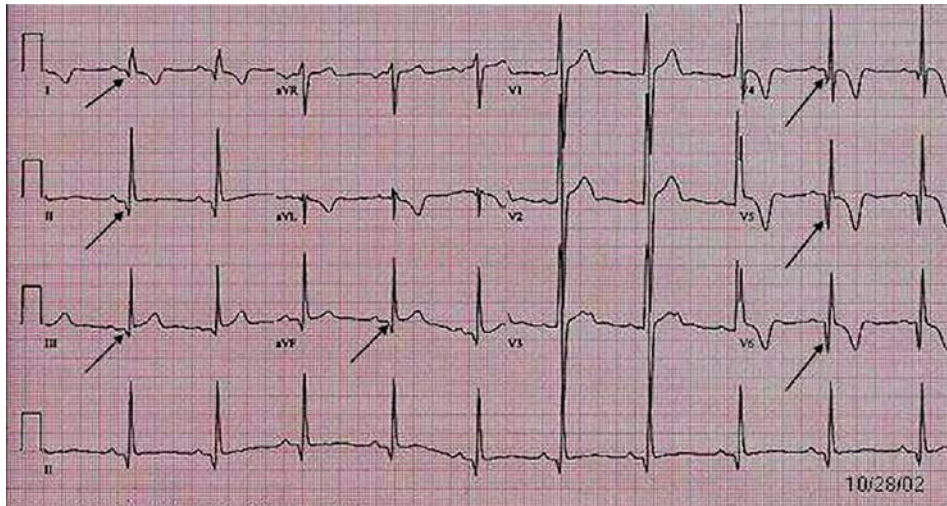
# Introduction

- Hypertrophic cardiomyopathy is the most common genetic cardiomyopathy, affecting approximately 1:500 people across multiple geographies, ethnicities and races.
- It is usually caused by a *sarcomeric mutation* transmitted in an autosomal-dominant inheritance pattern with incomplete penetrance and variable expression.
- As the yield of genetic testing is only about 35-60% depending on patients selection, ***the diagnosis of HCM is still clinical and based on the demonstration of unexplained and usually asymmetric left ventricular hypertrophy by imaging modalities.***
- Histopathology may show hypertrophy, myocardial fiber disarray, myocardial fibrosis and small vessel coronary disease.



# *Electrocardiogram: first screening tool*

- Abnormal ECG patterns are common in HCM patients (up to 90% of probands) and may be present in advance of the appearance of hypertrophy on imaging.
  - Criteria for LVH are usually present: Increased precordial voltages and non-specific ST segment and T-wave abnormalities (LVH strain).
  - Deep, narrow “dagger-like” Q waves in the lateral and inferior leads.
  - Apical HCM - “giant T Wave Inversion” and no septal Q waves
  - An association exists between Wolf-Parkinson's White and HCM



## ***But the ECG may be normal in HCM...***

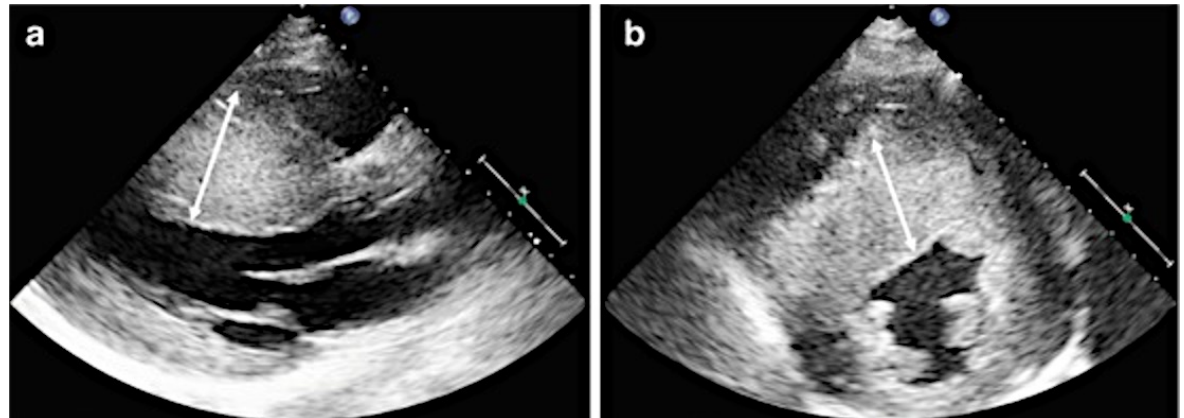
- There is a subset of patients with phenotypic expression of the disease by echocardiography that has a normal ECG.
  - Among 2,485 patients with an echocardiographic evidence of HCM seen at the Mayo Clinic 135 (5.4%) had a normal ECG. They had less severe phenotypic expression of HCM.

(McLeod et al. JACC Vol. 54, No. 3, 2009)

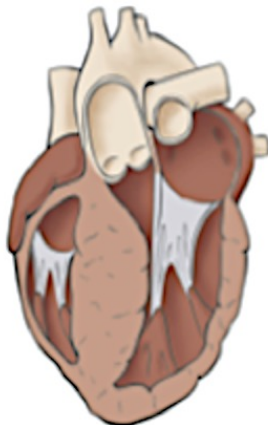
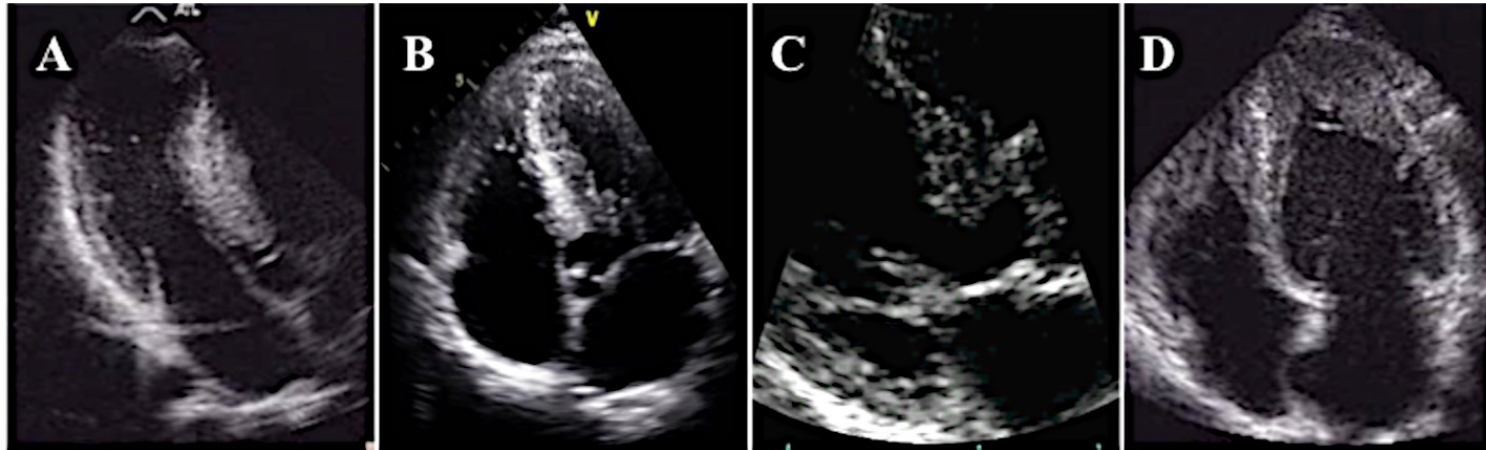
***Normal ECG  $\neq$  No clinical HCM***

