Benign and Malignant Early Repolarization Syndrome

Korean Heart Rhythm Society, Seoul
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Mayo Clinic

June 23rd, 2017
28M Suffers VF Arrest

- Standing at a computer at work
- EMS documents VF, single shock
- Good neurologic recovery
- Coronary angiography normal
- ECG normal, EPS negative
- ICD implanted, treated with carvedilol
Five Years Later

- Brief LOC while watching a movie on Christmas morning
- ICD shock terminated VF
ECG Review.....
What is Going on Here.....?

Idiopathic VF?

Early repolarization?

Are there implications for his family?

Is there a role for genetic testing?

How can we prevent further ICD shocks?
What Causes the Early Repolarization Pattern?
Early descriptions: Hypothermia
Generation of the Cardiac AP

Phase 0: Depolarization
Phase 1: Notch
Phase 2: Plateau
Phase 3: Repolarization
Phase 4: Resting Potential
Generation of the Surface ECG

0 mV

-85 mV

Outward

Inward

ECG

QRS

ST

T

Epicardium

Endocardium

I_{na}

I_{Ca}

I_{TO}

I_{ks}

I_{kr}

Endocardium

0 mV

-85 mV
“J” wave (Increased $I_{TO}$ in RVOT Epicardium)

Increased $I_{TO}$ in RVOT epicardium results in:

1. Prominent phase 1 notch
   - Results in R’
2. Loss of AP dome
   - Results in ST elevation

Based on Yan and Antzelevitch Circ, 1999
Phase II Reentry

ECG

QRS  ST  T

Outward  Inward

$I_{TO}$  $I_{kr}$

Functional reentry

0 mV

-85 mV

Epicardium  Endocardium
Phase 2 Reentry and VF

Endo

Epi 1

Epi 2

ECG

J wave

J wave

50 mV

50 mV

50 mV

500 msec
Pause
VPB
Accentuation of J-point elevation
VPB
Accentuation of J-point elevation
Prominent J-point elevation
Short coupled VPB
Short coupled VPB
Short coupled VPB
Ventricular fibrillation
<table>
<thead>
<tr>
<th>J Point</th>
<th>ST segment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notched</td>
<td>Ascending</td>
</tr>
<tr>
<td>Slurred</td>
<td>Ascending</td>
</tr>
<tr>
<td>Slurred</td>
<td>Horizontal</td>
</tr>
</tbody>
</table>
What Is the Significance of the Pattern?
Differential Diagnosis

- Juvenile ST pattern
- Pericardial disease
- Hypothermia
- Hypertensive heart disease
- Athlete’s heart
- Myocardial ischemia
- STEMI (i.e., anteroseptal myocardial infarction)
- Fragmented QRS (terminal notching)
- Hypocalcemia
- Hyperkalemia
- Arrhythmogenic right ventricular cardiomyopathy
- Takotsubo cardiomyopathy
- Neurologic causes (intracerebral bleeding, acute brain injury)
- Myocarditis
- Chagas disease
- Cocaine use

NORMAL VARIANT?

STEMI = ST segment elevation myocardial infarction
Antzelevitch Heart Rhythm, 2016
ERP in the General Population

Prevalence of ERP by Sex and Age in the H2K and FHS cohorts

Noseworthy JACC, 2010
## Clinical Correlates of ERP
### Independent Predictors of ERP in Multivariable Regression Model

