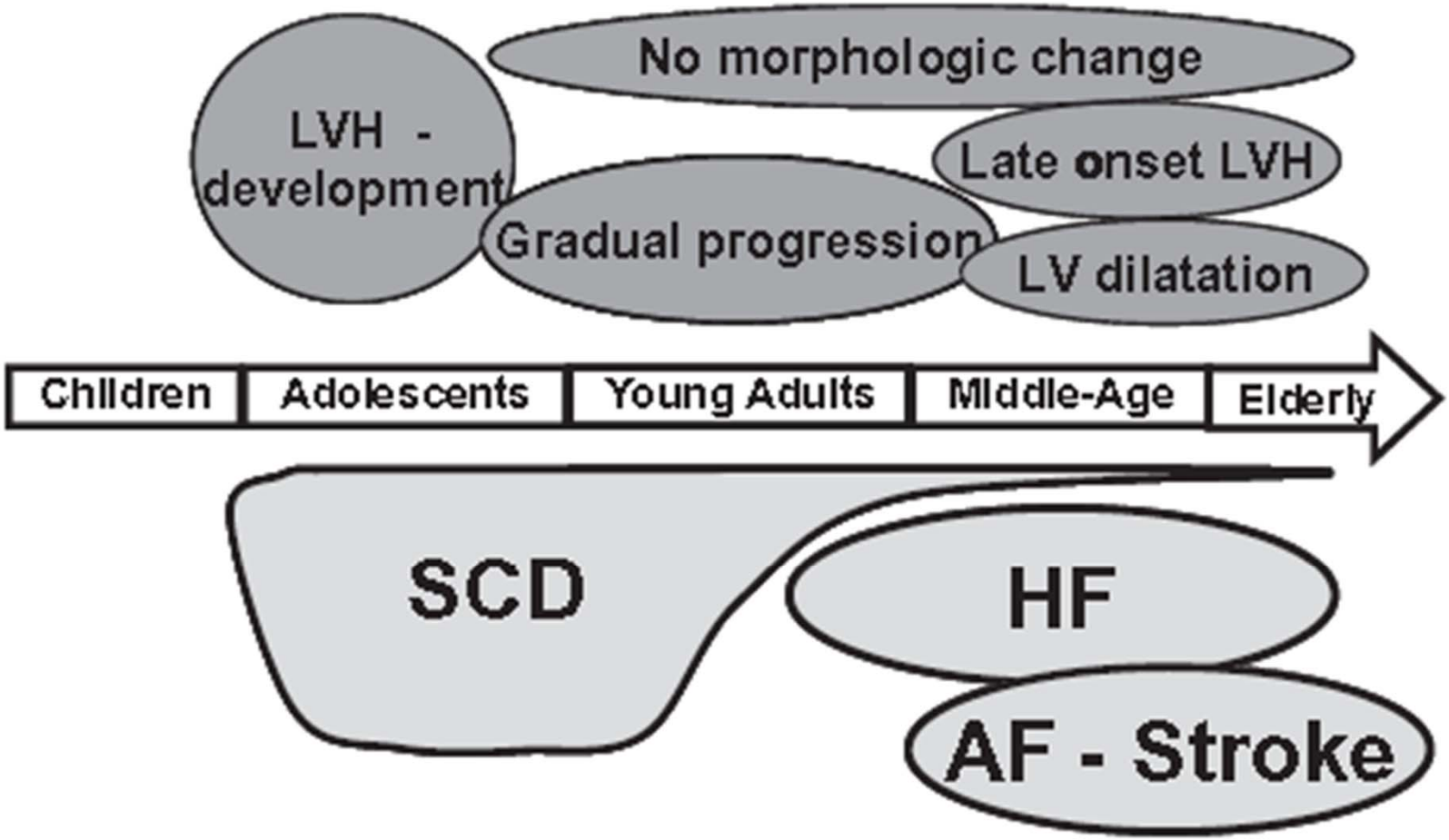
Role of Echocardiography for Prognosis of Hypertrophic Cardiomyopathies

Mi-Jeong Kim

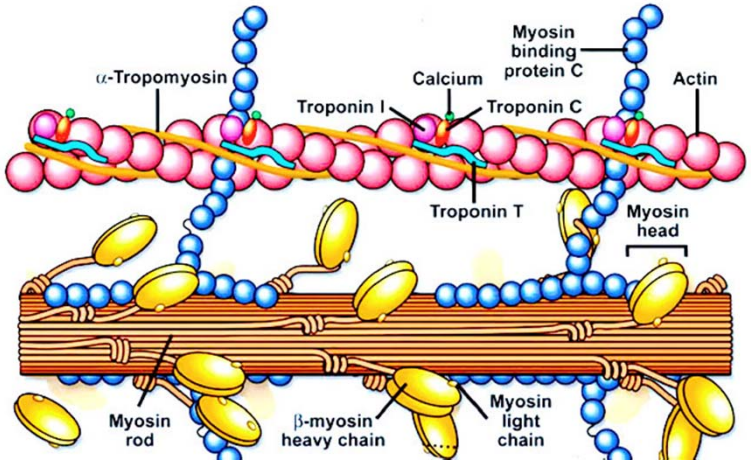
Incheon St.Mary`s Hostpial

The Catholic University of Korea

HCM: A Lifelong LV Remodeling Process



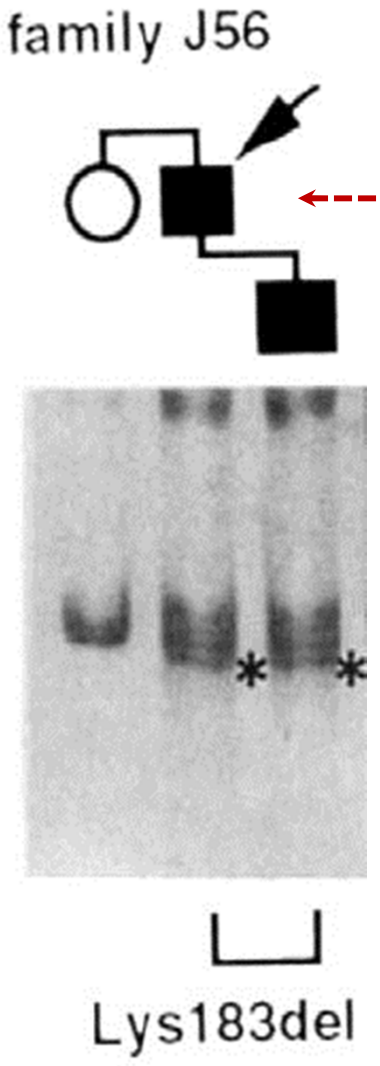
Genetic Basis of HCM



MYH7	β-Myosin heavy chain	25-40%
MYH6	α-Myosin heavy chain	Rare
MYBPC3	Cardiac myosin-binding protein C	25-40%
TNNT2	Cardiac troponin T	3-5%
TNNI3	Cardiac troponin I	1-5%
TPM1	α-tropomyosin	1-5%
…	…	…

- Over 400 mutation at >20 genes identified in HCM
- Yield for commercially available genetic test: 50-70% depending on the company
- Myofilament/sarcomeric HCM (thick/thin/giant filament), Z-disc HCM, calcium-handling HCM

Distinct mutation cannot dictate clinical phenotype



Same mutation in cardiac troponin I
(deletion of lysine 183; TNNI3-delK183)

