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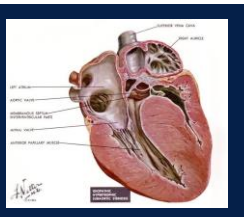

In the Thick of It: Hypertrophic Cardiomyopathy

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October 9th, 2015

Overview

- History
- Epidemiology
- Diagnosis
- Pharmacological Management
- Non-Pharmacological Treatment
- Risk Factors for Sudden Cardiac Death (SCD)
- ICD Indications
- Evolving Therapies

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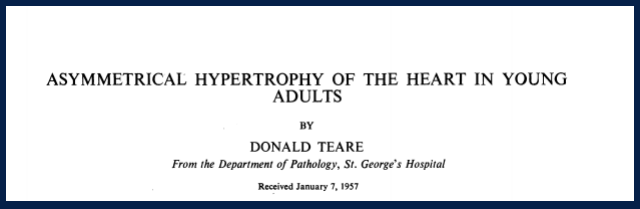
HCM: History



ASYMMETRICAL HYPERTROPHY OF THE HEART IN YOUNG ADULTS

BY

DONALD TEARE

From the Department of Pathology, St. George's Hospital

Received January 7, 1957

- First described in 1957 by Dr. Donald Teare from St George's hospital in London
- Described 8 cases of asymmetric septal hypertrophy seen on autopsy in patients ages 14-44
- Noted that the tumors had "occurred in a group where cardiac incapacity is rare"

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HCM History

- In 1964, Morrow and Braunwald published in a case series of 64 patients at the National Heart Institute (Bethseda, MD)
- They termed these patients "idiopathic hypertrophic subaortic stenosis"

Figure 3. Eugene Braunwald (left) and Barry Maron (right) at the American Heart Association meeting in Orlando, Florida, 2011.

Dr Braunwald wrote: "at this time, we are aware of no method of management that can specifically and favorably influence the course of the patient"

Braunwald E, et al. Circulation 1964:30:3-1119

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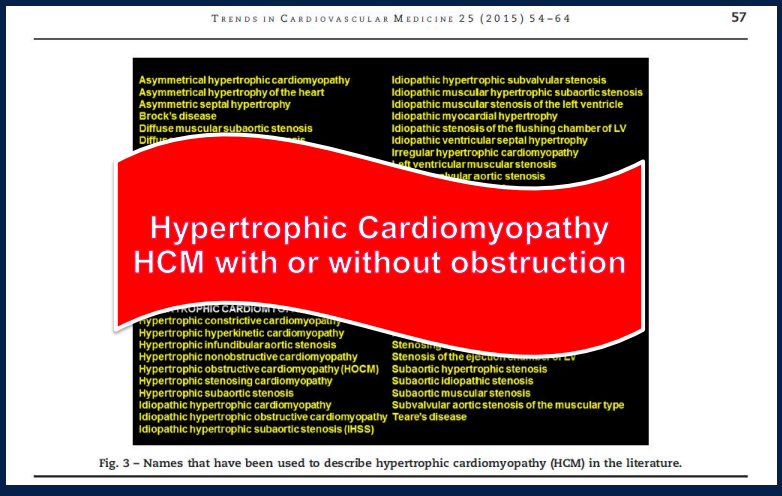

Fig. 3 – Names that have been used to describe hypertrophic cardiomyopathy (HCM) in the literature.

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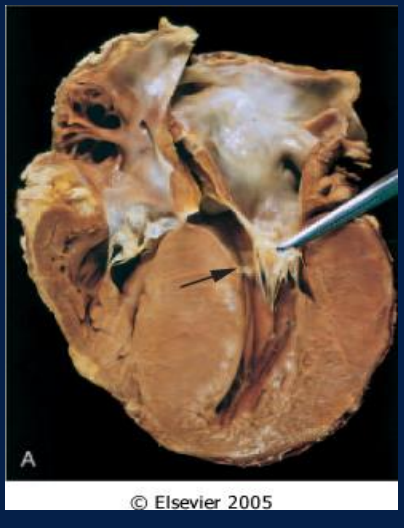
Hypertrophic Cardiomyopathy: Definition

- Thickened, non-dilated heart
- Absence of other Cardiac/Systemic Diseases
- Secondary to genetic mutation



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Epidemiology

- MC inherited cardiac disease
- Estimated prevalence of HCM 1 in 500 (0.2% general population)
- Global disease, reported in all continents
- Affects both genders, racial and ethnic origins

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Genetics

- Secondary to a genetic mutation in genes encoding proteins of the cardiac sarcomere
- Mutations in any one of 10 sarcomeric genes; over 200 mutations identified
- Autosomal Dominant with incomplete penetrance and variable phenotypic expression
- Little correlation between mutation type and clinical outcome

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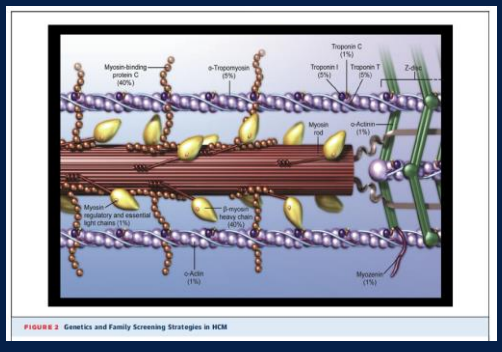
Genetic Mutations

- Most common mutations
  1) B-myosin heavy chain (40%)
  2) Myosin-binding protein C (40%)
  3) Cardiac troponin T (5%)



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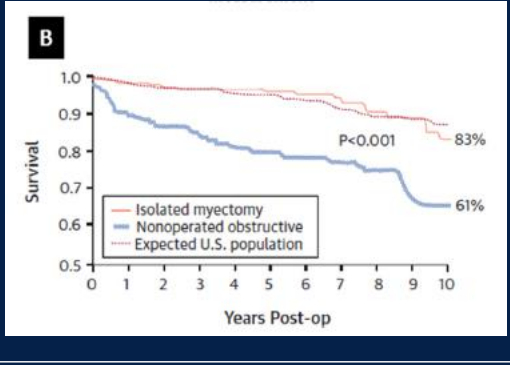
Natural History

- More recent retrospective data: 1% annual mortality
- Evidence that HCM patients frequently capable with normal life expectancy



Gersh BJ, Maron BJ et al, 2011 ACCF/AHA guidelines for the diagnosis and treatment of hyertrophic cardiomyopathy

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HCM: Natural Course

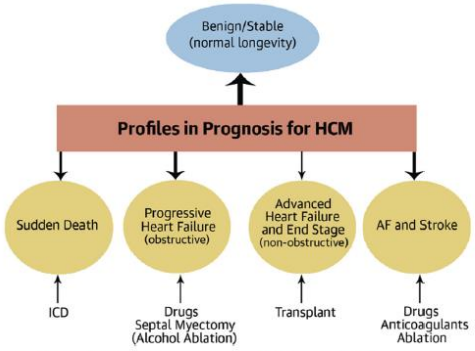

Fig. 6 – Adverse pathways within the broad HCM clinical spectrum. Individual patients may be subject to disease progression with 1 or more of these complications, each of which is associated with potentially effective treatment options. Alternatively, most HCM patients probably experience benign course without requiring major interventions. AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator.

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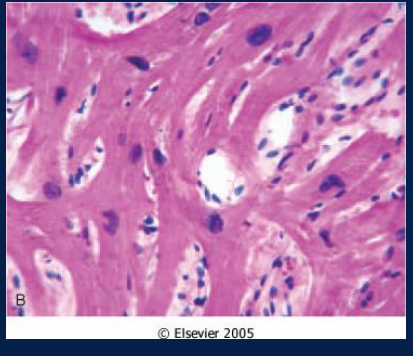
Pathology

- Disarray Myocyte/Myofibril
- Genetic defects encoding for cardiac sarcomeric proteins result in:
  1) Cardiomyocyte hypertrophy
  2) Cardiomyocyte dysfuction
  3) Myofibril disarray
  4) Interstitial fibrosis



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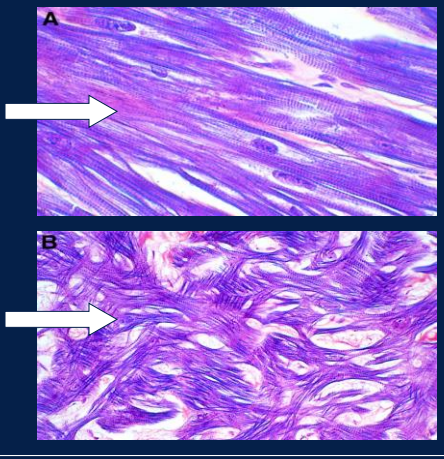
Myocyte/Myofibril Disarray

