Repetitive syncopal episodes in a child with documented ventricular tachycardia and particular ECG patterns

Episodios sincopales repetitivos en un niño con taquicardia ventricular documentada y un patrón de ECG particular

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English

Pediatric clinical-cardiological case

Child, 2 years 6 months, 14 kg. History of diabetes mellitus and hypertension in paternal grandparents and uncles. A cousin with arrhythmias (unknown, but without syncope or serious symptoms).

He has three brothers: 14 years healthy, 10 years oligophrenic and 4 years healthy.

No history of sudden death in their first degree relatives.

Personal history: at one year of age, he presented with a sudden episode (≈10 minutes) of flaccidity, diaphoresis, cyanosis, polypnea, with spontaneous recovery. On the occasion he went to emergency medical service, where he was diagnosed as an infectious process of the upper respiratory tract. In a short period of time he was diagnosed with the picture known as sob spasm or "Breath-Holding Spells" (this is a picture in which the child periodically becomes breathless after a prolonged expiration, by crying or anger. This picture has been known in France as *"spasme du sanglot"*, a name which was proposed by Robert Debre in 1948). These manifestations were observed on at least 5 occasions during one year and were accompanied by cyanosis and diaphoresis. 12 hours before the current admission, he presented a new sudden picture of flaccidity, diaphoresis, cyanosis, polypnea, seizures and prolonged hypothermia (approximately 3 hours), spontaneously improving (the picture was interpreted as a respiratory infection again. In the following morning, the parents noticed prolonged symptoms (several hours) of diaphoresis, flaccidity and polypnea. The attending physician directed him to the intensive care unit where the ECG-1 was performed, being medicated with 30 mg of propranolol orally. After ≈30 minutes after the placement of a central catheter the ECG-2 was performed, which showed the reversal of the ECG-1 tachyarrhythmic event, which was spontaneously reverted to a bradycardic rhythm (which lasted ≈8 hours due to the effect of β-blockers, then moved to sinus rhythm, without new evidences of pauses or nodal rhythm)

Echocardiogram performed 24 hrs after the last event was considered normal.

24-hour Holter performed during a feverish peak of 38 degrees Celsius, presented during the afternoon.

Precordial high nodal rhythms that go along with the ECG-2.

Questions:

What is the probable diagnosis (s)? Why?

What would be the most appropriate diagnostic / therapeutic approach?

Spanish

Caso clínico-cardiológico pediátrico

Niño, 2 años 6 meses, 14 kg. Antecedentes de diabetes mellitus tipo 2 e hipertensión en abuelos y tíos paternos, un primo con arritmias (se desconoce, pero sin sincope o síntomas graves)

Tres hermanos: 14 años sano, 10 años oligofrénico y 4 años sano.

Sin antecedentes de muerte súbita en sus familiares directos.

Historia personal: con un año de edad, presentó de forma súbita episodio de aproximadamente 10 minutos de flacidez, diaforesis, cianosis, polipnea, con recuperación espontanea. En la ocasión acudió a servicio médico de emergencia, donde le diagnosticaron apenas proceso infeccioso de vías respiratorias altas. En un corto periodo de tiempo le diagnosticaron el cuadro conocido como espasmo del sollozo (esta es una condición en que el niño periódicamente queda apneico tras una espiración prolongada, por llanto o ira). Este cuadro fue observado en por lo menos 5 ocasiones durante un año y siempre se acompañó de cianosis y diaforesis. 12 horas antes del actual ingreso, presentó nuevo cuadro súbito de flacidez, diaforesis, cianosis, polipnea, convulsiones e hipotermia prolongado (≈3 horas), mejorando de forma espontanea (el evento fue interpretado como infección respiratoria). A la madrugada siguiente, los padres notaron cuadro prolongado (varias horas) de diaforesis, flacidez y polipnea. El médico tratante lo encamina a la unidad de terapia intensiva donde se realiza el primer ECG (ECG-1), siendo medicado con 30 mg de propranolol vía oral. Pasado ≈30 minutos a la colocación de un catéter central se realiza el ECG-2, en el que se constata la reversión del evento taquiarrítmico, el cual es sustituido pot un ritmo lento de ≈8 horas y atribuido al efecto bradicardisante del β-bloqueador, luego pasa a ritmo sinusal. Precordiales altas en ritmo nodal que van junto con el ECG-2.

Holter de 24 horas (último slide).

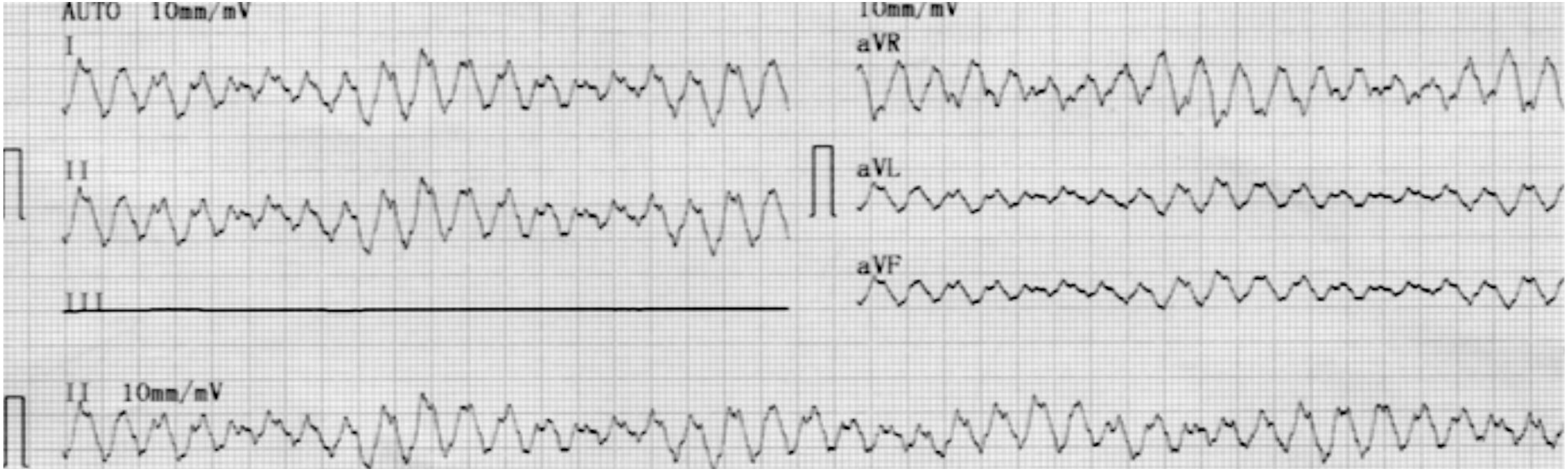
Ecocardiograma realizado 24 horas después del ultimo evento fue considerado normal.

Holter de 24 horas realizado durante un pico febril de 38 grados centígrados, que presentó durante la tarde.

Preguntas:

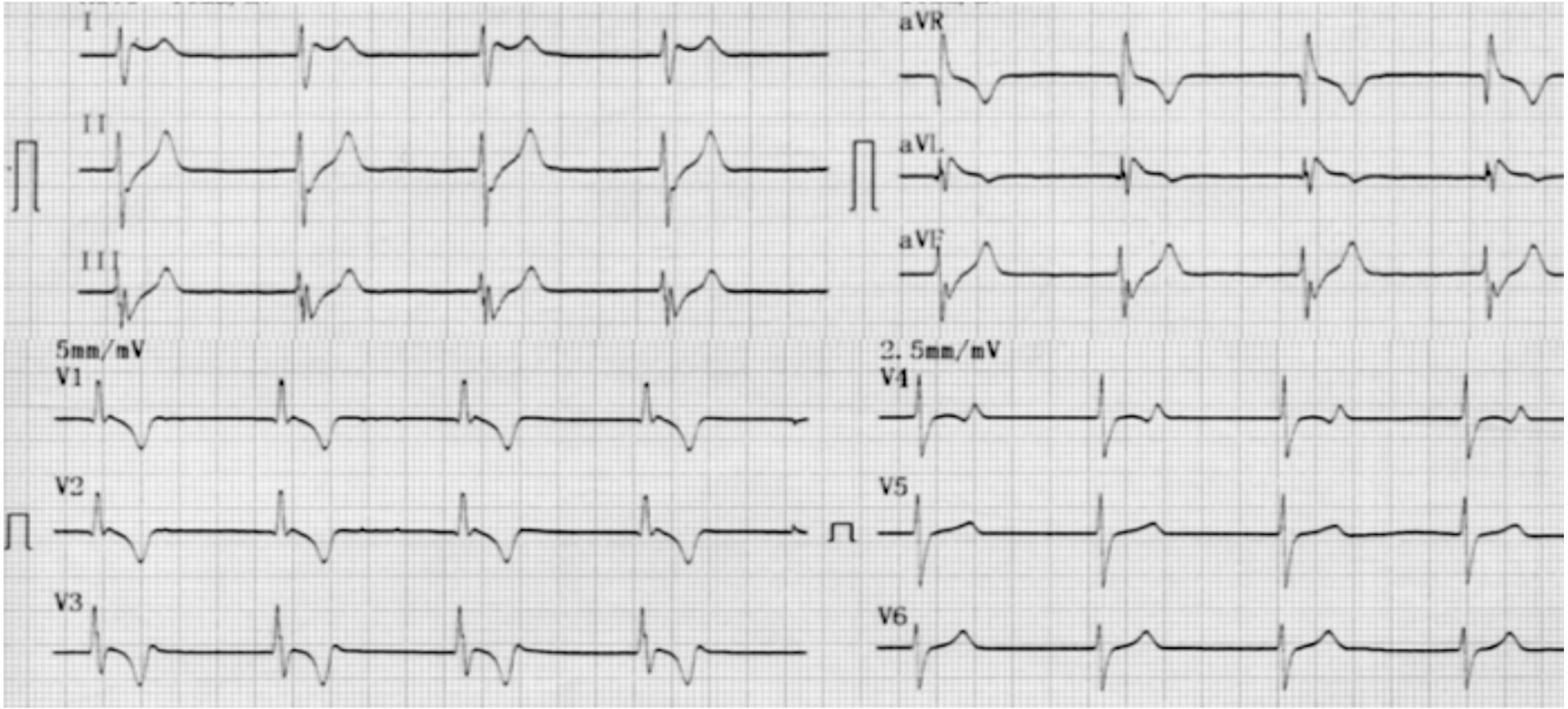
1. Cual es/son los probables diagnósticos? Por qué?
2. Cual seria el más adecuado abordaje diagnóstico/terapéutico?

ECG-1 Only limb leads (with artifact in III)



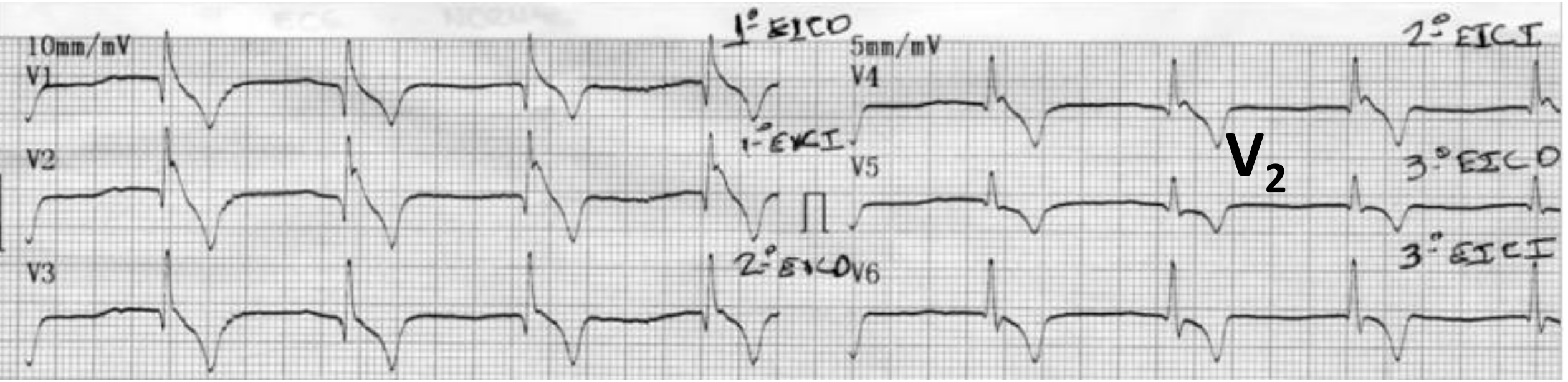
Diagnosis:

ECG-2 After spontaneous reversion

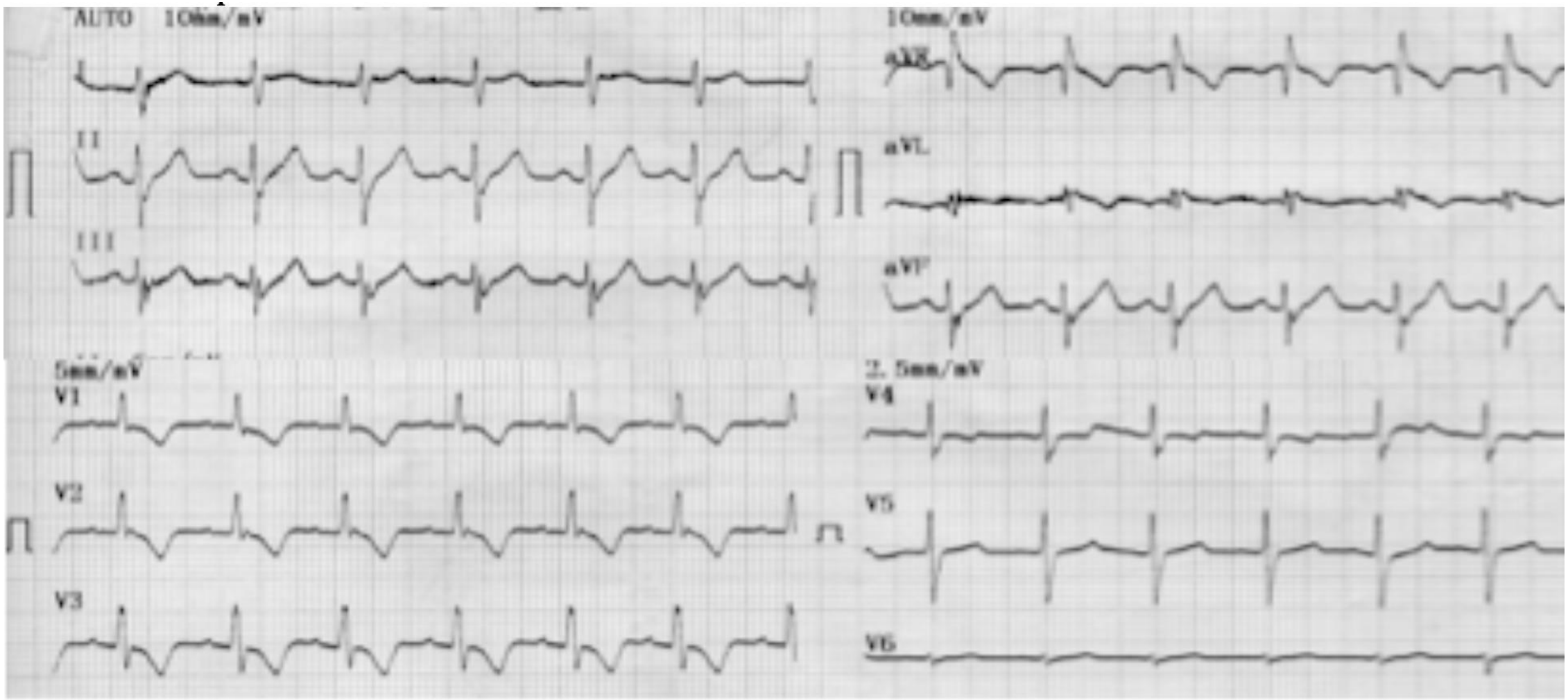


Diagnosis:

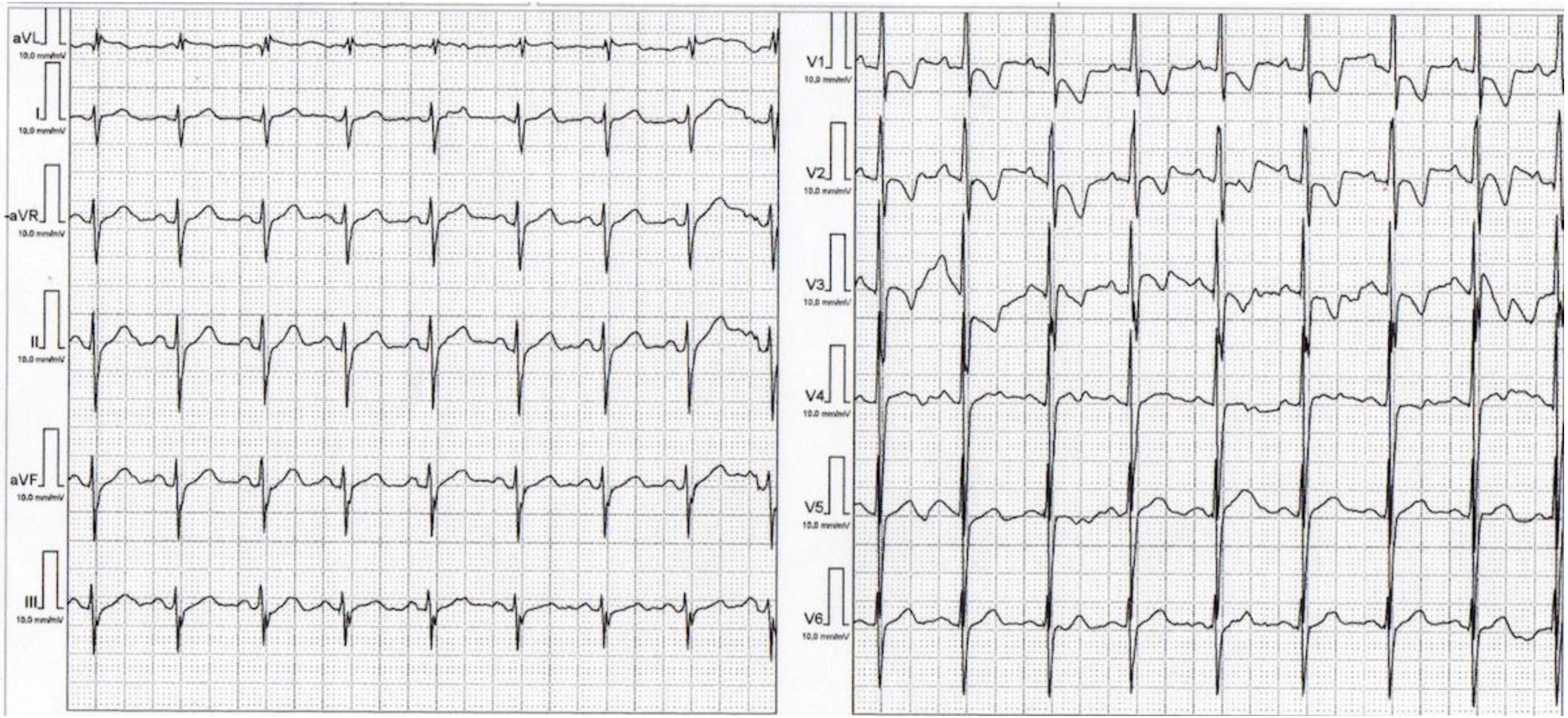
ECG-3 Precordial leads



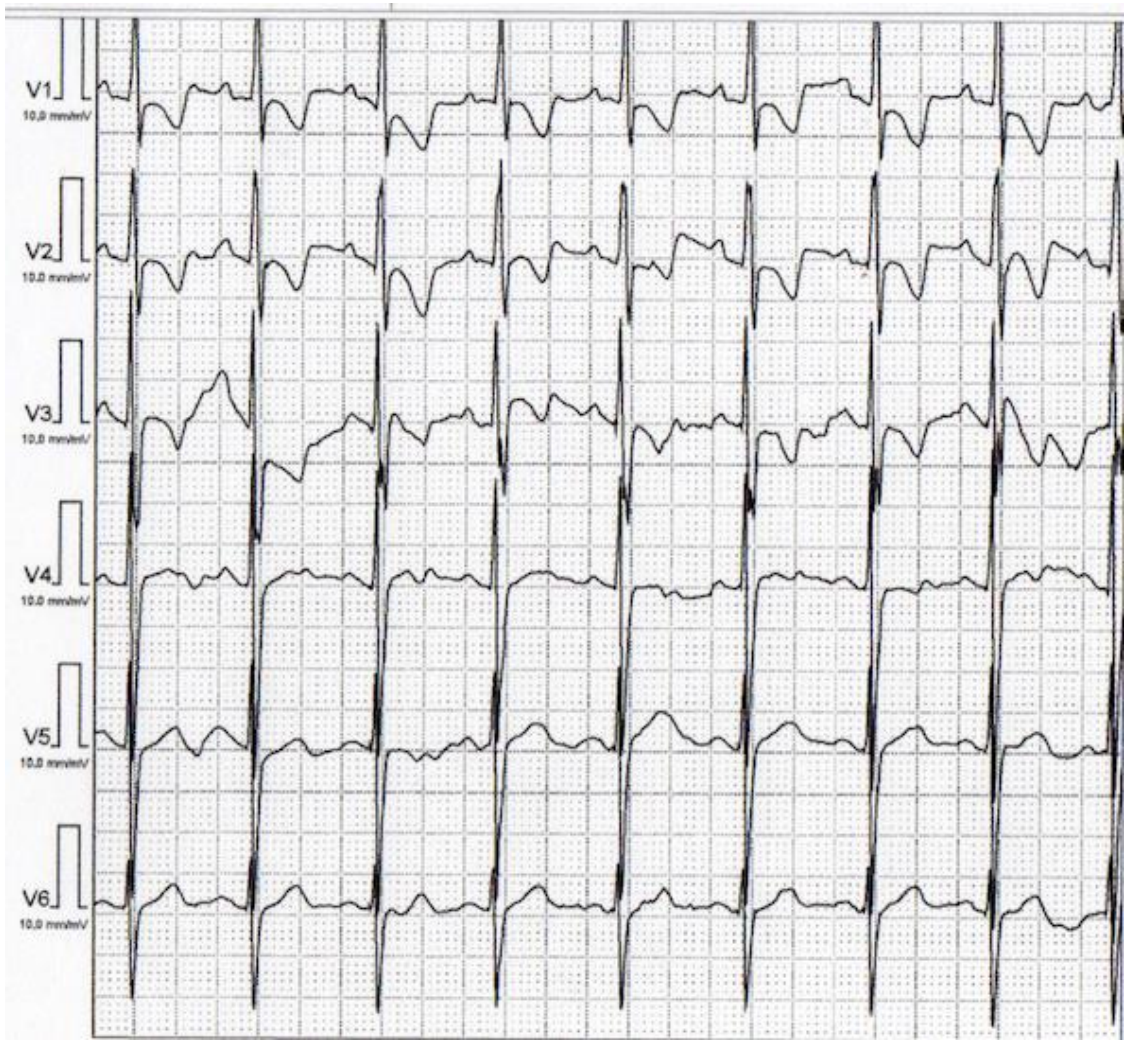
ECG-4 performed 8 hours later



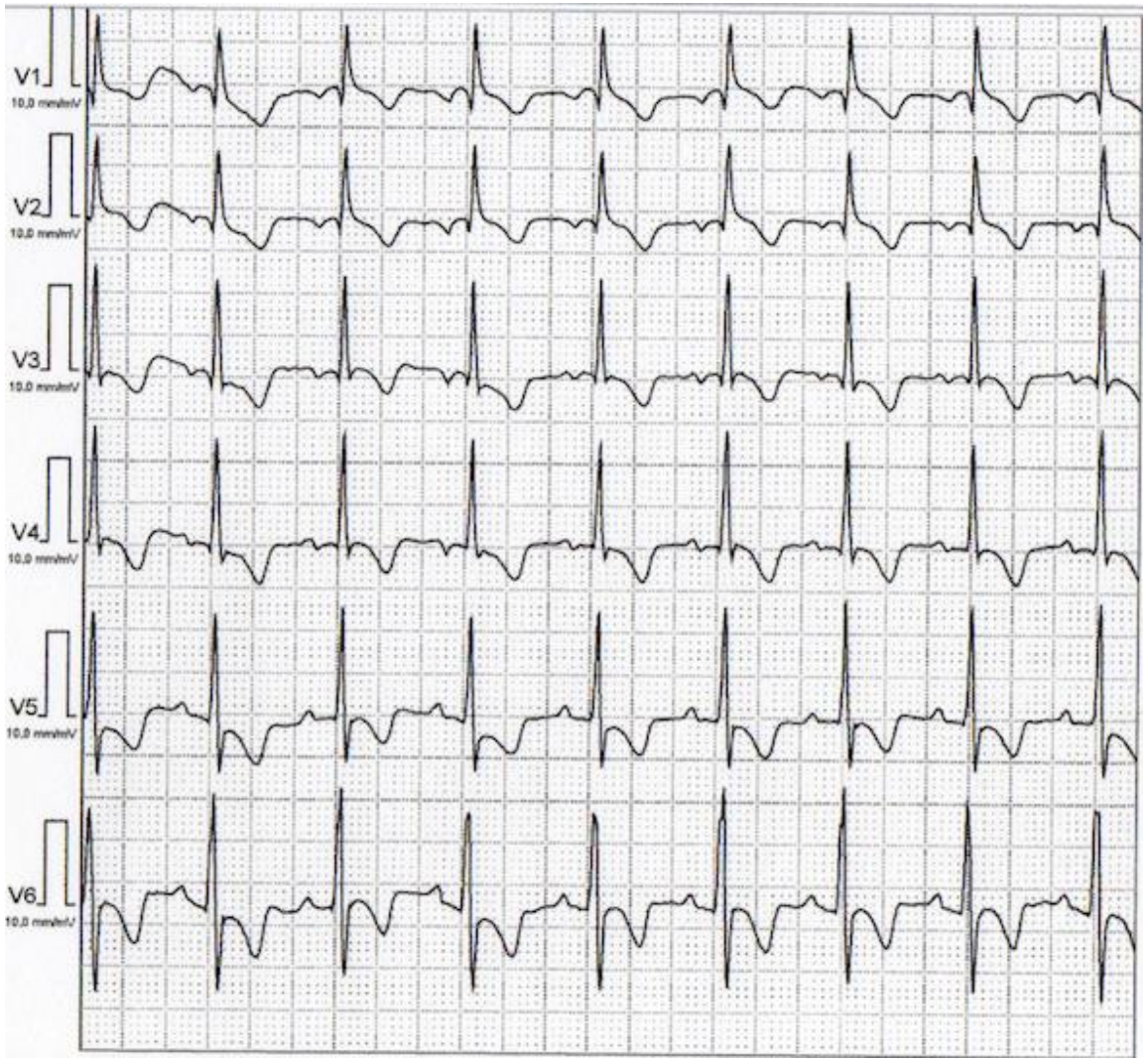
ECG-5 performed on March 14th, 2019



ECG-5 performed on March 14th, 2019

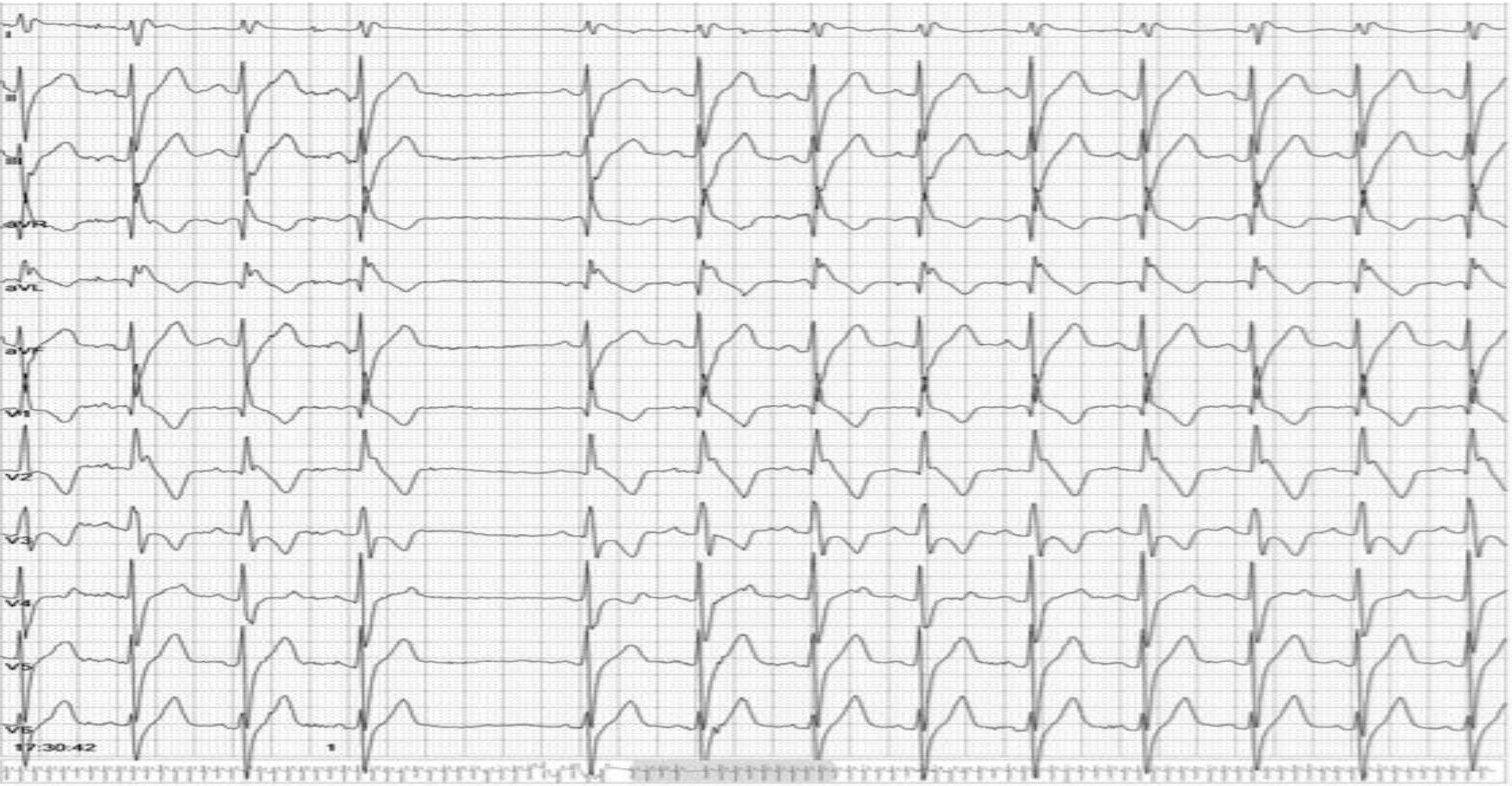


ECG-6 only precordial leads performed on the same day



Dynamic repolarization pattern

Holter Monitoring 24hs with feverish patient on March 14th, 2019



Colleagues opinions

Looks like early repolarization possibly J wave syndrome. Do you have recording of tachycardia ?

Needs Ajmaline or Proc. Challenge as well as genetic studies. If this is form of Brugada important considerations re ICD VS epicardial ablation. If this Brugada syndrome would check with Brugada and Nedamanee re experience with ablation in youngsters. A potential cure is much better than lifelong ICD and Quinidine .

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Professor of Medicine

Superb case for which my diagnosis is BRUGADA SYNDROME. However:

ECG 1: this may interpreted by most people as “POLYMORPHIC VT” pseudo-Torsades. However it is well known that infants with BrS usually present with “MONOMORPHIC VT” rather than VF or PVT. Therefore we should also discuss the possibility of DOUBLE TACHYCARDIA including some atrial tachycardia/flutter simultaneously with monomorphic VT. This may explain also why the baby did not die.

ECG 2: AV junctional rhythm with obvious type 2-Brugada changes in ECG lateral leads (leads I and aVL) not on right precordial leads.

