Dear Andrés. I want to hear your opinion of this ECG. The Brugada ECG/syndrome is very rare in Finland. Would you classify this as type 1 Brugada? You may send the case to the forum, if it seems appropriate and not too simple. The 3 last ECGs are recorded in the cath lab and it may be somewhat difficult to do measurements from them.
The case was introduced by our electrophysiologists Mäkynen and Inkovaara.
Best regards
Kjell

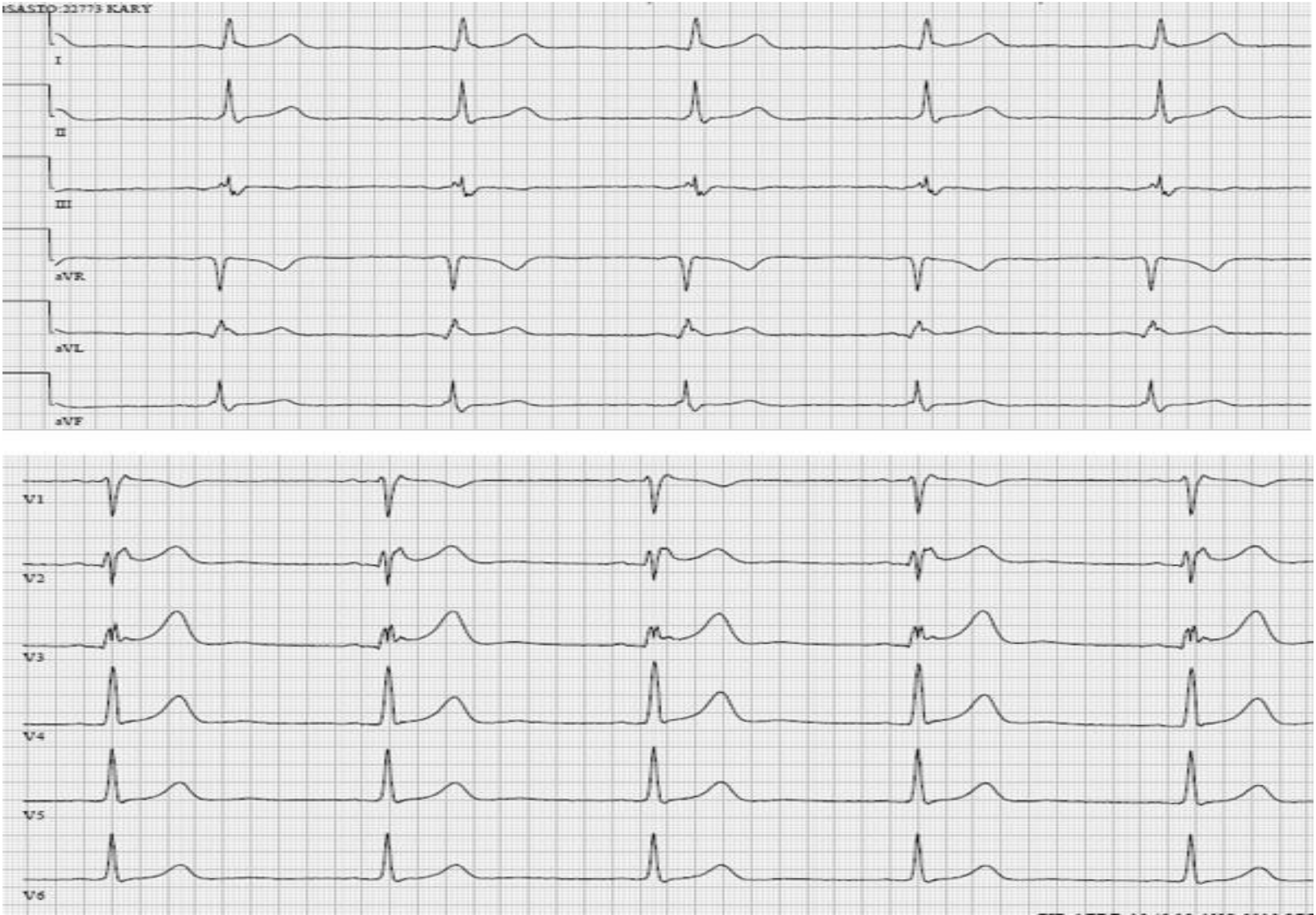
Dear all: Our dear friend Nikus from Finland sends us this precious case,
We are waiting for your valuable opinions.
Questions:
Which is the clinical/ECG diagnosis?
Which is the appropriate approach?
Andrés

Asymptomatic 37 years old male

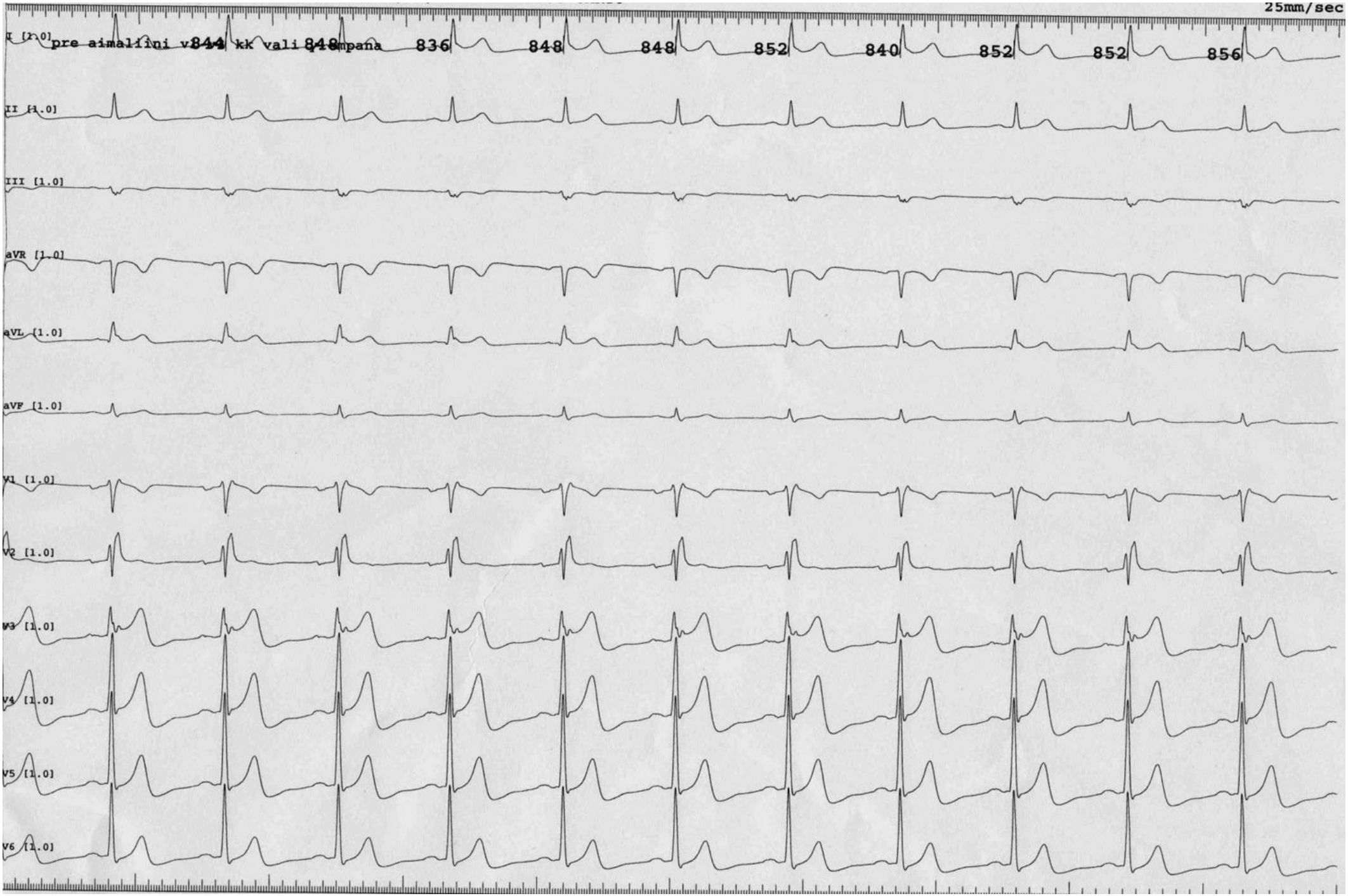
Family background:

- 1 year old child with syncopal attacks
- Sisters child: sudden death during sleep, 6 years old
- Cousin: sudden death immediately after swimming, 15 year old
- Echo normal

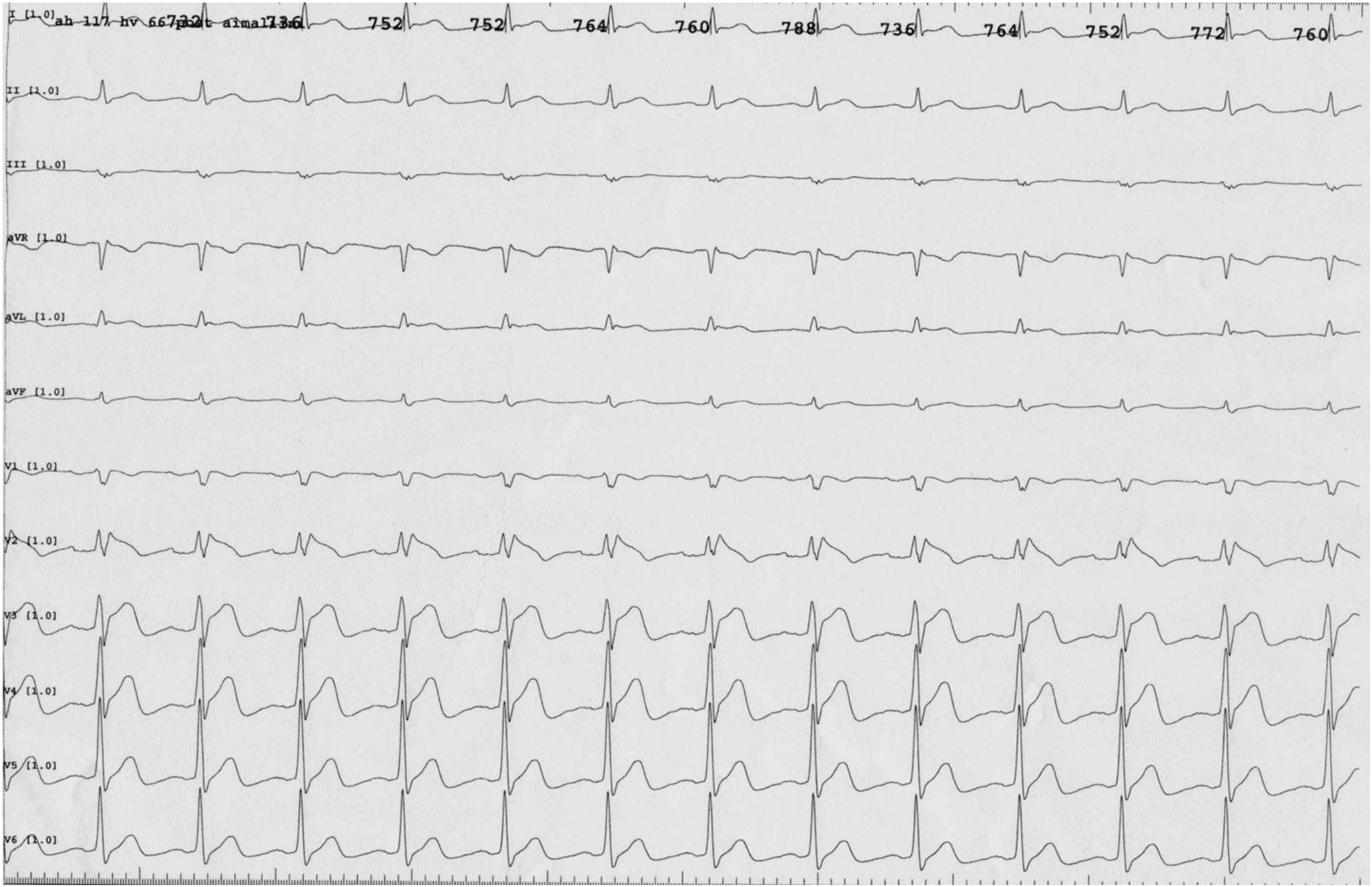
Standard ECG 50 mm/sec!!! (In Finland, this is the standard speed and not 25mm/sec)



