Arrhythmogenic Cardiomyopathy: Controversies to guide future directions

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Arrhythmogenic Cardiomyopathy: Introduction - Controversies

- Nomenclature
- **Diagnosis**
- Aetiology
- Pathogenesis
- Management

Cardiomyopathy

- Chronic disease of the heart muscle

Dysplasia

  - From the Greek *dys* (bad, disordered, abnormal) and *plassein* (to form)
- When applied to organ/ macroscopic structure (e.g., hip), a developmental anomaly
- When applied to tissue/ cells, refers to proliferation of abnormal/ immature/ poorly differentiated/ pre-malignant cells
- Neither scenario applies to ARVC

Name defines the brand, person, place,…… disease

Name defines a phenotype

Churchill

Ronaldo

Madonna

Evolution of nomenclature

1982
Arrhythmogenic Right Ventricular Dysplasia

1994
Diagnosis of Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy

2010
Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy / Dysplasia (ARVC/D)

2011
Arrhythmogenic Cardiomyopathy

Diagnosis

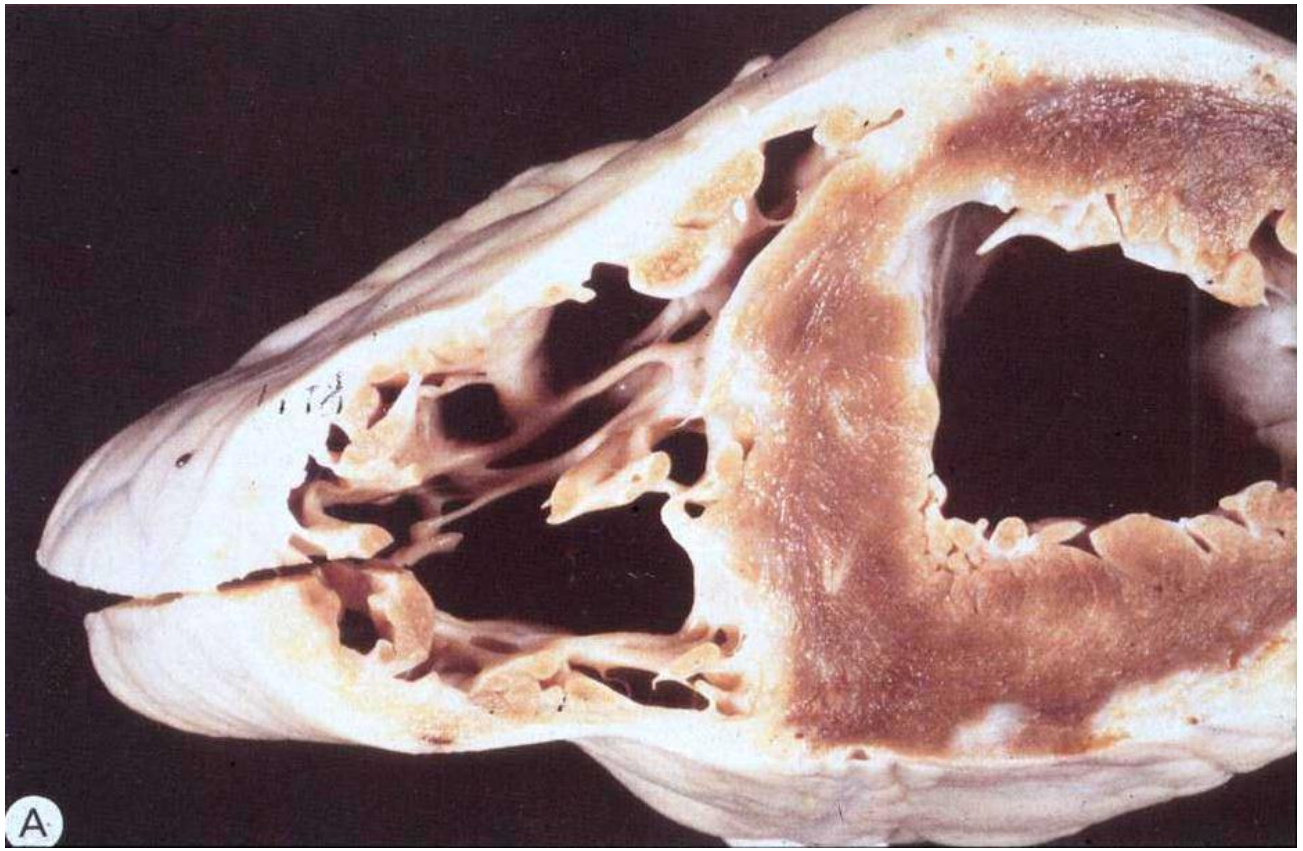
What constitutes a ‘diagnosis’?

- Pathology
- Clinical phenotype
- Genetics

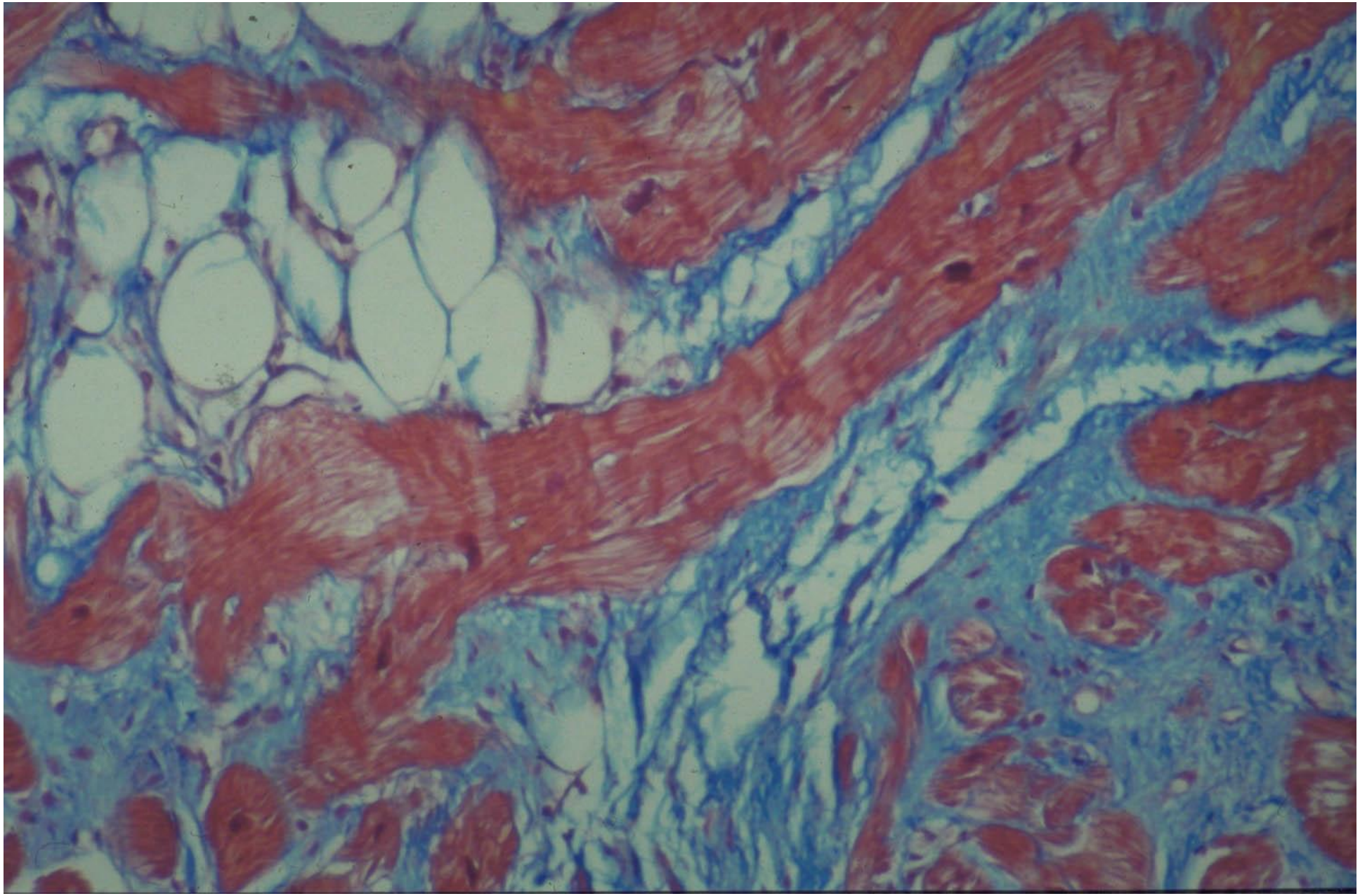
Perspectives in ARVC

- Pathologist — presentation with sudden death – regional RV disease
- Arrhythmologist — presentation with arrhythmias – LBBB VT
- Geneticist — pedigree evaluation – broad phenotype / incomplete disease expression

