Arrhythmogenic Cardiomyopathy

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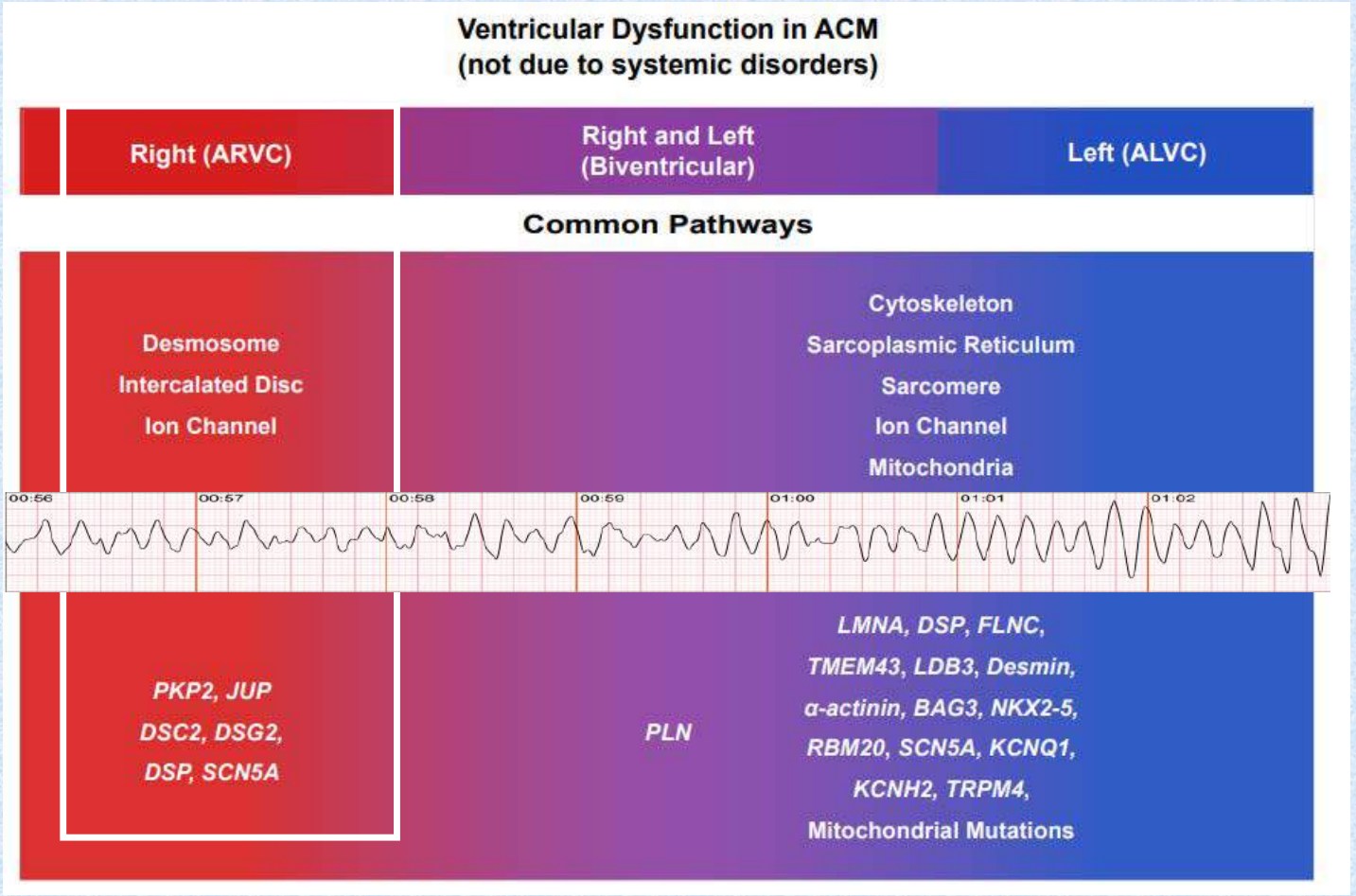
Disclosures:

1.Consultant, Medtronic, Inc

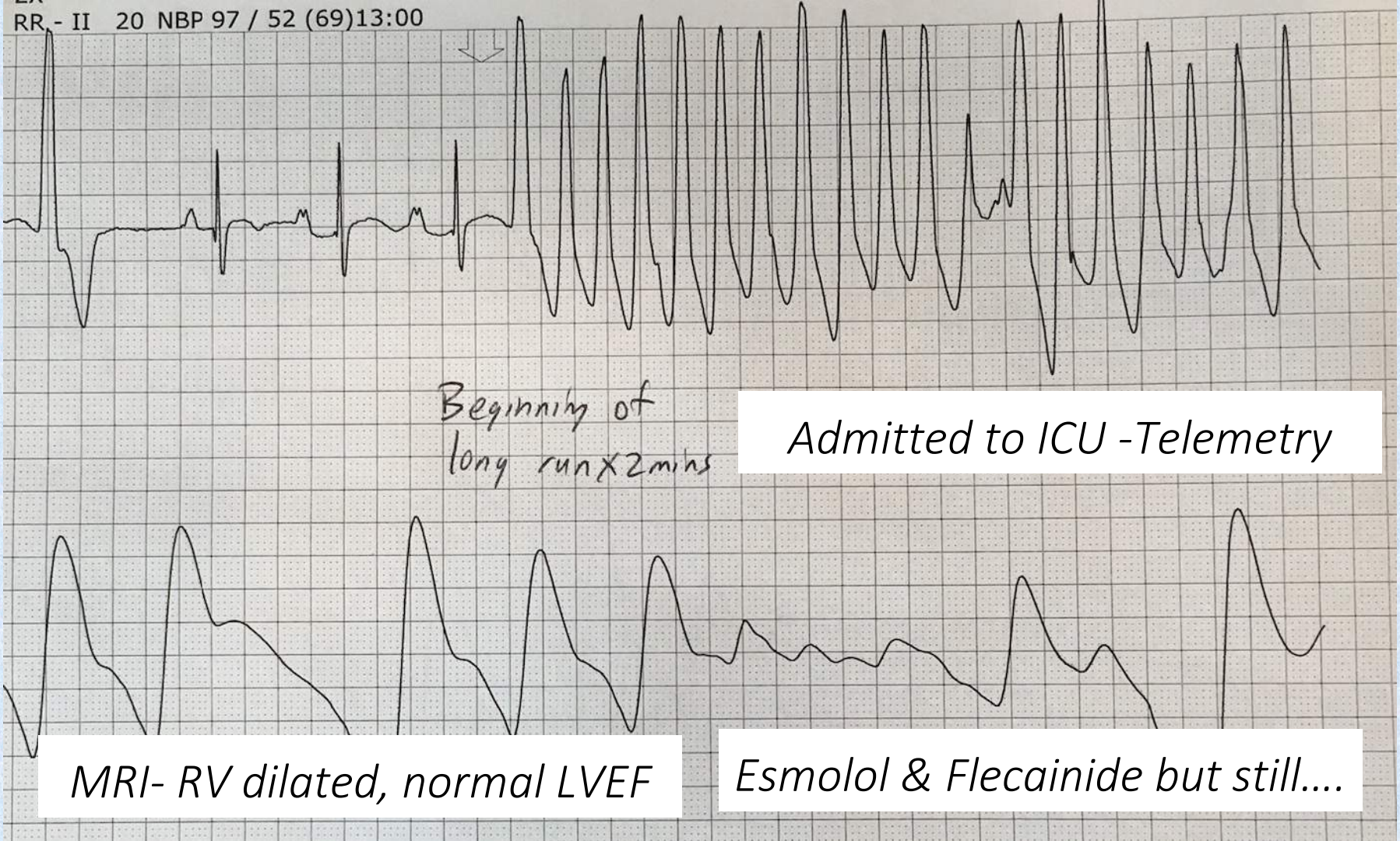
2. Talk on behalf of : Dr. Mitchell Cohen



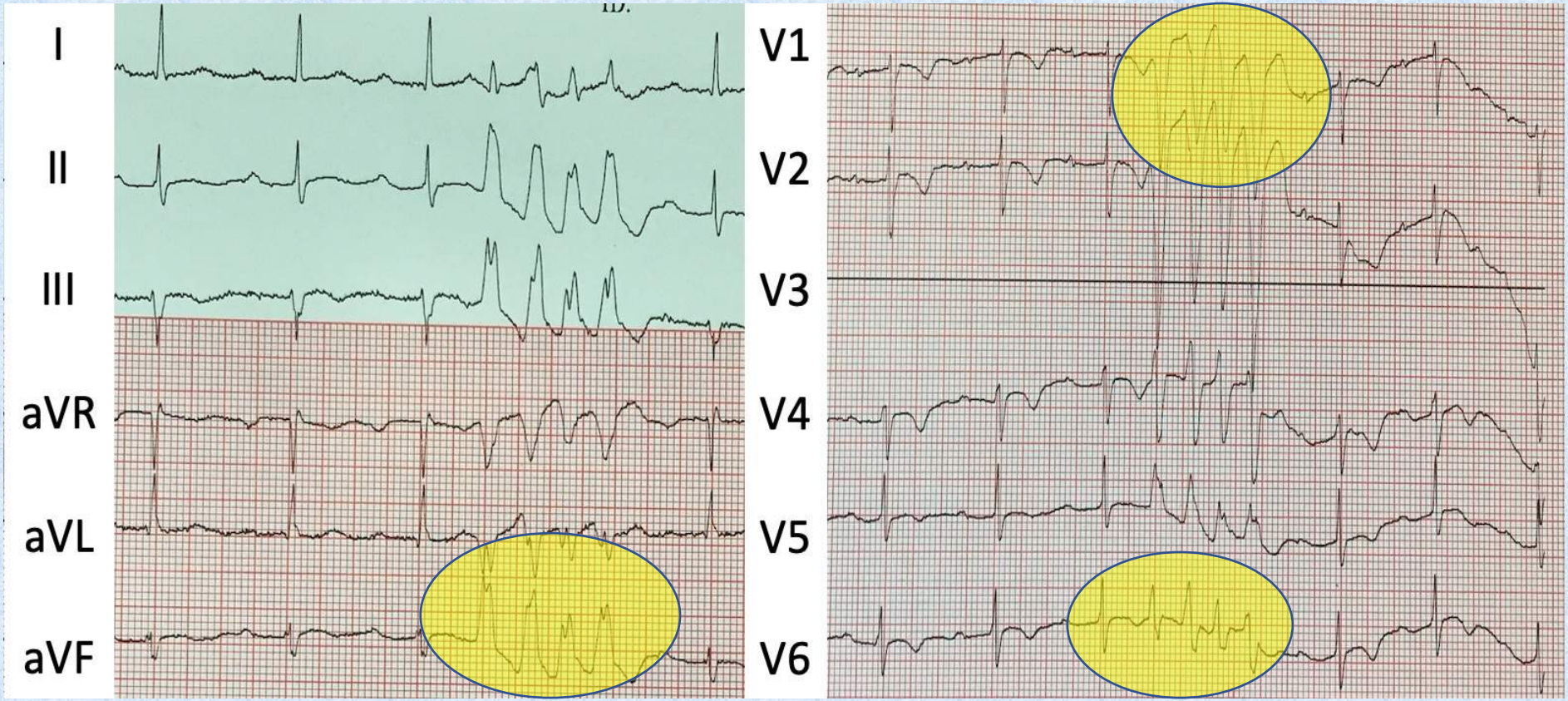
Towbin, Heart Rhythm 2019

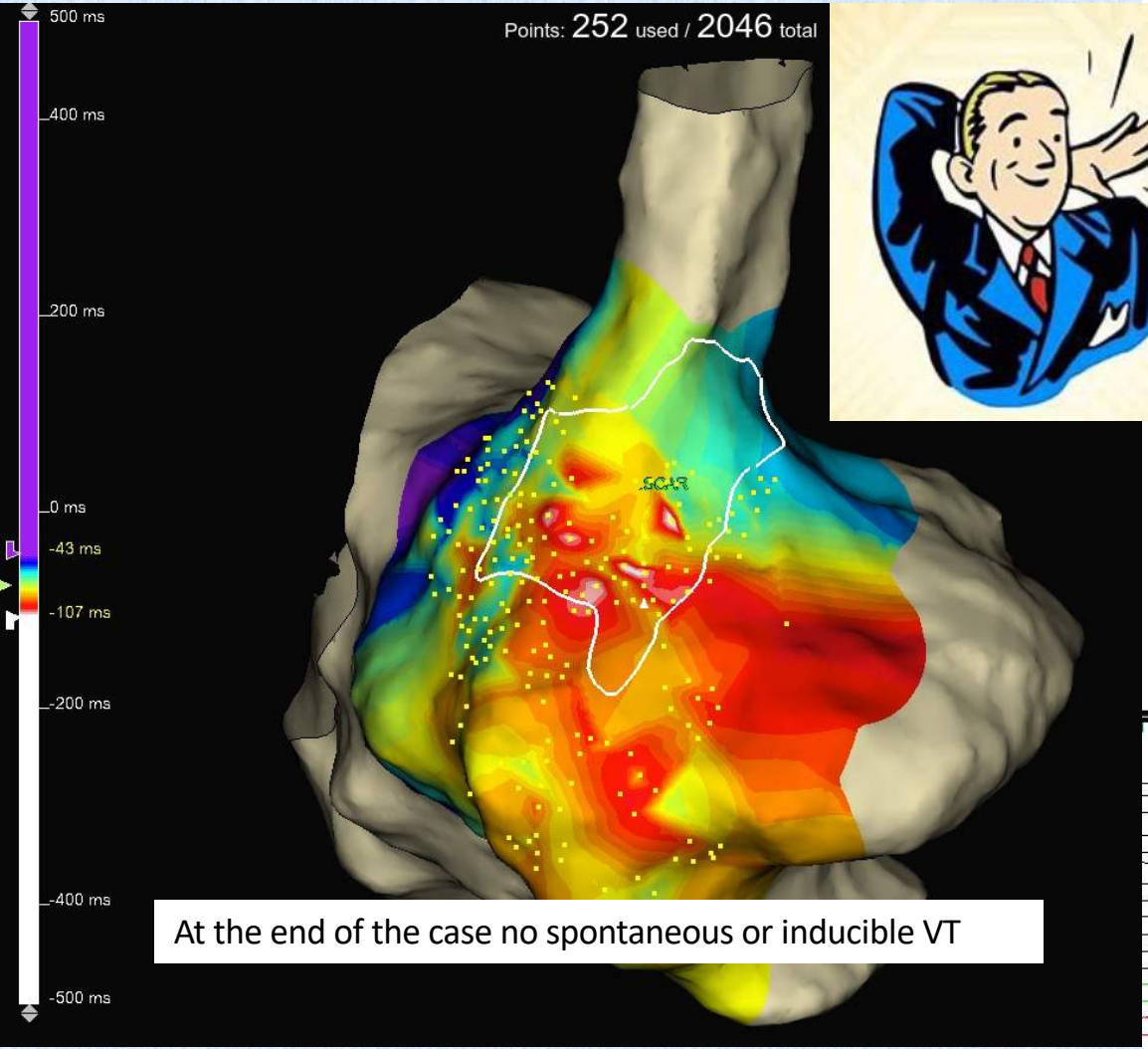
Case Presentation (January 2022)

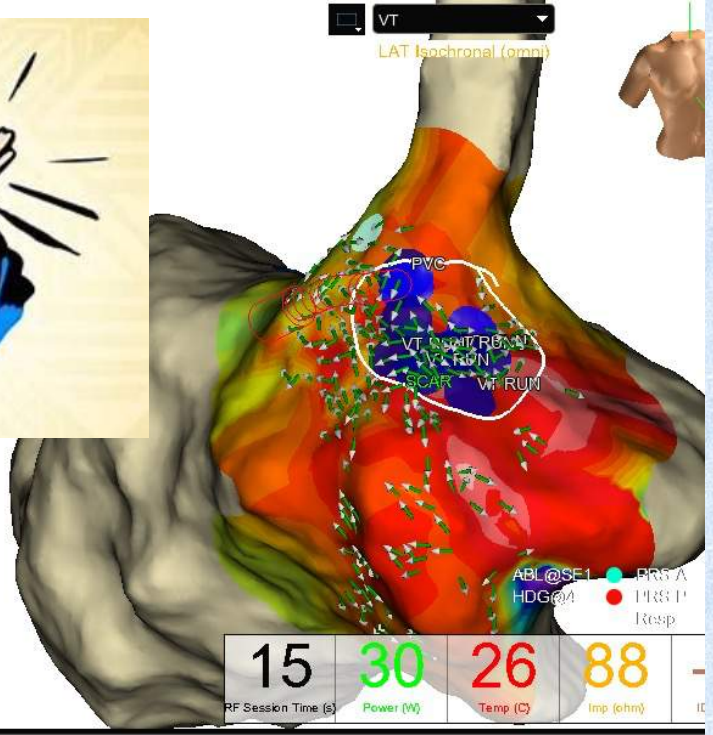
- 16-yo girl walking around Costco with a friend
- "*Tells her friend that her heart is racing*", faints and wakes up on the floor of the store with all of these people standing around her.
- A similar experience has happened 1-2 times per year since 7th grade (now in 11th grade)
- Moved to Northern Virginia - 7 years ago from Ghana
- Family History: Unremarkable (no SCD, no unexplained syncope)

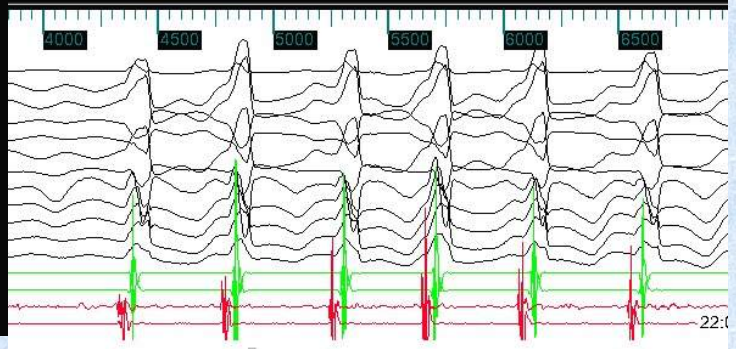

RR - II 20 NBP 97 / 52 (69)13:00
Beginning of long run x 2 mins
Admitted to ICU -Telemetry
MRI- RV dilated, normal LVEF
Esmolol & Flecainide but still….

