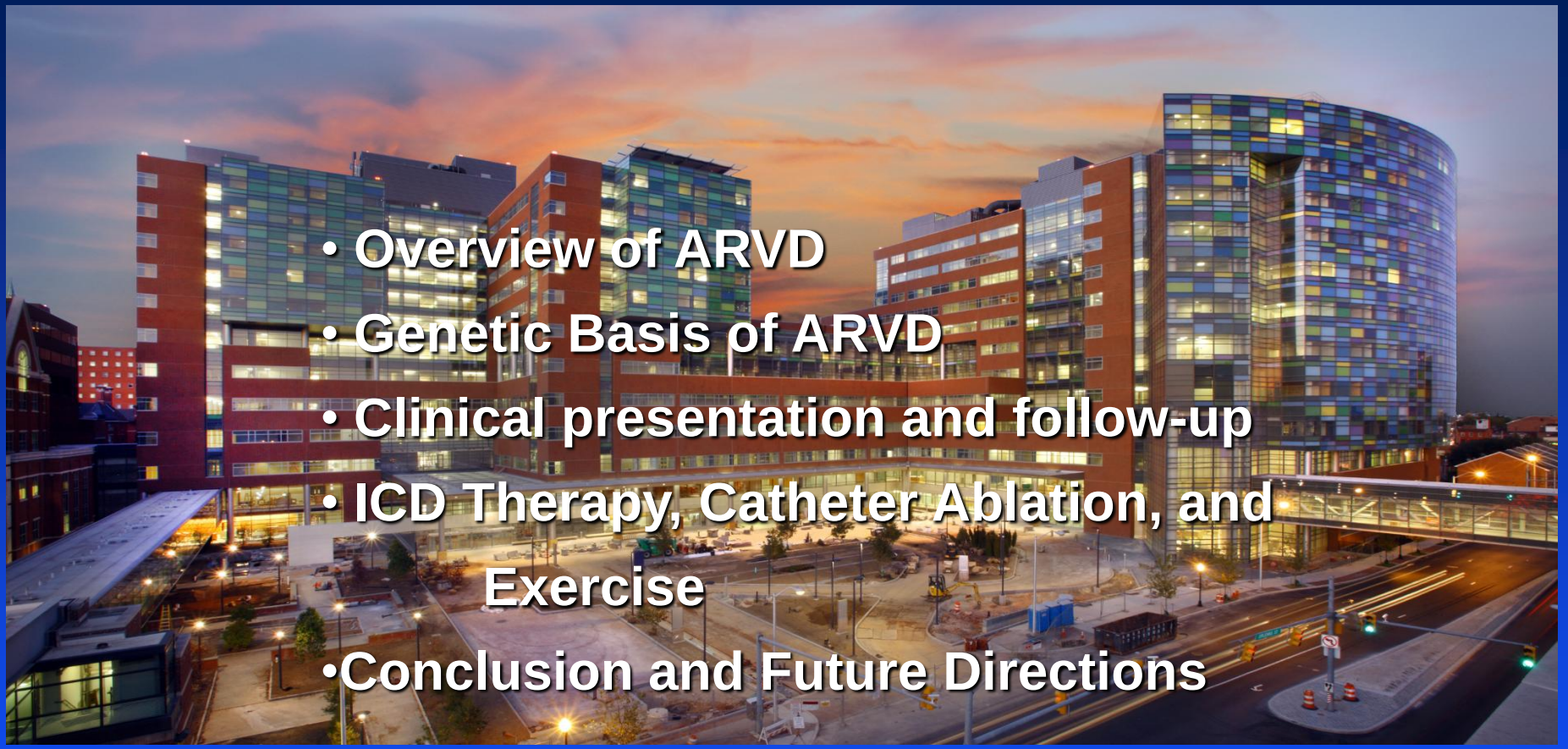
Arrhythmogenic Right Ventricular Dysplasia: State of the Art in 2013



Hugh Calkins MD
Nicholas J Fortuin Professor of Cardiology
Professor of Medicine
Director of Electrophysiology
Johns Hopkins Medical Institutions

Arrhythmogenic Right Ventricular Dysplasia Overview

- Genetically determined cardiomyopathy
- Characterized by:
  - Progressive replacement of the right ventricular myocardium with fatty & fibrous tissue
  - Ventricular arrhythmias of right ventricular origin
  - A left dominant form of ARVD has been described leading to some to refer to the disease as "arrhythmogenic cardiomyopathy".

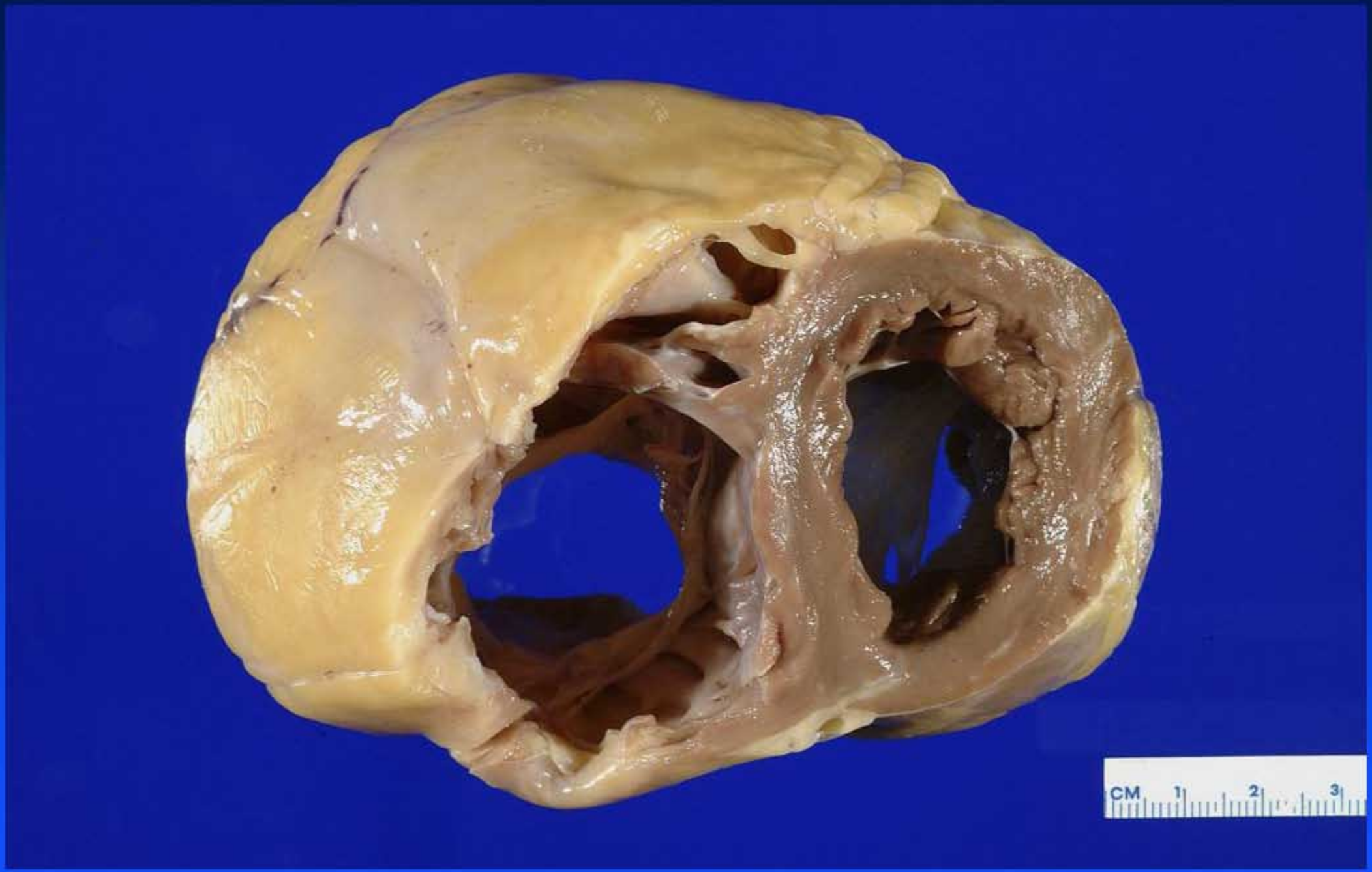
Right Ventricular Dysplasia: A Report of 24 Adult Cases

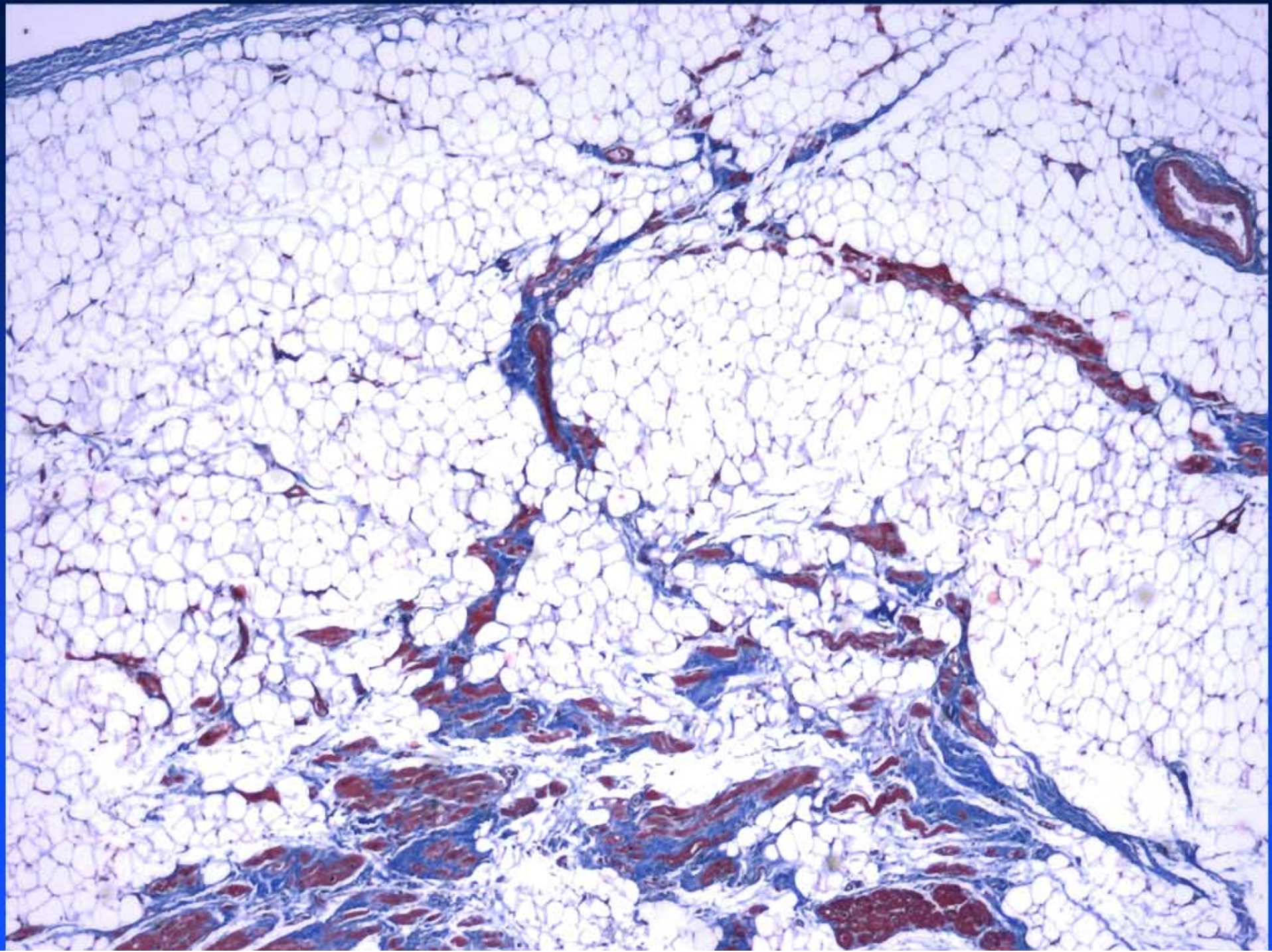
FRANK I. MARCUS, M.D., GUY H. FONTAINE, M.D., GERARD GUIRAUDON, M.D., ROBERT FRANK, M.D., JEAN L. LAURENCEAU, M.D., CHRISTINE MALERGUE, M.D., AND YVES GROSGOGEAT, M.D.

