J-wave syndromes genetic basis and ECG examples

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Similarities between BrS and ERS

Both entities display several clinical similarities, suggesting similar pathophysiology. (**Priori 20013; Antzelevitch 2016**)

1. **Gender:** Both are much more frequent in the male gender. The possible mechanism(s) is testosterone modulation of ion currents underlying the epicardial AP notch
2. **Average age of first event:** the highest incidence of VF or SCD occurs in the third or fourth decade of life. In both syndromes
3. **Both do not present apparent or macroscopic structural heart disease**.
4. **Both frequently present conduction disturbance in the right His system.**
5. **Both may present discrete QRS interval widening.** In the ERP of athletes' hearts, a mild increase in QRS duration is observed (100 ms to 110 ms); in 15% of the cases caused by physiological hypertrophy of the RVOT, which is translated in the ECG into the appearance of final r' wave that does not exceed 5 mm and that is lower than the preceding S in the same lead: rSr'. In BrS, as we have e a selective increase of QRS duration in the right precordial leads (Pitzalis 2003).
6. **Heart rate:** the appearance of accentuated J waves and ST segment elevation are generally associated with bradycardia or pauses, and VF events have been proposed to occur mostly during sleep or at a low level of physical activities.

7. **Dynamicity of ECG repolarization:** It is high in both entities. This is caused autonomic modulation of ion channel currents underlying early phases of the epicardial AP
8. **Both may display saddleback pattern quite frequently.**
9. **Predominant moment of event occurrence:** VF/PVT often occurs during sleep or at a low level of physical activity. Additionally, VT/VF are triggered by PVCs with short coupled intervals triggered by phase 2 reentry See next 12-Lead ECG figure 1