- Normal Myocardium:
  - Myocytes in parallel
  - Myofibrils in parallel along long axis of cell
- HCM Myocardium:
  - Myocyte/Myofibril disarray
  - Organization around foci of connective tissue



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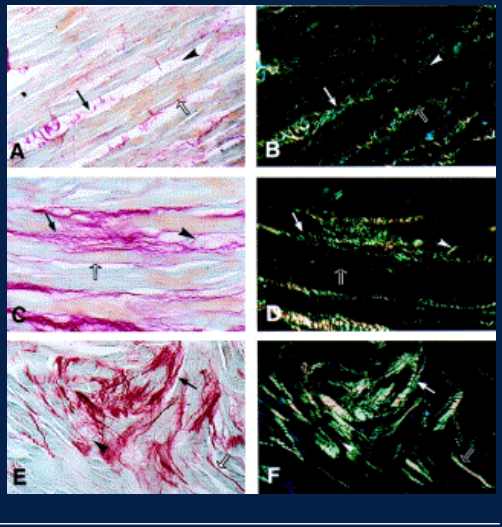
Pathology: ↑ Collagen Matrix

- Increased collagen matrix in HCM hearts
- Present at young age
- Expands during growth
- Contributes to hypertrophic process
- Interstitial and perivascular deposition



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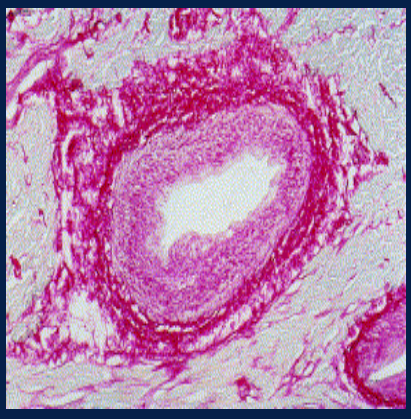
Microvascular Changes

- Genetic defect also causes microvascular changes
- Increased intimal and medial collagen deposition →narrowed lumen
- Limited vasodilator reserve →chronic ischemia→ ↑collagen matrix (replacement fibrosis)
- Not limited to areas of hypertrophy



1. Picture: Shirani JACC 2000; 35: 36-44

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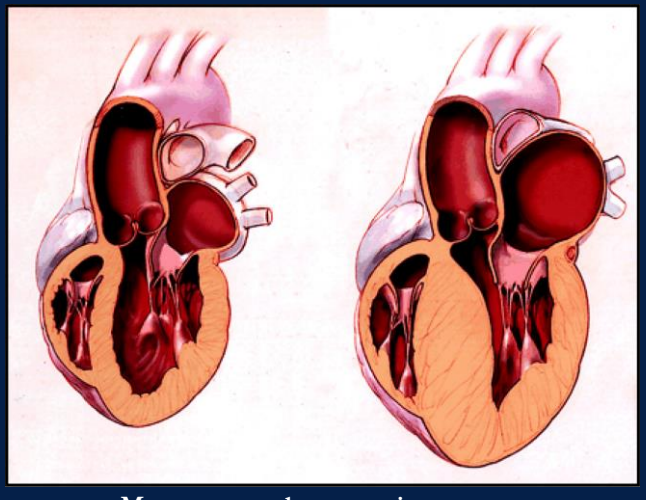
Variants of HCM



Most commonly at anterior septum

Nishimura R et al. Circulation 2003;108:e1133-135

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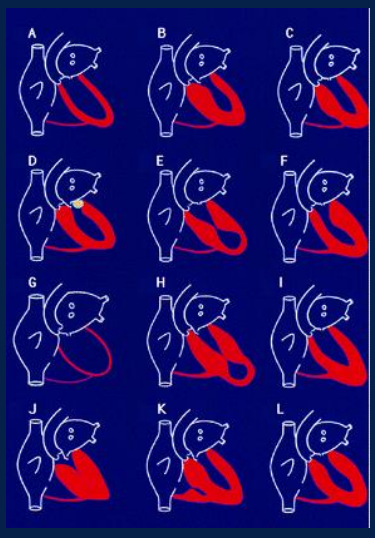
Variants of HCM



- A: NI or mild hypertrophy
- B: IHSS or LVOT obstructive HCM
- C: Asymmetric septal hypertrophy (ASH)
- D: Elderly HCM
- F: Reversed ASH
- G: LV thinning, low EF, RAE/LAE
- H: Mixed LVOT and midcavity obstructive HCM
- I: Apical HCM
- J: Cavity obliteration
- K: BiV hypertrophy and obstruction
- L: Symmetric hypertrophy.

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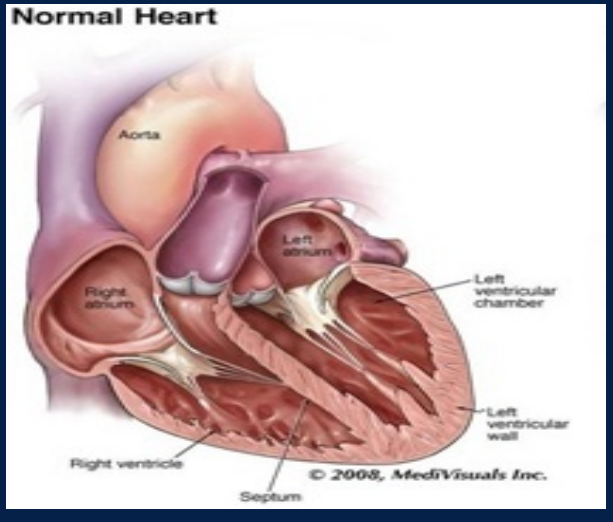
Physiology: LVOTO



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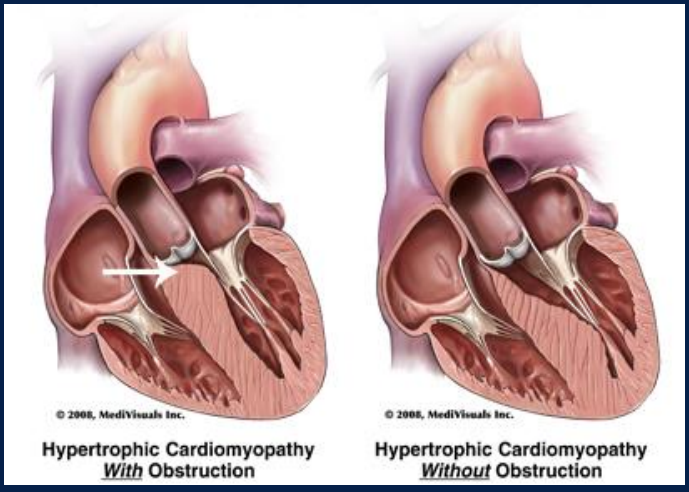
Physiology: LVOTO



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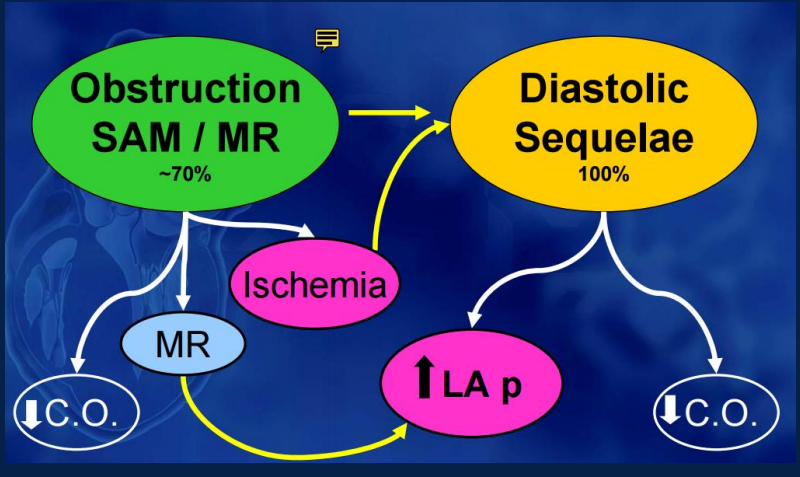
Pathophysiology