Left Bundle, Inferior Axis (RVOT) -NSVT



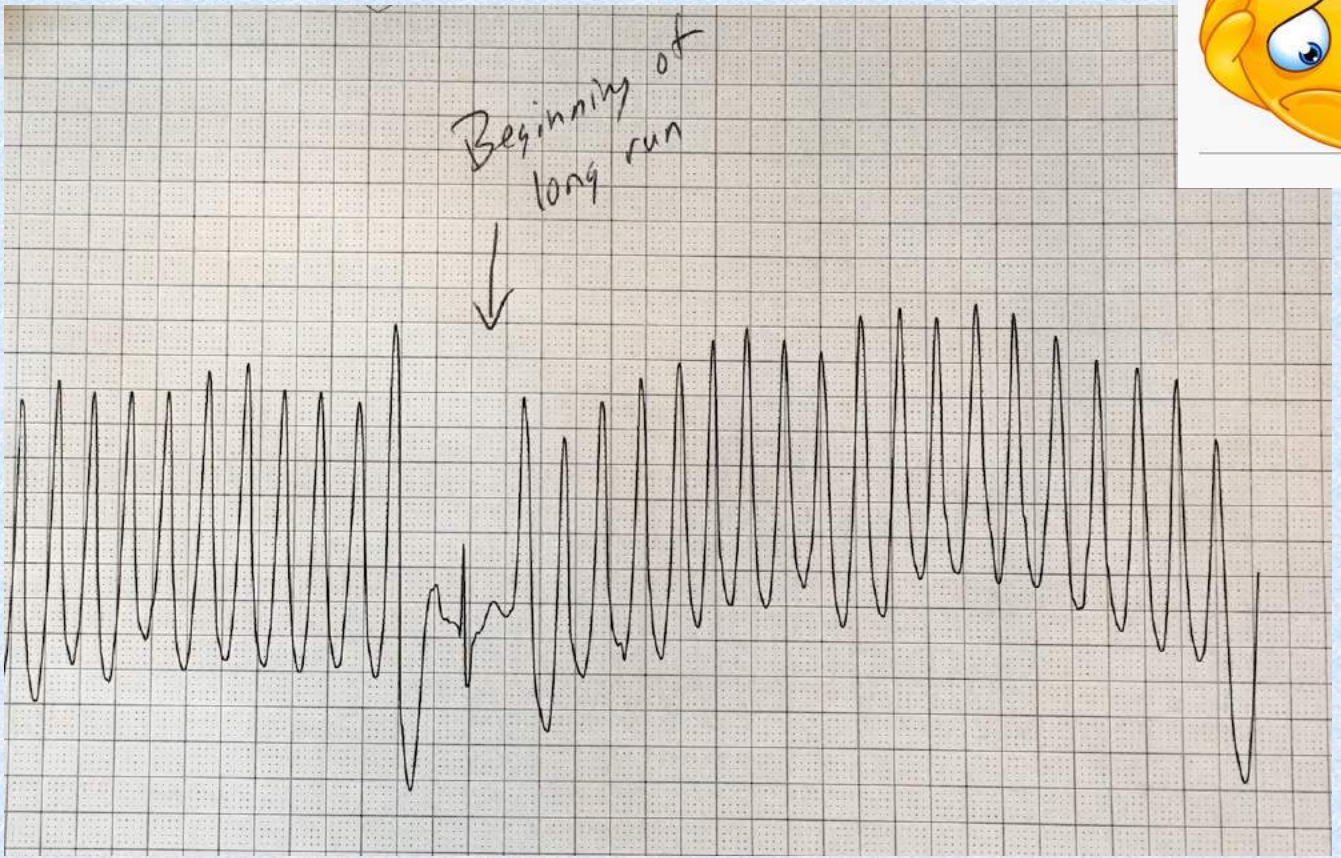




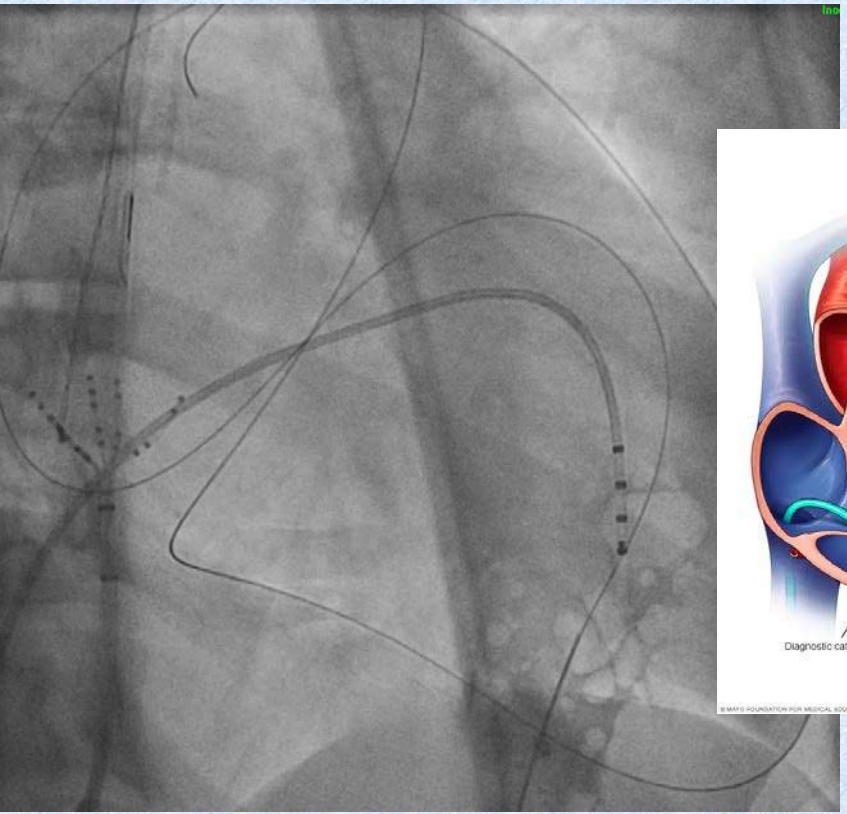


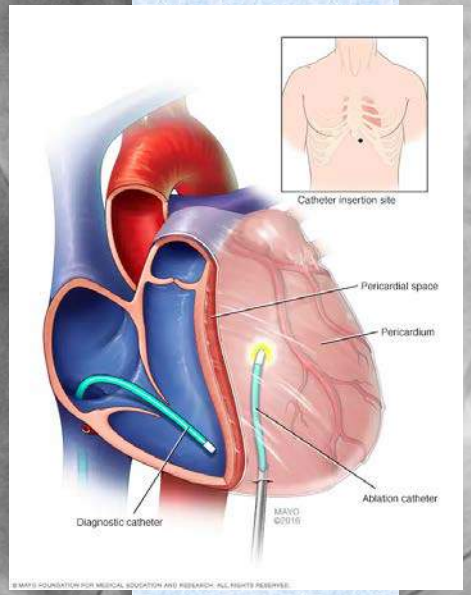
At the end of the case no spontaneous or inducible VT