Kimura et al. Nat Genet 1997;16:379-82

HCM is Heterogeneous Disease
With Extreme Phenotypic Variations

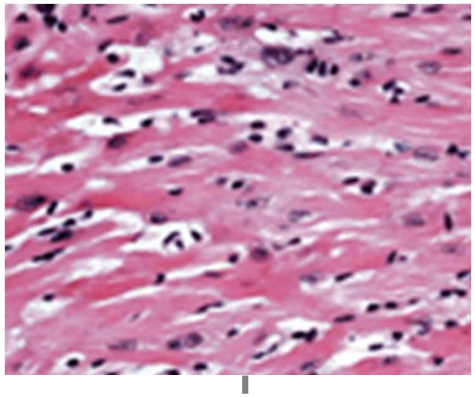
Disease gene + Mutation

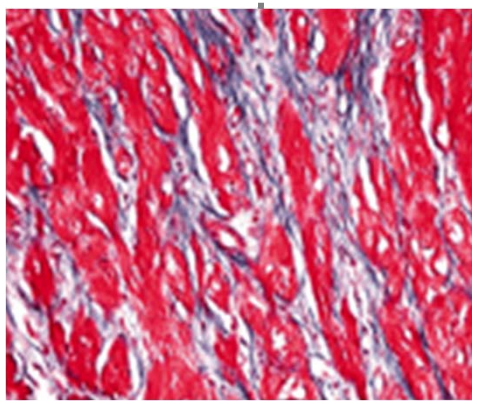
Modifier gene

Environment

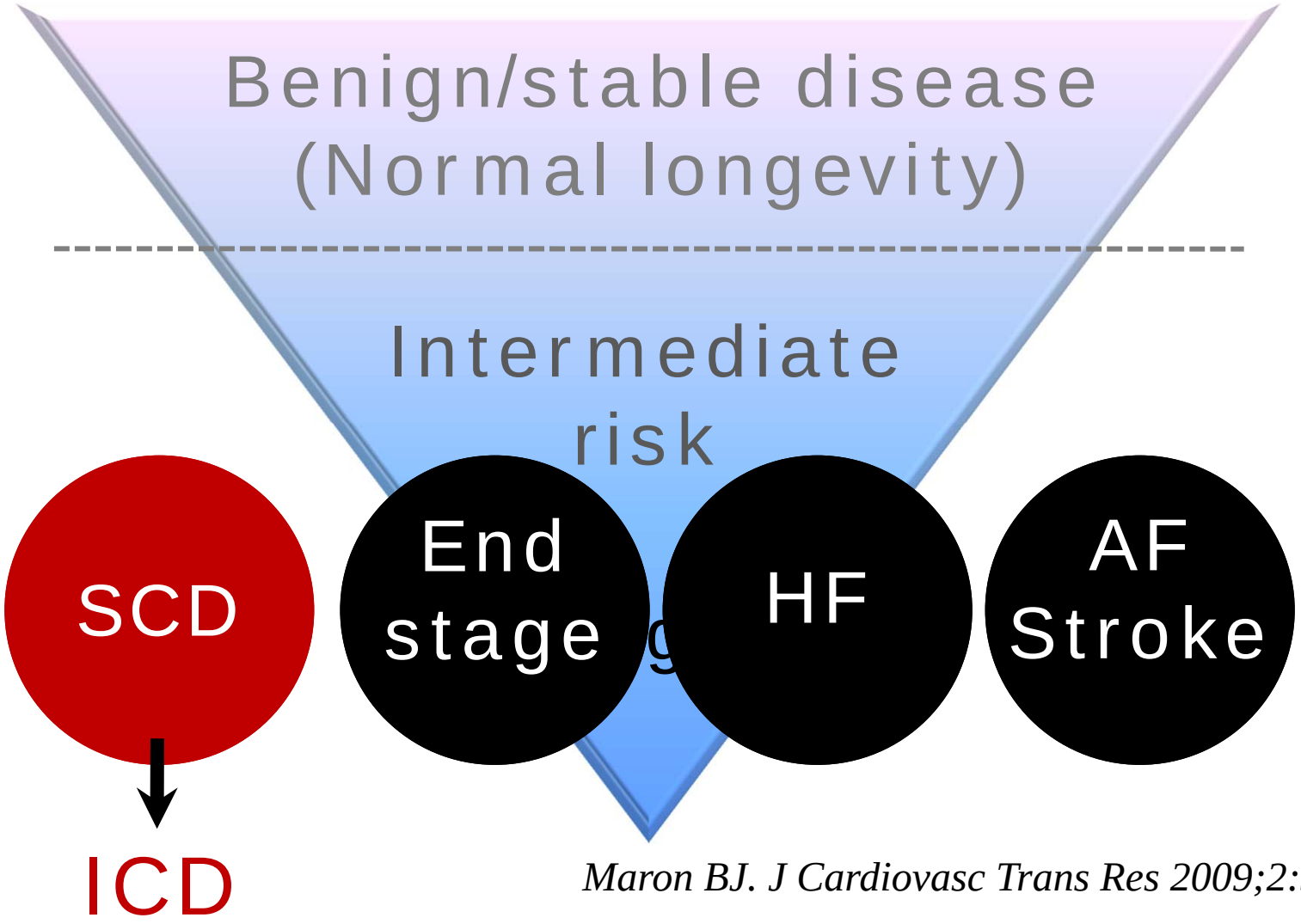
Phenotype

Variable
expression, penetrance





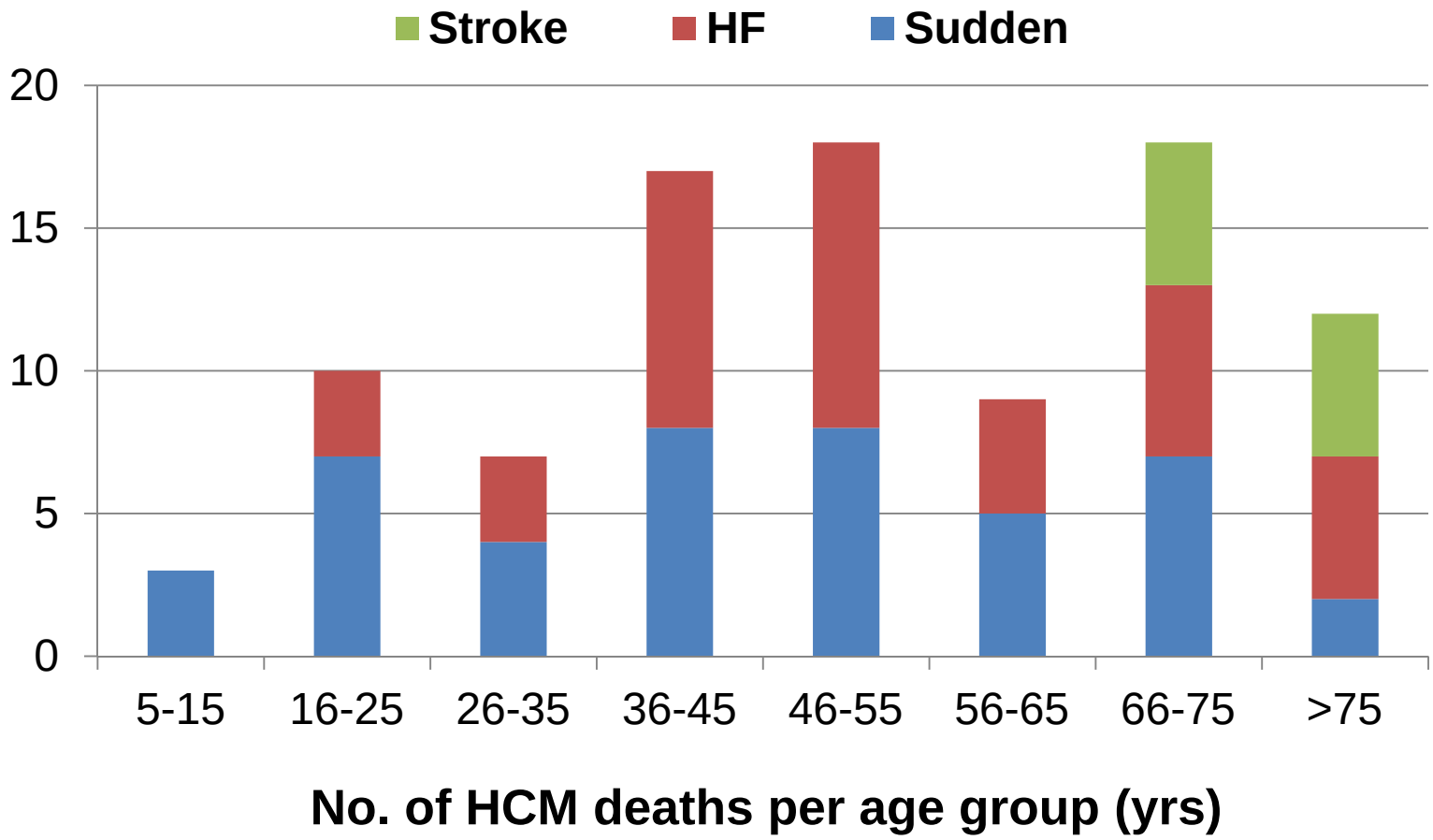
HCM: Profiles in Prognosis



Maron BJ. J Cardiovasc Trans Res 2009;2:368-80

Mode of death in HCM

86 deaths in 744 HCM pt, 8±7 yr f/up (non-referral based cohort, USA/Italy)



Maron et al. Circulation 2000;102:858-64

ACC/AHA/ESC guidelines for ICD in HCM

- **Sustained VT and/or VF (Class I, B)**
- **Primary prophylaxis for ≥1 major clinical risk factor for SCD (Class IIa, C)**
- **EP testing may be considered for risk assessment for SCD (Class IIb, C)**

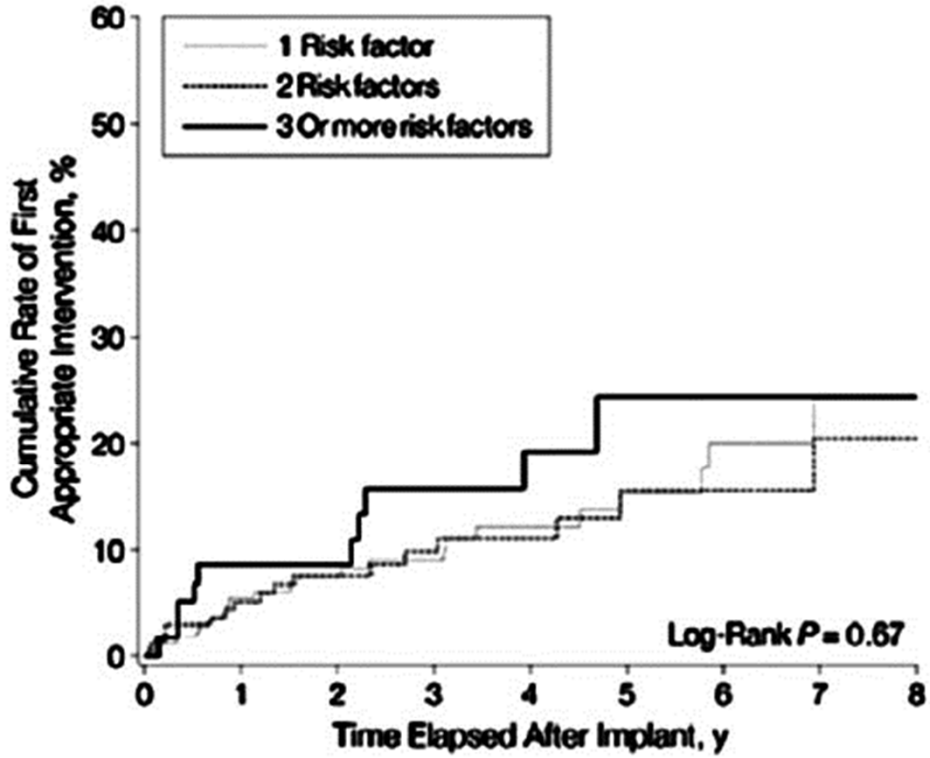
Europace 2010; 12:1156–1175

Conventional Risk Factors for Sudden Death in HCM

Major	Possible in Individual Patients
Cardiac arrest (ventricular fibrillation)	Atrial fibrillation
Spontaneous sustained ventricular tachycardia	Myocardial ischemia
Family history of premature sudden death	LV outflow obstruction
Unexplained syncope	High-risk mutation
LV thickness greater than or equal to 30 mm	Intense (competitive) physical exertion
Abnormal exercise blood pressure	
Nonsustained ventricular tachycardia (Holter)	

