Symptomatic Caucasian middle-aged woman with a family history of sudden death, Brugada type 1 electrocardiographic pattern and other peculiarities

PHRASE OF THE DAY: Accept the project that scares you a little. This will be the one that will teach you the most.

Dear Dr Pérez-Riera,

I would be very happy if you would agree sending you an ECG of a patient in order to ask you for your opinion.
It is an ECG from a 53y old female patient who suffered from syncope and has a positive family history for sudden cardiac death and has complete right bundle branch block.
My question would be if you would consider her ECG as a Brugada type I ECG pattern?
In order not to bias you I wouldn´t tell you my opinion before.
With best regards from Germany

Britt Maria
Dr. med. Britt-Maria Beckmann

Outpatient clinic für patients with inherited arrhythmia syndromes

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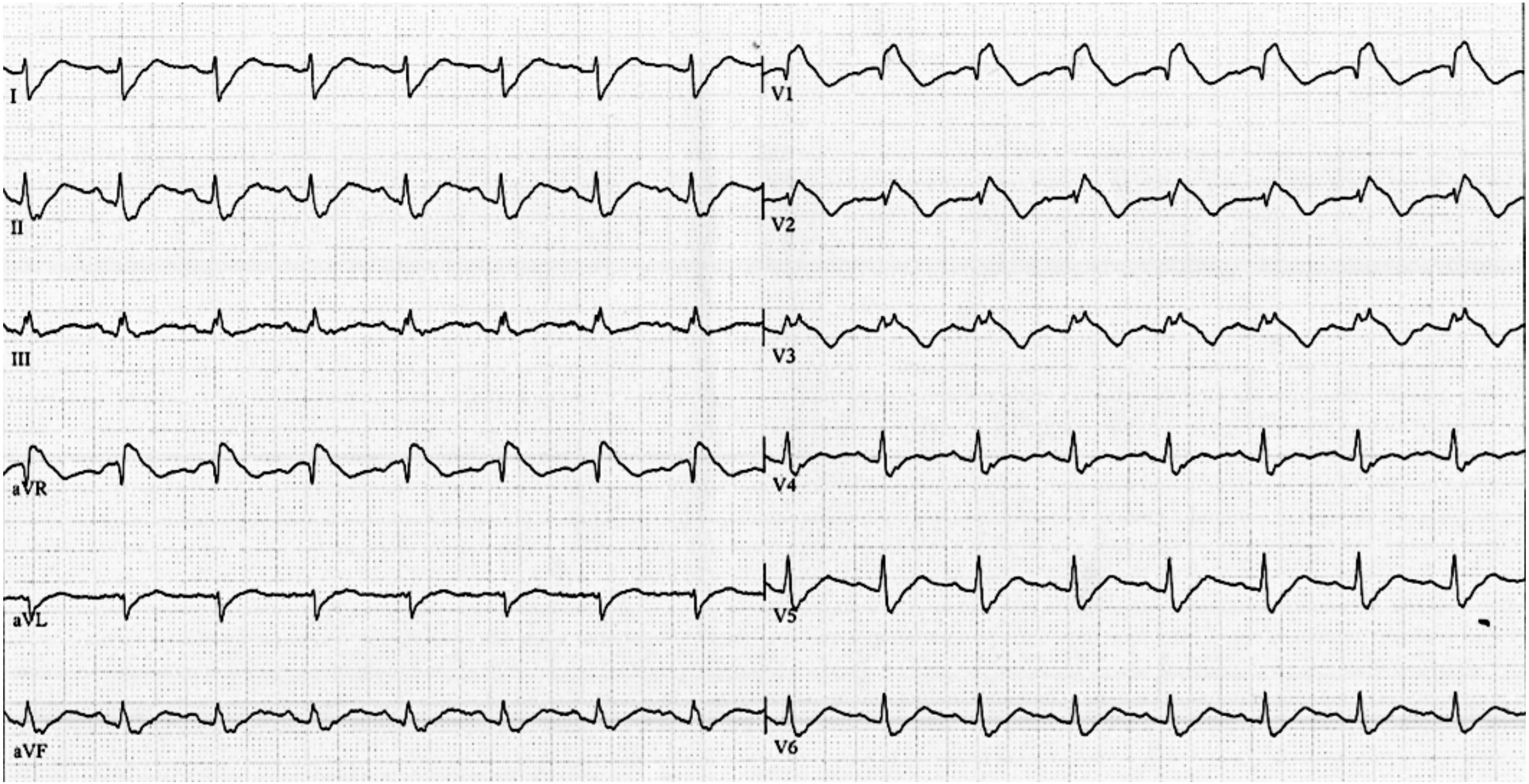
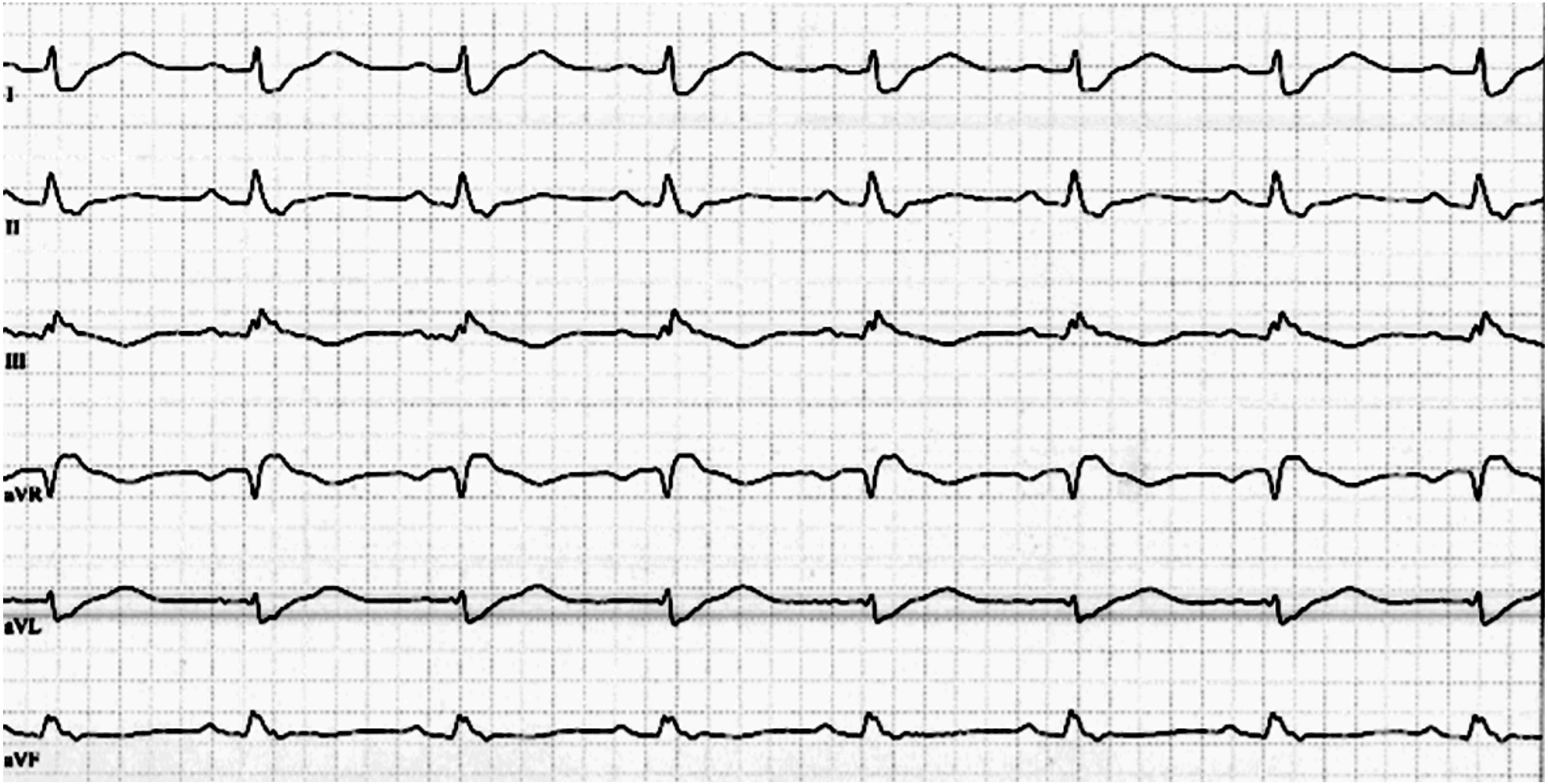
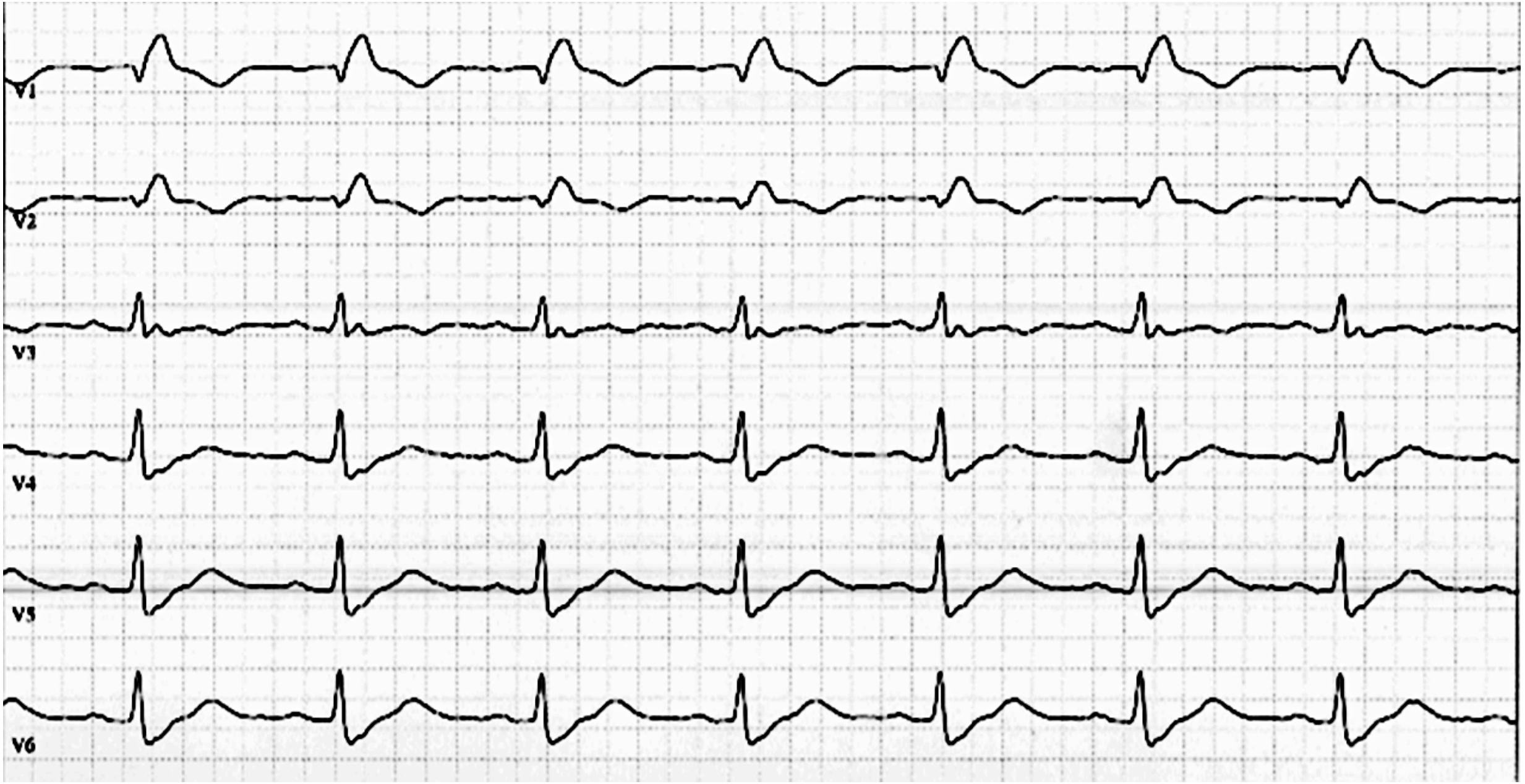
ECG-1


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
25mm/s 10mm/mV 0.01-100Hz 50Hz ADS 12SL 20.1

ECG-2 Limb leads 50mm/s



ECG-2 Precordial leads 50mm/s



Type 1 Brugada pattern plus fractionated QRS in lead III and V3, possible Brugada patterns in aVR and J wave in lead III. Worrisome risk features as well as history. Would lean towards genetic testing and ICD implant.

Melvin **Scheinman, MD**

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Dear Dr Beckmann:

I have the feeling you are preparing us some surprise but let's go anyway…..

First, in order one can ascertain the diagnosis of Brugada-ECG in this relatively young woman we need to be sure that the patient does not have any other cardiac or extracardiac condition that could result in a similar ECG. Therefore physical examination, echocardiogram and ECG exercise testing are mandatory.

I do believe that the ECG shown is consistent with a Type 1-Brugada ECG. Such tracing in females may indicate a poorer arrhythmic prognosis than in males. I also note a deep S wave in lead I that has been suggested by Calo et al. (1) to also indicate a worse arrhythmic prognosis. I do not see clearly fragmented QRS.

The positive family history of sudden cardiac death (SCD) is interesting despite we do not have information about the degree of familial relationship nor the age at which SCD occurred in the family relative. In any case, discrepant results exist about the predictive value of family history of SCD in first degree relatives at a young age (2, 3).

I would like to comment on the present case on the light of the results we have collected on 59 females with arrhythmic events in Brugada syndrome in the Multicenter International Survey (SABRUS) (Milman, Belhassen et al., unpublished data). Two papers dealing with SABRUS have already been recently published (4,5) while the one dealing with gender differences has been submitted for publication.