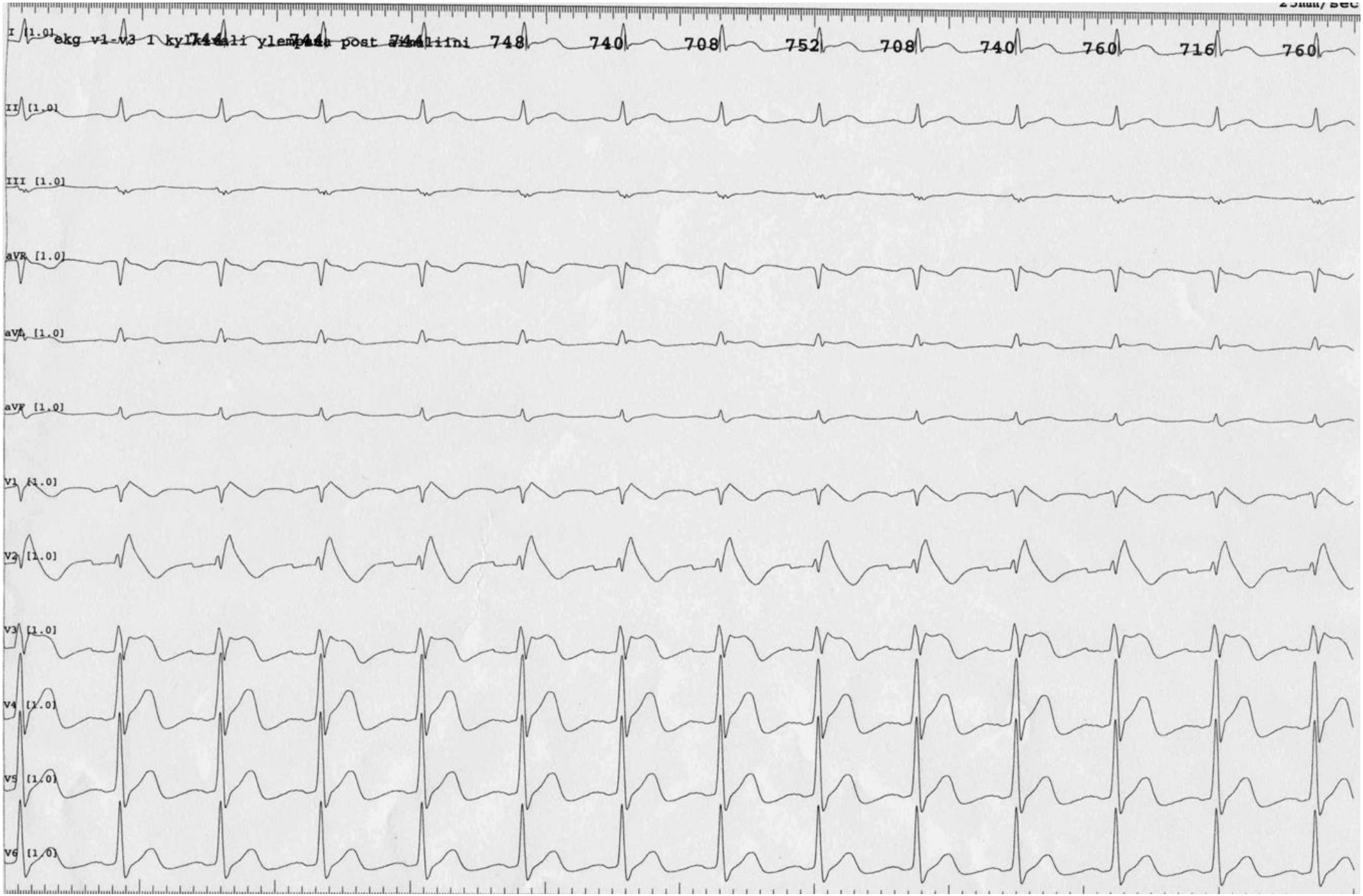
Before ajmaline in cath lab recorded from +1 intercostal space higher, 25 mm/sec



With ajmaline infusion, 25 mm/sec



With ajmaline, + 1 intercostal space higher recording 25 mm/sec



Colleague’s opinions

Hi Andrés and Nikus,

1. Type 1 Brugada pattern
2. Positive Ajmaline test
3. Asymptomatic with high family burden
4. Alternatives are:
    a. Close Follow-up
    b. Risk stratification with EPS (debatable): If positive (VF induction), ICD
    c. ICD given spontaneous type 1 and high family burden.

I would also recommend Genetic profile to determine the gene involved and facilitate family screening.

Adrian Baranchuk, MD FACC FRCPC
Associate Professor of Medicine and Physiology - Cardiac Electrophysiology and Pacing - Director, EP Training Program - Kingston General Hospital - FAPC 3, 76 Stuart Street K7L 2V7, Kingston ON Queen's University - Canada

Spanish
El ECG del adulto es la parte fácil del caso. Tiene un test de Ajmalina positivo (patrón Brugada tipo I con la droga).
Lo difícil es saber que hacer con esta respuesta. Lo mas probable es que este paciente y esta familia NO tengan síndrome de Brugada. Esta afirmación se basa en lo siguiente: En esta familia los sintomáticos son apenas los niños (el hijo de un año con síncopes, dos sobrinos (o sobrinas) muertos a los 6 años y a los 15 años de edad respectivamente).
El síndrome de Brugada es una enfermedad genética y por tanto está presente al nacimiento. Por otro lado, el síndrome de Brugada muy raramente produce arritmias en la infancia. Tenemos grandes series con cientos y hasta mil individuos con el síndrome (1029 en FINGER). Seria muy muy raro tener una familia con Brugada donde TODOS los miembros sintomáticos sean exclusivamente niños.
Hay que hacer ECGs del bebe con síncope y de los padres de los niños muertos. Todos los familiares tienen que hacer ECG, prueba de esfuerzo y ecocardiograma.
La enfermedad que más victima varios miembros de la misma familia es la taquicardia ventricular polimórfica catecolamigérgica (CPVT). El hecho de que uno de los integrantes tuvo muerte al dormir NO excluye CPVT.
Si llegamos a la conclusión que la familia es portadora del síndrome de Brugada (cosa que no va a ser fácil porque uno de los niños muertos es hijo de la hermana (mujer) que podría pasar el gen mutante sin tener el electrocardiograma, inclusive no con ajmalina (porque el test de ajmalina es menos conclusivo en mujeres, inclusive mujeres con historia de fibrilación ventricular (Are women with severely symptomatic Brugada syndrome different from men? J Cardiovasc Electrophysiol 2008).
Nuestro paciente no tiene síntomas. Tiene el patrón de Brugada tipo I únicamente con ajmalina. Según esto su pronóstico es excelente mismo que la familia tenga Brugada.
Yo le haría un Holter de 12 derivaciones para ver que no aparece el patrón Brugada tipo I espontáneo durante la noche. Si esto ocurre el pronóstico muda aumentando el riesgo. Este paciente tiene además otros signos electrocardiográficos de riesgo, incluyendo repolarización precoz en I, aVL y quizá fragmentación del QRS (los invito a ver "Risk Statification in Brugada syndrome: http://www.sciencedirect.com/science/article/pii/S1547527115011285).
Si llegamos a la conclusión que la familia es postadora del síndrome de Brugada y UNICAMENTE si el holter es positivo, le administraría quinidina . Yo no hago estudios electrofisiológicos porque creo que no tienen valor predictivo.
Sami Viskin

Head of cardiology hospital, laboratory and ECG ergometry at the Tel Aviv Medical Center, “Soraski” (“Ichilov”).

English: The adult ECG is the easy part of the case. He presents a positive ajmaline test (Brugada type I pattern with the drug). What is difficult to know is what to do with this response. Most likely, this patient and this family do NOT have Brugada syndrome (BrS). This statement is based on the following: in this family the symptomatic relatives are only the children (the 1-year-old child with syncope, two nephews or nieces dead at 6 years and 15 years respectively). BrS is a genetic disease and thus, it is present at birth and it very rarely produces arrhythmias in childhood. There are large series with hundreds and even thousands with the syndrome (1029 in FINGER) that show this. It would be very rare to have a family with Brugada in which ALL symptomatic members are exclusively children. ECGs of the baby with syncope should be made, as well as of the parents of the dead children. All relatives have to undergo ECG, stress test and echo.

The disease with more victims within a single family is catecholaminergic polymorphic ventricular tachycardia (CPVT). The fact that one of the members died while sleeping does NOT exclude CPVT. If we arrive to the conclusion that the family is carrier of BrS (which won't be easy as one of the dead children is the child of the sister (woman) that may pass along the mutant gene without having the characteristic ECG, even without ajmaline because the ajmaline test is less conclusive in the female gender, even in women with history of ventricular fibrillation [**Are women with severely symptomatic Brugada syndrome different from men? J CardiovascElectrophysiol 2008**]).

Our patient does not have symptoms. She has Brugada type I pattern only with ajmaline. According to this his prognosis is excellent, even if the family has Brugada. I would perform 12-lead Holter to see if spontaneous Brugada type I pattern appears, especially during the night. If this happens the prognosis changes, increasing the risk. This patient also has other risk ECG signs, including early repolarization in I, aVL and maybe QRS fragmentation (I invite you to read **Risk Statification in Brugada syndrome**: http://www.sciencedirect.com/science/article/pii/S1547527115011285).

If we reach the conclusion that the family is carrier of BrS and ONLY if the Holter is positive, I would administer quinidine. Personally, I do not indicate EPS because I think they do not have predictive value.

Sami Viskin

My diagnosis is that of Brugada-ECG type 2 at baseline and type 1 after ajmaline
The problem is mainly that of treatment with several possible options:

1. No treatment: with an estimate risk of #3% arrhytmic events during the next 6 years.
2. ICD ... now without any further exams.
3. EPS for risk stratification using the Pedro Brugada protocol (see recent paper of Conte and my Editorial comment in Circ Arrh Electrophys): no ICD if no inducible arrhythmias; ICD if inducible arrhythmia.
4. EP-guided therapy with quinidine if inducible VF (my paper on that is in press in Circ Arrh Electrophys): in my experience ZERO arrhythmic event during very long term follow-up in patients responding to quinidine who are compliant to the medication.
5. Finally, the last option that should (in my opinion) be only discussed but not attempted in the present case i.e. Epicardial ablation (see the recent paper by Josep Brugada in Circ Arrh Electrophys).

You will not be surprised if I do recommend Option # 3 (this option will allow the non-inducible patient at baseline to be only followed without drugs or ICD).

NB It is very interesting that know that Brugada syndrome is very rare in Finland.

Head of the Electrophysiology Laboratory,
Department of Cardiology, Tel-Aviv Medical Center, Tel-Aviv

Dear Andrés,

Thanks much for sharing an intriguing case with your ECG fans.

In my two cents it is risky jump to the conclusion without knowing the false positive rate of ajmaline tests and without assessment of his son who has syncope accordingly.

Most of BrS develop cardiac events around the 4th decade of the life span. The feature of early onset of syncope and sudden death in the family is atypical. Diagnosis however may be established if a BrS ECG pattern is captured in his son. Otherwise, genetic testing should be considered for the family.