SUMMARY Right ventricular dysplasia is characterized by an abnormality in the development of part of the right ventricular musculature. Patients with right ventricular dysplasia may present with ventricular tachycardia, supraventricular arrhythmias, right-heart failure or asymptomatic cardiomegaly. Twenty-two adult patients with right ventricular dysplasia who had recurrent ventricular tachycardia were seen during a 7-year period. The male/female ratio was 2.7:1. The mean age at the time of hospitalization was 39 years. All but one of the patients had ventricular tachycardia of a left bundle branch block configuration. With few exceptions, the T waves were inverted over the right precordial leads. The heart was usually enlarged and the pulmonary vasculature was usually normal. In six patients who had two-dimensional echocardiograms, all showed increased right ventricular diastolic dimensions. All patients had right ventricular angiography; the diagnosis of right ventricular dysplasia was substantiated during surgery in 12 patients and at autopsy in another. Two other patients who did not have arrhythmias had right ventricular dysplasia diagnosed by right- and left-heart angiography.

Our unique experience, when combined with a literature review of 34 adult cases, permits a composite clinical profile of this condition in the adult.

Circulation 65; 384- 398, 1982


CM
1
2
3



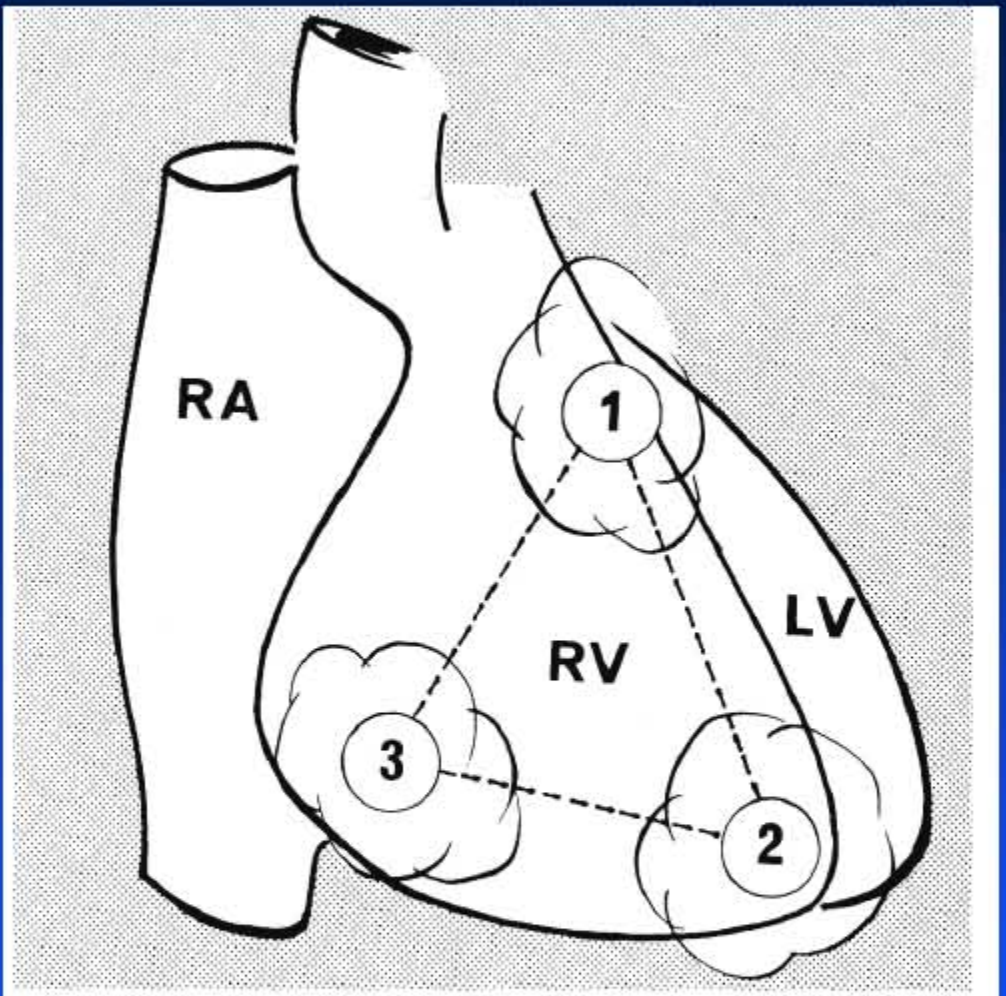
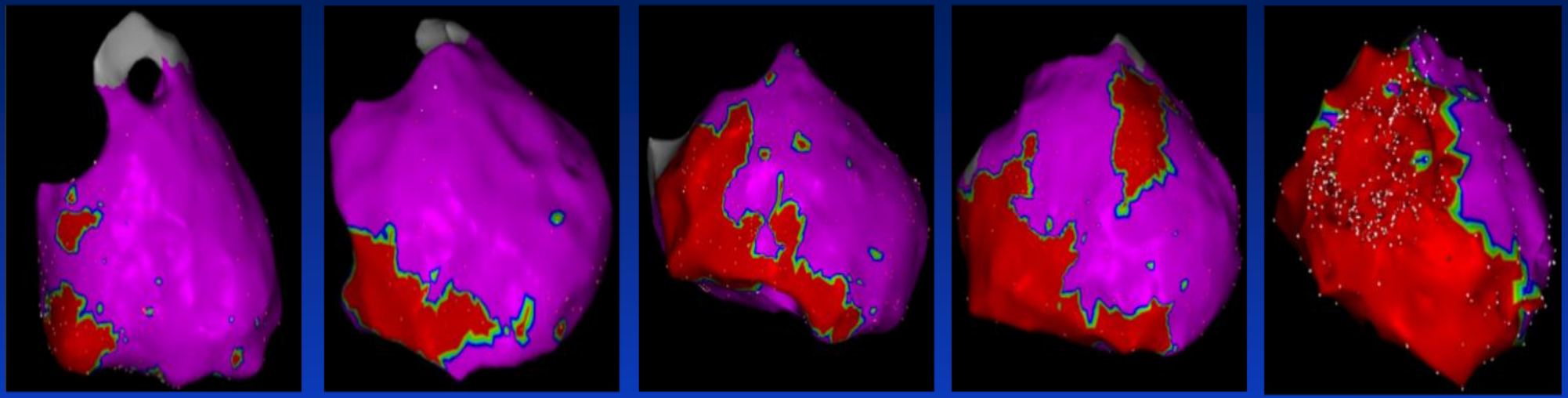


FIGURE 6. *The most frequent sites of dysplasia: (1) the anterior infundibulum, (2) the right ventricular apex and (3) the inferior or diaphragmatic aspect of the right ventricle (RV). These constitute the "triangle of dysplasia." LV = left ventricle, RA = right atrium.*

Circulation 65, No. 2, 1982.

The Triangle of RV Dysplasia Displaced

A



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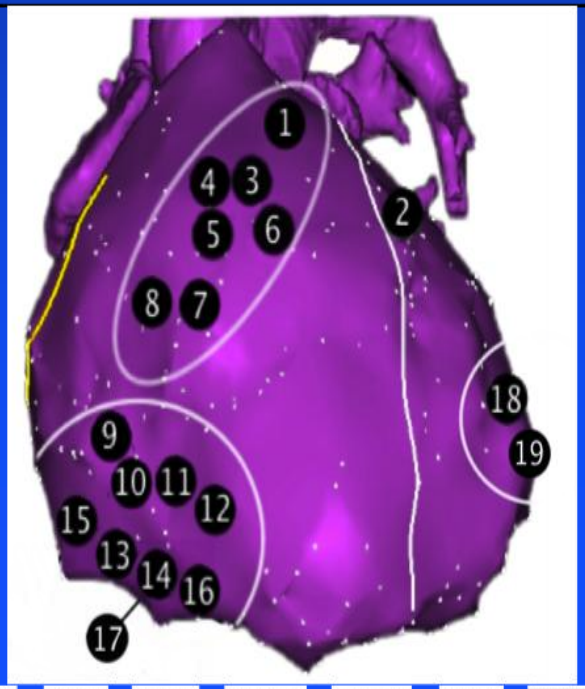

ARVD Overview: Epidemiology

- Prevalence: 1 per 2000 in Italy & 1 per 5000 in the US
- Equally common in men and women
- 20% of sudden deaths in young individuals in Italy
- 5% of sudden deaths in young individuals in the US

Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Proposed Modification of the Task Force Criteria

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European Heart J 2010; 31: 806-814.
Circ 2010; 121; 1533-41

ARVD Diagnostic Criteria

Parameter	1994 Criteria	2010 Criteria
RV Size and Function	Non quantitative	Quantitative
Biopsy (major)	Fibrofatty replacement	< 60% nl myocytes & fibrous replacement +/- fat
T wave inversion v2 and V3	Minor criteria in absence RBBB	Major criteria in absence of RBBB QRS > 120 msec
		Minor: T wave inv V1, V2 or in V4,V5, and V6 or T in V1-v4 w RBBB
Epsilon waves (major)	Epsilon or localized prolongation > 110 ms V1-V3	Episilon waves
SAECG (minor)	Late potentials	Quantitative, 1 of 3 parameters
TAD	NA	>= 55 msec in V1-v3
LBBB VT (minor)	Minor criteria	Major criteria if LB sup axis VT, minor criteria if not
Frequent PVCs (minor)	> 1000/ 24 hrs	> 500 / 24 hrs
Family History (Major)	Familial disease confirmed by autopsy or surgery	ARVD in first degree relative OR pathogenic mutation in patient
Family History (Minor)	FH of premature SCD < 35 yrs or family hx of ARVD	FH of ARVD where task force criteria unclear or premature SD < 35 yrs