## 2D Echocardiography

- Given its wide availability and relatively low cost, 2D echocardiography is the **initial imaging modality** for the diagnosis and management of HCM.
- Echocardiographic diagnostic criteria for HCM:
  - Unexplained maximal wall thickness (measured at end-diastole)  $\geq 15$  mm (or  $>2$  standard deviation for age, height and gender) in any myocardial segment
  - Septal/posterior wall thickness ratio of  $>1.3$  in a nondilated ventricle and  $>1.5$  in the setting of systemic hypertension.
- Ventricular hypertrophy in HCM is usually **asymmetric**, with involvement of **the basal anterior interventricular septum** in the majority of patients.

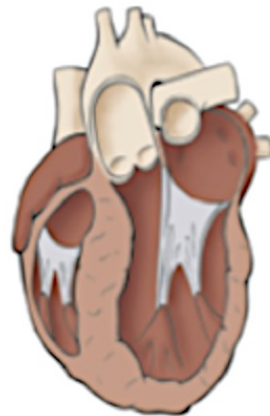


# *The different anatomic variants in HCM*



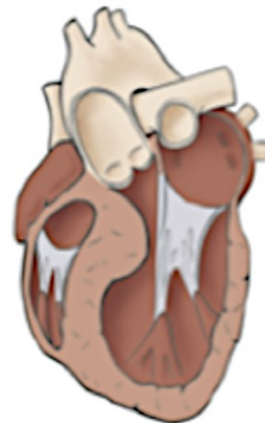
Reverse  
Septal  
curvature

**30-40%**



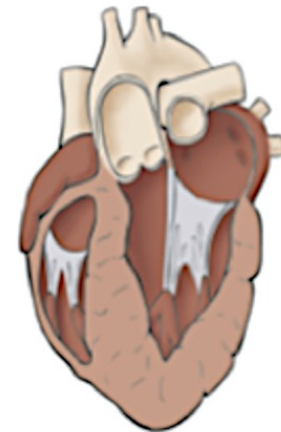
Neutral  
Septal  
curvature

**10%**



Sigmoid  
Septal  
curvature

**40-50%**

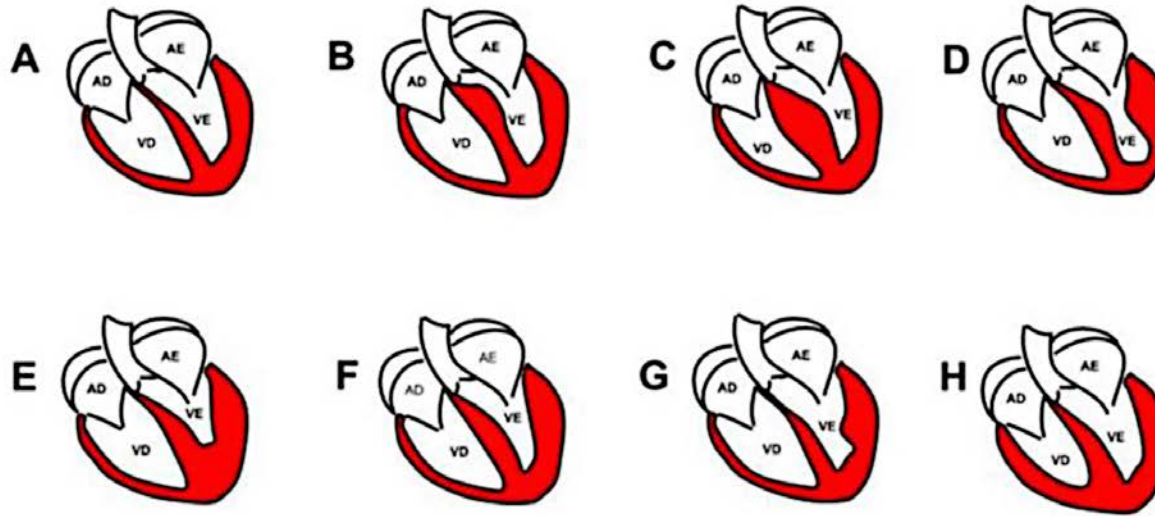


Apical  
hypertrophy

**10%**

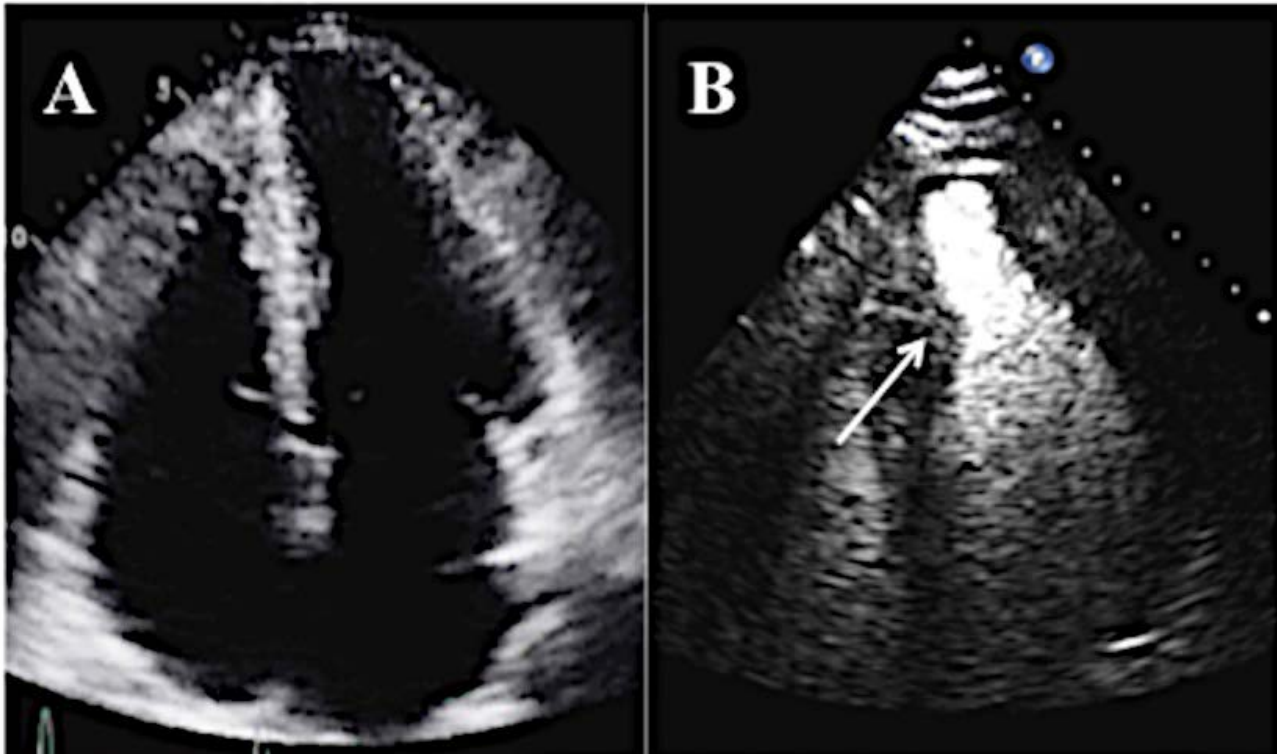
# Hypertrophy distribution

- The hypertrophy can range from focal segmental hypertrophy to diffuse global hypertrophy.
- In approximately 10% of patients the hypertrophy is limited to 1– 2 segments.
