Arrhythmogenic Right Ventricular Dysplasia: And Sudden Cardiac Death

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Professor of Medicine
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Johns Hopkins Medical Institutions

• Overview of ARVD
• Genetic Basis of ARVD
• Clinical presentation and follow-up
• ICD Therapy, Catheter Ablation, and Exercise
• Conclusion and Future Directions

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”.

Circulation 65; 384-398, 1982

Right Ventricular Dysplasia:
A Report of 24 Adult Cases

FRANK L. MARSH, M.D.; JULY H. FORDHAM, M.D.; GERARD GIBAUDON, M.D.; ROBERT FRANK, M.D.; JOSE L. LACROUX, M.D.; CHRISTINE MAECHTEL, M.D.; AND YVES GEHRIGEOFF, M.D.

SUMMARY Right ventricular dysplasia is characterized by an abnormality in the development of part of the right ventricular myocardium. Patients with right ventricular dysplasia may present with ventricular tachycardia, monomorphic ventricular tachycardia, right ventricular outflow tract tachycardia, or arrhythmogenic right ventricular dysplasia. Twenty-four adult patients with right ventricular dysplasia who had undergone ventricular rhythm disturbances were seen during a 3-year period. The male:female ratio was 2.2:1. The mean age at the time of hospitalization was 39 years. All but one patient had a history of cardiac symptoms prior to the onset of the disorder, and 10 patients had a history of syncope. Ventricular arrhythmias were noted over the right ventricular apex. The heart was usually enlarged, and the percussion and auscultation were normal. In 17 patients, there were no abnormalities noted by chest radiographs, and in the remaining 7, the right ventricle was noted to be dilated. The diagnosis of right ventricular dysplasia was substantiated by right ventricular angiography in 11 patients and in autopsy in another. Two other patients who did not have arrhythmias had right ventricular dysplasia diagnosed by right- and left-heart catheterization. A review, with a literature search of 14 adult cases, permits a composite clinical profile of this condition in the adult.

Circulation 65; 384–398, 1982
Cardiac Phenotype of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

Anneline S.J.M. te Riele, MD, Cynthia A. James, PhD, Binu Philips, MD, Neda Rashidi, MD, Arlette Rhimes, MD, Judith A. Groeneweg, MD, Brittney Murray, MS, Crystal Trudinger, MD, David P. Joseph, MD, Laureen F. van den Houten, MD, Wouter J.M. Cramer, MD, Birgitta K. Velthuis, MD, David A. Bluemke, MD, PhD, Stefan L. Zimmerman, MD, Ruth K. Kats, MD, Richard K.W. Moses, MD, Hugh Calkins, MD, and Harikrishna Tandri, MD
Results – CMR Left Ventricle

- Predominantly manifesting as subepicardial fat infiltration
  - Majority (80%) in posterolateral wall

Results – Epicardial Voltage Maps

Introduction - Study Design - Results - Conclusion
“Triangle of Dysplasia Displaced”

• Unique pattern of involvement

• RV apical involvement never isolated abnormality
  – Displacing RV apex from triangle of dysplasia in early ARVD/C

Role of Conduction Delay in ARVD/C?

Study Conclusion

• RV involvement follows a pattern
  – Limited: Subtricuspid region
  – Moderate: Extension to basal anterior region below RVOT
  – Severe: Global RV involvement

• LV involvement occurs at all stages of RV disease
  – Subepicardial fat infiltration in posterolateral wall

• Understanding disease mechanism
**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

**ARVD versus Idiopathic VT**

<table>
<thead>
<tr>
<th></th>
<th>ARVD</th>
<th>Idiopathic VT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prognosis</strong></td>
<td>SCD risk</td>
<td>excellent</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ICD</td>
<td>BB or cath abl</td>
</tr>
<tr>
<td><strong>Genetics</strong></td>
<td>inherited</td>
<td>not inherited</td>
</tr>
<tr>
<td><strong>Exercise induced</strong></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Young healthy patients</strong></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>LBI axis VT</strong></td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Other LV VTs</strong></td>
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<td>no</td>
</tr>
<tr>
<td><strong>Family history of SCD</strong></td>
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<td>no</td>
</tr>
<tr>
<td><strong>SAECG</strong></td>
<td>abnormal</td>
<td>normal</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td>abnormal</td>
<td>normal</td>
</tr>
<tr>
<td><strong>EPS</strong></td>
<td>reentrant VT</td>
<td>triggered/automatic VT</td>
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### ECG Comparison of VT in ARVD versus RVOT VT