2010 ARVD Diagnostic Criteria

Parameter	1994 Criteria	2010 Criteria
RV Size and Function	Non quantitative	Quantitative
Biopsy (major)	Fibrofatty replacement	< 60% nl myocytes & fibrous replacement +/- fat
T wave inversion v2 and V3	Minor criteria in absence RBBB	Major criteria in absence of RBBB QRS > 120 msec
		Minor: T wave inv V1, V2 or in V4,V5, and V6 or T in V1-v4 w RBBB
Epsilon waves (major)	Epsilon or localized prolongation > 110 ms V1-V3	Epsilon waves
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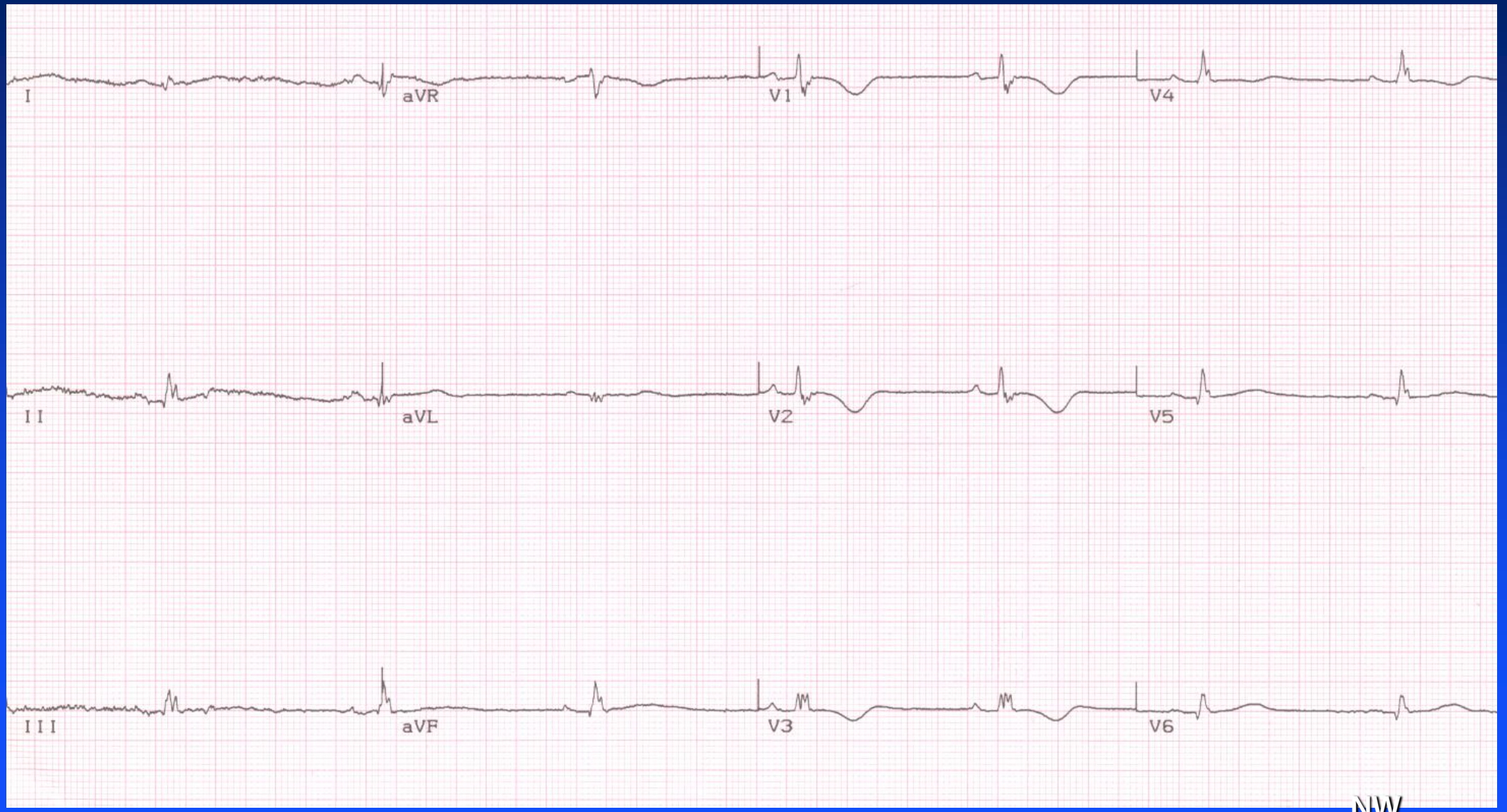
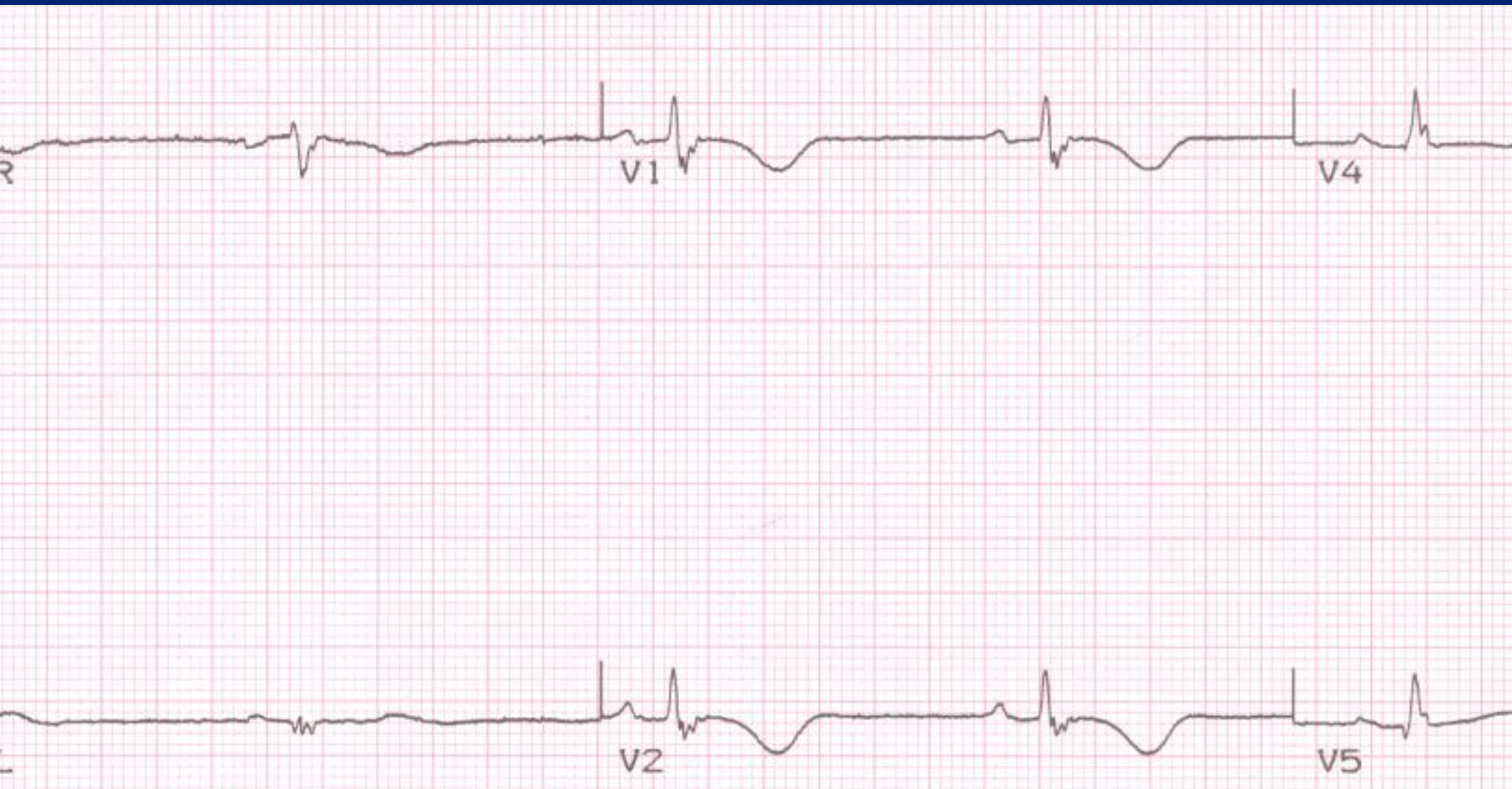
ECG Features of ARVD

