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Myocardial Mechanics & Hypertrophic Cardiomyopathy

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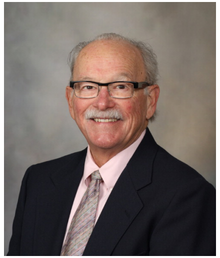
If I have seen further, it is by standing on the shoulders of giants – *Sir Isaac Newton*

Marek Belohlavek MD PhD
Biomedical Engineering



James Greenleaf PhD
Biomedical Engineering

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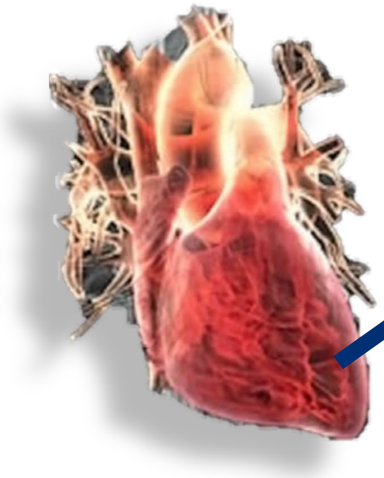
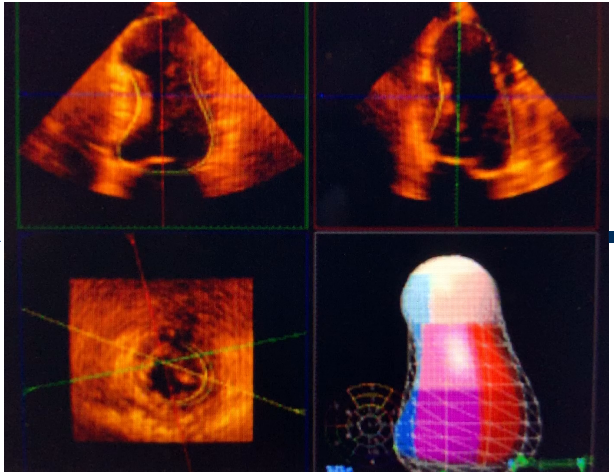
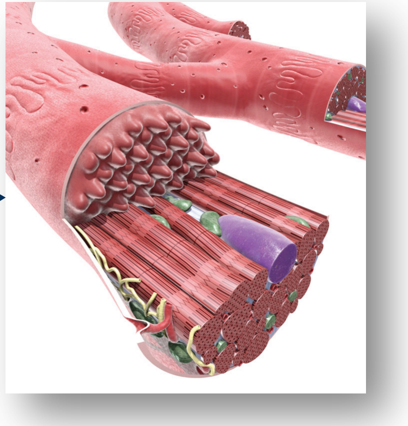
Johns Hopkins HCM Center of Excellence Team

Heart is a Mechanical Pump







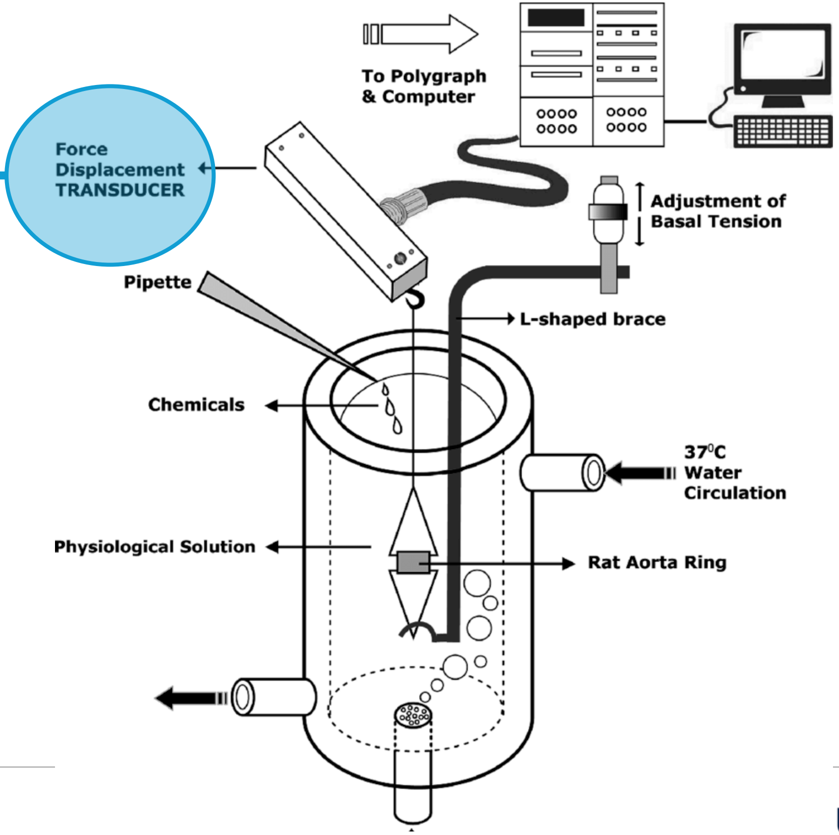
Heart is a pump
William Harvey

Clinically measure
chamber function

Ignores the muscle
No easy method

Direct Measurement of Muscle Function

Isolated cardiac muscle strips



Muscle Physiology

Length-tension

Velocity of shortening

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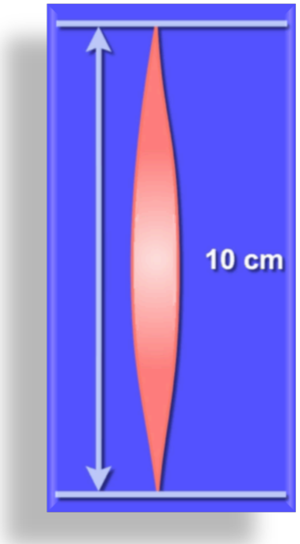
Heart is a Mechanical Pump