- QRSd 1 > 120 msec (88% sens, 48% spec)
- QRS transition at V6 (19% sens, 100% spec)
- Notching any lead (79% sens, 65% spec)
## ARVD Diagnostic Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1994 Criteria</th>
<th>2010 Criteria</th>
</tr>
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<tbody>
<tr>
<td>RV Size and Function</td>
<td>Non-quantitative</td>
<td>Quantitative</td>
</tr>
<tr>
<td>Biopsy (major)</td>
<td>Fibrofatty replacement</td>
<td>&lt; 60% of myocytes &amp; fibrous replacement +/- fat</td>
</tr>
<tr>
<td>T wave inversion v2 and V3</td>
<td>Minor criteria in absence of RBBB</td>
<td>Major criteria in absence of RBBB QRS &gt; 120 msec</td>
</tr>
<tr>
<td>Epsilon waves (major)</td>
<td>Epsilon or localized prolongation &gt; 110 ms V1-V3</td>
<td>Epsilon waves</td>
</tr>
<tr>
<td>SAECG (minor)</td>
<td>Late potentials</td>
<td>Quantitative, 1 of 3 parameters</td>
</tr>
<tr>
<td>LBBB VT (minor)</td>
<td>NA</td>
<td>&gt; 55 msec in V1-V3</td>
</tr>
<tr>
<td>Frequent PVCs (minor)</td>
<td>&gt; 1000/24 hrs</td>
<td>&gt; 500/24 hrs</td>
</tr>
<tr>
<td>Family History (Major)</td>
<td>Familial disease confirmed by autopsy or surgery</td>
<td>ARVD in first degree relative or pathogenic mutation in patient</td>
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<tr>
<td>Family History (Minor)</td>
<td>FH of premature SCD &lt; 35 yrs or family hx of ARVD</td>
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<td>Late potentials</td>
<td>Quantitative, 1 of 3 parameters</td>
</tr>
<tr>
<td>TAD</td>
<td>NA</td>
<td>&gt; 55 msec in V1-V3</td>
</tr>
<tr>
<td>LBBB VT (minor)</td>
<td>Minor criteria</td>
<td>Major criteria if LBB sup axis VT, minor criteria if not</td>
</tr>
<tr>
<td>Frequent PVCs (minor)</td>
<td>&gt; 1000/24 hrs</td>
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Outline

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

Intercellular Mechanical Junction (Desmosome)

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
• TGFβ3* (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 2% of patients
• No pathogenic mutation found in 50% of ARVD patients
Outline

- Overview of ARVD
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Johns Hopkins ARVD Experience
N = 100

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dx Alive</th>
<th>Autopsy Dx</th>
<th>Total</th>
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<tbody>
<tr>
<td>Age</td>
<td>29 ± 12</td>
<td>29 ± 15</td>
<td>29 ± 13</td>
</tr>
<tr>
<td>Male Gender</td>
<td>36 (52)</td>
<td>15 (48)</td>
<td>51</td>
</tr>
<tr>
<td>Athletic</td>
<td>37 (54)</td>
<td>12 (39)</td>
<td>49</td>
</tr>
<tr>
<td>Presenting Sx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palpitations</td>
<td>25 (36)</td>
<td>2 (6)</td>
<td>27</td>
</tr>
<tr>
<td>Syncope</td>
<td>20 (29)</td>
<td>5 (16)</td>
<td>25</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>23 (74)</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>Resuscitated SCD</td>
<td>1 (1.5)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15 (22)</td>
<td>15</td>
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</tbody>
</table>


Symptoms of ARVD

[Graph showing percentage of patients experiencing symptoms over time, including heart failure, SCD, VT, and any symptom]
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

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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.
Heart Rhythm 2013

67 ARVD patients
• 36 ± 18 yrs
• 4.4 ± 2.9 yrs fu
• 66% received an appropriate ICD therapy
• 21% received an ICD therapy for fast VT/VF (>240bpm)
• 24% incidence of inappropriate therapy

Circ 2010; 122: 1144 - 1152

106 ARVD patients
• 36 ± 18 yrs
• 4.8 ± 2.9 yrs fu
• 24% received an appropriate ICD therapy
• 16% received an ICD therapy for fast VT/VF (>240bpm)
• 19% received inappropriate ICD therapy

Predictors of appropriate therapy: syncope (p< 0.05) and NSVT (p = 0.07)

Palpitations: 40 pts (48%)
Syncope: 23 (27%)
Chest pain: 14 (17%)
Axs: 20 (24%)
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
Risk stratification scheme

- Probands with high risk ECG
- Probands with intermediate risk ECG and PVC count >760 on Holter
- Family members with high risk ECG and PVC count >760 on Holter
- Probands with low risk ECG
- Family members with high risk ECG and PVC count between 11-760 on Holter
- Family members with intermediate risk ECG and PVC count <760 on Holter
- Family members with 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.
• 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 with epicardial ablation).
• Mean follow up 88±66 months
Figure 1b. Complex Ventricular Ectopy