ACC/ESC Expert Consensus Comment on HCM. JACC 2003;42:1687-713

Conventional Risk Factors



No. at risk									
1 Risk factor	173	150	119	98	70	48	31	18	16
2 Risk factors	143	123	95	71	53	34	28	16	6
3 Or more risk factors	59	52	38	32	23	11	9	8	6

Maron BJ et al. JAMA 2007;298:405-412

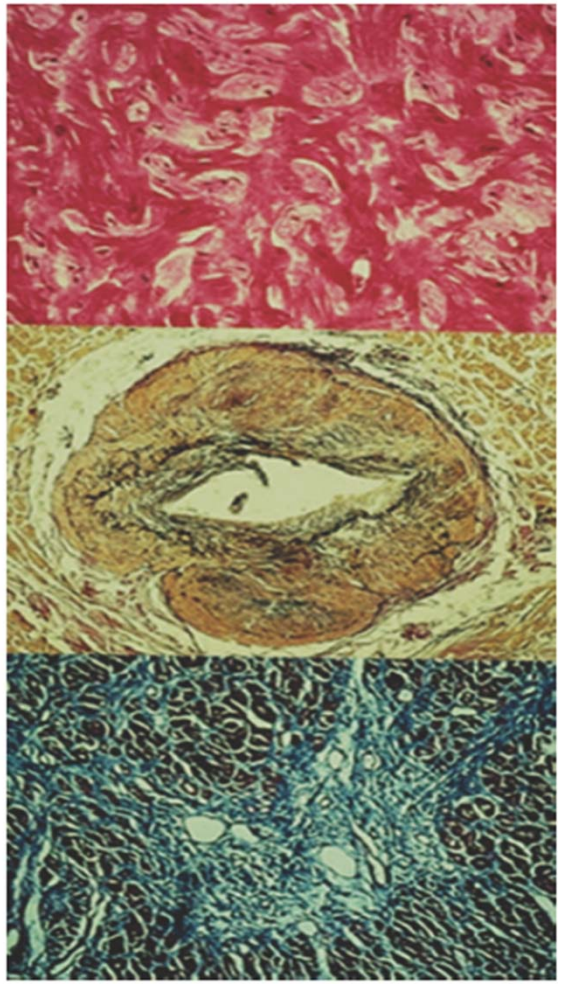
Clinical risk factors for ICD in HCM

- **1 risk factor can be enough for ICD**
- **Risk factors cannot be summed numerically**
- **Absence of risk factors does not declare immunity from SCD**
- **ICD decisions is based on individual considerations**

- Dr. Maron -

Substrates for arrhythmia

- **Myofiber disarray**
- **Ischemia- relative, fixed**
- **Fibrosis**
- **Marked systolic dysfunction**



Maron BJ. J Cardiovasc Trans Res 2009;2:368-80

CE-MRI findings in HCM

Myocardial fibrosis or scar (≈ DE in CE CMR)

- **High prevalence, particularly in areas with hypertrophy. (Moon et al. JACC 2003;41:1561-7)**
- **Associated with the occurrence of NSVT. (Adabag et al. JACC 2008;51:1369-74)**
- **Independent predictor of adverse cardiac events. (Bruder et al. JACC 2010;56:875-87, O`Hanlon et al. JACC 2010;56:867-74)**

Myocardial Scar Visualized by CMR Predicts MACE in Patients with HCM

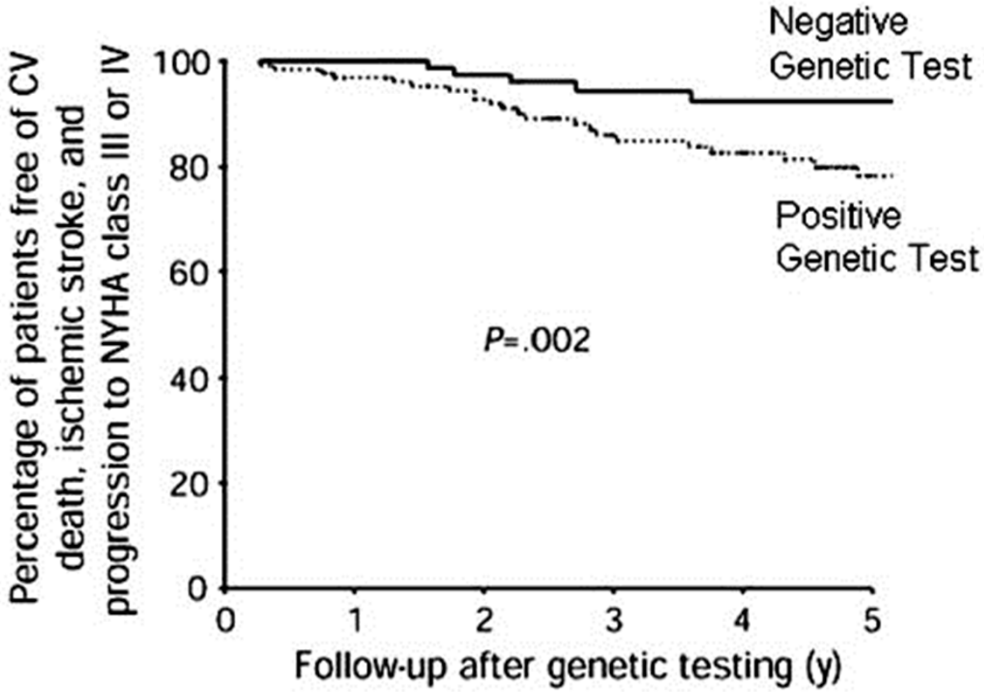
	No SCD (n=209)	SCD (n=22)	P value
Age	57 yr	60 yr	0.77
HCM type, septal	64%	62%	0.69
EF (by CMR)	71%	68%	<0.05
Max thickness	19 mm	21 mm	<0.05
LVOTO, %	21%	46%	0.33
LGE	66%	91%	0.10
LGE, %LV	1.9	11.2	<0.01
No of SCD RF			
0	76%	73%	NS
1	20%	18%	
2	3%	0	

Bruder et al. JACC 2010;56:875-87

“Positive HCM genetic test” associated with adverse outcome

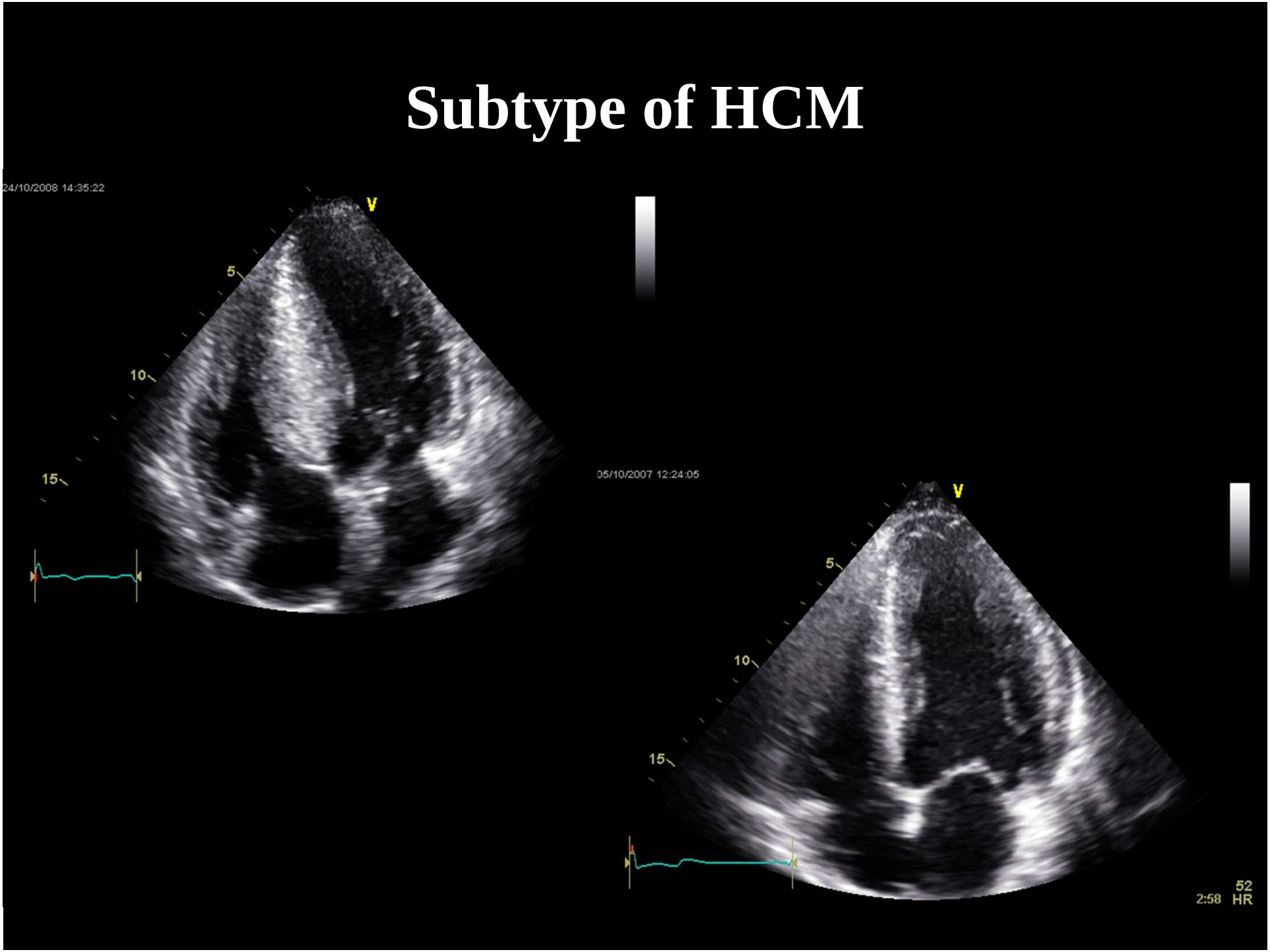
Characteristic	Positive	Negative	P-Value
Age at Dx (yr)	36±17	45±19	<0.001
MLVWT (mm)	23±7	21±6	0.002
FH of HCM	68%	59%	<0.001
ICD	25%	10%	<0.001