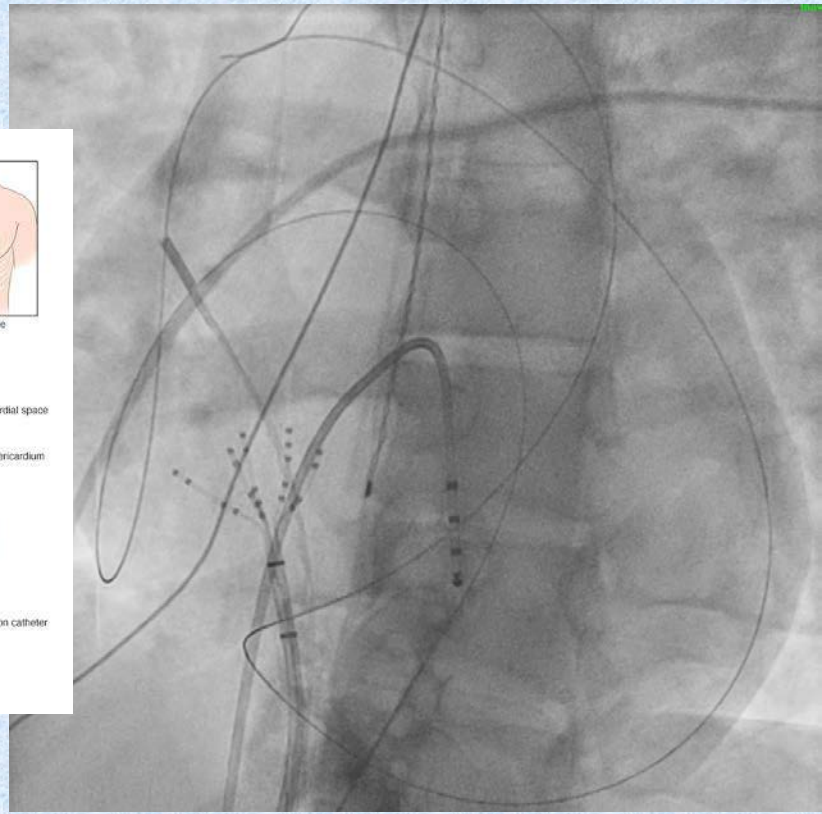
18 hours later in the ICU

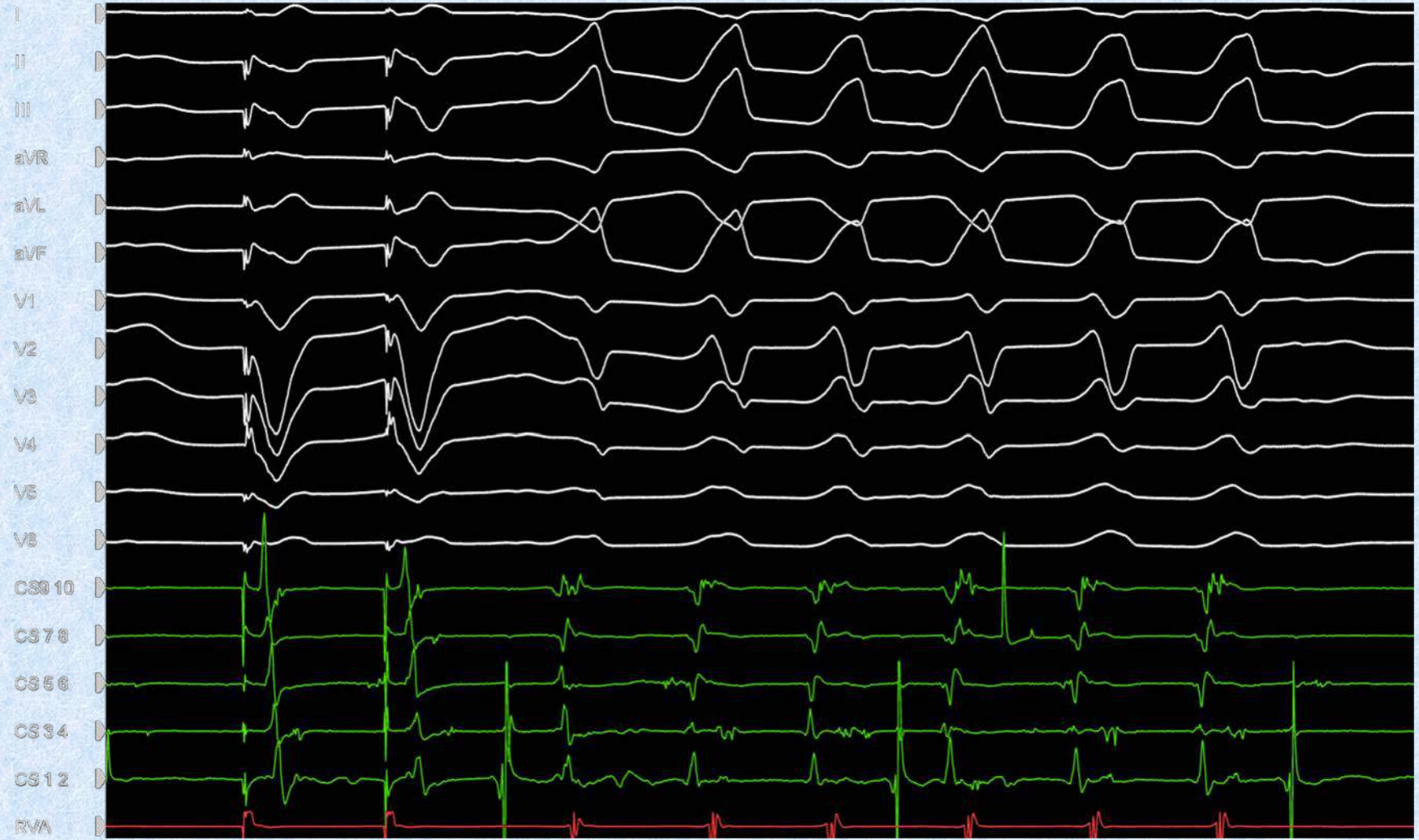


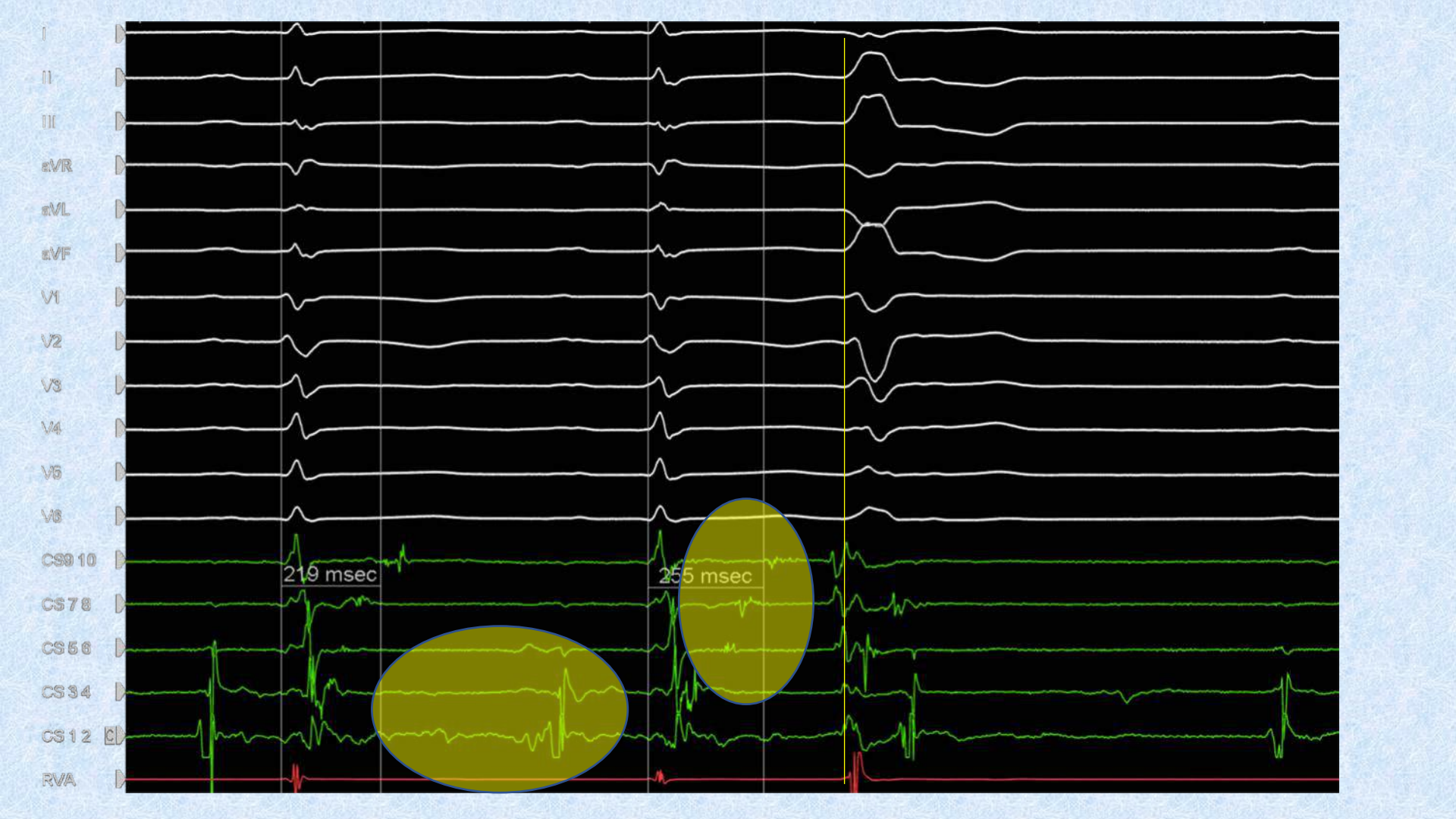
Back to the EP Lab - Pericardial Access

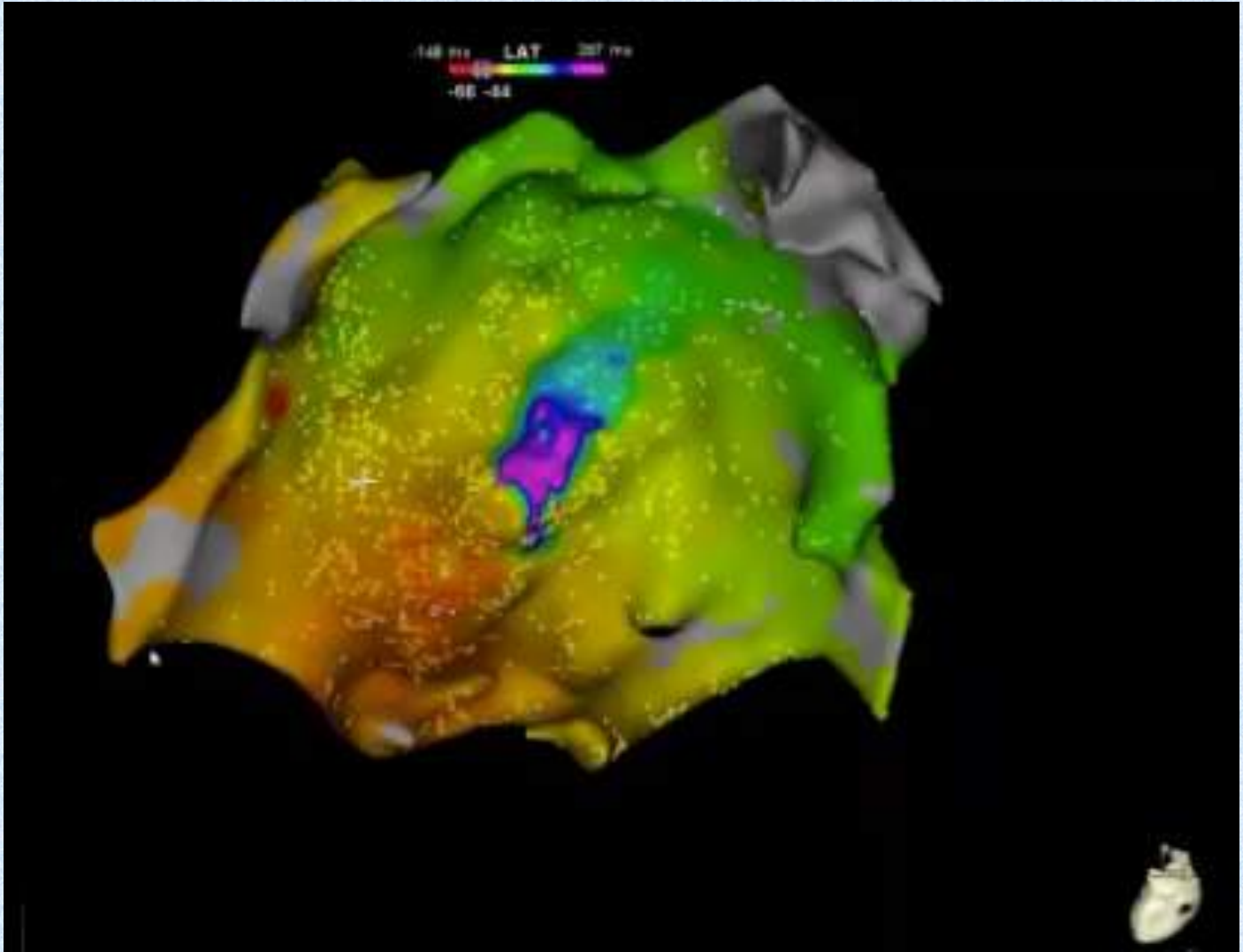


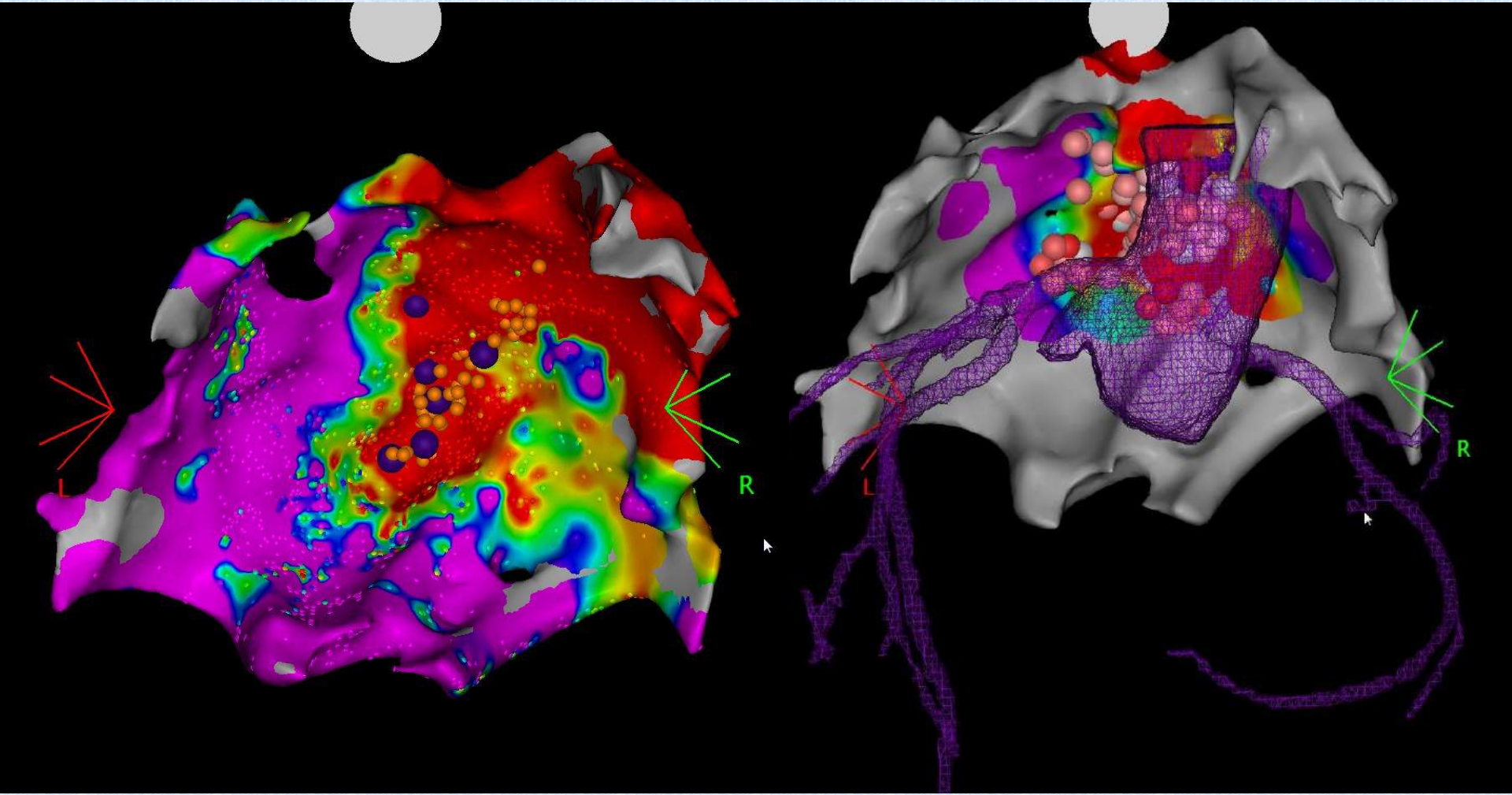





I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
CS9 10
CS7 8
CS5 6
CS3 4
CS1 2
RVA


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
CS9 10
CS7 8
CS5 6
CS3 4
CS1 2
RVA
219 msec
255 msec


LAT


L
R
L
R

Follow-Up

- The patient has no further VT events in 12 months
- Receives a single chamber ICD
- Discharged initially on atenolol and Flecainide
- + plakophillin ARVC mutation (patient is the proband)

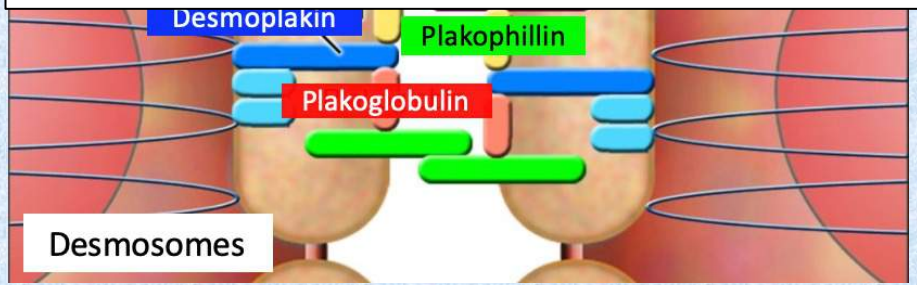
Misnomers We Have Heard – Let's Address Them

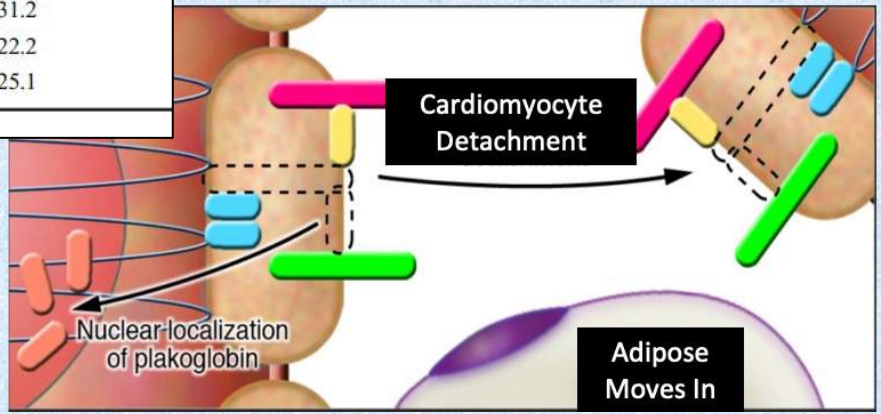
1. *"This is a disease of adults"*
2. *"If the ECHO and MRI are normal my patient cannot have ARVC"*
3. *"I just see LV dysfunction, must be old myocarditis"*
4. *"Genetic testing is so rarely positive in ARVC that it is useless"*
5. *"Sports restrictions are over exaggerated"*

Adherens Junctions

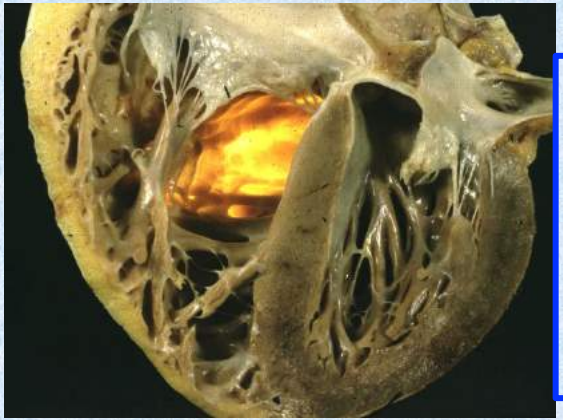
Gene	Encoded protein	Subcellular localisation	Chromosomal locus
JUP	Plakoglobin	Desmosome	17q21.2
DSP	Desmoplakin	Desmosome	6p24.3
PKP2	Plakophilin-2	Desmosome	12p11.21
DSG2	Desmoglein-2	Desmosome	18q12.1
DSC2	Desmocollin-2	Desmosome	18q12.1
CDH2	N-Cadherin	Area composita	18q12.1
LMNA	Lamin A/C	Nuclear envelope	1q22
DES	Desmin	Intermediate filament	2q35
CTNNA3	Alpha-T-catenin	Area composita	10q21.3
PLN	Phospholamban	Sarcoplasmic reticulum	6q22.31
RYR2	Ryanodine receptor 2	Sarcoplasmic reticulum	1q43
TGFB3	Transforming growth factor β3	Growth factor	14q24.3
TTN	Titin	Sarcomere	2q31.2
SCN5A	Sodium voltage-gated channel alpha subunit 5	Sodium channel Intercalated disk	3p22.2
TMEM43	Transmembrane protein 43	Nuclear envelope	3p25.1

