Hypertrophic Cardiomyopathy

Prof. Ralph Knöll

Lecture 3

25.10.11

Heartfailure 1

Systolic

Heartfailure:

- **Symptoms and signs of of heart failue**
- **EF<50%**
- **Diminished contractility (dp/dt)**

Relatively new concept!

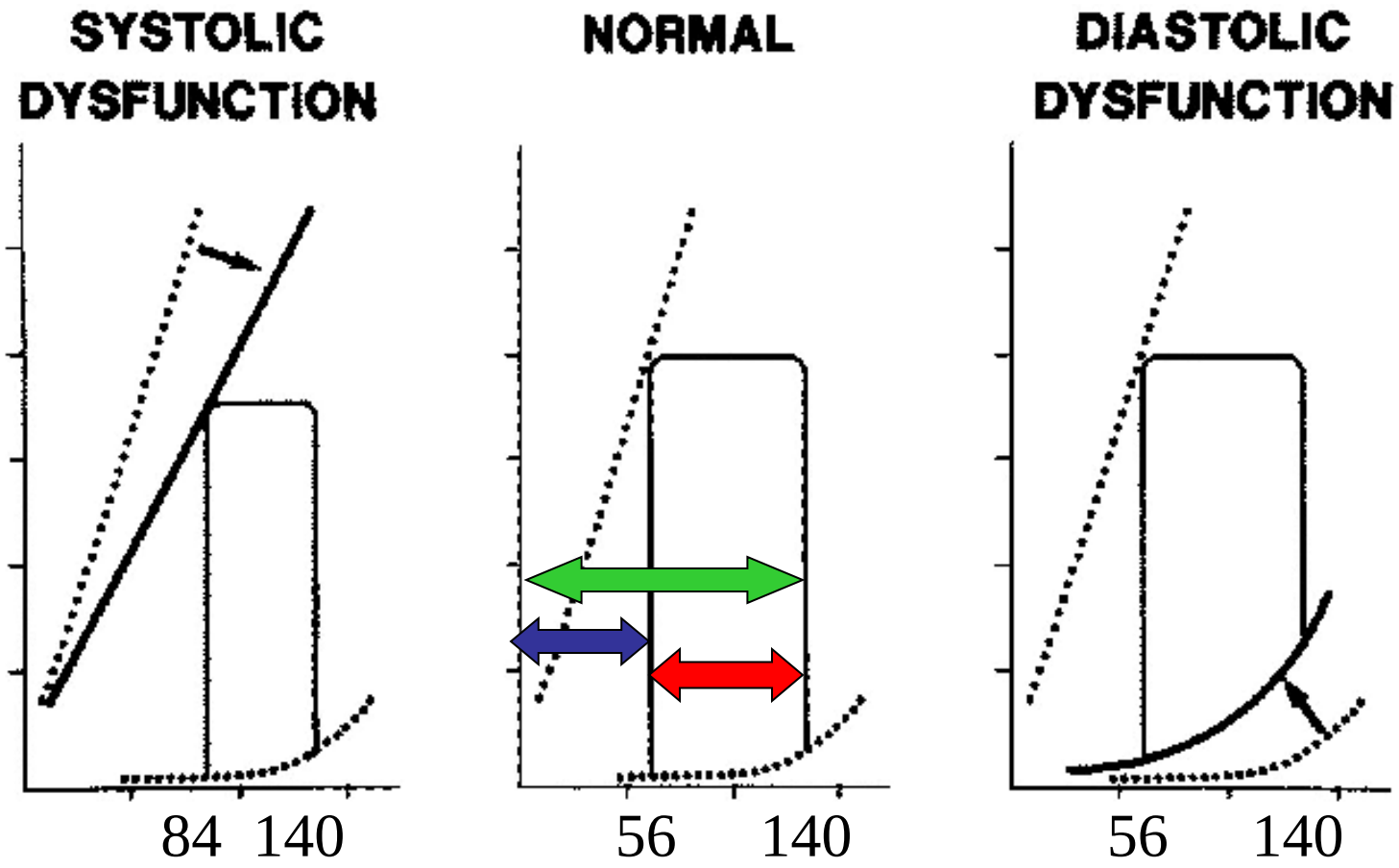
Does isolated diastolic heart failure really exist?

Diastolic

Heartfailure:

- **(Diagnosis only possible via analysis of myocardial function possible, such as echocardiography / angiography): Symptoms and signs of of heart failue**
- **EF>50%**
- **Abnormal diastolic function: ventricular relaxation dinimished, increased ventricular stiffness**

Systolic and Diastolic Heart Failure



Ejectionfraction (EF) = SV/EDV or EDV-ESV/EDV

Here: EF = 140 – 56 / 140 = 84 / 140 = 0,6 or 60%

(SV = Stroke Volume, EDV = enddiastolic Volume, ESV = endsystolic Volume)

Heartfailure 2

- **Acute:** all of a sudden, immediate heart failure (i. e. Myocardial Infarction or rupture during accident)
- **Chronic:** e. i. for a long time present (i. e. weeks, months, years - cardiomyopathy, slowly progredient heart valve disease)

Heartfailure 3

- **Right heart failure:** the right ventricle is primarily affected, blood pools back into the abdomen, liver and legs. Peripheral edema formed - typically around the ankles and in the lower legs or arms (i. e. Infarction of the right ventricle, tricuspidal valve failure pulmonal hypertonus)
- **Left heart failure:** the left ventricle is primarily affected, blood pools back into the lungs (lung-edema) low blood pressure (Infarction of the left ventricle, Mitral-valve failure, Aortic stenosis, arterial hypertension.

Global-heart failure: both ventricles are affected

Heartfailure 4

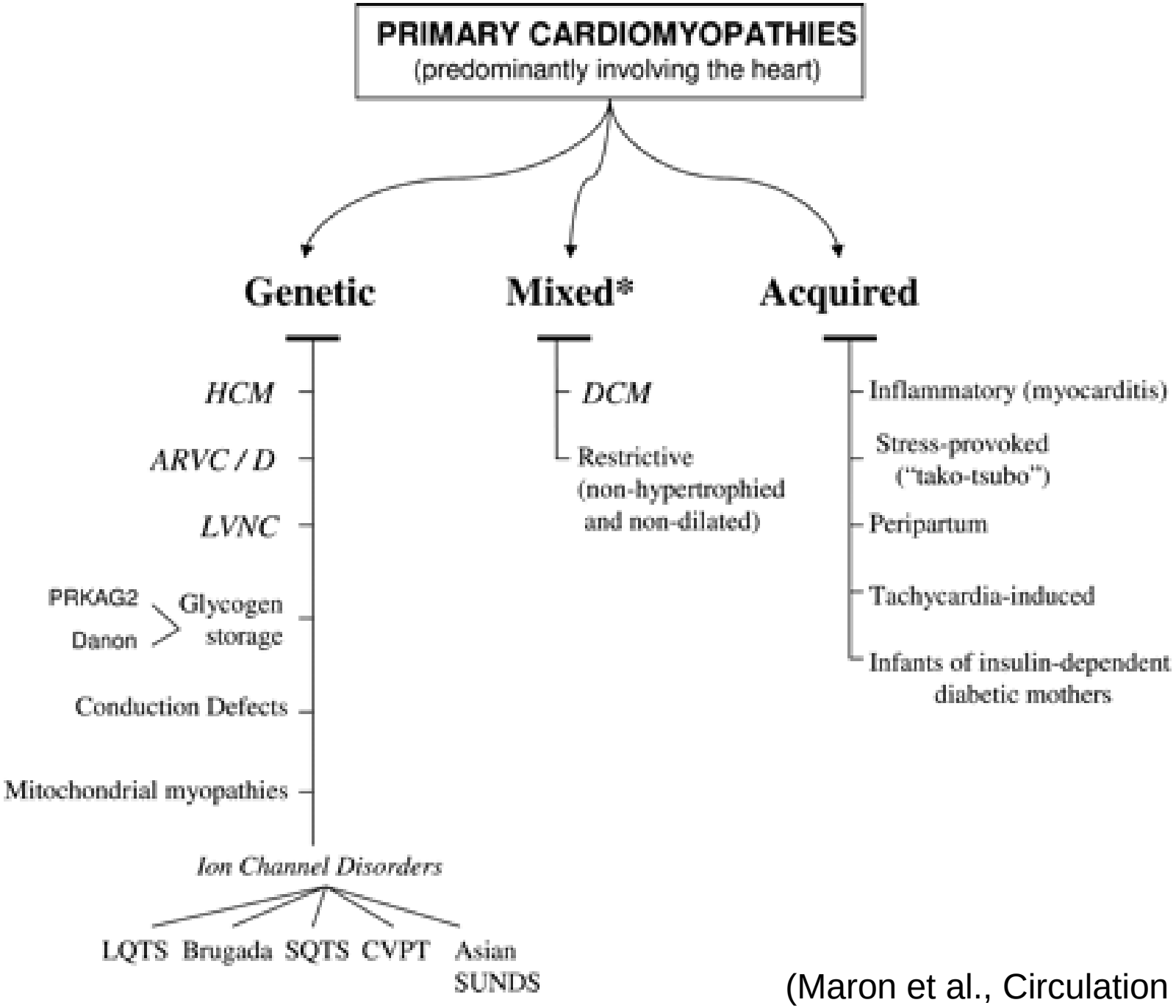
- **Backward failure:**

  of the left ventricle causes congestion of the pulmonary vasculature, and so the symptoms are predominantly respiratory in nature. Backward failure can be subdivided into failure of the left atrium, the left ventricle or both within the left circuit.

