ARVC: Diagnostic challenges

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Learning Objectives

A. Diagnosis using Revised Task Force Criteria

B. Diagnostic modalities outside Task Force Criteria

C. Quiz

D. Differential diagnosis

Introduction

- Genetics: Mutations in genes that encode constituents of intercalated discs of cardiomyocytes
- Histological hallmark: Cardiomyocyte loss and replacement of fibrous/ fibro-fatty tissues
- Characteristics: Arrhythmias, SCD & Progressive heart failure
- Prevalence: Estimated 1 in 5000 (M:F- 3:1)
- 10% of unexplained SCD in <69 yrs of age
- Median age of onset of symptoms: 29 yrs of age

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Review article

Almanac 2014: cardiomyopathies

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Diagnosis using revised TFC

- Integration of data from
  1. Imaging techniques
  2. Depolarisation abnormalities on ECG
  3. Repolarisation abnormalities on ECG
  4. Arrhythmias
  5. Family history
  6. Tissue diagnosis

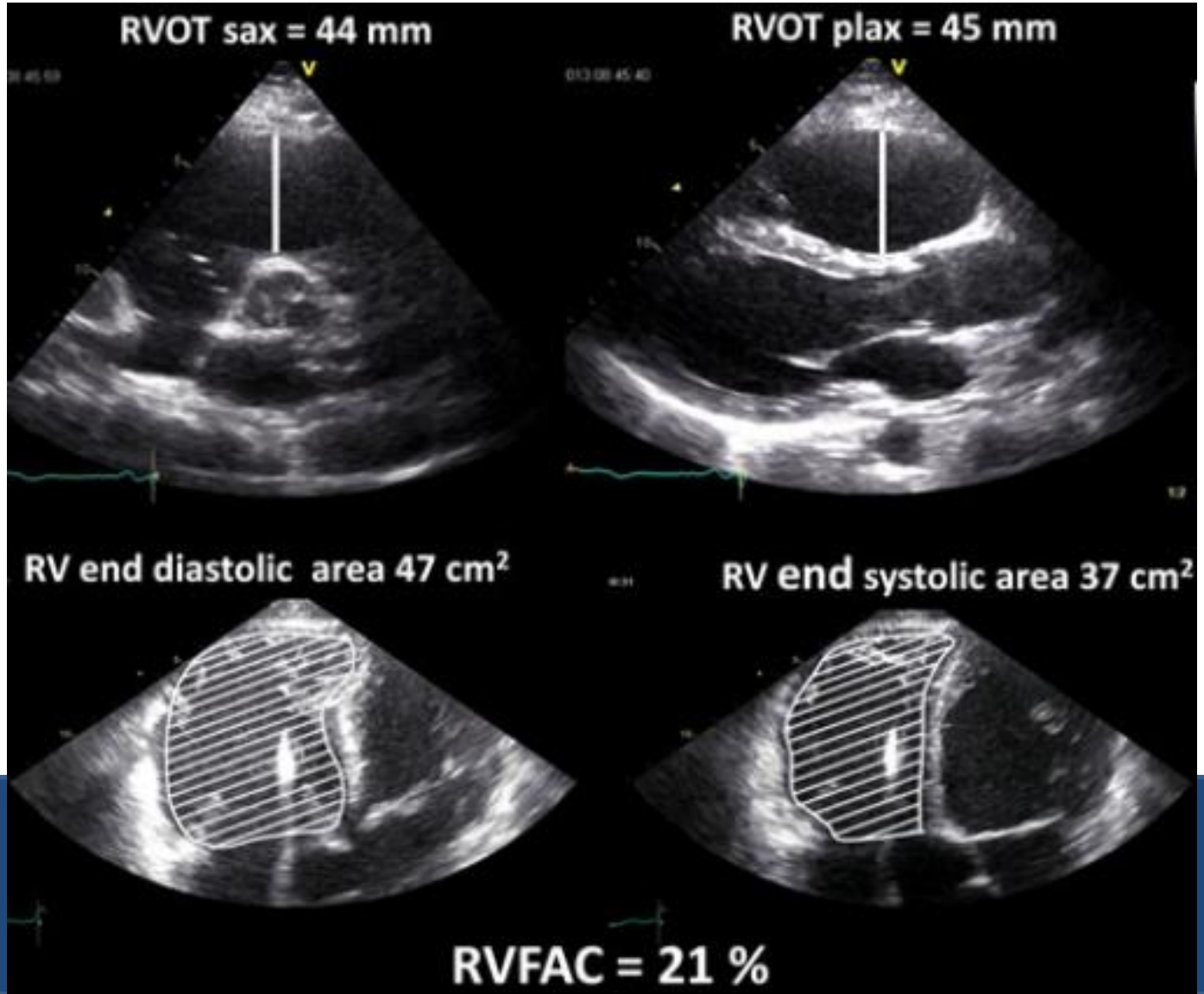
- Diagnostic groups

  – Possible: M(1) OR m(2)
  – Borderline: M(1)+m(1) OR m(3)
  – Definite: M(2) OR M(1)+m(2) OR m(4)

Imaging

Major Criteria	Minor Criteria
I. Imaging	
By 2D echo: Regional RV akinesia, dyskinesia, or aneurysm And 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) Fractional area change ≤33%	By 2D echo: Regional RV akinesia or dyskinesia And 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) Fractional area change >33% to ≤40%
By CMR: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 ml/m^2 (male) or ≥100 ml/m^2 (female) RV ejection fraction ≤40%	By CMR: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100 to <110 ml/m^2 (male) or ≥90 to <100 ml/m^2 (female) RV ejection fraction >40% to ≤45%
By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm	

Imaging by Echo



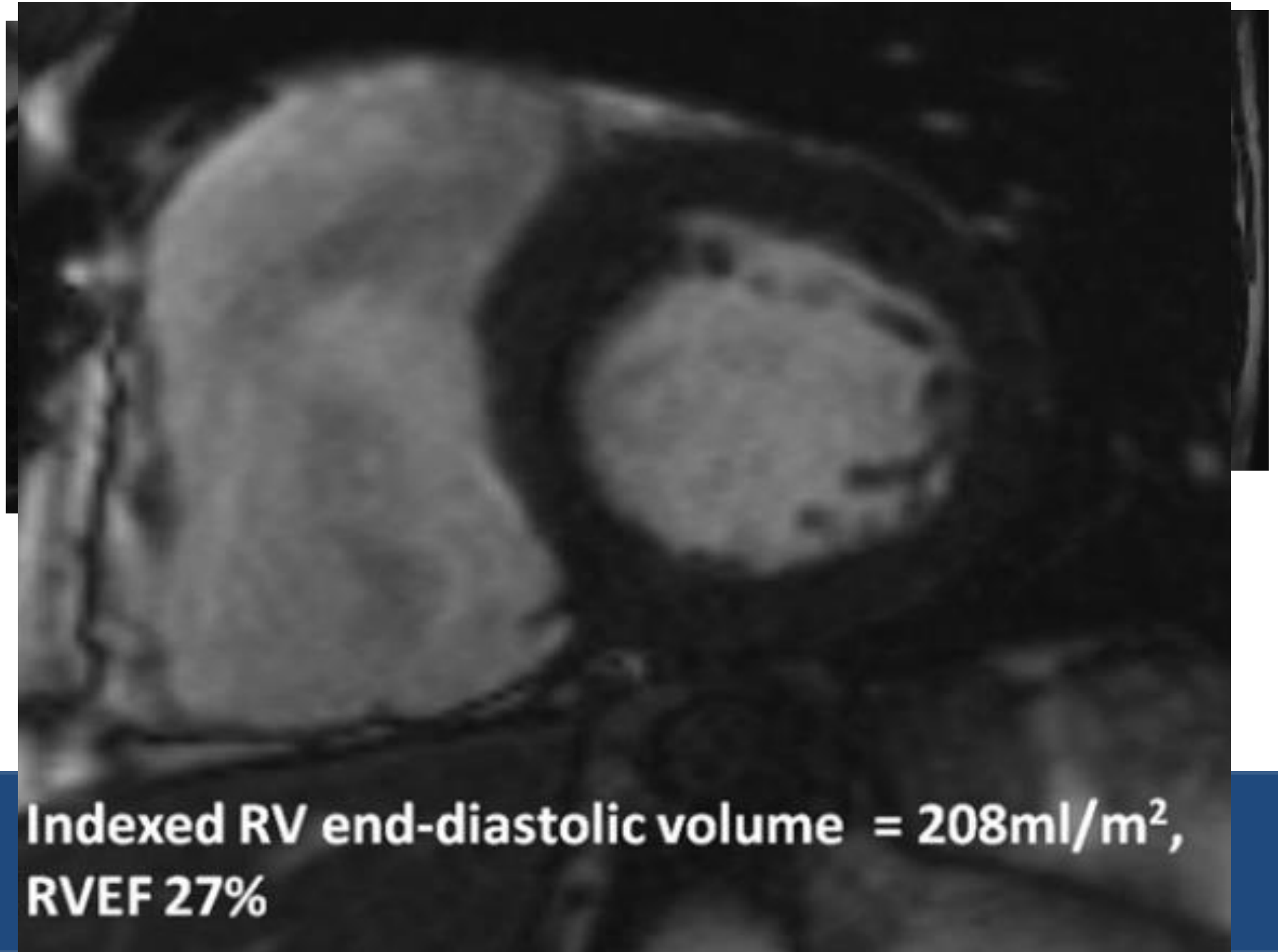
Imaging Criteria

	Value	Sensitivity, %	Specificity, %
Echocardiogram			
Major			
PLAX RVOT (diastole)	≥32 mm	75	95
Corrected for body size (PLAX/BSA)	≥19 mm/m²		
PSAX RVOT (diastole)	≥36 mm	62	95
Corrected for body size (PSAX/BSA)	≥21 mm/m²		
Fractional area change	≤33%	55	95
Minor			
PLAX RVOT (diastole)	≥29 mm	87	87
Corrected for body size (PLAX/BSA)	≥16 to ≤18 mm/m²*		
PSAX RVOT (diastole)	≥32 mm	80	80
Corrected for body size (PSAX/BSA)	≥18 to ≤20 mm/m²		
Fractional area change	≤40%	76	76
MRI†			
Major			
Ratio of RV end-diastolic volume to BSA			
Males	≥110 mL/m²		
Females	≥100 mL/m²	76	90♂
or		68	98♀
RV ejection fraction	≤40%		
Minor			
Ratio of RV end-diastolic volume to BSA			
Males	≥100 mL/m²		
Females	≥90 mL/m²	79	85♂
or		89	97♀
RV ejection fraction	≤45%		

