Asymptomatic Caucasian male with spontaneous Type 1 Brugada electrocardiographic Pattern. Anything else?

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Case report

Reason for the consultation: preoperative evaluation for nasal septum deviation surgery.

A 38-year-old Caucasian asymptomatic male. Recent complete check-up was absolutely normal.

He has a family history of sudden death in young first degree relative. His brother had sudden death at 23 years at rest.

Physical examination: unremarkable.

Electrocardiogram: see slides 3-5.

ECG/VCG correlation: see slide 6.

Transthoracic Echocardiogram: normal.

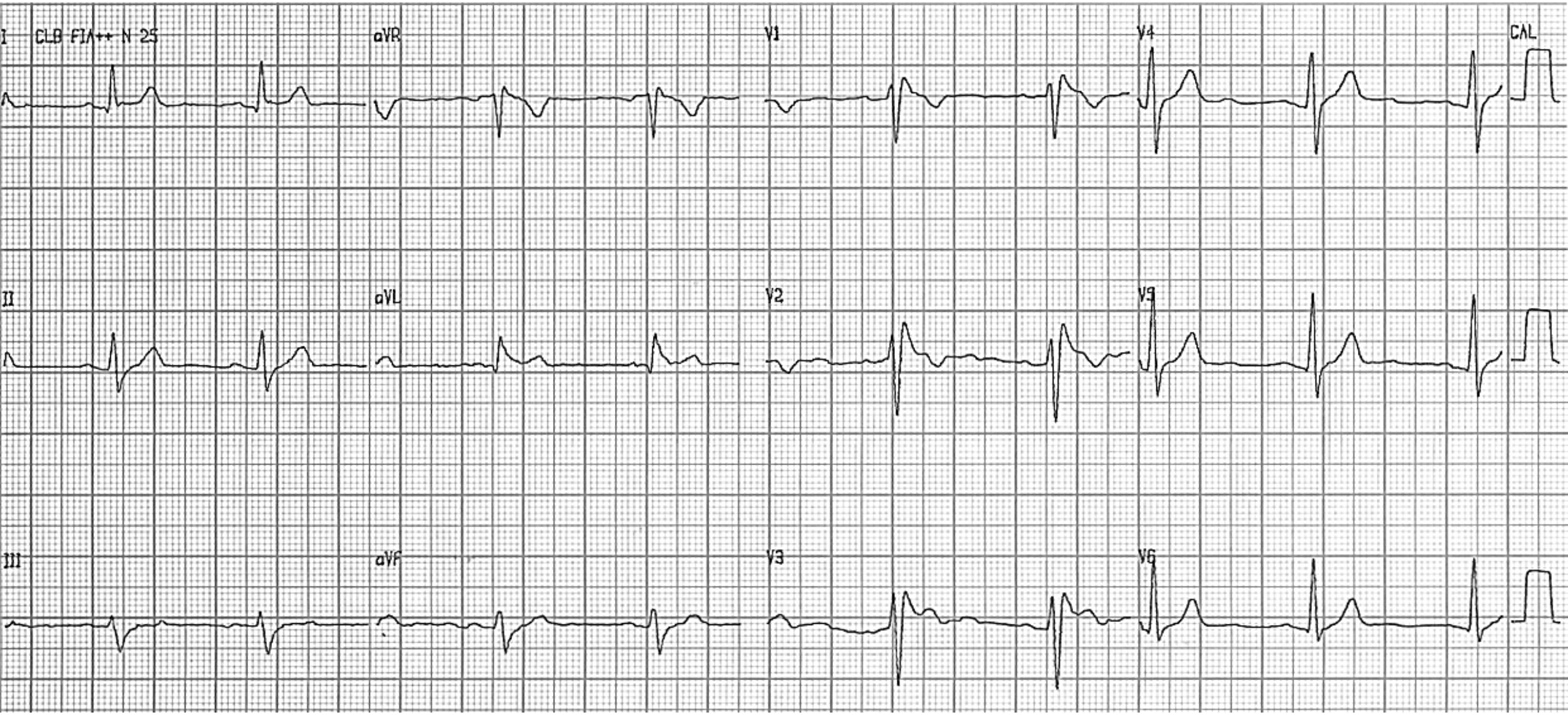
Laboratory investigations: unremarkable.

Questions:

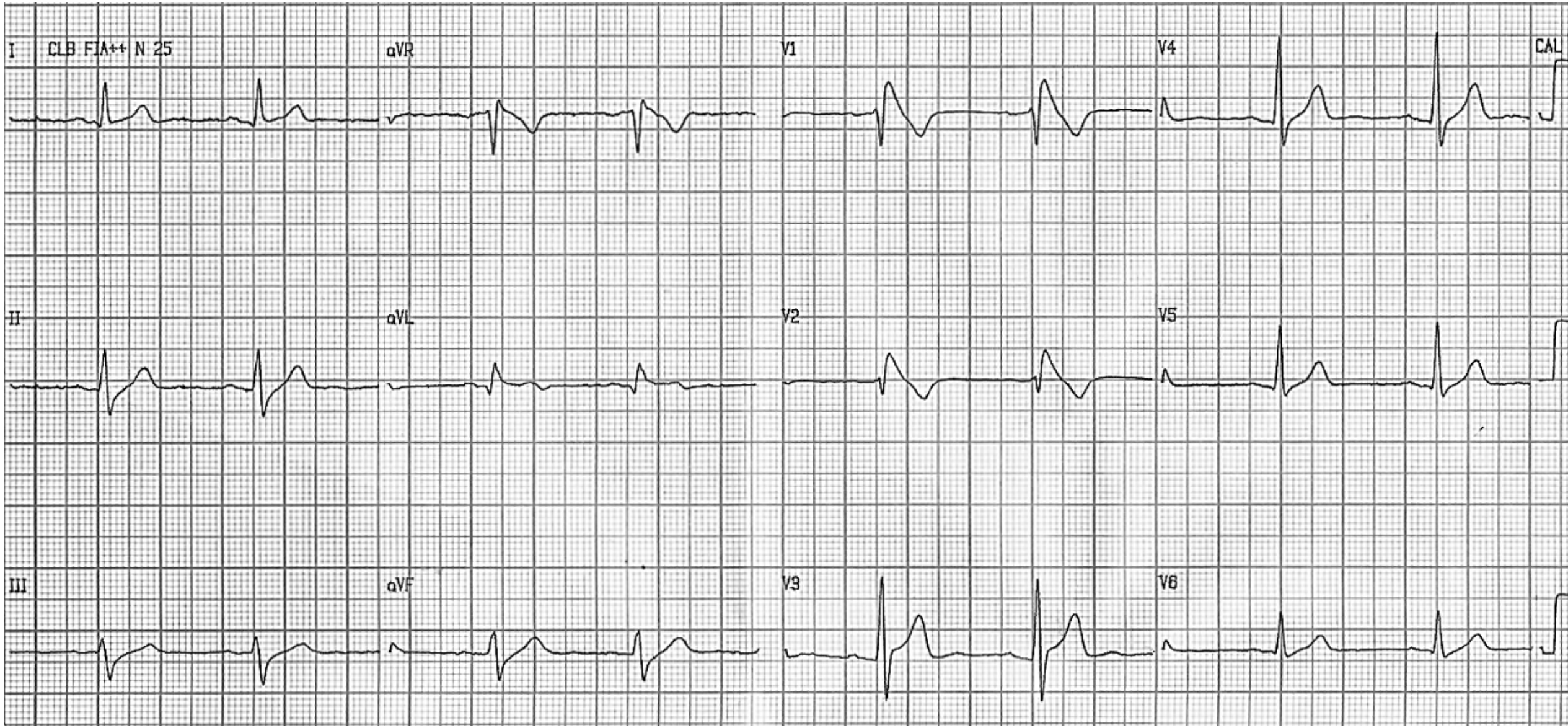
1) What is the electro-vectorcardiographic diagnosis?

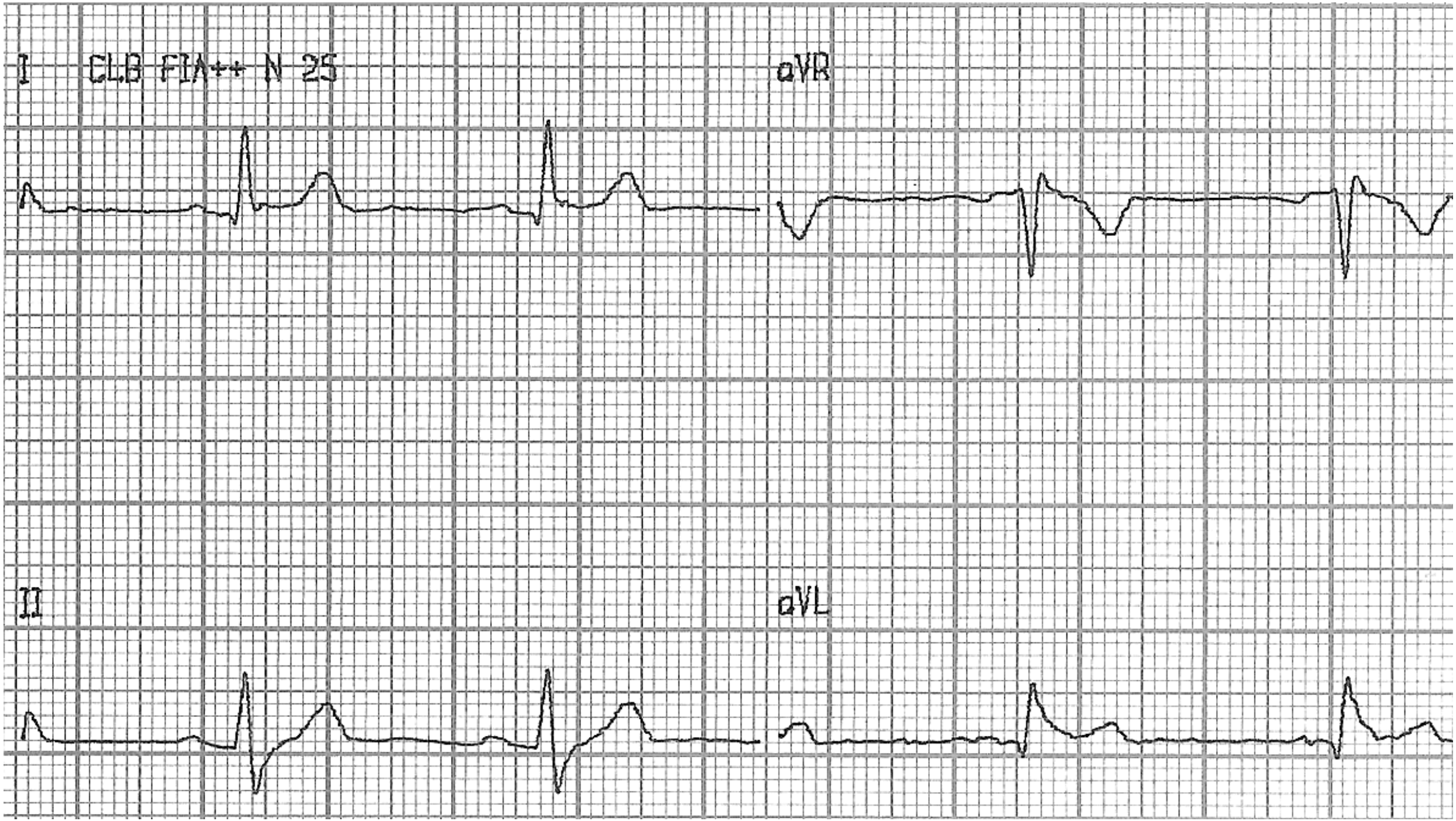
2) What is the appropriate therapeutic approach? And why?