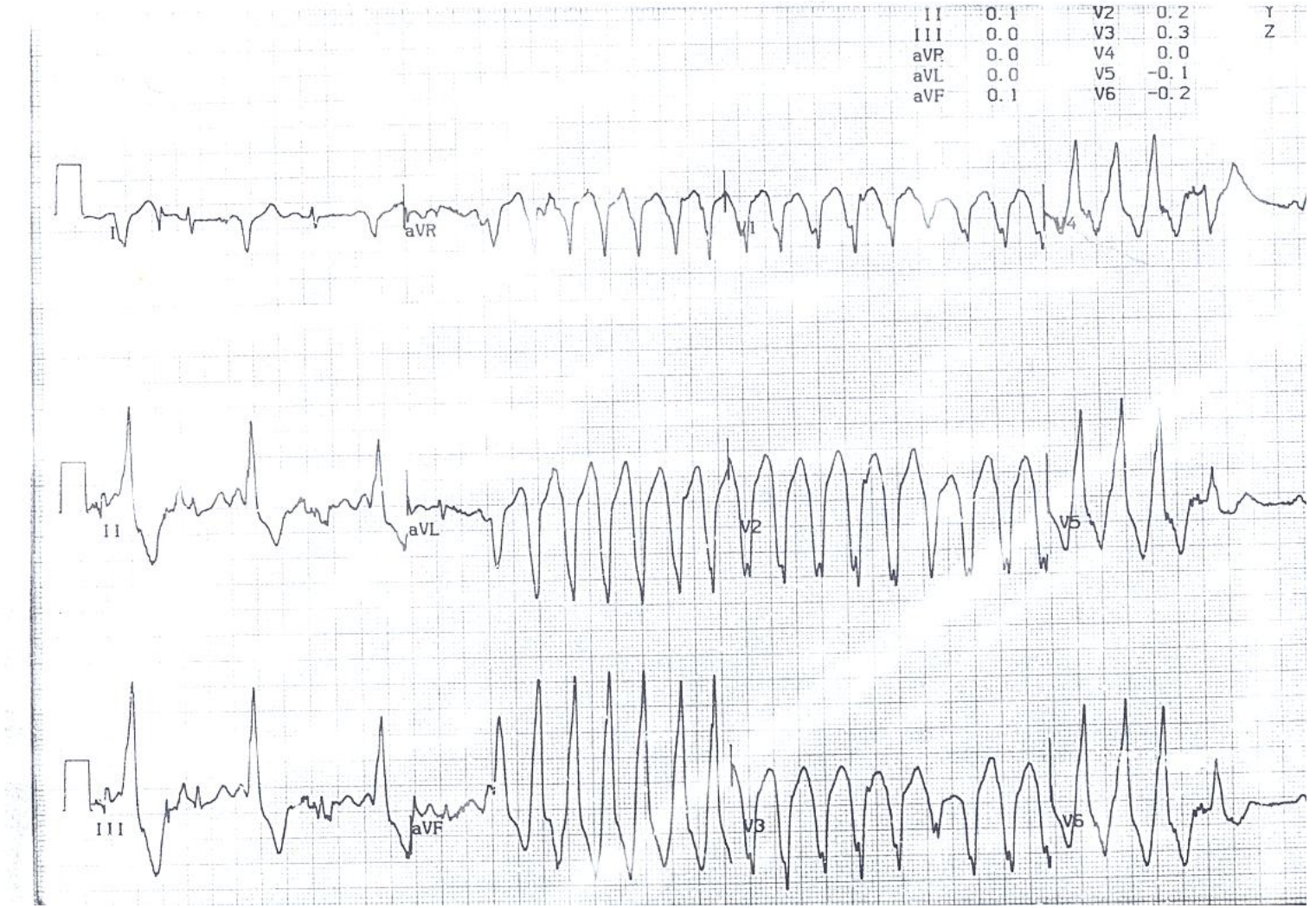
Arrhythmogenic Right Ventricular Cardiomyopathy



- Dx- structural, functional and electrophysiologic abnormalities, secondary to fibrofatty replacement of RV ± LV myocytes

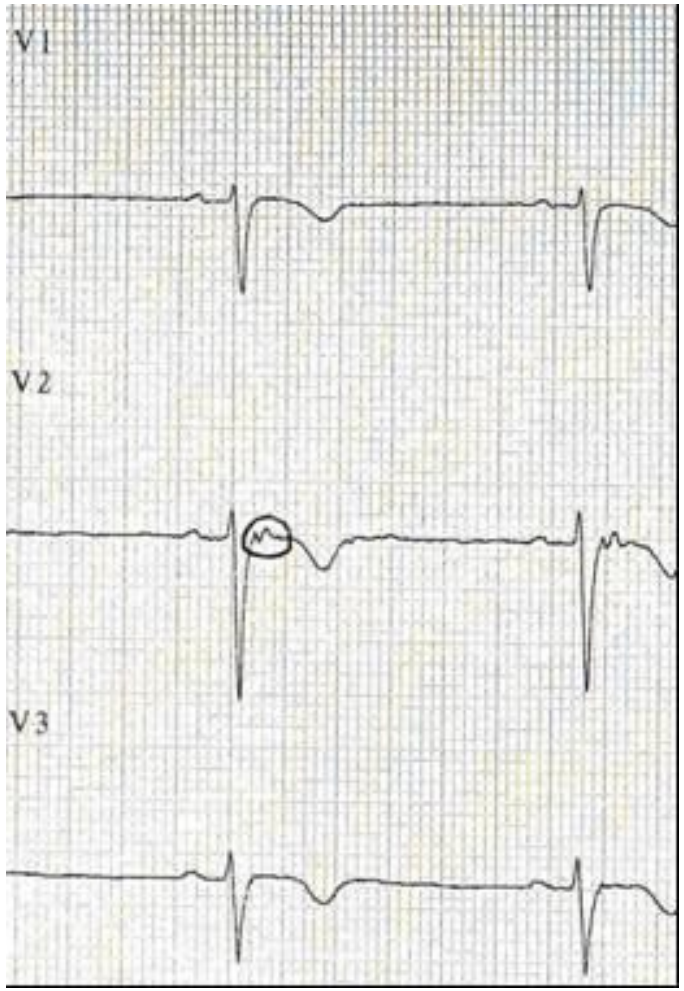


Exercise Test: 4.5min



ARVC

12/11/2003



02/02/2005

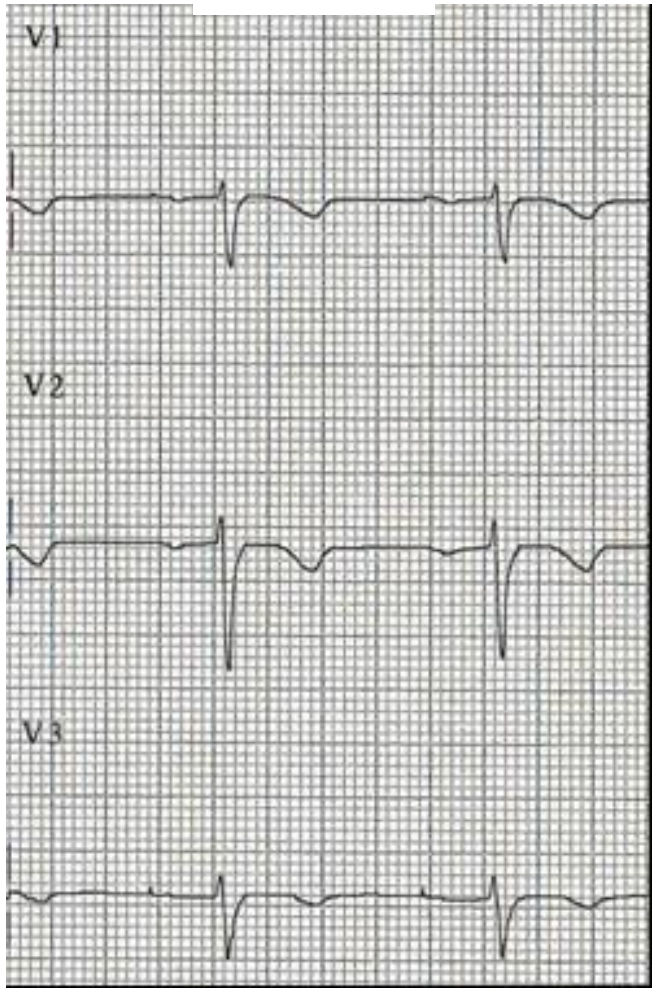
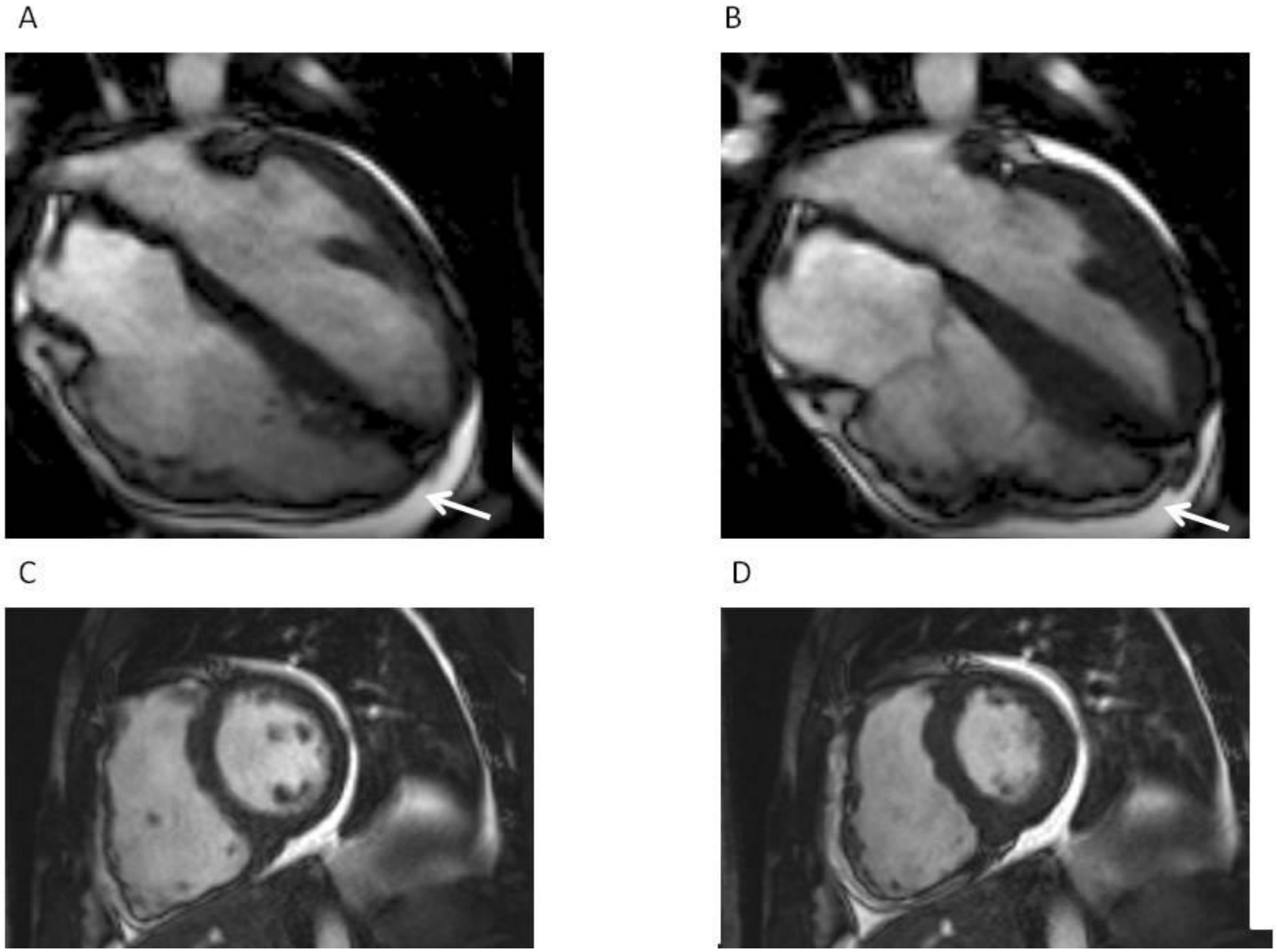