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Overall Population</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age at time of first procedure (years)</td>
<td>38 ± 13</td>
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<tr>
<td>Gender, male</td>
<td>45 (12)</td>
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<tr>
<td>ICD implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before first procedure</td>
<td>38 (43)</td>
<td></td>
</tr>
<tr>
<td>At follow-up*</td>
<td>44 (51)</td>
<td></td>
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<tr>
<td>No ICD</td>
<td>5 (5)</td>
<td></td>
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<td>Drugs, baseline / follow up</td>
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<tr>
<td>Amodarone</td>
<td>8 (9) / 18 (24)</td>
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<tr>
<td>Sotalol</td>
<td>15 (18) / 22 (26)</td>
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<tr>
<td>Dofetilide</td>
<td>0 (0) / 2 (2)</td>
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<td>Dronedarone</td>
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<td>Metoprolol</td>
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<tr>
<td>Flecainide</td>
<td>3 (3) / 1 (1)</td>
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</tr>
<tr>
<td>Propafenone</td>
<td>2 (2) / 1 (1)</td>
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Johns Hopkins Updated Results of Epicardial VT Ablation in ARVD

N= 19 patients

What About Exercise?

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

What Data Exists to Support These Recommendations?

- 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.
**Exercise Increases Penetrance and Arrhythmic Risk in ARVD/C**

**Purpose**
- To test whether in ARVD/C-associated desmosomal mutation carriers exercise influences:
  - Penetrance
  - Arrhythmic risk
  - Progression to heart failure

**Study Design**
- **Population**
  - 87 carriers of a single copy of an ARVD/C-associated desmosomal mutation (76 PKP2)
  - Age 11-88
  - Enrolled in the Johns Hopkins ARVD Registry
  - Subanalysis on 61 NOT presenting with a sustained VT/VF
- **Clinical Outcomes**
  - First sustained ventricular arrhythmia (VT/VF or ICD discharge)
  - Onset of stage C heart failure
  - Diagnosis of ARVD/C by 2010 Task Force Criteria at last follow-up

**Exercise**
- Structured telephone or in-person interviews
- Intensity, timing, and duration regularly performed exercise collected
- Exercise for each patient analyzed
  - **Endurance athlete -** Vigorous intensity participation for at least 50 hours/year in a sport with high dynamic demand (>70% Max O2 as defined by Bethesda Conference Classification of Sports).
  - Average annual hours/year of all exercise prior to and following clinical presentation.
Exercise history

- 56/87 (64%) endurance athletes
  - 37 long and middle-distance running
  - 27 basketball
  - 14 soccer
  - 8 competitive swimming
  - 5 cycling
  - 11 others (rowing, cross-country skiing, tennis, lacrosse, field hockey, squash)
- Median age starting first endurance sport - 14 years
- Median 284 hours/year (range 0-2657) exercise prior to presentation
- Median 155 hours/year (range 0-1658) after clinical presentation

Endurance athletes have worse clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Endurance athlete (n=56)</th>
<th>Non-endurance athlete (n=31)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>32 (57)</td>
<td>14 (45)</td>
<td>NS</td>
</tr>
<tr>
<td>Proband</td>
<td>30 (53)</td>
<td>8 (26)</td>
<td>0.028</td>
</tr>
<tr>
<td>Age at interview mean (SD)</td>
<td>42±15</td>
<td>45±22</td>
<td>NS</td>
</tr>
<tr>
<td>Age at clinical presentation</td>
<td>32±14</td>
<td>36±23</td>
<td>NS</td>
</tr>
<tr>
<td>Symptomatic presentation</td>
<td>38 (68)</td>
<td>9 (28)</td>
<td>0.001</td>
</tr>
<tr>
<td>Symptomatic at LFU</td>
<td>42 (79)</td>
<td>10 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age first symptom</td>
<td>35±13</td>
<td>41±21</td>
<td>0.15</td>
</tr>
<tr>
<td>Age first symptom at LFU</td>
<td>49±23</td>
<td>11±13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LFU, arrhythmia onset</td>
<td>31 (55)</td>
<td>8 (26)</td>
<td>0.008</td>
</tr>
<tr>
<td>VT/VF at presentation</td>
<td>8 (26)</td>
<td>19 (61)</td>
<td>NS</td>
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<td>33±11</td>
<td>37±19</td>
<td>NS</td>
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<tr>
<td>Stage C heart failure - LFU (yes)</td>
<td>10 (18)</td>
<td>0 (0)</td>
<td>0.012</td>
</tr>
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Lifetime survival free from sustained ventricular arrhythmias and heart failure is lower among athletes
Penetrance of ARVD/C is associated with exercise history

Exercise decreases survival from developing a first arrhythmia

Analysis of a subset of 61 participants who did not present clinically with a sustained ventricular arrhythmia

Only athletes developed a first arrhythmia in follow-up

Duration of exercise influences likelihood of a first VT/VF

Among 61 individuals who did not present with sustained VT/VF, survival free from a first arrhythmia was lower among those who had the highest average annual exercise both prior to and following diagnosis.
Changing exercise may decrease arrhythmic risk

61 cases not presenting with VT/VF:
Those doing most exercise/year both before and after clinical presentation were most likely to develop a first VT/VF in follow-up ($p=0.007$).

