Challenges in the management of genotype positive/phenotype negative HCM/NDLVC patients

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Definition

genotype

noun [C] • BIOLOGY • specialized

UK /ˈdʒiː.nə.taɪp/ **UK** /ˈdʒen.ə.taɪp/ **US** /ˈdʒiː.noʊ.taɪp/ **US** /ˈdʒen.oʊ.taɪp/

Add to word list

the particular type and arrangement of genes that each person, animal, plant, or organism has:

phenotype

noun [C] • BIOLOGY • specialized

UK /ˈfiː.nəʊ.taɪp/ **US** /ˈfiː.noʊ.taɪp/

Add to word list

the physical characteristics of something living, especially those characteristics that can be seen

Cambridge Dictionary

Considerations in genotype+/phenotype- patients

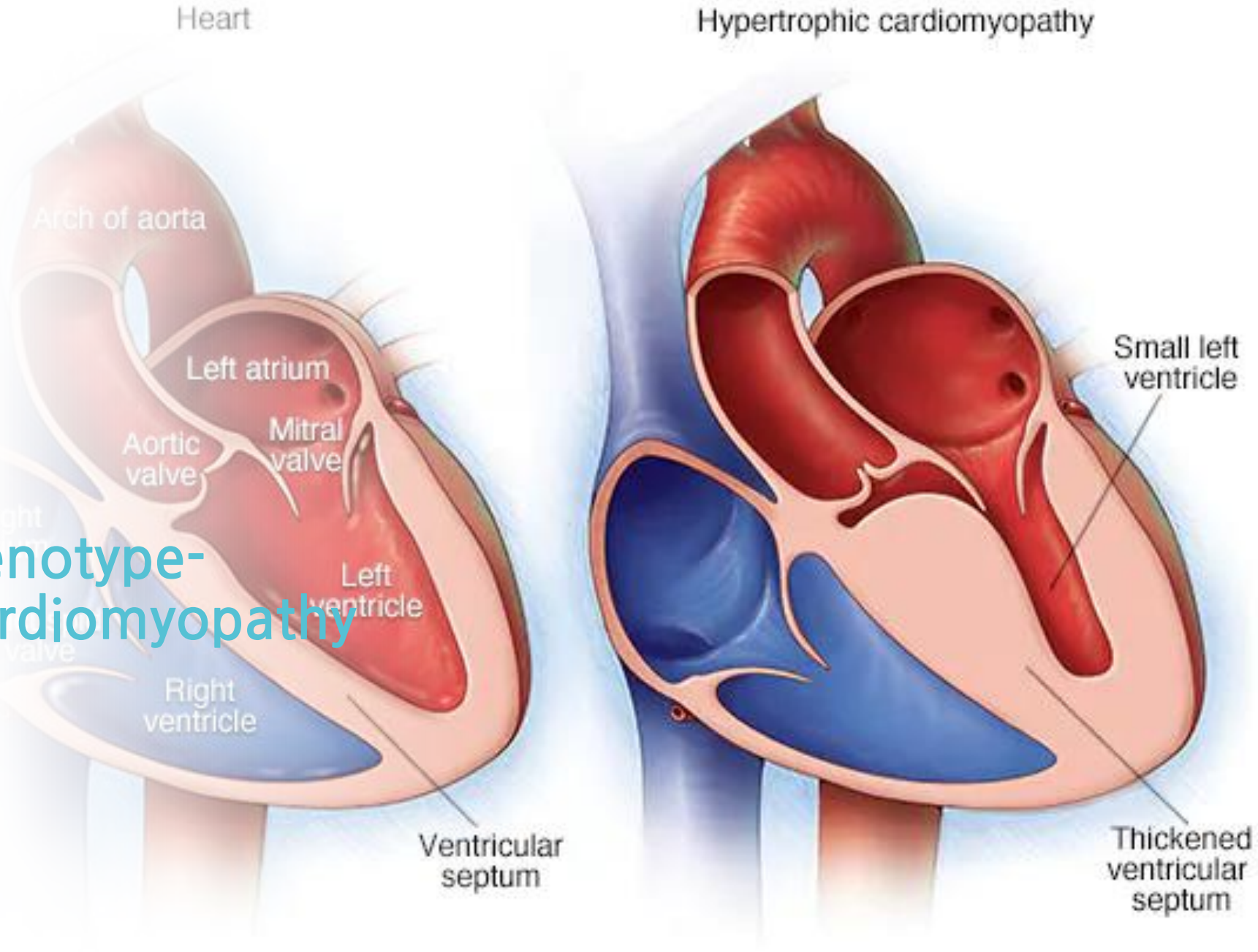
Risk of SCD and ventricular arrhythmias

Exercise recommendations

Preventative treatments

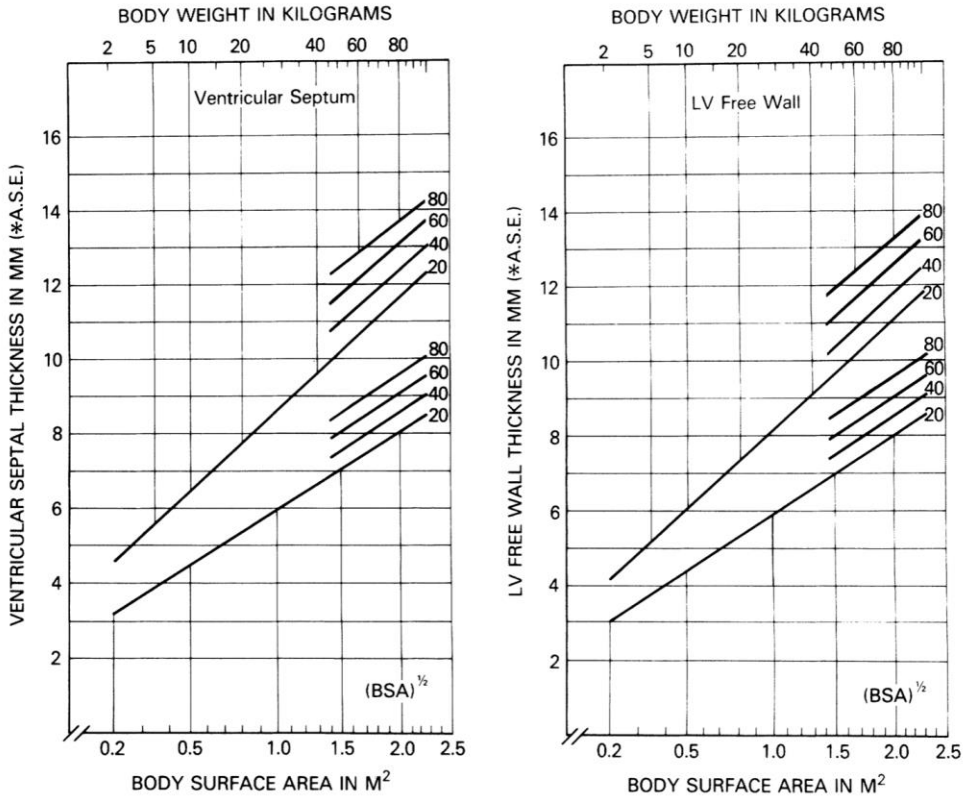
Follow up modalities used and planned interims

Genotype+/phenotype-
hypertrophic cardiomyopathy



Diagnostic criteria for HCM

- In an adult, HCM is defined by a **wall thickness ≥15 mm** in one or more LV myocardial segments—as measured by any imaging technique (echocardiography, CMR or CT)—that is not explained solely by loading conditions.
- In first-degree relatives of HCM patients, diagnosis is based on the presence of **LVH ≥13 mm**.
- The presence of other features (abnormal TDI, ECG, SAM etc.) is **non-diagnostic** but suggestive of early disease expression.



Henry WL, et al. Circulation. 1980.

Prevalence of HCM

Clinical prevalence

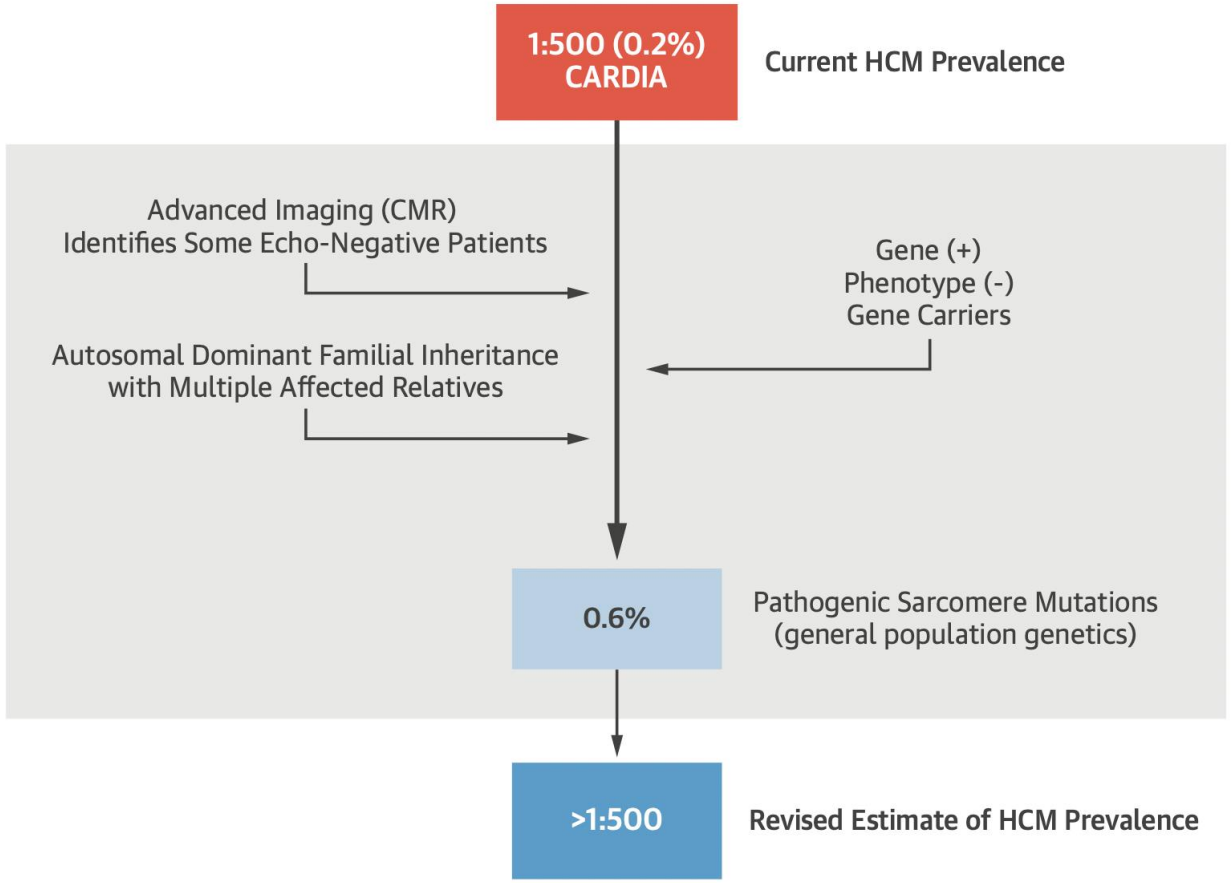
1/500

Variant prevalence

1/200

Semsarian C, et al. J Am Coll Cardiol. 2015.

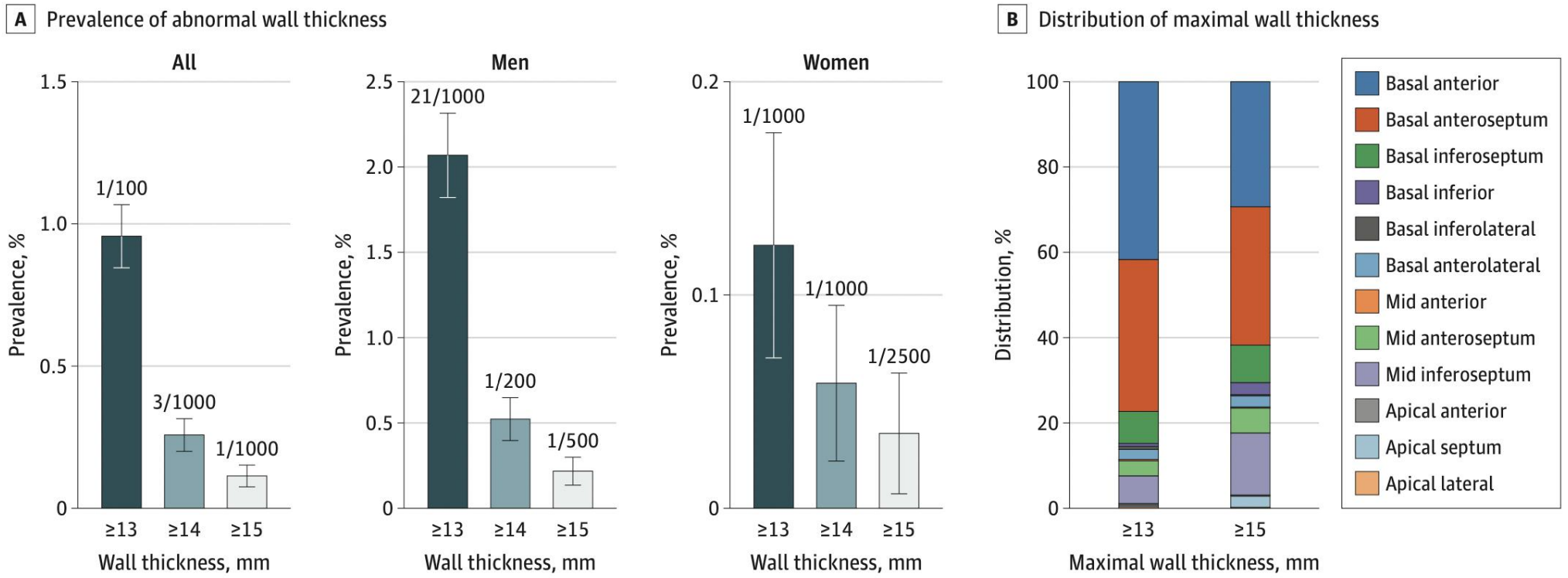
Potential reasons for the genotype/phenotype discrepancy



Semsarian C, et al. J Am Coll Cardiol. 2015.

Are the wall thickness criteria incorrect?

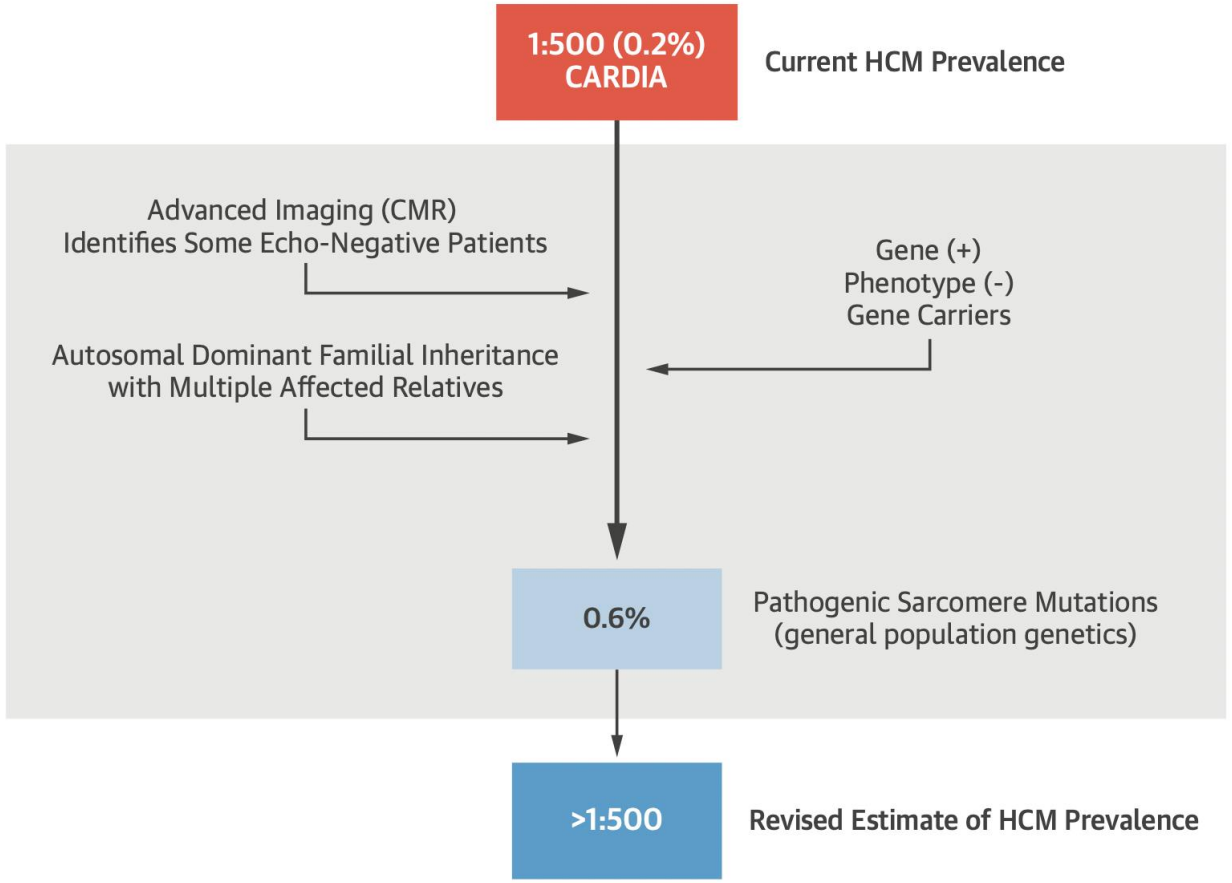
Figure. Prevalence of Left Ventricular Hypertrophy and Distribution of Maximal Wall Thickness



The value above each bar corresponds to the proportion of individuals with maximal wall thickness greater than the threshold value.

Lopes LR, et al. JAMA Cardiol. 2021.

Potential reasons for the genotype/phenotype discrepancy

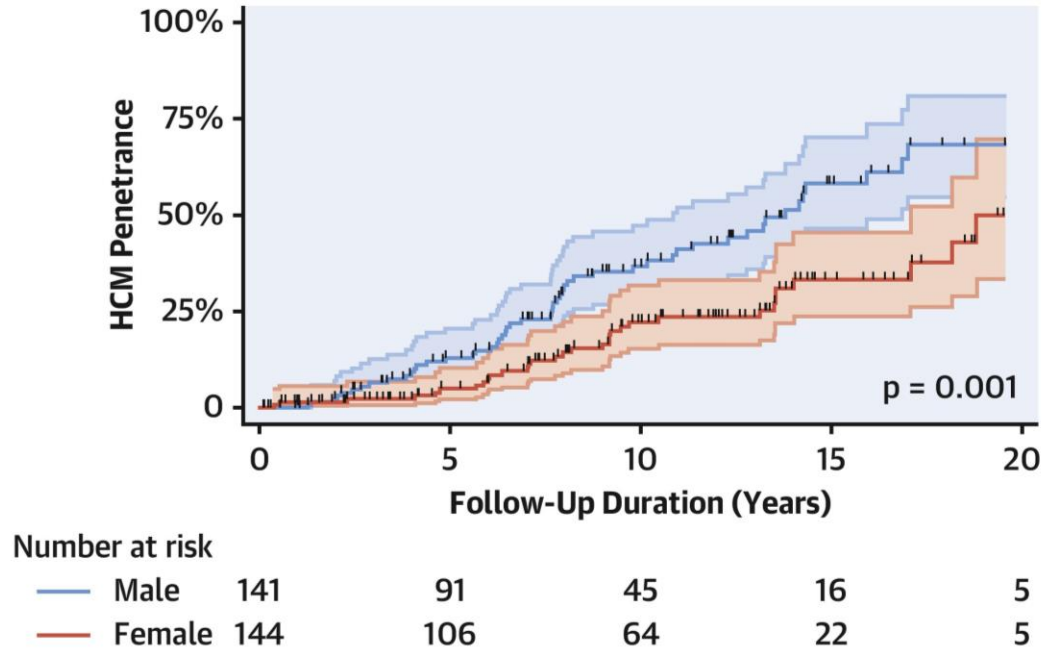


Semsarian C, et al. J Am Coll Cardiol. 2015.