My personal recommendation in the management of the present patient will require performance of 2 additional exams:

1. Diagnostic EPS (found positive in more than third of females with arrhythmic events in SABRUS).
2. Genetic testing (found positive for SCN5A mutation in almost half of females tested in females with arrhythmic events in SABRUS).

In case the patient has inducible VT/VF at EPS, I would first recommend EP-guided management therapy with quinidine (6) instead of implanting ICD. In case this approach is not feasible or if the patient is intolerant or not compliant to medication or if quinidine fails to prevent arrhythmia induction, ICD implantation will be mandatory.

In case the patient refuses EPS or has negative baseline EPS while he is SCN5A carrier I would also recommend implantation of an ICD.

References:

1. Calò L et al. A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome: The S-Wave in Lead I. J Am Coll Cardiol. 2016 Mar 29;67(12):1427-1440. doi: 10.1016/j.jacc.2016.01.024.
2. Sarkozy A et al. The value of a family history of sudden death in patients with diagnostic type I Brugada ECG pattern. Eur Heart J. 2011 Sep;32(17):2153-60. doi: 10.1093/eurheartj/ehr129. Epub 2011 Jul 4.

3. Sieira J et al. A score model to predict risk of events in patients with Brugada syndrome. Eur Heart J. 2017 Jun 7;38(22):1756-1763. doi: 10.1093/eurheartj/ehx119.
4. Milman A et al. Profile of Brugada Syndrome Patients Presenting with Their First Documented Arrhythmic Event. Data from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS). Heart Rhythm. 2018 Jan 8. pii: S1547-5271(18)30014-6. doi: 10.1016/j.hrthm.2018.01.014. [Epub ahead of print]
5. Milman A et al. Age of First Arrhythmic Event in Brugada Syndrome: Data From the SABRUS (Survey on Arrhythmic Events in Brugada Syndrome) in 678 Patients. Circ Arrhythm Electrophysiol. 2017 Dec;10(12). pii: e005222. doi: 10.1161/CIRCEP.117.005222. Epub 2017 Dec 18.
6. Belhassen B et al. Management of Brugada syndrome: Thirty-three- year experience using electrophysiologically guided therapy with class 1A antiarrhythmic Drugs. Circ Arrhythm Electrophysiol. 2015 Dec;8(6):1393-402. doi: 10.1161/CIRCEP.115.003109. Epub 2015 Sep 9.

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Dear Andres,
Thank you for sharing this interesting case.
At first glance, it obviously looks like a Brugada Type I ECG; however, looking at it carefully, I noticed the following:
1. The QT is above normal rage. I see an epsilon wave in leads V3 and V4.
2. The ST segment in aVR is not quite normal.
3. There are some early repolarization changes.
Putting all of these points together, I favor ARVC/D.
Looking forward to seeing your comments.
Very best,

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Books

1. Cardiac Mapping: Editors: Shenasa, M., Borggrefe, M., Breithardt, G., Futura Publishing Inc., 1993.
2. Antiarrhythmic Drugs: Mechanisms of antiarrhythmic and proarrhythmic action, Editors: Breithardt, G., Borggrefe, M., Camm, JA., Shenasa, M.; Springler Verlag, 1995.
3. Cardiac Mapping 2nd Edition: Shenasa, M., Borggrefe, M., Breithardt, G., Blackwell -Futura Publishing Inc., 2003
4. Cardiac Mapping 3rd Edition: Shenasa M, Hindricks, G, Borggrefe, M., Breithardt, G., Wiley-Black well Publishing In., 2008
5. Cardiac Mapping 4th Edition: Shenasa M, Hindricks, G, Borggrefe, M., Breithardt, G., and Josephson, M., Wiley-Blackwell Publishing Inc., 2013.
6. A Practical Approach to the Management of Atrial Fibrillation: Shenasa M, Camm., Oxford University Press, 2014
7. ECG Handbook: contemporary challenges: Shenasa M, Josephson M, Estes M., Cardiotext, 2014.
8. Electrocardiography of Complex Arrhythmias: Shenasa M, Gerstenfeld E (Guest Editors). EP Clinics, 201

Spanish

Buenas tardes estimado Andrés! !! En ECG registrado a velocidad Standard parece un BRD y patrón de Brugada (En una mujer de 53 años!!!, tengo 58 ....) tipo 1.

En los registros a 50 mm/seg creo ver ondas épsilon (u ondas de Fontaine) en V1 a V3, aVR y en cara inferior. Ondas T negativas asimétricas de V1 a V3. Y fQRS inferior (peor pronóstico) hablaría de un retardo de la conducción en el triángulo de la displasia (TSVD-TEVD-PUNTA) génesis de las TV-FV que explicarían síncope y MS, incluso en familiares.

Se trataría entonces de una DAVD, que en no pocas ocasiones se registran trastorno de conducción de rama derecha hasta BCRD.

Además podrían coexistir ambas entidades (DAVD+BrS).

Un Ecocardiograma o mejor una RMN ayudarían en el diagnóstico.

Con admiración y cariño.

Dr Juan Carlos Manzzardo

Mendoza-Argentina

English

Good afternoon dear Andrés. In the ECG registered at standard speed looks like a RBBB + type 1 Brugada ECG pattern.

In the tracing at 50 mm/s, I see epsilon waves or Fontaine waves from V1 to V3, aVR and in the inferior leads.

Asymmetric negative T waves from V1 to V3, and fQRS in the inferior leads (worst prognosis), I would say of a conduction delay in the dysplasia triangle (RVOT-RVIT-apex) could originate the genesis of VT/VFs that would explain syncope and sudden death, even in relatives.

In addition, a record of right leads and Fontaine, could help to visualize the epsilon.With HC and ECG, we have: 1 major criterion for ARVD on ECG: epsilon waves, 2 minor: negative T waves from V1 to V3 in the presence of BRD and family history of MS.

I do not know if the fQRS are minor criteria by ECG or they are by SAECG.

It would be a ARVCD, which in a few occasions are registered IRBBB to CRBBB. In addition, both entities (ARVCD and BrS) could coexist.

An echocardiogram or better an CMRI would help in the differential diagnosis.

With admiration and affection.

Dr Juan Carlos Manzzardo

Mendoza-Argentina

Dear Andrés and friends,
Thank you for sharing this interesting case of a 53 year old woman with syncope. The strong family history of sudden death suggests that the syncope is of cardiac origin.

ECG #1 recorded at 25 mm/s shows sinus rhythm (~90 bpm), PR 160 ms, QRS ~160 ms, QT ~340 ms, and SAQRS +120 degrees. Late QRS forces are oriented rightward and anterior with classic rsR' (V2) of complete RBBB. Although there is right axis deviation I don't think there is LPFB because $R_{II} > R_{III}$. Coved ST segment elevation followed by T wave inversion is present in V1-3 and suggests Brugada type 1 pattern.

The 2nd ECG recorded at 50 mm/s is not the same ECG #1, although RBBB is still present. Coved ST segment elevation in V1-3 is no longer present and the SQRS is closer to +90 degrees.

I look forward to your opinion and that our colleagues.

Regards,
Frank G. **Yanowitz MD**
Professor of Medicine (Cardiology), University of Utah School of Medicine; Medical Director, Cardiac Rehabilitation at Intermountain Medical Center; Medical Director, IHC ECG Services.

Spanish
Querido Andrés:
Coincido con el análisis de Juan Carlos Manzzardo.
Hay que descartar una displasia arritmogénica del V.D.
Abrazo,
Mario Hening

English
Dear Andrés:
I agree with the Juan Carlos Manzzardo´s opinion.
I would rule out ARVCD.
Hug
Mario Hening

Spanish
Querido Amigo Andrés: No veo vector septal por ningún lado lo que me hace pensar que tiene una fibrosis septal? qR en V1 y V2 sin r inicial , onda T plana en cara inferior, el eje eléctrico en cuadrante normal. Sin aparente sobrecarga auricular. Para mi no es patrón de Brugada ni de displasia. Pienso que es cardiopatía isquémica. Además un sincope a los 53 años justifica descartar coronariopatía. Espero la opinión del grupo.
Un saludo.
Emilio **Marigliano MD**

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English
Dear friend Andrés: I do not see a septal vector anywhere, which makes me think that she has a septal fibrosis? qR in V1 and V2 without initial r, flat T wave in the inferior wall, with normal QRS axis. No apparent atrial overload. For me it is not Brugada's pattern nor ARVCD. I think it would be coronary artery disease (CAD). In addition, in a person of this age with syncope justifies to rule out CAD. I look forward to the group's opinion.
Regards.
Emilio Marigliano MD

Estimado Andrés, es un interesante planteo el versus Brugada/BCRD. Para Brugada, es infrecuente en mujer, pero puede ocurrir. Para un simple BCRD episodio sincopal y antecedentes de MS familiar, sobra. Claramente hay que definir que no existe una cardiopatía estructural. La RM cardíaca creo que es el mejor método.
Si la duda existe, y es oportuno dudar ante este caso, creo que la TECNICA DE CHIALE publicada en HR en 2012 podría clarificarnos y recientemente ISABEL publicó 2 casos analizando ECG/VCG en BR enmascarado y Brugada.
Si no hay displasia haría esto. Va a ser muy interesante lo que vos plantees ya que sos quien más experiencia tiene en estos casos. gran abrazo.
Oscar Pellizon.

Dear Andrés, Brugada syndrome (BrS) versus RBBB is an interesting proposal. BrS, is uncommon in women, but it can happen. The syncopal episode associated with the family history of sudden death are strong arguments in favor of BrS. We must determinate the eventual presence of structural heart disease. For this propose the CMRI is the choice method. If the doubt exists, I think that the Chiale's maneuver (Heart Rhythm. 2012 Jun;9(6):974-6. 12) could clarify this doubt. Recently, Dr. Isabel Konopka published 2 cases analyzing the masquerading RBBB with BrS using ECG/VCG.
If there is no dysplasia I would do this. It is going to be very interesting what you say since you are the one who has more experience in these cases.
Big hug.
Oscar Pellizon MD

Thank you dear friend Oscar for your lucid response. In relation to the Chiale´s maneuver, I do not believe that in this case it is necessary because the RBBB does not hide the Brugada type 1 pattern. The two ECG features are clearly seen. The septal or predivisional RBBB is observed in 28% of the cases in the BrS. In most cases, they are divisional blocks of the superior or subpulmonary division of the right bundle branch, which, differently from the trivial, septal RBBB has the final delay in the right posterior quadrant. Septal RBBB has right end conduction delay in the anterior right quadrant with “glove finger” shape in the horizontal plane.

Dear Andres and Britt,
I would indeed consider this a type-1 ECG for ECG 1. There are some aspects which I would like to highlight :
- there is a profound right ventricular conduction delay, with extreme wide S inferior and lateral, and broad R' in V1. There is also QRS fractionation
- the right axis and (not as impressive) PR lengthening also contribute to the conduction disorder
- V1 itself I would not consider type-1, there is still a clear and angle at the J point between the end of the QRS and start of ST
- in V2 however, the same angle at the J point is still present although of less magnitude and there is a more profound positive coved type angle in the ST segment about 40-60 ms later. The J point seems to be elevated exactly 0.2 mV on my screen (but I might overestimate). From this lead I would consider this Ecg as type-1 (although it would have been more clear when the angle at the J point would have disappeared).
- In V3 a similar aspect is seen but not quite high enough and not too relevant any more for the type-1 question because of V2. The QRS complex in V3 is rather peculiar
- the extreme conduction delay does question whether sodium channel blocking drugs or other provocative conditions are present. If not, and this is an unprovoked baseline ECG, I would be quite reluctant to give ajmaline because of the amount of conduction slowing already present.
- undoubtedly there will be more information on the syncopal episode, on imaging results and on the family history / family ECGs
- ecg 2 I would interpret as remarkable right conduction delay but not type-1 (nor type-2 or -3)
Surely I'm very interested in the opinion of our colleagues
Very best wishes

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My cardiology site of scientific interests

https://ekgvcg.wordpress.com

To my dear friends the Brugada brothers Pedro and Josep,
“The Doctors do not discover diseases, diseases are as old as the World, what Drs discover are very small signs which were previously overlooked…”
"Los médicos no descubren enfermedades; éstas son tan antiguas como el mundo mismo. Lo que los médicos descubren son signos ínfimos, que previamente habían sido pasados por alto."