Cyclic changes in Length & Thickness

Length Change — Strain

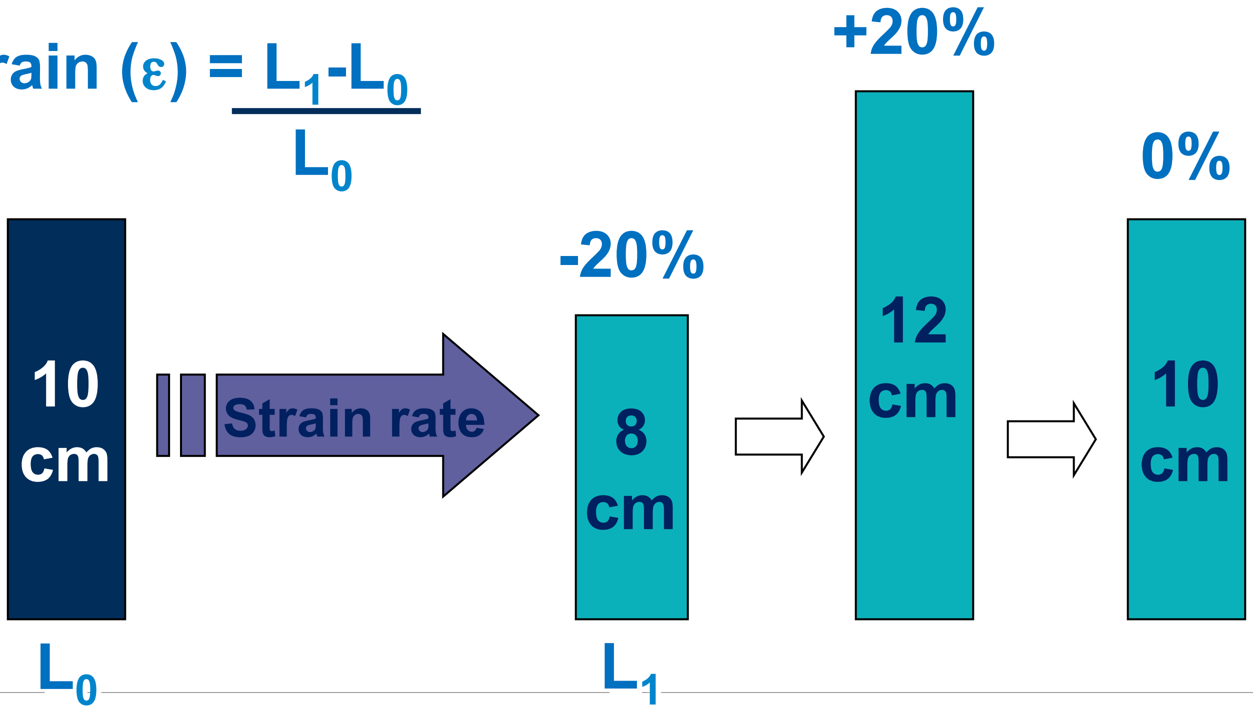
Rate of Length change — Strain Rate

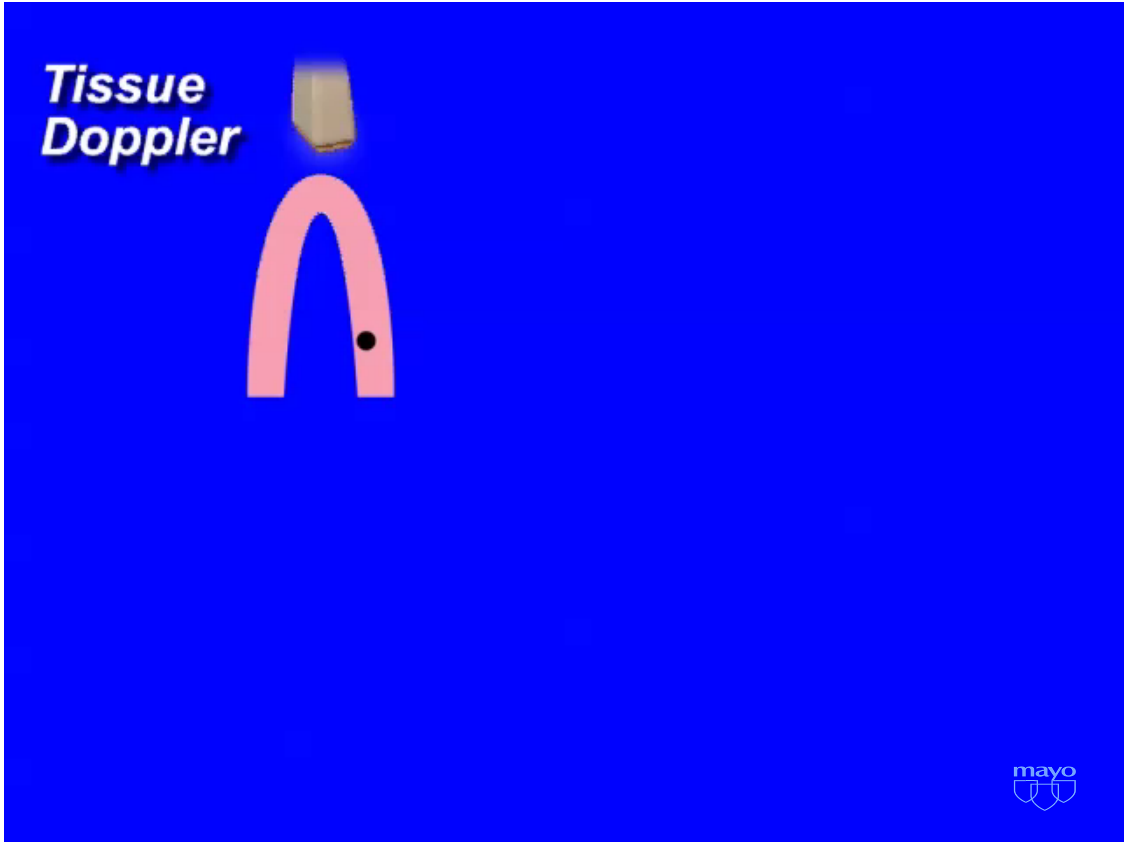
Events can be quantified

Strain used to describe elastic properties of cardiac muscle

Mirsky & Parmley 1973

$$\text{Strain } (\varepsilon) = \frac{L_1 - L_0}{L_0}$$





Displacement: tracks motion of a single point

Deformation: tracks 2 or more points in a segment – length change

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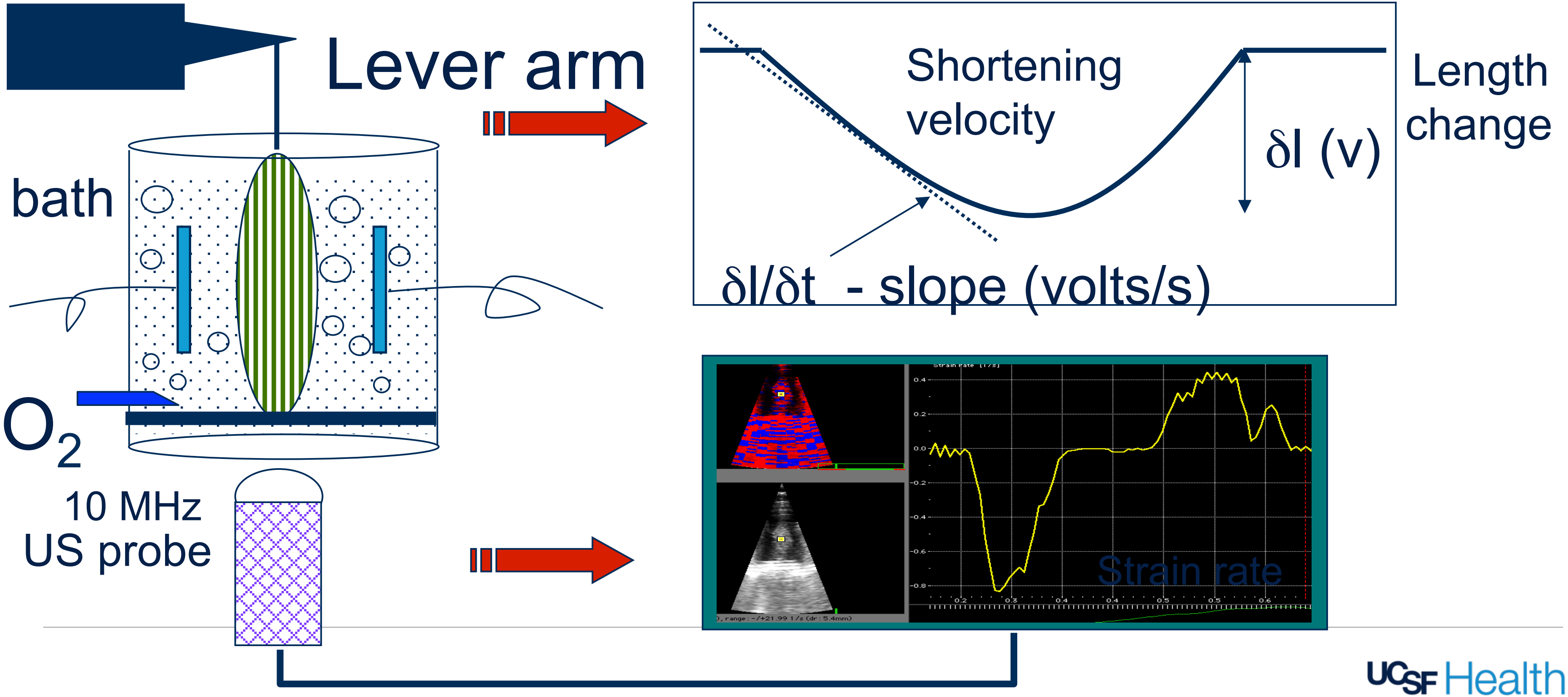
In vitro cardiac muscle – Simultaneous strain echocardiography and mechanics