Penetrance in HCM

285 adult and pediatric carriers of pathogenic/likely pathogenic sarcomere protein variants with no hypertrophic cardiomyopathy (HCM)

Penetrance of HCM at 15-year follow-up: 46% (95% CI: 38%-54%)



Risk factors for HCM

Male
HR: 2.91
(95% CI: 1.82-4.65)

Abnormal ECG
HR: 4.02
(95% CI: 2.51-6.44)

Lowest risk for HCM

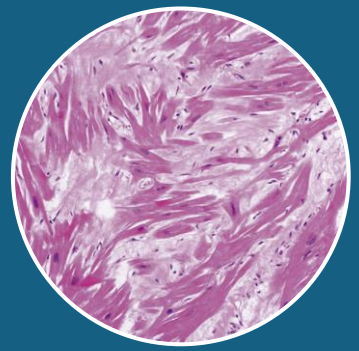
TNNI3 variants
HR: 0.19
(95% CI: 0.07-0.55)

Lorenzini M, et al. J Am Coll Cardiol. 2020.

From genotype to fulfilling criteria for HCM

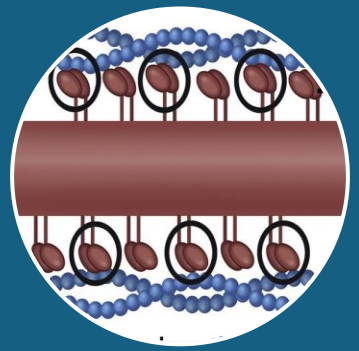
Genetic substrate

- Sarcomeric
- Non-sarcomeric
- ?Polygenic disease
- Epigenetics



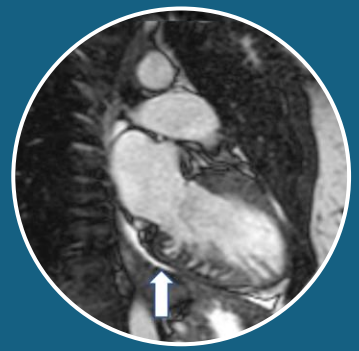
Microscopic changes

- Cell hypetrophy
- Disarray
- Small vessel disease
- Diffuse fibrosis
- Replacement fibrosis



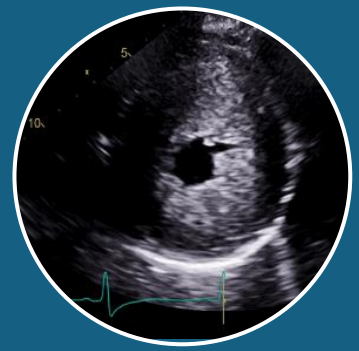
Functional changes

- Hypercontractility
- Ischemia due to hypoperfusion and supply/demand mismatch
- Diastolic dysfunction



Preclinical changes

- ECG abnormalities
- Mitral valve and apparatus abnormalities
- Myocardial crypts



Hypertrophic cardiomyopathy

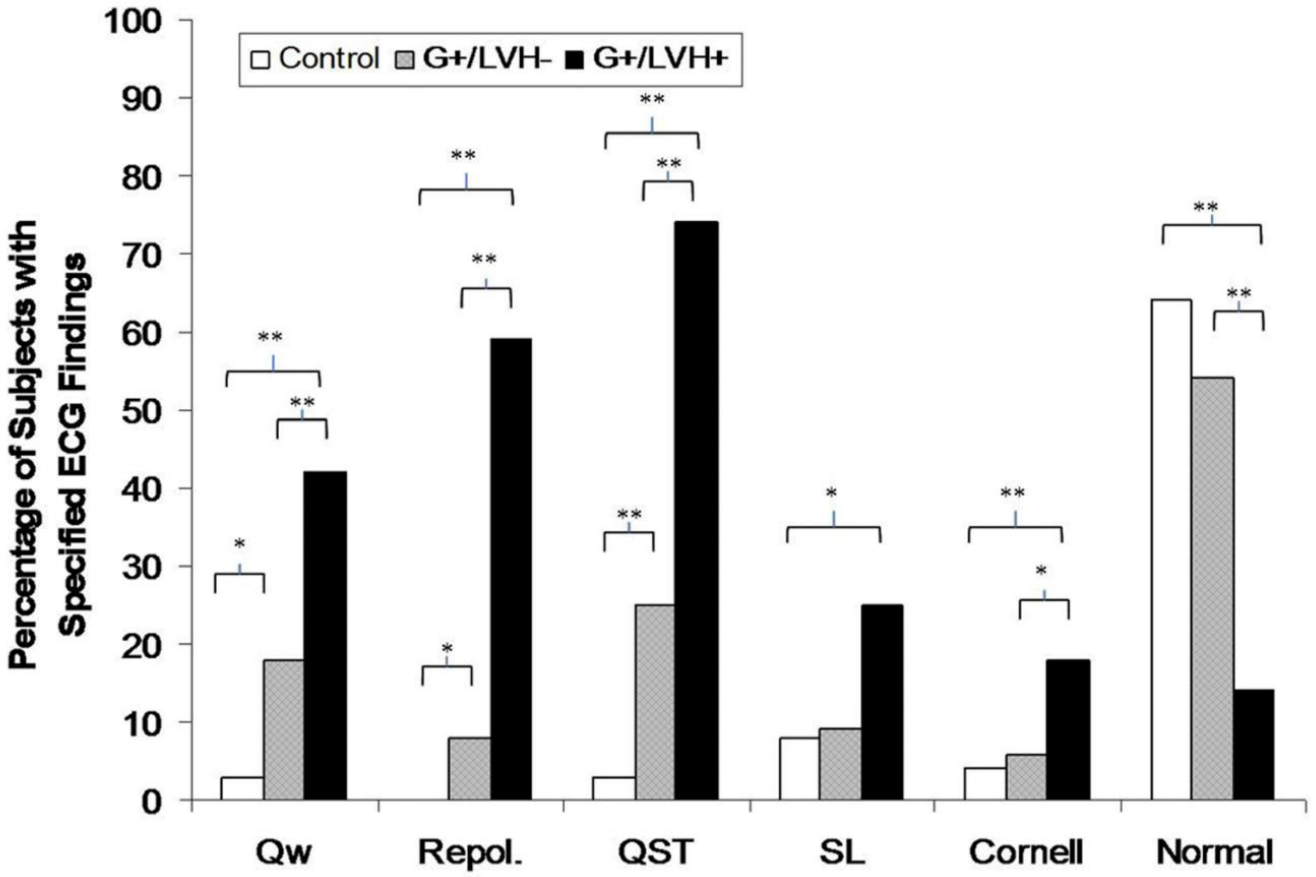
- Hypertrophy

A craftsman is only as good as his tools.

-Anonymous

Are genotype negative patients truly phenotype negative?

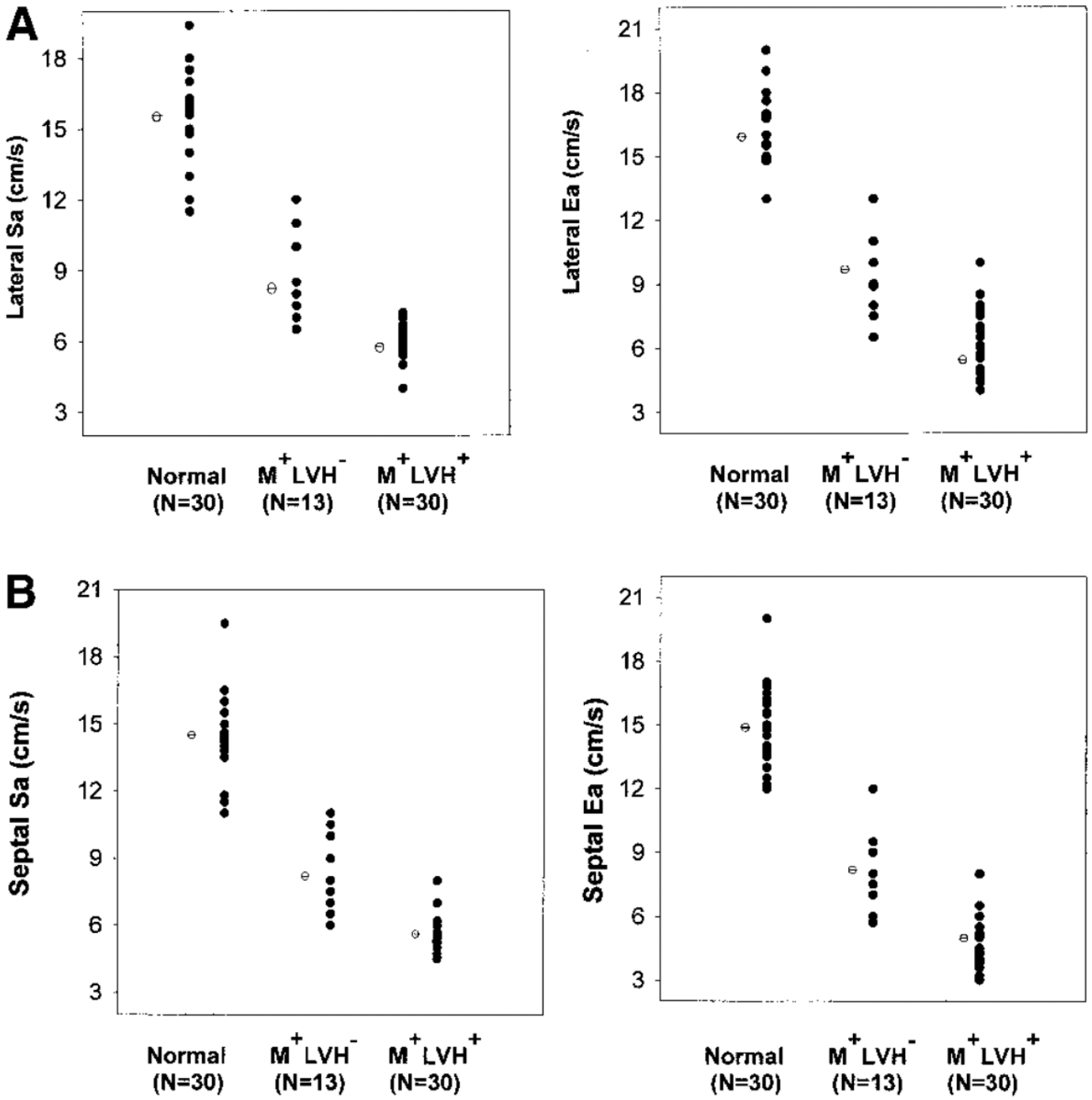
ECG abnormalities



Lakdawala NK, et al. Am J Cardiol. 2011.

Are genotype negative patients truly phenotype negative?

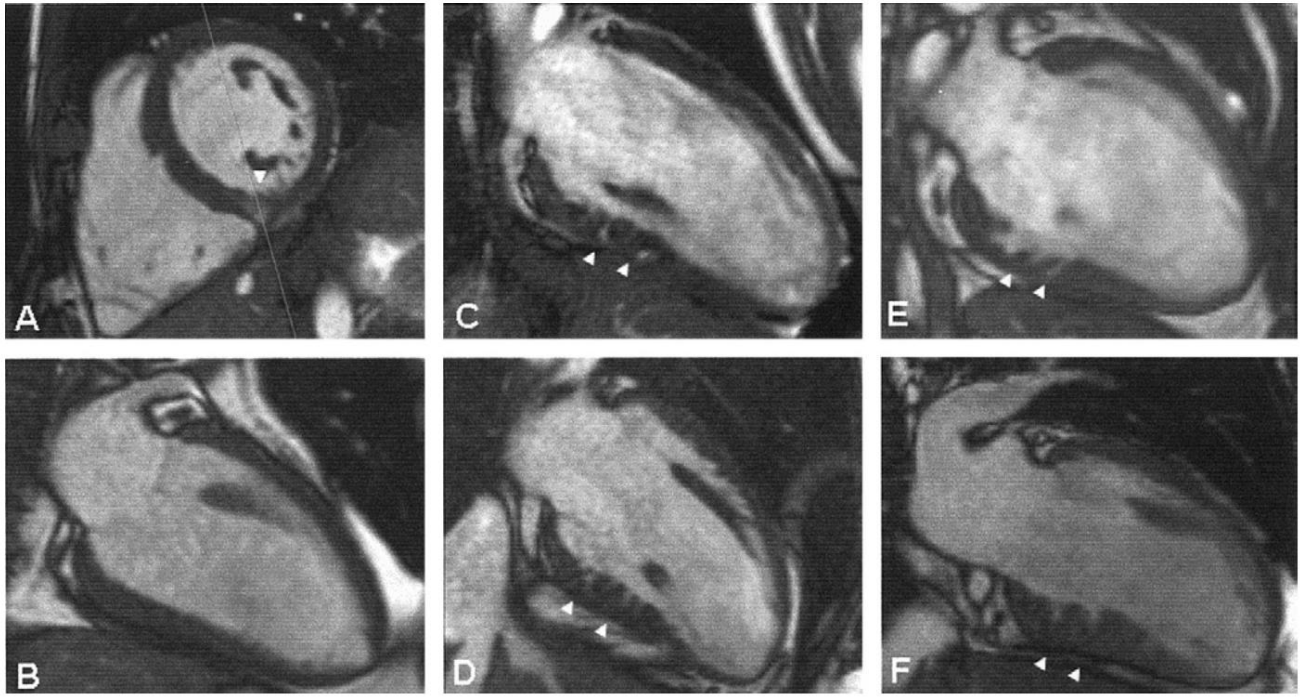
Myocardial mechanics

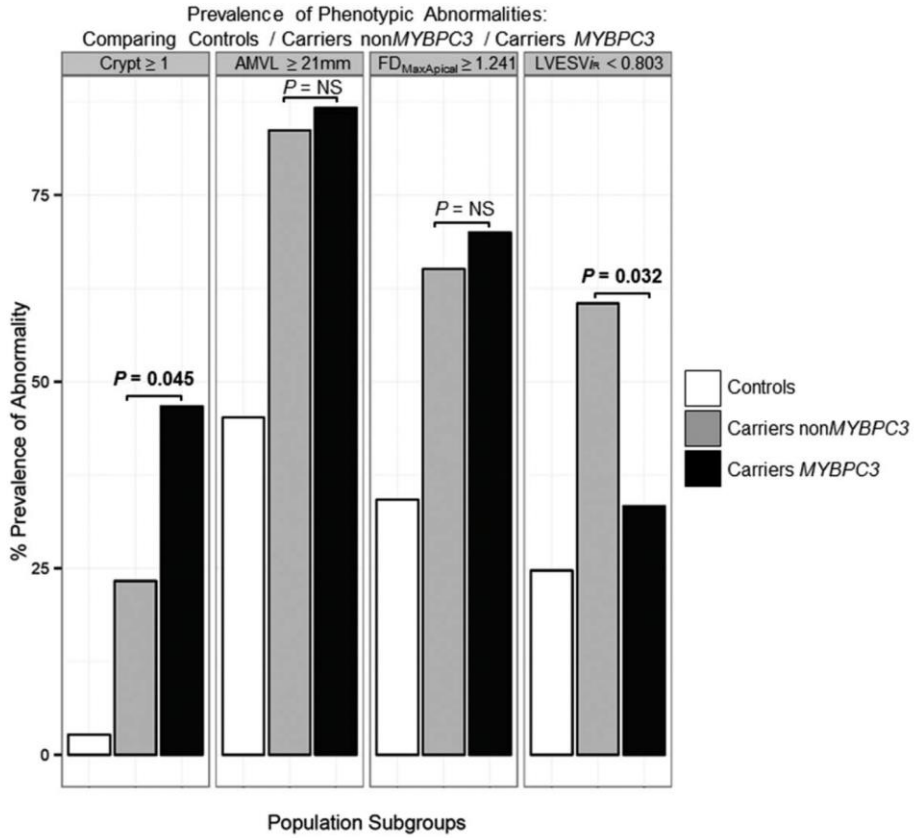


Nagueh SF, et al. Circulation. 2001.

Are genotype negative patients truly phenotype negative?

Myocardial crypts

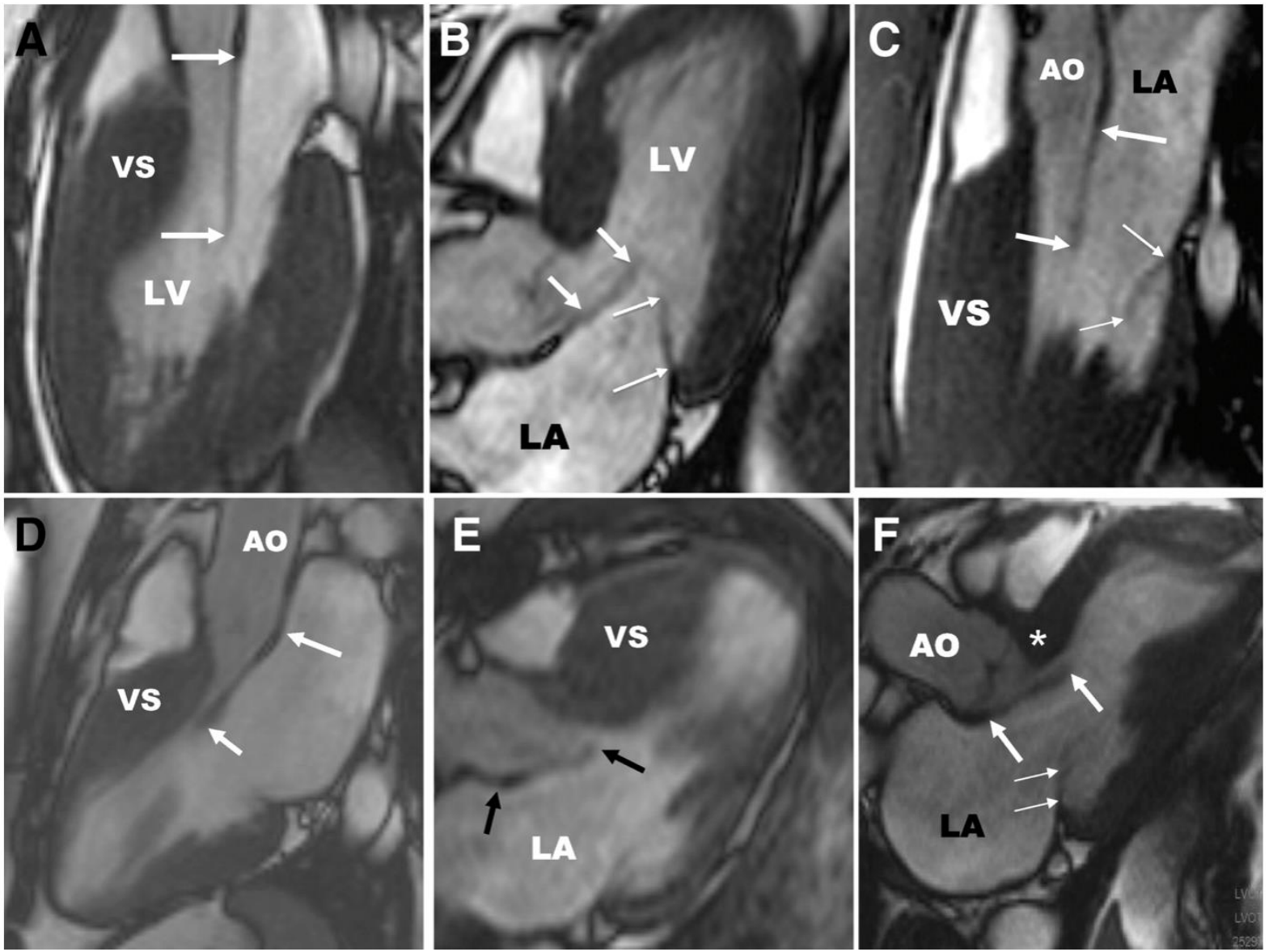




Germans T, et al. J Am Coll Cardiol. 2006. // Captur G, et al. Circ Cardiovasc Imaging. 2014.

Are genotype negative patients truly phenotype negative?