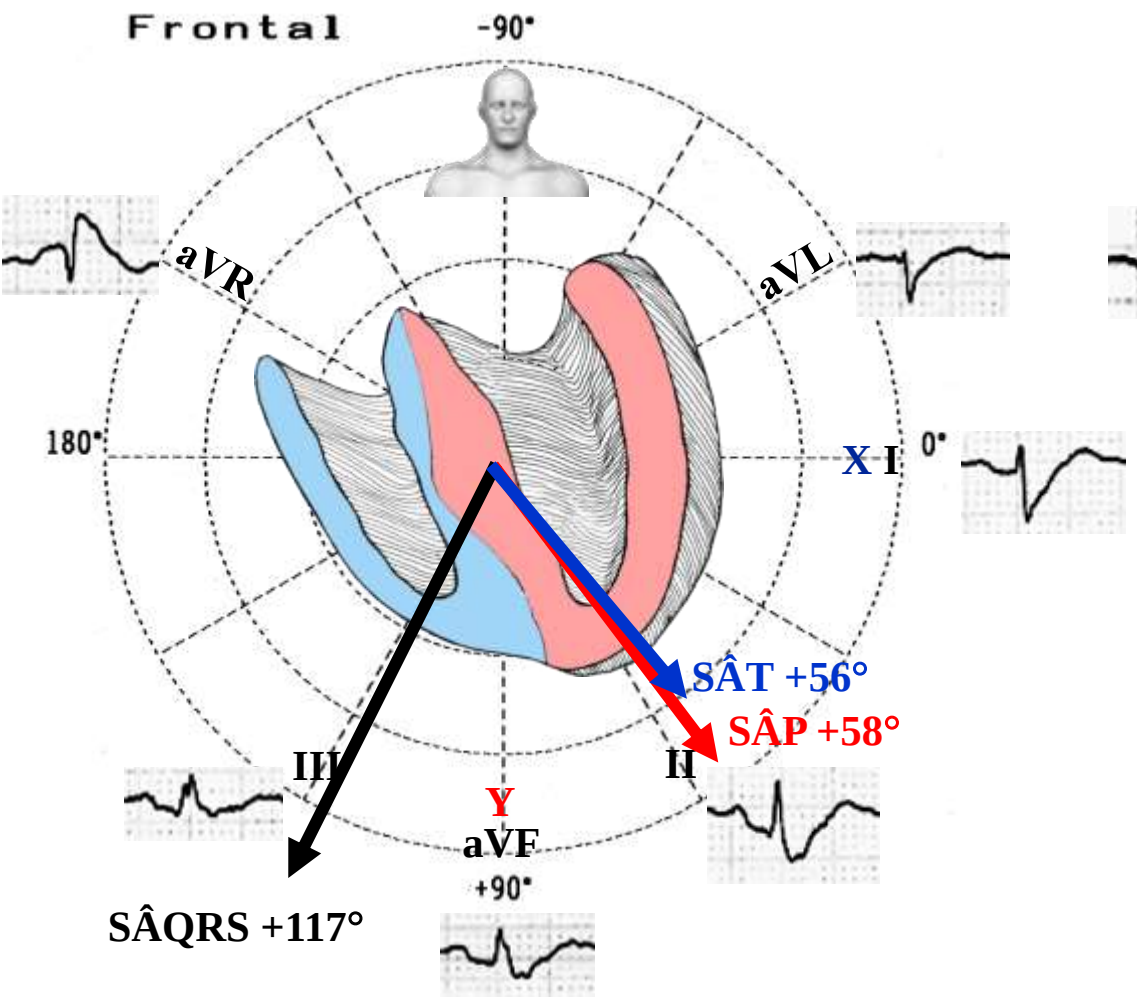
Best for both of you

Dear Maria Beckmann, here is my opinion:

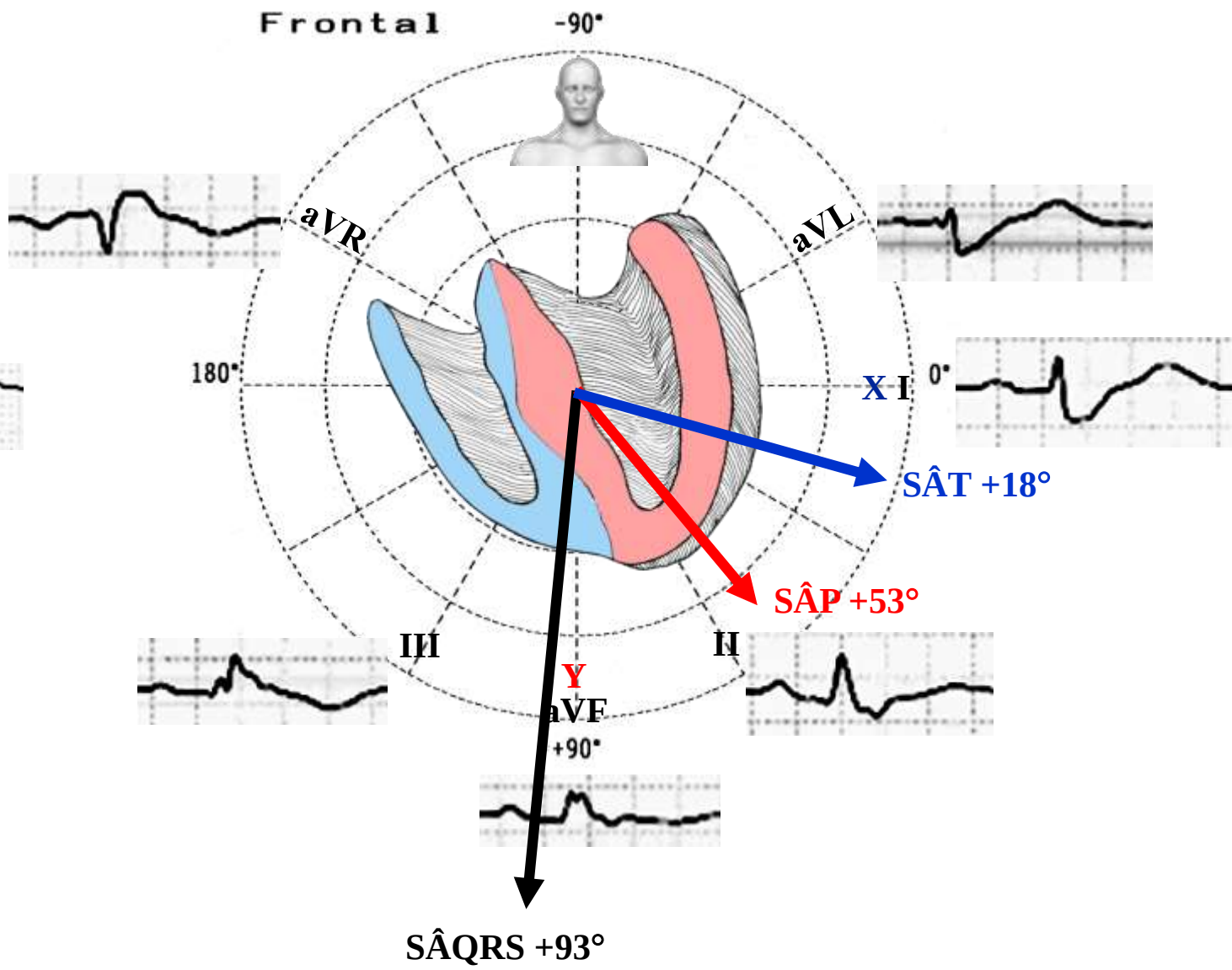
1. Sinus rhythm
2. Prolonged P wave duration: > 110 ms, typical of Brugada syndrome (BrS) with mutation.
3. QRS axis with right axis deviation QRS positive in III-aVR and aVF in 25mm/s +117°
4. Predivisional or troncular CRBBB
5. Type 1 Brugada pattern
6. Prolonged QTc duration =550ms: Phenotypic overlap of LQT3 + Brugada syndrome (BrS) + cardiac conduction disease (CCD), SCN5A-E1784K mutation? (**Veltmann 2003**) Overlapping of LQT3 and BrS in patients carrying the most common mutation is high. The ajmaline challenge represents an important step to rule out potential BrS overlapping in these patients before starting sodium channel blockers for the beneficial effect of QT shortening in LQT3.
7. The patient's ECG shows spontaneous coved-type ST-segment elevation and epsilon-like waves in II, aVF, III and from V1 to V4 (epsilon-like wave is observed on ECG 50mm/s): Overlapping characteristics of BrS and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)? (**Kataoka 2016**) A disease state combining both conditions has a different clinical course than uncomplicated BrS. A subgroup of BrS patients may demonstrate the features of ARVC/D after the initial BrS diagnosis. Structural heart diseases and histological findings consistent with ARVC/D have been revealed after autopsy of patients who were diagnosed with BrS and who died suddenly. Thus, careful observation of the changing clinical course is vital and may indicate the transformation from BrS to ARVC/D.

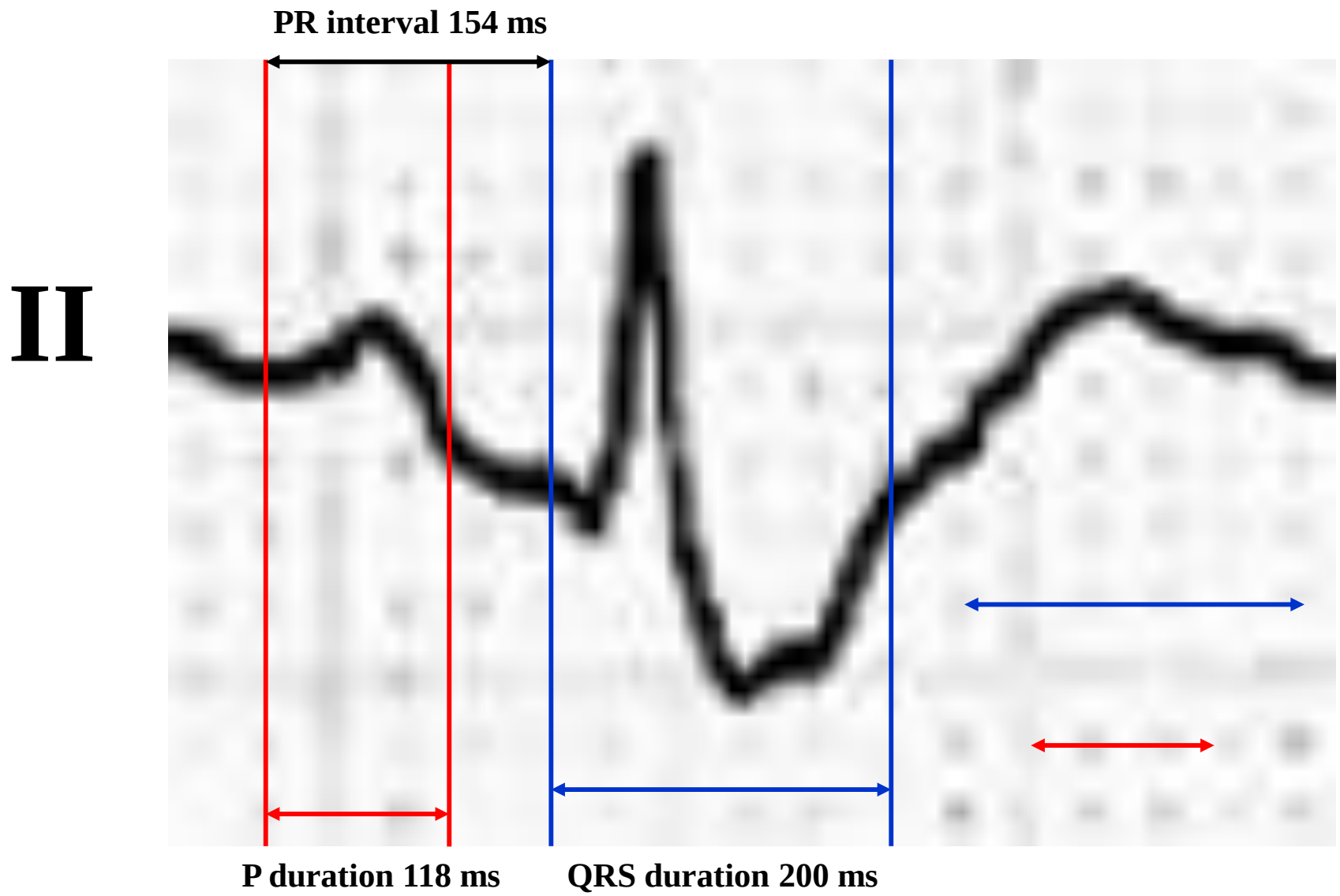
Conclusion: "sodium channel syndrome" (**Napolitano 2003**)? Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia? Overlapping syndrome ?(**Pérez-Riera 2016**) see next slide

ECG-1 at 25 mm/s



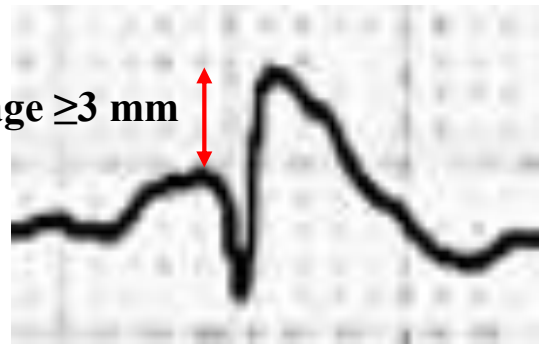
ECG-2 at 50 mm/s

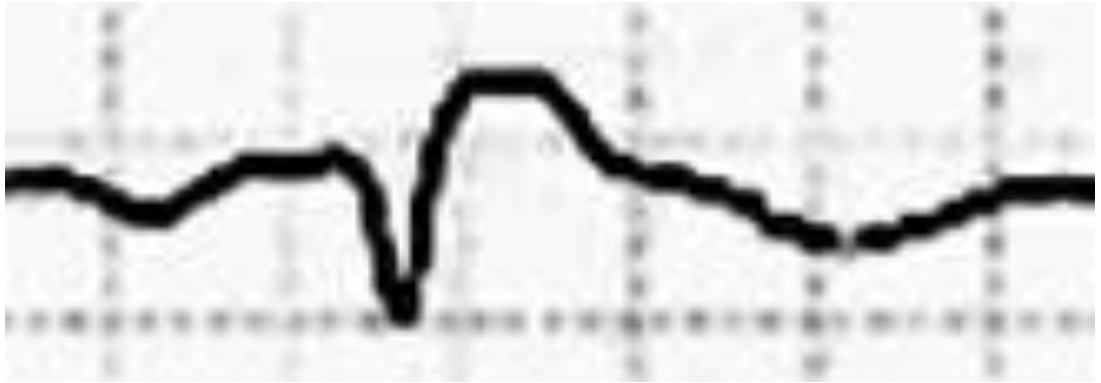




Basal P wave duration (Pd) is prolonged (Pd=118 ms – normal ≤110 ms). These atrial dromotropic disorders could be the substrate for reentrant atrial tachycardias such as AF. In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged (**Yokokawa 2007**). When the PR interval is prolonged it is observed predominantly in cases where the SCN5A gene mutation can be proven (carriers). The presence of a prolongued HV interval is possible in HBE by the existence of intra-His or infra-His block. PR prolongation consequence of HV split or HV prolongation is considered another ECG risk marker (**Miyamoto 2011**), absent in the presente case.

