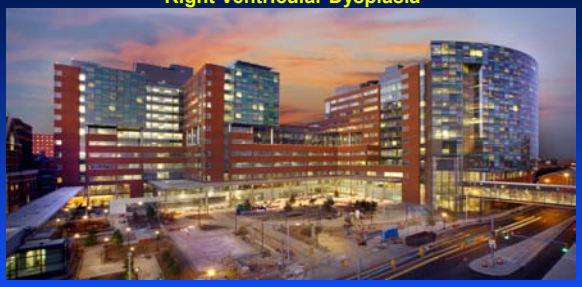
Insights on Diagnosis and Management of Arrhythmogenic Right Ventricular Dysplasia



Hugh Calkins MD
Nicholas J Fortuin Professor of Cardiology
Professor of Medicine
Director of the Johns Hopkins ARVD Program
(ARVD.COM)

COI

- The Johns Hopkins ARVD program receives research support from Medtronic and and St Jude Medical.
- Dr Calkins is a consultant for Medtronic and Boerringer Ingleheim.

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".

Establishing an Accurate Diagnosis

- Comprehensive evaluation including history, family history, exercise history, physical exam, ECG, SAECG, Holter, Echo, MRI, and stress test.
- Genetic testing when the diagnosis is suspected.
- Application of the 2010 Task Force Criteria.

Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Proposed Modification of the Task Force Criteria

Frank I. Marcus[1*] Chair, William J. McKenna[2] Co-Chair, Duane Sherrill[1], Cristina Basso[3], Barbara Bauce[3], David A. Bluemke[4], Hugh Calkins[5], Domenico Corrado[3], Moniek G.P.J. Cox[6], James P. Daubert[7], Guy Fontaine[10], Kathleen Gear[1], Richard Hauer[6], Andrea Nava[3], Michael H. Picard[11], Nikos Protonotarios[13], Jeffrey E. Saffitz[12], Danita M. Yoerger Sanborn[11], Jonathan S. Steinberg[9], Harikrishna Tandri[5], Gaetano Thiene[3], Jeffrey A. Towbin[14], Adalena Tsatsopoulou[13], Thomas Wichter[15], and Wojciech Zareba[8]

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	Epsilon 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
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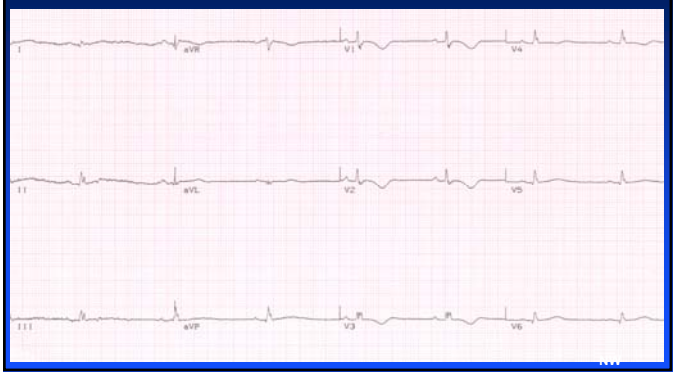
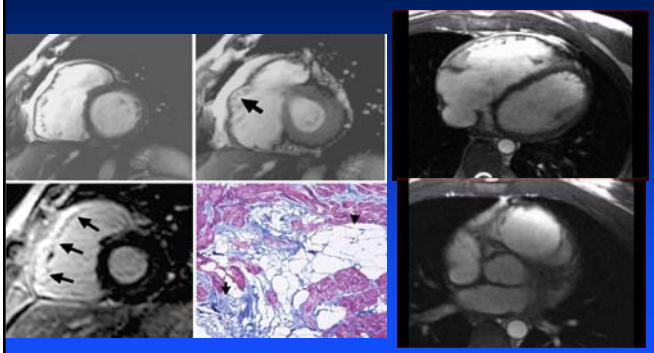
ECG Features of ARVD



MRI Features of ARVD



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

Please Remember:

1. MRI Imaging is not the "gold standard" for diagnosis of ARVD

2. MRI imaging is the most common reason for "over diagnosis" of ARVD

3. The most common reasons for overdiagnosis of ARVD include:

- Lack of awareness of the diagnostic criteria for ARVD
- Failed recognition that presence of myocardial fat and wall thinning are not diagnostic for ARVD.
- Failed recognition that RV wall motion abnormalities may result from a RV free wall tether between RV and sternum, pectus excavatum, and a RV moderator band.
- Overdiagnosis of an apical aneurysm. Recall that ARVD spares the apex which is only impacted in the very severe form of the disease.

