Arrhythmogenic Right Ventricular Dysplasia: State of the Art in 2013

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- 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”.
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.
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.
The Triangle of RV Dysplasia Displaced
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

Frank I. Marcus1* Chair, William J. McKenna2 Co-Chair, Duane Sherrill1, Cristina Basso3, Barbara Bauce3, David A. Bluemke4, Hugh Calkins5, Domenico Corrado3, Moniek G.P.J. Cox6, James P. Daubert7, Guy Fontaine10, Kathleen Gear1, Richard Hauer6, Andrea Nava3, Michael H. Picard11, Nikos Protonotarios13, Jeffrey E. Saffitz12, Danita M. Yoerger Sanborn11, Jonathan S. Steinberg9, Harikrishna Tandri5, Gaetano Thiene3, Jeffrey A. Towbin14, Adalena Tsatsopoulou13, Thomas Richter15, and Wojciech Zareba8
<table>
<thead>
<tr>
<th>Parameter</th>
<th>1994 Criteria</th>
<th>2010 Criteria</th>
</tr>
</thead>
<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% nl myocytes &amp; fibrous replacement +/- fat</td>
</tr>
<tr>
<td>T wave inversion v2 and V3</td>
<td>Minor criteria in absence RBBB</td>
<td>Major criteria in absence of RBBB QRS &gt; 120 msec</td>
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<td>Minor: T wave inv V1, V2 or in V4, V5, and V6 or T in V1-v4 w RBBB</td>
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<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>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 LB sup axis VT, minor criteria if not</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>
</tr>
<tr>
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<td>FH of premature SCD &lt; 35 yrs or family hx of ARVD</td>
<td>FH of ARVD where task force criteria unclear or premature SD &lt; 35 yrs</td>
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ECG Features of ARVD
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
Intercellular Mechanical Junction (Desmosome)

Armadillo Proteins  Desmosomal Cadherins  Plakins

Intermediary filaments Desmin and Actin

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**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dx Alive N = 69</th>
<th>Autopsy Dx N = 31</th>
<th>Total N=100</th>
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<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></td>
<td>23 (74)</td>
<td>23</td>
</tr>
<tr>
<td>Resuscitated SCD</td>
<td>1 (1.5)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>15 (22)</td>
<td></td>
<td>15</td>
</tr>
</tbody>
</table>

Symptoms of ARVD

- Heart failure
- SCD
- VT
- 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

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

JACC 2011

Baltimore, Maryland

- 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**
Figure A: Cumulative Event (Appropriate ICD therapy) free survival
- Non inducible at EPS: 32, 21, 11, 4, 2, 1, 1
- Inducible at EPS: 40, 19, 10, 2, 1, 1, 1

Log Rank (Mantel-Cox) p=0.003

Figure B: Cumulative Event (Appropriate ICD therapy) free survival
- No NSVT: 43, 29, 15, 5, 2, 2, 2
- NSVT: 41, 13, 7, 1, 1, 0, 0

Log Rank (Mantel-Cox) p < 0.001

Figure C: Cumulative Event (Appropriate ICD therapy) free survival
- PVC >1000/24 hrs: 23, 14, 9, 3, 2, 1, 1

Log Rank (Mantel-Cox) p=0.017

Figure D: Cumulative Event (Appropriate ICD therapy) free survival
- Proband: 54, 24, 10, 3, 1, 0, 0
- Family member: 30, 18, 12, 3, 2, 2, 2

Log Rank (Mantel-Cox) p < 0.001

EPS Pos
NSVT
PVCs > 1000
Proband Status
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

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Composite outcome (%)</th>
<th>Sustained VT</th>
<th>Appropriate ICD intervention</th>
<th>Resuscitated SCD</th>
<th>SCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>215</td>
<td>86 (40)</td>
<td>58</td>
<td>19</td>
<td>8</td>
<td>1</td>
</tr>
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</table>
Risk stratification scheme

- **High risk (≥50%)**
  - 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

- **Intermediate risk (15-50%)**
  - 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

- **Low risk (<15%)**
  - 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

Changsung Kim¹, Johnson Wong¹, Jianyan Wen¹,², Shirong Wang¹, Cheng Wang¹, Sean Spiering³, Natalia G. Kan³, Sonia Forcades³, Pier Lorenzo Puri³,⁴, Teresa C. Leone⁵, Joseph E. Marine⁶, Hugh Calkins⁶, Daniel P. Kelly⁶, Daniel P. Judge⁶ & Huei-Sheng Vincent Chen¹,⁷

presentation of ARVD/C is 26 years⁸. We used previously published methods¹⁰ to generate iPSC lines from fibroblasts of two patients with ARVD/C and PKP2 mutations¹¹,¹². Mutant PKP2 iPSC-CMs demonstrate abnormal plakoglobin nuclear translocation and decreased β-catenin activity¹³ 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-α-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-like milieu underlies ARVD/C pathologies, enabling us to propose novel disease-modifying therapeutic strategies.
Thank you