Mitral apparatus abnormalities

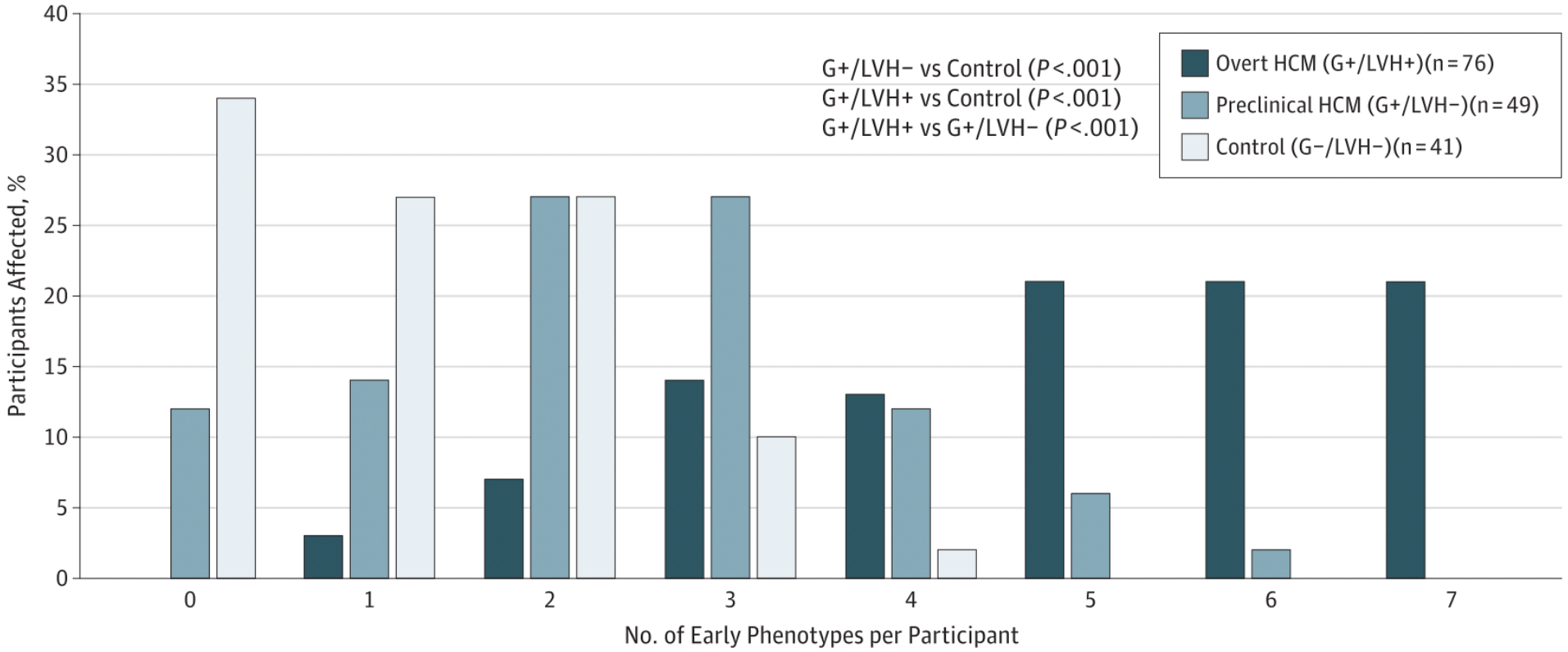


Maron MS, et al. Circulation. 2011.

Are genotype negative patients truly phenotype negative?

Overall prevalence of secondary abnormalities

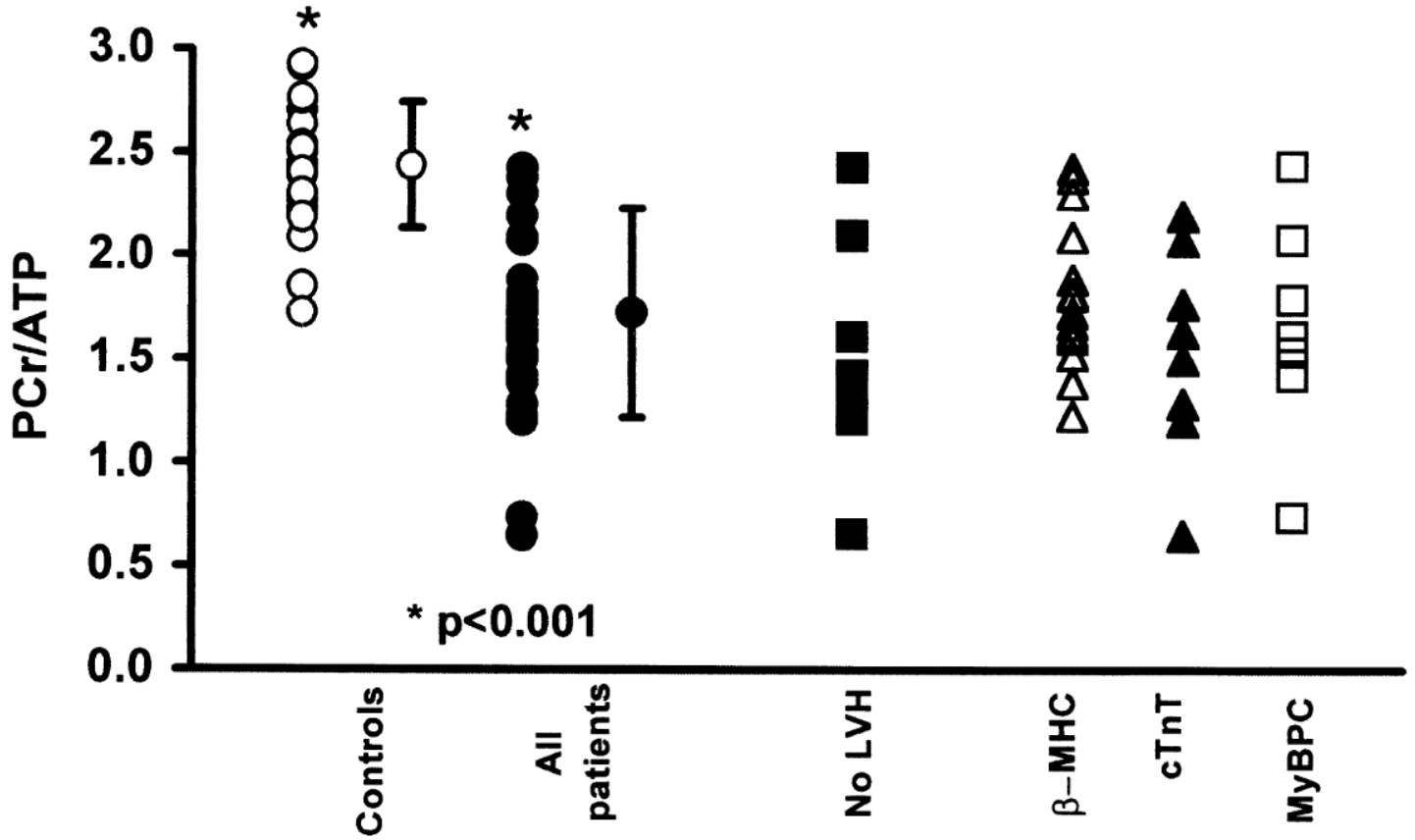
Figure 1. Burden of Early Phenotypic Abnormalities in Sarcomere Mutation Carriers Compared With Controls



Ho CY, et al. JAMA Cardiol. 2017.

Are genotype negative patients truly phenotype negative?

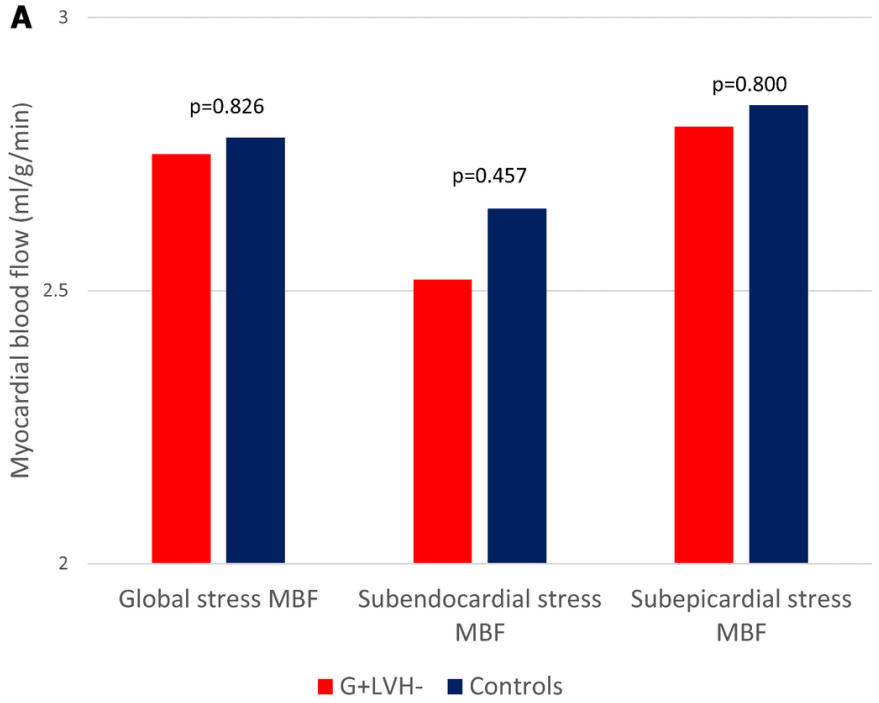
Myocardial energetics

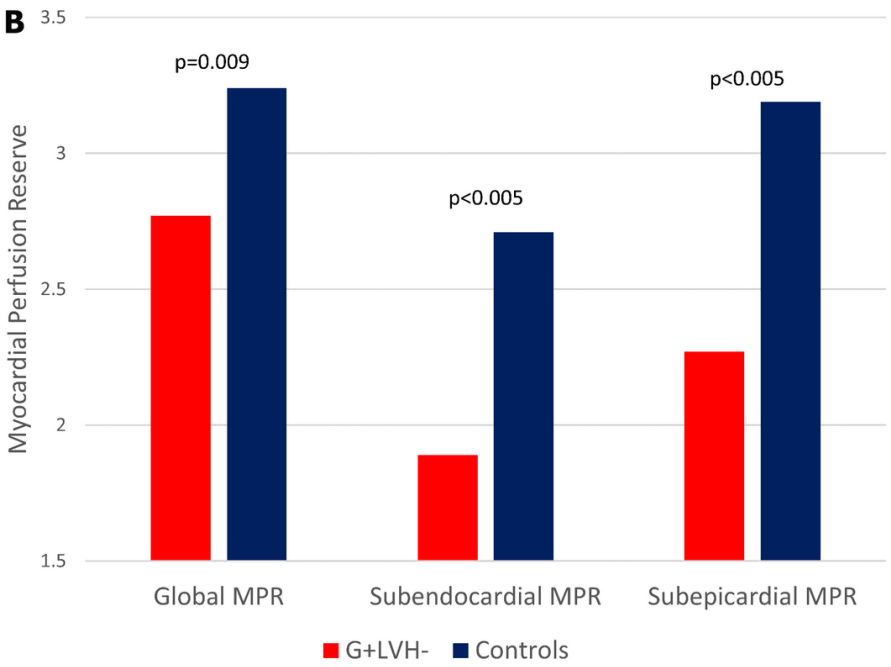


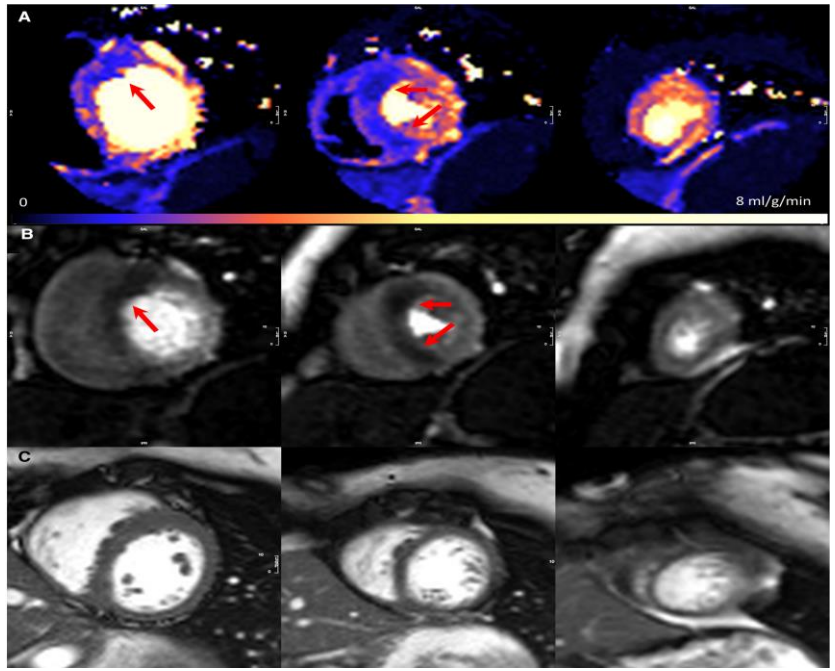
Crilley JG, et al. J Am Coll Cardiol. 2003.

Are genotype negative patients truly phenotype negative?

Small vessel disease and ECV expansion







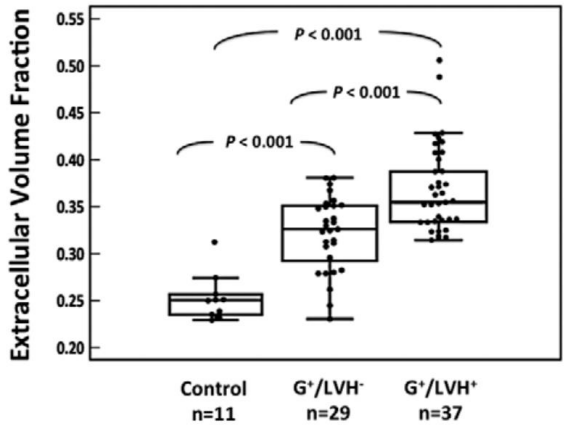
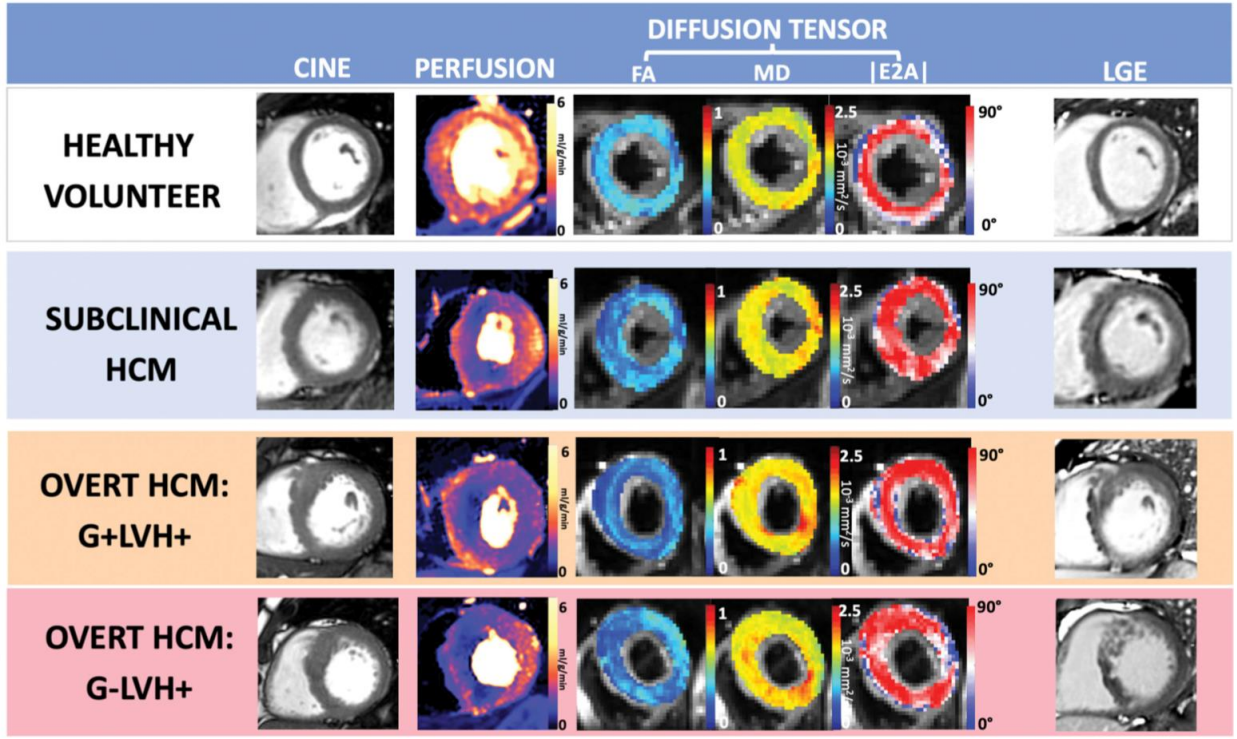


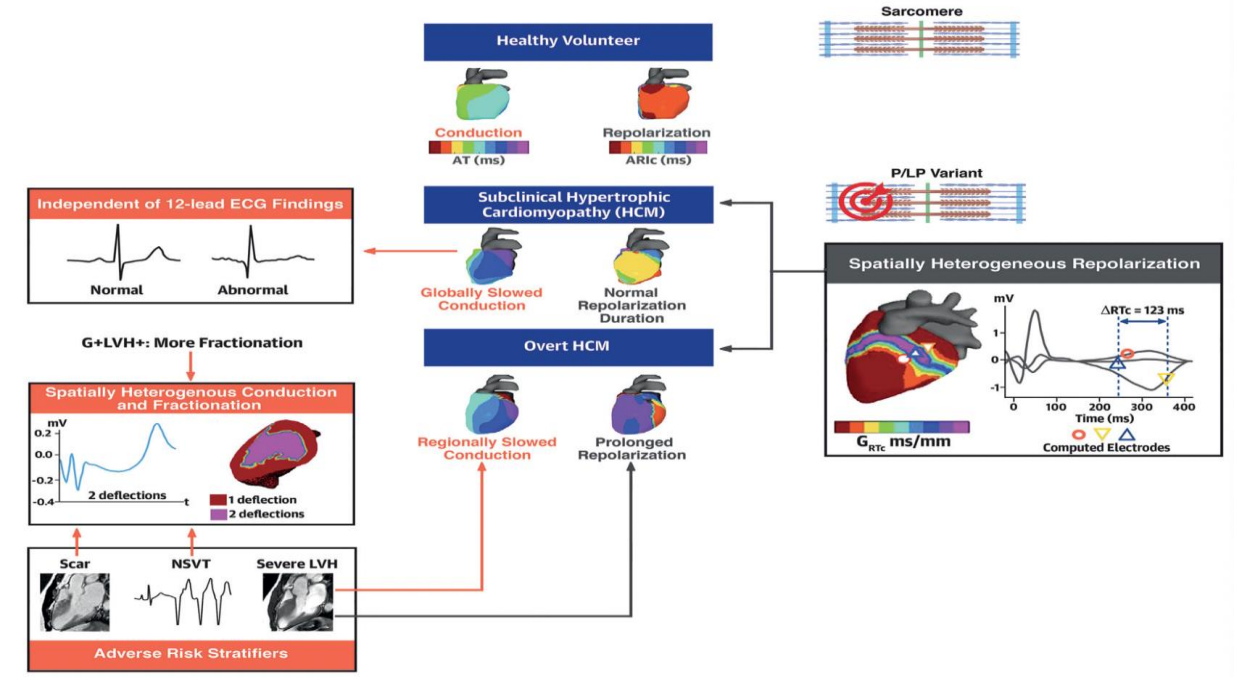
Figure 2. The myocardial extracellular volume (ECV) is significantly increased in hypertrophic cardiomyopathy (HCM) sarcomere mutation carriers with and without left ventricular hypertrophy (LVH). Compared with normal controls, ECV was 22% higher in G+/LVH– subjects and 33% higher in patients with G+/LVH+ HCM. ECV in overt HCM subjects was 9% higher than G+/LVH– subjects ($P \leq 0.001$ for all comparisons).

Ho CY, et al. Circ Cardiovasc Imaging. 2013.
Hughes RK, et al. J Am Heart Assoc. 2021.

Are genotype negative patients truly phenotype negative?

Disarray and electrical heterogenicity





Joy G, et al. Circulation. 2023.
Joy G, et al. J Am Coll Cardiol. 2024.

Clinical risk profile of genotype positive/phenotype negative patients

Total cohort of asymptomatic patients = 76

HCM n=31 patients

No HCM n=45 patients

Penetrance 41%

Table 3 **Risk factors for sudden cardiac death in hypertrophic cardiomyopathy mutation carriers**

	HCM	No HCM
NSVT	2	1
Abnormal blood pressure response	3	1
Syncope	0	0
MWT ≥30 mm	0	0
Positive family history		
Two or more first-degree SCD <40 years	0	0
One first-degrees SCD <40 years	2	2
Any SCD	27	25

HCM, hypertrophic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; MWT, maximal septal wall thickness; SCD, sudden cardiac death.

Michels M, et al. Eur Heart J. 2009.