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

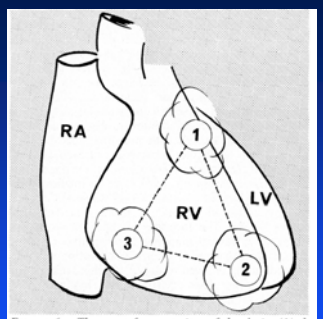
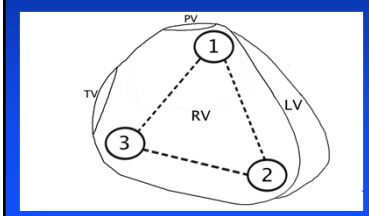


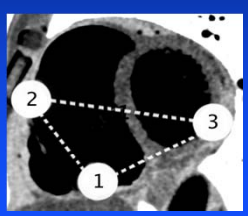
FIGURE 6. *The most frequent sites of dysplasia: (1) the anterior infundibulum, (2) the right ventricular apex and (3) the inferior or diaphragmatic aspect of the right ventricle (RV). These constitute the "triangle of dysplasia." LV = left ventricle, RA = right atrium.*

Circulation 65, No. 2, 1982.

"Triangle of Dysplasia Displaced"
Te Riele et al JCVEP 2013

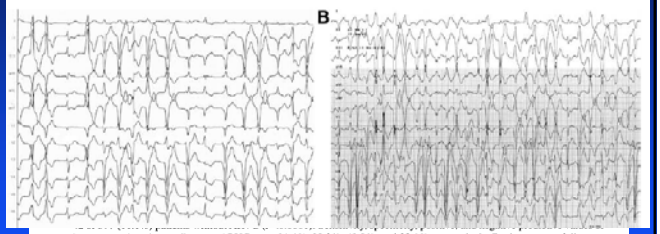
- ARVD preferentially impacts the RV basal inferior wall, the RV basal anterior wall, and the posterolateral LV.
- RV apical involvement never isolated abnormality





Original Article

Diagnostic Value of Isoproterenol Testing in Arrhythmogenic Right Ventricular Cardiomyopathy



isoproterenol testing to diagnose ARVC were 91.4%, 88.9%, 43.2%, and 99.1%, respectively. During a mean follow-up period of 5.6±4.4 years, 6 additional patients met diagnostic criteria for ARVC. Importantly, initial isoproterenol testing was positive in 6 of 6 (100%) of these patients. Survival free from ARVC diagnosis was significantly lower in the positive isoproterenol group than in the negative isoproterenol group (P<0.0001, exact log-rank test).

Conclusions—Ventricular arrhythmogenicity during isoproterenol testing is highly sensitive (sensitivity, 91.4%) for the diagnosis of ARVC, particularly in its early stages. (***Circ Arrhythm Electrophysiol.* 2014;7:590-597.**)

Diagnostic Value of isoproterenol Testing in ARVC Denis, Haissaguerre

412 patients referred for PVC evaluation or suspected ARVD

Isoproterenol infusion: 45 mcg/min isoproterenol for 3 minutes, continuous ECG during and 10 min post, all BB and Ca blockers stopped.
Positive test: 1) polymorphic PVCs and > 1 couplet, 2) sustained or nonsustained Monomorphic or polymorphic VT with LBBB morphology (with exclusion of RVOT VT) occurring during the infusion or within 10 minutes post. The test was stopped with positive test and if VT aten 5 mg for 1 min infused.

ARVD diagnosed in 35 patients at initial evaluation.