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Framingham Heart Study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 10 yrs</td>
<td>0.84 (0.71-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>4.10 (2.80-5.80)</td>
<td>1.0 x 10^{-14}</td>
</tr>
<tr>
<td>Cornell voltage, per mV</td>
<td>0.41 (0.28-0.61)</td>
<td>1.4 x 10^{-5}</td>
</tr>
<tr>
<td>Sokolow-Lyon, per mV</td>
<td>3.20 (2.50-4.10)</td>
<td>1.3 x 10^{-20}</td>
</tr>
<tr>
<td>Systolic BP, per 10 mm Hg</td>
<td>0.82 (0.72-0.92)</td>
<td>0.001</td>
</tr>
<tr>
<td>RR interval, per 100 ms</td>
<td>1.20 (1.10-1.30)</td>
<td>4.3 x 10^{-5}</td>
</tr>
<tr>
<td><strong>Health 2000 Survey</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 10 yrs</td>
<td>0.95 (0.80-1.12)</td>
<td>0.51</td>
</tr>
<tr>
<td>Male vs. female</td>
<td>2.74 (1.80-4.20)</td>
<td>5.6 x 10^{-6}</td>
</tr>
<tr>
<td>Cornell voltage, per mV</td>
<td>0.22 (0.15-0.32)</td>
<td>3.9 x 10^{-16}</td>
</tr>
<tr>
<td>Sokolow-Lyon, per mV</td>
<td>4.30 (3.40-5.40)</td>
<td>1.8 x 10^{-34}</td>
</tr>
<tr>
<td>Systolic BP, per 10 mm Hg</td>
<td>0.78 (0.69-0.88)</td>
<td>7.8 x 10^{-5}</td>
</tr>
<tr>
<td>QTc interval, per 20 ms</td>
<td>0.61 (0.51-0.72)</td>
<td>1.0 x 10^{-8}</td>
</tr>
<tr>
<td>QRS interval, per 10 ms</td>
<td>0.77 (0.63-0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Noseworthy JACC, 2010
Prognostic Significance
Case-Control Study: ERS present in 31% of 206 idiopathic VF cases

HR 2.1 (1.2-3.5); P=0.008

Haissiguerre NEJM, 2008
Prognostic Significance
Cohort Study: general population

Cardiac Death

Survival free of death from cardiac causes

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at risk</th>
<th>No J-point elevation</th>
<th>J-point elevation &gt;0.2 mV in inferior leads</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10,234</td>
<td>9,961</td>
<td>8,357</td>
</tr>
<tr>
<td>10</td>
<td>9,961</td>
<td>9,561</td>
<td>8,357</td>
</tr>
<tr>
<td>20</td>
<td>8,357</td>
<td>8,357</td>
<td>6,485</td>
</tr>
<tr>
<td>30</td>
<td>6,485</td>
<td>6,485</td>
<td>1,708</td>
</tr>
<tr>
<td>40</td>
<td>1,708</td>
<td>1,708</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Survival free of death from cardiac causes

P<0.001

Arrhythmic Death

Survival free of death from arrhythmia

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at risk</th>
<th>No J-point elevation</th>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Survival free of death from arrhythmia

P<0.001

Haissiguerre NEJM, 2009

No J-point elevation

J-point elevation >0.2 mV in inferior leads

10,864 middle-aged subjects (mean [±SD] age, 44±8 years)
How Does This Compare to Other ECG Findings?

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Subjects</th>
<th>Relative Risk (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged QTc interval</td>
<td>668</td>
<td>1.20 (1.02-1.42)</td>
<td>0.03</td>
</tr>
<tr>
<td>Left ventricular hypertrophy according to Sokolow-Lyon criteria</td>
<td>3,410</td>
<td>1.16 (1.05-1.27)</td>
<td>0.004</td>
</tr>
<tr>
<td>End-point elevation in inferior leads</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.1 mV</td>
<td>384</td>
<td>1.28 (1.04-1.59)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;0.2 mV</td>
<td><strong>36</strong></td>
<td><strong>2.98 (1.85-4.92)</strong></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

36/ 10,864 people (0.33%)
“Malignant Form?”