- **Forwardfailure:**

  of the left ventricle causes

  symptoms of poor systemic circulation such as dizziness, confusion and cool extremities at rest.



(Maron et al., Circulation 2006)

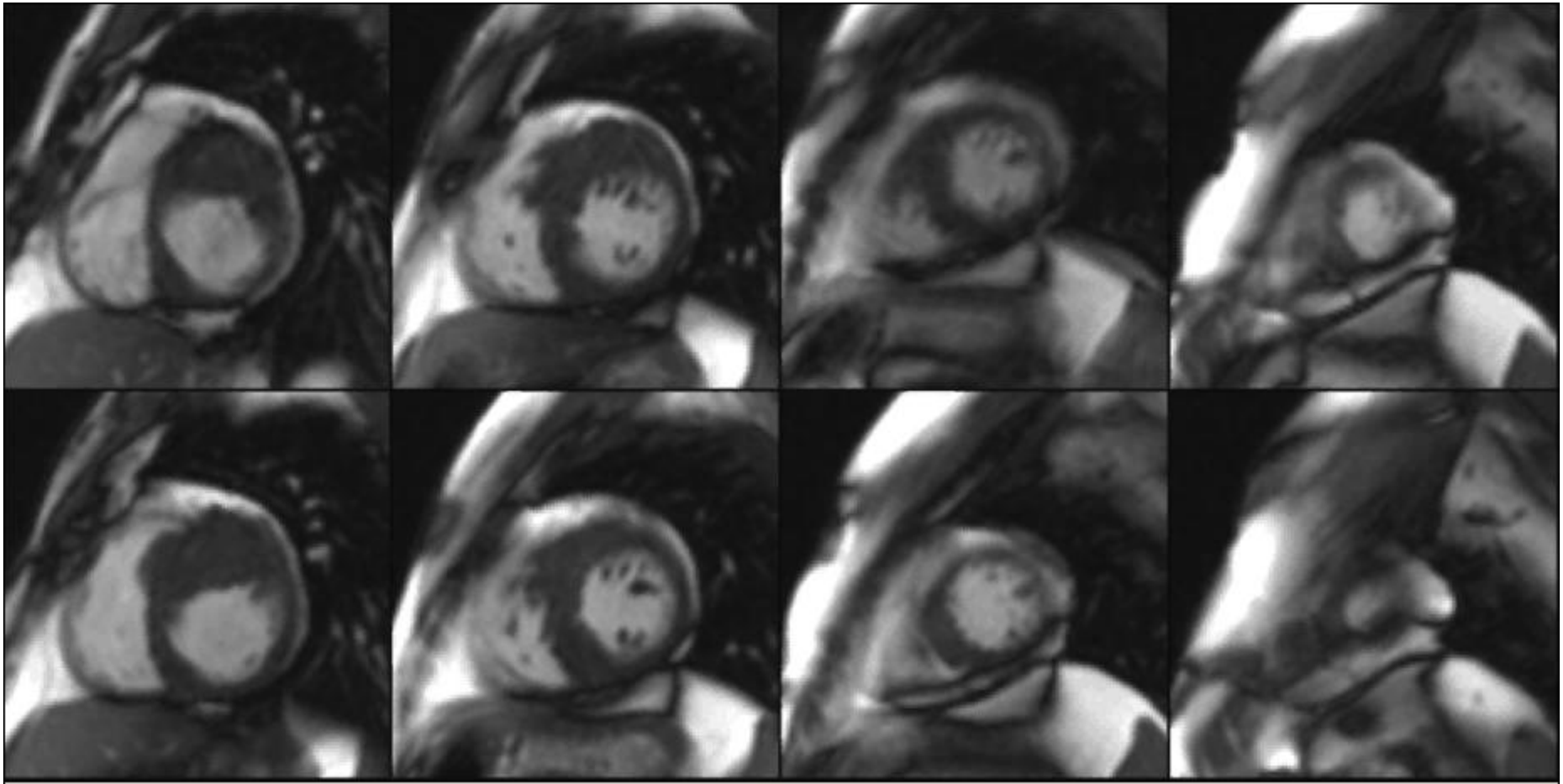
Hypertrophic Cardiomyopathy (HCM)

- Definition: HCM is characterized morphologically and defined by a hypertrophied, nondilated LV in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident (Maron et al., Circulation 2006).

Hypertrophic Cardiomyopathy (HCM)

- So what are the "....in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident?"
- Hypertension
- Valve diseases (aortic constriction)

Hypertrophic Cardiomyopathy (HCM)



Hypertrophic Cardiomyopathy (HCM)

- 2 types: Hypertrophic obstructive cardiomyopathy (HOCM) 25% of all cases
  Hypertrophic non-obstructive cardiomyopathy (HNCM) 75% of all cases

- Pathology: Hypertrophied septum
  in relation to wall thickness, relatively small ventricle
  Heart weight > 500 g

- Histology: myocardial dysarray (characteristic, but not specific)

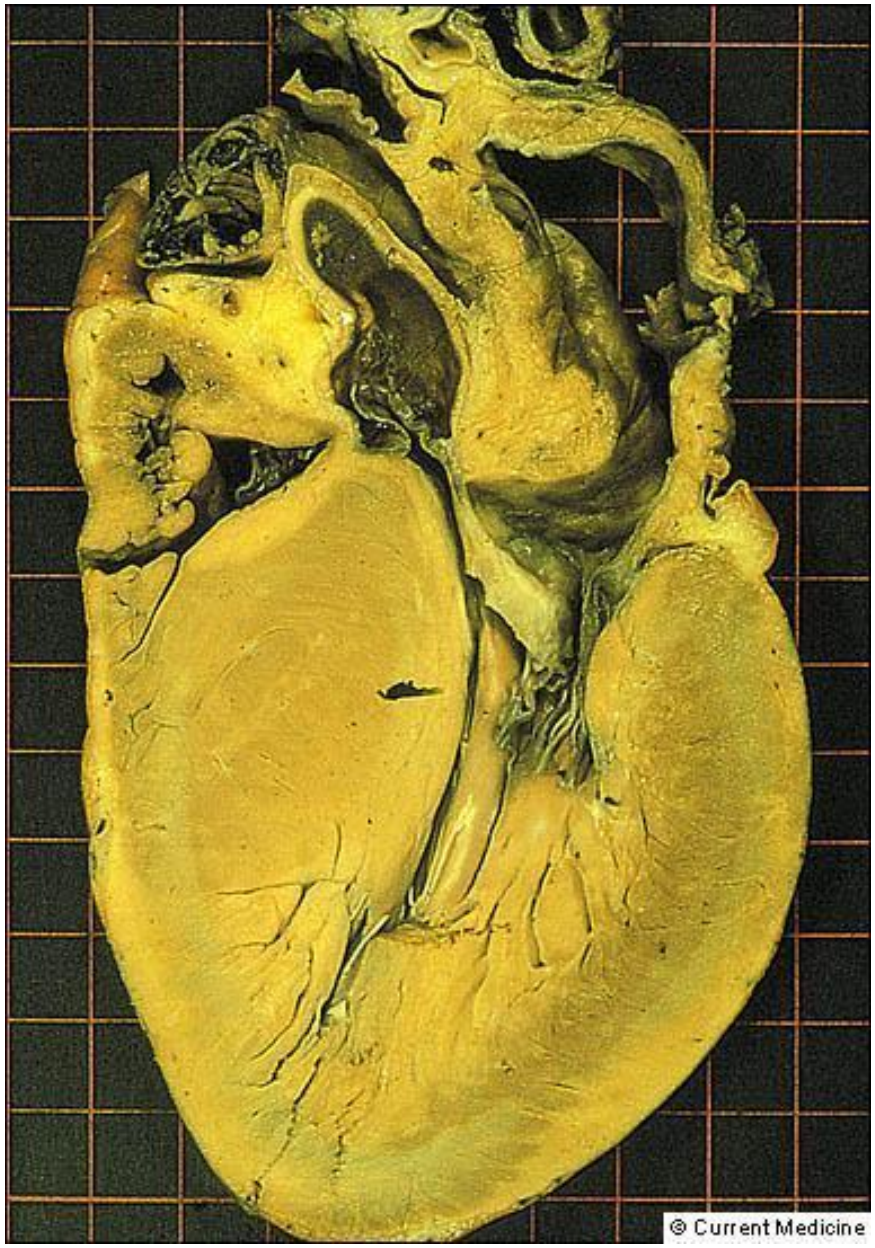
Hypertrophic Cardiomyopathy (HCM)

- HCM is a clinically **heterogeneous** but relatively common **autosomal dominant** genetic heart disease (1:500 of the general population for the disease phenotype recognized by echocardiography) that probably is the most frequently occurring cardiomyopathy.