Iso testing positive in 32 / 35 (91%) patients with ARVD versus 42 of 377 (11%) without ARVD

Sensitivity, specificity, pos and neg predictive values were 91%, 89%, 43%, and 99%

During 5 years fu 6 additional pts diagnosed with ARVD. Iso testing had been positive in 100%.

Risk Stratification for SCD Risk Important Variables

- History of sudden cardiac death
- History of sustained ventricular tachycardia
- Proband status
- Extent of disease
- PVC frequency on 24 hour Holter
- Cardiac syncope
- Exercise Plans
- Results of EP Testing
- Patient values and preferences

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

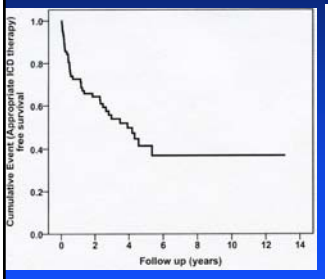
JACC 2011

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

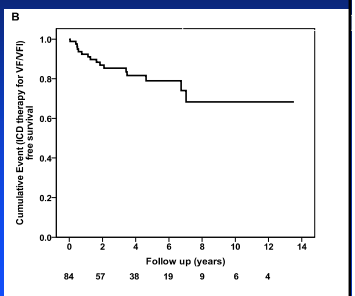
- Palpitations: 40 pts (48%)
- Syncope: 23 (27%)
- Chest pain: 14 (17%)
- Asx: 20 (24%)

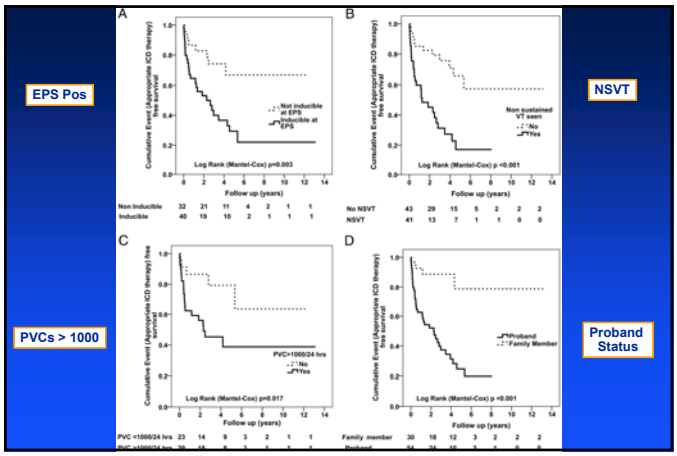
Incidence and Predictors of ICD Therapy in Primary Prevention ARVD Patients