- *As the hypertrophy is often noncontiguous, all LV segments should be carefully examined from base to apex in all available views.*



## ***Apical HCM is easy to miss on 2D echocardiogram***

- The addition of intravenous contrast agents can aid in the accurate diagnosis of these patients, especially in the setting of suspected apical aneurysms and clots by providing better LV cavity delineation.

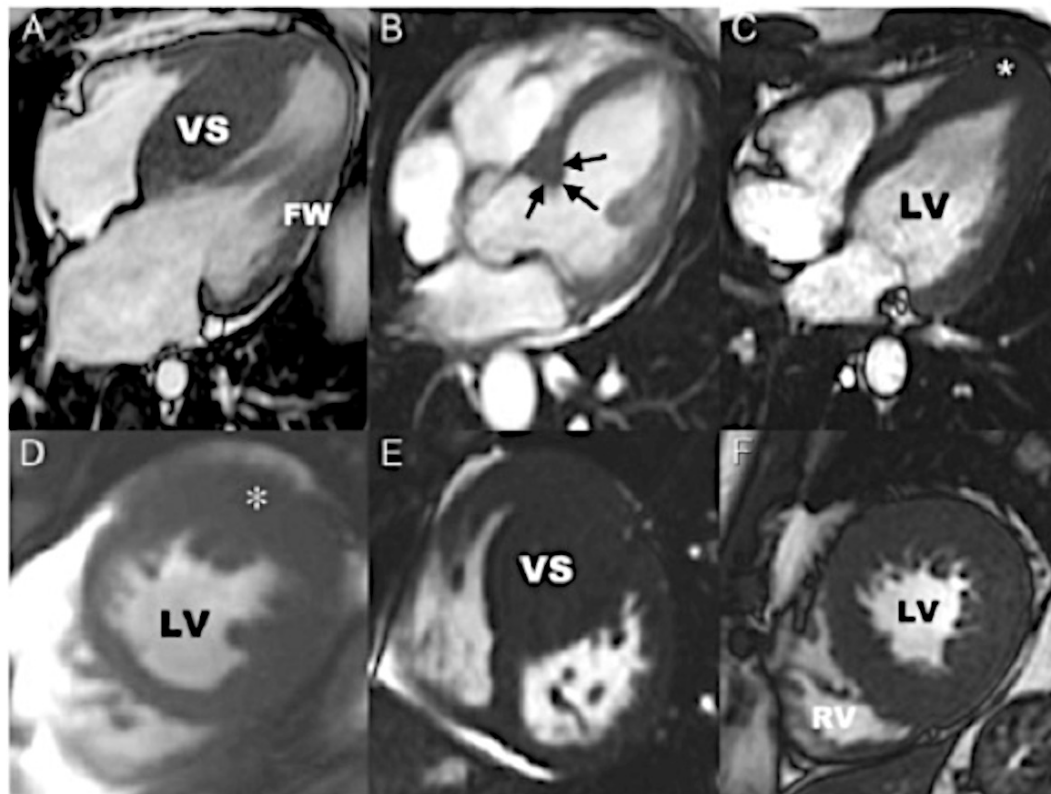


## *Echo limitations*

- Although traditionally 2D echocardiography has been the gold standard for the clinical diagnosis of HCM, it has several limitations:
    - The quality of the image relies on the acoustic window
    - Endocardial delineation is sometimes suboptimal and the short-axis view is often elliptic instead of round.
- Suboptimal measurement of the wall thickness particularly when the hypertrophy is mainly limited to the *apex, anterior free wall or posterior septum*

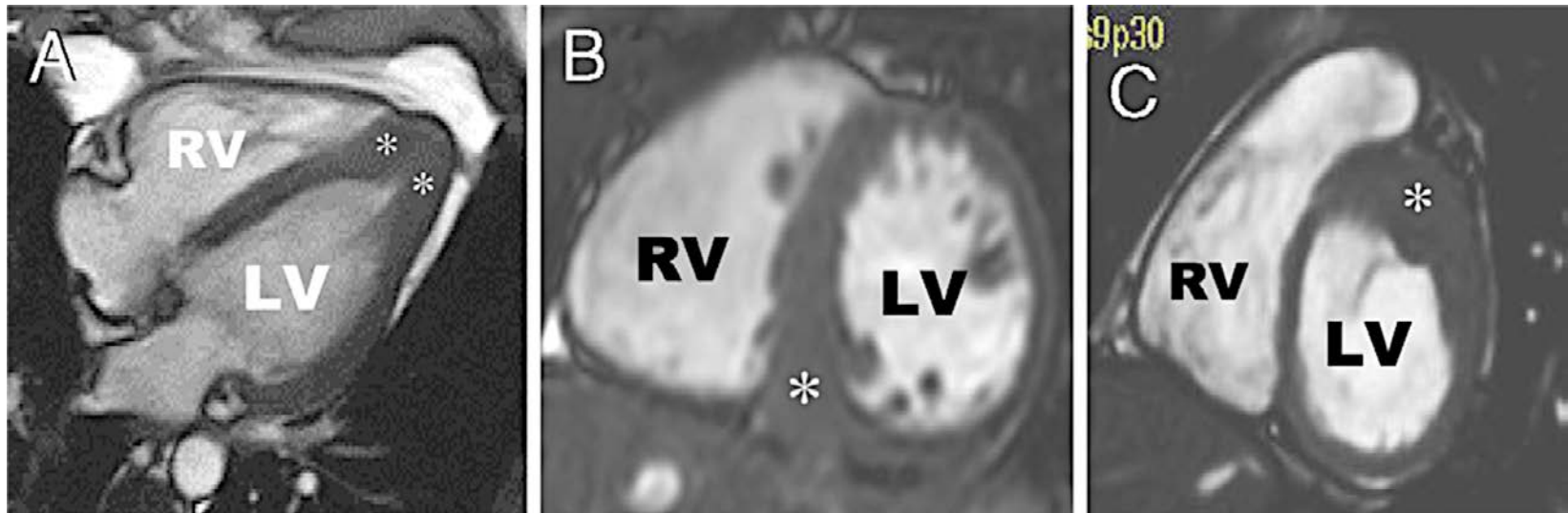
# Cardiac MRI

- CMR bright blood imaging produces excellent contrast between the blood pool and the myocardium at high spatial and temporal resolution, without limitation of imaging window or plane and without ionizing radiation.
- Echocardiographic diagnostic criteria for HCM also apply to CMR.

