Young woman with repetitive syncopal episodes and strong family background

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Case report

AK: 25 year old  Caucasian woman

- Extensive work up for recurrent syncope and exertional chest pain
- 5 episodes over last 2 months
- No prodrome or seizure activity
- Somewhat related to exercise or sitting-to-standing
- Family History: one cousin died (cardiac arrest) at age of 27; uncle died at age of 30, unknown cause
- Transthoracic echo: normal RV and LV function; normal valves; LVEF: 65%
- Treadmill stress echo: 11 METS exercise capacity; no arrhythmia, no ST-T abnormalities; normal wall motion
- 30 day event monitor: one 11 beat irregular ventricular tachycardia;
- CT angiogram: normal coronary arteries; Ca²⁺ score: ‘0’

Note: Exercise capacity is reported in terms of estimated metabolic equivalents of task (METs). The MET unit reflects the resting volume oxygen consumption per minute (VO2) for a 70-kg, 40-year-old man, with 1 MET equivalent to 3.5 mL/min/kg of body weight.

Questions:
1. Which is the most probable clinical diagnosis? Why?
2. What are the appropriate steps for the diagnosis?
Fastest Ventricular Tachycardia: 117 BPM at 05:11:30 d14
Dear friend:
The young patient has a Brugada's syndrome type I. She has a family background (one cousin died (cardiac arrest) at age of 27; uncle died at age of 30). Next step to make an ajmaline test.

Eduardo Quiñones MD Córdoba Argentina

Dear compatriot: you affirm that this young woman has an spontaneous type 1 electrocardiographic pattern consequently I do not see need to perform the ajmaline test if we admit that she has spontaneous the type 1 electrocardiographic pattern.

Andrés.
Estimados Maestros, buenas noches!

Historia de síncopes recurrentes y 2 parientes (tío y primo) con MS menores de 30 años.

ECG basal, ritmo sinusal, PR normal, patente de BrS tipo 1, onda P (-) en V1, probable colocación alta de electrodo, con signos de malignidad (fQRS en cara inferior, aVL y V2), y onda "J" en I y aVL. Angulo beta más de 50° y base del triángulo 160 mseg.

Monitor de 30 días una TVNS lenta e irregular, de sólo 11 latidos, no creo que sea la causa del síndrome, aunque aparece en la noche, momentos de las TV polimórficas y FV causas de la MS en Brugada.

Los estudios complementarios normales, indican que no hay cardiopatía estructural.

Conducta: estudio electrofisiológico (EEF) y si se induce ARF con navegador del TSVD e implante de CDI.

Cordiales Saludos, a la espera de la opinión de los expertos

Dr. Juan Carlos Manzzardo

English

Dear Masters, good evening!

History of recurrent syncope's and 2 relatives (uncle and cousin) with SCD under 30 years.

Negative P wave in V1, probable high electrode placement, with signs of malignancy (fQRS in inferior wall aVL and V2), and "J" wave, in I and aVL. β angle > 50° and base of triangle 160 msec.

30-day monitor a slow and irregular TVNS of only 11 beats, I do not think it is the cause of syncope, although it appears at night, moments of the polymorphic TV and FV causes of SCD in Brugada syndrome.

Normal complementary studies indicate that there is no structural heart disease.

Conduct: electrophysiological study (EEF) and if RFA is induced with TSVD navigator and ICD implantation.

Best regards, waiting for the opinion of the experts

Juan Carlos Manzzardo, MD, Mendoza, Argentina
Dear Frank, Raimundo & Andrés:
Thank you for sharing this superb case with us. This is a 25-year-old woman of unknown ethnical origin with recurrent syncope and at least 1 documented episode of non sustained (11 beats), irregular, not very fast (max 149/min) VT. We do not know if the patient felt syncope at the time of NSVT. In addition, there is a strong family of sudden death occurring at young age. The patient has apparently no organic heart disease. The ECG does not suggest long or short QT syndrome; however it does suggest a "minor form" of Brugada syndrome (BrS) which is very usual in females with BrS (see very suggestive pattern in leads I and aVL as well as V1-V2). The first step is to confirm the diagnosis. Since the patient is living in the U.S.A, both ajmaline and flecainide are not available so we should use IV procainamide for unmasking type 1 Brugada-ECG. In my experience, only small doses of the drug may be necessary. In any case, this test should be carefully done since it may occasionally result in pro-arrhythmic effects. Please look to one on my papers where a very small dose of Flecainide in a young 25-year female resulted in frequent short coupled RVOT-VPC's (Belhassen 2004) and also look to the superb recent paper by Poli et al. (Poli 2017)

Management: since she is living in the USA, the patient will receive an ICD that will certainly allow recording of a malignant rapid polymorphic VT/VF. I personally believe, based on my experience, that ICD is certainly not the best therapy for this kind of patient since they will continue suffering from syncopal tachyarrhythmias and receive multiple ICD discharges.

My policy in this type of patients is to perform diagnostic EPS, attempting to induce VF and assess if quinidine effectively prevents VF induction. If so, it is possible to avoid ICD implantation (Belhassen 2016; Milman 2017). In case of recurrent arrhythmias and impossibility to use quinidine, epicardial ablation should be considered in selected U.S centers. I also recommend genetic testing: our recent analysis of 678 patients with arrhythmic events and BrS (the Multicenter SABRUS survey) has shown that SCN5A mutations are very frequently observed (50-70%) in this type of female patient. This information might be important for future patient's progeniture. Finally I believe that the documented VT during Holter monitoring in this patient does not explain the syncope; however, I do not exclude that this arrhythmia has some relationship with the "Brugada process" on the RVOT epicardium.

Bernard Belhassen, MD
Professor Emeritus of Cardiology, Sackler Faculty of Medicine, Tel Aviv University,
Former Director of Cardiac Laboratory
Tel-Aviv Medical Center, Israel
Thank you, Dr. Belhassen for your wonderful comments on this case. Regarding her ethnicity, she is Caucasian. I look forward to more comments, and I will follow up with her doctors regarding further workup and outcomes.

Regards,
Frank

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Looks like a Brugada pattern in both V1 and V2 also J waves in I and aVl so called peripheral Brugada. This is a high risk pattern and would suggest ICD or Quinidine at a minimum. If she symptomatic with VT would treat with Quinidine and consider Ablation. The VT is monomorphic and relatively slow which is unusual for Brugada Perhaps something else is in play
In addition should undergo genetic testing and cascade family screening for Brugada syndrome.

Melvin Sheinman, MD
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Dear Frank, Raimundo and Andrés,
I would first ask what about the parents ECG of this young woman? Cardiac MRI? QRS and ST segment morphology at night during the holter recording? The circumstances of syncope occurrence are atypical. Any warning signs, trauma? A vasovagal origin has to be ruled out (tilt test).
Chest pain: Abnormal coronary implantation?
Malignant early depolarization syndrome?
The idioventricular rhythm has no relationship with the syncope history.
Genotyping: a KCND3 gain-of-function mutation?
Long term implantable Holter recordings?

Kind regards,

Philippe Chevalier MD PhD.
Louis Pradel Cardiology Hospital of Lyon, France

Pr. Philippe Chevalier, MD PhD is the head of the Rhythmology unit of HCL and the coordinator of the National Reference Center for inherited arrhythmia. He is an internationally recognized clinical expert in the field of cardiac arrhythmias. He has been implicated in more than 10 clinical studies. He is the principal investigator and coordinator of a European multicenter study on molecular markers of sudden death. He develops fundamental studies on the pathophysiology of AF. He organized every year the national congress of “les journées de rythmologie” in Lyon. Regularly invited to international cardiology congress, he is also a member of several societies (French Society of Cardiology, American Heart Association). His research led him to be present in more than 347 publications in refereed journals.
Hola Potro: Presenta patrón espontáneo de Brugada con signos de alteraciones de la repolarización en DI y aVL, sincope, VT documentada con antecedentes familiares de muerte súbita. Me llama la atención no la han referido para realizar RNM cardiaca, o lei mal el resumen?

Que sea 10 veces más frecuente en hombres no significa que no pueda presentarse en mujeres y justamente por dicho motivo la presencia de todo lo descrito hace que esta mujer tenga un mayor riesgo.

Como presenta episodios sincopales a repetición, la ablación del TSVD asociado a quinidina evitan numerosas descargas del CDI o tormentas eléctricas. En el estudio FINGER busca estratificar los factores de riesgo en pacientes asintomáticos con patrón tipo I espontáneo, lo que no es este caso.

Tiene alto riesgo de MS no encuentro motivos para no indicar CDI, que pensando en un comportamiento maligno realicen las medidas coadyuvantes está perfecto (quinidina, ablación del TSVD).

Me resulta difícil comprender la controversia o dudas en este caso.

Previo a colocar CDI sino realizo, completaría con RNM cardiaca y estudio genético en la paciente y sus familiares.

Un cordial saludo

English: Hi Andrés. She presents spontaneous Brugada pattern with signs of repolarization alterations in I and aVL, syncope, VT documented with a family history of sudden death. I wonder that they have not been referred to perform cardiac MRI, or I misread the summary?

As Brugada syndrome is ≈10 times more frequent in men, it does not mean that it can not present in women, and because of this reason the presence of everything that was described makes this woman have a greater risk.

As she presents syncopal episodes to repetition, the ablation of the RVOT associated with quinidine prevents high number of ICD discharges or electrical storms. The FINGER study tries to stratify risk factors in asymptomatic patients with spontaneous type I pattern, which is not the case.

She has a high risk of SD, and I do not see any reason not to indicate ICD, which, thinking of a malignant behavior make the necessary adjuvant measures (quinidine, RVOT ablation).

I find it difficult to understand the controversy or doubts in this case.

Before placing ICD, it would complement with CMRI and genetic study in the patient and her relatives.

Regards

Martín Ibarrola, MD, Buenos Aires, Argentina
Portuguese: A causa da síncope com certeza é arrítmica e a etiologia muito provavelmente está associada a alguma miocardiopatia não evidenciada no ecocardiograma. Falam a favor de uma miocardiopatia a presença de fragmentação do QRS na porção descendente da derivação III e a documentação de uma TVNS monomórfica no loop recorder. A avaliação isolada do ECG não me permitiu esclarecer a etiologia.
Passos seguintes:
1º: ECG-AR
2º: RNM cardíaca.
3º: Estudo eletrofisiológico para definir a etiologia da síncope e estratificar o risco.
Forte abraço,

English: The cause of syncope is certainly arrhythmic, and the etiology is most likely associated with some cardiomyopathy not shown on the echocardiogram. The presence of QRS fragmentation in the descending portion of lead III and the documentation of a monomorphic NSV in the recorder loop are in favor of a cardiomyopathy. The isolated evaluation of the ECG did not allow me to clarify the etiology.
Following steps:
1º: SAECG
2º: CMRI.
3º: EPS to define the etiology of syncope and to stratify the risk.

Hugs
Acácio Fernandes Cardoso, MD
Spanish: Hola amigos
En respuesta a las preguntas:
1. Diagnóstico ECG: patrón tipo1 de Brugada por la elevación de punto J 2mm en V1 con elevación del segmento ST (tipo coved) descendente seguido de onda T negativa y simétrica. No considero patrón tipo 2 SADDLE BACK, por lo que no utilizaría mediciones de ángulo beta, ni de su base, ya que en V1 no hay rSr' que es lo que llevaría a realizar las mismas.
2. Que pasos a seguir?
   a. Descartar fenocopias (drogas, trastornos electrolíticos, cardiopatías estructurales, etc) según lo descripto por Andrés Pérez Riera
   b. Inmediato estudio electrofisiológico con hasta 3 extra-estímulos. Caso sea inducible, indicaría ablación por RF de tracto de salida del VD (1) o CDI como prevención primaria de la muerte súbita
Es mi humilde opinión, saludos cordiales.