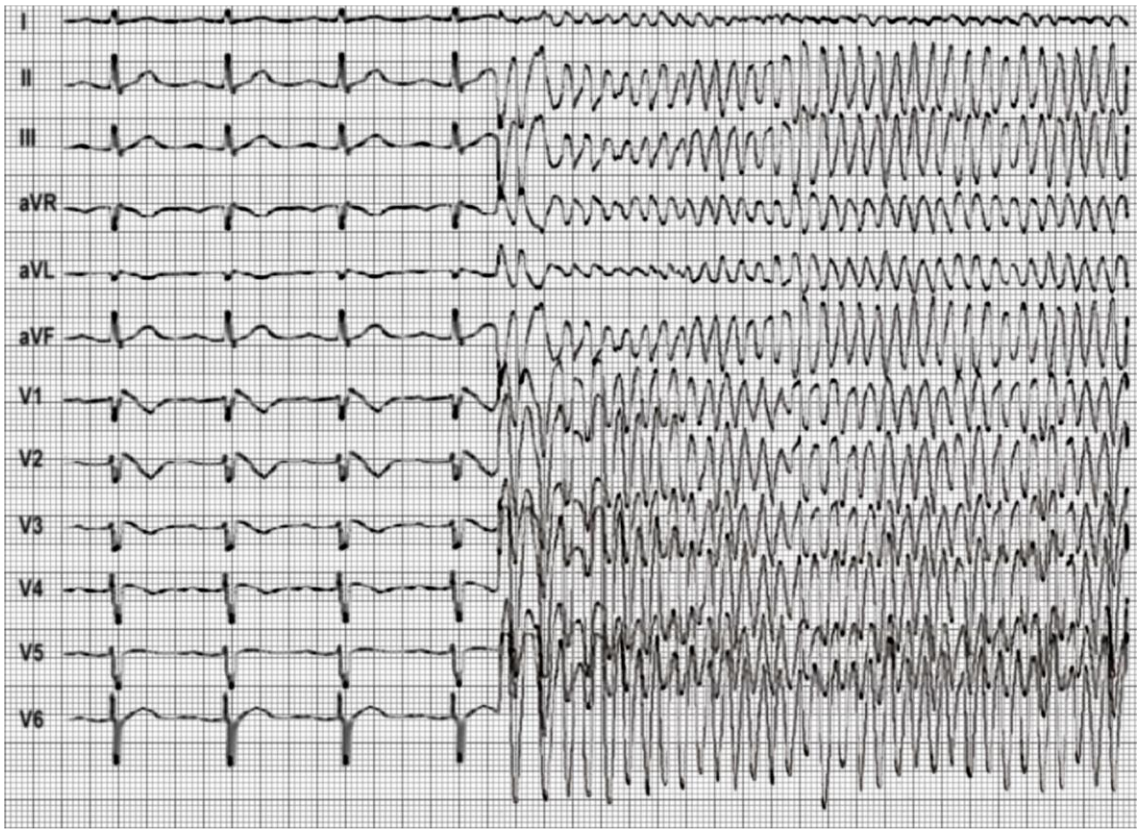


Figure 1: 12-leads ECG with Type 1 Brugada ECG pattern (Coved), premature ventricular contractions with short coupling followed by sustained polymorphic VT degenerating to VF induced by ajmaline. As a result of the spontaneous type 1 ECG pattern, the ajmaline test is not indicated.

10. Both may reverse ventricular repolarization pattern during early phase of treadmill stress testing.
11. Both improve ventricular repolarization with intravenous isoproterenol, probably because the drug reduces repolarization dispersion which triggers VF events (Hiss 1962).
12. Both have a shortening of phase 2 action potential due to electrophysiological substrate, in the ventricular epicardium thickness by intensification of the notch in phase 1, mediated by the *I*to channel (Yan 1996).
13. Both may have modification in the *I*to and I_{Ca}++-L channels by electrophysiological substrate, which explains the J point and ST segment elevation causing intensification of the notch in phase 1 and decrease in phase 2 duration in the ventricular epicardium thickness (Antzelevitch 2000).
14. Both may affect in different degrees, ventricular repolarization in the right precordial leads (Bianco 2001) as well as in the lateral wall (V4-V6) and inferior leads I, II, and III (atypical forms of BrS).
15. Both may be associated with rare variants
16. Genetic mutation shared: BrS and ER Syndrome shared several gene mutations such as

Genetic defects associated with ER Syndrome and genetic mutation shared with BrS

	Locus	**Gene/protein**	**Gene shared with BrS**	**Ion channel**	**% of probands**
ERS1	12p11.23	KCNJ8, Kir6.1	BrS8	$\uparrow I_{K\text{-}ATP}$	Rare
ERS2	12p13.3	CACNA1C, $Ca_v1.2$	BrS3	I_{Ca}	4.1%
ERS3	10p12.33	CACNB2b, $Ca_v\beta2b$	BrS4	I_{Ca}	8.3%
ERS4	7q21.11	CACNA2D1, $Ca_v\alpha2\delta1$	BrS9	I_{Ca}	4.1%
ERS5	12p12.1	ABCC9, SUR2A	Brs13	$\uparrow I_{K\text{-}ATP}$	Rare
ERS6	3p21	SCN5A, $Na_v1.5$	BrS1	$\downarrow I_{Na}$	Rare

			Gene shared with BrS		
ERS7	3p22.2	SCN10A, $Na_v1.8$	BrS17	$\downarrow I_{Na}$	Rare
ERS8	1p13.2	KCND3, $K_v4.3$	BrS10	$\uparrow I_{TO}$	Rare
ERS9 or IVF	7q36.2	DPP6/Dipeptidyl aminopeptidase-like protein 6	Familial idiopathic VF (1)	$\uparrow I_{TO}$	Rare
ERS10 (2) (2020)	3p24	GPD1L/ glycerol-3-phosphate dehydrogenase 1-like	BrS2 (3) 2007 + SIDS (4) 2007	$\downarrow I_{Na}$	Rare

Alders, M., et al, 2009.; Jun Fan,et al 2020.; London B,et al.2007.; Van Norstrand DW, et al.2007)