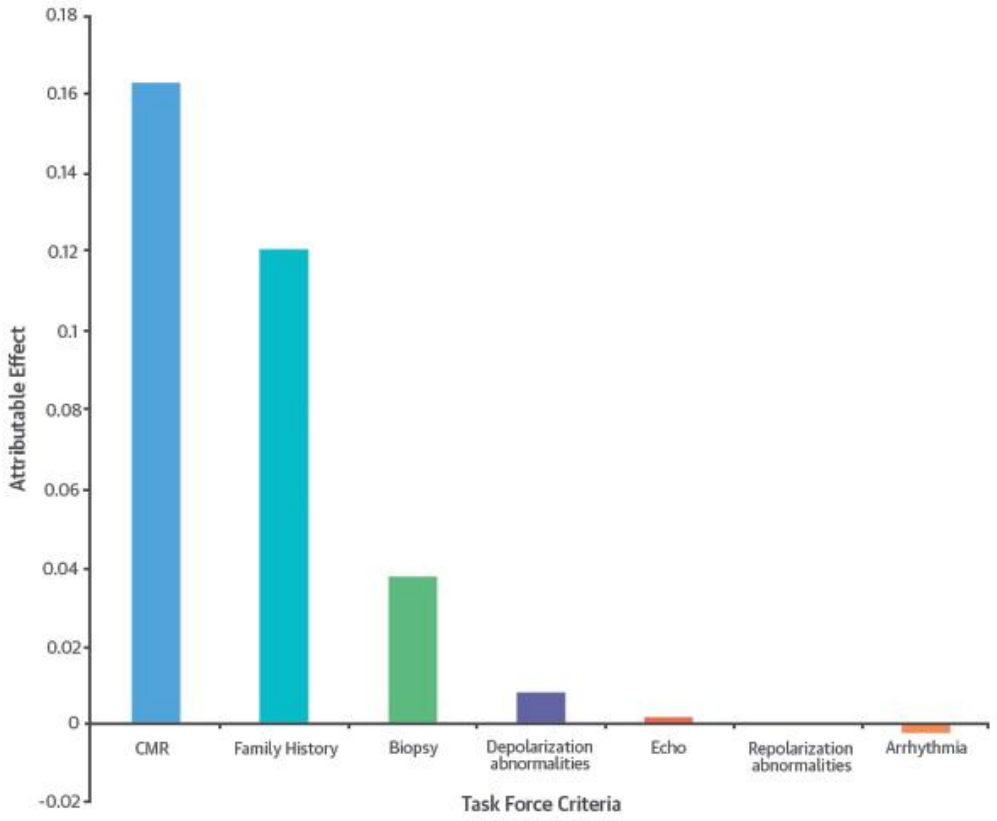
Imaging by Angiography

Sensitivity and Specificity of Angiographic Findings in Adults with ARVC

Study	Angiographic Finding	Sensitivity (%)	Specificity
Daubert et al.[61]	Slow dye evacuation of RV		Low
	Deep fissuring in anterior wall		Low
	Localized akinetic or dyskinetic bulges	90	
	Wide, deep fissuring of apex or inferior wall	33	
Chiddo et al.[63]	Localized akinesia/dyskinesia	48	High
	Small conical outpouchings persisting in systole	40	
	Apical deep fissuring	8	
Conte et al.[64]	Aneurysmal formations of the right ventricle		100%
Daliento et al.[65]	Transversly arranged hypertrophic trabeculae separated by deep fissures	96	87.50%
	Posterior subtricispid and anterior infuldibular wall bulgings		
Peters et al.[66]	Segmental hypokinesia	72	
	Diffuse hypokinesia	28	
Hebert et al.[67]	RV ejection fraction < 35%	32	100%


Indexed RV end-diastolic volume = 208ml/m²,
RVEF 27%

Revised TFC in Children



Importance of CMR Within the Task Force Criteria for the Diagnosis of ARVC in Children and Adolescents

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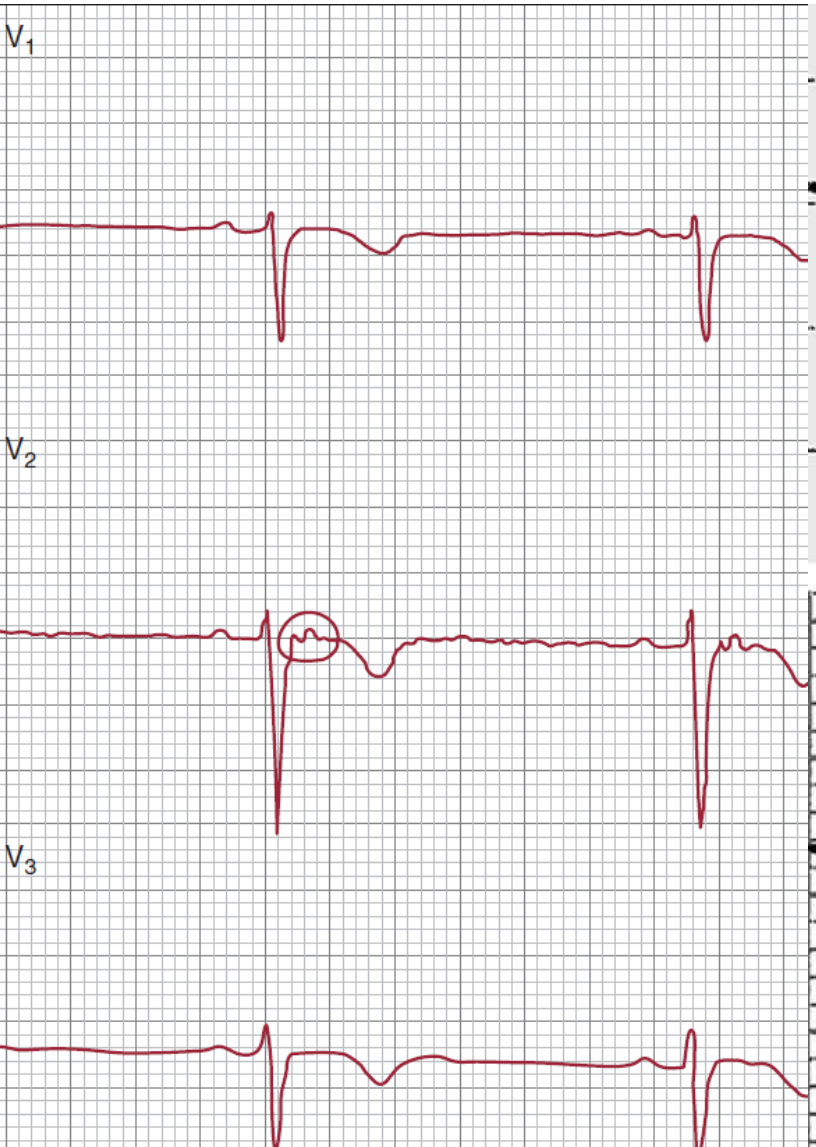
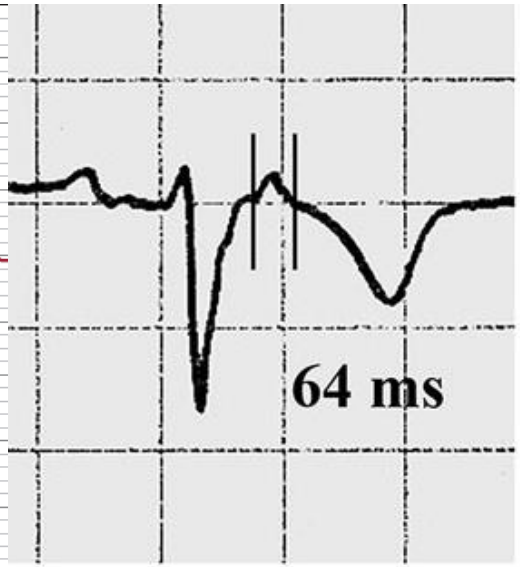
Etoom, Y. et al. J Am Coll Cardiol. 2015; 65(10):987-95.

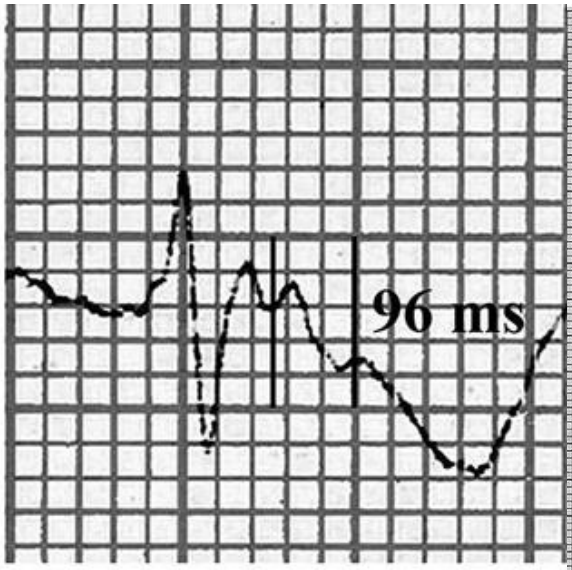
Depolarisation abnormalities

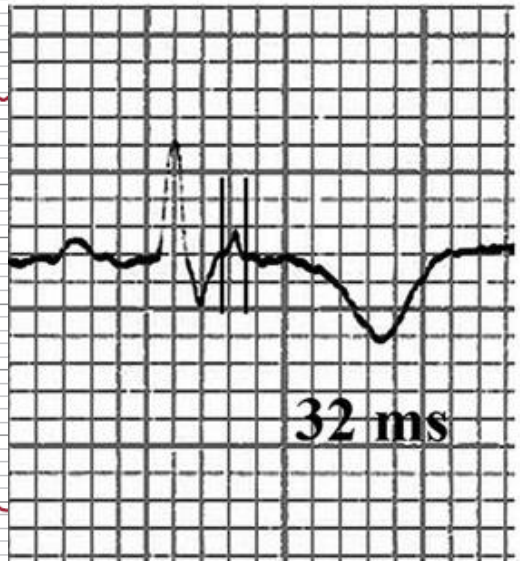
Major Criteria	Minor Criteria
IV. Depolarization/Conduction Abnormalities	
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T-wave) in the right precordial leads (V_1 to V_3)	Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG Filtered QRS duration (fQRS) ≥114 ms Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms Root mean square voltage of terminal 40 ms ≤20 μV Terminal activation duration of QRS ≥55 ms measured from the nadir of the S-wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block