Presence of aVR sign





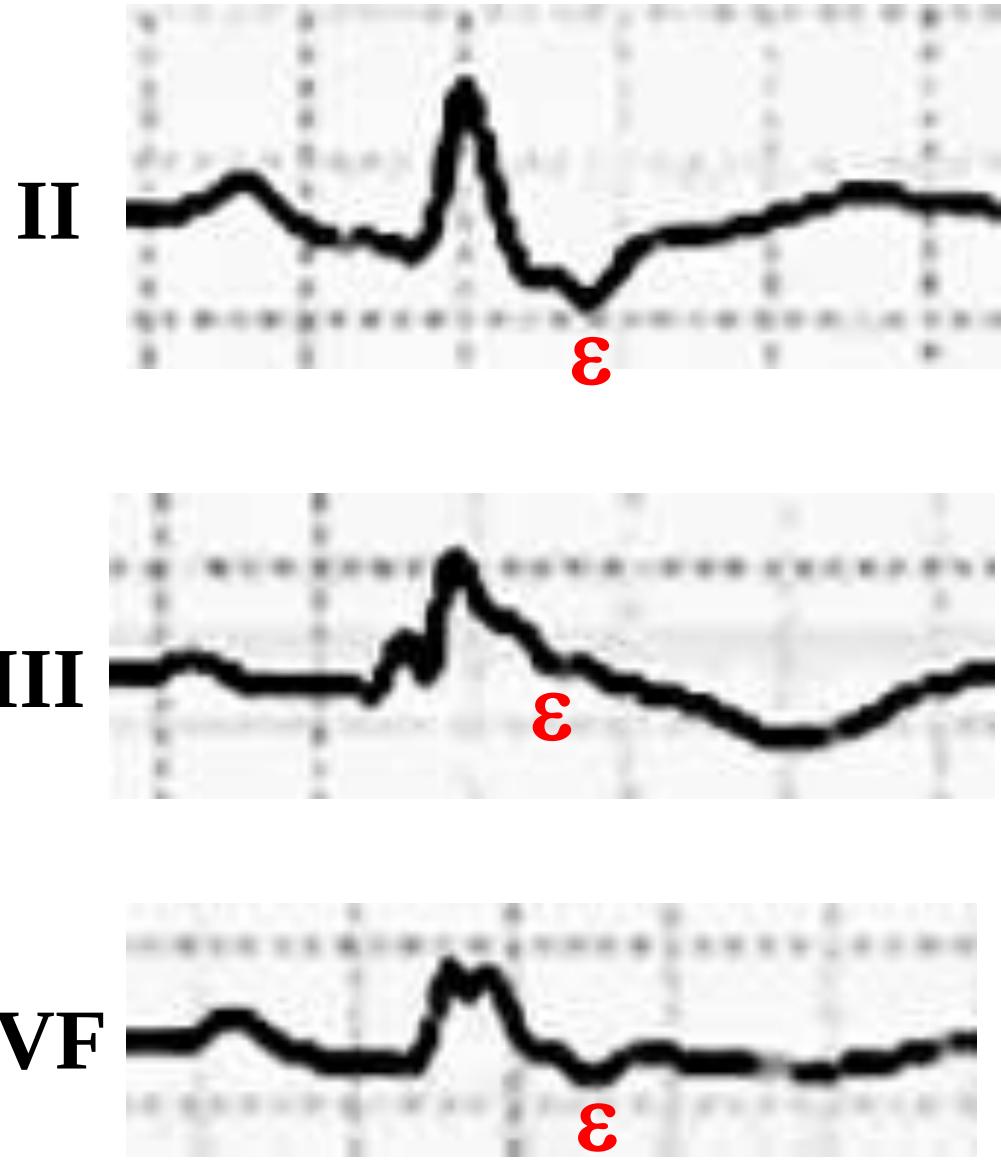
The aVR sign: Presence of prominent final R wave on aVR lead; R wave ≥3 mm or R/q ≥0.75 in lead aVR (aVR sign). It is indicative of slow conduction at the RVOT. It may contribute to the induction of VF by PVS **(Babai Bigi 2007)**.

50 mm/s épsilon-like waves

Epsilon potentials(ε), epsilon waves, or Fontaine waves are specific ECG markers that reflect ventricular conduction delay in ARVC/D. ε are commonly observed in subjects with spontaneous or drug-induced type 1 ECG pattern of BrS as well. These depolarization abnormalities may be related to subtle underlying structural abnormalities (**Letsas 2011**).
Recognition of ε waves are extremely important aspects of the ECG findings in ARVD/C. The characteristics of these potentials are

I. **Intrinsic features:** ε waves are one or more small notches or oscillations in the ECG signal**.** Wang et al **(Wang 2010)** describe 3 different morphologies of ε waves: wiggle waves, small spike waves, and smooth potential waves that formed an atypical prolonged R' wave. The most common configuration was small spiked waves.

II. **Location**: they are found at the end of QRS, in the J point, or at the onset of ST segment. The definition of ε waves remains difficult because within the QRS complex notches or deflections are called fragmentation of the QRS complex (f-QRS). The f-QRS at the beginning, on the top, and at the end of the QRS complex (termed "pre-, top-, and postsilons") was proposed as a typical extension of the definition of ε waves **(Kukla 2012).**



IV. **Leads**: observed in the right precordial leads. If the epsilon wave is of a large magnitude, a reciprocal epsilon wave may be seen in V5 or V6.This may indicate that large part of the RV is depolarizing late. When there is extensive scarring of both the right and left ventricle, epsilon waves may be observed from V1 to V6, reflecting extensive ventricular wall involvement **(Saprungruang 2013)**.

V. **Frequency in ARVC/D:** present in approximately 15-30% of cases usingonly the standard 12-lead ECG(S-ECG). This percentage increases using a modified ECG protocol adding right-sided precordial leads (R-ECG) and the Fontaine bipolar precordial lead (F-ECG).The detection rate of epsilon wave using combined methods is near 40**% (Wang 2010).**

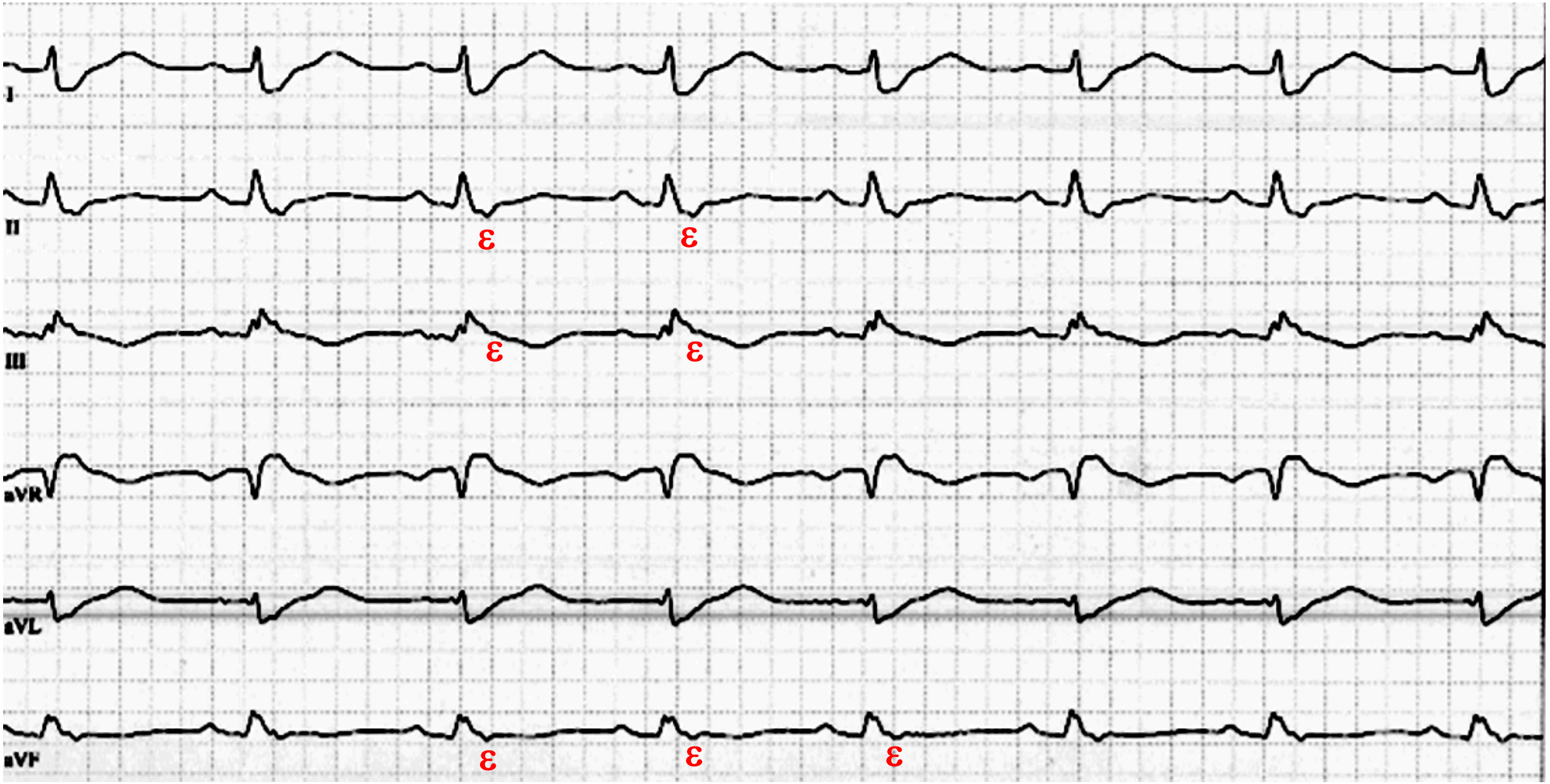
VI. **High resolution ECG:** epsilon waves are observed more frequently with this method.

VII. **Pathognomonic character**: in spite their importance in the diagnosis of ARVC/D, epsilon waves are not pathognomonic of this disease as they have been described in other diseases associated with myocardial scarring or damage including: right ventricular infarction **(Zorio 2005)**, inferior or lateral(old dorsal) infarction, sarcoidosis **(Santucci 2004)**,sickle cell anemia**(Hurst 1998)** and others. Specific ECG markers that reflect ventricular conduction delay in ARVC/D are commonly observed in subjects with spontaneous or drug-induced type 1 Brugada pattern. These depolarization abnormalities may be related to subtle underlying structural abnormalities**(Letsas 2011)**.

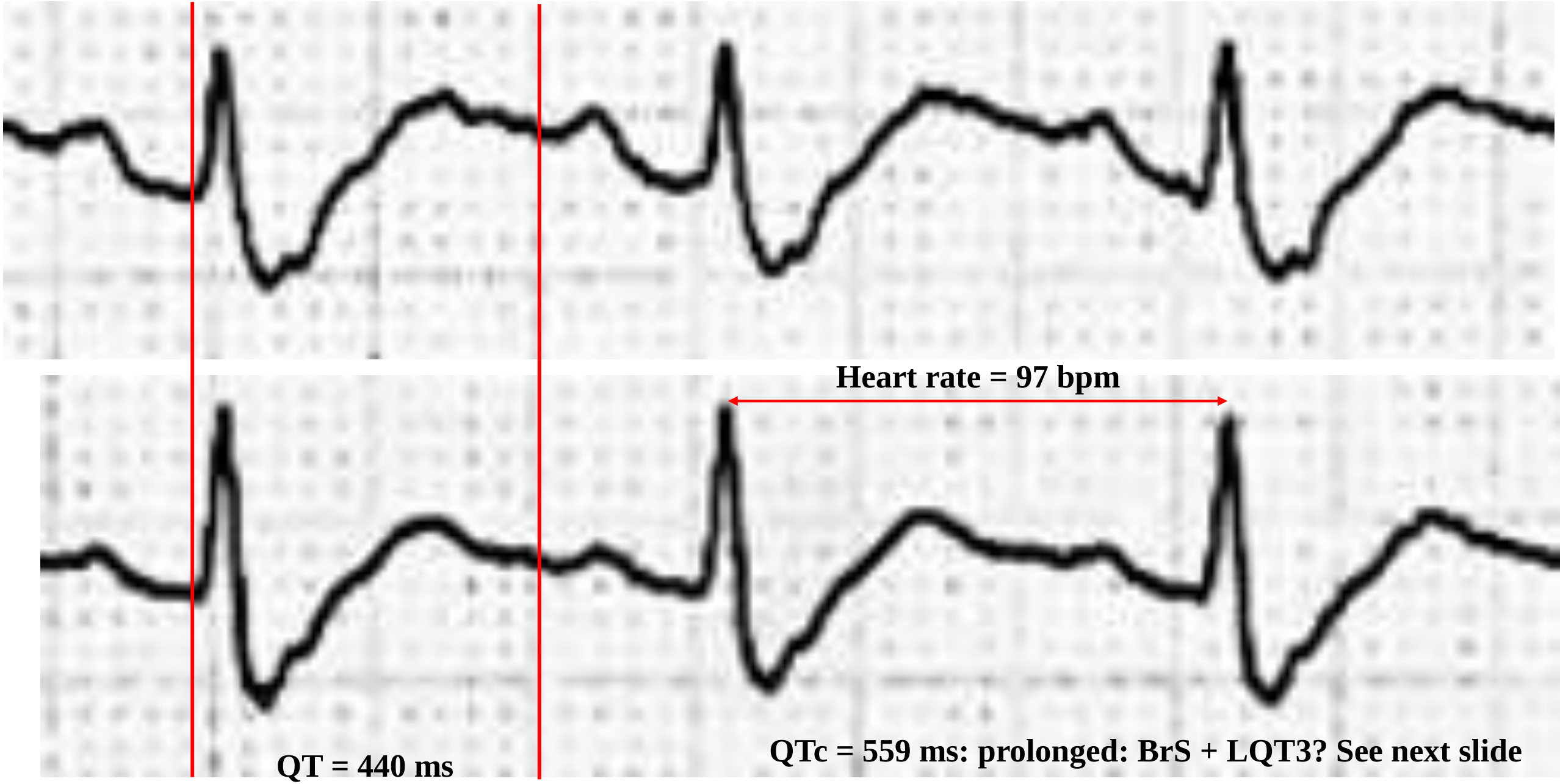
VIII. **Meaning:** epsilon waves are a reflection of delayed conduction of the right ventricle and are considered to be one of the major diagnostic criteria on the Revised Task Force criteria 2010 **(Fontaine 1999, McKenna 1994)**. They are late posterior potentials (PP) that occur in the RV free wall in patients with ARVC/D and rarely in others entities. Inversion T waves in leads V1-V3 and/or **ε**-waves are found in 70% of patients with ARVC/D. Epicardial electrophysiological studies in dysplastic areas of the RV reveal that late potentials occurring at the end of the QRS complex, in the J point, or at the onset of the ST segment can be explained by fibro-fatty replacement of myocardial tissue **(Fontaine 1984)**.