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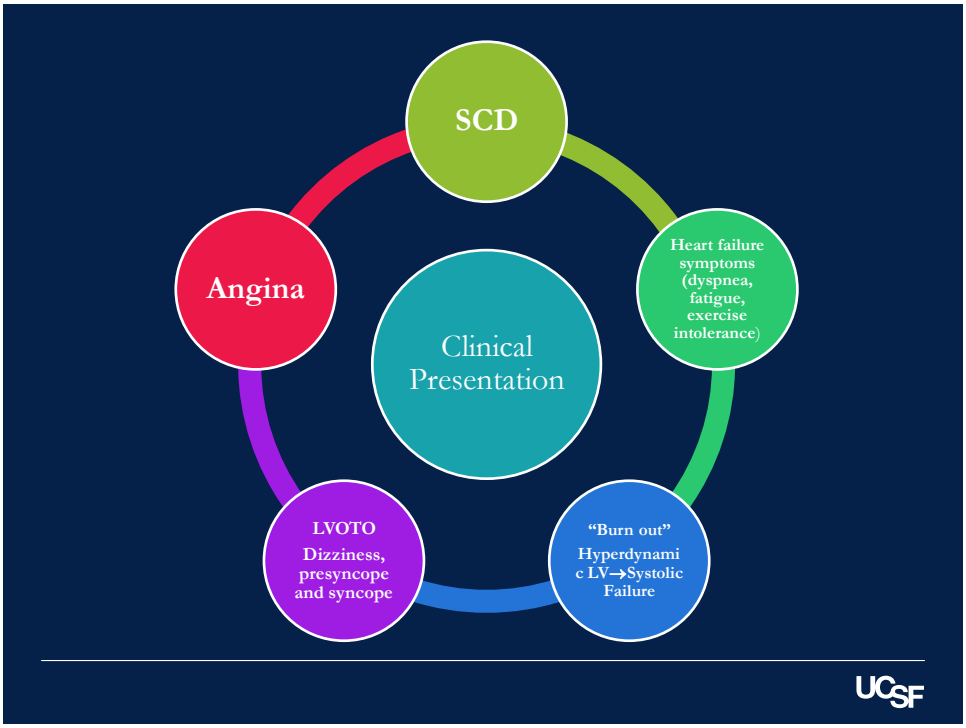
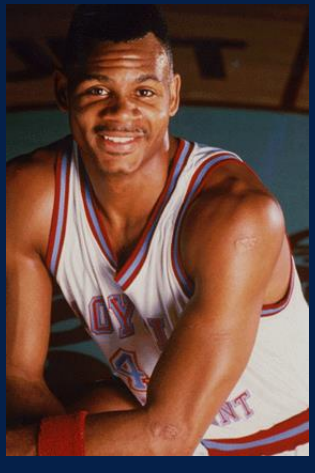
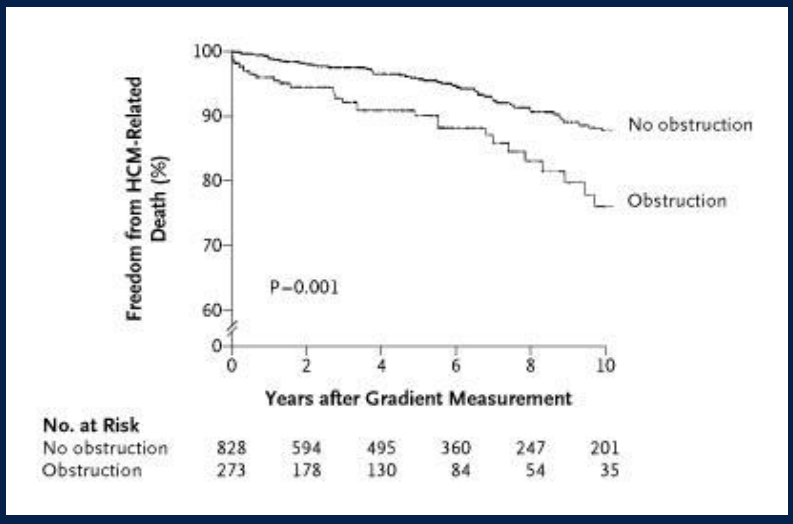


HCM and Sudden Cardiac Death

- Young adults under 30-35
- Primary VT / VF
- Most common initial presentation
- Most common cause of SCD in the youth (35%).
- Assoc with sedentary, modest, or vigorous physical activity



Probability of Hypertrophic Cardiomyopathy (HCM)–Related Death among 273 Patients with a Left Ventricular Outflow Gradient of at Least 30 mm Hg under Basal Conditions and 828 Patients without Obstruction at entry.



Maron MS et al. N Engl J Med 2003;348:295-303.

The NEW ENGLAND JOURNAL of MEDICINE

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Heart Failure

- 50% of HCM patients
- Sx: DOE
- Due to mechanical impedance to LV outflow, usually due to SAM
- Because SCD had decreased due to increasing penetration of ICD, death due to HF emerging as predominant mode of demise

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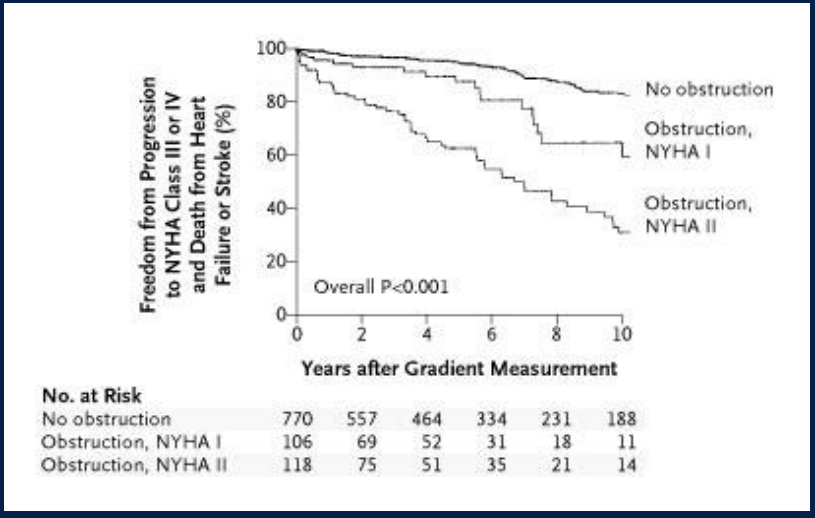
Probability of Progression to Severe Heart Failure (NYHA Class III or IV) or Death from Heart Failure or Stroke among 224 Patients with Left Ventricular Outflow Tract Obstruction and 770 Patients without Obstruction.



No. at Risk

No obstruction	770	557	464	334	231	188
Obstruction, NYHA I	106	69	52	31	18	11
Obstruction, NYHA II	118	75	51	35	21	14

Maron MS et al. N Engl J Med 2003;348:295-303.

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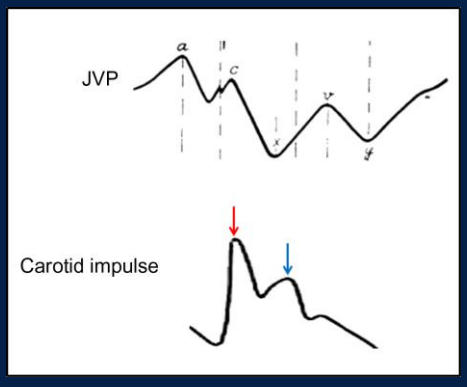
Physical Exam

Physical Exam

- Many patients may have normal PE
- Parasternal Lift/apical impulse
- Prominent A-wave
- Palpitation of Carotid Artery: bi-fid, brisk waveform



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Murmur

Mid-Systolic Murmur at Apex radiating to axilla Due to SAM	Mid-systolic, cresendo-decrescedo murmur, LLSB Due to Turbulant flow through outflow tract

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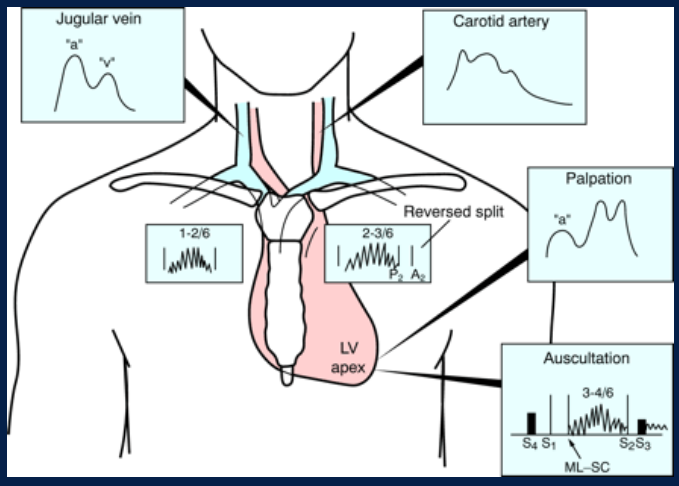
Physical Findings



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ECG Findings in HCM

- Abnormal in >95% of pts.
- Abnormal in 75% of asymptomatic relatives.
  - Normal ECG does not provide reliable prognostic info about outcome.
- Wide variety of abnormalities
  - LVH
  - Lateral precordial TWI
  - Tall R or Deep S waves
    - Only weakly correlate with magnitude of LVH
    - Do not differentiate HCM from HOCM.
- None is characteristic or predictive of future events.