Characteristic	HR	95% CI	P-Value
Positive Test	4.3	1.5-12.5	0.008
Age (per yr)	1.03	1.01-1.06	0.017
LVOTO (≥30mmHg)	1.33	0.7-2.7	0.43
Atrial Fibrillation	1.67	0.7-3.8	0.22

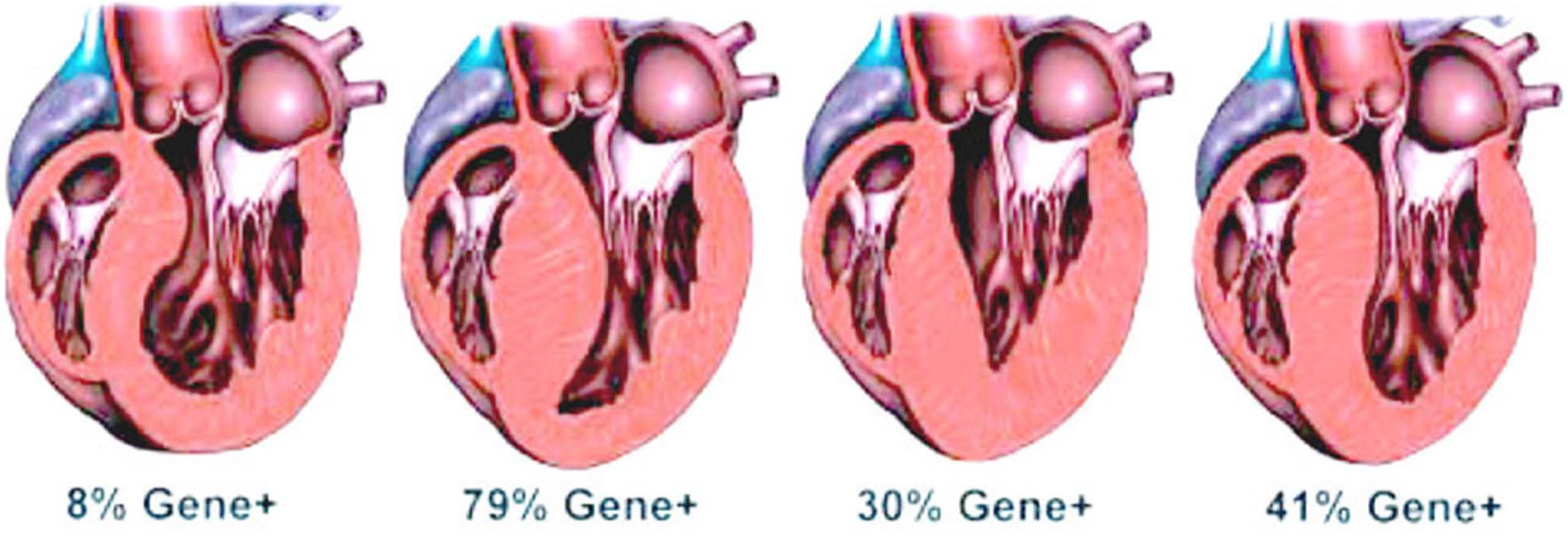


Van Driest SL, Ackerman MJ et al. Mayo Clin Proc. 2005;80:739 –744

Subtype of HCM



Echocardiography-guided genetic testing in HCM: Septal Morphological Features Predict the Presence of Myofilament Mutations



Sigmoid (ovoid LV cavity)

Reverse curve (crescent)

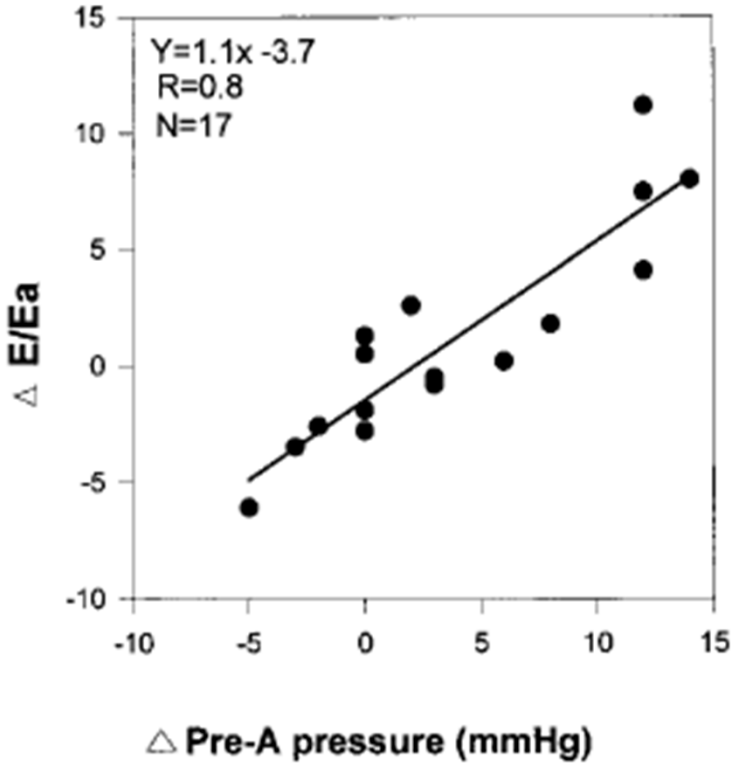
Apical

Neutral

Binder et al. Mayo Clin Proc 2006;81:459-467

Diastolic dysfunction

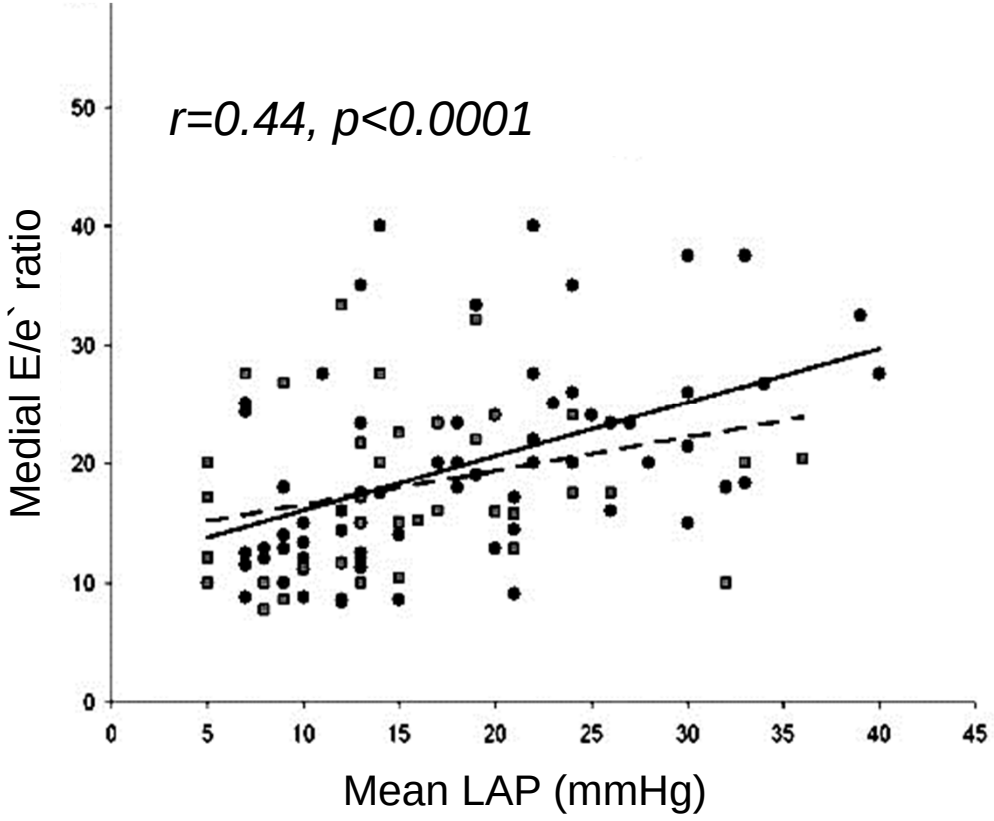
- **Early manifestation in *ALL* patients.**
- **Subtle changes even in preclinical disease.**

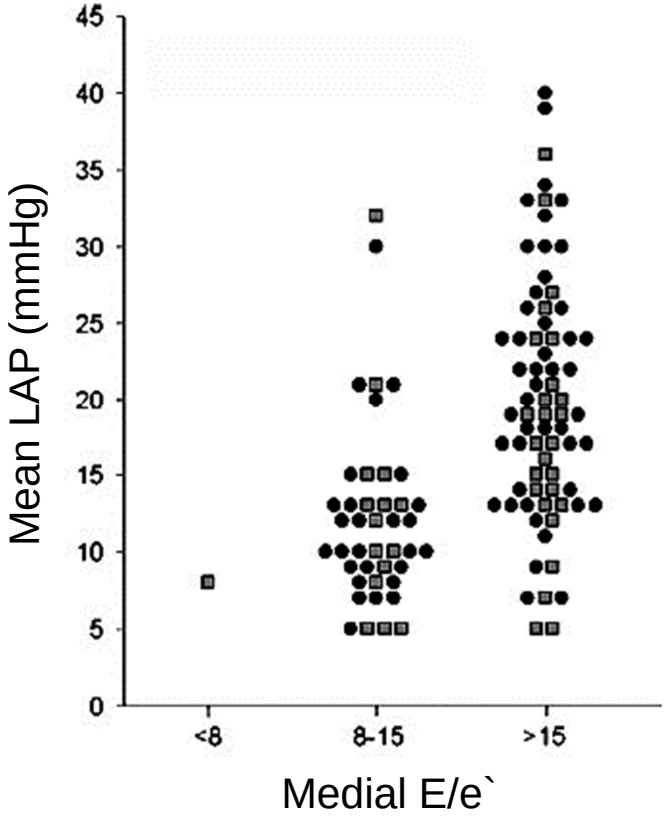


Nagueh et al. Circulation 1999;99;254-261

Evaluation of LV Filling Pressures by Doppler Echo in Patients With HCM: Correlation With Direct LA pressure Measurement at Cardiac Catheterization