IX. **Epsilon waves and their relationship to VT:** the presence of these waves are indicative of slow and fragmented conduction leading to reentry circuits which, in turn, result in monomorphic ventricular tachycardia (M-VT) with a LBBB morphology by originating in the RV**(Aldakar 1998, Sajeev 2004)**.

ECG-2 Limb leads 50mm/s



25 mm/s


Heart rate = 97 bpm
QT = 440 ms
QTc = 559 ms: prolonged: BrS + LQT3? See next slide

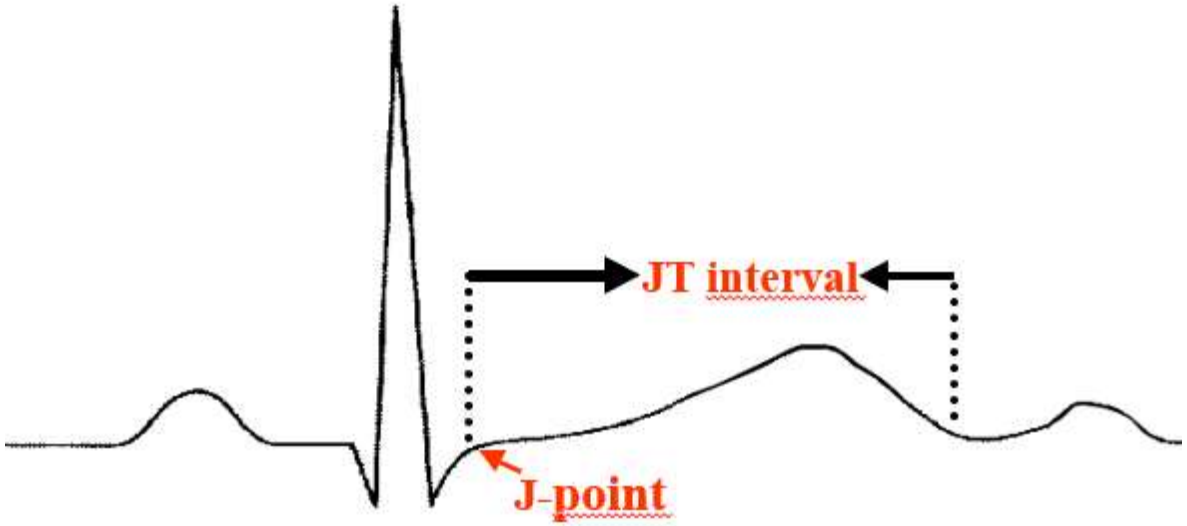
The JT and JTc intervals the posible value in the present case

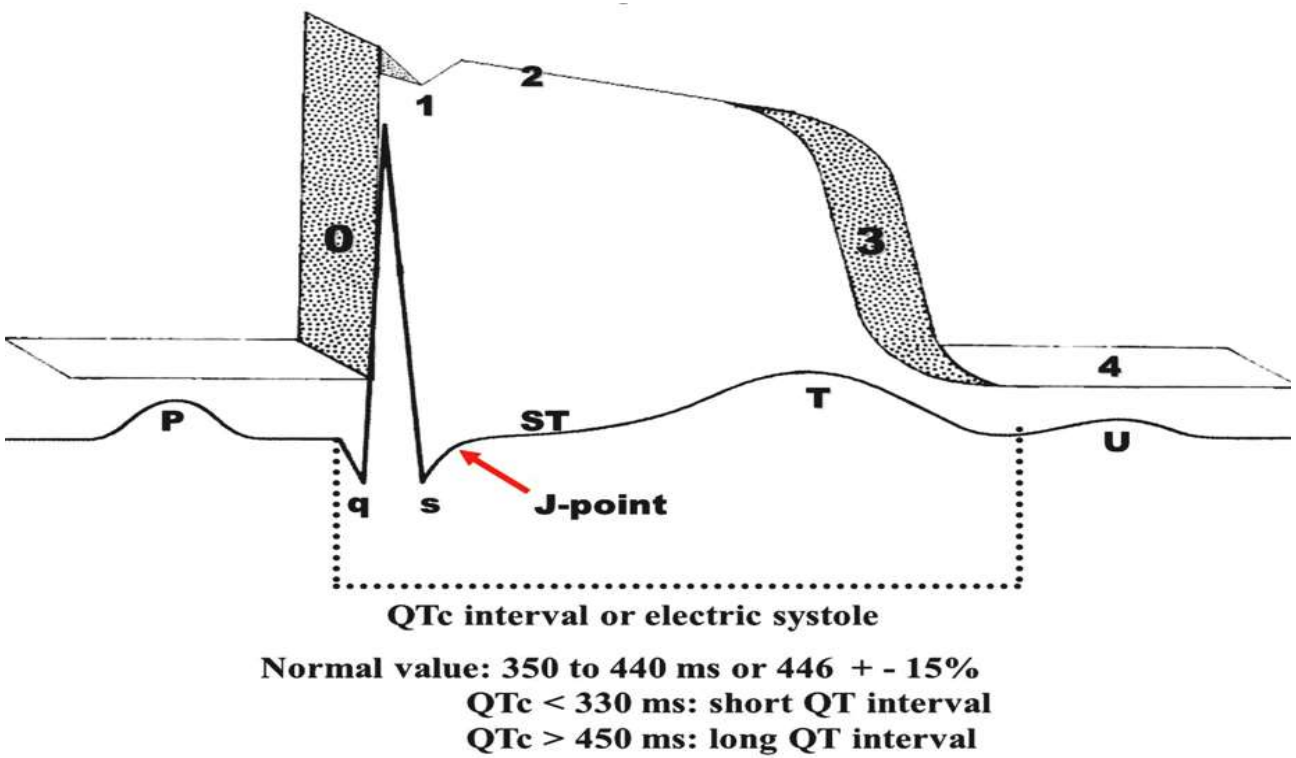
JT and JTc intervals: interval that extends from the J point to the end of the T wave.

The QTc interval constitutes the classical measurement of ventricular repolarization; however, the parameter includes ventricular depolarization. Thus, when there is bundle branch blocks(RBBB/LBBB), nonspecific intraventricular conduction disturbance or ventricular preexcitation, the measurement of ventricular repolarization by QTc may be incorrect. In such cases, the measurement of JTc is more accurate than the QTc interval, because it excludes depolarization.

The measurement of JTc may be useful to identify LQTS cases with borderline values, where QTc interval could be normal in rest ECG.

We find an example in patients carriers of tetralogy of Fallot who underwent surgery, and as a consequence of RV ventriculostomy, developed CRBBB. In these cases, JTc interval measurement is more sensitive than the QTc interval to detect prolonged repolarization The same think probably occur in the present case.

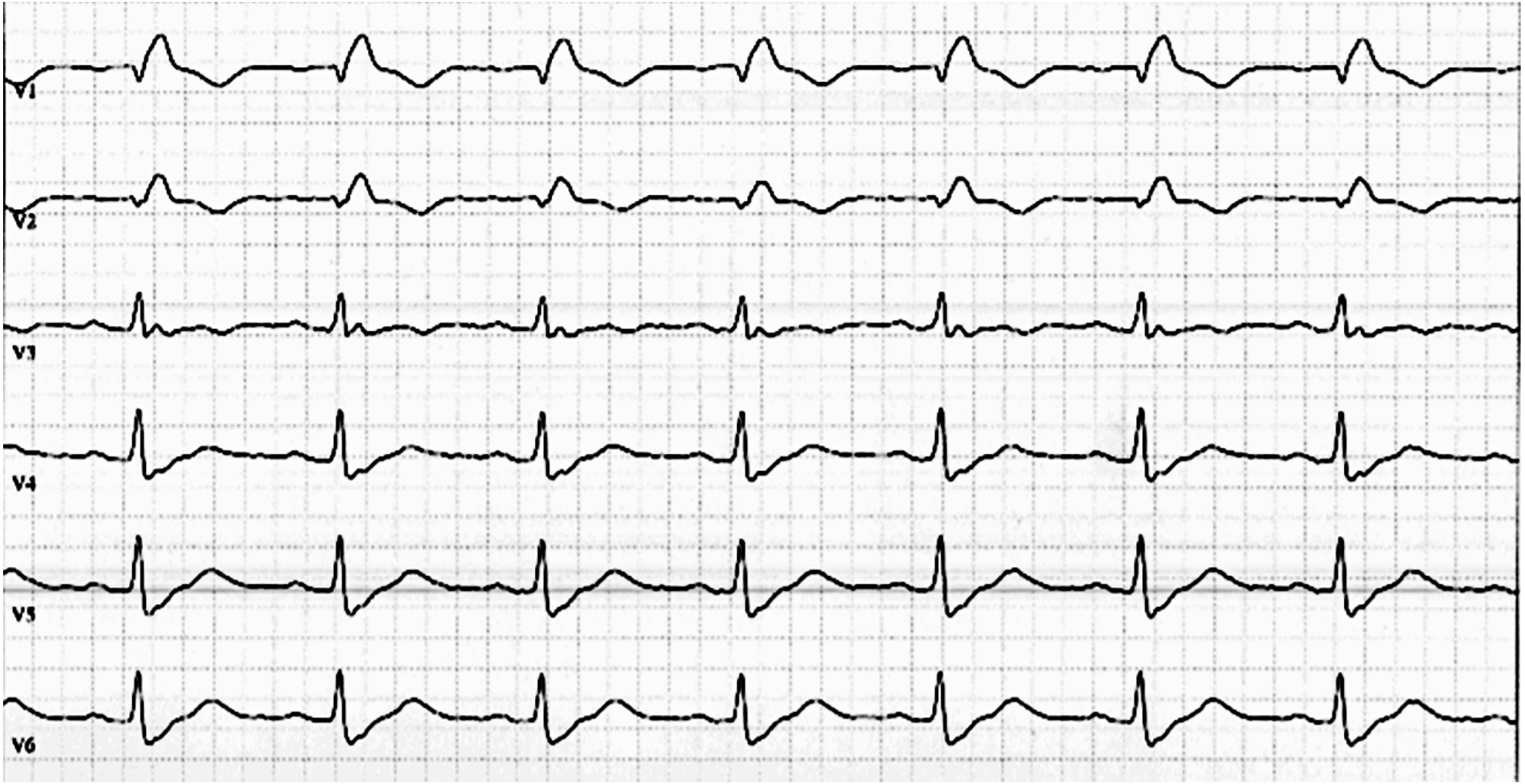


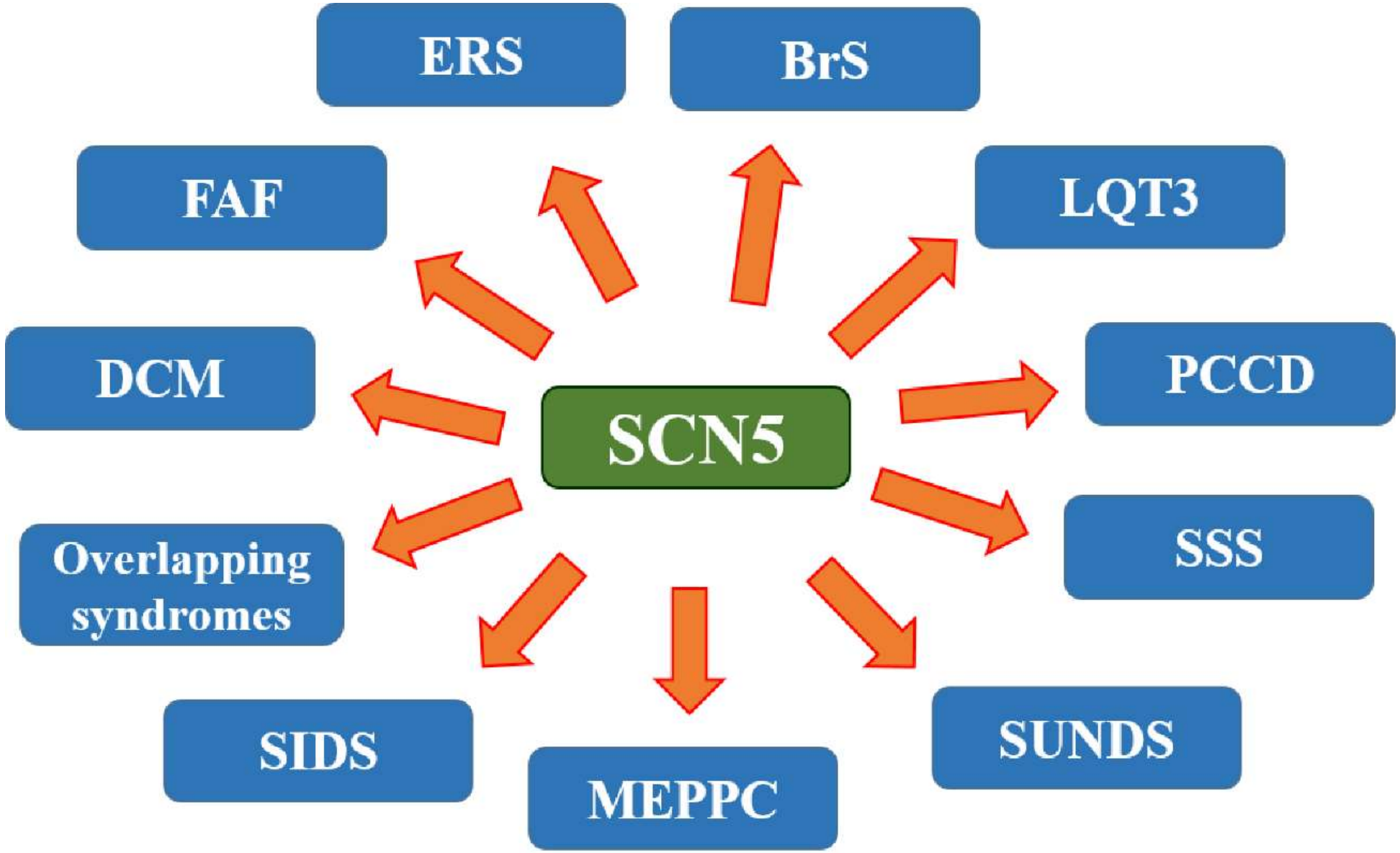


BrS and LQT3 variant in association (overlapping phenotype)