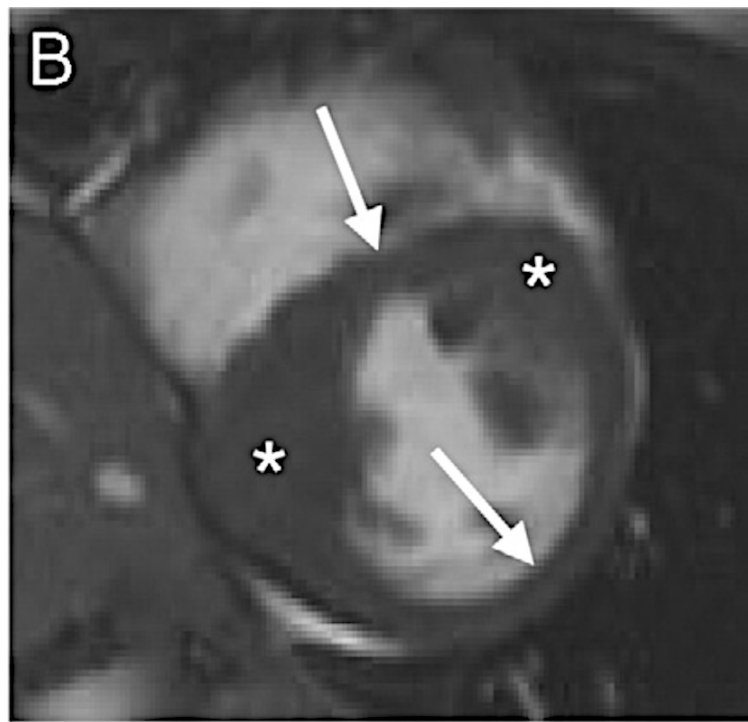
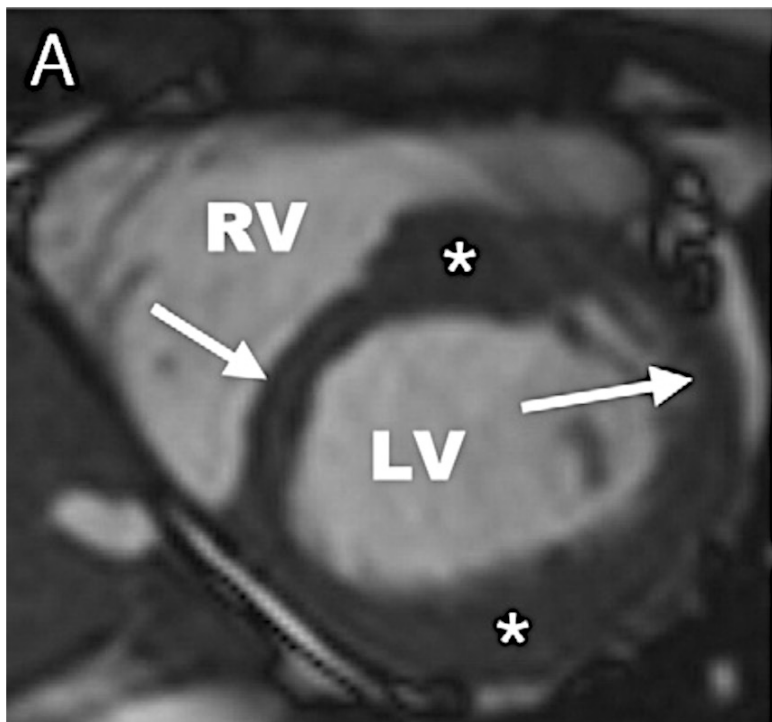


## ***Locations under recognized by 2D echocardiography***

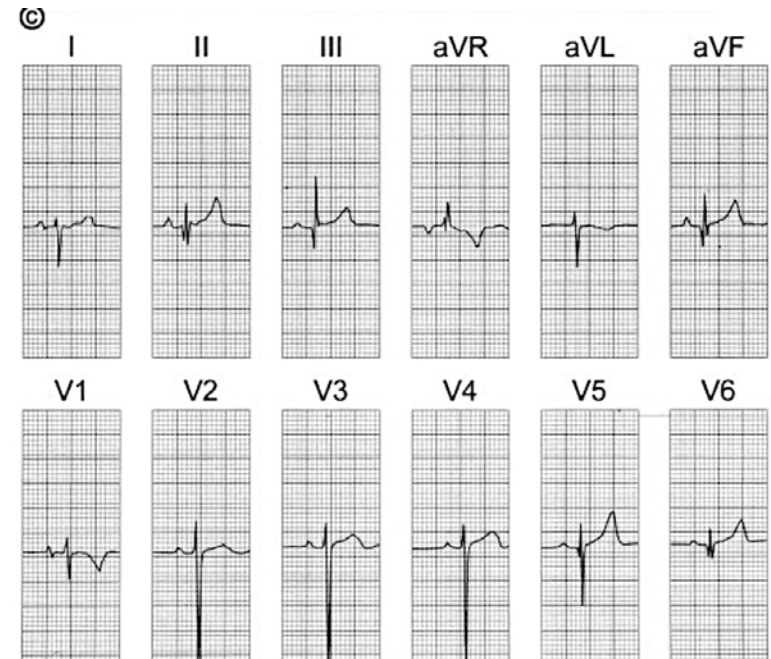
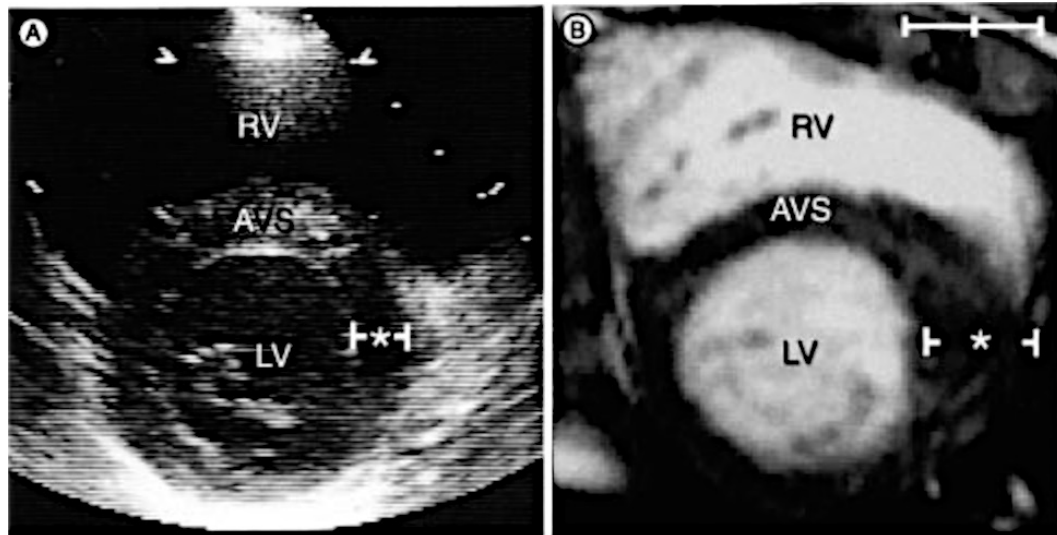
- In a study by Maron et al. on a large cohort of patients with HCM (n = 333), echocardiography underestimated or missed hypertrophy in 12% of patients.
- Those patients had segmental LV hypertrophy, which was largely confined to the *apex*, *posterior septum* or *anterolateral free wall*.



