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der Universität Heidelberg

Universitätsklinikum Mannheim

Early repolarization syndrome: mith or reality?

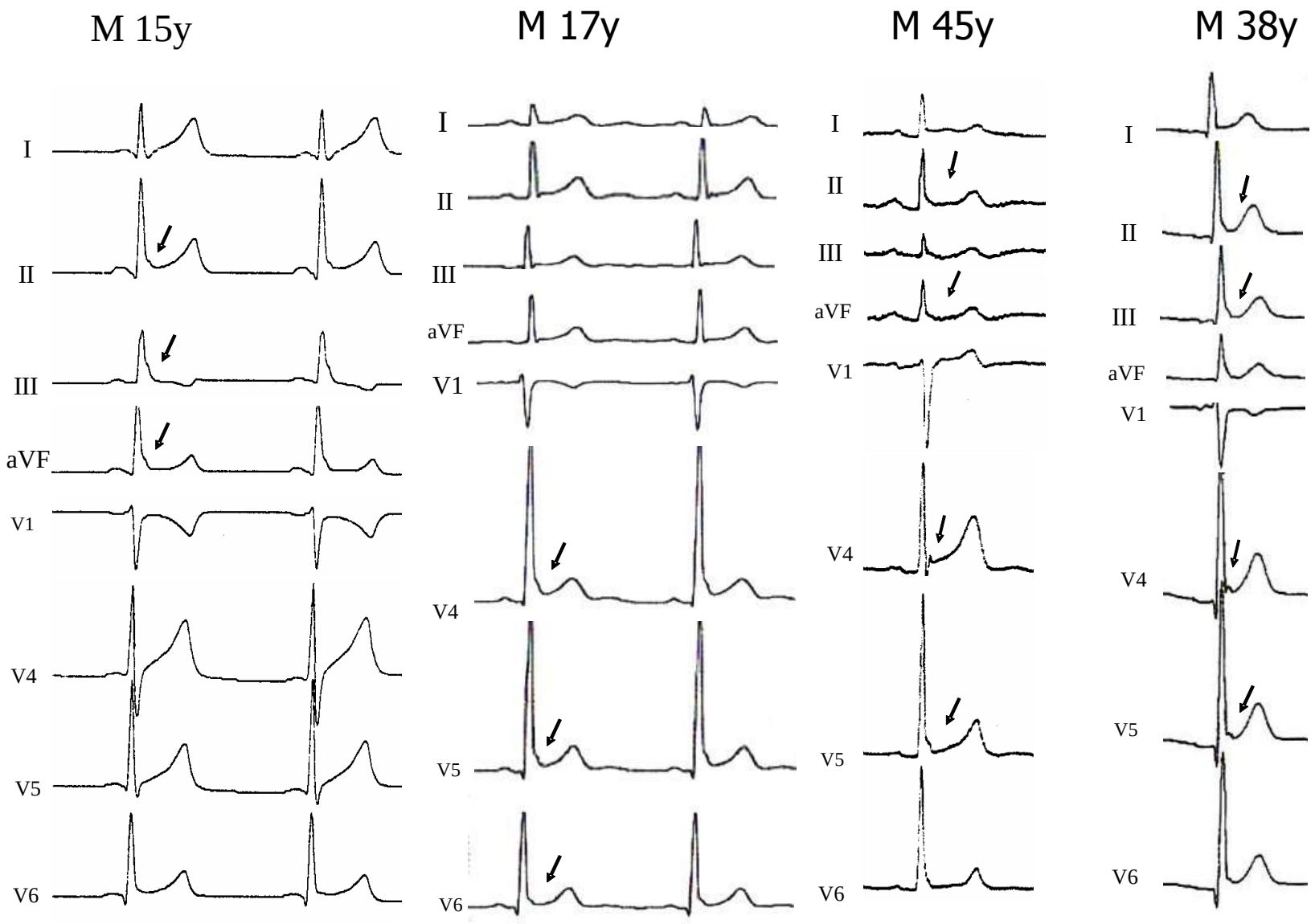
Prof. Dr. Martin Borggrefe

Mannheim

Advances in Cardiovascular Arrhythmias and Great Innovations in Cardiology

Turin, October 20-22, 2011

Early Repolarization Syndrome

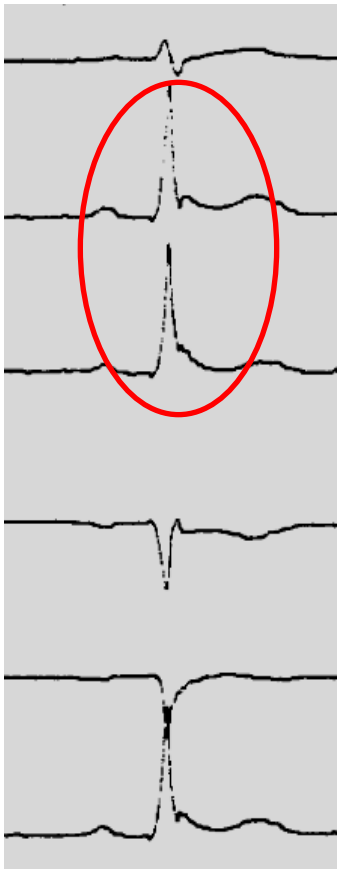


Early Repolarization Syndrome

Screening of all idiopathic VF from ICD databases

Early repolarization on Baseline ECGs defined as:

- **Slurring (late delta) or notch at the end of QRS, with J point>0.1mV in ≥ 2 leads**
- **Left precordial and/or inferior and/or lateral ECG leads (excluding V1-V3 for Brugada/ARVD)**



Haïssaguerre et al, N Engl J Med 2008;358:2016-23.

Early Repolarization Syndrome

Prevalence ~ 5% of the population

Haïssaguerre et al, N Engl J Med 2008

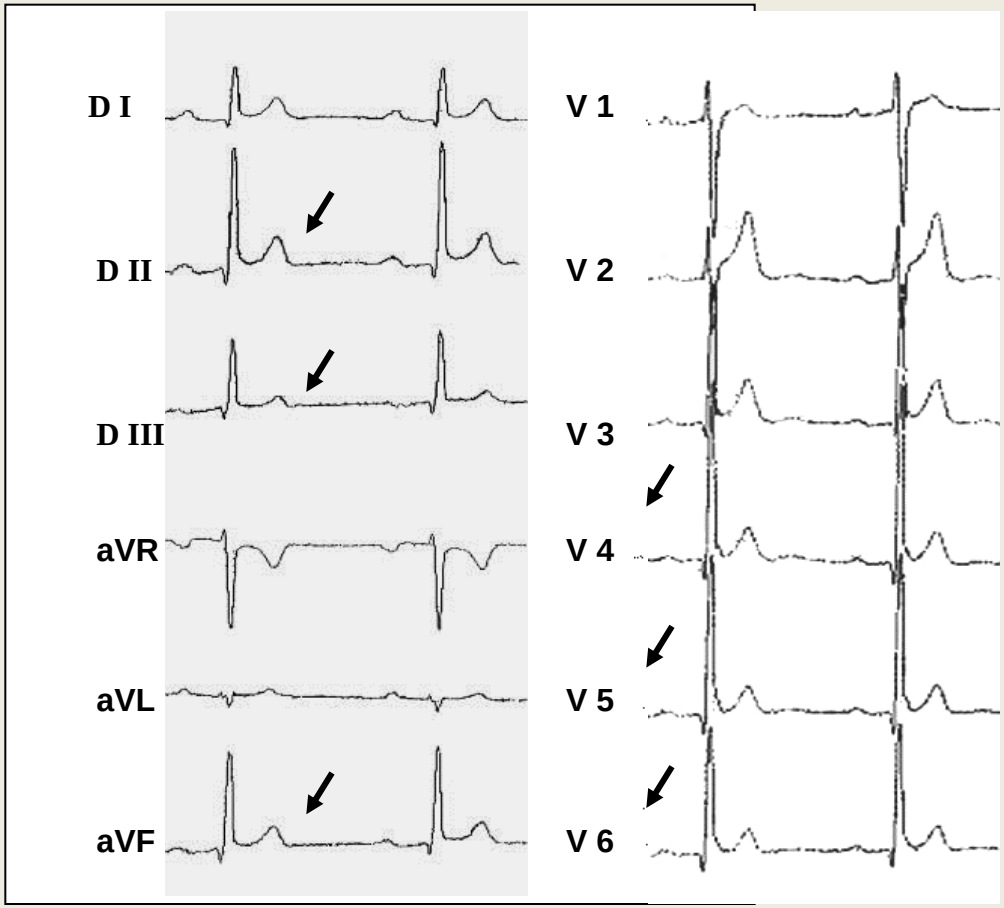
First description: 1936

Shipley and Hallaran

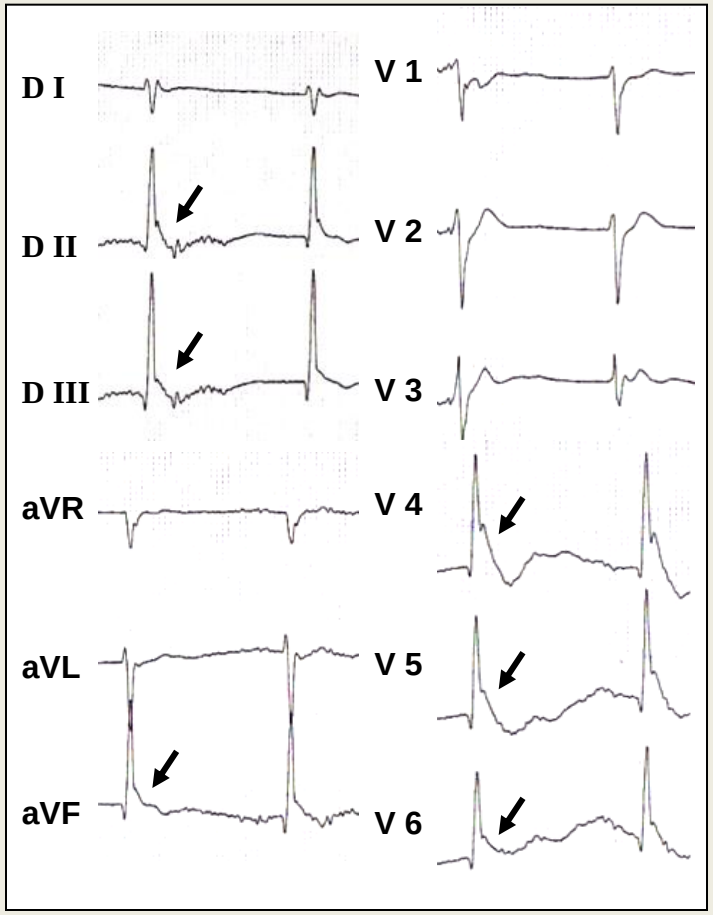
- **normal variant**
- **“normal RS-T segment elevation variant”**
- **“juvenile ST pattern”**

Early Repolarization Syndrome

M 22yrs



April 2004



March 2006

Early Repolarization Syndrome

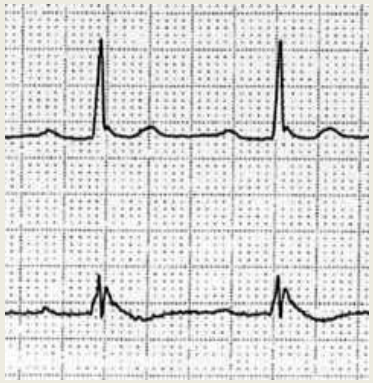
Ventricular Fibrillation with 'Early Repolarization'

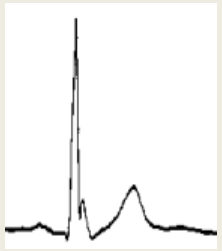
- **Incidence of early repolarization**

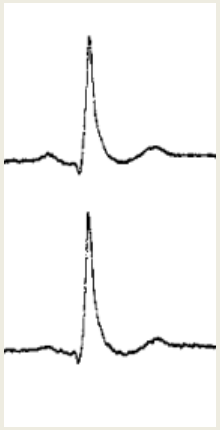
  31% ie 66 pts with IVF vs 4% in controls (p=0.002)

- **Amplitude of J point**

  2.15±1.2mm in IVF vs 1.05±0.2mm in controls







Haïssaguerre et al, N Engl J Med 2008;358:2016-23.