17. Ameliorative response to quinidine and bepridil by Ito inhibition and possible vagolytic In ERS therapeutic efficacy of quinidine is accepted, there is no consensus on dose..1 g/d may be required.
18. Response to isoproterenol denopamine and milrinone: Ameliorative response caused by increased ICa and faster heart rate
19. Ameliorative response to cilostazol in both entities, consequence of increased ICa, reduced Ito and faster heart rate
20. Both have ameliorative response to pacing by reduced availability of Ito due to slow recovery from inactivation
21. Both have vagally mediated accentuation of ECG pattern consequence of direct effect ot inhibit ICa and indirect effert to incrase Ito due to slowing of heart rat
22. Both have augmented J-wave by fever consequence fo accelerated inactivation of INa and accelerated recovery of Ito form inactivation.
23. Both have augmented J wave during hypothermia by slowed activation of ICa, leaving Ito unopposed. Increased phase 2 reentry but reduced pVT due to prolongation of APD. (**Morita et al 2007**)

Genes associated with BrS and Early Repolarization Syndrome

Gene/ OMIM	BrS	ERS	Protein /Locus	Functional effect/author
SCN5A/ # 601144	Yes BrS1	Yes	Cardiac sodium channel alpha subunit (Nav1.5) / Locus on chromosome 3p21	Loss of function, reduced Na1 current (**Chen Q et al 1998**). 20-30% of all cases.
GPD1-L/ # 911778	Yes BrS2	No	Glycerol-6-phosphatedehydrogenase / Locus on chromosome 3p22.3	Loss of function, reduced Na1 current (**London B et al 2007**)
CACNA1c/ # 114205	Yes BrS3	Yes	L-type calcium channel α subunit (Cav1.2) / Locus on chromosome 12p13.3	Loss of function, reduced Ca21 current (**Antzelevitch C et al 2007**)
CACNB2/ 114205	Yes BrS4	Yes	L-type calcium channel β subunit (Cav1.2) / Locus on chromosome 10p12.33-p12.31	Loss of function, reduced Ca21 current(**Antzelevitch C et al 2007**)
SCN1B/ # 612838	Yes BrS5	No	Cardiac sodium channel beta1 subunit /19q13.1	Loss of function, reduced Na1 current (**Watanabe H et al 2008**)
KCNE3/ # 613119	Yes BrS6	No	Transient outward current beta subunit-transient outward current /11q13-14	Gain of function, increased K1 Ito current (**Delpon E et al 2008**)
SCN3B/ # 6081214	Yes BrS7	No	Cardiac sodium channel beta-3 subunit / 11q23.3	Loss of function, reduced Na1 current (**Hu D et al 2009**)
HCN4 # 613123	Yes BrS8	Yes	Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4/ Locus on chromosome 15q24.1	↑$I_{K=ATP}$ 2% (**Ueda K, et al 2009**.) (**Crotti, L, et al.2012**) (**Barajas-Martinez H, et al. 2012**)
CACNA2D1	Brs 10		Cavα2δ−1/Locus on chromosome 7q21-22	Loss-of-function LOF
RANGRF	BrS11		MOGI/17p13.1	Loss-of-function LOF Rare (Olesen MS, et al, 2011)
KCNE5(*KCNE1L*)	BrS12		MiRP4/Locus on chromosome Xq22.3	Kv4.3, I_{to} Gain-of-function (GOF) (Ohno S, et al, 2011)
KCND3	BrS13? Or BrS9		Potassium Voltage-gated Channel, Shal-related Subfamily, Member 3/Locus on chromosome: 1p13.2	↑I_{to} Gain-of-function (GOF) (Postma,A.V 2000) (Giudicessi, J. R et al 2012)