Clinical risk profile of genotype positive/phenotype negative patients

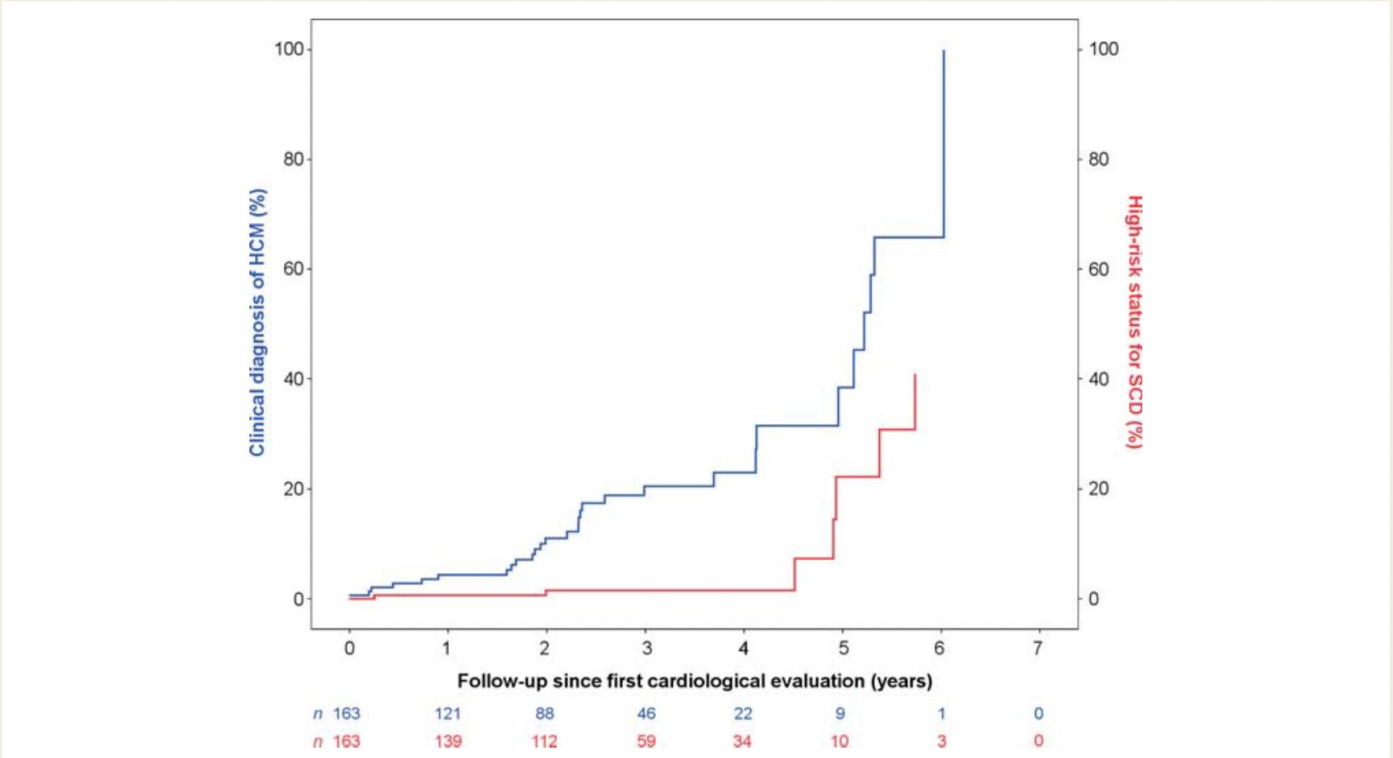
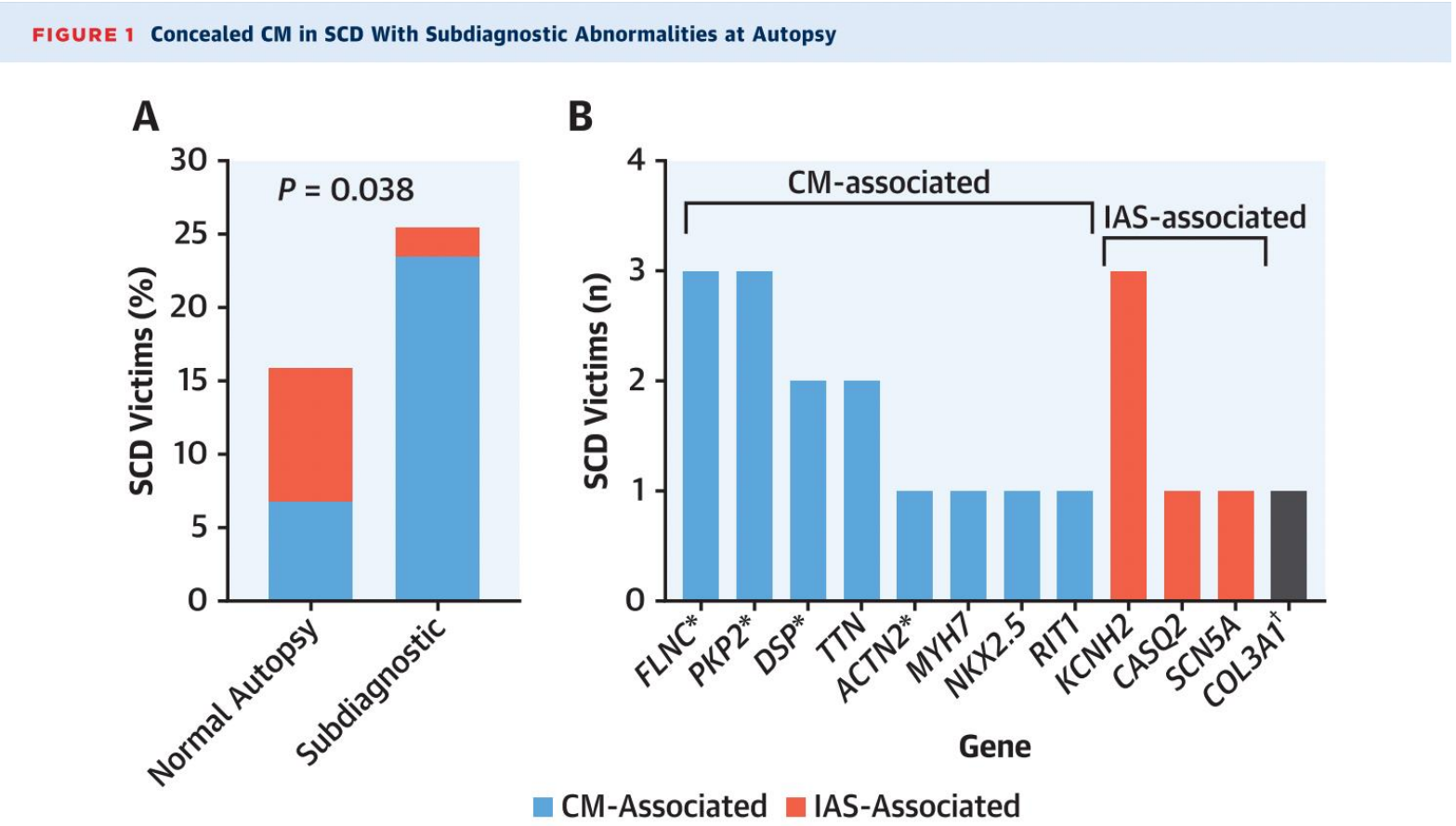


Figure 4 Clinical diagnosis of hypertrophic cardiomyopathy and high-risk status for sudden cardiac death (manifest hypertrophic cardiomyopathy and ≥2 risk factors) during follow-up in mutation carriers not diagnosed with manifest hypertrophic cardiomyopathy at first cardiological evaluation.

Christiaans I, et al. Eur Heart J. 2011.

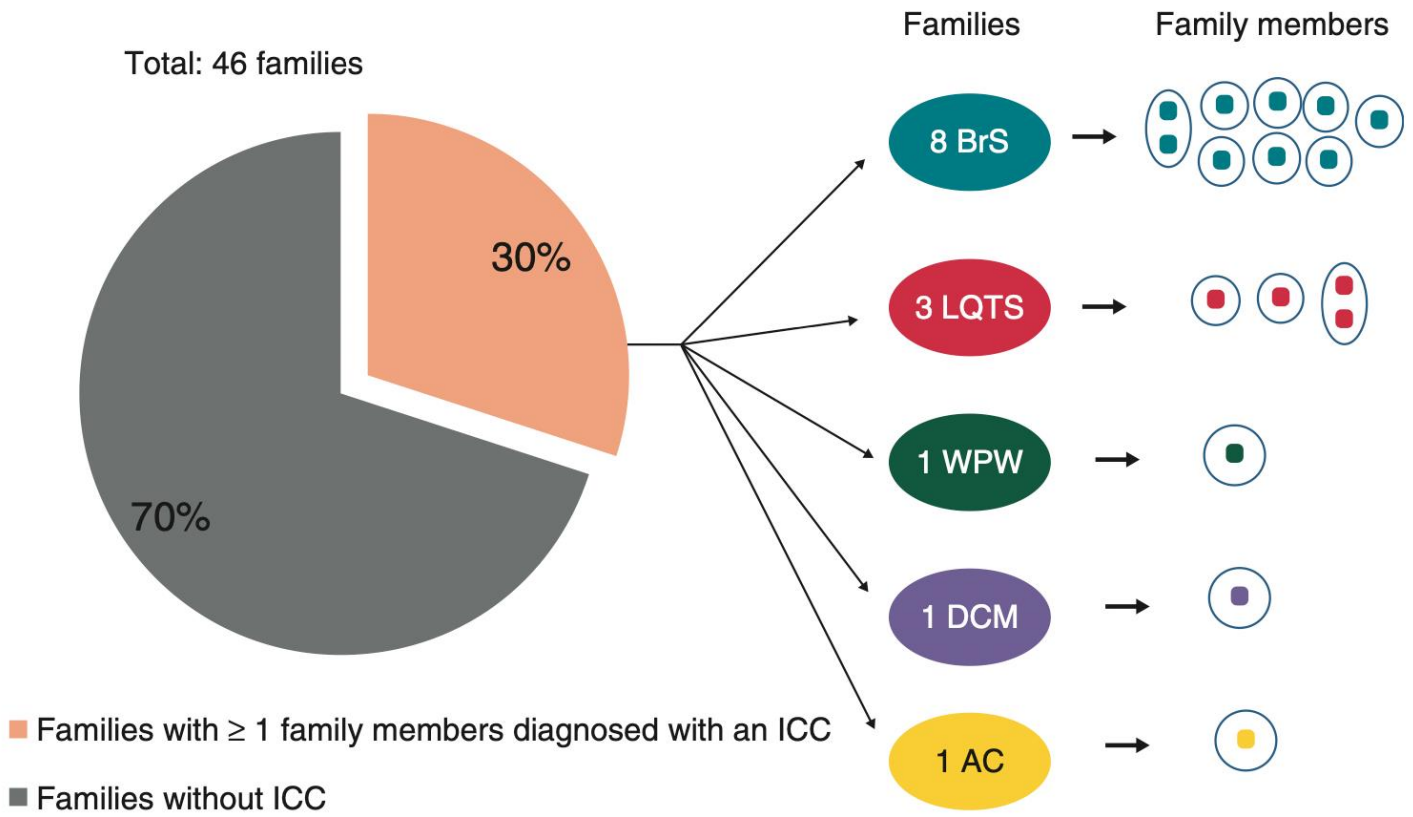
HCM related P/LP variants in SCD with non-diagnostic heart autopsies



N=91 SCD victims with normal or subdiagnosit c autopsies

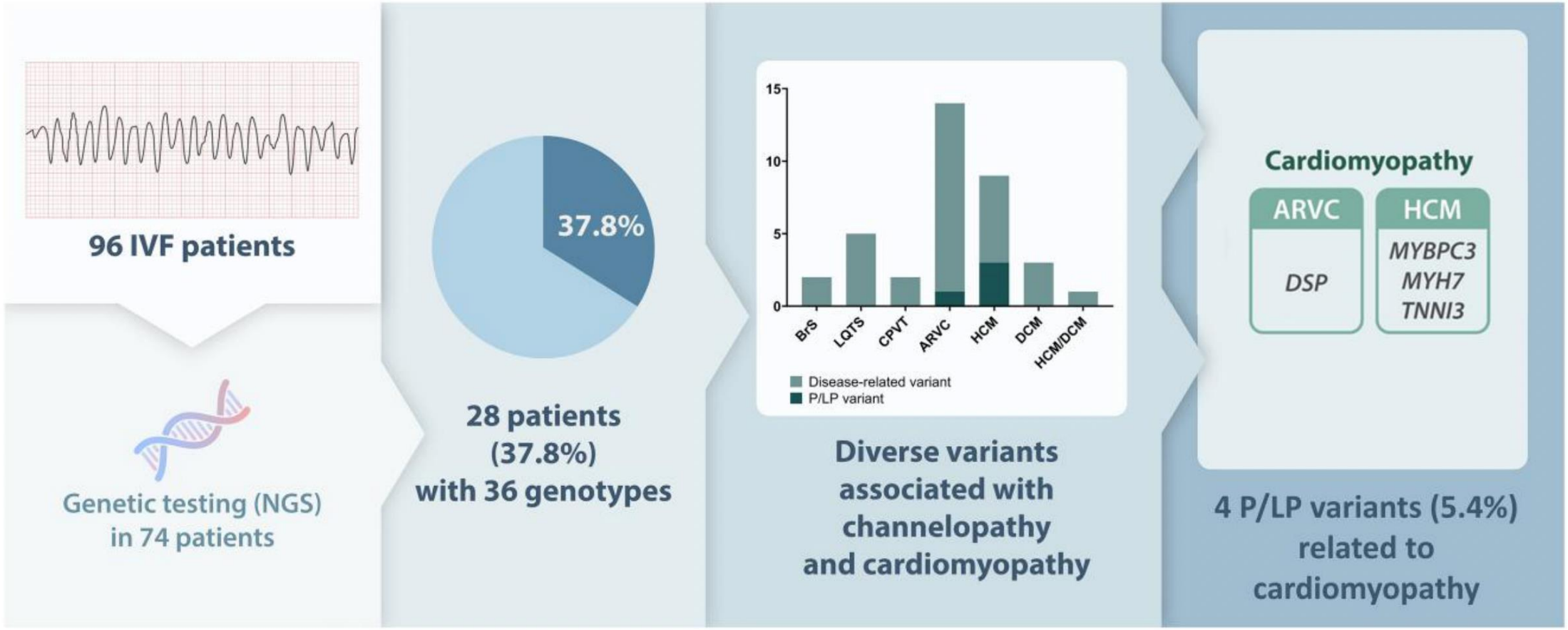
Isbister JC, et al. J Am Coll Cardiol. 2022.

HCM related P/LP variants in SCD with idiopathic LVH in heart autopsies



Finocchiaro G, et al. Europace. 2020.

HCM related P/LP variants in idiopathic fibrillation



Jeong JH, et al. Europace. 2023.

HCM related P/LP variants in idiopathic fibrillation

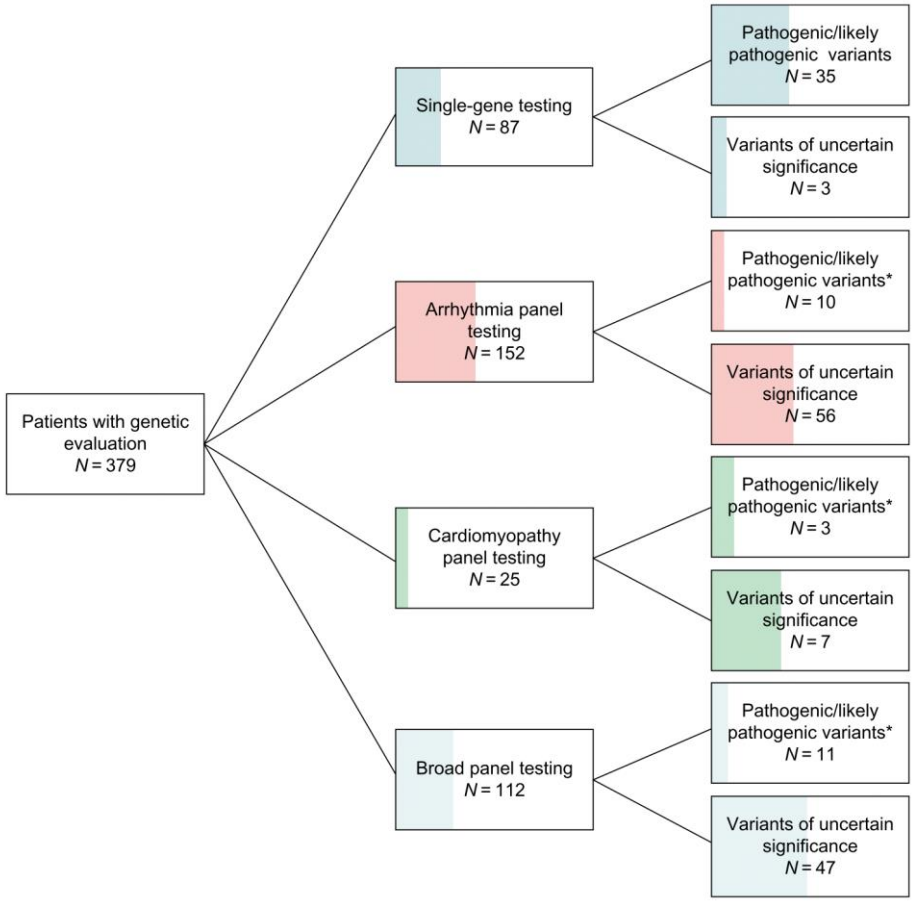


Table 2 Genes with LP/P variants stratified by type of genetic testing that revealed the LP/P variant

Single-gene testing	Arrhythmia panel testing	Cardiomyopathy panel testing	Broad panel testing
DPP6 (33)	*DPP6* (5)	*MYH7* (1)	*DPP6* (1)
PLN (1)	*PLN* (1)	*TTN* (1)	*CPT2* (1)
RYR (2)	*RYR2* (1)		*FLNC* (1)
RBM20 (1)	*KCNQ1* (1)		*MYL2* (1)
TTN (1)	*SCN5A* (1)		*NEB* (1)
			RYR2 (1)
			TTN (2)
			SCN5A (1)
			PPA2 (1)
			TRDN (1)

Genes (number of patients with a variant) are listed.

Verheul LM, et al. Europace. 2023.

Cardiac events in genotype positive/phenotype negative HCM patients during exercise

JAMA Cardiology | Original Investigation

Vigorous Exercise in Patients With Hypertrophic Cardiomyopathy

Rachel Lampert, MD; Michael J. Ackerman, MD, PhD; Bradley S. Marino, MD; Matthew Burg, PhD; Barbara Ainsworth, PhD, MPH; Lisa Salberg; Maria Teresa Tome Esteban, MD, PhD; Carolyn Y. Ho, MD; Roselle Abraham, MD; Seshadri Balaji, MBBS, PhD; Cheryl Barth, BS; Charles I. Berul, MD; Martijn Bos, MD; David Cannom, MD; Lubna Choudhury, MD; Maryann Concannon, MSW; Robert Cooper, MD; Richard J. Czosek, MD; Anne M. Dubin, MD; James Dziura, PhD; Benjamin Eidem, MD; Michael S. Emery, MD; N. A. Mark Estes, MD; Susan P. Etheridge, MD; Jeffrey B. Geske, MD; Belinda Gray, MBBS, PhD; Kevin Hall, MD; Kimberly G. Harmon, MD; Cynthia A. James, PhD; Ashwin K. Lal, MD; Ian H. Law, MD; Fangyong Li, MS; Mark S. Link, MD; William J. McKenna, MD; Silvana Molossi, MD, PhD; Brian Olshansky, MD; Steven R. Ommen, MD; Elizabeth V. Saarel, MD; Sara Saberi, MD, MS; Laura Simone, MS; Gordon Tomaselli, MD; James S. Ware, MD; Douglas P. Zipes, MD; Sharlene M. Day, MD; for the LIVE Consortium

Characteristic	Nonvigorous (n = 961)	Vigorous (n = 699)	Cohen *d* or *h*	Vigorous noncompetitive (n = 440)	Vigorous competitive (n = 259)	Cohen *d* or *h*
Phenotype negative, No. (%)	52 (5.4)	74 (10.6)	−0.19	26 (5.9)	48 (18.5)	−0.40
Overt HCM, No. (%)[a]	909 (94.6)	625 (89.4)	0.19	414 (94.5)	211(71.9)	0.40

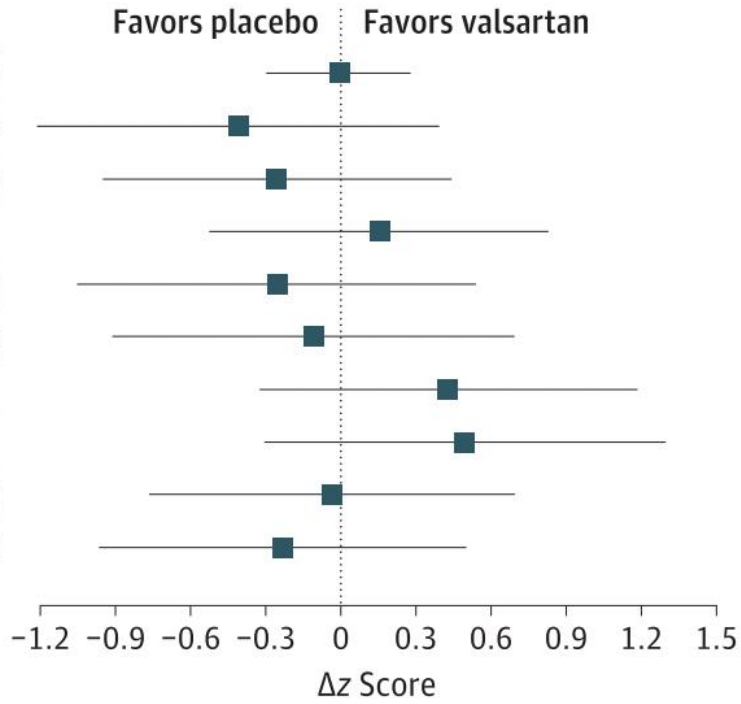
Number of events in genotype positive, phenotype negative patients = 0

Lampert R, et al. JAMA Cardiol. 2023.