Early Repolarization Syndrome

Sudden Cardiac Arrest Associated with Early Repolarization

Michel Haïssaguerre, M.D., Nicolas Derval, M.D., Frederic Sacher, M.D., Laurence Jesel, M.D., Isabel Deisenhofer, M.D., Luc de Roy, M.D., Jean-Luc Pasquié, M.D., Ph.D., Akihiko Nogami, M.D., Dominique Babuty, M.D., Sinikka Yli-Mayry, M.D., Christian De Chillou, M.D., Patrice Scanu, M.D., Philippe Mabo, M.D., Seiichiro Matsuo, M.D., Vincent Probst, M.D., Ph.D., Solena Le Scouarnec, Ph.D., Pascal Defaye, M.D., Juerg Schlaepfer, M.D., Thomas Rostock, M.D., Dominique Lacroix, M.D., Dominique Lamaison, M.D., Thomas Lavergne, M.D., Yoshifusa Aizawa, M.D., Anders Englund, M.D., Frederic Anselme, M.D., Mark O'Neill, M.D., Meleze Hocini, M.D., Kang Teng Lim, M.B., B.S., Sebastien Knecht, M.D., George D. Veenhuyzen, M.D., Pierre Bordachar, M.D., Michel Chauvin, M.D., Pierre Jais, M.D., Gaelle Coureau, Ph.D., Genevieve Chene, Ph.D., George J. Klein, M.D., and Jacques Clémenty, M.D.

N Engl J Med 2008;358:2016-23.

Early Repolarization Syndrome

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

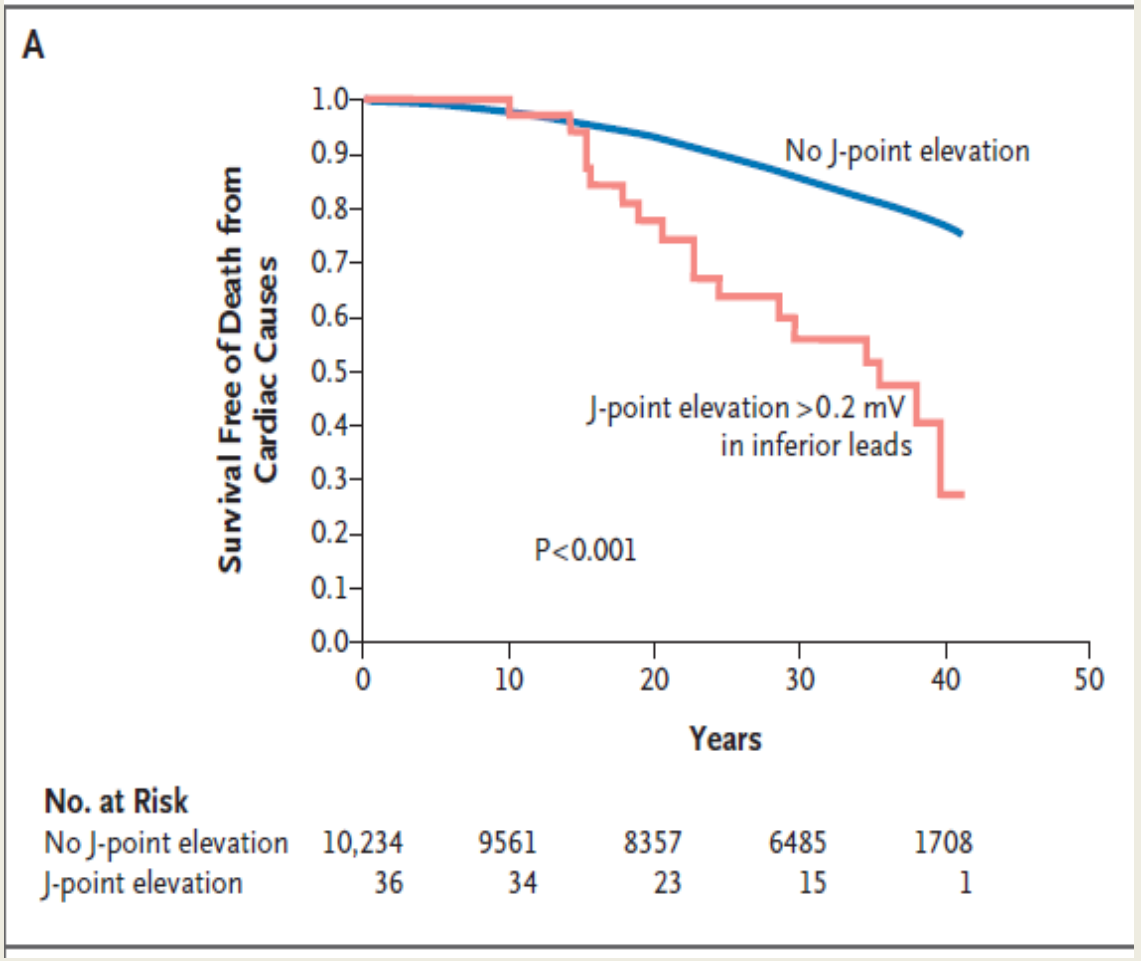
Long-Term Outcome Associated with Early Repolarization on Electrocardiography

Jani T. Tikkanen, B.S., Olli Anttonen, M.D., M. Juhani Junttila, M.D., Aapo L. Aro, M.D., Tuomas Kerola, M.D., Harri A. Rissanen, M.Sc., Antti Reunanen, M.D., and Heikki V. Huikuri, M.D.

N Engl J Med 2009; 361:2529-37

Early Repolarization Syndrome

Death from Cardiac Causes and from Arrhythmia in Subjects with J-Point Elevation



Tikkanen et al, N Engl J Med 2009; 361:2529-37

Early Repolarization Syndrome

OPEN ACCESS Freely available online

PLoS MEDICINE

Association of Early Repolarization Pattern on ECG with Risk of Cardiac and All-Cause Mortality: A Population-Based Prospective Cohort Study (MONICA/KORA)

Moritz F. Sinner[1☯], Wibke Reinhard[2☯], Martina Müller[1,3☯], Britt-Maria Beckmann[1], Eimo Martens[1], Siegfried Perz[4], Arne Pfeufer[5,6], Janina Winogradow[2], Klaus Stark[2], Christa Meisinger[3], H.-Erich Wichmann[3,7,8], Annette Peters[3], Günter A. J. Riegger[2], Gerhard Steinbeck[1], Christian Hengstenberg[2☯], Stefan Kääb[1☯*]

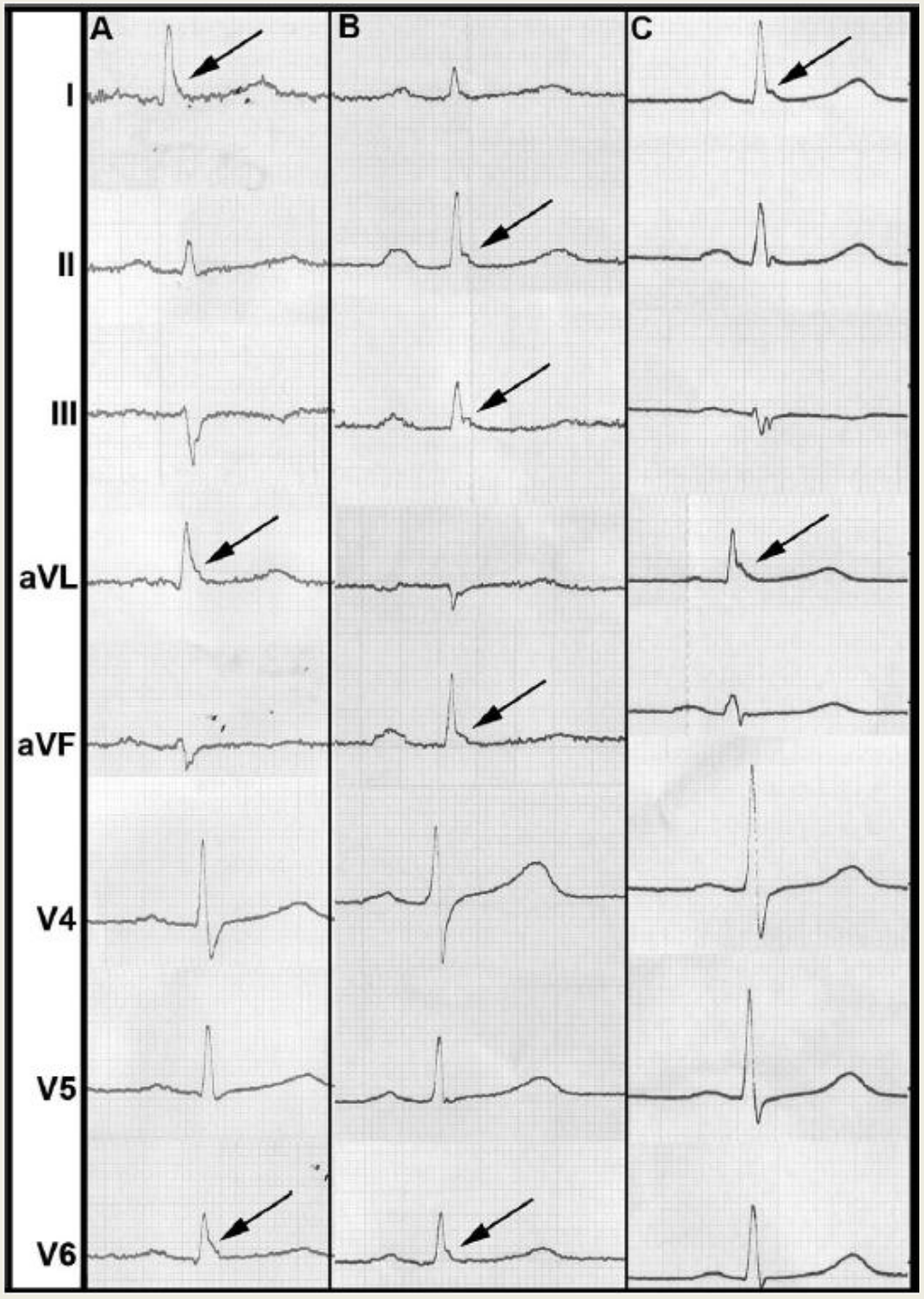
1 University Hospital Munich, Campus Grosshadern, Medical Department I, Ludwig-Maximilians University Munich, Munich, Germany, **2** Klinik und Poliklinik für Innere Medizin II, Universitätsklinikum Regensburg, Regensburg, Germany, **3** Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany, **4** Institute of Biological and Medical Imaging, Helmholtz Zentrum München, Neuherberg, Germany, **5** Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany, **6** Institute of Human Genetics, Technical University Munich, Munich, Germany, **7** Institute of Medical Informatics, Biometry and Epidemiology, Chair of Epidemiology, Ludwig-Maximilians-Universität, Munich, Germany, **8** Klinikum Grosshadern, Munich, Germany