As far as the treatment: I do agree with MEL SCHEINMAN that epicardial ablation should be discussed despite the very young age. However the patient should be treated just now with QUINIDINE; I am aware of a single case of 3-year old infant baby treated by epicardial ablation and recently published(1). Very soon will be published in JACC a paper from SABRUS by Yoav Michowitz and coworkers dealing with Arrhythmic Events in the Young with Brugada Syndrome: Characterization, Management and Risk Factors for Recurrence (57 patients)

Bernard Belhassen
THE HEART INSTITUTE; HADASSAH MEDICAL CENTER, JERUSALEM

Reference

1. de Asmundis C, Chierchia GB, Baltogiannis GG, et al. Concomitant Brugada syndrome substrate ablation and epicardial abdominal cardioverter-defibrillator implantation in a child. Heart Rhythm Case Rep. 2018 Mar 17;4(6):214-218. doi: 10.1016/j.hrcr.2017.12.004 See next two slides

Final comments by

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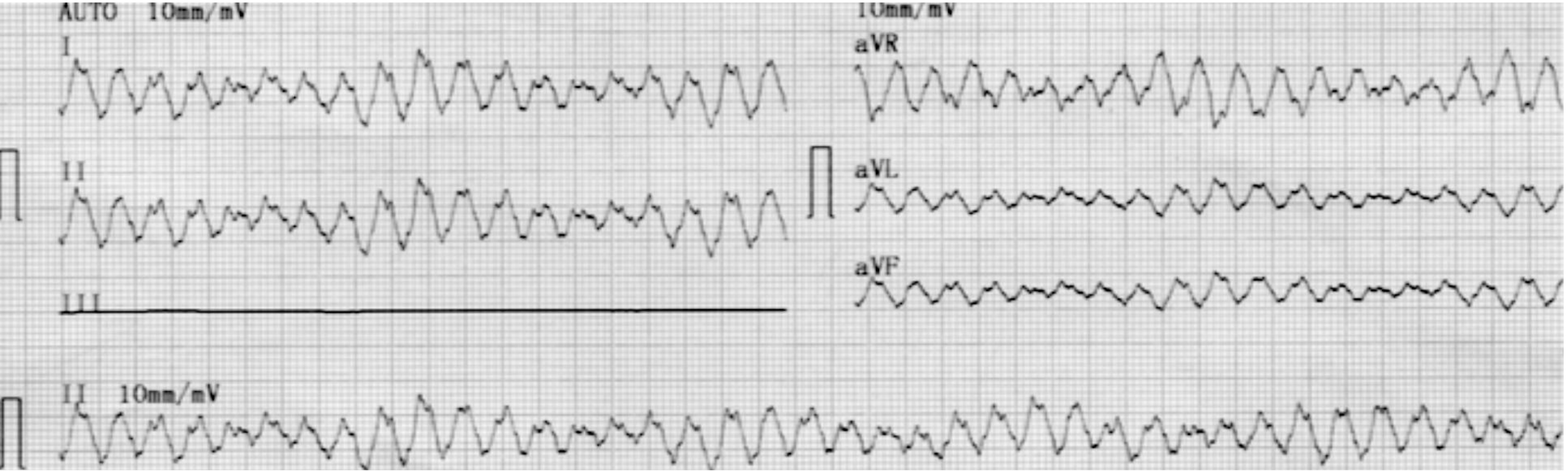
ECG / VCG Pérez-Riera | my cardiology site of scientific interests

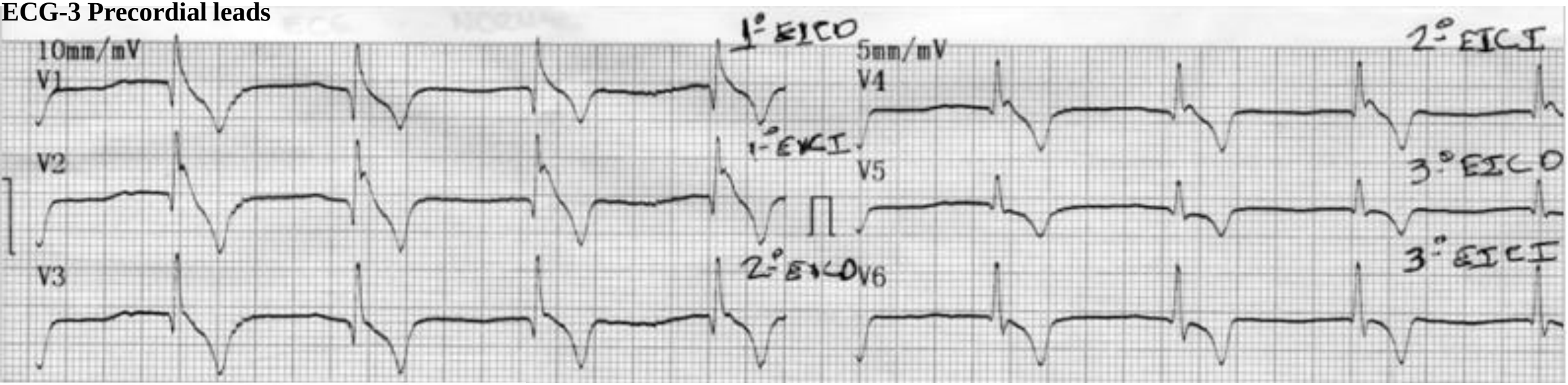
https://ekgvcg.wordpress.com/

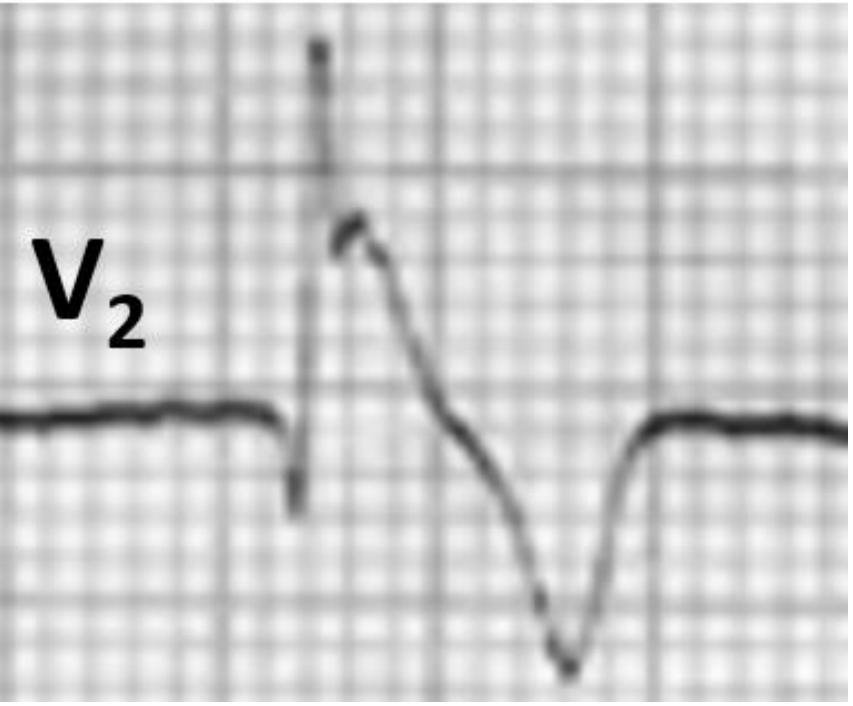
ECG-1 Only limb leads (with artifact in III)



Sustained monomorphic ventricular Tachycardia (SMVT): regular wide QRS complex (≥120 ms), HR ≥100bpm, the consecutive beats have a uniform and stable QRS morphology and the arrhythmia lasts ≥30 seconds or causes hemodynamic collapse in <30 seconds. Reentry is the dominant arrhythmia mechanism in BrS. There is debate over how the reentrant substrate develops, whether it is due to dromotropic disturbance, repolarization abnormality, or both(**Eckhardt LL 2015**). However, there is some consensus that BrS–related arrhythmias belie their origin in the heterogeneity in the RVOT and may include minimal structural heart disease. MVT has been reported in BrS and is noted to occur more commonly in children.(**Chockalingam P 2012**)

ECG-3 Precordial leads



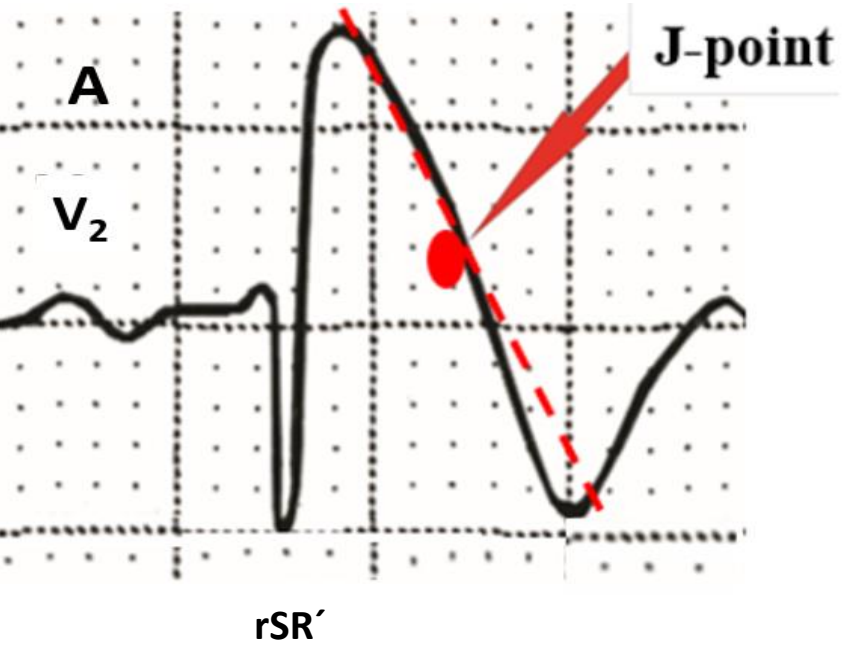


Spontaneous Type 1 Brugada ECG pattern
Notched J-wave

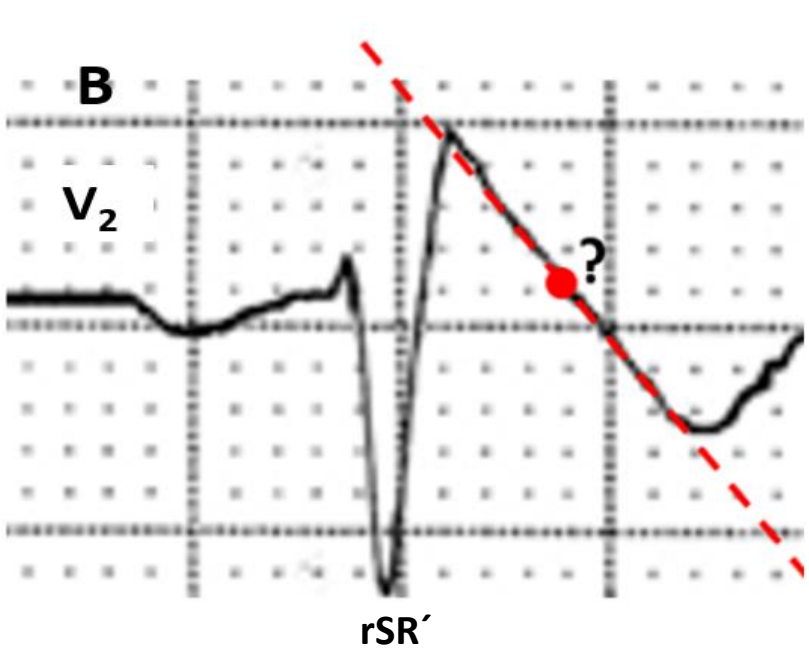
HR 62bpm, nodal rhythm + spontaneous Type 1 Brugada ECG pattern or coved-type characterized by rSr', qR or rSR' pattern, J-point and ST segment elevation ≥ 2mm followed by negative T wave in at least one right precordial lead (≥ 1 right precordial lead) positioned in the second, third, or fourth intercostal space(**Priori SG 2013**). Nagayama et al compared 15 BrS patients with drug-induced (D-BrS) and 29 with spontaneous type 1 ECG (SP-BrS). All patients had had a previous VF episode. In each Age and family history were comparable between groups. Inferolateral early repolarization was observed in 87% D-BrS at least once but in only 3 SP-BrS (10%). Immediately after VF, inferolateral ER was accentuated in 9 of 10 D-BrS, while type 1 ECG was accentuated in 12 of 16 SP-BrS. fQRS in the right precordial lead and aVR sign(R wave ≥0.3mV or R/q ≥0.75 in lead aVR) were absent in D-BrS but present in 20 (69%) and 11 (38%, P<0.01) SP-BrS, respectively. There was no prognostic difference between groups(**Nagayama T 2019**). Type 1 Brugada ECG pattern is the keystone in the diagnosis of BrS. Spontaneous coved-type or type I pattern is considered a noninvasive risk marker in BrS without requiring any further evidence of malignant arrhythmias(**Antzelevitch C 2017**).

Type 1 Brugada ECG SUBTYPES patterns on right precordial leads

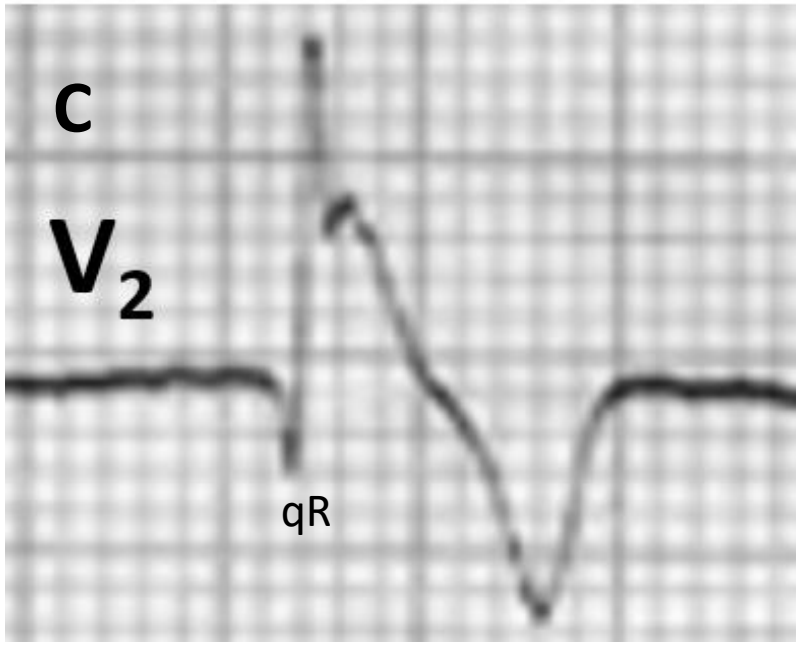
Sub-type A slurring convex upward



Sub-type B rectilinear oblique descendent



Sub-type C Notched J-wave



J-point and ST segment elevation ≥ 2mm followed by negative T wave in at least one right precordial lead (≥ 1 right precordial lead) positioned in the second, third, or fourth intercostal space(**Priori SG 2013**).

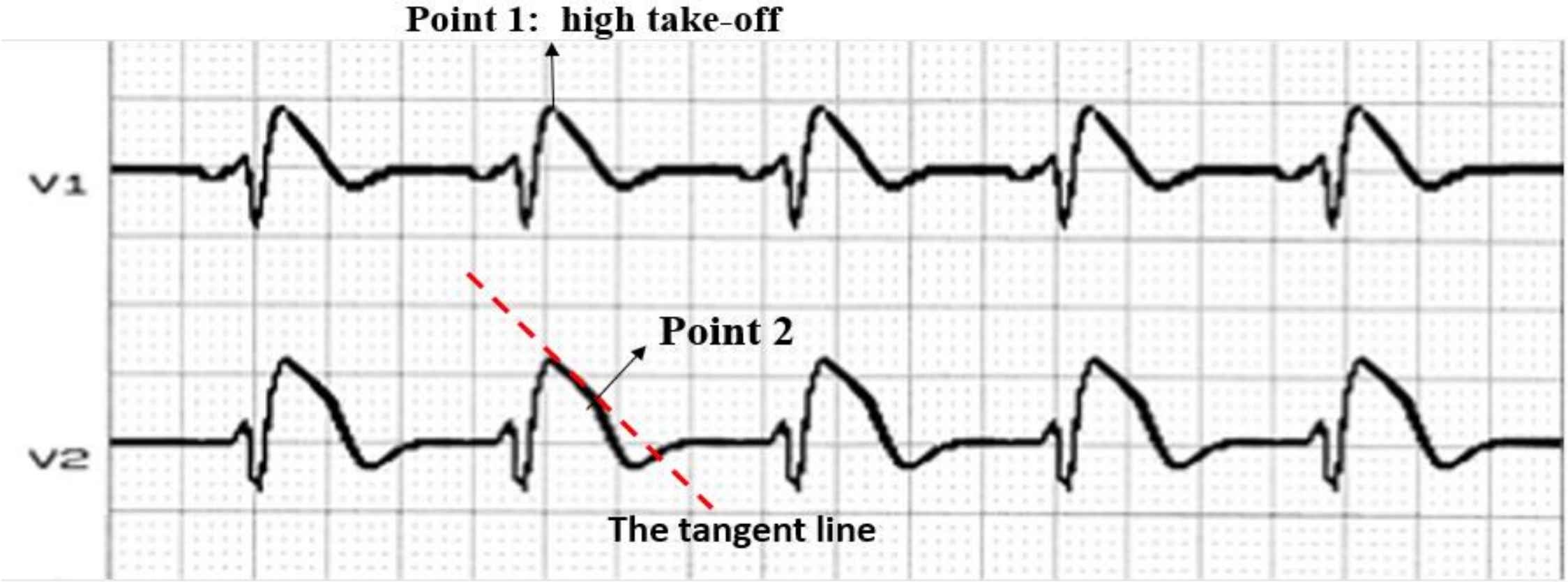
A) ST segment elevation slurring with upper convexity;

B) ST segment elevation slurring descending rectilinear.

To determine the location of point J (end of QRS) we use the tangent line method that accompanies the descending ramp of R' (dotted line). It is considered that the point J is located at the moment that the tangent line separates from the descending ramp of R' wave. When this is rectilinear (B) it is difficult to determine the exact location of the J point and consequently the QRS duration and r-J interval.

Where is the correct location of the end of the QRS complex (the J-point)?

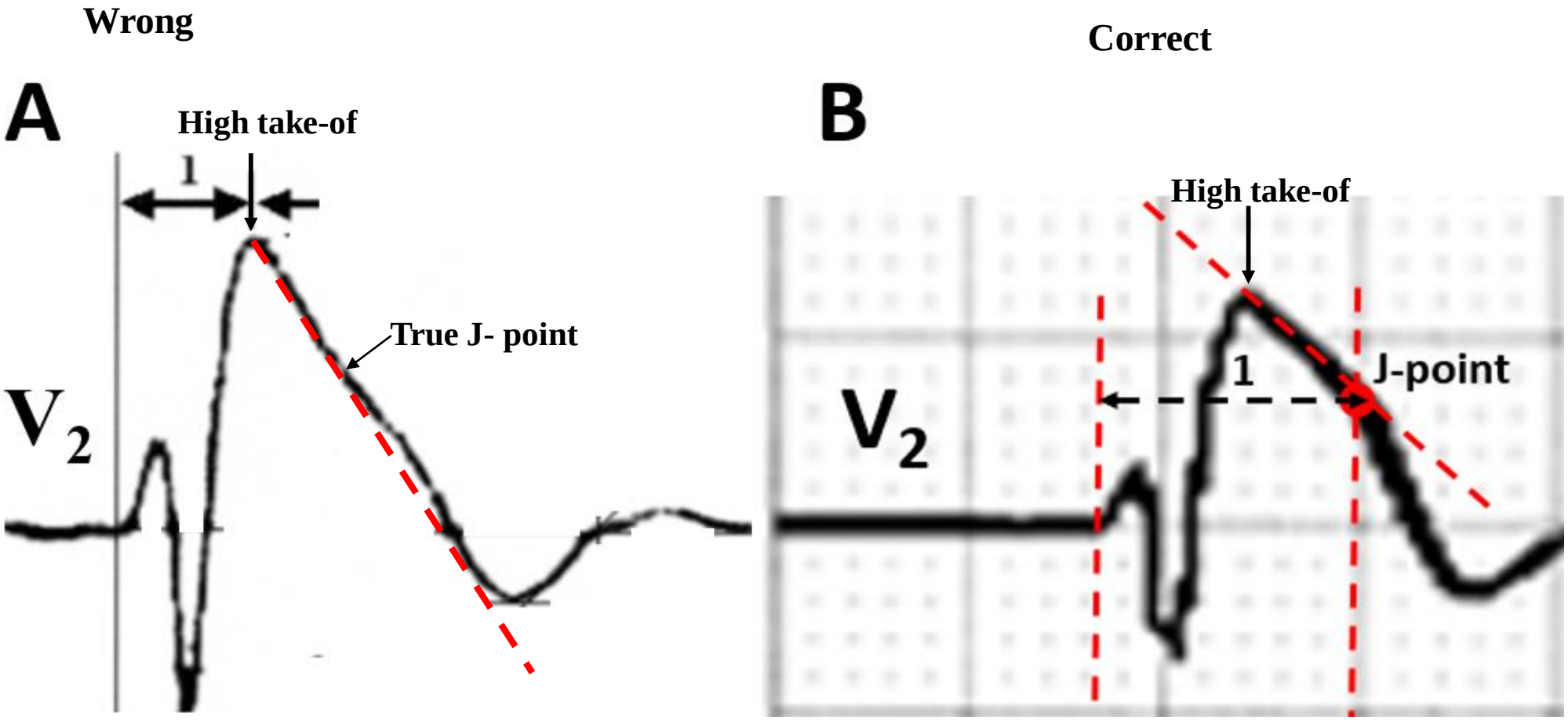
Is it at point 1 or point 2?



Answer: the correct answer is on point 2, because point 1 corresponds to the high take-off and point 2 to J point, that is to the end of the QRS and beginning of ventricular repolarization.

r -J interval: It it's the interval from QRS onset to J point in V_1 or V_2. This value is important because a QRS duration ≥120ms in V_2 and a r -J interval ≥ 90ms in V_6, are noninvasive markers of event risk.

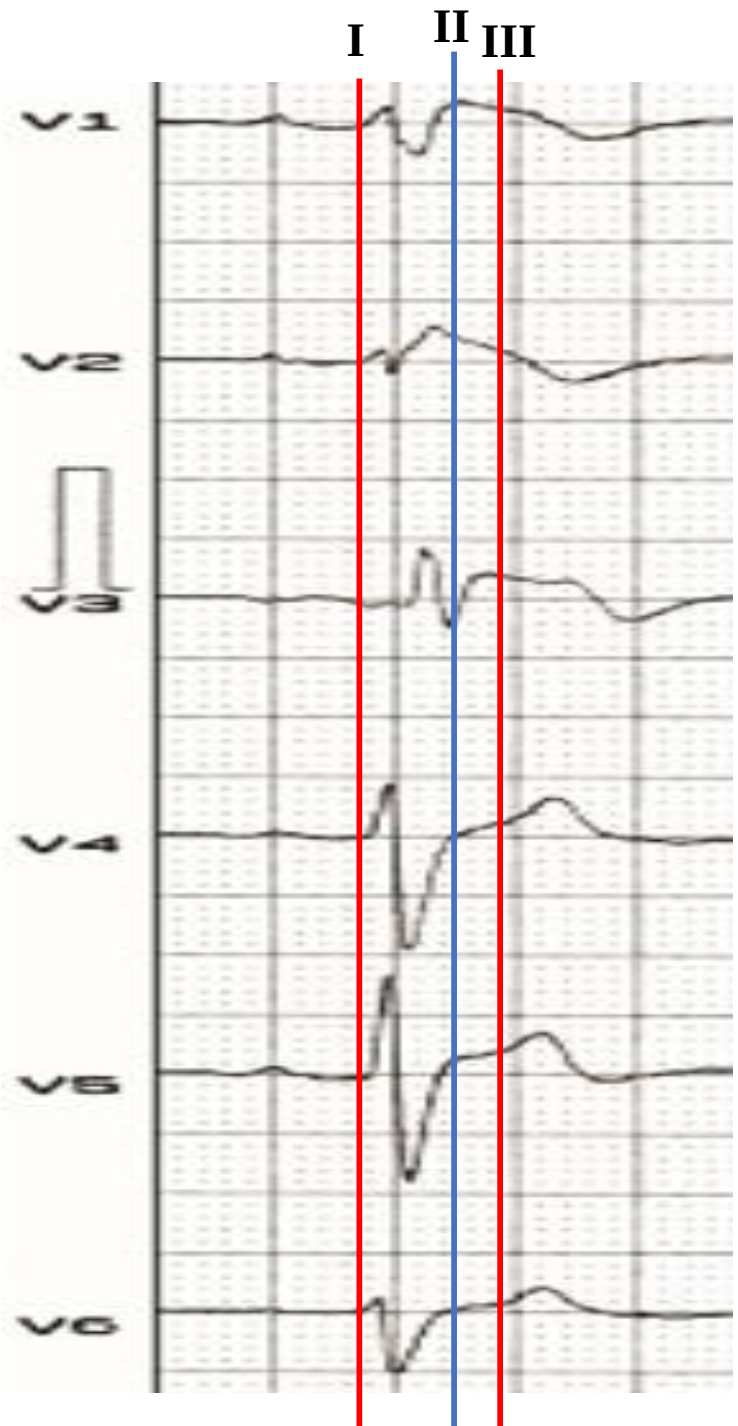
Wrong and correct measurements of the r-J interval



A is wrong because it extends from onset of QRS to high take-of. When this measurement in lead V2 ≥ 90 ms is predictors of recurrence of cardiac events in symptomatic patients. Consequently, the measurements of Takagi's manuscript are wrong. (**Takagi M 2007**)
B measurement is correct because it extends from onset of QRS to true J point determinate by tangent line.

Pitzalis et al (**Pitzalis 2003**) In BrS with type 1 pattern identified selective prolongation of QT interval duration in the right precordial leads (V_1 to V_3) in comparison to the left ones (V_4 to V_6). As the QT interval is made up by ventricular depolarization (QRS) plus ventricular repolarization (ST/T).

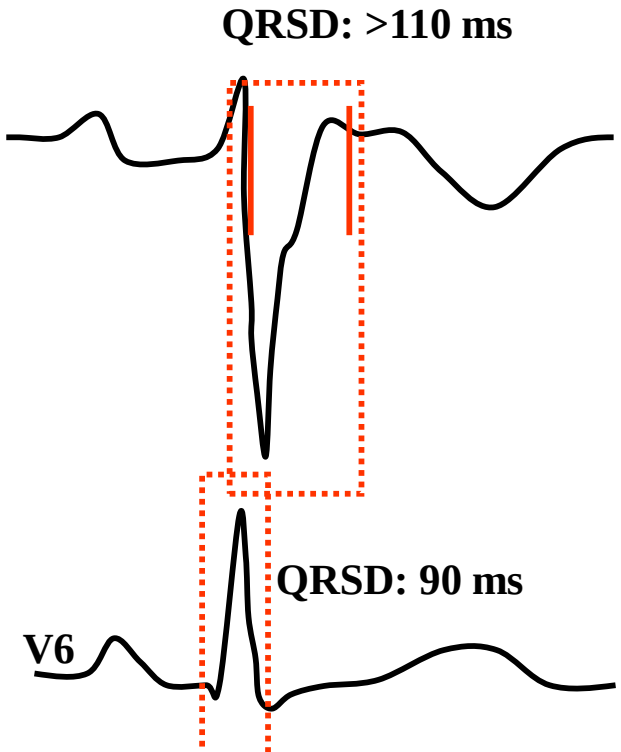
We think that this selective prolongation represents a certain degree of parietal block in the RVOT, as the one observed in ARVC/D. If the QT interval is prolonged only from V_1 to V_3, being normal or lesser from V_4 to V_6, it is clear that this increase may be due to prolongation of ventricular depolarization (QRS complex) and/or by ST/T prolongation (repolarization). If we admit that in BrS there is some degree of branch block, clearly the QT interval prolongation is due partly to this. The QTc interval constitutes the classical measurement for ventricular repolarization; however, this parameter includes ventricular depolarization (QRS), and therefore represents the so-called electric systole, which includes depolarization (QRS) and ventricular repolarization (ST/T = JT interval).



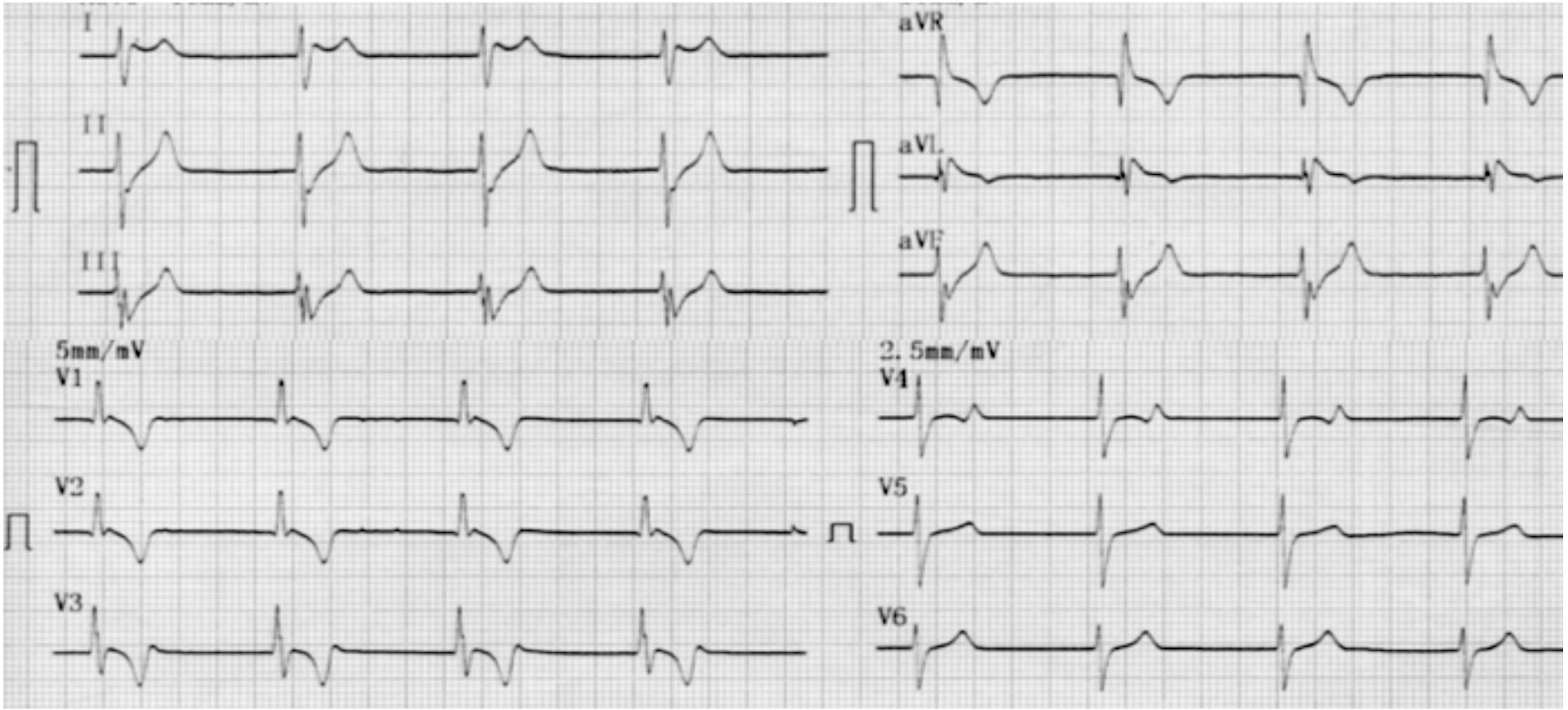
Increase in QRS complex duration (>110º) in right precordial leads, in absence of CRBBB: parietal block

I. Onset of the QRS complex
II. Termination of the QRS complex from V4-V6
III. Termination of the QRS complex from V1-V3.

QRSD of $^{V1+V2+V3}/_{V4,V5,\ V6} \geq 1.2$. This feature is considered typical of ARVC/D, but it is also observed in BrS (**Pitzalis 2003**).