The defects on the SCN5A gene that encode the alpha subunit of the cardiac Na+ current may cause both the LQT3 variant and BrS. Both are allelic disorders with a common genotype. Evidence shows the existence of an overlapping of phenotypes between BrS and LQT3 variant. Bezzina et al (**Bezzina 1999**) described a large family that displays an SCN5A mutation, where in all the members of the family a mixed ECG pattern was observed, characterized by RBBB, J point and ST segment elevation from V1 to V2, long QT interval and high tendency to nocturnal SCD. The genotype study of these patients revealed the insertion of 3 nucleotides (TGA) in the 5537 position, which would cause an insertion of aspartic acid (1795insD) in the C-terminal domain of the protein of the SCN5A gene. Some class I antiarrhythmic agents have been used to differentiate these diseases. Endovenous flecainide can cause ST segment elevation in some patients carriers of the LQT3 variant (**Cerrone 2001; Khan 2004**). An SCN5A mutation (1795insD) in the C terminus results in a clinical phenotype combining QT prolongation and ST segment elevation, indicating a close interrelationship between BrS and the LQT3 variant. Two novel mutations on the same codon, Y1795C (LQT-3) and Y1795H (BrS), have marked and opposing effects on channel gating consistent with activity associated with the cellular basis of each clinical disorder. Y1795H speeds and Y1795C slows the onset of inactivation. The Y1795H, but not the Y1795C, mutation causes a marked negative shift in the voltage dependence of inactivation, and neither mutation affects the kinetics of the recovery from inactivation. Interestingly, both mutations increase the expression of sustained Na+ channel activity compared with wild type (WT) channels, although this effect is most pronounced for the Y1795C mutation, and both mutations promote entrance into an intermediate or a slowly developing inactivated state. This data confirms the key role of the C-terminal tail in cardiac Na+ channel gating, illustrates how subtle changes in channel biophysics can have significant and distinct effects in human disease, and, additionally, provides further evidence of the close interrelationship between BrS and LQT3 at the molecular level (**Rivolta 2001**). Pfahnl et al. (**Pfahnl 2007**) identified a threonine-to-isoleucine missense mutation at position 353 (T353I) adjacent to the pore-lining region of domain I of the cardiac sodium channel (SCN5A) in a family with BrS. Both male and female carriers are symptomatic at young ages, have typical Brugada-type ECG changes, and have relatively normal QTc. The clinical presentation of patients carrying the T353I mutation is that of BrS and could be explained by a cardiac Na(+) channel trafficking defect. However, when the defect was ameliorated with mexiletine, a Na(+) channel blocking agent the mutated channels had biophysical properties consistent with LQTS. The lack of phenotypic changes associated with the LQTS could be explained by a T353I-induced trafficking defect reducing the number of mutant channels with persistent currents present at the sarcolemma.

ECG-2 Precordial leads 50mm/s





Representation of numerous phenotypes consequence of SCN5A gene mutations: Early repolarization syndrome (ERS), Brugada síndrome (RrS), Progressive Cardiac Conduction Disease(PCCD) or Lenegre diseasse, Sick Sinus Syndrome(SSS), Sudden unexplained nocturnal death syndrome (SUNDS), Multifocal Ectopic Purkinje-related Premature ontraction(MEPPC), Sundden Infant Death Syndrome(SIDS) Overalpping syndromes, Dilated Cardiomyopathy(DCM), and Familial Atrial Fibrillation (FAF)(**Pérez-Riera 2016**).

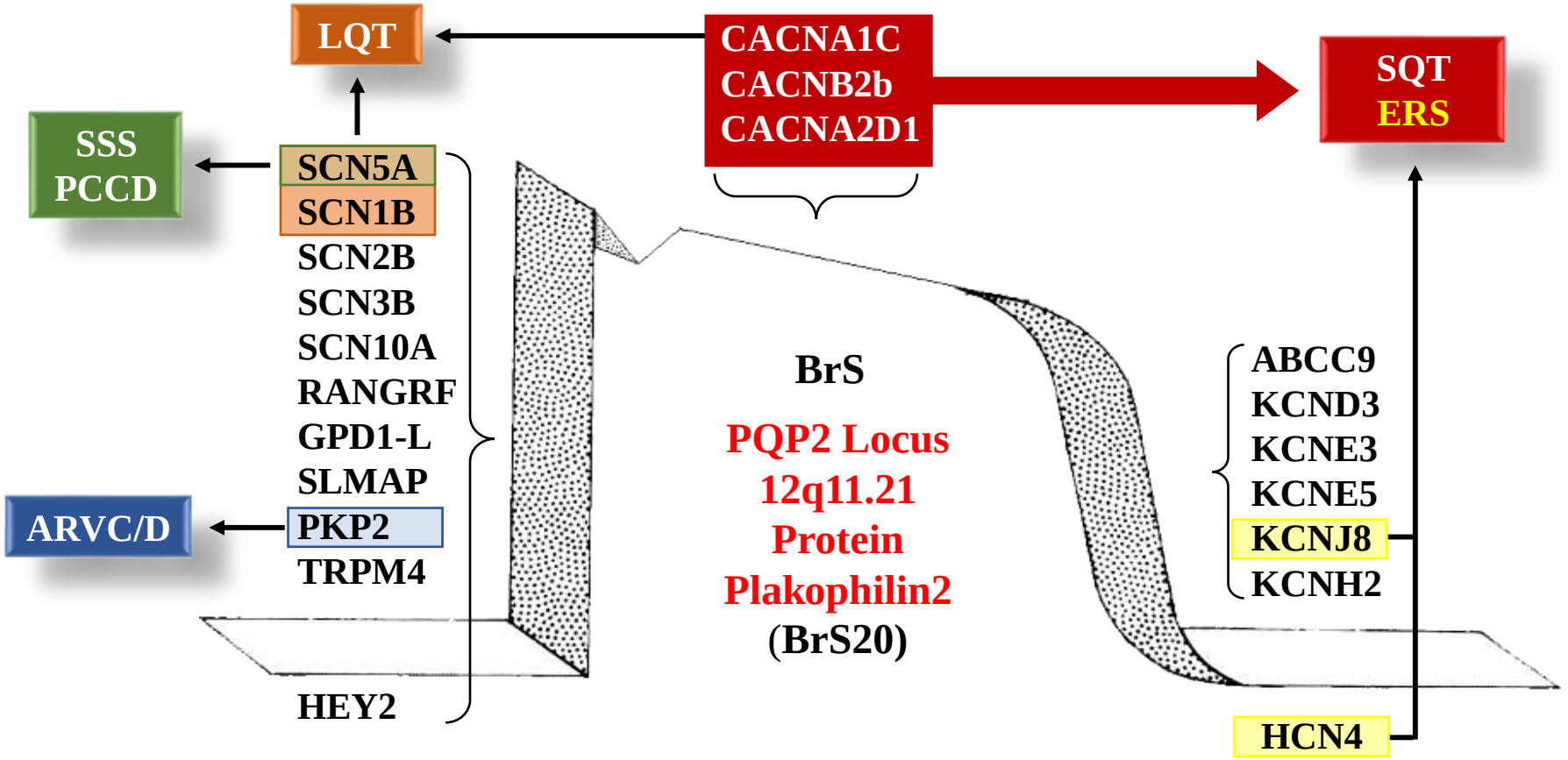
Brugada syndrome versus ARVC/D and suspected overlap of BrS and ARVC/D

Although presentation of the overlapping disease state may vary among patients, past investigations have demonstrated some common features of the overlap. First, sodium channel blockers can induce BrS ECG in a subgroup of patients with ARVC/D(**Peters 2004**) and epsilon-like waves are seen in some patients with type 1 ECG. Epsilon-like waves are more common in drug-induced type 1 ECGs than in spontaneous type 1 ECGs (**Letsas 2011**). Rather than using the term "epsilon wave," we use the term "epsilon-like wave" because distinguishing the epsilon wave from the fragmented QRS wave was difficult. The epsilon wave is located between the end of the QRS complex and beginning of the T-wave. In contrast, a fragmented QRS (f-QRS) is defined as the presence of additional spikes within the QRS complex. In patients with BrS, defining the end of QRS complex is difficult, and it is still controversial where the J wave represents depolarization component or repolarization component. Therefore, occurrence of additional spikes at the end of QRS complex or immediately after the QRS complex in BrS is not certain. The term "epsilon-like wave" has been used to avoid such discrepancies in ECG interpretation (**Letsas 2011**). Some studies revealed that epsilon potentials and fQRS fragmentation have similarly high diagnostic values, and epsilon-like potentials in different leads at the beginning, top, or end of the QRS complex are typical ECG findings in patients with ARVC/D (**Zhang 2006**). Second, imaging studies have revealed RV wall motion abnormalities or RV dilatation, which are characteristic of ARVC/D, in some patients with BrS(**Catalano 2009; Papavassiliu 2004**). Third, the fibro-fatty replacements required to diagnose ARVC/D have been detected during endocardial biopsies of patients with type 1 ECG(**Zumhagen 2009**). Finally, specific gene mutations involving ARVC/D have been identified in some patients with BrS(**Koopmann 2007**). These overlapping features are considered a result either of genetic interactions or of the combined influence of BrS' electrophysiological abnormalities and ARVC/D′s structural abnormalities. Accordingly, ARVC/D patients can satisfy the diagnostic criteria of BrS, and BrS patients can satisfy the diagnostic criteria of ARVC/D. A disease state combining both conditions has a different clinical course than uncomplicated BrS. A subgroup of BrS patients may demonstrate the features of ARVC/D long after the initial BrS diagnosis. Structural heart diseases and histological findings consistent with ARVC/D have been revealed after autopsy of patients who were diagnosed with BrS and who died suddenly(**Tada1998**). Thus, careful observation of the changing clinical course is vital and may indicate the transformation from BrS to ARVC/D. Detailed evaluation in the cases of suspected overlap of BrS and ARVC/D is also needed to determine a better treatment course for these patients. In this case, we used a range of methods, from physical examination to genetic testing (BrS- and ARVC/D-specific), to confirm dual diagnosis and to determine a better course of treatment. Since this patient experienced an episode of syncope, demonstrated epsilon-like waves in spontaneous type 1 ECG, and showed RV dilatation and RV wall motion abnormalities, a diagnosis of overlap disease of BrS and ARVC/D for the patient can be asserted with certainty.

Differential diagnosis between ARVCD and BrS

Clinical characteristics	ARVCD	BrS
Age	25-35	35-40
Sex (M/F)	M>F (3:1)	M>F (8:1)
Race	Caucasian predominance	Asian predominance
Distribution	Endemic (Veneto/Italy, Naxos Island)	Endemic (Southeast Asia: Thailand, Philippines, Japan)
Inheritance	AD or AR	AD or new mutations
Chromosomes	1, 2, 3, 6, 10, 14, 17	3
Gene, Locus and protein	**ARVC1** TGFβ-3 cause myocardial fibrosis, **ARVC2** RYR2 CPVT1/ regulates intra-cellular Ca(2+) concentration by releasing Ca(2+) reserves from the sarcoplasmic reticulum (SR), It mutation cause impaired Calcium handling, **ARVC3** chromosome 11.42-q43, **ARVC4** chromosome 2q32.1-q32.3, **ARVC5** TMEM-43 gene fibrofatty infiltration, severe ICD **ARVC6** chromosome 10p12-14, **ARVC7** desmin, *DSP* **ARVC8** *DSG2desmoplakin* **ARVC9** PKP2 plakophilin **ARVC10**, DSC2 desmoglein-2 **ARVC11** *JUP desmocollin impaired desmossomal fuction* **ARVC12,** *TMEM43*, *RYR2*, *RPSA*, *TGFB3* Plakoglobin (Naxos disease)	*SCN5A Locus 3p21 Protein Nav1.5, (**BrS1**), GPD1L Locus 3p24, protein G3PD1L (**BrS2**), CACNA1C locus 12p.13.3 protein Cav1.2 (**BrS3**), CACNB2 Locus 10p12.33 protein Cavβ2(**BrS4**), SCN1B Locus 19q13.1 Protein Navβ1(**BrS5**), KCNE3 Locus 11q13-14 Protein MiRP2, Ito/Iks (**BrS6**), SCN3B Locus 11q23,2 Protein Navβ3(**BrS7**), HCN4 Locus 7q35 Protein kv11.1, Ikr (**BrS8**),KCNJ8 Locus 12p12.1 Protein kir6.1,IK-ATP (**BrS 9**),CACNA2D1 Locus 7q21-22 Protein Cavα2δ-1 (**BrS 10**), RANGRF Locus 17p13.1 Protein MOG1* (**BrS11**) CACNA2D1 Locus 7q21-22 Protein Cavα2δ−1 (**BrS12**) KCND3 Locus 1p13.2 Protein Kv4.3, Ito (**BrS13**) HCN4 Locus 15q24.1 Protein If (**BrS14)** SLMAP Locus 3p21.2-p14.3 Protein SLMAP (**BrS15)** *TRPM4 Locus 19q13.33 Protein NSCCa* (**BrS16**) SCN2B Locus 11q23 Protein Navβ2 (**BrS17)** SCN10A Locus 3p22.2 Protein Nav1.8 (**BrS18)** HEY2 Locus 6q22 Protein Nav1.5 (**BrS19) PQP2 Locus 12q11.21 Protein Plakophilin2 (BrS20)** ABCC9 Locus12q11.21 Protein SUR2A (sulfonylurea receptor subunit 2A, IK-ATP (**BrS21).**