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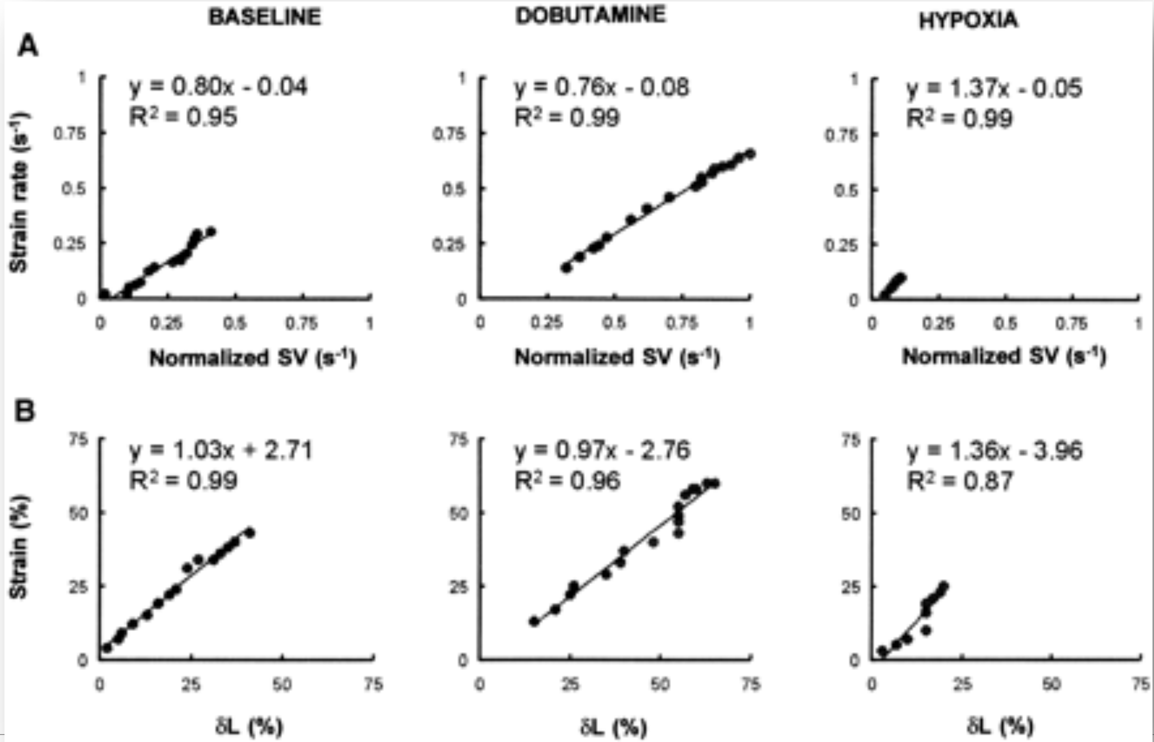
Validating Ultrasound-based strain

Ultrasound measurements correlate closely with muscle length change



Abraham 2003

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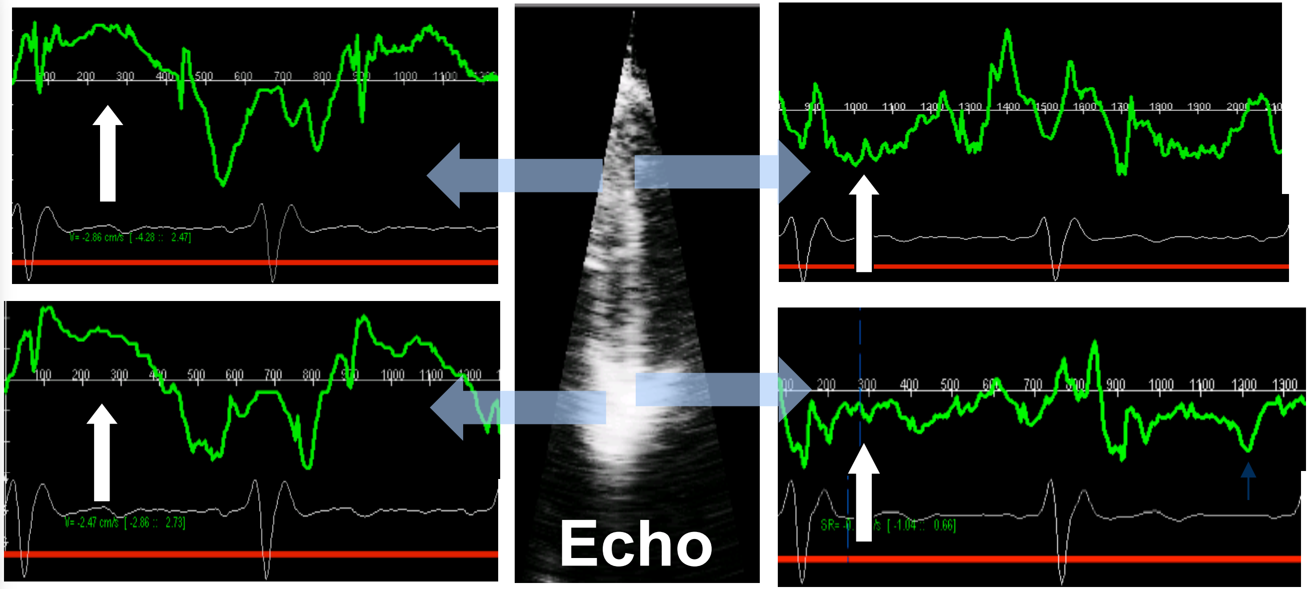
Deformation (Strain) is less susceptible to tethering