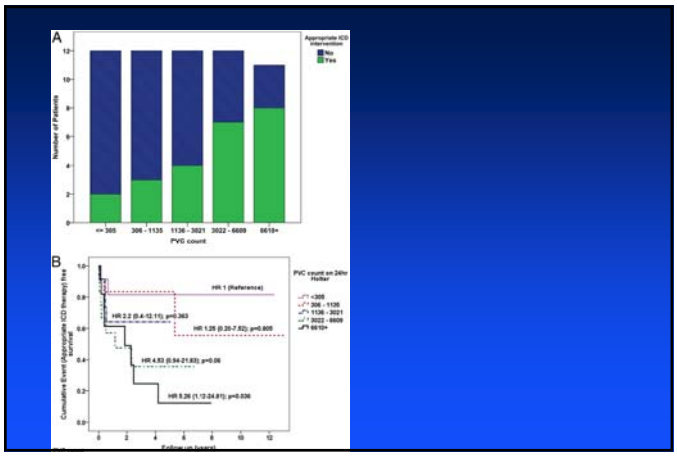
Appropriate ICD Therapy

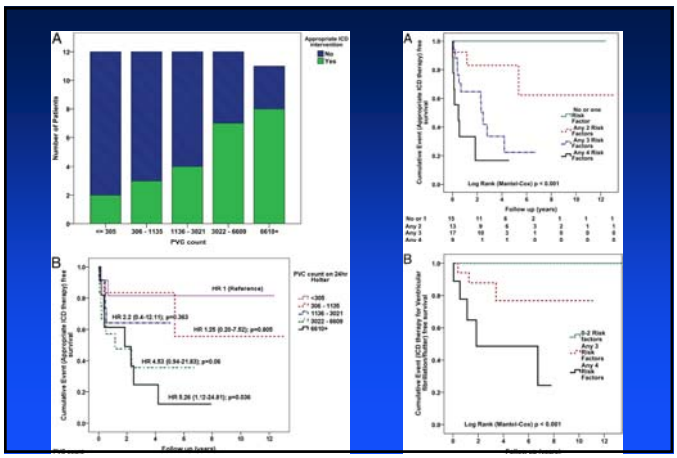


ICD interventions for VFL/VF




EPS Pos
NSVT
PVCs > 1000
Proband Status
A
B
C
D
Log Rank (Mantel-Cox) p=0.003
Log Rank (Mantel-Cox) p <0.001
Log Rank (Mantel-Cox) p=0.017
Log Rank (Mantel-Cox) p <0.001
Follow up (years)


A
B
PVC count


A
B
PVC count
Log Rank (Mantel-Cox) p < 0.001

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.

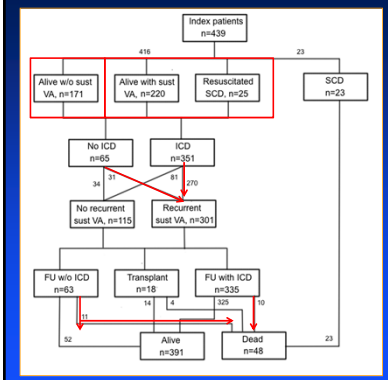
ARVD/C: A Transatlantic experience in 1001 index patients and at risk family members

Aditya Bhonsale, Cindy James, Anneline te Riele, Dennis Dooijes, Crystal Tichnell, Abhishek Sawant, Brittney Murray, Jeroen van der Heijden, Harikrishna Tandri, Pieter Doevendans, Daniel Judge, Arthur Wilde, Peter van Tintelen, Richard Hauer, and Hugh Calkins

JOHNS HOPKINS MEDICINE

ICIN Netherlands Heart Institute

Detailed Outcomes of Index patients



87% of 245 pts received an ICD for seconday prevention.

81% of 171 pts received an ICD for primary prevention.

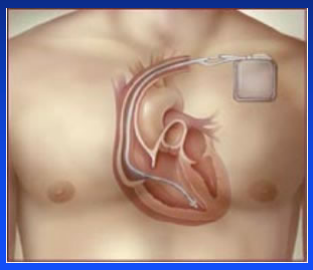
270/351 pts with ICD (77%) had sust VA during fu as compared with 31 of 65 pts (48%) without ICD

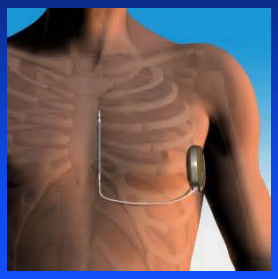
Among pts with ICD, 10 died (3%) 2 of SCD, 3 of heart failure, 2 of a combination of heart failure and arrhythmias, and 3 of non-cardiac causes

Among pts without an ICD, 11 died (17%) : 10 died of SCD and 1 of heart failure.

The SCD incidence was higher in pts without an ICD compared to those with ICD(16% vs. 0.6%).

Which ICD Should They Get?





Methods for Minimizing Symptoms and ICD Shocks

- Stop exercising – especially stop competitive and endurance sports. Think pack years of smoking.
- Take beta blockers.
- Take ACE inhibitors, especially if significant disease.
- Consider taking antiarrhythmic medications if recurrent sustained VT or symptomatic nonsustained VT (sotolol, flecainide, tikosyn, amiodarone)
- Consider catheter ablation if AA drugs do not work or have side effects.

What Data Exists to Support The Recommendation to Stop Exercising ?