Genes associated with Brugada syndrome and other inherited arrhythmia diseases



Outward K+ current → Gain of function

Inward Ca2+ current → Loss of function

Inward Na+ current → Loss of function

Symptoms	Palpitation, syncope, cardiac arrest	Syncope, cardiac arrest (if AF, palpitation)
Circumstances	Effort	Nocturnal
Pathology	Fibrofatty replacement	Collagen and epicardial and interstitial fibrosis are increase in the RVOT, The Cx43 is reduced (structural heart disease). Sudden structural changes, such as RVOT dilation may point to a localized arrhythmogenic substrate.
Atrial arrhythmias	Late secondary	Early primary (20%)
Ventricular teachycardia	Monomorphic with LBBB pattern	Polymorphic. Monomorphic is posible
Mechanism	Scar-related reentry	Phase 2 reentry
Distribution	Endemic (Veneto/Italy, Naxos Island)	Endemic (Southeast Asia: Thailand, Philippines, Japan)
Inheritance	AD or AR	AD or new mutations
Chromosomes	1, 2, 3, 6, 10, 14, 17	3
ECG changes	Fixed mostly	Dynamic variable
Epsilon waves on ECG	Major criteria	Excepcional
β Stimulation (isoproterenol infusion)	↑	↓ Can be useful in suppressing arrhythmic storms.
Quinidine	Not indicated	For the treatment of electrical storm and prevention of recurrent shocks. Can be useful in patients qualify for an ICD but present a contraindication to the ICD or refuse it and/or have a history of documented supraventricular arrhythmias that require treatment.
ECG changes	Fixed mostly	Dynamic variable, transient

Treatment	ARVCD	BrS
Chinese herb extract Wenxin Keli	Not indicated	It inhibits the Ito current, acting to diminish the AP notch and thus to suppress the substrate and trigger for VT or VF
Cilostazol	Not indicated	Used by inhibition of transient outward current Ito
Cilostazol + bepridil	Not indicated	Possible utility in presence of J-wave syndrome (**Shinohara 2014**)
Flecainide in combination with sotalol/ metoprolol	The addition of flecainide in combination with sotalol/metoprolol may be an effective antiarrhythmic strategy for the control of ventricular arrhythmias in patients with ARVC refractory to single-agent therapy and/or catheter ablation(**Ermakov 2017**).	No
Radiofrequency catheter ablation (RFCA)	RFCA of VT in ARVC patients should be considered a potentially effective strategy for eliminating frequent VT episodes and ICD shocks rather than a curative therapeutic approach, until long-term efficacy has been consistently documented. Research into the optimal mapping and ablation techniques are promising and ongoing (**Romero 2017**).	Epicardial RFCA offers an alternative therapy for patients with BrS, especially when ICD shocks are encountered. It may be an effective approach to treat VTs in BrS patients with arrhythmic storms. Arrhythmogenic electrophysiological substrate elimination by RFCA results in ECG normalization and VT/VF noninducibility. Substrate-based ablation is effective in potentially eliminating the arrhythmic consequences of this genetic disease (**Pappone 2017**).
Implantable cardioverter-defibrillator (ICD)	Recurrence of SVT/VF is frequent in high-risk patients with ARVC. The prognosis is favorable for ARVC patients treated with an ICD for prevention of SCD. The most important parameters to consider when determining arrhythmic risk include electric instability, the frequency of PVCs and SVT; proband status; extent of structural disease; cardiac syncope; male sex; the presence of multiple mutations or a mutation in TMEM43; and the patient's willingness to restrict exercise and to eliminate participation in competitive or endurance exercise(**Callkins 2017**).	Survivors of a cardiac arrest, documented spontaneous sustained VT with or without syncope. ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.

Expert consensus recommendations on BrS diagnosis:

1. BrS is diagnosed in patients with ST-segment elevation with type 1 morphology ≥2 mm in ≥1 lead among the right precordial leads V1, V2, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.
2. BrS is diagnosed in patients with type 2 ST-segment elevation in ≥1 lead among the right precordial leads V1, V2 positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.

Expert consensus recommendations on BrS therapeutic interventions:

Class I

1. The following lifestyle changes are recommended in all patients with diagnosis of BrS:
   a) Avoidance of drugs that may induce or aggravate ST-segment elevation in right precordial leads (for example, visit Brugadadrugs.org),
   b) Avoidance of excessive alcohol intake.
   c) Immediate treatment of fever with antipyretic drugs.
2. ICD implantation is recommended in patients with a diagnosis of BrS who:
   a) Are survivors of a cardiac arrest and/or
   b) Have documented spontaneous sustained VT with or without syncope.

Class IIa

3. ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.
4. Quinidine can be useful in patients with a diagnosis of BrS and history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours.
5. Quinidine can be useful in patients with a diagnosis of BrS:
   a) Who qualify for an ICD but present a contraindication to the ICD or refuse it and/or
   b) Have a history of documented supraventricular arrhythmias that require treatment.
6. Isoproterenol infusion can be useful in suppressing arrhythmic storms in BrS patients.

Class IIb

7. ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).
8. Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type I ECG.
9. Catheter ablation may be considered in patients with a diagnosis of BrS and history of arrhythmic storms or repeated appropriate ICD shocks.

Class III

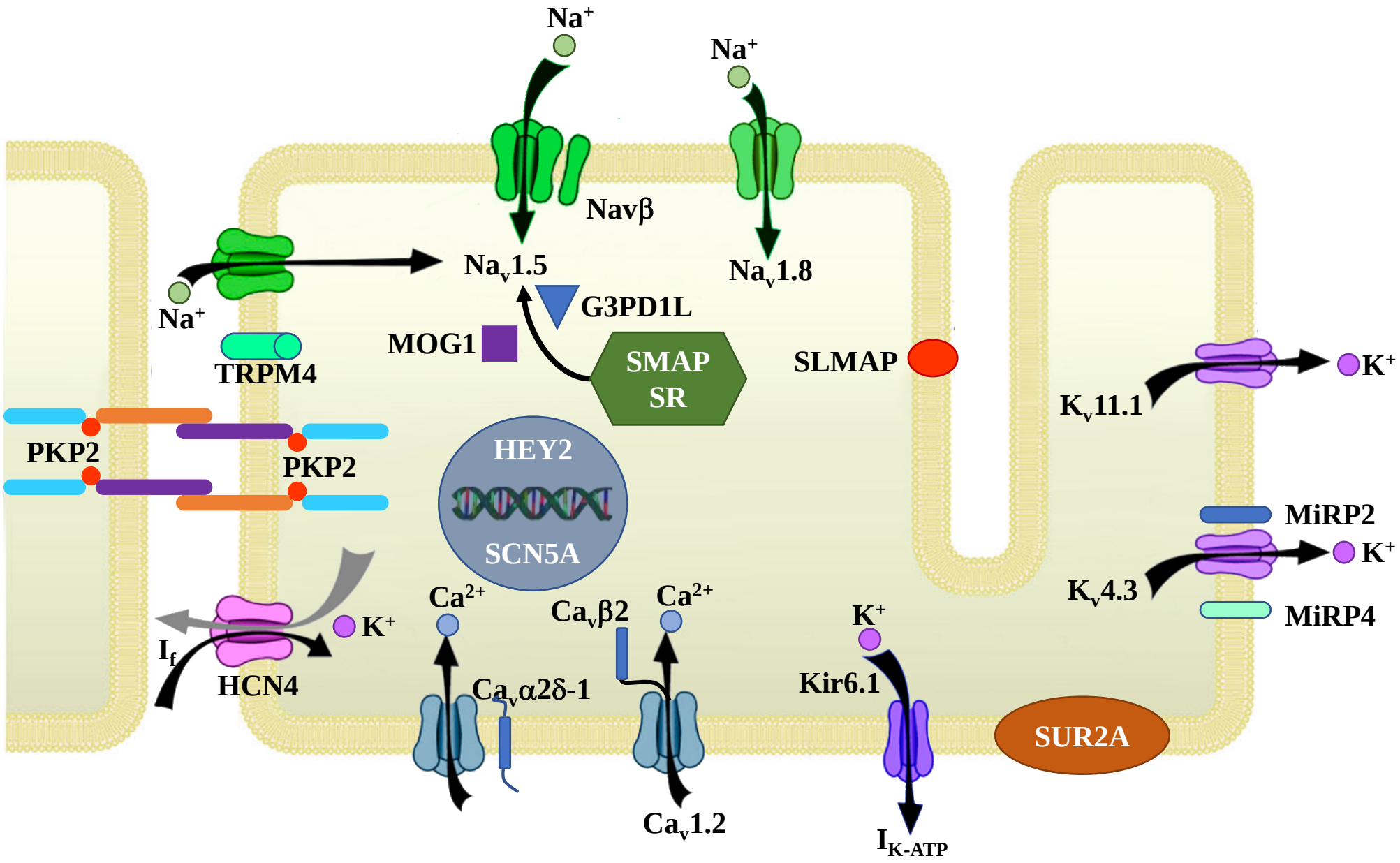
10. ICD implantation is not indicated in asymptomatic BrS patients with a drug-induced type I ECG and on the basis of a family history of SCD alone (**Priori 2013**).

ICD: BrS patients with first arrhythmic event documented after prophylactic ICD implantation exhibited their arrhythmic event at a later age with a higher incidence of positive family history of SCD and SCN5A mutations compared to those presenting with an aborted cardiac arrest. Only 75% of patients who suffered an arrhythmic event after receiving a prophylactic ICD complied with the 2013 Class II indications, suggesting efforts are still required for improving risk stratification (**Milman 2018**).

Sudden cardiac arrhythmia	Genes
Long QT Syndrome (LQTS)	*KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5*
Brugada Syndrome	*SCN5A Locus 3p21 Protein Nav1.5, (**BrS1**), GPD1L Locus 3p24, protein G3PD1L (**BrS2**), CACNA1C locus 12p.13.3 protein Cav1.2 (**BrS3**), CACNB2 Locus 10p12.33 protein Cavβ2(**BrS4**), SCN1B Locus 19q13.1 Protein Navβ1(**BrS5**), KCNE3 Locus 11q13-14 Protein MiRP2, Ito/Iks (**BrS6**), SCN3B Locus 11q23,2 Protein Navβ3(**BrS7**), HCN4 Locus 7q35 Protein kv11.1, Ikr (**BrS8**),KCNJ8 Locus 12p12.1 Protein kir6.1,IK-ATP (**BrS 9**),CACNA2D1 Locus 7q21-22 Protein Cavα2δ-1 (**BrS 10**), RANGRF Locus 17p13.1 Protein MOG1* (**BrS11**) CACNA2D1 Locus 7q21-22 Protein Cavα2δ−1 (**BrS12**) KCND3 Locus 1p13.2 Protein Kv4.3, Ito (**BrS13**) HCN4 Locus 15q24.1 Protein If (**BrS14**) SLMAP Locus 3p21.2-p14.3 Protein SLMAP (**BrS15**) *TRPM4 Locus 19q13.33 Protein NSCCa* (**BrS16**) SCN2B Locus 11q23 Protein Navβ2 (**BrS17**) SCN10A Locus 3p22.2 Protein Nav1.8 (**BrS18**) HEY2 Locus 6q22 Protein Nav1.5 (**BrS19**) PQP2 Locus 12q11.21 Protein Plakophilin2 (**BrS20**) ABCC9 Locus12q11.21 Protein SUR2A(sulfonylurea receptor subunit 2A, IK-ATP (**BrS21**).
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	*RYR2 (CPVT1), CASQ2 (CPVT2), TRDN (CPVT3), ANK2 (CPVT4),TRD (CPVT5), KCNJ2* (**Pérez-Riera 2017**)
WPW Syndrome	*PRKAG2*
Short QT Syndrome (SQTS)	*KCNH2 (SQT1), KCNQ1 (SQT2), KCNJ2 (SQT3), CACNA1C (SQT4), CACNB2b (SQT5), CACNA2D1 (SQT6), CAVE3 (SQT7?)*
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	TGFβ-3 (ARVC1) myocardial fibrosis, RYR2CPVT1/ARVC2 impaired Calcium handling, ARVC3 chromosome 11.42-q43, ARVC4 chromosome 2q32.1-q32.3, ARVC5 TMEM-43 gene fibrofatty infiltration, ARVC6 chromossome 10p12-14, ARVC7 desmin, *DSP desmoplakin* (ARVC8), *PKP2 plakophilin* (ARVC9), *DSG2*(ARVC10), DSC2 desmoglein-2 (ARVC11), *JUP desmocollin impaired desmossomal fuction* (ARVC12), *TMEM43, RYR2, RPSA, TGFB3*
Familial Sick Sinus Syndrome (SSS)	*SCN5A, HCN4*