Juan Jose Sirena, MD
Santiago del Estero, Argentina

English: Hello friends
In response to the questions:
1. ECG diagnosis: Brugada type 1 pattern by J ST-SE ≥2mm (coved type) followed by negative and symmetric T wave. I do not consider type 2 Brugada pattern (saddle back), so I would not use beta angle measurements, and nor its base, since in V1 there is no rSr' which is what would lead to them.
2. What steps to follow?
   a) Discard phenocopies (drugs, electrolytic disorders, structural heart disease, etc.) as described by Andrés Pérez Riera
   b) Immediate EPS with up to 3 extra-stimuli. If inducible, it would indicate RFCA of the RVOT epicardium (1) or ICD implantation as the primary prevention of SCD.
It is my humble opinion, best regards.
Juan Jose Sirena, MD
Santiago del Estero, Argentina
Amigos
Brugada tipo 1 com períodos que não se registra no ECG. Achado possível em BRUGADA com casos anteriores similares já relatados neste FIAI. Síncope. TVNS no “Holter" de 30 dias. Mortes súbitas em familiares de 1º grau, fQRS. CDI e quinidina se necessário. Conordo com muitas das opiniões nesta abordagem e como Martin e El Potro não vejo razões de dúvidas neste caso. Abraços a todos
Adail P. Almeida, MD

Friends
Brugada type 1 with periods not recorded on the ECG. Possible finding in BRUGADA with similar previous cases already reported in this FIAI. Syncope. TVNS in the 30-day "Holter." Sudden deaths in first-degree relatives, fQRS, CDI, and quinidine if necessary.
I agree with many of the opinions in this approach and as Martin and Andrés see no reason for doubt in this case.
Hugs to all
Adail Paixão -Almeida, MD Vitória da Conquista Bahia
Final comments by

Andrés Ricardo Pérez-Riera, MD PhD
Design of Studies and Scientific Writing Laboratory of the ABC School of Medicine, Santo Andre, Brazil
Vectorcardiography section editor at Journal of Electrocardiology

https://ekgvcg.wordpress.com/
CV Lattes: http://buscatextual.cnpq.br/buscatextual/visualizacv.do?id=K4244824E7
Questions:
1. Which is the most probable clinical diagnosis? Why?
ECG diagnosis: Atypical type 1 Brugada pattern. Why atypical? Answer: Because the ST-segment elevation in right precordial leads is not convex to the top (coved type) or rectilinear oblique descendent. Let’s see:

a) Characteristic of ST-segment shape in genuine Brugada syndrome

The present case

"minor form" of Brugada syndrome (BrS) which is frequent in females with BrS

b) Fragmented QRS (see explanation later)

c) Malignant early repolarization pattern (ERP) in lateral leads I and aVL. Because it is associated with repetitive syncopes, it is probably considered an early repolarization syndrome (ERS), which currently is diagnosed in the presence of J-point elevation 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT in the setting of idiopathic VF. Consequently, it is not possible to affirm that the present case is an ERS.

d) In the present case we observe totally negative P wave in V1, probably caused by by high placing of the right precordial electrodes (see explanation in slides 74-78).
Irregular rhythm (fusion beats), heart rate 149bpm: Non-sustained (three or more ventricular complexes) QRS duration ≥120ms, accelerated idioventricular rhythm (AIVR) results when the rate of an ectopic ventricular pacemaker exceeds or is similar to that of the sinus node. Isorhythmic AV dissociation because sinus and ventricular complexes occurring at identical rates. Often it is associated with increased vagal tone and decreased sympathetic tone. It is caused by enhanced automaticity of ventricular pacemaker, although triggered activity may play a role especially in ischemia and digoxin toxicity. AIVR is classically seen in the reperfusion phase of an acute STEMI, e.g. post thrombolysis. Usually a well-tolerated, benign, self-limiting arrhythmia (see slide 61).

2. What are the appropriate steps for the diagnosis?
   a) To eliminate the possibility of visible structural heart disease by CMRI and eventual phenocopy following recommended steps in the literature. Brugada phenocopies are clinical entities that present with an ECG pattern identical to either the type 1 or type 2 Brugada patterns yet differ etiologically from true Brugada syndrome (BrS). The pattern presents in association with an identifiable condition and, upon resolution of that condition, the ECG pattern normalizes. Brugada phenocopy is not due to a congenital sodium channel abnormality. Indeed, the defining feature of Brugada phenocopy is the absence of true congenital Brugada syndrome. Therefore a provocative test with a sodium channel blocking agent such as ajmaline, flecainide, or procainamide will not reproduce the ECG pattern (Baranchuk 2012). The diagnostic criteria for Brugada phenocopies are (I-V are mandatory) (Baranchuk 2012; Anselm 2013-2014):
      • An ECG pattern that has a type-1 or type-2 Brugada morphology
      • The patient has an underlying condition that is identifiable
      • The ECG pattern resolves upon resolution of the underlying condition
      • There is a low clinical pretest probability of true Brugada syndrome determined by a lack of symptoms, medical history, and family history
      • The results of provocative testing with a sodium channel blocker such as ajmaline, flecainide, or procainamide are negative
      • Provocative testing is not mandatory if surgical RVOT manipulation has occurred within the last 96 hours.
      • The results of genetic testing are negative (desirable but not mandatory because the SCN5A mutation is identifiable in only 20% to 30% of probands affected by true BrS).
      • Correction of hypokalemia.
   b) Primary ICD implantation following last guideline (see next slide).
Additional measurements:
- Avoid drugs (brugadadrugs.org)
- Reduce fever immediately (paracetamol)
- Avoid excessive alcohol consumption
- Quinidine, if ICD indicated but refused or contraindicated (Class IIa). Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with frequent ICD discharges. Additionally, RFCA of epicardial RVOT can eliminate the BrS phenotype and warrants further study. Patients with BrS underwent epicardial mapping to identify areas of abnormal electrograms as target for RFCA. Substrate identification consisted in mapping right ventricle epicardial surface before and after flecainide (2 mg/kg per 10 minutes). After RFCA, flecainide and remap confirmed elimination of abnormal substrate, Brugada pattern, and VT/VF inducibility. Substrate elimination resulted in Brugada pattern disappearance and no VT/VF inducibility with minimal complications. After a median follow-up of 5 months, ECG remained normal despite flecainide (Brugada J 2015).
1. **Fragmented QRS (fQRS): The present case**

fQRS is defined as additional spikes within the QRS complex with normal QRS duration (QRSd). If QRSd is ≥120 ms, it is called wide fQRS (wfQRS). fQRS is a convenient marker of myocardial scar evaluated by ECG recording. fQRS was also a predictor of mortality and arrhythmic events.
Fragmented QRS overview

The QRS complex represents the electrical depolarization of ventricular myocardium. In the case of an undisturbed depolarization, the QRS complex has a normal configuration and duration, but abnormal electrical conduction leads to widening of the QRS complex. The block of one of the bundle branches results in a typical bundle branch block pattern. A QRS complex that cannot be classified as bundle branch block due to an atypical configuration is called nonspecific intraventricular conduction delay or pre-excitation type Wolff-Parkinson-White. If the QRS complex has normal duration and contains notched R or S waves, various RsR' patterns in at least 2 contiguous ECG leads is called a fragmented QRS (fQRS). If QRS duration is prolonged, the proper nomenclature is wide fragmented QRS (w-fQRS). The underlying pathophysiology is manifold and include myocardial scars induced by ischemic art disease, myocardial fibrosis due to other diseases, primary cardiac pathologies as well as systemic diseases with cardiac involvement. Pathologies on the cellular level, such as ion channel dysfunctions, also correlate with fragmented QRS. Besides the diagnostic relevance, fragmented QRS is known to have prognostic properties, for example in identifying high risk patients with coronary artery disease, cardiomyopathy, Brugada syndrome and acquired long QT syndrome; however, fQRS may also be detected in ECGs of healthy individuals (Steger 2015). fQRS is a novel ECG marker with more sensitivity and less specificity than Q wave. A combination of fQRS with Q wave in a 12-lead ECG results in up to 74% sensitivity and 92% specificity (Sadeghi 2016). fQRS frequency y and QRS duration were found to increase in obstructive sleep apnea syndrome (OSAS) patients. Both parameters are related with increased cardiovascular mortality. Considering the prognostic importance of ECG parameters, it may be reasonable to recommend more detailed evaluation of OSAS patients with fragmented or prolonged QRS complexes with respect to presence of cardiovascular diseases (Sayin 2015). Risk stratification of sudden cardiac death (SCD) is challenging. fQRS is proposed as a non-invasive ECG marker associated with mortality and SCD. Results from individual studies including small numbers of patients are discrepant. Rosengarten et al. (Rosengarten 2015) performed a meta-analysis of studies evaluating fQRS as a risk stratification tool to predict all-cause mortality and SCD. Electronic databases and bibliographies were systematically searched (1996-2014). Twelve studies (5009 patients) recruiting patients with coronary artery disease or non-ischemic cardiomyopathy were included. fQRS was associated with an all-cause mortality relative risk of 1.71 (CI 1.02-2.85) and a relative risk of SCD of 2.20 (CI 1.05-4.62). Subgroup analysis demonstrated greater mortality and SCD risk in those with LVEF >35% and SCD risk in those with QRS duration <120 ms. Fragmented QRS is associated with all-cause mortality and the occurrence of SCD and may be suited as a marker of SCD risk. The incremental benefit of fQRS should be assessed in a randomized, prospective setting. fQRS on initial presentation with acute coronary syndrome(ACS) is not predictive of subsequent events but, if present 6 months later, could be predictive of an adverse outcome (Akbarzadeh 2013). Regression of fQRS could be a maker of electrical reverse remodeling following CRT (Yang 2015). fQRS complex, as a sign of myocardial scar, predicts non-responsiveness to CRT. fQRS may help selecting of CRT candidates (Assadian Rad 2015).
Fragmented QRS in Brugada Syndrome

VT/VF inducibility is unable to identify high-risk patients, whereas the presence of a spontaneous type I ECG, history of syncope, ventricular effective refractory period <200 ms, and QRS fragmentation seem useful to identify candidates for prophylactic implantable cardioverter defibrillator.

Fragmented wide QRS complex in a 35-year-old Asian male patient with BrS. f-QRS appears to be a marker for the substrate for spontaneous VF in BrS and predicts patients at high risk of syncope. It is a conduction abnormality within the QRS complex (Morita 2008).
Presence of a “notch” within a non-wide QRS complex in two adjacent leads ($V_1-V_2$): f-QRS. It is a non-invasive marker of events (Das 2009).

**Entities where fQRS is used as a non-invasive marker of events** (Das 2009)

- **Coronary artery disease** (Das 2007; 2009; 2010) where it represents a conduction delay of the stimulus and is associated to an increase in mortality and arrhythmic events in these patients. The incremental benefit of fQRS should be assessed in a randomized, prospective setting.

- **Non-ischemic cardiomyopathies** (Das 2010). In non-ischemic dilated cardiomyopathy with narrow QRS to predict dyssynchrony (Tigen 2009)

- **Idiopathic dilated cardiomyopathy** (Sha 2011)

- **Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)** (Peters 2008)
Hypertrophic cardiomyopathy. fQRS is associated with HF with hospitalization in HCM patients who had a unique distribution of gene mutations. TNNI3 (Femenia 2012; Nomura 2015)

Acquired and congenital long QT syndrome (Yuce 2010; Haraoka 2010) fQRS plays an important role in the appearance of TdP in patients with acquired long QT interval Cardiac sarcoidosis (Homsi 2009)

Congenital heart diseases (Moss 2010)

Severe aortic valve stenosis. (Ağaç 2014; Canpolat 2015)

Chagas disease (Baranchuk 2012; 2014 a;b)

Coronary artery ectasia (CAE) (Sem 2014)

Brugada syndrome (Haraoka 2010)

Myocardial scar (Das 2008)

Behçet's disease: QRS duration is greater and fQRS complexes are more frequent in patients with Behçet's disease. These findings may indicate subclinical cardiac involvement in BD. Given the prognostic significance of ECG parameters, it is reasonable to evaluate patients with BD with prolonged and fQRS complexes more in detail such as late potentials in signal averaged ECG in terms of cardiac involvement (Sayin 2013)

Systemic lupus erythematosus (SLE): A careful cardiovascular evaluation and follow-up is essential to continuously improve survival in SLE. For this purpose, fQRS may be used for the early detection in patients with SLE (Demir 2014)
 ➢ **Hypertension:** fQRS is a common electrocardiographic phenomenon in patients with hypertension. Although the diagnostic value for LVH is limited, the presence of fQRS on ECG is associated with a higher risk for worse LVH (*Zhang 2015*).