Eletrocardiograma realizado com derivações precordiais convencionais / ECG preformed with conventical right precordial leads

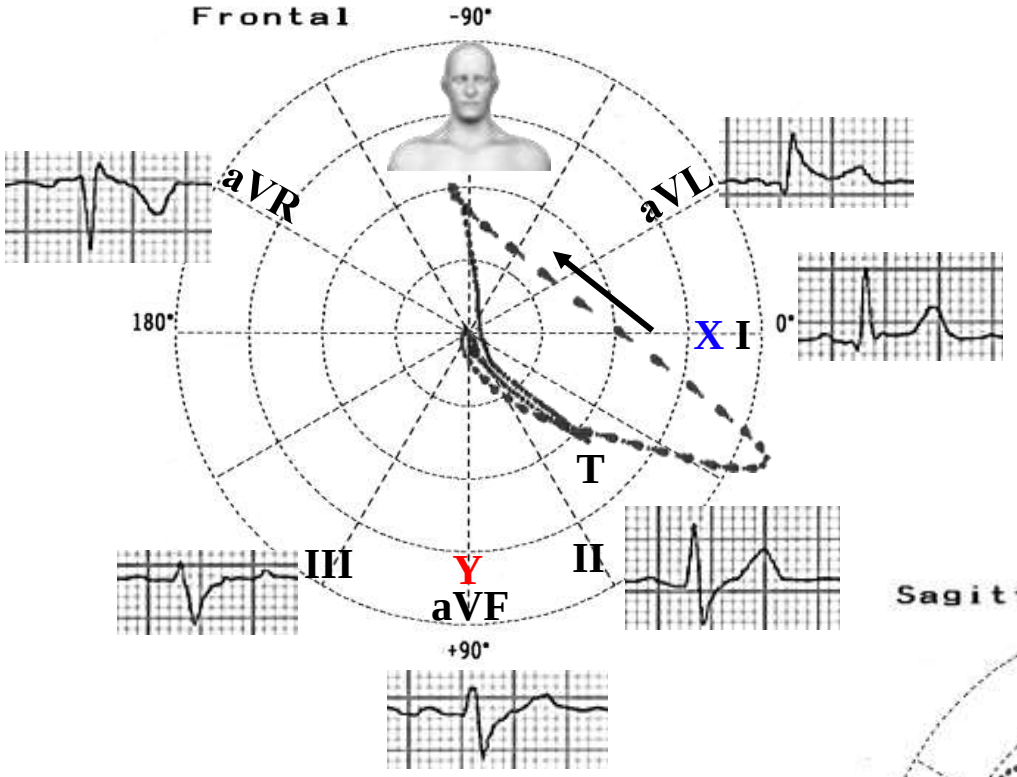


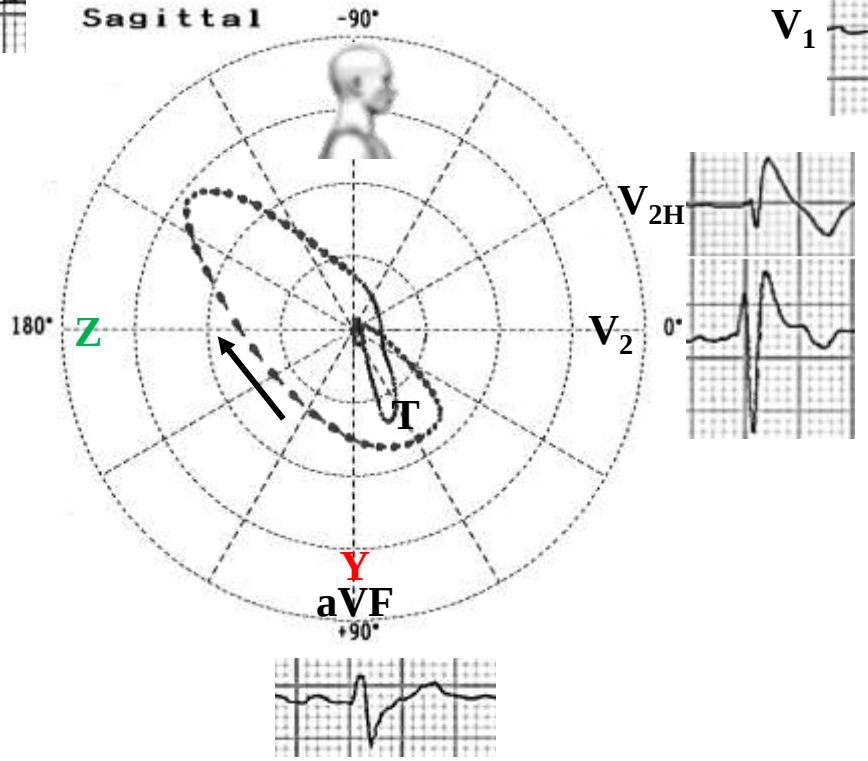
Eletrocardiograma realizado com derivações precordiais diretas altas / ECG preformed with high right precordial leads

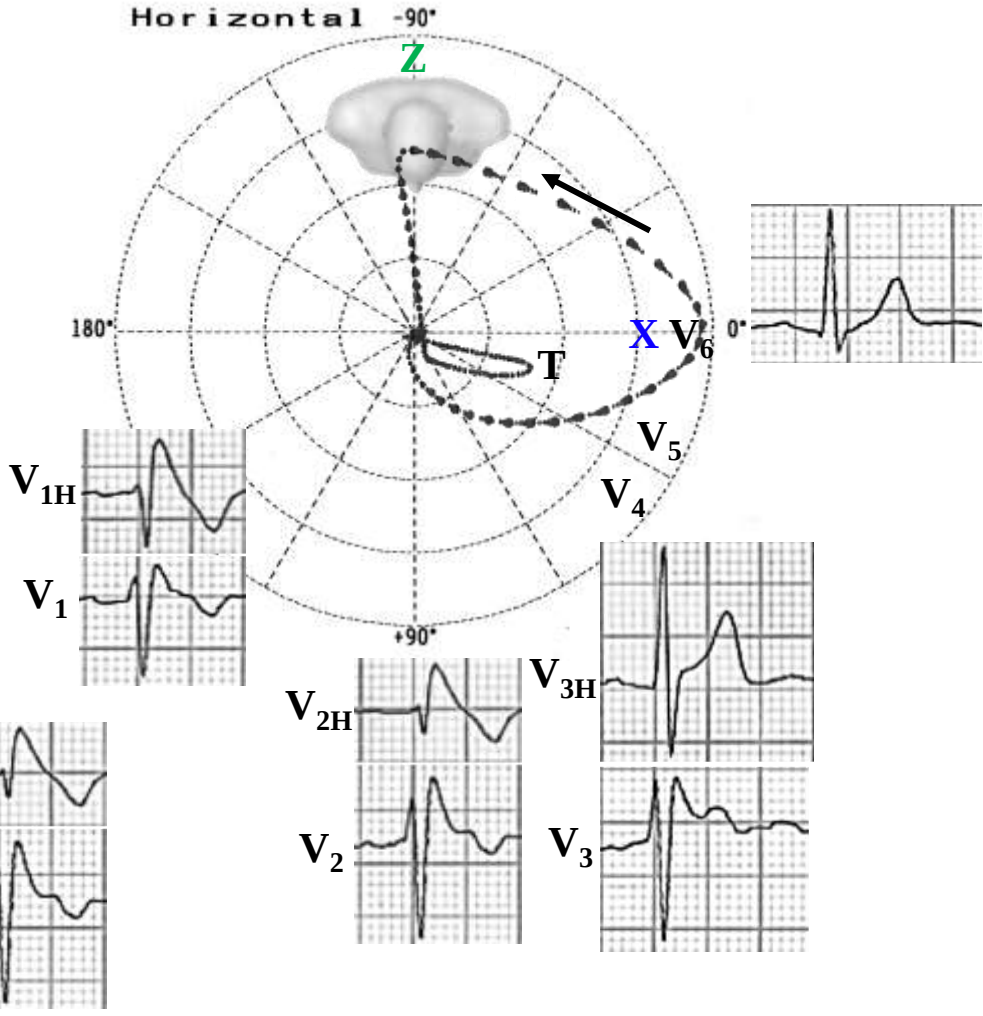



I CLB FIA++ N 25
aVR
II
aVL

ECG/VCG correlation in the three planes







Colleagues opinions

Spanish

Hola Potro tiene además criterios para bloqueo del fascículo anterior izquierdo y una duración del QRS de 120 mseg con retraso de fuerzas finales del QRS lo que puede interpretarse como BRD. Lo que me llama más la atención es el trastorno de repolarización en DI y aVL con el punto J elevado. Pueden ser una combinación de ambas canalopatías (BrS+ ERS). Patrón de Brugada espontáneo y repolarizacion precoz maligna.
Es difícil estratificar el riesgo encontrándose asintomático. Muchos indicarían un EEF e inducción de arritmias. El examen genético contribuirá para el screening de familiares pero no dará pronóstico.
Lo más probable es que se indique CDI profiláctico. Con o sin EEF.
Un abrazo y VCC no la sé descifrar.
Martín Ibarrola, MD Provincia de Buenos Aires Argentina