HCN4	BrS14		Hyperpolarization-activated Cyclic Nucleotide-gated Potassium Channel 4 /Locus on chromosome 15q24.1	GOF ↑IK^+ Rare (Crotti, L, et al 2012)
SLMAP	BrS15 and Cerebral Cavernous Malformations, 3		Sarcolemma Menbrane Associated Protein /Locus on chromosome 3p21.2-p14.3	↓INa^+ modulating the intracell, ular trafficking of hNav1.5 channel. (Ishikawa T, et al. 2012)
TRPM4	Br16		NSCCa/Locus on chromosome 19q13.33	Abnormal resting potential. Rare (Hui Liu, et al 2013)
SCN2B * 601327			Sodium Voltage-gated Channel, Beta Subunit 2Navβ3/Locus 11q23.3	Loss-of-function(LOF) Rare (Riuro, H et al 2013)
SCN10A * 604427	BrS18		Sodium Voltage-gated Channel, Alpha Subunit 10Nav1.8/Locus on chromosome 3p22.2	↓INa^+ Loss-of-function(LOF) Rare (Fukuyama M 2016)
HEY2 * 604674	Yes BrS19	No	Hes related family bHLH transcription factor with YRPW motif 2Nav1.5/Locus on chromosome 6q22.31	Loss-of-function(LOF) (Christiaan C Veerman, et al 2017)
PKP2	Yes BrS20	No ARVC9	Plakophilin-2 PKP2/Locus on chromosome 12p11.21 12p13	Loss-of-function (LOF) ↓INa^+ (**Cerrone M et al, 2013, 2014**)
ABCC9 * 601439	Yes Brs 21	Yes	ATP-BINDING CASSETTE, SUBFAMILY C, MEMBER 9 *SUR2A* (sulfonylurea receptor subunit 2 A), IK-ATP)/ /Locus on chromosome *12p12.1*	Gain-of-function GOF/ (**Hu D et al 2014**)

Differences between the ERS and BrS

1) The region of the heart most affected (right ventricular outflow tract in BrS vs. left ventricular inferior region in ERS
2) Leads affected: BrS: right precordial leads. ER syndrome II, III a, VF, V4, V5, V6; I, aVL, Both: inferolateral
3) The presence of (discrete) structural abnormalities in BrS and not perhaps in ERS;
4) Higher incidence of late potentials in signal-averaged ECGs in BrS vs. lower incidence of LPs in ERS,
5) Effect of sodium channel blockers on surface ECG: Increased J-wave manifestation in BrS and Reduced J-wave manifestation in ER syndrome. The reduction of J wave in the setting of ER syndrome is thought to be due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.
6) Higher prevalence of atrial fibrillation in BrS vs. ERS.
7) Structural changes, including mild fibrosis and reduced expression of Cx43 in RVOT or fibrofatty infiltration in cases of AC. Imaging studies have also revealed wall motion abnormalities and mild dilation in the region of the RVOT in BrS. On the other hands in ER syndrome structural changes are unknow.

Genetic basis of Brugada syndrome Sodium, potassium and calcium

Gene	Frequency	Functional abnormalities
INa^+channel dysfunction		
SCN5A	20-30%	LOF ↓INa^+
SCN10A	Rare	LOF ↓INa^+
SCN1B	Rare	LOF ↓INa^+
SCN2B	Rare	LOF ↓INa^+
SCN3B	Rare	LOF ↓INa^+
GPD1L	Rare	LOF ↓INa^+
MOGI1	Rare	LOF ↓INa^+
SLMAP	Rare	LOF ↓INa^+
PKP2	Rare	LOF ↓INa^+

The cardiac potassium K^+ channels (Crotti L et al 2020)

Cardiac K^+ channels are membrane-spanning proteins that allow the passive movement of K^+ ions across the cell membrane along its electrochemical gradient. They regulate the resting membrane potential, the frequency of pacemaker cells and the shape and duration of the cardiac action potential. Normal K^+ channel function is essential to maintain electrical stability in the heart. Gene mutations that alter the assembly, trafficking, turnover or gating of cardiac K^+ channels can cause LQTS, SQTS, J-wave syndromes and AF.

1. **Delayed Rectifier Potassium(K^+) Currents/Channels**

    a) The rapidly activating component of the delayed rectifier K^+ current, I_{Kr}**,** rapid-rates of activation onset. Name: Kv11.1 (HERG), Gene:KCNH2, Human Crhomosomal location:7q35–36

    b) The slowly activating component of the delayed rectifier K^+ current, I_{Ks} , slow-rates of activation onset: Name: Kv7.1 (KVLQT1), Gene: KCNQ1. Human Crhomosomal location 11p15.5

    c) The ultrarapid (I_{Kur}) ultra-rapid rates of activation onset. Name:KCNA5, Gene:12p13.3, Human Crhomosomal location: 12p13.3