- ARVD is a disease of desmosomal dysfunction.
- Desmosomes are structures that connect cells together.
- During exercise pressures in the RV increase three fold and the RV dilates increasing wall stress.
- Most ARVD patients, especially those that present at young ages are high level athletes.
- Exercise is a common trigger of arrhythmias and sudden death in ARVD patients.
- One mouse study demonstrates the provocative role of exercise in a model of ARVD.
- Two clinical studies from Johns Hopkins demonstrate that exercise is bad in patients at risk for developing ARVD

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

Cynthia A. James, ScM, PrD, Aditya Bhonsale, MD, Crystal Tichnell, MGC, Brittney Murray, MS, Stuart D. Russell, MD, Harikrishna Tandri, MD, Ryan J. Tedford, MD, Daniel P. Judge, MD, Hugh Calkins, MD

Baltimore, Maryland

	Overall (N = 87)	Endurance Athlete (n = 56)	Not Endurance Athlete (n = 31)	p Value
Male	46 (53)	32 (57)	14 (45)	NS
Proband	36 (41)	28 (50)	8 (26)	0.028
Age at interview, yrs	44 ± 18	42 ± 15	45 ± 22	NS
Presentation				
Age at clinical presentation, yrs	35 ± 17	32 ± 14	38 ± 20	NS
Type of presentation				
Symptomatic presentation	44 (51)	36 (64)	8 (26)	0.002
Resuscitated SCD	3 (3)	2(4)	1 (3)	
Asymptomatic	40 (46)	18 (45)	22 (71)	
Sustained VT/VF at presentation	26 (30)	18 (32)	8 (26)	NS

(J Am Coll Cardiol 2013;62:1290–7)

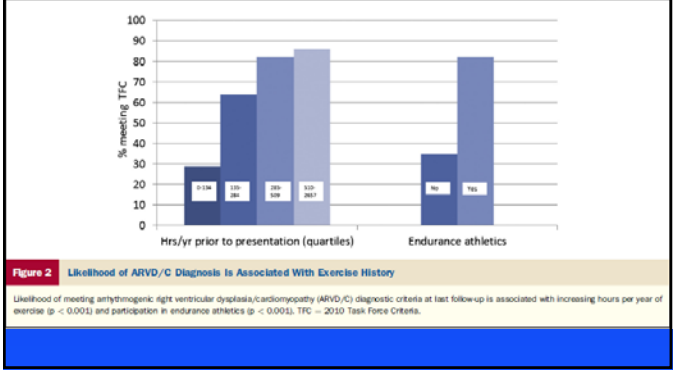


Figure 2 Likelihood of ARVD/C Diagnosis Is Associated With Exercise History

Likelihood of meeting arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) diagnostic criteria at last follow-up is associated with increasing hours per year of exercise ($p < 0.001$) and participation in endurance athletics ($p < 0.001$). TFC = 2010 Task Force Criteria.

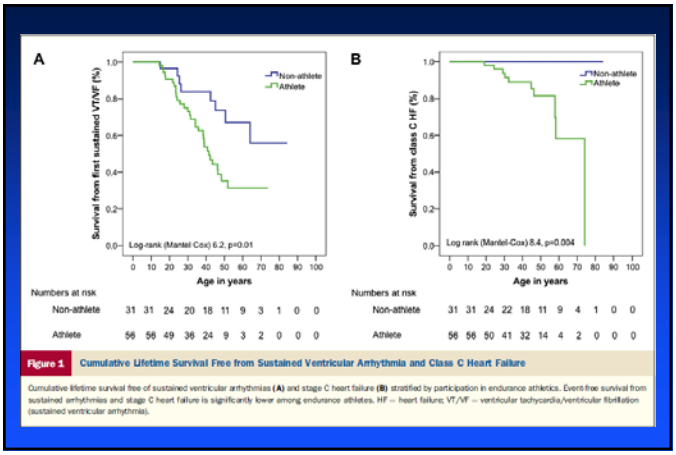
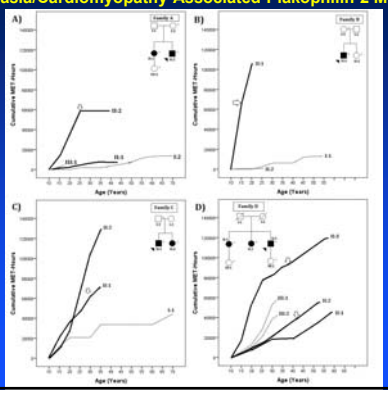