Figure 4



ARVC/D Diagnostic Criteria

Marcus et al, Circulation 2010

	Major	**Minor**
2-D echo and MRI	RV dysfunction/aneurysm ↑ volume (95% sp)	RV dysfunction ↑ volume (87% sp)
Tissue characterization on endomyocardial biopsy	Fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue. Residual myocytes <60% by morphometric analysis, or <50% if estimated	Fibrous replacement of the RV free wall myocardium in at least one sample, with or without fatty replacement of tissue. Residual myocytes 60-75% by morphometric analysis, or 50-65% if estimated
Electrocardiogram **Repolarization abnormalities**	Inverted T waves in the right precordial leads (V_1, V_2 and V_3) or beyond in people >14 years of age, in the absence of complete RBBB (QRS ≥ 120 msec)	Inverted T waves in leads V_1 and V_2 in the absence of complete RBBB, or in V_4, V_5, or V_6
Electrocardiogram **Depolarization abnormalities**	Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T-wave)	Terminal activation duration of QRS ≥55 ms measured to the end of the QRS, including R prime, in V_1 or V_2 or V_3, in the absence of complete RBBB. Late potentials by signal averaged ECG in at least one of the 3 parameters in the absence of a QRS duration of ≥110 msec on the standard ECG Filtered QRS duration (fQRS) ≥ 114 msec Duration of terminal QRS < 40 µV (LAS) ≥ 38 ms RMS voltage of terminal 40 ms ≤20 µV
Arrhythmias	Non-sustained or sustained VT of LBBB morphology excluding typical RVOT morphology (positive QRS in II, III, aVF and negative in aVL	Non-sustained or sustained VT of LBBB morphology of RVOT axis (see above) or of unknown axis. > 500 ventricular extrasystoles / 24 hours by Holter
Family history / Genetics	Familial disease confirmed pathologically at necropsy or surgery in a first-degree relative A pathogenic** mutation in the proband or carrier status of pathogenic desmosomal mutation in a family member, who may be a healthy carrier***	Familial disease confirmed in a first-degree relative who meets Task Force Criteria without ARVC/D pathogenic desmosomal mutation(s) A desmosomal mutation in the proband which is normal and/or not proven to be disease causing

Definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories

Borderline: 1 major and 1 minor or 3 minor from different categories

Suspected: 1 major or 2 minor from different categories

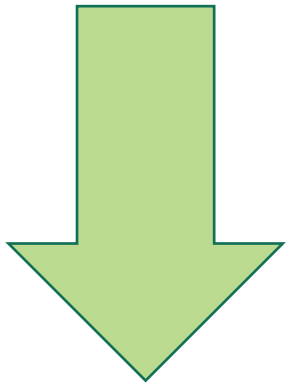
Unlikely: 1 minor

Presentation of ARVC

- Concealed phase
  - Sporadic ventricular ectopic beats
  - Subtle ECG/morphological abnormalities
  - Sudden death can occur
- Overt phase
  - Arrhythmia symptoms, sustained VT
  - Diffuse RV/LV structural abnormalities
  - Sudden death can occur
- Advanced disease
  - ↑ dilatation, ↓ contractility of RV, LV
  - Heart failure symptoms, sustained VT

Clinical Presentation of ARVC

Phenotype differs in relation to stage of disease (age)



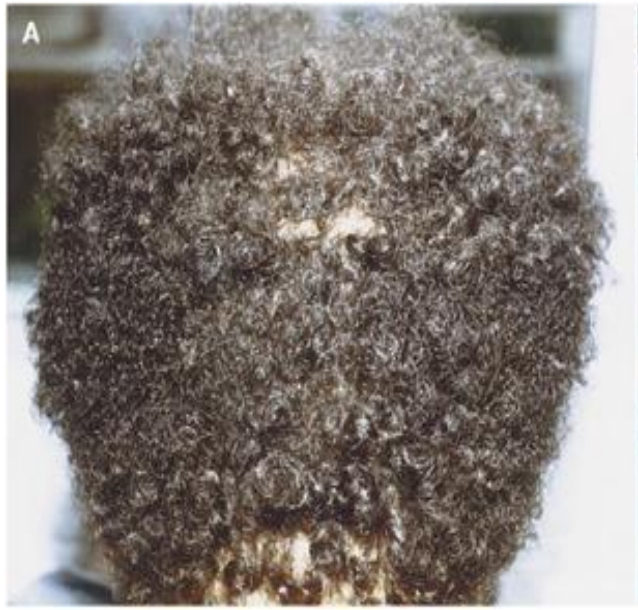
Is this sufficiently taken into account in current diagnostic criteria?

Autosomal Dominant ARVC Loci

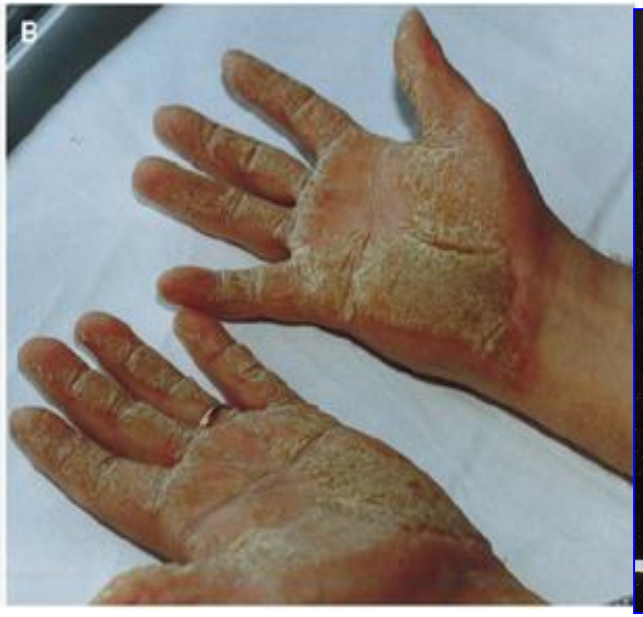
ARVC1	14q23-24	Rampazzo, 1994
ARVC2	1q42-43	Rampazzo, 1995
ARVC3	14q12-22	Severini, 1996
ARVC4	2q32	Rampazzo, 1997
ARVC5	3p23	Ahmad, 1998
ARVC6	10q22.3	Melberg, 1999
ARVC7	10p12-14	Li, 2000

Naxos Disease

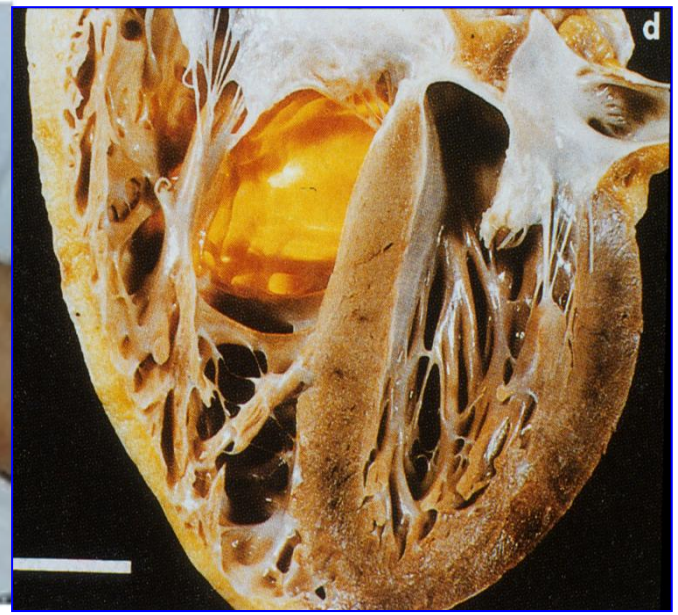
Autosomal recessive mutation in plakoglobin resulting in truncation of C-terminal amino acids