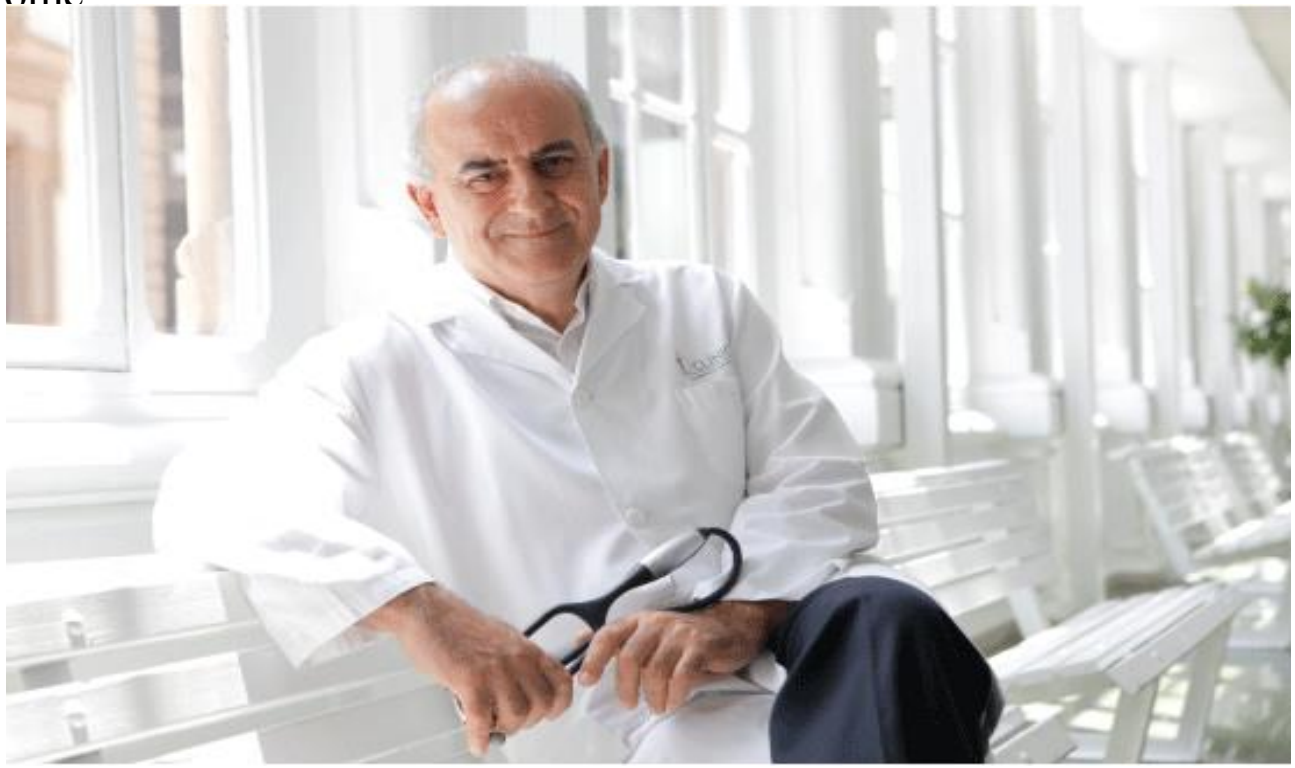
Sincerely yours,

Li Zhang
Associate Professor, Lankenau Institute for Medical Research
Honorary Professor, First and Second Affiliated Hospitals of Xi'an Jiaotong Univ. School of Medicine
Director, Cardiovascular Outcomes Research,
Main Line Health Heart Center
Chair, Electrophysiology, Chinese American Heart Association

For me there is no doubt
This is a clearly positive test

Dr. Josep Brugada Terradellas, MD, PhD, FESC.
Cardiologist, Specialist in Biology and Sport Medicine, MBA Management in Health Services. Medical Director of Hospital Clínic de Barcelona, head of the Arrhythmia Section of the Pediatric Hospital Sant Joan de Déu and Past President of the European Heart Rhythm Association. So far, he has published more than 574 original papers in the most relevant international journals, Prof. Brugada held also the post of Deputy Editor of the European Journal of Cardiology. He is member of several scientific societies and is Professor of Medicine at the University of Barcelona since 1998.

Regarding the field of research, he discovered, treated and found the genetic cause (along with his brother Pedro and Ramon) of a rare syndrome causing Sudden Death, which is known in the scientific literature as "Brugada Syndrome"



Dear Andres,

In this case, the family history is the most important element that facilitates the diagnosis. The ECGs obtained with precordial leads positioned in the second intercostal space and following Ajmaline administration, confirm the diagnosis of Brugada syndrome.
Although the patient has survived 37 years with no symptoms, I would recommend him to have an ICD implanted based .on the strong family history. I would also recommend genetic testing.

Thank you for sharing these interesting cases!

Mario González
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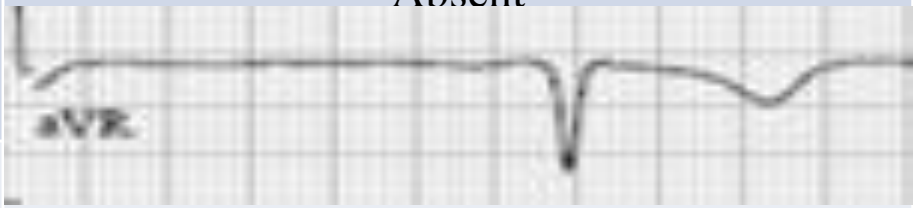
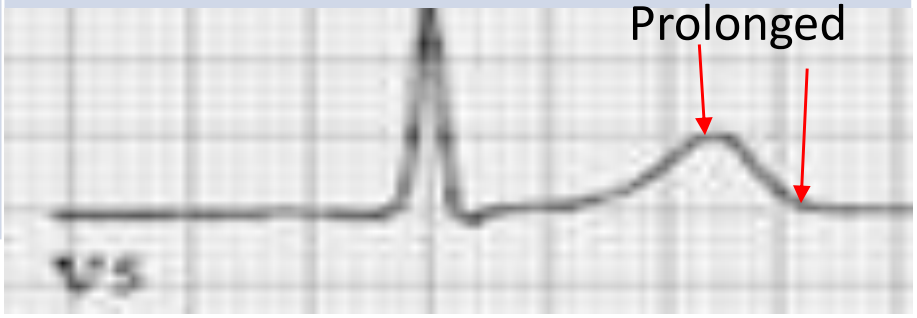
Final comments by Andrés Ricardo Pérez-Riera M.D. Ph.D.

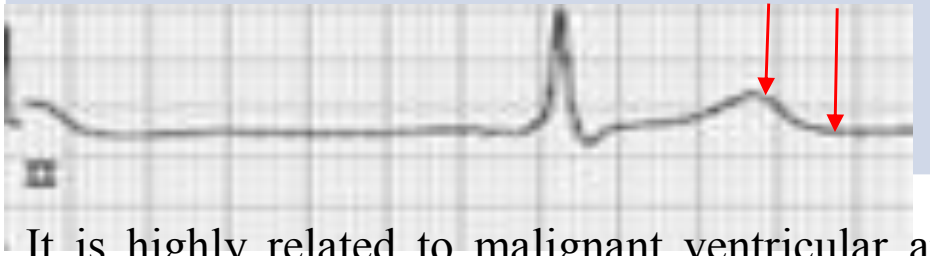
Electrocardiographic analysis

1. **Baseline ECG:**
    1. Type 2 ECG Brugada pattern +
    2. Early repolarization pattern: J wave syndromes +
    3. QRS fragmentation or fractionated QRS complexes(**f-QRS**)
2. **ECG after Ajmaline challange:** positive. Intravenous administration of class IC antiarrhythmic drugs is an established tool to unmask the diagnostic Brugada ECG pattern in patients with suspected BrS and non-diagnostic ECG (**Antzelevitch 2005**). Current data indicate that ajmaline is the most effective drug for the diagnosis of BrS, mainly because of its kinetics and strength of rate-dependent sodium channel blocking effects.(**Wolpert 2005**).
3. **Risk stratification in the proband**
    1. **PRELUDE registry data** (**Priori 2012**) show that 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 ICD. In the present case the proband has not spontaneous type 1 ECG Brugada pattern and he is asymptomatic but he has QRS fragmentation. I think that is indicated an EPS for to study the ventricular effective refractory period following PRELUDE registry, The objectives this registry were: 1) to evaluate the impact of different protocols of ventricular inducibility on the predictive value of PES; 2) to evaluate prospectively the predictive value of PES; and 3) to search for novel outcome predictors in BrS.
    2. **FINGER study** In the largest series of BrS patients, event rates in asymptomatic patients were low. Inducibility and family history of SCD were not predictors of cardiac events (**Probst 2010**)
    3. The presence of spontaneous type 1 ECG increases the risk for VF in all studies whereas the presence of f-QRS and early repolarization (ER) correlates with increased risk in several studies. Signal averaged techniques using late potentials (LP) and microscopic T-wave alternans show some promising results in small studies that need to be confirmed. (**Adler 2015**).

4. Arrhythmic events in asymptomatic BrS patients are not insignificant. Ventricular arrhythmias inducibility, spontaneous type I ECG and presence of sinus node dysfunction might be considered as risk factors and used to drive long term management. (Sieira 2015)

5. A meta-analysis for risk stratification concluded that a history of syncope or SCD, the presence of a spontaneous Type I Brugada ECG, and male gender predict a more malignant natural history. Our findings do not support the use of a family history of SCD, the presence of an SCN5A gene mutation, or EPS to guide the management of patients with a Brugada ECG. (Gehi 2006)

Predictors of malignant natural history in BrS	The present case
History of syncope or aborted cardiac arrest or documented sustained VT	Abstent low risk (around 0.5% annually) and therefore not indicated for ICD.
Spontaneous type 1 ECG Brugada pattern "coved-type" (≥ 0.2 mV) ST elevation followed by a negative T wave	Absent: Low risk
Male gender	Present
Inferolateral early repolarization in association	Present
f-QRS	Present
Atrial fibrillation/SSS/AV block	Absent
Prominent final R wave on aVR lead R wave ≥ 3 mm or R/q ≥ 0.75 in lead aVR aVR sign (Babai 2007) consequence of HV split or HV prolongation	Absent 
ST elevation after exercise/ meal/full stomach/glucose	
QT prolongation, longer T_{peak}–T_{end} Increased Tpeak-Tend interval in the precordial leads (Maury 2015).	Prolonged 



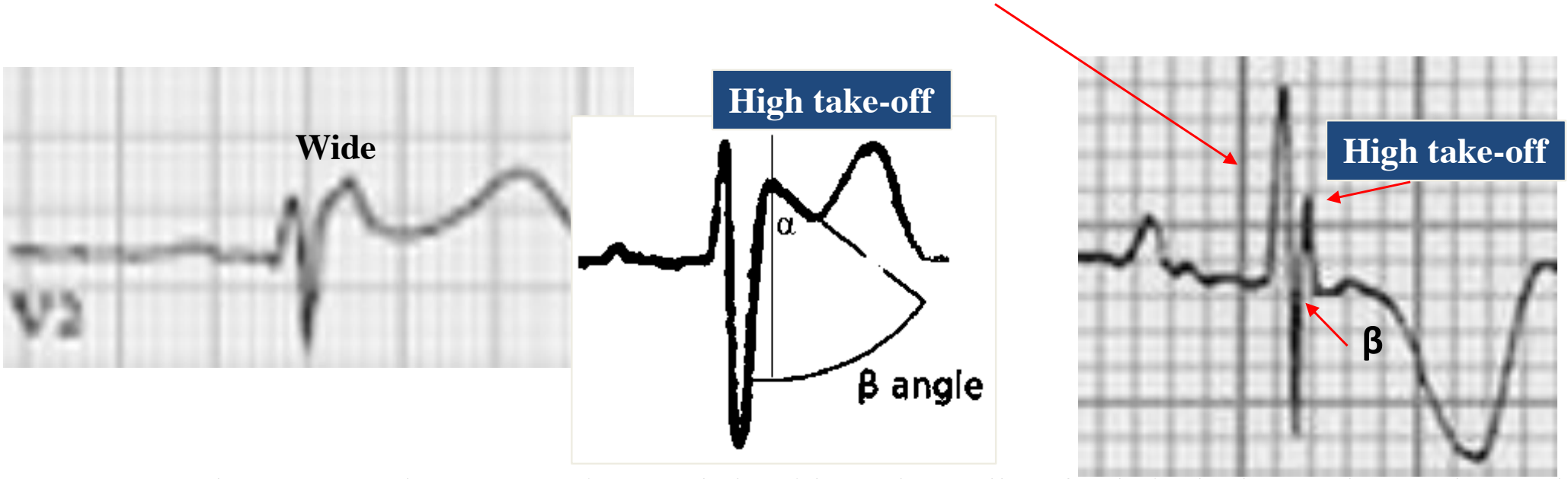
It is highly related to malignant ventricular arrhythmias in this large cohort of patients with BrS.