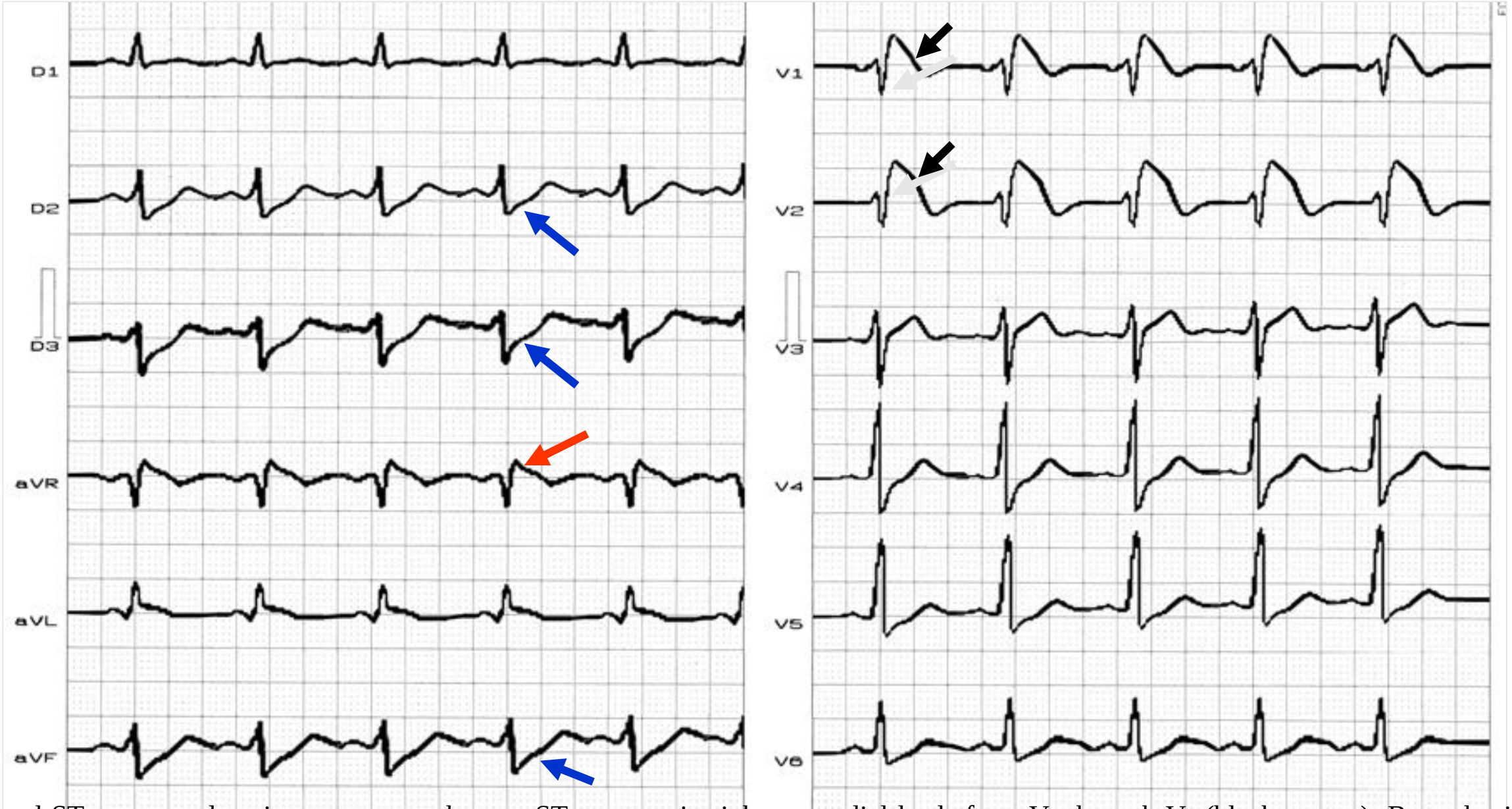
ECG-2 After spontaneous reversion



Diagnosis: Type 2 Brugada ECG pattern(saddle back pattern) in lateral lead I and type 1 in aVL: Early repolarization pattern because is registered in lateral leads

Reciprocal changes (mirror image) are observed in inferior leads. We described reciprocal changes in the BrS similar to STSEMI See next slide

Typical type 1 ECG Brugada pattern with reciprocal changes in the inferior leads



J point and ST segment elevation, convex to the top, ST segment in right precordial leads from V_1 through V_2 (black arrows): Brugada sign or idiopathic J wave. Unipolar aVR lead that heads toward the RV epicardium above the outflow tract, which shows subtle ST segment and J point elevation (red arrows). Inferior leads show reciprocal changes or mirror images (blue arrows) like STSEAcute Myocardial Infarction;

Reciprocal changes or mirror image

Ventricular walls	Facing leads	Reciprocal leads
Inferior	II, III = aVF 	Septal V1-V2 / I - aVL 
Septal	V1-V2	Inferior
Anterior	V3 - V4	Does not have
Lateral	I, aVL, V5, V6	V1 a V3

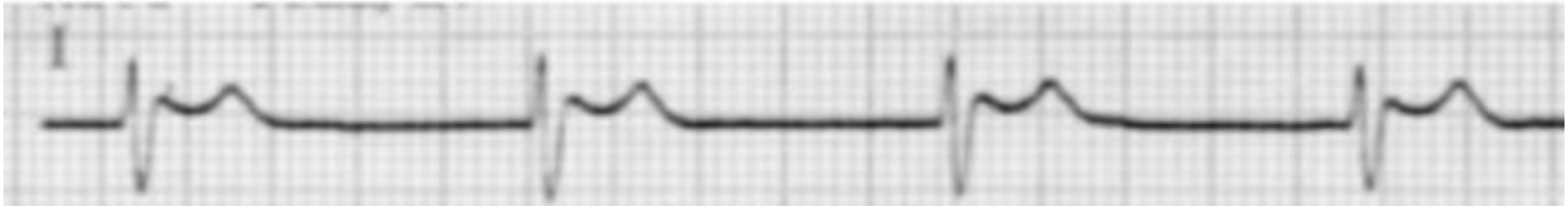
The presence of reciprocal changes in the 12-lead ECG can help distinguish true AMI from AMI mimics. The contour of the ST segment can also be useful, since a straight or ascending convex ST segment (not concave) favors the diagnosis of AMI.

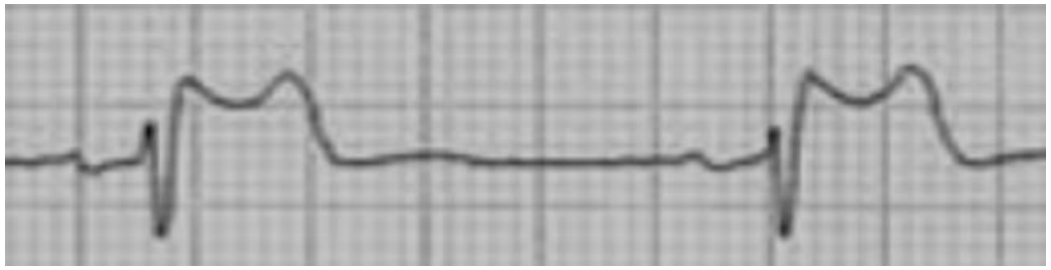
The dorsal or posterior wall does not exist !!! (**Bayés de Luna 2006**.)

The lateral wall includes the leads I, aVL, V5 and V6. The term high lateral wall is incorrect and should be eliminated !!! (**Bayés de Luna 2006**.).

Apical region in reference to V5-V6 should also be eliminated (**Bayés de Luna 2006**.)

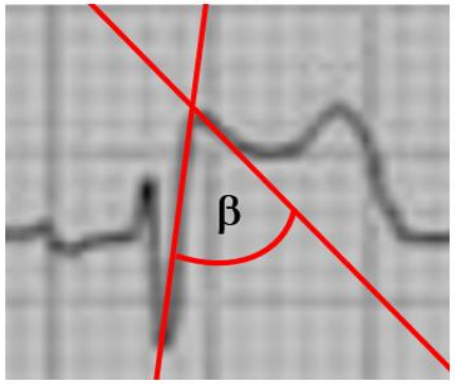
Although the breakdown of this paradigm occurred more than a decade ago, cardiologist continue to use the erroneous terms "dorsal infarction", high lateral infarction "How difficult it is to paradigm changes Dear Professor Bayés;





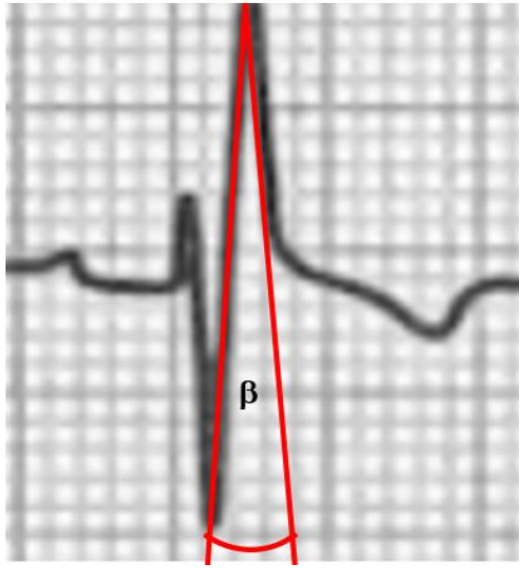
Type 2: It has triphasic pattern in right precordial leads rSr' or rSR' pattern ≥2 mm J-point an STSE with saddleback appearance trough that is still ≥1 mm ST-segment elevation and, followed by a positive or biphasic T-wave. In the present case we have the type 2 ECG pattern in lateral I lead. Type 2 Brugada pattern has characteristic broad β-angle always > 36° and "innocent" incomplete RBBB an acute β-angle (12° in mean).(**Ohkubo K 2011**)

Type 2 Brugada ECG pattern



Characteristic broad β angle

"Innocent" incomplete RBBB: acute β angle



Main causes of Incomplete Right Bundle Branch Block for differential diagnosis with type 2 Brugada syndrome

1. *Normal variant, ordinary or "innocent" Incomplete Right Bundle Branch Block.*
2. *Athlete heart*
3. *Pectus excavatum*
4. *Straight-back syndrome*
5. *Secundum atrial septal defect (OS-ASD)*
6. *Arrhythmogenic Right Ventricular Cardiomyopathy Dysplasia(AEVC/D)*
7. *Facioscapulohumeral muscular dystrophy without cardiac symptoms*
8. *Brugada syndrome 28% of cases*. (**Maury P, 2013**)

1. Incomplete Right Bundle Branch Block as a normal variant, ordinary or "innocent"

IRBBB as a a normal variant, commonly seen in children (of no clinical significance) and in the general population in <10%. IRBBB is not uncommon in a healthy school age population and is observed to have high inter-reader variability. It was associated with increased use of echocardiographic exam but was not associated with increased rate of echocardiographic findings when compared with rates for normal ECGs. (**Meziab O, 2018**) The QRS duration must be > 100ms and < 120ms(if < 100 ms normal variant predominates.), there should be a terminal R' wave in lead V_1 often called "R prime" and denoted by R, rR',rsR' rSR' or qR patterns, R' wave of aVR, prominent and/or broad; wide S wave in lateral leads I, aVL, V5 and V6. Although IRBBB is not related to an increased risk of death in 20 years from cardiovascular diseases, such block is frequently a manifestation of primary abnormality of the cardiac conduction system in middle-aged men. Men with IRBB had a significantly

greater risk of developing left axis deviation. The associations between IRBB and left axis deviation are unrelated to age and body weight (**Liao YL, 1986**). Complete RBBB and IRBBB are two to three times more common among men than women. Complete RBBB is associated with increased cardiovascular risk and all-cause mortality, whereas IRBBB is not. Contrary to common perception, CRBBB in asymptomatic individuals should alert clinicians to cardiovascular risk. (**Bussink BE, 2013**) Men with IRBBB had a significantly greater likelihood of developing complete RBBB. In cases genuine "innocent" IRBBB, the angle formed by the ascending and descending ramp of R' is acute with an average 12° (between 8° to 20°) (**Ohkubo K, 2011**) on the other hand in type 2 Brugada ECG pattern this angle is broad figure β.

Vectorcardiograms in patients with Brugada type 1 ECG pattern have distinctive characteristics compared with healthy individuals with incomplete and complete RBBB. These differences relate to the spatial location of the end conduction delay (right superior and posterior quadrant in the BrS group) and the morphology, size, and velocity of inscription of afferent and efferent limbs of the T loop (circular, small, of symmetrical limbs) and with a 1:1 length/width ratio.(**Peréz-Riera AR,. 2012**)

2. Athlete heart

IRBB is reported in 30% to 60% of athletes. This pattern is believed to be secondary to a mild conduction delay as a consequence of increased right ventricular cavity size and/or remodeling (structural cardiac adaptations) right ventricle with slowing of conduction from exercise-induced RVH (**La Gerche A, 2011**.) Competitive exercise does not induce cardiac damage in individuals with healthy hearts, but does induce physiological functional and structural cardiac adaptations which have positive effects on life expectancy.

3. Pectus excavatum

Pectus excavatum It is a deformity of the chest that consists of backward displacement of the sternum and costal cartilages giving rise to a depression in the xiphisternal area, Electrocardiographic findings are caused by alterations in the intrathoracic position of the heart. Characterized by negative P waves in V_1 leads, qr pattern in V1 (the right auricular chamber, being situated exactly underneath the exploratory electrode of Vl would permit the direct transmission of intracavitary potentials to that lead.) or triphasic rsr'in V1 consequence of cardiac rotation, signifies the depolarization of the basal portion of the RV as well as the higher parts of the interventricular septum, and further, that it is present whenever the mean activation vector of these regions is oriented forward and to the right, either as a consequence of hypertrophy and dilatation of these basal portions or because of a marked rotation of the heart. SÂQRS axis with backward orientation on horizontal plane, and negative T waves in V1 in 100% of cases. (**Martins de Oliveira J, 1958.**) We report a case of an electrocardiographic BrP in a patient with pectus excavatum deformity in the absence of true BrS using currently defined BrP diagnostic criteria. Brugada phenocophy criteria are:

1. The ECG pattern has a type 1 or type 2 Brugada pattern.
2. The patient has an underlying condition that is identifiable.
3. The ECG pattern resolves after resolution of the underlying condition.
4. There is a low clinical pretest probability of true Brugada syndrome determined by lack of symptoms, medical history, and family history.
5. Negative provocative testing with sodium channel blockers such as ajmaline, flecainide, or procainamide.
6. Provocative testing not mandatory if surgical RVOT manipulation has occurred within the last 96 hours. vii. The results of genetic testing are negative (desirable but not mandatory because the SCN5A mutation is identified in only 20% to 30% of probands affected by true Brugada syndrome) (**Awad SF, 2013**):

4. Straight-back syndrome

It is a ‘pseudo-heart disease’ that can mimic congenital abnormalities, especially atrial septal defect. It typically occurs in young thin individuals who have a reduced sagittal diameter of the thoracic cage because of the absence of a normal thoracic kyphosis. The often-prominent murmur is caused by compression of the right ventricular outflow tract by the sternum and therefore is reduced with deep inspiration. Accentuated but physiologic splitting of the second heart sound and incomplete RBBB in the ECG are common associated findings. (**Esser SM, 2009**)

5. Secundum atrial septal defect.

An ostium secundum atrial septal defect (ASD-OS) is a defect in the fossa ovalis in the center or middle part of the interatrial septum, causing a left-to-right shunt and volume overload of the right atrium and right ventricle. Children are rarely symptomatic, but long-term complications after age 20 yr include pulmonary hypertension, heart failure, and atrial arrhythmias. Adults and, rarely, adolescents may present with exercise intolerance, dyspnea, fatigue, and atrial fibrillation. A soft grade 2 to 3/6 midsystolic murmur at the upper left sternal border with wide and fixed splitting of the 2nd heart sound (S2) is the rule (**Rodriguez R, 1968**) These findings may be absent on infants. It is confirmed on transthoracic echocardiography. The 12-lead **ECG** will show an incomplete right bundle branch block, (Triphasic morphology of QRS complexes in V3R, V1 and V2 with QRS <120 ms duration) some evidence of volumetric right ventricular enlargement/hypertrophy (RVH); prominent and broader final R wave in aVR reflecting right end conduction delay in RVOT. frequent notch near the apex of the R wave of inferior leads: "Crochetage" (notch) (**Cohen JS, 2000**.). The sign correlates with severity. The specificity of this sign for the diagnosis was remarkably high when present in all three inferior limb leads (≥92%), even when comparison was limited to patients with an incomplete RBBB (≥95.2%). Early disappearance of this pattern was observed in 35.1% of the operated-on patients although the RBBB pattern persisted. A crochetage pattern of the R wave in inferior limb leads is frequent in patients with ASD, correlates with shunt severity and is independent of the RBBB pattern. Sensitivity and specificity of this

sign are remarkably high when it is associated with an incomplete RBBB or present in all inferior limb leads (**Heller J, 1996**.).

6. Arrhythmogenic Right Ventricular Cardiomyopathy Dysplasia

Terminal activation delay (TAD), incomplete right bundle branch block (IRBBB), complete right bundle branch block (CRBBB) and epsilon waves (subtricuspid region) are depolarization abnormalities that represent delayed activation on RV free wall mainly on the right ventricular outflow tract in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C).(**Pérez-Riera AR, 2019.**). CRBBB and IRBBB are infrequent findings in ARVC. CRBBB is characterized by r'/s ratio<1. There are no significant T wave inversions ≥ V4. IRBBB is characterized by ST segment elevation in right precordial leads but not by T wave inversions ≥ V4(**Peters S, 2012**).

Corrado et al studied 16 members of a family affected by a syndrome of RBBB, ST segment elevation and SCD, including the following studies: ECG, Holter monitoring, ECG monitoring, stress testing, echocardiography and SA-ECG. Two members had EPS and angiographic study. Endomyocardial biopsy was performed in one living patient, and postmortem examination, including study of the specialized conduction system, was performed in one victim of SCD. Five years before a fatal cardiac arrest, the proband had been resuscitated from SCD due to VF. Serial ECGs showed a prolonged PR interval, RBBB, left-axis deviation and persistent ST segment elevation in the right precordial leads, in the absence of clinical heart disease. Postmortem investigation disclosed right ventricular dilation and myocardial atrophy with adipose replacement of the right ventricular free wall as well as sclerotic interruption of the RBB. A variable degree of RBBB and upsloping right precordial ST segment was observed in 7 family members; four of the seven had structural right ventricular abnormalities on echocardiography and late potentials on SA-ECG. A sib of the proband also had a prolonged HV interval, inducible VT and fibrofatty replacement on endomyocardial biopsy. IRBBB may be associated to ST segment elevation in V1 and V2 (**Corrado D, 1996.**). BrS and ARVC/D clinical features can coexist in a single patient, and EPS might be useful for determining the phenotype of overlapping disease (e.g., BrS-like or ARVC/D-like). (2) An overlapping disease state of BrS

and ARVC/D can change phenotypically during its clinical course. Therefore, careful examination and attentive follow-up are required for patients with BrS or ARVC/D. (**Kataoka 2016**) A remarkable overlap in clinical features has been demonstrated between these conditions.

The pathophysiology of the ECG features and the arrhythmogenic substrate are disputed but increasing evidence is emerging that minor structural abnormalities in the right ventricular outflow tract (RVOT) area underlie the disease. Structural changes were reported in an explanted heart and by biopsy specimens in a small number of cases,(**Coronel R, 2005**.)(**Frustaci A. 2005**.).

Patients with BrS compared with normal subjects showed: (**Catalano O, 2009**)

Higher incidence of mild RV wall-motion abnormalities (50% vs 17%);

Reduced radial fractional shortening in more than two segments, reduction of outflow tract ejection fraction, enlargement of the inflow tract diameter in short-axis; in four-chamber long-axis view) and area and of global RV end-systolic volume; but comparable outflow tract dimensions, global RV end-diastolic volume, LV and atria. As such, BrS may have to be regarded as part of ARVC spectrum (**Corrado D, 2016**) Candidate genes in BrS patients not carrying a SCN5A mutation showed enrichment for another desmosomal gene, the DSC2 coding for desmocollin-2 (**Di Resta C, 2015**), supporting the hypothesis of a possible continuum between the 2 diseases.

7. **Facioscapulohumeral muscular dystrophy without cardiac symptoms**

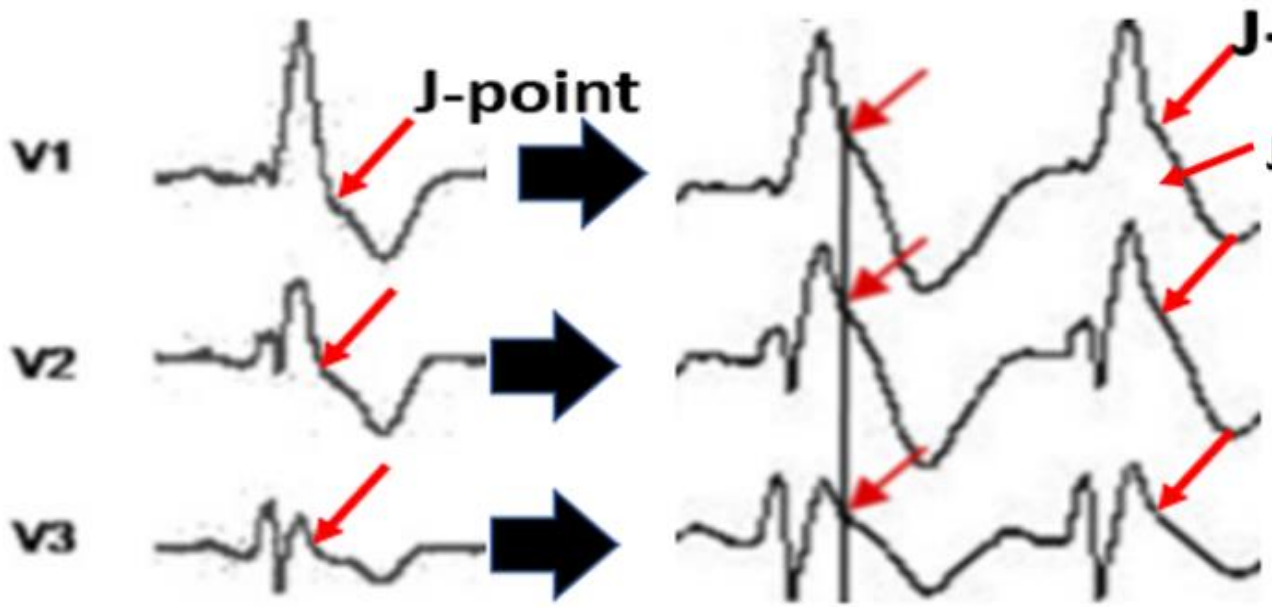
Baseline ECG demonstrated incomplete RBBB in 33%, complete RBBB in 4%, and other minor abnormalities in 16%. Comparison of incomplete RBBB in facioscapulohumeral muscular dystrophy without cardiac symptoms with the normal population showed a higher prevalence of incomplete RBBB (9.7 times higher) and of complete RBBB (4.8 times higher).(**van Dijk GP 2014**)

8) Brugada syndrome: RBBB is observed only in 28% of cases. **(Maury P, 2013)**

Are CRRB or IRBB electrocardiographic hallmark in the Brugada syndrome? The answer is No. IRBBB and CRBBB can be found in a percentage close to 30% of cases (**Maury P, 2013**). The characteristic type 1 ECG Brugada pattern can be masked by the presence of CRBBB and exposed by resolution of the block, through drugs (**Rolf S2005**) (**Veltmann C 2009**)or pacing maneuvers: "Chiale maneuver" (**Chiale PA2012**) (**Peréz-Riera AR2012**)(**Tomita M 2012**) (**Aizawa Y, 2013**)(**Pérez-Riera AR, 2017**)(**Baranchuk A 2014 and Baranchuk A 2014**)

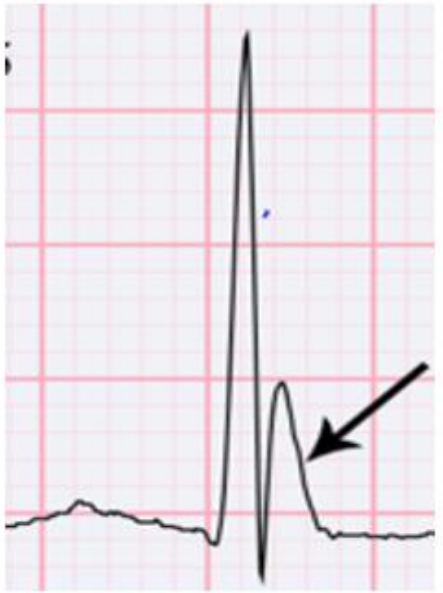
Basal ECG right precordial leads

ECG right precordial leads immediately after IV ajmaline

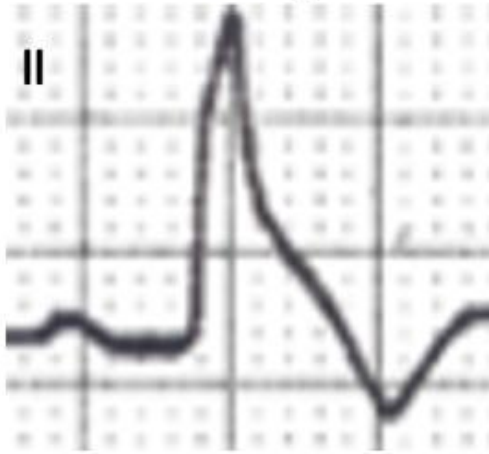


J- wave with "slurring" shape followed by negative symmetric T-wave

J-notched

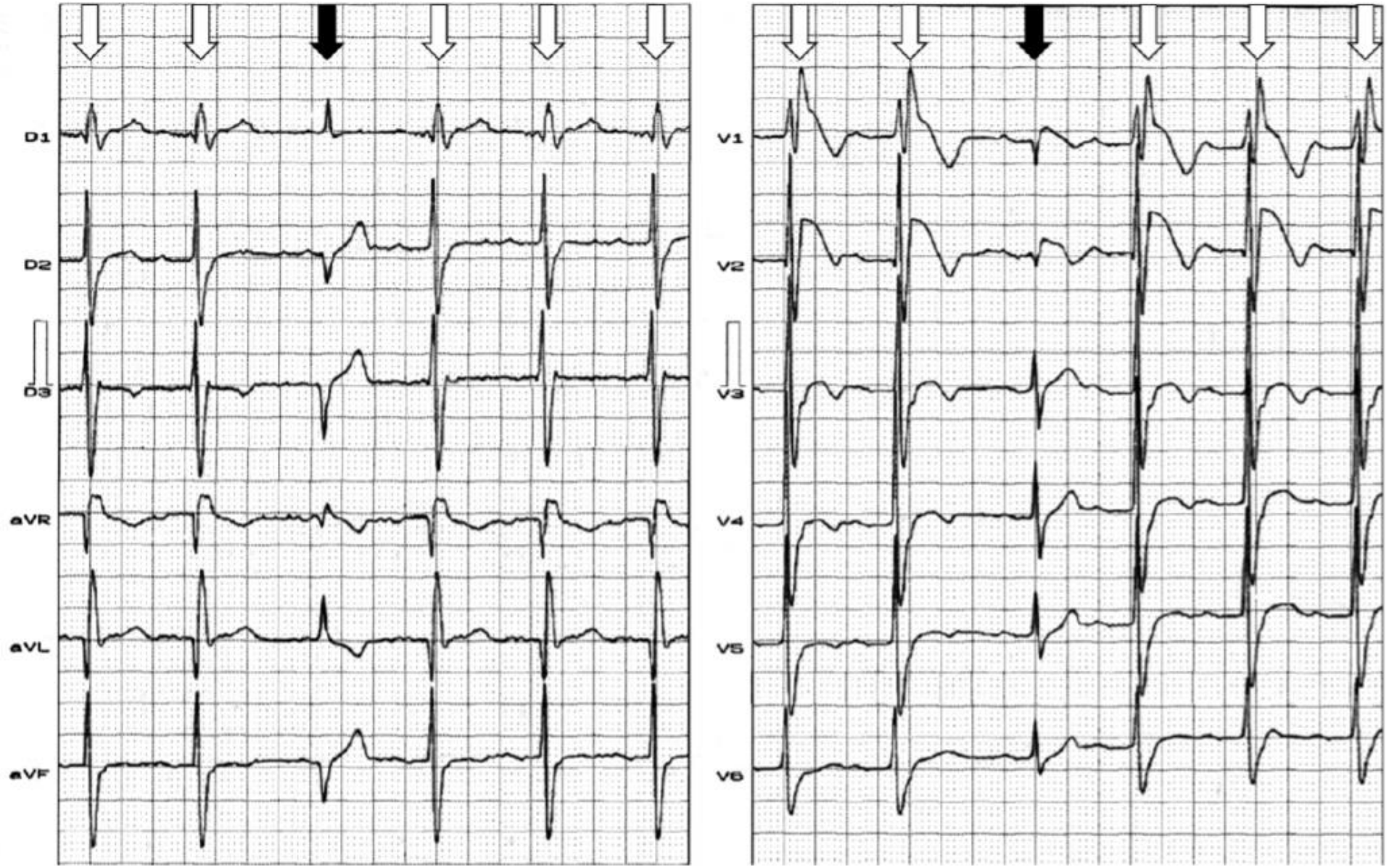


J-slurring

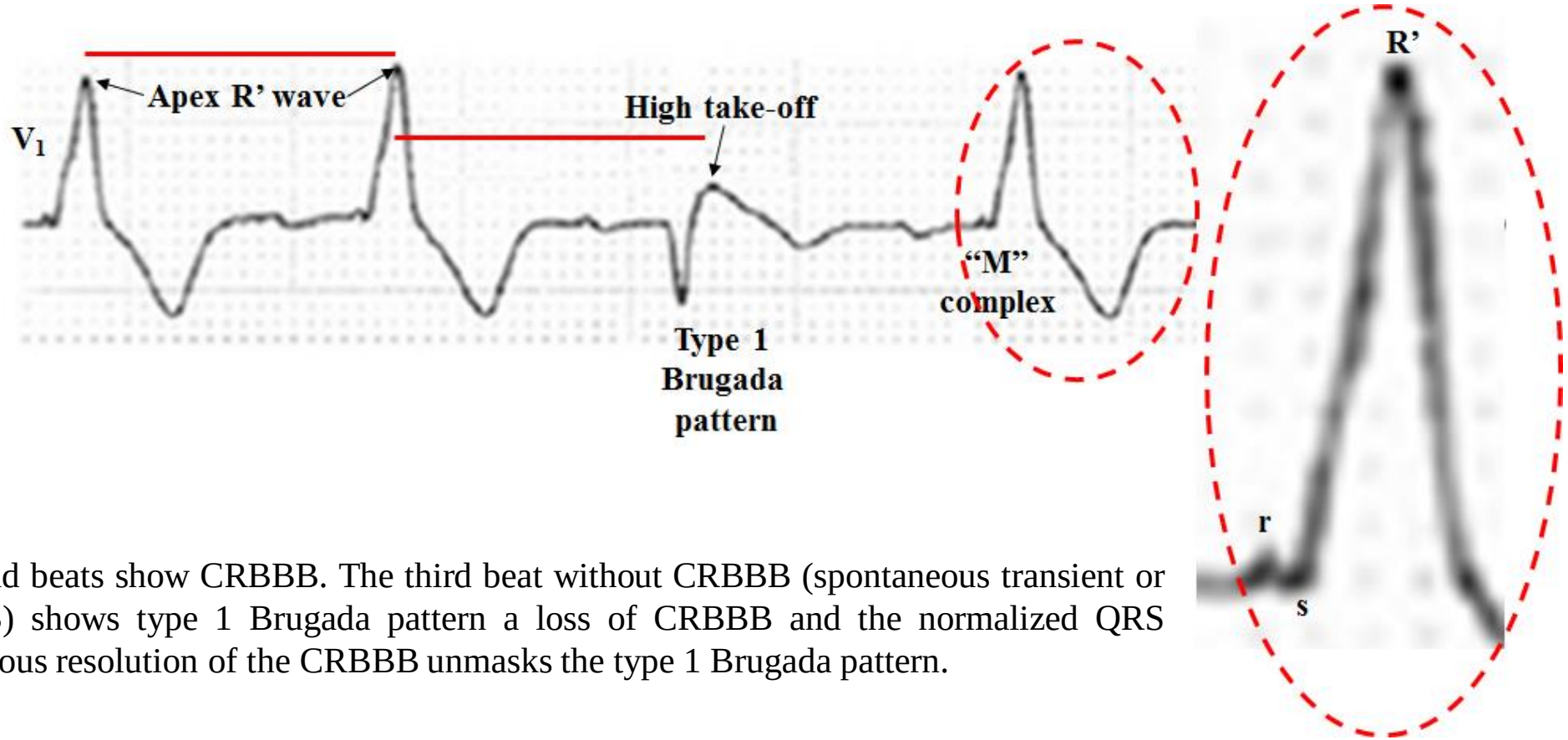


The Brugada type 1 ECG pattern is hidden by the BCRD: The J point is located further down, followed by negative asymmetric T wave.

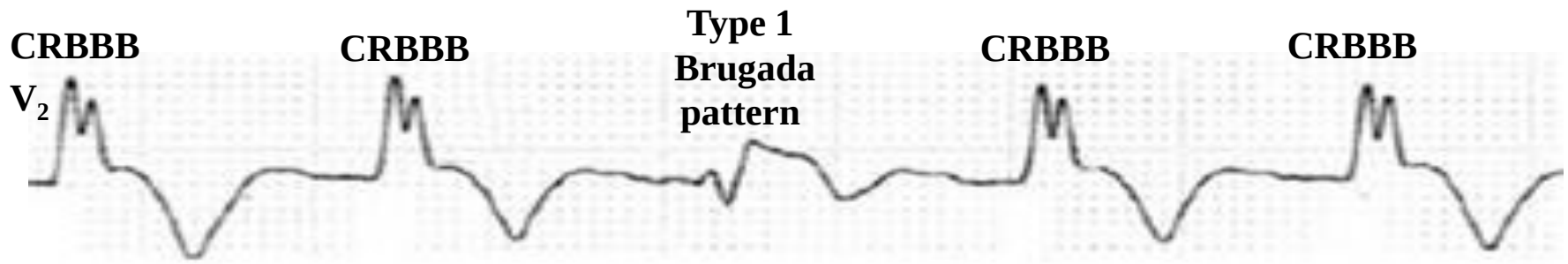
Ajmaline unmasks type 1 ECG Brugada pattern: J-point J is located higher up



All beats (white arrows) except the 3rd one in each panel show first degree AVB with CRBBB. The 3rd beat in each panel shows a fusion beat with a narrow QRS which is resulted from the “Chiale’s maneuver” by right apical ventricular pacing with appropriately timed A-V intervals. Third beat (black arrows) shows first degree AVB and typical LAFB and type 1 Brugada pattern(**Pérez-Riera 2017**).



The first and second beats show CRBBB. The third beat without CRBBB (spontaneous transient or intermittent RBBB) shows type 1 Brugada pattern a loss of CRBBB and the normalized QRS complex. Spontaneous resolution of the CRBBB unmasks the type 1 Brugada pattern.