## *Noncontiguous hypertrophy*



# *An example of a case missed by 2D echocardiography*

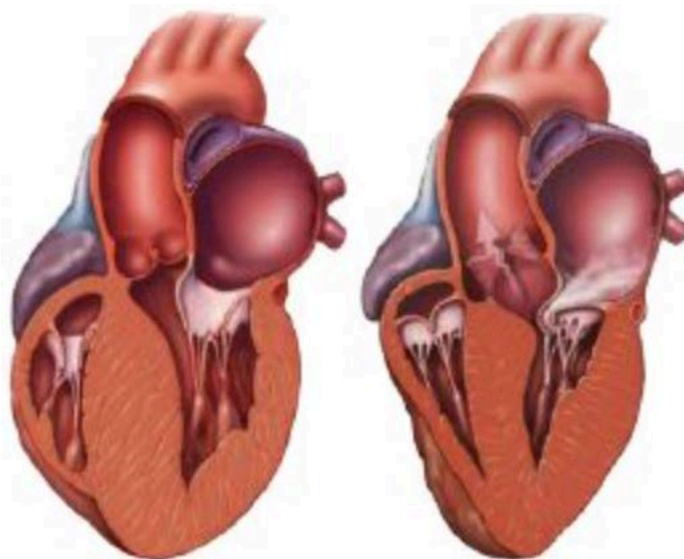


## *When should we use Cardiac MRI for HCM diagnosis?*

- CMR should be integrated into the initial evaluation of all patients if available.
- It is of greatest importance in the “*borderline patient*”:
  - LV myocardium is not well visualized by the echocardiogram
  - The echocardiographic data are inconclusive
  - The electrocardiogram is abnormal but the echocardiogram is normal
  - Members of high-risk families with non-diagnostic findings on echocardiogram
- To differentiate HCM from other conditions including amyloidosis, hypertensive heart disease and athlete’s heart.

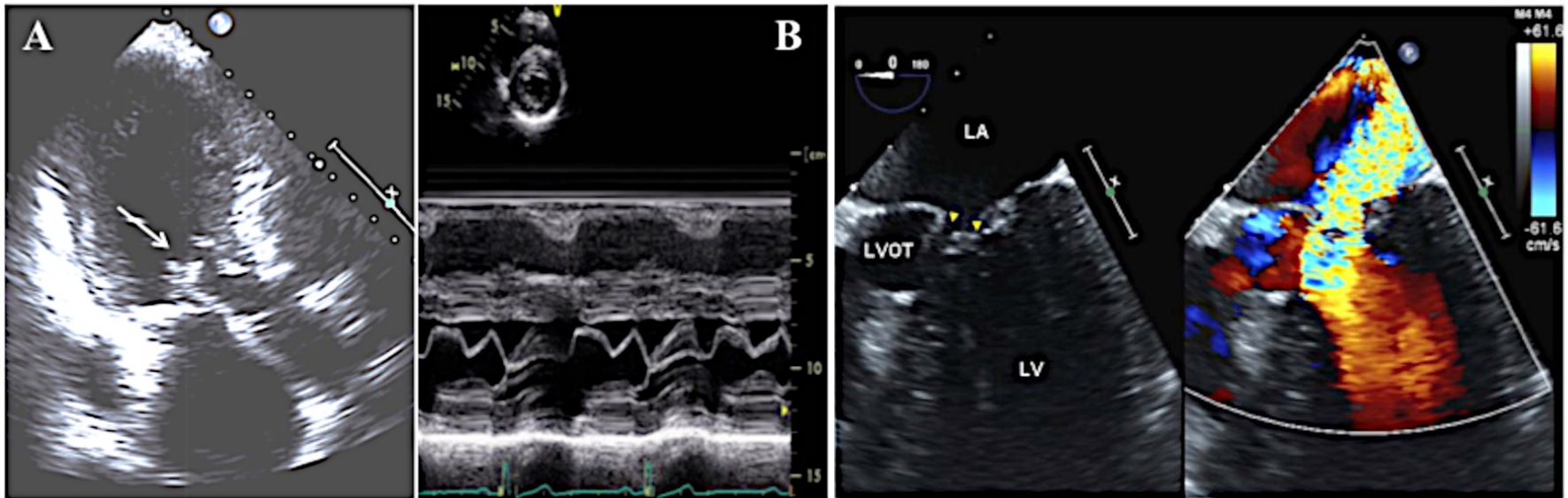
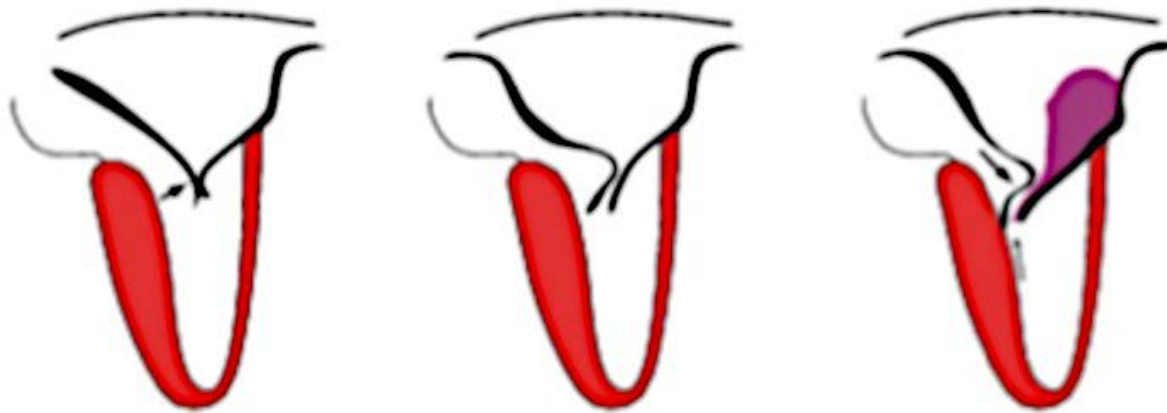
## ***How not to miss LVOT obstruction***

- Obstruction is defined as a peak gradient  $>30$  mmHg at rest or after provocation (Valsalva maneuver, standing and exercise).
- About one-third of the patients demonstrate LVOTO at rest while another third have LVOTO only on provocation.
- LVOTO is usually of hemodynamic importance when the gradient is  $\geq 50$  mmHg.