Sinner et al, PLOS Medicine 2010; 7:e1000314

Early Repolarization Syndrome

ERP Prevalence n (%)	n Study Population (%)	n Death from Cardiac Causes (%)	n Death from Any Cause (%)
Total n	6,213	511	1,496
Overall	812 (13.1)	89 (17.4)	244 (16.3)
Antero-lateral leads	275 (4.4)	25 (4.9)	78 (5.2)
Inferior leads	474 (7.6)	58 (11.4)	149 (10.0)
Combined antero-lateral and inferior leads	63 (1.0)	6 (1.2)	17 (1.1)
Slurring morphology	590 (9.5)	58 (11.4)	161 (10.8)
Notching morphology	219 (3.5)	31 (6.1)	83 (5.6)
Men	439 (7.1)	60 (11.7)	160 (10.7)
Women	372 (6.0)	29 (5.7)	84 (5.6)
35–54 y	422 (11.9)	20 (19.0)	57 (15.4)
55–64 y	277 (14.3)	51 (20.8)	120 (18.0)
65–74 y	114 (15.6)	18 (11.2)	67 (14.6)

Sinner et al, PLOS Medicine 2010; 7:e1000314



Representative examples of ERP from our study population

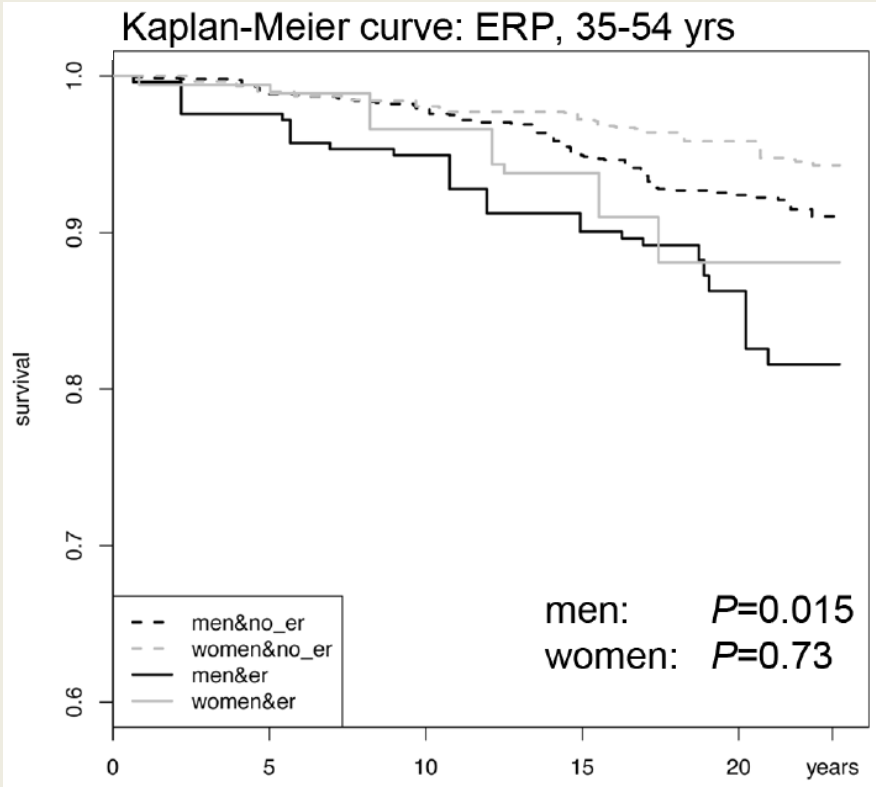
Sinner et al, PLOS Medicine 2010; 7:e1000314

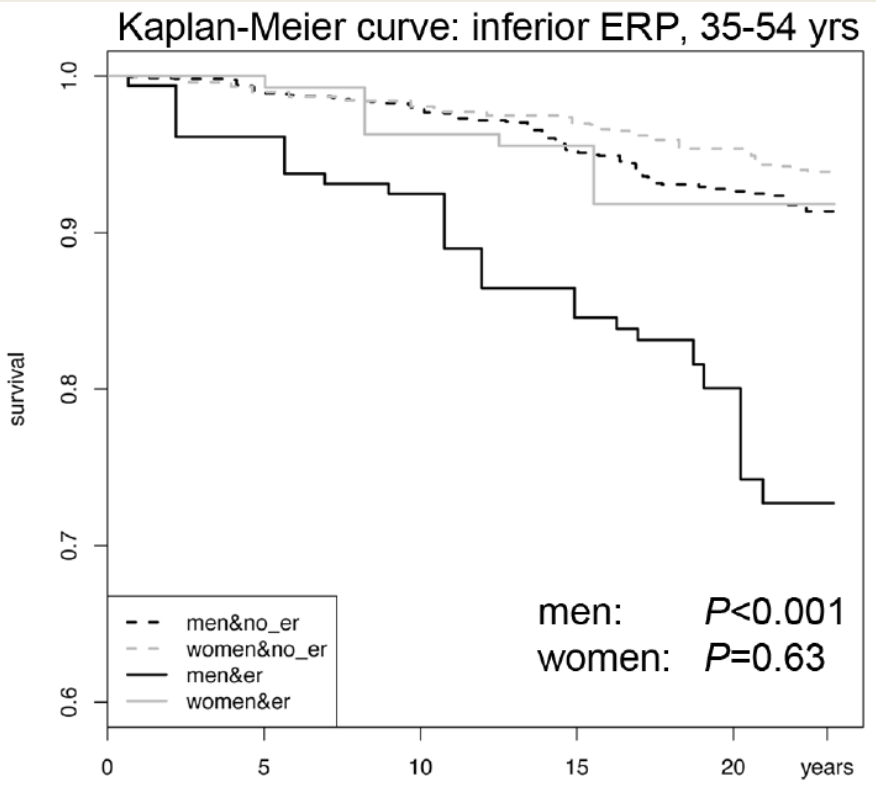
Association of ERP with cardiac mortality

Sinner et al, PLOS Medicine 2010; 7:e1000314

Study population	Substrata	ERP in any localization		ERP in inferior localization	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
All					
Main effect	ERP	3.44 (1.52–7.80)	0.003	3.71 (1.44–9.53)	0.007
	ERP x age	0.95 (0.92–0.99)	0.005	0.96 (0.92–1.00)	0.049
Age-strata	35-54 y	1.96 (1.05-3.68)	0.035	3.15 (1.58-6.28)	0.001
	55-64 y	1.12 (0.70-1.78)	0.63	1.33 (0.78-2.27)	0.29
	65-74 y	0.59 (0.25-1.44)	0.25	1.18 (0.48-2.92)	0.72
Women					
Main effect	ERP	5.97 (0.85-42.04)	0.073	1.58 (0.14-17.42)	0.71
	ERP x age	0.93 (0.86-1.00)	0.56	0.99 (0.90-1.09)	0.91
Age-strata	35-54 y	1.25 (0.34-4.58)	0.73	1.48 (0.30-7.29)	0.63
	55-64 y	0.99 (0.39-2.50)	0.99	1.80 (0.57-5.63)	0.32
	65-74 y	0.63 (0.15-2.72)	0.54	0.77 (0.10-6.14)	0.81
Men					
Main effect	ERP	2.69 (1.10-6.60)	0.030	4.32 (1.59-11.68)	0.004
	ERP x age	0.96 (0.93-1.00)	0.058	0.96 (0.92-1.00)	0.039
Age-strata	35-54 y	2.65 (1.21-5.83)	0.015	4.27 (1.90-9.61)	<0.001
	55-64 y	1.16 (0.67-2.02)	0.60	1.28 (0.67-2.42)	0.45
	65-74 y	0.67 (0.21-2.08)	0.49	0.77 (0.10-6.14)	0.81

Early Repolarization Syndrome





Individuals at Risk

					men					
1,500	1,467	1,427	1,364	545	ERP-negative	1,418	1,388	1,345	1,284	631
259	250	230	211	88	ERP-positive	162	153	138	119	52
					women					
1,677	1,667	1,640	1,614	828	ERP-negative	1,759	1,737	1,712	1,679	856
179	178	173	168	158	ERP-positive	135	135	130	129	129

Sinner et al, PLOS Medicine 2010; 7:e1000314

Early Repolarization Syndrome

Epidemiology

Prevalence: 1-9% of the general population

15-70% of IVF cases

⇒ **4-10-fold SD risk ↑**

Early Repolarization Syndrome

Epidemiology aspects

Gender: young (black) males

⇒ large I_{To} density

- Age <30
- Physical activity
- Vagal tone
- Slow heart rate
- (spinal cord injury)

Early Repolarization Syndrome

Electrocardiographic features (I)

- Heart rate: sinus bradycardia
- I° AV block: 5-39%
- Vertical electrical axis
- QRS duration ~90±10 ms
- Tall R waves

Early Repolarization Syndrome

Electrocardiographic features (II)

- St segment elevation
  - elevation greater in precordial leads (prominent V_4)
  - distinct J wave in leads V_4–V_6
- Localization of ST elevation
  - inferior
  - lateral

  } ⟹ "risky elevation"
  - mid precordial ⟹ "benign elevation"

Early Repolarization Syndrome

J-Point Elevation in Survivors of Primary Ventricular Fibrillation and Matched Control Subjects

Incidence and Clinical Significance

Raphael Rosso, MD,* Evgeni Kogan, MD,* Bernard Belhassen, MD,* Uri Rozovski, MD,* Melvin M. Scheinman, MD,§ David Zeltser, MD,* Amir Halkin, MD,* Arie Steinvil, MD,* Karin Heller, MD,* Michael Glikson, MD,† Amos Katz, MD,‡ Sami Viskin, MD*

Tel Aviv and Beer-Sheva, Israel; and San Francisco, California

J Am Coll Cardiol 2008; 52: 1231-1238

Early Repolarization Syndrome

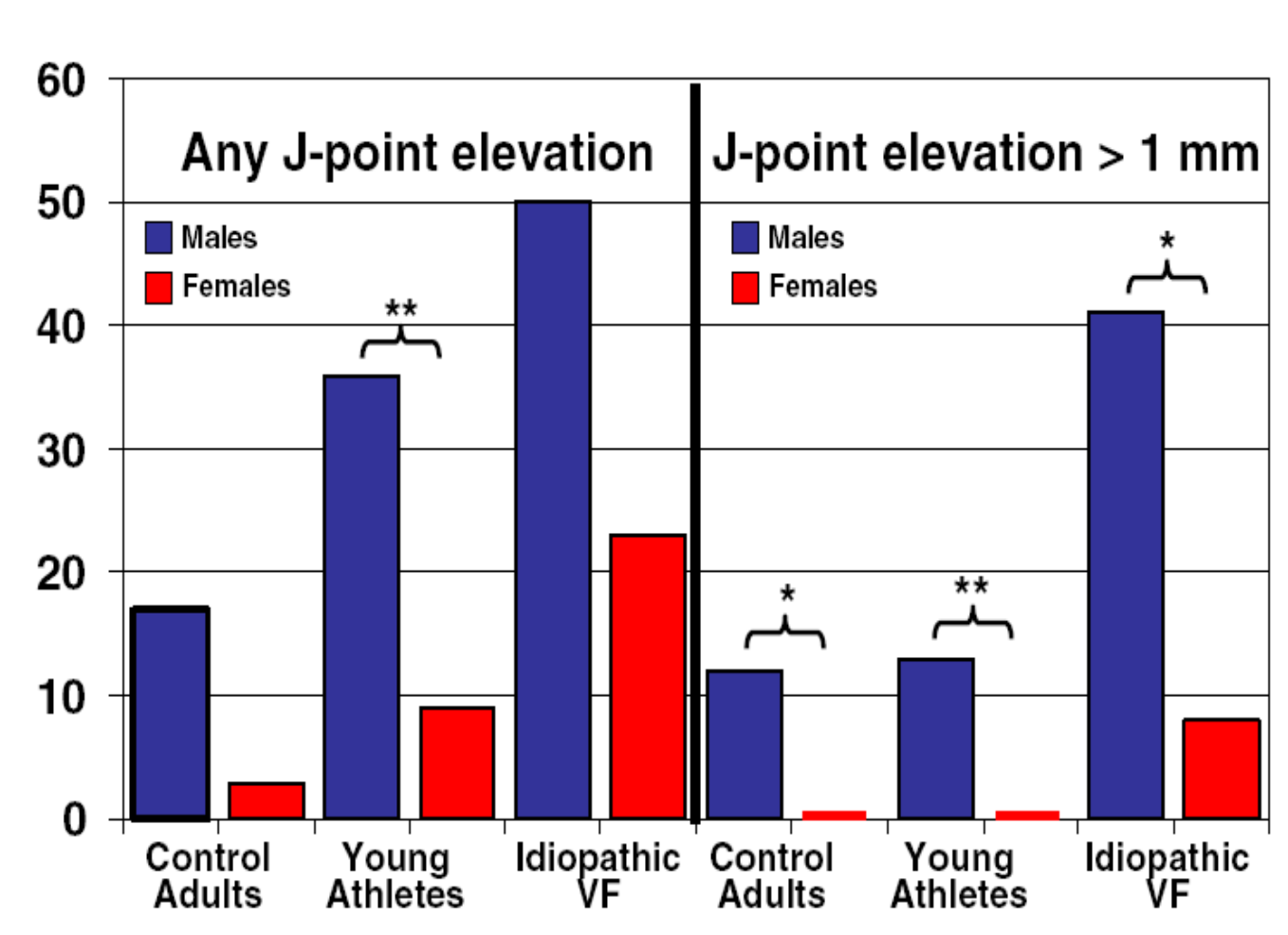
Incidence of J-Point Elevation Among 45 Patients With Idiopathic VF and 124 Healthy Control Subjects Matched for Age and Gender