- Advantage in regional pathologies – testing in HCM model



TDI - Displacement

Strain - Deformation

Abraham 2002

Hypertrophic Cardiomyopathy

COMMON Inherited heart disease

?1:300 regardless of sex & ethnicity

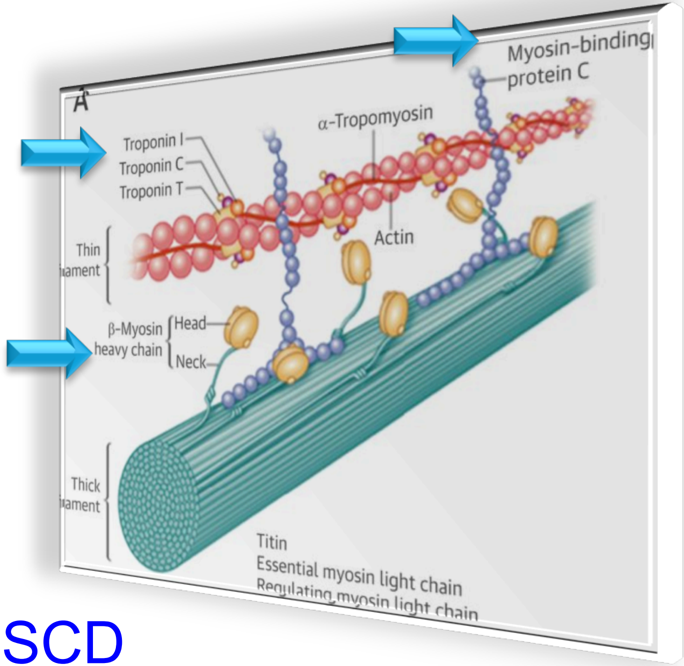
Gene MUTATIONS

Sarcomeric proteins

VARIABLE presentation

Healthy – Angina – HF – Arrhythmias – SCD

Most common cause of SCD in Athletes



Semsarian 2015

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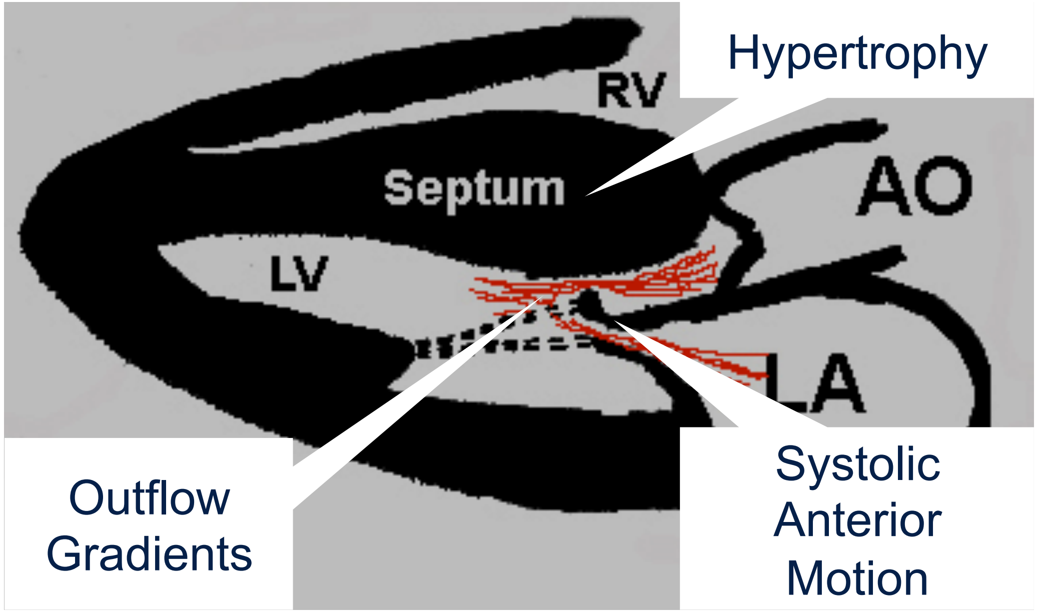
Hypertrophic Cardiomyopathy

Key Features

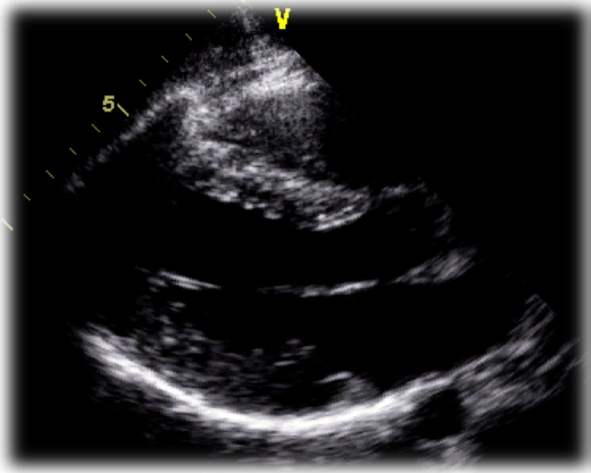
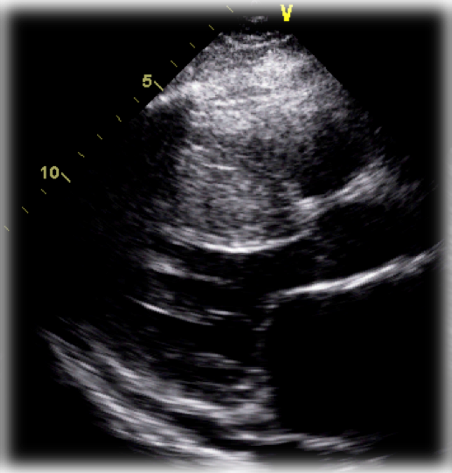
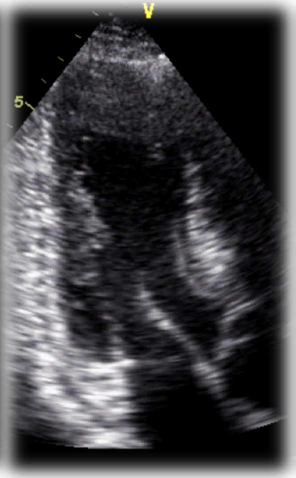
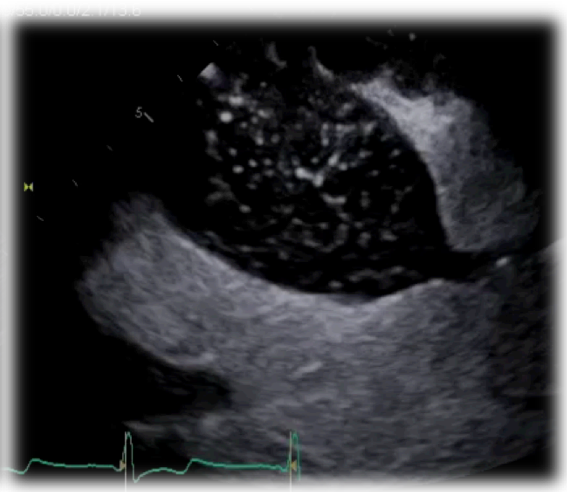
Variable Phenotype

- **Hypertrophy**
  Degree - Location
- **SAM**
  Presence - Absence
- **Gradients**
  Present - Rest - Exercise
- **Function – mostly normal**



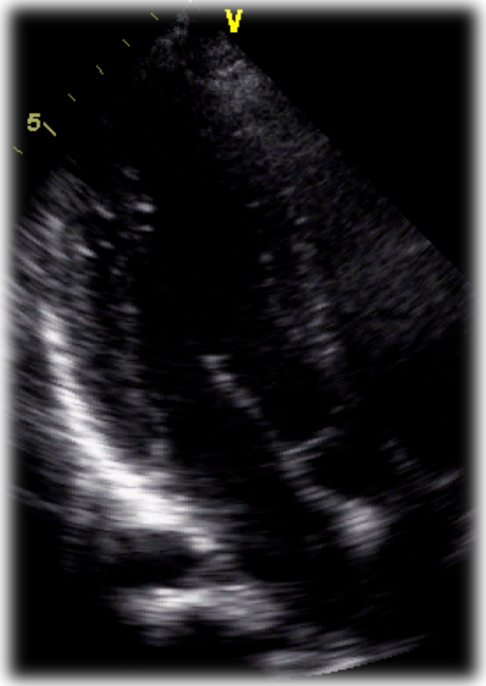
Strain uniquely suited for HCM Evaluation