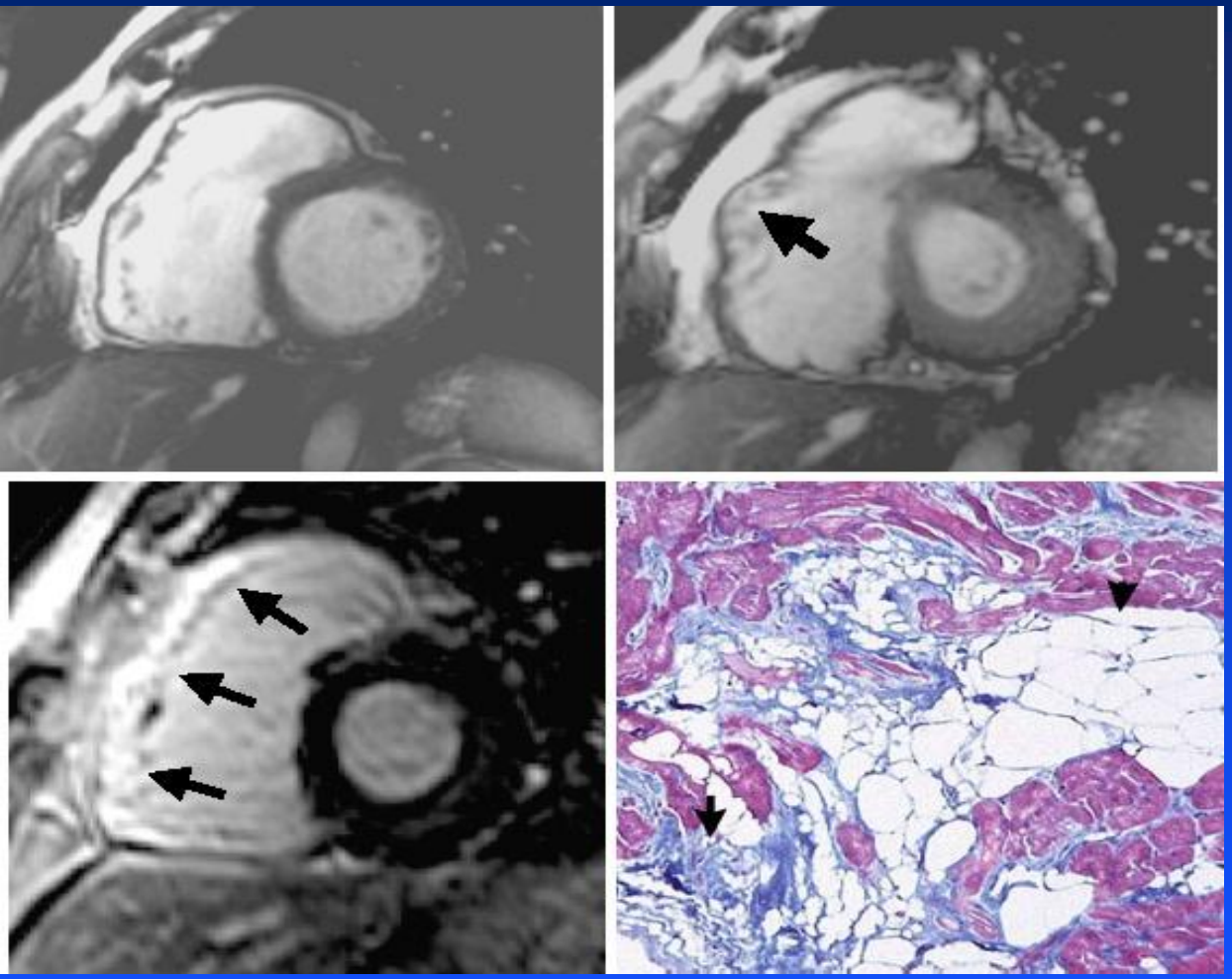


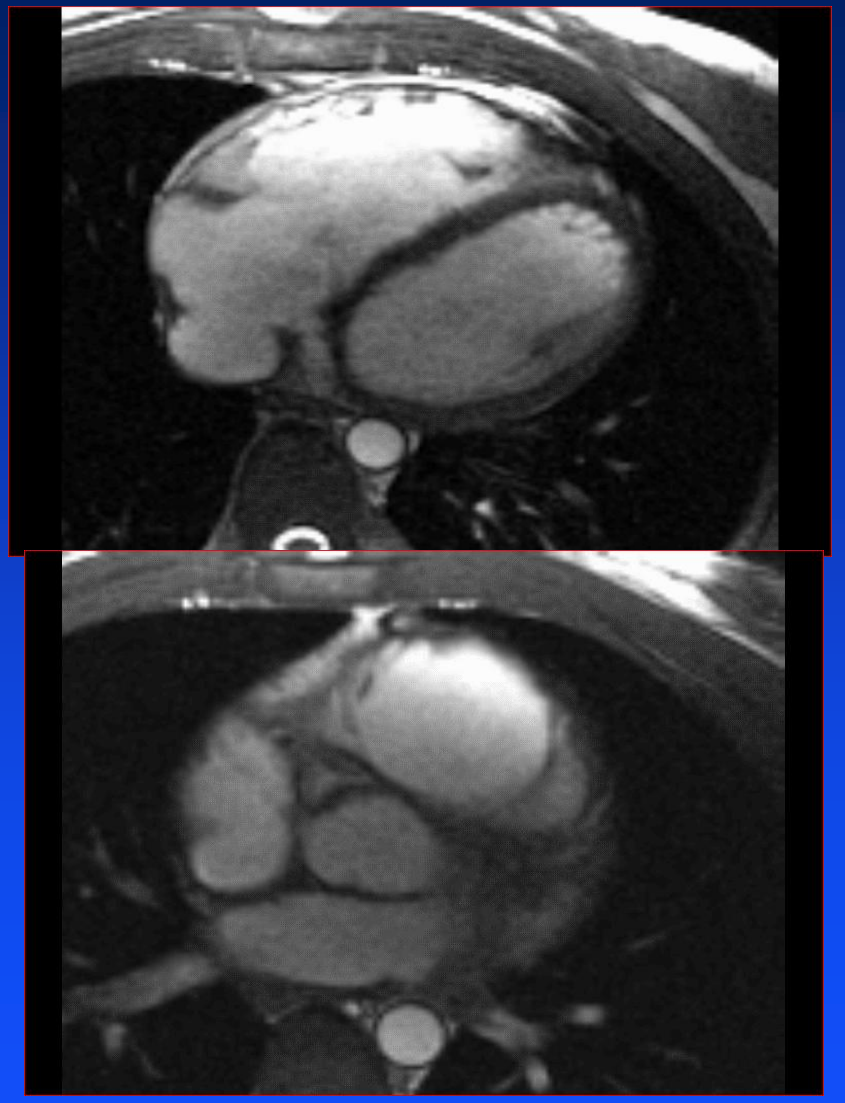
NW

ECG Features of ARVD



MRI Features of ARVD

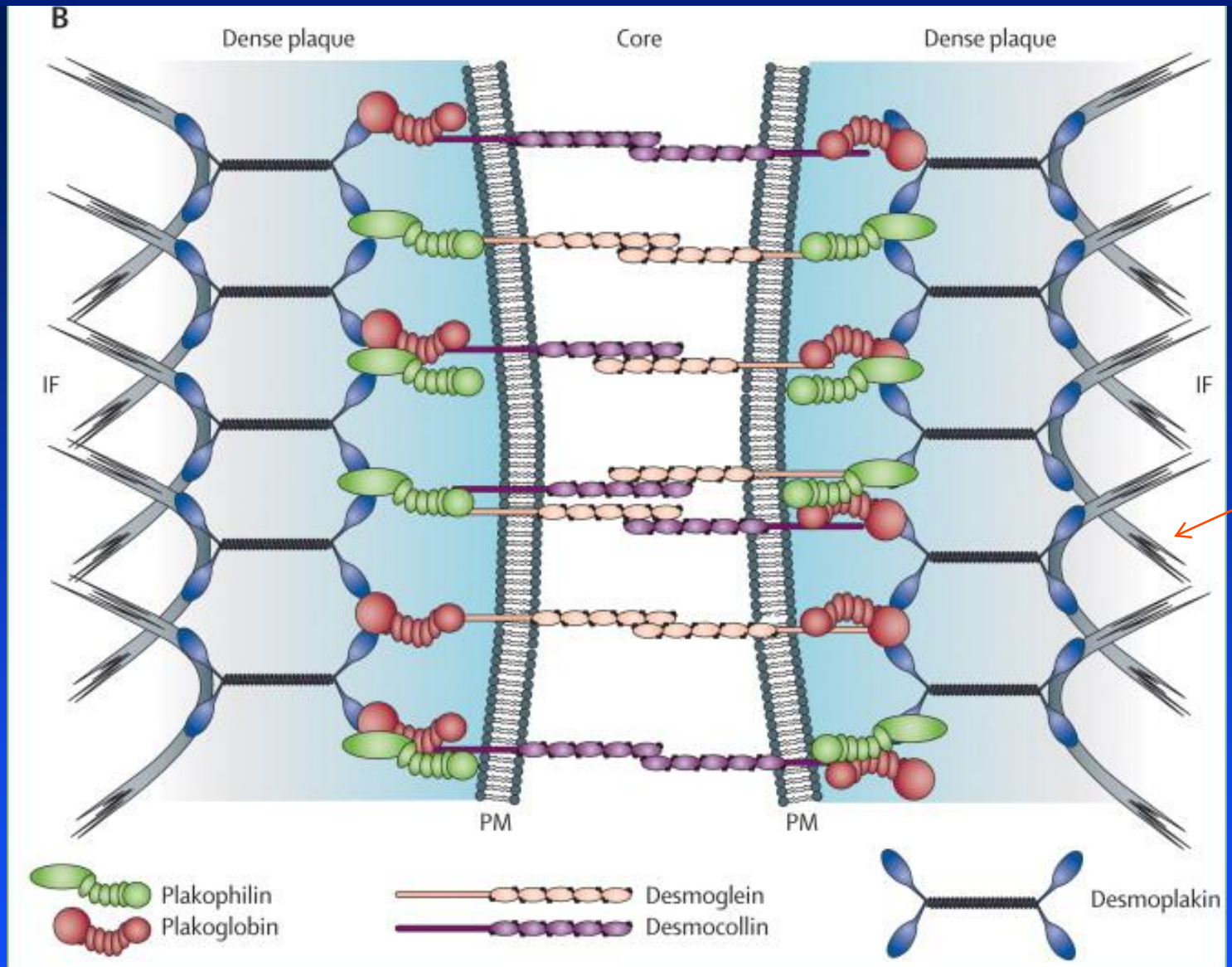




Tandri, et al JACC 2005;45:98-103

Outline

- Overview of ARVD
- **Genetic Basis of ARVD**
- Clinical presentation and follow-up
- ICD Therapy, Catheter Ablation, and Exercise
- Cases from the Clinic
- Conclusion



Intermediary filaments Desmin and Actin

Armadillo Proteins **Desmosomal Cadherins** **Plakins**

Intercellular Mechanical Junction (Desmosome)

Basso et al. Lancet 2009; 373; 1289=1300

ARVD Genetic Mutations: 2013

- *PKP2* (plakophilin-2) - 25% of cases
- *DSG2* (desmoglein-2) - 10% of cases
- *DSP* (desmoplakin) - 10% of cases
- *DSC2* (desmocollin-2) - 3% of cases
- *JUP (*plakoglobin) Naxos syndrome – rare, recessive
- *RYR2** (ryanodine receptor) - atypical disease – catech PMVT
- *TGFB3** (transforming growth factor) - rare, profibrotic mitotic
- TMEM43* Newfoundland, highly penetrant, lethal, nuclear pore
- Compound heterozygosity (two mutations one gene) seen in 7% of patients. Digenic heterozygosity (mutations in more than one gene) seen in 5% of patients
- No pathogenic mutation found in 50% of ARVD patients