Any room for preventative treatment in HCM?

Figure 2. Primary and Secondary Trial Outcomes

Source	Δ Placebo	Δ Valsartan
Composite outcome	−0.01 (−0.20 to 0.18)	−0.02 (−0.20 to 0.16)
Maximum LVWT	0.24 (−0.32 to 0.80)	−0.17 (−0.69 to 0.34)
E′ velocity	0.14 (−0.34 to 0.62)	−0.12 (−0.56 to 0.33)
S′ velocity	−0.11 (−0.58 to 0.36)	0.04 (−0.39 to 0.47)
LV end-diastolic volume index	0.14 (−0.41 to 0.68)	−0.12 (−0.63 to 0.39)
LV end-systolic volume index	0.06 (−0.49 to 0.61)	−0.05 (−0.57 to 0.46)
LV mass index	−0.22 (−0.74 to 0.29)	0.20 (−0.28 to 0.68)
LAVI	−0.26 (−0.81 to 0.29)	0.23 (−0.28 to 0.74)
TnT	0.03 (−0.47 to 0.54)	−0.01 (−0.47 to 0.46)
NT-proBNP	0.14 (−0.36 to 0.65)	−0.09 (−0.56 to 0.38)



Vissing CR, et al. JAMA Cardiol. 2023.

Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis

A Scientific Statement From the American Heart Association and American College of Cardiology

Participation in competitive athletics for asymptomatic, genotype-positive HCM patients without evidence of LV hypertrophy by 2-dimensional echocardiography and CMR is reasonable, particularly in the absence of a family history of HCM-related sudden death *(Class IIa; Level of Evidence C)*.

2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the Management of Hypertrophic Cardiomyopathy: A Report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines

2. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive sports of any intensity is reasonable.[6,7]	2a	B-NR

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Participation in all competitive sports, if desired, may be considered for individuals who are gene positive for HCM but phenotype negative.	IIb	C

2023 ESC Guidelines for the management of cardiomyopathies

HCM		
High-intensity exercise and competitive sport should be considered in genotype-positive/ phenotype-negative individuals who seek to do so.[1124]	IIa	C

Screening

What do the guidelines say?

Recommendations for Individuals Who Are Genotype-Positive, Phenotype-Negative Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	**LOE**	**Recommendations**
1	**B-NR**	1. In individuals who are genotype-positive, phenotype-negative for HCM, serial clinical assessment, electrocardiography, and cardiac imaging are recommended at periodic intervals depending on age (every 1-2 years in children and adolescents and every 3-5 years in adults) and change in clinical status (Figures 1 and 2, Table 7).[1–5]
2a	**B-NR**	2. In individuals who are genotype-positive, phenotype-negative for HCM, participation in competitive sports of any intensity is reasonable.[6,7]
3: No benefit	**B-NR**	3. In individuals who are genotype-positive, phenotype-negative for HCM, ICD is not recommended for primary prevention.[2–6,8]

1	**B-NR**	10. Screening: In individuals who are genotype-positive, phenotype-negative, echocardiography is recommended at periodic intervals depending on age (1-2 years in children and adolescents, 3-5 years in adults) and change in clinical status (Figure 1, Table 7).[39–43]

Table 7. Screening With Electrocardiography and 2D Echocardiography in Asymptomatic Family Members*

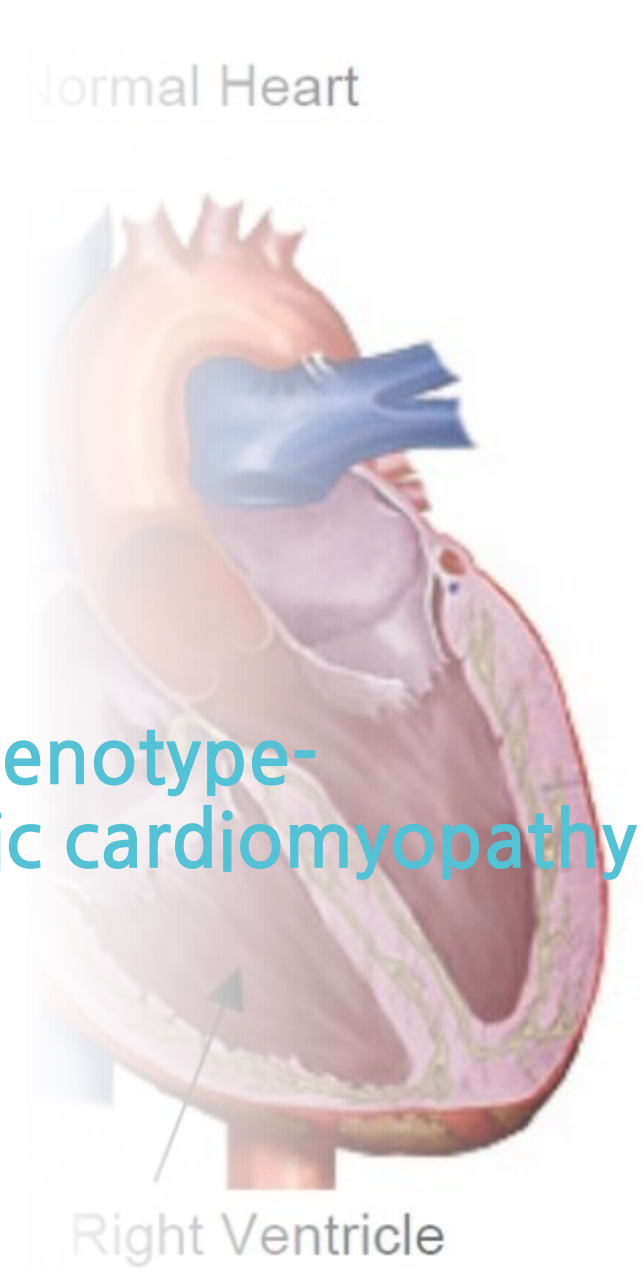
Age of First-Degree Relative	Initiation of Screening	Repeat ECG, Echo
Pediatric		
Children and adolescents from genotype-positive families, and families with early onset disease	At the time HCM is diagnosed in another family member	Every 1-2 y
All other children and adolescents	At any time after HCM is diagnosed in a family member but no later than puberty	Every 2-3 y
Adults	At the time HCM is diagnosed in another family member	Every 3-5 y

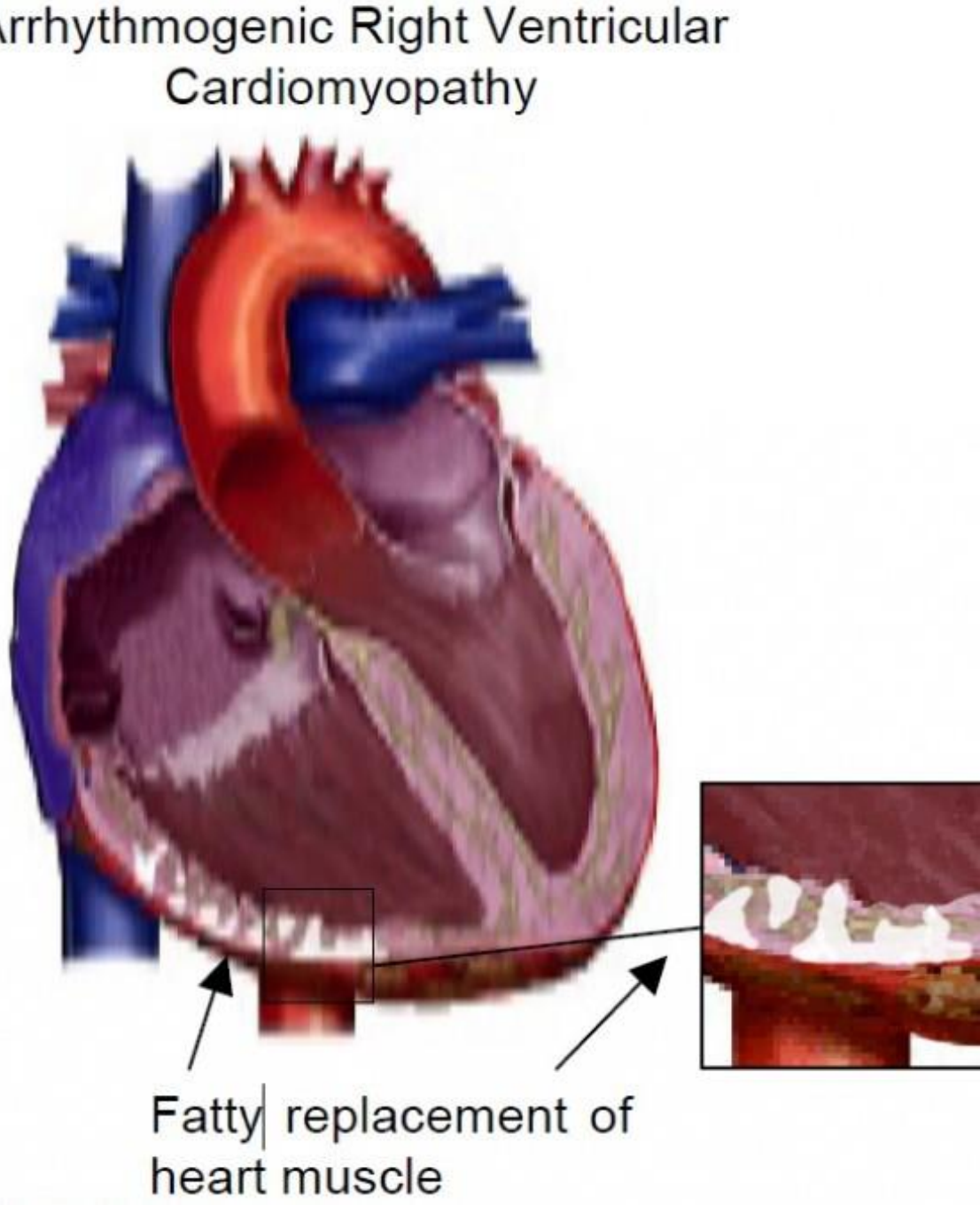
*Includes all asymptomatic, phenotype-negative, first-degree relatives deemed to be at risk for developing HCM based on family history or genotype status and may sometimes include more distant relatives based on clinical judgment. Screening interval may be modified (eg, at onset of new symptoms or in families with a malignant clinical course or late-onset HCM).

ECG indicates electrocardiogram; Echo, echocardiogram; and HCM, hypertrophic cardiomyopathy.

Because of the low risk of sudden death, phenotype-negative individuals are not restricted from competitive sports and are not routinely monitored with ambulatory electrocardiography and exercise stress testing unless the family history indicates a high risk for SCD or as part of precompetitive athletic screening. This is appropriate every 1 to 2 years to assess the safety of ongoing competitive athletics participation.

Genotype+/phenotype-
arrhythmogenic cardiomyopathy





Are gene carriers truly phenotype negative?

The relation of exercise with electrical instability

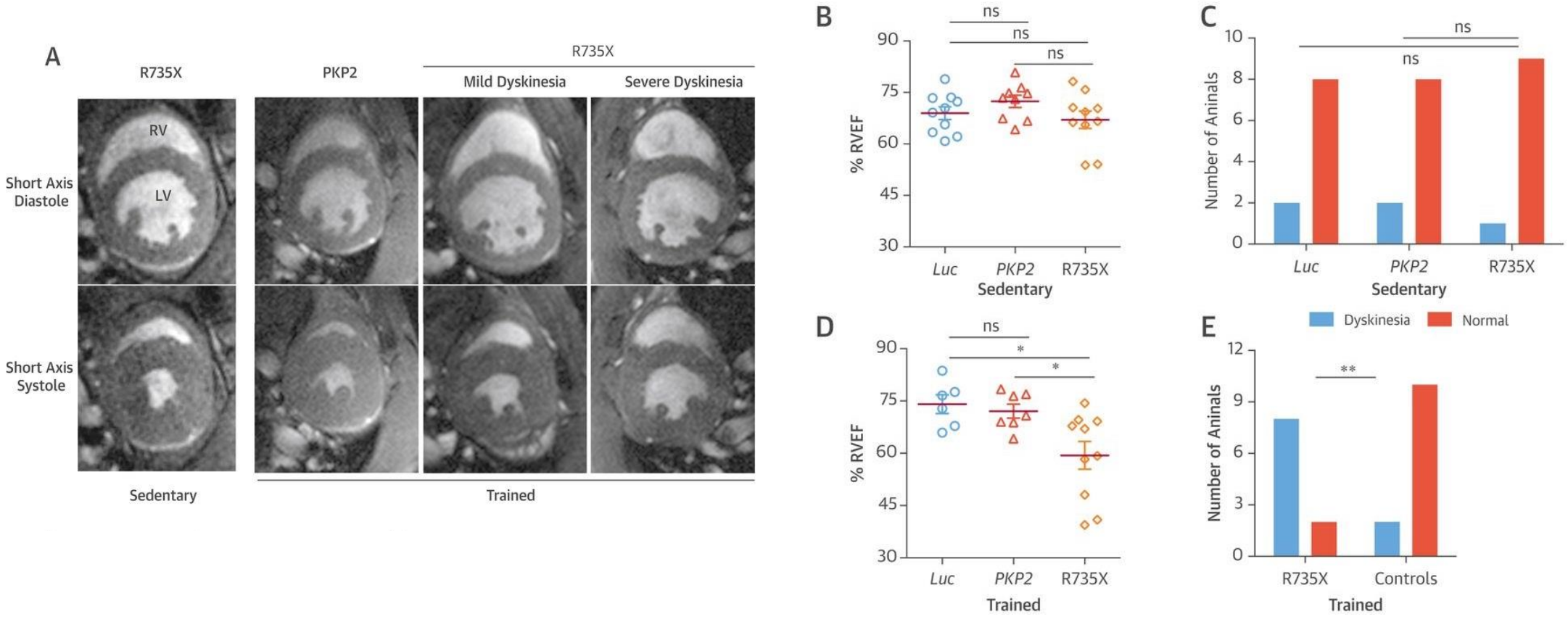
Table 3 Summary Data Comparing Asymptomatic Gene Carriers With Patients With Symptomatic (VT) ARVC

Variable	Healthy Controls (n = 70)	Asymptomatic ARVC Gene Carriers (n = 47)	Patients With Symptomatic ARVC (n = 25)	p Value (Controls vs. Asymptomatic Gene Carriers)	p Value (Asymptomatic Gene Carriers vs. Patients With Symptomatic ARVC)
Age (yrs)	35.8 ± 15.2	36.7 ± 18.1	40.7 ± 10.9	0.78	0.24
Men	28 (40%)	18 (38%)	18 (72%)	1.00	0.01
Genotype					
PKP2	—	43 (91%)	19 (76%)	—	0.09
Structural RV abnormalities					
Major criterion	—	1 (2%)	16 (64%)	—	<0.0001
Minor criterion	—	1 (2%)	0 (0%)	—	1.00
Resting ECG abnormalities					
TWI in leads V_1 to V_3	0/70	0/45 (0%)	9 (36%)	1.00	<0.0001*
Epsilon waves	0/70	0/45 (0%)	6 (24%)	1.00	0.002*
TAD ≥55 ms	—	10/45 (22%)	11/24 (45)	—	0.06
SAECG (≥1 criterion)	—	10/41 (24%)	17/21 (81)	—	<0.0001
Exercise ECG abnormalities					
Epsilon waves	0/70	6/45 (13%)	3/18 (17%)	0.003	0.70
PVCs					
Any	11/70 (11%)	27 (57%)	23 (92%)	<0.0001	0.003
Superior axis	1/70 (1%)	10 (21%)	21 (84%)	0.0004	<0.0001
TAD ≥ 55 ms	—	11/36 (31%)	8/12 (67%)	—	0.04

Perrin M, et al. J Am Coll Cardiol. 2013.

The relation of exercise with the development of ARVC

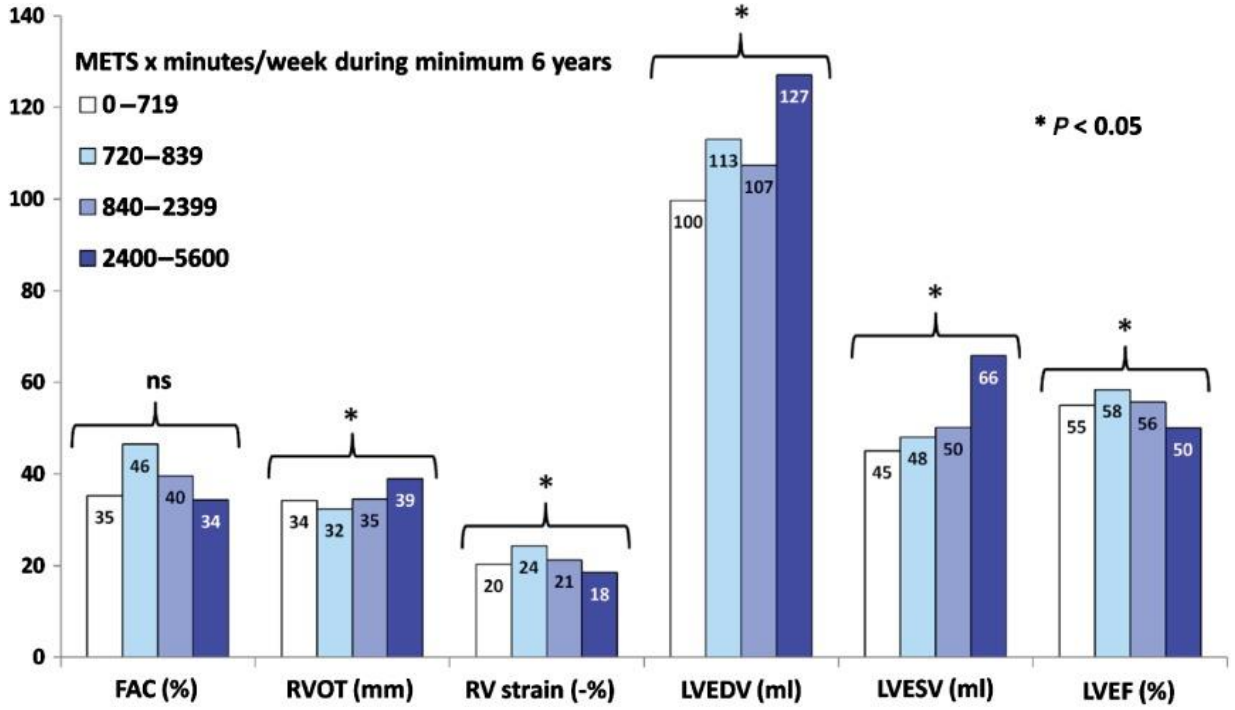
Workload dependent structural changes (animal model)

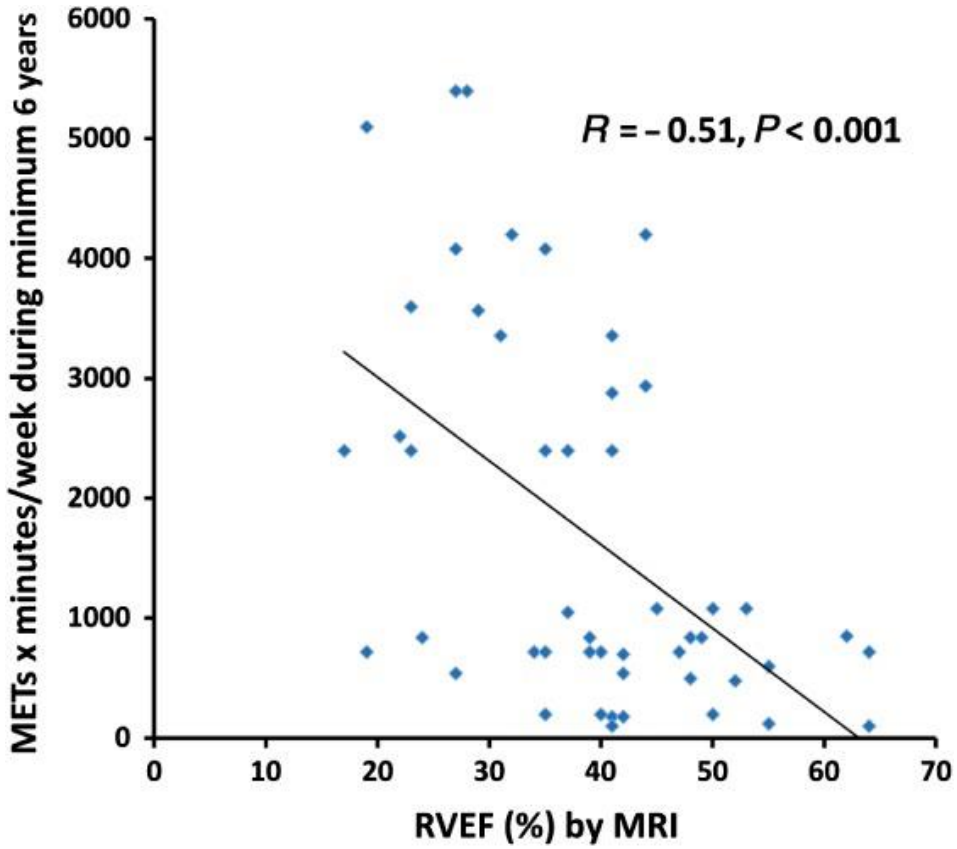


Cruz FM, et al. J Am Coll Cardiol. 2015.