Woolly hair

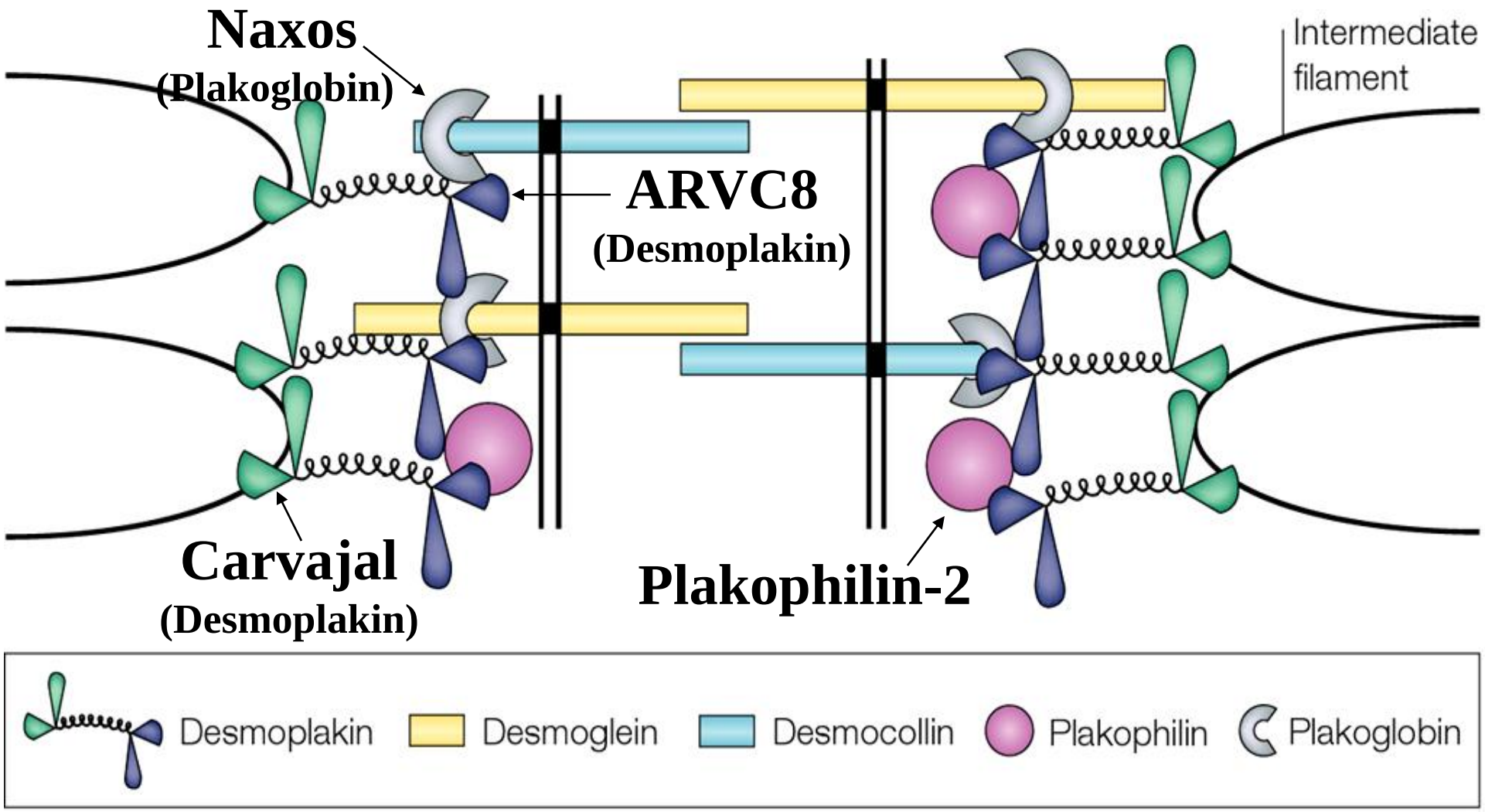


Palmoplantar keratoderma

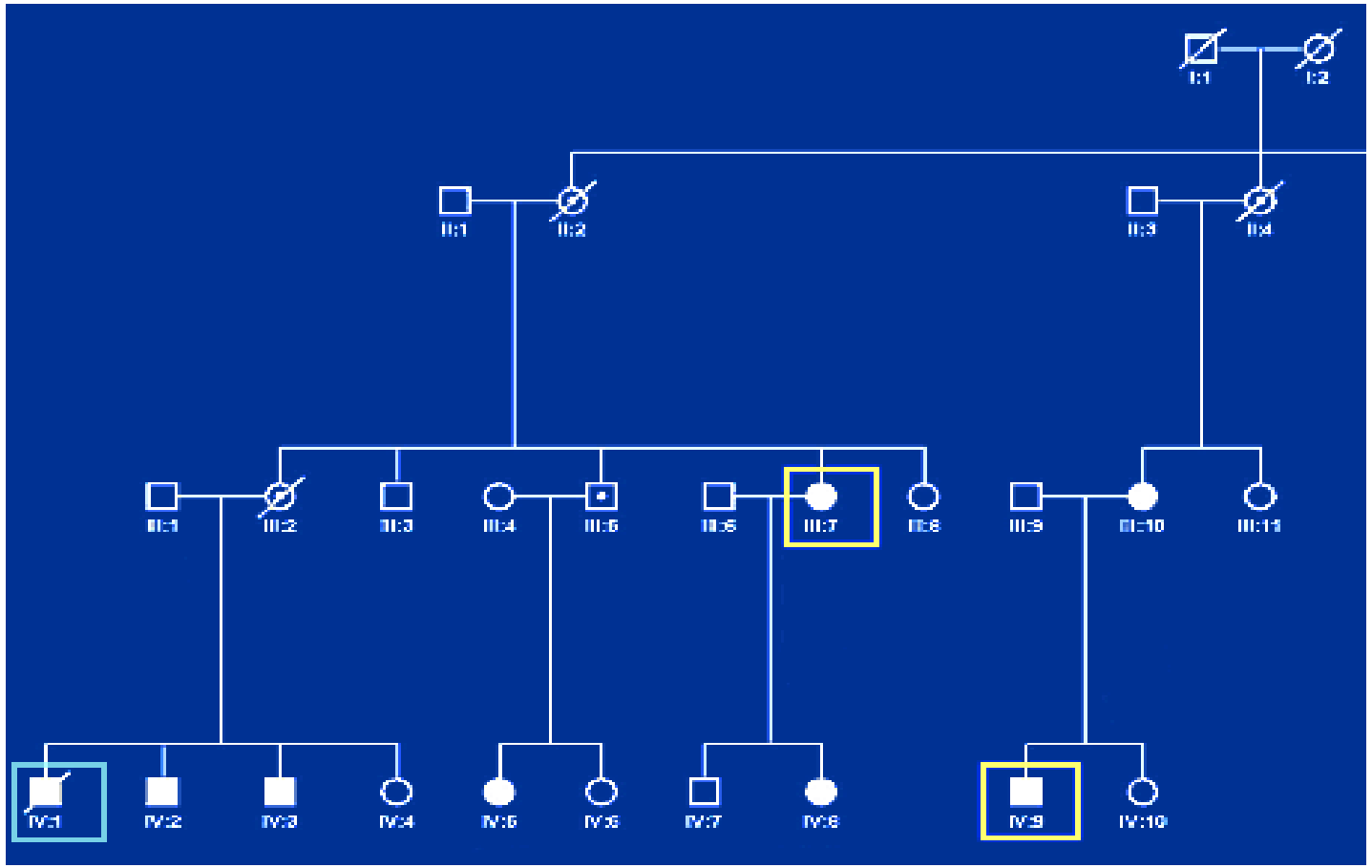


Arrhythmogenic RV Cardiomyopathy

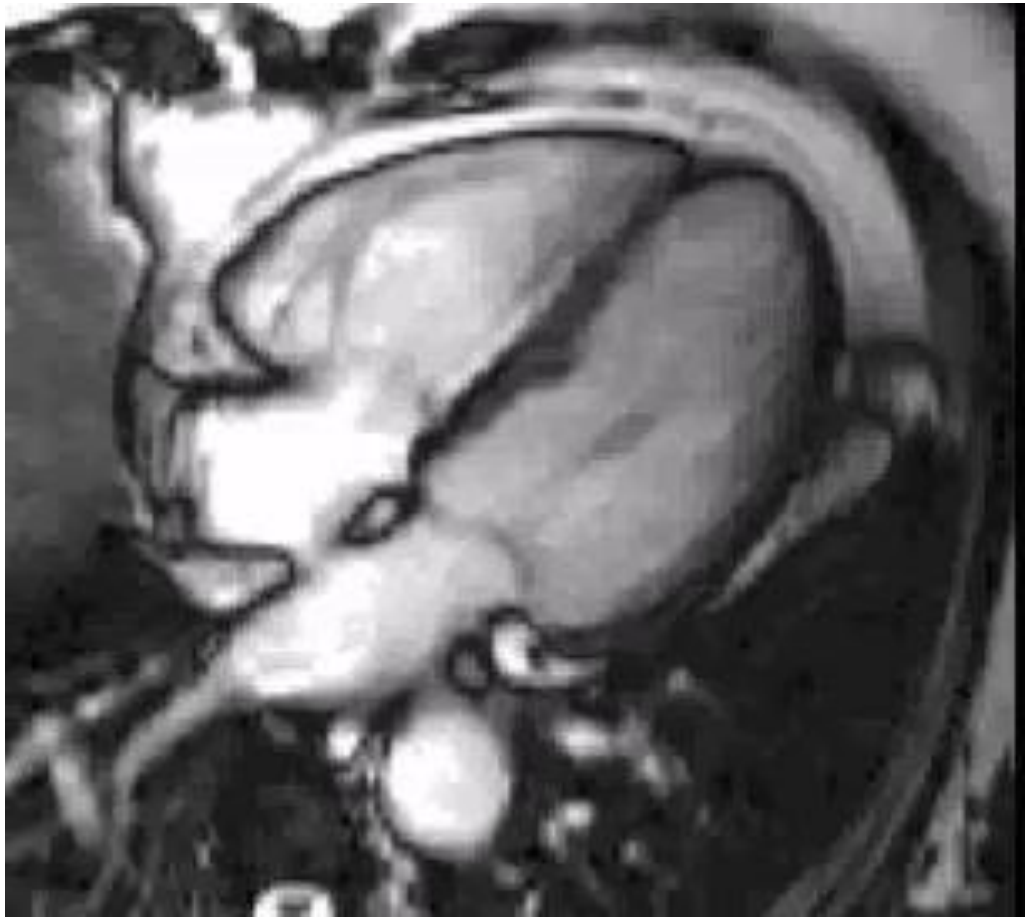
Disease-Causing Mutations in Desmosomal Proteins