 ➢ **Radiotherapy:** Radiotherapy for breast cancer induces development of fQRS on ECG. Cardiac radiation dose is independently associated with the development of FQRS (*Adar 2015*).

 ➢ **Nephrotic syndrome (NS) (*Tin 2015*):** This parameter can be used in the prediction of myocardial functions in this entity (*Özkan 2014*). An important factor to be concerned in the patient with NS is the medication. In the case of long-term use of steroid, the effect on the QRS can be expected (*Ito 1976*), and this might decrease the utility of fQRS detection.

 ➢ **Iron overload in patients with beta-thalassemia major (TM):** Since cardiac involvement is the primary cause of mortality in TM patients, the early diagnosis of cardiac dysfunction is of vital importance. The search for fQRS in the ECGs of these patients, particularly when cardiac T2* values, measured by cardiac MR cannot be determined and followed, is a non-expensive and easy-to-attain method for therapy management (*Bayar 20115*).

 ➢ **Obstructive sleep apnea syndrome (OSAS)** fQRS frequency y and QRS duration were found to increase in OSAS patients. Both parameters are related with increased cardiovascular mortality. Considering the prognostic importance of ECG parameters, it may be reasonable to recommend more detailed evaluation of OSAS patients with fQRS or wide QRS complexes with respect to presence of cardiovascular diseases (*Sayin 2015*).

 ➢ **Familial Mediterranean fever (FMF):** FMF patients displayed a statistically significant increase in frequency of fQRS. Doppler-derived diastolic index was statistically significantly impaired in FMF patients with fQRS as compared with the patients without fQRS. fQRS might be a new noninvasive marker for cardiac involvement in FMF patients (*Celik 2015*).
Mutations in several genes have been associated with early repolarization syndromes (ERS), but the clinical benefit of genetic testing in these patients is currently questionable. Brugada syndrome (BrS) and ERS differ with respect to the magnitude and lead location of abnormal J waves and are thought to represent a continuous spectrum of phenotypic expression termed J-wave syndromes (Antzelevitch 2015). The ECG finding of early repolarization (ER) is common in the general population with a prevalence of 1–2%, and was previously thought to be benign (Mehta 1995). However, ER in 2009 has been associated with an increased risk of ventricular fibrillation (VF) and SCD (Haïssaguerre 2009), and it has been suggested that it represents one facet of a larger group of ‘J-wave syndromes’, a spectrum of ER-associated condition, including BrS (Antzelevitch 2010). Currently, we know numerous gene defects associated with both the ERS and BrS.
History

Early repolarization (ER) was first described in 1936 by Shipley and Hallaran when they performed four-lead electrocardiograms (ECGs) on 200 healthy 20 to 35-year-old individuals and noticed an elevated ST segment in lead II in 25% of males and 16% of females (Shipley 1936). In 1938, Tomaszewski described this variant in a man who died from hypothermia (Tomaszewski 1938). The term "early repolarization" was coined by Grant in 1951 in his study on spatial vector electrocardiography (Grant 1951). In 1953, Osborn described the J wave, which also became known as Osborn wave in hypothermic dogs (Osborn 1953). The Osborn wave can be seen in both cardiac and non-cardiac disorders including neural/brain injury, increased vagal tone, hypercalcemia, and hypothermia (Derval 2011).

ER has historically been considered a normal variant, but it is becoming more evident through numerous case controls and population based studies that it is associated with an increased incidence of arrhythmic sudden cardiac arrest. Its link to malignant potential was suggested in 1984, when Otto et al. discussed idiopathic ventricular fibrillation (VF) that occurred in the sleep of three young Southeast Asian males with J waves and no structural heart disease (Otto 1984). Among patients with a history of idiopathic VF, Haïssaguerre et al. found an increased prevalence of ER in 2008 (Haïssaguerre 2008).

Epidemiology

Multiple cohort studies have estimated that the prevalence of ER occurs in up to 13% of the general population (Jones 2015; Haruta 2011; Sinner 2010; Rosso 2008; Tikkanen 2009). Over 75% of ER occurs in men who also have a higher degree of J point elevation (Tikkanen 2009). This is thought to be related to an increase in outward potassium current in men caused by higher levels of testosterone, which also increases the J wave (Benito 2010; Antzelevitch 2010). Men also represent 75% of ER malignant cases (Haïssaguerre 2008; Tikkanen 2009). J point elevation is found more frequently among patients with idiopathic VF than among healthy subjects (Sinner 2010). The frequency of J point elevation among young athletes was higher than among healthy adults but lower than among patients with idiopathic VF (Rosso 2008). African Americans also tend to have the ER pattern more often, but the arrhythmic risk in this population is uncertain (Perez 2012). In a case-control study, subjects with idiopathic VF have higher prevalence of ER (31%) than healthy control subjects (5%) (Haïssaguerre 2008). While ER is relatively prevalent in the general population, the incidence of idiopathic VF is low. The arrhythmic events usually occur at higher age (>55 years). In asymptomatic individuals before age of 45 years, the risk of SCD is three per 100,000 and the SCD risk is 11 per 100,000 with J waves and 30 per 100,000 with horizontal ST segment elevation. In a meta-analysis by Wu et al., the estimated absolute risk for arrhythmic death in patients with ER was 70 per 100,000 (Wu 2013).
The challenge in studying ERP is the lack of agreement on definition. Historically, the term ER was first used to describe ST-segment elevation (ST-SE) in the absence of chest pain (Wasserburger 1961) to differentiate these findings from acute myocardial infarction or pericarditis. In the absence of chest pain, these findings were considered benign (Klatsky 2003). ERP can represent distinct pathological conditions, including acute myocardial injury or infarction, Takotsubo cardiomyopathy (Zhong-qun 2013), pericarditis, and hypothermia (Osborn waves) (Osborn 1953). In the absence of these conditions, ERP is considered a normal ECG variant pattern, given its frequency in the population (Maury 2013). The study of ERP is complicated by the presence of not 1 but several key characteristics that must be considered, including the localization and number of leads in which ERP is present, the character of the QRS complex and J point (notching or slurring), the magnitude and duration of the J-point elevation, the elevation of the ST segment, and concomitant ECG findings such as J-wave augmentation or short coupled premature ventricular contractions (PVCs) (Nam 2008; 2010).

ERS: it is diagnosed in the presence of J-point elevation 1 mm in ≥ 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT in the setting of idiopathic VF (Priori 2013). Because terminal QRS slurs and notches are common, the consensus statement recommended that the diagnosis of ERS in family members should not be based on ECG findings alone. Familial cases (Nunn 2011) are currently associated with six genetic variants (see next slide) in several ion channel-encoding genes (Haïssaguerre 2009). As noted earlier, the definition was unclear because the J point was not clearly defined (Yong 2013).
I. Ventricular repolarization components on the electrocardiogram

- Transmural voltage gradient during early ventricular repolarization: phases 1 and 2 of AP
- Electrical heterogeneity among ventricular endocardium and epicardium during repolarization.
- The ventricular epicardium denotes an AP with a prominent transient outward K⁺ current (I_{to})-mediated notch.
- The AP of the endocardium shows a much smaller I_{to} current.
- J waves are associated with Phase 2 reentrant arrhythmias.

II) Ventricular depolarization components on the electrocardiogram

- QRS fragmentation (fQRS)
- QRS duration ≥120 ms in V2 and II
- Epsilon wave
- Right End Conduction Delay
- Parietal block
- QT peak
- QT end
- r-J interval
- Late potentials (LPs)
Transmembrane APs from epicardium, endocardium and midmyocardium (M cells): repolarization mechanism

A prominent AP notch in the epicardium mediated by $I_{to}$ channels is responsible for the appearance of J wave on the ECG of BrS, IVF.
Early repolarization mechanism in Brugada syndrome repolarization mechanism

Gene mutations SCN5A and other

↓I_{Na}; ↓I_{Ca}

I_{to}; ↑I_{K-ATP}

Type 1 Brugada Pattern

↓I_{Na}; ↓I_{Ca}

I_{to}; ↑I_{K-ATP}

Fever
Ischaemia
Multiple Drugs
Cocaine
Alcohol
Hypokalaemia
Hypothermia

Short-coupled PVCs/
Polymorphic VT
Phase 2 reentry VT

Self-terminating
VT/VF

Sustained VF

VT/VF
Depolarization mechanism

I. fQRS: defined as ≥ 2 notches of the R wave or in the nadir of the S wave in at least 2 consecutive leads.

II. QRSd ≥120 ms in V2 and II, fQRS are powerful depolarization marker for VF/SCD is a significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I in patients with BrS (Calò 2016)

III. QT-interval prolongation in right precordial leads (Pitzalis 2003)

IV. Presence of LPs on SAECG: 1) Total filtered QRSd (fQRS) ≥114 ms; 2) Root Mean Square voltage (RMS40) of the terminal 40 ms of the fQRS complexes ≥20 µV; 3) Duration of low-amplitude signals 40 µV of the f-QRS complexes (LAS_{40}) ≥38 ms; 4) LP is identified when 2 of the criteria are satisfied; 5) Right End Conduction Delay on VCG
r–J interval, defined as the time between the earliest deflection of the QRS complex and J wave
RECD in the right posterior quadrant: Depolarization mechanism

Type 1 Brugada pattern

T-loop: Rounded, small, with symmetrical inscription velocity of afferent and efferent limbs and a 1:1 length/width ratio: Repolarization mechanism.
T LOOPS CHARACTERISTICS IN ALL THREE GROUPS

GROUP I
Type-1 Brugada ECG Pattern
Frontal Plane

GROUP II
IRBBB
Frontal Plane

GROUP III
CRBBB
Frontal Plane

Horizontal Plane

CW: Clockwise Rotation, CCW Counter-clockwise Rotation
The 10 to 20ms initial forces are directed to left and downward (in LAFB this forces are directed to right and downward). Counterclockwise rotation (CCWR) with extreme left axis deviation, SII>SIII, prominent final R wave in aVR and prolonged R-peak time in this lead.
Abnormal expression of cardiac neural crest cells in heart development (Elizari 2007) in fact this theory is also eclectic because it admits both mechanisms: depolarization and repolarization. The cardiac neural crest (CNC) cells are a subpopulation of cranial neural crest discovered nearly 33 years ago by ablation of premigratory neural crest. The CNC cells are necessary for normal cardiovascular development.