The relation of exercise with the development of ARVC

Workload dependent structural changes (human studies)



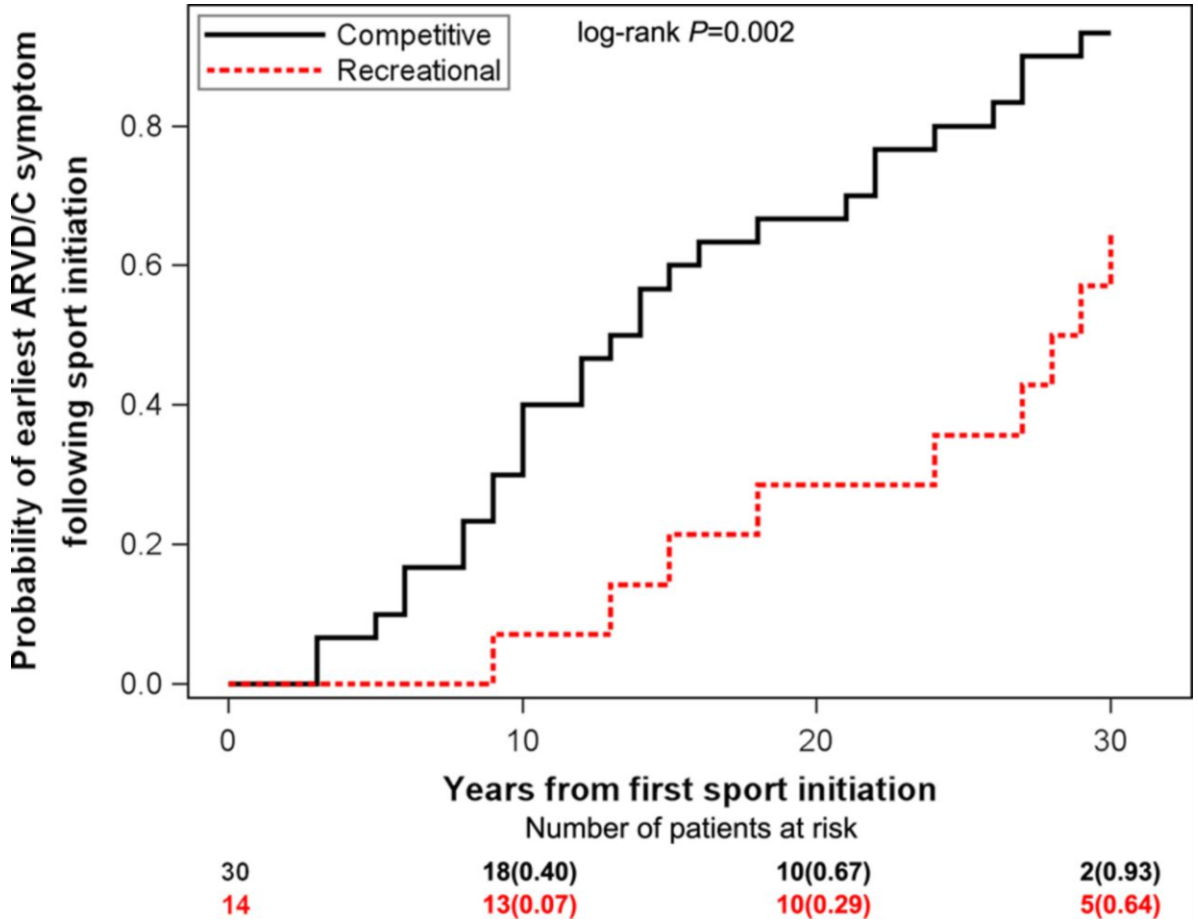


N=110 patients, 45 phenotype negative gene carriers

Saberniak J, et al. Eur J Heart Fail. 2014.

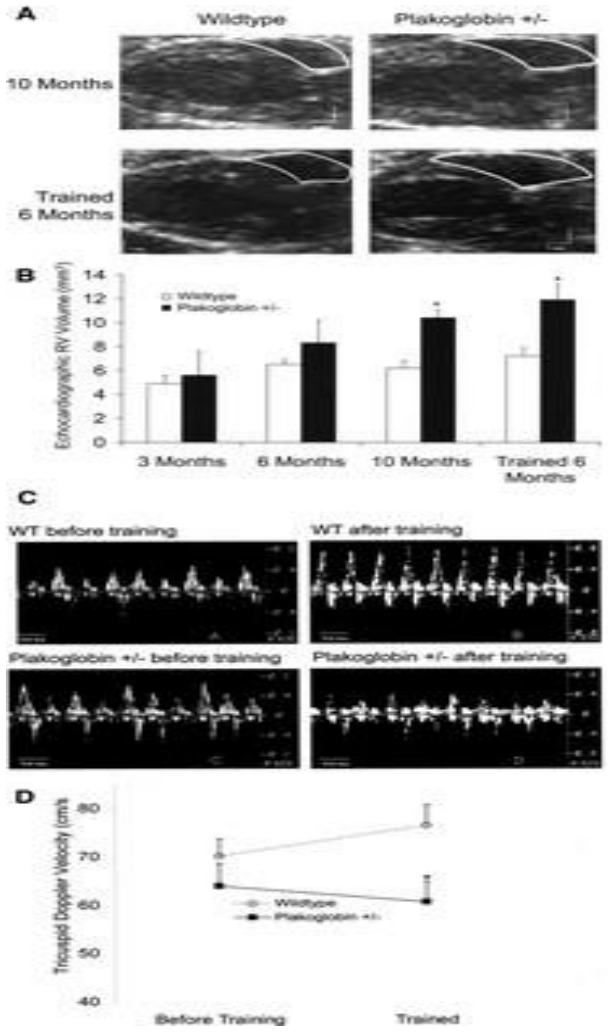
The relation of exercise with the development of ACM

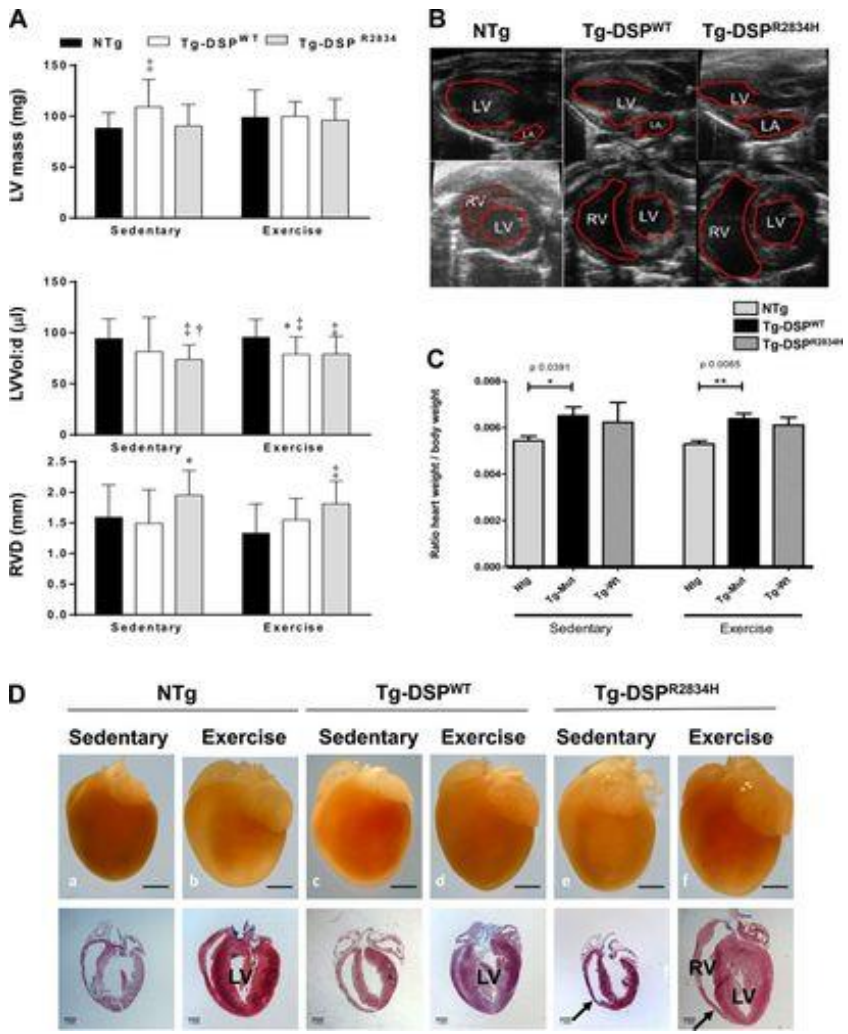
Exercise leads to symptoms regardless of age



Ruwald AC, et al,. Eur Heart J. 2015.

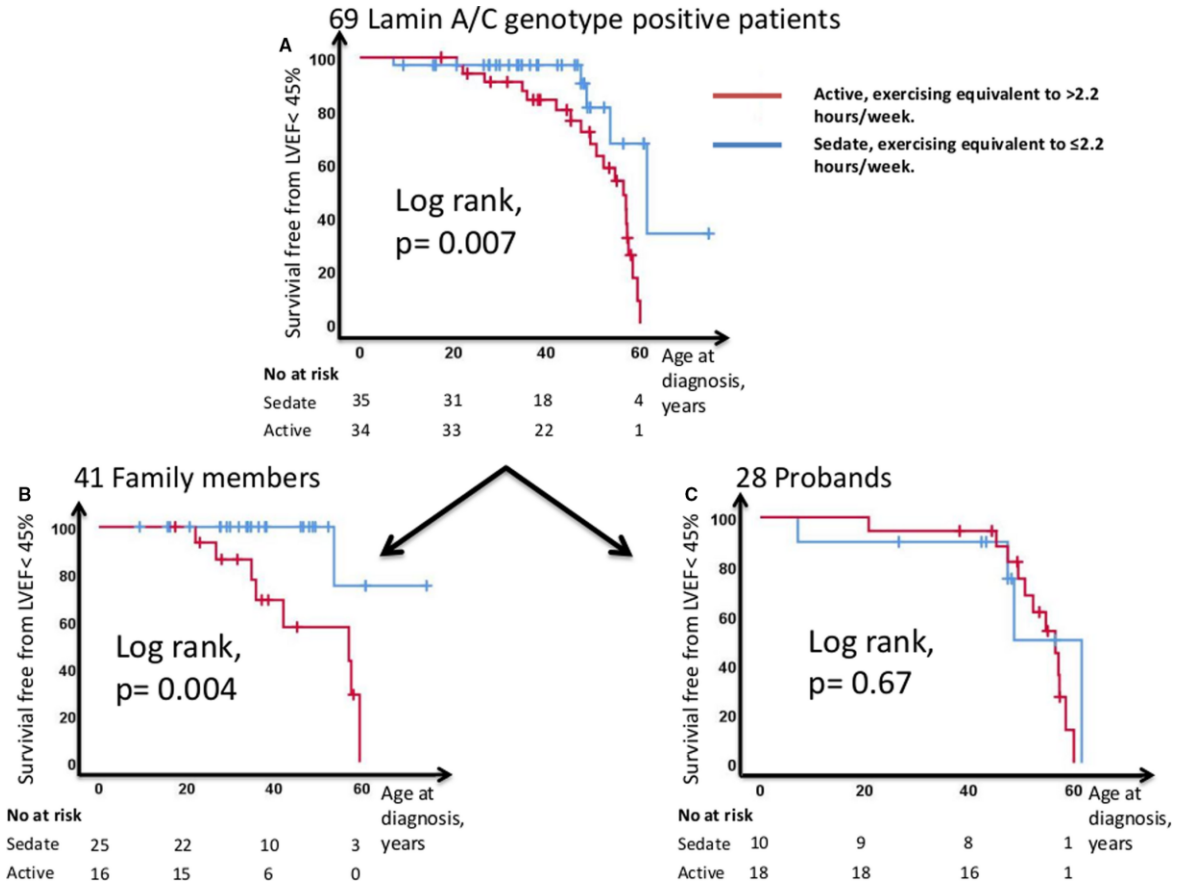
Maladaptation to exercise is independent of genotype





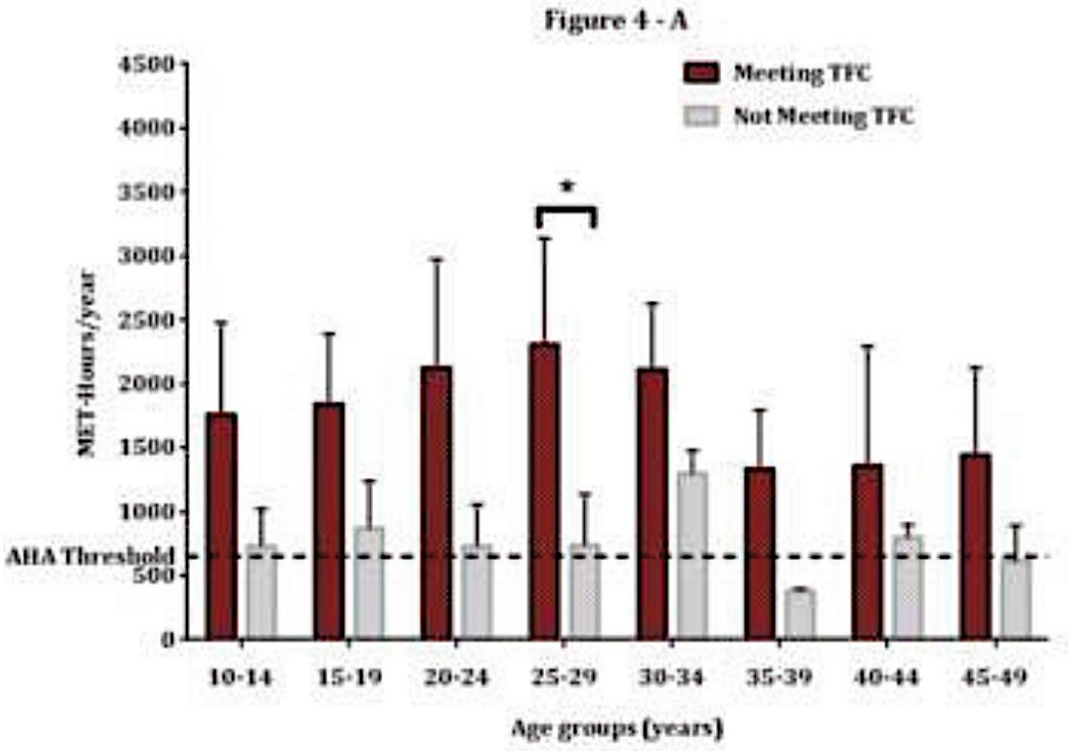
Kirchhof P, et al. Circulation. 2006. // Martherus R, et al. Am J Physiol Heart Circ Physiol. 2016.