English

Hy Andrés: He has also left anterior fascicular block criteria and a QRS duration of 120 msec with terminal conduction delay of the QRS forces, which can be interpreted as RBBB.
What strikes me most is the repolarization disorder in I and aVL with the J point elevation. It can be a combination of both channelopathies (BrS + ERS). Spontaneous type 1 ECG Brugada pattern and malignant early repolarization pattern.
It is difficult to stratify the risk being asymptomatic. Many would indicate an EPS and induction of arrhythmias.
The genetic test will contribute to the screening of relatives but will not give a prognosis.
Most likely, prophylactic CDI is indicated. With or without EEF.
The VCC I can not decipher.
A hug
Martín Ibarrola MD Provincia de Buenos Aires Argentina

Answer to Martin:

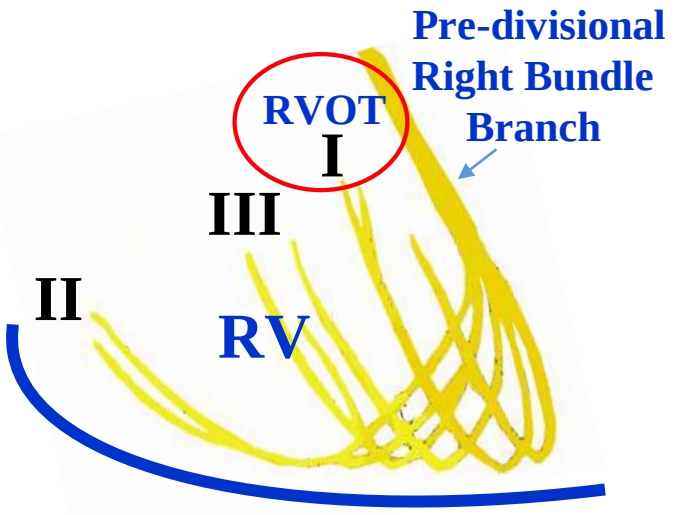
Dear Martin, your analysis seemed very interesting to me, although we could disagree on some points. I would like to say to everyone that the first thing to keep in mind is the difference between the terms Early Repolarization Syndrome (ERS) and Early Repolarization Pattern (ERP):

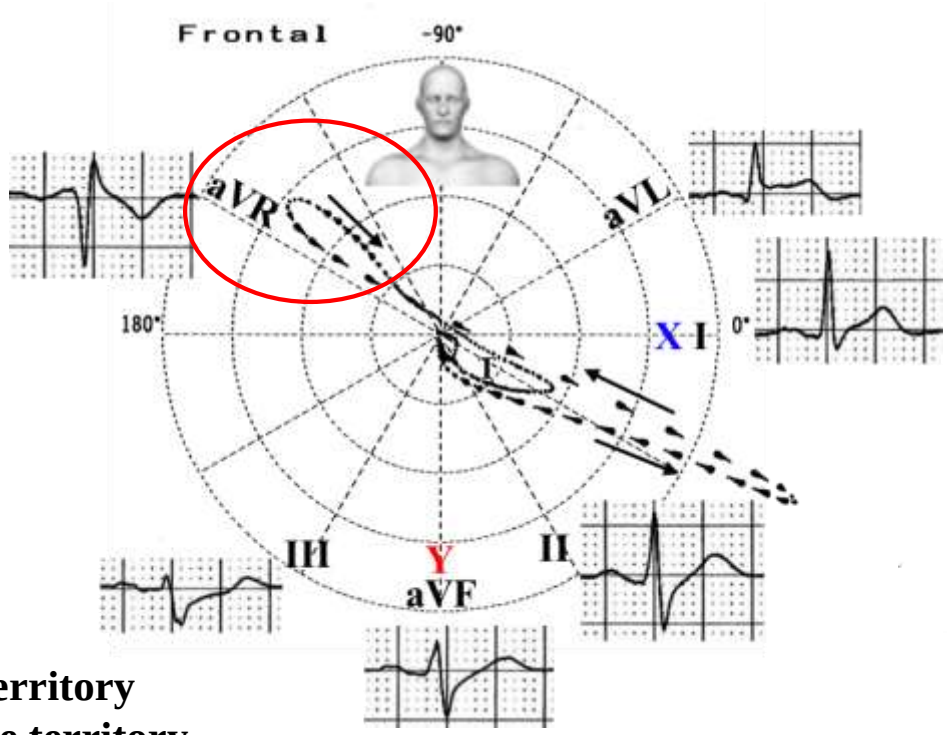
The presence of early repolarization syndrome (ERS) is characterized by the J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads recorded on a standard 12-lead ECG that occurs in a patient resuscitated from cardiac arrest by unexplained polymorphic VT/VF. As our patient is asymptomatic he does not fit into the definition of ERS. ERS can also be diagnosed in a victim of sudden cardiac death (SCD) with a negative non-molecular autopsy and a review of the medical history with a previous ECG showing a J-point elevation of ≥1 mm in ≥2 contiguous inferior and/or lateral leads on a standard 12-lead ECG. ERP is defined in the presence of a notch in the final part of the QRS, that is, in the descending slope of an R wave with a point J ≥0.1 mV in ≥2 contiguous leads of the 12-lead ECG, excluding V1 to V3, or the presence of an abrupt change in the final descending ramp of the R ("slurring") that is completely above the baseline, on the descending slope of a prominent R wave; 2) J peak (notching peak) is ≥0.1 mV in ≥2 contiguous 12-lead ECG leads, excluding right precordial leads V1 to V3; and 3) QRS duration <120 ms (**Sugrue A, et al., 2018, Macfarlane PW, et al. 2015, Patton KK, et al. 2016**). Consequently, if you measured 120 ms of QRS duration it would be out of the definition. However, a QRS duration of 120 ms could be just in the right precordial leads and not in the rest of the leads, V4, V5 and V6. Do not forget that the parietal block is characterized by a QRS duration in V1 + V2 + V3 may be longer than the sum of the QRS duration of V4 + V5 + V6. The same thing that happens in RV dysplasia ($^{V1 + V2 + V3}$ / $_{V4 + V5 + V6}$≥1.2). In classic ARVD, the evidence of right parietal block is manifested by QRS duration in right precordial leads ≥ 10 ms and greater QRS duration in the right precordial than in the left precordial (**Marcus FI, 2000**). The QRSD ratio of $^{V1 + V2 + V3}$ / $_{V4 + V5 + V6}$ ≥1.2 is observed in approximately 65% of cases in ARVD (**Nasir K et al . 2004**). QRSD> from V1 to V3 has 91% sensitivity, 90% specificity for ARVC / D (**Nasir K et al. 2003**).

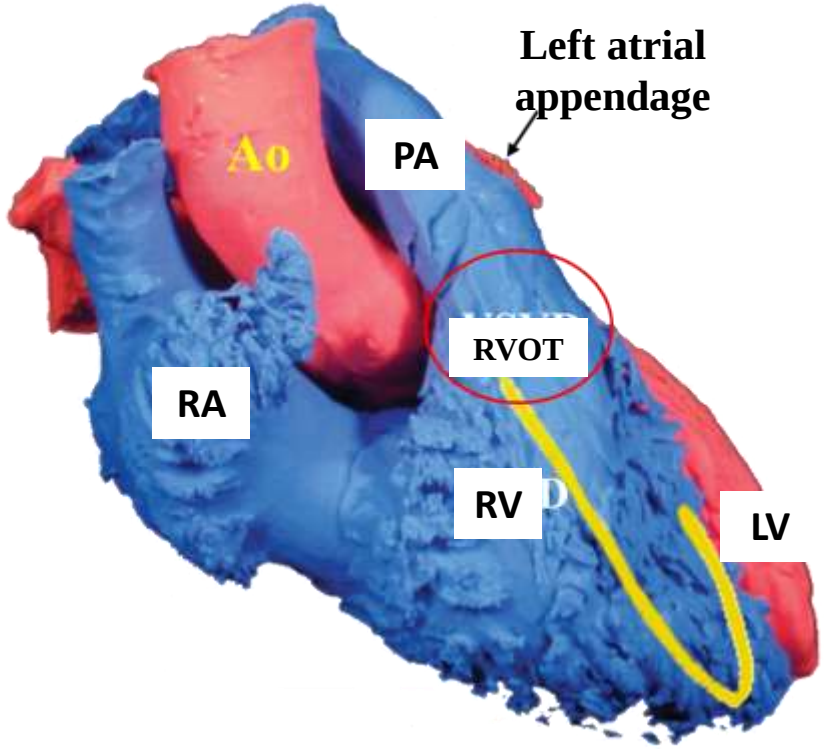
In BrS this is explained because in the territory of the RV outflow tract there is less expression of connexin 43 which causes the final conduction delay in RVOT without necessarily being due to a genuine septal or pre-divisional RBBB, at most a block in the superior or subpulmonary division of the right branch in the RV free wall that enters in the affected RVOT (**Pitzalis MV, et al. 2003.**).. See ludic explanation in the next 4 slides.