Sudden cardiac arrhythmia	Genes
Cardiac conduction disease (CCD) or Lenègre disease	SCN5A on chromosome 3 (coding for the Na^+ channel alpha subunit)
Hypertrophic Cardiomyopathy (HCM)	*MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3, MYH6, LAMP2, PRKAG2, CSRP3, GLA, VCL, TNNC1, TTR, TTN, TCAP, MYLK2, MYOZ2, MYO6*
Dilated cardiomyopathy (DCM)	*DES, TNNT2, MYH7, CSRP3, PLN, TCAP, ABCC9, LMNA, DMD, TAZ, TTN, VCL, EYA4, EMD, ACTN2, SGCD, ACTC1, TNNI3, TPM1, MYBPC3, LDB3, MYH6, CTF1, ANKRD1*
Dilated cardiomyopathy with Cardiac conduction defect (DCM+CCD)	*SCN5A, LMNA*
Left ventricular noncompaction (LVNC)	*LDB3, TAZ, MYH7, MYBPC3, ACTC1, TNNT2, SCN5A, LMNA, DMPK, DTNA, AMPD1, PMP22, LMX1B, YWHAE*
Restrictive cardiomyopathy (RCM)	*MYH7, TNNI3, TNNT2*
Familial Atrial Fibrillation (FAF)	*KCNQ1, KCNE2, KCNJ2, KCNH2, SCN5A, KCNA5, NPPA, NUP155, GJA5, ABCC9, GATA4, GATA5, GATA6, KCNE1L*
Long QT Syndrome (LQTS)	*KCNQ1, KCNH2, SCN5A, ANK2, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP9, SNTA1, KCNJ5*

Schematic representation of a cardiomyocyte exhibiting the proteins involved in Brugada syndrome pathogenesis



Dear Andres,
Thanks a lot for your interpretation!
My opinion is:

1) Sinus rhythm
2) Prolonged P Wave duration>110ms
3) QRS axis with right axis deviation QRS positive in III-aVR and aVF
4) CRBBB
5) Type 1 Brugada pattern
6) Prolonged QTc duration =550ms : *due to the cRBBB I wouldn´t consider QTc as clearly prolonged*
7) *Genetic testing is still not perfomed as the patients insurance until now wasn´t willing to cover the costs, but we´ll try again*
8) *A cardiac MRI was performed 4 years ago without signs of ARVC but we´ll follow careful obervation of a possible transformation*

Hence, at present we would agree with the working diagnosis: “Sodium channel syndrome/Diffential diagnosis :Brugada syndrome and possible arrhythmogenic right ventricular cardiomyopathy/dysplasia”.

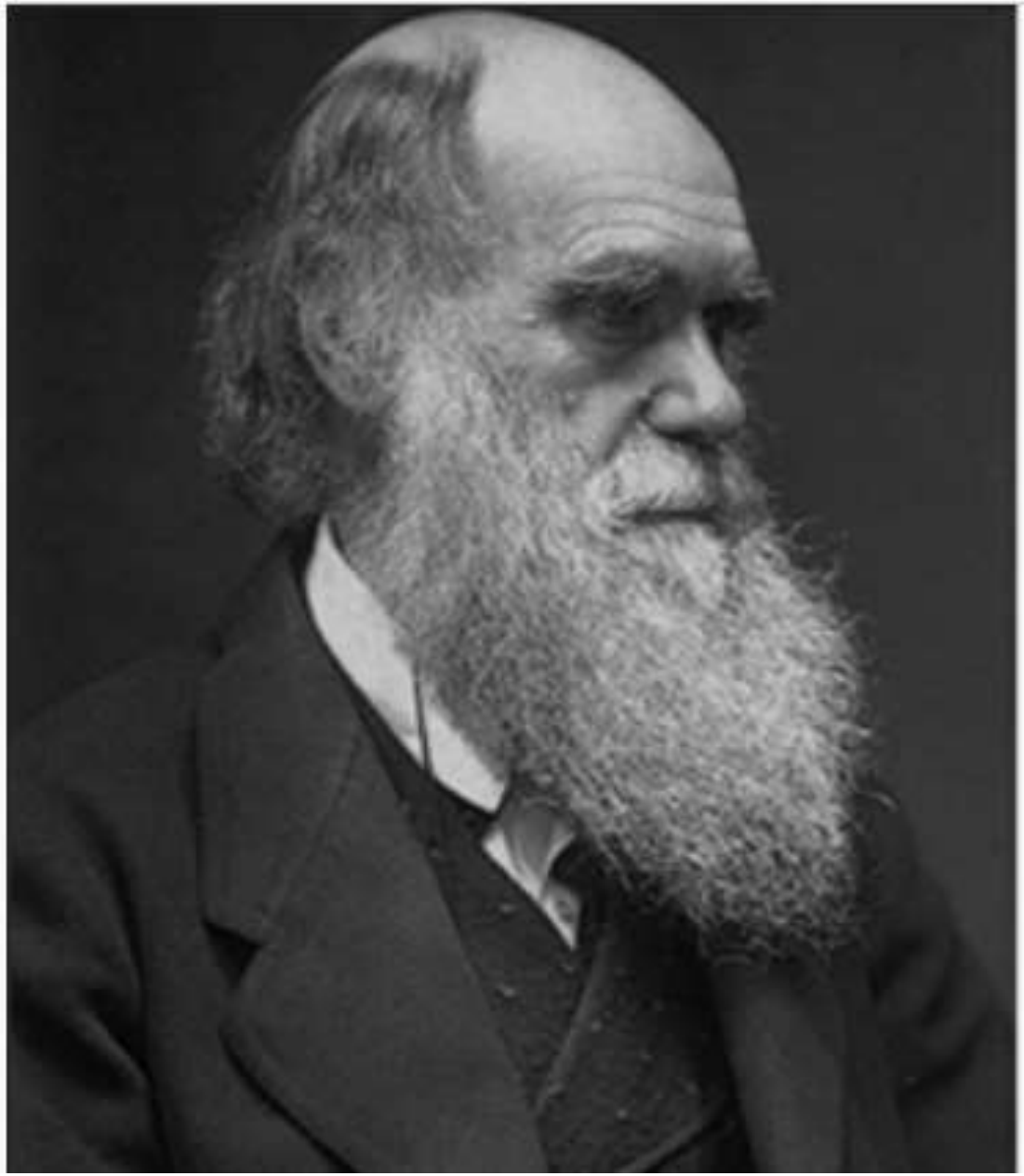
I highly appreciated your valuable opinion
Best regards
Britt

References

1. Aldakar M, Perchet Hm Coutte R, et al. Association of an epsilon wave and syncope. Presse Med. 1998;27(37):1893-6.
2. Babai Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm. 2007;4(8):1009-12.
3. Bezzina C, Veldkamp MW, van Den Berg MP, et al. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. Circ Res. 1999;85(12):1206-13.
4. Calkins H, Corrado D, Marcus F.Risk Stratification in Arrhythmogenic Right Ventricular Cardiomyopathy.Circulation. 2017;136(21):2068-82.
5. Catalano O, Antonaci S, Moro G. Magnetic resonance investigations in Brugada syndrome reveal unexpectedly high rate of structural abnormalities. Eur Heart J. 2009;30(18):2241-8
6. Cerrone M, Crotti L, Faggiano G, et al. Long QT syndrome and Brugada syndrome: 2 aspects of the same disease? Ital Heart J 2001;2(3 Suppl):253-7.
7. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm. 2017;14(4):564-9.
8. Fontaine G, Frank R, Tonet JL, et al. Arrhythmogenic right ventricular dysplasia: a clinical model for the study of chronic ventricular tachycardia. Jpn Circ J. 1984;48(6):515-38.
9. Fontaine G, Fontaliran F, Hébert JL, et al. Arrhythmogenic right ventricular dysplasia. Annu Rev Med. 1999;50:17-35.
10. Hurst JW. Naming of the Waves in the ECG, With a Brief Account of Their Genesis. Circulation 1998:98(18),1937-42.
11. Kataoka S, Serizawa N, Kitamura K, et al. An overlap of Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia. J Arrhythm. 2016;32(1):70-3.
12. Khan IA, Nair CK. Brugada and long QT-3 syndromes: two phenotypes of the sodium channel disease. Ann Noninvasive Electrocardiol. 2004;9(3):280-9.
13. Koopmann T.T., Beekman L., Alders M. Exclusion of multiple candidate genes and large genomic rearrangements in SCN5A in a Dutch Brugada syndrome cohort. Heart Rhythm. 2007;4(6):752–5.
14. Kukla P, Jastrzebki M, Kurdzielewicz W. Higher right precordial leads and Fontaine leads: the better detection of QRS fragmentation and epsilon wave in arrhythmogenic right ventricular dysplasia-cardiomyopathy. Kardiol Pol. 2012;70(9):958-9.

15. Letsas K.P., Efremidis M., Weber R. et al. Epsilon-like waves and ventricular conduction abnormalities in subjects with type 1 ECG pattern of Brugada syndrome. Heart Rhythm. 2011;8(6):874–8.
16. McKenna WJ, Thiene G, Nava A, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. Br Heart J 1994;71(3):215-8.
17. Milman A, Andorin A, Gourraud JB, et al. Profile of Brugada Syndrome Patients Presenting with Their First Documented Arrhythmic Event. Data from the Survey on Arrhythmic Events in BRUgada Syndrome (SABRUS). Heart Rhythm. 2018. pii: S1547-5271(18)30014-6.
18. Miyamoto A, Hayashi H, Makiyama T, et al. Risk determinants in individuals with a spontaneous type 1 Brugada ECG. Circ J. 2011;75(4):844-51.
19. Napolitano C, Rivolta I, Priori SG. Cardiac sodium channel diseases. Clin Chem Lab Med. 2003;41(4):439-44.
20. Papavassiliu T., Wolpert C., Flüchter S. Magnetic resonance imaging findings in patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2004;15(10):1133–8.
21. Pappone C, Brugada J, Vicedomini G, et al. Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome. Circ Arrhythm Electrophysiol. 2017;10(5):e005053.
22. Pérez-Riera AR, Daminello Raimundo R, Akira Watanabe R, Figueiredo JL, de Abreu LC. Cardiac sodium channel, its mutations and their spectrum of arrhythmia phenotypes. J Hum Growth Dev. 26(3):281-96.
23. Pérez-Riera AR, Barbosa-Barros R, de Rezende Barbosa MPC, Daminello-Raimundo R, de Lucca AA Jr, de Abreu LC. Catecholaminergic polymorphic ventricular tachycardia, an update. Ann Noninvasive Electrocardiol. 2017 Oct 19. doi: 10.1111/anec.12512.
24. Peters S., Trümmel M., Denecke S. Results of ajmaline testing in patients with arrhythmogenic right ventricular dysplasia–cardiomyopathy. Int J Cardiol. 2004;95(2-3):207–10.
25. Pfahnl AE, Viswanathan PC, Weiss R, et al. A sodium channel pore mutation causing Brugada syndrome. Heart Rhythm. 2007;4(1):46-53.
26. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932-63.
27. Rivolta I, Abriel H, Tateyama M, et al. Inherited Brugada and long QT-3 syndrome mutations of a single residue of the cardiac sodium channel confer distinct channel and clinical phenotypes. J Biol Chem 2001;276:30623-30.

28. Romero J, Grushko M, Briceño DF, Natale A, Di Biase L. Radiofrequency Ablation in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). Curr Cardiol Rep. 2017;19(9):82.
29. Sajeev CG, Javakumar TG, Krishnan MN, et al. Epsilon wave. Int J Cardiol. 2004; 93:315.
30. Santucci PA, Morton JB, Picken MM, JB, et al. Electroanatomic mapping of the right ventricle in a patient with a giant epsilon wave, ventricular tachycardia, and cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2004;15:1091-4.
31. Saprungruang A, Tumkosit M, Kongphatthanayothin A. The Presence of Epsilon Waves in All Precordial Leads (V1 -V6) in a 13-Year-Old Boy with Arrhythmogenic Right Ventricular Dysplasia (ARVD). Ann Noninvasive Electrocardiol. 2013;18(5):484-6.
32. Shinohara T, Ebata Y, Ayabe R, et al. Combination therapy of cilostazol and bepridil suppresses recurrent ventricular fibrillation related to J-wave syndromes. Heart Rhythm. 2014;11(8):1441-5.
33. Tada H, Aihara N, Ohe T. Arrhythmogenic right ventricular cardiomyopathy underlies syndrome of right bundle branch block, ST-segment elevation, and sudden death. Am J Cardiol. 1998;81(4):519–22.
34. Veltmann C, Barajas-Martinez H, Wolpert C, et al. Further Insights in the Most Common SCN5A Mutation Causing Overlapping Phenotype of Long QT Syndrome, Brugada Syndrome, and Conduction Defect. J Am Heart Assoc. 2016;5(7). pii: e003379.
35. Wang J, Yang Bm Chen H, et al. Epsilon waves detected by various electrocardiographic recording methods: in patients with arrhythmogenic right ventricular cardiomyopathy. Tex Heart Inst J. 2010;37(4):405-11.
36. Yokokawa M, Noda T, Okamura H, et al. Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5A-positive probands and the SCN5A-negative probands. Am J Cardiol. 2007;100(4):649-55.
37. Zhang L, Riera ARP, Pu J. Are epsilon waves in ARVD “the right precordial leads only” phenomena? Europace. 2006;8(Suppl 1):S265/4.
38. Zorio E, Arnau MA, Rueda J, et al. The presence of epsilon waves in a patient with acute right ventricular infarction. Pacing Clin Electrophysiol. 2005;28(3):245-7.
39. Zumhagen S, Spieker T, Rolinck J. Absence of pathognomonic or inflammatory patterns in cardiac biopsies from patients with Brugada syndrome. Circ Arrhythm Electrophysiol. 2009;2(1):16–23.



"It is not the strongest species that survive, nor the most intelligent, but the most responsive to change."

CHARLES DARWIN

ORIGIN OF SPECIES