Outline

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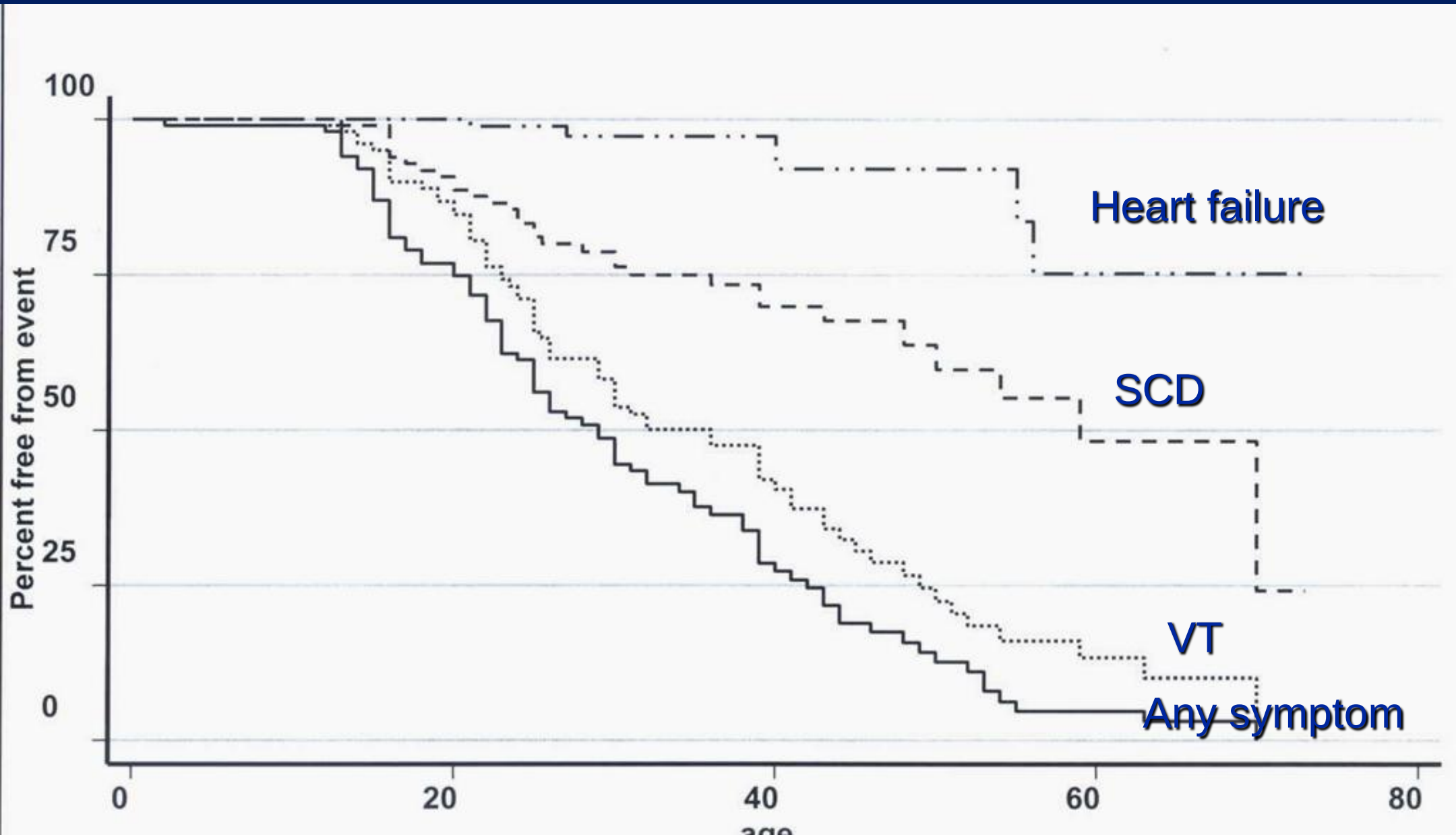
Johns Hopkins ARVD Experience
N = 100

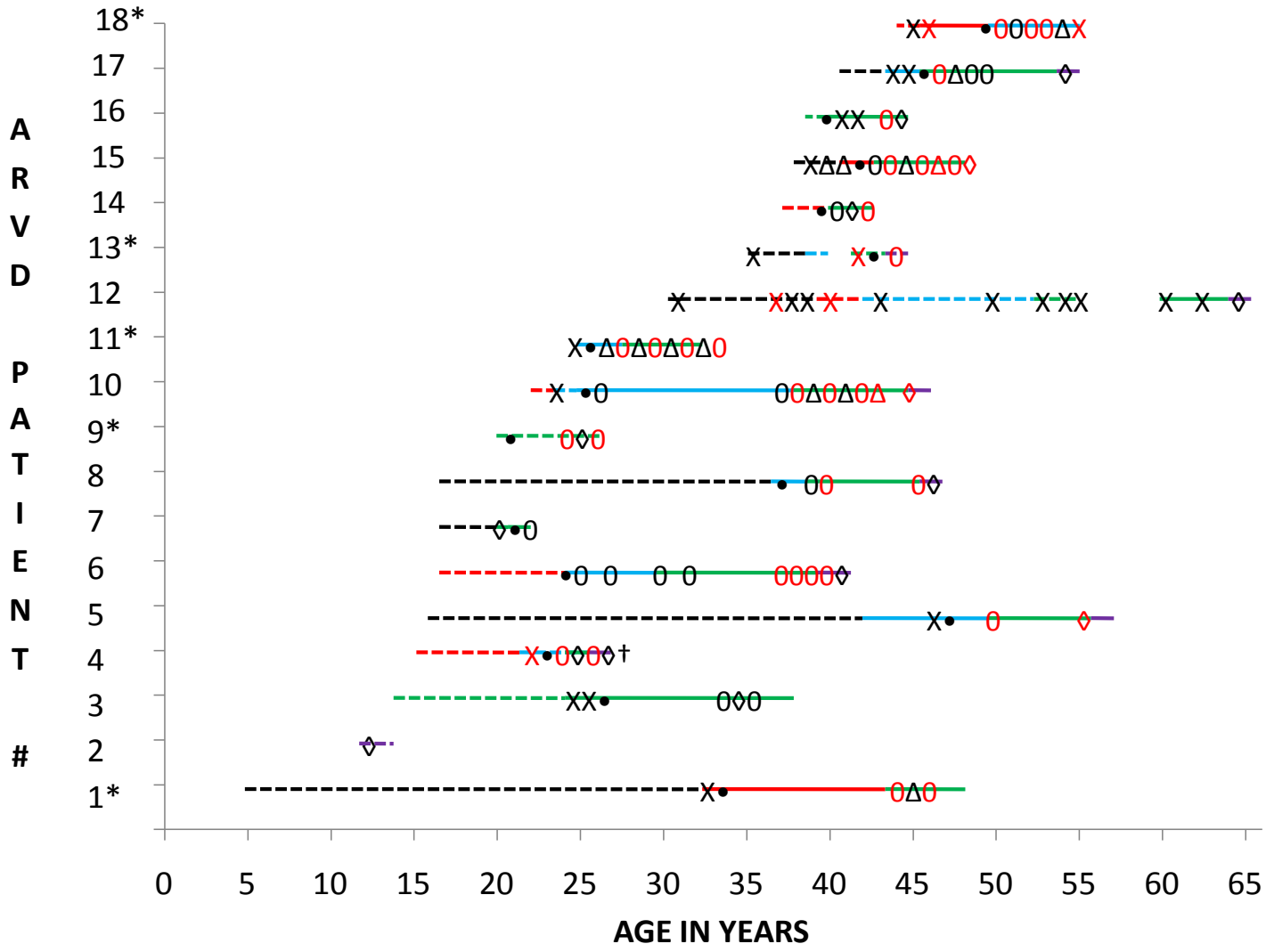
Characteristic	Dx Alive N = 69	Autopsy Dx N = 31	Total N=100
Age	29 ± 12	29 ± 15	29 ± 13
Male Gender	36 (52)	15 (48)	51
Athletic	37 (54)	12 (39)	49
Presenting Sx			
Palpitations	25 (36)	2 (6)	27
Syncope	20 (29)	5 (16)	25
Sudden Death		23 (74)	23
Resuscitated SCD	1 (1.5)		1
Asymptomtic	15 (22)		15

Dalal, Calkins et al Circ 2005;112:3823-3832.

Symptoms of ARVD



Cardiac Transplantation in ARVD/C



- N = 18
- Male (61%)
- Sx onset 24 ± 13 yr
- Tx age 40 ± 14 yrs

- VT in 28%
- CHF in 28%

- Tx for CHF in 13
- Tx for VT in 5

HF stage: black,red,blue,green,purple
X –VT, O appropr ICD tx, Δ cath abl, * tx for vt

Tedford JACC 2011

Outline

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- Genetic Basis of ARVD
- Clinical presentation and follow-up
- **ICD Therapy, Catheter Ablation, and Exercise**
- Cases from the Clinic
- Conclusion

Who Should get an ICD ?

- ARVD patients who have experienced sustained VT or VF.
- ARVD patients who meet task Force Criteria and are probands.
- Selected family members of ARVD probands who meet Task Force Criteria and have other high risk markers such as frequent PVCs, NSVT, and / or arrhythmic syncope.

Incidence and Predictors of Implantable Cardioverter-Defibrillator Therapy in Patients With Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Undergoing Implantable Cardioverter-Defibrillator Implantation for Primary Prevention

Aditya Bhonsale, MD, Cynthia A. James, PHD, Crystal Tichnell, MS, Brittney Murray, MS, Dmitri Gagarin, MD, Binu Philips, MD, Darshan Dalal, MD, Ryan Tedford, MD, Stuart D. Russell, MD, Theodore Abraham, MD, Harikrishna Tandri, MD, Daniel P. Judge, MD, Hugh Calkins, MD