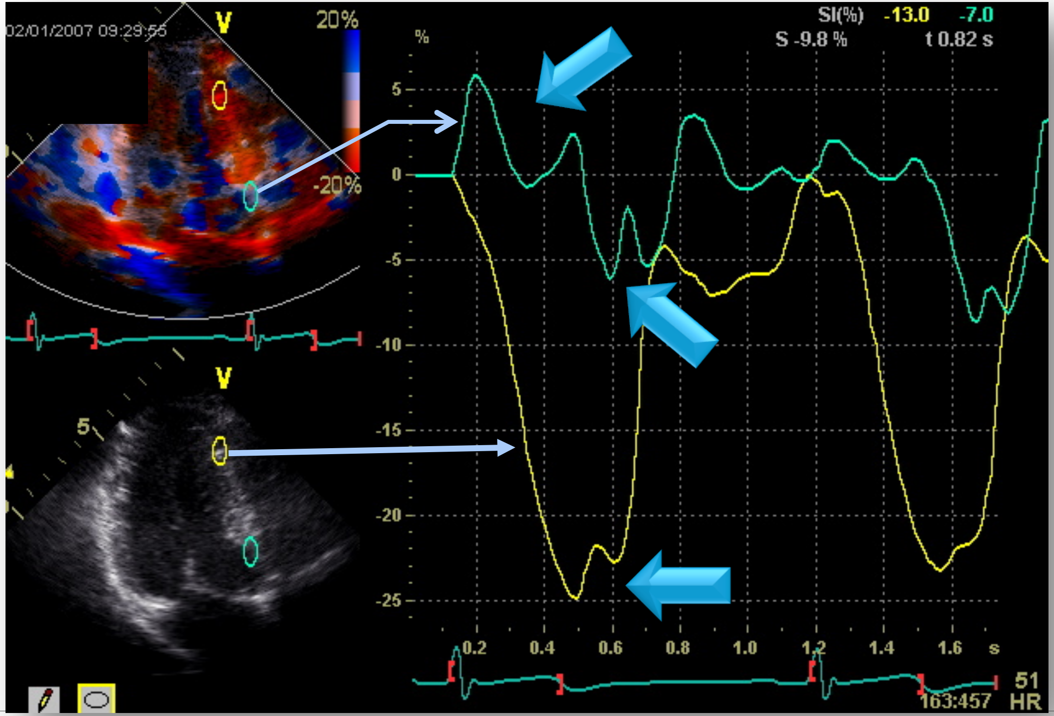
Overt Regional and Global Function normal at rest and stress – regardless of morph

Strain uniquely suited for HCM eval

Normal Regional and Global Function – Regional Mechanics/strain abnormality





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Racial differences in HCM phenotype?

Lars Sorensen

Prevalence similar to Whites

↓

High rates of SCD

↓

Low diagnosis rates

Blacks have high SCD rates but low Rx rates

Clinical
Imaging
Mechanics

Maron 1995; Maron 2003; Movahed 2010

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HCM in Blacks vs. Whites – ? SCD profiles

Clinical and Echo Characteristics

Differences

- Hx HTN (NS)
- ↑ Angina
- Rest/stress gradients ↓
- Exercise time ↓

Similarities

- Dyspnea
- Syncope
- NYHA class
- IVS thickness
- EF/DD grade

Sudden Death Risk Profile

	African-American (68)	Caucasian (161)	Total (229)	P-value
Syncope	21%	14%	16%	0.19
ABPR	33%	29%	30%	0.57
NSVT (Holter)	20%(n=40)	22%(n=102)	21%	0.84
Fam Hx SCD	11%	14%	13%	0.54
Wall ≥3 cm	15%	6%	9%	0.04
≥1 risk factor	60%	55%	56%	0.42
Hx SCD	5%	3%	4%	0.60

Morphology, Function and Mechanics

- **Hypertrophy**
  Similar Degree – Different Location
- **SAM**
  Less Frequent
- **Gradients**
  Not Elevated
- **Function**
  EF normal
  Worse myopathy

	AA (68)	C (161)	Total	p-
Max Wall	2.2±0.6	2.1±0.5	2.1±0.5	0.25
LVEF (%)	65±8	66±10	65±10	0.47
Apex	1.1±0.5	0.9±0.4	0.9±0.4	0.01
Apical LVH	27%	7%	13%	<0.001
Apical HCM	10%	3%	5%	0.02
GLS	13.9±3.5	15.7±3.2	15.2±3.4	0.003

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Possible Reasons for low DIAG rates

Summary and Clinical Management Pointers

Key HCM features less frequent

- LESS septal hypertrophy
- LESS SAM
- LESS LVOT obstruction

LVH attributed to Hypertension

- Patterns of LVH

Low threshold for Advanced Imaging

Contrast Echo
CMR

BP monitoring

Screen Family

Genetics

How important is OBSTRUCTION in HCM?

Is Non obstructive HCM truly benign?

Prevailing view – HCM is a disease of OBSTRUCTION

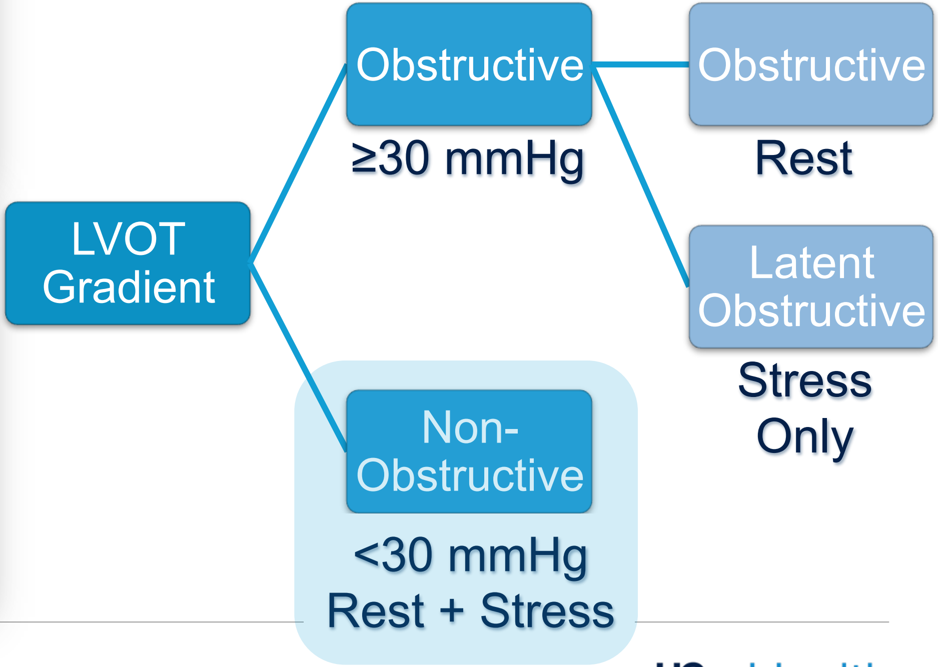
Iraklis Pozios

STATE-OF-THE-ART REVIEW 2014

Hypertrophic Cardiomyopathy

Present and Future, With Translation Into Contemporary Cardiovascular Medicine

HEART FAILURE WITHOUT OBSTRUCTION. About one-third of HCM patients have the nonobstructive form with absent or small (<30 mm Hg) outflow gradients at rest and with physiological exercise (16). The majority of nonobstructive HCM patients experience a relatively stable clinical course without significant symptoms, high-risk profile, or the necessity of major treatment options (111).