Symptomatic HCM (n=100, NYHA III/IV 82%)



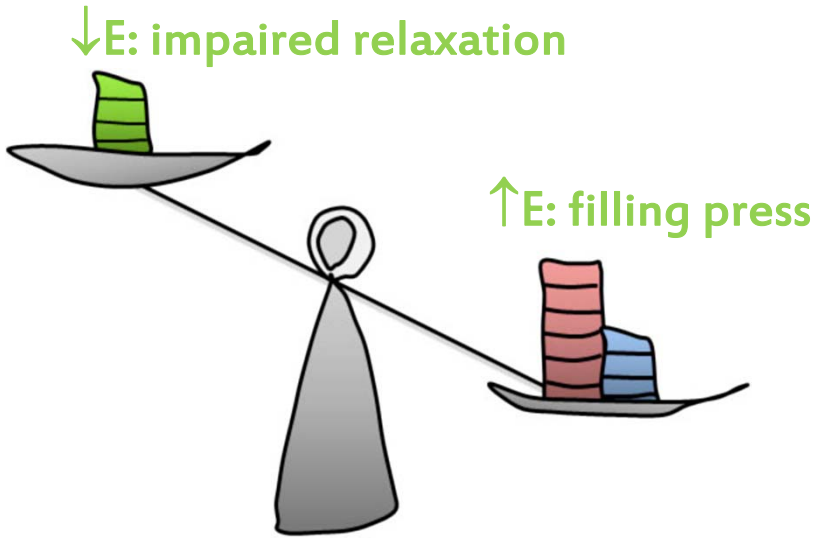


Geske, Nishimura et al. Circulation 2007;116:2702-8

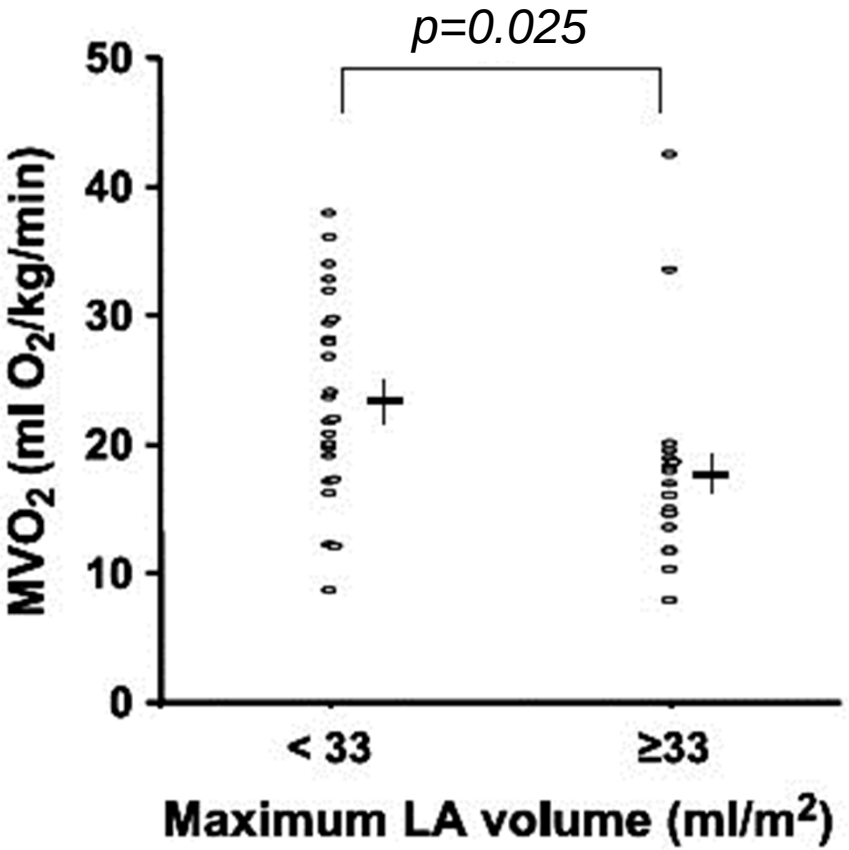
Diastolic dysfunction in HCM:
Complex interplay of multiple mechanisms

Reduced LV distensibility
- **ventricular hypertrophy**
- **myocardial disarray**
- **interstitial fibrosis - modulated by GF, cytokines**
- **LV shape and geometry: small LV systolic volumes, LV cavity obliteration**

Increased elastic recoil
Reduced preload



LA volumetric remodeling is predictive of functional capacity in non-obstructive HCM