T_{peak}–T_{end} = 200 ms/ 50mm/seg

Macroscopic T wave alternans	?
QRS prolongation in V2 (≥ 120 ms) (**Junttila 2008**)	Present
Prolonged PR interval (> 200 ms) (***Miyamoto 2011***). consequence of HV split or HV prolongation	Absent
Abnormal late potentials on signal-averaged ECG	?
Ventricular effective refractory period < 200 ms	?
QTc interval more than 460 ms in lead V2 (**Take 2011**) and QT-interval prolongation in right precordial leads. Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block. (**Pitzalis 2003**)	?

Early onset of syncope and sudden death such as the present case in the family is very unusual
Current guidelines recommend ICD implantation only in patients with spontaneous type 1 ECG pattern, and either history of aborted cardiac arrest or documented sustained VT (class I), or syncope of arrhythmic origin (class IIa) because they are at high risk of recurrent arrhythmic events (up to 10% or more annually for those with aborted cardiac arrest).

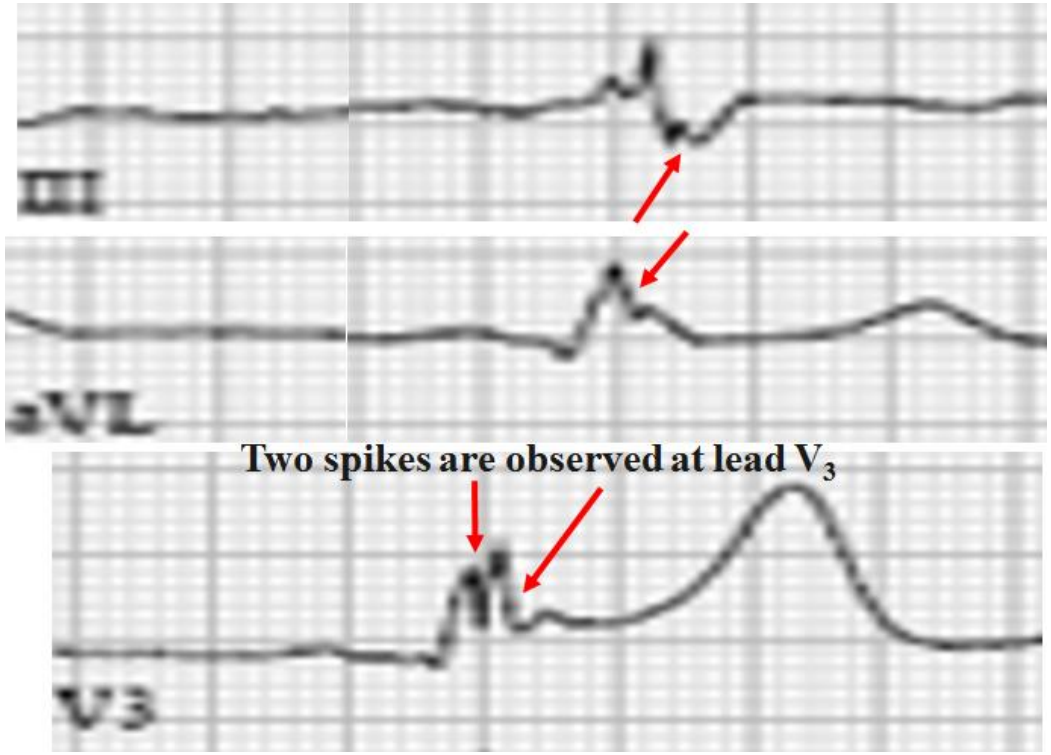
Type 2 Brugada pattern **versus** **ordinary "innocent" incomplete RBBB**



Type 2 Brugada pattern: The r´ wave is rounded, wide and usually of relatively low voltage The angle between the upslope of the S-wave and the downslope of the r'-wave is broad. (β angle) > 58°. (**Chevalier 2011**) Descending arm of r´ coincides with beginning of ST segment (J-point) Duration of the base of the triangle of r´ at 5mm from high take-off > 3.5mm The QRS duration is longer in Brugada pattern type 2 than in other cases of IRBBB with r´ in V1 and there is a mismatch between V1 and V6. In Brugada pattern the QRS complex end is earlier in V6 than in V1-V2.

β angle	> 58° broad	Acute
α angle	Mayor	Minor
T-wave	Positive or plane	Negative
Duration of triagle base from the high take-off at 5mm	Greater than 3.5 mm	Minimal
High take-off	Wide	Acute

Fragmented QRS (f-QRS)



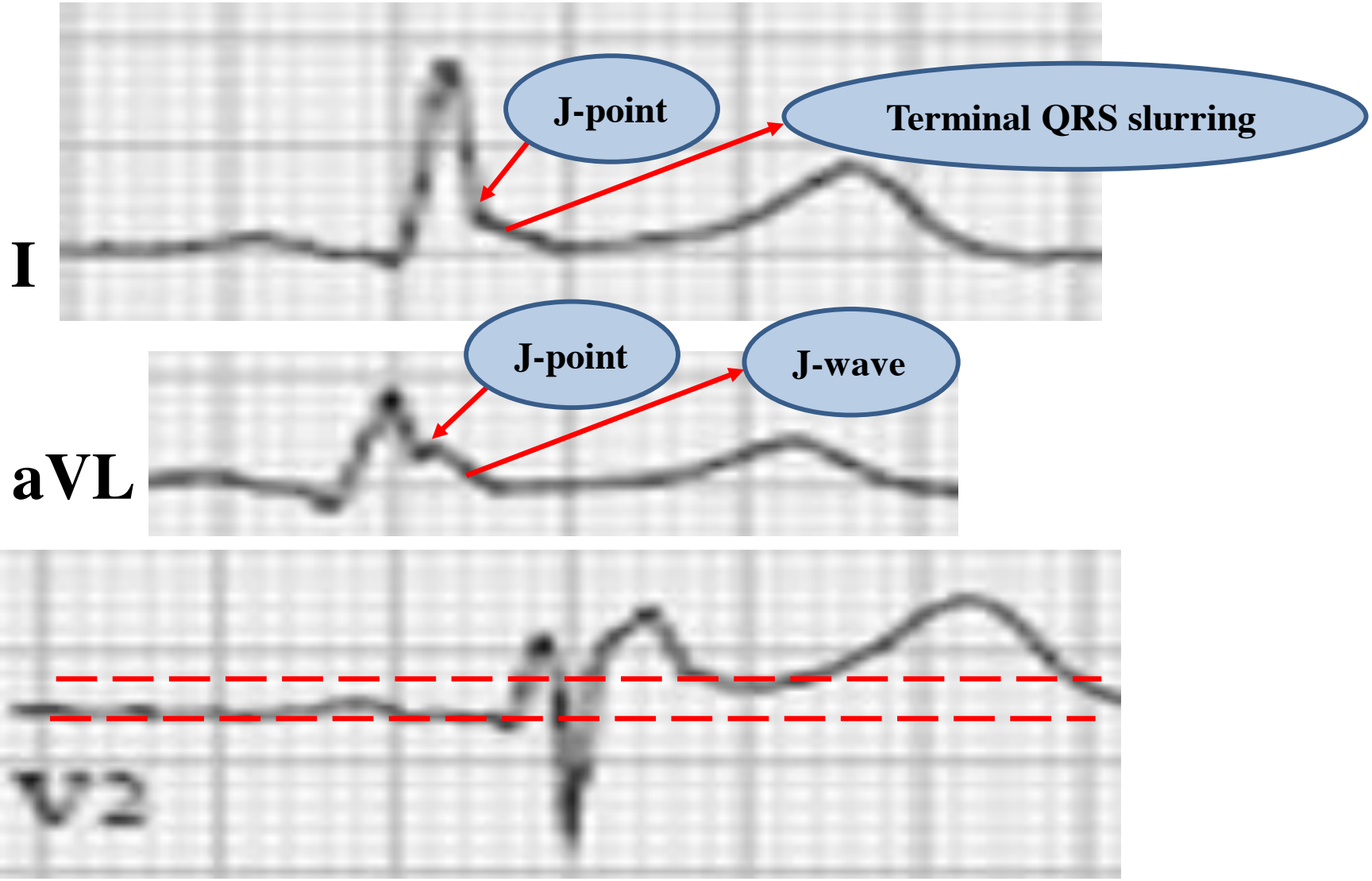
f-QRS appears to be a marker for the substrate for spontaneous VF in BrS and predicts patients at high risk of syncope. It is a conduction abnormality within the QRS complex (**Morita 2008**).

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

- **Coronary artery disease (Das 2010)** where it represents a conduction delay of the stimulus and is associated to an increase in mortality and arrhythmic events in these patients.
- **Non-ischemic cardiomyopathies (Das 2010). In non-ischemic dilated cardiomyopathy with narrow QRS to predict dyssynchrony (Tigen 2009)**
- **Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (Peters 2008)**
- **Cardiac sarcoidosis (Homsi 2009)**
- **Congenital heart diseases (Moss 2010)**
- **Brugada syndrome (Haraoka 2010)**
- **Acquired long QT syndrome (Yuce 2010)**

The existence of fQRS plays an important role in the appearance of Torsades de Pointes (TdP) in patients with acquired long QT interval.

Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities with high risk



Early repolarization pattern

A and B classic definition of ER always with ST segment elevation

A) ER with only ST segment elevation.

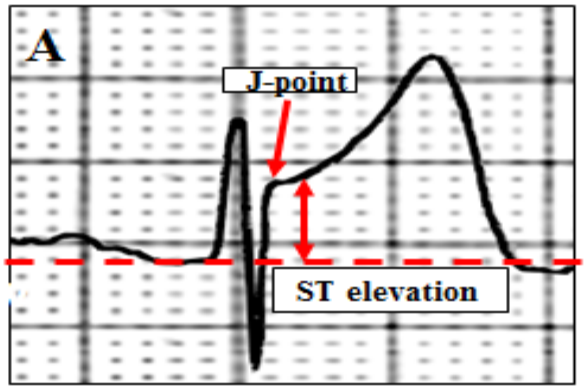
B) ER with ST segment elevation and J-point at the end of J wave.