Notching (44%) more common than slurring (5%) in SCD survivors

Merchant, Noseworthy AJC 2009
Spectrum of disease

ER syndrome, resuscitated cardiac arrest

Family history for sudden cardiac death

Dynamic augmentation of J waves

Short coupled PVCs

Co-existing disorder (Brugada or SQTS)

Prominent (>0.2 mV) J waves

Widespread/global J-waves/ER pattern

ER waves in the inferior leads

Anterior/lateral ER, ascending ST segments
How Do We Diagnose Early Repolarization Syndrome?
## Diagnostic Criteria for ERS

<table>
<thead>
<tr>
<th>Points</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Clinical History</strong></td>
<td></td>
</tr>
<tr>
<td>A. Unexplained cardiac arrest, documented VF or polymorphic VT</td>
<td>3</td>
</tr>
<tr>
<td>B. Suspected arrhythmic syncope</td>
<td>2</td>
</tr>
<tr>
<td>C. Syncope of unclear mechanism/unclear etiology</td>
<td>1</td>
</tr>
</tbody>
</table>

ER = Early repolarization; ERS = early repolarization syndrome; PVC = premature ventricular contraction; VF = ventricular fibrillation; VT = ventricular tachycardia
Consensus Statement: 2016

Early Repolarization (ER) Expert Consensus Recommendations on Early Repolarization Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ER syndrome is diagnosed in the presence of J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT</td>
</tr>
<tr>
<td>2</td>
<td>ER syndrome can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG</td>
</tr>
<tr>
<td>3</td>
<td>ER <strong>pattern</strong> can be diagnosed in the presence of J-point elevation $\geq 1$ mm in $\geq 2$ contiguous inferior and/or lateral leads of a standard 12-lead ECG</td>
</tr>
</tbody>
</table>
Is it a Genetic Syndrome?
Individual pedigrees: seven genes implicated

- KCNJ8
- ABCC9
- CACNA1C
- CACNB2
- CACNA2D1
- SCN5A
- SCN10A

\[ \text{I}_{\text{K-ATP}} \]

\[ \text{I}_{\text{Na}} \]

\[ \text{L-type calcium} \]

<20% of ERS probands
What about at the population level?
ERP May Be Heritable

<table>
<thead>
<tr>
<th>Sibling Recurrence risks and ORs for ERP in Siblings of ERP + Individuals, Unadjusted and Adjusted for Age and Sex, in the FHS</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP rate in general population</td>
<td>0.06 (0.05-0.07)</td>
<td></td>
</tr>
<tr>
<td>ERP rate in siblings of ERP + subjects</td>
<td>0.11 (0.03-0.19)</td>
<td></td>
</tr>
<tr>
<td>Sibling recurrence risk ((\lambda_s))^*</td>
<td>1.90 (1.31-2.70)</td>
<td></td>
</tr>
<tr>
<td>OR for ERP in sibs (unadjusted)</td>
<td>2.20 (1.00-4.90)</td>
<td>0.047</td>
</tr>
<tr>
<td>OR for ERP in sibs (adjusted)</td>
<td>2.00 (0.88-4.40)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
ERP GWAS Interesting Candidates
Genetic architecture is still unknown…

The most biologically relevant finding was intronic to \textit{KCND3}: rs17029069 (odds ratio 1.46; 95\% confidence interval 1.25–1.69; $P=8.5\times10^{-7}$).

Sinner, Noseworthy Heart Rhythm, 2012
What About Early Repolarization Pattern in Athletes?
# ERP Prevalence in Athletes

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Athlete characteristics</th>
<th>Prevalence of ERP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosso et al, (16), 2008</td>
<td>Non-competitive amateur endurance runners</td>
<td>22</td>
</tr>
<tr>
<td>Tikkanen et al, (13), 2011</td>
<td>Finnish and American amateur and collegiate athletes combined</td>
<td>31.5</td>
</tr>
<tr>
<td>Noseworthy et al, (7), 2011</td>
<td>Collegiate rowers and football players</td>
<td>25.1</td>
</tr>
<tr>
<td>Junttila et al, (5), 2011</td>
<td>Collegiate athletes</td>
<td>30</td>
</tr>
<tr>
<td>Swaitowiec et al, (26), 2009</td>
<td>Olympic athletes (variety of sports)</td>
<td>23.3</td>
</tr>
<tr>
<td>Zoneraich et al, (27), 1977</td>
<td>Marathon runners</td>
<td>58</td>
</tr>
<tr>
<td>Bianco et al, (28), 2001</td>
<td>Top-ranking distance runners, soccer players, cyclists</td>
<td>89</td>
</tr>
</tbody>
</table>