	Idiopathic VF		Control Subjects				
	n	%	n	%	p Value*	OR	95% CI
Any lead							
Any J-point elevation	19	42.2%	16	13.0%	0.001	3.2	1.7–6.3
J-point >1.0 mm	14	31.1%	11	8.9%	0.002	3.4	1.5–7.5
Inferior leads							
Any J-point elevation	12	26.7%	10	8.1%	0.006	3.2	1.4–7.5
J-point >1.0 mm	8	17.8%	8	6.5%	0.052	2.6	1.0–7.1
Leads I and aVL							
Any J-point elevation	6	13.3%	1	0.8%	0.009	16.9	2.0–140.3
J-point >1.0 mm	5	11.1%	0	0			
Leads V_4 to V_6							
Any J-point elevation	3	6.7%	9	7.3%	0.860	0.9	0.2–3.3
J-point >1.0 mm	3	6.7%	6	4.9%	0.686	1.3	0.3–5.3

Rosso et al, J Am Coll Cardiol 2008; 52: 1231-1238

Early Repolarization Syndrome

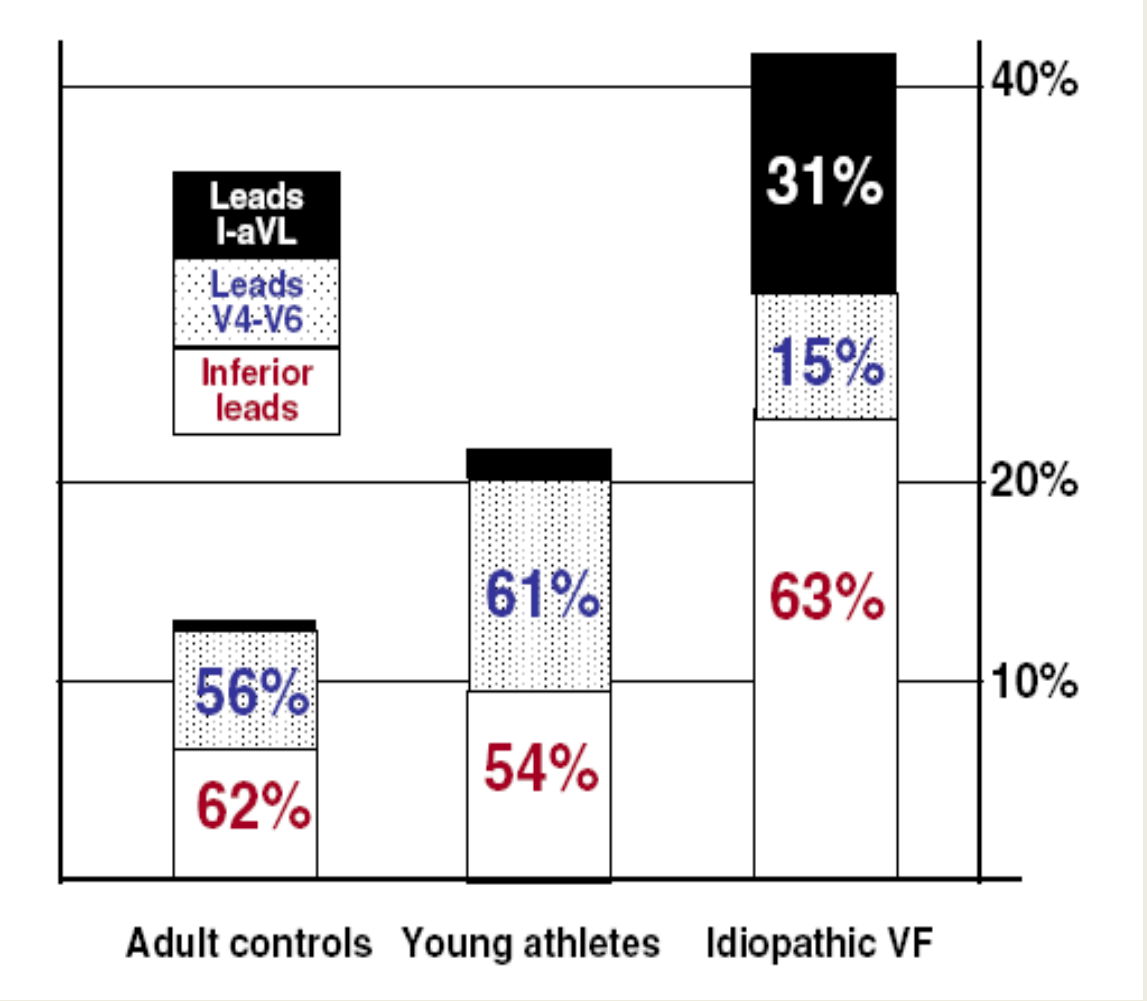
Incidence of Influence of Gender on the Incidence of J-Point Elevation in the Different Patient Groups



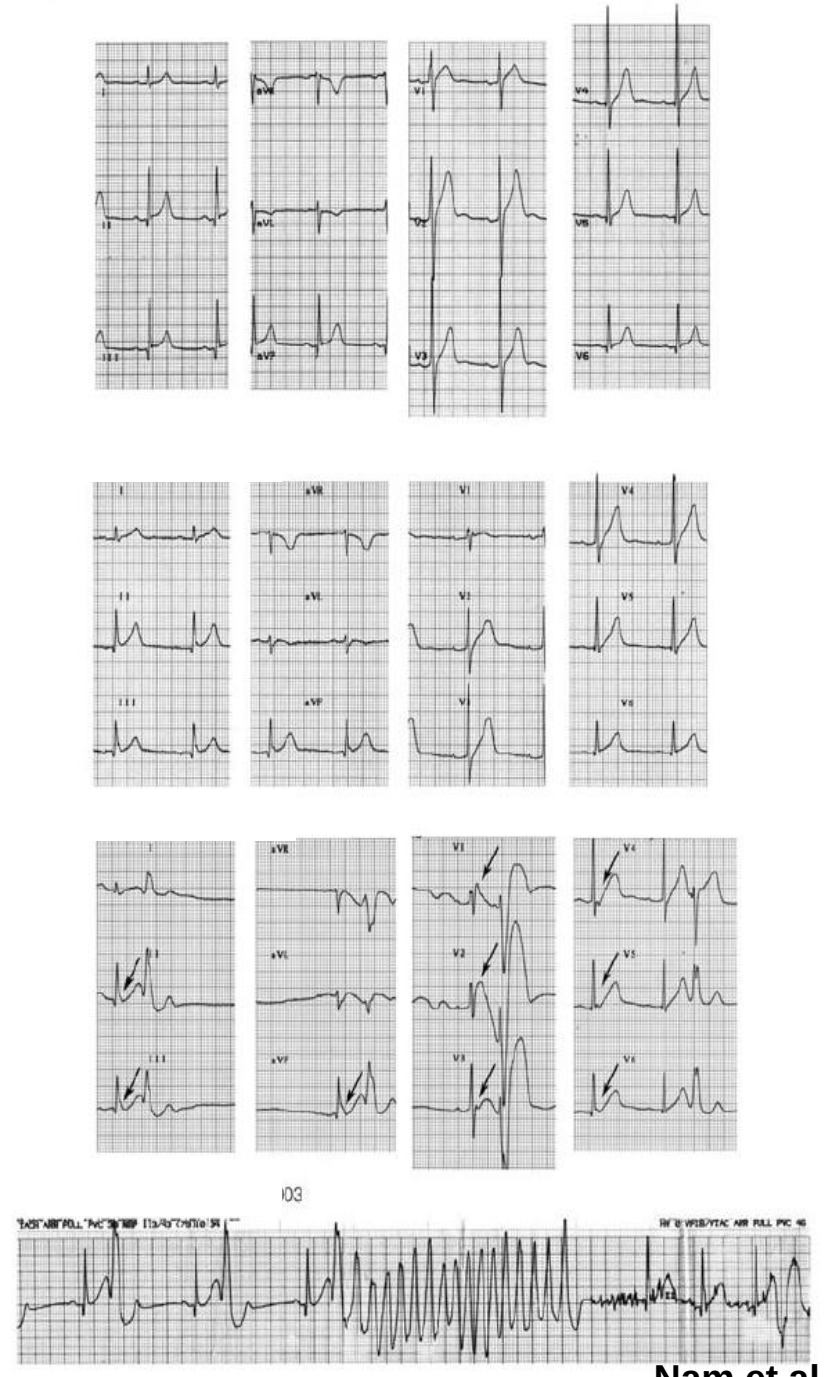
Rosso et al, J Am Coll Cardiol 2008; 52: 1231-1238

Early Repolarization Syndrome

Distribution of J Waves Among Patients With Idiopathic VF, Matched Control Subjects, and Healthy Athletes