Hypertrophic Cardiomyopathy (HCM)

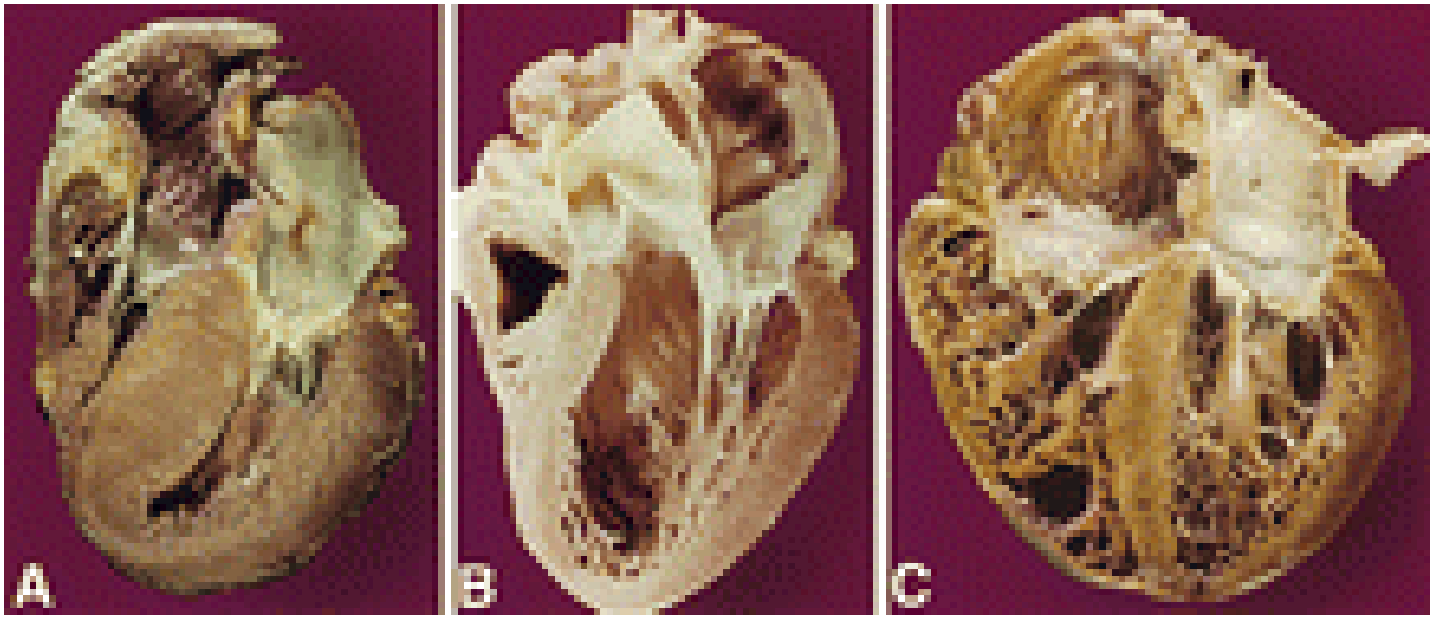
- Data from the United States indicate that HCM is the **most common cause of sudden cardiac death in the young (including trained athletes)** and is an important substrate for heart failure disability at any age.
- **Variable penetrance**
- **Age dependent penetrance**

Asymmetric septal hypertrophy



Heartfailure

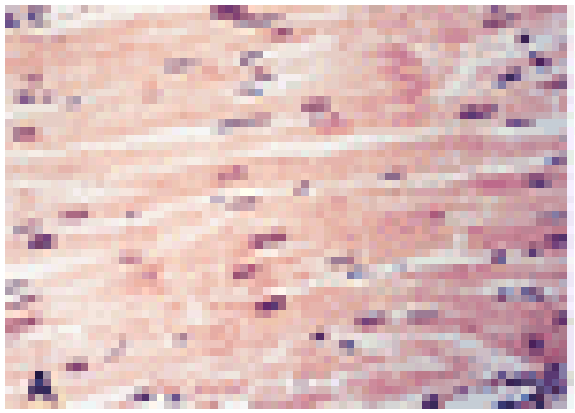
HCM Normal DCM



Seidman & Seidman, Cell, 2001

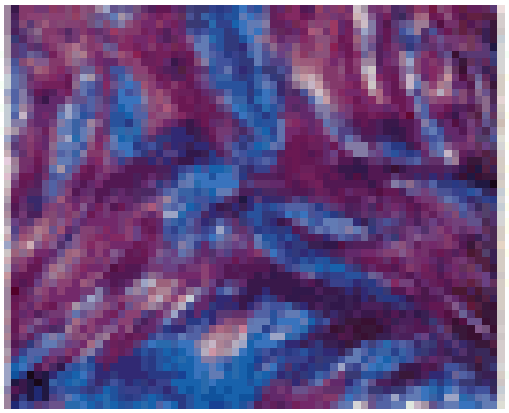
Heartfailure - Histology

H&E



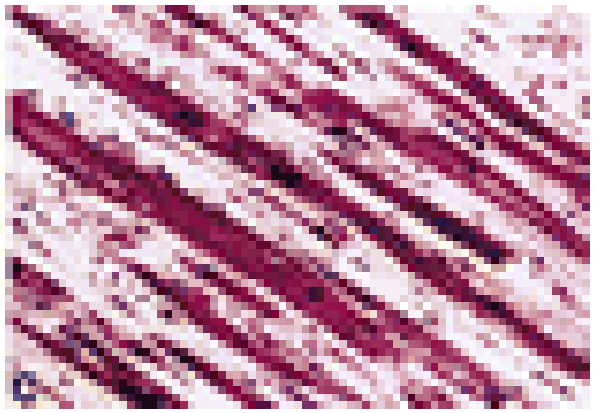
Normal (no interstial fibrosis; elongated, symmetric cardiomyocytes)

Mason Tricrome



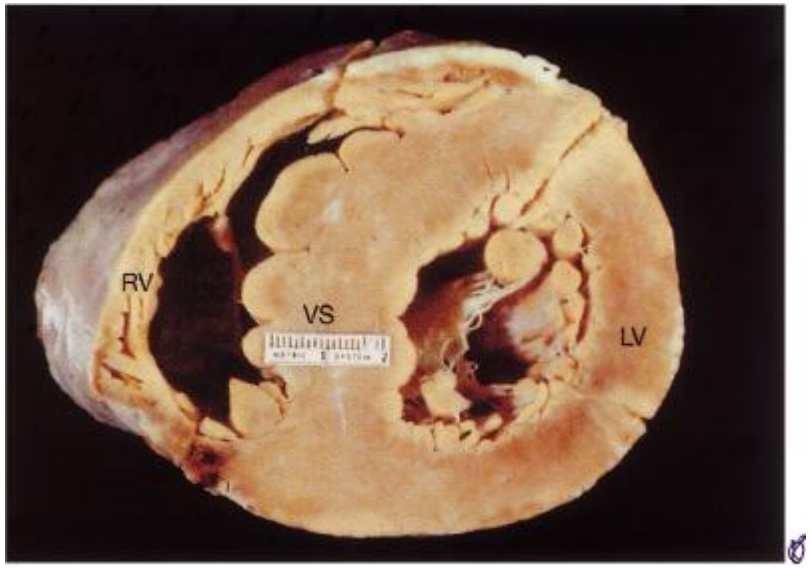
HCM
(Blue: Interstial fibrosis
red: disarray hypertrophied cardiomycytes)

H&E

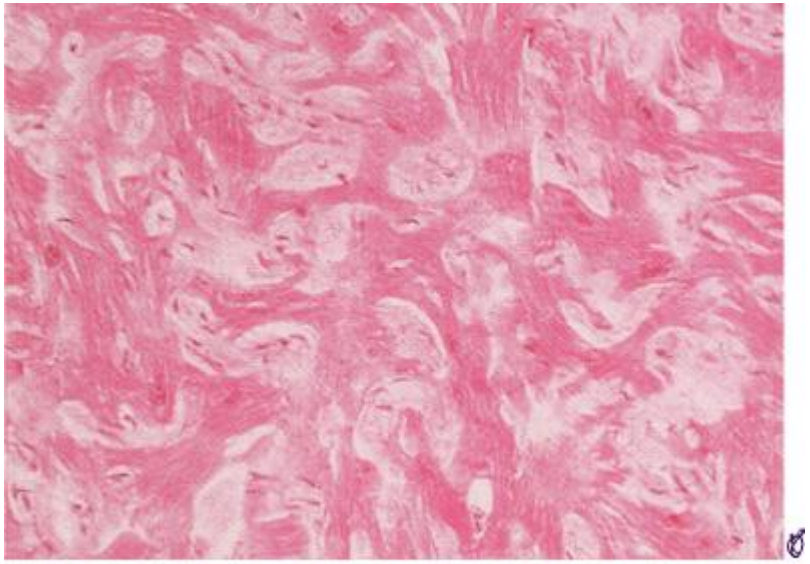


DCM (red: no disarray; hypertrophied, degenerating cardiomyocytes; pink: interstitial fibrosis)

HCM – Morphology, Histology



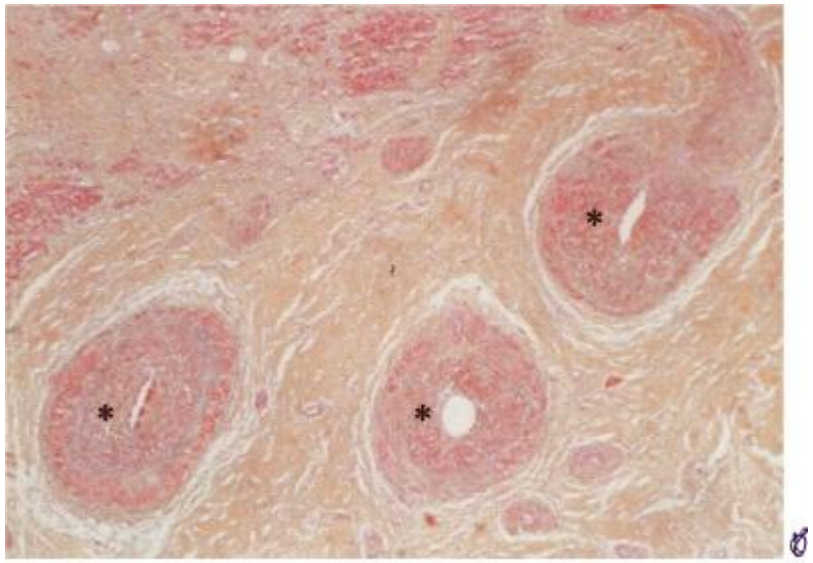
A



B

A, Gross heart specimen of a 13-year-old male athlete with disproportionate thickening of the interventricular septum (VS) compared with the left ventricular (LV) free wall. **B,** Histological specimen showing marked cellular disarray with hypertrophied cells arranged in a chaotic pattern.