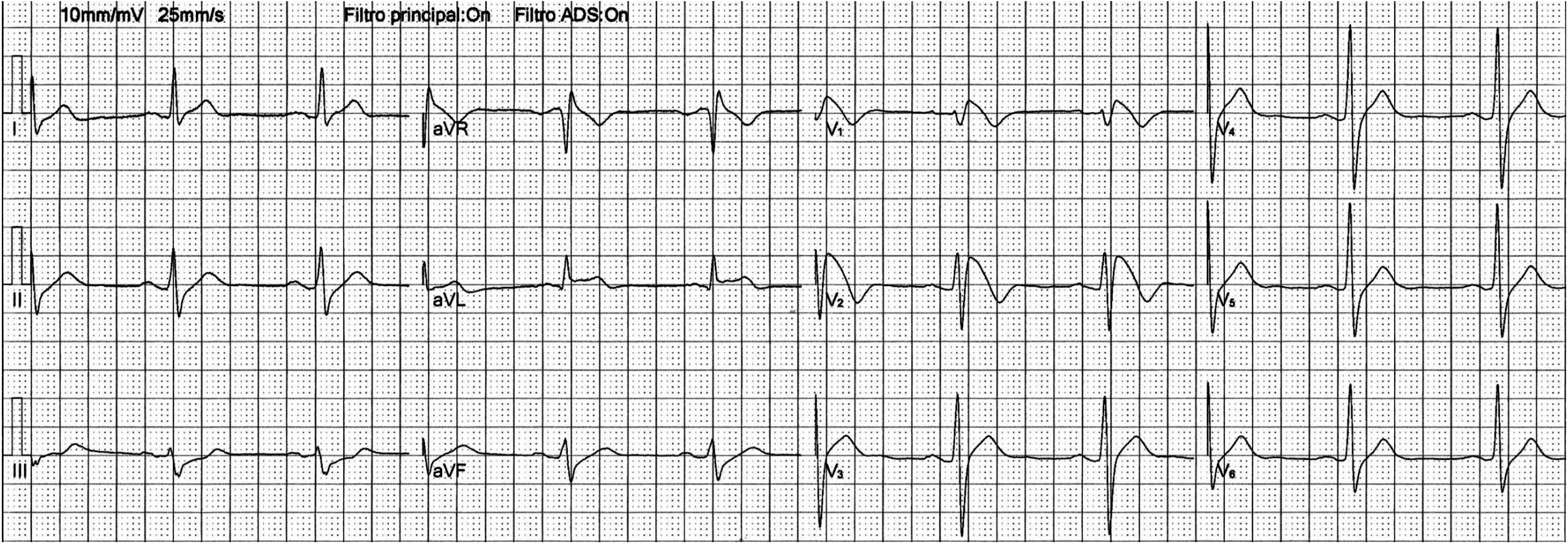


The Value of the Vectorcardiogram in Brugada Syndrome

Introduction

In the initial description of Brugada syndrome (BrS) by the Brugada brothers (**Brugada P 1992**) and in older studies they have reported discussing other features in the electrocardiogram (ECG), the presence of incomplete or complete right bundle branch block (IRBBB/CRBBB) was demonstrated as part of the phenomenon. Maury et al.(**Maury P 2013**) found right bundle branch block RBBB only in 28% of BrS patients **[Luna Filho B. 1989**]. In addition, several patients with BrS and type 1 electrocardiographic Brugada pattern did not meet criteria of incomplete right bundle Branch block (IRBBB) (QRS duration between 110 and 120 ms in adults, between 90 and 100 ms in children between 4 and 16 years of age, and between 86 and 90 ms in children less than 8 years of age) or complete RBBB (QRS duration greater than or equal to 120 ms in adults, greater than 100 ms in children ages 4 to 16 years, and greater than 90 ms in children less than 4 years of age.): rsr, rsR, or rSR in leads V1 or V2. The R or r deflection is usually wider than the initial R wave. . S wave of greater duration than R wave or greater than 40 ms in leads I and V6 in adults and normal R-wave peak time in leads V5 and V6 but > 50 ms in lead V1. (Fig. 12.1) (**Surawicz B 2009**). Finally, type 1 ECG Brugada pattern rarely is concealed by the presence of CRBBB. BrS masked by CRBBB is associated with the same risk of fatal ventricular tachyarrhythmia as other types of BrS [**Maury P 2013**].

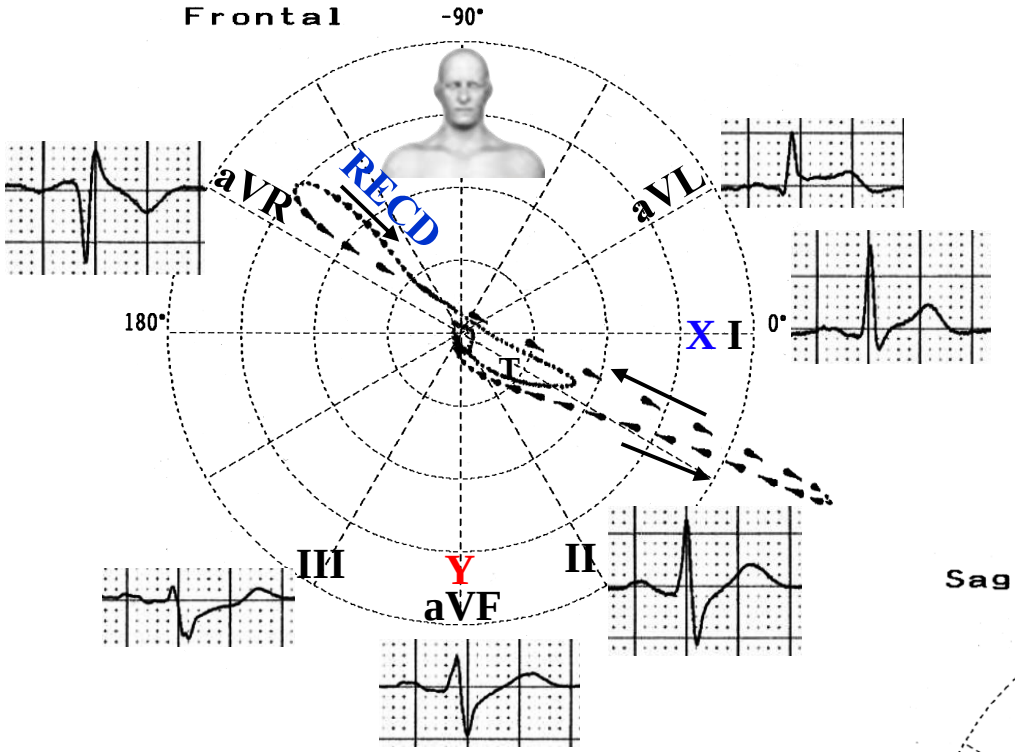
In this presentation , we will show the main vectorcardiographic features of type 1 ECG Brugada pattern We carefully analyzed an extensive series of 121 ECGs/VCGs from BrS patients with spontaneous or induced by provocative test type 1 ECG From the total sample, 102 ECG/VCGs came from the Department of Clinical and Experimental Cardiology, Academic Medical Center, Amsterdam, The Netherlands; and 19 ECG/VCGs came from our series (total of 121 ECG/VCGs). Examples in next slides……



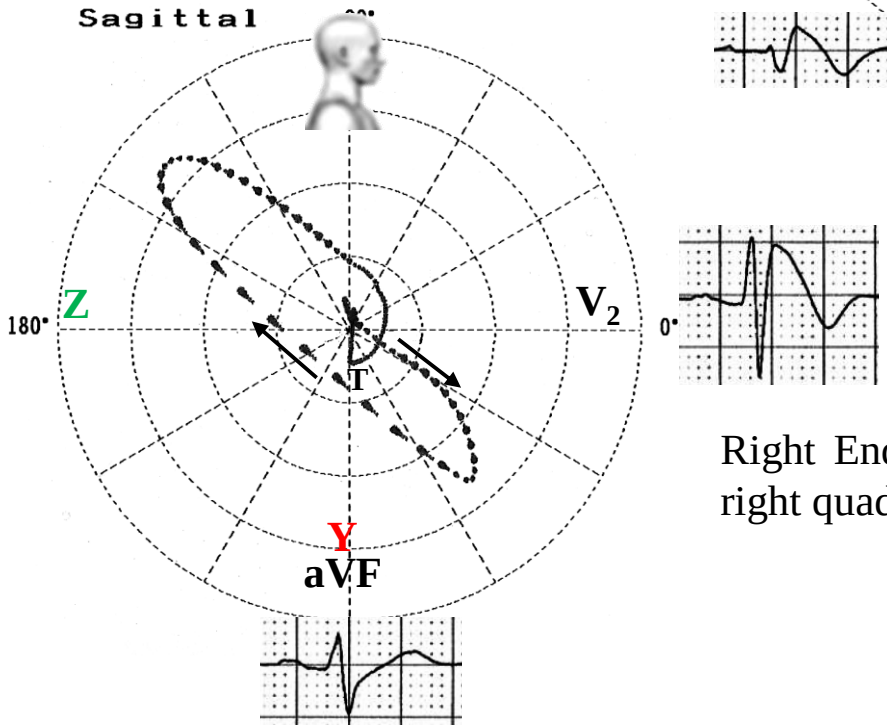
Sinus rhythm, HR 58 bpm, P axis +50°, prolonged P-wave duration 150 ms, PR interval 200 ms, P voltage 1 mm, QRS axis -20°, final R in aVR typical of spontaneous Brugada type 1 pattern. The increase in P-wave duration in the general population is a risk marker for sudden cardiac death and AF (Maheshwari A. Am J Cardiol. 2017 May 1;119(9):1302-1306). Patients carriers of Brugada syndrome with SCN5A mutations display more conduction abnormalities in ECG (P wave, PR and QRS intervals) and present a higher risk of cardiac events (Yamagata K. Circulation. 2017 Jun 6;135(23):2255-2270). Spontaneous Brugada type 1 pattern, in isolation or associated to other risk parameters like QT dispersion, Tp-e interval increase, etc. (Castro Hevia J. Int J Cardiol. 2019 Feb 15;277:130-135).

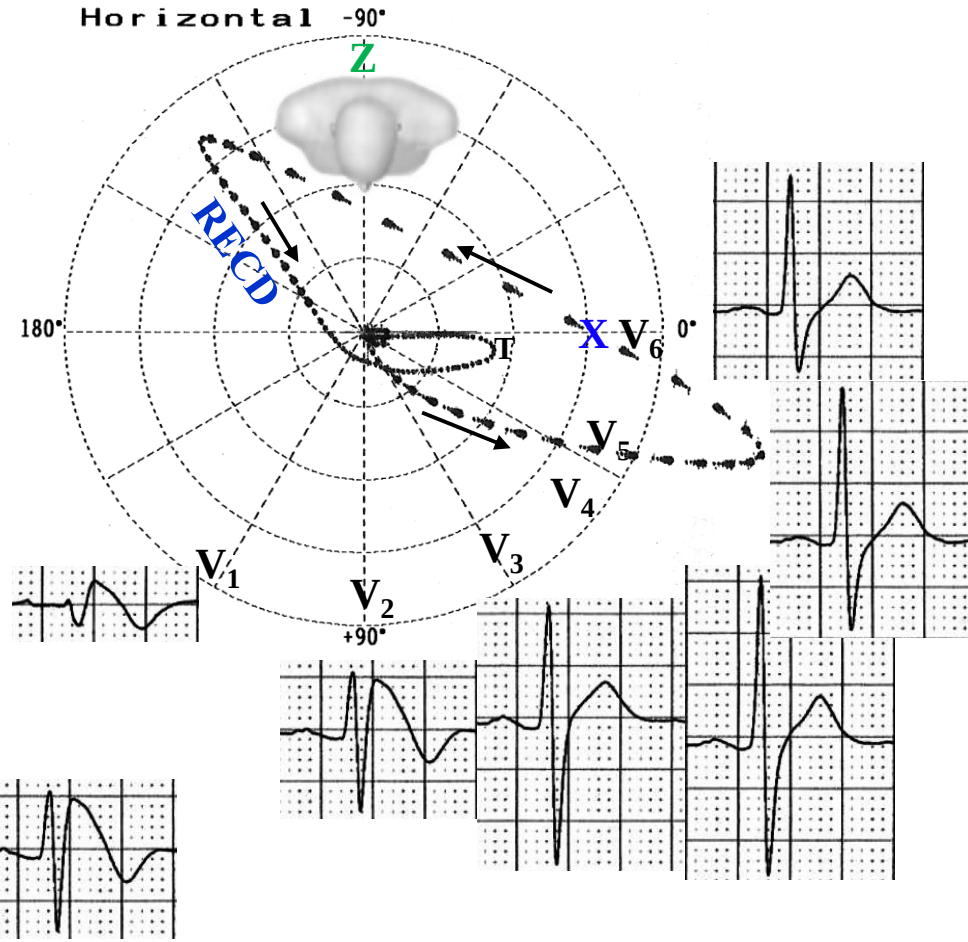
Conclusion: prolonged P wave + Brugada type 1 pattern + probable right end conduction delay (**RECD**) through the superior or subpulmonary fascicle (or contingent) of the right bundle branch on the free wall of right ventricle.

ECG/VCG correlation in the FP, HP and RSP



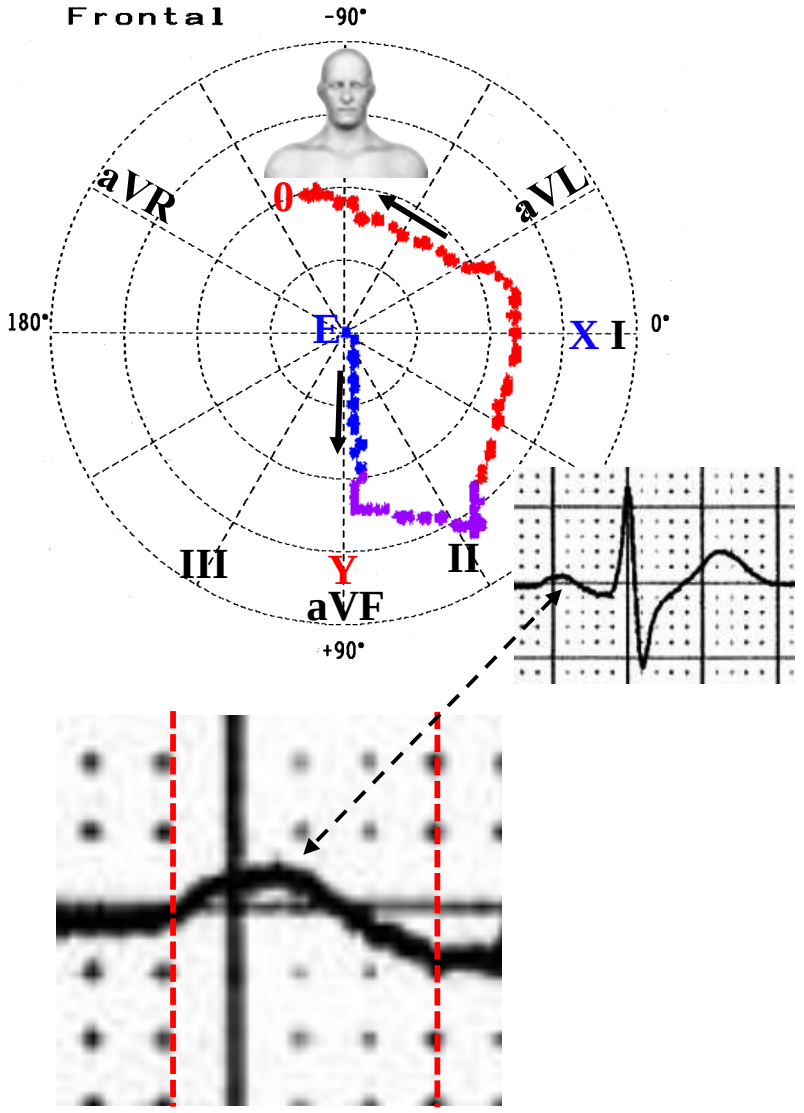
Right End Conduction Delay (**RECD**) on top right quadrant near aVR(-150°) correspondent to RVOT area: **depolarization mechanism**

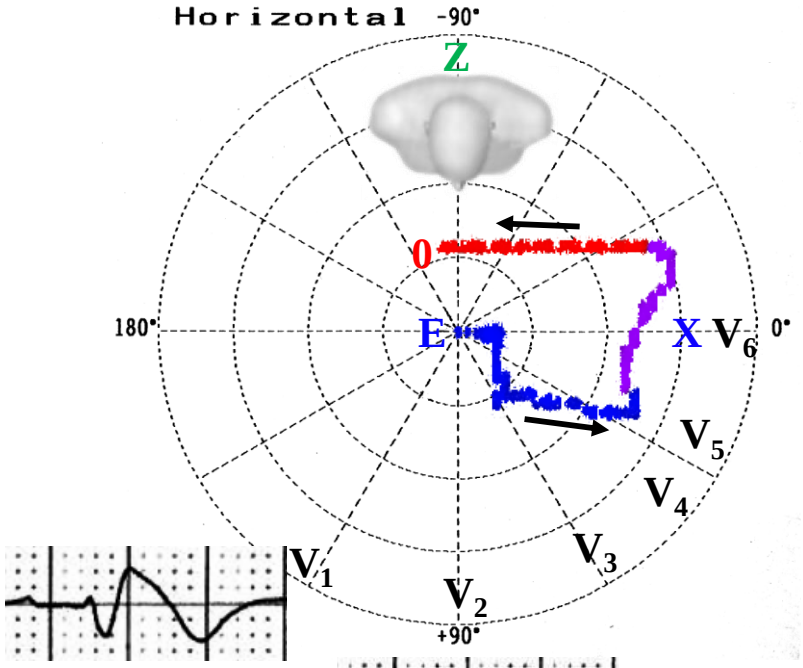


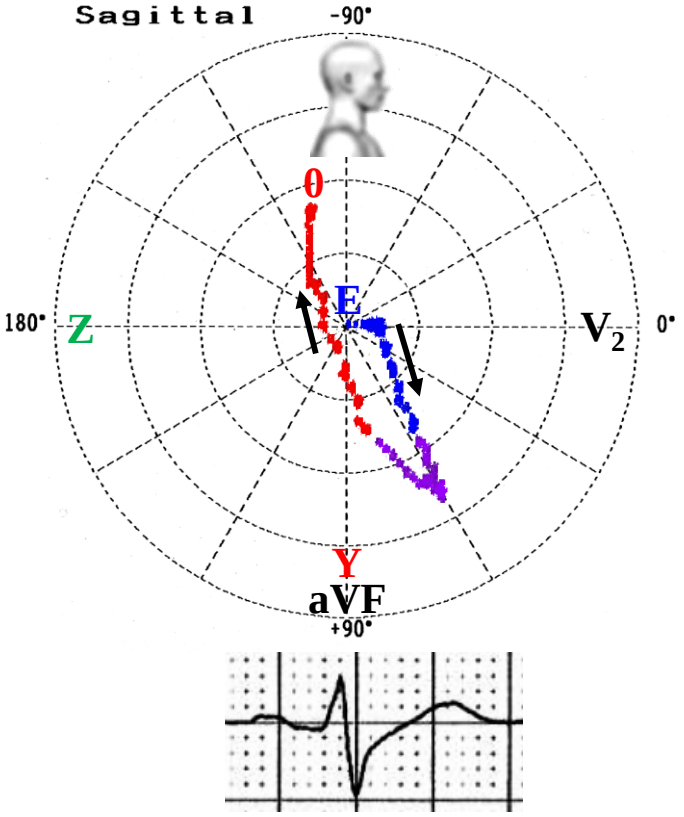


Right End Conduction Delay (**RECD**) on posterior right quadrant: **depolarization mechanism**

Enhanced P loop and wave in the three planes

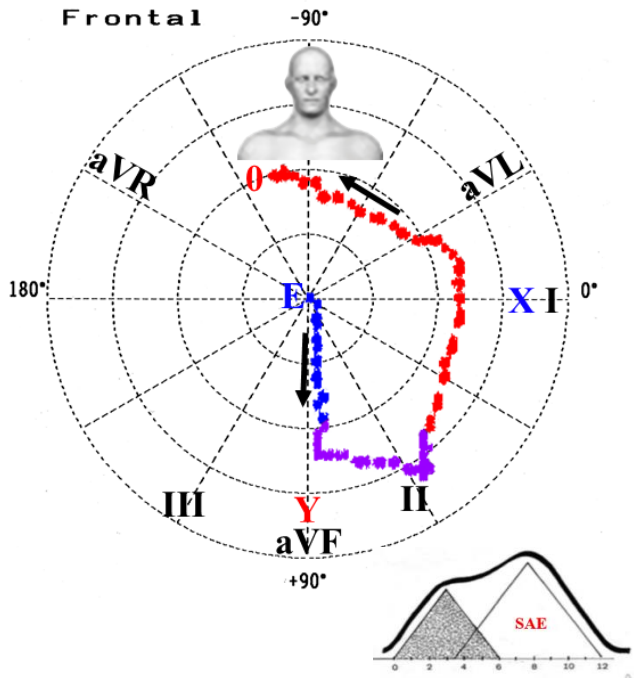


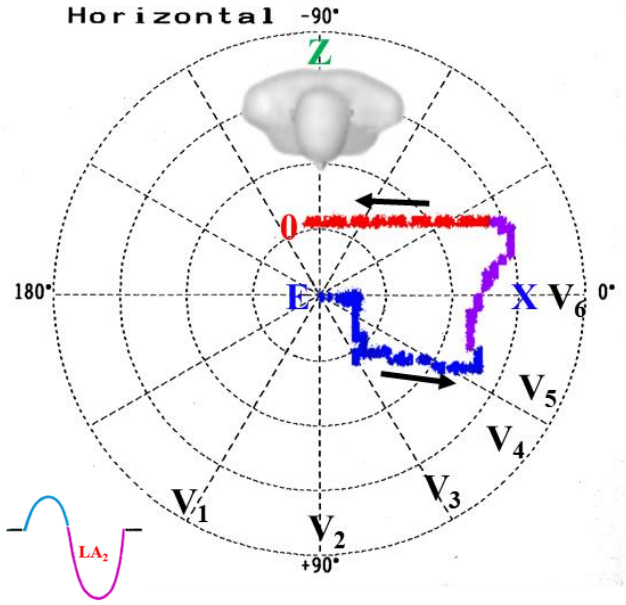


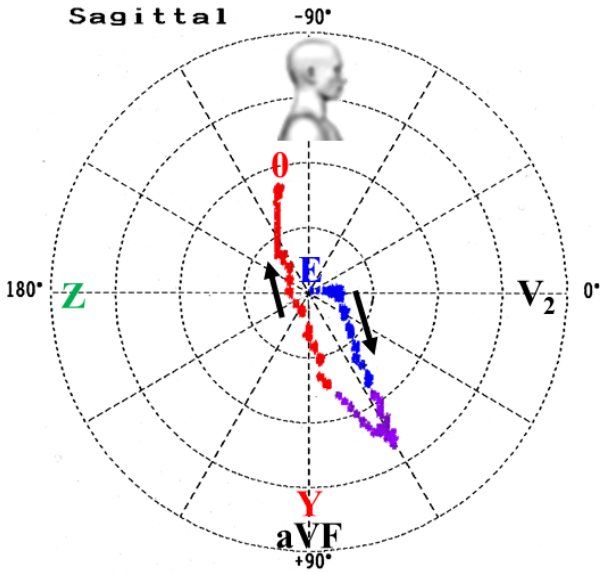


Prolonged P wave (150 mm = LAE)

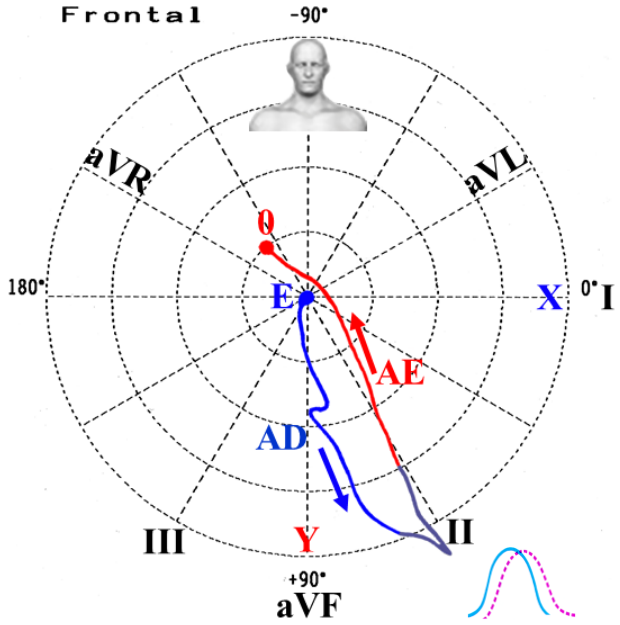
Enhanced P loop in the three planes in this particular case

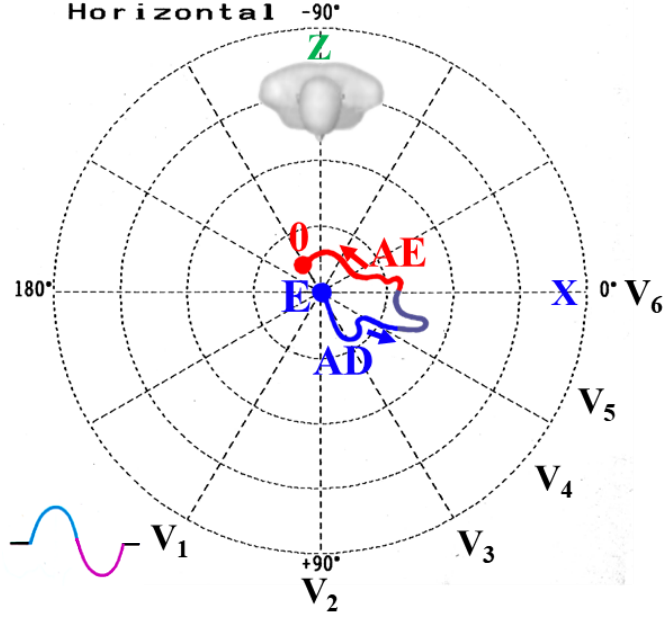


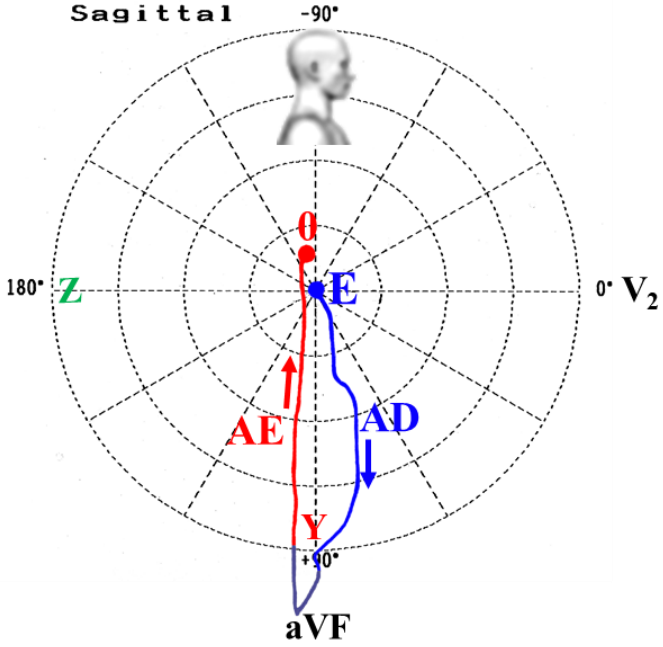




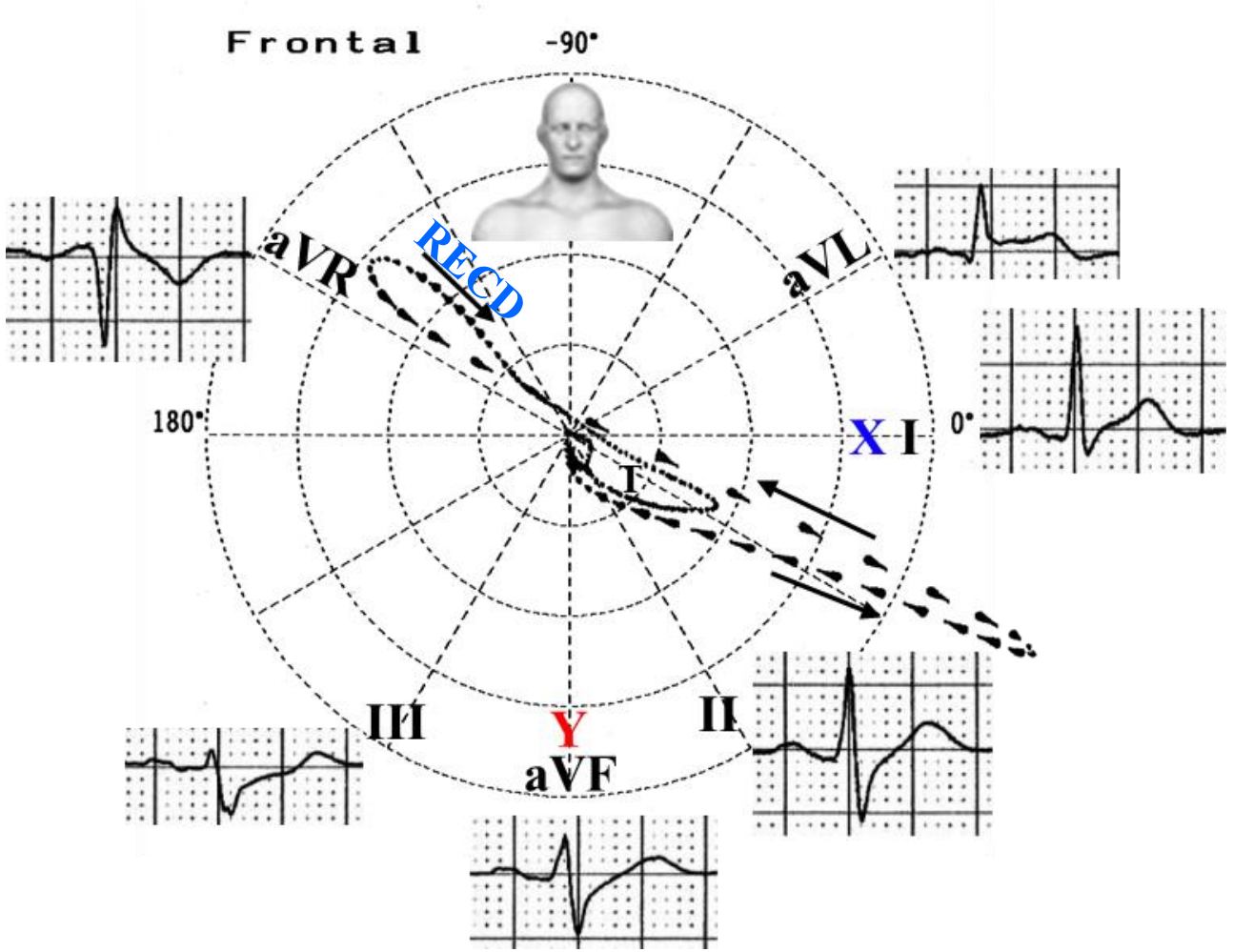
Normal P loop in the three planes





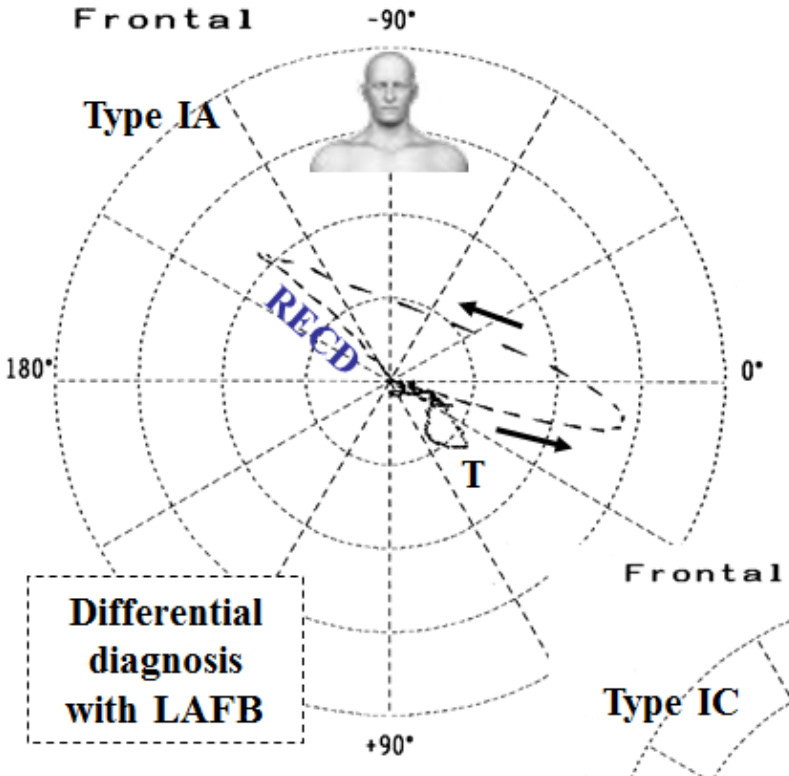


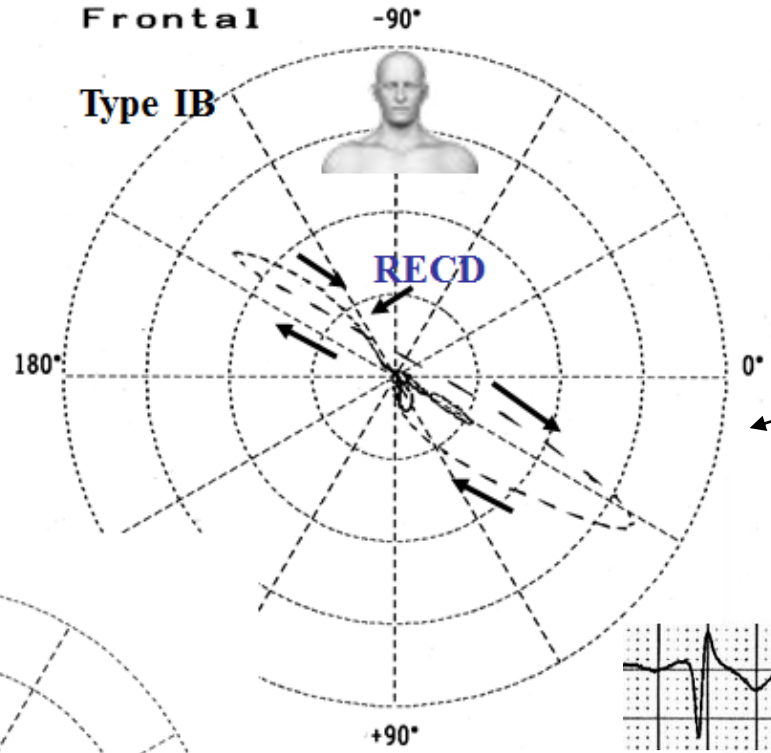
ECG/VCG correlation in the frontal plane