AF in HCM

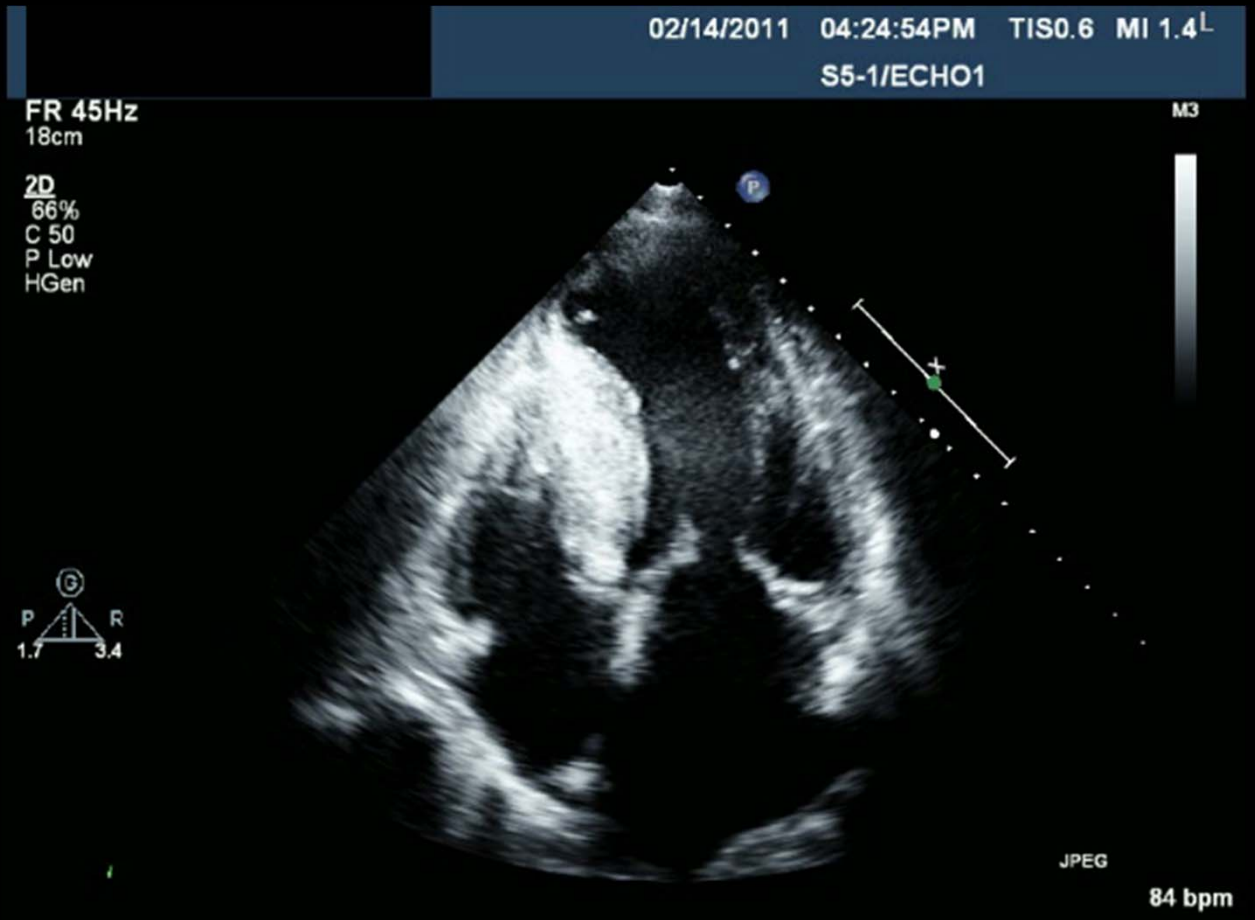
- 5-fold risk of general population

- 1/3 of HCM

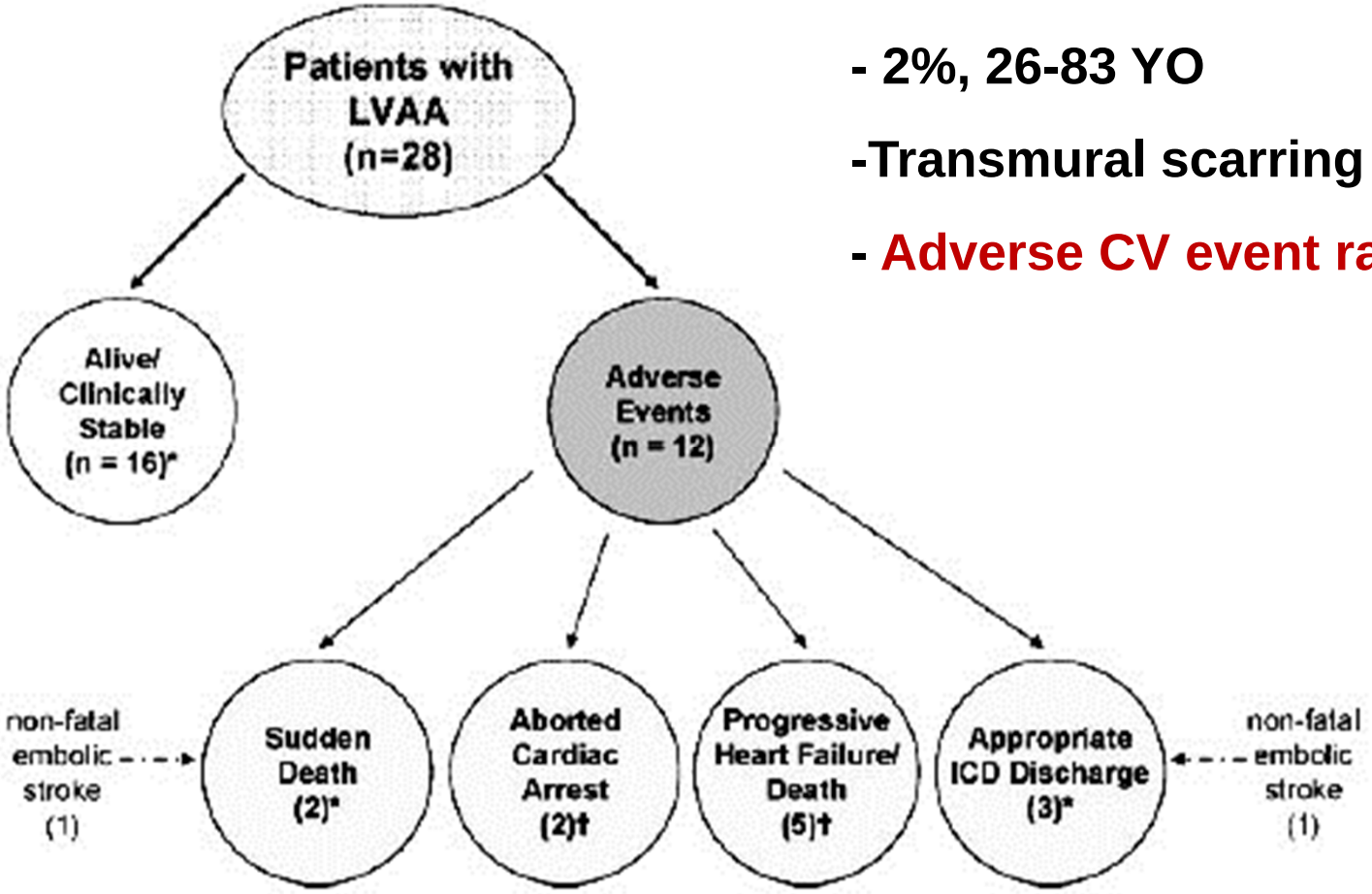
- HF, stroke

Sachdev et al. Am Heart J 2005;149:730-736

Systolic Dysfunction
- Dilated Phase in the Course of HCM



LV Apical Aneurysm



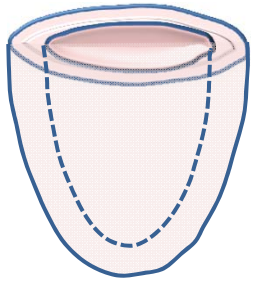
- 2%, 26-83 YO
-Transmural scarring in CMR
- Adverse CV event rate= 11%/yr

Maron MS, Circulation 2008;118:1541-9

Limitation of Conventional Echocardiography

Stable condition (balanced)

Intrinsic myocardial contractility ~ loading condition



Increased loading
Reduced contractility ***(Unstable)***

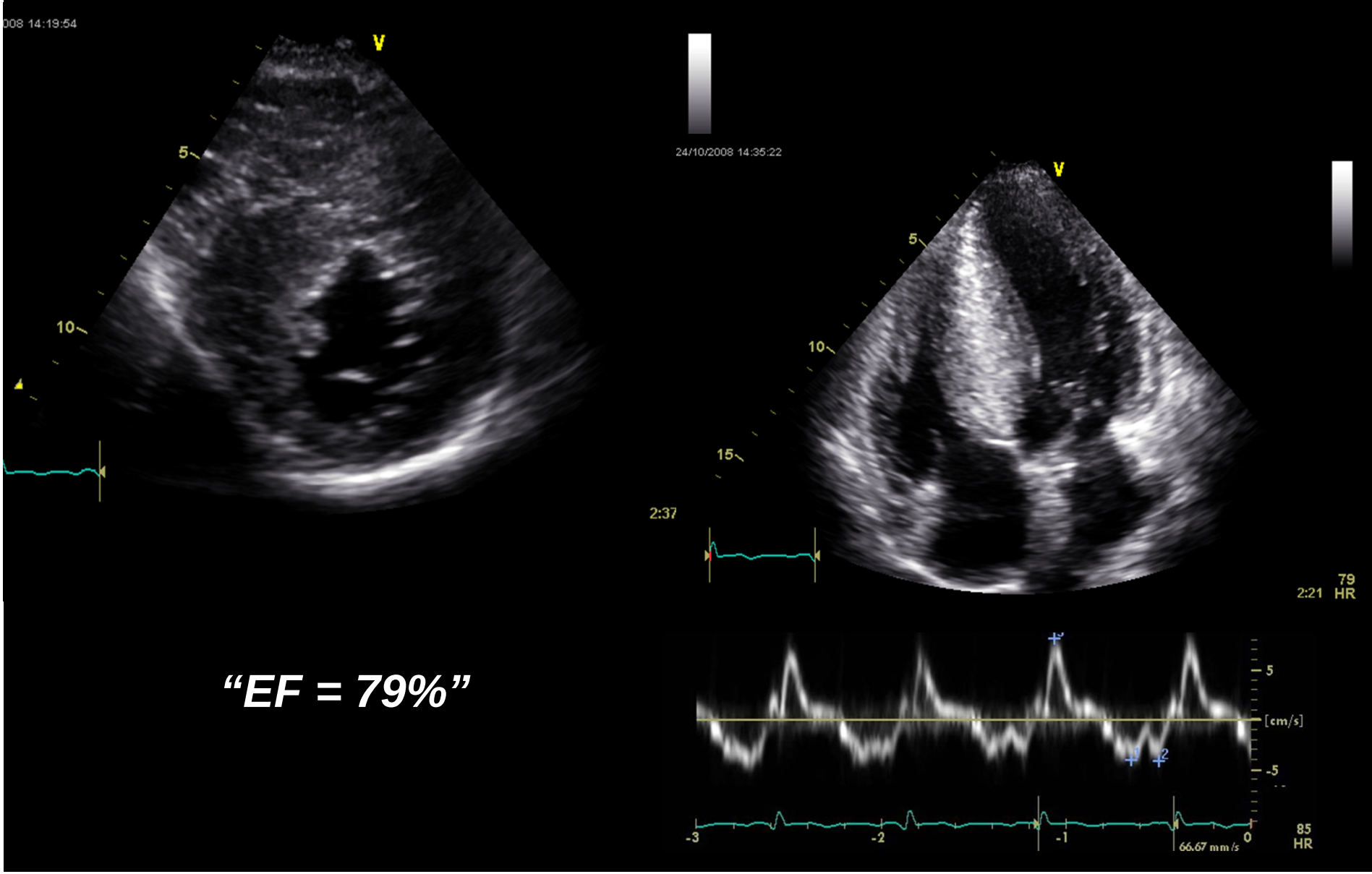
molecular/pathologic change

Remodeling

Dysfunction
(systolic/diastolic)

Conventional echo
- ***Geometry***
- ***Volume-dependent index***
- ***Blood flow velocity***

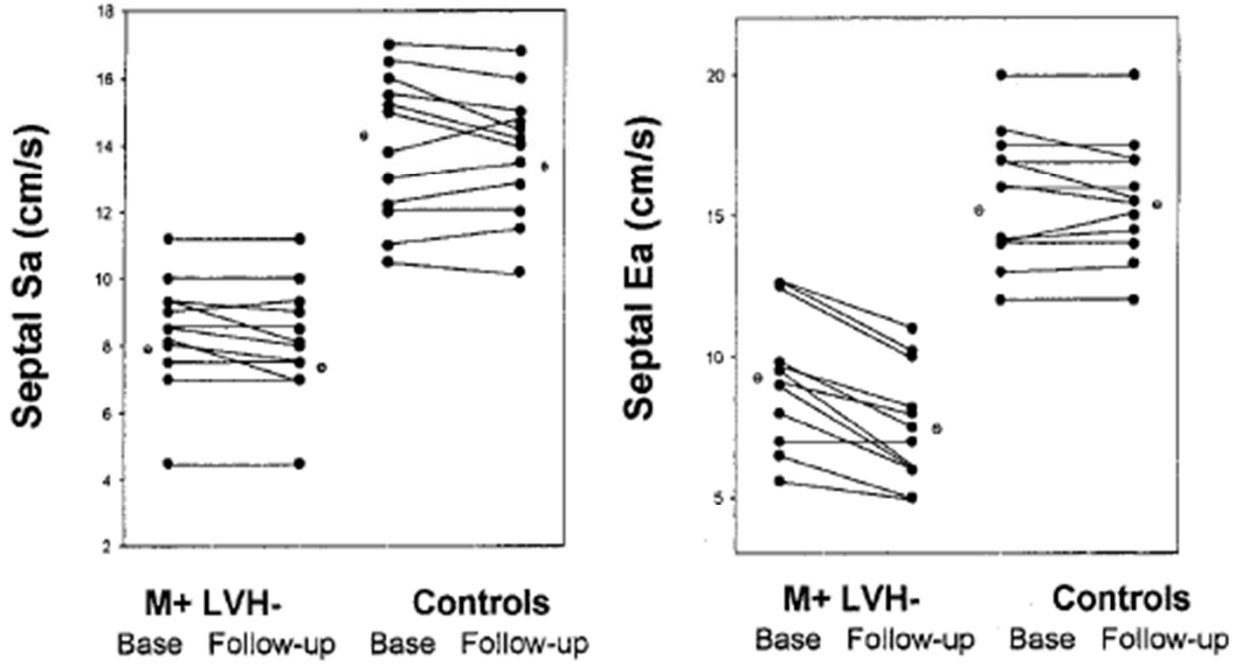
Apparent Super-normal Function



"EF = 79%"