Baltimore, Maryland

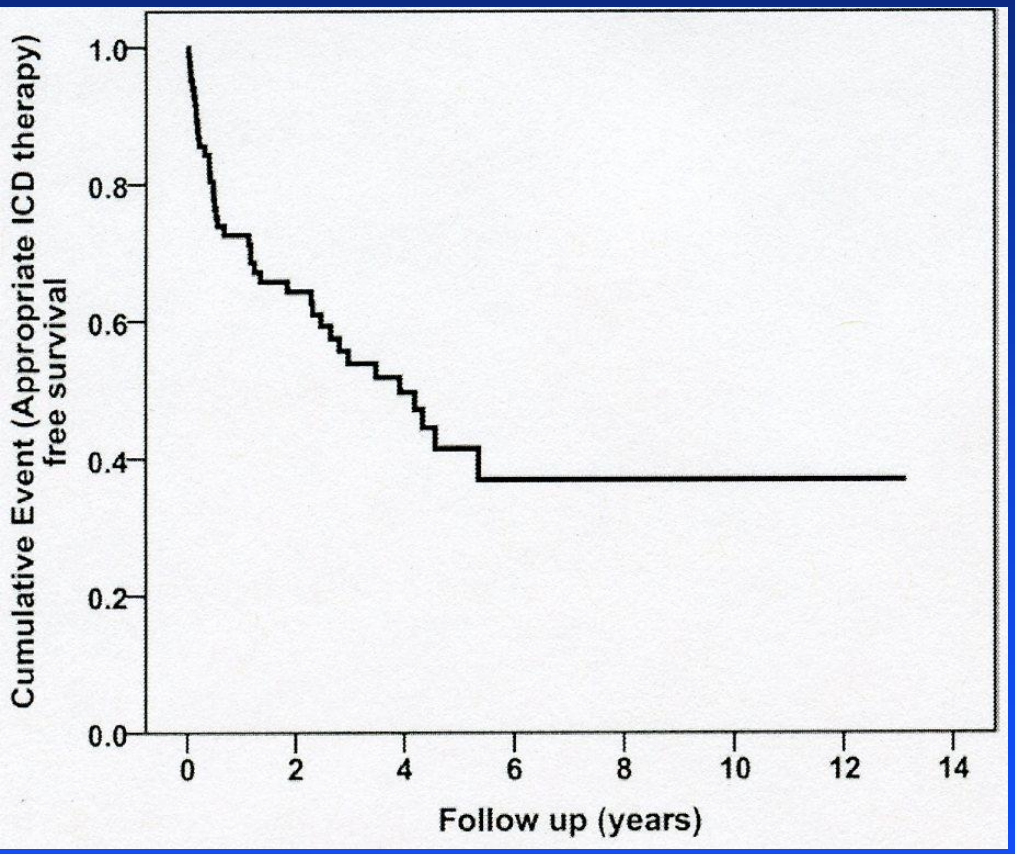
JACC 2011

- 84 patients
- 31.9 ± 11.9 yrs
- 39 men (46%)
- 4.73 ± 3.39 years

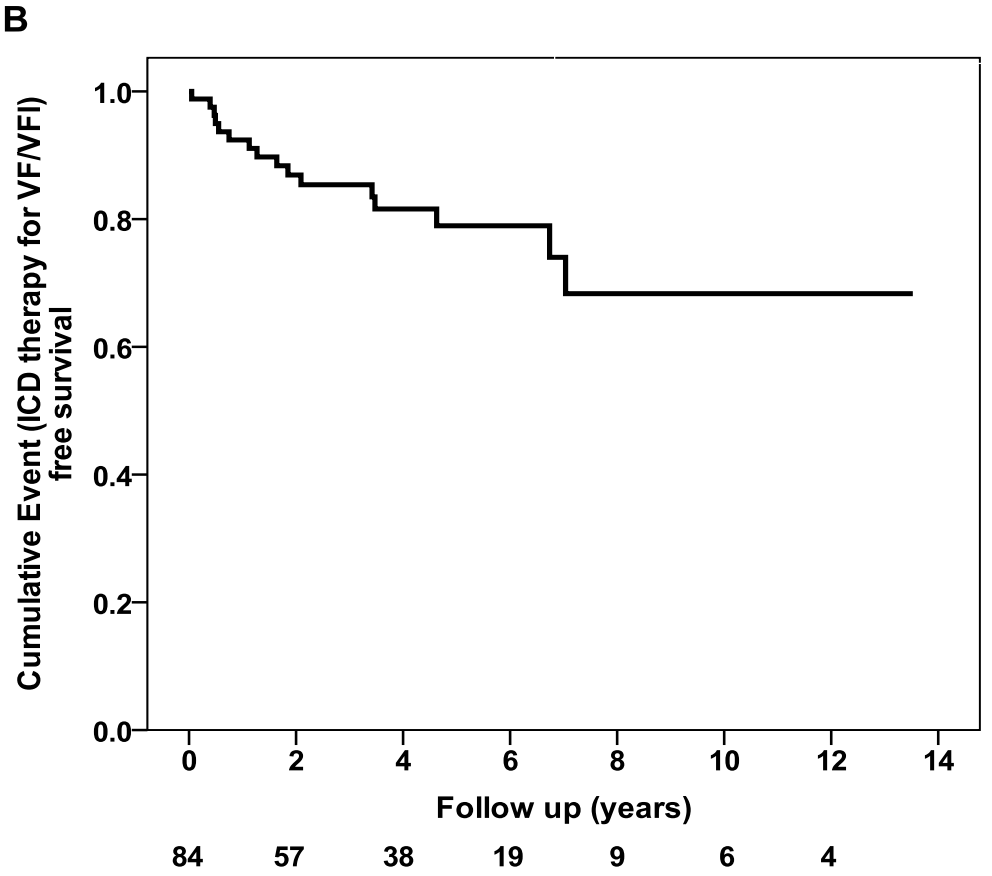
- Palpitations: 40 pts (48%)
- Syncope: 23 (27%)
- Chest pain: 14 (17%)
- Asx: 20 (24%)

Incidence and Predictors of ICD Therapy in Primary Prevention ARVD Patients

Appropriate ICD Therapy



ICD interventions for VFL/VF



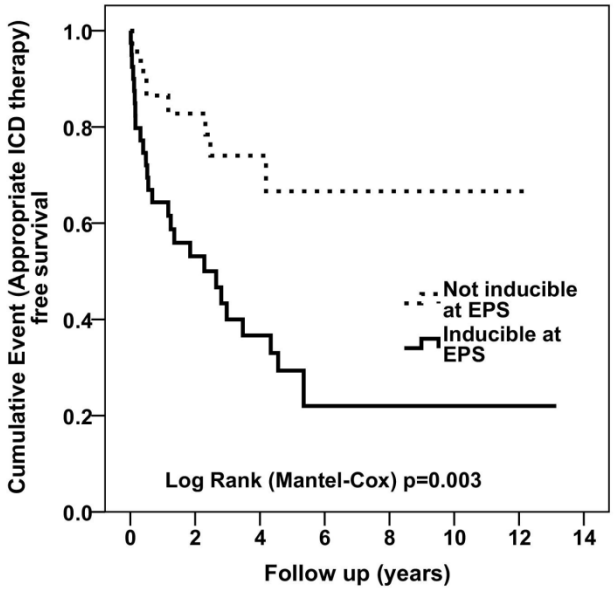
EPS Pos

NSVT

PVCs > 1000

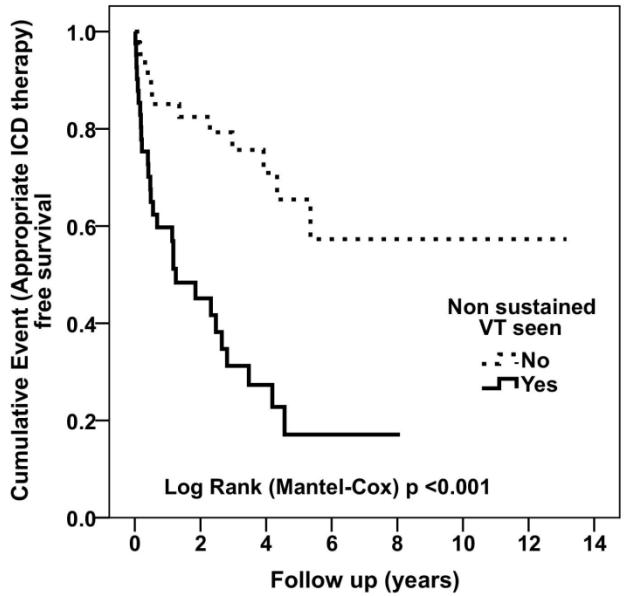
Proband Status

A



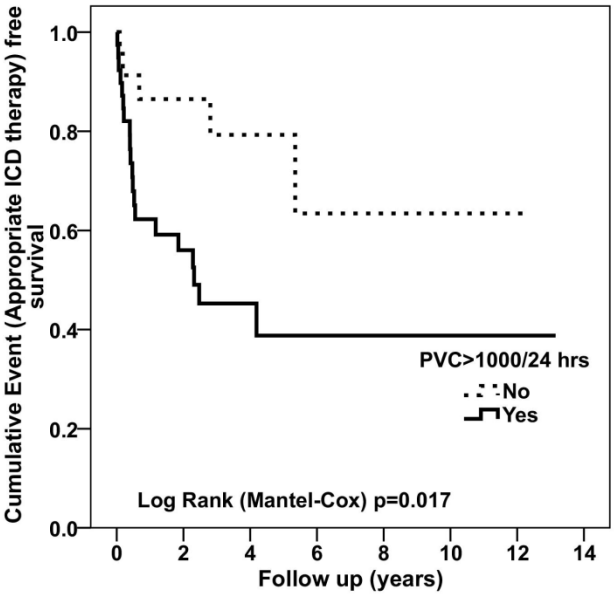
Non Inducible	32	21	11	4	2	1	1
Inducible	40	19	10	2	1	1	1

B



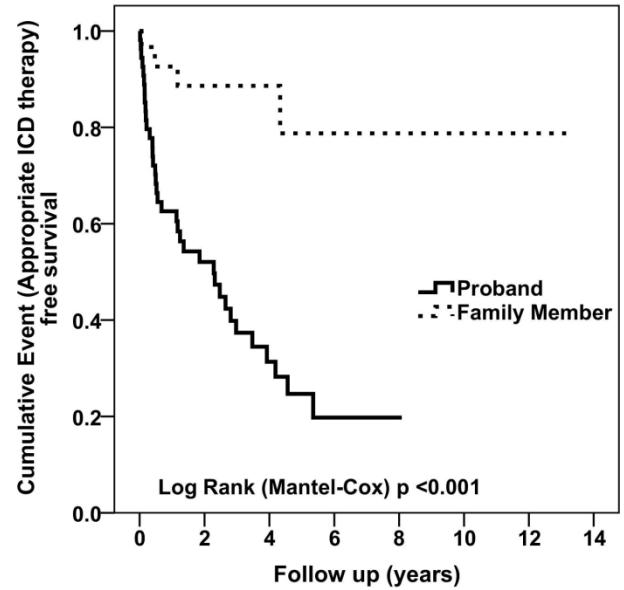
No NSVT	43	29	15	5	2	2	2
NSVT	41	13	7	1	1	0	0