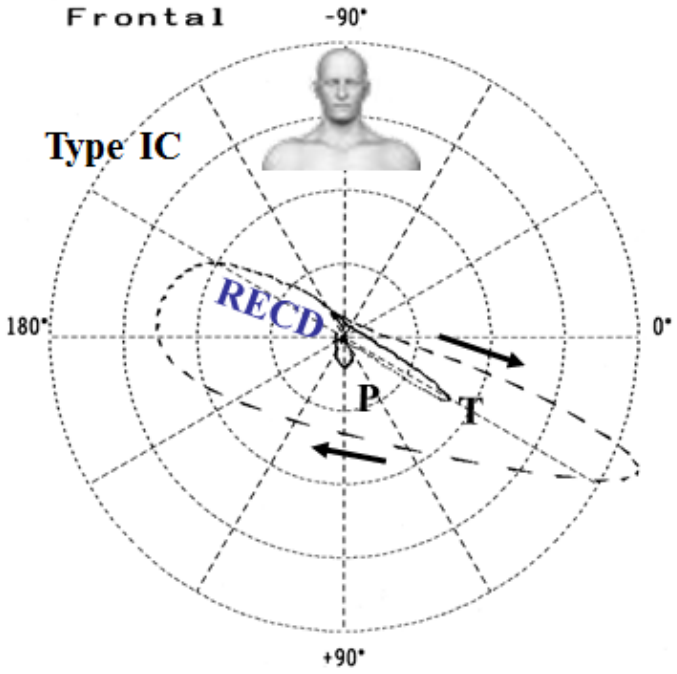


Typical right end conduction delay (**RECD**) through the superior or subpulmonary fascicle of the right bundle branch. This delay is near aVR lead, corresponding to the RVOT, which explains the final R of aVR. Our classification of right end conduction delays through the superior fascicle(OR CONTINGENT) of the right bundle branch we called type 1, which in turn are divided into three subtypes (1A, 1B and 1C) according to the QRS loop rotation in the frontal plane. In this case, it is subtype 1B. See next slides

The 3 VCG types of right end conduction delays through the superior fascicle of the right bundle branch

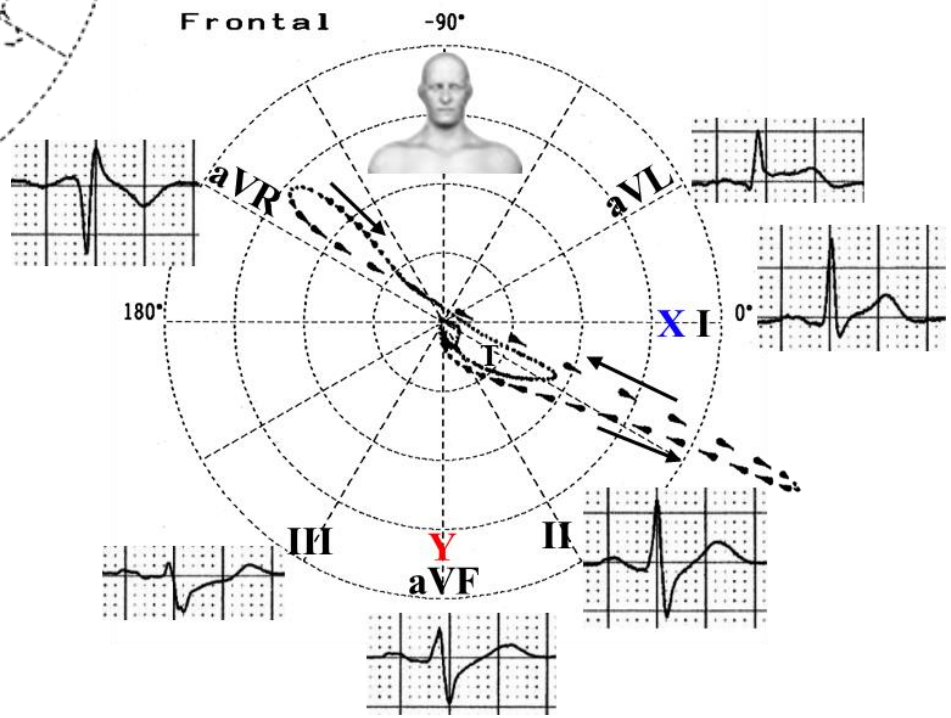






Differential diagnosis with LAFB

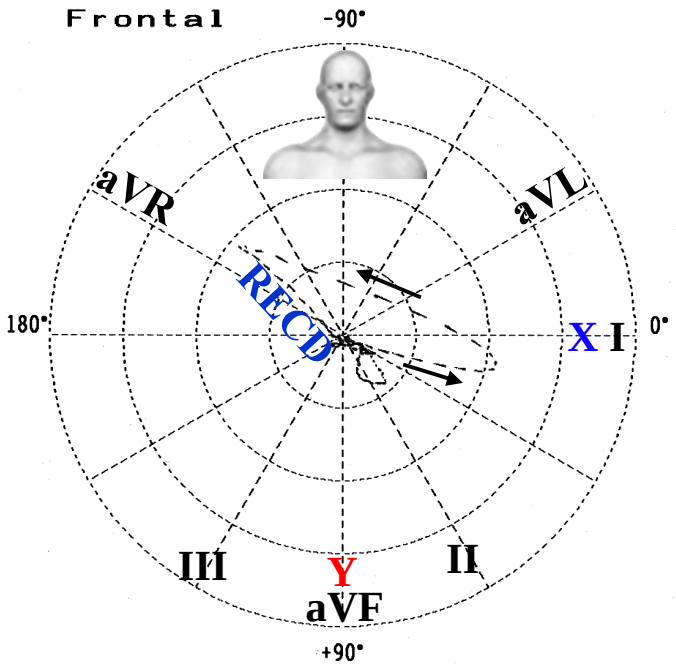
QRS loop with eight shape and its final part located in the right upper quadrant close to aVR with very close dashes (RECD). This type resembles the propellers of a single-engine plane.



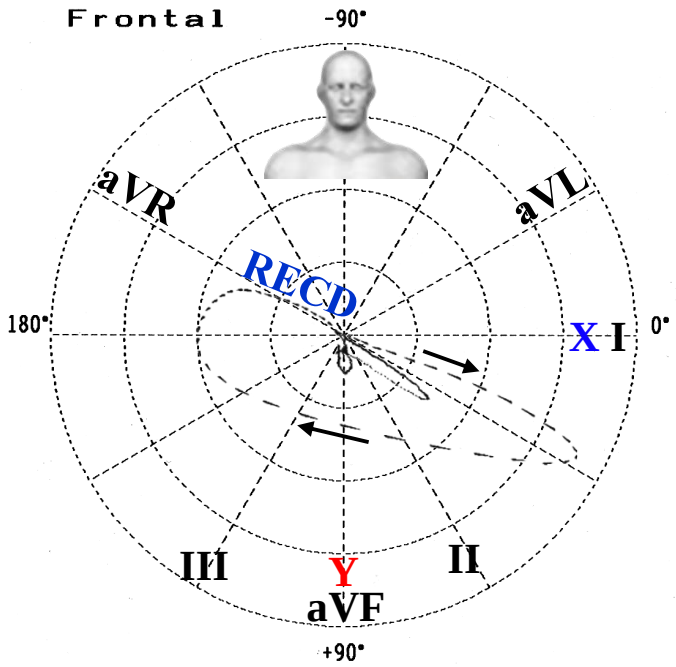
This case is a right end conduction delay subtype 1B

QRS loop types in the frontal plane

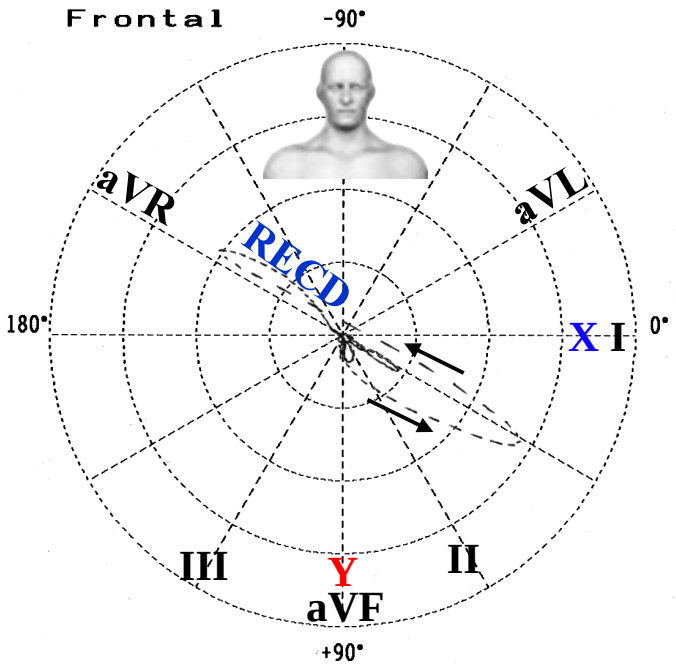
RECD type IA: CCW



RECD type IB: CW

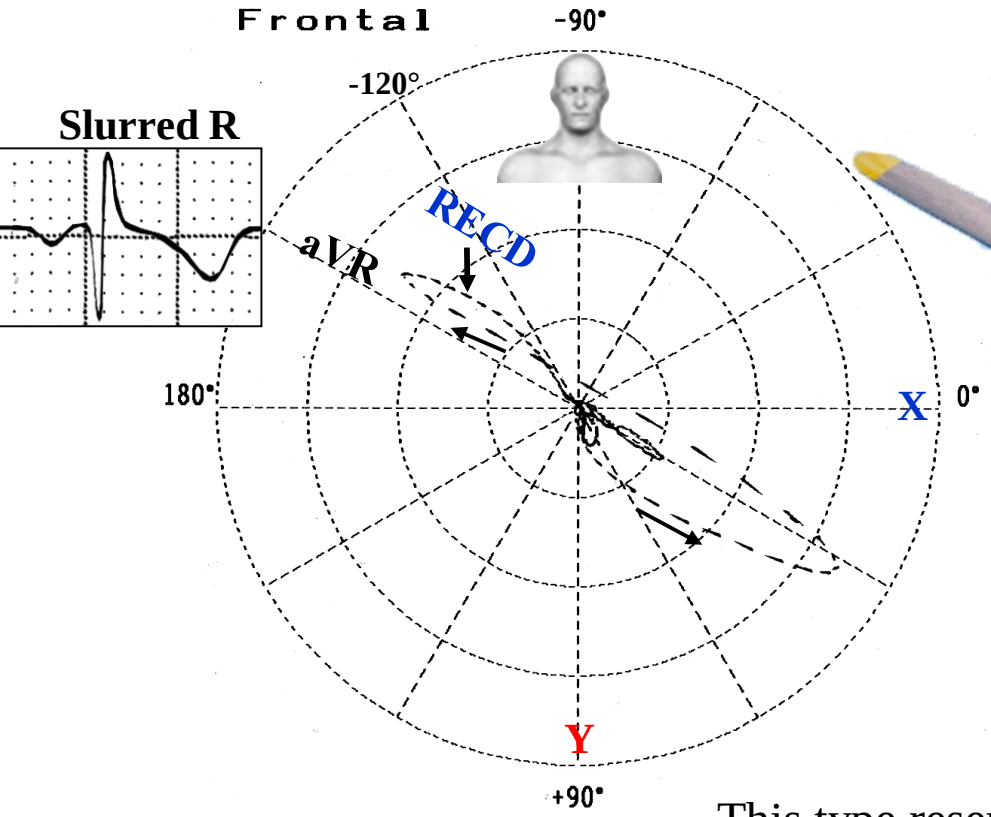


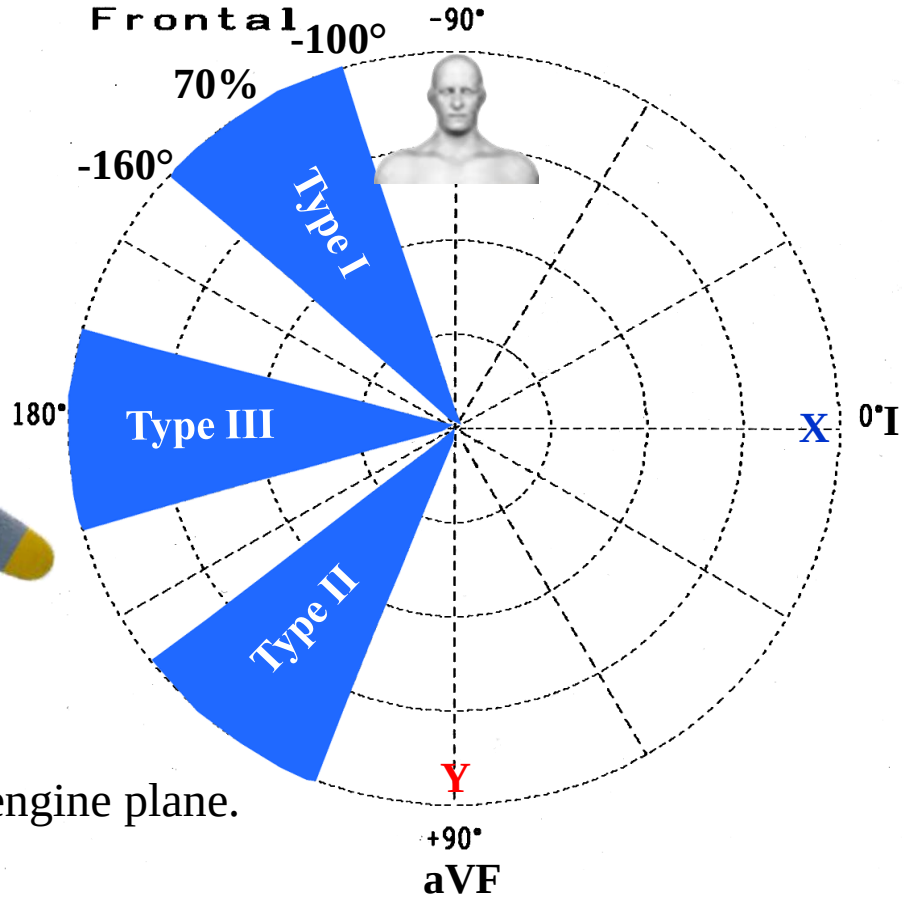
RECD type IC: in eight



The figure shows the three possible types of QRS loop rotations in BrS in the frontal plane. Type IA - QRS loop with counterclockwise rotation (CCW) and extreme superior QRS axis deviation: Right Superior Fascicular Block. >90% of the Brugada patients shows RECD in the right superior quadrant near aVR (RVOT).

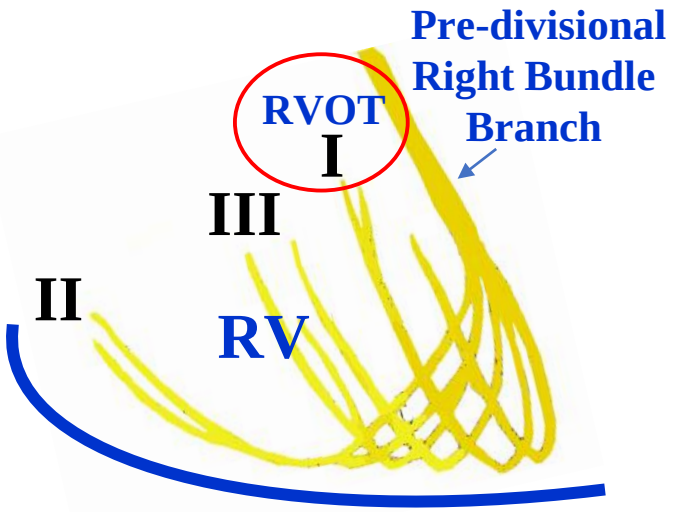
Right End Conduction Delay (RECD), subtype 1B

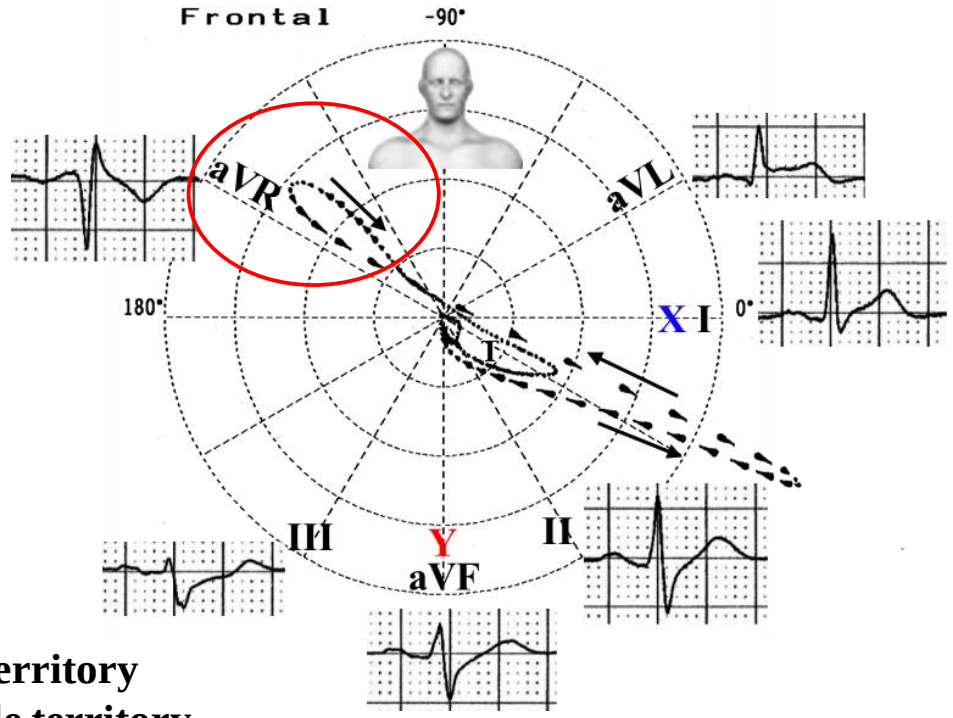


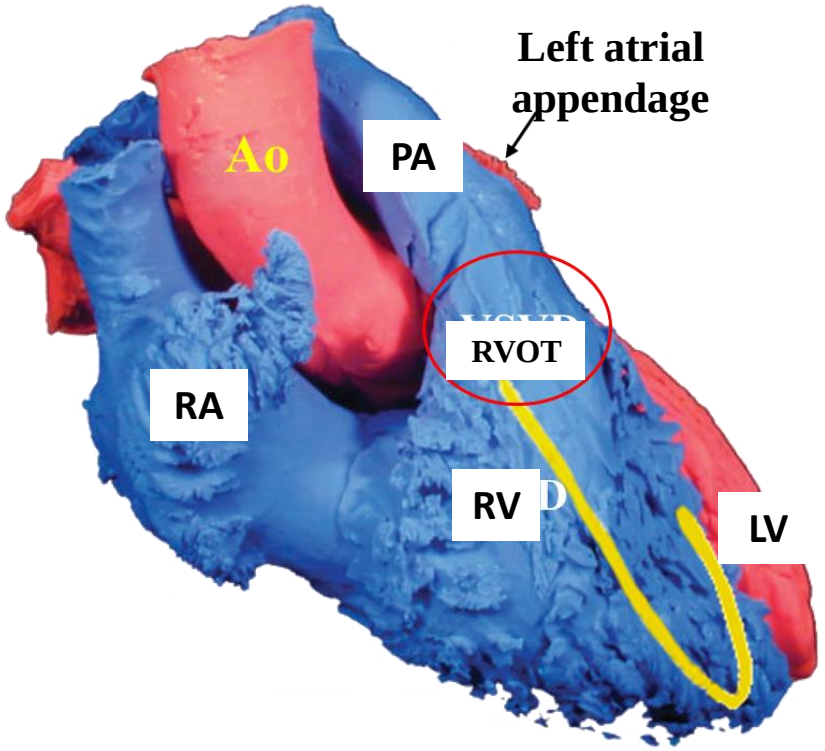


This type resembles the propellers of a single-engine plane.

Distribution of the three fascicles of the His bundle right branch in the RV free wall

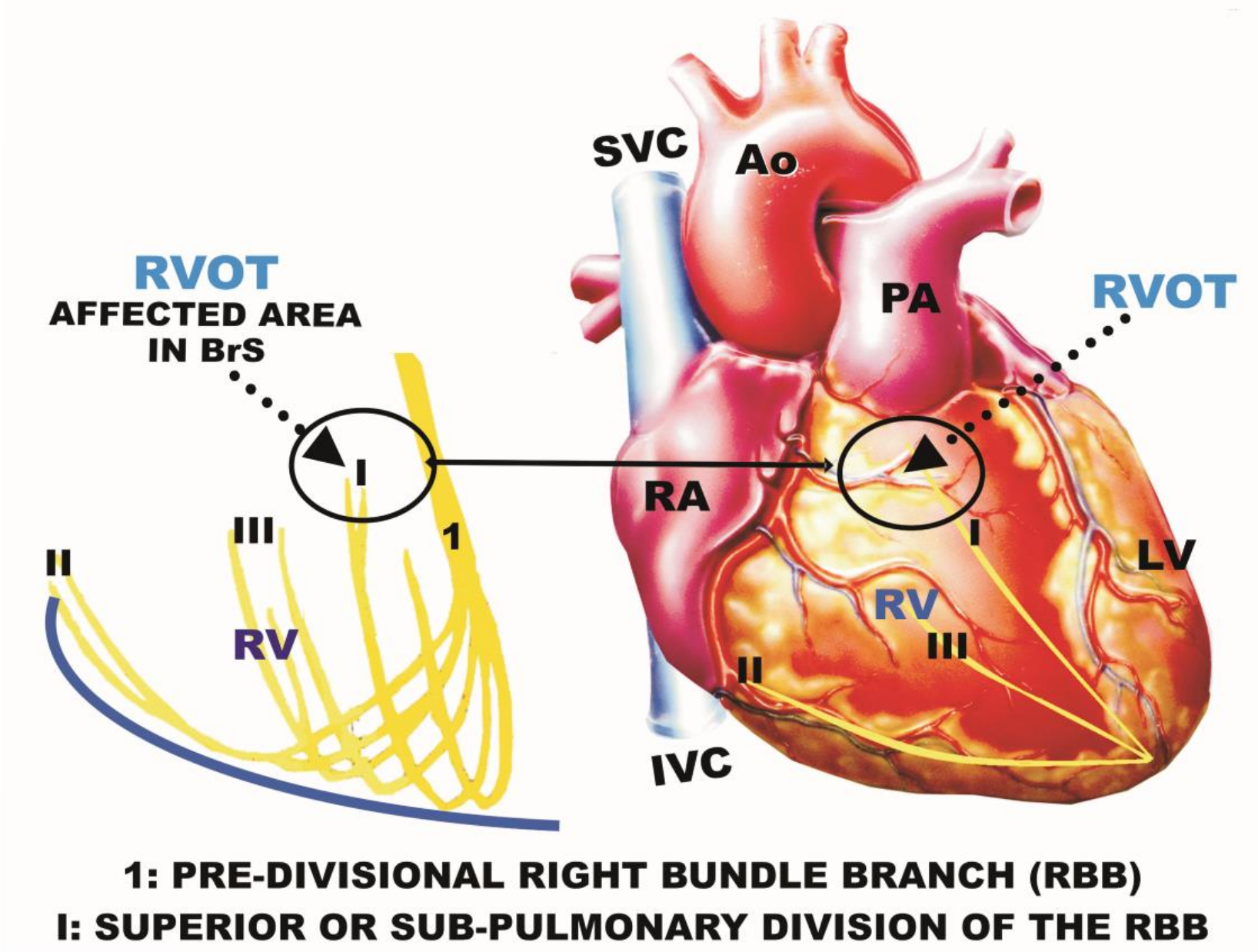






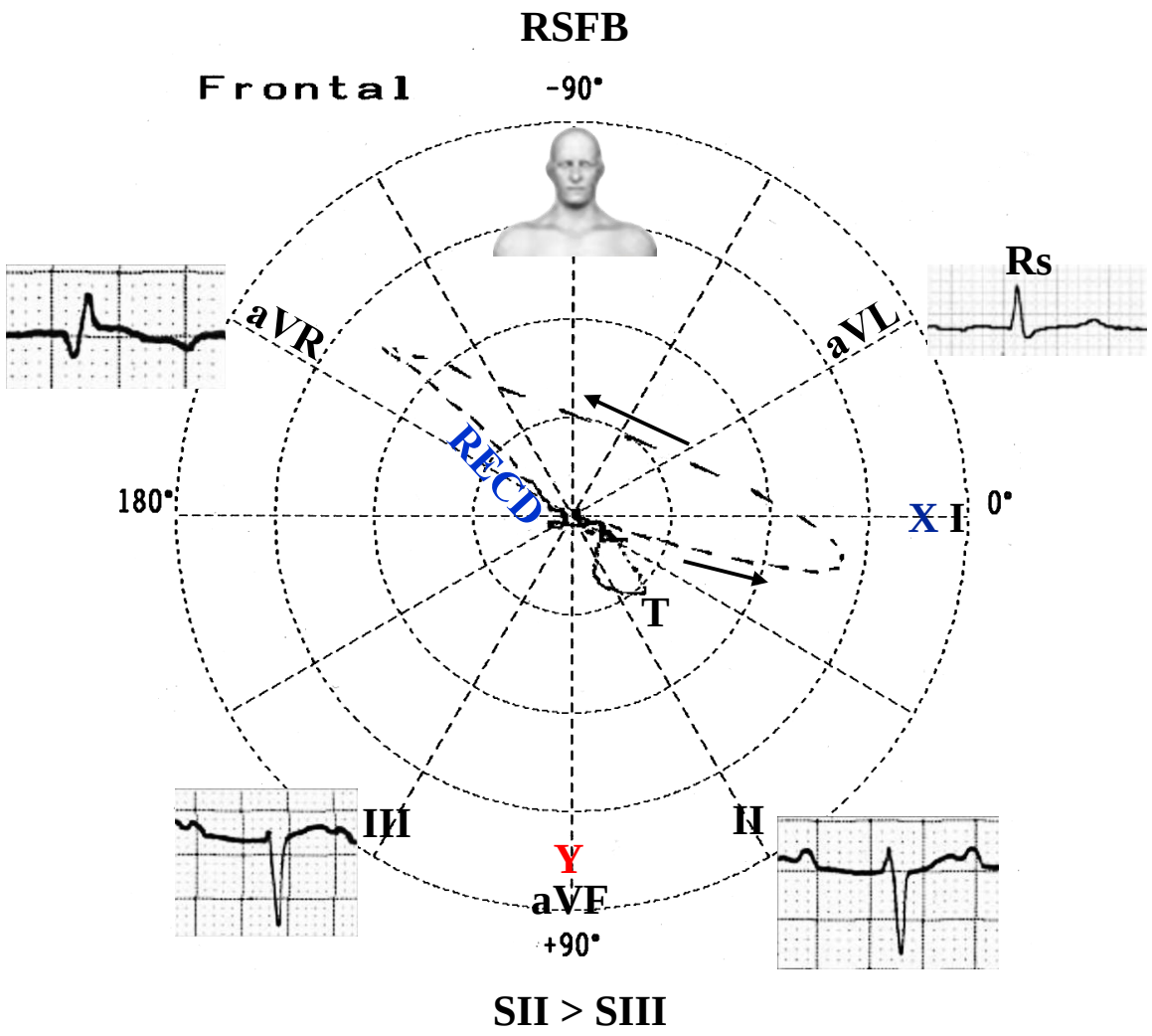
I – Superior or subpulmonary fascicle territory
II – Inferior or posterior-inferior fascicle territory
III – Middle fascicle territory

Structural epicardial alterations in the right ventricular outflow tract (RVOT) are the substrate for the conduction anomalies in Brugada syndrome (BrS). Electroanatomic mapping of endocardial unipolar voltage is an emerging tool that identifies accurately epicardial anomalies in the RVOT in BrS. Endocardial unipolar voltage mapping of the RVOT detects electroanatomical abnormalities in patients with BrS. Wide areas of abnormalities in endocardial unipolar voltage reflect structural epicardial abnormalities in the RVOT of patients with BrS (Letsas KP. Europace. 2018 Jun 1;20(FI1):f57-f63). BrS is associated to interstitial subepicardial fibrosis and a reduction in gap junction expression (connexin-43) in the RVOT, responsible for abnormal potentials, and its ablation abolishes BrS phenotype and arrhythmias risky for life. BrS is also associated to an increase in collagen throughout the heart. Abnormal myocardial structure and conduction are, therefore, responsible for BrS (Nademanee K. J Am Coll Cardiol. 2015 Nov 3;66(18):1976-1986).

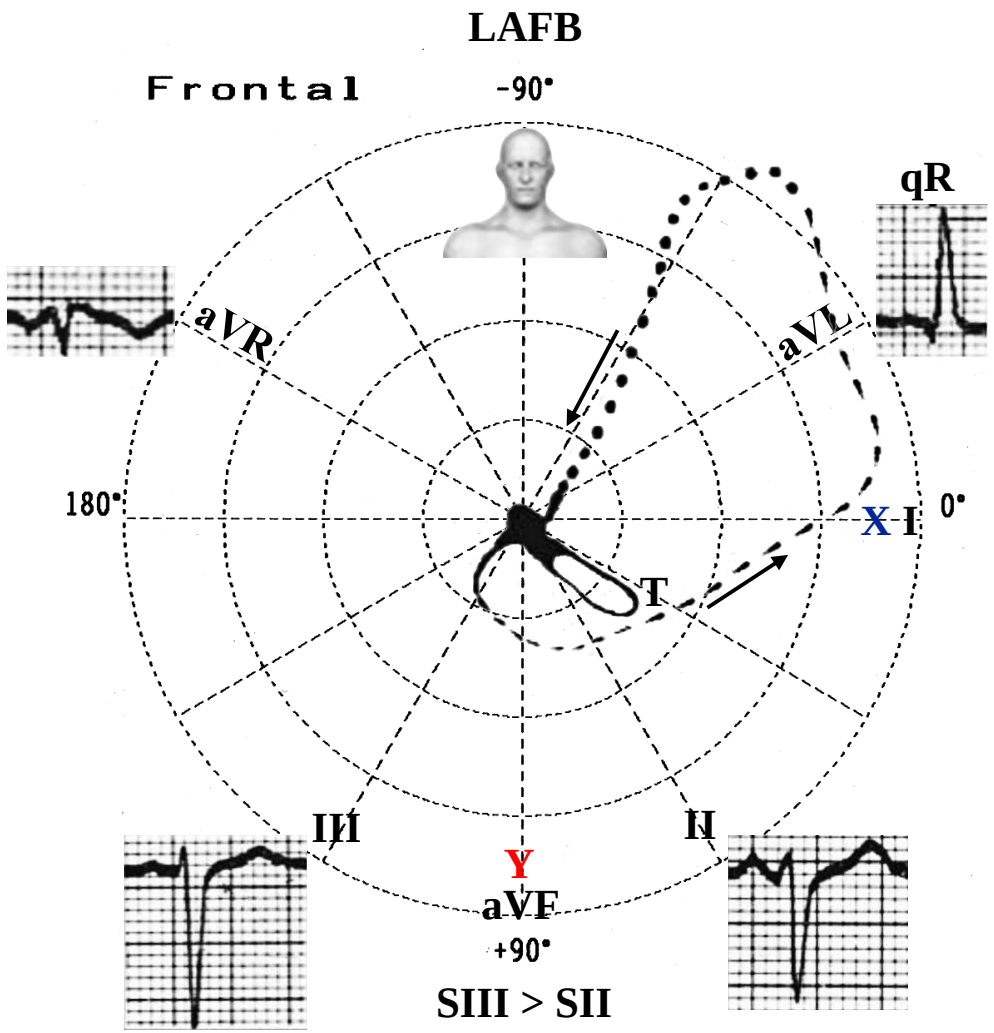


The figure shows the three hypothetical clusters of fibers (I, II and II) on the free wall of the right ventricle, and the partial superior right Hissian system affected in BrS: “Right Superior Fascicular Block” (depolarization mechanism).