HCM - Histology



C

C, Histological specimen showing several abnormal intramural coronary arteries, with markedly thickened walls and narrowed lumina. RV = right ventricle; hematoxylin and eosin stain in B and C;

HCM causing mutations

TABLE 59–4 Molecular Defects Linked to the Various Cardiomyopathies

Genomic Defect	Cardiomyopathy		
	Hypertrophic	*Dilated*	*Restrictive*
Sarcomere			
Myosin heavy chain	M	M	
Myosin essential light chain	M		
Myosin regulatory light chain	M		
Cardiac actin	M	M	
Troponin T	M/D	D	
Troponin I	M		M
Alpha-tropomyosin	M	M	
Myosin-binding protein C	M/D		
Titin/titin-related Protein			
Titin	M	M/D	
Telethonin (T-cap)		M	
Z-disk-associated Proteins			
Muscle LIM domain protein		M	
Sarcolemma Cytoskeleton			
Dystrophin		D	
Beta-sarcoglycan		D/Dup	
Delta-sarcoglycan		M	
Alpha-dystrobrevin		M	
Metavinculin		D	
Intermediate Filaments			
Desmin		M	
Lamin A/C		M	

D = deletion; Dup = duplication; M = missense.

Adapted from Chien KR: Genotype, phenotype: Upstairs, downstairs in the family of cardiomyopathies. J Clin Invest 111:175, 2003.

Number of sarcomeric gene mutations in hypertrophic cardiomyopathy (Schlossarek et al., J Mol Cell Cardiol 2011)

Gene name	Symbol	Number of mutations
β-myosin heavy chain	*MYH7*	218
Cardiac myosin-binding protein C	*MYBPC3*	185
Cardiac troponin T	*TNNT2*	36
Cardiac troponin I	*TNNI3*	30
α-tropomyosin	*TPM1*	12
Regulatory myosin light chain	*MYL2*	10
Cardiac α-actin	*ACTC1*	7
Essential myosin light chain	*MYL3*	5
α-actinin 2	*ACTN2*	4
Muscle LIM protein	*CSRP3*	3
Muscle RING-finger protein 1	*TRIM63*	3
Myozenin 2 (calsarcin 1)	*MYOZ2*	2
Nexilin	*NEXN*	2
Telethonin	*TCAP*	2
Titin	*TTN*	2
Vinculin	*VCL*	2
Cardiac troponin C	*TNNC1*	1
α-myosin heavy chain	*MYH6*	1
Obscurin	*OBSCN*	1

Hypertrophic Cardiomyopathy (HCM)

For many years it was unclear, whether cardiomyopathies do have a genetic cause or do have a genetic basis. However, 20 years ago, the first mutation in a patient / family affected by HCM was shown:

the R403Q β Myosin heavy chain mutation (MYH 7)

A molecular basis for familial hypertrophic cardiomyopathy: An α/β cardiac myosin heavy chain hybrid gene

Gary Tanigawa[a], John A. Jarcho[b], Susan Kass[a], Scott D. Solomon[b], Hans-Peter Vosberg[c], J. G. Seidman[a] and Christine E. Seidman[b, a]

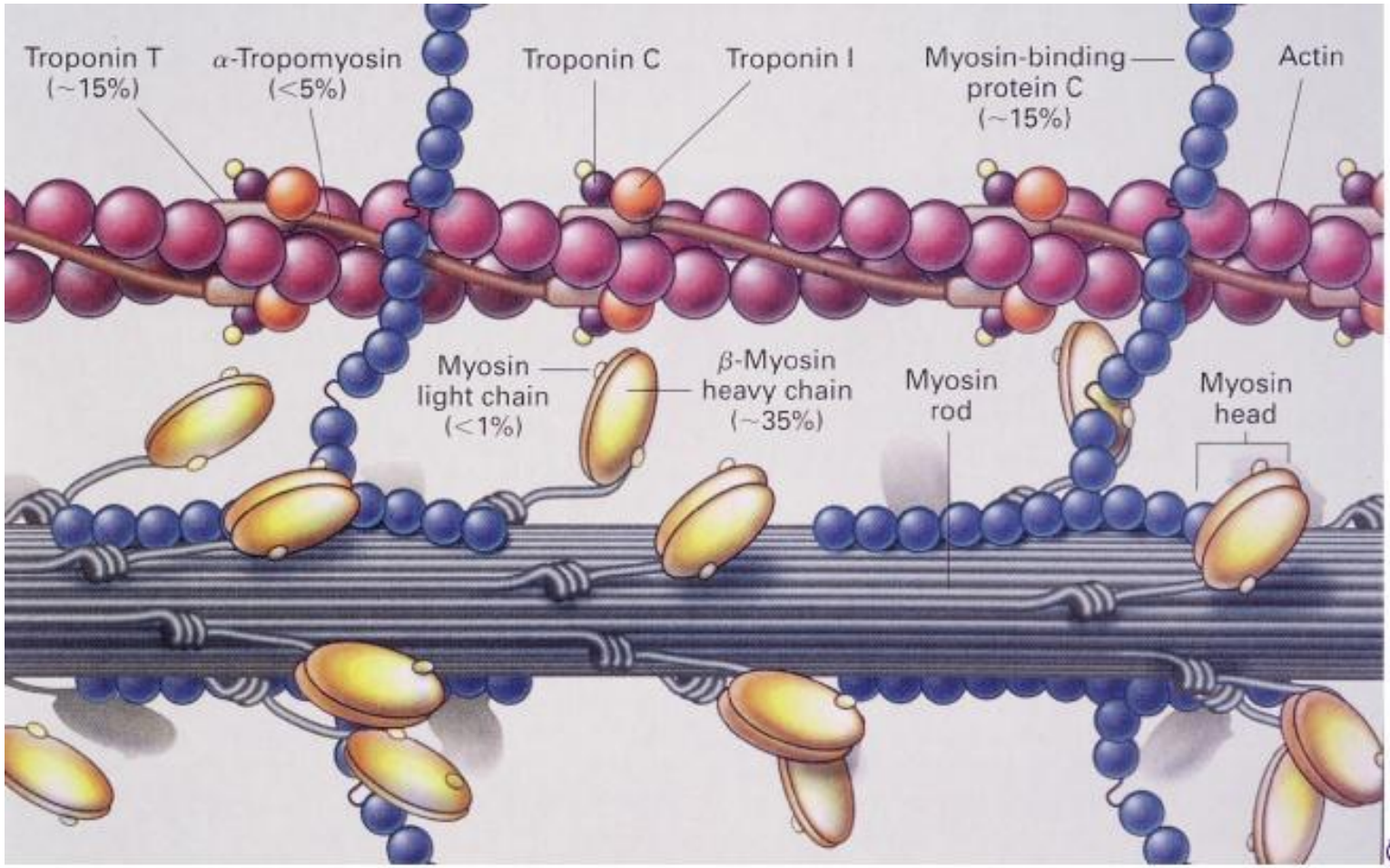
[a] Howard Hughes Medical Institute and Department of Genetics Harvard Medical School, Boston, Massachusetts 02115, USA

[b] Cardiovascular Division Brigham and Women's Hospital, Boston, Massachusetts 02115, USA

[c] Department of Cell Physiology Max-Planck Institute for Medical Research, Heidelberg, Federal Republic of Germany

Received 20 July 1990.