Rosso et al, J Am Coll Cardiol 2008; 52: 1231-1238

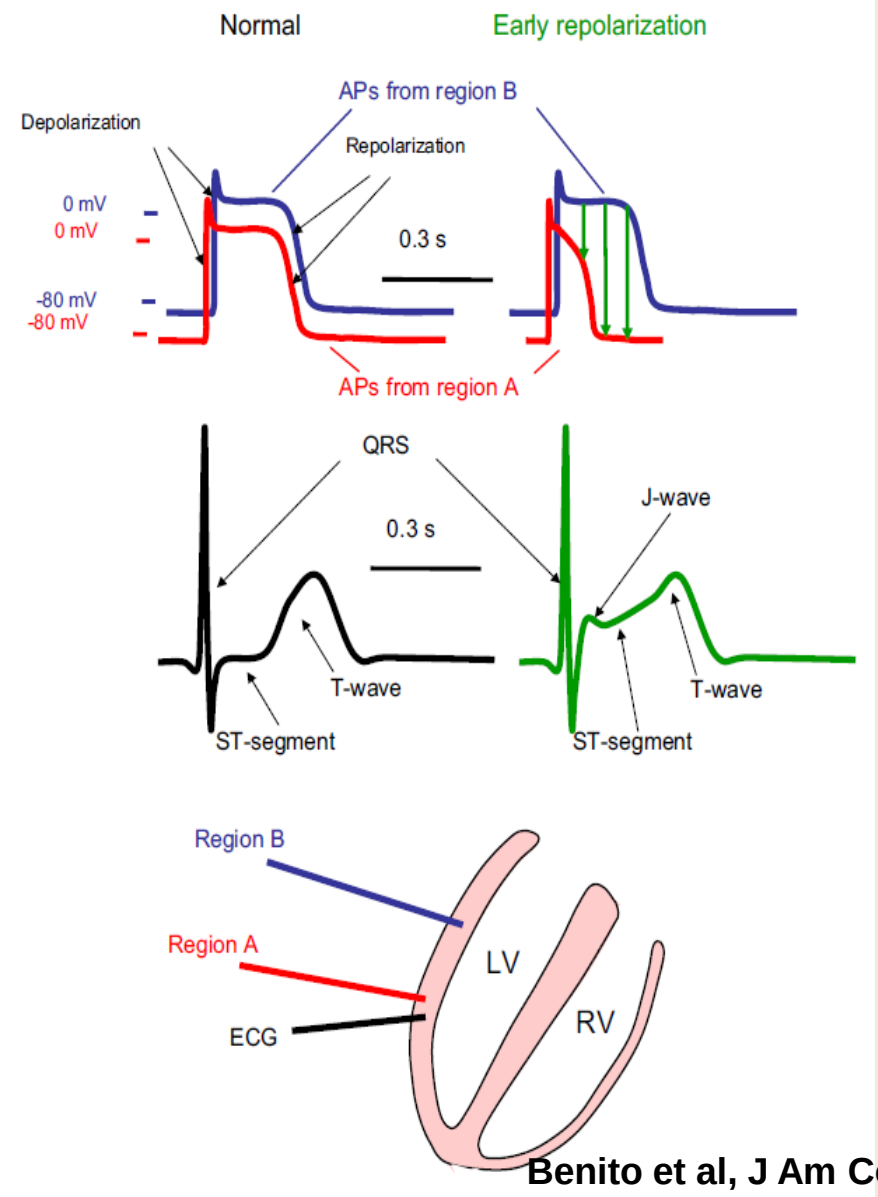


J-ST-T waves before and after electrical storm

Nam et al, Eur Heart J 2010; 31:330-339

Early Repolarization Syndrome

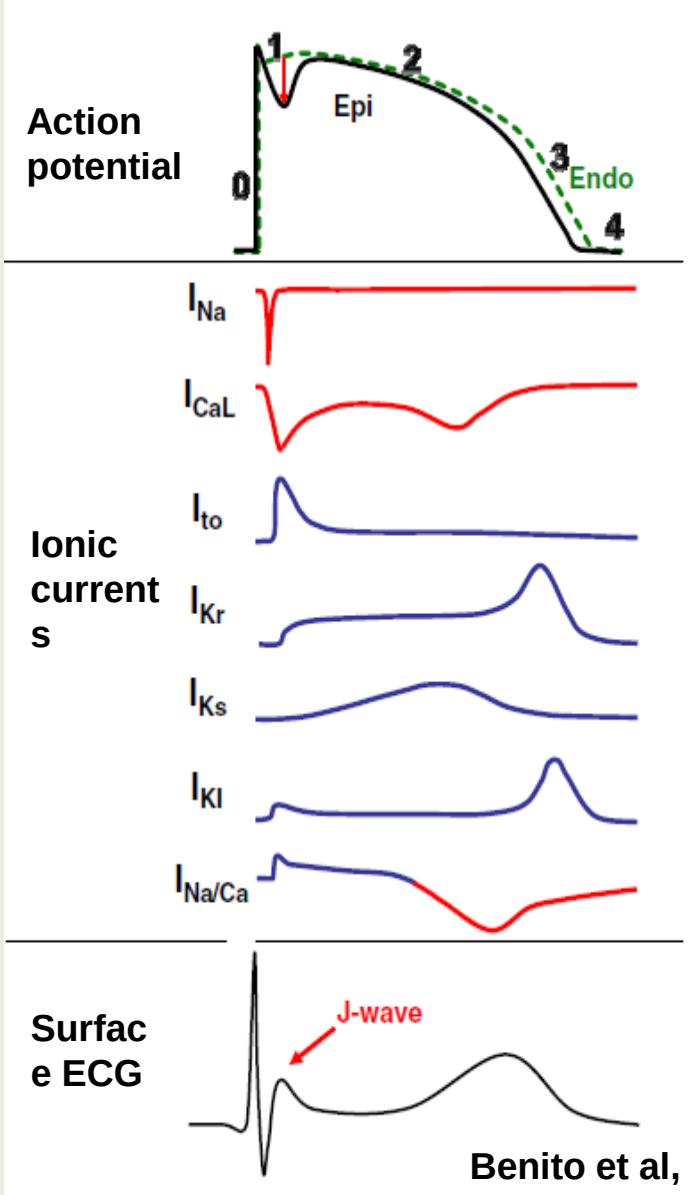
Potential Mechanism of Early Repolarization



Benito et al, J Am Coll Cardiol 2010;56:1177–86

Early Repolarization Syndrome

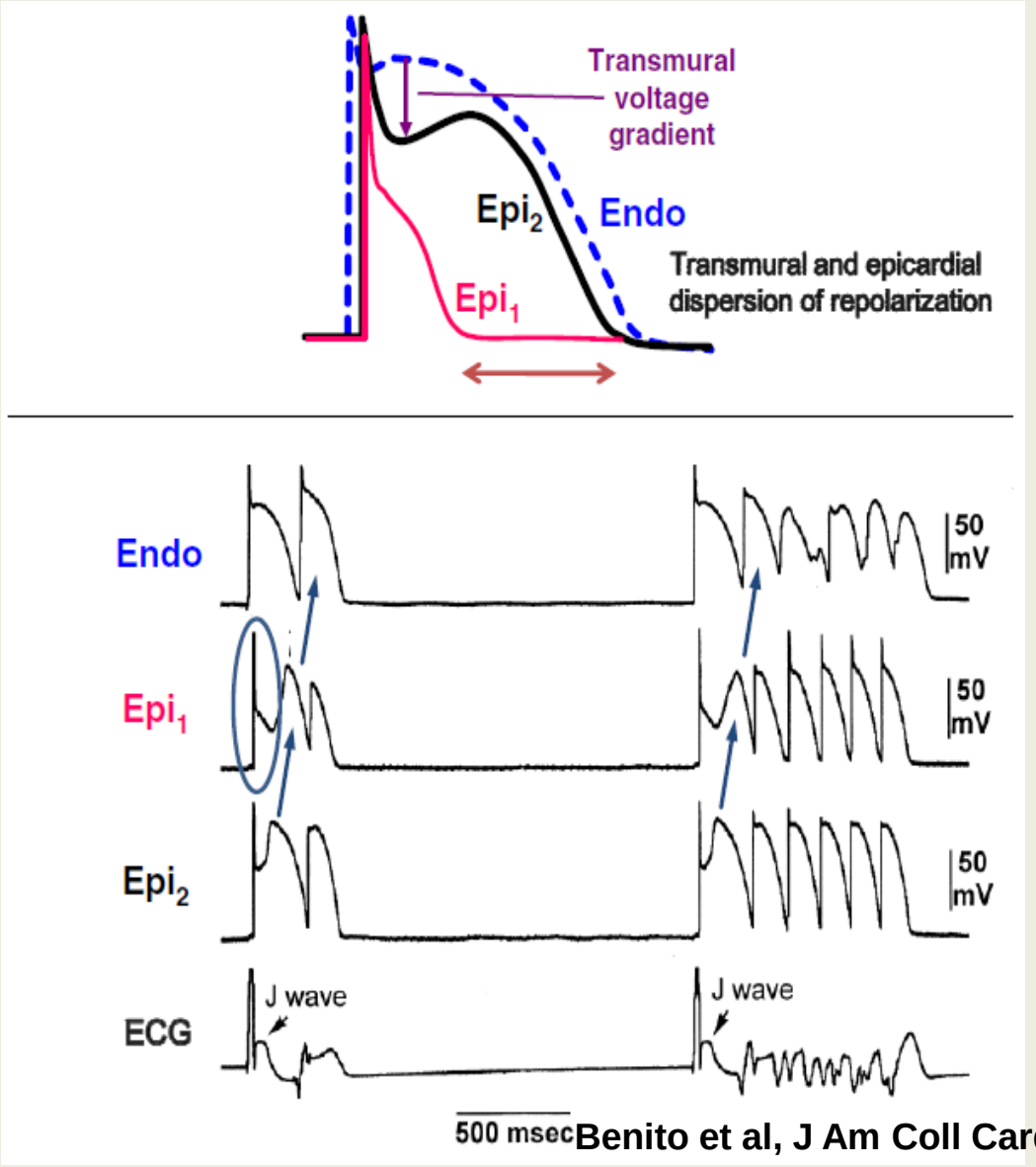
APs in Epicardium and Endocardium With the Main Underlying Ionic Currents