C



PVC <1000/24 hrs	23	14	9	3	2	1	1
PVC >1000/24 hrs	39	18	8	3	1	1	1

D

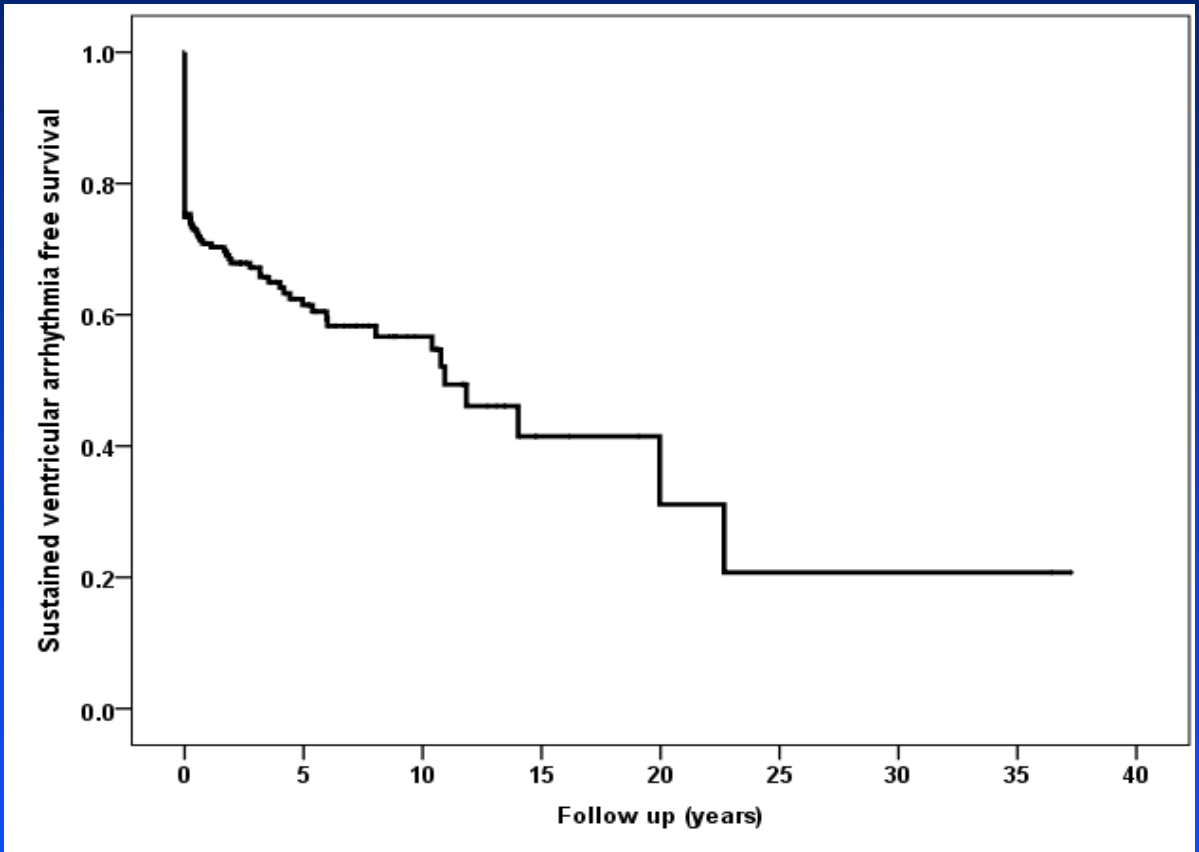


Family member	30	18	12	3	2	2	2
Proband	54	24	10	3	1	0	0

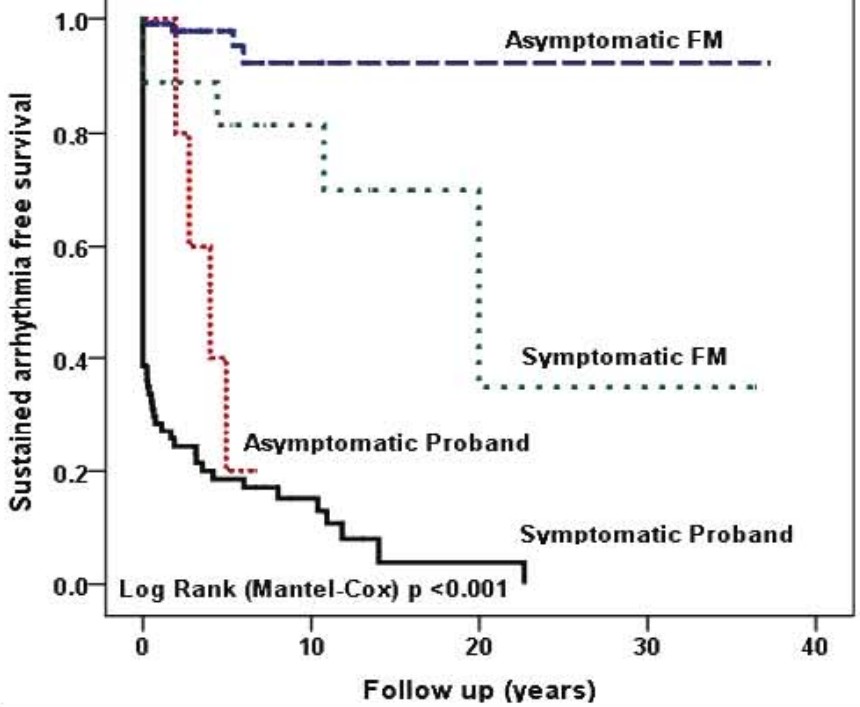
Risk Stratification in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Associated Desmosomal Mutation Carriers

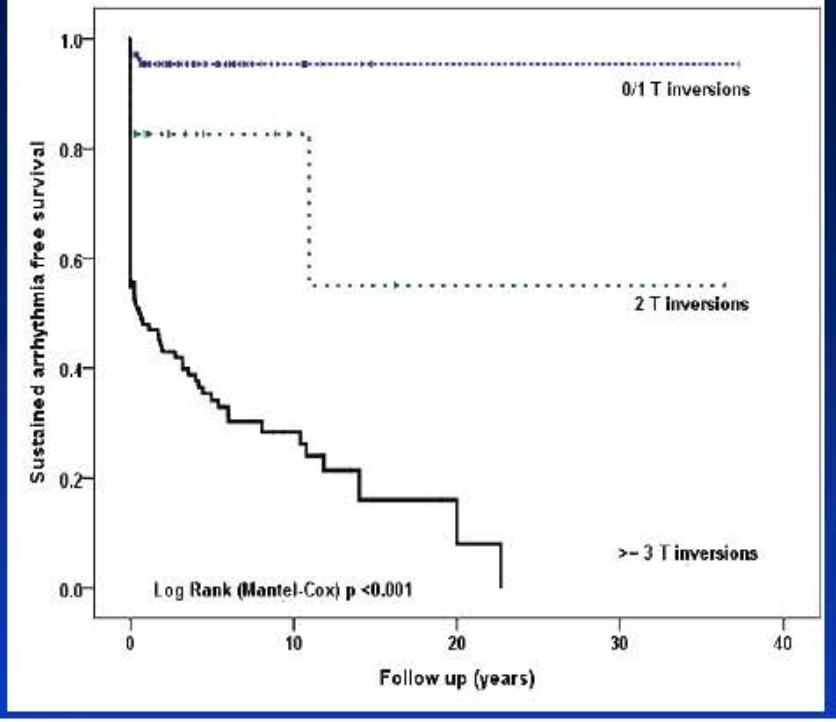
- 215 patients from 104 families with ARVD associated desmosomal mutations
- Review of medical records, clinical evaluation, and patient interview
  - Demographics
  - Symptoms
  - Family history
- Prospective follow up
- ARVD/C Diagnosis

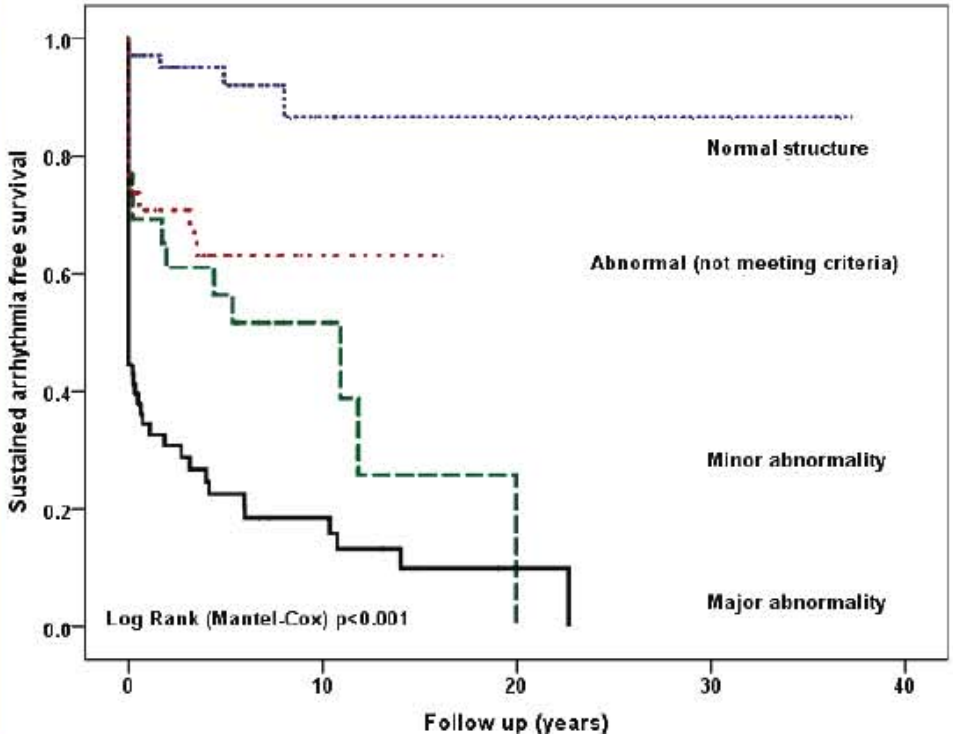
Arrhythmic outcome

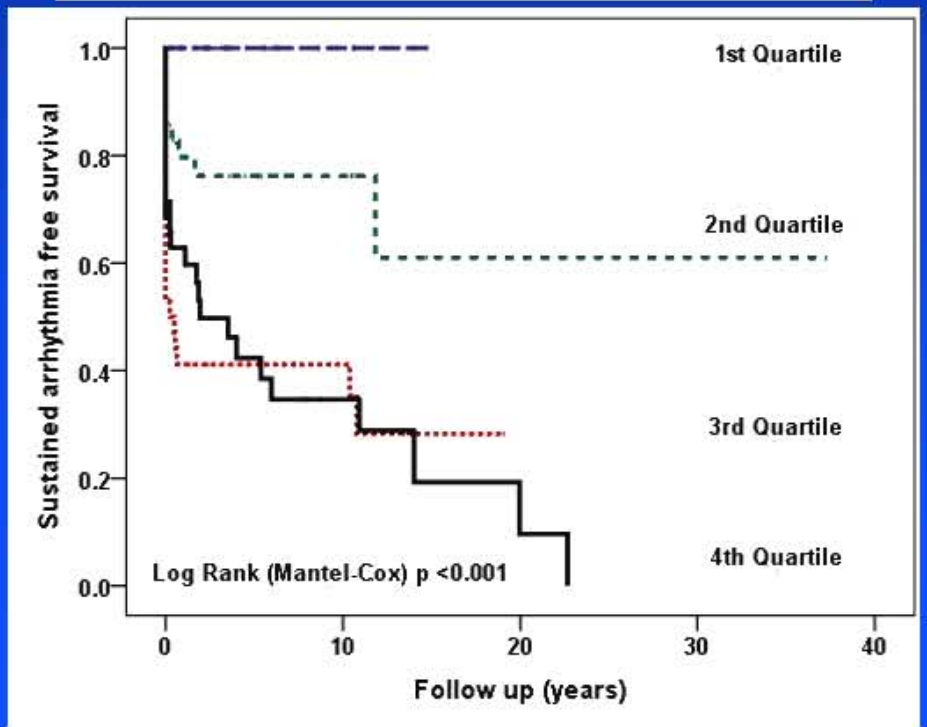


No. of patients	Composite outcome (%)	Sustained VT	Appropriate ICD intervention	Resuscitated SCD	SCD
215	86 (40)	58	19	8	1