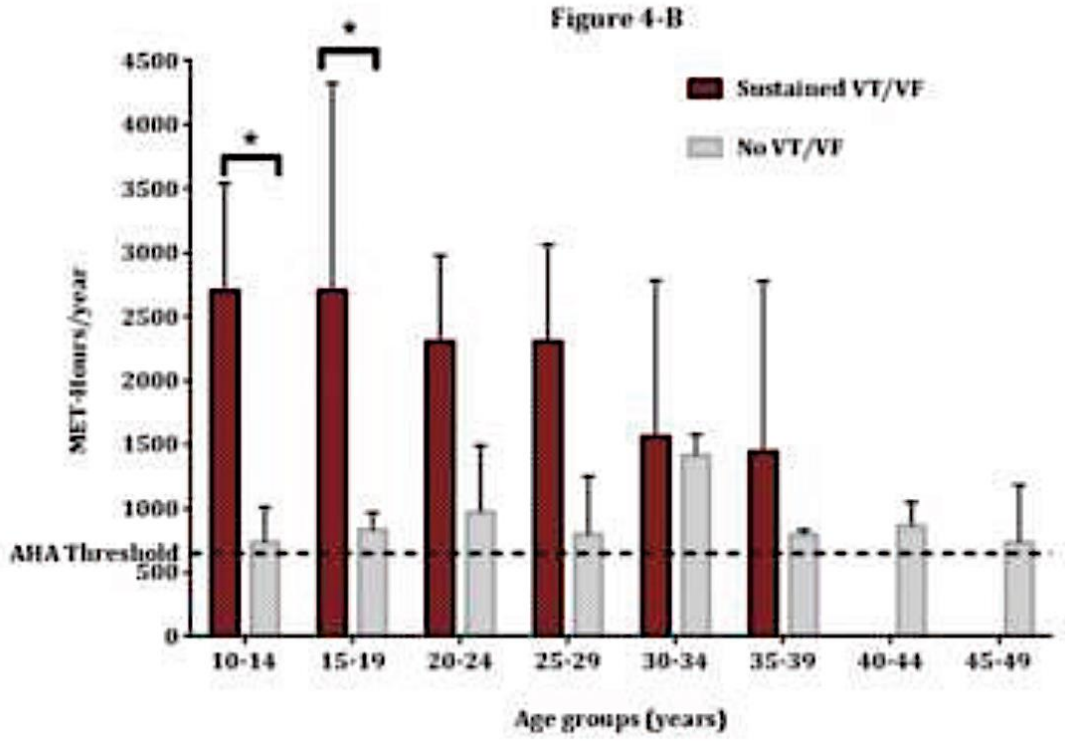
Exercise in LMNA carriers



Skjølsvik ET, et al. J Am Heart Assoc. 2020

Avoidance of exercise is protective against phenotype development and arrhythmia

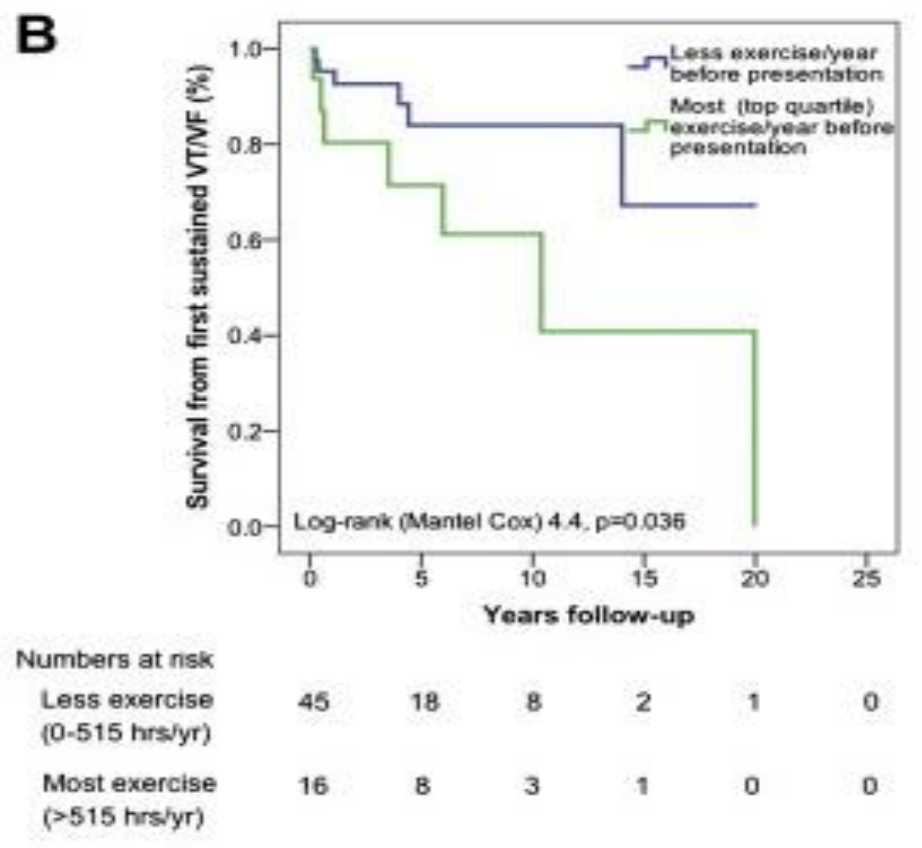


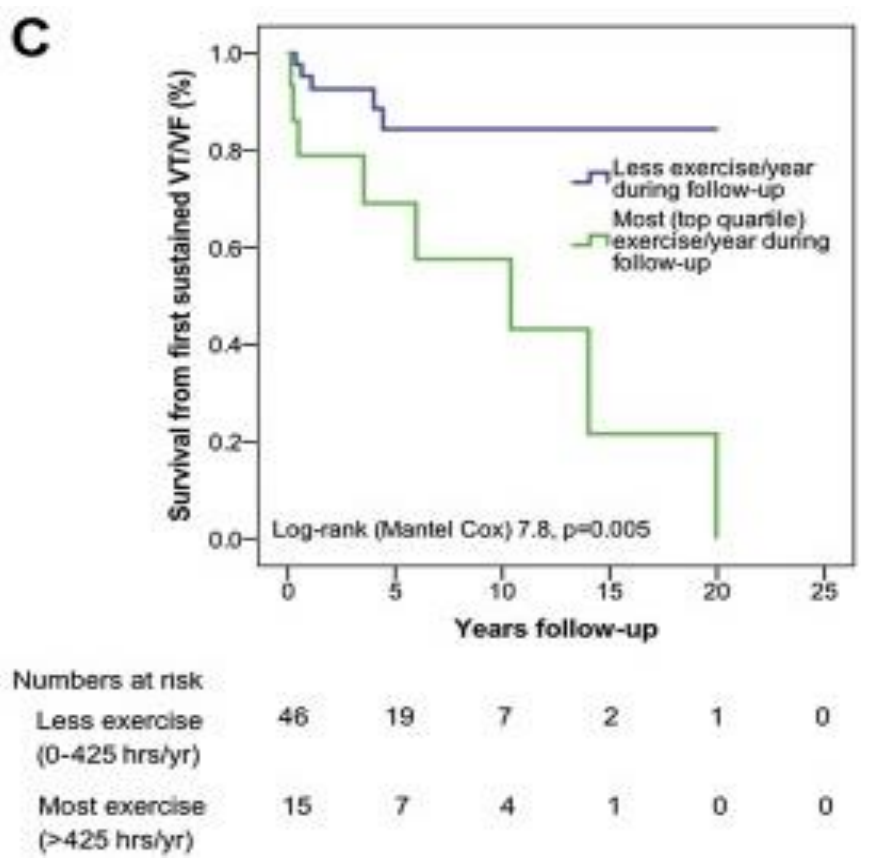


N=28 unaffected PKP2 mutation carriers

Sawant AC, et al. Heart Rhythm. 2016.

Avoidance of exercise is protective even after phenotype expression

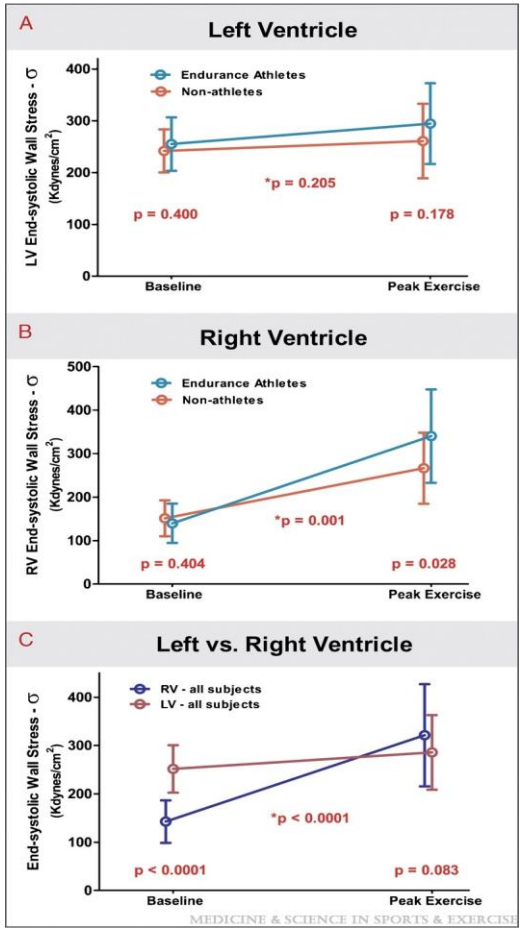


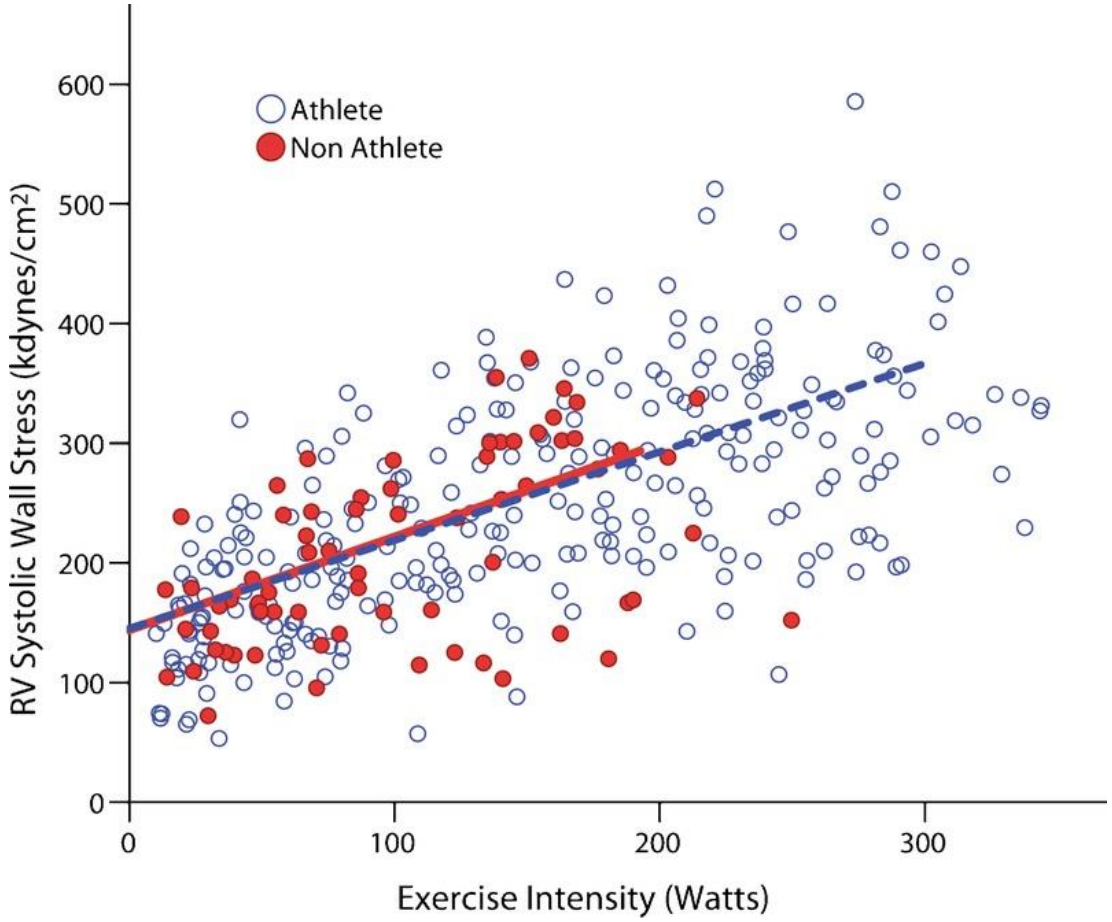


N=87 desmosomal gene carriers, 57/87, 66% meeting TFC

James CA, et al JACC. 2013.

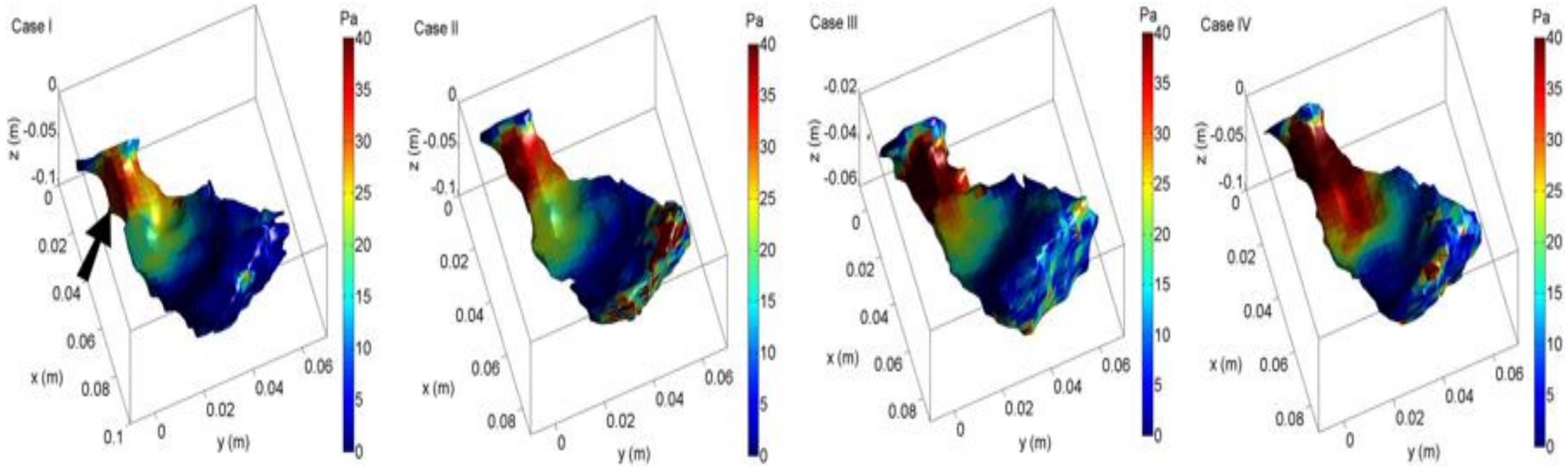
Exaggerated RV adaptation to exercise





La Gerche A, et al. Med Sci Sports Exerc. 2011.

RV wall shear stress is dependent on cardiac output...

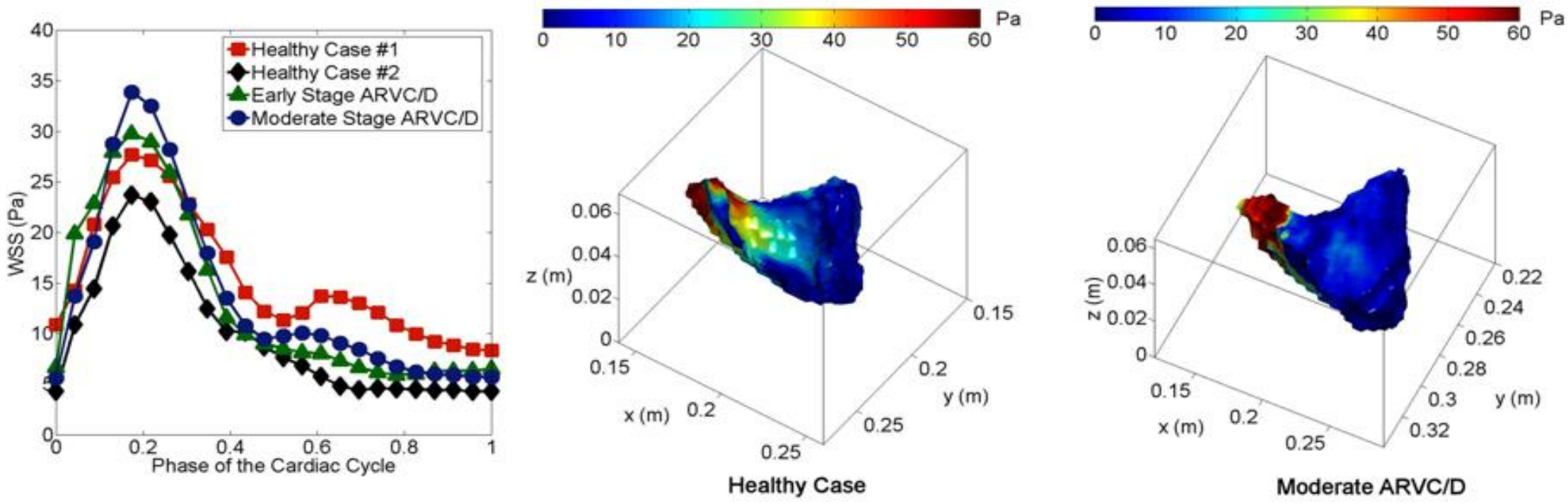


Spatial distribution of WSS at peak systole for varying cardiac output levels obtained using 3D-PTV in vitro

(Case I: 4.05 L/min, Case II:4.44 L/min, Case III:4.65 L/min, Case IV:5.32 L/min)

Gülan U et al. Scientific Reports. 2019.

...and genotype/phenotype.



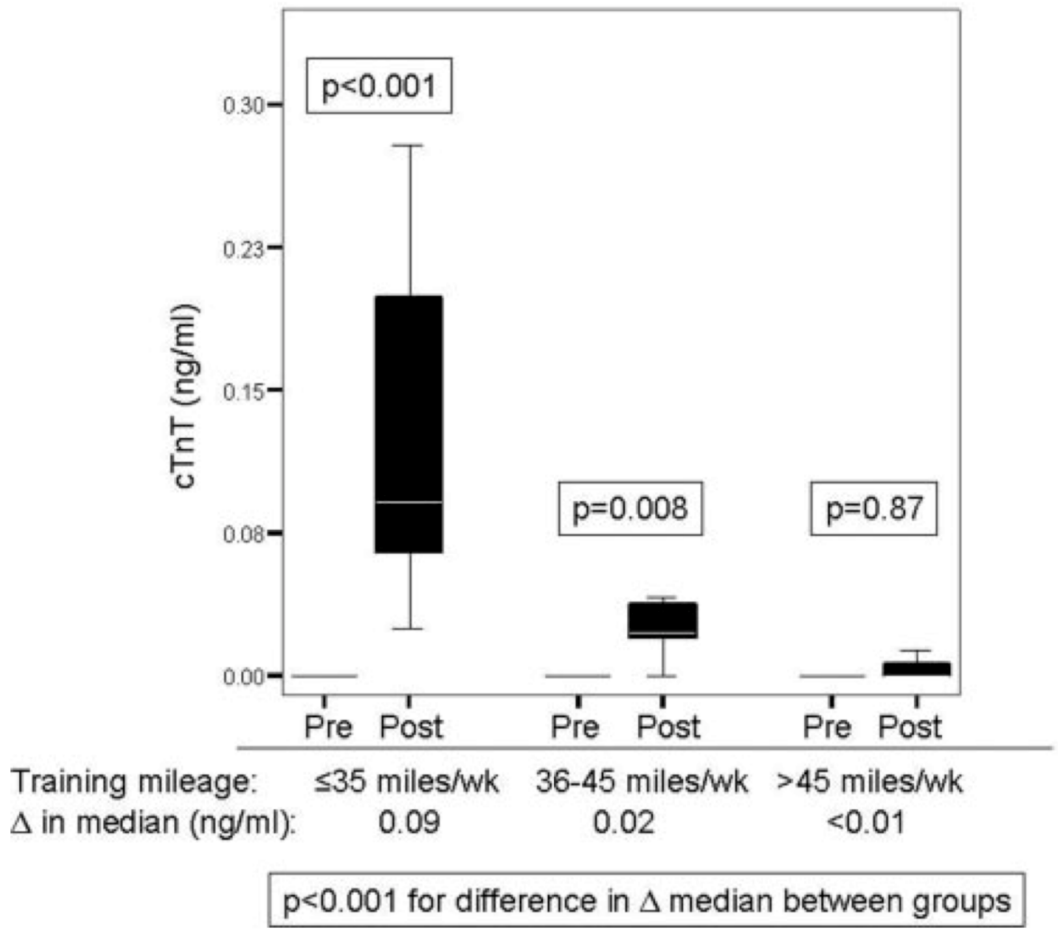
Time evolution of WSS averaged over the RVOT for healthy, early ARVC/D and moderate ARVC/D cases (left) obtained using in vivo PC-MRI. Spatial distribution of WSS at peak systole for the healthy case (middle) and moderate ARVC/D case (right).

Gülan U et al. Scientific Reports. 2019.

Troponin elevation is associated with RV functional changes in exercise

TABLE 2. Baseline and Postmarathon Echocardiographic Indices (n=60)

Variable	Baseline	After the Marathon	*P*
Left atrial dimensions, mm	34±4	33±3	0.17
Left atrial area, cm^2	19±3	18±3	0.49
Right atrial area, cm^2	17±2	16±3	0.45
LV end-diastolic volume, cm^3	110±20	105±23	0.11
LV end-systolic volume, cm^3	44±10	43±10	0.35
RV dimensions, mm	35±4	41±4	0.001
RV diastolic area, cm^2	17±4	20±3	0.008
RV systolic area, cm^2	10±2	13±2	0.004
LV ejection fraction, %	60±6	59±6	0.44
RV area change, %	41±7	33±7	<0.001
Mitral E-wave filling velocity, $m \cdot s^{-1}$	0.9±0.1	0.6±0.2	<0.001
Mitral A-wave filling velocity, $m \cdot s^{-1}$	0.5±0.1	0.7±0.12	<0.001
Ratio of mitral E/A	1.6±0.4	1.0±0.4	<0.001
TD-derived E′ lateral, $cm \cdot s^{-1}$	12±2	8±2	<0.001
TD-derived A′ lateral, $cm \cdot s^{-1}$	5±1	8±2	<0.001
TD-derived E′ septal, $cm \cdot s^{-1}$	10±2	8±2	<0.001
TD-derived A′ septal, $cm \cdot s^{-1}$	5±1	8±2	<0.001
RV base			
V_{ENDO}, $cm \cdot s^{-1}$	11±2	9±2	0.007
ϵ, %	18±7	14±4	<0.001
SR, s^{-1}	1.2±0.4	1.2±0.3	0.25
RV mid			
V_{ENDO}, $cm \cdot s^{-1}$	11±2	7±2	0.001
ϵ, %	27±6	21±5	<0.001
SR, s^{-1}	1.6±0.4	1.5±0.4	0.62
RV apex			
V_{ENDO}, $cm \cdot s^{-1}$	8±2	6±1	0.007
ϵ, %	38±8	29±7	<0.001
SR, s^{-1}	2.4±0.6	2.3±0.6	0.86

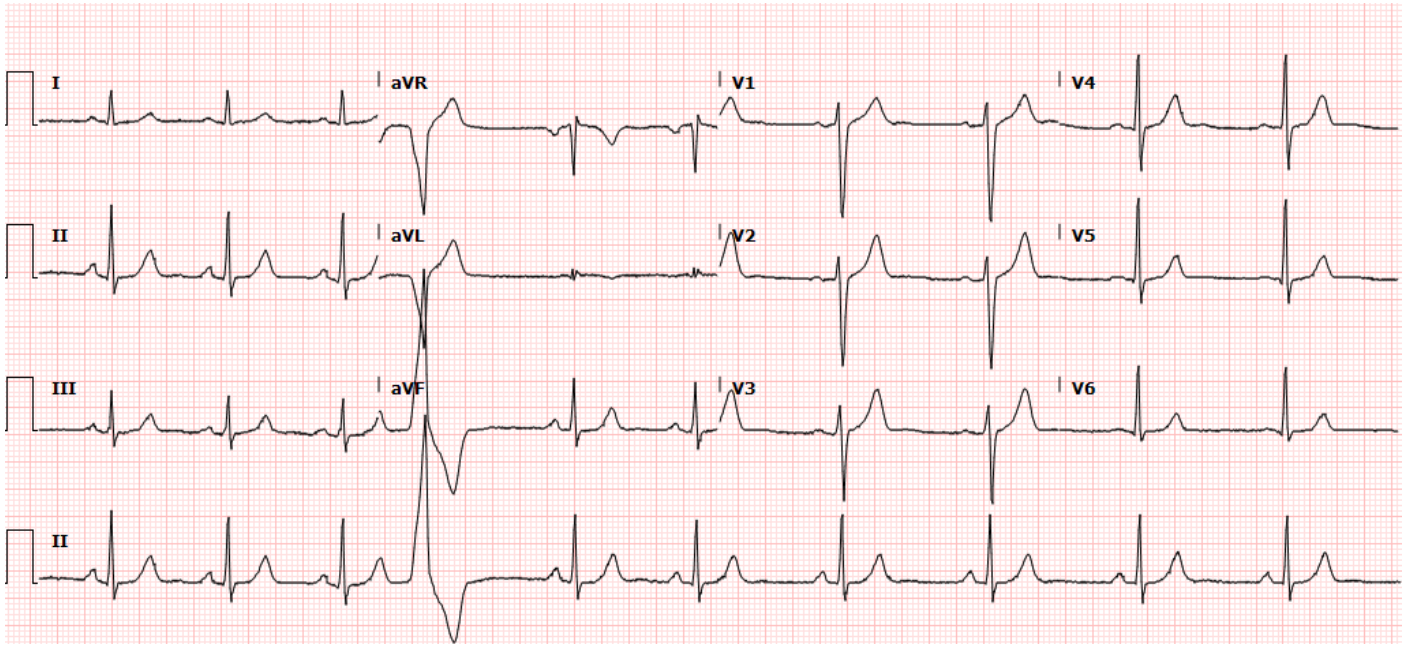


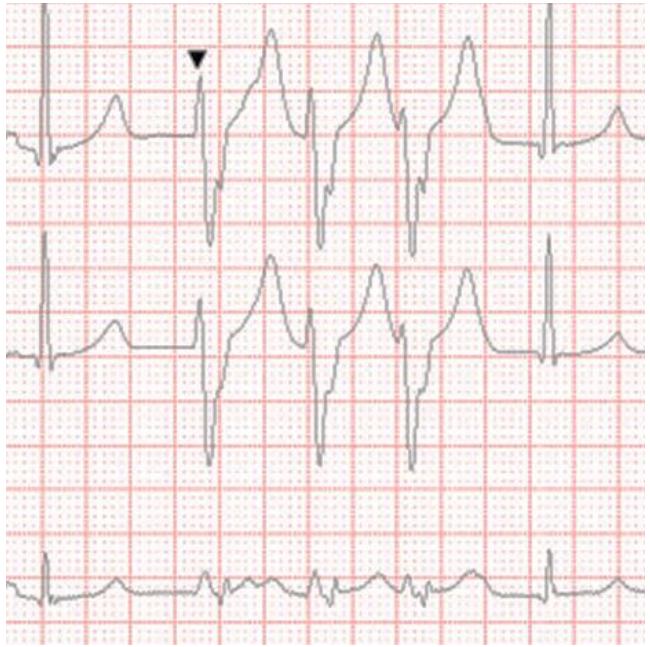
Neilan TG, et al. Circulation. 2006.