Arrhythmogenic LV cardiomyopathy

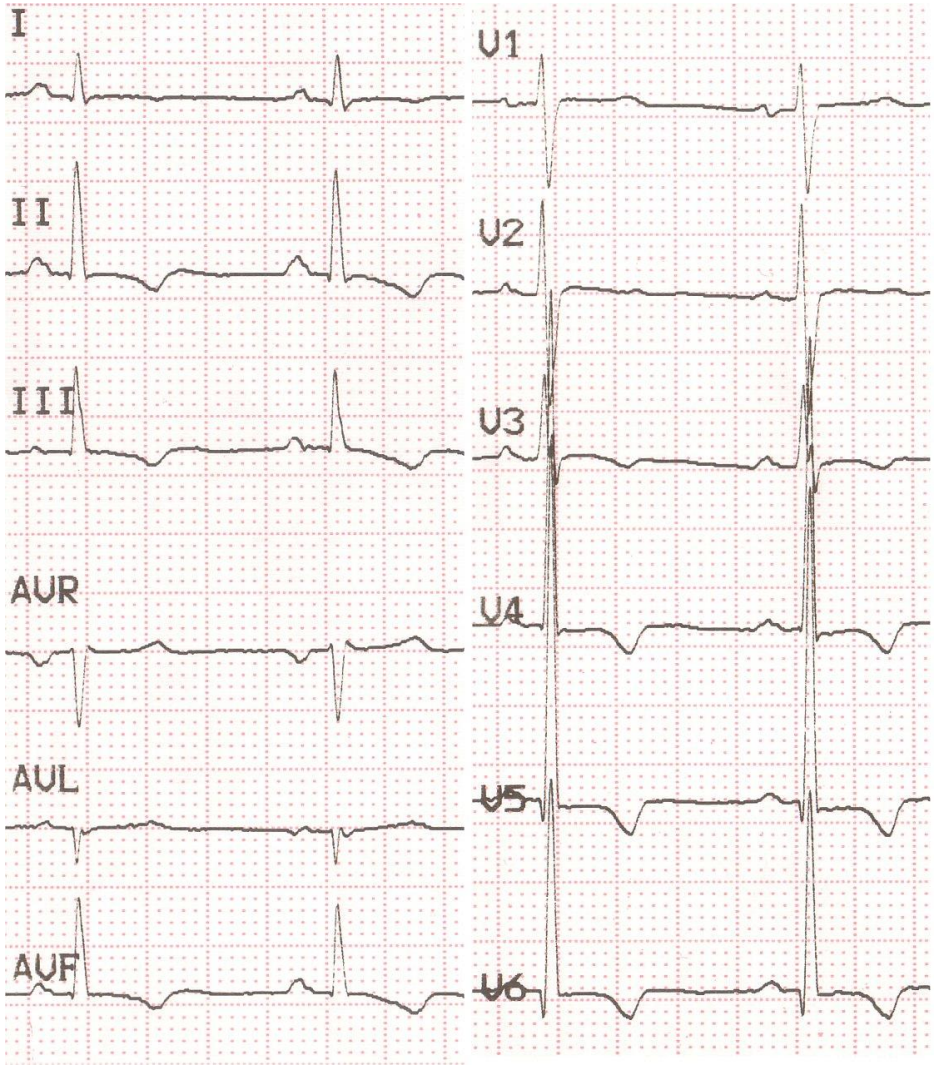


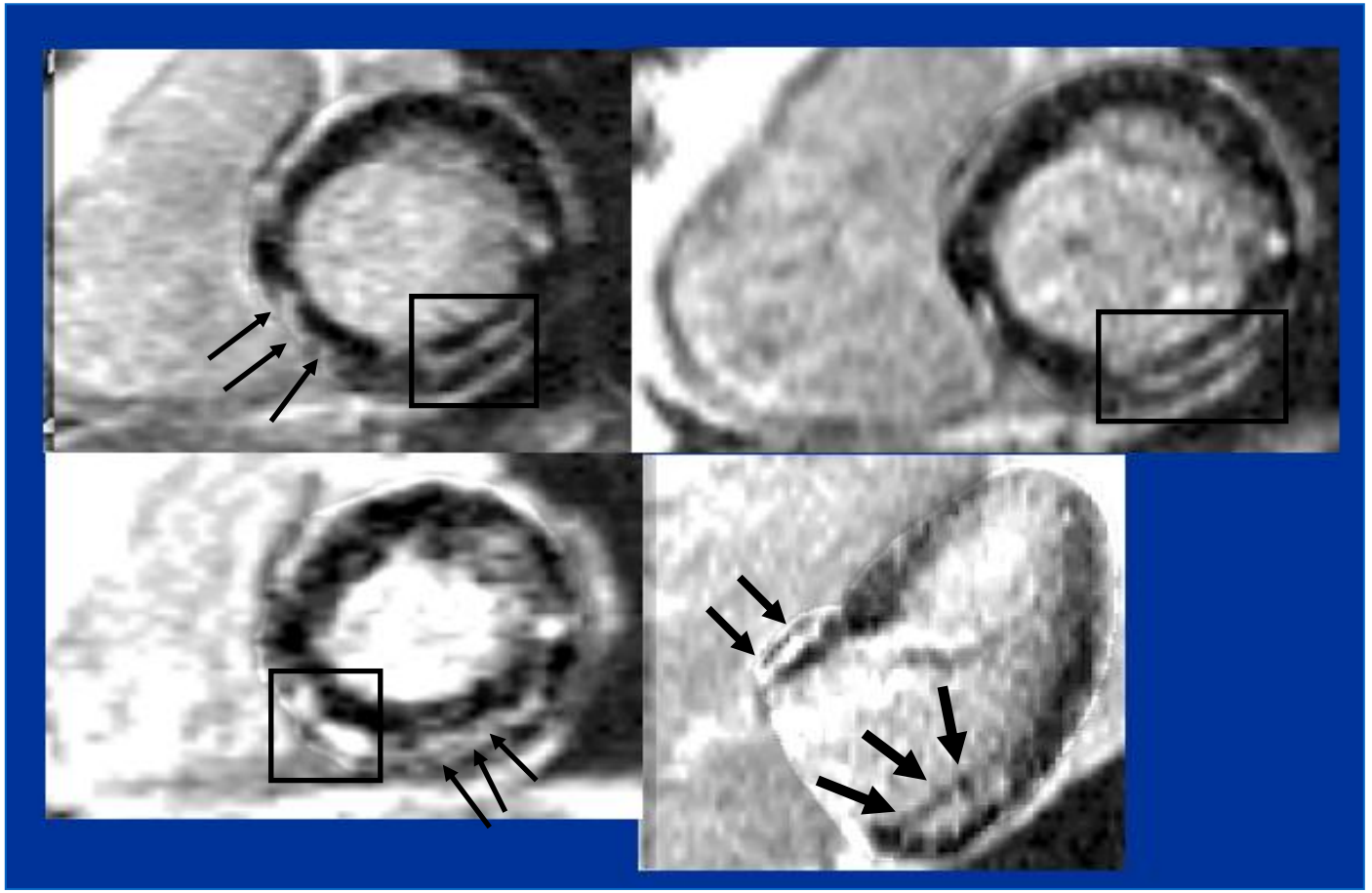
Case III.7 – True FISP ciné



Four-chamber view

ALVC Desmoplakin (2034insA mutation)

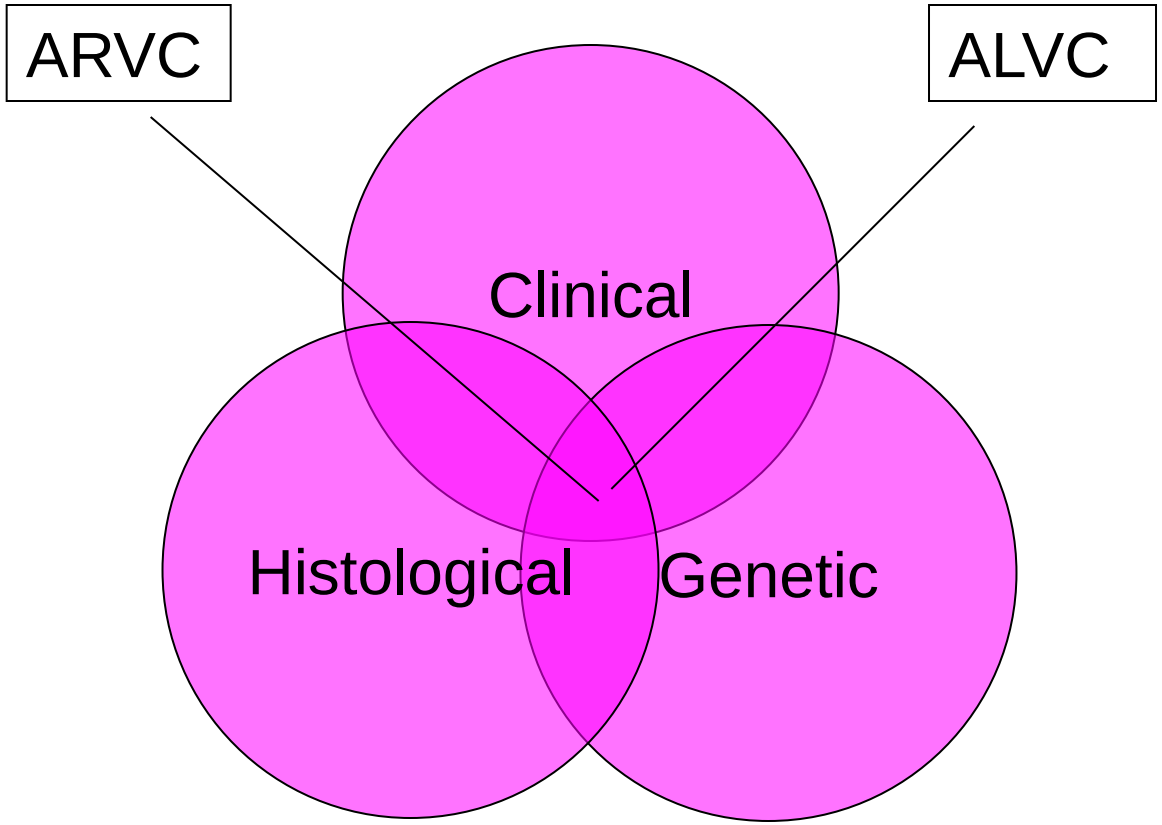




Circulation, 2005; 112(5):636-42

ID	Age	LVED % pred	LVED mm	LVES mm	FS %	Abn CMR gad	ECG	VT/ VES/ 24hrs
II.6	67	142%	64	48	25	ICD *in situ*	T↓ II, III, VF, V4-6	RBBB VT*
III.7	62	109%	50	28	44	positive	T↓ II, III, VF, V4-6	RBBB VT*
III.10	47	120%	53	34	36	ND	N	1316 R&L VES
III.17	41	98%	42	26	38	ND	T↓ II, III, VF	7 L VES#
III.20	46	128%	64	45	29	ND	T↓ II, III, VF, V3-6	815 L VES
IV.2	36	118%	51	35	31	ICD *in situ*	↓R V1-2, T↓ V3	LBBB VT*
IV.3	39	113%	50	33	34	ND	N	3661 R&L VES
IV.5	31	105%	48	32	33	positive	N	1795 L VES
IV.8	36	125%	54	38	29	ND	T↓ II, III, VF, V4-6	5938 L VES
IV.9	28	127%	58	43	26	positive	T↓ V4-6	5612 L VES
IV.14	22	117%	54	36	33	positive	T↓ II, III, VF	47 L VES