C and D New concept of ER without ST segment elevation (Pérez 2012)

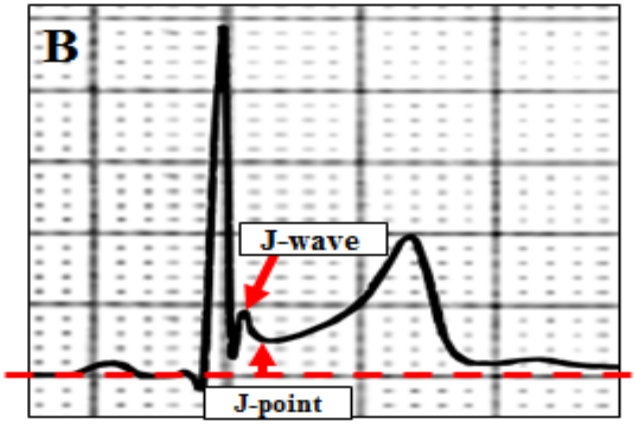
C) J-point elevation and terminal QRS slurring without ST segment elevation.

D) J-wave without ST segment elevation.

A and B classic definition of early repolarization: with ST segment elevation

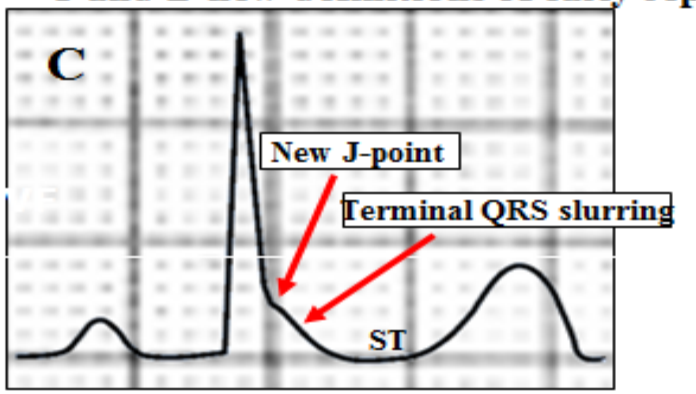


Without J wave and STSE

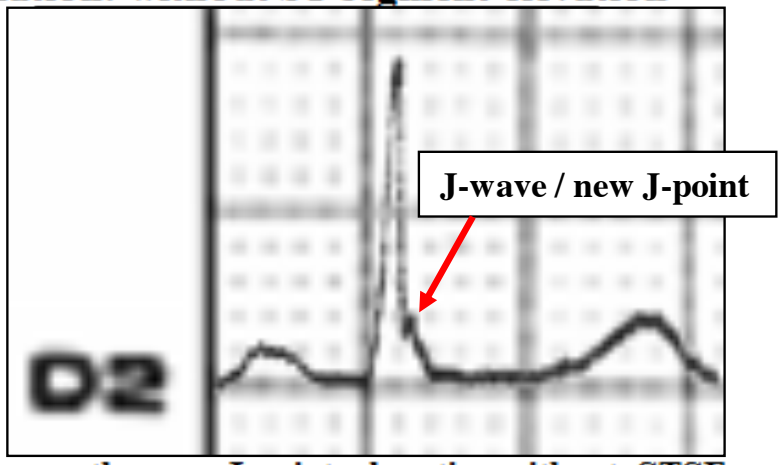


With J wave and STSE

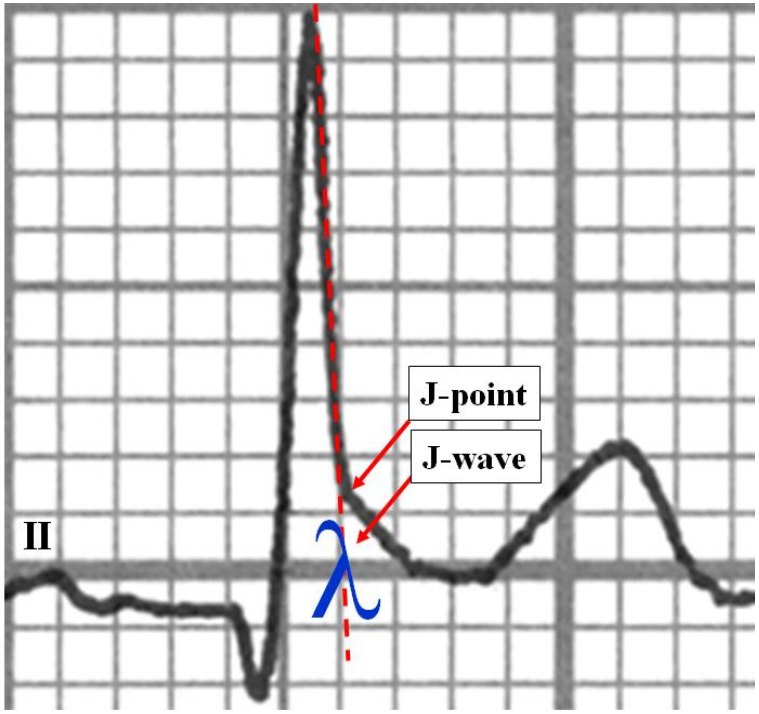
C and D new definitions of early repolarization: without ST segment elevation



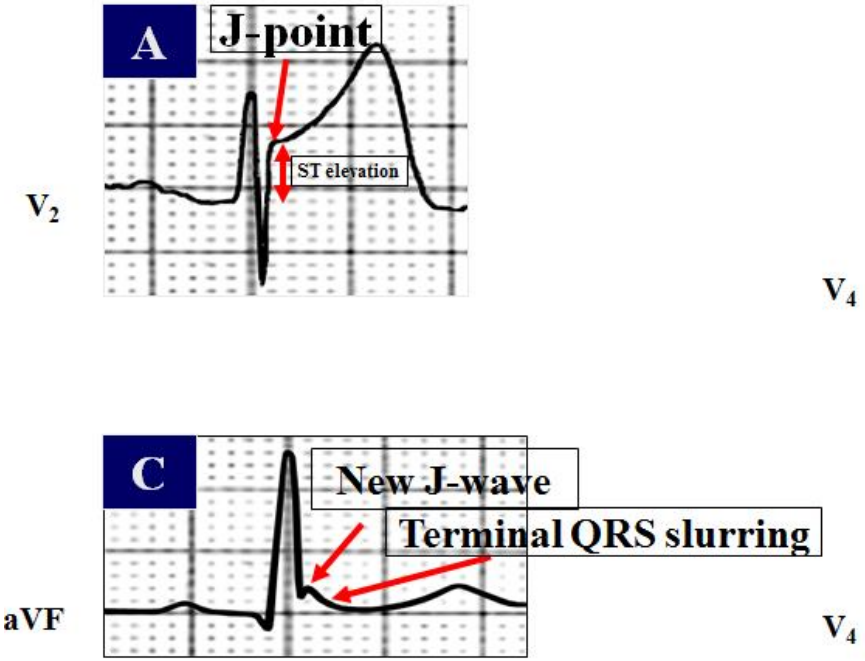
Slurred QRS downstroke without STSE



J-wave or the new J-point elevation without STSE



The first point of inflection of R wave descendent ramp is considered the real J-point. In these cases "The tangent line" method is ideal. ST-segment elevation = 0.8mm. We considered an atypical C type variant of early repolarization pattern. The lambda aspect is a marker of fatal arrhythmias.



Classic definition of ERP always with ST segment elevation

A) ERP with only ST segment elevation

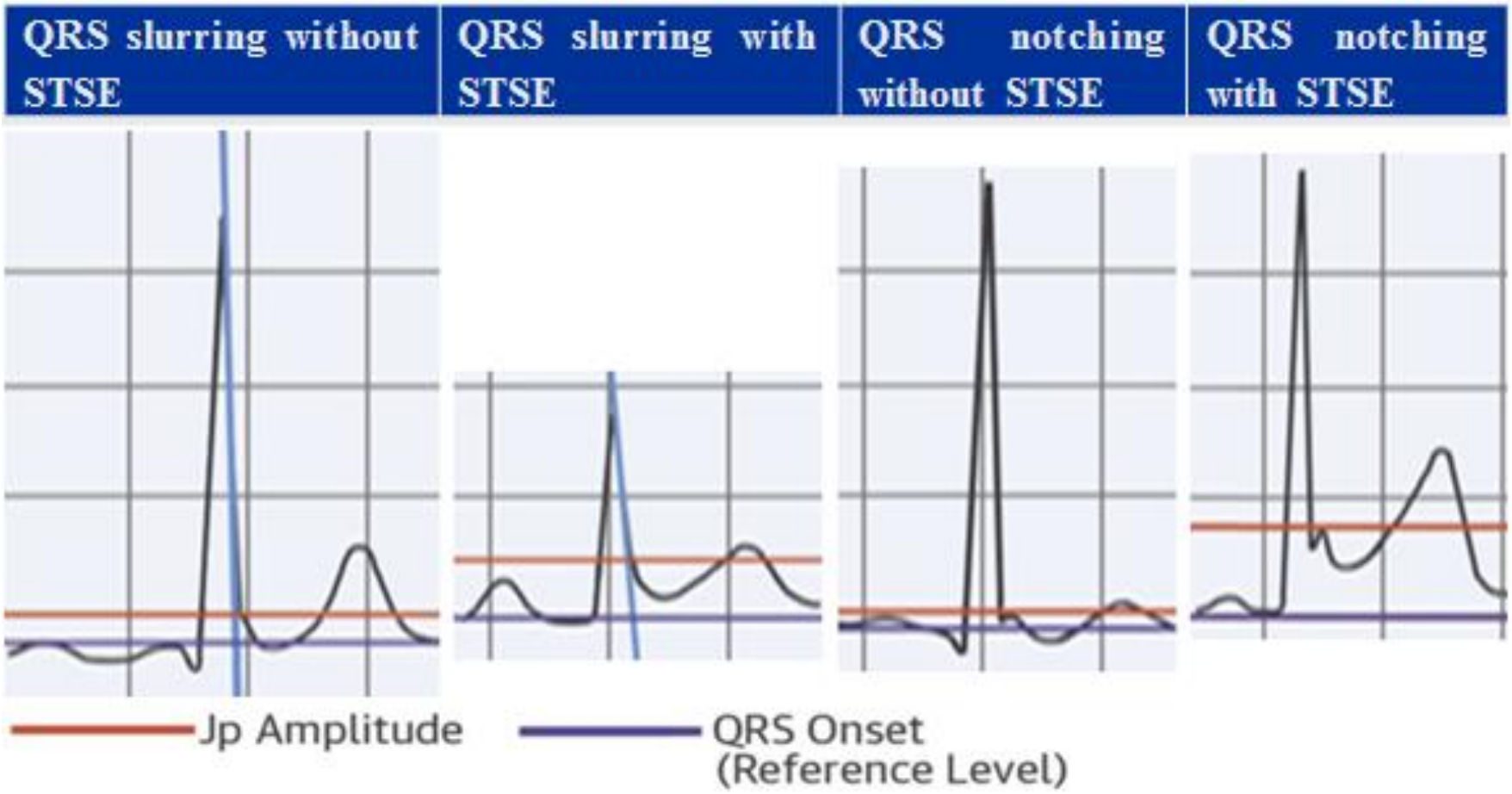
B) ERP with ST segment elevation and J-point at the end of J wave.

New definition of ERP without ST segment elevation

- J-point elevation and terminal QRS slurring without ST segment elevation. The first point of inflection of R wave descendent ramp is considered the real J-point. In these cases "The tangent line" method is ideal.
- J-wave without ST segment elevation (Pérez 2012).

Early Repolarization Pattern new consensus definition (Macfarlane 2015)

The new definition of ERP requires the peak of an end-QRS notch and/or the onset of an end-QRS slur as a measure, denoted Jp, to be determined when an interpretation of early repolarization is being considered. One condition for early repolarization to be present is Jp ≥ 0.1 mV, while ST-segment elevation is not a required criterion.



The upper red line indicates the notch or slur amplitude, J peak (Jp), while the lower blue line indicates the baseline used as a reference with respect to which amplitudes should be measured. The light blue lines indicate tangents to the initial component of the R-wave downslope. All of these waveforms are illustrations of the early repolarization pattern.