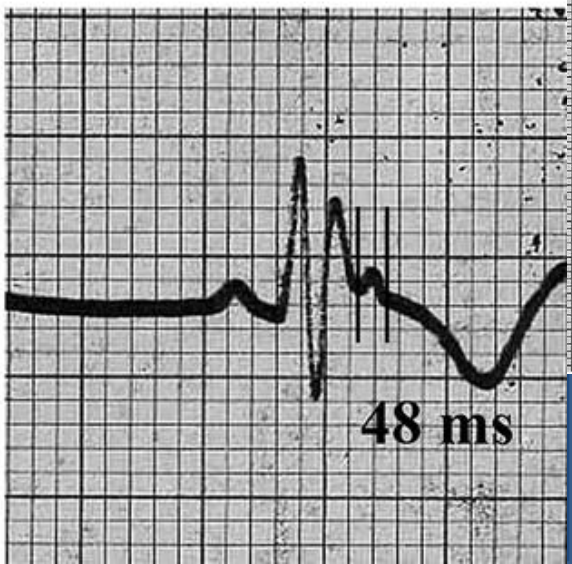
Depolarisation changes: Epsilon



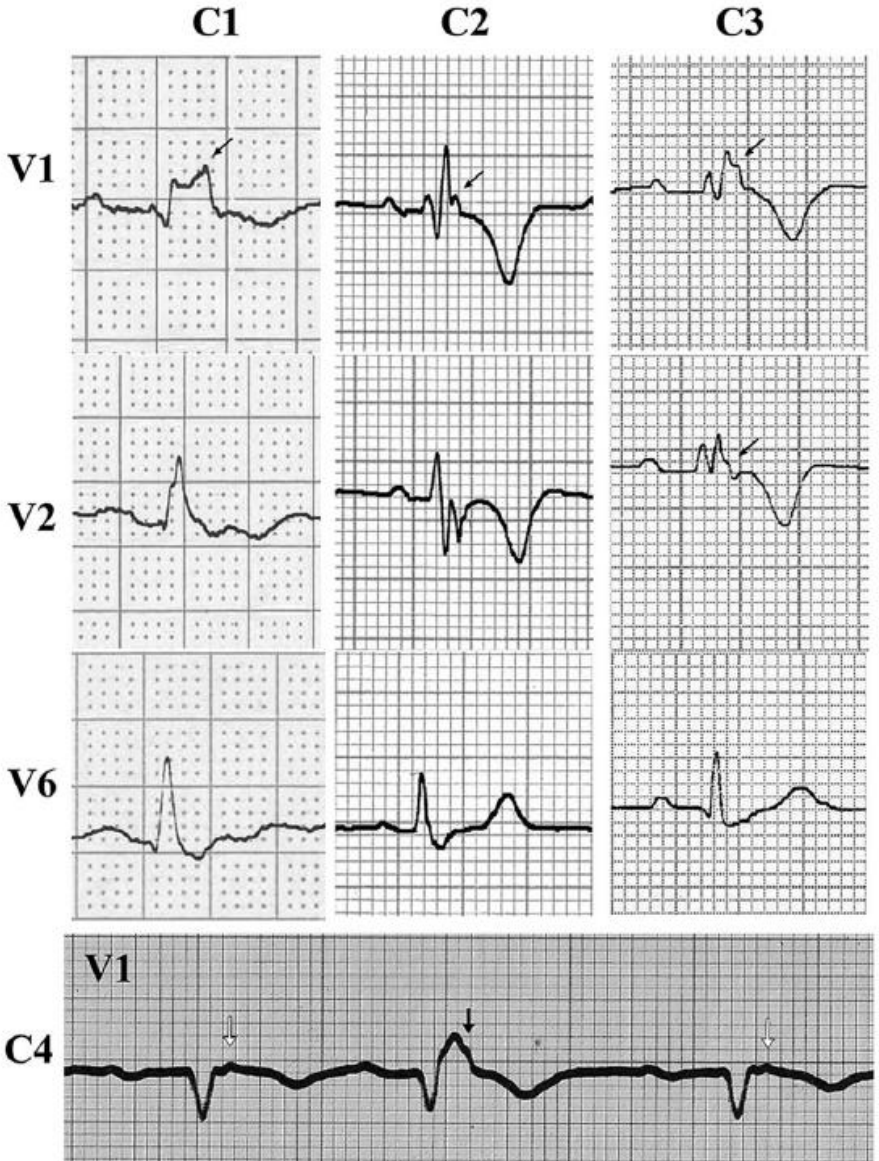








Depolarisation changes & Epsilon



Depolarisation changes: SAECG

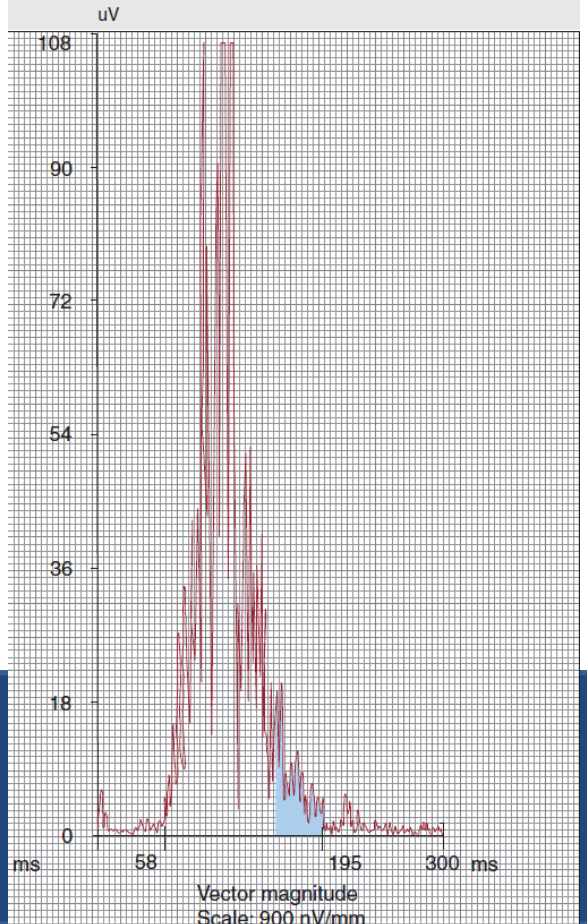
- Late Potentials> 1 of 3 features

1. Filtered QRS duration
   fQRS **≥114 ms**

2. Low Amplitude Signal duration
   (duration of terminal QRS), 40 mV:
   LAS40 **≥ 38 ms**

3. Root-mean-square voltage of
   terminal 40 ms:
   RMS40**≤20 mV**

		X	Y	Z	Vector
QRSD	(ms)	137.00	117.50	122.50	137.00
QRS	(μV)	26.37	28.11	27.79	45.44
QRS 40	(μV)	3.10	7.66	5.77	5.41
LAS	(ms)	77.50	58.00	64.50	77.00



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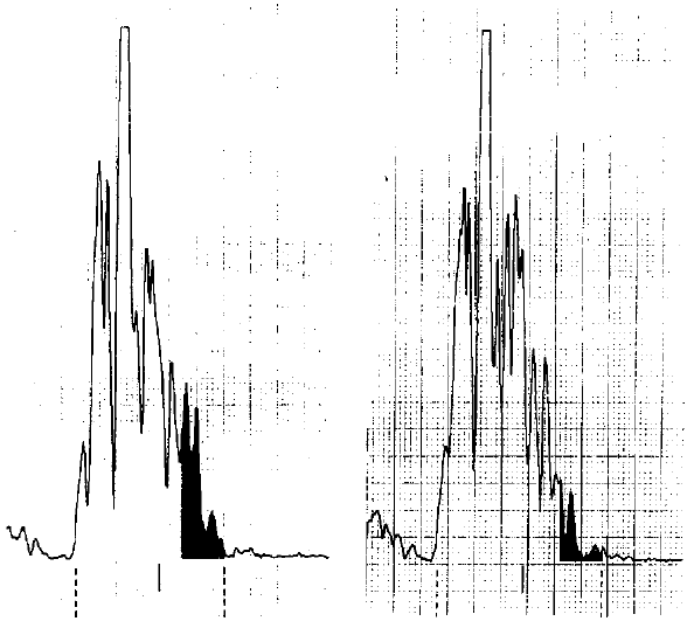
SAECG: Serial testing



	Unfiltered QRS (ms)	QRS25 (ms)	LAS25 (ms)	RMS25 (μV)	QRS40 (ms)	LAS40 (ms)	RMS40 (μV)	QRS80 (ms)	LAS80 (ms)	RMS80 (μV)
Patient 1: First control	134	142	24	28	137	60	17	131	67	7
↓ 10 months	131	163	53	8	154	74	6	130	60	8

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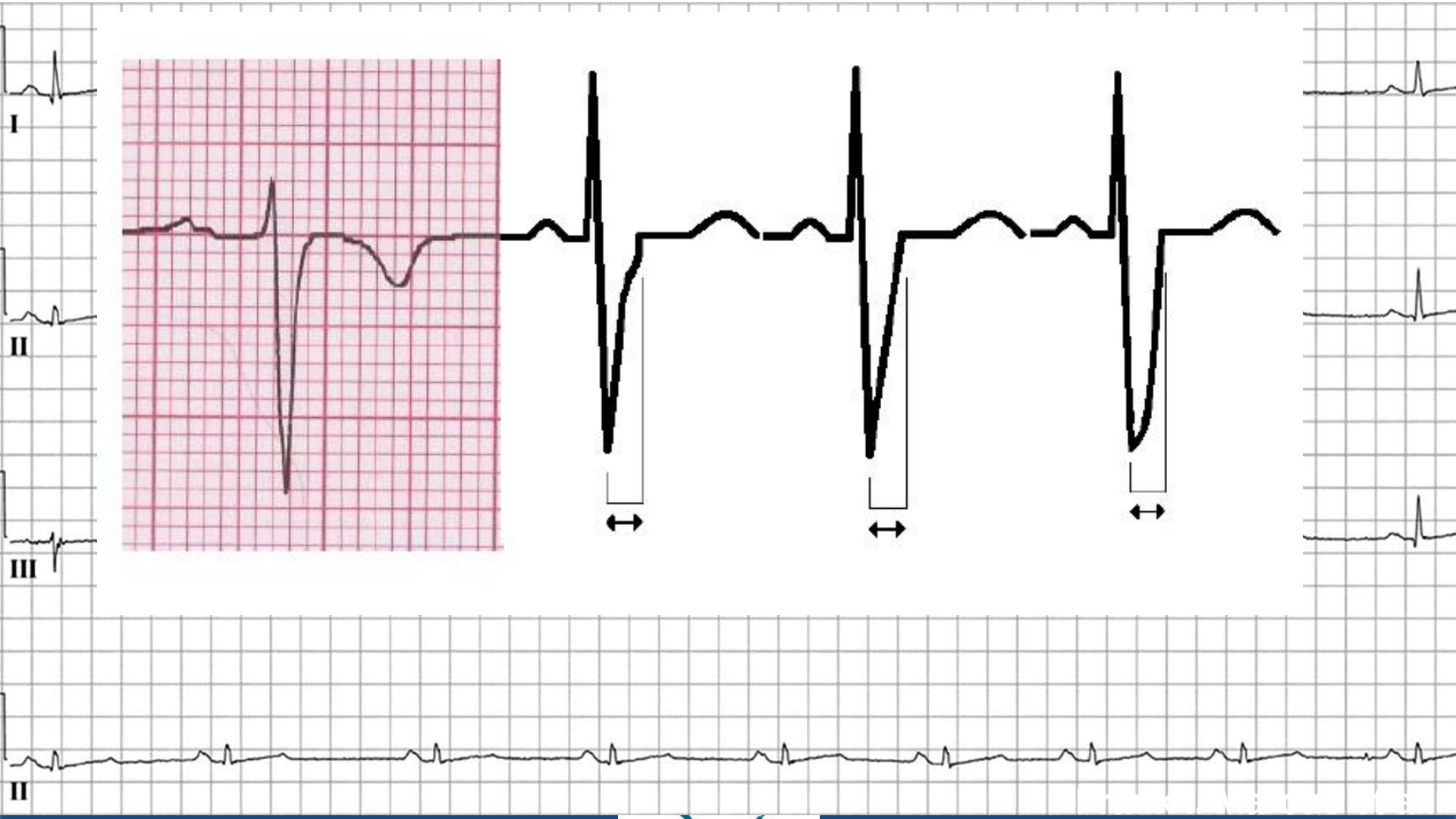
Signal-Averaged Electrocardiographic Parameter Progression as a Marker of Increased Electrical Instability in Two Cases with an Overt Form of Arrhythmogenic Right Ventricular Cardiomyopathy