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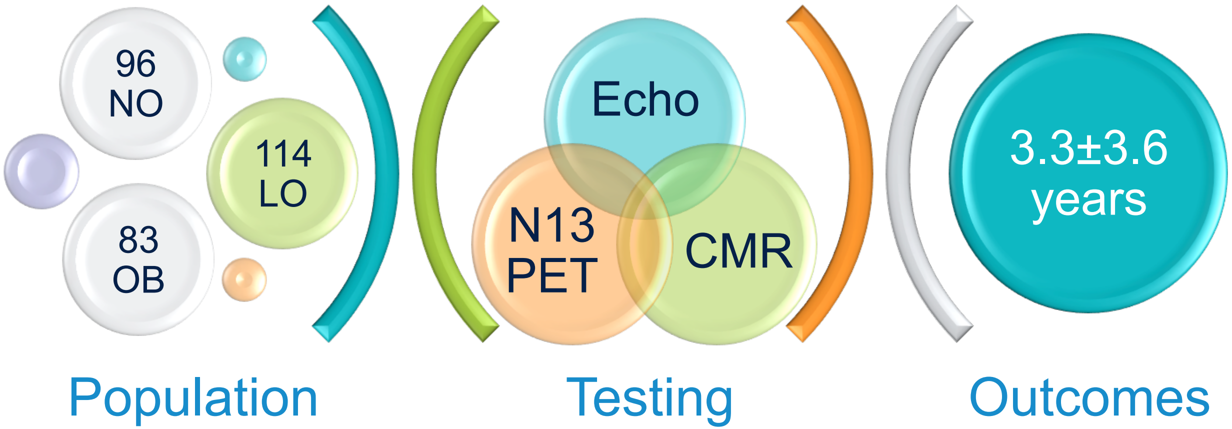
Study Population (n~300)



No Differences
Max LV thickness
EF
Diastology
Obs-HCM
Larger LA size
Higher E/e’ ratio

- OBS HCM – older; more NYHA II
- Non OBS HCM – Hx of VT/VF; NSVT;
- No differences – FU period; men; angina; SCD risk factors; βB use

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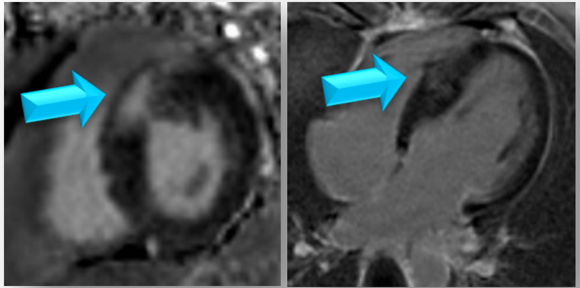
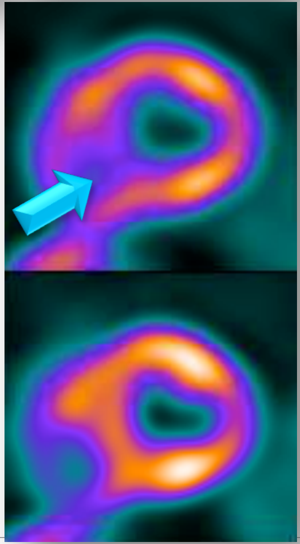
Scar Burden + Microvascular Ischemia

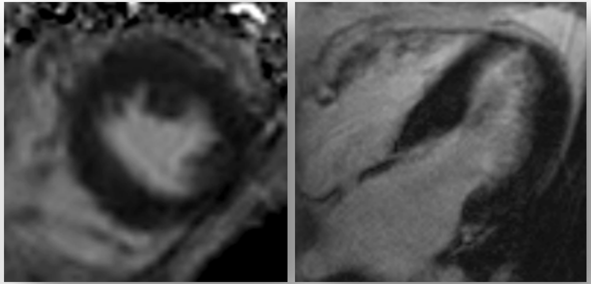


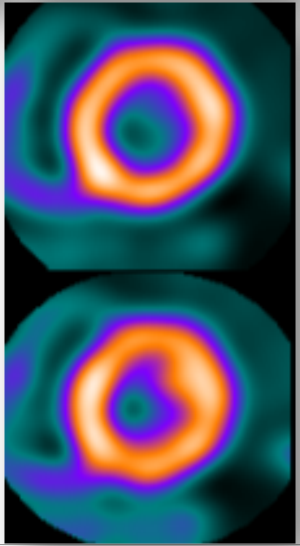


Scar
(n=77)
21% LVM
≥20% = 30%

Ischemia
(n=34)
SDS≥2
82%

Non Obs

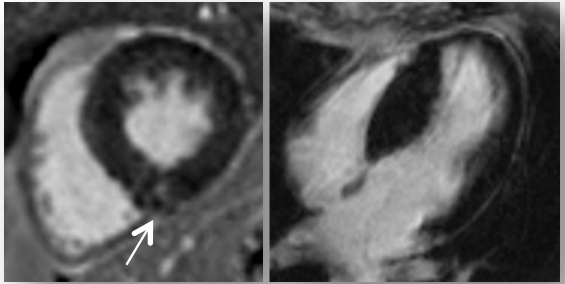


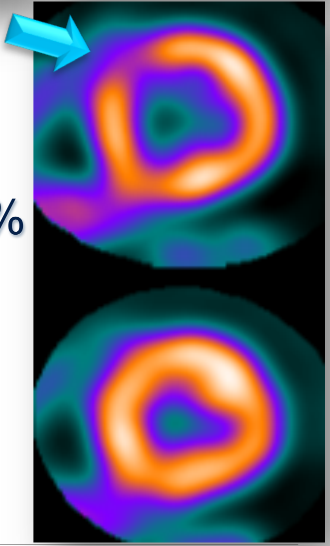


Scar
(n=105)
11% LVM
≥20% = 18%

Ischemia
(n=28)
SDS≥2
54%

Labile





Scar
(n=72)
16% LVM
≥20% = 11%

Ischemia
(n=21)
SDS≥2
76%

Obs

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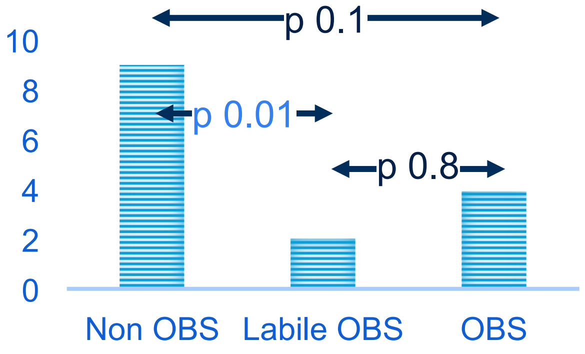
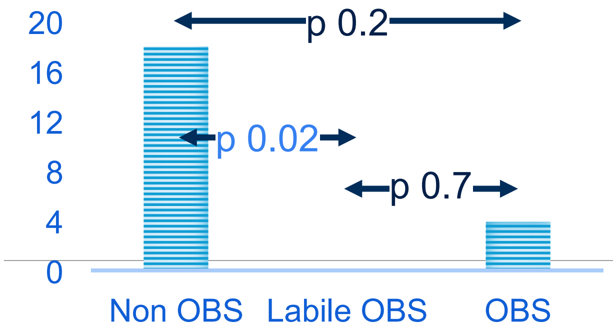
Arrhythmias/Appropriate ICD dc