A practical guide to early repolarization

KEY POINTS (Adler 2015)

- The historical early repolarization definition includes two electrocardiographic phenomena, J-point elevation and ST-segment elevation; however, contemporary studies associating early repolarization with CA/SCD use only J-point elevation in their definition.
- Mutations in several genes have been associated with ERS, but the clinical benefit of genetic testing in these patients is currently questionable.
- SCD preventive measures (e.g., ICD implantation) are limited mainly to symptomatic patients with early repolarization (i.e., patients with ERS).

ERS patients are rare and have a high risk of recurrent cardiac events. ICD implantation and possibly quinidine are the recommended treatments in this group. On the other hand, asymptomatic individuals with early repolarization are very common and, as a group, have a good prognosis. Sudden death preventive measures in these asymptomatic patients are limited to rare and unique cases.

J wave syndromes (Li 2015)

	Inherited				Acquired	
Characteristics	**ERS type 1**	**ERS type 2**	**ERS type 3**	**BrS**	**Ischemia mediated VT/VF**	**Hypothermia mediated VT/VF**
Average age of first event	35 years				30-40 years	
Anatomic location	Anterolateral left ventricle	Inferior left ventricle	Left and right ventricles	RVOT	Left and right ventricles	Left and right ventricles
Leads displaying J point/J wave	I, V4-V6	II, III, aVF	Global	V1-V3	Any of 12 leads	Any of 12 leads
Response of J wave/ST elevation to Bradycardia or pause	↑	↑	↑	↑	NA	NA
Response of J wave/ST elevation to Na-channel blockers	↓→	↓→	↓→	↑	NA	NA
Male predominance	75%			80%		
VT/VF	Rare common in healthy athletes	Yes	Yes, electrical storm	Yes	Yes	Yes
Sex dominance	Male	Male	Male	Male	Male	Male
Response to quinidine					Limited data	
J wave/ST elevation	↓	↓	↓	↓		

	Inherited				Acquired	
Characteristics	**ERS type 1**	**ERS type 2**	**ERS type 3**	**BrS**	**Ischemia mediated VT/VF**	**Hypothermia mediated VT/VF**
VT/VF	↓	↓	↓	↓		↓
Response to isoproterenol			**Limited data**		**NA**	**NA**
J wave/ST elevation	↓	↓		↓		
VT/VF	↓	↓		↓		
Gene mutations	**CACNA1C, CACNB2B**	**KCNJ8, CACNA1,CACNB2B KCNJ8, CACNA1, CACNB2B**	**CACNA1C**	**SCN5A, CACNA1C, CACNB2B, GPD1L, SCN1B, KCNE3, SCN3B, KCNJ8, CACNA2D1, KCND3, MOG1, ABCC9, HCN4, KCNH2, KCNE5**	**SCN5A**	**Not available.**

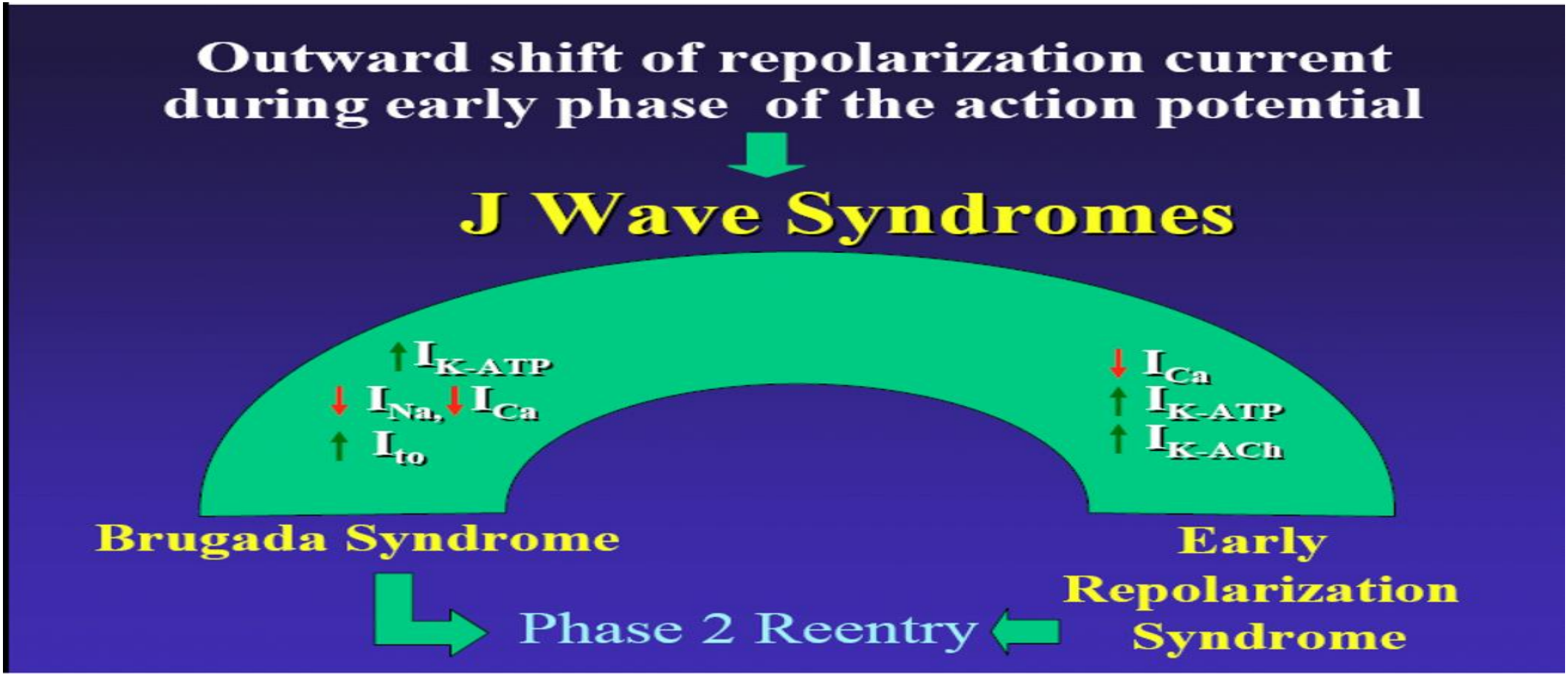
ERS: Early repolarization syndrome; BrS: Brugada syndrome; VT: Ventricular tachycardia; VF: Ventricular fibrillation; NA: Not available

J wave syndromes

J wave syndromes are a spectrum of variable phenotypes characterized by the appearance of prominent ECG J waves with a risk of VF, including the inherited BrS, ERS, IVF with J wave in inferior leads as well as acquired arrhythmias linked to the acute ST-SEMI 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**). J wave is a positive deflection immediately following the QRS complex of the ECG or be in part buried inside of the QRS as notching or slurring. J wave may be accompanied by an STSE, traditionally referred to as an **ERP (Antzelevitch 2011**). J wave 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 of the ECG (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 recognized in subjects with central nervous system disorders (**Hersch 1961**),severe 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 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**). I_{to} is rapidly activated and deactivated (**Wettwer 1993**). It is following the phase 0 of the AP (**Niwa 2010**). Once activated, the outward flow of K^+ from inside the cells constitutes Ito and causes the transmembrane potential to decrease. This decrease of the transmembrane potential is known as early repolarization coincident with J point. 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 epicardium, rather than endocardium, produces a transmural voltage gradient during phase 1 of AP that is, contributory to registration of J waves on the ECG. The higher density of Ito in the epicardium compared to the midmyocardial (M) region and significantly greater than the endocardial region of canine and 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_{to} is reduced following faster heart rate, resulting in a decrease in the amplitude of the J waves.



J wave Syndromes. Schematic hypothesis that an outward shift in repolarizing current due to a decrease in Na^+ or Ca^{2+} channel currents or an increase in I_{to}, I_{K-ATP} or I_{K-ACh}, or other outward currents can give rise to accentuated J waves associated with the BrS, ERS and IVF.(**Antzelevitch 2010**).

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 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 ≈ 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, 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 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. 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 (**Antzelevitch 2001**)**.**

Acquired J Wave Syndromes

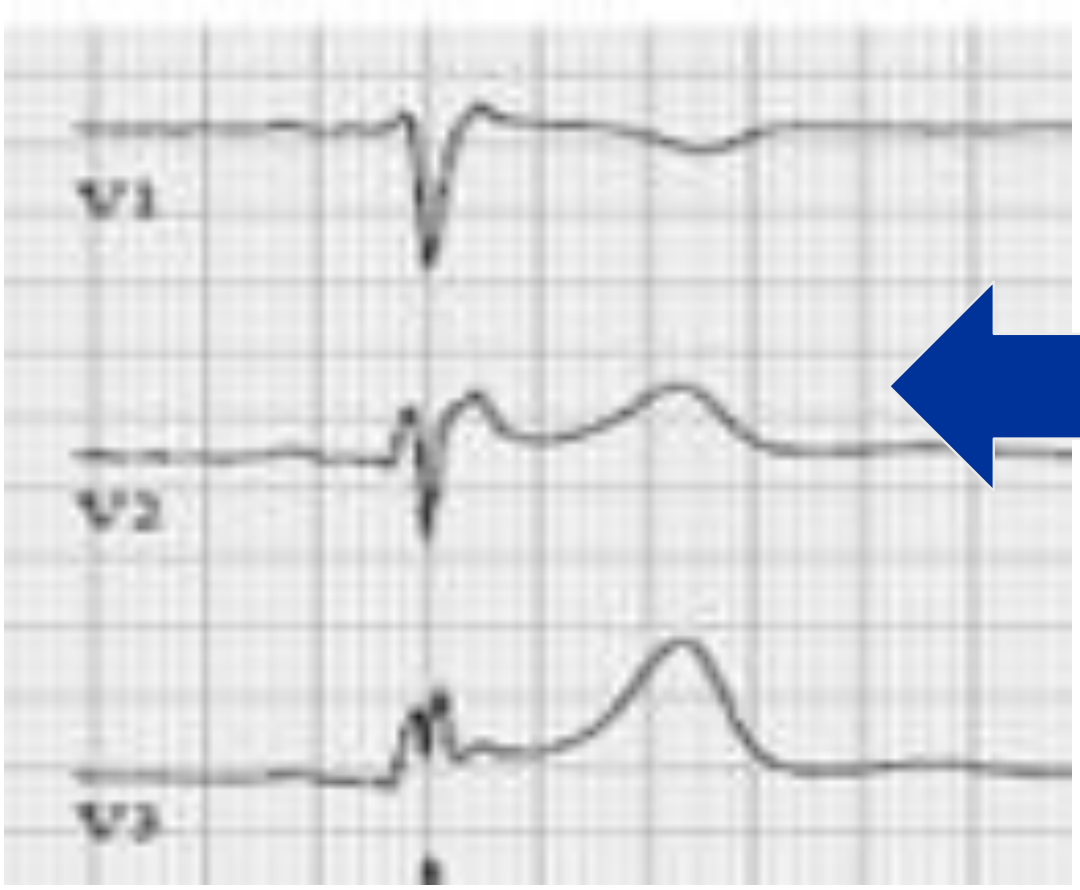
J wave syndromes can be acquired, which share the similar properties with those of inherited J wave syndromes, including ECG features and the underlying mechanism for VF (Antzelevitch 2010; Cui 2010). Hypothermia-induce J wave is well-known, and the study that showed J wave accentuation prior to VF can 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 to a prominent J wave (Antzelevitch 2011). It seems that there is no prominent gender-related discrepancy in 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 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 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 right compared to LV epicardium may be responsible for an increased incidence of ischemia-induced VF. This is further supported by clinical observation of 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).