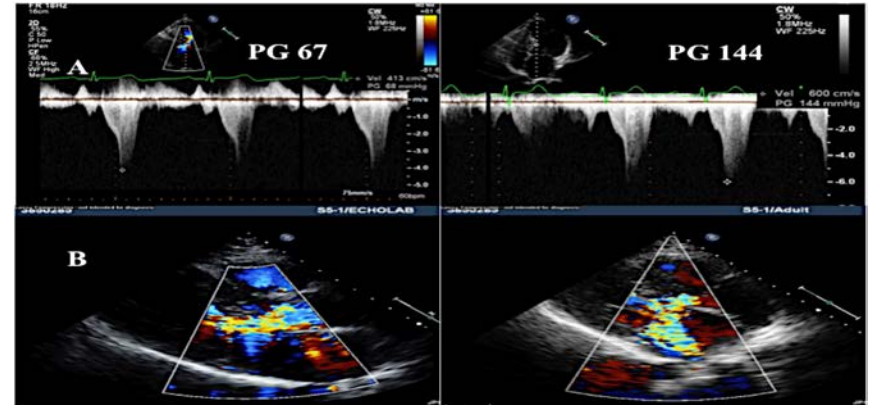
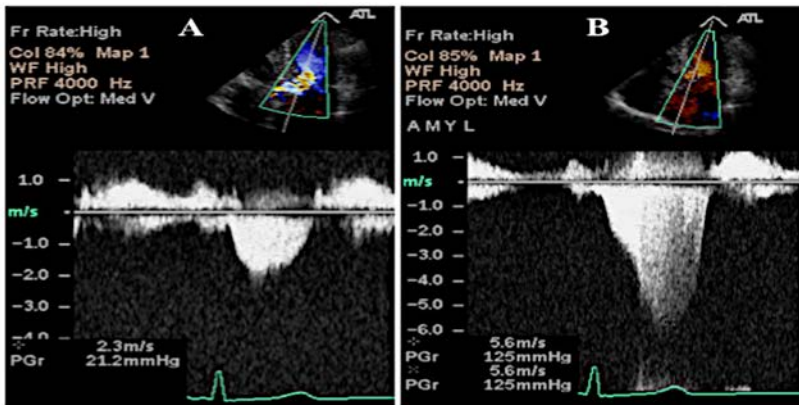
## How not to miss LVOT obstruction

- Systolic anterior motion of the mitral valve causes impingement of the mitral valve leaflets upon the hypertrophied basal septum, which may result in *dynamic LVOTO*.



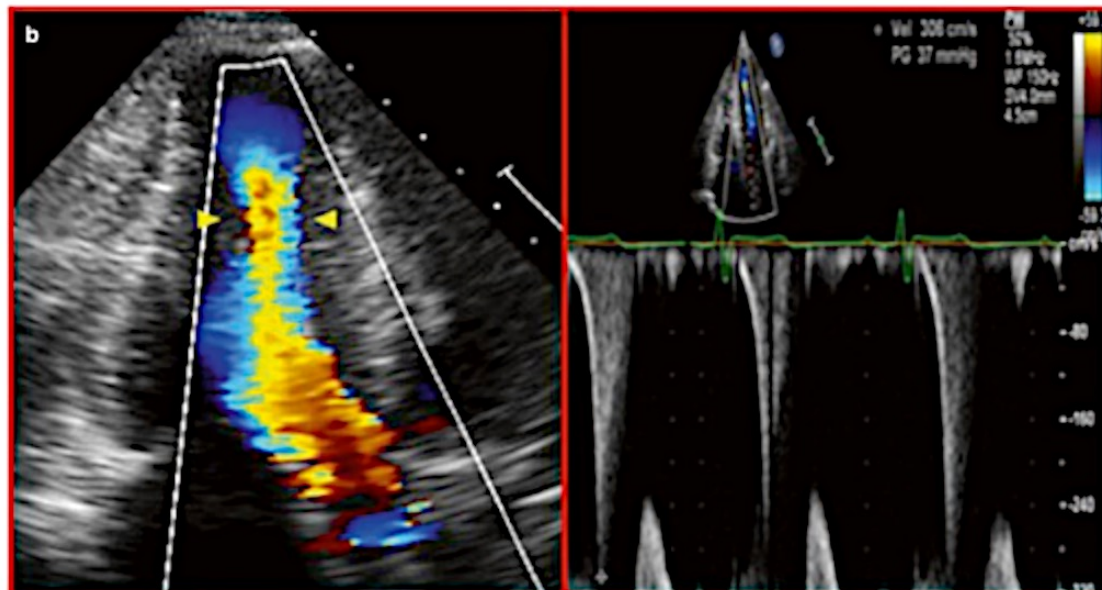
# How not to miss LVOT obstruction

- *It is important to assess LVOT gradients on provocation in symptomatic patients with gradients < 50 mmHg.*
- compared with exercise echocardiography Valsalva maneuver has a lower sensitivity (40%) and may underestimate the magnitude of a provokable LVOT gradient.



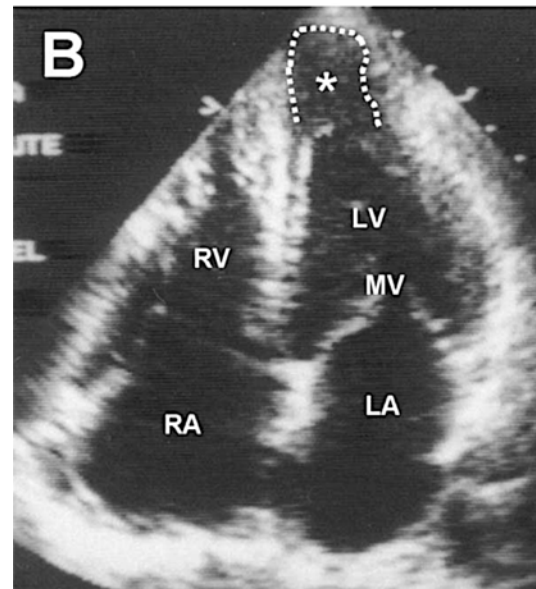
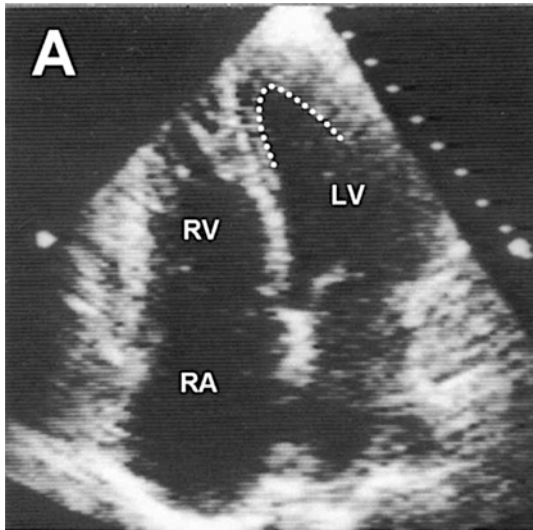
## *Mid cavity obstruction*

- Systolic apposition of the mid-LV walls with a mid-ventricular systolic gradient of  $>30$  mmHg
- Approximately 10% of patients exhibit mid cavity obstruction.
- Usually occurs when the hypertrophy predominantly involves the mid-septum and the corresponding free wall near the papillary muscles with apex of normal thickness.
- The diagnosis of mid-cavity obstruction requires a separation of the apical cavity and the basal segments of the LV.