Depolarisation changes: TAD

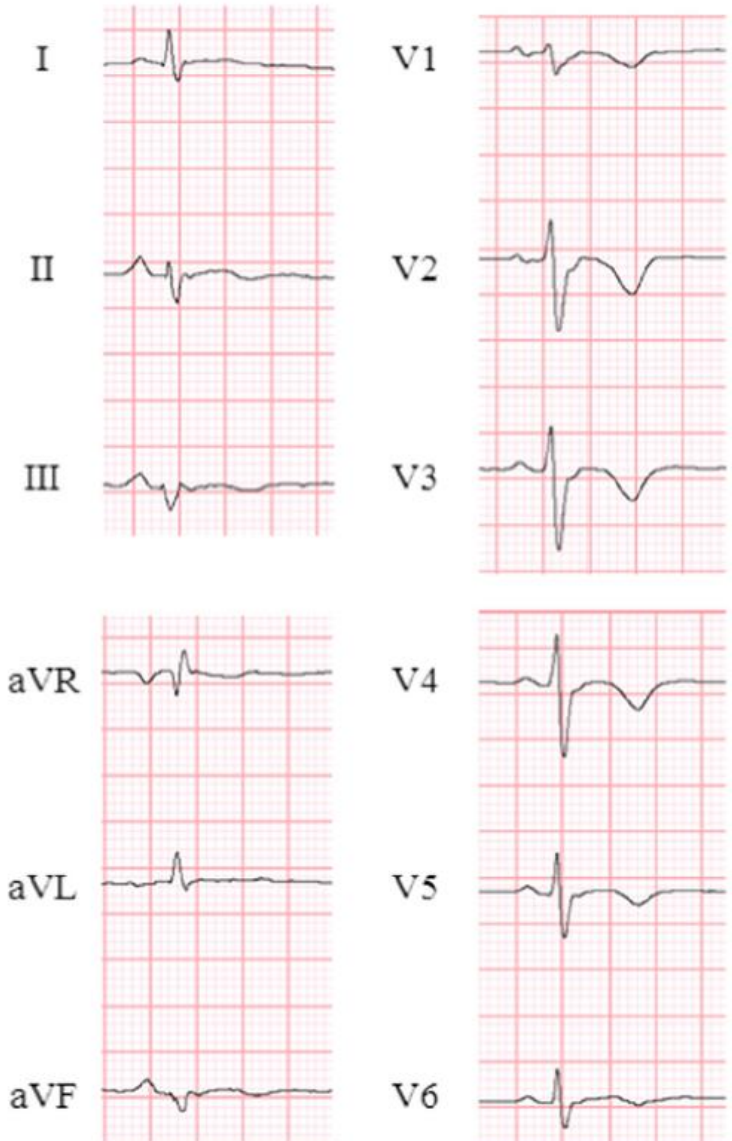


Circulation. 2010

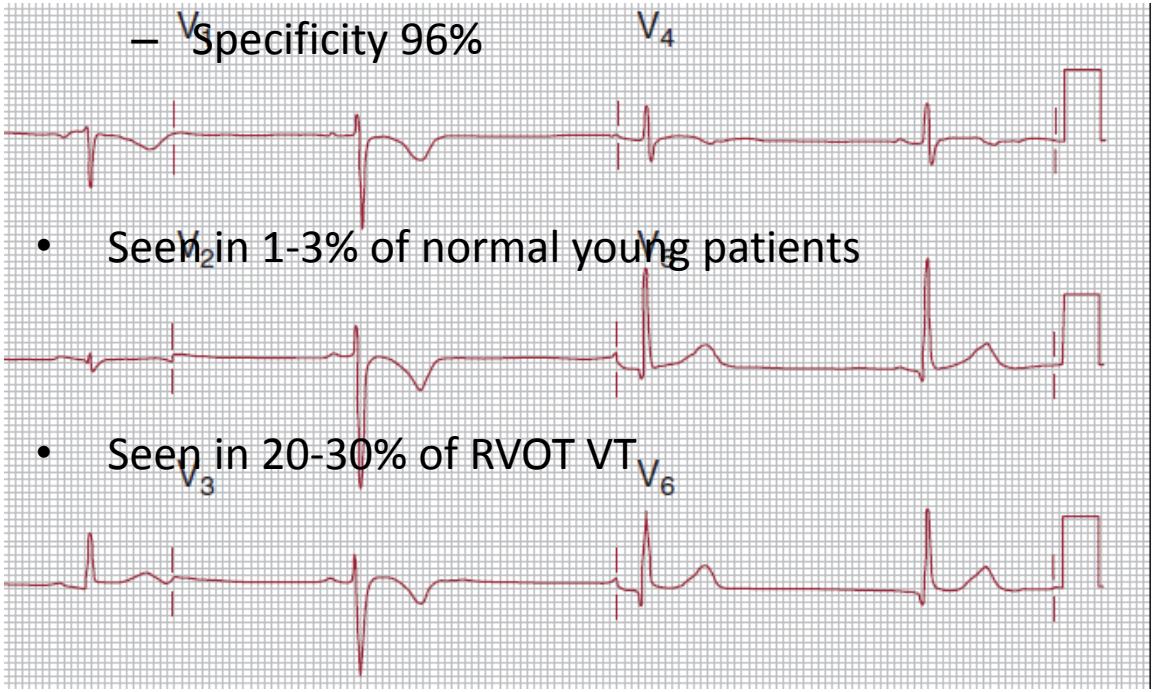
Repolarisation changes

Major Criteria	Minor Criteria
III. Repolarization Abnormalities	
Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block

Repolarisation changes: TWI



- Seen in 32-50% of ARVC
  - Sensitivity 47%
  - Specificity 96%
- Seen in 1-3% of normal young patients
- Seen in 20-30% of RVOT VT



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Bomma C, Rutberg J, Tandri H, Nasir K, Roguin A, Tichnell C, Rodriguez R, et al. Misdiagnosis of arrhythmogenic right ventricular right ventricular dysplasia/cardiomyopathy. J Cardiovasc Electrophysiol 2004; 15:300–306.

Electrical abnormalities

Table 2
Incidence of electrical abnormalities on ECG, SAECG, and 24-hour Holter monitor in several series of patients with ARVC/D

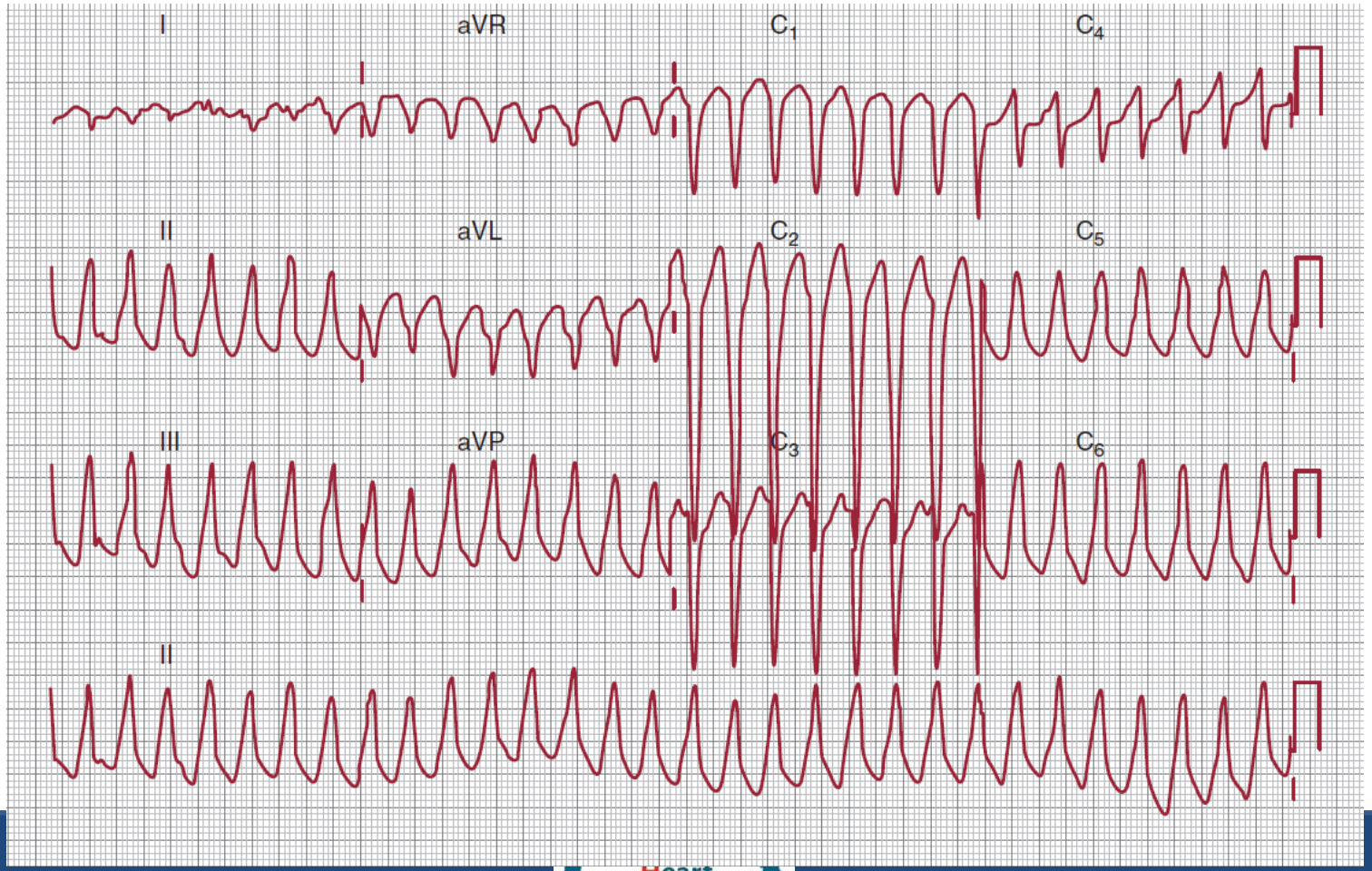
Publications	Nava et al [1]	Peters and Trummel [10]	Dalal et al [12]	Cox et al [13]	NIH registry data
No. of patients	136	265	69	42	95
1. Depolarization and conduction abnormalities					
(*a*) Epsilon waves	4%	23%	29%	10%	1%
(*b*) Localized QRS >110 ms in V_1, V_2, or V_3 (in absence of RBBB)		70%	58%	26%	24%
(*c*) QRS duration ratio $\frac{V_1+V_2+V_3}{V_4+V_5+V_6}$ >1.2		98%		35%	17%
(*d*) Prolonged S-wave duration			91%[a]	52%[a]	34%[b]
Terminal activation delay				71%[c]	
(2) Repolarization abnormalities					
Inverted T waves V_1					18%
V_1 and V_2					6%
$V_1 + V_2 + V_3$	19%	31%	81%[d]	67%	16%
Beyond V_3	18%	23%			31%
Only V_4, V_5, V_6					3%
(3) LBBB, VT on ECG Holter or exercise test					
(*a*) Sustained VT			77%	42%	35%
(*b*) 1000 PVCs/24 h on Holter			67%	28%	57%

[a] Prolonged S-wave duration from nadir of S wave to isoelectric line >55 milliseconds in leads V_1–V_2.
[b] From nadir of S wave to end of depolarization (R′).
[c] From nadir of S wave to end of all depolarization including an epsilon wave.
[d] T ↓ V_1 to V_3 or beyond.

Arrhythmias

Major Criteria	Minor Criteria
V. Arrhythmias	
Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL), or of unknown axis >500 ventricular extrasystoles per 24 h (Holter)

Arrhythmias



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Editorial

Diagnostic Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

Criterios diagnósticos para la miocardiopatía arritmogénica del ventrículo derecho

Giovanni Quarta and Perry M. Elliott*

Inherited Cardiac Diseases Unit, The Heart Hospital, University College London, London, United Kingdom