HRS/EHRA/APHRS consensus recommendations for diagnosis and management of ERS

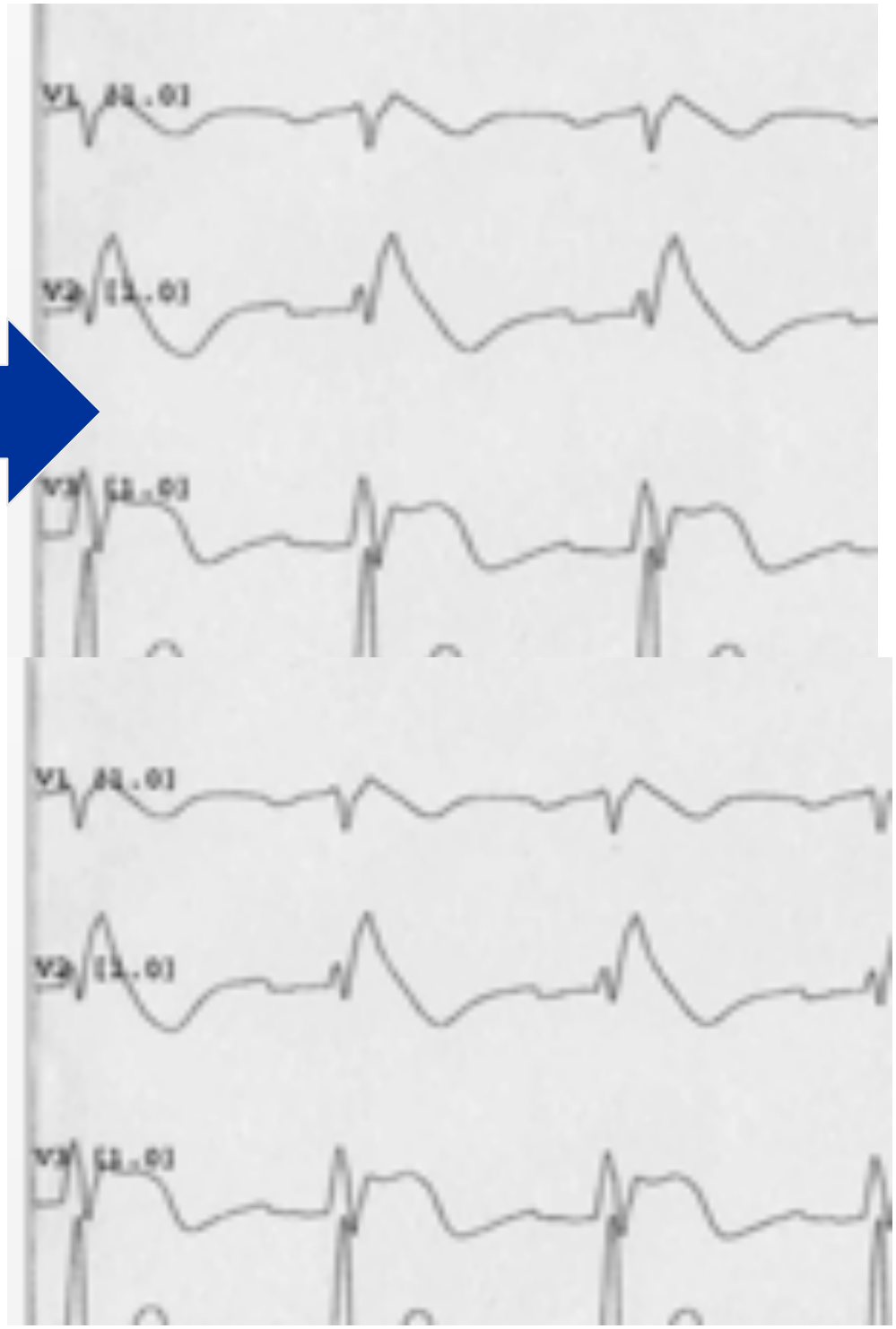
Expert consensus recommendations on early repolarization diagnosis (Priori 2013)	
(1) ERS is diagnosed in the presence of J-point elevation 1mm in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT	
(2) ERS can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation 1mm in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG	
(3) ER pattern can be diagnosed in the presence of J-point elevation 1m in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG	
Expert consensus recommendations on early repolarization therapeutic interventions	
Class I	(1) ICD implantation is recommended in patients with a diagnosis of ER syndrome who have survived a cardiac arrest
Class IIa	(2) Isoproterenol infusion can be useful in suppression of electrical storms in patients with a diagnosis of ER syndrome (3) Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ER syndrome
Class IIb	(4) ICD implantation may be considered in symptomatic family members of ER syndrome patients with a history of syncope in the presence of ST-segment elevation >1mm in two or more inferior or lateral leads (5) ICD implantation may be considered in asymptomatic individuals who demonstrate a high-risk ER ECG pattern (high J-wave amplitude, horizontal/descending ST segment) in the presence of a strong family history of juvenile unexplained SD with or without a pathogenic mutation
Class III	(6) ICD implantation is not recommended in asymptomatic with an isolated ER ECG pattern

APHRS, Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; ER, early repolarization; HRS, Heart Rhythm Society; ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