15 genes

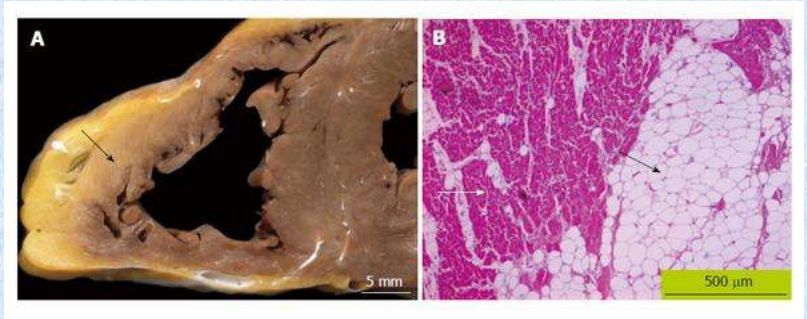


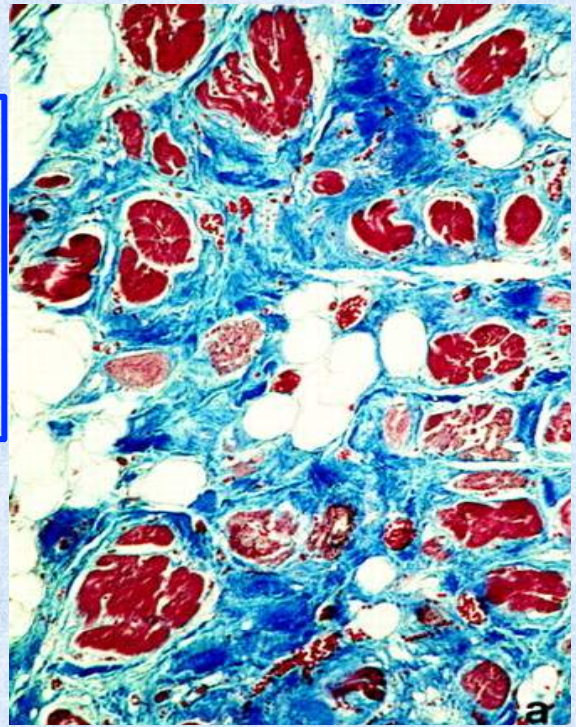


Histopathology



-Fibro-fatty tissue replacement
-Scar Zone for slow conduction and VT circuits
-Exercise exaggerates desmosomal dysfunction





Basso Circulation 1996;94:983-991
Corado, NEJM 2018

Diagnosis of ARVC

2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy

Jeffrey A. Towbin, MS, MD (Chair),[1,2] William J. McKenna, MD, DSc (Vice-Chair),[3]
Dominic J. Abrams, MD, MRCP, MBA,[4] Michael J. Ackerman, MD, PhD,[5,*]

Complicated set of diagnostic criteria

Need 4 points (2 major, 1 major + 2 minor, or 4 minor TFC points) from different groups for definite diagnosis

4 points = definite ACM

3 points = borderline ACM

2 points = possible ACM

Christopher J. McLeod, MBChB, PhD, FHRS,[5] Luisa Mestroni, MD,[22]
Silvia G. Priori, MD, PhD,[23,24,25] Jeffrey E. Saffitz, MD, PhD,[26]
Shubhayan Sanatani, MD, FHRS, CCDS,[27,¶¶] Wataru Shimizu, MD, PhD,[28,##]
J. Peter van Tintelen, MD, PhD,[29,30] Arthur A.M. Wilde, MD, PhD,[24,29,31]
Wojciech Zareba, MD, PhD[32]

Global or Regional Dysfunction and Structural Alteration		
ECHO	Regional RV akinesia, dyskinesia, or aneurysm and one of the following (end diastole):	
	1. PLAX RVOT ≥ 32 mm (PLAX/BSA ≥19 mm/m^2)	1. PLAX RVOT ≥ 29 mm (PLAX/BSA ≥16 to <19 mm/m^2)
	2. PSAX RVOT ≥36 mm PLAX/BSA (≥ 21 mm/m^2)	2. PSAX RVOT ≥32 to < 36 mm PLAX/BSA (≥ 18 to <21 mm/m^2)
	3. Fractional area change of ≤ 33%	3. Fractional area change of > 33% to ≤ 33%
MRI	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:	
	1. Ratio of RV end-diastolic volume to BSA ≥110 ml/m^2 (male patients) or ≥100 ml/m^2 (female patients)	1. Ratio of RV end-diastolic volume to BSA 100 to <110 ml/m^2 (male patients) or 90 to <100 ml/m^2 (female patients)
	2. RV ejection fraction ≤ 40%	2. RV ejection fraction 41 - 45%
RV Angiography	Regional RV akinesia, dyskinesia, or aneurysm	

Tissue Characterization of the Wall		
Endomyocardial Biopsy (>1 sample)	<60% residual myocytes on morphometric analysis (or <50%, if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one EMB sample	60-75% residual myocytes, on morphometric analysis (or 50-65%, if estimated) and fibrous replacement of the RV free-wall myocardium, with or without fatty replacement of tissue, in at least one EMB sample
ECG	Repolarization Abnormalities	
	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in patients older than 14 yr of age (in the absence of complete RBBB, QRS ≥120 msec)	Inverted T waves in leads V1 and V2 in patients older than 14 yr of age (in the absence of complete RBBB) or in V4, V5, or V6; Inverted T waves in leads V1, V2, V3, and V4 in patients older than 14 yr of age (in the presence of complete RBBB)

Arrhythmias		
	Depolarization/Conduction Abnormalities	
ECG	Epsilon wave (reproducible low-amplitude signals from end of QRS complex to onset of the T wave) in the right precordial leads (V_1, V_2, and V_3)	Late potentials on signal-averaged ECG in at least one of three parameters in the absence of a QRS complex duration of ≥110 msec on the standard ECG: a. Filtered QRS complex duration, ≥114 msec b. Duration of terminal QRS complex <40 μV (low-amplitude signal duration), ≥38 msec c. Root-mean-square voltage of terminal 40 msec, ≤20 μV Terminal activation duration of QRS complex, ≥55 msec, measured from the nadir of the S wave to the end of the QRS complex, including R′, in V1, V2, or V3, in the absence of complete RBBB
ECG & Holters	Nonsustained or sustained ventricular tachycardia with a left bundle-branch block and superior axis pattern (negative or indeterminate QRS complex in leads II, III, and aVF and positive QRS complex in lead aVL)	Nonsustained or sustained ventricular tachycardia of RV outflow configuration with a left bundle-branch block and inferior axis pattern (positive QRS complex in leads II, III, and aVF and negative QRS complex in lead aVL) or unknown axis, or >500 ventricular extrasystoles per 24 hr (on Holter monitoring)

Family History		
Family History	ARVC confirmed in a first-degree relative who meets current task- force criteria.	History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether current task-force criteria are met.
	ARVC confirmed pathologically at autopsy or surgery in a first-degree relative, or	Premature sudden death (at <35 yr of age) due to suspected ARVC in a first-degree relative, or
	Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation	ARVC confirmed pathologically or by current task-force criteria in a second-degree relative

BSA=body surface area; MR; PLAX=parasternal long-axis; PSAX=parasternal short-axis; RBBB=right bundle branch block

Phenotypic Manifestations of Arrhythmogenic Cardiomyopathy in Children and Adolescents

Elizabeth S. DeWitt, MD,[a,b] Stephanie F. Chandler, MD,[a,b] Robyn J. Hylind, MS, CGC,[a,b] Virginie Beausejour Ladouceur, MD,[a,b] Elizabeth D. Blume, MD,[b] Christina VanderPluym, MD,[b] Andrew J. Powell, MD,[b] Francis Fynn-Thompson, MD,[c] Amy E. Roberts, MD,[b] Stephen P. Sanders, MD,[b,d] Vassilios Bezzerides, MD, PhD,[a,b] Neal K. Lakdawala, MD,[e] Calum A. MacRae, MD, PhD,[e] Dominic J. Abrams, MD, MBA[a,b]

N=32 patients < 21 years of age
Mean age: 15.1 ± 3.8 years

ABSTRACT

BACKGROUND Arrhythmogenic cardiomyopathy (ACM) is a variably penetrant disease increasingly identified in young patients.

OBJECTIVES This study sought to describe the diverse phenotype, genotype, and outcomes in pediatric and adolescent patients.

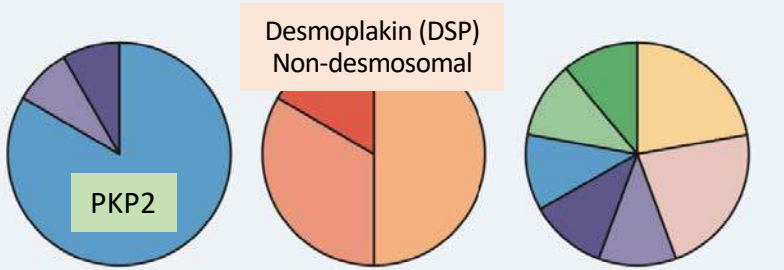
METHODS Records from 1999 to 2016 were reviewed for individuals age <21 years with a consistent personal or family history. Patients were categorized by right ventricular (RV), left dominant (LD), or biventricular subtypes using 2010 Task Force Criteria or proposed features of LD disease, encompassing electrocardiographic, structural, histological, and arrhythmic characteristics. Genetic variants classified as pathogenic and/or likely pathogenic by 2015 American College of Medical Genetics and Genomics criteria in recognized disease-associated genes were included.

RESULTS Manifest disease was evident in 32 patients (age 15.1 ± 3.8 years), of whom 22 were probands, including 16 RV, 7 LD, and 9 biventricular ACM. Nondiagnostic features were seen in 5 of 15 family members. RV disease was associated with cardiac arrest and ventricular tachycardia ($p = 0.02$) and prevalence of *PKP2* variants ($p < 0.01$), whereas biventricular disease was associated with a younger age of onset ($p = 0.02$). LD ACM was associated with variants in *DSP* and *LMNA*, and biventricular ACM with more a diverse etiology in desmosomal genes. Cardiac arrest was observed in 5 probands (age 15.3 ± 1.9 years) and ventricular tachycardia in 10 (age 16.6 ± 2.7 years), 6 probands, and 4 family members. Features suggestive of myocardial inflammation were seen in 6 patients, with ventricular tachycardia and/or cardiac arrest in 3 patients. Cardiac transplantation was performed in 10 patients. There were no deaths. In RV and biventricular disease, electrocardiographic preceded imaging features, whereas the reverse was seen in LD disease.

CONCLUSIONS ACM in the young has highly varied phenotypic expression incorporating life-threatening arrhythmia, heart failure, and myocardial inflammation. Increased awareness of early onset, aggressive disease has important implications for patient management and familial screening. (J Am Coll Cardiol 2019;74:346–58)

	Right Dominant (ARVC)	Left Dominant AVC	Biventricular (AVC)
NUMBER	16	7	9
FEMALE/MALE	6/10	3/4	5/4
PROBAND	11 (69%)	3 (43%)	8 (89%)
Age at Diagnosis	16.7 yrs	15 yrs	12.1 yrs
Cardiac Arrest	19%	19%	11%
Ventricular Tachycardia	56%	43%	22%
CARDIAC TRANSPLANT	0 (0%)	2 (29%)	8 (89%)