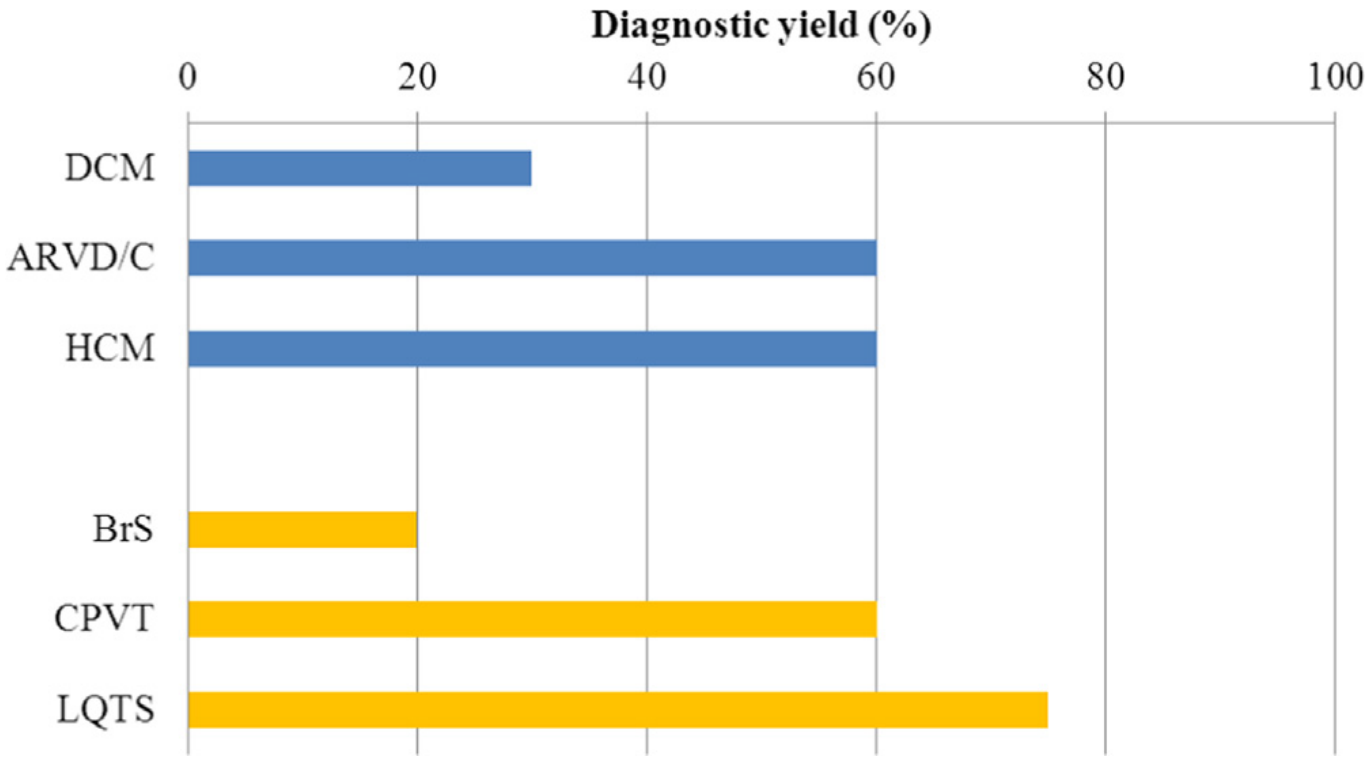
Rev Esp Cardiol. 2012;65(7):599–605

Family history

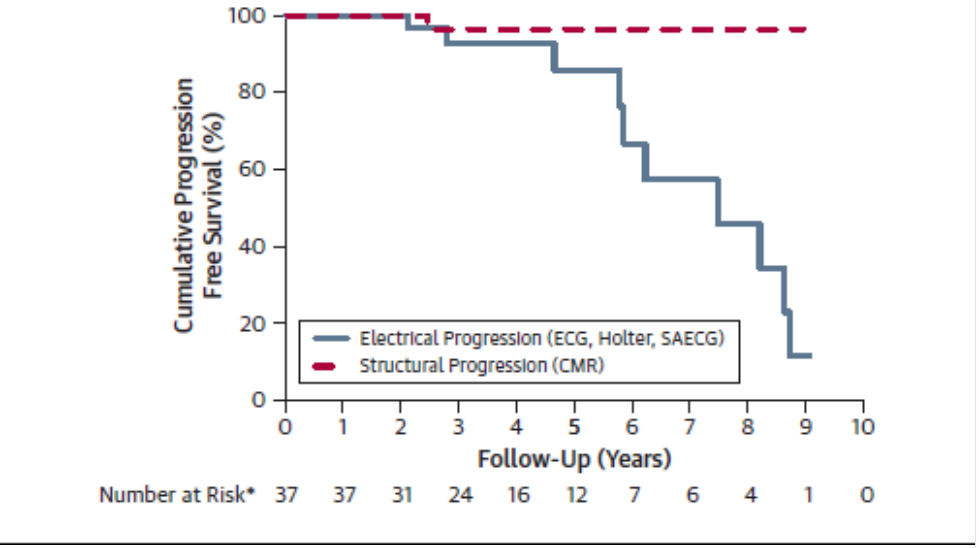
Major Criteria	Minor Criteria
VI. Family History	
ARVC confirmed in a first-degree relative who meets current TFC	History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current TFC
ARVC confirmed pathologically at autopsy or surgery in a first-degree relative	Premature sudden death (<35 years of age) due to suspected ARVC in a first-degree relative
Identification of a pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation	ARVC confirmed pathologically or by current TFC in a second-degree relative

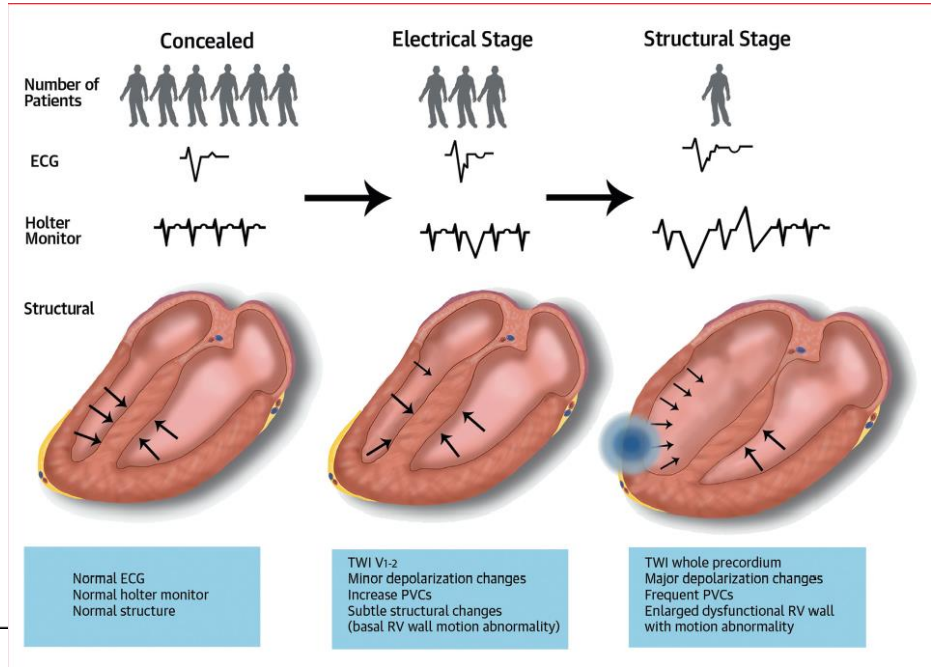
Genetics

- Inherited as Autosomal dominant trait in up to 50% of cases
- Incomplete penetrance
- Variable clinical expression



Family history & Progression





Anneline S. J. M. te Riele, MD,*† Cynthia A. James, PhD,† Neda Rastegar, MD,‡ Aditya Bhonsale, MD,
Brittney Murray, MS,† Crystal Tichnell, MGC,† Daniel P. Judge, MD,† David A. Bluemke, MD, PhD,‡§
Stefan L. Zimmerman, MD,‡ Ihab R. Kamel, MD, PhD,‡ Hugh Calkins, MD,† Harikrishna Tandri, MD†

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Yield of Serial Evaluation in At-Risk Family Members of Patients With ARVD/C

Tissue Diagnosis: Myocardial Bx

Major Criteria	Minor Criteria
II. Endomyocardial Biopsy	
Residual myocytes (60% by morphometric analysis or 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes (60% to 75% by morphometric analysis or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

Tissue diagnosis

Criterion	Sensitivity (%)	Specificity (%)
Major global/regional dysfunction of RV (echo, MRI, or angiography)	30	98
Minor/mild global or segmental dilatation or hypokinesis	58	76
RV wall thinning on MRI	58	79
Tissue characterization on Bx by the pathologist of "fibrofatty replacement"	62	91
Quantitative morphometric analysis on Bx of >18% fibrosis	56	71
T inversion in right precordial ECG	66	64
Epsilon waves or QRS prolongation	39	100
Any SAECG parameter beyond 2 Z-values	66	65
Any SAECG parameter beyond 1.5 Z-values	78	64
Frequent PVCs	48	54

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From the Labatt Heart Centre, The Hospital for Sick Children and Research Institute, University of Toronto, Ontario, Canada

Useful modalities outside TFC

- Tpe assessment
- Isoproterenol challenge
- Exercise Stress Test
- EPS, Voltage maps for scar assessment

Repolarisation change: Tpe (Tpeak-Tend)

The ECG Data of ARVC and RVOT-VT Patients

Variable	ARVC (n = 25)	RVOT-VT (n = 13)	P Value
T_{peak}–T_{end} in V1 (ms)	137.1 ± 32.6	93.8 ± 16.9	<0.001
T_{peak}–T_{end} in V2 (ms)	133.2 ± 35.5	104.7 ± 16.9	0.01
T_{peak}–T_{end} in V3 (ms)	125.7 ± 31.5	99.1 ± 19.6	0.09
T_{peak}–T_{end} in V4 (ms)	121.9 ± 26.5	92.3 ± 19.7	0.001
T_{peak}–T_{end} in V5 (ms)	123.1 ± 26.5	99.5 ± 20.1	0.04
T_{peak}–T_{end} in V6 (ms)	126.9 ± 32.2	89 ± 11.3	<0.001
Epsilon wave	2 (8)	0	-
Precordial T-wave inversion (V1–3)	16 (64)	1 (7)	0.002
QT ms	433.8 ± 93.2	384.1 ± 45.0	0.079
QTc ms	438.5 ± 78.4	388.2 ± 63.6	0.087
R–R interval ms	884.9 ± 264.4	819.5 ± 247.2	0.46
QRS duration >110 ms in V1–3	16 (64)	0	-
TAD prolongation >55 ms	12 (48)	1 (7)	0.004

Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. J Electrocardiol 2008; 41:575–580.

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Usefulness of T_{peak}–T_{end} Interval to Distinguish Arrhythmogenic Right Ventricular Cardiomyopathy from Idiopathic Right Ventricular Outflow Tract Tachycardia

EBRU GOLCUK, M.D.,* KIVANC YALIN, M.D.,†,‡ AHMET KAYA BILGE, M.D.,† ALI ELITOK, M.D.,† TOLGA AKSU, M.D.,* TAYLAN AKGUN, M.D.,§ EKREM BILAL KARAAYVAZ, M.D.,† SAMIM EMET, M.D.,† and KAMIL ADALET, M.D.†

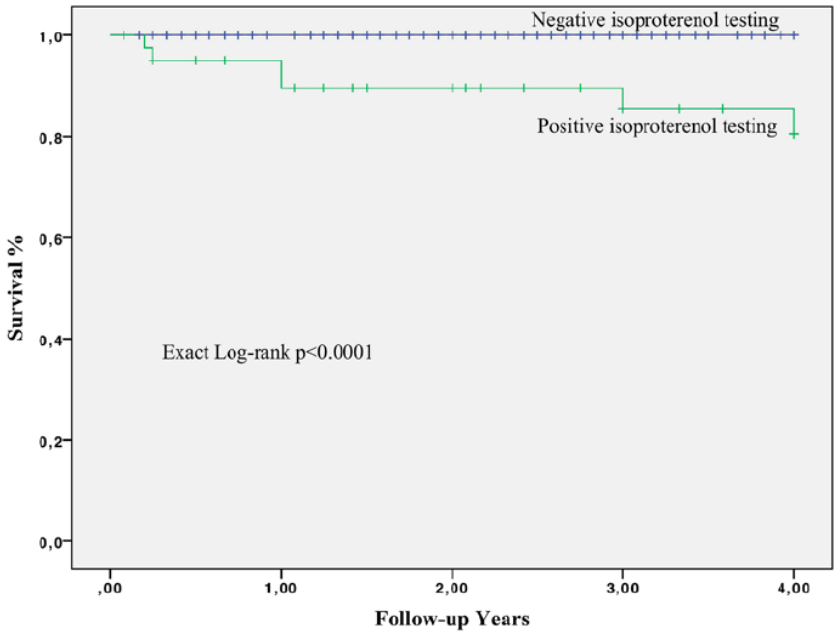
Isoproterenol testing

I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

Table 3.
Based on

Positive isoproteren testing

Negative isoproteren testing



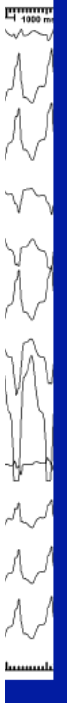
Year	0	1	2	3	4
Positive isoproterenol testing	42	35	29	23	18
Negative isoproterenol testing	335	295	264	235	220

ing

e predictive
e=43.2%

e predictive
e=99.1%

12 (100)



Diagnostic Value of Isoproterenol Testing in Arrhythmogenic Right Ventricular Cardiomyopathy

Arnaud Denis, MD; Frédéric Sacher, MD, PhD; Nicolas Derval, MD; Han. S. Lim, MBBS; Hubert Cochet, MD, PhD; Ashok J. Shah, MD; Matthew Daly, MBChB; Xavier Pillois, PhD; Khaled Ramoul, MD; Yuki Komatsu, MD; Adlane Zemmoura, MD; Sana Amraoui, MD; Philippe Ritter, MD; Sylvain Ploux, MD; Pierre Bordachar, MD, PhD; Mélèze Hocini, MD; Pierre Jaïs, MD; Michel Haïssaguerre, MD

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Circ Arrhythm Electrophysiol August 2014

ETT in Asymptomatic carriers

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

Mark J. Perrin, MBBS, PHD,* Paul Angaran, MD,† Zachary Laksman, MD,† Hanfei Zhang, BSc,* Liane F. Porepa, MD,† Julie Rutberg, MSc,* Cynthia James, PHD,‡ Andrew D. Krahn, MD,† Daniel P. Judge, MD,‡ Hugh Calkins, MD,† Michael H. Gollob, MD*

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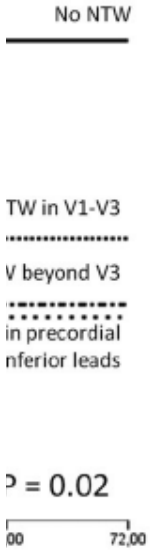
Exercise Testing in Asymptomatic Gene Carriers Exposes a Latent Electrical Substrate of Arrhythmogenic Right Ventricular Cardiomyopathy

EPS & Voltage maps- abnormal

TABLE 2

Differences of Percentage Right Ventricular Electroanatomic Scar According to the Presence or Absence of Major ECG Abnormalities and Late Potentials