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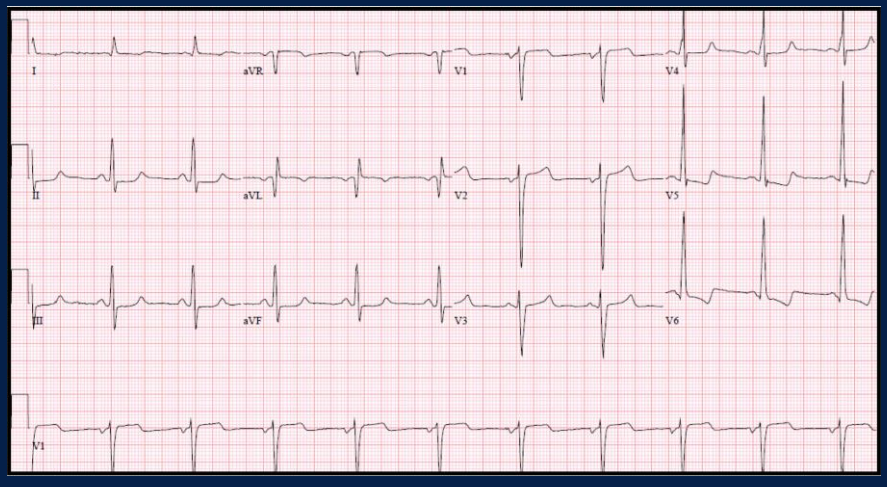
Diagnosis EKG



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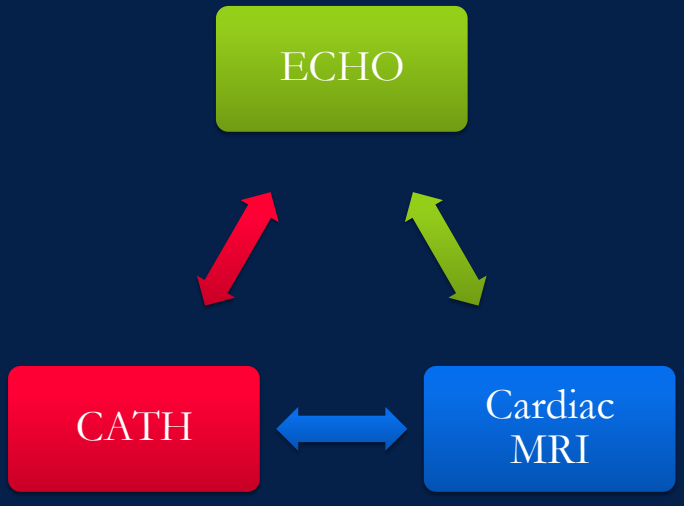

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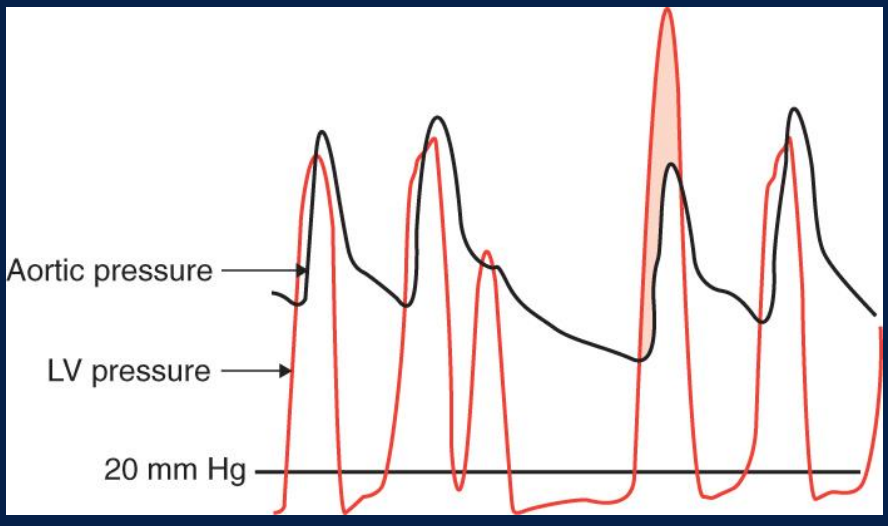
CATH



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Diagnosis: 2D Echo

- Majority of HCM cases diagnosed by 2D Echo
- Hypertrophied but nondilated LV
- Increased wall thickness ranging from mild (≥15mm) to massive (≥30mm)
- Septal/Posterior Wall ratio > 1.3
- Only 2D image slices (does not provide complete 3D view of RV/LV)

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HCM Diagnosis: 2D Echo

- Echo can also estimate LVOT gradient
- Gradients ≥ 30 mm Hg and elevated LV cavity pressures reflect mechanical obstruction to flow
- *Gradient is dynamic

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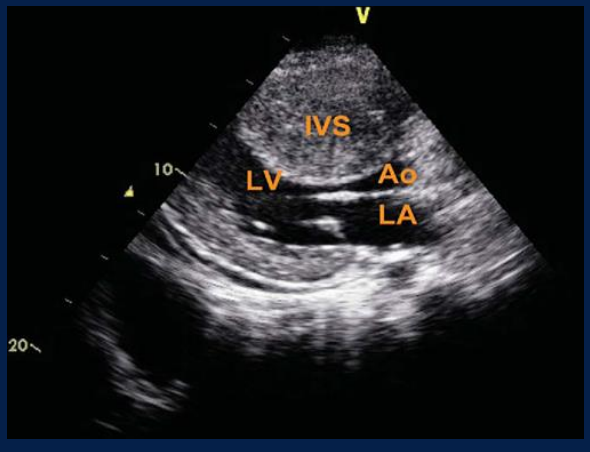

Diffuse hypertrophy variant of hypertrophic cardiomyopathy (HCM).

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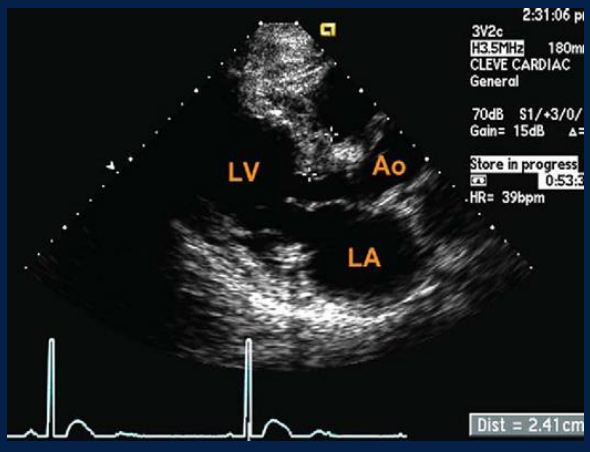
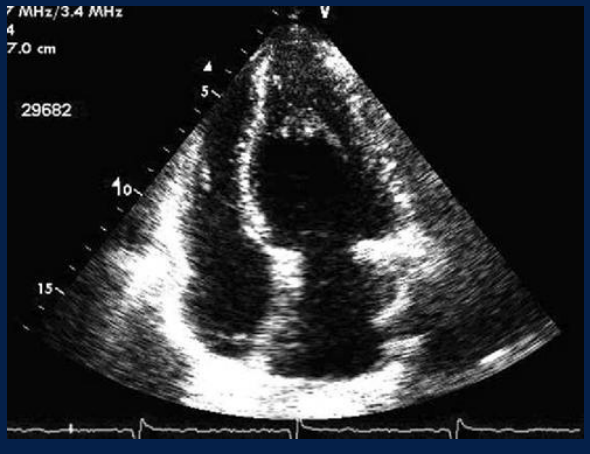


Proximal septal hypertrophy variant of hypertrophic cardiomyopathy (HCM).



Apical hypertrophy variant of hypertrophic cardiomyopathy (HCM)

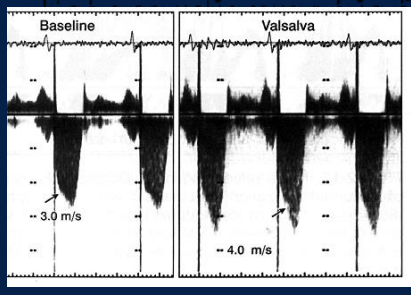
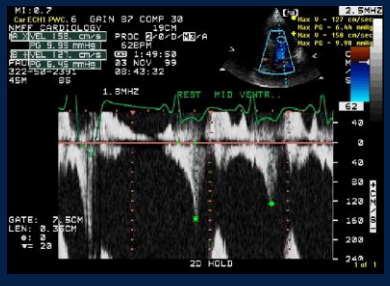


FIG. 12-9. Continuous-wave Doppler spectra obtained from the apex demonstrating dynamic left ventricular (LV) outflow tract obstruction. Note the typical late-peaking configuration resembling a dagger or ski slope (*arrow*). The baseline **(left)** velocity is 2.8 m/sec, corresponding to the peak LV outflow tract gradient of 31 mm Hg ($= 4 \times 2.8^2$). With the Valsalva maneuver **(right)**, the velocity increased to 3.5 m/sec, corresponding to the gradient of 50 mm Hg.