Hypertrophic Cardiomyopathy (HCM)



Expression of mutant alleles

Table 1 Direct measurements of mutant protein expression

Gene	Mutation	Fraction mutant protein in tissue	Reference
MYH7	Val606Met (HCM)	12%	[59]
MYH7	Gly584Arg (HCM)	23%	[59]
MYH7	Arg403Gly (HCM)	50%	[60]
TNNC1	Gly159Asp (DCM)	40%	[55]
ACTC	Glu99Lys (HCM)	38%	[61]
TPM1	Asp175Asn (HCM)	47–53% (skeletal muscle)	[62]

Hypertrophic Cardiomyopathy (HCM)

- Mutations in sarcomeric genes are a major cause of HCM.
- Mutations in genes encoding force generating parts of the sarcomere are a major cause of HCM **(i. e. Is HCM a disease of the „force generation“?)**

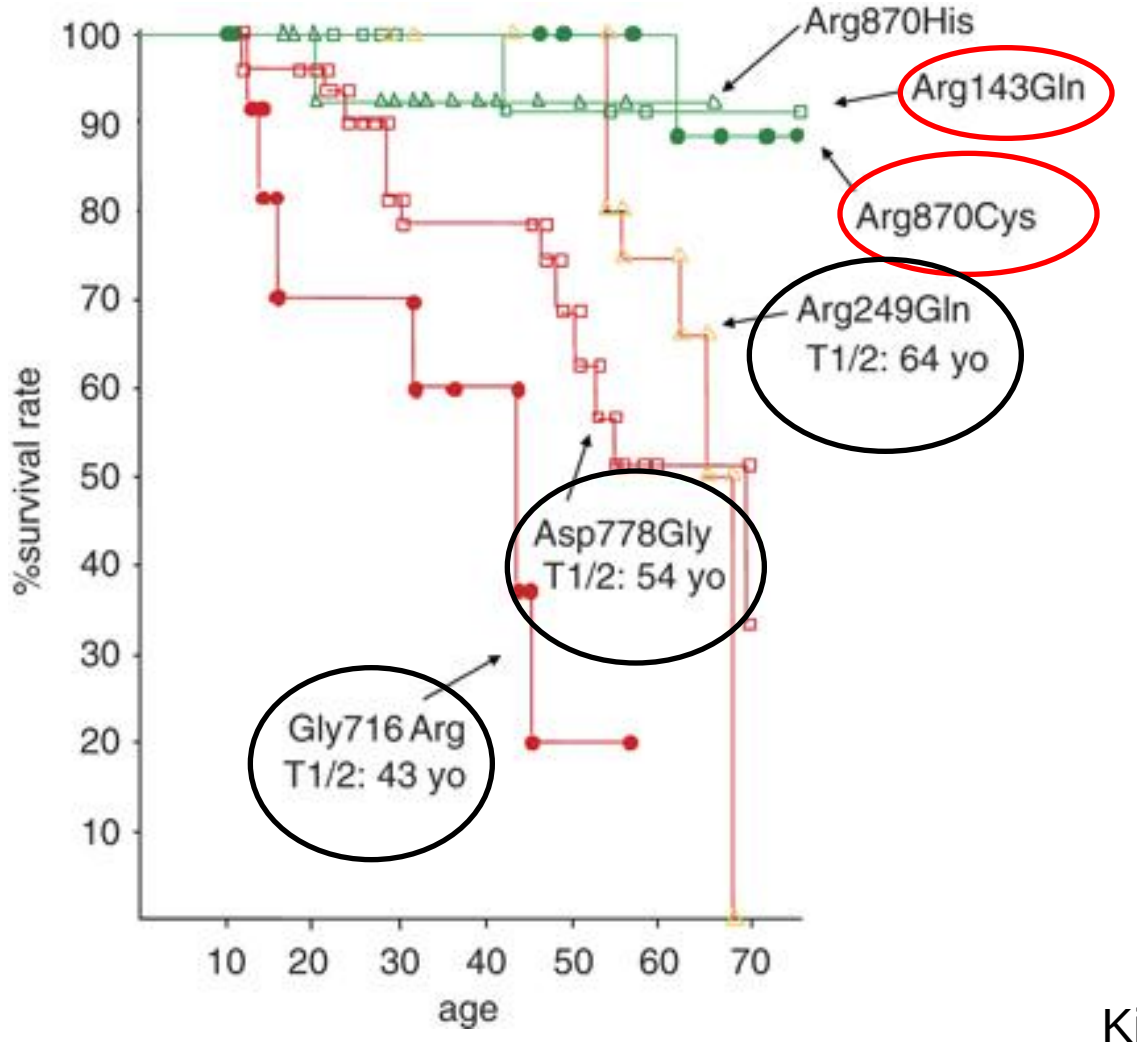
Hypertrophic Cardiomyopathy (HCM)

- Mutations in genes encoding force generating parts of the sarcomere are a major cause of HCM **(i. e. Is HCM a disease of the „force generation“?)**
- **Indeed, some MYH7 chain mutations are associated with a decrease in power generation and it was initially thought that the observed hypertrophy might represent a „compensatory mechanism“ <u>BUT</u>: most of the HCM causing mutations are associated with increased power production.**

Hypertrophic Cardiomyopathy (HCM)

- Watkins et al., proposed that the MYH7 mutations leading to an amino acid change with charge alteration was associated with poor survival prognosis.
- **This fits for the Arg249Gly, Gly716Arg, and the Asp778Gly mutation.**
- **But not for the Arg143Gln and Arg870Cys**

Survival of HCM patients with different MYH7 mutations



Kimura, J human Genetics 2010

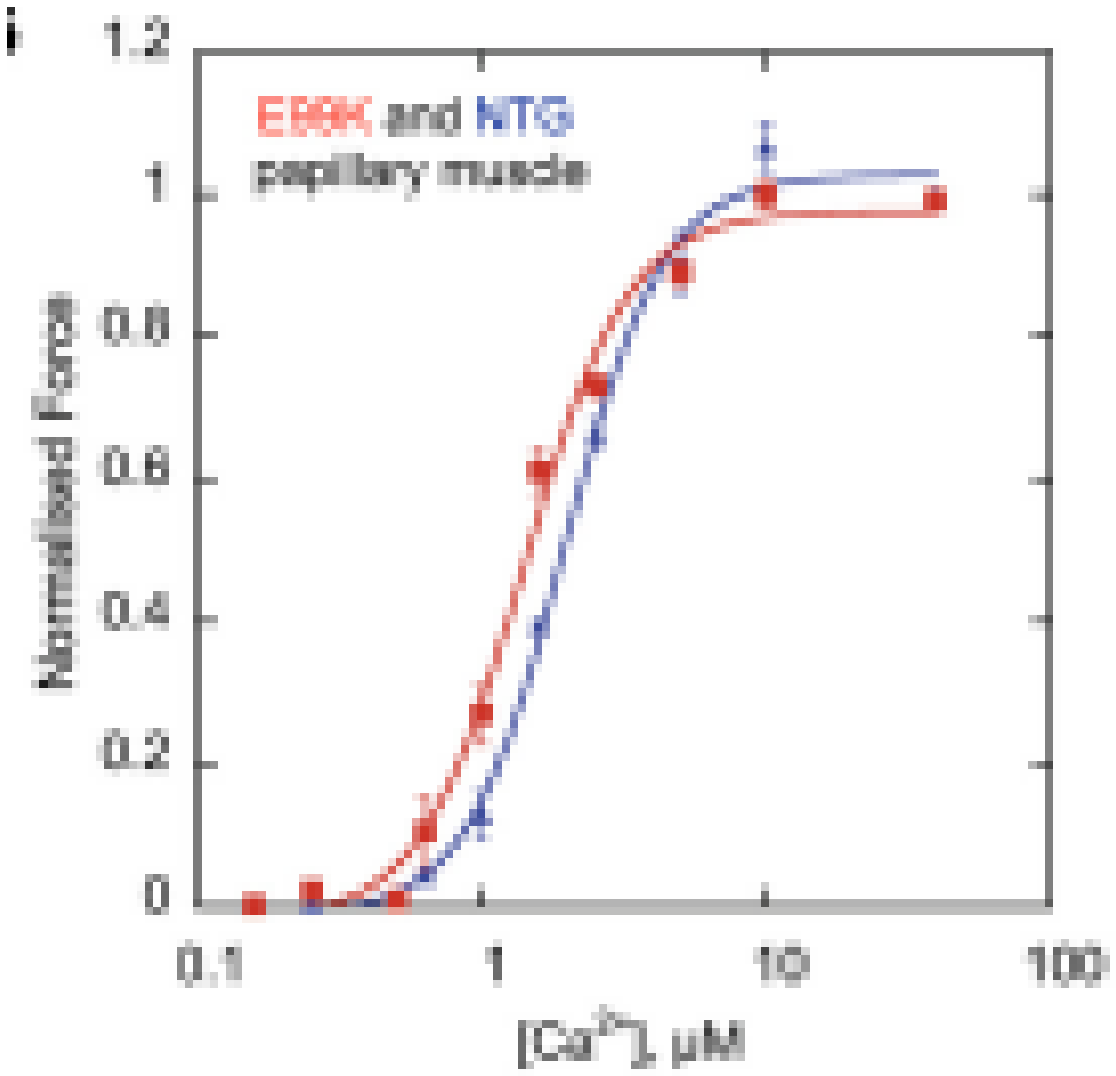
Hypertrophic Cardiomyopathy (HCM)

- As such, this hypothesis was changed so that amino acid changes associated with charge alteration in functionally important domains of myosin heavy chain (i. e. ATP binding domain, converter domain and myosin light chain interacting domain) are correlated with poor survival.