2. **Inward rectifying K^+ channels**

    a) I_{K1}**, "**The transient outward current"**.** Name: Kir2.1 (IRK1), Gene: KCNJ2, Human Crhomosomal location: 17q23.1–24.2

    b) I_{KATP} ATP-sensitive K^+ channels, K_{ATP} Name: Kir6.2 (BIR), Gene:KCNJ11, Human Crhomosomal location:11p15.1

    c) I_{KAch} The acetylcholine-activated K^+ current, $\boldsymbol{I}_{KAch}$ Name: Kir3.1 (GIRK1), Gene: KCNJ3, Human Crhomosomal location: 2q24.1 11p15.1

    d) **Transient outward currents**

    e) $\boldsymbol{I}_{tof}$ $\boldsymbol{I}_{to1}$ 4-aminopyridine (4-AP)-sensitive, calcium-independent K^+ current (I_{to1}) is rapidly activated and inactivated in response to depolarization

    f) I_{to2} $\boldsymbol{I}_{to2}$ 4-AP-insensitive, Ca^{2+}-activated Cl^- or K^+ current (I_{to2})

    g) **Intracellular cation activated currents**

    h) IKNa,

    i) IKCa) and at least one

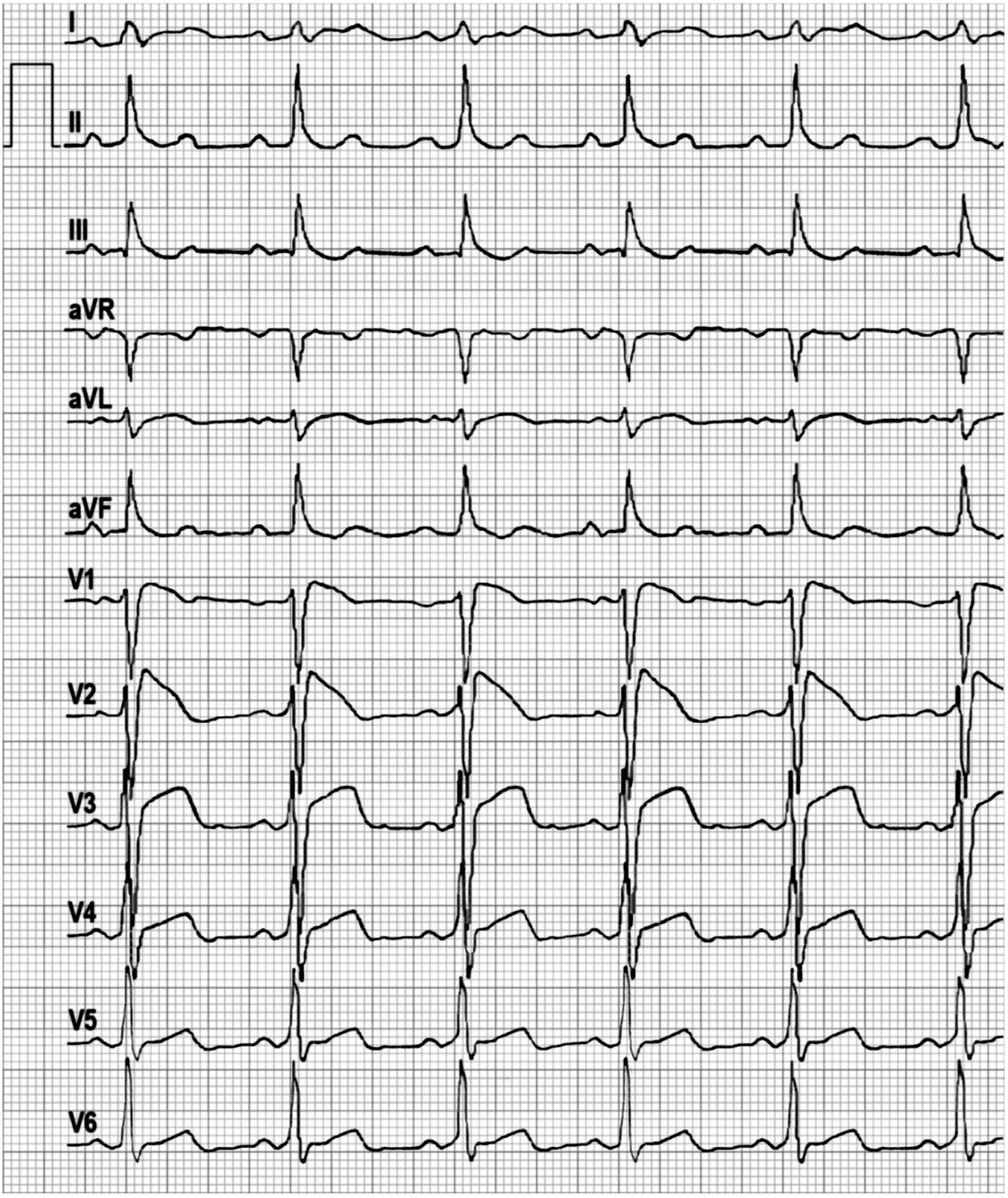
    j) "background leak" current (IKleak)