	RV-EAS Area%		
ECG Abnormalities	**Yes**	**No**	**P**
Left axis deviation	18.9 (10.3–33.8)	24.8 (5.4–31.7)	0.98
Right axis deviation	20.4 (4.9–32.8)	23.8 (8.8–31.8)	0.87
S wave > 60 milliseconds	24.8 (5.6–31.6)	14.8 (7.9–31.9)	0.88
Low-QRS voltages	30.8 (8.1–33.9)	19.1 (5.1–31.4)	0.34
dQRS > 110 milliseconds	28.9 (11.0–33.0)	12.3 (5.1–31.4)	0.14
Epsilon waves	30.0 (10.1–37.0)	15.6 (5.1–27.8)	0.04
Negative T waves†	29.6 (13.1–32.2)	4.9 (4.5–6.4)	<0.001
Late potentials on SAECG	29.6 (10.3–31.7)	10.6 (5.1–32.2)	0.30



Electrocardiographic Predictors of Electroanatomic Scar Size in Arrhythmogenic Right Ventricular Cardiomyopathy: Implications for Arrhythmic Risk Stratification

Journal of Cardiovascular Electrophysiology *Vol. 24, No. 12, December 2013*

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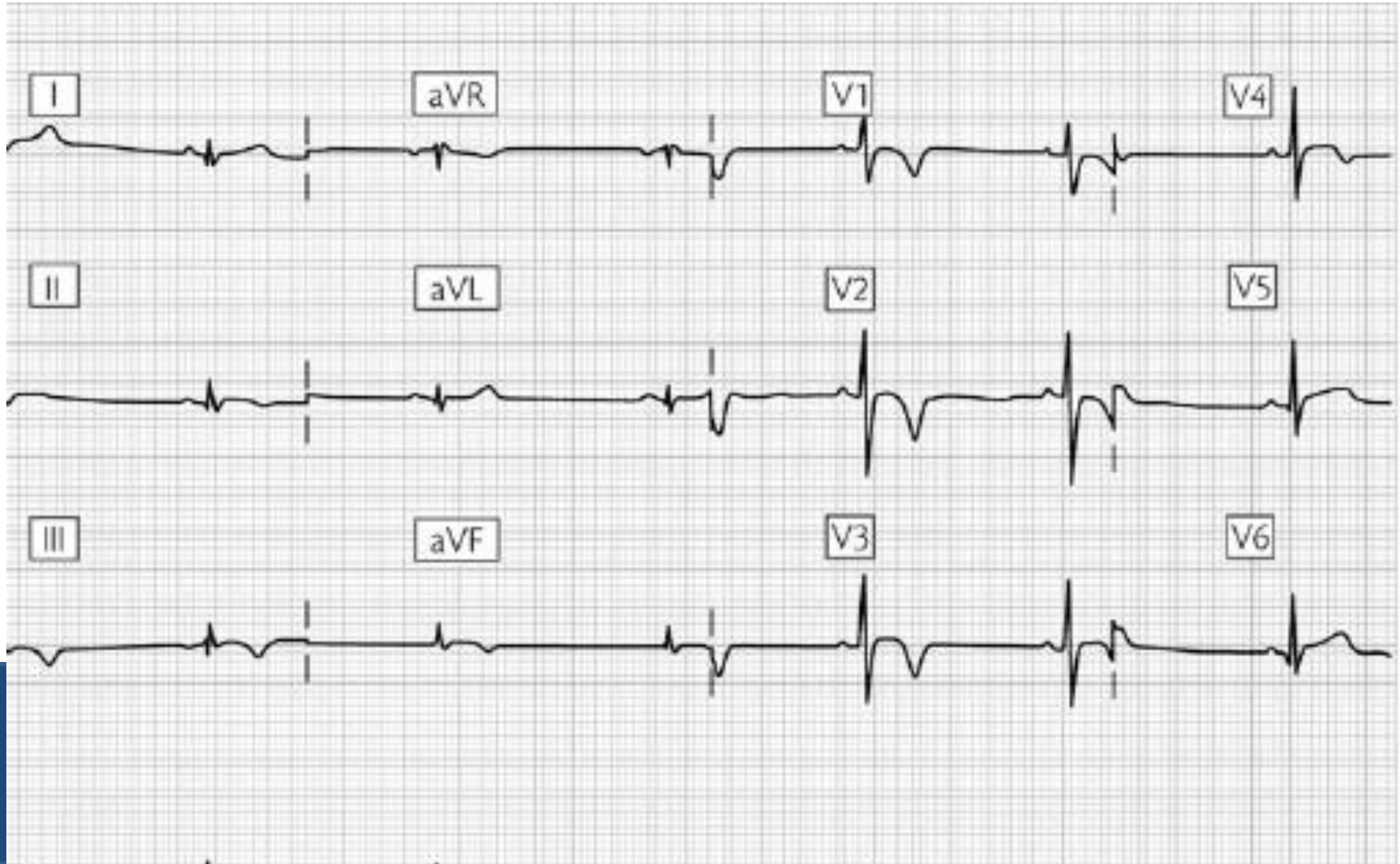
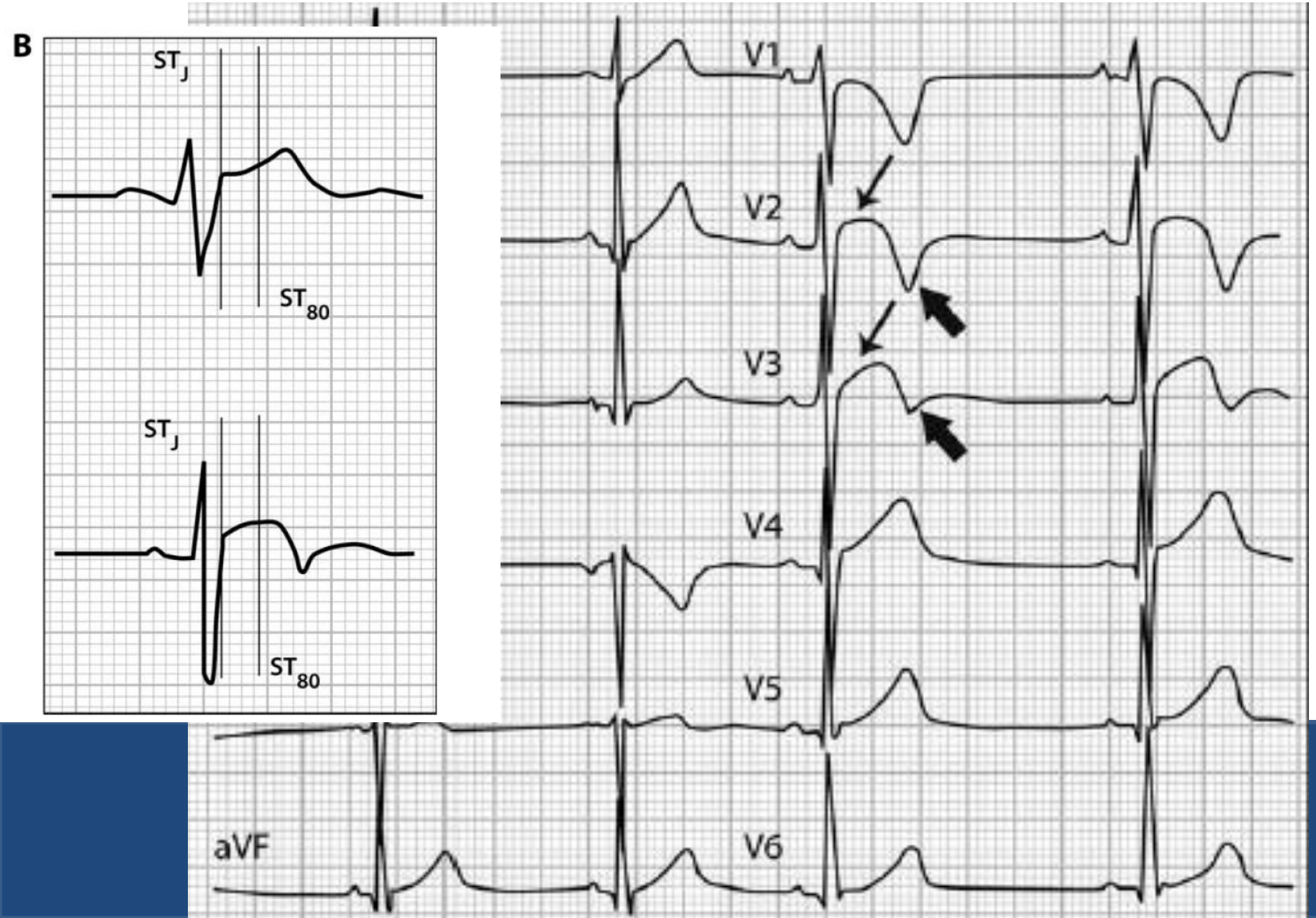
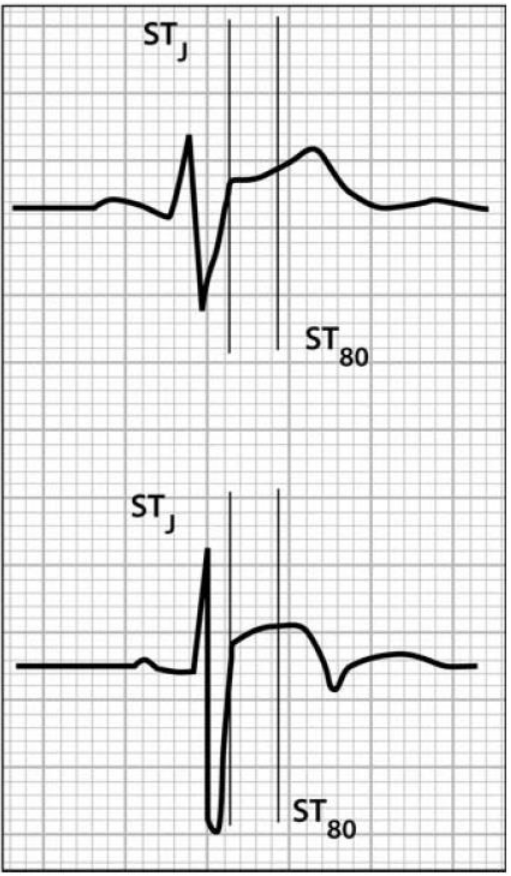
Quiz-1: Athlete referred for pre-participation evaluation