Arrhythmogenic Cardiomyopathy



“Dilated Cardiomyopathy”

(unexplained LV dilatation / impaired contraction)

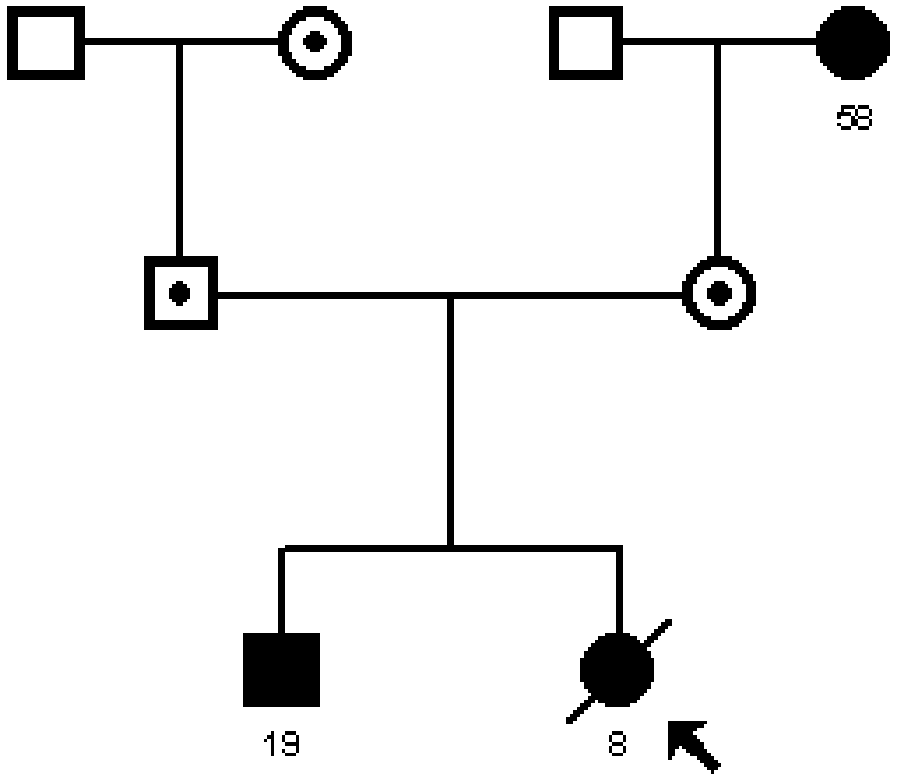
Clinical Presentation		**Genes**
• Heart Failure	→	cytoskeletal, sarcomere, Z disc
• Arrhythmia (CD, VT/VF, SD)	→	desmosomal, lamin, SCN5A

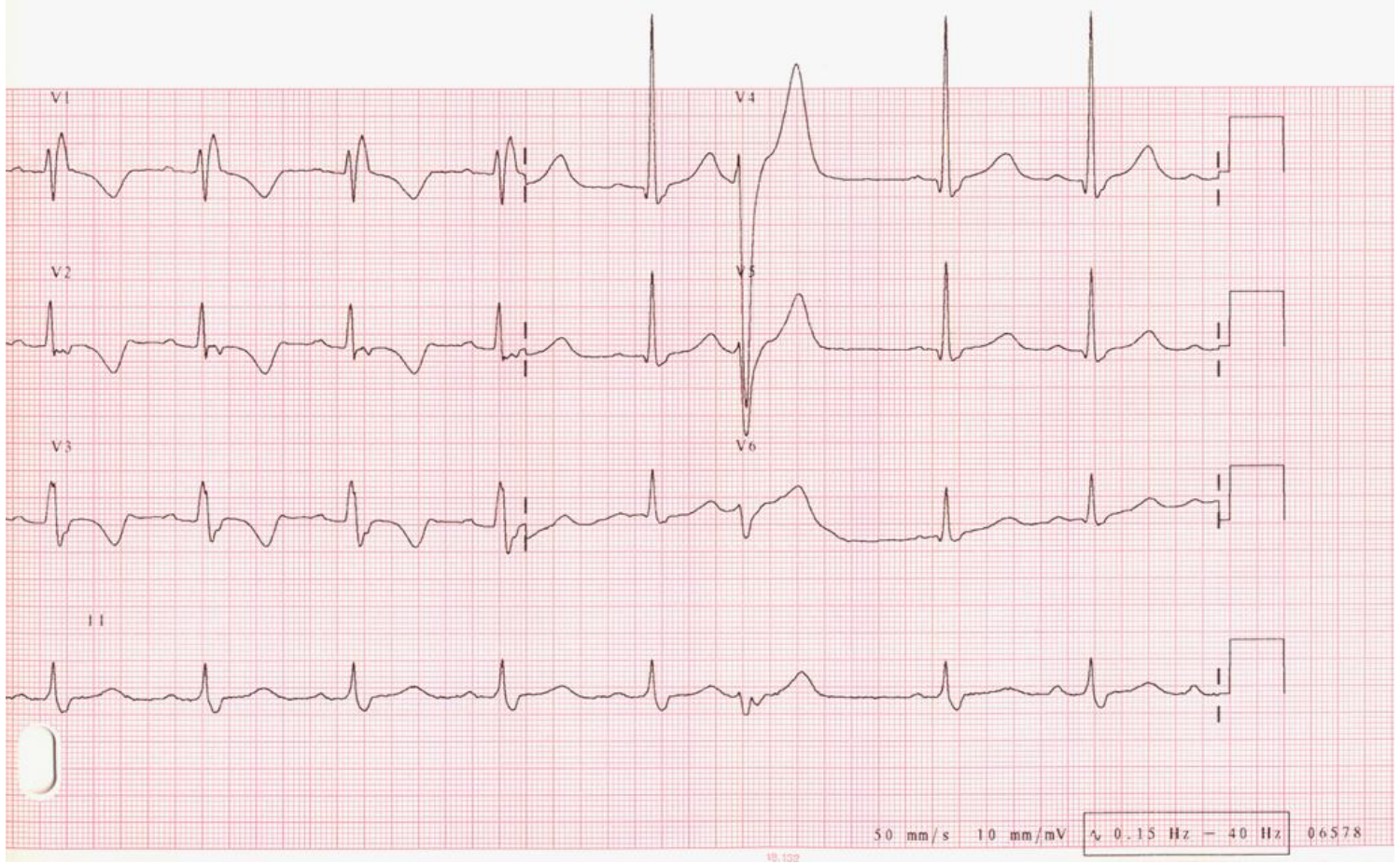
Arrhythmogenic Cardiomyopathy

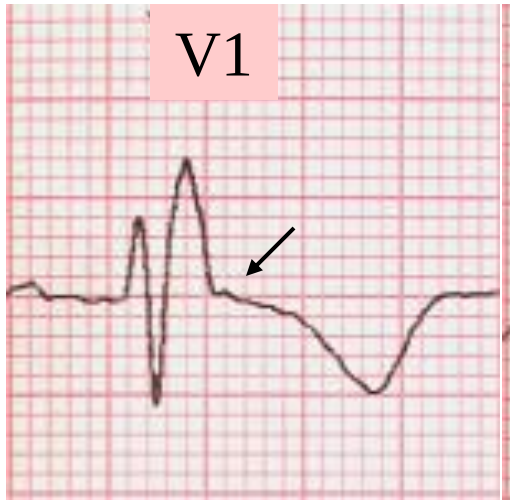
genotype		phenotype
Desmosomal	-	ARVC / ALVC, hair/skin abnormalities
Lamin	-	conduction disease, ventricular arrhythmia /sudden death, dilated cardiomyopathy, lipodystrophy, muscular dystrophy
SCN5A	-	Brugada Syndrome, conduction disease, AF, ventricular tachycardia / ventricular fibrillation, DCM
PLN	-	low voltage ECG, VT/VF, DCM/ACM
TMEM43	-	sudden death M>F
FLNC	-	sudden death, DCM, ACM
RBM20	-	DCM, AF, ?ventricular arrhythmia/sudden death as an early feature
Desmin	-	skeletal myopathy, DCM, arrhythmia (?early vs late manifestation)