Calcium channels and BrS

Type	OMIM	Gene	Protein
BrS3	**114205**	**CACNA1C**	**$Ca_V1.2$ – α subunit of voltage-dependent calcium channel carrying the L-type calcium current $I_{Ca(L)}$**
BrS4	**600003**	**CACNB2**	**$Ca_V\beta2B$ – β-2 subunit of the voltage-gated calcium channel carrying the L-type calcium current $I_{Ca(L)}$.[17]**
BrS5	**600235**	**SCN1B**	**$Na_V\beta1$ – β-1 subunit of the sodium channel carrying the sodium current I_{Na}**

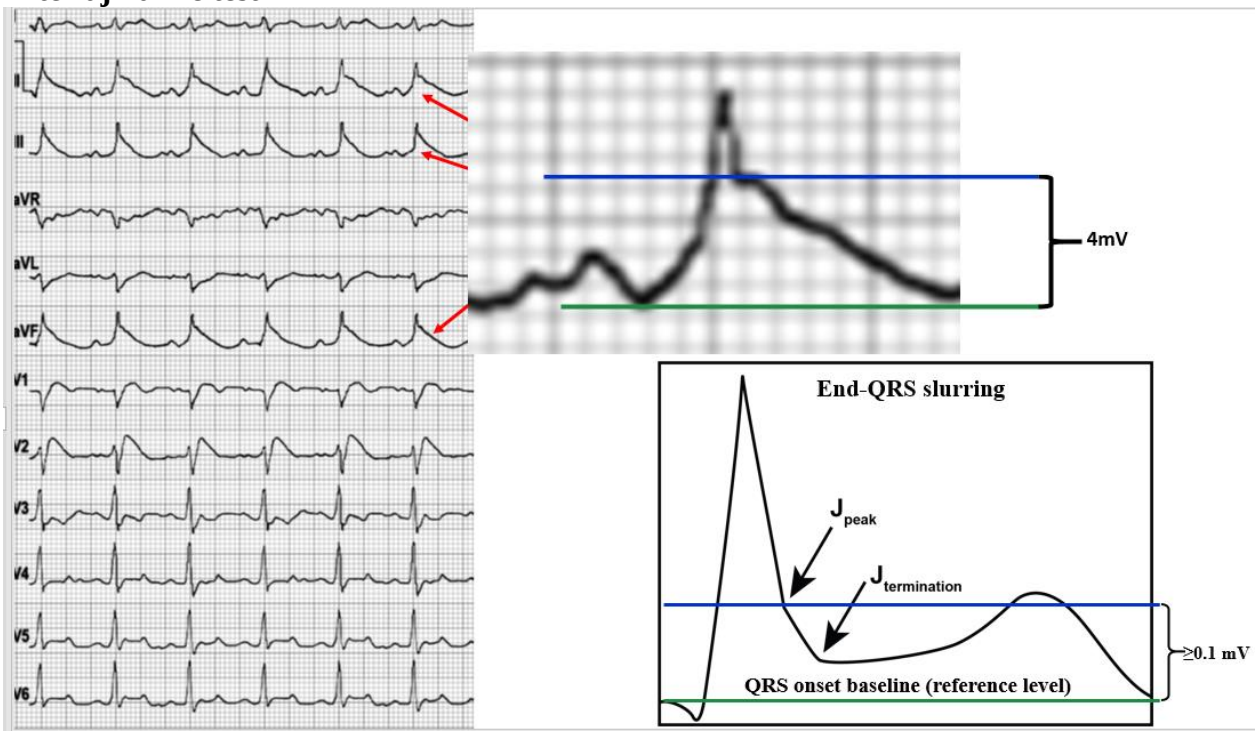
Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, et al. (January 2010). "An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing". Heart Rhythm. 7 (1): 33–46. doi:10.1016/j.hrthm.2009.09.069. PMC 2822446. PMID 20129283.