VT/VF

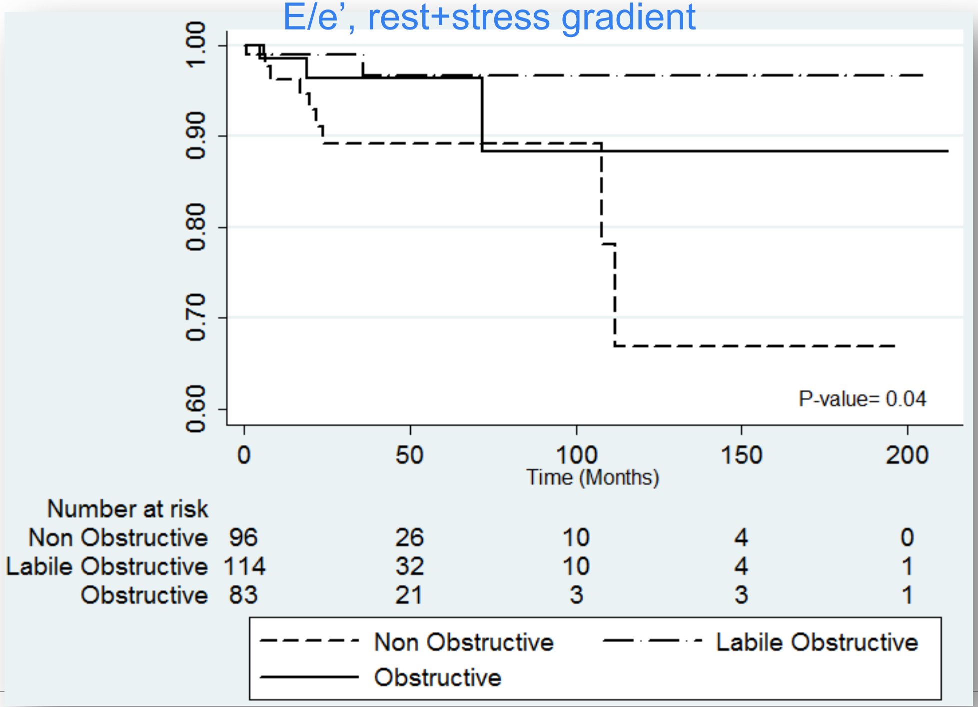


ICD DC



Event Free Survival

After adjusting for NSVT, NYHA, LGE, PET, EF, LA, IVS, E/e', rest+stress gradient



Pozios 2015

	Gradient	LVH	SAM	LGE	Microvas	VT/VF
Non-OBS	< 30	++	(-)	++	+++	+++
Labile-OBS	< 30 rest ≥ 30 stress	++	(-/+)	+	+	+/-
OBS	≥ 30	++	++	+	++	++

Summary observations:

Non obstructive HCM not benign

All need advanced characterization + Risk stratification

Labile possibly benign - ? Less aggressive intervention

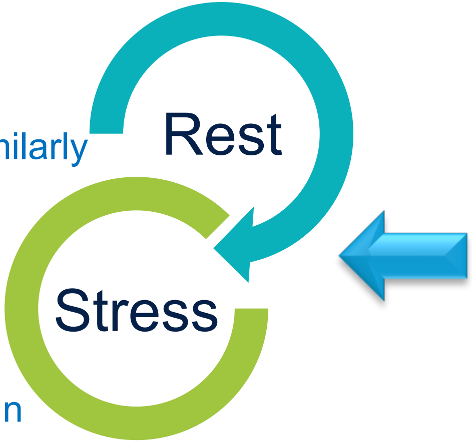
Pozios 2015

Why is Non- OBS HCM not benign?

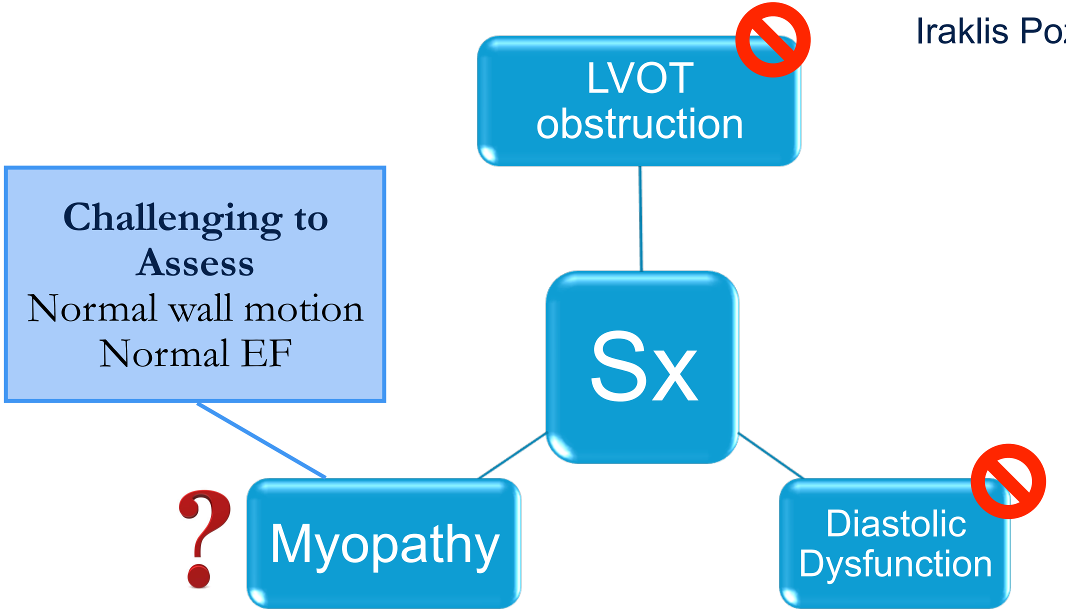
What is the Role of the underlying MYOPATHY?

Iraklis Pozios

Myocardial mechanics similarly abnormal



? Differences in how mechanics responds to stress



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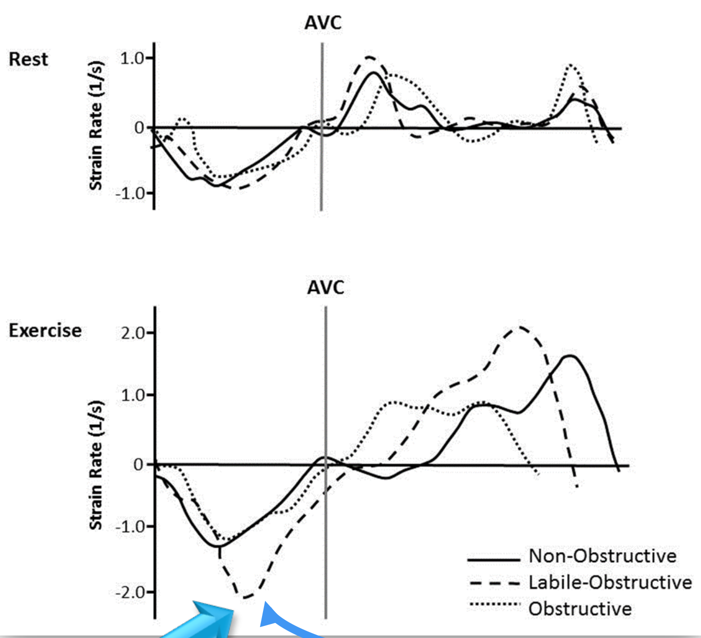
Rest – Stress Response of Myocardial Mechanics in HCM