Could exercise promote inflammation?

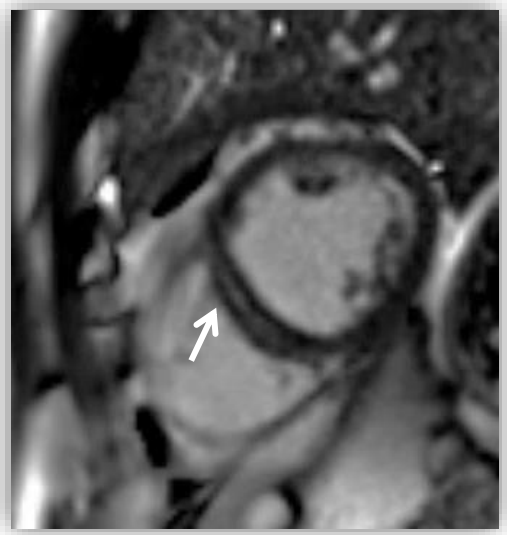
55-year-old previously asymptomatic male, PKP2 mutation +, phenotype -

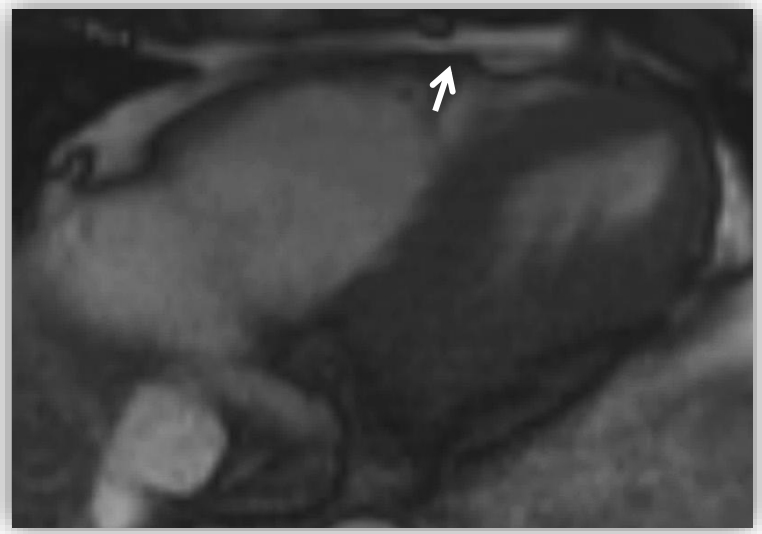
- 01/2018: started high intensity interval exercise at the gym
- 03/2018: he noticed significant palpitations. 24h Holter: 14307 VEs (16%), 2x NSVTs (monomorphic Triplets). hsTnT negative.





Courtesy of Dr Alexandros Protonotarios



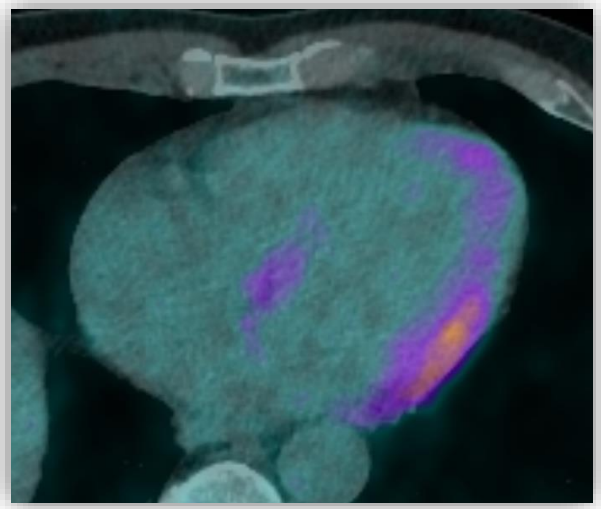


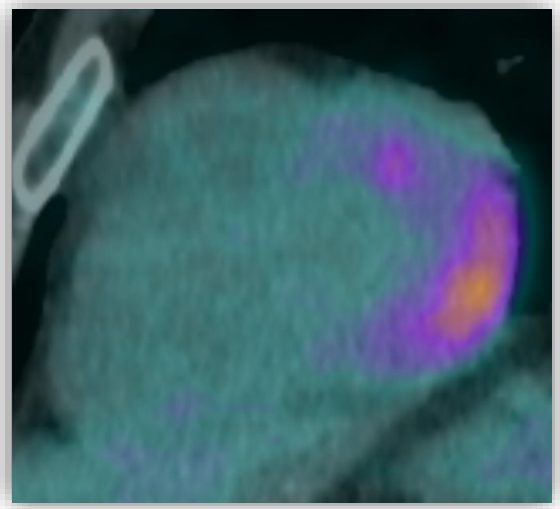
CMR

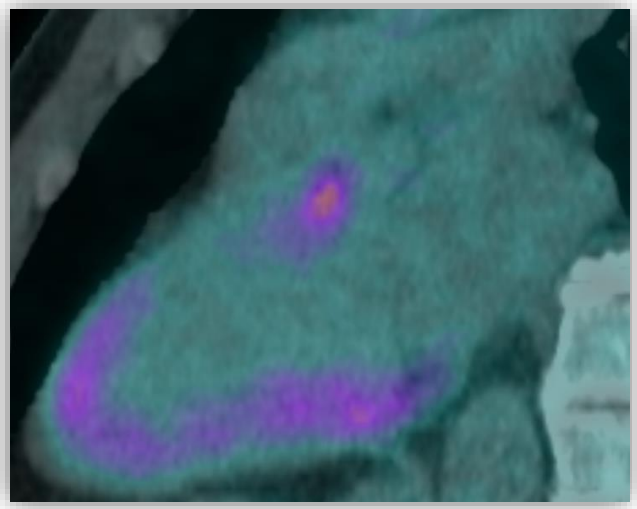
Normal biventricular size,
minor dyskinetic area of the RV free wall
Minor mid-wall LGE at the midseptum

FDG-PET (cardiac protocol)

Heterogenous LV myocardial uptake compatible with active myocardial inflammation.

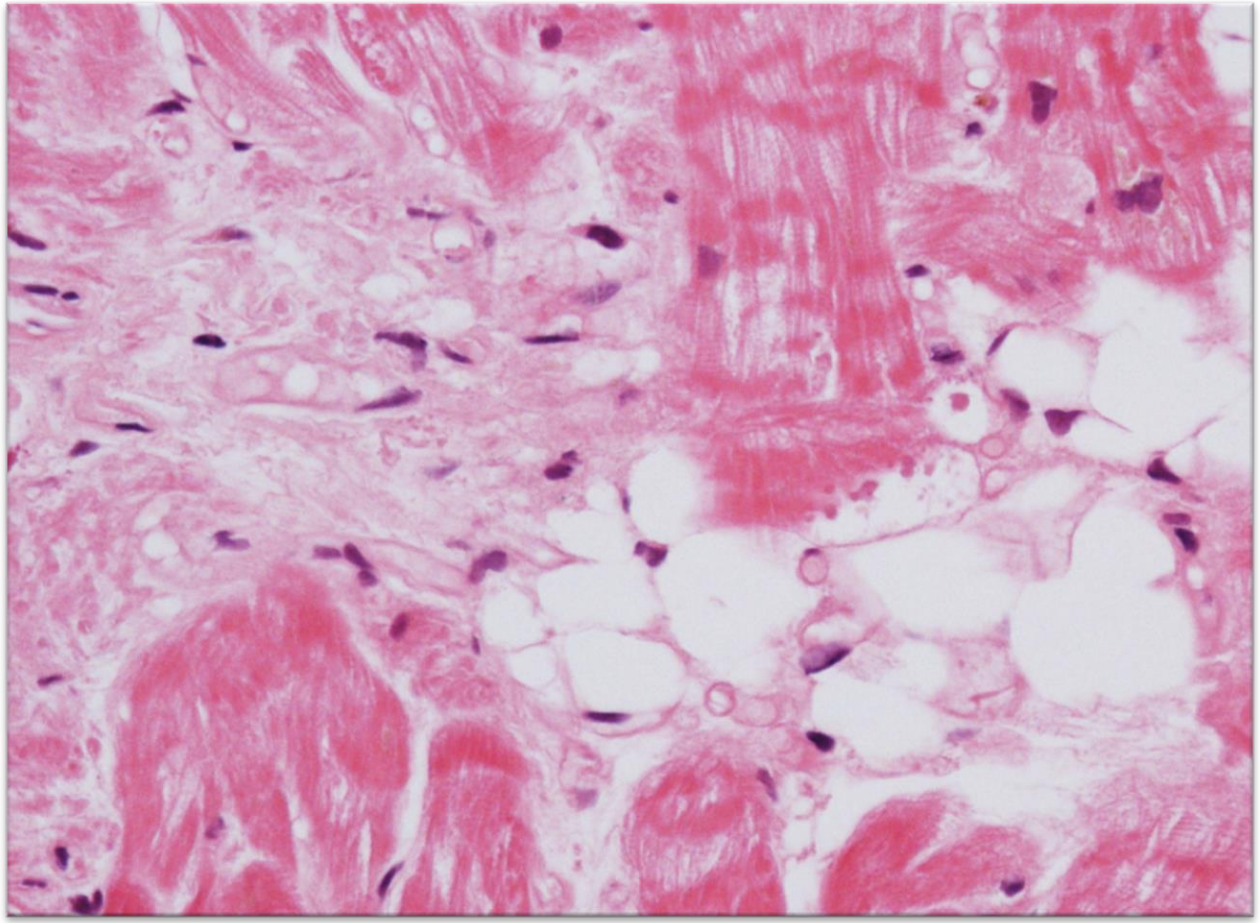






Courtesy of Dr Alexandros Protonotarios

EMB: fibrofatty replacement and myocardial apoptosis. No inflammatory infiltrates identified.

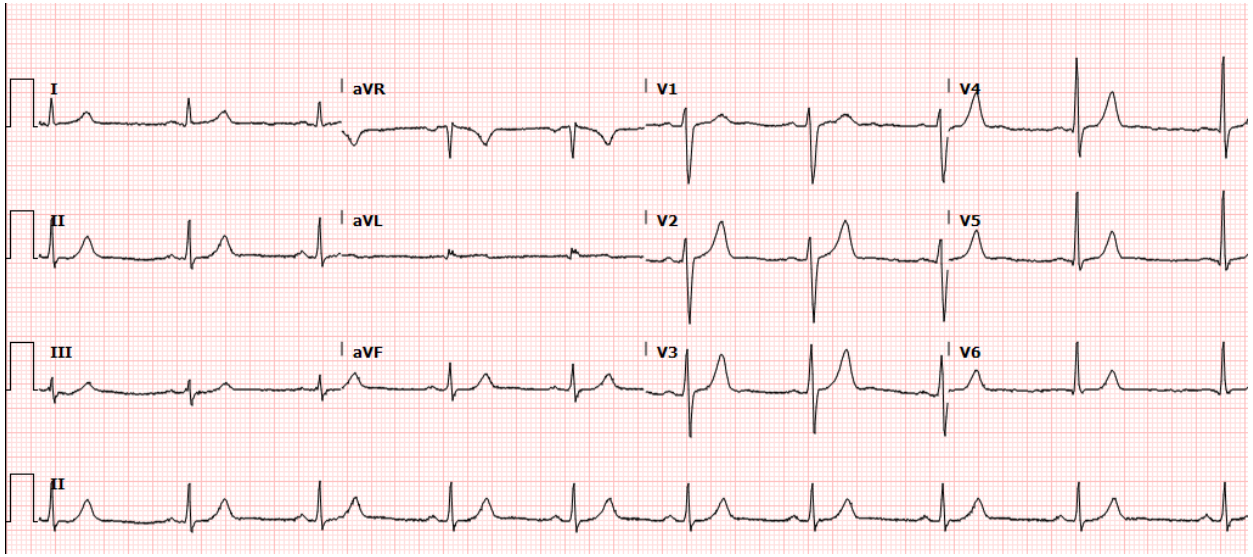


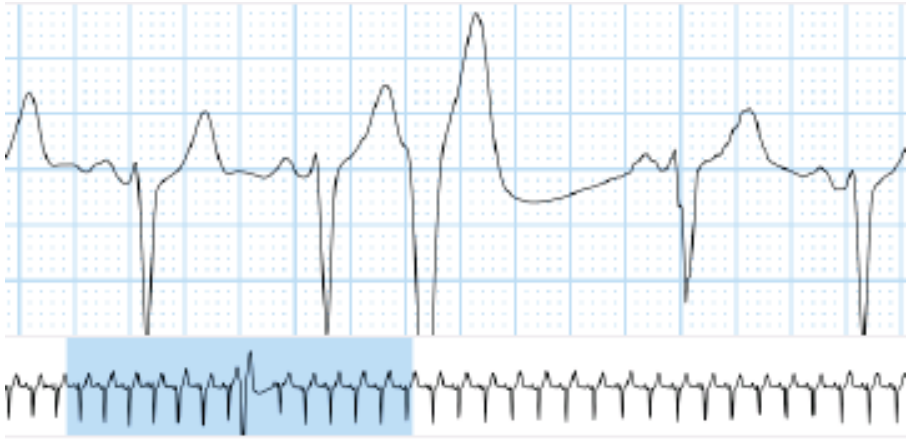
Courtesy of Dr Alexandros Protonotarios

Could exercise promote inflammation?

55-year-old previously asymptomatic male, PKP-2 mutation +, phenotype -

- Started on Bisoprolol 2.5 mg od and advised to avoid intensive exercise
- Repeat 24h Holter: 8 VEs. No complex ventricular arrhythmias
- Hot phase of ARVC or exercise induced inflammation?

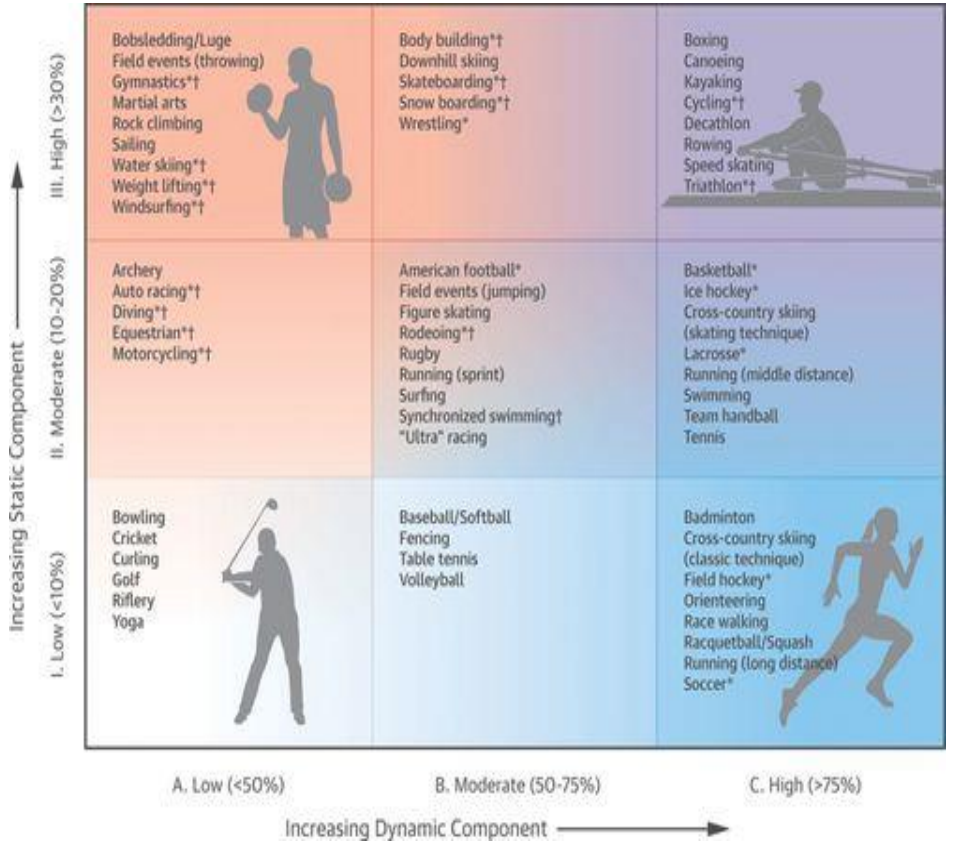




Courtesy of Dr Alexandros Protonotarios

Current recommendations

- **AHA/ACC 2015:** Athletes with a possible diagnosis of ARVC should not participate in most competitive sports, with the possible exception of low-intensity class 1A sports (Class III; Level of Evidence C).
- **EAPC/ESC 2019:** Athletes who are genetic carriers of pathogenic AC-associated desmosomal mutations (even in the absence of phenotypic expression of the disease) should not participate in competitive sports. These athletes should be advised to limit their exercise programmes to leisure-time activities and remain under clinical surveillance (Class IIa/Level of Evidence C).



Maron BJ, et al. Circulation. 2015. // Pelliccia A, et al. Eur Heart J. 2019.

Conclusions

Hypertrophic cardiomyopathy

- Hypertrophy may be insufficient as the sole diagnostic criterion
- Risk factors and events do occur in phenotype negative patients but they are very rare.
- Novel imaging/EP and hybrid techniques may allow for a more detailed understanding of such occurences in phenotype negative patients.
- Current guidelines do not suggest restriction of exercise but focus on early detection of phenotypical conversion.

Arrhythmogenic/NDLV cardiomyopathy

- Less structured pathophysiology compared to HCM
- The phenotype here may only be arrhythmia, even in the absence of structural abnormalities
- Two major concerns
  - Events
  - Disease progression
- Both may increase with exercise.
- Current guidelines suggest restriction of exercise and are in favor of predictive treatment