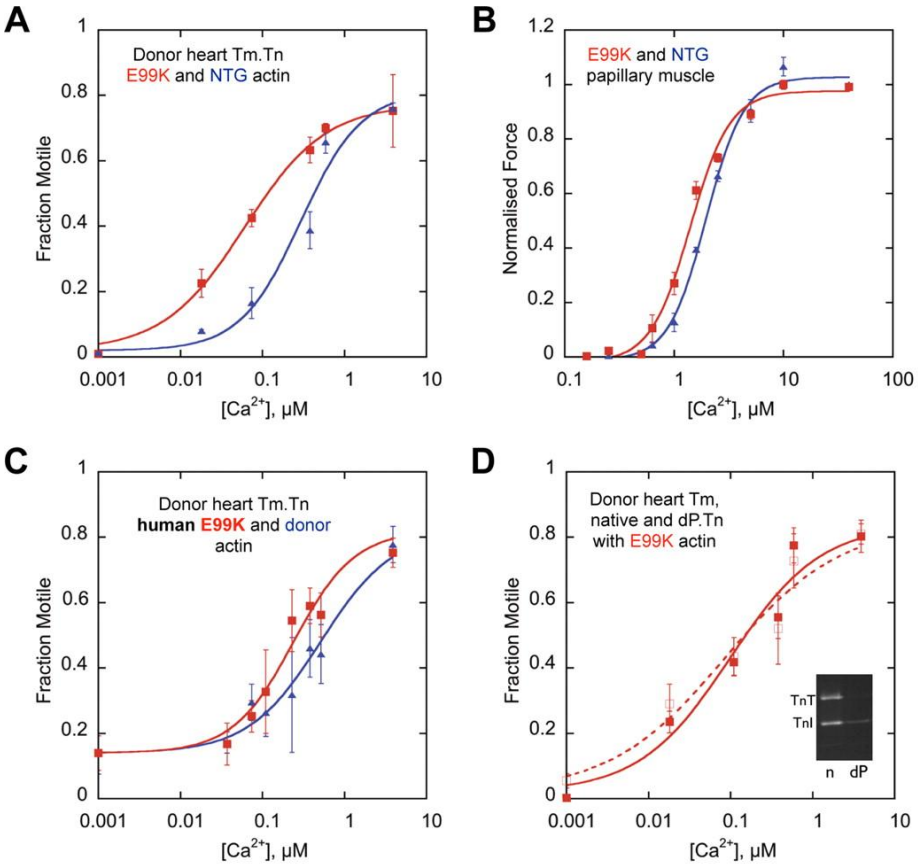
Hypertrophic Cardiomyopathy (HCM)

- Mutations in genes causing an increase in calcium sensitivity **(i. e. is HCM a disease of the „calcium sensitivity“?) (Prof. Steve Marston)**

Calcium Sensitivity



Ca2+ activation curves comparing ACTC E99K (red squares) with wild-type actin (blue triangles).



	number of hearts	number of assays		Wild-type actin	E99K actin	p , paired t test
skinned trabecula muscle	4	4	EC_{50}, isometric tension, μM	1.93±0.02	1.48±0.09	p=0.0027
Actin.Tm.Tn	5	5	EC_{50}, fraction motile, μM	0.35±0.09	0.15±0.05	p=0.02
Actin.Tm.Tn Human sample 2	1	5	EC_{50}, fraction motile, μM	0.42±0.10	0.34±0.12	p=0.017

Song W et al. J. Biol. Chem. 2011;286:27582-27593

Gene	Mutation	Change in Ca^{2+}-sensitivity	Change in crossbridge turnover rate	Reference
ACTC	E361G	+0.02	Normal	[51, 56]
	R312H	+0.30	Reduced	[51, 63]
MYBPC3	R326Q			[6]
	T494I			[6]
	E619K			[6]
	N948T			[74]
MYH7	A223T			[74]
	S532P		Reduced	[4, 75]
	S642L			[74]
	F764L		Reduced	[76, 75]
	I201T			[76]
	T412N			[76]
	A550V			[76]
	L517M			[77]
	K637E			[6]
	Q734E			[77]
	T1019N			[76]
	L1038P			[6]
	R1193S			[76]
	E1426K			[76]
	R1634C			[76]
	R1832C			[6]
TNNT2	R131W	−0.23	Reduced	[5, 53]
	R141W	−0.09	Reduced	[5, 53]
		−0.20		[70]
	A171S			[78]
	R205L	−0.46	Reduced	[5, 53]
	ΔK210	−0.34	Reduced	[4, 53]
		−0.10		[70]
		+0.2 (100%) −0.35 (50%)		[54]
	D270N	−0.19	Reduced	[5, 53]
	K247R	+0.01	Reduced	[6, 79]
TNNC1	G159D	−0.25	Reduced	[5, 53]
		+0.22		[55]
TNNI3	K36Q	−0.39	Reduced	[80]
	N185K	−0.38	Reduced	[80]
TPM1	E40K	−0.17	Reduced	[81]
		−0.08		[82]
	E54K	−0.47	Normal	[81]
		+0.28 (100%) +0.01 (50%)		[54]
	E207K	−0.27	Reduced	[83]

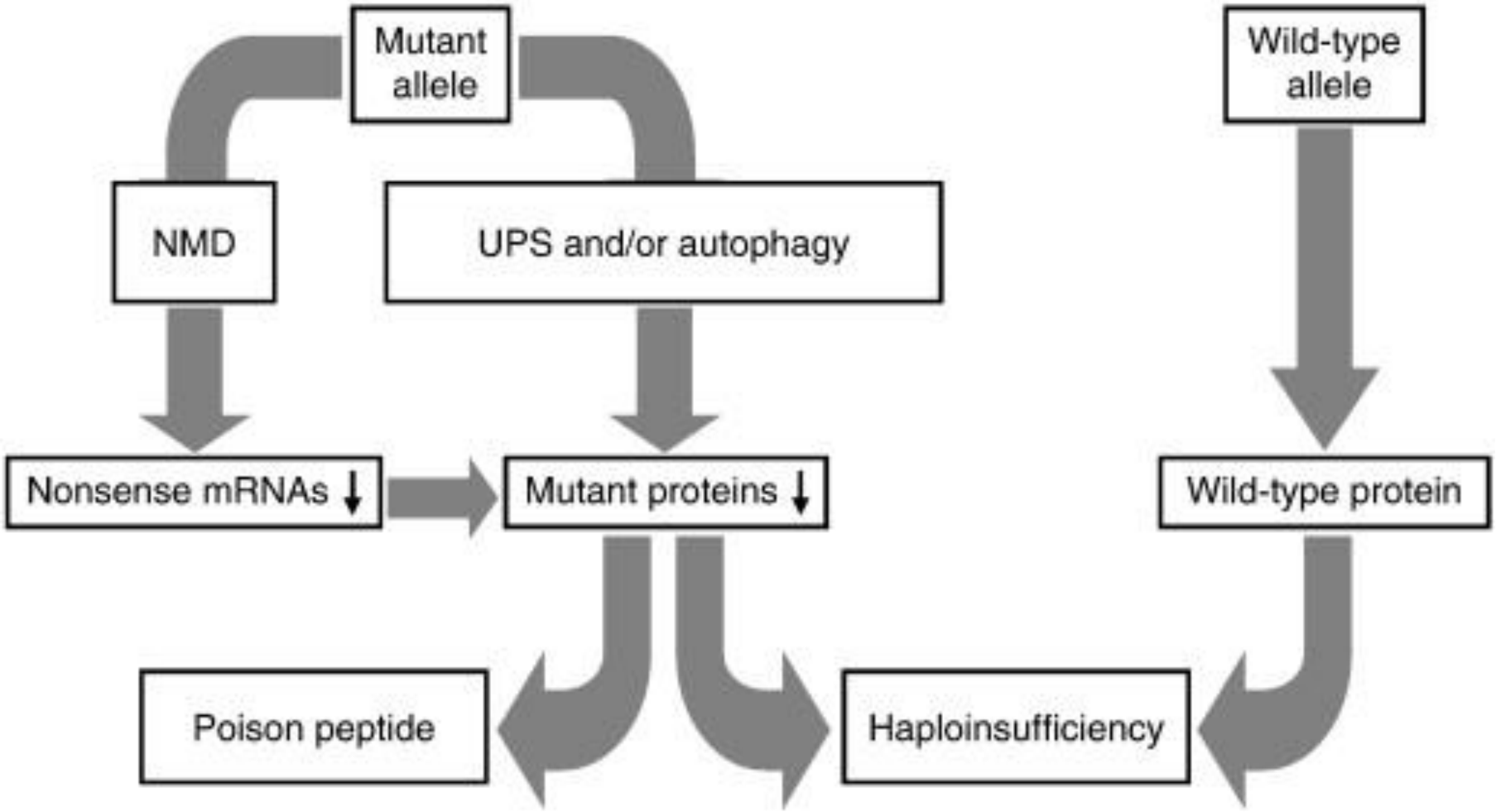
Gene	Mutation	System	Ca^{2+}-sensitivity, ΔpCa_{50}	Switch-off at pCa9	Max turnover rate	Reference
ACTC	E99K	TG mouse tissue, motility	+0.39	Normal	Normal	[56]
		Human tissue, motility	+0.12	Normal	Normal	[56]
		TG mouse tissue, force	+0.11	Normal		[56]
		Baculovirus, motility	+0.05	Normal		[63]
MYBPC3	IVS17+4A>T truncated at 868	Human tissue, skinned cells	+0.1			[19]
	c.2864_2865delCT truncated at 860	Human tissue, skinned cells	+0.06			[20]
MYL2	R58Q	Recombinant exchange, force	+0.11			[64]
	D166V	TG mouse tissue, force	+0.25		Reduced	[35]
MYH7	R403Q	Human tissue, motility			Increased	[25]
		Recombinant, motility			Increased	[65]
		TG mouse tissue, force	+0.15	Normal		[29]
	R453C	TG mouse tissue, force	+0.30	Normal		[30]
	R719Q	Recombinant, motility			Normal	[65]
	R719W	Recombinant, motility			Normal	[65]
	D778G	Recombinant, motility			Increased	[65]
	L908V	Human tissue, motility			Increased	[25]
TNNI3	R145G	Recombinant, ATPase	+0.56	None		[66]
		Recombinant, ATPase	+0.32	Incomplete	Increased	[67]
		Recombinant exchange, force	+0.16			[67]
	R145Q	Recombinant, ATPase	+0.23	Incomplete	Increased	[67]
		Recombinant exchange, force	+0.10			[67]
	R162W	Recombinant, ATPase	+0.11	Incomplete	Normal	[67]
		Recombinant exchange, force	+0.06			[67]
		Recombinant, ATPase	+0.13	Incomplete		[66]
	ΔK182	Recombinant, ATPase	+0.18	Normal	Normal	[67]
		Recombinant exchange, force	+0.1			[67]
	K206Q	Recombinant, ATPase	+0.18	Normal		[67]
		Recombinant exchange, force	+0.04			[67]
	G203S	Recombinant, ATPase	+0.10	Normal		[67]
		Recombinant exchange, force	+0.02			[67]
TNNT2	Exon 16/17del (truncated at 267)	Recombinant, ATPase	+0.43	None	Normal	[13]
	R92Q	Recombinant, ATPase	+0.24	Incomplete		[52]
		Recombinant exchange, force	+0.18			[69]
	I79N	Recombinant exchange, force	+0.15	Incomplete		[69]
	R94L	Recombinant exchange, force	+0.11			[70]
	F110I	Recombinant exchange, force	+0.37	Incomplete	Decreased	[69]
	ΔE160	Recombinant exchange, force	+0.15			[70]
	E163K	Recombinant exchange, force	+0.07	Incomplete	Increased	[69]
	R278C	Recombinant exchange, force	+0.34	Incomplete	Increased	[69]
TPM1	A63V	Recombinant, ATPase, motility	+0.30			[71]
	K70T	Recombinant, ATPase, motility	+0.33			[71]
	D175N	Recombinant, motility	+0.082	Normal	Normal	[72]
		Human tissue (skeletal), force	+0.09	Normal	Normal	[62]
		TG mouse tissue, force	+0.10			[73]
	E180G	Recombinant, motility	+0.115	Normal	Normal	[72]