CNC cells migrate from the neural tube to the circumpharyngeal ridge (i.e. circumpharyngeal crest), caudal pharyngeal arches (third, fourth, and sixth), and outflow tract (OFT) just before asymmetrical remodeling of the aortic arch arteries. Some of the CNC cells migrate in and envelop the nascent aortic arch arteries, while others continue to migrate and eventually colonize to later form the aorticopulmonary septum.
## Genetic defects associated with ERS

<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene/Protein</th>
<th>Ion Channel</th>
<th>% of Probands</th>
<th>Locus</th>
<th>Gene/Protein</th>
</tr>
</thead>
</table>
| ERS1    | 12p11.23  
KCNJ8, Kir6.1 variant S422L     | ↑K<sub>ATP</sub> |               | ERS1    | 12p11.23     |
| ERS2    | 12p13.3  
CACNA1C, Cav1.2                   | ↓I<sub>Ca</sub> | 4.1%          | ERS2    | 12p13.3      |
| ERS3    | 10p12.33  
CACNB2b, Caβ32b                    | ↓I<sub>Ca</sub> | 8.3%          | ERS3    | 10p12.33     |
| ERS4    | 7q21.11   
CACNA2D1, Cavα2β                   | ↓I<sub>Ca</sub> | 4.1%          | ERS4    | 7q21.11      |
| ERS5    | 12p12.1   
ABCC9, SUR2A                       | ↑I<sub>K-ATP</sub> | Rare          | ERS5    | 12p12.1      |
| ERS6    | 3p21     
SCN5A, Na<sup>V</sup> 1.5         | ↓I<sub>Na</sub> | Rare          | ERS6    | 3p21         |

**ERS1:** Delaney et al demonstrated that the *KCNJ8*-S422L variant is associated with both increased AF susceptibility and ER in the lateral leads indicating a role for Kir 6.1 K<sub>ATP</sub> channel in both ventricular and atrial repolarization. The *KCNJ8*-S422L mutation has been shown to shorten repolarization in ventricular tissue, yet with the identification of this mutation among patients with lone AF it is possible that expression of this mutation in the atrium could also shorten repolarization to increase AF susceptibility. Further evidence for *KCNJ8* as a candidate gene for ERS was provided by the finding of ER on the ECG of a mutation-positive proband and a mutation-positive first-degree relative (Delaney 2012). Barajas-Martínez demonstrated that KCNJ8 is a susceptibility gene for BrS and ERS and point to S422L as a possible hotspot mutation. Their findings suggest that the S422L-induced gain of function in ATP-sensitive potassium channel current is due to reduced sensitivity to intracellular ATP (Barajas-Martínez 2012).

**ERS2** Liu et al demonstrated that the loss-of-function CACNA1C-Q1916R mutation contributed to ERS-related SCD, and the phenotypic incomplete penetrance was modified by the SCN5A-R1193Q variant and sex. These findings suggest that phenotypes of ERS are modified by multiple genetic factors, which supports the theory that ERS may be an oligogenic disease (Liu 2017).
**Diagnosis**

ER is diagnosed on ECG as a sharp, well-defined positive deflection or notch immediately following a positive QRS complex at the onset of the ST segment, or the presence of slurring at the terminal part of the QRS complex (since the J point elevation may be hidden in the terminal part of the QRS complex, resulting in slurring of the terminal QRS complex). It is present when J point elevation is ≥0.1 mV or 1mm in two adjacent leads. The notch or the onset of the slur should be entirely above the baseline, and the angle between the tangent to the slur and the initial R downslope exceeds 10 degrees (Macfarlane 2015). ER can occur with ST segment elevation (with or without a J wave) or without ST segment elevation (with a J wave or a slurred QRS downstroke). The ST elevation is defined by ≥1 mm in at least two adjacent leads. The ST changes seen in early repolarization are different than the ST changes seen with acute ischemia/infarction that are due to current flow, called "injury current," across the area between ischemic and non-ischemic myocardium (Rautaharju 2009).

ER pattern (ERP) describes ECG findings of ER in the absence of symptomatic arrhythmias. If ERP is accompanied with a history of resuscitated idiopathic VF and/or polymorphic VT, is denominated early repolarization syndrome (ERS) (Priori 2013). ER falls under the category of J wave syndromes, which are a phenotypic spectrum of J wave disorders, including ERS, the BrS, and arrhythmias linked to ST-SEMI and hypothermia (Li 2015).
ERS3: Burashnikov et al observed that mutations in the LTCCs are detected in a high percentage of probands with J-wave syndromes associated with inherited cardiac arrhythmias, suggesting that genetic screening of Ca(v) genes may be a valuable diagnostic tool in identifying individuals at risk. These results are the first to identify CACNA2D1 as a novel BrS susceptibility gene and CACNA1C, CACNB2, and CACNA2D1 as possible novel ERS susceptibility genes (Burashnikov 2010).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Effect of Mutation on Current</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ8</td>
<td>K\textsubscript{ir}6.1</td>
<td>↑\textit{I}_{\text{KATP}}</td>
<td>12p11.23</td>
</tr>
<tr>
<td>ABCC9</td>
<td>SUR2</td>
<td>↑\textit{I}_{\text{KATP}}</td>
<td>12p12.1</td>
</tr>
<tr>
<td>KCNE5</td>
<td>MiRP4</td>
<td>↑\textit{I}_{\text{to}}</td>
<td>Xq22.3</td>
</tr>
<tr>
<td>DPP10</td>
<td>DPL2</td>
<td>↑\textit{I}_{\text{to}} (due to E5D polymorphism)</td>
<td>2q14.1</td>
</tr>
<tr>
<td>CACNA1C</td>
<td>Ca\textsubscript{V1.2} \alpha\textsubscript{1c}</td>
<td>↓\textit{I}_{\text{Ca.L}}</td>
<td>12p13.33</td>
</tr>
<tr>
<td>CACNB2B</td>
<td>Ca\textsubscript{V1.2} \beta\textsubscript{2b}</td>
<td>↓\textit{I}_{\text{Ca.L}}</td>
<td>10p12.33-p12.31</td>
</tr>
<tr>
<td>CACNA2D1</td>
<td>Ca\textsubscript{V1.2} \alpha2\delta1</td>
<td>↓\textit{I}_{\text{Ca.L}}</td>
<td>7q21.11</td>
</tr>
<tr>
<td>SCN5A</td>
<td>Na\textsubscript{V1.5} \alpha</td>
<td>↓\textit{I}_{\text{Na}}</td>
<td>3p21</td>
</tr>
<tr>
<td>SCN10A</td>
<td>Na\textsubscript{V1.8}</td>
<td>↓\textit{I}_{\text{Na}}</td>
<td>3p22.2</td>
</tr>
</tbody>
</table>
The present case corresponds to ER without ST-SE and notched
Malignant Early Repolarization Syndrome with diffuse J waves without ST segment elevation: Idiopathic ventricular fibrillation

This tracing belongs to a young Asian man with a strong family history of sudden death. He presents a history of frequent syncopal episodes occurring at rest. ECG: Sinus bradycardia (heart rate 42bpm), P, QRS and T axis +60°. Diffuse J wave with slur and notch at the end of QRS in all leads except aVR (mirror image) and aVL.
Classical case of type 3 diffuse J-wave with ERS (Yang 1996; Antzelevitch 2005)

J wave across the precordial leads

Reciprocal change or mirror image

Normal QRS axis +60°
Comments: The drug reduces the magnitude of the Ito channel – mediator of phase 1 and consequently normalizes the elevation of the ST segment. Additionally, it could improve repolarization due to its vagolytic effect (M2 muscarinic receptor block) and to the exacerbation of reflex sympathetic tone.

A: Basal tracing. We observe J-wave across all precordial and inferior leads.

B: ECG after two days after oral quinidine 1500 mg/day
Scope of the problem

ER is associated with increased risk of IVF in the absence of pre-existing heart conditions, and there is also an increased risk of VT and VF in patients with acute coronary events who have baseline ER pattern (Adler 2013; Oh 2013). ER has not been associated with non-arrhythmic cardiac diseases (Viskin 2016). As the evidence associating ER with sudden arrhythmic death is increasing, research has been focusing on ways to distinguish between benign and malignant patterns of ER in attempts to risk stratify patients for optimal management.

Risk Stratification: Various ECG parameters have been studied as prognostic indicators in patients with ER. Tikkanen et al. studied the ST-segment morphology in Finnish and American young healthy athletes. ST segments were classified as either horizontal/descending (≤0.1 mV within 100 ms after the J point; downsloping ST segment elevation is characterized by a STJ [J point]/ST80 [the point 80 ms after the J point] ratio >1) or rapidly ascending/upsloping (>0.1 mV elevation throughout the ST segment). The majority of these athletes (>85%) with ERP had the ascending ST variant. When comparing these athletes to ECGs from a large population, it was shown that the horizontal/descending variant of ST segments were more strongly associated with SCD as compared to patients without ER, and the upsloping pattern did not show significant association with sudden arrhythmic death (Roten 2016). However, the horizontal/descending variant is commonly seen in healthy adults and this may result in over-diagnosis of malignant pattern of ER (Viskin 2016). Roten et al. compared ECGs of patients with ER and VF with those of asymptomatic patients with ER pattern and found that patients with VF had significantly longer QTc intervals, had J wave and with higher J wave amplitudes, higher frequency of low-amplitude T waves, and lower T/R ratio (leads II or V₃) (Roten 2016). Among these parameters, low T/R ratio was most strongly associated with malignant ER. Cristoforetti et al. analyzed the slope of the J wave in ERS patients (the J wave slope is the angle between an ideal line drawn from J point perpendicular to isoelectric line and tangent to the J wave, resulting in a J angle) and the J wave duration (interval between the onset of J point [or J₀] and intersection of tangent to J wave with isoelectric line or the change in slope of the J wave into the ST/T wave, depending on which comes first), and compared these parameters to healthy athletes with ERP. ERS patients had longer duration of J waves (>60 ms) and had significantly wider J angle (>30°) than ERP patients. Longer J wave duration with wider J angle was shown to be associated with higher arrhythmic risk (Cristoforetti 2016). Other ECG parameters associated with malignant ER are the presence of ER in inferior/inferolateral leads (ERS type 2) or global ER (ERS type 3), and shifting of ER into a BrS pattern (involvement of the anterior precordial lead or ERS type 4) (Mahapatra 2016). Aizawa et al. studied J waves occurring after sudden RR-interval prolongations (pauses) caused by benign arrhythmias, and found that "pause-dependent augmentation" of J waves was associated with IVF with 100% positive predictive value and specificity (Mahida 2015). Thus, the dynamicity of the J wave (instantaneous J/ST changes or the accentuation of ER by arrhythmias) is associated with SCD. Exercise ECG testing has been shown to unmask high-risk ERPs. Bastiaenen et al., studied the exercise tolerance testing (ETT) and ajmaline provocation testing on 229 patients with history of aborted SCD, sustained ventricular arrhythmia, unexplained syncope,
and/or a positive family history of SCD with no definitive cardiac etiology. 26 of these patients had baseline ERP, and of these, ajmaline provocation and ETT led to the disappearance of all lateral ERPs and rapidly ascending ST segment patterns. In patients with horizontal/descending ST segment patterns, 40% of ER persisted in ajmaline provocation and 75% of ER persisted in ETT. Inferior ER persisted in 44% during ajmaline provocation and 40% during ETT. Patients with persistent ER had in increased likelihood of symptoms (mainly unexplained syncope) than patients with diminished ER during exercise tolerance testing (Bastiaenen 2013; Atta 2013).