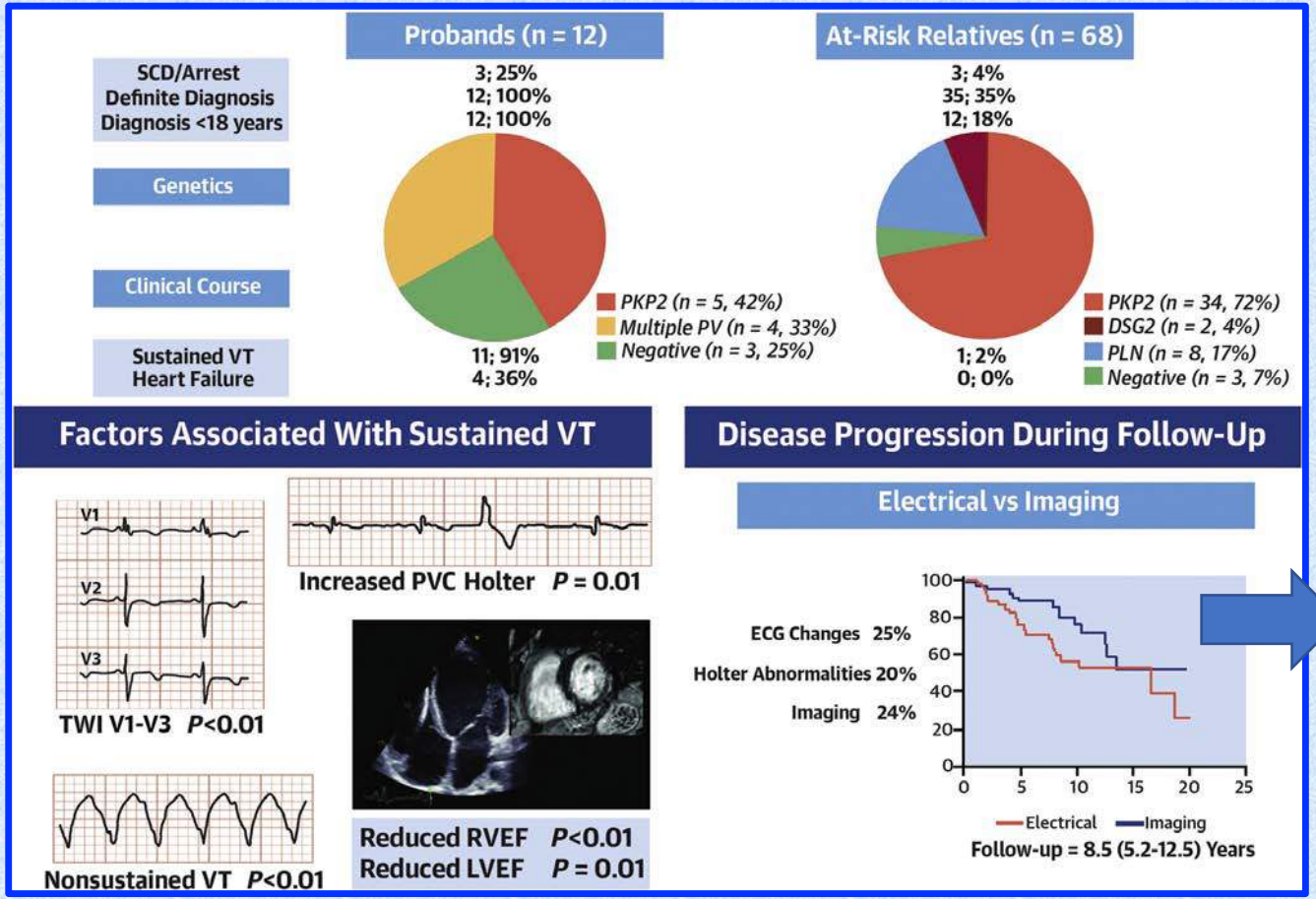
GENETIC FINDINGS



Predominantly Plakophillin-2

Once again, not a disease of just adults

The ARVC Registry Study



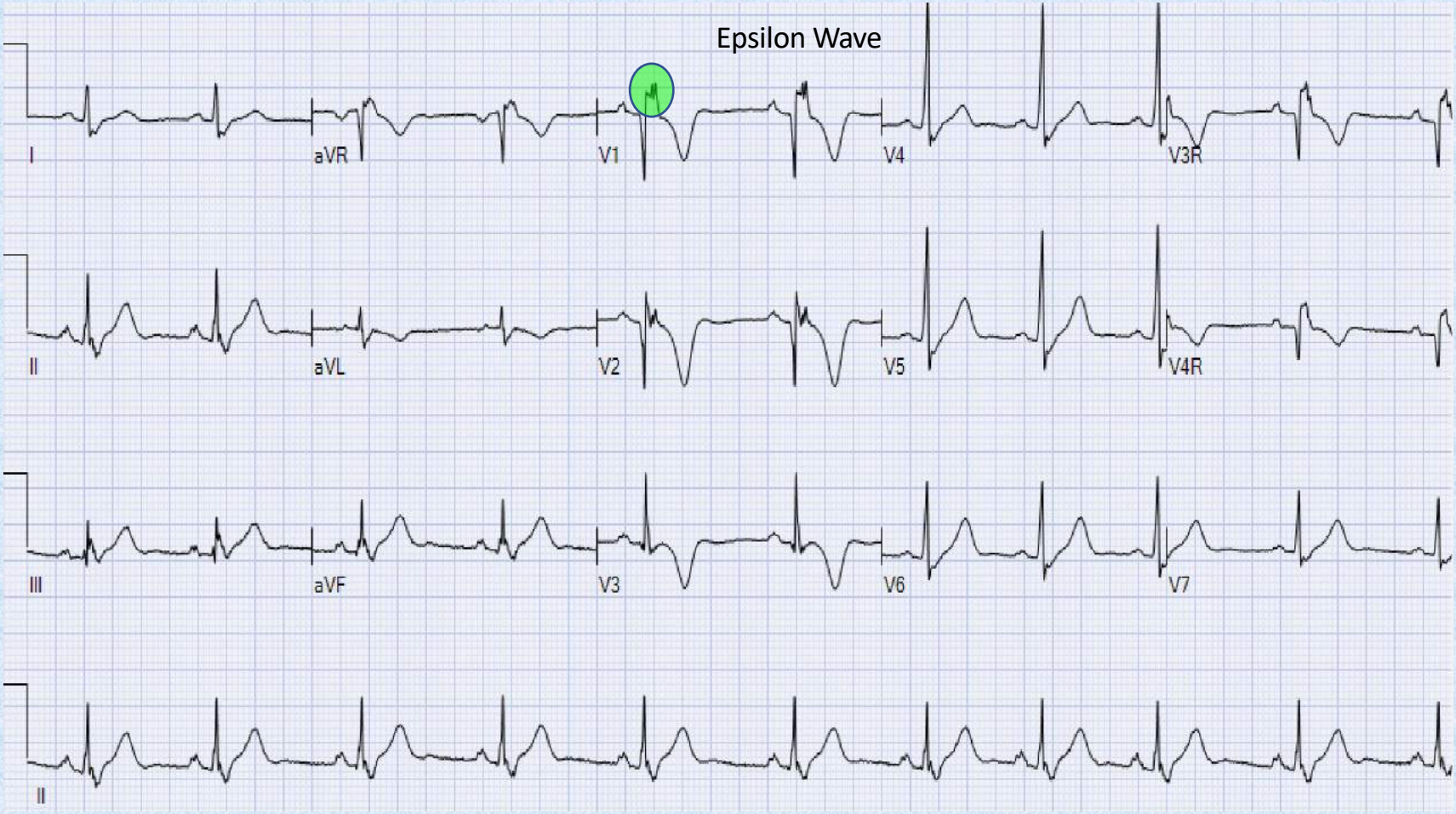
IN *CHILDREN*, ELECTRICAL DISEASE PROGRESSION *PRECEDED* IMAGING CHANGES

-VE% on Holter

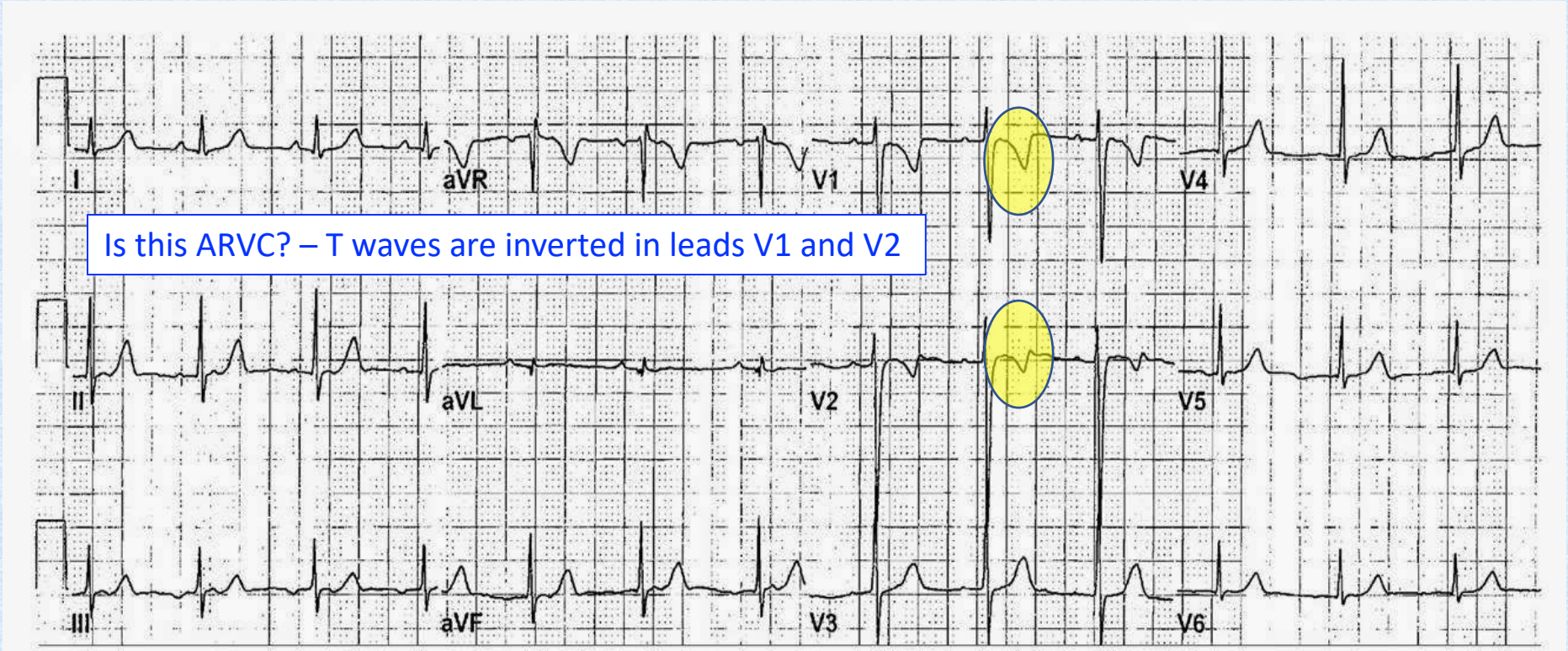
-ECG changes

Roudijk et al JACC EP 2022

If only it were this easy…21 year-old clear ARVC ECG

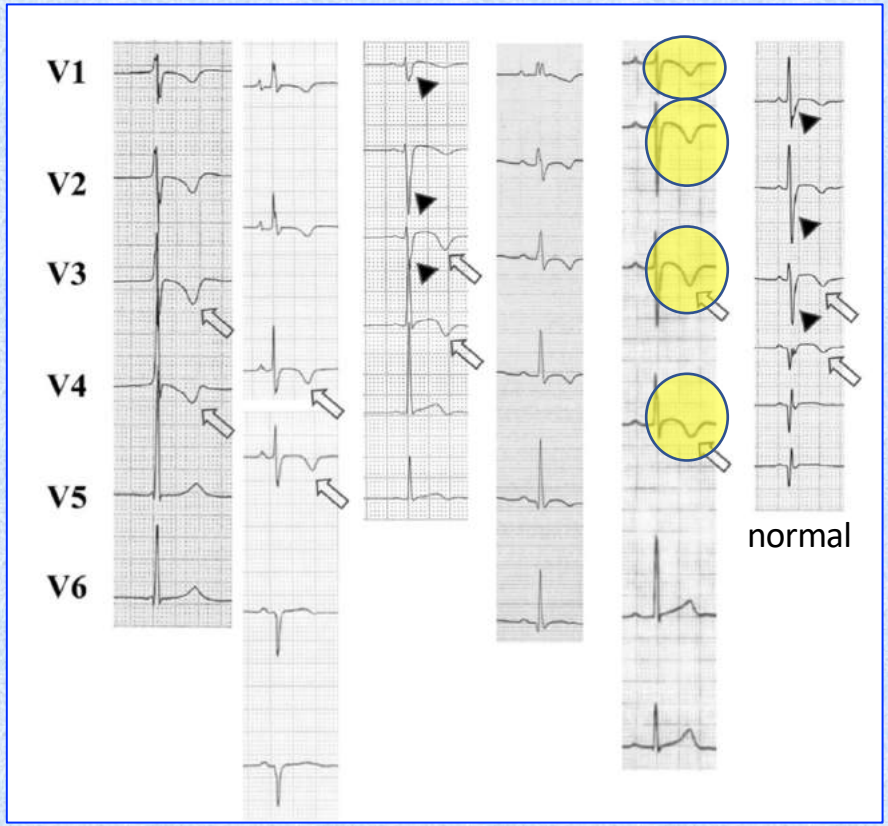


Healthy 14 year-old (juvenile pattern)



Is this ARVC? – T waves are inverted in leads V1 and V2

Impact of the T-wave characteristics on distinguishing arrhythmogenic right ventricular cardiomyopathy from healthy children



T wave inversion gets bigger in ARVC patients going from V1 out -whereas in healthy children tends to get smaller (60% vs. 0.55%

Imamura International Journal of Cardiology2020

Misnomers I Have Heard – Let's Address Them

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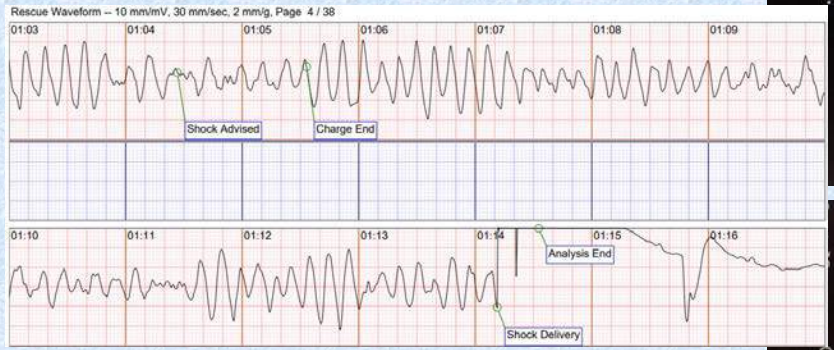
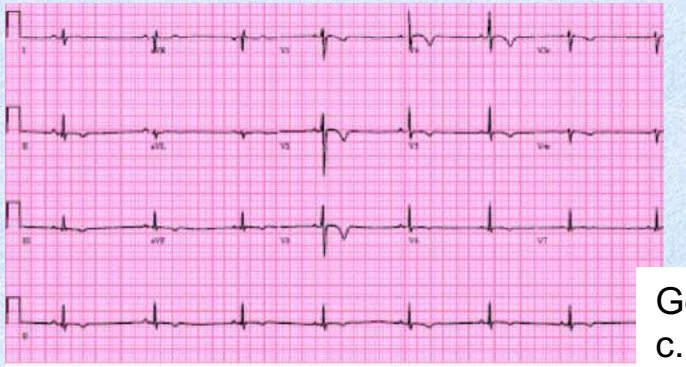
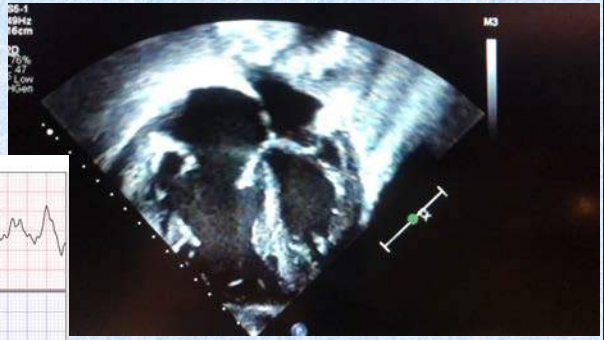
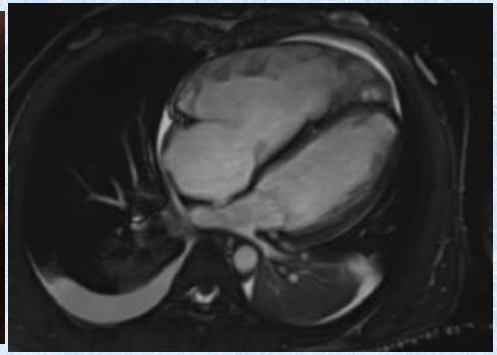
5. *"Sports restrictions are over exaggerated"*

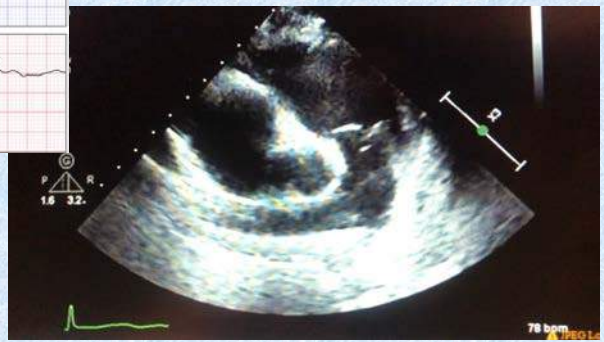
11 y.o (50 kg.)healthy male, no FH, Cardiac arrest after Basketball in school

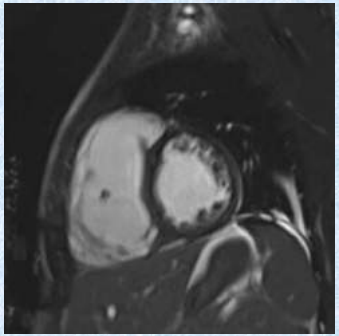












Gene: PKP2
c.1237C>T (p.R413*)

CMR: RVEF: 24% with a
RVEDV 242 cc/sq m, RVESV183 cc/sq m
LGE +++

Misnomers I Have Heard – Let's Address Them

1. ~~*"This is a disease of adults"*~~
2. *"If the ECHO and MRI are normal my patient cannot have ARVC"*
3. *"I just see LV dysfunction, must be old myocarditis"*
4. *"Genetic testing is so rarely positive in ARVC that it is useless"*
5. *"Sports restrictions are over exaggerated"*

ARVC Task Force Criteria

Demographics								
Family	Patient #	Age at Diagnosis, yrs	Structural	Tissue	Repolarization	Depolarization	Arrhythmia	Family History and Genetics
A	1	13.9	++		++	+		++
B	1	15.2			++	+	+	++
C	1	16.8	++		++	+	+	++
C	2	18.3			+	+		++
D	1	15.0			++	+	+	++
E	1	14.5	++		++	+	+	
F	1	22.1	+		++	+	+	++
G	1	14.2			++	+	+	++
H	1	20.2				+	+	++
H	2	21.8	+		++	+	+	
I	1	18.4			++	+	+	++
J	1	12.0	++		+	+	+	++
K	1	16.5	++		++		+	++
L	1	14.3	++		+		+	++
M	1	17.6			++	+	+	
N	1	16.1			+	+		++

Misnomers – Let's Address Them

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5. *"Sports restrictions are over exaggerated"*

ARVC PHASES
Natural History

Early Concealed Phase

non-apparent or subtle RV changes
(patients can still be at risk for SCD)

Electrical Phase

Characterized by T-wave inversions, PVCs
and VT with left bundle branch pattern

Structural Phase

structural modifications progressed into RV
and/or LV dilation and potentially heart failure

Early Phase

Are there Triggers in the “Early Phase” that accelerate Phenotypic Conversion ?

- Myocardial inflammation may play a role
- Exercise may play a role

-A deficiency in Plakophillin alters sarcoplasmic reticulum regulation of calcium homeostasis.

-Adrenergic mediated release (? Exercise) of calcium can trigger VT

Martins, Int J Cardiol, 2018

Myocardial inflammation detected by cardiac MRI in Arrhythmogenic right ventricular cardiomyopathy: A paediatric case series

CMR results at admission and follow-up.