MID LV GRADIENT

From Oh JK et al

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Diagnosis: Cardiac MR

- Echo only provides 2D image of heart; often difficult to assess apex
- MRI: superior in identifying patients with apical aneurysms
- Allows one to identify fibrosis with delay Gd
- LGE seen >50% of patients
- Absence of LGE is associated with lower risk of SD and a source of reassurance
- Conversely, SD risk is proportional to the amount of LGE, with >15% (of LV mass) equivalent to a 2 fold

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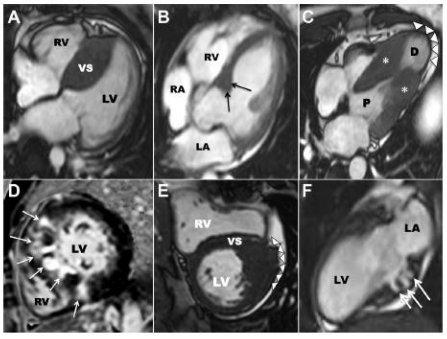

FIGURE 1 Cardiovascular Magnetic Resonance Images Demonstrate Diversity of the Hypertrophic Cardiomyopathy Phenotype

(A) Asymmetric hypertrophy of ventricular septum (VS), sparing the left ventricular (LV) free wall. **(B)** Focal hypertrophy sharply confined to basal anterior septum **(arrows)**. **(C)** Thin-walled apical aneurysm **(arrowheads)** with muscular mid-ventricular apposition of hypertrophied septum and LV wall **(asterisks)**, and distinct proximal (P) and distal (D) chambers. Adapted with permission from Maron et al. (19). **(D)** Extensive, transmural late gadolinium enhancement involving ventricular septum **(arrows)**. **(E)** Massive thickening (i.e., 33 mm) confined largely to anterolateral LV wall, greatly underestimated by echocardiography **(arrowheads)**. Adapted with permission from Maron et al (9). **(F)** Genotype positive-phenotype negative HCM family member with 3 myocardial crypts penetrating thickness of basal inferior wall **(arrows)**. Adapted with permission from Maron et al. (55). LA = left atrium; RA = right atrium; RV = right ventricle.

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Cardiomyopathy/Focal LGE and Outcomes in Hypertrophic Cardiomyopathy

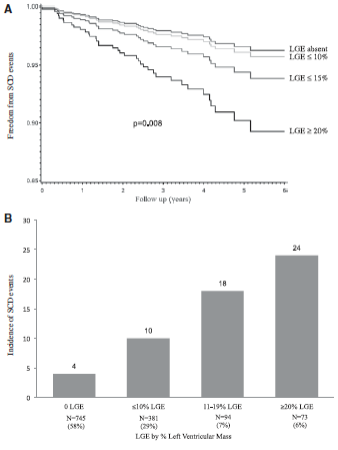

Figure 2. Relation between extent of late gadolinium enhancement (LGE) and sudden cardiac death (SCD) events in 1293 patients with hypertrophic cardiomyopathy. **A**, Hazard plot based on multivariable Cox regression analysis (P=0.008). **B**, Incidence of SCD events increased progressively and in direct relation to the extent of LGE (P<0.001).

Chat RH, Maron, BJ et al. Circulation 2014:130;484-495

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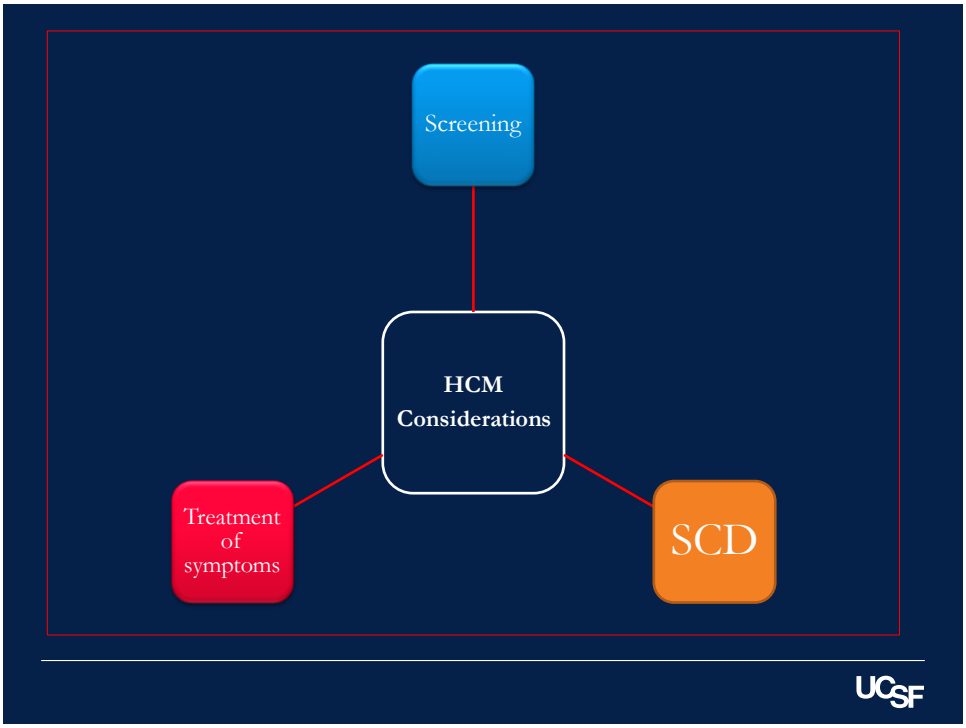
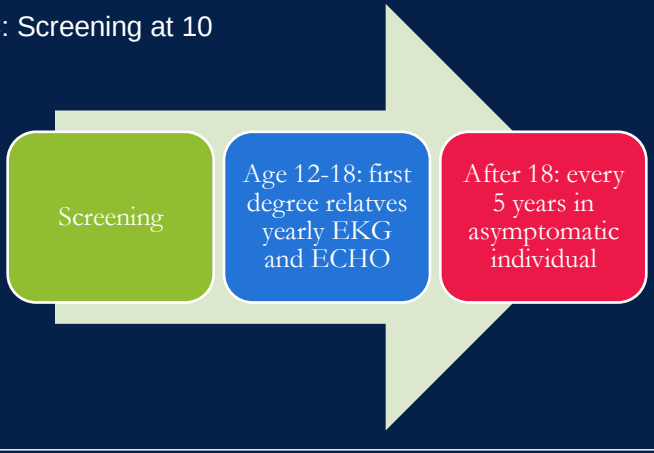


Screening

- AHA: Screening age 12
- ESC: Screening at 10



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Screening

If mutation is identified in an HCM patient, genetic testing is the preferred screening for the 1st degree relative

If patient does not have known mutation, then imaging is necessary for family screening

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Treatment: Lifestyle Changes

- Avoid volume depletion
- Physical Activity: Avoid completive sports and burst activity
- Avoid Strenuous activity
- Low level exercise as part of aerobic lifestyle is allowed

Table 4. Recommendations for the Acceptability of Recreational (Noncompetitive) Sports Activities and Exercise in Patients With HCM*

Intensity Level	Eligibility Scale for HCM†
High	
Basketball (full court)	0
Basketball (half court)	0
Body building‡	1
Gymnastics	2
Ice hockey‡	0
Racquetball/squash	0
Rock climbing‡	1
Running (sprinting)	0
Skiing (downhill)‡	2
Skiing (cross-country)	2
Soccer	0
Tennis (singles)	0
Touch (flag) football	1
Windsurfing§	1
Moderate	
Baseball/softball	2
Biking	4
Hiking	3
Modest hiking	4
Motorcycling‡	3
Jogging	3
Sailing§	3
Surfing§	2
Swimming (laps)§	5
Tennis (doubles)	4
Treadmill/stationary bicycle	5
Weightlifting (free weights)‡‖	1
Low	
Bowling	5
Brisk walking	5
Golf	5
Horseback riding‡	3
Scuba diving§	0
Skating¶	5
Snorkeling§	5
Weights (nonfree weights)	4

ACC/ACCF Hypertrophic Cardiomyopathy Guidelines

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Pharmacological Management

- Majority of patients experience HF symptoms secondary to diastolic dysfunction
- Symptoms often occur in the setting of preserved LV function
- Worsening HF can predispose patients to development of AFib
- HF symptoms and AFib are the targets of pharmocological therapy

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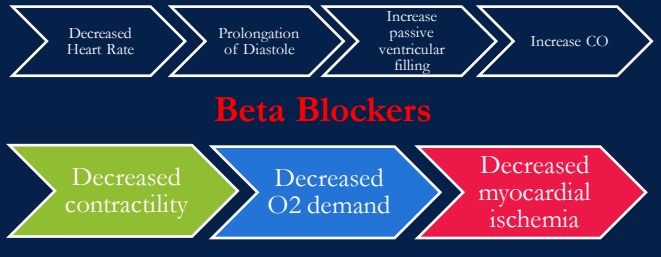
Pharmacological Management: B-Blockers