Andrés y Raimundo.

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

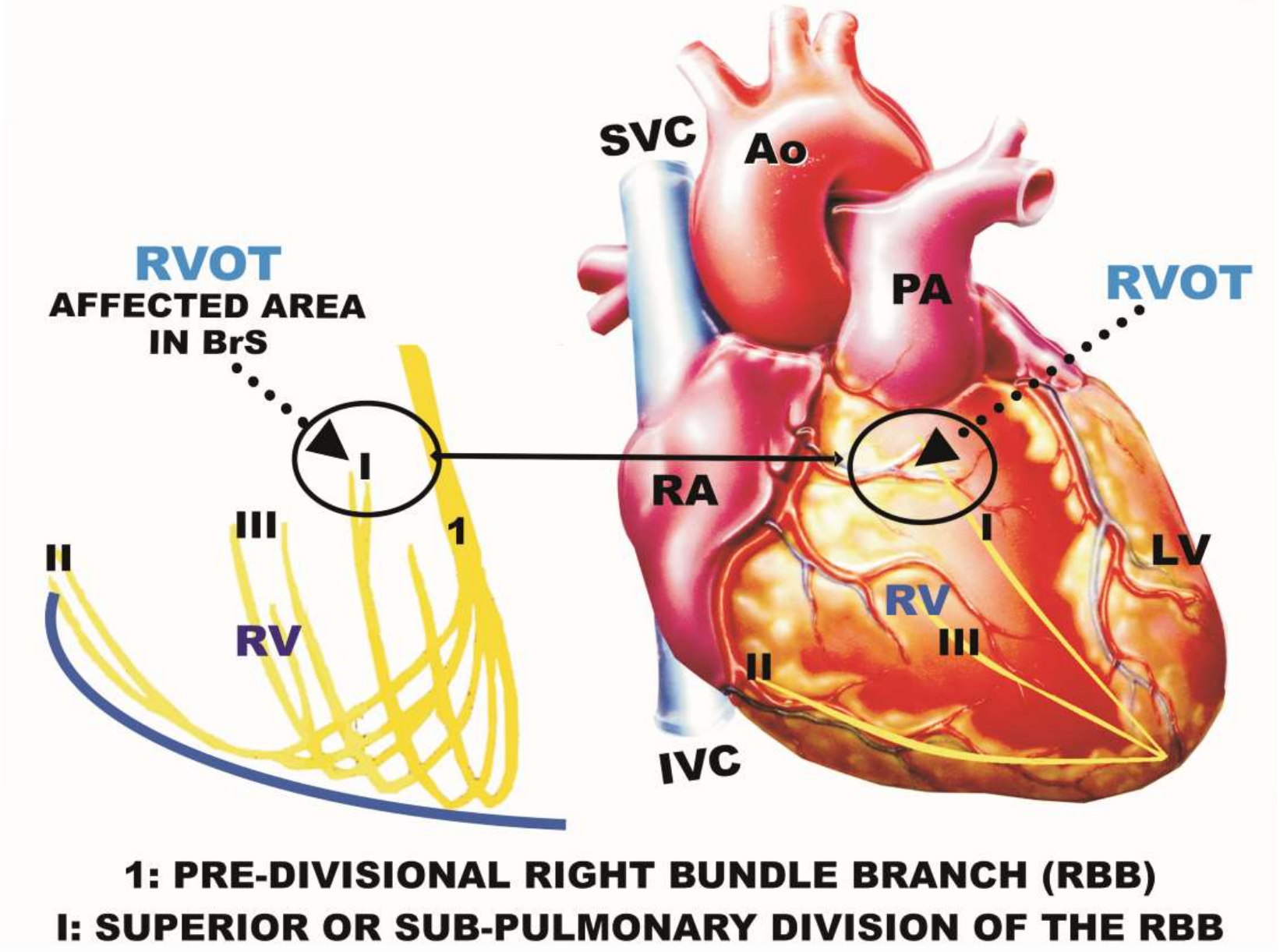






I – Superior or subpulmonary fascicle territory
II – Inferior or posterior-inferior fascicle territory
III – Middle fascicle territory

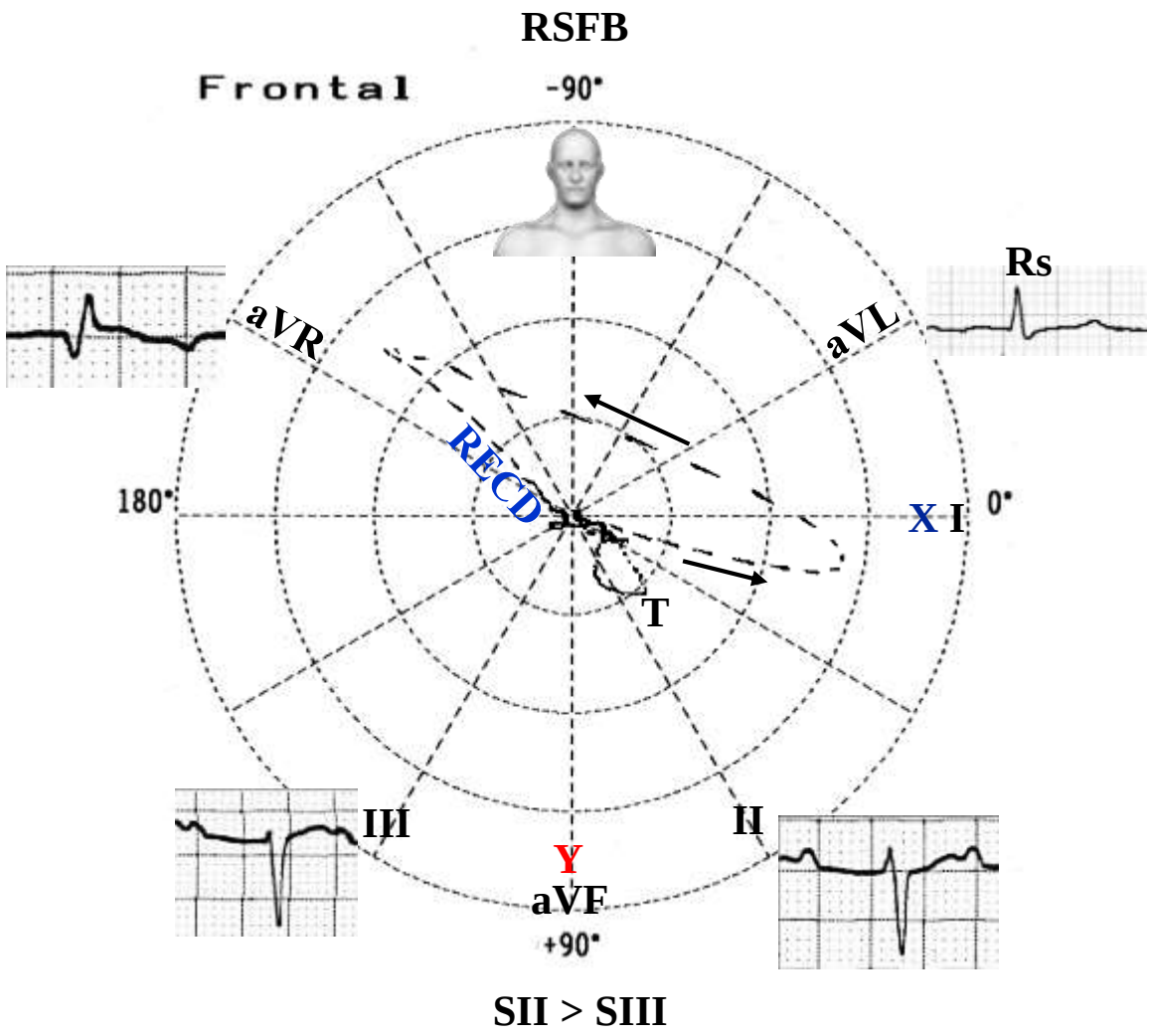
Structural epicardial alterations in the right ventricular outflow tract (RVOT) are the substrate for the conduction anomalies in Brugada syndrome (BrS). Electroanatomic mapping of endocardial unipolar voltage is an emerging tool that identifies accurately epicardial anomalies in the RVOT in BrS. Endocardial 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.et al 2015**).