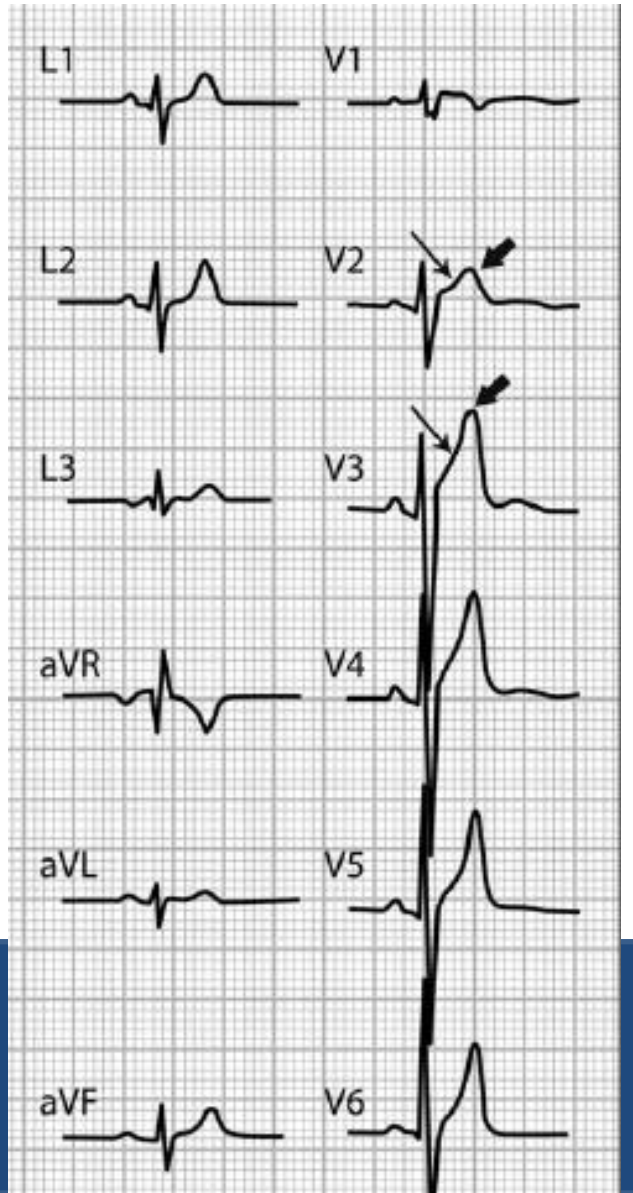


Quiz-2: Healthy Athlete from Africa



Quiz-3: Olympic screening





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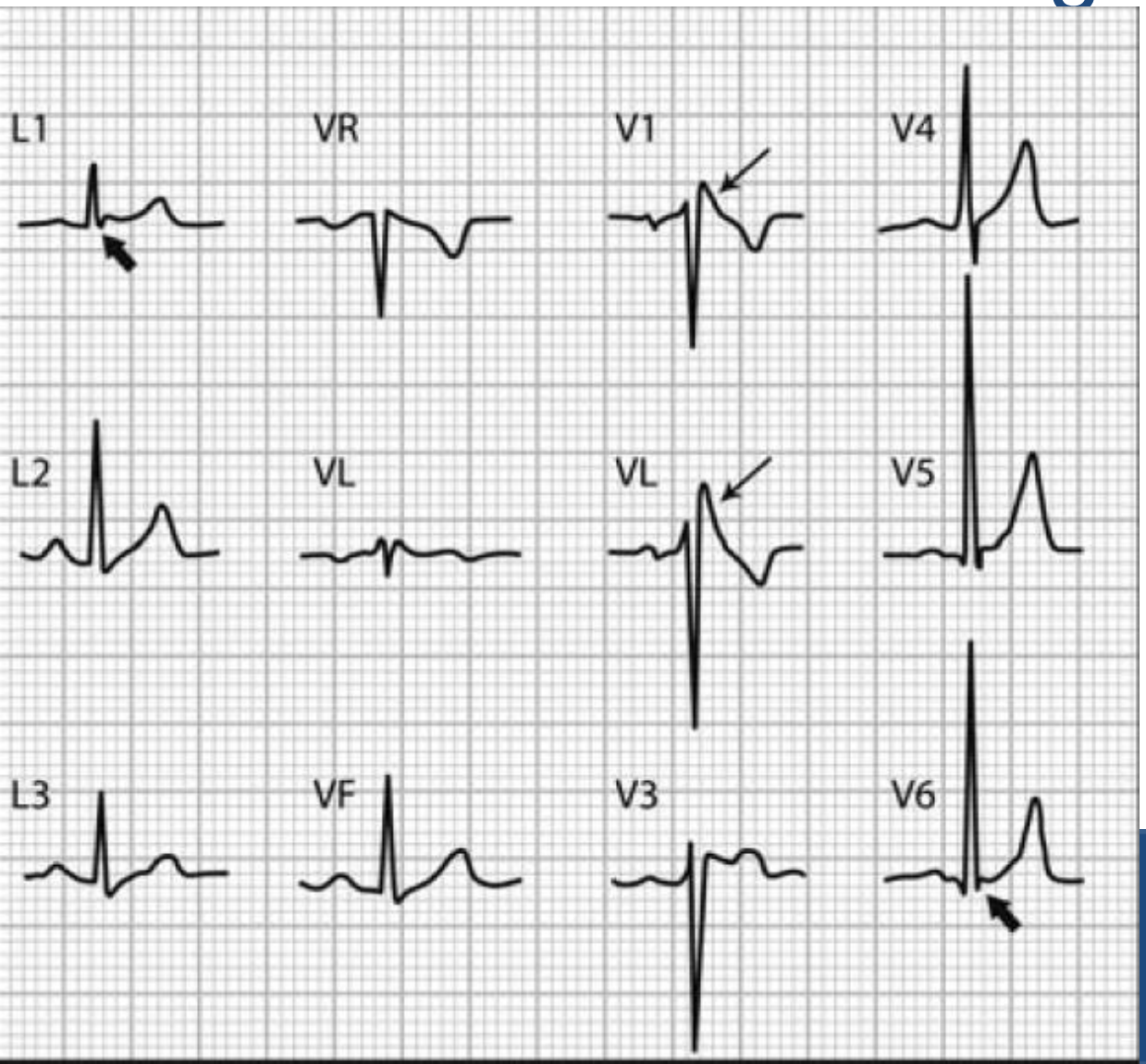
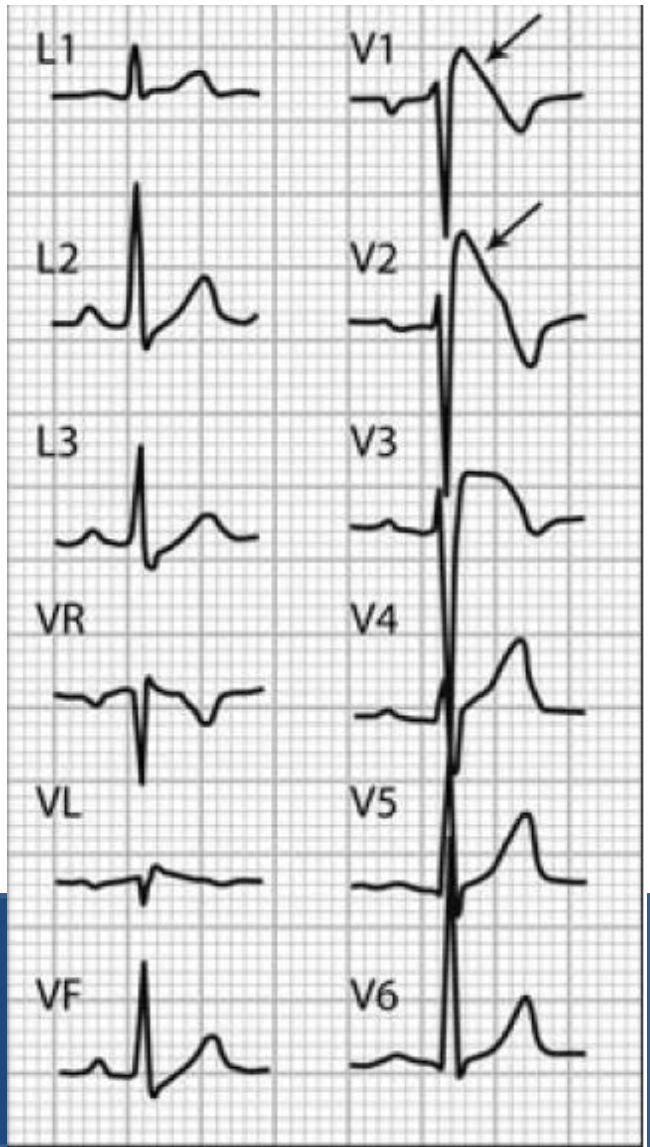
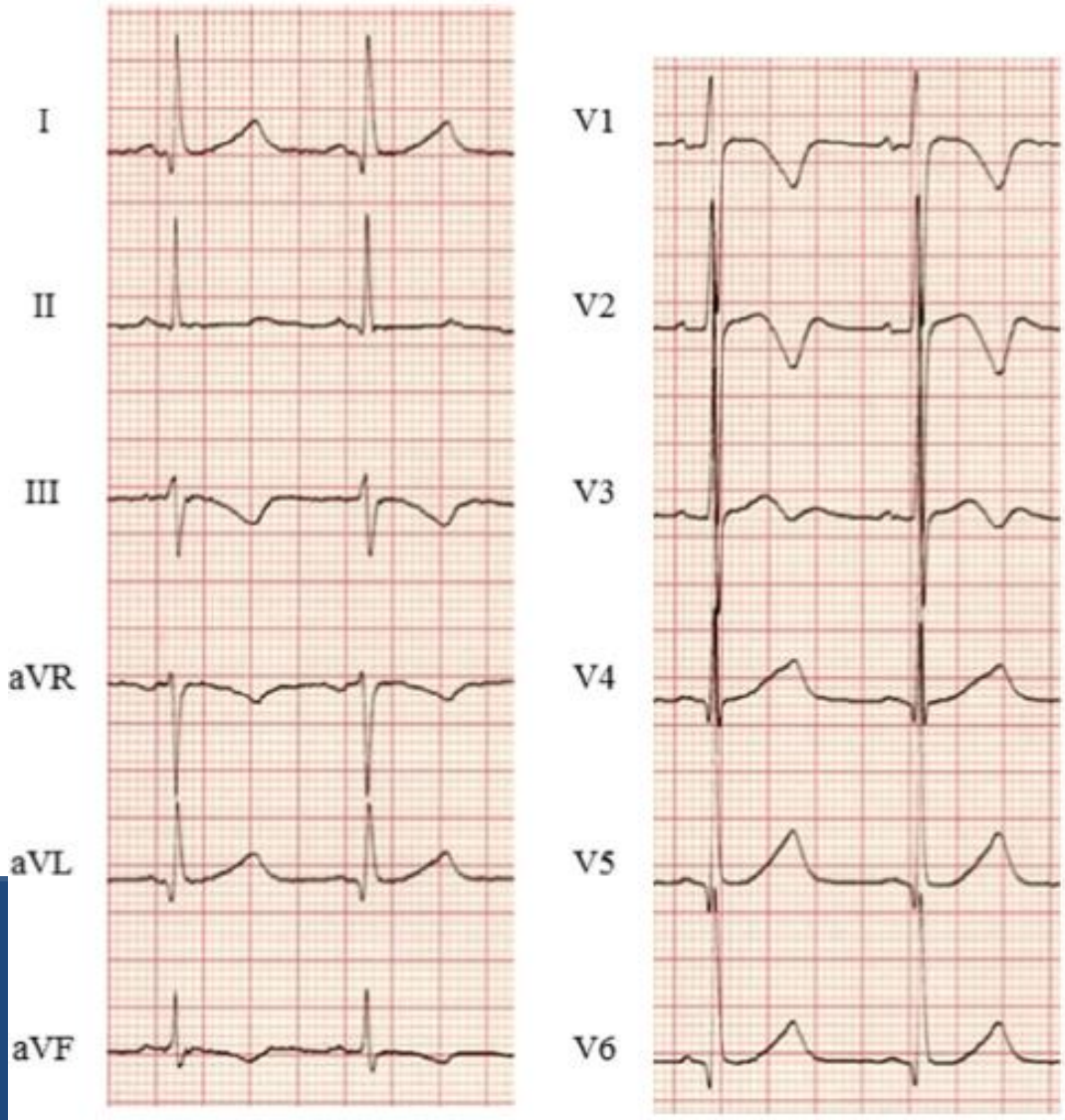
Quiz-4: Athlete referred for screening