- Mainstay of therapy for HF symptoms
- Negative chronotropy and inotropy



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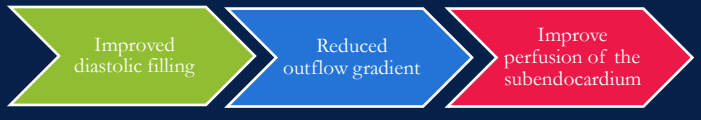
Pharmacological Management: Verapamil

- Negative inotropic/chronotropic effects:



- Often used in patients intolerant to B-blockers
- Refrain from using in patients with resting outflow obstruction (systemic vasodilator)

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Pharmacological Management: Disopyramide

- Introduced into treatment regimen in 1982
- Type IA anti-arrhythmic
- Only drug to improve outflow gradients at rest
- Symptomatic benefit via negative inotropic effect
- Anticholinergic side effects
- Increases A-V nodal conduction (concomitant Bblocker)
- QT prolongation

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Pharmacological Management: The rest…

- Avoid ACE-I, ARBs and dihydropyridine CCB: ↓Afterload ↑LVOT gradient
- Diuretics should be given cautiously
- No need to treat asymptomatic patients
- No data to support OR contradict empiric, prophylactic treatment in young asymptomatic patients
- Antibiotic Prophylaxis Recommended

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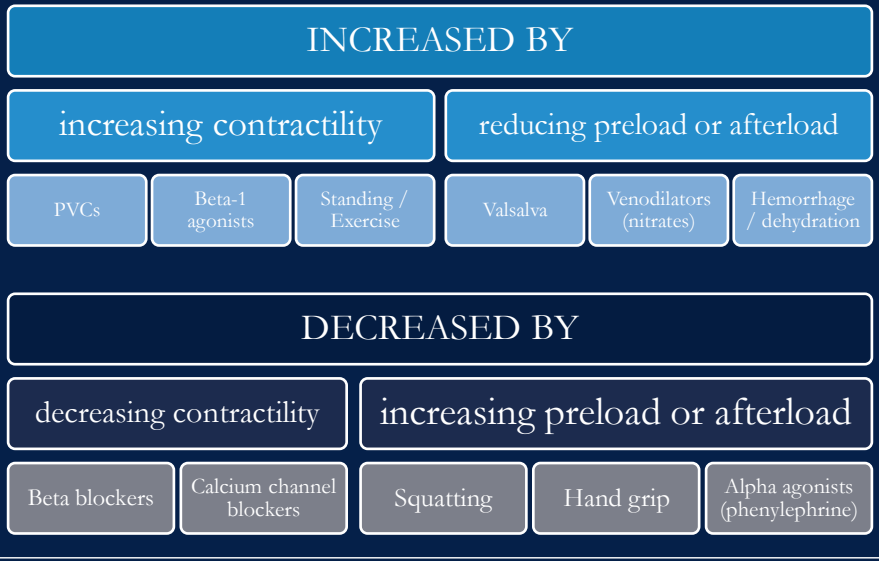
LVOT Gradient



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Pharmacological Management: End Stage Disease

- "Burn out" stage is characterized by LV systolic failure, chamber dilation and wall thinning
- 5% of HCM patients
- Managed like typical systolic HF
- Afterload reduction via ACE-I, ARBs
- Diuretics for hypervolemia
- No evidence of beneficial effect from B-blocker therapy

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Pharmacological Management: Afib

- AF/AFL MC disease complication and sustained arrhythmia
- Occurs in 25% of HCM patients
- Average Age: 55, rare in young children/young adults
- Not well tolerated with outflow obstruction
- Not uncommon in patients with SHF/advanced HF

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Pharmacological Management: Afib

- Electrical of Pharmacological cardioversion within 48 hours of presentation
- Rate control with Bblockers, Verapamil and Digoxin
- Anticoagulation with coumadin
- **Amiodarone most effective in preventing recurrences**

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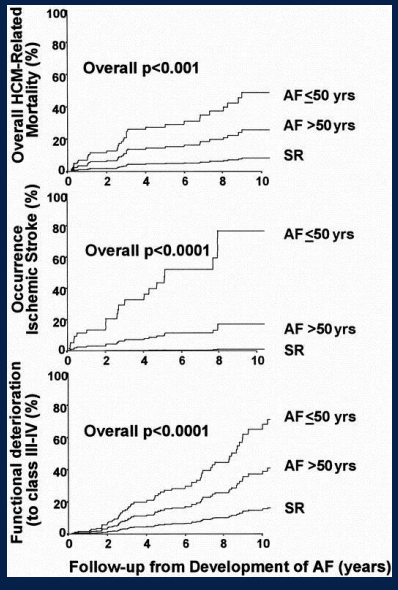

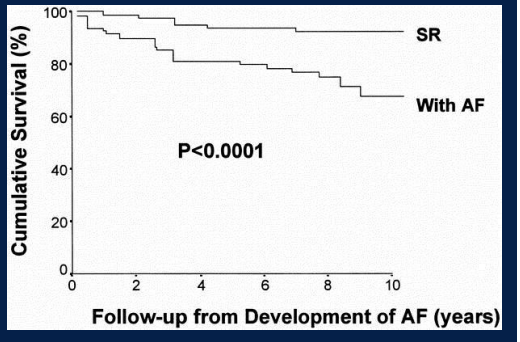

Olivotto I et al. *Circulation*, 2001, 104:2517-24

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Non-Pharmacological Therapies: Surgical Myectomy

- Known as the “Morrow Procedure”
- Gold standard for treatment of drug refractory LVOTO
- Resection of small amount of proximal septum (5-10g) through an aortotomy

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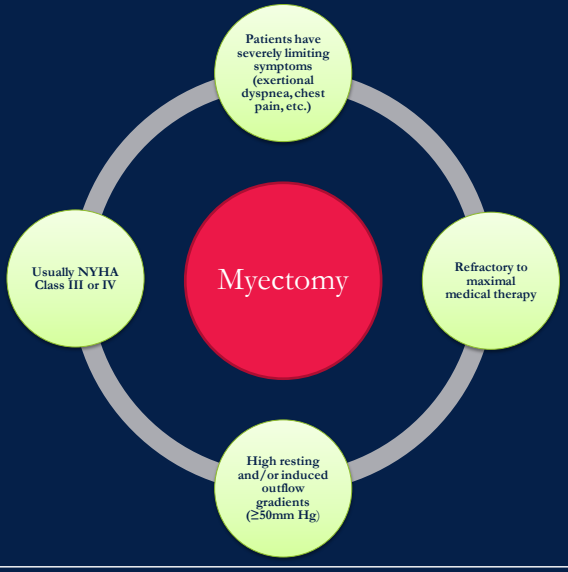
Indications



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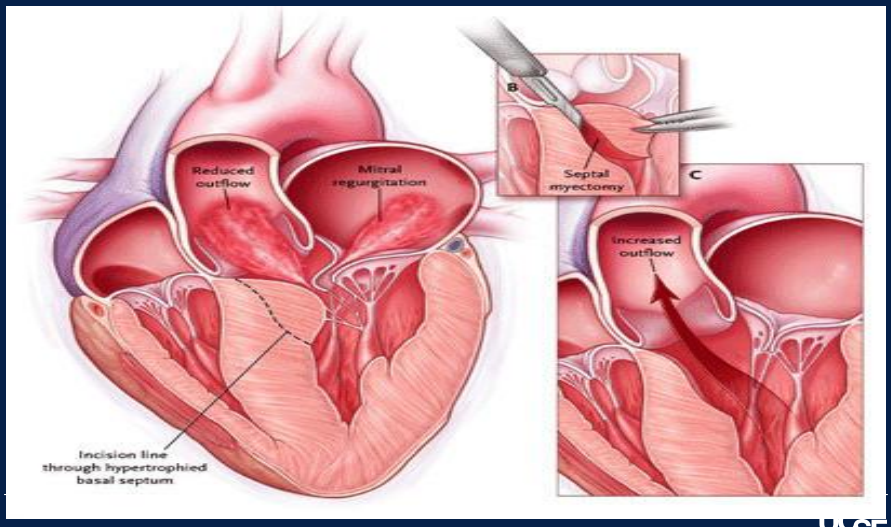
Morrow Procedure



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Morrow Procedure

Benefits:

1)↓ LVOTO (90% of patients)

2)↓ SAM/MR

3)Normalization of LV systolic and end diastolic pressure

4)Symptomatic improvement (70% of patients)

5)Operative mortality <1% experience centers

Risks:

- Ventricular septal perforation
- Incomplete or complete LBBB
- Complete heart block
- Mortality < 2%