ECG/VCG differential diagnosis between right superior fascicular block (RSFB) and left anterior fascicular block (LAFB) (Pérez-Riera AR 2005)



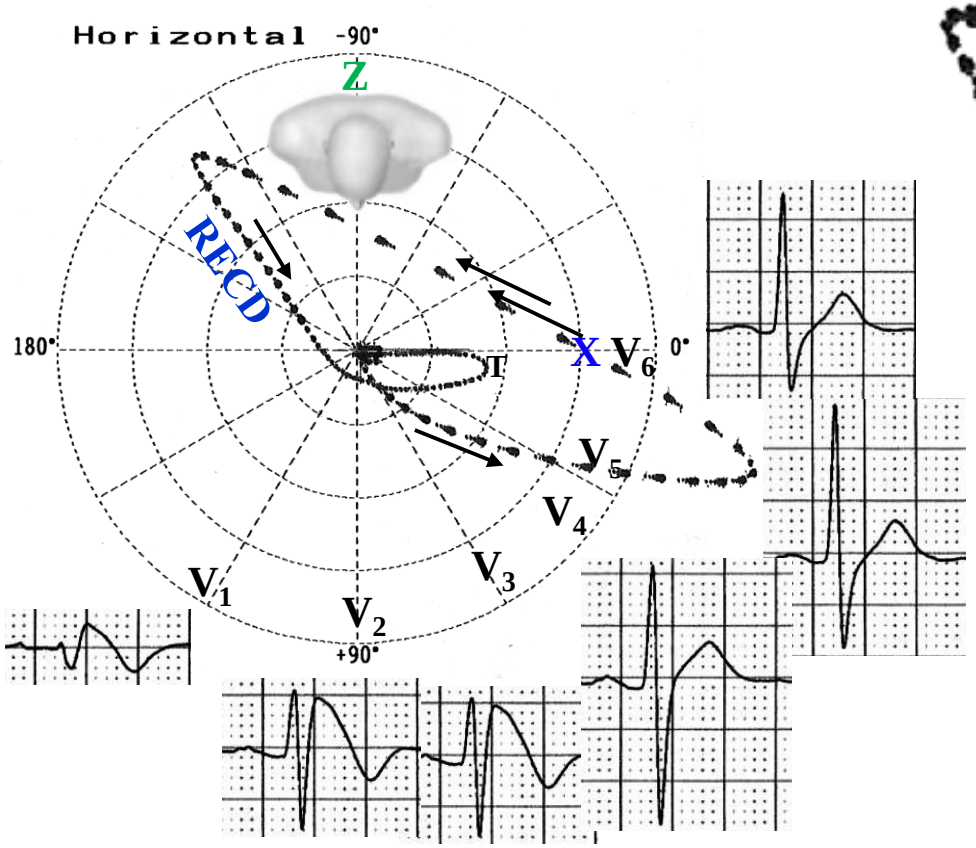
SII > SIII



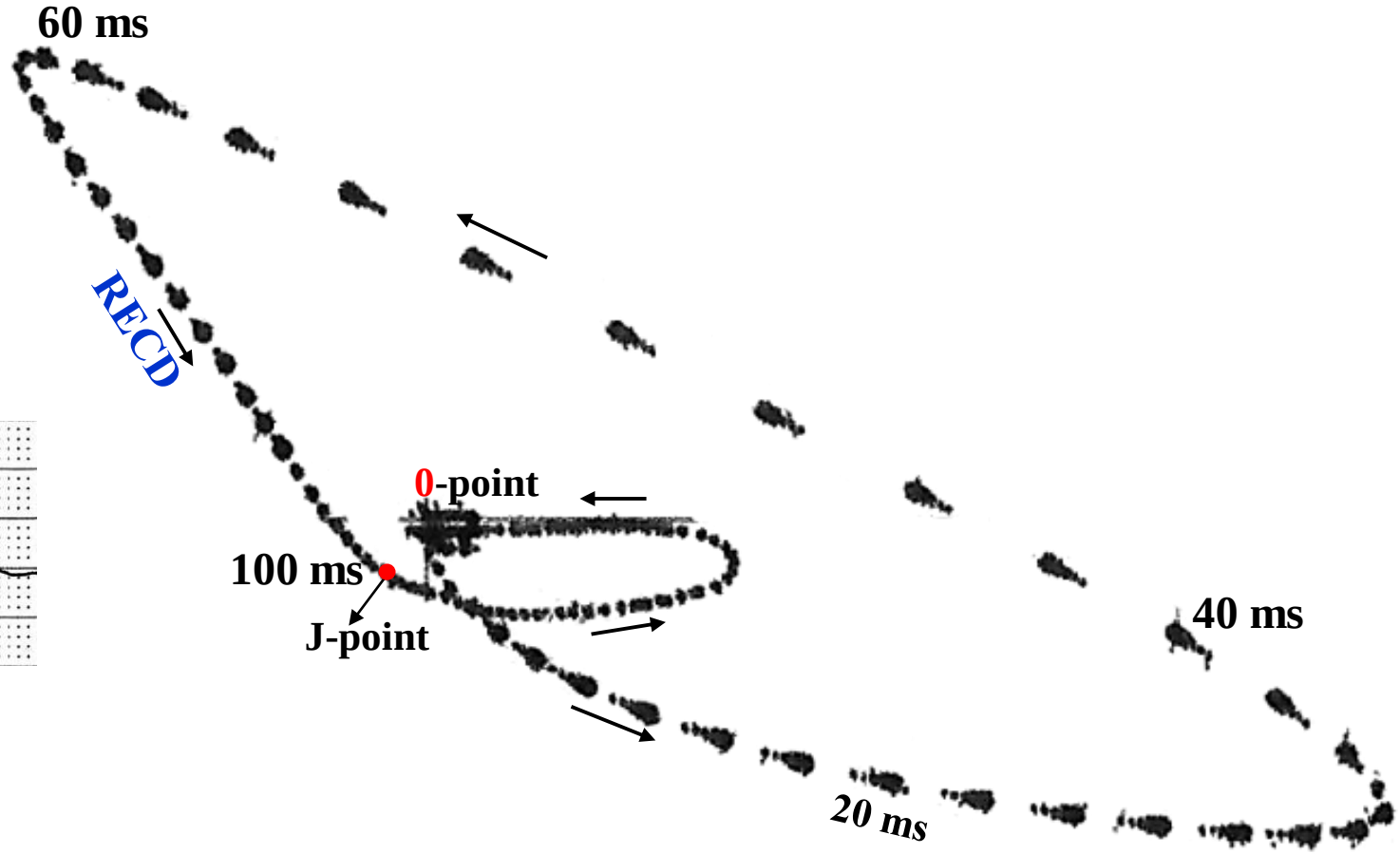
SIII > SII

	LAFB	RSFB
Initial 10 ms vector of QRS loop	Heading downward and to the right	Heading downward and to the left
QRS morphology in I & aVL	qR pattern	Rs
SII/SIII ratio	SIII>SII	SII>SIII
Location of end conduction delay (ECD)	In the left superior quadrant when present	In the right superior quadrant (Pastore 1983)
Prominent R wave in aVR (R-wave ≥ 0.3 mV)	Absent	It could be present and it is called aVR sign (Babai Bigi 2007).
Morphology of QRS loop of vectorcardiogram in the horizontal plane	Similar to normal	Similar to type-C right enlargement pattern: initial vector to the front and leftward, counterclockwise rotation and 20% or more of the area of the loop located in the right posterior quadrant in the horizontal plane (Luna Filho 1989)

ECG/VCG correlation in the horizontal plane

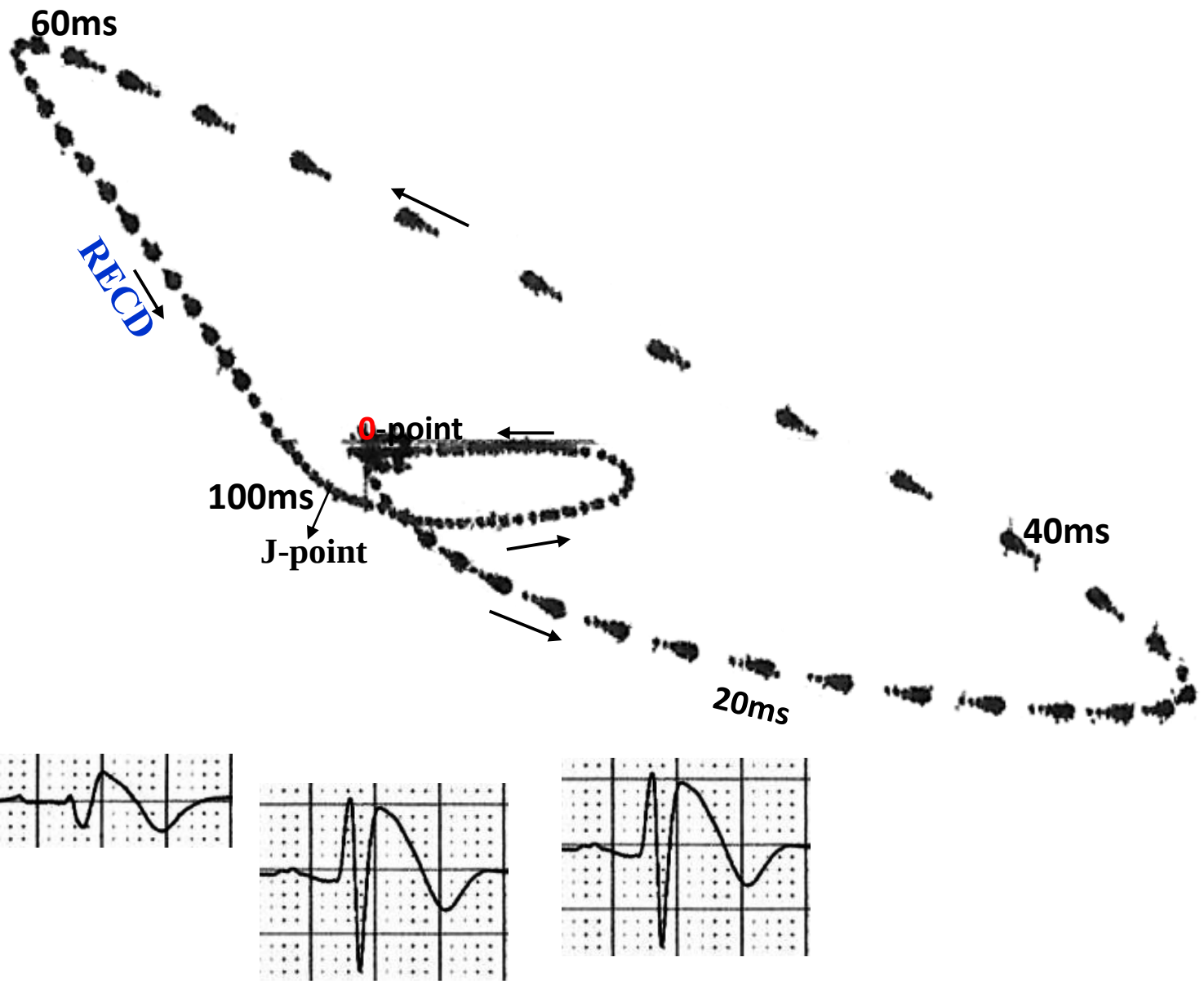


QRS and T loops characteristics in the horizontal plane

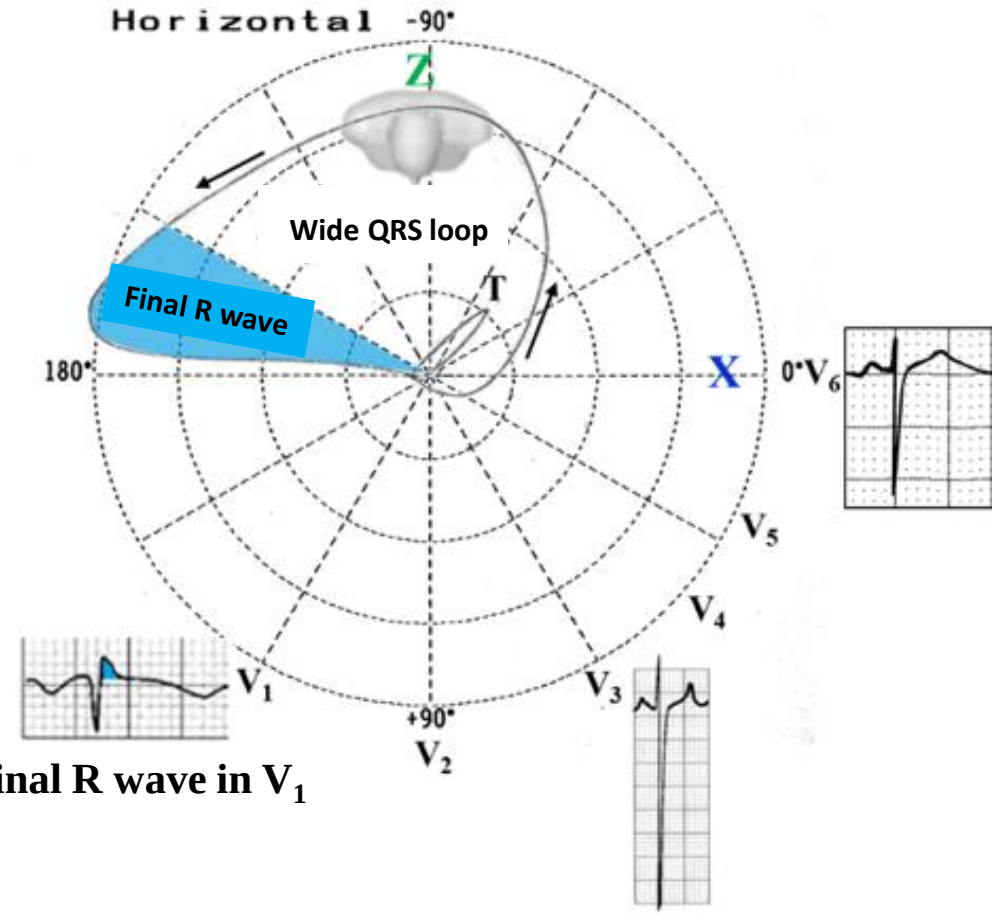


Initial 20ms forces directed to front and leftward, rapid passage from left to right between 40ms to 60ms and the final 40ms with Right End Conduction Delay (**RECD**) on posterior right quadrant: **depolarization mechanism.** J-point in the front and the right related the point 0. Both points are very distant from each other, which marks the elevation of point J and the ST segment typical of Brugada type 1 pattern, The T-loop pointing left as a finger, with both efferent and afferent limbs with slow and similar speed inscription. The QRS loop remembers the type C right ventricular overload typical of chronic obstructive pulmonary disease(COPD) or emphysema (**Luna filho B 1989**).

QRS and T loops characteristics in the horizontal plane in Brugada type 1 pattern

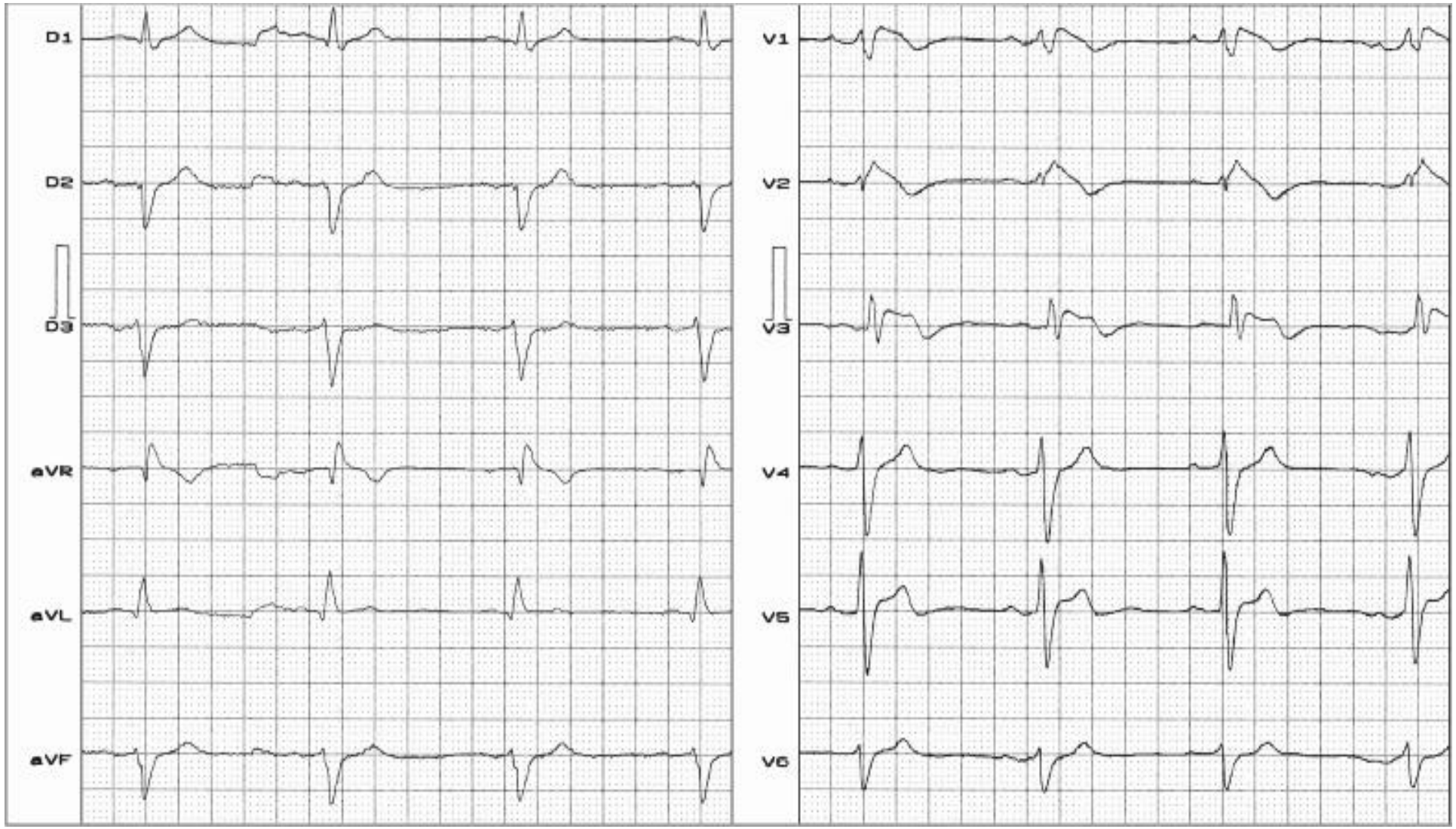


QRS and T loops in RVH type C, III or special



Final R wave in V_1

Name: MK; **Age:** 38 y/o; **Gender:** Male; **Ethnic Group:** Asian; **Weight:** 68 kg; **Height:** 1.70 m

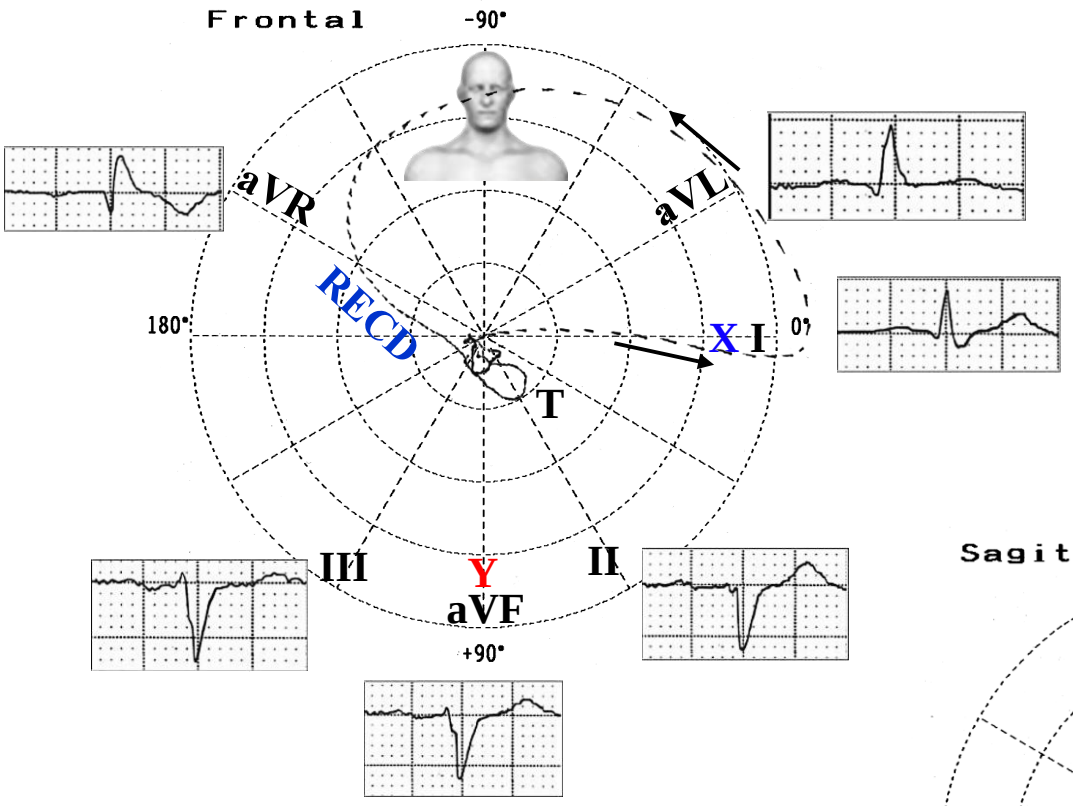


Clinical diagnosis: Syncope. Positive familiar background of sudden death in young (≤35 y/o) first-degree relative. Genetic research performed: negative.

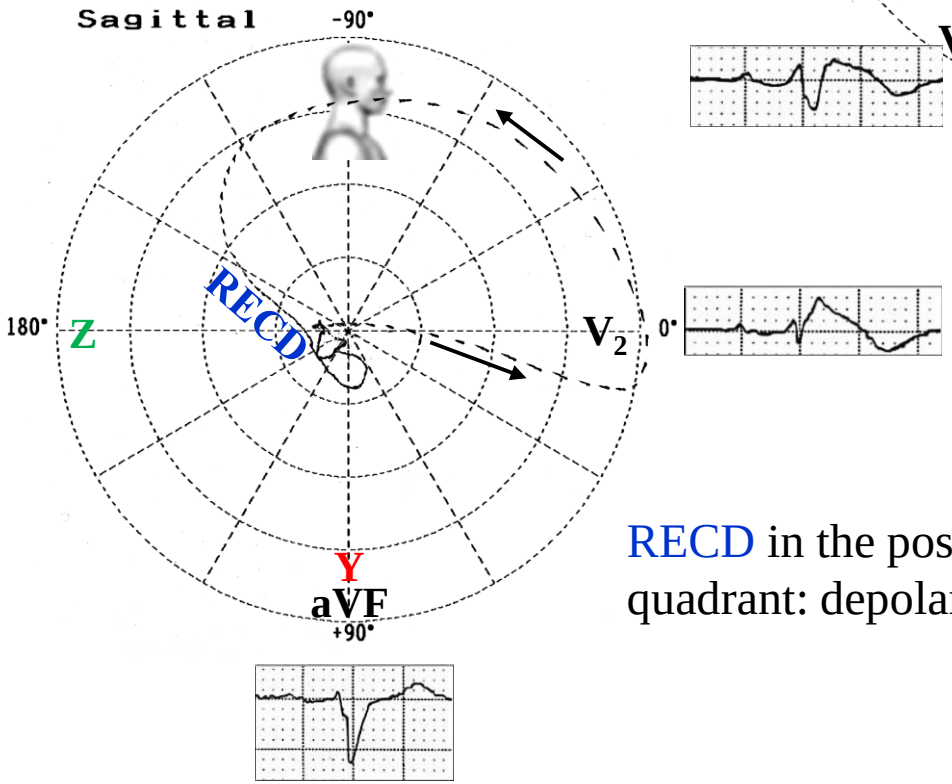
ECG diagnosis: Sinus bradychardia (HR <60 bpm), Brugada type 1 ECG pattern, prolonged QRS duration, aVR signal: final R wave of aVR lead >3 mm, fQRS in V1-V2.

Extreme left axis deviation: Left anterior fascicular block? or Right superior fascicular block?

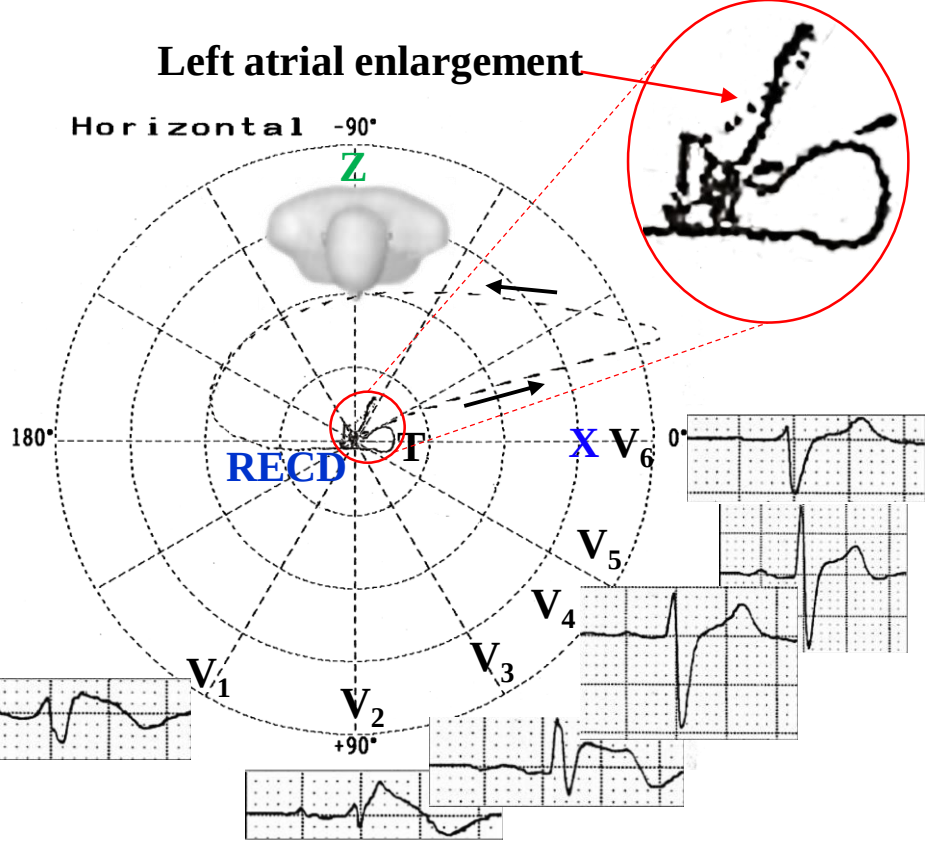
ECG/VCG correlation



RECD in the right superior quadrant (RVOT): depolarization mechanism; round, small T wave: repolarization mechanism; extreme left axis deviation + CCW rotation = pseudo LAFB; SIII>SII; broad final R wave in aVR



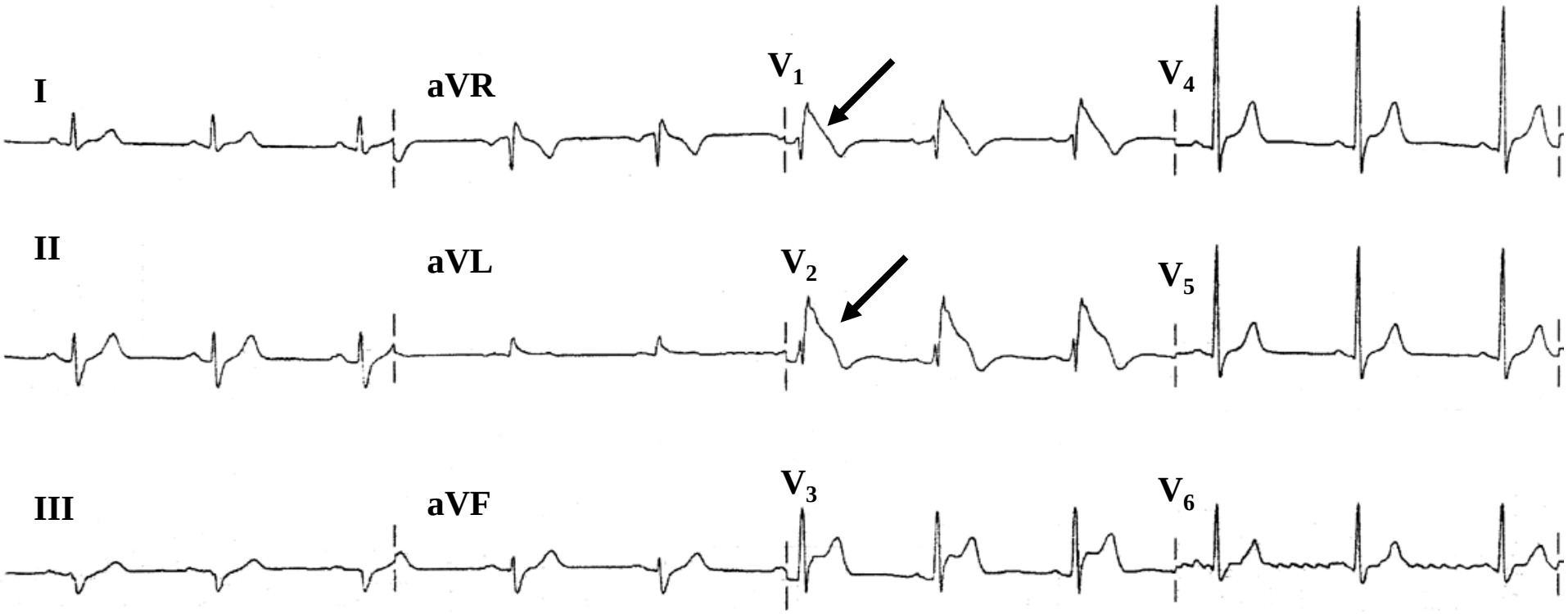
Left atrial enlargement



RECD in the posterosuperior quadrant: depolarization mechanism

ECG with typical type 1 Brugada pattern and final part broadening by superior fascicle block of RBBB

Male, 56-year-old patient (03/16/2002). He complained of atypical precordial pain.