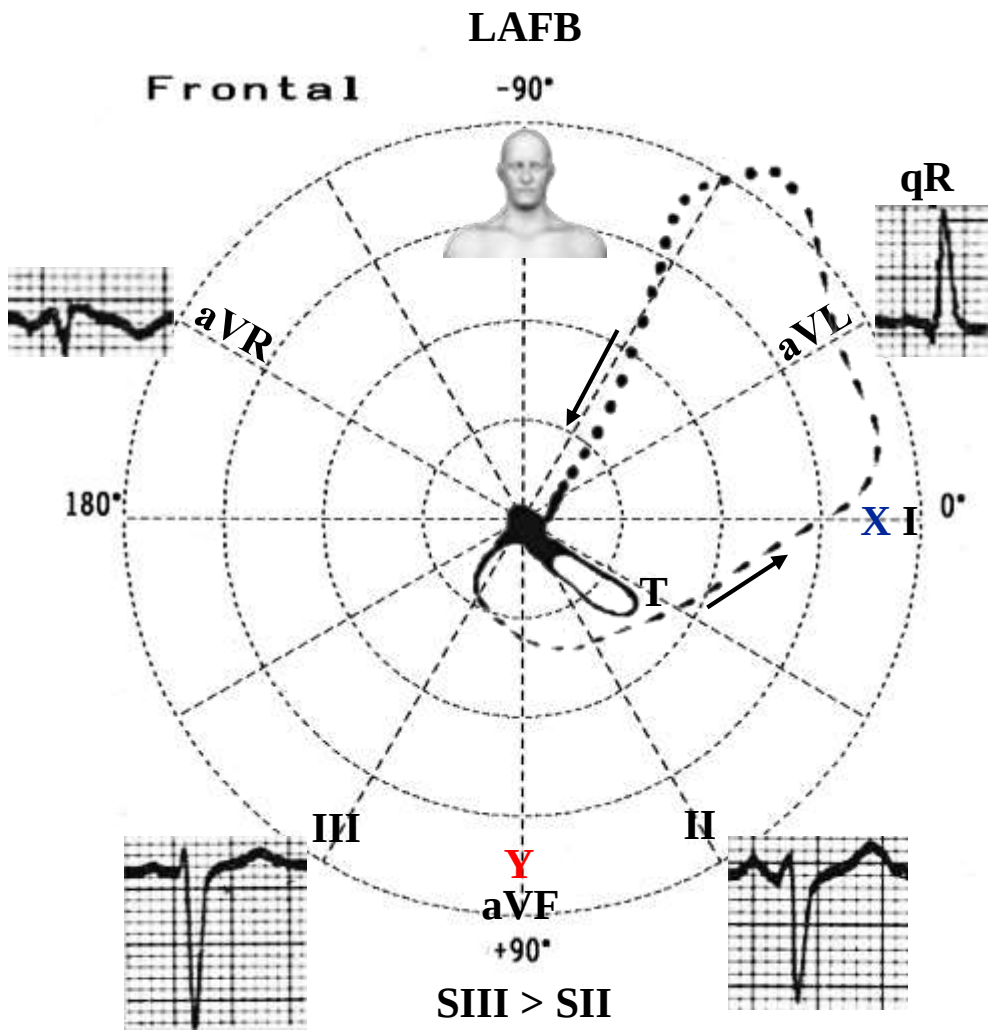


BrS is associated with epicardial surface and interstitial fibrosis and reduced gap junction expression (Cx43) in the epicardial RVOT, and increased collagen throughout the heart (**Nademanee K et al. 2015**).

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 et al. 2005)





	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 CA et al. 1983**)
Prominent R wave in aVR (R-wave ≥ 0.3 mV)	Absent	It could be present and it is called aVR sign (**Babai Bigi MA, et al. 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 B et al. 1989**)

LAFB: Left Anterior Fascicular Block. RSFB: Right Superior Fascicular Block

Spanish

Respuesta a Martin Querido Martin tu análisis me pareció muy interesante, aunque pudiéramos estar en desacuerdo en algunos puntos. Me gustaría comentar para todos que lo primero que hay que tener en mente es la diferencia de los términos de **Síndrome de Repolarización Precoz** "Early Repolarization Syndrome" (ERS) y el de **Patrón de Repolarización Precoz** "Early Repolarization pattern (ERP)"**:**

La presencia del síndrome de repolarización precoz (ERS) está caracterizada por la elevación del punto J ≥ 1 mm en ≥2 derivaciones inferiores y / o laterales contiguas registrado en un ECG estándar de 12 derivaciones y que ocurre en un paciente resucitado de parada cardiaca por TV polimórfica /FV por lo demás inexplicable. Como nuestro paciente es asintomático él no se encaja en la definición de ERS. El síndrome de repolarización precoz (ERS) también se puede diagnosticar en una víctima de muerte cardiaca súbita (SCD) con una autopsia no molecular negativa y una revisión de la historia clínica con un ECG previo que muestre una elevación del punto J ≥ 1 mm en ≥2 derivaciones inferiores y / o laterales contiguas en un ECG de 12 derivaciones estándar. El patrón de repolarización precoz (ERP) se diagnostica en presencia de una elevación del punto J ≥ 1 mm en ≥2 derivaciones inferiores y / o laterales contiguas de un ECG estándar de 12 derivaciones. Además, ERP se define en la presencia de una muesca ("notch") en la parte final del QRS, es decir en la pendiente descendente de una onda R con un punto J ≥0.1 mV en ≥2 derivaciones contiguas del ECG de 12 derivaciones, excluyendo V1 a V3. o la presencia de una muesca o cambio brusco en la rampa descendente final de la R ("slurring") que se encuentra completamente por encima de la línea de base, en la pendiente descendente de una onda R prominente; 2) El pico J (pico de muesca o ligadura) es ≥0.1 mV en ≥2 derivaciones contiguas del ECG de 12 derivaciones, excluyendo las derivaciones precordiales derechas V1 a V3; y 3) duración del QRS <120 ms (**Sugrue A, et al. Clin Electrophysiol. 2018; Macfarlane P et al 2015; Patton KK, et al. 2016**). Consecuentemente, si mediste 120ms de duración del QRS estaría fuera de la definición. No obstante, ocurre que posiblemente 120ms de duración del QRS sea apenas en las precordiales derechas y no en el resto de las derivaciones, V4 V5 y V6. No te olvides que el bloqueo parietal caracterizado por una duración del QRS en **V1+V2+V3** puede ser mayor que la suma de la duración del QRS de **V4+V5+V6**. La misma cosa que ocurre en la displasia de VD ($^{\mathbf{V1+V2+V3}}/_{\mathbf{V4+V5+V6}} \geq 1.2$). En la DAVD clasica la evidencia de bloqueo parietal derecho se manifiesta por duracion del QRS en precordiales derechas "≥110 msec y duración del QRS mayor en las precordiales derechas que en las izquierdas (**Marcus FI. 2000**). La relación QRSD de $^{V1+V2+V3}$ / $_{V4,\ V5\ y\ V6}$ o ≥ 1.2 se observa en aproximadamente 65% de los casos en la DAVD (**Nasir K et al. 2004**). QRSD ≥ de V1 a V3 tiene 91% de sensibilidad, 90% especificidad para ARVC/D (**Nasir K et al. 2003**). En el síndrome de Brugada esto se explica porque en el territorio del tracto de salida del VD existe menor expresión de la conexina 45, lo que ocasiona el retardo final de conducción en el RVOT sin que necesariamente sea debido a un BRD genuino septal o pre-divisional a lo sumo un bloqueo en la división superior o subpulmonar de la rama derecha en la pared libre del VD que entra en el tracto de salida del VD afectado (**Pitzalis MV, et al. 2003.**).

English

He has a history of a young brother with sudden death at rest, which is very important for suspicion of BrS. Sinus rhythm, normal P wave length and normal PR interval. The QRS axis is not deviated to the left (it has R> S in II), The QRS has RBBB morphology, absence of f-QRS, the aVR sign, normal QTc interval, Tp-Te around 90 msec: No ECG signs of arrhythmic risk with exception of spontaneous type 1 Brugada pattern.

The ST segment has elevation in DI and aVL and probable concomitant PR segment depression. (Spodick positive?) but has no clinic for pericarditis). In the registry with high leads positions, there is a Brugada type 1 pattern. The QRS duration is close to 200 msec measured with the tangent to point J, and e V1, V2. V3 wider than in the left precordial leads V4-V5-V6, (QRSd ratio $^{V1 + V2 + V3}$ / $_{V4 + V5 + V6}$ ≥1.2).-Also, it seems that both registers are not simultaneous, in the 1st the transition is in V4 , higher voltage in left leads, and elevation in DI and aVL, in 2nd trace with high right leads, the transition is before V3, the voltage of V5 and V6 is less, has less elevation in DI and aVL. In addition, the T wave is biphasic (plus/minus), There is mild depression of the ST segment in inferior derivations, added elevation of the ST segment in DI and aVL, ruling out STEACS. (Patient asymptomatic). Although the echocardiogram is normal, it would not rule out ARVC/D because eventually they are superimposed entities, it would request a Cardiovascular Magnetic Resonance Image. Additionally, perhaps the genetic screening help

The FP-VCG looks like a terminal or Right End Conduction Delay (RECD), located in the upper right quadrant, if it were a LAFB the QRS loop would be predominantly located in the upper left quadrant. The HP-VCG the QRS loop looks like a RBBB with counterclockwise rotation and followed by flat, elongated and asymmetrical T wave. In the BrS the T-loop is predominantly rounded and symmetrical. In short Brugada pattern masked by RBBB, which is evidenced only by making high right derivations.I do not know how to explain why ST segment elevation in DI and aVL. Its management and treatment are controversial.

Juan Manzzardo MD Mendoza Argentina

Spanish

Tiene antecedentes de un hermano joven con muerte súbita en reposo, lo que es muy importante para sospecha de BrS.

Ritmo sinusal, duración de onda P e intervalo PR normales con imagen de BCRD, sin QRS fragmentado, sin el signo de aVR, intervalo QTc normal, Tp-Te alrededor de 90 mseg. Sin signos electrocardiográficos de riesgo arrítmico. Elevación del segmento ST en DI y aVL y probable concomitante depresión del segmento PR. (Spodick positivo? pero no tiene clínica para pericarditis). En el registro con derivaciones altas hay patrón de Brugada tipo 1. La duración del complejo QRS próximo de 200 mseg medido con la tangente al punto J, y e V1, V2. V3 más anchos que en las precordiales V4V5V6, (relación ($^{V1 + V2 + V3}$ / $_{V4 + V5 + V6}$≥1.2). > 1,2. Además parecen que ambos registros no son simultáneos. En el 1° la transición está en V4, mayor voltaje en derivaciones izquierdas, y elevación en DI y aVL , en 2° trazado con las derivaciones derechas altas, la transición está antes que V3, el voltaje de V5 y V6 es menor, tiene menos elevación en DI y e (n aVL, además la onda T es bifásica plus/minus. El eje del QRS no está desviado a la izquierda (tiene R > S en DII)

Si bien el ecocardiograma es normal no descartaría DAVD por ser eventualmente entidades superpuestas, solicitaría una RMN y quizás la genética ayude. Hay leve depresión del segmento ST en derivaciones inferiores, sumado elevación del segmento ST en DI y aVL , descartar SCACEST. (Pac asintomático). El VCG en plano frontal parece un retardo final de conducción (RECD), ubicado en cuadrante superior derecho, si fuese un LAFB el asa del QRS estaría predominantemente en el cuadrante superior izquierdo.