Patient	Age at first CMR (years)	LV EF at first CMR	T2 criteria	EGE criteria	LGE criteria	LV localization	Last CMR at follow-up	RV compromise at follow-up	Last LV EF
1	11	55%	Yes	Yes	Yes	Septal basal	RV and LV septal fibrosis	Right ventricular fibrosis without ARVC criteria	55%
2	15	65%	Yes	Yes	Yes	Lateral	Normal	RV dyskinesia on ventriculography and fibrosis at biopsy	55%
3	5	23%	No	Yes	Yes	Anterior, lateral, apical	NA	Dilatation and severe dysfunction	15%
4	10	60%	No	Yes	Yes	lateral	ARVC major criteria	Dilatation and dysfunction	54%
5	12	53%	Yes	Yes	Yes	Anterior, lateral, apical	ARVC major criteria	Dilatation and severe dysfunction	42%
6	2	20%	Yes	Yes	Yes	Anterior, lateral, apical	NA	NA	NA

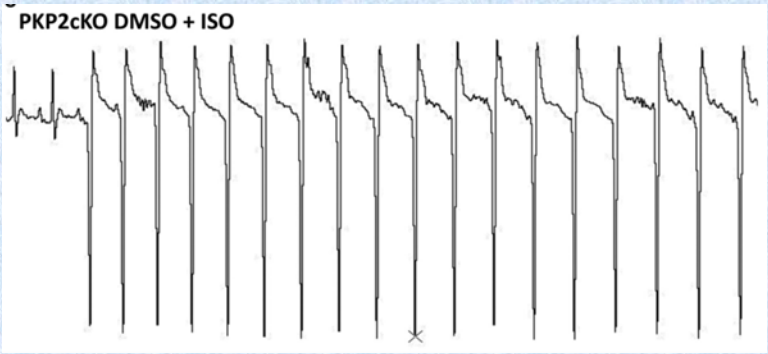
Patient	Gender	Age at admission (years)	Follow-up (years)	Family history	Number of myocarditis-like episodes	Gene	ECG during myocarditis-like episode	ECG during follow-up	NYHA at last follow-up
1	F	11	8	Yes	6	DSG2	Ti V1–2	Unchanged	I
2	M	15	7	No	3	PKP2	Ti V1–3	Unchanged	I
3	M	5	1	No	2	DSP	Arrhythmic storm with RBBB VT	Normal	Transplant
4	M	10	6	Yes	1	DSP	Unspecific QRS prolongation	Epsilon wave	I
5	M	12	3	Yes	2	PKP2	Right precordial STe and Ti; LBBB VT	Ti V3–6 and inferior limb leads	II

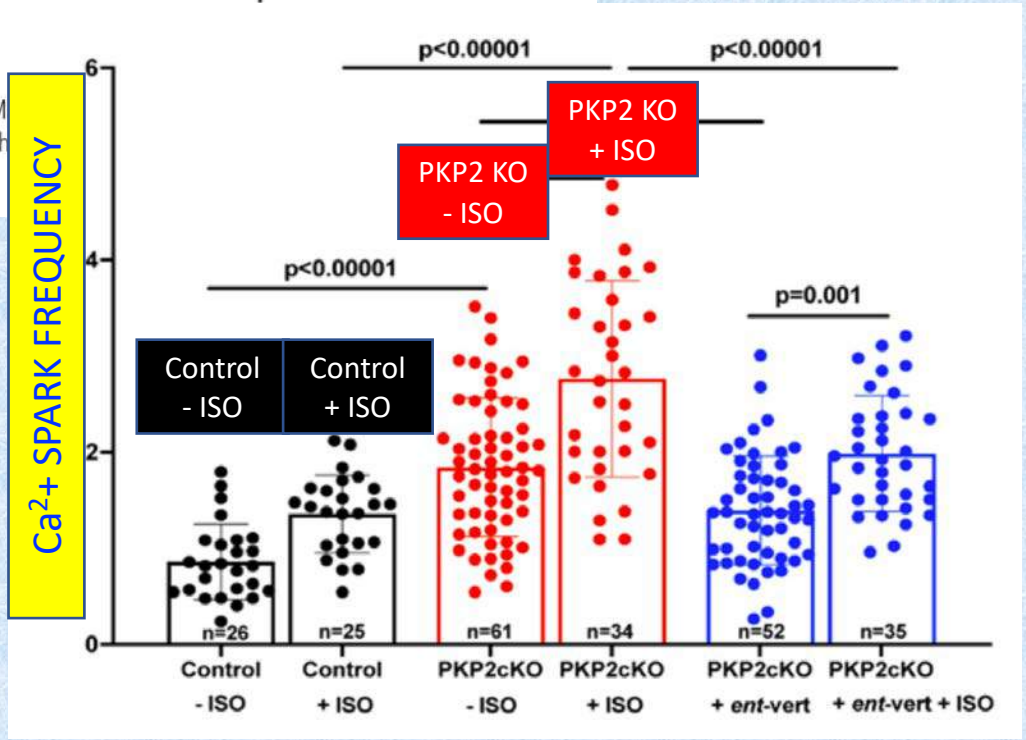
Circulation. 2022;145:1480–1496

ORIGINAL RESEARCH ARTICLE

Exercise Causes Arrhythmogenic Remodeling of Intracellular Calcium Dynamics in Plakophilin-2–Deficient Hearts

Chantal J.M. van Opbergen, PhD*; Navratan Bagwan, PhD*; Svetlana R. M
Abigail N. Smith, PhD; Daniel J. Blackwell, PhD; Jeffrey N. Johnston, Ph
Marina Cerrone, MD; Alicia Lundby, PhD†; Mario Delmar, MD, PhD†





Misnomers I Have Heard – Let's Address Them

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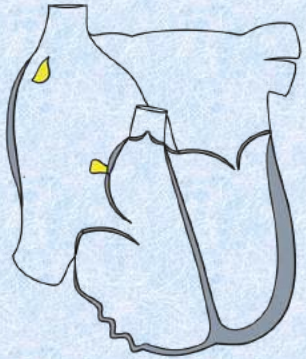
Definition of Arrhythmogenic Cardiomyopathy

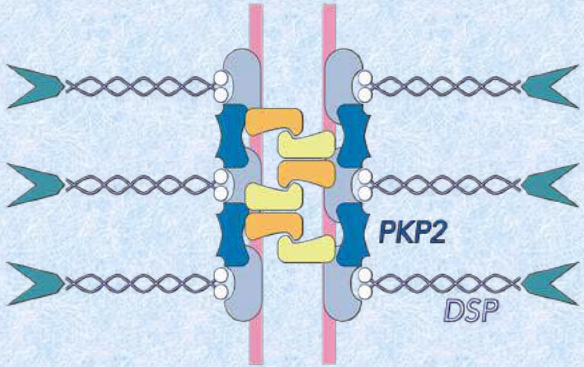
ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY



RV dilatation/dysfunction
RV VT
ECG - V1-V3

Δ 2010 Task Force Criteria
Genetics:

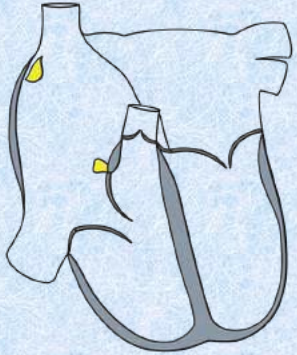
Plakophillin-2 (abnormal ECG)
Desmocollin
Desmoglein



CARDIAC DESMOSOME

Genetic testing in ARVC assessing for desmosomal mutations generally approaches 40-50%.

LEFT DOMINANT ARRHYTHMOGENIC CARDIOMYOPATHY



LV dilatation/dysfunction
LV VT
LV LGE on MRI
ECG - 1,aVL, V4-V6

Δ 2008/Padua criteria
Genetics:

Desmoplakin
Normal ECG and
subepicardial LV scar

50% Genetically Elusive- Now What?

ESC European Society of Cardiology

European Heart Journal (2018) **39**, 3932–3944
doi:10.1093/eurheartj/ehy567

FASTTRACK CLINICAL RESEARCH
Arrhythmia/electrophysiology

An autoantibody identifies arrhythmogenic right ventricular cardiomyopathy and participates in its pathogenesis

Diptendu Chatterjee[1], Meena Fatah[1], Deniz Akdis[2], Danna A. Spears[3], Tamara T. Koopmann[1], Kirti Mittal[1], Muhammad A. Rafiq[1], Bruce M. Cattanach[4], Qili Zhao[5], Jeff S. Healey[6], Michael J. Ackerman[7], Johan Martijn Bos[7], Yu Sun[5,8], Jason T. Maynes[9], Corinna Brunckhorst[2], Argelia Medeiros-Domingo[10], Firat Duru[2,11], Ardan M. Saguner[2], and Robert M. Hamilton[1]*

Anti-DSG2 antibodies are a sensitive and specific biomarker for ARVC

- In 12 of 12 cases of definite ARVC and 7 of 8 cases of Borderline ARVC in human samples, autoantibodies to the desmosomal protein DSG2 were present on western blots
- Autoantibodies were absent (in 11) from sera of 12 control subjects

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5. *"Sports restrictions are over exaggerated"*

Heart Rhythm Disorders

Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers

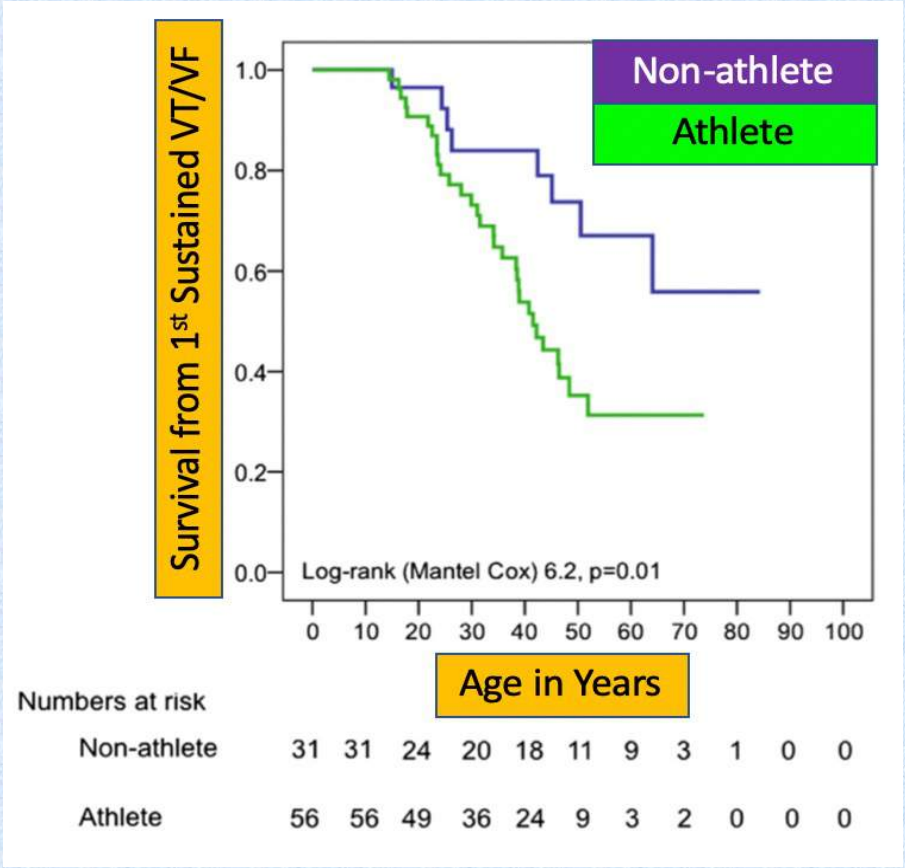
Cynthia A. James, ScM PhD

Journal of the American College of Cardiology 2013 http://dx.doi.org/10.1016/j.jacc.2013.06.033

Dominated by PKP2 carriers 87%

Endurance sports >75% VO2

Proband Status of Athletes
50% athletes
26% non-athletes



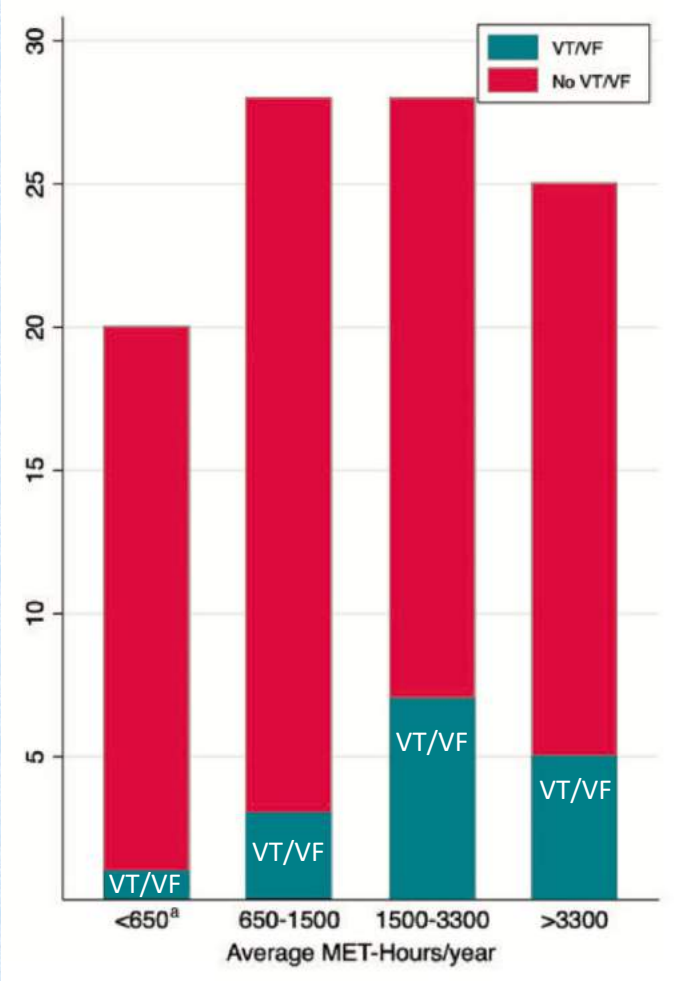
Exercise restriction is protective for genotype-positive family members of arrhythmogenic right ventricular cardiomyopathy patients

Weijia Wang [1,2]*, Crystal Tichnell[1], Brittney A. Murray[1], Julia Agafonova[1], Julia Cadrin-Tourigny[1], Stephen Chelko[1], Harikrishna Tandri[1], Hugh Calkins[1], and Cynthia A. James[1]

- 101 family members (40.5 +/- 19.3 years)
- *PKP2 = 82%*
- *Exercise - METs/hr/year*
- Correlation between exercise duration & ARVC/VT (F>M)

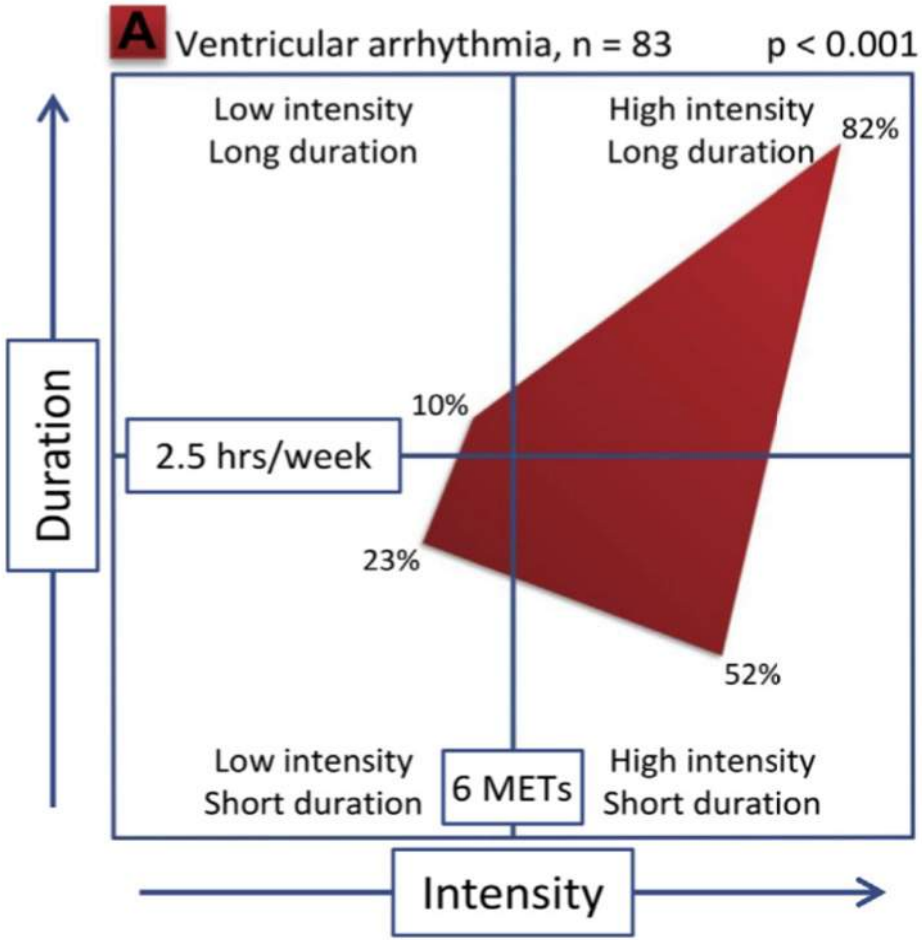
- AHA recommendation = 650/METs/hr/year
- 3 METS = walking at 3 miles an hour
- 3 METs * 30 mins * 2 per day = 1095/METs/hr/year