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Description</th>
<th>Results</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>J wave amplitude &amp; ST segment morphology</td>
<td>≥0.1 mV, horizontal/descending ST segment</td>
<td>RR = 1.43 [1.05 – 1.94]</td>
<td>Tikkanen et al. (Tikkanen 2011)</td>
</tr>
<tr>
<td></td>
<td>≥0.2 mV, horizontal/descending ST segment, inferior leads</td>
<td>RR = 3.14 [1.56 – 6.30]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥0.1 mV, ascending ST segment</td>
<td>RR = 0.89 [0.52 – 1.55]</td>
<td></td>
</tr>
<tr>
<td>QTc Interval</td>
<td>Per 10 ms</td>
<td>OR = 1.15 [1.02 – 1.30]</td>
<td>Roten et al (Roten 2016)</td>
</tr>
<tr>
<td></td>
<td>QTc &gt; 420 ms</td>
<td>OR = 11.77 [4.23 – 32.79]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>QTc &gt; 400 ms</td>
<td>OR = 3.5 [1.96 – 6.25]</td>
<td></td>
</tr>
<tr>
<td>T waves</td>
<td>Low amplitude (&lt;0.1 mV and &lt;10% of R-wave amplitude in lead I, II, or V4 – V6</td>
<td>OR = 12.41 [5.38 – 28.61]</td>
<td>Roten et al. (Roten 2016)</td>
</tr>
<tr>
<td>T/R ratio (lead II or V5)</td>
<td>&lt;0.25</td>
<td>OR = 6.93 [3.98 – 12.07]</td>
<td>Roten et al. (Roten 2016)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.20</td>
<td>OR = 6.45 [3.82 – 10.89]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.15</td>
<td>OR = 5.73 [3.22 – 10.20]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.10</td>
<td>OR = 11.15 [4.81 – 25.85]</td>
<td></td>
</tr>
<tr>
<td>J wave duration</td>
<td>&gt;60 ms</td>
<td>Controls = 0%</td>
<td>Cristoforetti et al. (Cristoforetti 2016)</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Cases = 55.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls = 35.05 ± 10.33 ms &lt; Cases = 69.48 ± 27.93 ms (p &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>J wave slope</td>
<td>&gt;300</td>
<td>Controls = 8.3%</td>
<td>Cristoforetti et al (Cristoforetti 2016)</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>Cases = 55.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Controls = 20.00° ± 6.84° &lt; Cases = 32.59° ± 10.4° (p &lt; 0.001)</td>
<td></td>
</tr>
</tbody>
</table>
Currently, the term ER is used to refer to nonspecific ST-SE in algorithms used in commercial ECG machines (GE Healthcare; Phillips 2005). The 2009 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations for the standardization and interpretation of the ECG define ER as “a normal variant commonly characterized by J-point elevation and rapidly upslping or normal ST segment followed by tall positive T waves” (Rautaharju 2009). ERP was originally considered a normal variant with a benign outcome (Goldman 1953; Otto 1984). However, in the 1980s, abnormalities of the J point were associated with idiopathic VF and SD in isolated case reports (Goldman 1953). In 2000, Gussak and Antzelevitch (Gussak 2000) published experimental models demonstrating that under conditions predisposing to ST-SE, ERP resembled BrS in arrhythmogenicity. The arrhythmogenic hypothesis gained support in 2008 with the seminal publication by Haïssaguerre and colleagues (Haïssaguerre 2008) reporting that survivors of idiopathic sudden cardiac arrest were found to have terminal QRS slurring or notching at a greater frequency than control patients. These slurs and notches were described as ERP, and the authors did not require the presence of ST-SE in their definition. A series of population studies subsequently used the ER term to refer to terminal QRS slurring or notching without requiring ST-segment elevation (Noseworthy 2011). Thus began the semantic confusion that continues to this day. To complicate matters further, several studies have identified ER in reference to the J point. Traditionally, the J point has been characterized as the junction at the end of the QRS complex and beginning of the ST segment, a definition used by the 2009 American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society ECG standardizations document (Rautaharju 2009). Despite differences in magnitude and location, because the ERS and BrS are characterized by similar clinical features and J-wave abnormalities, they are often described as representing parts of a continuum of J-wave syndromes (Antzelevitch 2011). Historically, terminal QRS slurs and notches have been considered part of the QRS complex, a finding supported by the 1985 Common Standards of Electrocardiography Working Party (Guideline 1985). More recently, ERP has been defined by QRS slurring and notching, with the J point defined as the top of the terminal QRS slur or peak of the QRS notch, and is recognized as being the result of phase 1 of the action potential (Yan 1996). The lack of consensus in definitions of ERP and of J-point abnormalities results in difficulty in the interpretation of the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society expert consensus on the inherited arrhythmia syndromes (Priori 2013). The ERP was defined as ≥1-mm J-point elevation in ≥2 contiguous inferior or lateral leads. The authors recognize that ERP could refer to ST-SE. However, the consensus document focuses on J-point elevation without a precise definition. The authors most likely refer to the J point as the top of the QRS slurs or notches described by Haïssaguerre et al (Haïssaguerre 2008) and those found in familial cases of idiopathic VF (Nunn 2011), but these definitions are not clear (Yong 2013). It is critical to standardize the definitions of ERP. The definition of ERP is an umbrella term that can mean any of the following: ST-SE in the absence of chest pain, terminal QRS slurring, or terminal QRS notching. Clinical studies that use the term ER should clearly state which of these ECG patterns is being used. Some have suggested elimination of ER terminology altogether (Surawicz 2011). Others have suggested using the term
Terminology: The following definitions are proposed to help standardize the terminology used in conjunction with ERP.

ERP: An umbrella term that can refer to ST-SE in the absence of chest pain, terminal QRS slur, or terminal QRS notch. When used, this term should be qualified or defined.

i) ECG criteria that suggest “benign” ERP

- HR: sinus bradycardia is frequent;
- Axes of QRS, ST segment and T wave, are oriented in the same direction in the FP;
- Deep and narrow Q waves followed by R wave of great voltage in left precordial leads;
- Terminal QRS slur, or terminal QRS notch;
- Transition area in precordial leads of sudden occurrence;
- J point and ST segment elevation, usually < 2 mm (exceptionally it may be > 5 mm) of superior concavity in middle and/or left precordial leads and possibly in inferior leads;
- Possible reduction in J point and ST segment elevation by sympathetic action and sympathomimetic drugs;
- Absence of reciprocal or mirror image (with exception in VR lead);
- Symmetrical T waves, with great width and polarity matching QRS;

J-wave pattern to differentiate ST-SE from QRS slur/notch (Froelicher 2013). Neither of these approaches has been widely adopted. When the term ERP is used, it should be qualified further such as ERP with ST-SE or ERP with terminal QRS slur/notch.
Inverse and significant correlation between J wave voltage (mm) and central temperature in hypothermia.
The tracing was obtained during cooling of the blood before a surgical procedure of the heart. Although the ECG obtained was somewhat expected, what was striking is that the progressive development and augmentation of the J wave was recorded. Most of the hypothermia cases are published in the moment when the patient is rescued and after recovery. On the other hand, in this case we can see the time course of changes up to the simulation of a monophasic action potential. Additionally, significant bradycardia is observed and the QT interval was too prolonged, something that usually is not given much attention in the published cases.

Courtesy from Prof. Dr. Raimundo Puerta from Cuba
2. Normothermic states

J-wave syndromes: a group of clinical entities that share similar molecular, ionic and cellular mechanism and marked by amplified J wave on the ECG and a risk of PVT/VF.

- BrS: J-wave in the right precordial leads V1-V3
- IVF
- SQTS
- LQTS

### Type 2

Type 2: ERP in the inferior (II, III, aVF) or inferolateral leads (II, III, aVF, V5-6). Intermediate risk.

### Type 3

Type 3: ERP global (inferior, lateral, and right precordial leads). Highest risk.

### Brugada syndrome

#### Concept

Clinical and electrocardiographic entity (without apparent structural heart disease) hereditary heterogeneous pattern with autosomal dominant transmission (33% of cases) or sporadic (67%), mainly caused by mutation in the SCN5A gene encoding the α subunit of Na+ channel (Na (v) 1.5) located on the short arm of chromosome 3 (locus: 3p21). Until present date, 20 types of genes affected are known. Clinically manifested by a tendency to syncope and/or sudden death in 60-80% of cases during night rest, with great male predominance (8:1), endemic in Southeast Asia (Thailand, Philippines) and Japan, predominantly in productive life time (young adult).

#### Diagnosis criteria

1. Absence of apparent structural heart disease
2. Absence of drugs effects, electrolyte disturbance and CHD
3. Documented PVT/VF
4. Family history of SCD at <45 years in first-degree relatives
5. Type 1 ECG Brugada pattern (coved-type) in proband and family members
6. Induction of VT/VF with Programmed Electrical Stimulation
7. Syncope, cardiac arrest or nocturnal agonal respiration.
Clinical diagnosis: Syncope. Positive familiar background of sudden death in young (≤35 y/o) first-degree relative. Genetic research performed: negative.

ECG diagnosis: Sinus bradycardia (HR <60 bpm), Brugada type 1 ECG pattern, prolonged QRS duration, aVR signal: final R wave of aVR lead >3 mm, fQRS in V1-V2.

Extreme left axis deviation: Left anterior fascicular block? or Right superior fascicular block?
ECG/VCG correlation in the frontal plane

Name: MK; Age: 38 y/o; Gender: Male; Ethnic Group: Asian; Weight: 68 kg; Height: 1,70 m

Broad final R wave

RECD on right Superior quadrant:
RVOT
Depolarization mechanism

CCW Rotation

Round, small T-Loop
Repolarization mechanism

Extreme Left Axis Deviation + CCW = LAFB
SIII>SII

+90°
ECG/VCG correlation horizontal plane

Name: MK; Age: 38 y/o; Gender: Male; Ethnic Group: Asian; Weight: 68 kg; Height: 1.70 m.
Twelve-lead ECG from the same 20-year-old man, recorded 72 hours later. The ERP persists, and there is now sinus bradycardia with a Brugada type 1 ECG pattern (coved type) in leads V1 to V3. The ST-segment elevation seen in lead aVR has been identified as a potential high-risk marker for ventricular arrhythmia in patients with BrS.
Inferolateral early repolarization patterns and magnitude of risk of sudden cardiac death. Estimated prevalence in the general population is manifested by width of the pyramid. Highest risk is on the top of the pyramid, and lowest on the bottom (Junttila 2012).

1. J-point with rapidly ascending ST segment followed by tall T wave considered a **Benign** form.

2. J-point with horizontal or descending ST segment, considered a **Malignant** form.

Primary electrical disorder ER with extensive repolarization abnormalities

- ST segment elevation ≥ 2mm in inferior leads shape horizontal or descendent
- ST segment elevation 01-2mm in inferior leads shape horizontal or descendent
- ST segment elevation 01mm in lateral leads shape horizontal or descendent
- ST segment elevation infero-ateral leads rapidly ascendent followed by tall T waves
<table>
<thead>
<tr>
<th>Early repolarization</th>
<th>Brugada syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age of first event 35 years</td>
<td>Average age of first event 30–40 years</td>
</tr>
<tr>
<td>Male predominance: 75%</td>
<td>Male predominance: 80%</td>
</tr>
<tr>
<td>Temporal variation in the expression of the ECG pattern</td>
<td>Temporal variation in the expression of the ECG pattern</td>
</tr>
<tr>
<td>Vagally mediated accentuation of ECG pattern</td>
<td>Vagally mediated accentuation of ECG pattern</td>
</tr>
<tr>
<td>Pattern with ascending ST-segment after J-point: lower risk</td>
<td>Pattern with ascending ST-segment after J-point, i.e. Type II and III ECG: lower risk</td>
</tr>
<tr>
<td>Normalization during quinidine exposure</td>
<td>Normalization during quinidine exposure</td>
</tr>
</tbody>
</table>
Short QT syndrome with early repolarization

The main features of congenital SQTS are:

➢ Absence of structural heart disease

➢ Familial clinical-electrocardiographic entity

➢ Autosomal dominant inheritance or sporadic, and genetically heterogeneous

➢ Constant and uniform very short QT and QTc intervals (QTc interval ≤330 ms)

➢ Positive family history for sudden cardiac death (SCD)

➢ Manifested by syncope, sudden death, dizziness and high tendency to appearance of episodes of paroxysmal runs of atrial fibrillation (AF)

➢ The response to exercise testing is a slight reduction of the QT interval during the increase in heart rate.

➢ Short refractory periods and tendency for inducible AF and VF were seen in electrophysiology studies (EPSs).

➢ Autopsy did not reveal any structural heart disease
Name: MTC; Sex: F; Age: 54 y/o; Date: March 20, 2014; Ethnic group: Caucasian. ECG of one sister of the proband.

Clinical diagnosis: Congenital short QT syndrome with mutation in Caveolin-3 (SQT7).