ERP = early repolarization pattern
Typical ‘malignant ERP’
**horizontal** ST segment

Typical ‘athlete ERP’
**ascending** ST segment
ERP in Athletes (n=879)

- No Non-Anterior ERP: 74.9%
- Isolated Lateral ERP: 21.3%
- Lateral and Inferior ERP: 3.8%
- Isolated Inferior ERP: 2.5%

Noseworthy Circ AE, 2011
### ERP in Athletes: Dynamic finding

#### All Sports (n=148)

<table>
<thead>
<tr>
<th></th>
<th>Preseason</th>
<th>Postseason</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sports (n=148)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERP 55 (37.2)</td>
<td>78 (52.7)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Inferior ERP subtype</td>
<td>6 (4.1)</td>
<td>12 (8.1)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

#### Football (n=78)

<table>
<thead>
<tr>
<th></th>
<th>Preseason</th>
<th>Postseason</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP 28 (35.9)</td>
<td>34 (44.9)</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>Inferior ERP subtype</td>
<td>3 (3.8)</td>
<td>6 (7.7)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

#### Crew (n=68)

<table>
<thead>
<tr>
<th></th>
<th>Preseason</th>
<th>Postseason</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERP 27 (39.7)</td>
<td>43 (63.2)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Inferior ERP subtype</td>
<td>3 (4.4)</td>
<td>6 (8.8)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Data are presented as n (%). Abbreviation as in Table 2. *compares preseason to postseason*
How Does ERS Differ from Brugada Syndrome?
Similarities between BS and ERS

- Male predominance
- Age of first event 30-50
- KCNJ8, CACNA1C, CACNB2, CACNA2D, SCN5A, ABCC9, SCN10A
- VF often occurs during sleep or at a low level of physical activity
- VT/VF trigger is phase 2 reentry
- Ameliorative response to quinidine, isoproterenol, cilostazol, pacing
- Vagally mediated accentuation of ECG pattern
- Accentuated by fever or hypothermia
# Differences between BS and ERS

<table>
<thead>
<tr>
<th></th>
<th>BrS</th>
<th>ERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Region</strong></td>
<td>RVOT</td>
<td>Inferior LV</td>
</tr>
<tr>
<td><strong>Leads</strong></td>
<td>V1-V3</td>
<td>Inferolateral</td>
</tr>
<tr>
<td><strong>Geography</strong></td>
<td>Common in Asia</td>
<td>ERP common in African descent, ERS not specific to region</td>
</tr>
<tr>
<td><strong>Late potential on SAECG</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>AF prevalence</strong></td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td><strong>Na blocker challenge</strong></td>
<td>Increased J-wave (I&lt;sub&gt;TO&lt;/sub&gt; effect)</td>
<td>Reduced J-wave manifestation (hidden in QRS)</td>
</tr>
</tbody>
</table>

Antzelevitch Heart Rhythm, 2006
How Do We Treat?
Expert Consensus Recommendations

**Class I**
- ICD in patients with ER syndrome + cardiac arrest

**Class IIa**
- Isoproterenol for electrical storms in ERS
- Quinidine + ICD for secondary prevention of VF

**Class IIb**
- Consider ICD in symptomatic family members of ERS patients with a history of syncope + ERP
- Consider ICD in asymptomatic pts with high-risk ERP + strong family history unexplained sudden death

**Class III**
- ICD implantation is not recommended asymptomatic patients with an isolated ER ECG pattern

Patton Heart Rhythm, 2016
Take Home Points

- ER pattern is common and may be benign in most people
- ERS shares some pathophysiology and clinical characteristics with Brugada syndrome
- Stepwise approach to diagnosis and treatment that considers symptoms, ECG, and family history