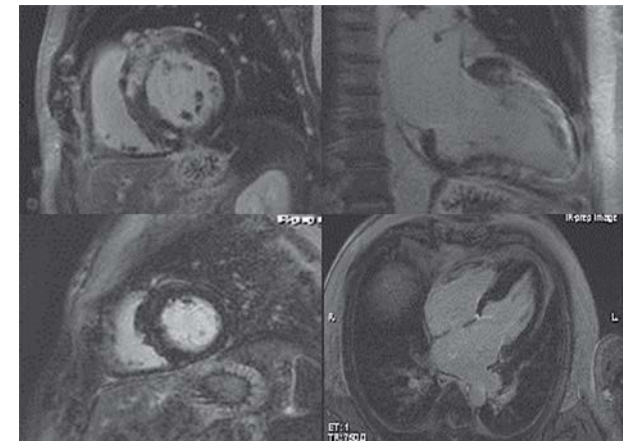
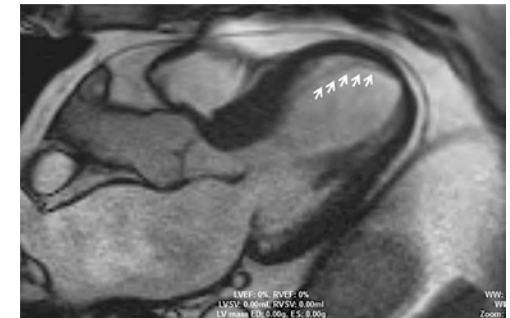
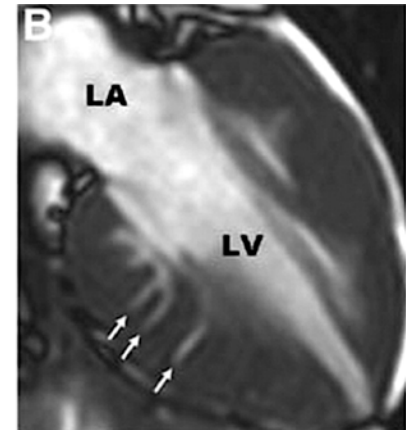
## ***Screening family members and preclinical diagnosis***

- 2D transthoracic echocardiogram is the first-line imaging modality for screening first-degree relatives of patients with HCM.
- The cut-off values of wall thickness for diagnosing first degree relatives of a patient with HCM are lower than in the index patients (>13 vs >15 mm).
- Screening is recommended yearly between the ages of 12– 21 and at least every 5 years thereafter, as late-onset hypertrophy can occur, and a significant proportion of patients are diagnosed at an older age.

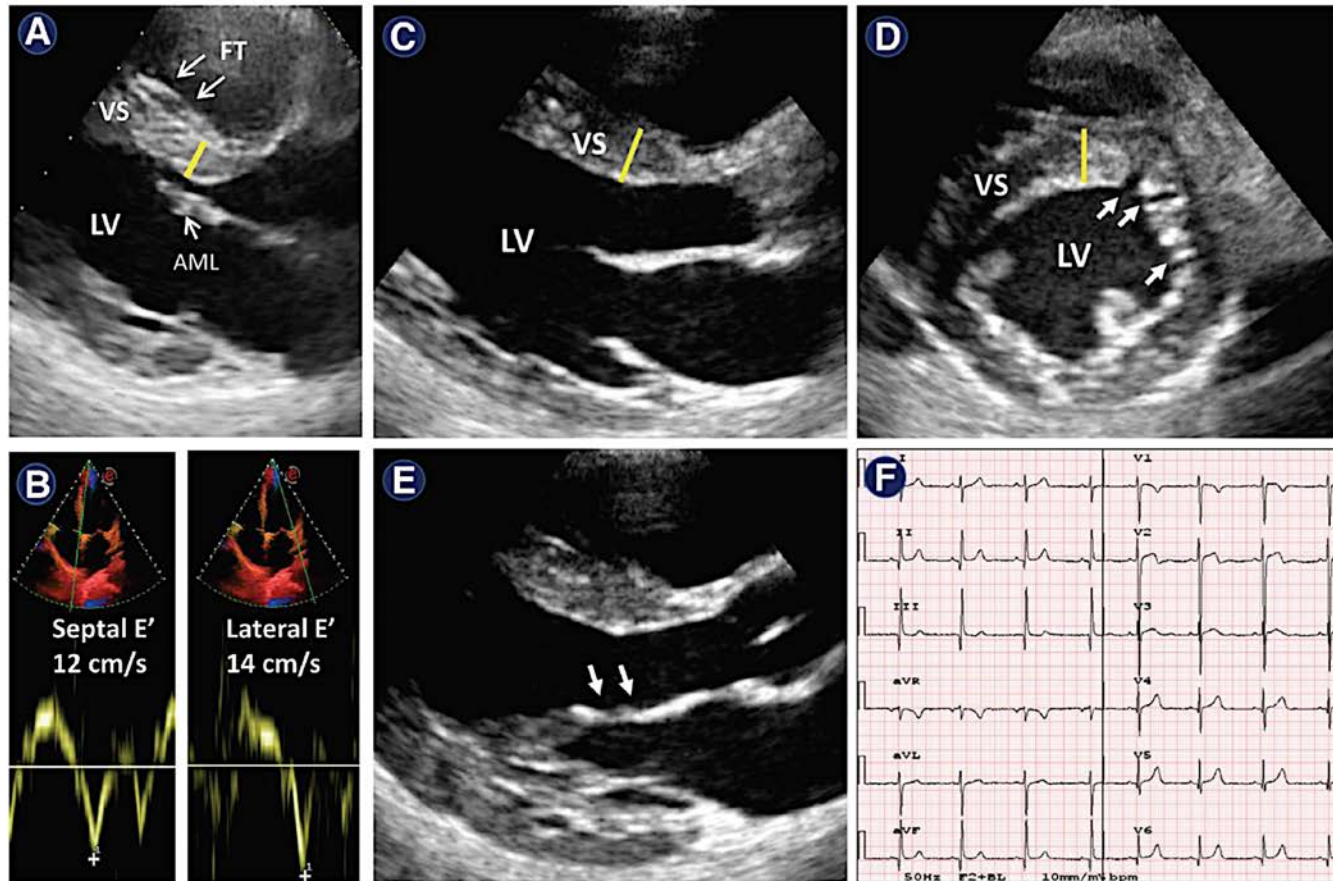


# Screening family members and preclinical diagnosis

- Several studies have investigated subtle echocardiographic abnormalities in genotype positive phenotype negative patients including reduced TDI systolic and early diastolic velocities and impaired regional longitudinal strain and apical rotation in gene carriers.
- CMR can detect subtle “*pre-hypertrophic*” features in genotype positive individuals with no hypertrophy including:
  - **Mitral valve apparatus abnormalities**: elongated mitral leaflets, papillary muscle hypertrophy, anterior displacement of the papillary muscles
  - **Crypts** (narrow, deep invaginations within the LV myocardium) in the basal and mild inferoseptum
  - **False tendons** running parallel to the IVS
  - **Late gadolinium enhancement**