El PH-VCG parece un patrón de BCRD con rotación antihorario seguido de onda T estrecha, de ramas asimétricas y alargada. En el BrS el bucle T es predominantemente redondeado y de ramas simétricas.

En resumen patrón de Brugada enmascarado por BCRD, que se pone en evidencia con solo hacer derivaciones derechas altas.

No sé explicar motivo para la elevación del segmento ST en DI y aVL.

Es controvertido su manejo y tratamiento.

Juan Manzzardo MD Mendoza Argentina

Final comments by……

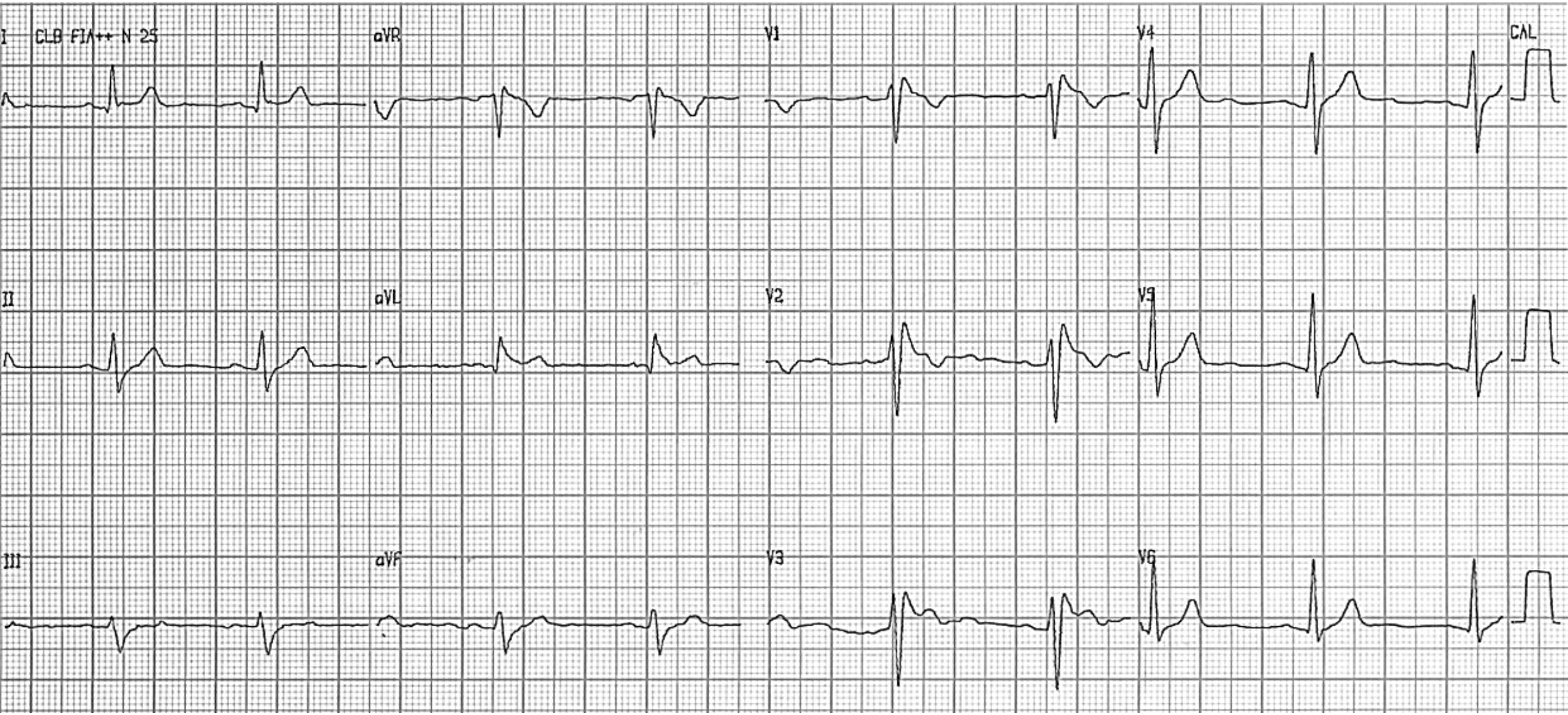
Raimundo **Barbosa-Barros MD&** Andrés Ricardo **Pérez-Riera MD PhD**

The fox

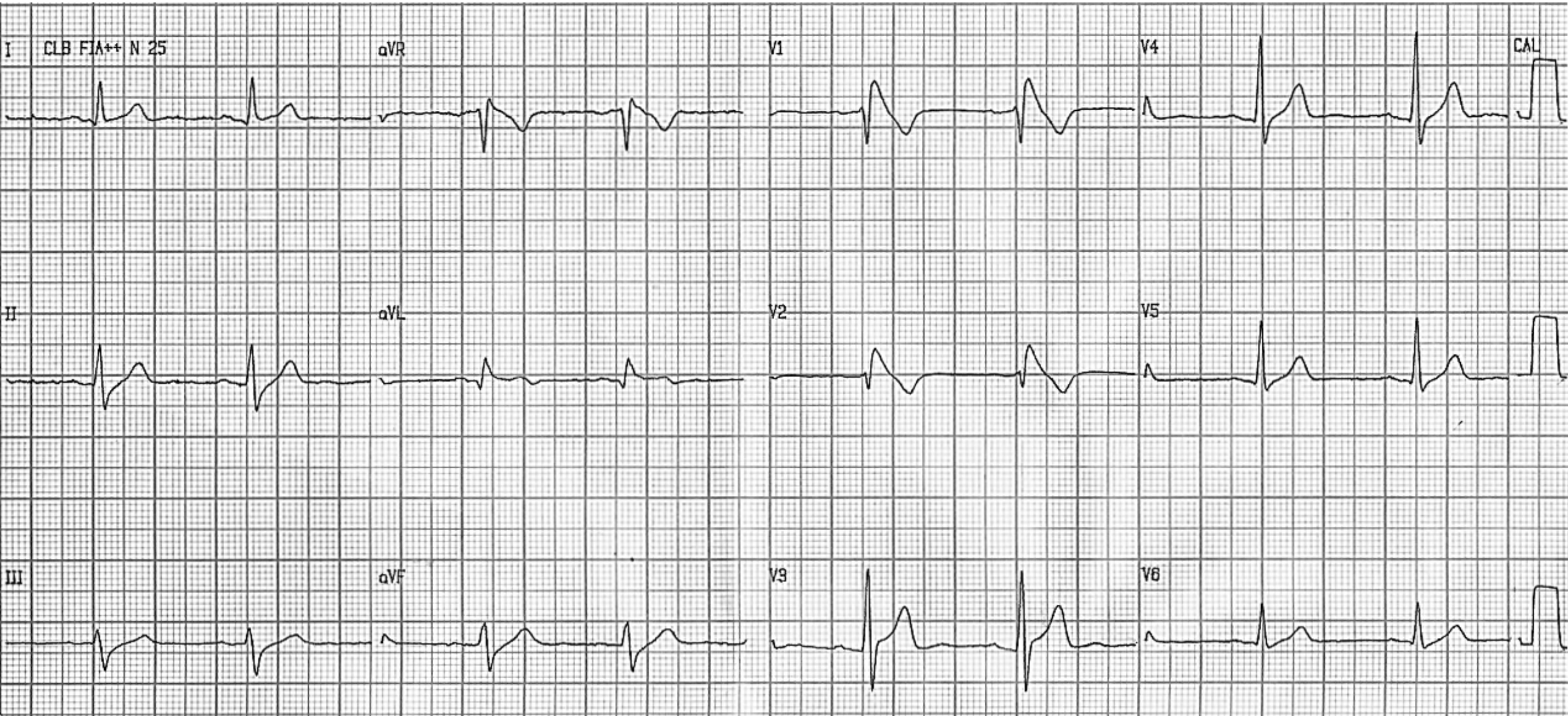
Andrés R Pérez Riera, MD

The "Paulista Colt"

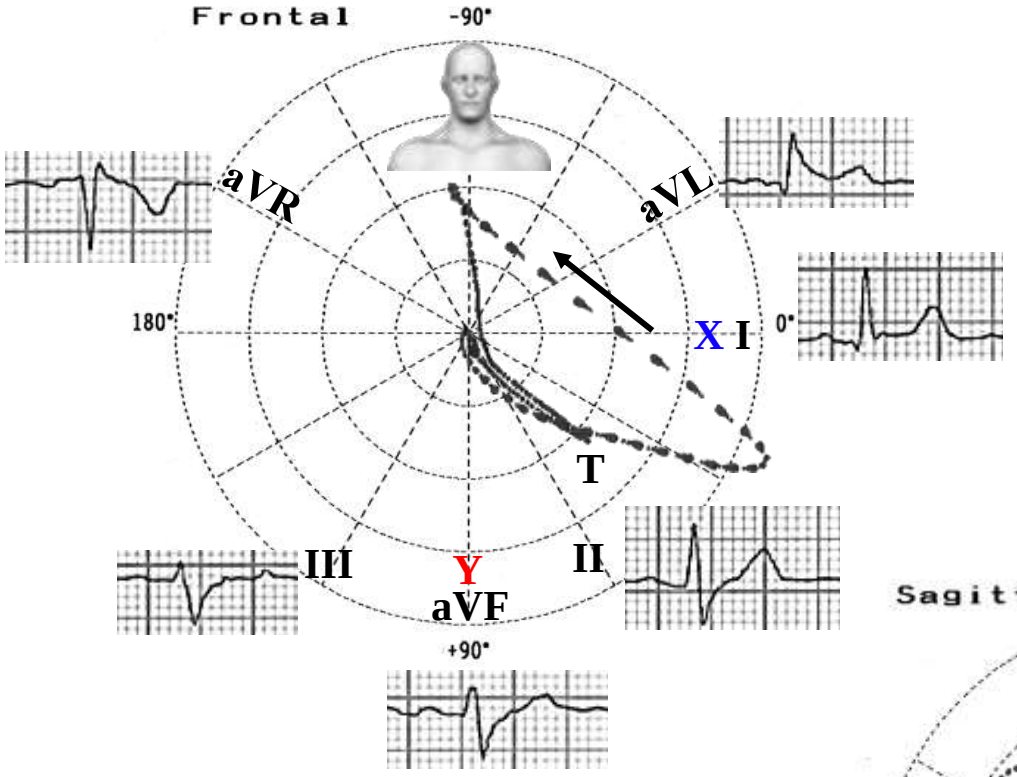
ECG preformed with conventional right precordial leads