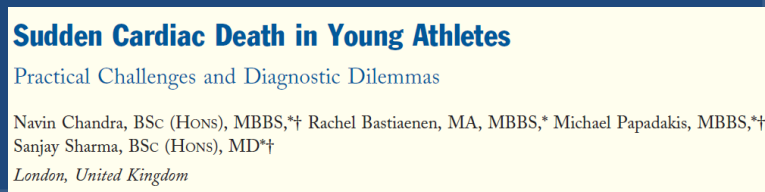


Quiz-5

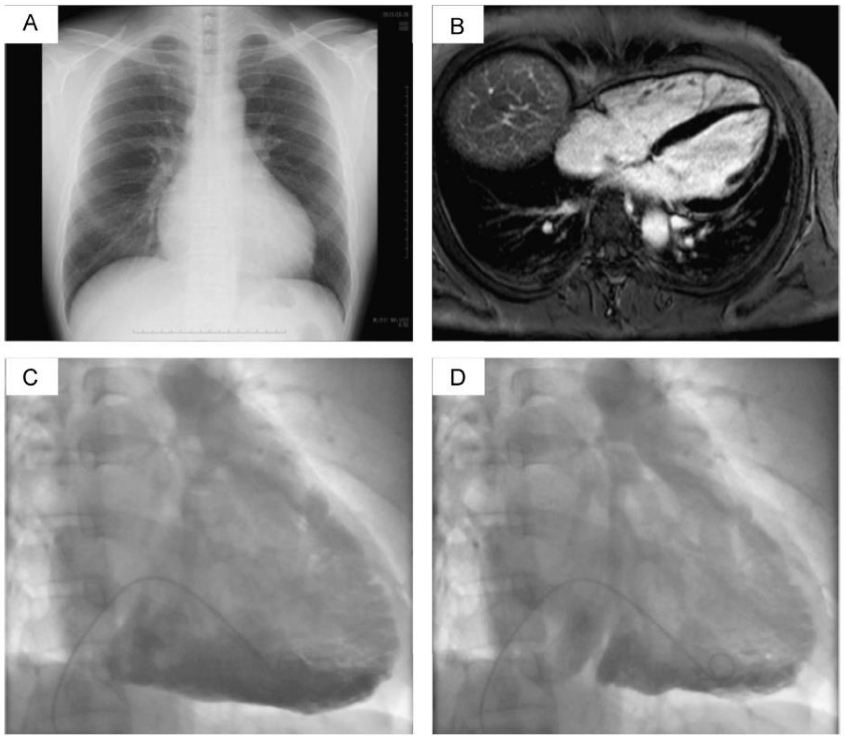


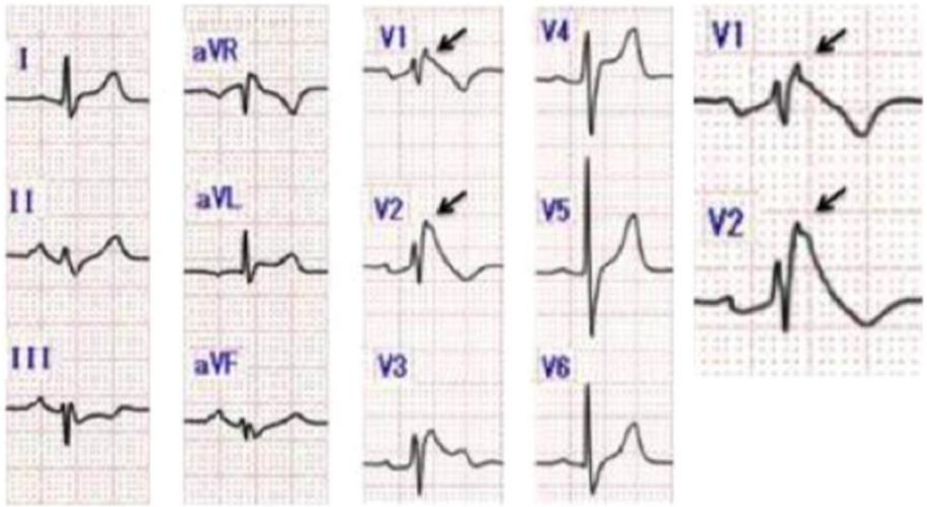
Differential Diagnosis

- BrS overlap
- RVOT VT (Malignant conversion)
- Race
- Athletes
- Congenital abnormalities and Acquired heart diseases
- Early repolarisation
- Sarcoidosis



BrS overlap





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An overlap of Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia

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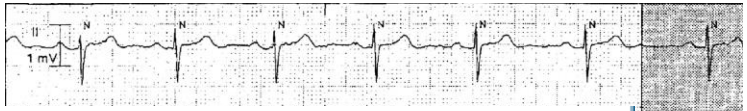
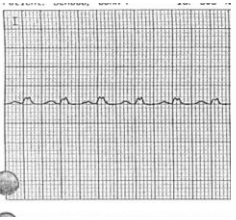
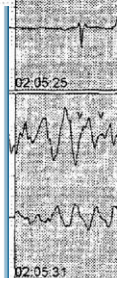
RVOT VT- Malignant conversion





ECG Findings in RVOT Tachycardia and in ARVC/D

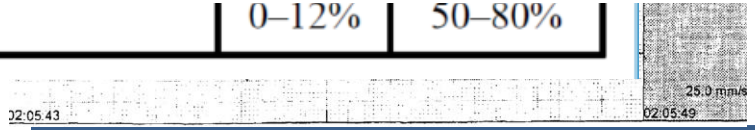
	RVOT	ARVC/D
T↓ V_1–V_3	0 –6%	37–81%



Univariate and Multivariate Logistic Regression Analysis

	Univariate Model			Multivariate Model		
Variables	**OR**	**95% CI**	**P Value**	**OR**	**95% CI**	**P Value**
QRS duration in lead I ≥125 ms	9.58	1.94–47.22	0.006	8.79	1.51–51.16	0.016
Transition R/S at lead V5 or later	6.15	1.46–26.0	0.014	8.59	1.47–50.33	0.017
Notched QRS in leads I and aVL	5.06	1.37–18.72	0.015	10.41	1.91–56.76	0.007

Positive SAECG	0–12%	50–80%



Electrocardiographic Difference between Ventricular Arrhythmias from the Right Ventricular Outflow Tract and Idiopathic Right Ventricular Arrhythmias

Marcus et al. J Cardiol 2009

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Malignant conversion of benign right ventricular outflow track ventricular tachycardia 18 years post-ablation

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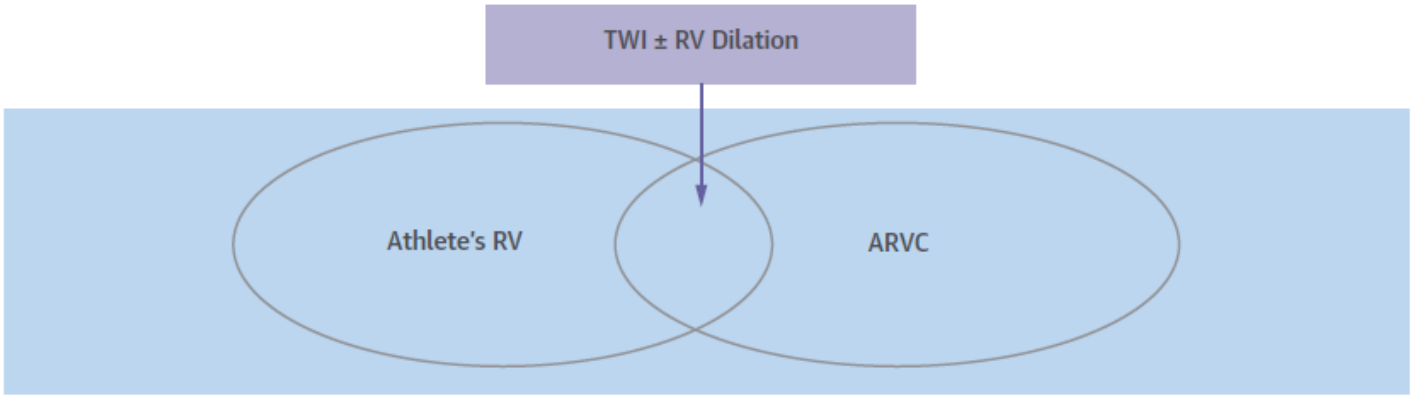
Athlete's Heart



Consider Athlete's RV	Poor Discriminators	Consider ARVC
Voltage LVH on ECG Voltage RVH on ECG V-Amp$_{max}$ >3.3 mV (male subjects) Biphasic TWI Convex STE + TWI Inferior / lateral ER RVD1/LVEDD ≤0.9 (echo) RVEDV/LVEDV ≤1.2 (CMRI)	Distribution of TWI Depth of TWI pRBBB QRS terminal activation time LAE on ECG RAE on ECG RV size (absolute or indexed) RVFAC (echo) 31%–40% Apical RV WMA at echo 0-2 abnormal SAECG parameters TWI pseudonormalization on ETT Lack of pseudonormalization	Syncope (nonvasovagal) Any exertional symptoms +VE FHx (ARVC, SCD, genetics) Q waves TWI + isoelectric ST-segment V-Amp$_{max}$ <1.8 mV (male subjects) ≥1 VE on resting ECG RVWT ≤3 mm RVFAC (echo) ≤30% RVEF (CMRI) ≤45% RV WMA or DGE (CMRI) 3 abnormal SAECG parameters ETT duration <12 min Increase in VE during ETT NSVT / VT (Holter, ETT) SBP rise < 20 mm Hg or ↓BP on ETT >500 VE / 24 h (unless all RVOT) >1,000 VE / 24 h (any morphology)

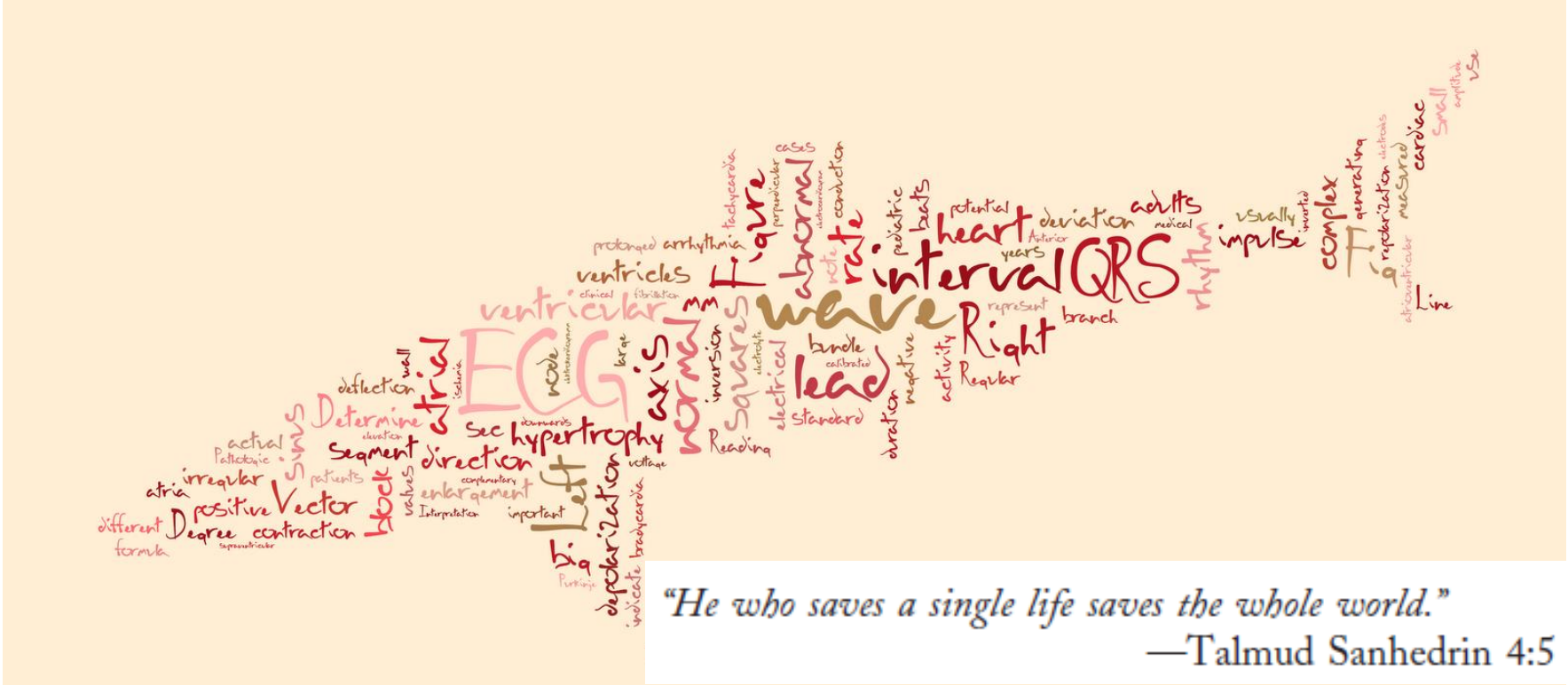
Clinical Differenti
Physiological Ren
Arrhythmogenic F
Cardiomyopathy i
Electrocardiograp

sse K. Jongman, MD,†
ırr-White, BSc (Hons), MBBS, PhD,§
jah R. Behr, MBBS, MD,*

Summary

- Integration of 6 domains of TFC in diagnosis
- Importance of serial monitoring
- Electrical changes precede structural changes
- Newer modalities outside TFC
- Differential diagnosis

Thanks for your attention



"He who saves a single life saves the whole world."

—Talmud Sanhedrin 4:5 (1)

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