# Screening family members and preclinical diagnosis



**Figure 2.** Nonhypertrophic stage and early phenotype. **A** and **B**, Twenty-six-year-old male patient with family history of hypertrophic cardiomyopathy, carrying the  $\beta$ -myosin heavy chain (MYH7) mutation Lys865Arg (NM\_000257.2 c.2594A>G). Parasternal long-axis view shows normal LV thickness values, with redundant mitral leaflets (**A**). Tissue Doppler imaging velocities of the mitral annulus appear reduced (**B**). **C** and **D**, Ten-year-old boy carrying the myosin binding protein C (MYBPC3) mutation Glu258Lys (NM\_000256.3 c.772G>A). Parasternal long- and short-axis views show mild increase in septal thickness (11 mm; **C** and **D**), with presence of crypts (**arrows**). **E**, Early systolic frame shows abnormal papillary insertion into the anterior mitral leaflet (**arrows**). Inferolateral Q waves are evident on the ECG (**F**). AML indicates anterior mitral leaflet; FT, false tendon, LV, left ventricle; and VS, ventricular septum.

# Genetic testing

- **Despite the discovery of more genes the yield is generally lower than 50%!**
- The yield differs between the different morphological variants, with higher detection rates in the reverse curvature (53-70%) and neutral septum (41-48%) variants compared with the sigmoid septum (8-23%) and apical hypertrophy (11-30%) variants.
- ***The best predictor for a positive genetic testing is family history of HCM.***
- Other predictors include: female sex, young age at diagnosis, family history of sudden death.



Ingles et al. Genet Med. 2013 Dec;15(12):972-7

Gruner et al. Circ Cardiovasc Genet. 2013;6:19-26

## ***HCM diagnosis in the context of HTN***

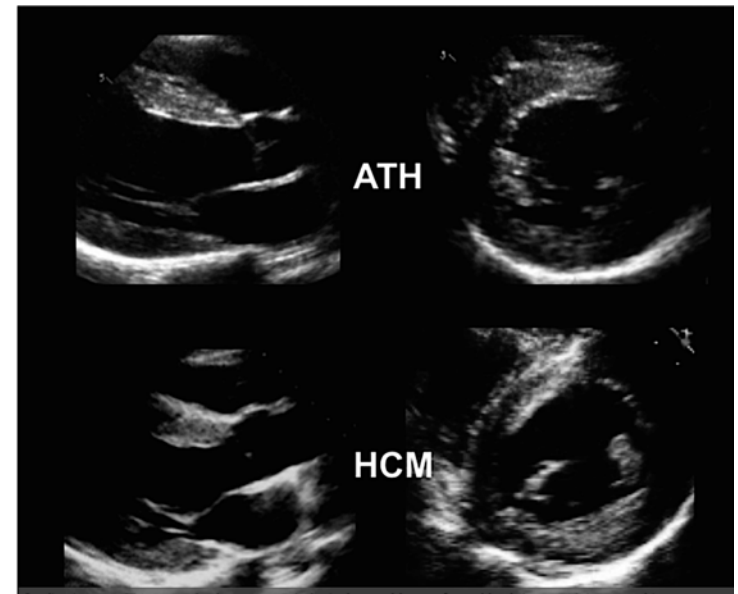
- As HTN is very prevalent, it is not uncommon for HTN and HCM to coexist.
- The maximal wall thickness rarely exceeds 15 mm in hypertensive heart disease
  - Afro-Caribbean patients and patients with renal failure often exhibit greater hypertrophy in response to HTN
- Usually concentric hypertrophy.
- In the early stages of the disease, the hypertrophy is often more prominent in the basal septum, yet a septal/posterior wall thickness ratio of >1.5:1 is extremely rare.
- ***SAM with LVOTO is not pathognomonic of HCM and can be seen in HTN.***
- Associated mitral valve apparatus abnormalities point to HCM.

## *Diagnosing HCM in the context of HTN*

- Myocardial strain is potentially helpful in differentiating HTN from HCM.
  - In HTN, systolic strain and systolic strain rate are only mildly reduced, whereas in HCM they are often markedly decreased.
- CMR may also aid in distinguishing hypertensive heart disease from HCM, as LGE is uncommon in HTN, compared with HCM where LGE may be seen in about two-thirds of the patients.

## *Differentiating HCM from Athlete's heart*

- LV wall thickness increases as a response to intense training.
  - Maximal wall thickness  $>16$  mm suggests HCM since the upper limit of physiological hypertrophy (in all ethnicities) seems to be an absolute wall thickness of 16 mm.
  - LVH is usually symmetric in athletes.
  - Chamber dilatation (LV cavity  $>55$  mm) and absence of concomitant mitral valve apparatus abnormalities also suggest an athlete heart.
  - Regression of hypertrophy ( $>2$  mm) after deconditioning supports athlete's heart, which can be accurately performed on CMR.



## *Differentiating HCM from Athlete's heart*

- Reduced longitudinal systolic strain is frequently seen in HCM, whereas athletes usually exhibit a normal or even supra-normal strain.
  - Reduced diastolic function assessed by tissue Doppler velocities and untwist are not likely to be encountered in athletes.
  - LA dilatation may be seen in both conditions, however; LA function, evaluated by strain, is reduced in HCM, whereas it is usually preserved in athlete's heart.
  - The presence of LGE supports HCM rather than athlete's heart.
- ECG is not particularly useful in distinguishing between these two entities. However, unusual and bizarre ECG patterns with strikingly increased voltages, prominent Q waves, or deep, negative T waves favor HCM.

## *Summary*

- The diagnosis of HCM is clinical
- Yield of genetic testing is generally <50%
- A normal ECG does not exclude HCM
- All LV segments should be carefully examined from base to apex in all available views on Echocardiogram
- In borderline cases CMR should be used
- Screening is recommended yearly between the ages of 12– 21 and at least every 5 years thereafter, as late-onset hypertrophy can occur
- A symptomatic patient with no LVOTO at rest should have a stress echo

***Any Questions....?***