ECG diagnosis: Sinus rhythm, HR = 68 bpm; P wave: ; SÂP + 32º, PR interval duration: 120 ms, PR segment depression (>0.5 mm) in II and V5, absence of ST segment, positive-negative T wave or “minus-plus T wave sign” in aVF, and QT = 280 ms; QTc = 295 ms.
El primer punto de inflexión de la rampa descendente de la onda R es considerado el punto J real. En estos casos el método de la “línea tangente” es ideal. Elevación del segmento ST = 0,8 mm. Consideramos una variante tipo C atípica de patrón de repolarización precoz. El aspecto de lambda es un marcador de arritmias fatales.
Irregular rhythm (fusion beats), heart rate 149bpm: Non-sustained (three or more ventricular complexes) QRS duration ≥ 120ms, accelerated idioventricular rhythm (AIVR) results when the rate of an ectopic ventricular pacemaker exceeds or is similar that of the sinus node. Isorhythmic AV dissociation because sinus and ventricular complexes occurring at identical rates. Often it is associated with increased vagal tone and decreased sympathetic tone. It is caused by enhanced automaticity of ventricular pacemaker, although triggered activity may play a role especially in ischemia and digoxin toxicity. AIVR is classically seen in the reperfusion phase of an acute STEMI, e.g. post thrombolysis. Usually a well-tolerated, benign, self-limiting arrhythmia.
I. **ST-segment elevation**: The elevation above the isoelectric baseline of the segment between the end of the QRS and the beginning of the T wave. The differential for ST-SE is broad and includes myocardial infarction (MI), Takotsubo, ventricular aneurysm and pericarditis. ST-SE in the absence of chest pain can be referred to as ERP with ST-SE.

II. **Terminal QRS notch**: A low-frequency deflection at the end of the QRS complex. These notches were initially described by Osborn (Osborn 1953) as J waves (referring to injury) during experimental hypothermia and later were called Osborn waves.

III. **Terminal QRS slur**: An abrupt change in the slope of the last deflection at the end of the QRS. It is also called lambda wave (Gussak 2004).

The ECG belong a symptomatic Thailand young man with strong familial antecedents of SD that shows persistent ST segment elevation in the inferior and apical leads, associated to concomitant reciprocal or mirror image in the anterior wall that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia (Riera 2004).
**V. J point:** Approximate point of convergence between the end of QRS complex and the onset of ST segment. It is considered the point at which the QRS complex finishes and the ST segment begins. The J-point is an essential landmark for measuring QRS duration and ST segment elevation and/or depression. J-point represents approximate the end of depolarization and the beginning of repolarization as determined by the surface ECG. There is an overlap of ≈10 milliseconds (Mirvis 1982). The J point is used to measure the degree of ST elevation or depression present. It is very important in ACS-ST segment elevation myocardial infarction (STEMI). The TP segment of precedent beat and the PRs or PQs segment (PRs), are used as reference as the isoelectric line. The point where the QRS ends and the ST segment begins (Rautaharju 2009). There is debate about whether terminal QRS slurs and notches should be considered part of the QRS segment, as recommended by the Common Standards of Electrocardiography Working Party (Guideline 1985). The J point should be measured with the peak representing the peak of the notch or onset of a slur when present.

**VI. J-point elevation:** An elevation of the J point ≥1 mm above the isoelectric baseline.

**VII. J wave:** The J wave (Gussak 1995), also referred to as the J deflection, "the camel's hump"/ camel-hump sign (Abbott 1976), “late delta wave”, elevated J-point (Yan 1996), hathook junction, hypothermic wave, prominent J wave, K wave, H wave, current of injury or Osborn wave (Ortak 2007): Hipothermal or cool wave (Maruyama 2004); Normotermal. Initially used by Osborn (Osborn 1953) to refer to notching at the end of the QRS seen during experimental hypothermia. However, it has more recently been used to refer to the presence of notches or terminal QRS slurs. For clarity, if this term is used, it should be further defined with the terminal QRS slur and notch terminology.

**VIII. Brugada ECG patternS:** A series of ST-segment abnormalities, including downward coved and saddleback ST-segment elevations, associated with SCD. These patterns were clearly defined in the BrS consensus statement (Antzelevitch 2005) and are located in precordial leads V₁ through V₃. Clinical studies, including those by Haïssaguerre et al (Haïssaguerre 2008), excluded these leads to differentiate ER from Brugada patterns.
ECG types from first consensus report (Wilde 2002)

**Type 1:** ST-segment elevation is triangular or coved to the top ("coved type") ≥2 mm (0.2 mV) elevation in >1 right precordial lead V₁-V₃ in the presence or absence of a sodium-channel blocker and followed by negative symmetrical T wave. Type 0 as coved-type ST elevation without a negative T wave (Take 2011).

**Type 2:** J point and ST segment elevation ≥2 mm (0.2 mV) with saddleback appearance, and remains at least 1 mm above the isoelectric line, followed by positive or biphasic T wave.

**Type 3:** J point and ST segment elevation <1 mm and with variable shape: whether coved type or saddleback appearance. In type 3, the terminal section of the ST segment never exceeds 1 mm above the isoelectric line. Note that type 2 and 3 patterns are characterized by the same general shape of the J-ST-T wave, but the ST segment elevation in type 3 pattern is slightly less than 0.1 mV.
New ECG classification

**Type 1 Brugada pattern:** J point and ST segment elevation $\geq$ 2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on the right precordial leads ($V_1$-$V_2$ or from $V_1$ through $V_3$) and/or high right precordial leads $V_{1H}$, $V_{2H}$ and $V_{3H}$.

**Type 2 Brugada pattern:** it has ST segment elevation with saddleback shape, high take-off angle broad, $\beta$ angle always $>36^\circ$ and the base of the triangle from high take-off of 5 mm.
the characteristics of the triangle formed by r’ enables the different criteria to be defined that are useful for diagnosis: a) the duration of the base of the triangle formed by r’ at 5 mm from the high take-off is greater than 5 mm, and b) the duration of QRS in Brugada type 2 syndrome is longer than in other cases with r’ in V1, and there is a mismatch between V1 and V6. See figure below.

**Type 1 Brugada pattern**

[High take-off ≥ 2 mm]

**Type 2 Brugada pattern**

[Base at 5 mm from high take-off]

[High take-off ≥ 2 mm]

[Negative T-wave]
In the new ECG criteria, only 2 ECG patterns are considered: pattern 1 identical to classic type 1 of other consensus (coved pattern) and pattern 2 that joins patterns 2 and 3 of the first consensus (saddle-back pattern) (Bayés de Luna 2012).

**Type 1 Brugada pattern in V1-V2:**
- At the end of QRS, there is ascending ST segment with a high take-off of at least 2 mm followed by a convex to the top or rectilinear downsloping ST segment. There are a few cases where high take-off is between 1 and 2 mm.
- There is no clear r’ wave.
- The high take-off does not correspond to the J-point.
- At 40 ms of take-off, the decrease in amplitude of ST segment is 4 mm (it is much higher in RBBB and athletes).
- ST segment at high take-off > ST segment at 40 ms > ST segment at 80 ms
- ST segment is followed by negative and symmetrical T-wave.
- The duration of QRS in V1 is longer than in RBBB and longer than in V6 (mismatch).

**Type 2 Brugada pattern in V1-V2:**
- High take-off that does not coincide with the J-point ≥ 2 mm.
- The descending arm of r’ coincides with the beginning of ST segment.
- ST segment upslope is at least 0.5 mm.
- ST segment is followed by positive T wave in V2.
- The characteristics of the triangle formed by r’ enables the differente criteria to be defined that are useful for diagnosis: a) the duration of the base of the triangle formed by r’ at 5 mm from the high take-off is greater than 3.5 mm, and b) the duration of QRS in Brugada type 2 syndrome is longer than in other cases with r’ in V1, and there is a mismatch between V1 and V6.
### Type 2 Brugada pattern versus ordinary “innocent” incomplete RBBB

<table>
<thead>
<tr>
<th></th>
<th>Type 2 Brugada pattern</th>
<th>Ordinary “innocent” incomplete RBBB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β angle</strong></td>
<td>&gt; 36°</td>
<td>Acute</td>
</tr>
<tr>
<td><strong>α angle</strong></td>
<td>Major</td>
<td>Minor</td>
</tr>
<tr>
<td><strong>T-wave</strong></td>
<td>Positive or plane</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Duration of triangle base from the high take-off at 5 mm</strong></td>
<td>Greater than 3.5 mm</td>
<td>Minimal</td>
</tr>
<tr>
<td><strong>High take-off</strong></td>
<td>Wide</td>
<td>Acute</td>
</tr>
</tbody>
</table>

### References

Proposal of classification of type 1 Brugada pattern

Right precordial leads

Subtype 1A
- STSE convex upward
- J-point

Subtype 1B
- STSE rectilinear oblique and downward

The dotted line is the tangent line

Inferior/lateral leads

Subtype 1C
- J-point

The dotted line is the tangent line
<table>
<thead>
<tr>
<th>Locus</th>
<th>Locus Position</th>
<th>Gene/Protein</th>
<th>Ion Channel</th>
<th>% of Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td>BrS1</td>
<td>3p21</td>
<td>SCN5A, Na(^{\text{v}})(^{\text{1.5}})</td>
<td>↓ I (\text{Na})</td>
<td>11-28%</td>
</tr>
<tr>
<td>BrS2</td>
<td>3p24</td>
<td>GPD1L</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS3</td>
<td>12p13.3</td>
<td>CACNA1C, Ca(^{\text{v}})(^{\text{1.2}})</td>
<td>↓ I (\text{Ca})</td>
<td>6.6%</td>
</tr>
<tr>
<td>BrS4</td>
<td>10p12.33</td>
<td>CACNB2b, Ca(^{\text{v}})(^{\beta 2b})</td>
<td>↓ I (\text{Ca})</td>
<td>4.8%</td>
</tr>
<tr>
<td>BrS5</td>
<td>19q13.1</td>
<td>SCN1B, Na(^{\text{v}})(^{\beta 1})</td>
<td>↓ I (\text{Na})</td>
<td>1.1%</td>
</tr>
<tr>
<td>BrS6</td>
<td>11q13-14</td>
<td>KCNE3, MiRP2</td>
<td>↑ I (\text{I}_{\text{o}})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS7</td>
<td>11q23.3</td>
<td>SCN3B, Na(^{\text{v}})(^{\beta 3})</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS8</td>
<td>12p11.23</td>
<td>KCNJ8, Kir6.1</td>
<td>↑ I (\text{K}_{\text{ATP}})</td>
<td>2%</td>
</tr>
<tr>
<td>BrS9</td>
<td>7q21.11</td>
<td>CACNA2D1, Ca(^{\text{v}})(^{2\alpha})</td>
<td>↓ I (\text{Ca})</td>
<td>1.8%</td>
</tr>
<tr>
<td>BrS10</td>
<td>1p13.2</td>
<td>KCND3, K(^{v})(^{4.3})</td>
<td>↑ I (\text{I}_{\text{o}})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS11</td>
<td>17p13.1</td>
<td>RANGRF, MOG1</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS12</td>
<td>3p21.2-p14.3</td>
<td>SLMAP</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS13</td>
<td>12p12.1</td>
<td>ABCC9, SUR2A</td>
<td>↑ I (\text{K}_{\text{ATP}})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS14</td>
<td>11q23</td>
<td>SCN2B, Na(^{\text{v}})(^{\beta 2})</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS15</td>
<td>12p11</td>
<td>PKP2, Plakophilin-2</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS16</td>
<td>3q28</td>
<td>FGF12, FHAF1</td>
<td>↓ I (\text{Na})</td>
<td>Rare</td>
</tr>
<tr>
<td>Locus</td>
<td>Gene/Protein</td>
<td>Ion Channel</td>
<td>% of Probands</td>
<td></td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>BrS17</td>
<td>3p22.2</td>
<td><em>SCN10A, Na</em>1.8</td>
<td>↓ I\text{Na}</td>
<td>~16.7%</td>
</tr>
<tr>
<td>BrS18</td>
<td>6q</td>
<td><em>HEY2 (transcriptional factor)</em></td>
<td>↑ I\text{Na}</td>
<td>Rare</td>
</tr>
<tr>
<td>BrS19</td>
<td>7p12.1</td>
<td><em>SEMA3A, Semaphorin</em></td>
<td>↑ I\text{o}</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Brugada syndrome diagnosis criteria (Antzelevitch 2005)**

1. Absence of apparent structural heart disease
2. Absence of drugs effects, electrolyte disturbance and CHD
3. Documented PVT/VF
4. Family history of SCD at <45 years in first-degree relatives
5. Type 1 ECG Brugada pattern (coved-type) in proband and family members
6. Induction of VT/VF with Programmed Electrical Stimulation
7. Syncope, cardiac arrest or nocturnal agonal respiration.
Algorithm for diagnosis, risk stratification, and treatment of Brugada syndrome

**Symptomatic**
- Aborted SCD ➔ ICD
- Documented VT with/without syncope ➔ ICD
- Spontaneous type 1 BrP + syncope ➔ ICD
- Electrical storm ➔ Isoprot. + (hydro) quinidine

**Asymptomatic**
- VT/VF induced by PVS ➔ ICD
- Spontaneous type 1 ECG BrP ➔ (Hydro) quinidine
- Drug-induced type 1 BrP + pos. fam. hist. ➔ ICD not indicated

**Definitive diagnosis**
Type 1 ECG, BrP, in V1 or V2 in standard position or higher (up to 2nd ICS), spontaneous or induced (ajmaline)

**General treatment measures**
- Avoid drugs (brugadadrugs.org)
- Reduce fever immediately (paracetamol)
- Avoid excessive alcohol consumption

**Class I**

**Class IIa**

**Class IIb**

**Class III**
Indication for therapy of patients with BrS. Recommendations with class designation are taken from Priori et al (Antzelevitch 2016). Recommendations without class designation are derived from unanimous consensus of the authors.