Benito et al, J Am Coll Cardiol 2010;56:1177–86

Early Repolarization Syndrome

Potential Mechanism for Early Repolarization Arrhythmogenesis



Benito et al, J Am Coll Cardiol 2010;56:1177–86

Early Repolarization Syndrome

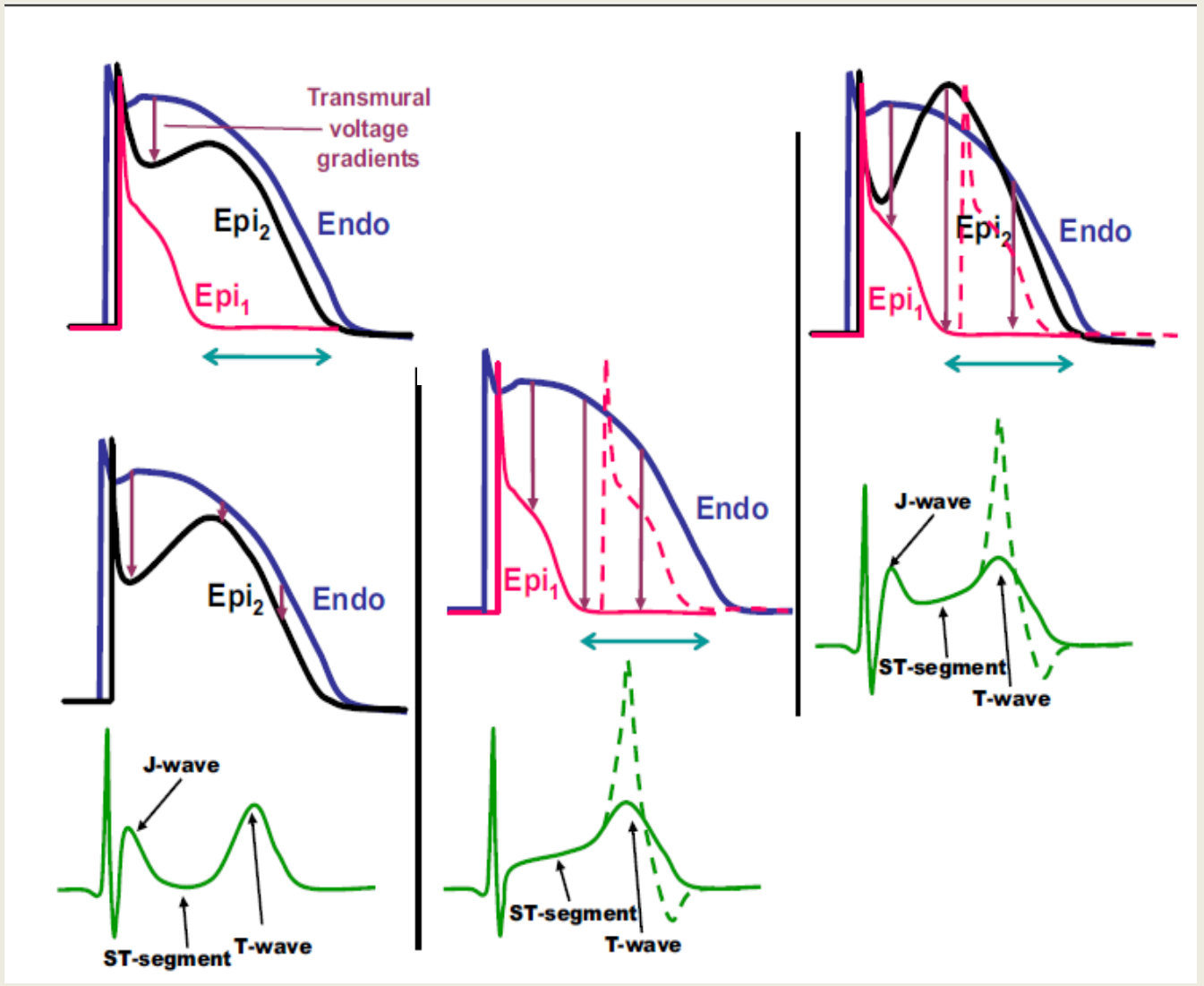
Inherited SCD syndromes involving ER

	ER Syndrome	Brugada Syndrome	Short-QT Syndrome
Gene mutations/ion current	*KCNJ8*/I_{KATP} (35) *CACNA1C*, *CACNB2B*/I_{CaL} (43)	*SCN5A*, *SCN1B*, *SCN3B*/I_{Na} (51,54,55) *GPD1-L*/I_{Na} (52) *CACNA1C*, *CACNB2B*/I_{CaL} (53) *KCNE3*/I_{to} (55)	*KCNH2*/I_{Kr} (59) *KCNQ1*/I_{Ks} (60) *KCNJ2*/I_{K1} (61) *CACNA1C*, *CACNB2B*/I_{CaL} (53)
ECG	J-wave; ST-segment elevation	J-wave; ST-segment elevation	Short-QT; peaked T waves
Drug therapy	Quinidine (16) Isoproterenol (15)	Quinidine (48) Isoproterenol (49)	Quinidine (50)

Benito et al, J Am Coll Cardiol 2010;56:1177–86

Early Repolarization Syndrome

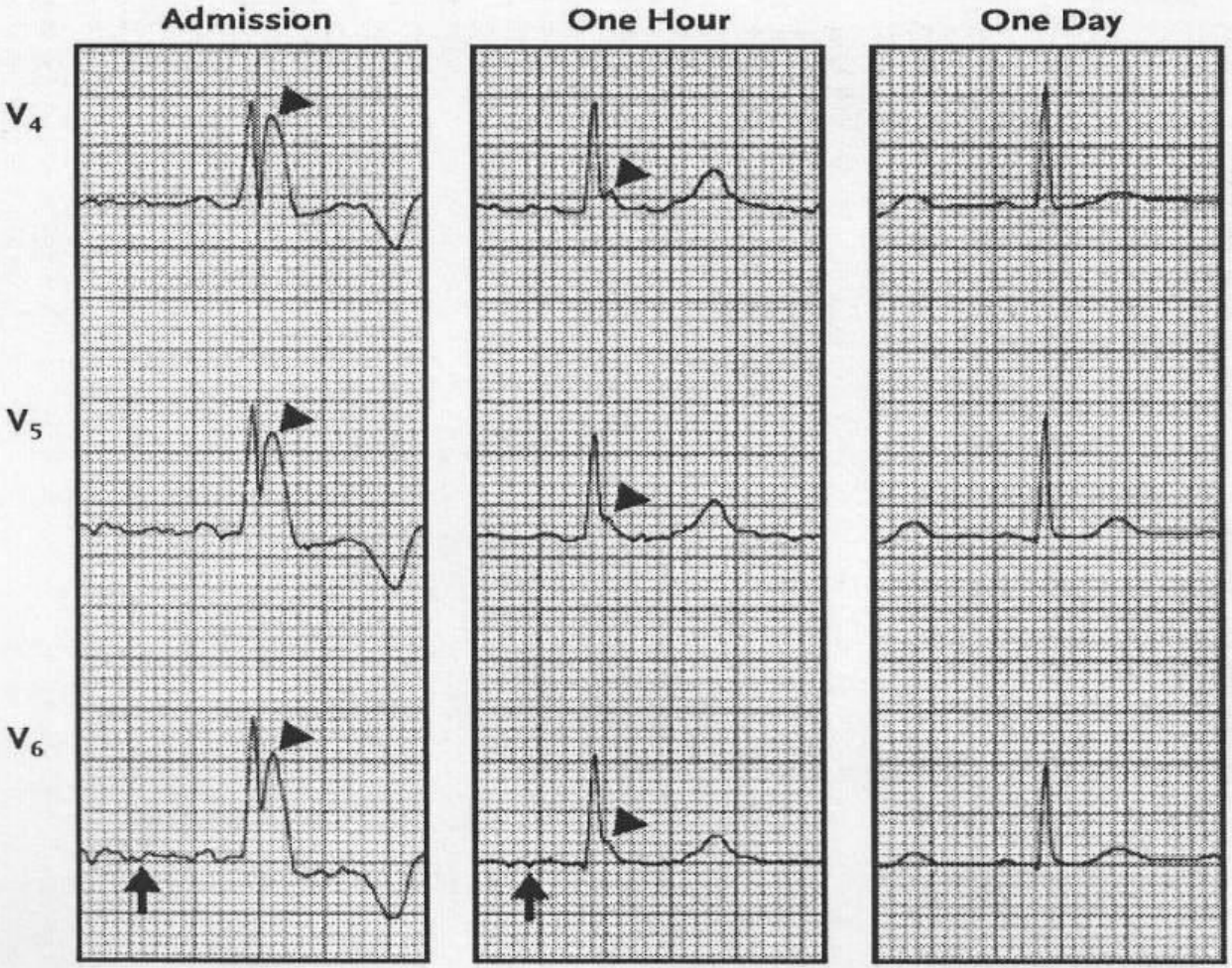
ER Effects on Action Potentials and ECG, Illustrating the Potential Role of J-Wave as a Marker of ER Risk



Benito et al, J Am Coll Cardiol 2010;56:1177–86

M 47years **Krantz NEJM 2005;352:2**

Giant Osborn Waves in Hypothermia



Temperature (C°)	24.1	29.4	36.6
Heart rate (beats/min)	50	70	98
QRS interval (msec)	184	119	71
QTc interval (msec)	516	502	403

Early Repolarization Syndrome

Possible mechanisms

Early voltage gradients (phase 1)

↓

J wave ⇢ phase 2 re-entry

Late voltage gradients

↓

ST-segment elevation

Early Repolarization Syndrome

Genetic findings

KCNJ8 gene → **inward rectifier ATP-dependent-K^+-channel**

CACNB2B gene → **Ca^+-channel submit**

Early Repolarization Syndrome

Unresolved issues

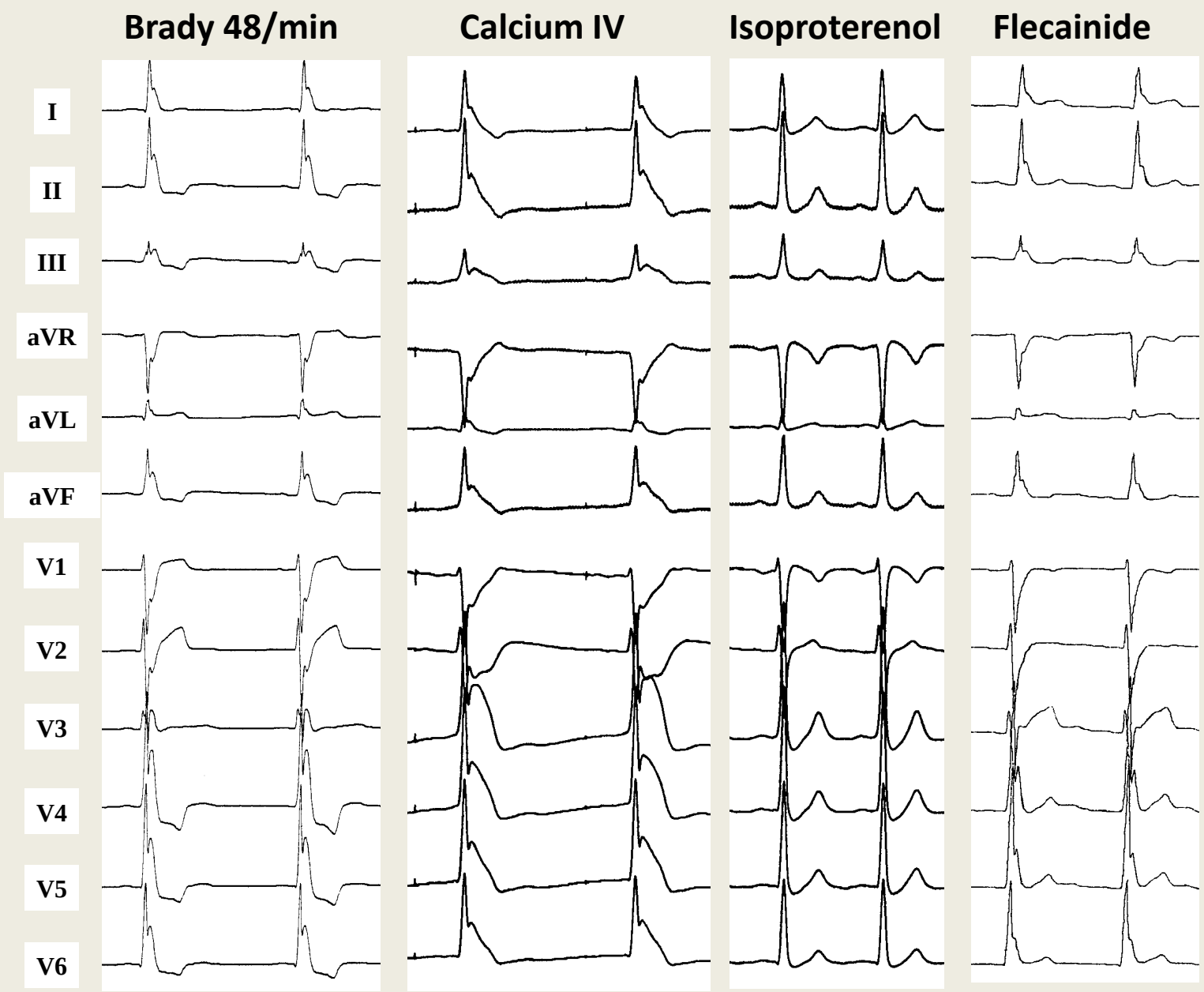
J wave = marker of risk ?

Regional ER = mechanisms ?

Brugada syndrome = right precordial ER ?