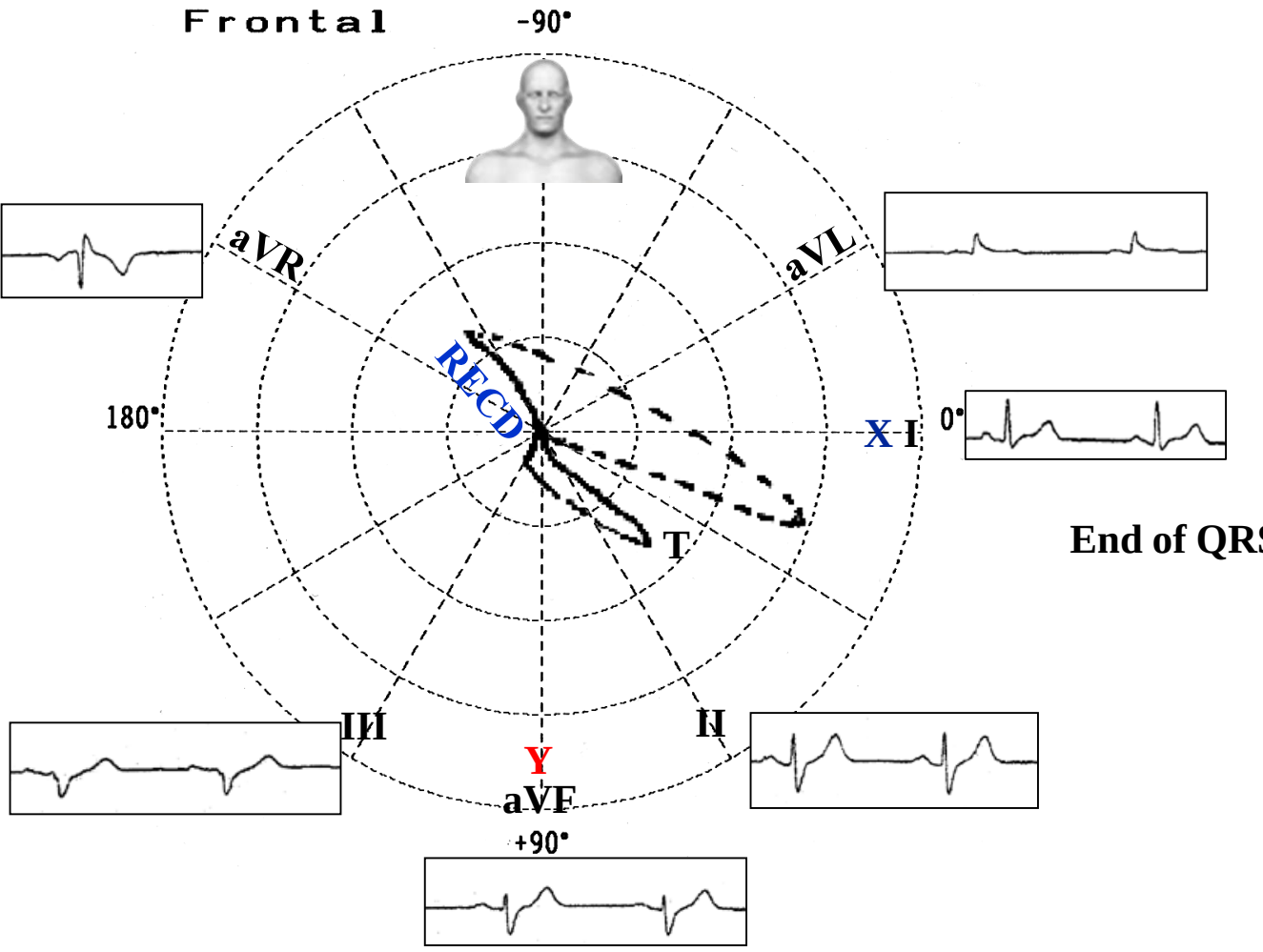


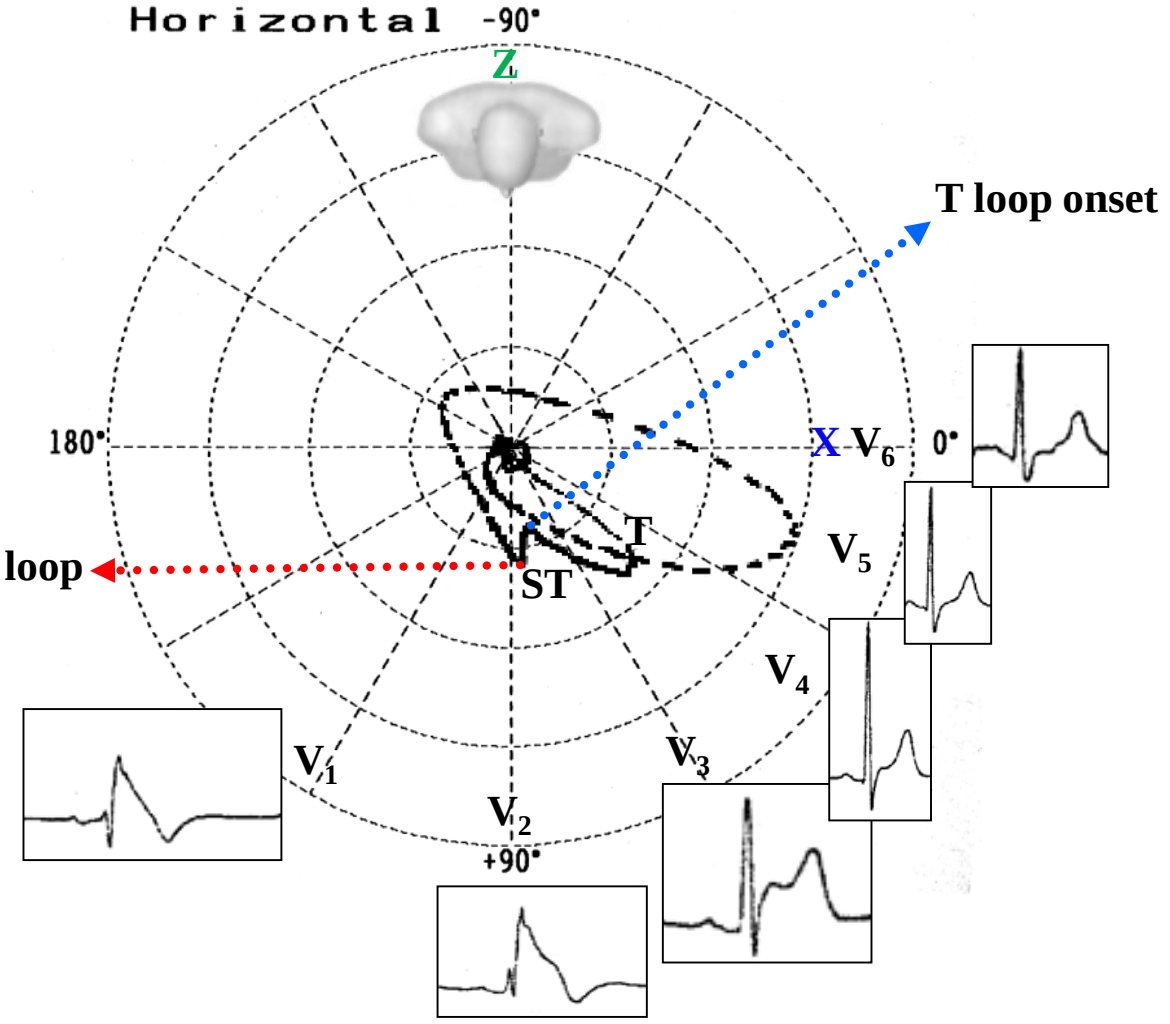
Final part widening by the superior, anterosuperior or subpulmonary fascicle of the RBB, type I according to our classification. Extreme shift of SAQRS to the left in the left superior quadrant –45°. ST segment and J point elevation with convex to the top morphology in V_1 and V_2 and saddle type in V_3. aVR with D wave broadening: "crista delay" or RV outflow tract widening. S waves in left precordial leads V_5-V_6. SII >SIII. This information is very important for a differential diagnosis with left anterior fascicular block. Structural heart disease was not detected with noninvasive and invasive methods.

Conclusion: ECG with typical Brugada type 1 pattern, and final part widening by superior fascicle block of RBB.

ECG/VCG correlation of Brugada syndrome in the frontal and horizontal planes

Male, 56 years old; Date: 03/16/2002.



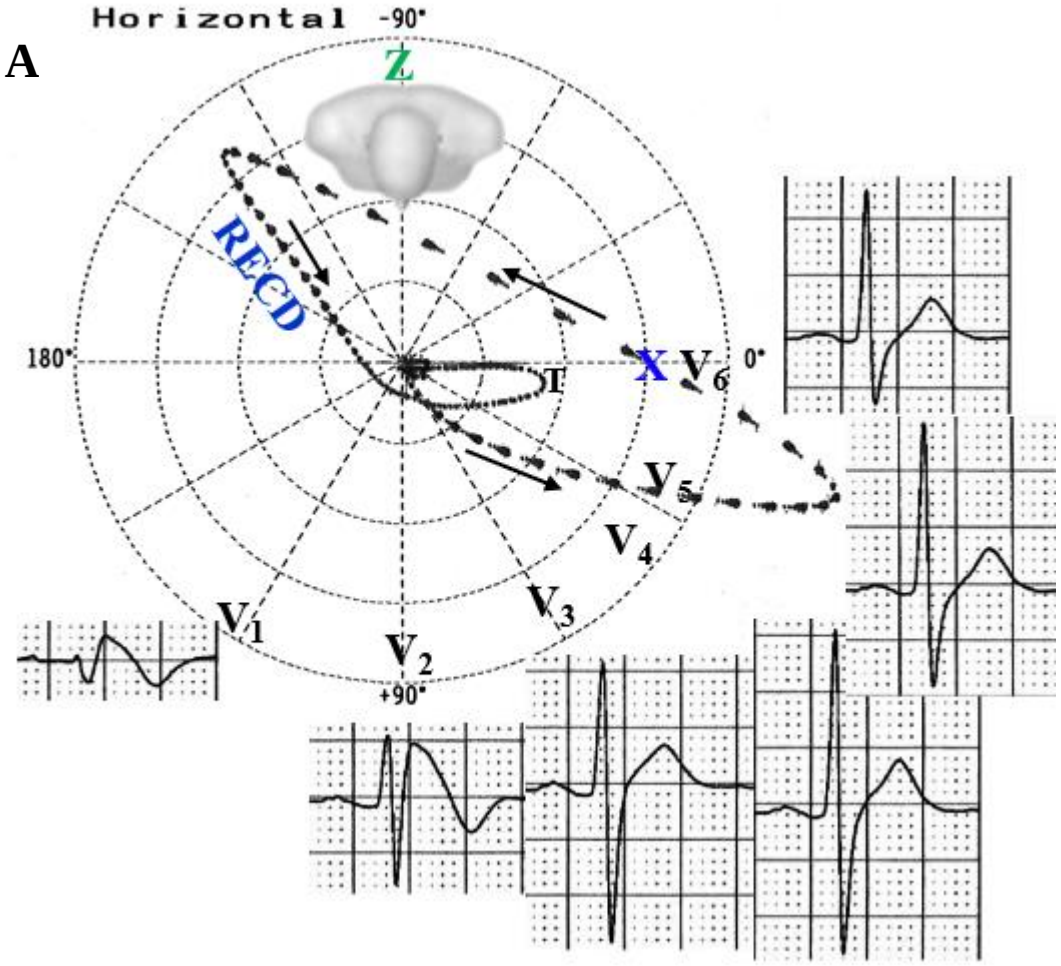


Conclusion: it is the first VCG of Brugada syndrome shown in world literature. End conduction delay (ECD) by superior fascicle of the RBB. Type IA of our classification.

The end of QRS loop does not coincide with T loop onset (as it occurs in normal conditions) since there is elevation both in the J point and the ST segment.

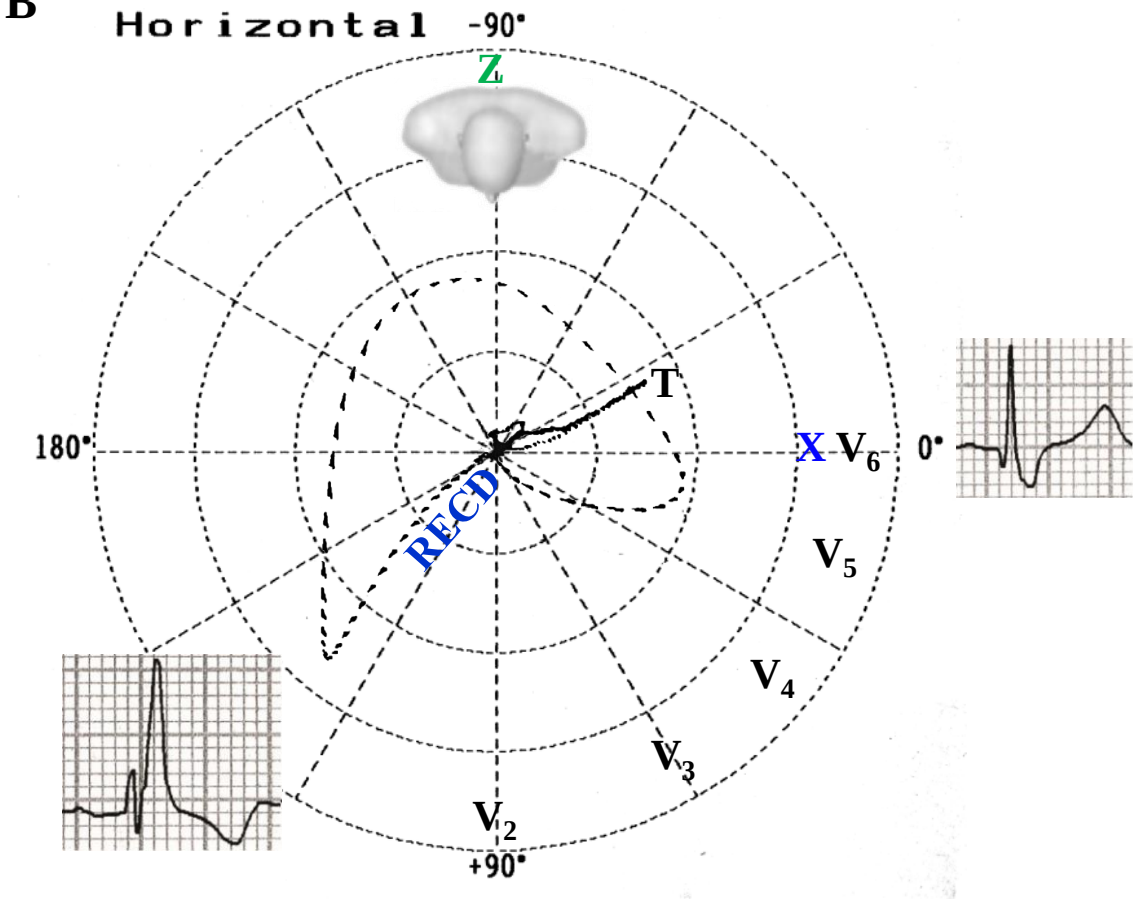
Truly RBBB pattern in the HP ECG/VCG correlation

A



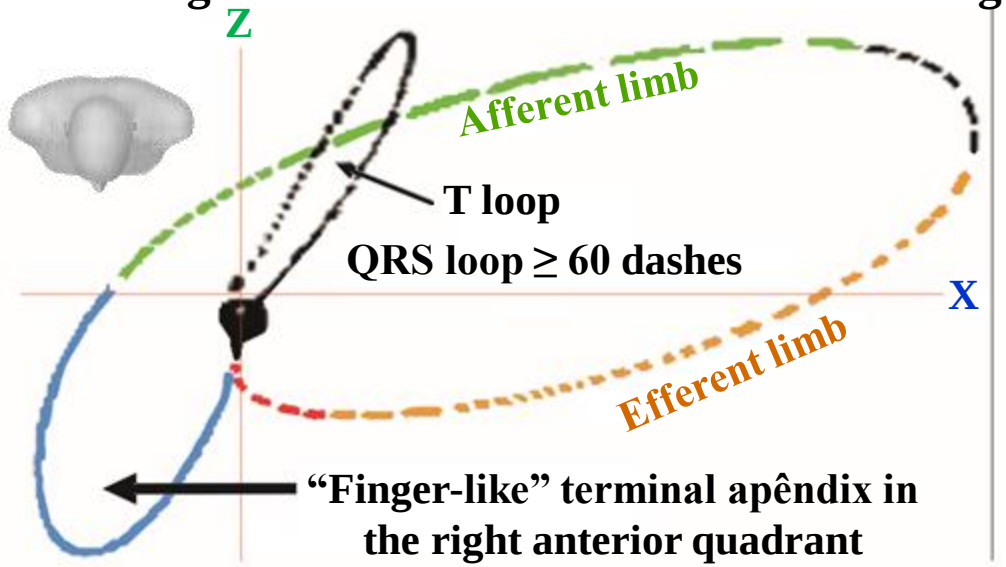
Right End Conduction Delay (**RECD**) on posterior right quadrant: **depolarization mechanism.** Sometimes T-loop is small, with rounded shape, efferent and afferent limb with similar velocities.

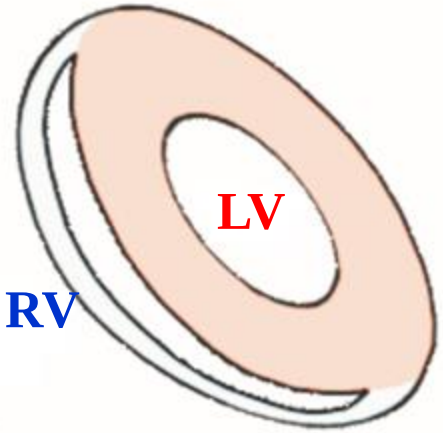
B



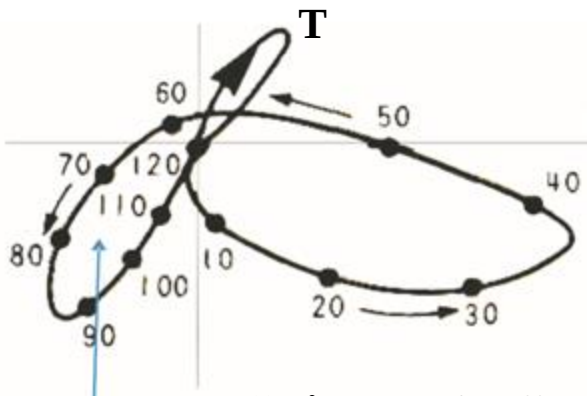
Right End Conduction Delay (**RECD**) on anterior right quadrant. T-loop has linear shape directed to back and leftward and efferent limb with slower velocity related afferent limb

Rigth Bundle Branch Block Vectorcardiograpnic types in the Horizontal Plane

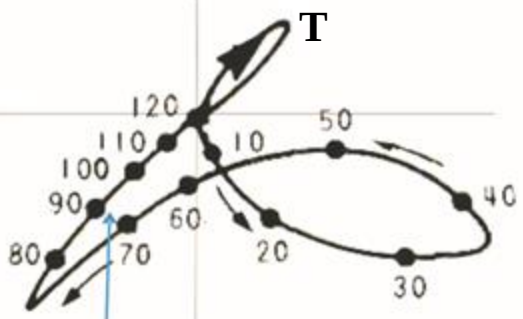




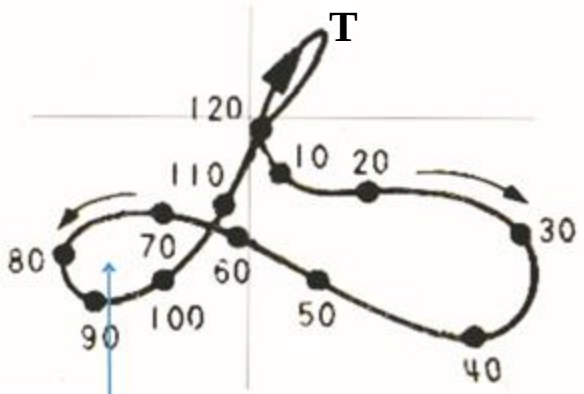
Grishman type or type I



Cabrera type or type II

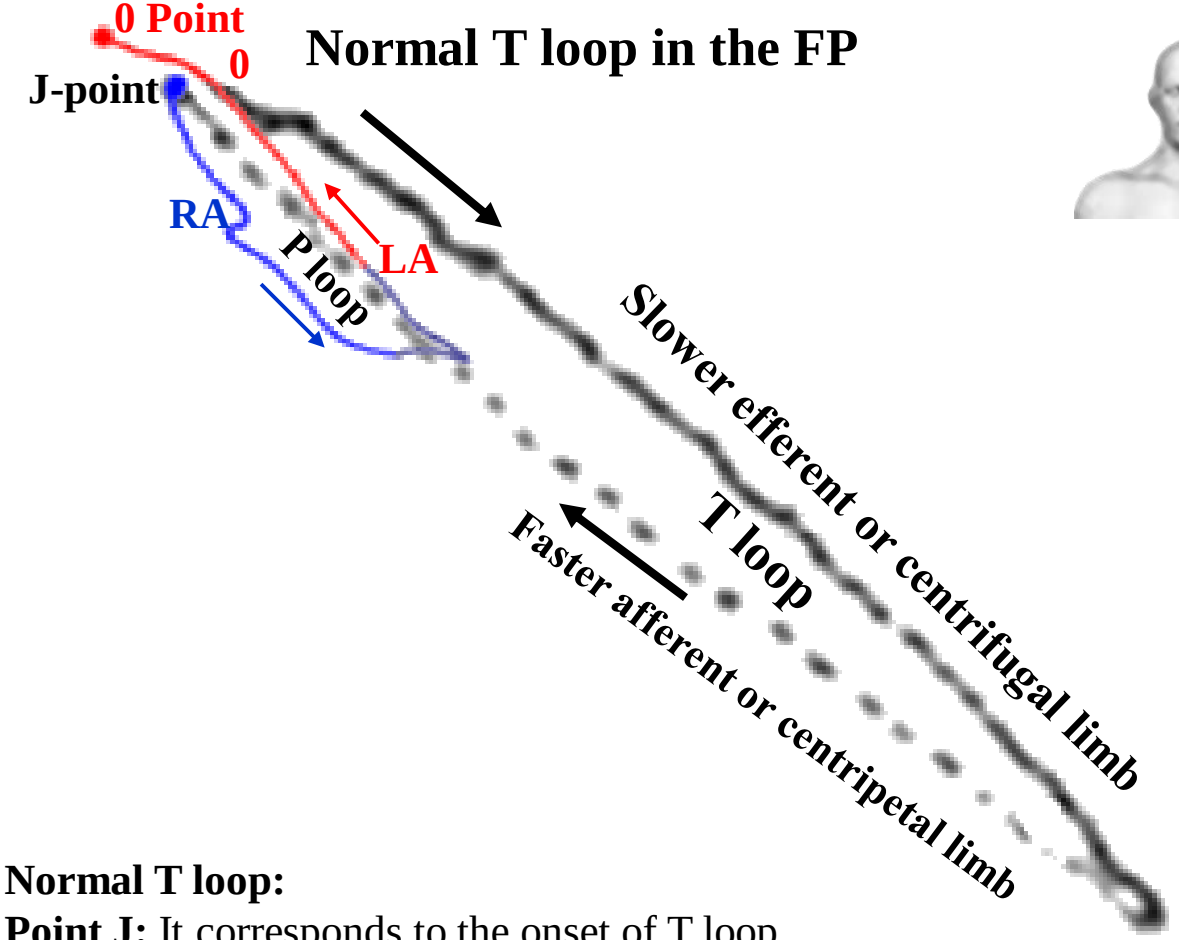


Type III or C

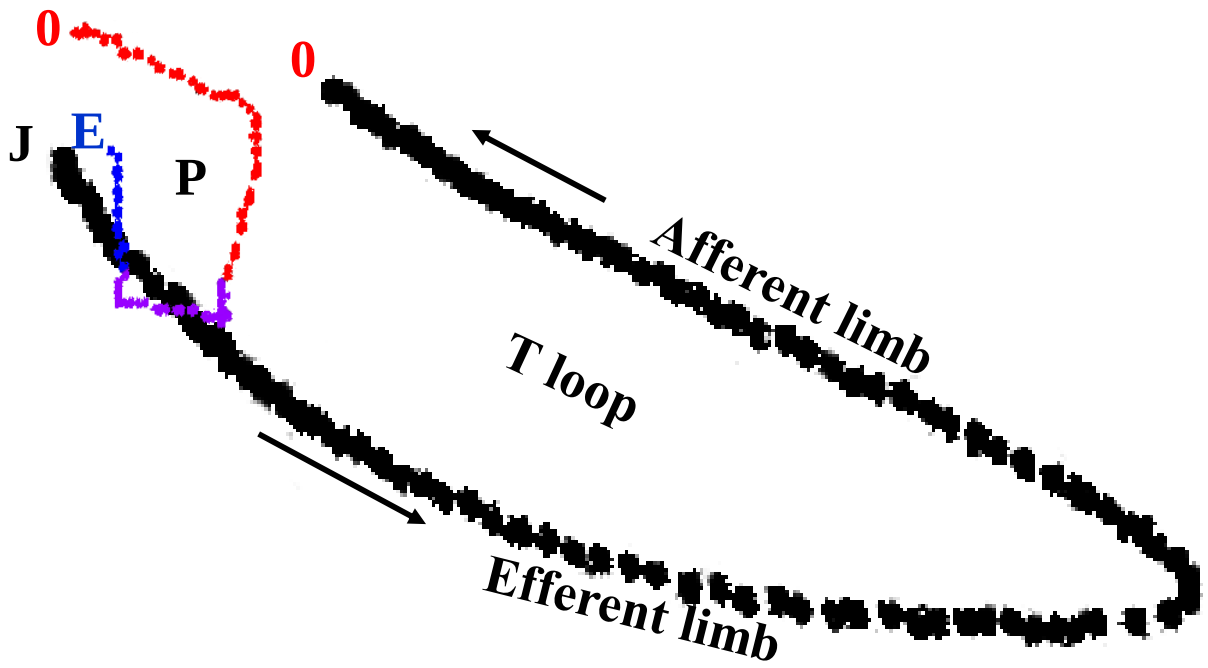


"Finger-like" terminal appendix in the right anterior quadrant

Normal T loop in the FP



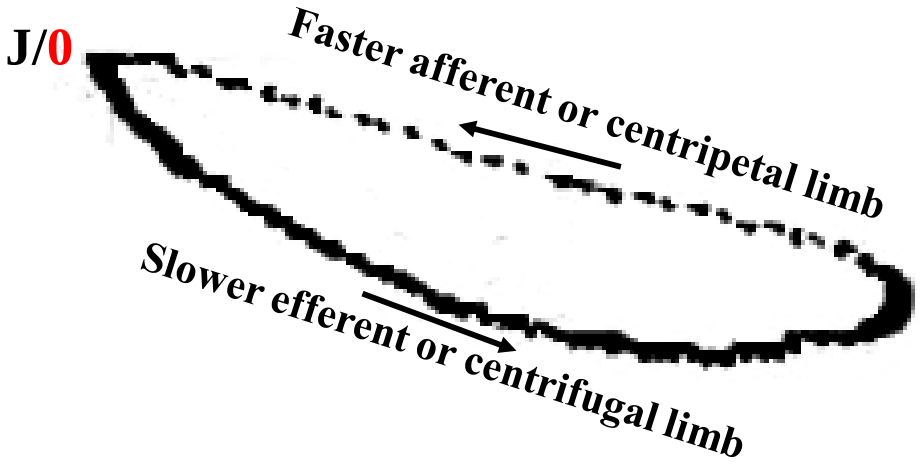
P and T loops in this case



Normal T loop:
Point J: It corresponds to the onset of T loop.
Point 0: It corresponds to the end of T loop.
Usually, the distance between both points is ≤**0.1 mV.**
Morphology: elongated, elliptic or almost linear.
Direction: to the left or below around +36° (10° to 70°).
Magnitude: 0.35 mV (0.15 to 0.63 mV).
Rotation: clockwise or counterclockwise.
QRS/T angle: ≤36°.

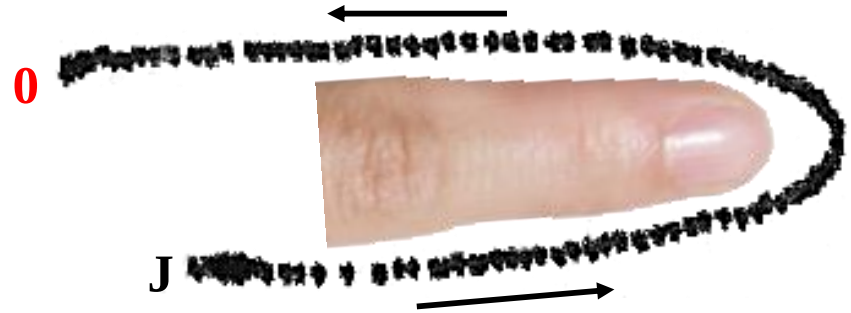
Points 0 and J are distant (>0.1 mV), indicating in ECG, J point and ST segment elevation ≥0.2 mV (2 mm).
Efferent and afferent limbs with similar conduction velocities: repolarization mechanism present.

Normal T loop in the HP



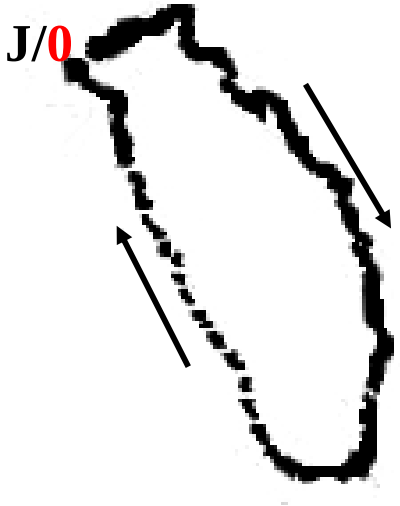
Points J and 0 together.
Shape: elongated, elliptic or linear.
Direction: to the left and front, around 23° (-14° to +45°).
Efferent limb of slower inscription than the afferent one.
Rotation: nearly always counterclockwise, except for the linear morphology.
Magnitude: mean 0.34 mV (0.15 to 0.60 mV).
QRS/T angle: it could be as wide as 93°.

T loop in type 1 Brugada pattern

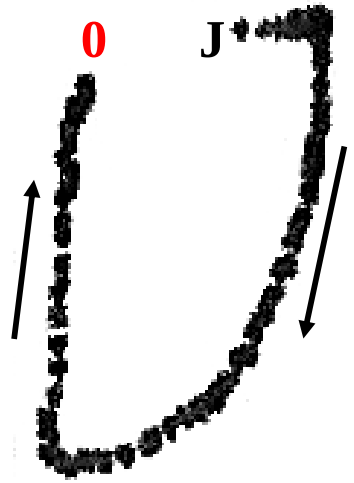


Points J and 0 are separated ≥2 mm, indicating J point and ST segment elevation. When both points are distant >1 mm it indicates ST segment elevation, which is not observed in VCG. This may be indicative of early repolarization pattern, Brugada syndrome with types 1 and 2 pattern, idiopathic ventricular fibrillation, congenital short QT syndrome, ST-segment elevation acute coronary syndrome, Prinzmetal variant angina, acute pericarditis in phase 1, left ventricular aneurysm of anterior wall.
Both the afferent and efferent limbs present slow inscription, dashes very close to one another.
Shape: elliptic or with “finger” shape.
Direction: to the left, around +5°.
Rotation: counterclockwise.
Magnitude: 0.34 mV.
QRS/T angle: 7°.

Normal T loop in the RSP



T loop in Brugada type 1 pattern in the RSP



	Normal T loop in RSP	T loop in Brugada type 1 pattern in RSP
Points J and 0	Together	Distant (point J above and opposite in relation to 0)
Velocity of efferent/afferent branch	Smaller efferent limb	Equal inscription velocity (slow)
Direction	58° (+30 to +110°)	+90° to +120°
Magnitude	0.30 mV (0.13 and 0.55)	Similar
Shape	Elliptic	Elliptic
Rotation	Clockwise	Clockwise

Antzelevitch C 2015 modified	BrS	ERS	Possible Mechanism(s)
Region Associated with highest arrhythmic risk	RVOT	Inferior myocardium	Higher levels of I_{to}
Male Predominance	Yes (>75%)	Yes (>80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	~35-40	~36-42	
Dynamicity of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
PVCs pattern	LBBB with inferior axix	LBBB with superior axix	Focus dependent QRS axis
Ameliorative response to quinidine	Yes	Yes	Inhibition of I_{to} and possible vagolytic effect
Ameliorative response to Isoproterenol and and milrinone	Yes	Yes	Increased I_{Ca} and faster heart rate
Ameliorative response to cilostazol	Yes	Yes	Increased I_{Ca}, reduced I_{to} and faster heart rate
Ameliorative response to pacing	Yes	Yes	Reduced availability of I_{to} due to slow recovery from inactivation
Radiofrequency epicardial ablation + sodium channel blocker infusion during the procedure	Yes in patients with recurrent ventricular arrhythmias refractory to medical treatment	?	Elimination of the arrhythmogenic substrate

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.

ERS is diagnosed in the presence of J-point elevation 1 mm in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT

ERS can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation 1 mm in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG

ER pattern can be diagnosed in the presence of J-point elevation 1 m in 2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.

High-Risk Features of Early Repolarization Patterns Seen on Routine Electrocardiograms (Darmoch F 2018)

1. J point distribution: Inferior or global distribution across all leads considered high risk compared to lateral distribution that is deemed low risk
2. J-wave amplitude: Amplitude ≥0.1 mV
3. ST segment shape: Horizontal or downsloping ST segment
4. **Coexisting electrical disorder: Conditions such as Brugada syndrome or congenital short QT syndrome (the present case)**
5. Dynamic J wave: High amplitude and transient augmentation of J wave patterns
6. Family history of sudden cardiac death: First-degree relative
7. History of resuscitation from cardiac arrest: Cardiac arrest resulting from documented or polymorphic VT or VF

J-wave syndromes including BrS and ERS is associated with life-threatening ventricular arrhythmias (**Calvo D, 2016)**

Similarities between BrS and ERS.

1. Male predominance
2. Occurrence of the first event predominantly at the middle age
3. Ventricular arrhythmias triggered by short-coupled PVCs during slower heart rates
4. Response toβ-agonists, quinidine and phosphodiesterase III inhibitors
5. Prominent I_{to} activity
6. Shared mutations of the genes.

Differences between BrS and ERS

1. Hyperthermia causing augmented J waves in BrS by inactivation of INa and recovery of Ito, hypothermia causing augmented J waves in early ERS by slower ICa and higher Ito activity
2. Right ventricular outflow tract involvement in BrS and inferolateral left ventricular involvement in ERS
3. Higher occurrence of late potentials and atrial fibrillation in BrS
4. Increased J wave manifestation with sodium channel blockers in BrS in contrast to decreased J waves in ERS.
5. BrS ECG pattern could be masked by therapeutic hypothermia.
6. When unipolar left ventricular epicardial electrograms used during provocation with sodium channel blockers, J waves increase whereas reduced J waves on the surface electrogram due to widening of QRS (**Nakagawa, S 2014**)

Expert consensus recommendations on early repolarization therapeutic interventions

1. Class I ICD implantation is recommended in patients with a diagnosis of ERS who have survived a cardiac arrest

2. Class IIa Isoproterenol infusion can be useful in suppression of electrical storms in patients with a diagnosis of ERS

3. Quinidine in addition to an ICD can be useful for secondary prevention of VF in patients with a diagnosis of ERS Class IIb

4. ICD implantation may be considered in symptomatic family members of ERS with a history of syncope in the presence of ST-segment elevation >1 mm 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 sudden death with or without a pathogenic mutation Class III

6. ICD implantation is not recommended in asymptomatic patients with an isolated ER ECG pattern

Brugada syndrome: Importance of genetic background

Currently, there is increasing evidence that BrS is an oligogenic disease (**Le Scouarnec S, 2015**.), with involvement of more than one genetic factor with different effect sizes (**Bezzina CR, 2013**.). The more of these genetic factors one has, the higher the likelihood of having a type 1 Brugada pattern. Currently, molecular genetic testing should be limited to SCN5A, SLMAP, SEMA3A, SCNN1A, and SCN2B(**Campuzano O, 2019)**. SCN5A and in SCN5A families (presymptomatic) and counselling should include an ECG, because phenotype positive genotype negative cases have been described within these families (**Probst V, 2009**.). There might be some role for genetic testing in risk stratification (**Yamagata K, 2017**.).