Figure 1 Cumulative Lifetime Survival Free from Sustained Ventricular Arrhythmia and Class C Heart Failure

Cumulative lifetime survival free of sustained ventricular arrhythmias (**A**) and stage C heart failure (**B**) stratified by participation in endurance athletics. Event-free survival from sustained arrhythmias and stage C heart failure is significantly lower among endurance athletes. HF = heart failure; VT/VF = ventricular tachycardia/ventricular fibrillation (sustained ventricular arrhythmia).

Youth Exercise Influences Disease Penetrance and Arrhythmic Outcomes in Families Segregating Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy-Associated Plakophilin-2 Mutations



What is the Role of Catheter Ablation?

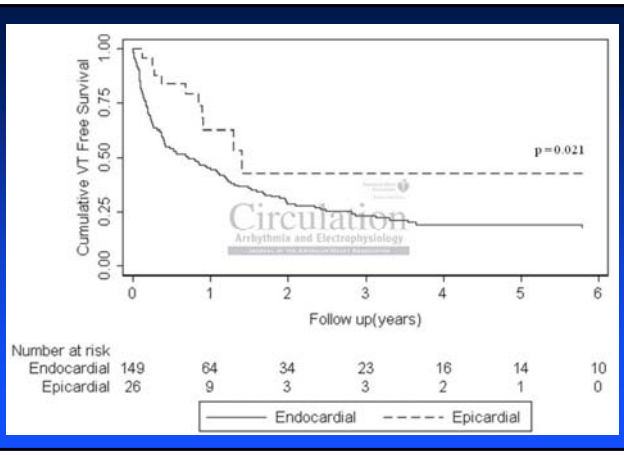
- EP testing and a limited endocardial ablation procedure is appropriate at the time of evaluation and / or diagnosis.
- Catheter ablation (endo +/ - epi) is recommended for patients receiving frequent ICD therapies despite antiarrhythmic drug therapy.
- Catheter ablation is appropriate prior to antiarrhythmic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

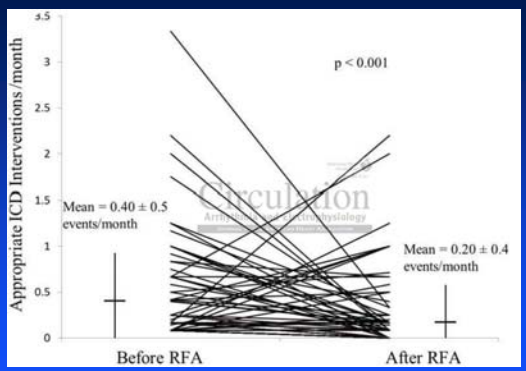
Outcomes of Catheter Ablation of Ventricular Tachycardia in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

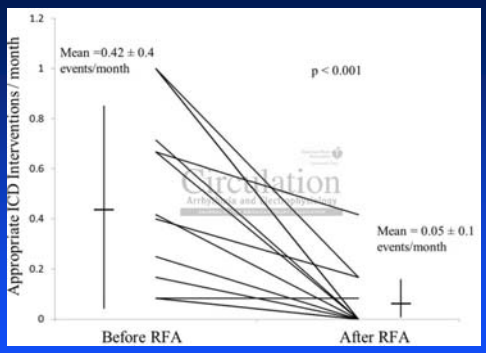
Binu Philips, Srinivasa Madhavan, Cynthia James, Crystal Tichnell, Brittney Murray, Darshan Dalal, Aditya Bhonsale, Saman Nazarian, Daniel P. Judge, Stuart D. Russell, Theodore Abraham, Hugh Calkins and Harikrishna Tandri

Circ Arrhythm Electrophysiol published online April 6, 2012;