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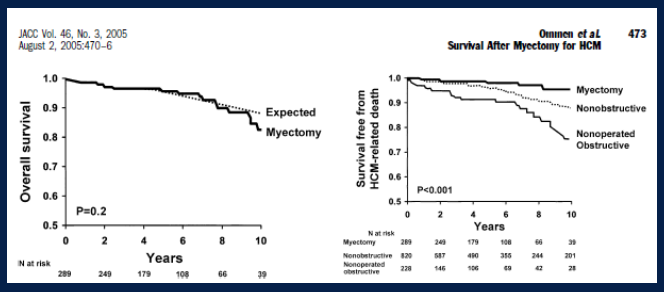

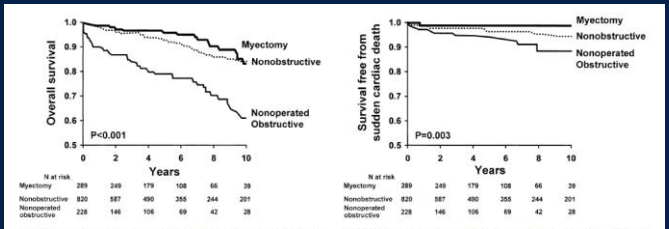

Figure 2. Survival free from all-cause mortality in three hypertrophic cardiomyopathy patient subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, $p < 0.001$; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, $p < 0.001$; myectomy versus nonobstructive hypertrophic cardiomyopathy, $p = 0.8$.

Figure 4. Survival free from sudden cardiac death among patients in three hypertrophic cardiomyopathy subgroups: surgical myectomy (n = 289), nonoperated with obstruction (n = 228), and nonobstructive (n = 820). Overall log-rank, $p = 0.003$; myectomy versus nonoperated obstructive hypertrophic cardiomyopathy, $p = 0.003$; myectomy versus nonobstructive hypertrophic cardiomyopathy, $p = 0.3$.

Ommen SR et al. JACC **Volume 46, Issue 3, Pages A1-A60, 403-566**

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Non-Pharmacological Treatment: Alcohol Septal Ablation (ASA)

- Introduced in 1995
- Infusion of 1-3cc of alcohol through 1st septal perforator branch
- Induces a myocardial infarction in small area of septum
- Thinning of septum and reduction in LVOTO

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Alcohol Septal Ablation (ASA)

- Contrast Echo used to select appropriate septal perforator
- Arteriogram gives visualization of septal branch
- Coronary balloon placed into septal branch and inflated
- Arteriogram repeated to ensure correct location and complete occlusion of branch
- Alcohol infused

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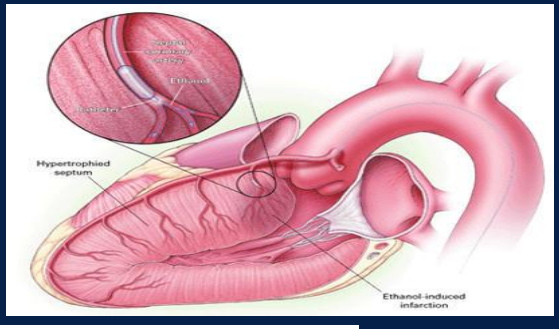
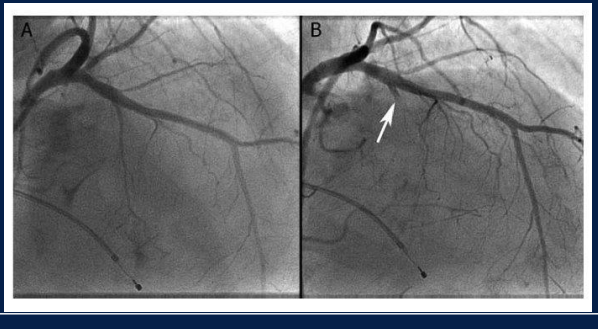
ASA Procedure





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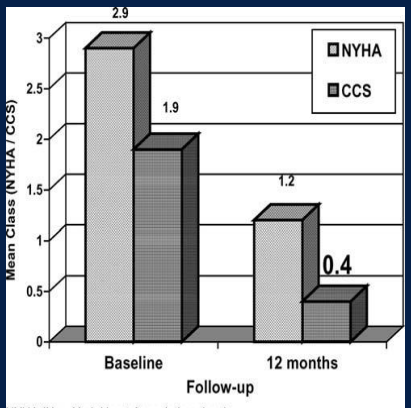
ASA Outcomes

- Benefits:
  - Reduction in LVOTO
  - Symptomatic Improvement
  - Improved NYHA Classification
  - Increased Exercise Capacity
- Risks:
  - High incidence of PPM placement (18.4%)
  - Massive MI
  - 4% mortality
  - ↑ SCD?



NYHA (New York Heart Association class), CCS (Canadian Cardiovascular Society class)

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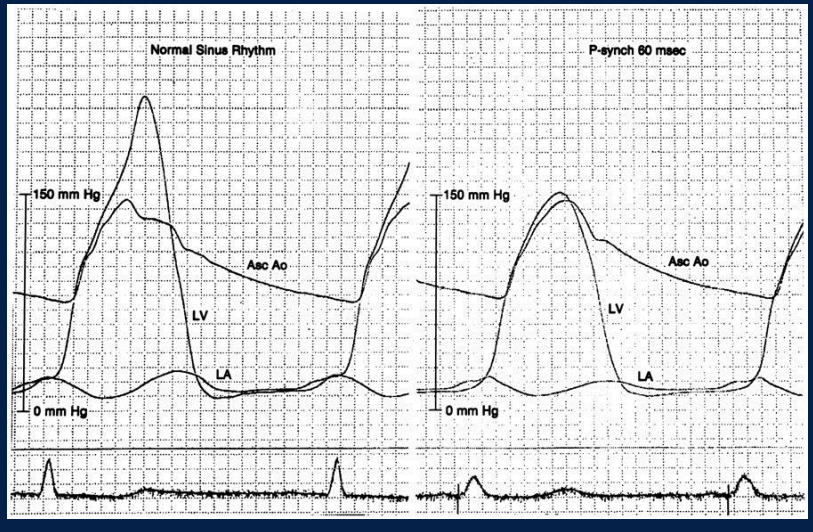
Effective dual-chamber pacing of the left ventricular outflow tract gradient in a patient with hypertrophic obstructive cardiomyopathy.



R. A. Nishimura et al. Circulation. 1997;96:1701

American Heart Association

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Non-Pharmacological Treatment: Dual Chamber Pacing

- Treatment modality for poor surgical or ASA candidates
- Typically reserved for elderly patients
- Alters wave of depolarization/contraction
- Subjective symptomatic improvement; little objective data available

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Non-Pharmacological Treatments: And the winner is…

- Myectomy is the gold standard for treatment of LVOTO
- Myectomy has shown superior results vs. dual chamber pacing
- Generally accepted that myectomy and alcohol septal ablation are superior to dual chamber pacing

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Myectomy vs. ETOH Septal Ablation

- No large, multi-center randomized controlled trials exist comparing myectomy vs. ASA
- Recent meta-analysis showed that both procedures reduce LVOT gradients
- Similar symptomatic improvement
- ASA resulted in higher rates of PPM placement
- ASA has higher rate of repeat intervention

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Table 3. Comparative Features of Septal-Reduction Therapies.

Therapy	Mortality	Residual Gradient	Effectiveness	Follow-up	Complications		Time to Resolution of Gradient
	%	*mm Hg*	*% of Patients*	*Yr*	*Type*	*% of Patients*	
Dual-chamber pacing	<1	<40	10–40	10	Infection or perforation	<2	4 wk
Septal myectomy*	<2–3	<10	>90	>30	Complete heart block Ventricular septal defect Aortic regurgitation	<3 <1 <1	Immediate
Septal ablation†	<2–3	<20	70–80	<5	Complete heart block Ventricular septal defect Large myocardial infarction	10–40 Unknown Unknown	8–12 wk

* Surgical septal myectomy is the only intervention that can treat concomitant problems, such as multivessel coronary disease, intrinsic mitral-valve disease, midventricular obstruction, and fixed subaortic obstruction.
† The true rates of death and complications may be underestimated, since complications may occur at a higher frequency in the inexperienced centers and may be underreported.