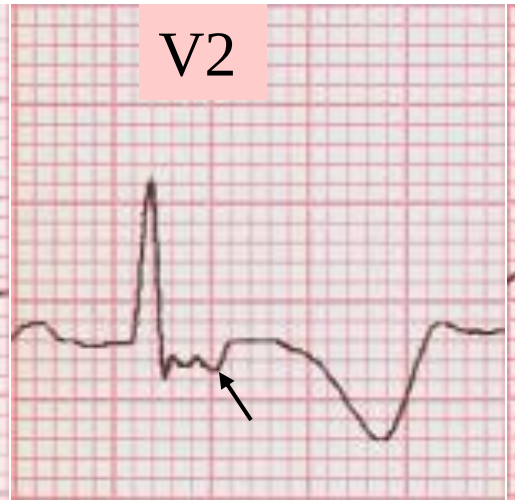
Naxos Disease
(SD 2.3% / yr)

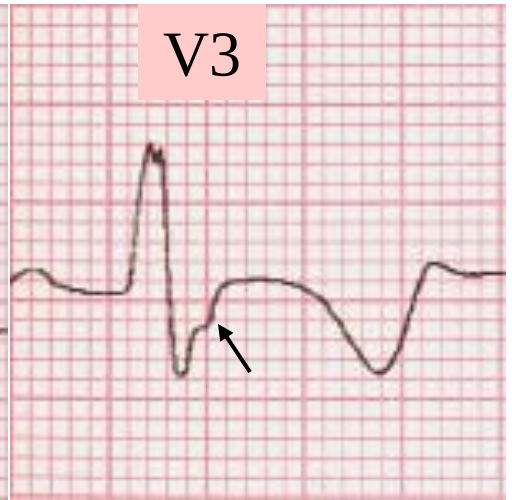
Age 5	asymp N ECG, N 2D echo frequent VES
Age 7	Abn ECG N 2D echo 14,451 VES 21 couplets
Age 8	Died – leukaemia PM: normal RV, LV



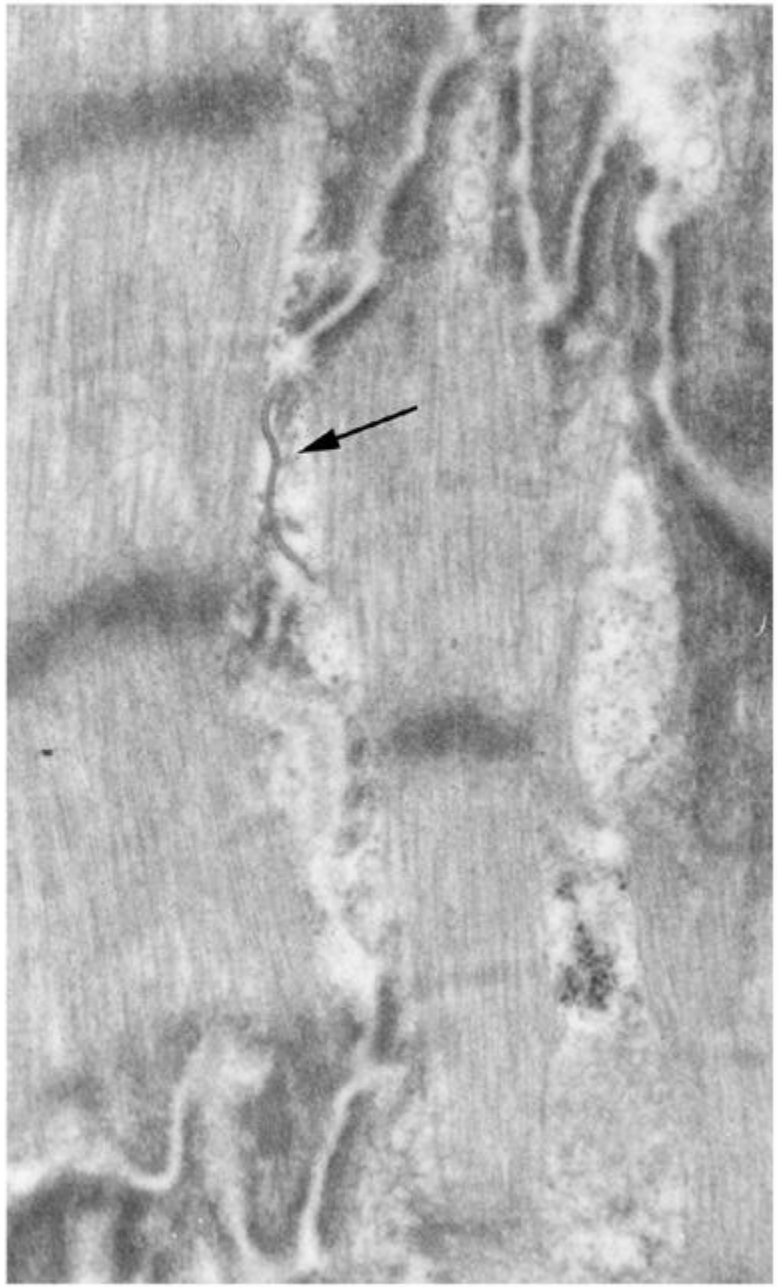

V1
V4
V2
V5
V3
V6
II
50 mm/s 10 mm/mV 0.15 Hz – 40 Hz 06578


V1

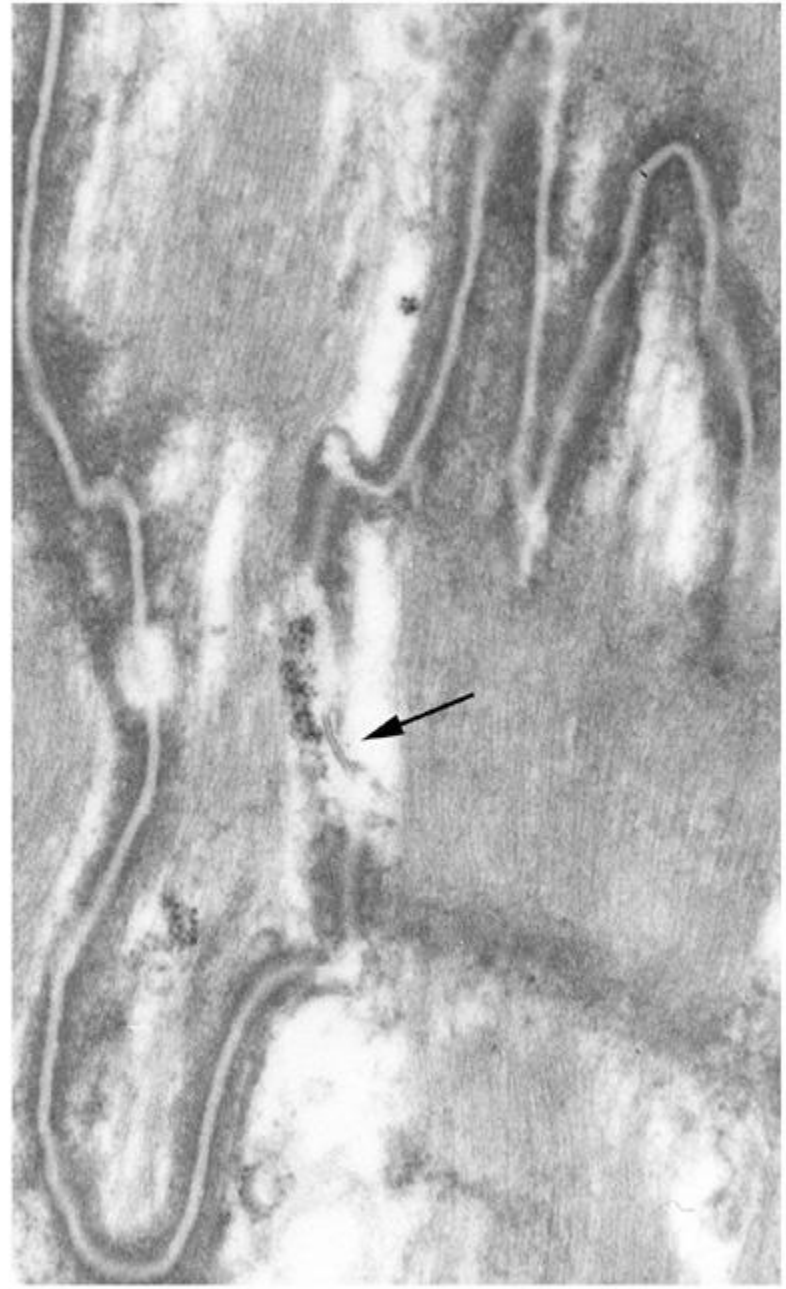

V2


V3

Control



Naxos LV



Mechanisms of electrocardiographic abnormalities and arrhythmia in desmosomal disease

late - macroreentry as a consequence of fibro/fatty myocyte replacement

early - abnormal electrical coupling as a consequence of altered mechanical coupling

Exercise and Disease Development

Cardiac Arrhythmogenic Remodeling in a Rat Model of Long-Term Intensive Exercise Training

Benito et al, Circulation 2011;123:13-22

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

James et al, JACC 2013;62(14):1290-7

Exercise in Arrhythmogenic Cardiomyopathy

- Data support endurance exercise as a contributor to disease development
- Data support exercise as a risk factor for life threatening ventricular arrhythmia