Hypertrophic Cardiomyopathy (HCM)

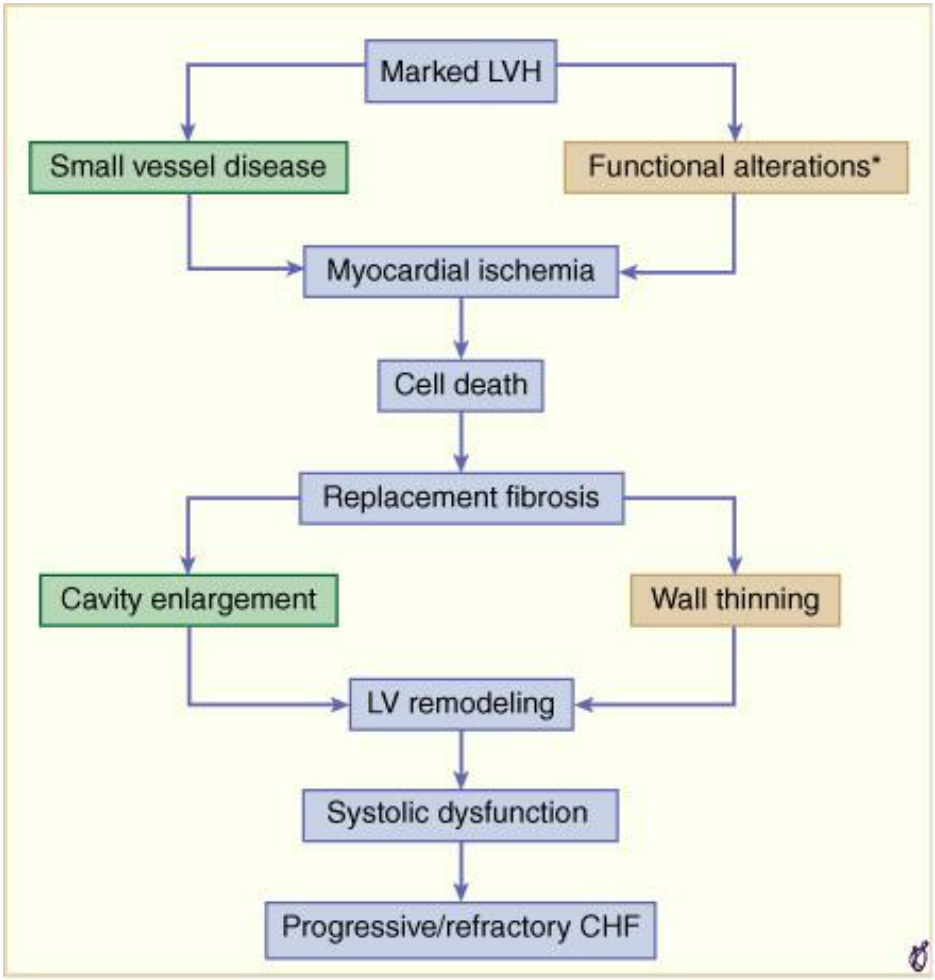
- **New hypothesis:** an increase in misfolded proteins (i. e. particularly mutant myosin binding protein C proteins) which the ubiquitine proteasome complex is unable to degrade timely, causes hypertrophy of cardiomyocytes.

  Moreover, other proteins, such as growth factors can‘t be degraded as well and may cause a further increase in hypertrophy.

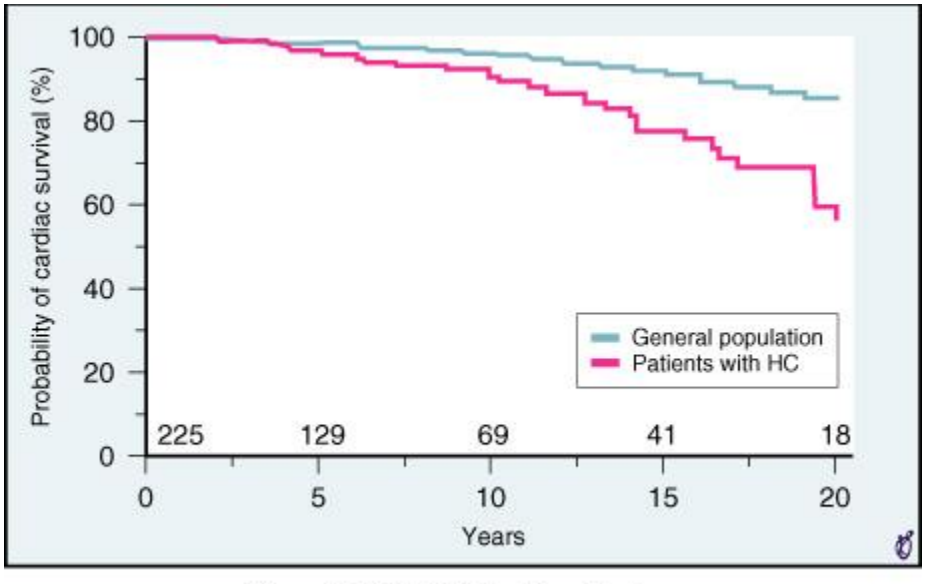
Hypertrophic Cardiomyopathy (HCM)



HCM and progression to heart failure



HCM - Prognosis



Kaplan-Meier survival curve of 225 community-based patients with hypertrophic cardiomyopathy (HC) and age-matched control subjects. The numbers above the horizontal axis refer to the number of patients at each follow-up period. The annual total mortality rate of the patients with HC was 1.3 percent.

Hypertrophic Cardiomyopathy (HCM)

Sarcomeric components	**Number of known mutations**	**Mutation (Example)**	**SCD Risik (sudden cardiac death)**
β MHC	>50	Arg403Q Val606Met	Minimal - high Minimal
CardiacTroponin T	11	Ile79Asn Arg92Gln	High ?
Cardiac Troponin I	6		Unknown
α-Tropomyosin	4	Asp175Asn	Minimal
Myosin bindending Protein C	11	Mutations in introns, Splice Sites	Minimal
Myosin light chain	6		Unknown

Hypertrophic Cardiomyopathy (HCM)

- **So why are some mutations associated with sudden cardiac death and others not?**
- **Simple answer:**

  No one knows it exactly, but:

1. About 5% of all HCM patients carry at least 2 different cardiomyopathy causing mutations (i. E. Homozyogous or compound heterozygous mutations)

Hypertrophic Cardiomyopathy (HCM)

2. **Environmental effects (sports? Biomechanical stress?)**
3. **Additional diseases (hypertonus? Valve diseases?)**
4. **Age dependent penetrance**
5. **Epigenetic effects (i. E. DNA methylation)**

Hypertrophic Cardiomyopathy (HCM)

6. **Imbalances within a single sarcomere due to the presence of 2 different sarcomeric proteins (i. E. 2 different βMHC with different kinetics and force generation may cause imbalances)**

Hypertrophic Cardiomyopathy (HCM)

What causes the arrhythmias?