- Male gender
- Vagal tone
- Response to quinidine/isoproterenol

F 14 y


Brady 48/min
Calcium IV
Isoproterenol
Flecainide
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
500msec

Early Repolarization Syndrome

Therapeutic considerations

Secondary prevention

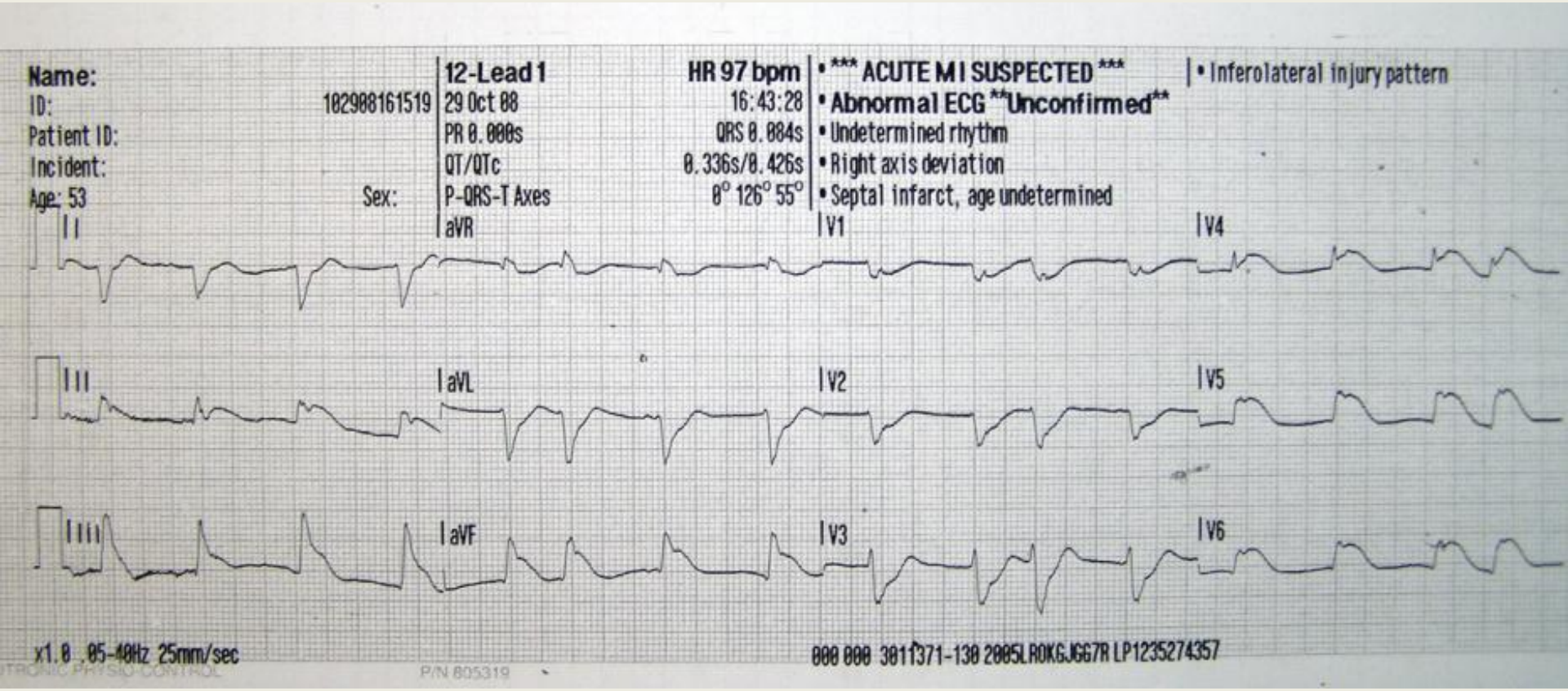
ER + VF ⟹ ICD

ER + electrical storm ⟹ isoproterenol, pacing, ablation ?

Primary prevention

?

Early Repolarization Syndrome



Early Repolarization Syndrome

The characteristic finding of this ECG is the

lambda like[1] or Gussak[2] shape ST elevation

which goes with the previously reported cases about electrical storm.

1) Gussak I, Bjerregaard P, Kostis J. Electrocardiographic "lambda" wave and primary idiopathic cardiac asystole: a new clinical syndrome? J Electrocardiol. 2004;37:105-107
2) Riera AR, Ferreira C, Schapachnik E, Sanches PC, Moffa PJ. Brugada syndrome with atypical ECG: downsloping ST-segment elevation in inferior leads. J Electrocardiol. 2004;37:101-104.

Early Repolarization Syndrome

Lambda-like ST segment elevation in acute myocardial infarction – a new risk marker for ventricular fibrillation? Three case reports

Uniesienie odcinka ST o kształcie litery lambda w ostrej fazie zawału serca – nowy wskaźnik ryzyka wystąpienia migotania komór? Opis trzech przypadków

Piotr Kukla[1], Marek Jastrzębski[2], Jerzy Sacha[3], Leszek Bryniarski[2]

[1] The H. Klimontowicz Hospital, Gorlice

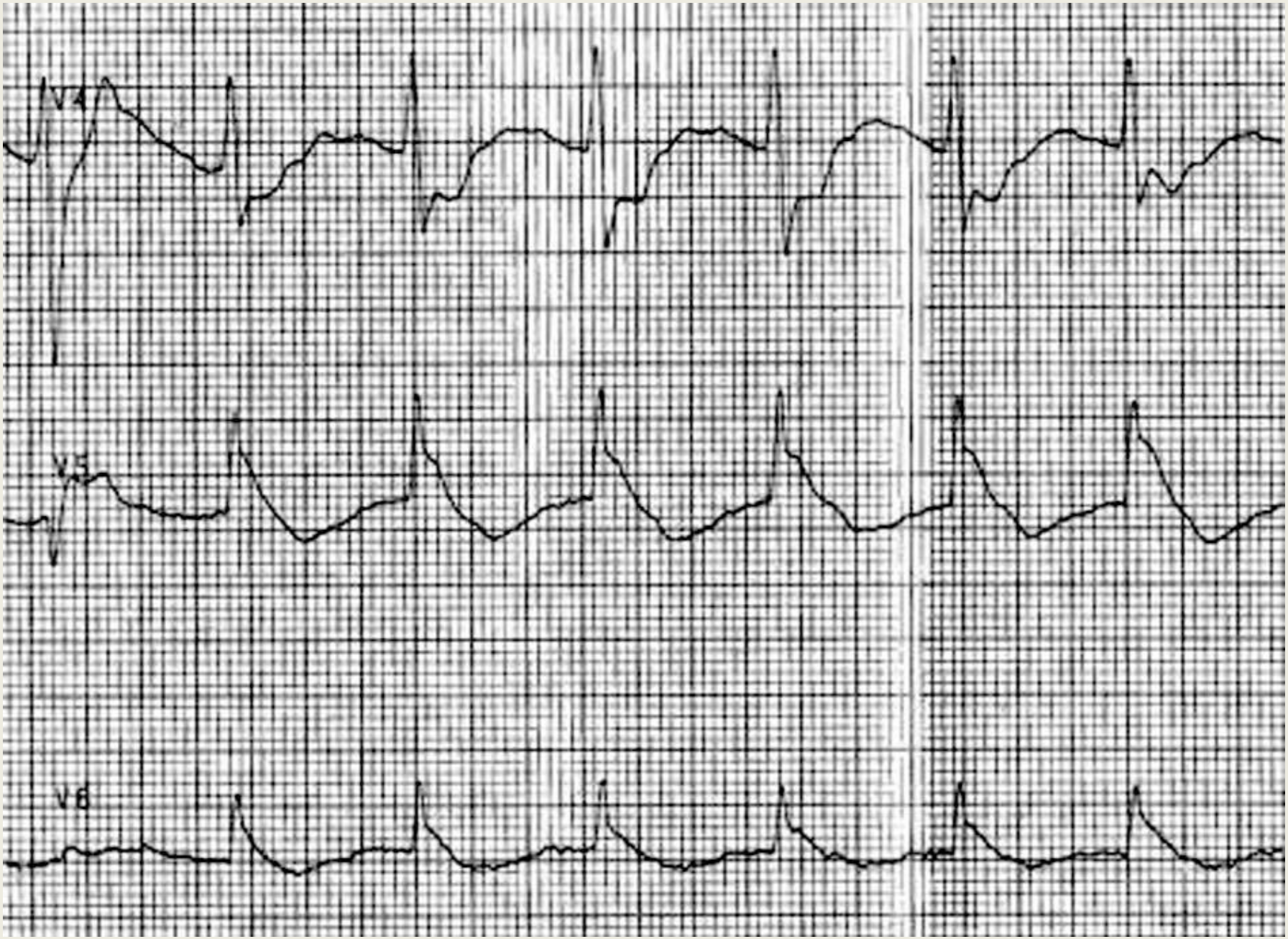
[2] 1st Departament of Cardiology, *Collegium Medicum*, Jagiellonian University, Kraków

[3] Department of Cardiology, Medical Center, Opole

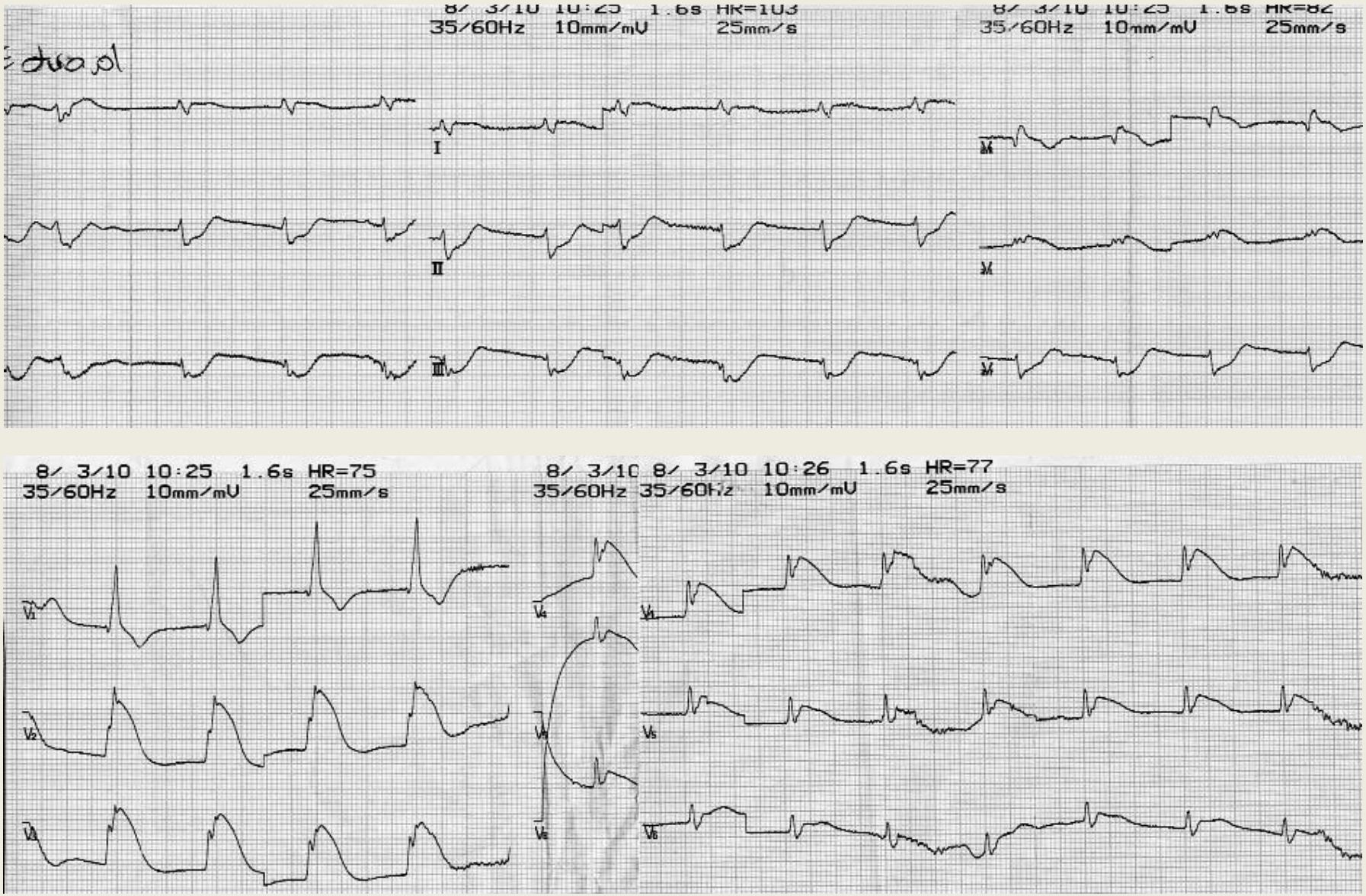
Kardiol Pol. 2008;66:873-7

Abstract

Sudden cardiac death (SCD) is responsible for almost 50% of all cardiac deaths in the U.S. The most common cause of SCD is coronary artery disease, especially during acute myocardial infarction (AMI). There are no publications concerning the shape of ST segment elevation in AMI and the risk of ventricular fibrilation (VF) or SCD. We present three cases with AMI and atypical ST segment elevation – lambda-wave-like complicated with episodes of VF.