ECG right precordial leads at baseline
Type 2 Brugada ECG patter



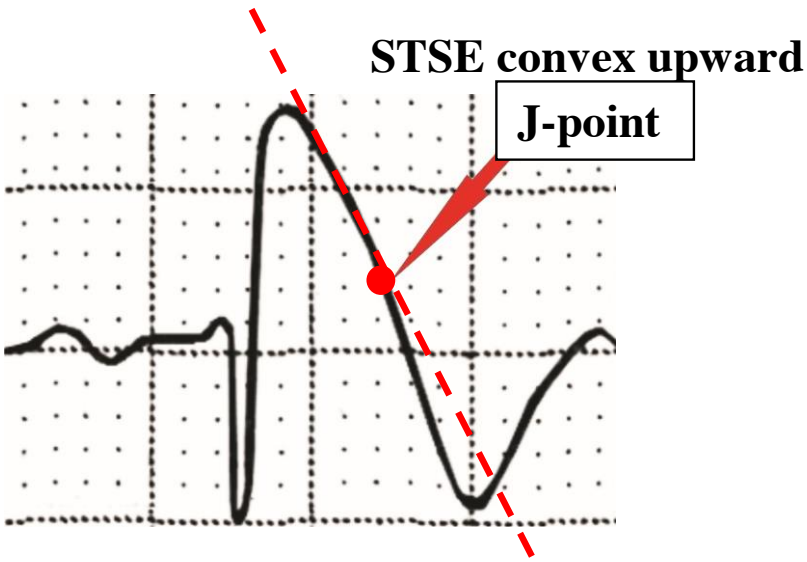
Positive After ajmaline challenge



Proposal of classification of type 1 Brugada pattern

Right precordial leads

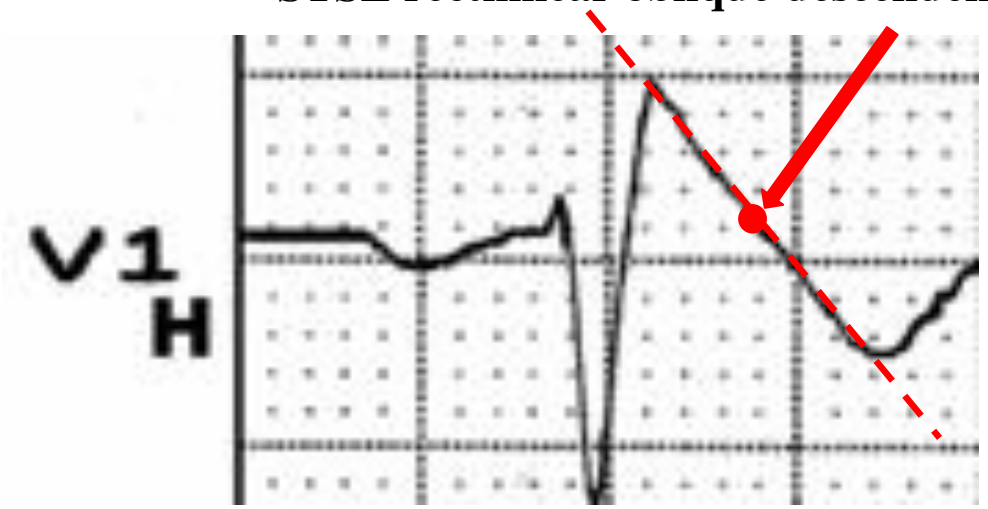
Subtype 1A



The dotted line is tangent line

Subtype 1B

STSE rectilinear oblique descendent



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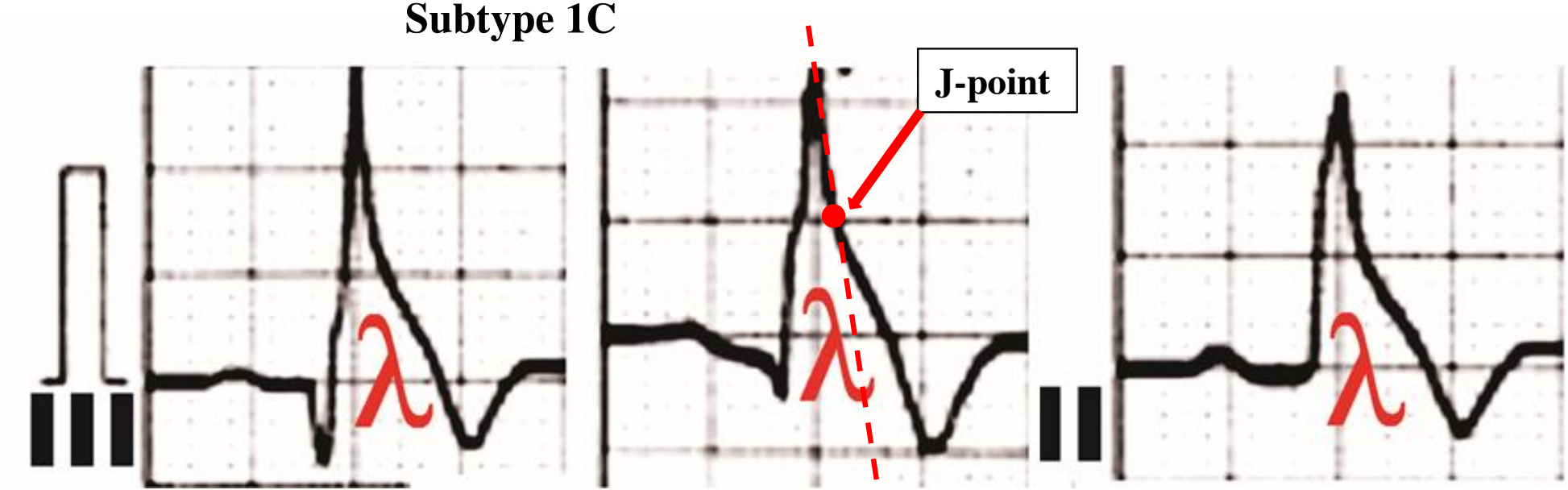
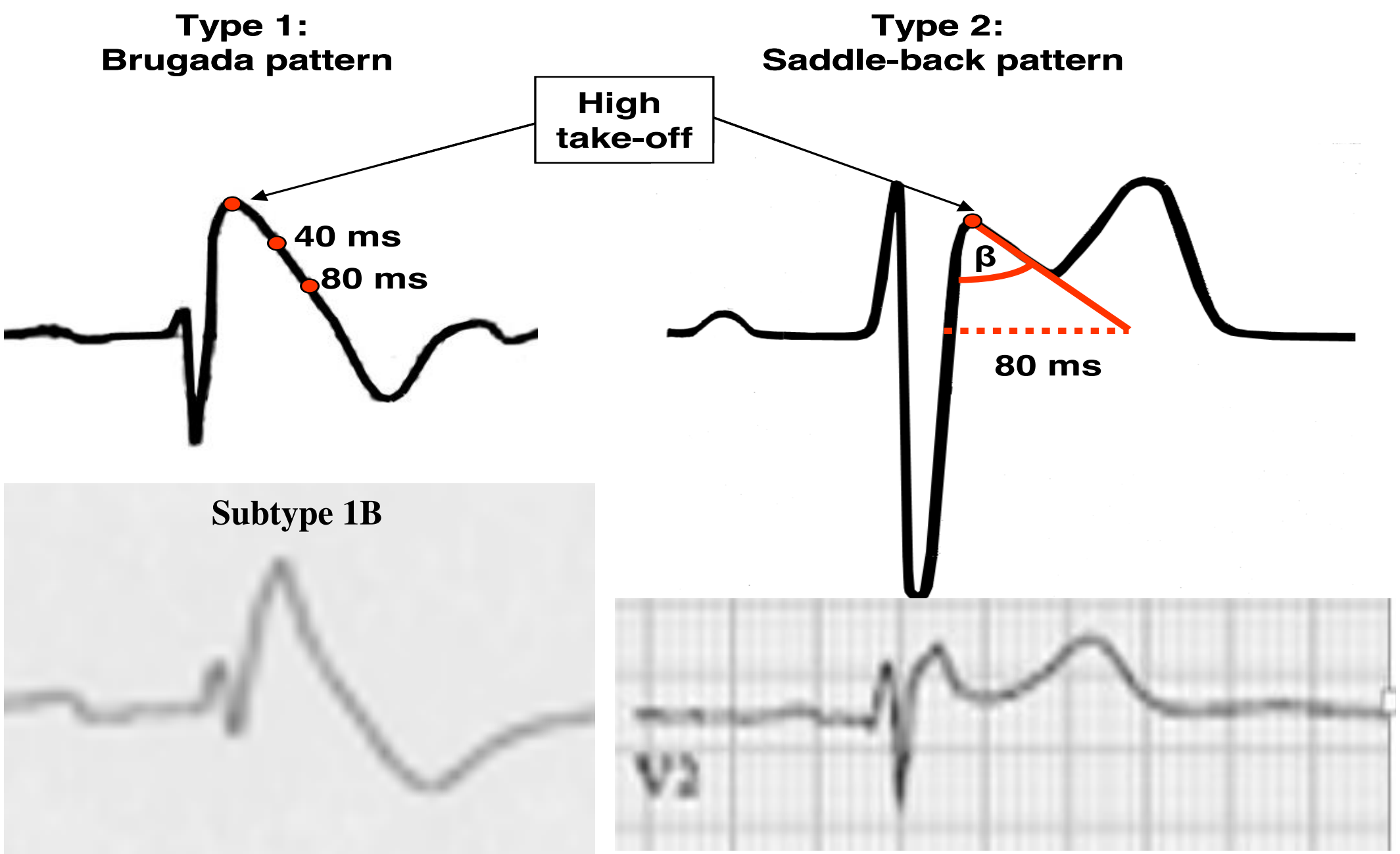
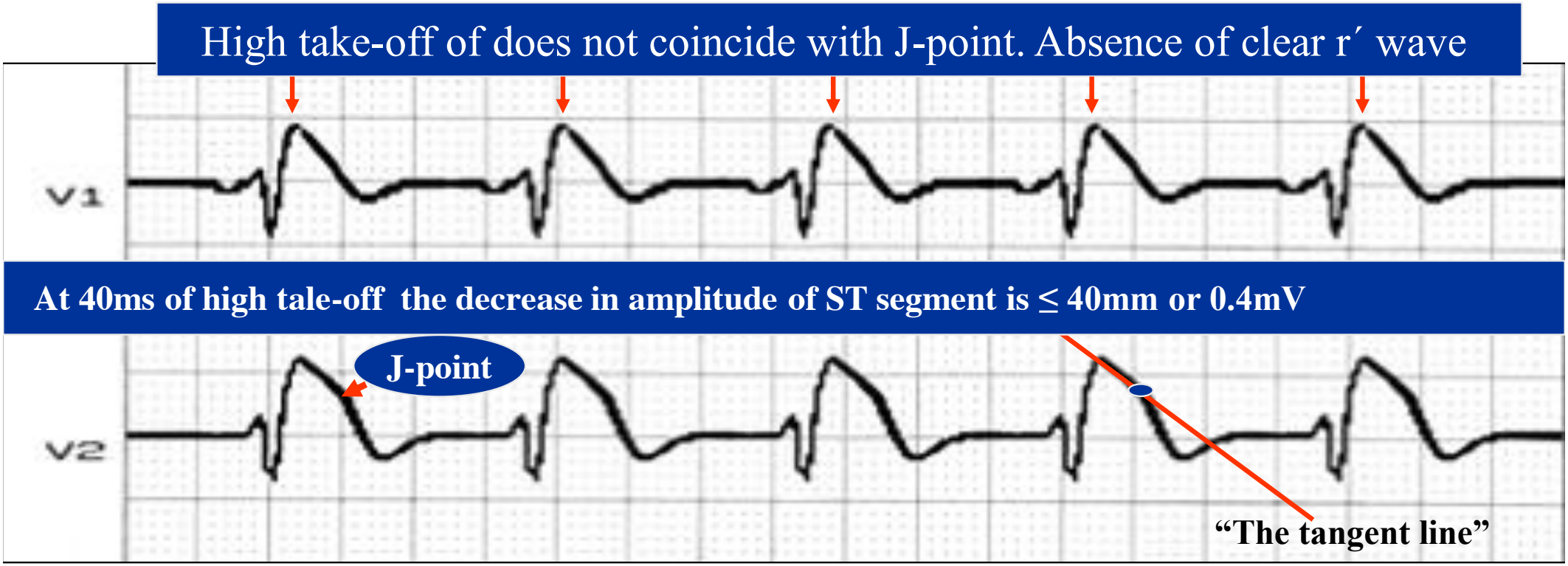
Inferior leads

Subtype 1C




Type 1:
Brugada pattern
Type 2:
Saddle-back pattern
High
take-off
40 ms
80 ms
β
80 ms
Subtype 1B
V2

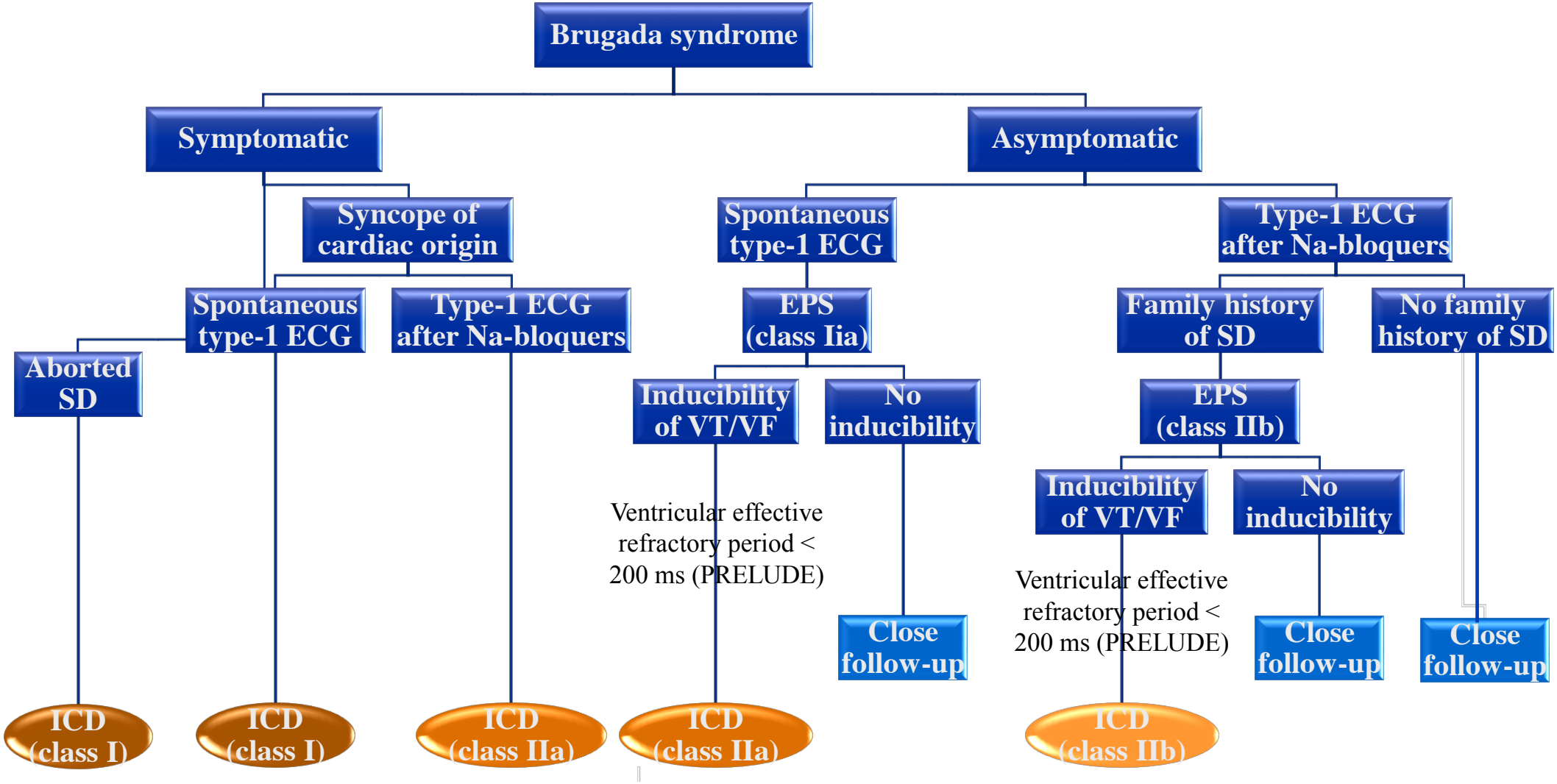
Brugada Type 1 ECG pattern



"Upwardly Convex" ST-segment elevation upwardly convex

Typical electrocardiographic pattern, Brugada Type 1: ST segment elevation ≥ 2 mm, upwardly convex and followed by inverted symmetric T wave in the right precordial leads (V1, V2 or V3). The QRS duration is longer than RBBB and there is a mismatch between V1 and V6. (**Nishizaki 2010**)

Indication for ICD implantation in patient with BrS (Antzelevitch 2005)



Class I: Designation indicates clear evidence that the procedure or treatment is useful or effective;
Class II: Conflicting evidence about usefulness or efficacy;
Class IIa: weight of evidence in favor of usefulness or efficacy;
Class IIb: Usefulness or efficacy less well established.

Farmacological approach to therapy in the Brugada syndrome

Action	Proved on
Ito blockers	
4-amynopiridine	Effective inexperimental models (suppression or phase-2 re-entry) Probable neurotoxity in humans
Quinidine	Effective inexperimental models (suppression or phase-2 re-entry) Showing effectiveness in clinical practice - ↓ Inducibility of VF - ↓ Spontaneous VF in follow-up - Adjunctive therapy in patients with ICD and multiple shocks - Effective in electrical storm - A possible option in children
Tedisamil	Effective inexperimental models (suppression or phase-2 re-entry)
AVE0118	Effective inexperimental models (suppression or phase-2 re-entry)
Ica activators	
Isoprotelenol (β-adrenergic agentes)	Effective inexperimental models (suppression or phase-2 re-entry) Effective in electrical storm
Cilostazol (phosphodiesterase III inibitors)	Controversial preliminary results in preventing VF
INa openers	
Dimethyl lithospermate B	Effective inexperimental models (suppression or phase-2 re-entry)

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