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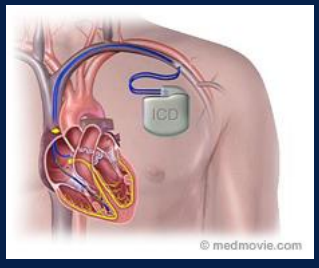
Sudden Cardiac Death

- HCM patients at risk for SCD
- Thought to be secondary to scar tissue formation serving as unstable substrate for VT/VF
- Typically occurs in adolescents and young adults
- Can often be initial presenting symptom in HCM



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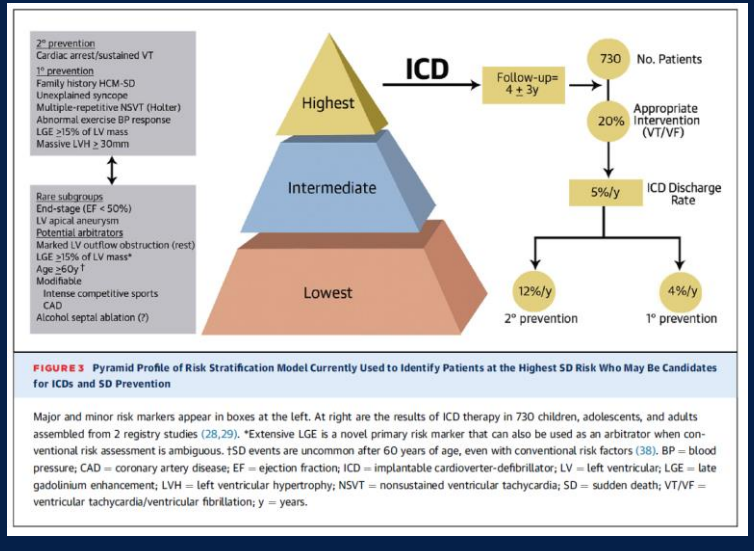

FIGURE 3 Pyramid Profile of Risk Stratification Model Currently Used to Identify Patients at the Highest SD Risk Who May Be Candidates for ICDs and SD Prevention

Major and minor risk markers appear in boxes at the left. At right are the results of ICD therapy in 730 children, adolescents, and adults assembled from 2 registry studies (28,29). *Extensive LGE is a novel primary risk marker that can also be used as an arbitrator when conventional risk assessment is ambiguous. †SD events are uncommon after 60 years of age, even with conventional risk factors (38). BP = blood pressure; CAD = coronary artery disease; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LGE = late gadolinium enhancement; LVH = left ventricular hypertrophy; NSVT = nonsustained ventricular tachycardia; SD = sudden death; VT/VF = ventricular tachycardia/ventricular fibrillation; y = years.

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LVAD?

- Generally not favorable due to small LV cavity size
- Recent case reports the use of LVAD with myectomy in BTT candidates
- Patients had similar flows and outcomes.

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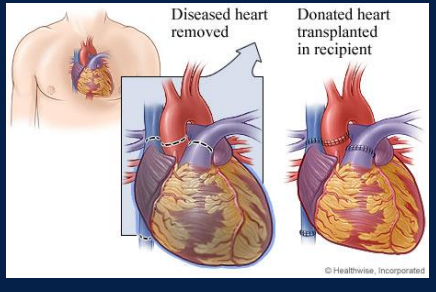
Heart Transplant

- For refractory HF and life-threatening arrhythmia's
- Only comprise 1% heart transplants



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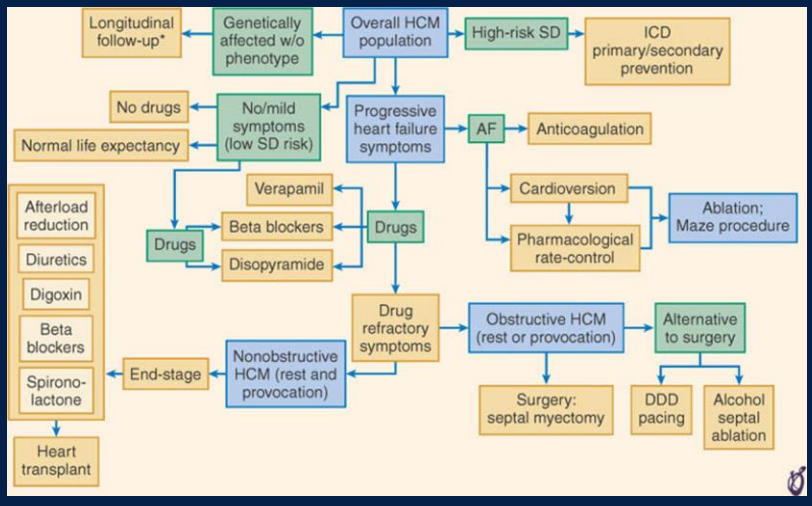

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Future Directions

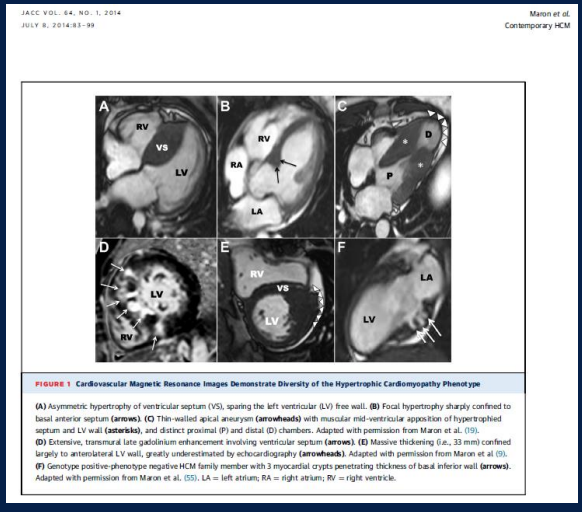

FIGURE 1 Cardiovascular Magnetic Resonance Images Demonstrate Diversity of the Hypertrophic Cardiomyopathy Phenotype

(A) Asymmetric hypertrophy of ventricular septum (VS), sparing the left ventricular (LV) free wall. **(B)** Focal hypertrophy sharply confined to basal anterior septum **(arrows)**. **(C)** Thin-walled apical aneurysm **(arrowheads)** with muscular mid-ventricular apposition of hypertrophied septum and LV wall **(asterisks)**, and distinct proximal (P) and distal (D) chambers. Adapted with permission from Maron et al. (59). **(D)** Extensive, transmural late gadolinium enhancement involving ventricular septum **(arrows)**. **(E)** Massive thickening (i.e., 33 mm) confined largely to anterolateral LV wall, greatly underestimated by echocardiography **(arrowheads)**. Adapted with permission from Maron et al. (9). **(F)** Genotype positive-phenotype negative HCM family member with 3 myocardial crypts penetrating thickness of basal inferior wall **(arrows)**. Adapted with permission from Maron et al. (55). LA = left atrium; RA = right atrium; RV = right ventricle.

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Conclusion

Dr Braunwald wrote: "at this time, we are aware of no method of management that can specifically and favorably influence the course of the patient"

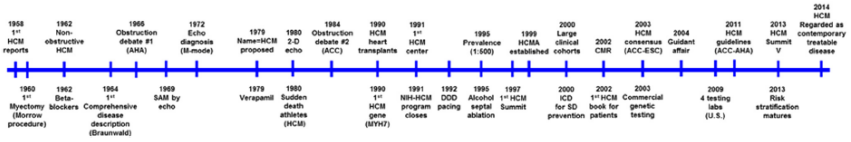

Fig. 1 – Timeline of the advances in HCM over 50 years. ACC = American College of Cardiology; AHA = American Heart Association; CMR = cardiovascular magnetic resonance; echo = echocardiography; ESC = European Society of Cardiology; HCMA = Hypertrophic Cardiomyopathy Association; ICD = implantable cardioverter-defibrillator; SD = sudden death.

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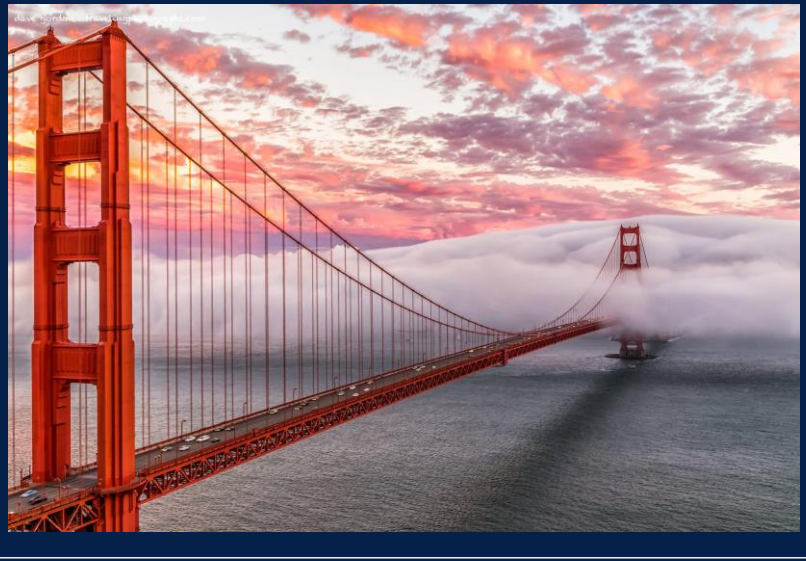
Thank You



Picture from: Traveling Photographs : Dave Gordon

PA: UCSF Lung Transplant Program

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