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).

BrS-1 (**Chen Q 1998**): **Locus:** 3p21-23; **OMIM:** 601144; **Gene:** SCN5A; **Protein:** NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa^+; **Channel affected:** INa^+ loss-of-function↓; **Percentage of probands:** 11-28%.

Amin et al (**Amin AS, 2011)** hypothesized based on a study of AF in a large cohort of BrS patients, that a reduced number of potentially triggering premature atrial contractions (PACs) in the presence of a more extensive substrate in SCN5A mutation carriers may account for AF being no more prevalent in patients with SCN5A mutations than in those without. Given the polemic and complex issues underlying the pathophysiology of BrS, one should regard this hypothesis as one potential mechanism of many that influence the prevalence of AF in BrS.

Mutations in SCN5A lead to a broad spectrum of phenotypes, however the SCN5A gene is not commonly involved in the pathogenesis of BrS and associated disorders. Studies have revealed significant overlap between aberrant rhythm phenotypes, and single mutations have been identified that evoke multiple rhythm disorders with common gating lesions

Phenotypes with SCN5A mutations

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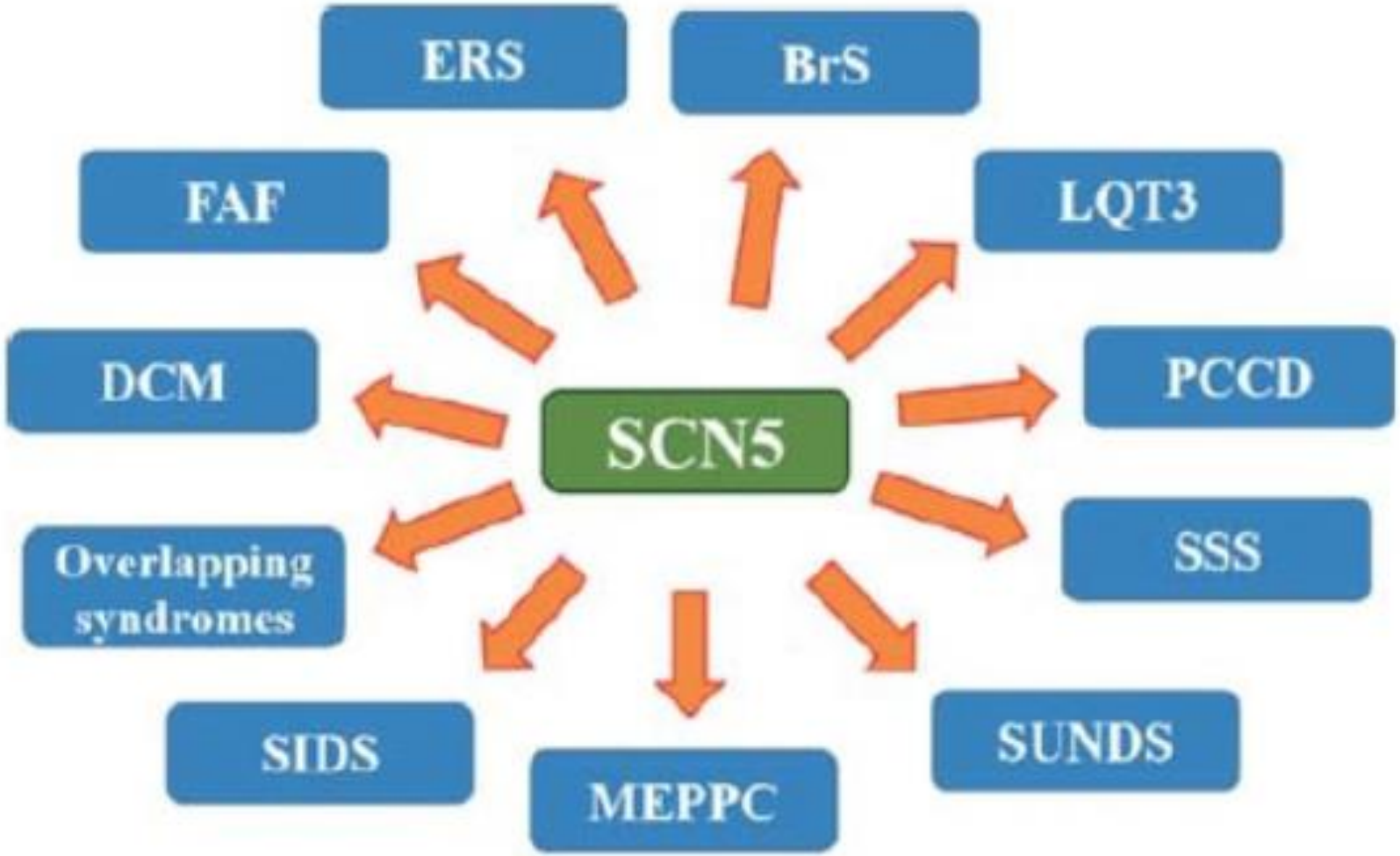

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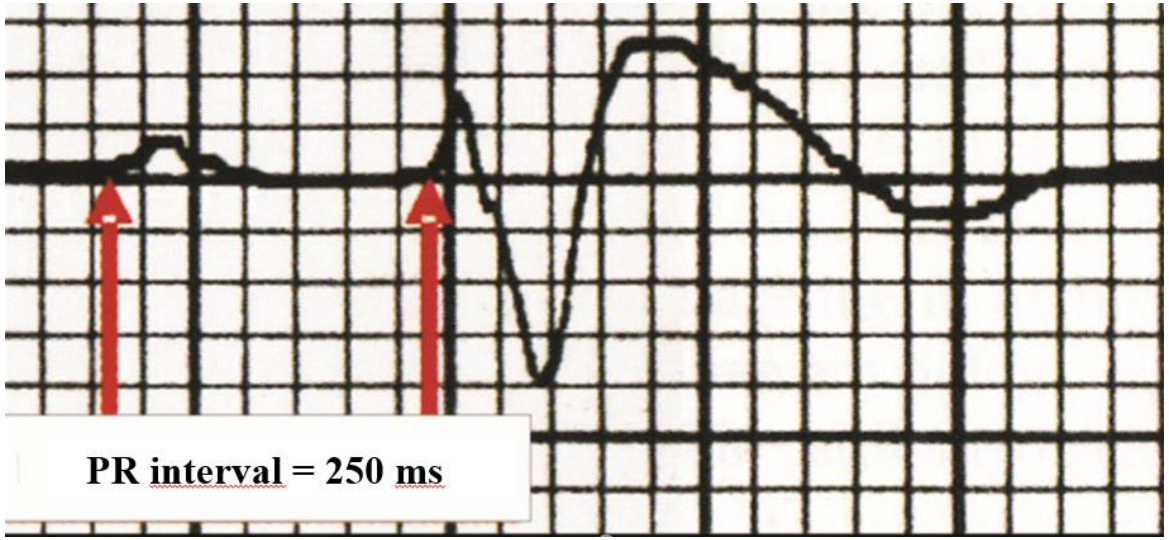
ERS: Early repolarization syndrome; BrS: Brugada syndrome; **LQT3:** Congenital long QT syndrome variant 3; **PCCD:** Progressive Cardiac Conduction Disease; or Lenègre disease; **SSS:** Sick Sinus Syndrome; **SUNDS:** Sudden Unexpected Nocturnal Death Syndrome; **MEPPC:** Multifocal Ectopic Purkinje-related premature Contractions; **SIDS:** Sudden Infant Death Syndrome; Overlapping syndromes **(Bezzina C 1999)**; **DMC:** Dilated Cardiomyopathy; **FAF:** Familial Atrial Fibrillation. (**Pérez-Riera AR, 2016).**

Nav1.5 consists of peak and late components (INa-P and INa-L). Mutant Nav1.5 causes alterations in the peak and late Na+ current and is associated with an increasingly wide range of genetic arrhythmias. More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopaties can be classified according to the alteration of INa-P and INa-L as gain-of-function (↑), loss-of-function and both (↓), few researchers have summarized the mechanisms in this way (**Han D, 2018**). Gain-of-function mutations in SCN5A lead to more Na^+ influx into cardiomyocytes through aberrant channel gating causing LQT3. Slowed or incomplete inactivation of the NaV1.5 channel results in an additional inward current, known as the late or persistent sodium current (Ipst), during the plateau phase of the ventricular action potential with ST segment prolongation and late T occurrence. Among the mutations in SCN5A associated with LQT3 is1795insD, which is characterized by the insertion of 3 nucleotides (TGA) at position 5537 C-terminal domain of the NaV1.5 protein **(Bezzina C., 1999)**. Carriers of this mutation may not only present with LQT3, but also with ECG features of sinus bradycardia, progressive cardiac conduction disease, and Brugada syndrome, thus creating the first described arrhythmic 'overlap syndrome' (**Remme CA., 2008)**. Interestingly, 1795insD is supposed to be a gain-of-function (↑) mutation in light of the QT prolongation, but a loss-of-function (↓) mutation in light of the sinus bradycardia, progressive cardiac conduction disease, and BrS. Additionally , and **MEPPC** ; loss-of-function (↓) mutations in SCN5A result in amplitude reduction in peak Na^+ current, further leading to channel protein dysfunction or cardiac conduction defect an entity with minor structural heart disease. In addition, both ↓) - and (↑) mutations may cause DCM and/or FAF. (**Wilde AAM 2018**).

On ECG PR interval prolongation is the only parameter that predicted the presence of a SCN5A mutation in BrS, additionally, late potentials on high resolution ECG LP were more frequently observed in SCN5A mutation carriers (**Robyns T, 2018**). SCN5A mutation is associated with an increased risk of drug-induced ventricular arrhythmia in patients without baseline type-1 ECG. In particular, Snon-missense and Smissense-TP are at high risk.(**Amin AS, 2018**).



Tracing of a symptomatic patient with BrS after intravenous ajmaline injection. First-degree atrioventricular block (PR interval = 216 ms) and Brugada type-1 ECG pattern in V_1 lead (positive test). In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes figures of 100 ms (**Yokokawa 2007**). This prolongation of the PR interval 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**).

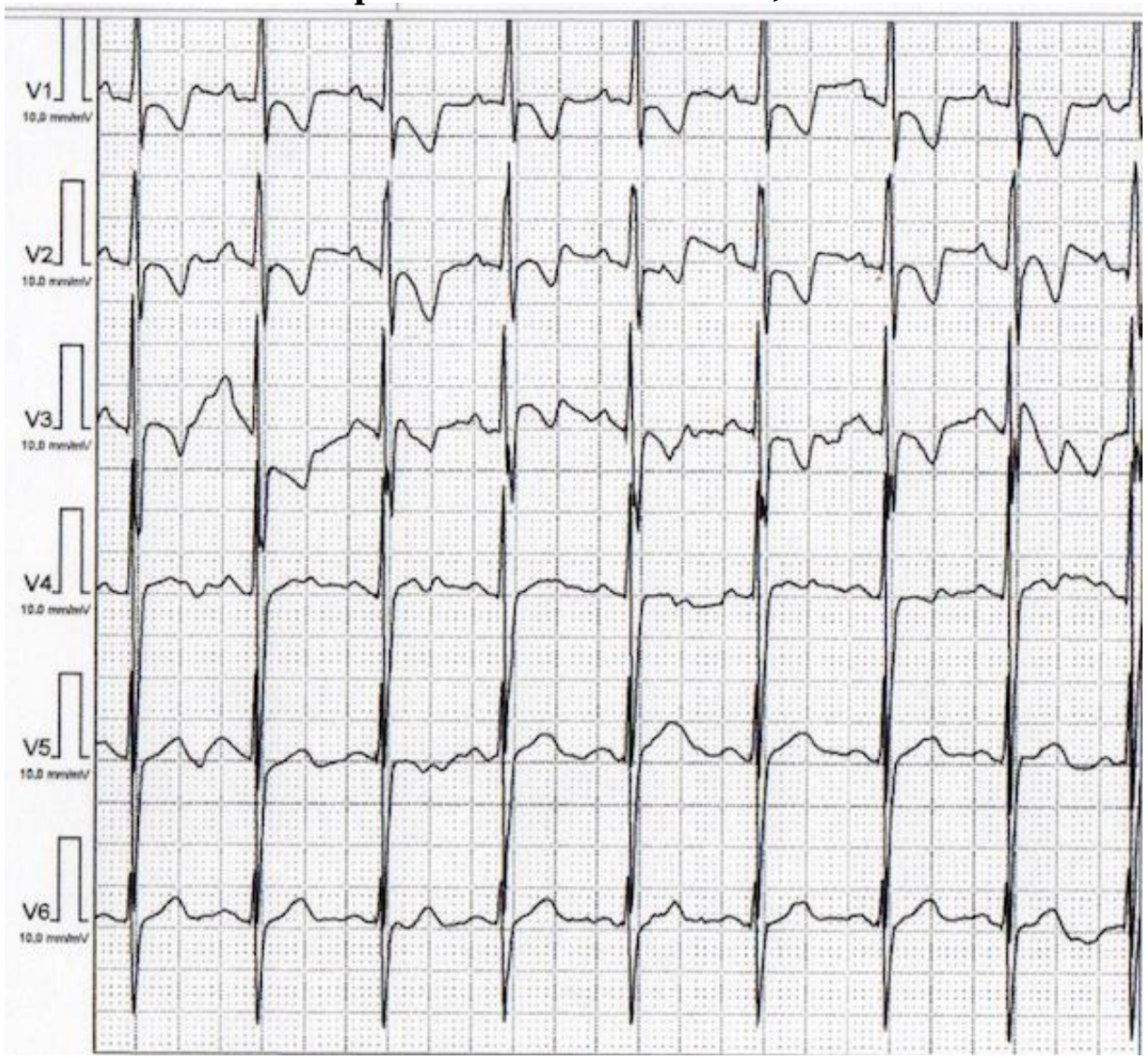
XII. BrS12 (**Ishikawa T 2012**)
Locus: 3p21.2-2-p14.3; **OMIM:** 602701; **Gene:** SLMAP; **Ion channel and effect**: INa+ loss-of-function; **Protein:** Sarcolemma membrane-associated protein, a component of T-tubes and the sarcoplasmic reticulum – influences trafficking of Nav1.5.T-tubules and sarcoplasmic reticulum are essential in excitation of cardiomyocytes, and sarcolemmal membrane-associated protein (SLMAP) is a protein of unknown function localizing at T-tubules and sarcoplasmic reticulum. The mutations in SLMAP may cause BrS via modulating the intracellular trafficking of hNav1.5 channel. **% of probands:** Rare.

XIX BrS-19 (**Boczek NJ, 2014**.)
Locus: 7p12.1; **OMIM:** 603961; **Gene:** SEMA3A, Semaphoring; Ion channel and effect: Ito gain-of-function; **Protein:** NaV1.5- α subunit of the cardiac sodium channel carrying the sodium current INa; **% of Probands**: Rare. Boczek et al were the first to demonstrate SEMA3A as a naturally occurring protein that selectively inhibits Kv4.3 and SEMA3A as a possible BrS susceptibility gene through a Kv4.3 Ito gain-of-function mechanism

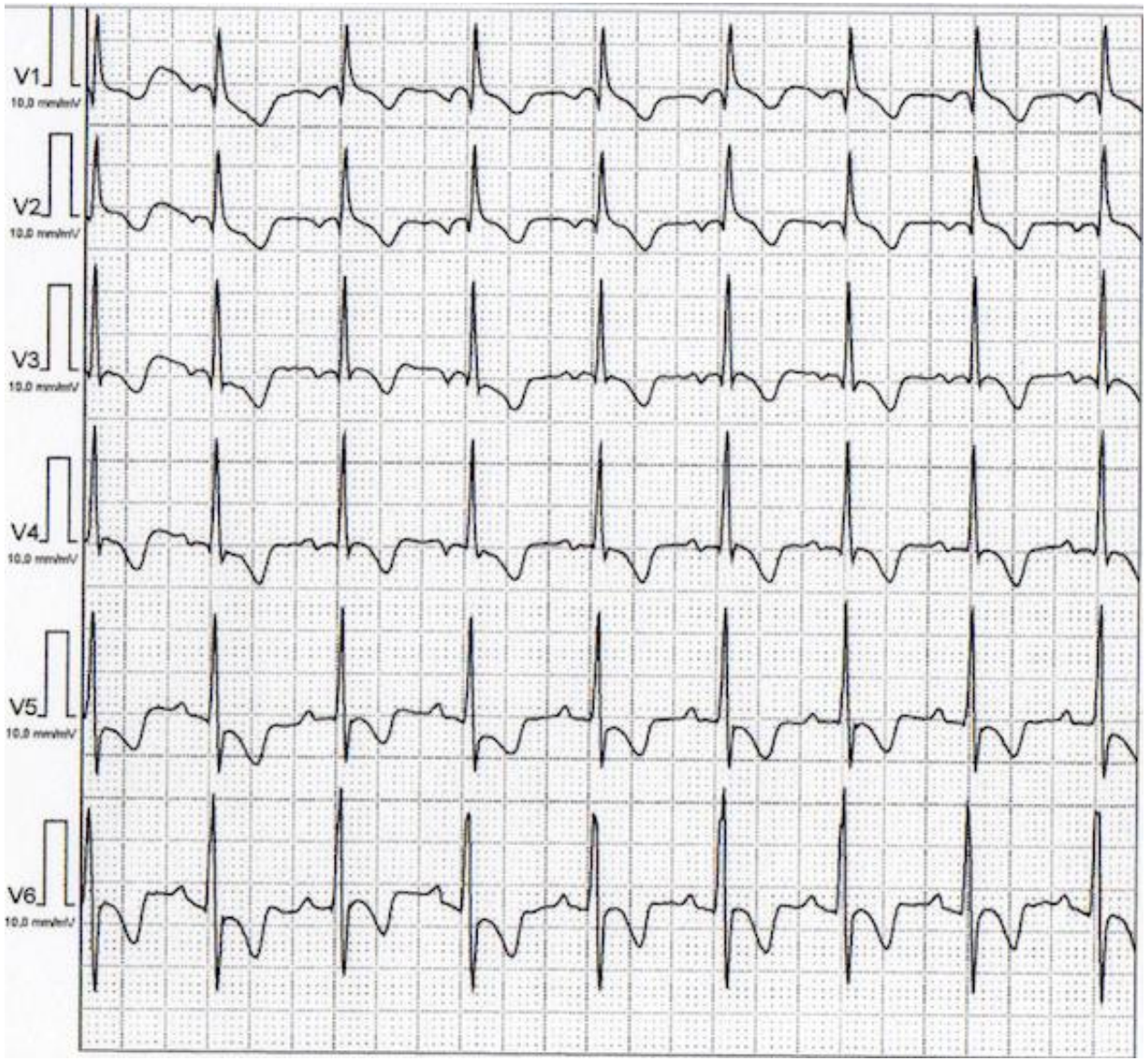
XIV BrS14 (**Riuro H,2013**):
Locus: 11q23**; OMIM:** 601327; **Gene:** SCN2B, Navβ2; Ion channel and effect: INa+ loss-of-function; **Protein:** Navβ2-β -2subunit of the cardiac sodium channel carrying the sodium current INa; **% of Probands:** Rare. Riuró et al. identified a novel missense mutation in the sodium β2 subunit encoded by SCN2B, in a woman diagnosed with BrS. They studied the sodium current from cells coexpressing Nav 1.5 and wild-type (β2WT) or mutant (β2D211G) β2 subunits. Electrophysiological analysis showed a reduction in INa density when Nav 1.5 was coexpressed with β2D211G. Single channel analysis showed that the mutation did not affect the Nav 1.5 unitary channel conductance. Instead, protein membrane detection experiments suggested that β2D211G decreases Nav 1.5 cell surface expression. The effect of the mutant β2 subunit on the INa strongly suggests that SCN2B is a candidate gene associated with BrS.

SCNN1A Sodium Channel Epithelial 1 Alpha Subunit (**Juang JM,2014**): These authors study identified four novel BrS-associated genes and indicated the effectiveness of this disease-targeted sequencing across ion channel genes for non-familial BrS patients without SCN5A variants. It is is a Protein Coding gene. Diseases associated with SCNN1A include Bronchiectasis with or without elevated Sweat Chloride 2 and Pseudohypoaldosteronism, Type I, Autosomal Recessive. Among its related pathways are Ion channel transport and Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds. Gene Ontology (GO) annotations related to this gene include actin binding and sodium channel activity.

ECG-5 performed on March 14th, 2019

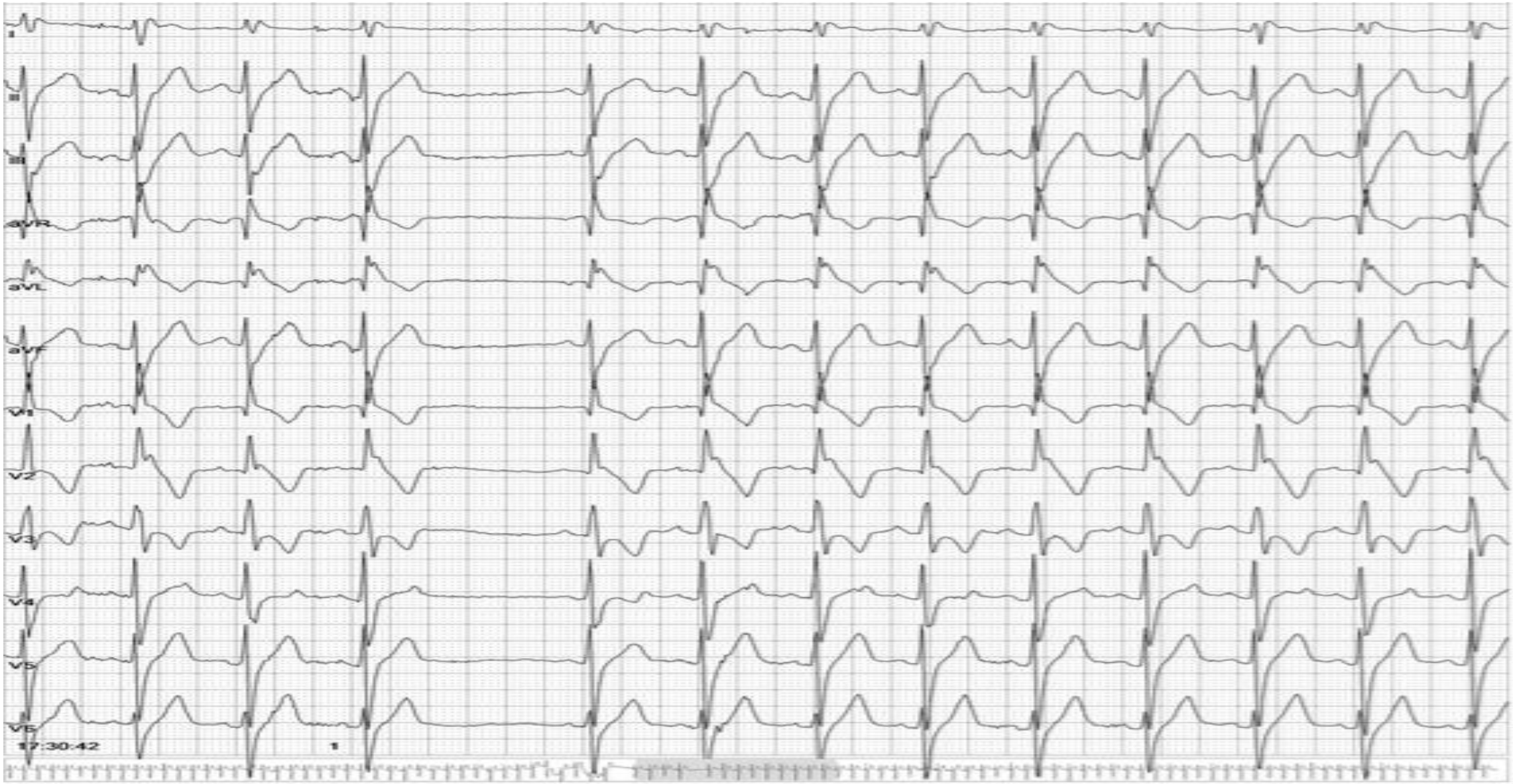


ECG-6 only precordial leads performed on the same day



Dynamic repolarization pattern in precordial leads on the same day: ST segment depression followed by T-wave inversion across precordial leas

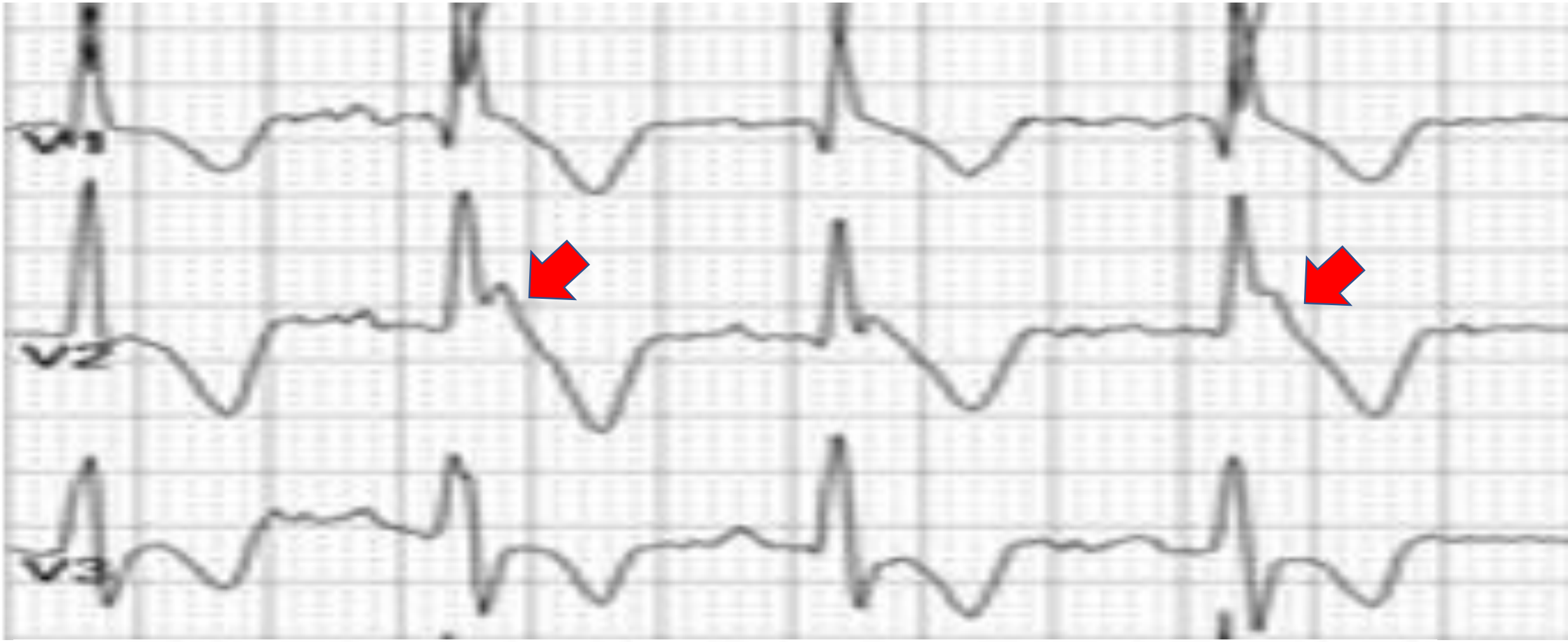
Holter Monitoring 24hs with feverish patient on March 14th, 2019

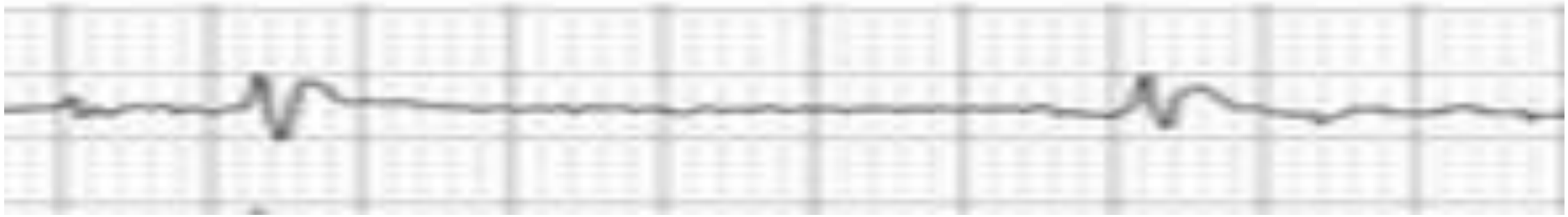


Early repolarization pattern in inferolateral leads + type 1 Brugada Pattern on right precordial leads + Prolonged PR interval + sinus arrest or sinus pause. It is defined as lasting ≥ 2.0” suggesting sinus node dysfunction.

The diagnosis of BrS is very unusual in children's, with a low penetrance rate (,20%) even in known SCN5A mutation carriers.(**Gonzalez-Corcia MC 2016**) Despite its rarity, symptomatic BrS during a young age is a malignant condition related to a very high risk of arrhythmic events and SCD .(**Gonzalez Corcia MC 2017**) Any episode of VT occurring in a pediatric patient should be highly suspicious for BrS and the syndrome systematically considered in the differential diagnosis. MVT triggered by fever in infants with SCN5A mutations has already been reported in the literature(**Rodríguez-Mañero M 2016**); however, the current literature has not provided sufficient information to determine an association between MVT and the SCN5A mutation because of the rarity and inconsistency of the available data. The incidence of MVT described in a large cohort of patients with BrS implanted with an ICD was 4.2%. The efficacy of ICDs in preventing SCD is well established for patients with symptomatic BrS.(**Conte G 2105**) However ICD related complications, such as endocardial lead fractures or dislodgments and device infections, occur more frequently in children than in the adults. Implant epicardial ICD leads using a minimally invasive approach is feasible and may be safer than an transvenous approach.(**Irfan G 2017**) The lead insertion technique and the final lead positions need to accommodate the child's growth in order to keep the device functional as long as possible. Implantation of epicardial leads, which avoids the tricky passage below the clavicle through the subclavian vein, seems to be better for children and young men because a wider range of movements and physical activities are allowed, and the risk of fractures and dislodgments may be reduced. Consensus that the epicardial RVOT is the arrhythmogenic substrate for BrS was reported (**Nademanee K 2010**). The anterior wall of the RVOT epicardium in symptomatic BrS patients was found to be characterized by low-voltage, prolonged, and fractionated potentials(**Zhang P, 2016**). Nademanee et al(**Nademanee K 2017**) reported the importance of sodium channel blocker infusion during the procedure in order to identify the entire epicardial area involved and ablate it completely. Radiofrequency epicardial ablation of these clustered potentials could normalize the type 1 Brugada ECG pattern and make VT/VF noninducible. RVOT substrate Today, this procedure is indicated as a last possible therapeutic treatment to manage symptomatic BrS

Intermitent or transient type 1 Brugada ECG pattern on right precordial leads: Brugada syndrome





patients with recurrent ventricular arrhythmias refractory to medical treatment. It seems to be a safe and feasible procedure, effective during short-term follow-up in restoring electrical stability and improving quality of life. However, the therapeutic impact of epicardial RVOT substrate ablation during the entire natural course of BrS is not known yet because long-term data are not available, and even less is known about the syndrome in the pediatric population. Combined approach of epicardial RVOT ablation and ICD implantation with epicardial leads in a 3-year-old child and the persistence of good clinical outcome 1 year after the procedure. However, data regarding the overall effect during the patient's lifetime are not available, and in particular nothing is known about the possible different longterm results between children and adults.

Summary: What is the probable diagnosis (s)? Overlapping BrS + ERS Why? Transient Spontaneous type 1 Brugada pattern+ J-waves inferolateral leads + significative conduction disturbance+ dynamic repolarization changes. Genetic testing in probands and relatives may result in many more children being diagnosed with BrSWhat would be the most appropriate diagnostic / therapeutic approach?

Immediately oral quinidine + ICD + epicardial RFCA with ajmaline infusion Children less than 12 years of age may require a higher dosage of quinidine on a per kilogram of body weight basis. Proper selection of quinidine dosage, careful adjustment of dosage according to age, and regular monitoring of drug response and serum drug concentration are essential steps to a rational management of quinidine therapy in children. Doses of quinidine is from 7.7 to 45.6 mg/kg/day and from 179 to 921 mg/m2/day. Children require larger quinidine doses on a body weight basis and respond to a wide range of plasma quinidine concentration. Asymptomatic offspring of proband be screened by resting ECG, with high positioning of the anterior leads on the chest. If such screening is negative, whether or not genetic information is available, obtaining an ECG during a febrile illness is recommended, as this may unmask the Brugada ECG phenotype. Intensity of follow-up can be tailored based on the presence or absence of a Brugada pattern. While awaiting the ECG during a febrile illness, avoidance of medications contraindicated in BrS is prudent. https://www.brugadadrugs.org

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