**Type 1 Brugada pattern**

- Avoid drugs that may induce or aggravate ST segment elevation in right precordial leads ([www.brugadadrugs.org](http://www.brugadadrugs.org))
- Avoid cocaine and excessive alcohol intake
- Immediately treat fever with antipyretic drugs (Class I)

**Symptomatic**

- Electrical storm
  - Isoproterenol ± quinidine (Class IIa)
    - Presumably arrhythmic origin
    - ICD (Class I)
    - Close follow-up
- Prior cardiac arrest sustained VT
  - ICD (Class IIa)
    - Repeat appropriate shocks
    - RVOT ablation (Class IIb)
- Syncope seizure NAR
  - Close follow-up with/without ILR

**Asymptomatic**

- Spontaneous and fever-induced type 1 Brugada pattern
  - Based on patient and ECG characteristics (age, gender, Jp amplitude, QRS fragmentation...)
  - Inducible VT/VF with up to 2 ES
  - ICD (Class IIb)
- Type 1 Brugada pattern induced by Na channel blocker
  - Close follow-up

**Quinidine, if ICD indicated but refused or contraindicated (Class IIa)**

ES: extra stimulus at right ventricular apex; ICD: implantable cardioverter defibrillator; ILR: implantable loop recorder; NAR: nocturnal agonal respiration; RVOT: right ventricular outflow tract; VF: ventricular fibrillation; VT: ventricular tachycardia
The first \(1/3\) of the P wave corresponds to right atrial activation, the final \(1/3\) corresponds to left atrial activation; the middle \(1/3\) is a combination of the two. In lead V1 the right and left atrial waveforms move in opposite directions. This produces a biphasic P wave “plus-minus” with the initial positive deflection corresponding to right atrial activation and the subsequent negative deflection denoting left atrial activation. This separation of right and left atrial electrical forces in lead V1 means that abnormalities affecting each individual atrial waveform can be discerned in this lead. Elsewhere, the overall shape of the P wave is used to infer the atrial abnormality. The P wave is typically biphasic in V1, with similar sizes of the positive and negative deflections. Negative P wave in V1 is the key to identifying high placement of V1-V2 electrodes in nonpathological subjects. (García-Niebla 2012) The P wave negative, indicating high placement of V1-V2 in patients without cardiac disease. (Bayés de Luna 2007.) The misplacement of precordial lead electrodes is perhaps the most frequent error found when ECGs are performed. The degree of inexactitude in the placement of precordial electrodes is closely related with the level of technical training of the professional performing the technique (Rajaganeshan 2008). A total of 120 subjects were recruited within 2 days from six hospitals. They comprised physicians, nurses and cardiac technicians involved in the clinical assessment and care of patients with suspected cardiac disease. Subjects were asked to complete a questionnaire and marked on two diagrams of the chest wall the positions they would place precordial electrodes V1-V6. This study showed wide inter-individual and inter-group variations in the placement of electrodes. Notably, V1 and V2 were frequently incorrectly positioned in the second intercostal space, especially by physicians. The correct position of V1 in the fourth right intercostal space was identified by 90% of cardiac technicians, 49% of nurses, 31% of physicians (excluding cardiologists) and--most disappointing of all--only 16% of cardiologists (\(p<0.001\) for inter-group differences). Because incorrect positioning of the precordial electrodes changes the ECG significantly, patients are at risk of potentially harmful therapeutic procedures. Equally, doctors who are aware of the possibility of lead misplacement may be inclined to ignore some ECG changes that may be genuine evidence of ischemia. The only safe solution is proper precordial electrode placement, which requires training and an environment supporting precision. Totally negative P wave in V1 in healthy subjects, suggests that V1 is recording the tail of the resulting vector instead of the head due to atrial depolarization.

Another cause of negative P wave in V1 is pectus excavatum or funnel chest. Tanner et al studied 36 consecutive patients with funnel chest treated surgically at the Division of General Thoracic Surgery of the University Hospital of Bern were screened for this study. Biphasic plus-minus P waves in lead V1 with a dominant negative force were found in 73% of preoperative ECGs, and 12 patients (33%) showed a completely negative P wave in V1 (Tanner 2016). See next slide.
P wave negative in V1 indicating high placement of V1-V2 in patients without structural heart disease. The misplacement of precordial lead electrodes is perhaps the most frequent error found when ECGs are performed.

The present case
Normal P-loop in a patient with normal thorax morphology in the right sagittal plane

Positive or biphasic plus-minus P-wave in the right sagittal plane
VCG P-loop in a patient with pectus excavatum in the right sagittal plane

Negative P-wave in the right sagittal plane, because all P-loops are located in the negative hemifield, consequence of posterior displacement of the atria. P-loop is totally positive in corrected Z and Y leads of VCG.
Localization of right precordial leads and accessory high parasternal leads (Butz 2010)

$V_1$ – over the 4th intercostal space, just to the right of the sternum.
$V_2$ – over the 4th intercostal space, just to the left of the sternum
$V_3$ – midway between $V_2$ and $V_4$.
$V_{1H}$ – over the 3rd or 2nd intercostal space, just to the right of the sternum.
$V_{2H}$ – over the 3rd or 2nd intercostal space, just to the left of the sternum.
IX. **Epsilon wave right precordial epsilon potentials or Fontaine wave:** Epsilon waves (ε): (30%) late potentials or low amplitude and short duration oscillations near the J point (immediately after) is considered a major criterion. Its wave constitute a mayor criteria for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (Wu 2009): A low-frequency terminal QRS deflection present in the anteroseptal precordial leads in patients with arrhythmogenic right ventricular cardiomyopathy. The morphology can be variable but is often a broad, low-amplitude terminal QRS notch. The characteristics are: intrinsic features - they are small notches or oscillations in variable quantities (1, 2, 3 or more); location - at the end of QRS in the J point or onset of ST segment (there is no consensus about this); leads - observed in right precordial leads, however Dr. Li Zhang et al, found the ε wave in the leads of the frontal plane, especially in inferior leads; frequency in ARVC/D - approximately 15-30% of cases in 12-lead ECG. This percentage increases if we use the ECG with the modified protocol; value of criterion - considered to be a major criterion for diagnosis by the Task Force for ARVC/D diagnosis (McKenna 1994; Fontaine 1999); high resolution ECG: observed more frequently with this method; pathognomonic character: in spite of the characteristics in ARVC/D, they are not pathognomonic, since they have been described in other diseases associated with myocardial damage: RV infarction, inferior or dorsal (Zorio 2005), sarcoidosis (Santucci 2004), sickle cell anemia (Hurst 1998), etc; meaning: late posterior potentials (PP) that occur in the RV free wall in patients with ARVC/D; inversion of T wave in leads V1-V3 and/or ε wave found in 70% of patients with ARVC/D. Epicardial electrophysiological studies in dysplastic areas reveal the LP that occur at the end of the QRS complex, in the J point, and at the onset of the ST segment, are explained by fibro-fatty substitution of myocardial tissue (Fontaine 1984).

X. **Pattern versus syndrome:** Pattern refers to an ECG characteristic, whereas syndrome is a collection of clinical findings (which may include certain ECG characteristics) that share a pathophysiological mechanism. A Brugada pattern, for example, refers to the ECG characteristic, whereas BrS is the disease entity that requires the presence of a type I Brugada pattern and clinical signs such as syncope or ventricular arrhythmias.

XI. **ERS:** it is diagnosed in the presence of J-point elevation 1 mm in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT. Familial cases have been described (Nunn 2011) and associated with rare genetic variants in several ion channel-encoding genes (Haïssaguerre 2009). In the 2013 Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society inherited arrhythmia expert consensus statement, ERS was defined by J-point elevation of 1 mm in ≥2 contiguous inferior or lateral leads in the setting of idiopathic VF (Priori 2013). As noted earlier, the definition was unclear because the J point was not clearly defined (Yong 2013). Because terminal QRS slurs and notches are common, the consensus statement recommended that the diagnosis of ERS in family members should not be based on ECG findings alone.
**IX. J-wave syndrome**

**J-wave syndrome**: Terminal QRS slurs or notches associated with cardiac arrest. This is often used as an umbrella term that includes BrS, ERS and IVF (Burashnikov 2010). J wave syndromes are a spectrum of variable phenotypes characterized by the appearance of prominent electrocardiographic J waves (or Osborn waves) with a risk of VF, including the inherited Brugada syndrome (BrS), traditional ERS, IVF with J wave in inferior leads as well as acquired arrhythmias linked to the acute ST-SE MI and hypothermia. Although they may bear differences with regard to the ECG lead location, amplitude, and underlying causes of J wave, these disease entities share a similar ionic and cellular basis, risk factors, and similar clinical outcomes. J wave syndromes were first defined by Yan et al., in a Chinese journal in 2004 (Yan 2004) and has gained worldwide recognition. J wave is a positive deflection immediately following the QRS complex of surface ECG or is in part buried inside of the QRS as notching or slurring. The J wave may be accompanied by an ST-SE, traditionally referred to as an ERP (Antzelevitch 2011). J wave (QRS slurring or notching) was first reported in an experimental model of hypercalcemia (Kraus 1920), followed by hypothermia-induced J waves in an accidentally frozen man by Tomaszewski, who described the wave as a very slowly inscribed deflection between the QRS complex and the ST segment (Tomaszewski 1938). Shipley and Hallaran described J wave in healthy young individuals shortly afterward (Shipley 1936). J wave was later named as Osborn wave after being highlighted by a landmark study in which Osborn described hypothermia-induced J wave in hypothermic dogs and its accentuation prior to VF (Osborn 1953). J waves have been increasingly recognized in subjects with CNS disorders (Hersch 1961), hypercalcemia (Sridharan 1984), BrS (Brugada 1992; Yan 1996), IVF (Kalla 2000; Haïssaguerre 2008), and myocardial ischemia (Yan 2004; Jastrzebski 2009). Especially, J wave has gained a great deal of attention after determining it as a sign of a substrate capable of generating fatal VT/VF. Underlying ionic and cellular basis of Ito-mediated J wave was elucidated in the days when the arterially perfused ventricular wedge preparation was first developed in 1996 (Yan 1996). Ito is the main current contributing to the repolarizing phase 1 of the AP. It is a result of the movement of K+ from the intracellular to the extracellular (Niwa 2010). Ito is rapidly activated and deactivated (Wettwer 1993). It is activated after the fast increase of the membrane potential following the phase 0 of the AP (Niwa 2010). Once activated, the outward flow of (K+) ions from inside the cells constitutes Ito and causes the transmembrane AP to decrease. This decrease of the transmembrane AP is known as repolarization. Ito is then quickly deactivated, stopping the repolarization and ending the phase 1 of the AP (Niwa 2010; Wettwer 1993). A distinct AP notch mediated by Ito in the epicardium, rather than the endocardium, produces a transmural voltage gradient during early ventricular repolarization that is, contributory to the registration of J waves in the ECG. The higher density of Ito in the epicardium compared to the midmyocardial (M) region and significantly greater than the endocardial region of the canine ventricle. Similar results were obtained in subepicardial and subendocardial myocytes from human ventricles (Wettwer 1994; Näbauer 1996). Factors that affect the gating properties of Ito or ventricular activation sequence can modify the appearance of the J wave.
Genetic forms

J-wave syndromes: a group of clinical entities that share similar molecular, ionic and cellular mechanism and marked by amplified J wave on the ECG and a risk of PVT/VF.