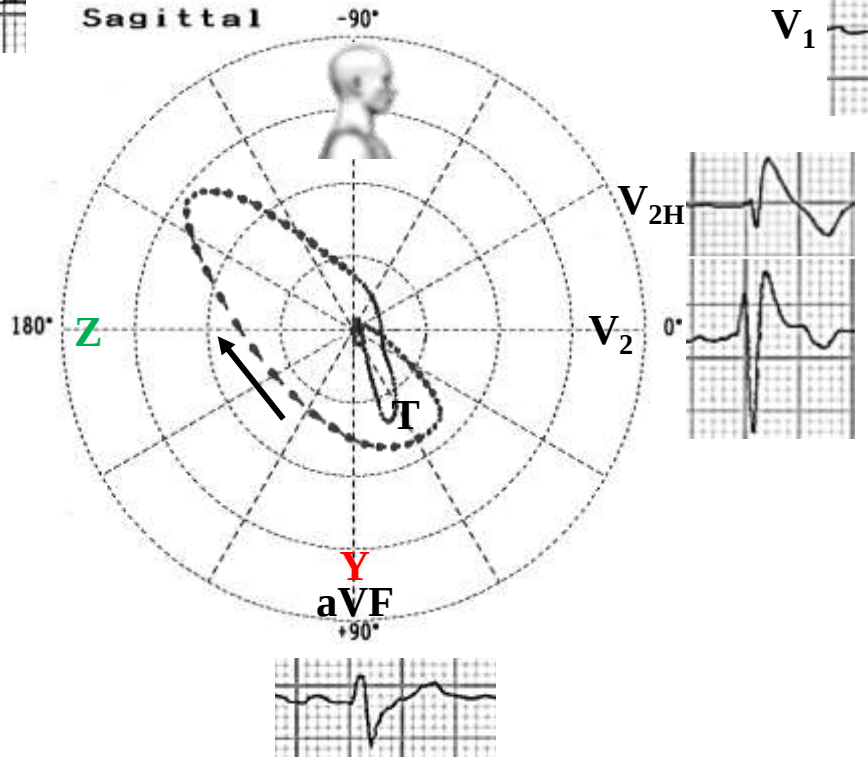


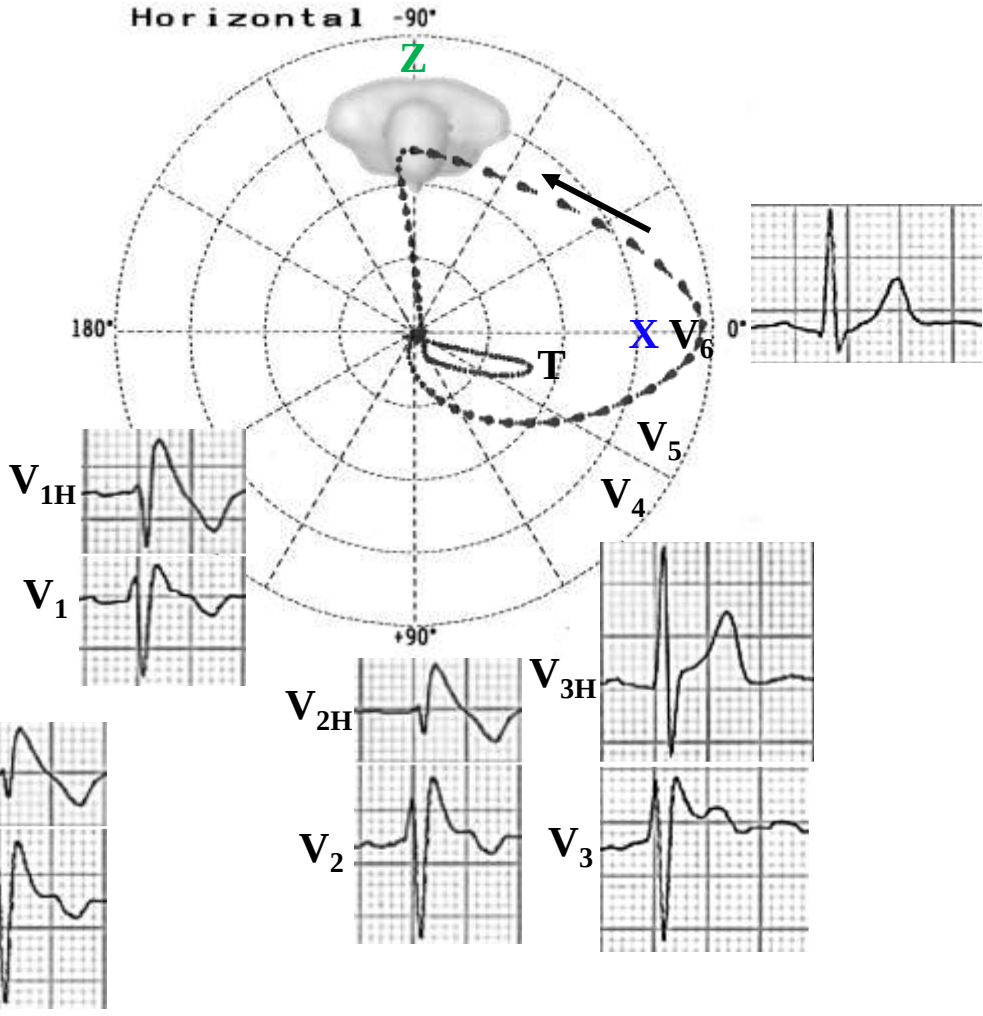
ECG preformed with High right precordial leads