Among those who doing the most exercise at presentation, those who reduced exercise were less likely to develop a first VT/VF than those who reduced exercise ($p=0.04$).
Study Conclusions

- Exercise increases penetrance, risk of ventricular arrhythmias, and likelihood of developing heart failure among ARVD/C desmosomal mutation carriers.
- Modification of exercise habits may alter risk of developing a first arrhythmia.
- Exercise negatively influences cardiac structure and function among mutation carriers.

Clinical implications

- Restriction from frequent and vigorous, endurance exercise for ARVD/C associated mutation carriers is important.
- There may be an opportunity to change outcomes through counseling about exercise reduction at presentation.
- Risks of more modest exercise for this population remains unknown. Weighing other cardiovascular and social benefits of exercise is important.

Conclusions

- ARVD is a rare but important cause of sudden cardiac death.
- 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.
- Catheter ablation of VT plays an important role in management.
- Vigorous exercise increase the chance of developing ARVD and results in a greater chance of ventricular arrhythmias and heart failure. Because of this we advise against exercise.
- We are eager to enroll all patients with ARVD in the Johns Hopkins ARVD registry.
ARVD in the Real World

D.P.
- 46 year old engineer with a device company
- Track star – track scholarship at Purdue
- Excellent health until 2008 when developed sustained VT when jogging (LB superior axis, CL 260 msec)
- Evaluation revealed ARVD: CT scan mild dyskinesis and fat infiltration at base. EPS pos for inducible VT.
- PKP2 mutation identified
- 1/27/2011 Jogging with friends and received shock for VT CL 240 msec.
- 4/15/2011: He received another shock while running.
- Two children mutation negative, no family history.

DP
C.S.
- 52 year old man who works at a nuclear power plant.
- Highly athletic throughout life.
- Exercise of treadmill at work daily running 5 miles per day.
- h/o palpitations and IRBBB for past 5 years.
- 4/22/11 Syncope while on treadmill.
- VT detected by paramedics and cardioverted.
- ECG cw ARVD
- MRI – dilated RV, mod decreased function to 30%, free wall aneurysm
- Holter while on atenolol 425 PVCs
- Negative genetic screen for 7 known genes
K.L.

- 49 year old woman who survived a cardiac arrest and was diagnosed with ARVD.
- Nonathletic until 35 years of age when decided to start running. She started competing regionally and nationally.
- At time of her cardiac arrest she was running 80 miles per week at minimum.
- 10/3/2010 – 7 min into 5K felt nauseaus, lay down, paramedics, ECG “nl”

K.L.

- Saw cardiologist, Holter showed “nothing concerning” and cleared to resume running.
- 1/11/2011 Because it has snowed decided to run at gym instead of outside. Was on treadmill for 20 min when had a witnessed cardiac arrest. Was resuscitated with an AED.
- MRI borderline consistent with ARVD: fat, fibrosis, RVEF 48%
- SaECG – abnormal
K.L.
1/11/2011

K.L.

R.S.
• 24 year old man of Indian descent referred for second opinion re ARVD.
• Very athletic – 3 season varsity athlete in high school, currently runs or plays basketball for 2 hours each day
• He is in graduate school for an MBA at JHH.
• Over past 6 months recurrent episodes of heart racing while exercising.
• Presented to ER.
C.B.

- 14 year volleyball star from Texas
- Resuscitated from cardiac arrest during volleyball game.
- Evaluation revealed ARVD. ICD Implanted
- No longer exercises.
- Is a trainer on the volleyball team.
- PKP2 mutation: Gln323fs
A.B.

- 12 yo
- Volleyball star
- Asymptomatic
- ECG T inv V1 and V2
- Abnl SAECG
- Normal Holter
- Normal MRI
- PKP2 Gln323fs
B.B.

- 41 yo
- Mom
- Asymptomatic
- ECG T inv V1 to V3
- Normal Holter
- Normal MRI
- Does not want ICD.
- PKP2 Gln323fs

B.B.

B.B.

B.B.
Conclusions

- 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.
- Catheter ablation of VT is not curative.
- We are eager to enroll all patients with ARVD in the Johns Hopkins ARVD registry.

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Thank You