- **Without apparent structural heart disease**
  - BrS: J-wave in the right precordial leads V1-V3
  - Overlapping between BrS and ERS
  - Idiopathic VF
  - SQTS; LQTS

- **With structural heart disease**
  - Concealed forms of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) (*Nava 1988*)

Acquired forms

- Ischemia- mediated VT/VF: Vasospastic angina, Prinzmetal J waves/ Ischemic J-Waves
- Miscellaneous
  - Hypercalcemia
  - Brain injury
    - Subarachnoid hemorrhage
    - Acute intracranial hypertension
    - Transient postictal hemiplegia (Todd's paralysis) (*O'Connell 2013*)
  - Damage to sympathetic nerves in the neck: or spinal cord injury leading to loss of sympathetic tone
  - Cardiopulmonary arrest from over sedation (*Shinde 2007*)
  - Accessory third papillary muscle with a prominent J-wave
  - Hypervagotonia.
It is a result of the movement of K+ from the intracellular to the extracellular (Niwa 2010). $I_{o}$ is rapidly activated and deactivated (Wettwer 1993). It is activated after the fast increase of the membrane potential following the phase 0 of the AP (Niwa 2010). Once activated, the outward flow of (K+) ions from inside the cells constitutes Ito and causes the transmembrane potential to decrease. This decrease of the transmembrane potential is known as repolarization. Ito is then quickly deactivated, stopping the repolarization and ending the phase 1 of the AP (Niwa 2010; Wettwer 1993). A distinct AP notch mediated by Ito in the epicardium, rather than the endocardium, produces a transmural voltage gradient during early ventricular repolarization that is, contributory to the registration of J waves in the ECG. Several lines of evidence determined the higher density of Ito in the epicardium compared to the midmyocardial (M) region and significantly greater than the endocardial region of the canine ventricle. Similar results were obtained in subepicardial and subendocardial myocytes from human ventricles (Wettwer 1994; Näbauer 1996). Factors that affect the gating properties of Ito or ventricular activation sequence can modify the appearance of the J wave. For example, because of its slow recovery from inactivation, $I_{o}$ is reduced following faster heart rate, resulting in a decrease in the amplitude of the J waves.

**Phase 2 Reentry, An Initiator for Ventricular Fibrillation**

If the Ito-mediated epicardial AP notch is deep enough, complete loss of epicardial AP dome may occur. During transition to complete loss of the epicardial AP dome, a few electrical alterations occur (Yan 2004): The dome is markedly delayed immediately prior to its complete loss, resulting in paradoxical AP prolongation “downslope ST segment elevation,” which in fact is a giant J wave, followed by a negative T wave (Shu 2005); once the epicardial AP dome is completely lost, AP duration shortens $\approx 40\%$ (Yan GX 1999) causing a marked increase in TDR (Antzelevitch 2010); complete loss of the dome is often heterogeneous across the epicardium: that is, a complete loss of the dome with significantly AP shortening occurs in some areas, but the delayed AP dome remains in others (Yan 1999; Yan 2003). Due to a marked difference in AP duration and the property of the delayed dome similar to ER (Guo 2007), the dome may produce a new AP in the areas where complete loss of epicardial AP is present, leading to the formation of short-coupled PVCs, which can be capable of originating PVT/VF.
Because it is the propagation of the dome at AP phase 2, it is termed as phase 2 reentry, also demonstrated in humans. Phase 2 reentry is the initiator for VF in all of the J wave syndromes regardless of the locations of J wave on the ECG (D) (Antzelevitch 2001).

Schematic representation of RV epicardial action potential (AP) changes thought to underlie the ECG manifestation of Brugada syndrome.
The underlying biological mechanisms and pathogenesis of ERP and ERS have been areas of substantial focus over the past 2 decades, and many elegant studies have contributed to our current understanding (Koncz 2014). Some controversy exists as to whether the electrocardiographic findings represent ER, late depolarization, or neither (Nademanee 2011). The repolarization hypothesis suggests that the presence of the ERP reflects regional heterogeneity in the dispersion of repolarization currents (Antzelevitch 2010). Shifts favoring decreased inward sodium or calcium channel current or increased transient outward potassium current ($I_{to}$), for example, may drive this dispersion of repolarization. Augmented dispersion of repolarization predisposes to phase 2 reentry, allowing premature ventricular contractions to trigger VF. A transmural voltage gradient from ventricular epicardium to endocardium, caused by the prominence of epicardial $I_{to}$, results in the J wave. Increased net repolarization current results in an augmented voltage gradient causing an accentuation of the phase 1 notch of the action potential and J waves or ST-segment elevation (Yan 1996). Meticulous studies of canine left ventricular wedge preparations have shown accentuation of the action potential notch in the epicardium enhanced by vagal tone, associated with increased level of $I_{to}$ current, and reversed by quinidine and isoproterenol, supporting the repolarization hypothesis (Koncz 2014). The depolarization hypothesis proposes that slowed conduction in the right ventricular outflow tract with fractionated and late potentials contributes to arrhythmogenicity (Nademanee 2011).

Several observations have raised speculation that a genetic basis for ERP exists. First, ERP has been reported to occur more frequently among relatives of individuals who experienced idiopathic sudden cardiac arrest than control subjects (Nunn 2011). Second, a widespread heritable basis for ERP has been reported (Reinhard 2011). Data from the Framingham study and British cohorts suggest that there is evidence of heritability of ERP with a 2- to 2.5-times increased risk in siblings and offspring of subjects with inferolateral ERP (Reinhard 2011). Third, ERP has been observed as a feature of other genetic arrhythmia syndromes such as Brugada syndrome (McIntyre 2012) and short-QT syndrome (Watanabe 2010). Furthermore, some genetic variants reported to be associated with ERP have been associated with other arrhythmia syndromes, including Brugada syndrome (Barajas-Martínez 2012). Indeed, rare genetic variants in genes governing cardiac repolarization have been observed in candidate gene screening studies performed in affected individuals, including KCNJ8 (Medeiros-Domingo 2010), SCN5A (Watanabe 2011), and L-type calcium channel subunits (Burashnikov 2010). In contrast, despite the widespread heritable component reported to underlie ERP, a large-scale meta-analysis of genome-wide association studies did not identify any common variants significantly associated with ER (Sinner 2012). The authors speculate that heterogeneity in the definition of ERP may have contributed to the null findings of this analysis. In aggregate, these observations underscore the limited understanding of the genetic basis of the condition at present. It is conceivable that various genetic forms of ERP exist, ranging from highly penetrant mendelian forms of the condition to complex polygenic forms.
Acquired J Wave Syndromes

J wave syndromes can be acquired, and they share similar properties with those of inherited J wave syndromes, including ECG features and the underlying mechanism for VF (Antzelevitch 2010; Cui 2010). Hypothermia-induced J wave is well known, and the study that showed J wave accentuation prior to VF can be dated back to 1953 (Osborn 1953). Hypothermia can produce distinct J waves, resulting in phase 2 reentry and VF (Gurabi 2014). Note, hypothermia-induced J waves can be confined to some selected leads or manifest globally in all leads. Under normal conditions, much of the J wave is buried inside the QRS complex. With hypothermia, the epicardial AP notch is evidently accentuated, and transmural conduction is slowed bringing about a prominent J wave (Antzelevitch 2011). It seems that there is no prominent gender-related discrepancy in the manifestation of hypothermia-induced VF. This may be due to the powerful potential of hypothermia to significantly amplify the magnitude of J waves, which can then abate the basically gender-related diversity of the J wave. Another more common type of acquired J wave syndromes is ischemia-induced J wave syndrome (Yan 2004; Cui 2010; Wang 2008; Li 2009). During the early phase of acute MI in canine experiments, phase 2 reentry causes R-on-T ectopic beats capable of initiating VF (Yan 2004). Intrinsically, much higher density of Ito in the right compared to the left ventricular epicardium may be responsible for an increased incidence of ischemia-induced VF. This is further supported by the clinical observation of a higher incidence of primary VF in individuals with acute inferior MI who have right ventricular involvement (8.4%) than those without (2.7%), or with an anterior MI (5.0%) (Mehta 2001).
J-wave syndrome with structural heart disease
1. Concealed forms of arrhythmogenic dysplasia of the right ventricle

36-year-old patient, episode of VF

The authors interpreted this tracing as early repolarization pattern. Today we know that this is the typical type 1 ECG Brugada pattern, which from the vectorcardiographic point of view is diagnosed as RECD by one of the RB fascicles of the RBB (Nava 1988).
Clinical diagnosis: 56-year-old female who presented to the emergency department with a decreased level of consciousness following intensification of a two-week long worsening headache. The patient's past medical history was significant for hypertension for which she was on no medication. On physical exam, she was unconscious (Glasgow Coma Scale (GCS) 6).

ECG diagnosis: Wide-complex QRS VT (160 ms) at a rate of 294 bpm with visible fusion and capture beats. Monophasic R-waves in leads V1–V2 indicated left ventricular origin.
ECG diagnosis: The patient was electrically cardioverted and a second ECG performed after 8 minutes demonstrated rapid AF at 188 bpm and massive J-waves (maximal amplitude: 0.47 mV in lead II) with ST-segment elevation in the inferolateral leads and ST-segment depression in the anterior leads (V1–V4).
Computed tomography of the brain showing a massive intraparenchymal hematoma.
Clinical diagnosis: ECG performed subsequent postictal confusion/hemiplegia with left-sided upper and lower extremity hemiparesis: cerebral and cardiac hypoperfusion (ischemia) following a postictal event with an increase in sympathetic tone.

ECG diagnosis: Lambda waves or slurring at the end of QRS complex in the setting of cerebral injury such as trauma or hemorrhage; however, ECG evidence of a dynamically displaced J-point has not been previously described in the setting of postictal hemiplegia.
During myocardial ischemia in patients with Prinzmetal vasospastic angina. J-wave augmentations caused by myocardial ischemia during coronary spasms has lambda wave morphology. The presence and augmentation of J waves, especially prominent J waves with the characteristic ST-elevation patterns, were associated with VF (Sato 2012).

We show a continuous Holter monitoring below belonging to a man who had coronary revascularization a time ago, during an episode of angina and concomitant ST segment elevation and ischemic giant J-wave "lambda-like type” associated with Premature Ventricular Contractions with Bigeminy sequence and very short coupling. The PVCs disappear immediately after cessation of vasospastic ischemia with administration of sublingual nitrate.

**Observation:** the pattern is very similar with ECG-2 from the present case because we have f-QRS + lambda wave.
Association of f-QRS in at least two contiguous leads on the 12-lead ECG + Wide QRS complexes + J-waves ≥0.1 mV combined with a descending/horizontal ST segment constitute a malignant ER pattern (Misuzawa 2014). Identifying patients with higher risk of fatal arrhythmias after CABG surgery. All are components of multifactorial risk for increased morbidity and mortality, sudden cardiac death and recurrent cardiovascular events.
4. Hypercalcemia

Comparative of monophasic action potential with surface ECG in normal conditions and in hypercalcemia

QTC interval shortening, Q-oTc interval shortening: interval from Q wave onset to T wave onset corrected according to HR.
Q-aT interval decrease: interval between QRS onset to T wave apex. Values below 270 ms are diagnostic.

Almost absent ST segment
J-waves in hypercalcaemia are presumably due to an increase in the calcium-activated outward current and a decrease in the inward calcium current. This lead to all-or-none repolarization of the action potential (end of Phase 1 in the epicardium), creating an Ito channel-mediated transmural voltage gradient during ventricular repolarization.
References


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