Asymptomatic FM
Symptomatic FM
Asymptomatic Proband
Symptomatic Proband
Log Rank (Mantel-Cox) p <0.001
Sustained arrhythmia free survival
Follow up (years)


0/1 T inversions
2 T inversions
>= 3 T inversions
Log Rank (Mantel-Cox) p <0.001
Sustained arrhythmia free survival
Follow up (years)


Normal structure
Abnormal (not meeting criteria)
Minor abnormality
Major abnormality
Log Rank (Mantel-Cox) p<0.001
Sustained arrhythmia free survival
Follow up (years)

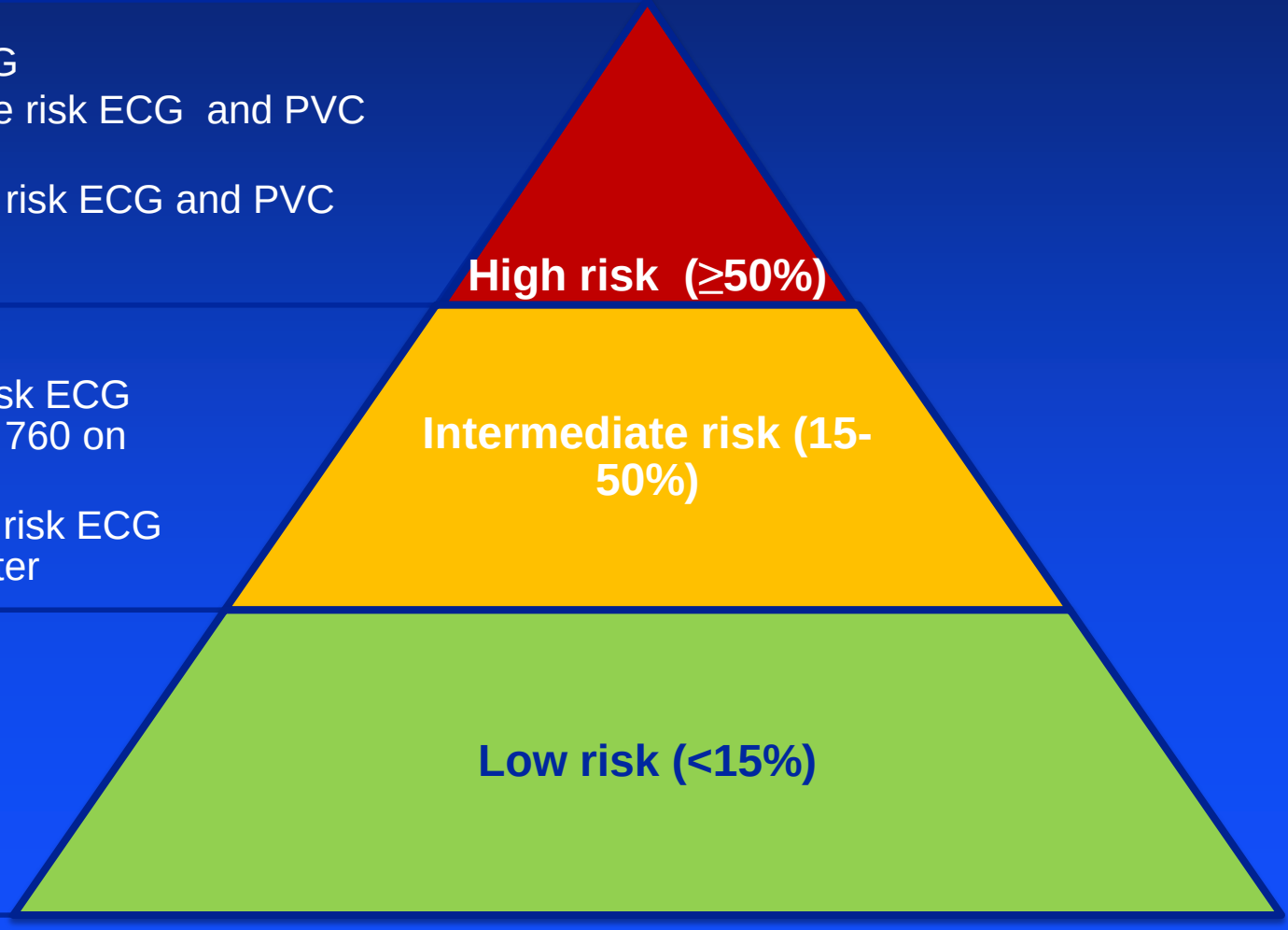

1st Quartile
2nd Quartile
3rd Quartile
4th Quartile
Log Rank (Mantel-Cox) p <0.001
Sustained arrhythmia free survival
Follow up (years)

Risk stratification scheme

- Probands with high risk ECG
- Probands with a intermediate risk ECG and PVC count >760 on a Holter
- Family members with a high risk ECG and PVC count >760 on a Holter

- Probands with low risk ECG
- Family members with high risk ECG and PVC count between 11- 760 on Holter
- Probands with intermediate risk ECG and PVC count <760 on Holter

- Family members with a high risk ECG and <10 PVC on a Holter
- Family members with a low or intermediate risk ECG



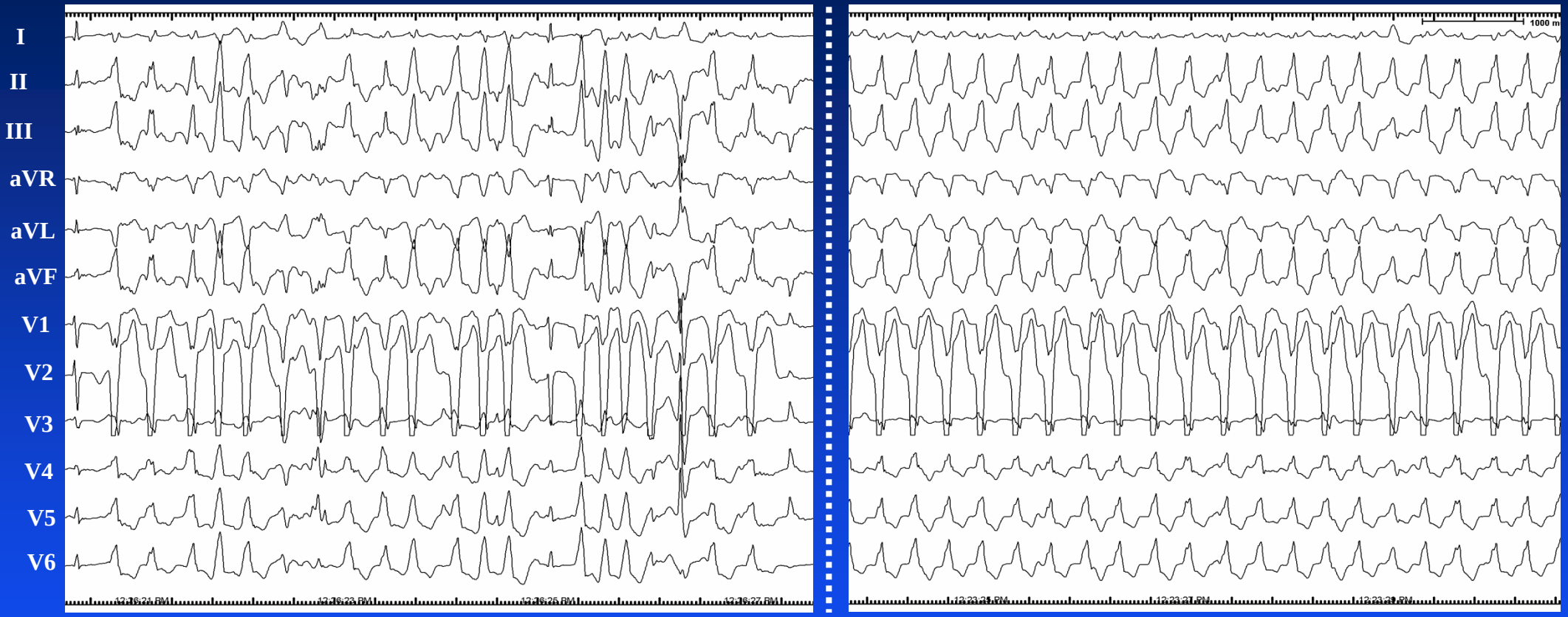
What is the Role of Catheter Ablation?

- EP testing and a limited endocardial ablation procedure is appropriate at the time of evaluation and / or diagnosis.
- Catheter ablation (endo +/ - epi) is recommended for patients receiving frequent ICD therapies despite antiarrhythmic drug therapy.
- Catheter ablation is appropriate prior to antiarrhythmic drug therapy when performed in experienced centers.

Figure 1b.

Complex Ventricular Ectopy

Sustained VT



What About Exercise?

- Patients with ARVD are advised to avoid high level athletics.
- Recommended activities include walking, bowling, and golf.

Conclusions and Future Directions

- ARVD is a rare but important cause of sudden cardiac death.
- Increasing evidence suggests that ARVD is a disease of desmosomal dysfunction.
- Diagnosis of ARVD is challenging and requires a comprehensive evaluation with both noninvasive and invasive testing.
- Identification of genetic and clinical risk factors for sudden death remains an active area of investigation.
- We recommend ICD implantation for all probands who meet Task Force criteria for ARVD.
- Outcomes of VT ablation have improved with an epicardial approach.

ARVD.COM

Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs

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presentation of ARVD/C is 26 years[8]. We used previously published methods[1,10] to generate iPSC lines from fibroblasts of two patients with ARVD/C and *PKP2* mutations[11,12]. Mutant *PKP2* iPSC-CMs demonstrate abnormal plakoglobin nuclear translocation and decreased β-catenin activity[13] in cardiogenic conditions; yet, these abnormal features are insufficient to reproduce the pathological phenotypes of ARVD/C in standard cardiogenic conditions. Here we show that induction of adult-like metabolic energetics from an embryonic/glycolytic state and abnormal peroxisome proliferator-activated receptor gamma (PPAR-γ) activation underlie the pathogenesis of ARVD/C. By co-activating normal PPAR-alpha-dependent metabolism and abnormal PPAR-γ pathway in beating embryoid bodies (EBs) with defined media, we established an efficient ARVD/C *in vitro* model within 2 months. This model manifests exaggerated lipogenesis and apoptosis in mutant *PKP2* iPSC-CMs. iPSC-CMs with a homozygous *PKP2* mutation also had calcium-handling deficits. Our study is the first to demonstrate that induction of adult-like metabolism has a critical role in establishing an adult-onset disease model using patient-specific iPSCs. Using this model, we revealed crucial pathogenic insights that metabolic derangement in adult-lik milieu underlies ARVD/C pathologies, enabling us to propose novel disease-modifying therapeutic strategies.

Thank you