- 87 ARVD patients
- ICD implanted in 82, no ICD in 5
- 175 VT ablation procedures (mean = 2.3 per patient)
- Procedures performed at 80 EP centers
- 62% underwent ablation prior to AA drug therapy
- 26 epicardial VT ablation procedures in 23 patients
- Two major complications (death and delayed MI both withepicardial ablation.
- Mean follow up 88±66 months





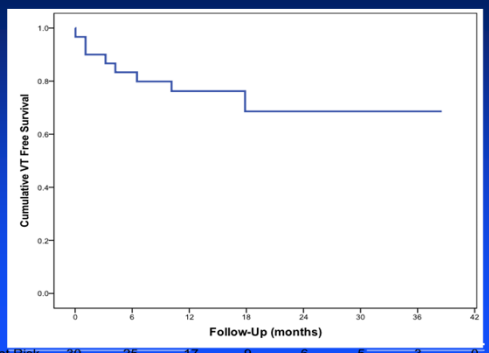


Outcomes and VT Recurrence Characteristics after Epicardial Ablation of Ventricular Tachycardia in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

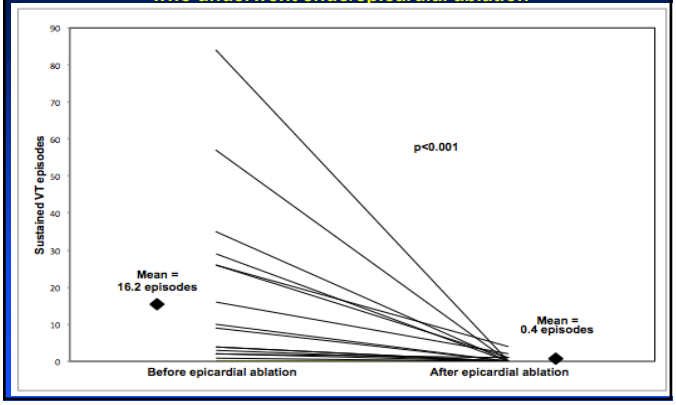
Patient Population

- 30 ARVD patients
- ICD implanted in30
- 15 had failed one or more endocardial ablation procedures
- Procedures performed at Johns Hopkins
- 80% had previously failed AA drug therapy, including amiodarone in 15
- No major complications
- Mean follow up 20±12 months (range 3 – 51 months)
- 30% on AA drug therapy at follow-up (none on amiodarone)

VT free survival in 30 subjects who underwent epi+endo ablation



VT burden in the year before/after ablation for 30 subjects who underwent endo/epicardial ablation



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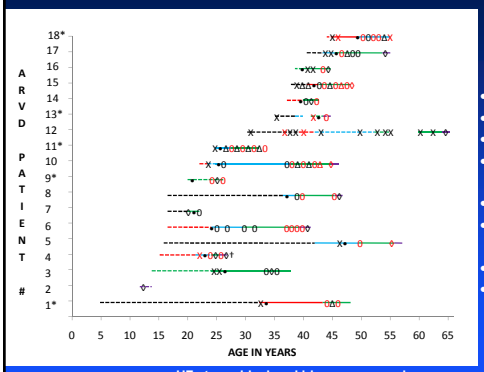
Methods for Preventing Progression of ARVD/C

- Stop exercising – especially stop competitive and endurance sports. Think pack years of smoking.
- Take beta blockers.
- Take ACE inhibitors, especially if significant disease.

Cardiac Transplantation in ARVD/C



- N = 18
- Male (61%)
- Sx onset 24 ± 13 y
- 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

Conclusions

- Management of ARVD can be considered as a four legged stool.
- First, make sure you make an accurate diagnosis.
- Second – risk stratify the patient for SCD risk and implant an ICD if indicated.
- Third, minimize ICD therapies with exercise restriction, medications, and catheter ablation.
- Fourth, prevent progression with exercise restriction and ACE inhibitors.
- We are eager to enroll all patients with ARVD in the Johns Hopkins ARVD registry.

ARVD.COM


THANK YOU!