Stress response blunted in Non-OBS and OBS; normal in LABILE



Matched for

Age, men, BMI, co-morbidities, medications

No differences

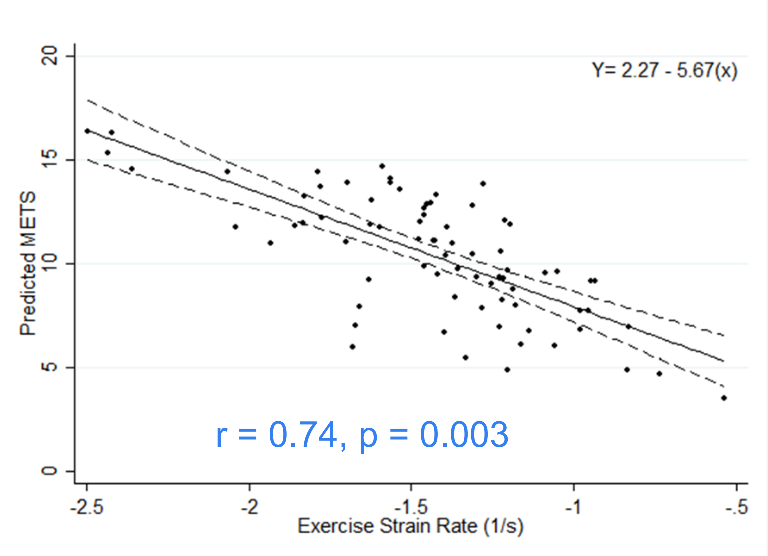
EF, Septal thickness, E/A, E/e', % MPHR

Mechanical Reserve: % augment in regional mechanics with stress

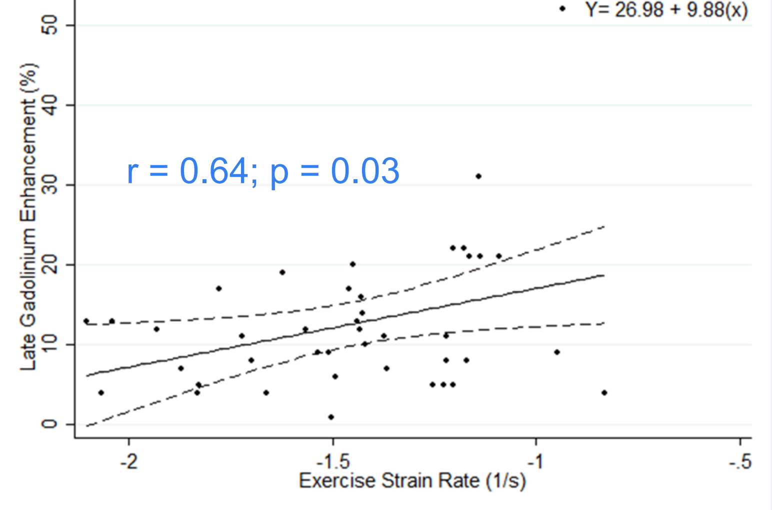
Exercise sSR

Non-OBS HCM – worst stress sSR & worst Mechanical Reserve

Adjusted for age, sex, BMI, rest gradient; E/e ratio



Patients with LGE>15%



- Independently predicts METs
- Correlates (inversely) with LGE
- With PRESERVED EF

Pozios 2017

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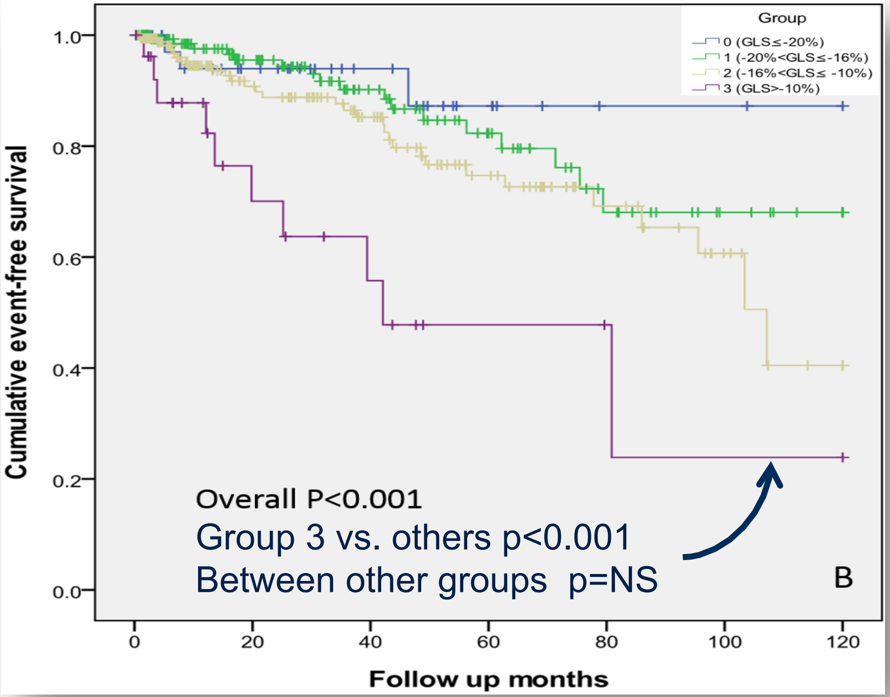
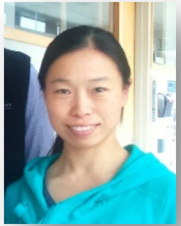
Resting Mechanics predict outcomes?





Hongyun Liu

Composite end point (n=400)

Death

VT/VF

Heart transplant

HF exacerbation

Mechanics vs. Events

Strain <10 poor

>16% better

>20% close to actuarial

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GLS independently predicts outcomes

Rest GLS <10% predicts 3.5x events compared to GLS>16%

Variables	Univariate Cox regression		Multivariate Cox regression	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Sex	0.358 (0.215-0.598)	<0.001	0.446 (0.236-0.841)	0.013
LA	1.691 (1.232-2.321)	0.001	1.472 (1.030-2.104)	0.034
E/e'	1.037 (1.022-1.052)	<0.001	1.106 (0.995-1.038)	0.144
LVOT_rest	1.008 (1.000-1.016)	0.043	1.003 (0.993-1.013)	0.547
NYHA	1.588 (1.101-2.289)	0.013	1.290 (0.849-1.960)	0.233
GLS -10% vs. <-16%	4.632 (2.164-9.915)	<0.001	3.541 (1.457-8.602)	0.005

p = NS for Age, BMI, EF, E/A, stress LVOT, IVS, Fam Hx, Hx SCD

Liu 2017

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Myocardial Mechanics in HCM

Unique role given overt normal function – substantial mechanical abnormalities

Myocardial Mechanics → **Echo Strain** → **HCM Physiology**

- Non Invasive **Strain**
- Quantitative
- Sensitive
- Superior to EF/WM

→

- Similar to Physio
- Deformation superior in regional pathology

→

- Racial Difference
- Non OBS not benign
- Outcomes in HCM
- Risk Assessment
- ? New Mx approach

***Ongoing**: Mouse models; treatment effects; metabolic function; personalized/precision medicine*

It takes a village……..

Aurelio Pinheiro
Lea Dimaano
Hsin-Yueh Liang
HongChang Luo
Hong-yun Liu
Dai-yin Lu
Lars Sorensen
Iraklis Pozios
Ioannis Ventoulis
Styliani Vakrou
Berekete Haileselassie
Fatih Yalcin

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Informatics Sciences
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