Example
12-lead ECG before ajmaline challenge



Type 1 Brugada pattern and slurring J-wave insinuation in the inferior leads (before ajmaline injection).

After ajmaline test



Typical J-wave syndrome ERP+ type 1 Brugada ECG pattern

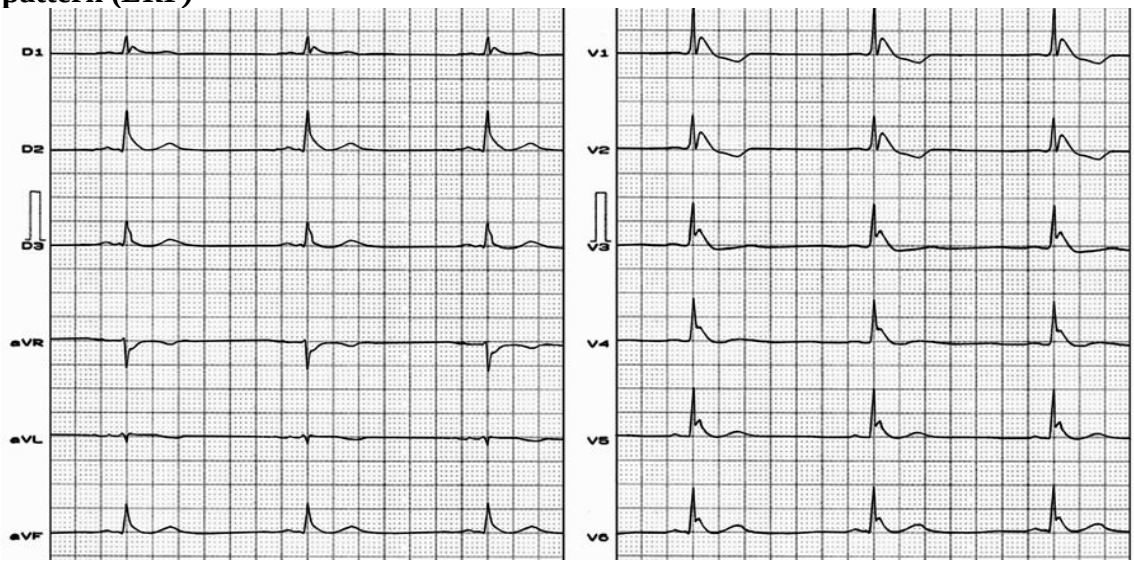
HEART WALLS CURRENT NOMENCLATURE

I Lateral	aVR	V1 Septal	V4 Anterior
II Inferior	aVL Lateral	V2 Septal	V5 Lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Lateral