Again, not really clear but:

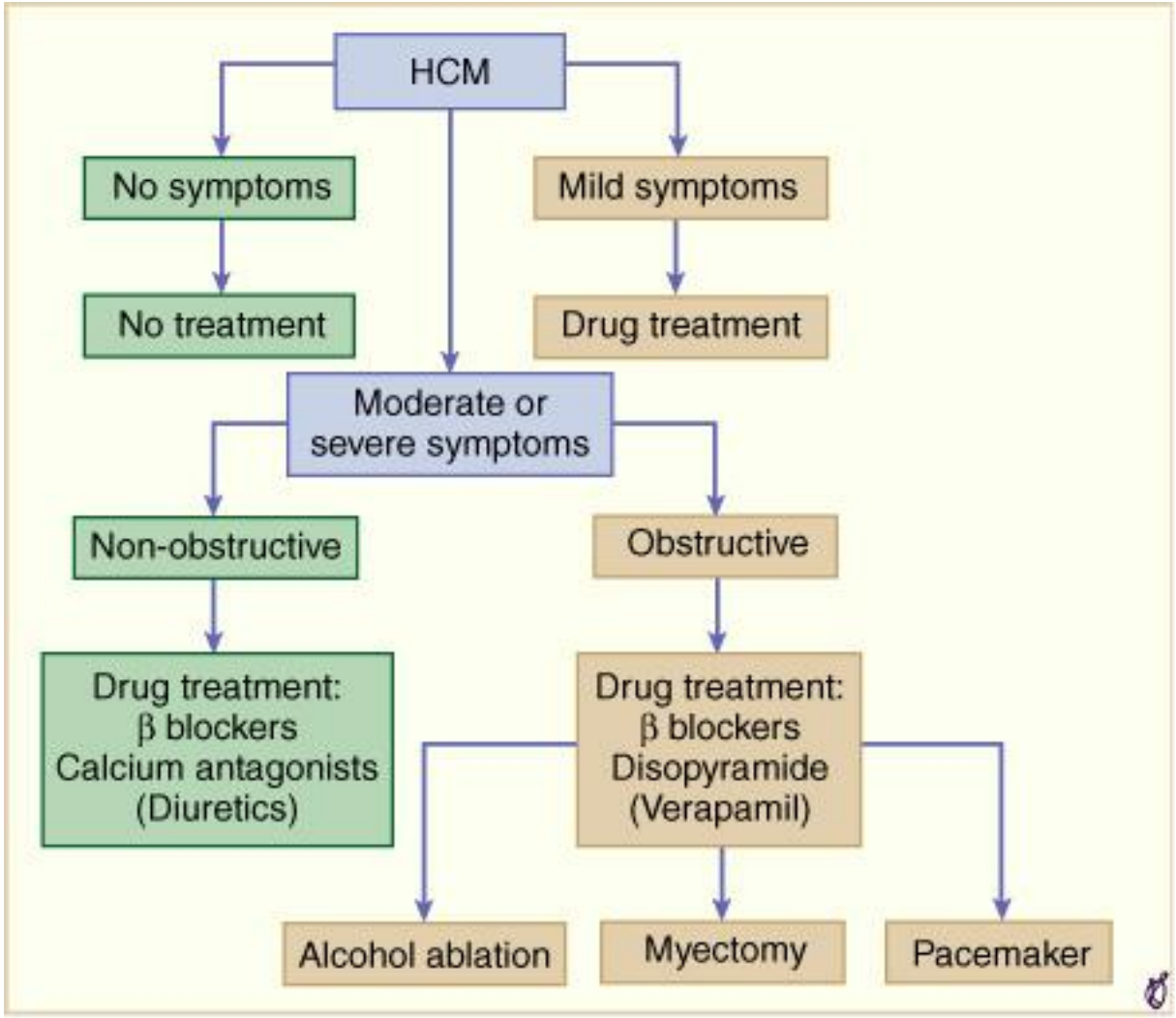
1. **Ischemia is a major trigger for arrhythmias in any cardiac disease**
2. **Mechano-electrical feedback might be affected**

Hypertrophic Cardiomyopathy (HCM)

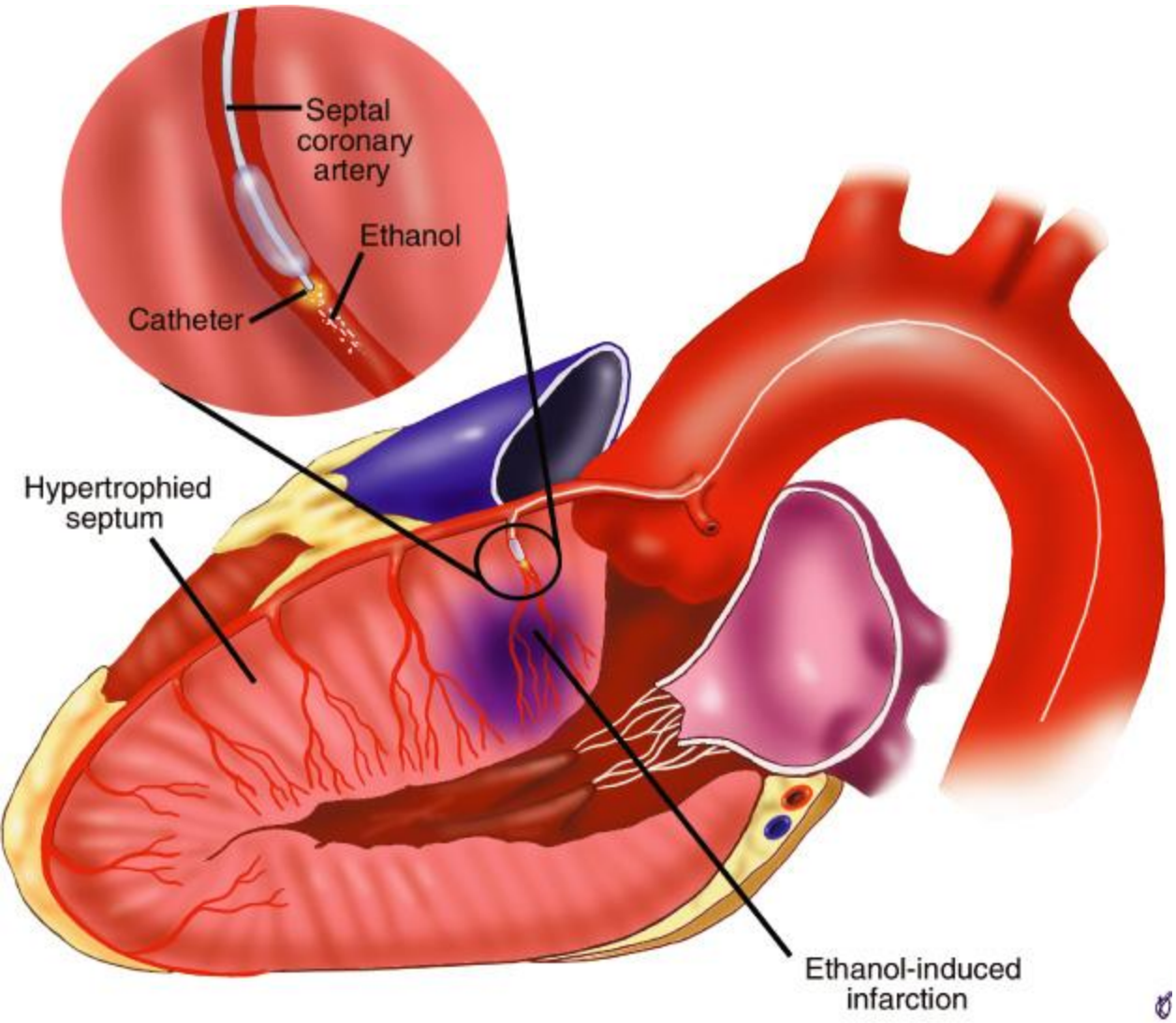
Also unclear how HCM causing mutations are linked to:

1. **Fibrosis?**
2. **Hypertrophy itself?**

HCM - Therapy



Alcohol ablation



Drawing demonstrating technique of ethanol infusion into a septal artery in hypertrophic cardiomyopathy. The insert shows a balloon occluding the septal artery and the alcohol-induced septal infarction.

HCM - Ischemia

TABLE 59–5 Possible Mechanisms for Ischemia in Hypertrophic Cardiomyopathy

Increased Myocardial Oxygen Demand	Reduced Myocardial Perfusion
Myocardial hypertrophy	Small vessel disease
Diastolic dysfunction	Abnormal vascular responses
Myocyte disarray	Myocardial bridges
Left ventricular outflow obstruction	Increased coronary vascular resistance
Arrhythmias	

From McKenna WJ, Behr ER: Hypertrophic cardiomyopathy: Management, risk stratification, and prevention of sudden death. Heart 87:169, 2002.

HCM - Prognosis

TABLE 59–7 Factors Associated with an Adverse Outcome in Hypertrophic Cardiomyopathy

History of sudden cardiac death
Family history of premature death
"Malignant" causal mutations
"Malignant" modifier genes
History of syncope
Magnitude of LV hypertrophy
Extent of myocyte disarray
Extent of interstitial fibrosis
Early onset of disease
Myocardial ischemia on perfusion tomography
Abnormal blood pressure response to exercise
Nonsustained VT on Holter monitor
LV outflow tract obstruction

LV = left ventricular; VT = ventricular tachycardia.

Adapted from Marian AJ: On predictors of sudden cardiac death in hypertrophic cardiomyopathy. J Am Coll Cardiol 41:994, 2003.

Thank you very much
for your attention

Hypertrophic Cardiomyopathy (HCM)

- Mutations in the following genes have been found in HCM:

1. Chr. 10, β Myosin heavy chain (MYH 7)
2. Chr. 1, cardiac troponin T (TNNT2)
3. Chr. 15, α-Tropomyosin (TMSA)
4. Chr. 11, Myosin Binding protein C (MYBPC 3)
5. Chr. 3, essential myosin light chain (MYL 3)
6. Chr. 12, regulatory myosin light chain (MYL 2)
7. Chr. 19, cardiac troponin I (TNNI 3)
8. Actin
9. Titin
10. α Myosin heavy chain