Functional Impairment Primarily Affects the Longitudinal Myocardial Fibers

Tissue Doppler Imaging Predicts the Development of Hypertrophic Cardiomyopathy in Subjects With Subclinical Disease



Nagueh et al. Circulation 2003;108:395-398

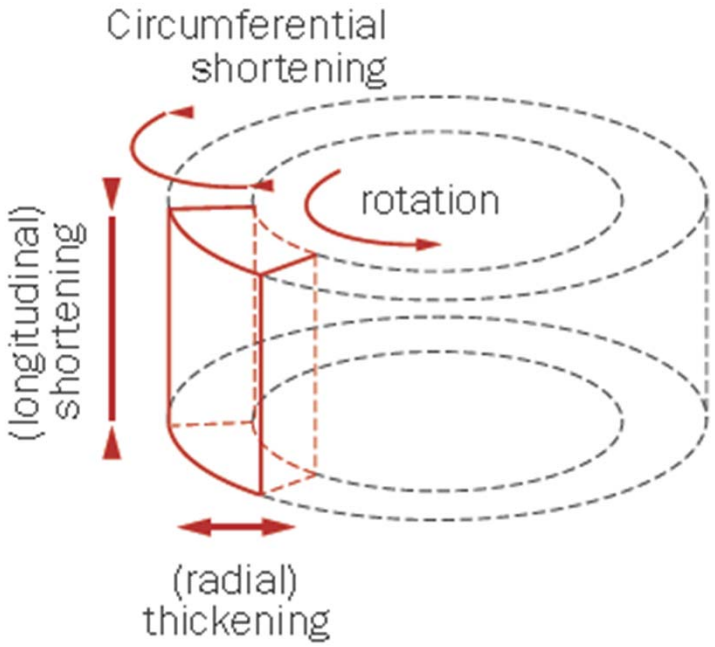
Limitation of Conventional Echocardiography

- **Assess changes in late stage results**
- **Assess global cardiac function by volume-based index**
- **Exclusive concentration on radial function rather than longitudinal function**
- **Omit the complex shear deformation in 3D space**

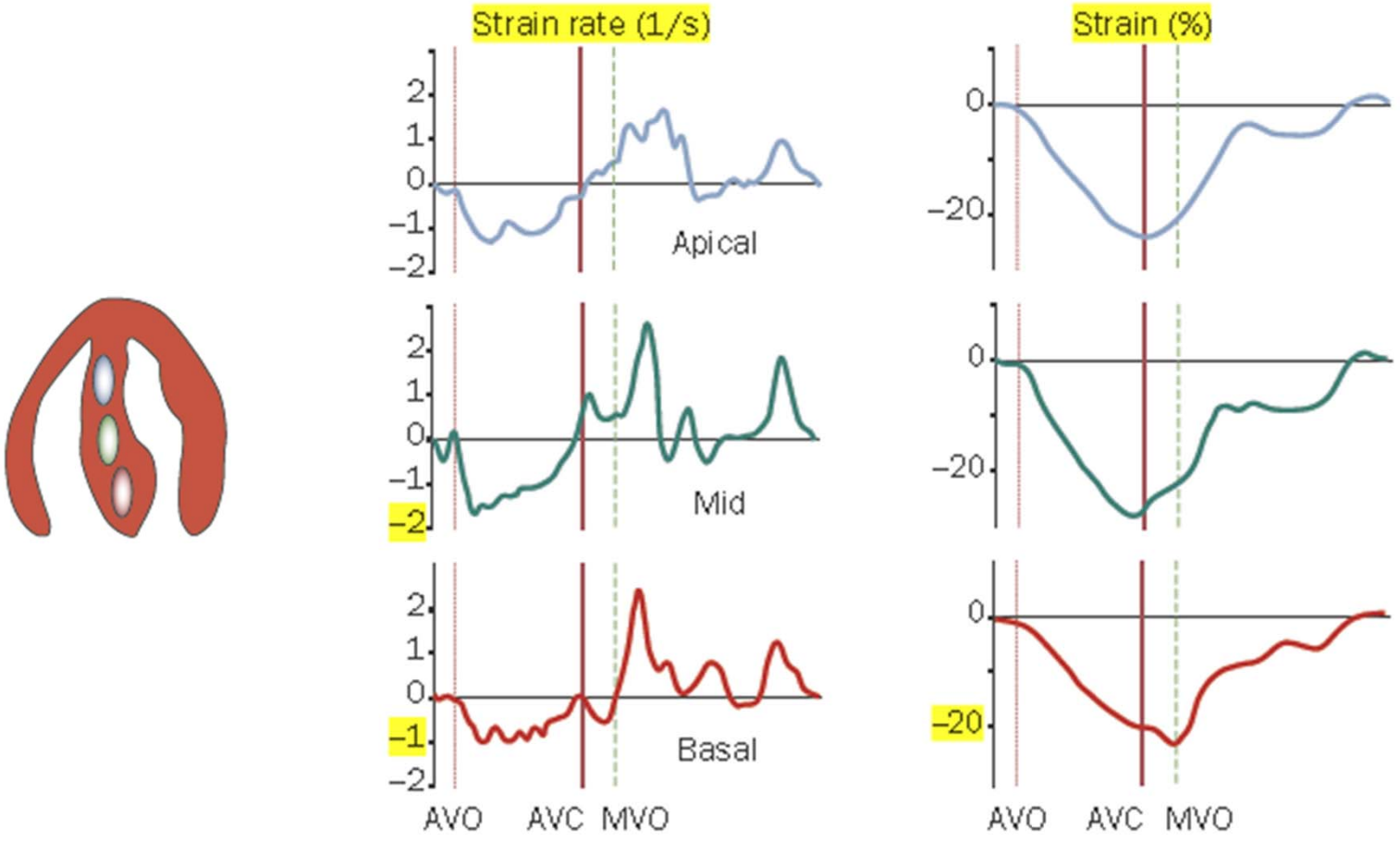
Major Components of Normal Cardiac Motion/deformation

- **Longitudinal lengthening and shortening**
- **Radial thinning and thickening**
- **Circumferential lengthening and shortening**

- **Base–apex twist**
- **Epicardial–endocardial**
  - **Circumferential**
  - **Longitudinal shear**



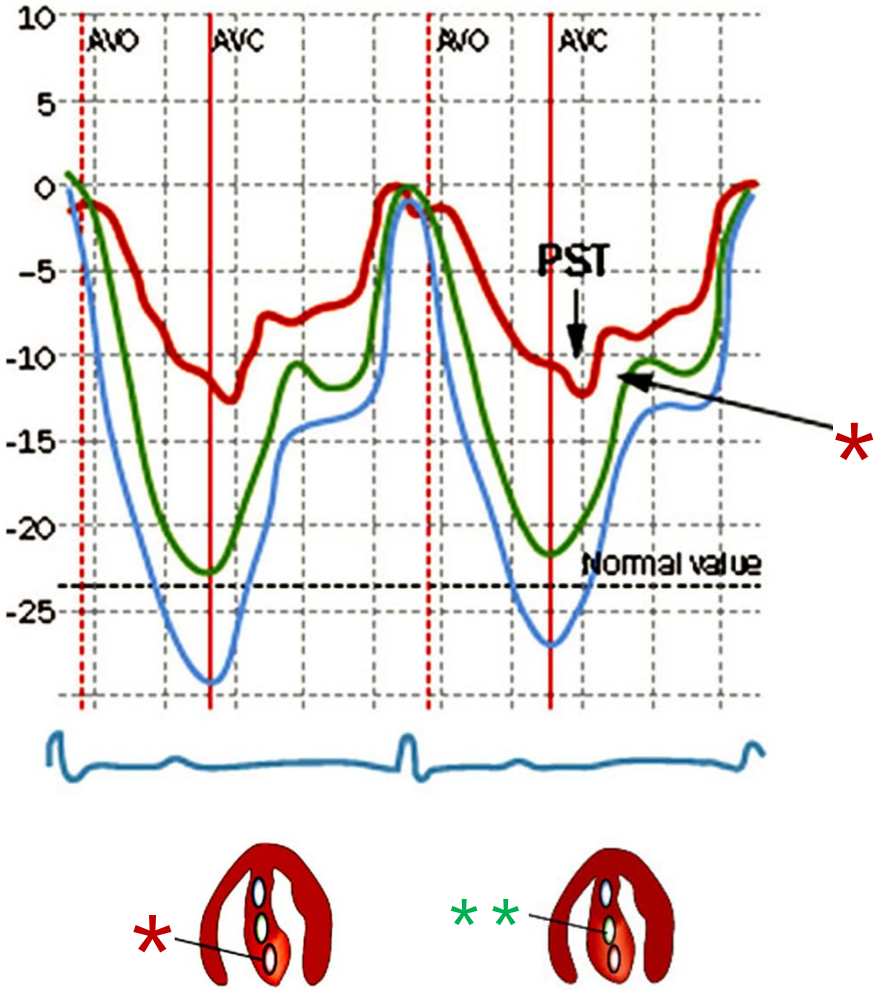
Major Components of Normal Cardiac Motion/deformation