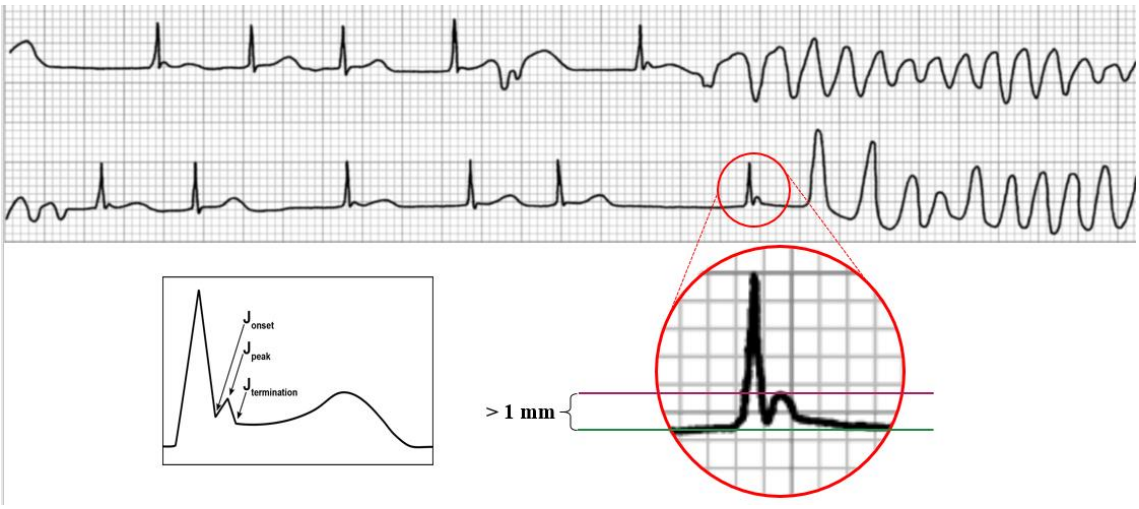
1) **Type 1: which displays an early repolarization pattern (ERP) predominantly in the lateral precordial leads, is prevalent among healthy young male athletes**
2) **Type 2: An ERP in inferior and lateral leads: It is associated with moderate level of risk**
3) **Type 3: An ERP in inferior, lateral and right precordial leads (Anteroseptal): Type 3 highest risk**

Expert Recommendations for the Diagnosis of ER Pattern and Syndrome Modified from (Priori S.G et al. (2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 10:1932–1963. DOI: 10.1016/j.hrthm.2013.05.014)
Early Repolarization syndrome (ERS) is diagnosed in the presence of J-point elevation ≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated form otherwise unexplained polymorphic/VF
ERS can be diagnosed in a SCD victim with a negative autopsy and medical chart review, with a previous ECG demonstrating J-point elevation ≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ERP can be diagnosed in the presence of J-point elevation≥ 1mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG
ER Pattern or better inferolateral J waves is defined as elevation of the J point in ≥2 contiguous leads evaluated at baseline using 12-lead ECG.(**Haïssaguerre M, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med Overseas Ed 2008;358:2016–23**.) with an amplitude of the inferolateral J-point elevation of ≥0.1mV above the baseline level, either as QRS slurring or notching in any of the inferior (II, III and aVF), lateral (V4 , V5, V6, I and aVL leads.(**Macfarlane PW, et al. The early repolarization pattern: a consensus paper. J Am Coll Cardiol 2015;66:470–7**.) and slurring or notching they have to happen in the final 50% of the R-wave downslope. The QRS interval in patients with inferolateral J waves had to be <120ms. J-point amplitude is evaluated at the peak of the notch or at the onset of slur. A greater amplitude of the ST segment 100 ms after the end of the J wave (ie, the end of notch or slur) versus that observed at the end of the J wave indicated an ascending ST segment. A lower or equal amplitude of the ST segment 100 ms after the end of the J wave versus that observed at the end of the J wave indicated a horizontal or descending ST segment. (**Macfarlane PW, et al. 2015**)

Difusse Early Repolarization Pathological J-wave syndrome or early repolarization pattern (*ERP)*



Subtype 3 shows an ER pattern registered globally in the inferior, lateral and right precordial leads. This variant is associated with the highest level of risk for the development of VF storms (Nam 2008). In subtype 3, the Brugada waves may be seen together with giant J waves in other ECG leads. Although the Brugada waves are not called ER, their underlying mechanism is identical to that of the ER patterns



J-point elevation is dynamic as (↑) increases during atrial fibrillation with long R-R intervals. In the present case, the value is > 1 mm. We consider this case an ERS because the ERP is associated with unexplained polymorphic VT.