V4
V5
V6

Early Repolarization Syndrome



Electrical storm in acute myocardial infarction

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In the USA, the annual rate of acute myocardial infarction (AMI) is close to one million, and almost one quarter of patients with AMI will die suddenly due to the development of fatal ventricular tachyarrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF) [1]. Although in more than half of such cases SCD occurs as the first symptom of coronary artery disease [2], conventional cardiovascular risk factors are not predictive of 'coronarogenic' SCD [3]. The search for identification of patients at risk for SCD, including those with AMI, has intensified in recent years. Promising results from experimental and clinical studies have emphasized the pivotal role of family history and subclinical mutation in cardiac channels in the development of repetitive life-threatening arrhythmias during acute ischemia, commonly described as 'electrical storm'.

The term 'electrical storm (ES)' is commonly defined as a state of transient critically impaired electrical stability of the heart culminating in a sequence of life-threatening ventricular tachyarrhythmias (either self-terminating or requiring multiple electrical defibrillations) within a short time (typically during a 24-hour period), although there has been no consistency in the definition of this term. ES is highly resistant to prevention and treatment and is associated with pure clinical outcome, even in patients with implantable cardioverter-defibrillators [4]. Most frequently ES is observed in patients with: (a) primary electrical diseases (PED) of the heart, (b) acute ischemic ('coronarogenic') event, (c) hypothermia during aggressive rewarming, and (d) drug-associated cardiac toxicity. Neither the mechanism/s nor the precipitating factors for ES are well defined, although genetic mutation of cardiac ion channels or gap junctions are considered as a highly likely predisposing factor for ES in ACS. For instance, Dr. Dan Hu et al. [5] have identified ES in 1 out of 19 consecutive patients who developing VF during AMI. The patient with ES was the only one carrying the SCN5A mutation. Interestingly, this patient developed his first VF at age 70 years and only in the setting of AMI.

In the article by Dr. Piotr Kukla [6] published in this issue of the Journal, the authors present three patients with AMI associated with multiple episodes of polymorphic VT and VF that were observed during a short period of time

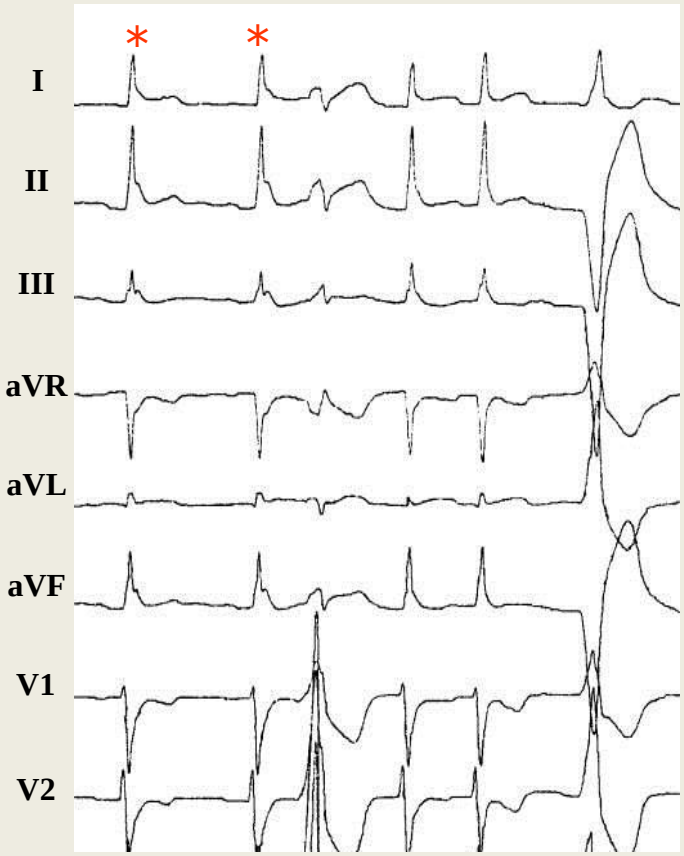
Early Repolarization Syndrome

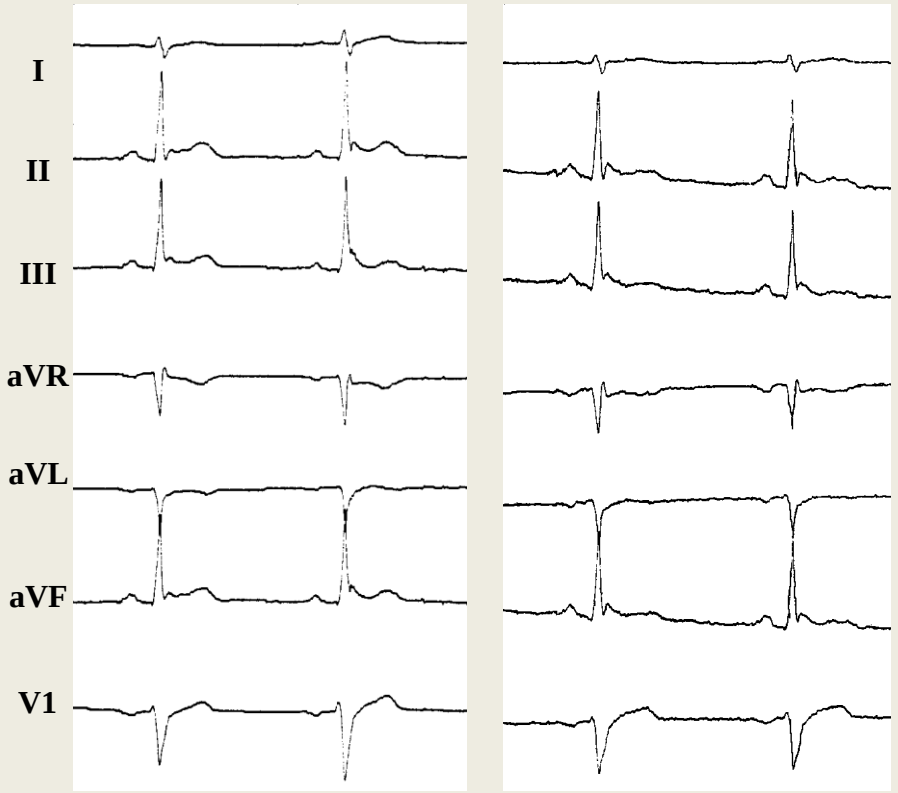
Summary

Thus, early repolarization syndrome is reality !

Early Repolarization Syndrome

Repolarization wave but not depolarization





Gradual/beat to beat fluctuations in contrast with QRS- attenuation during effort – possible accentuation by vagal maneuvers- No/little change with NaBlocker- HV normal

Rare late potentials -No endocardial activity synchronous of J-wave

Early Repolarization Syndrome

The less common causes of ST segment elevation (I)

1. Brugada syndrome
2. **Idiopathic ventricular fibrillation related to a prominent J wave in the inferior leads** (a variant of BrS with ST-segment elevation in the inferior leads but no coved or saddleback ST-segment elevation in the right precordial leads) [31] Gussak et al. [32] named this wave as lambda wave due to its morphology
3. **Arrhythmogenic right ventricular dysplasia:** Sometimes, the electrocardiographic phenotype is impossible to differentiate from the electrocardiographic pattern in BrS [33, 34]. In these cases, observed in the socalled minor or concealed forms, only magnetic nuclear resonance is useful in differentiating both entities
4. J wave syndrome
   - 4.1. J wave in hypothermal patients
   - 4.2. J wave in normothermal patients [35]
   - 4.2.A. Nervous system injuries: Acute brain injury i.e. subarachnoid hemorrhage, cardiac arrest, and dysfunction of cervical sympathetic system [36]
   - 4.2.B. Extreme hypercalcemia [37–42]
5. **Marked hyperpotassemia** [43]
6. **Myocardial bridging of the left anterior descending artery** [44]
7. Mitral valve prolapse syndrome [45]
8. **Prinzmetal's angina secondary to coronary artery spasm:** Reversible ST segment elevation [45]
9. **Acute aortic dissection of the ascending aorta (type A)** [46]

Pérez Riera et al, Cardiol J 2008;15:4-16

Early Repolarization Syndrome

The less common causes of ST segment elevation (II)

10. **Transient left ventricular apical ballooning syndrome, transient apical ballooning syndrome without coronary stenosis, tako-tsubo cardiomyopathy or "broken heart":** An acute and unique cardiac syndrome characterized by typical ischemic chest symptoms (chest pain or dyspnea), with ECG that shows ST-segment elevation and T-wave inversion, and minor elevated cardiac enzyme levels. Cardiac atheterization reveals absence of coronary stenosis. Left ventriculography and cardiac magnetic resonance imaging shows apical akinesia and compensatory hypercontractility of the basal ventricular segments (apical bal looning). Left ventricular systolic function recovers from ejection fraction. Wall abnormalities return to normal can occur after as long as 3 months. This new clinical entity may have a catecholamine-mediated neurogenic mechanism as the etiopathogenic substrate
11. **Acute myocarditis or myopericarditis [47]**
12. Chagasic cardiomyopathy [48]
13. **Hypertrophic cardiomyopathy:** The electrocardiographic features of hypertrophic cardiomyopathy are numerous, including ST segment elevation that may simulate other ST segment elevation syndromes [49]
14. **After mitral valvuloplasty [50]**
15. **Septic noncardiogenic shock [51]**
16. Cardiac tumor [52]
17. **Acute pancreatitis:** It is considered a stress-related cardiomyopathy similar to transient apical ballooning syndrome without coronary stenosis [53]. More than 50% of the patients with acute pancreatitis have ECG abnormalities, and these changes could be related also to electrolyte alterations [54]
18. **Anaphylactic reaction/anaphylactic shock [55]**
19. **Gallbladder disease:** Acute cholecystitis or biliary colic may be associated with angina pectoris, arrhythmias, or nonspecific ST-T wave changes on the ECG. A vagally mediated cardio-biliary reflex is the presumed cause of these changes. The signs and symptoms of gallbladder and heart disease may overlap, making diagnosis difficult [56]

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Comparison of ECG

	ERV	Acute pericarditis	AMI	BrS type 1
ST segment appearance	Concave to the top	Concave to the top	Concave to the top	Convex to the top
Pathological Q waves	Absent	Absent	Present	Absent
Mirror image changes	Only in aVR	Absent	Present	Possible
Leads involved	Limb and precordial	Limbs and precordial	Segmentary pattern	Right precordial
R voltage	Normal or minimally augmented	Normal	Lost	Normal
PR interval	Not affected	Possible depression	Variable	50% prolongation
ST/T ratio in lead V6	< 0.25	> 0.25	Not applicable	Not applicable

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