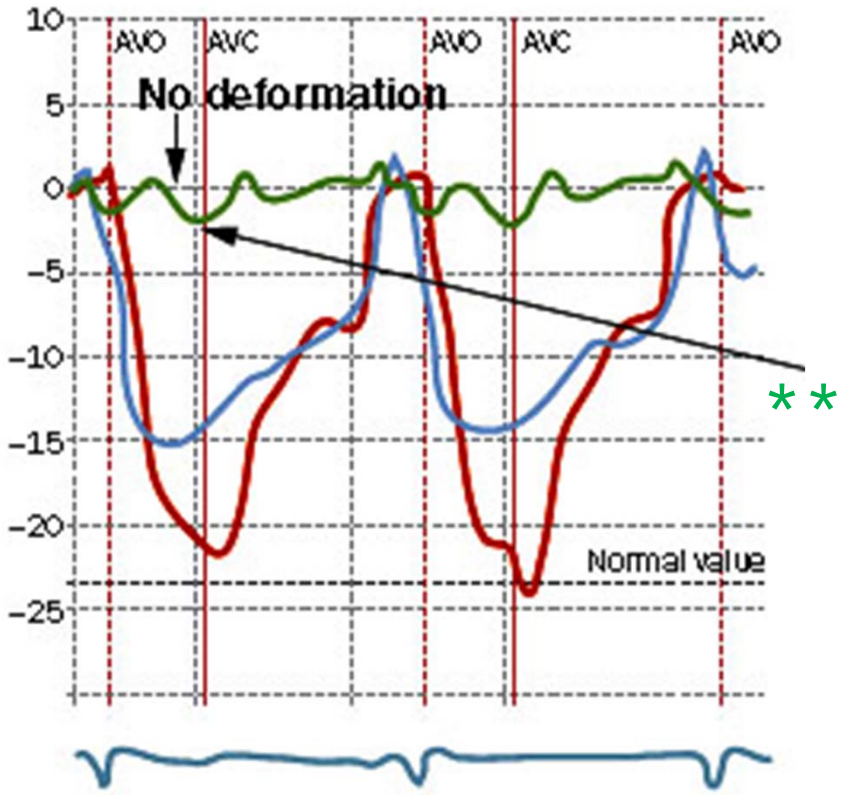


Nat Rev Cardiol 2010;7:384-96

Longitudinal Strain Curve Profiles

Hypertension vs HCM

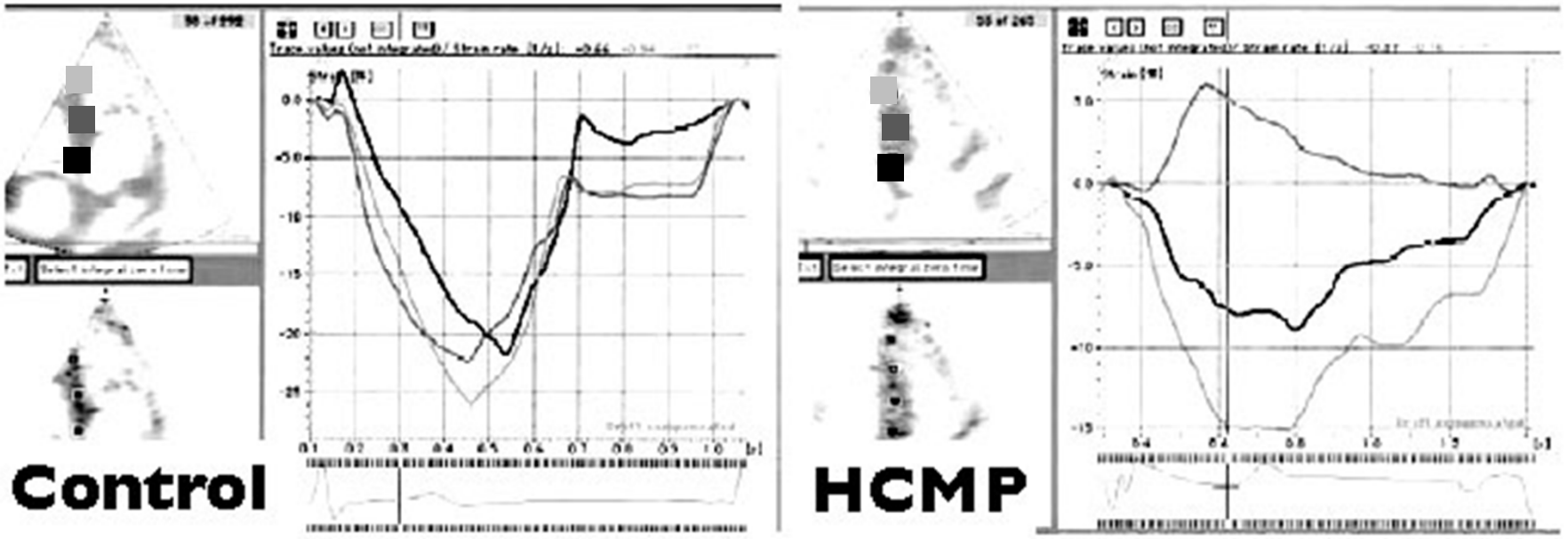




Nat Rev Cardiol 2010;7:384-96

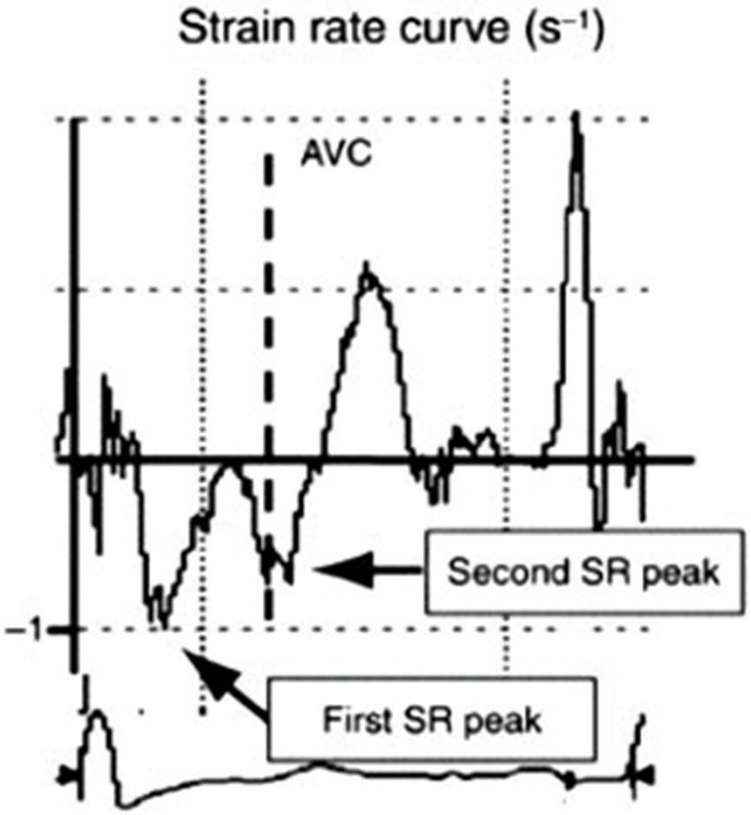
Rotational Mechanics Also Reduced

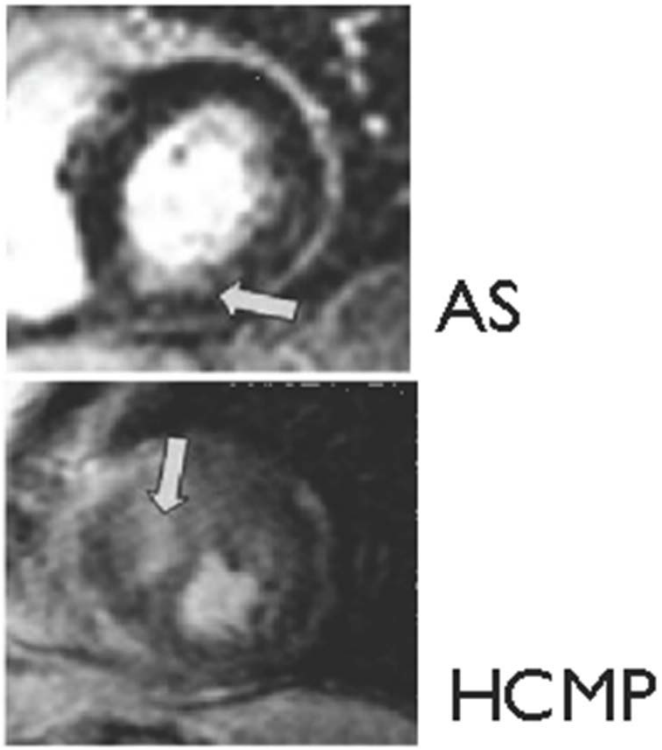
Use of Strain Imaging in Detecting Segmental Dysfunction in Patients With Hypertrophic Cardiomyopathy



Yang H, Garcia MJ et al. J Am Soc Echocardiogr 2003;16:233-9

Characteristic Deformation Pattern in HCM with Fibrosis





Eur J Heart J 2007;28:3020-6

Roles of Deformation Imaging in HCM

- **Regional vs Global function**
- **Longitudinal vs Radial function**
- **Systolic vs Diastolic function**
- **Early functional change**

  vs Late morphology of remodeling
- **Localizing abnormal myocardial tissue**

Risk Assess in HCM; Role of Imaging

- **Conventional echo**
  - **Clinical diagnosis of HCM (LVH), EF, diastolic dysfunction, etc**
  - **Clinical risk factors of prognosis of HCM**

- **New tool for Abnormal tissue-detection (CMR, 2D deformation image)**