In patients with Plakophillin mutations (F>M) vigorous exercise increases disease expression (? more stress on RV)



Harmful Effects of Exercise Intensity and Exercise Duration in Patients With Arrhythmogenic Cardiomyopathy

Øyvind H. Lie, MD,[a,b,c] Lars A. Dejgaard, MD,[a,b,c] Jørg Saberniak, MD,[a,b] Christine R
Mathis K. Stokke, MD, PhD,[a,b,c,d] Thor Edvardsen, MD, PhD,[a,b,c,e] Kristina H. Haugaa



Treatment Strategies and Algorithms for Risk Stratification

1. Lifestyle changes
2. Pharmacological intervention
3. Implantation of an ICD
4. Catheter ablation of ventricular tachyarrhythmias,
5. Heart transplantation patients with end-stage heart failure or therapy-resistant arrhythmias (rarely, pediatric patients with ARVC)

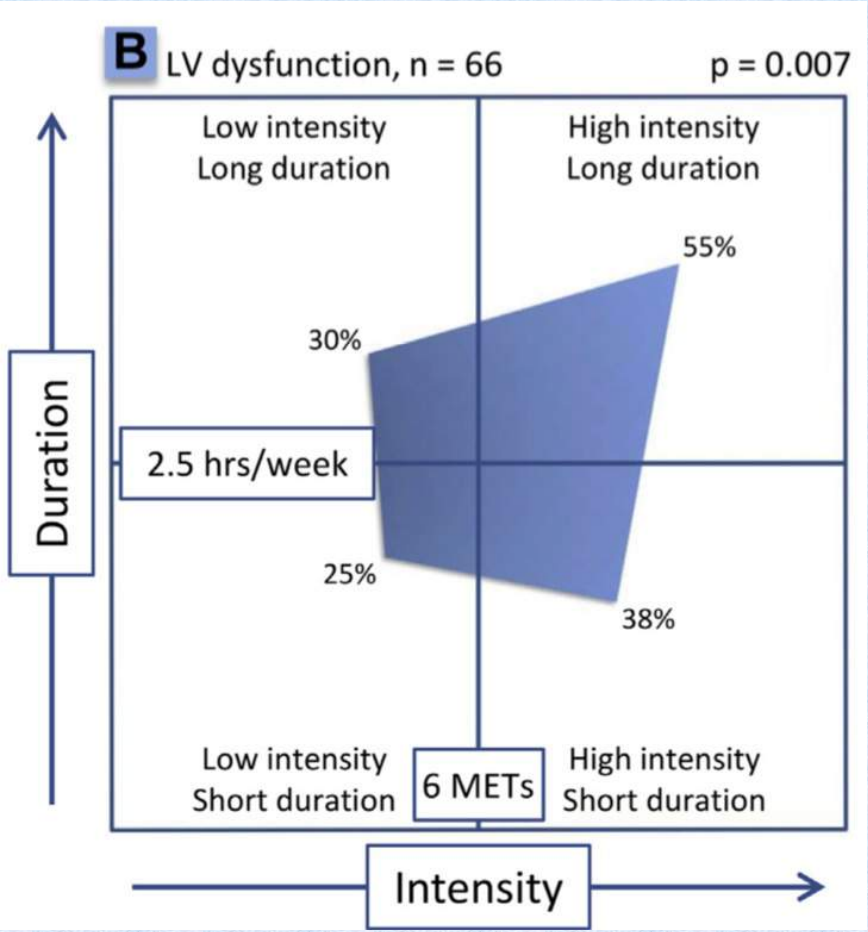

The Children's Hospital of Philadelphia

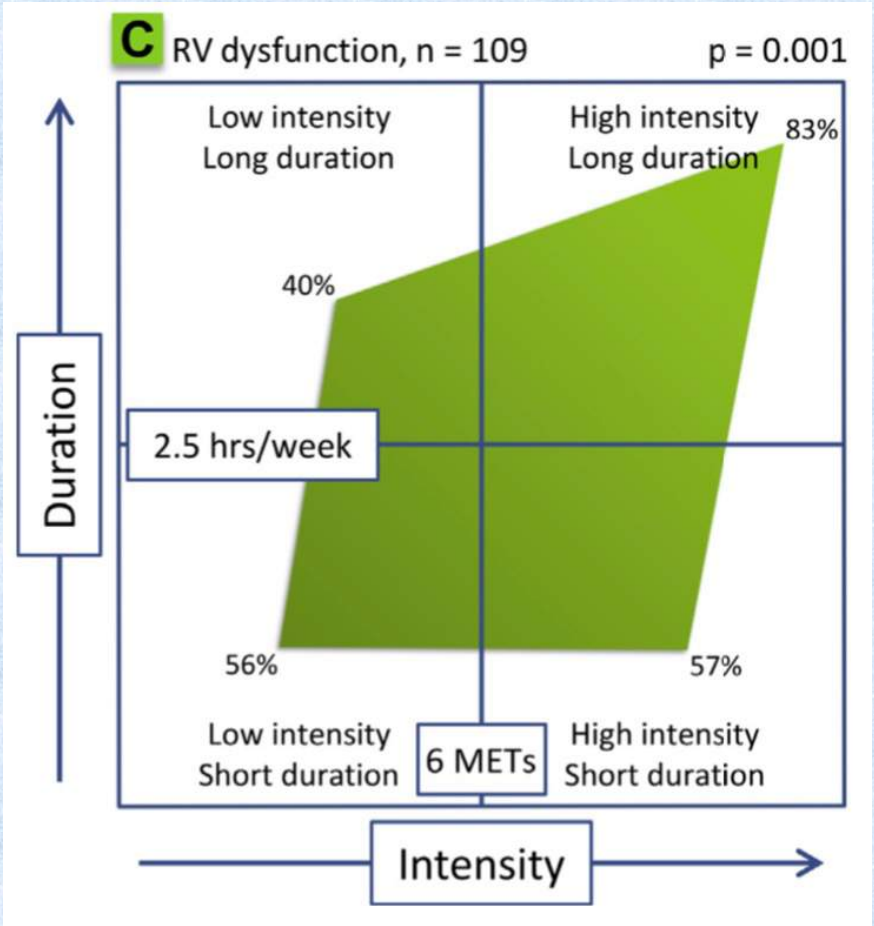

LEGES
SINE MORIBUS
VANAE

SAVE THE DATE

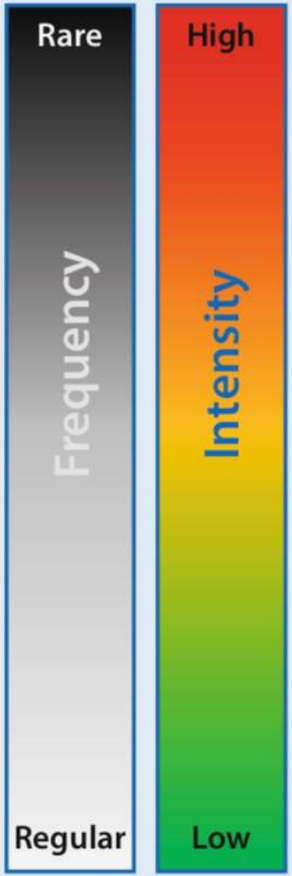
8th World Congress of
Pediatric Cardiology
and Cardiac Surgery
AUGUST 27TH -
SEPTEMBER 1ST, 2023
WASHINGTON D.C

http://www.wcpccs2023.org/

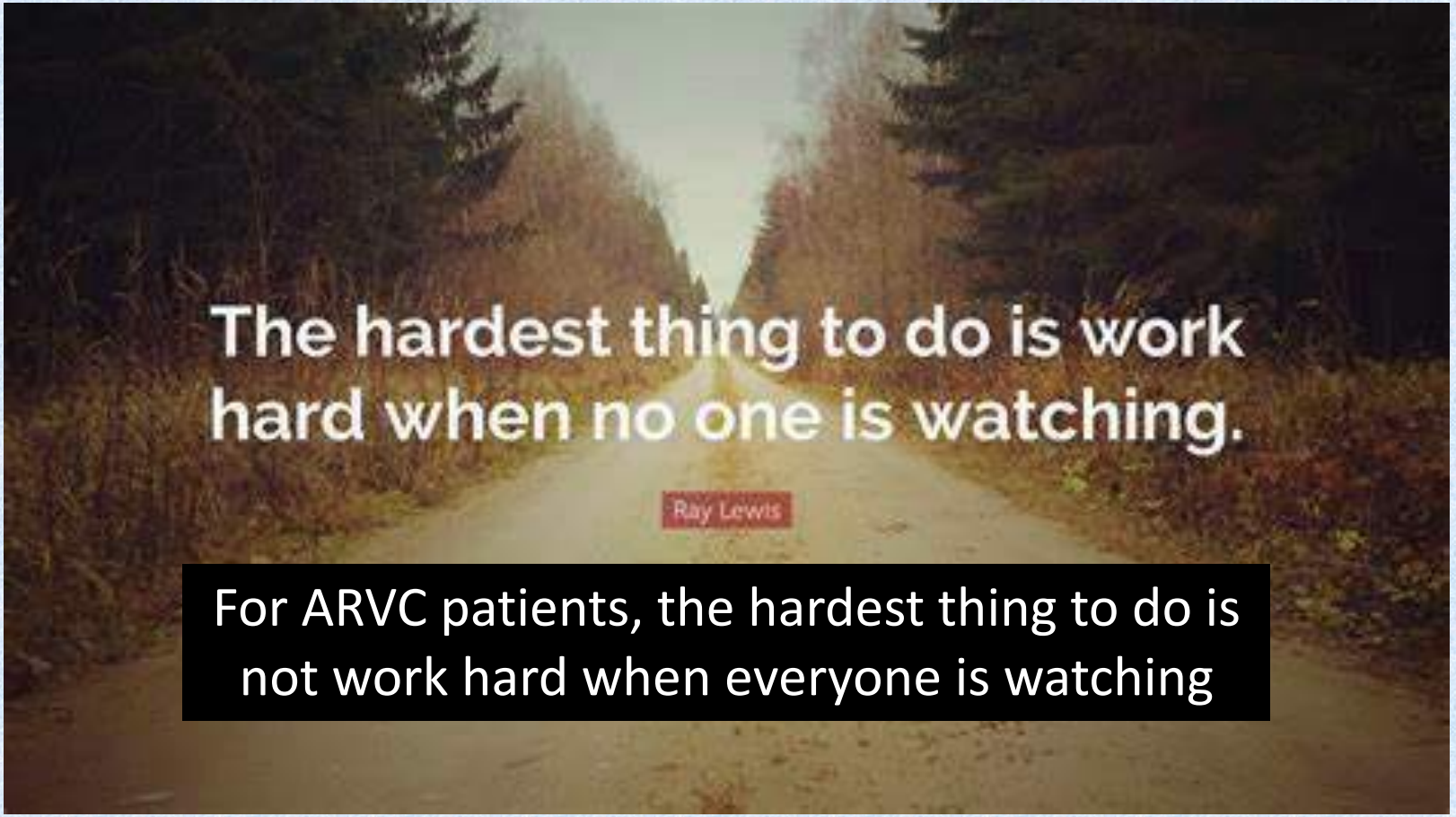




INTENSITY IS MORE CONCERNING In ARVC THAN DURATION (Long Walk Better than a 20 MINUTE HIIT CLASS



METS	Exemplary sports
16	Competitive cycling
15	Cross-country ski racing (>13 km/h)
12	Canoeing, rowing crew in competition
10	Soccer, competitive
9.8	Running (10 min, 1.6 km)
8	Basketball game
5.8	Swimming laps / freestyle (moderate effort)
5.3	Downhill skiing (moderate effort)
5	Walking for exercise (6 km/h)
4.8	Golf
3.5	Walking for pleasure or transportation
3.3	Sailing, wind surfing
3	Canoeing, rowing for pleasure
2.5	Yoga



For ARVC patients, the hardest thing to do is not work hard when everyone is watching

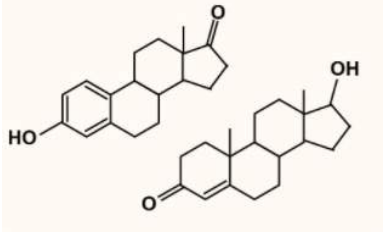
Pragmatic Advice to the ARVC Patient

- Endurance exercise should be avoided.
- Exercise should be limited to less than 2.5 hours (?) per week
- Intense exercise should be avoided. Patients should be
- Moderate static strength-based exercise may be reasonable

Variable Expressivity, Incomplete Penetrance, Epigenetics, Chance

Primary Disease Mutation

Other Modifiers (i.e histone)

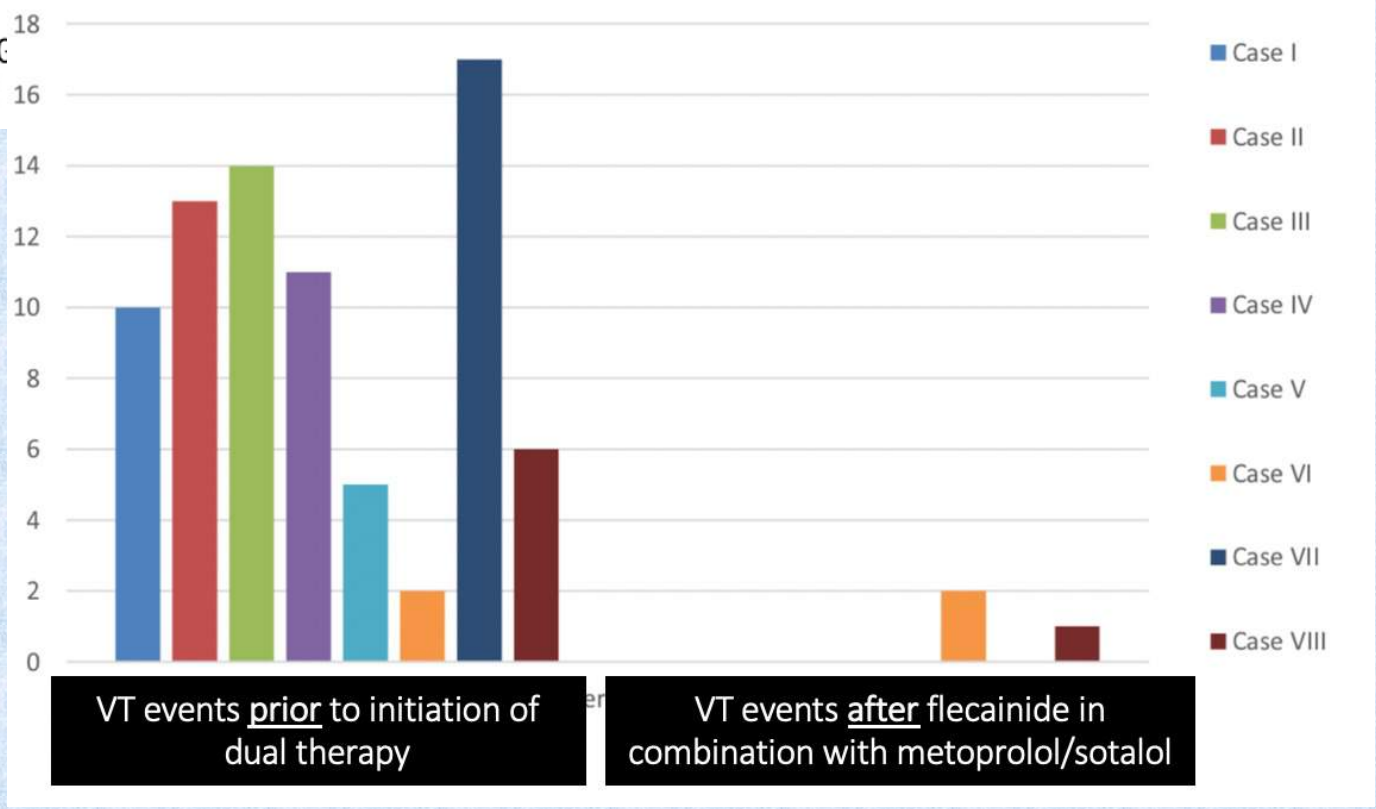


Sex Linked Modifiers

Epigenetic Modifications

Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy

Simon Ermakov, MD, Edward P. C
Melvin M. Scheinman, MD, FHRS



ARVC Risk calculator

Prediction risk at 5 years of sustained VA (> 100 bpm)