ARVD – Marcus, Circulation 1982

24 patients

- 22 LBBB VT
- 2 CHF

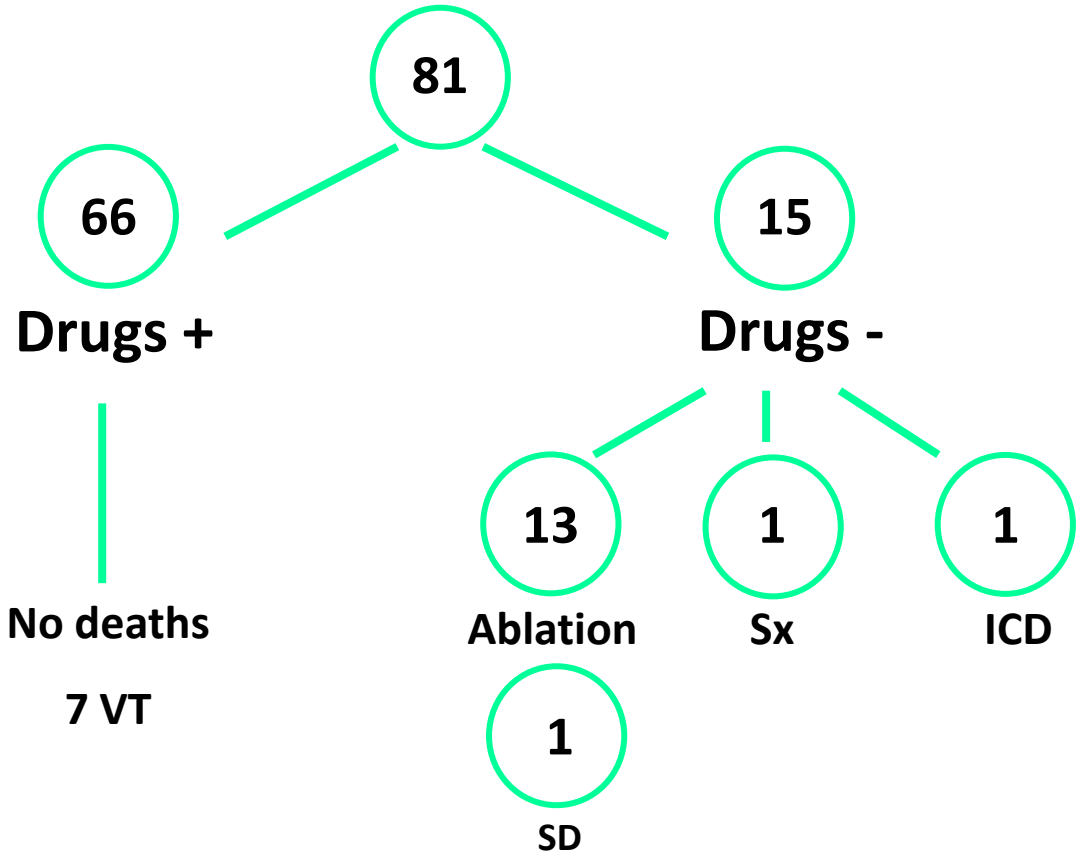
Treatment

- 10 drugs (BB, Class I, amio)
- 12 surgery (epicardial mapping)

F/U 1 – 7, mean 3 yrs

- 20 alive
- 2 died perioperatively
- 1 CHF 3 yrs
- 1 non cardiac

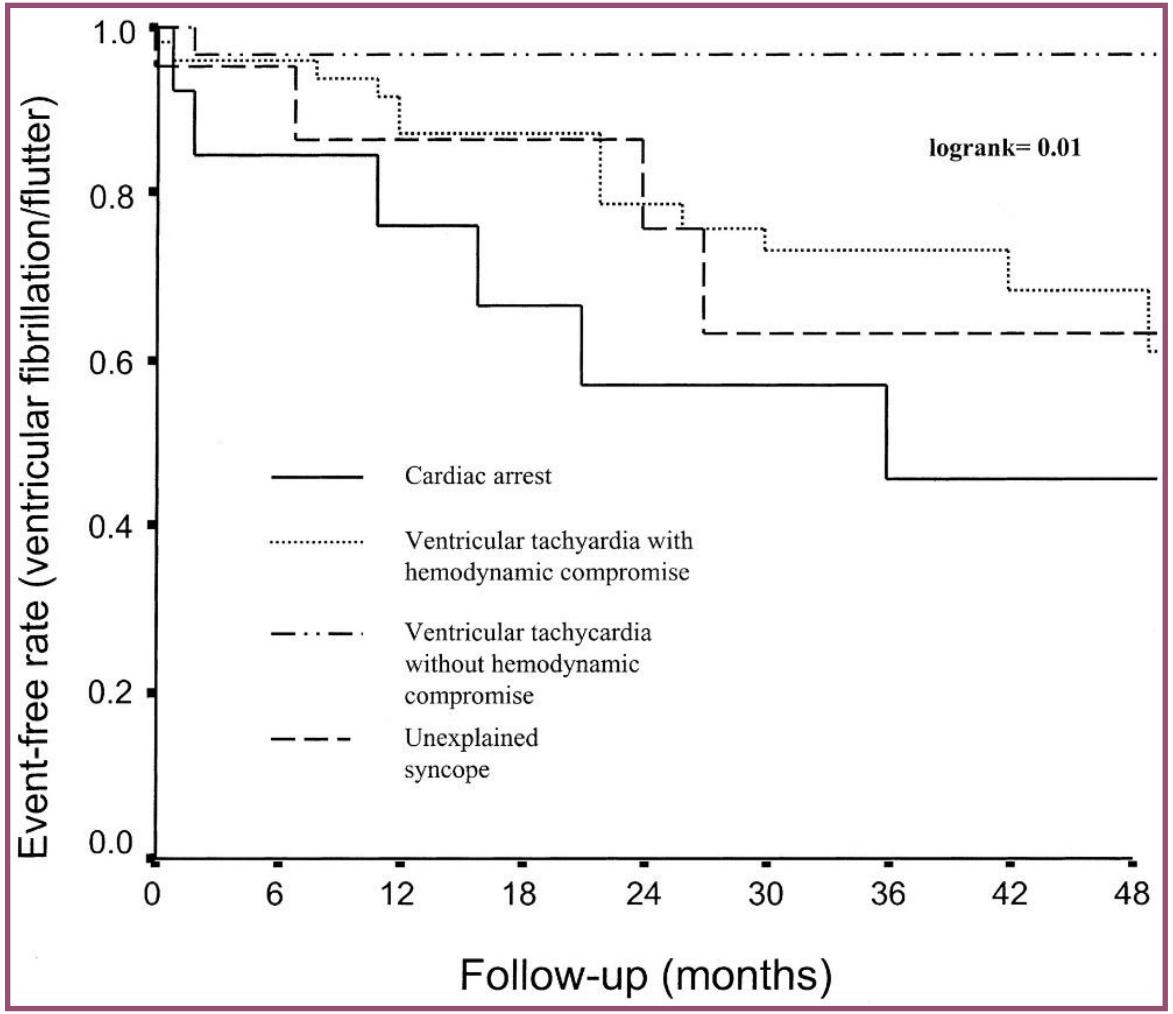
EP guided antiarrhythmic drug treatment in ARVC



Wichter et al, Circulation 1992

ICD benefit in patients with ARVC

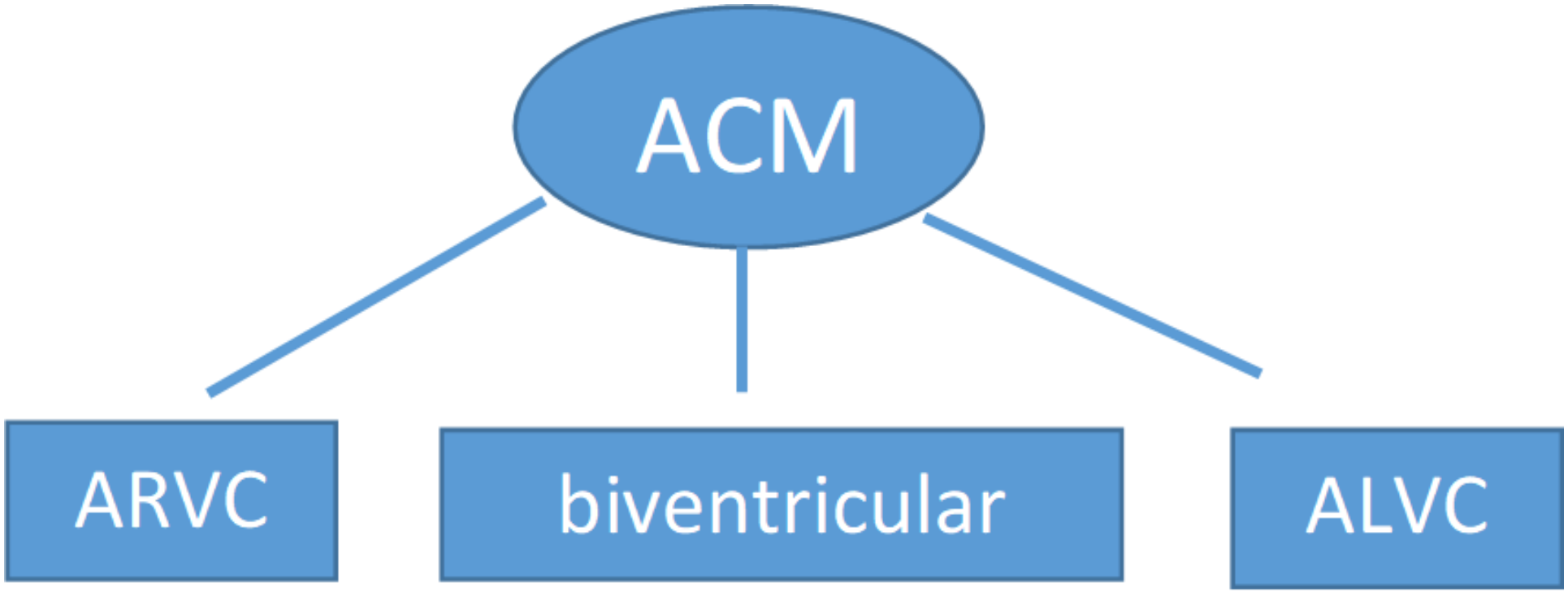
- 132 patients with ICDs
- Mean age 40±15
- 39 months F/U



Corrado et al, Circulation 2003

Issues for Resolution

- Should diagnostic criteria be modified to incorporate occult and/or later stages of disease?
- Is the distinction of heart failure versus arrhythmogenic DCM valid and/or useful?
- Do mechanisms of arrhythmia and should the approach to risk assessment differ in occult versus overt disease?
- Does an aggressive approach to EPS and ICD use contribute to disease progression in ACM?
- Is an ICD pro-arrhythmic in ACM?
- Should asymptomatic mutation carriers be recommended to restrict endurance exercise?


ACM
ARVC
biventricular
ALVC