- Sex
- Age
- Recent syncope
- No of leads with TWI
- 24h PVC count
- NSVT
- RVEF

Derivation cohort

C Index 0.77, Calibration slope 0.93

ARVC Risk calculator validation

Jordà P. *et al.*

- C-index 0.7
- Calibration slope 1.01
- Agreement between predicted and observed events

Protonotarios A. *et al.*

- C-index 0.75
  (C-index gene positive 0.82 > gene negative 0.65)
- Calibration slope 0.52
- Overall overestimation of predicted risk

Open questions / concerns

- High rate of VA without SCD in ARVC patients
- VA instead of SCD as end-point for the model
- Over-estimation of risk at the lower end of spectrum
- Patient selection (RV-dominant form, gene positive: PKP2 carriers)
- Lack of prospective validation
- Threshold for ICD-implantation

www.arvcrisk.com

mitchell.cohen@inova.org

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5. *~~"Sports restrictions are over exaggerated~~"*

Clinical Characteristics and Follow-Up of Pediatric-Onset Arrhythmogenic Right Ventricular Cardiomyopathy

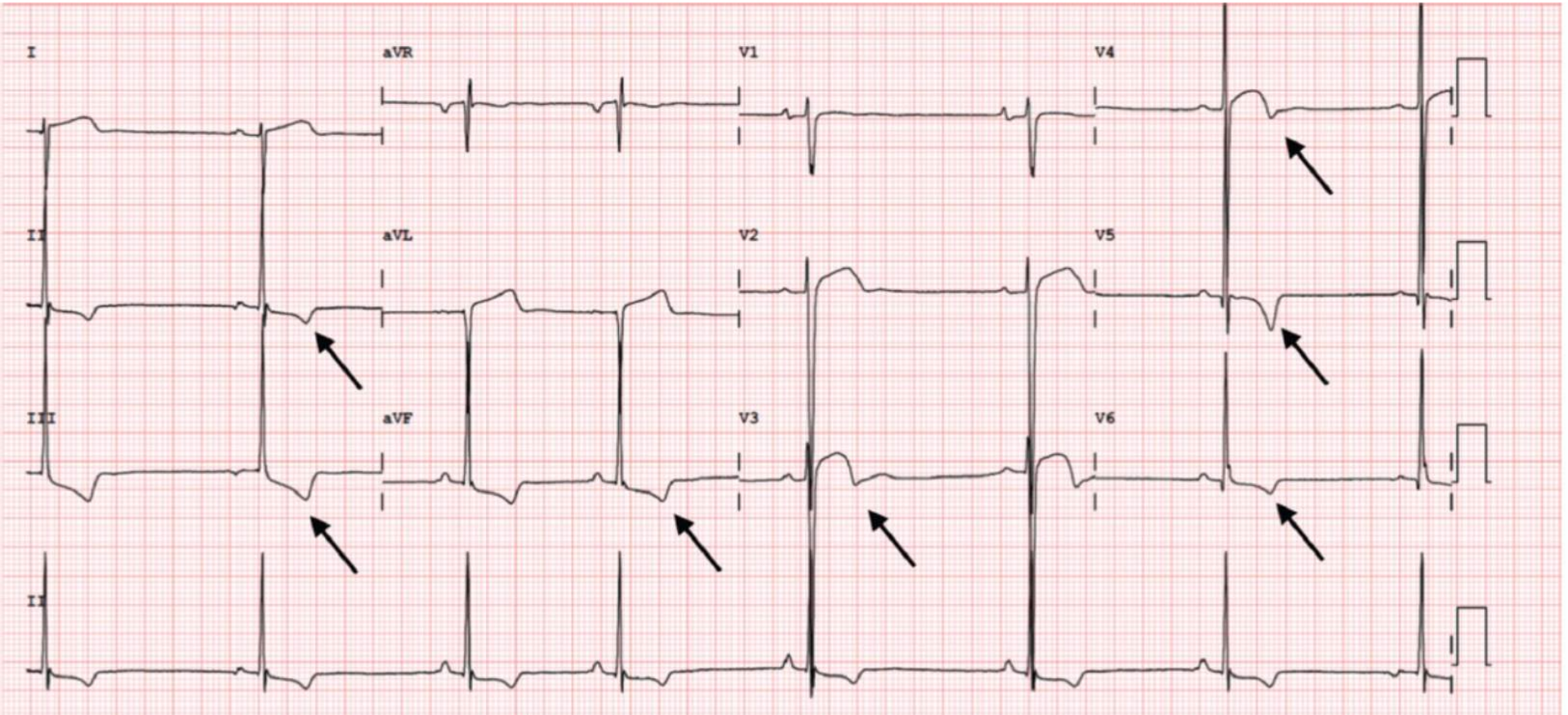
Robert W. Roudijk, MD,[a,b] Lisa Verheul, MD,[a] Laurens P. Bosman, MD,[a,b] Mimount Bourfiss, MD,[a] Johannes M.P.J. Breur, MD, PhD,[c] Martijn G. Slieker, MD, PhD,[c] Andreas C. Blank, MD, PhD,[c] Dennis Dooijes, PhD,[d] Jeroen F. van der Heijden, MD, PhD,[a] Freek van den Heuvel, MD, PhD,[e] Sally-Ann Clur, MD, PhD,[f] Floris E.A. Udink ten Cate, MD, PhD,[g] Maarten P. van den Berg, MD, PhD,[h] Arthur A.M. Wilde, MD, PhD,[i] Folkert W. Asselbergs, MD, PhD,[a,j,k] J. Peter van Tintelen, MD, PhD,[b,d] Anneline S.J.M. te Riele, MD, PhD[a,b]

	Overall	Probands	Relatives
Demographic characteristics of all patients	N = 80	n = 12	n = 68
Male	38 (48)	8 (67)	30 (44)
Age at presentation, y	13.5 [10.5-16.7]	16.8 [13.7-17.1]	13.2 [10.1-15.3]
Type of presentation			
Ventricular tachycardia	8 (10)	7 (58)	1 (2)
Resuscitated sudden cardiac arrest	3 (4)	2 (17)	1 (2)
Sudden cardiac death	3 (4)	1 (8)	2 (3)
Symptomatic	5 (6)	2 (17)	3 (4)
Cascade screening	61 (76)	0	61 (90)

TABLE 3 Characteristics of Patients Presenting Alive, Stratified According to Any VT Event

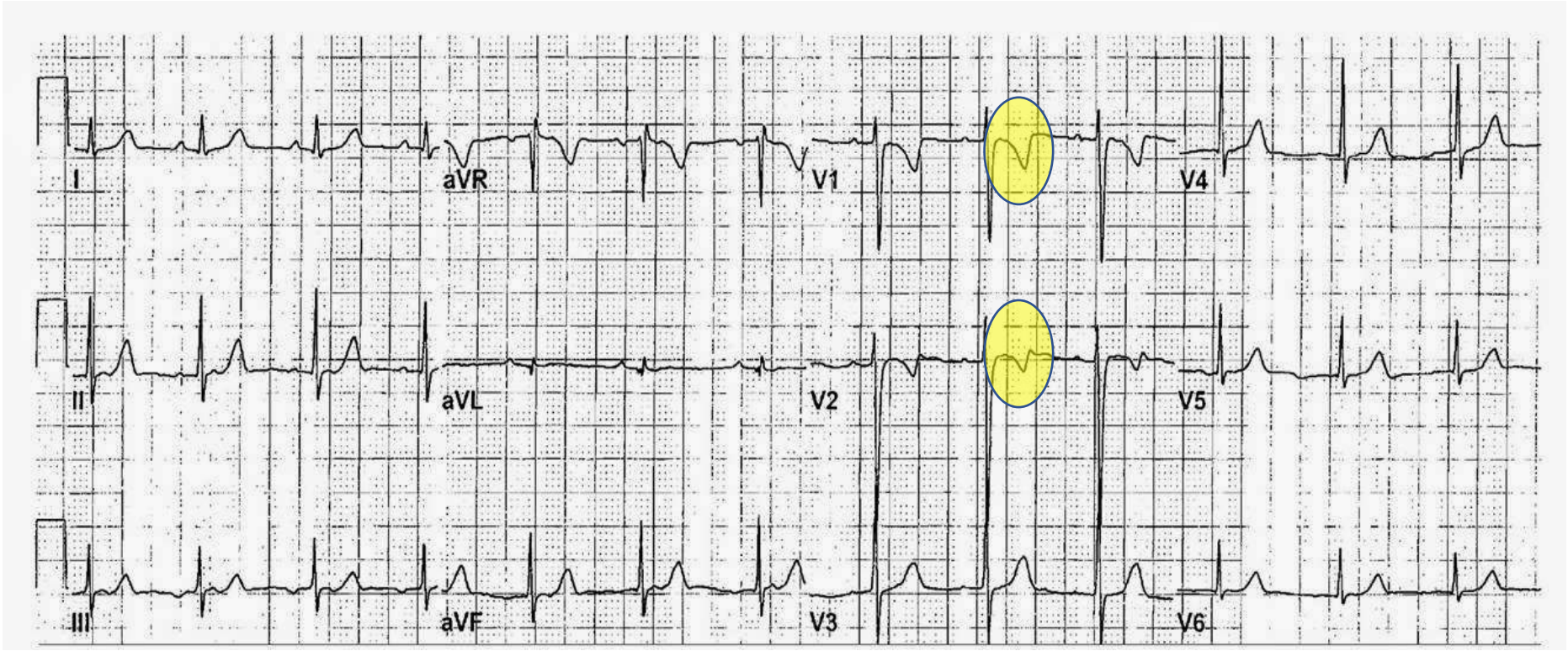
	VT (n = 12)	No VT (n = 65)	*P* Value
Demographic characteristics			
Proband status	10 (83)	1 (2)	<0.01
Male	10 (83)	27 (42)	<0.01
Pathogenic genetic variant	9/12 (75)	42/44 (96)	0.06
ECG and Holter monitoring			
T-wave inversion in V_1-V_3	9 (75)	2 (3)	<0.01
No. of PVCs/24 h	3241 [413-6,892]	3 [1-285]	0.01
NSVT	5/11 (46)	5/63 (8)	<0.01
Imaging			
LVEF	54 [49-59]	60 [57-64]	0.01
RVEF	32 [24-33]	53 [47-57]	<0.01
Late gadolinium enhancement on CMR	3/4 (75)	4/18 (22)	0.09

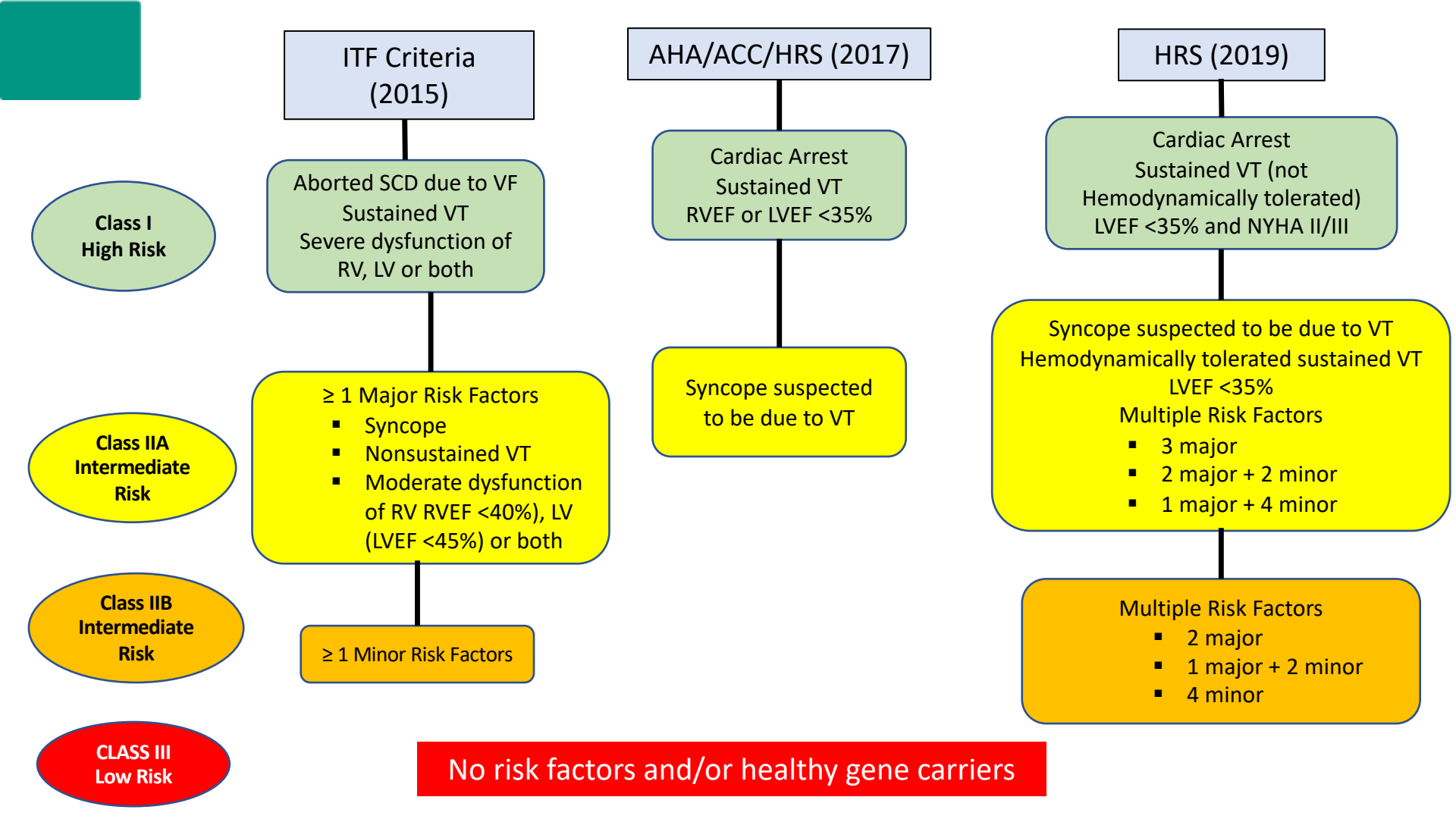
Oh this must be it…… *No this is an athletic 16 year-old black male*



European Cardiology Review 2020;15:e61

Healthy 14 year-old (juvenile pattern)




ITF Criteria (2015)
AHA/ACC/HRS (2017)
HRS (2019)
Class I High Risk
Aborted SCD due to VF
Sustained VT
Severe dysfunction of RV, LV or both
Cardiac Arrest
Sustained VT
RVEF or LVEF <35%
Cardiac Arrest
Sustained VT (not Hemodynamically tolerated)
LVEF <35% and NYHA II/III
Class IIA Intermediate Risk
≥ 1 Major Risk Factors
Syncope
Nonsustained VT
Moderate dysfunction of RV RVEF <40%), LV (LVEF <45%) or both
Syncope suspected to be due to VT
Syncope suspected to be due to VT
Hemodynamically tolerated sustained VT
LVEF <35%
Multiple Risk Factors
3 major
2 major + 2 minor
1 major + 4 minor
Class IIB Intermediate Risk
≥ 1 Minor Risk Factors
Multiple Risk Factors
2 major
1 major + 2 minor
4 minor
CLASS III Low Risk
No risk factors and/or healthy gene carriers