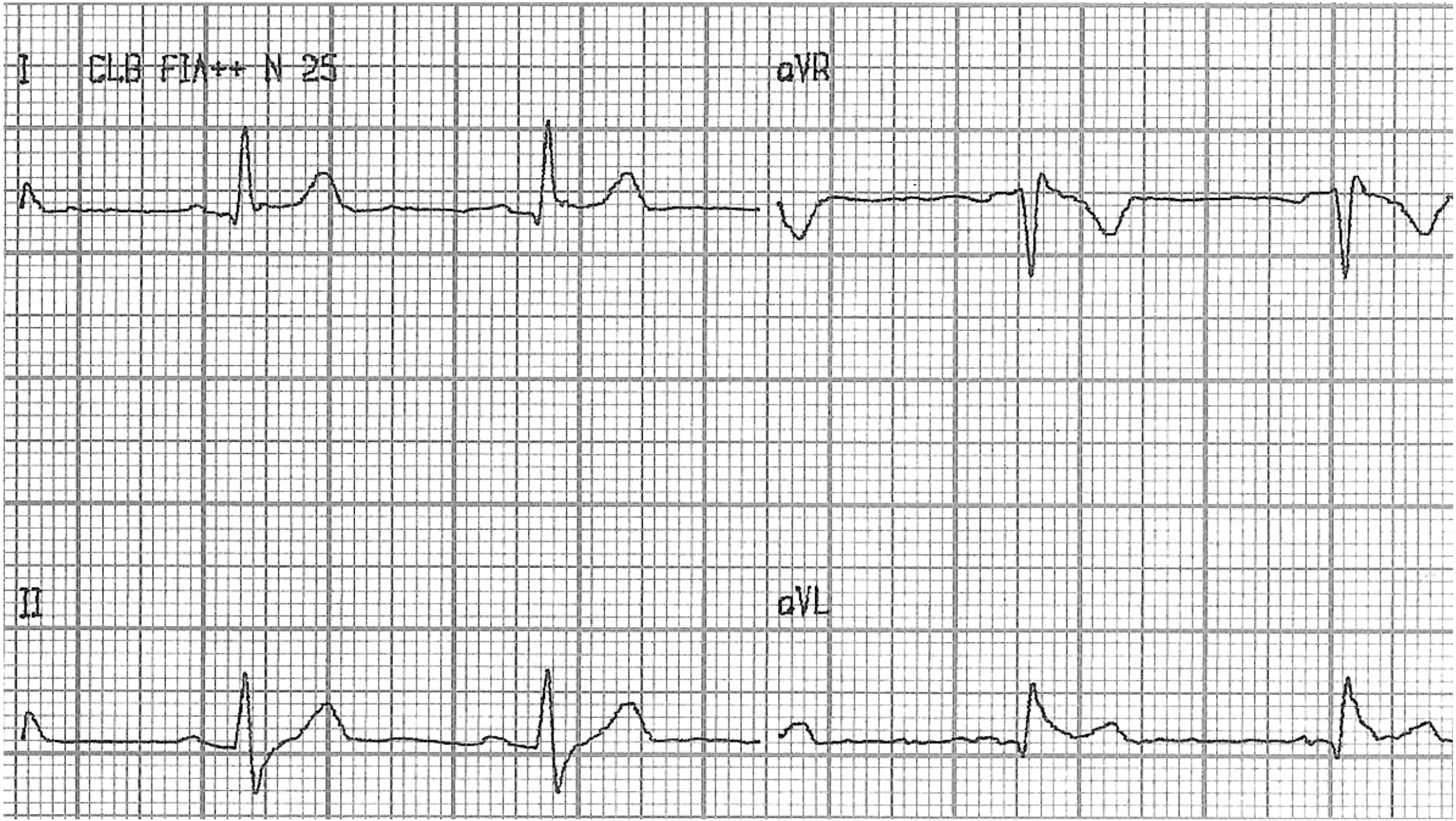


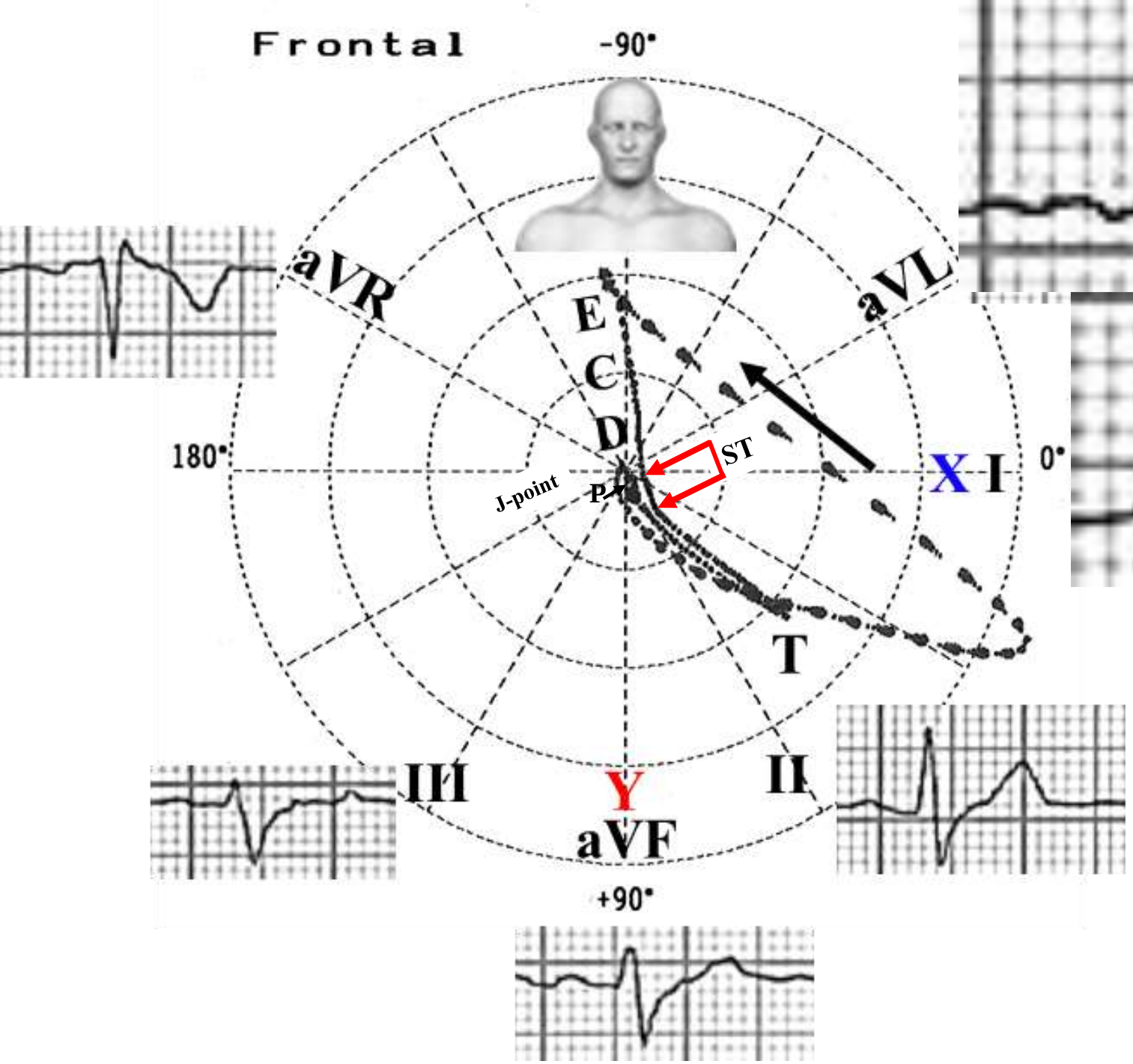
ECG/VCG correlation in the three planes

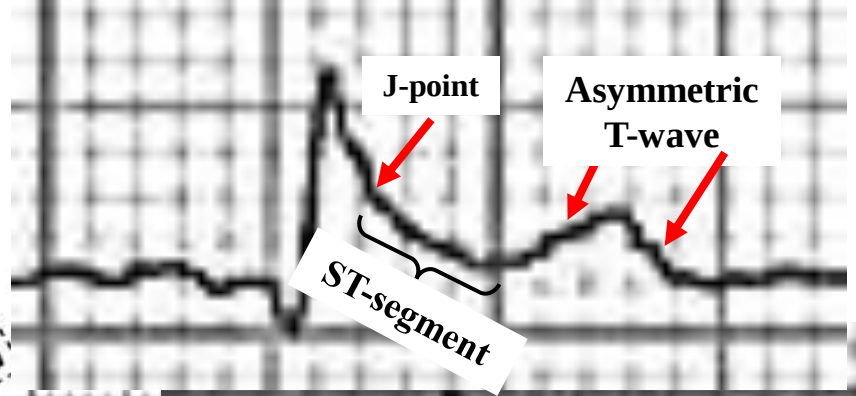


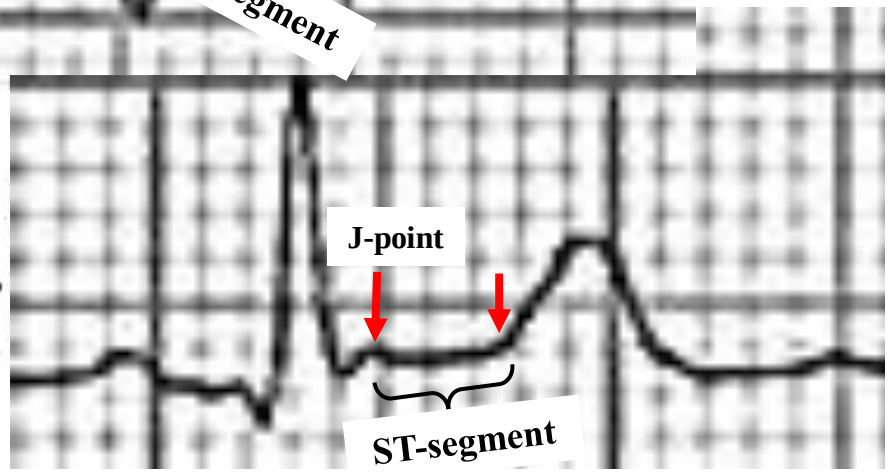





I CLB FIA++ N 25
aVR
II
aVL

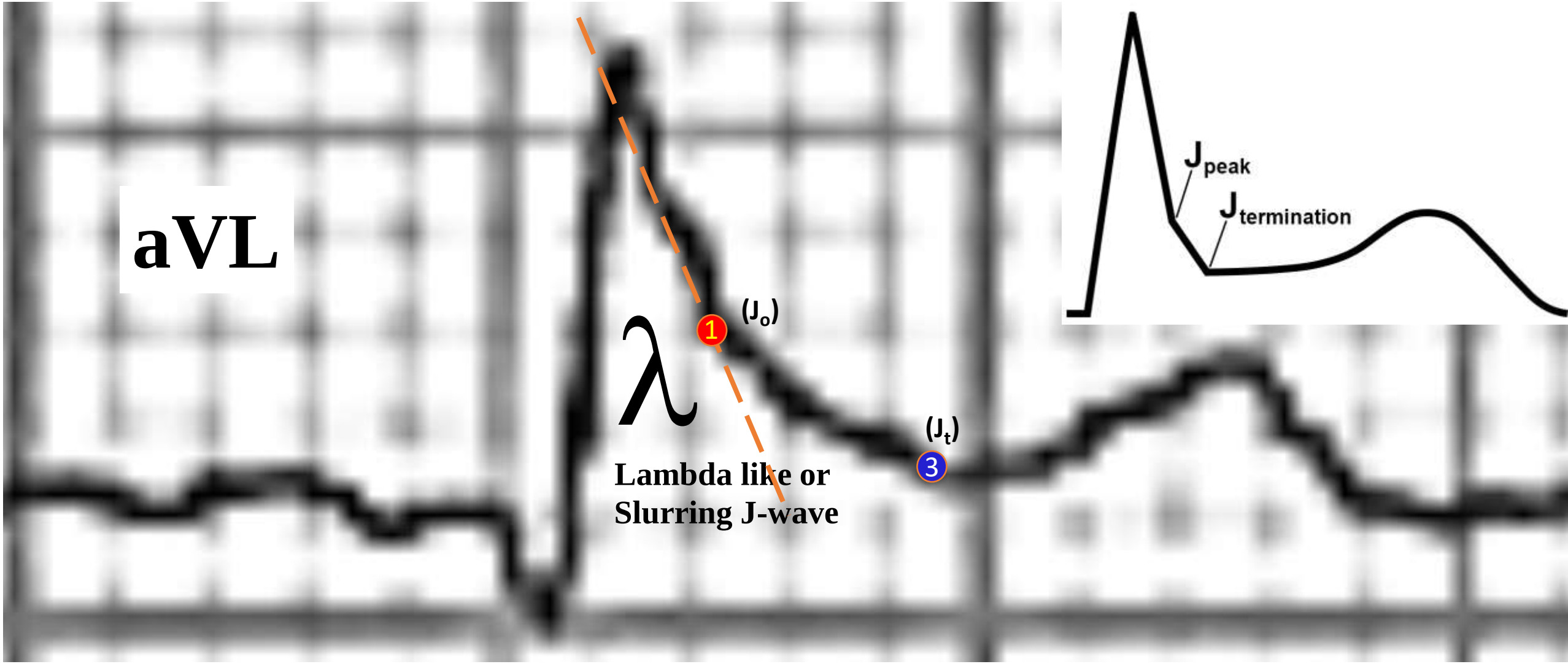






ECD: End Conduction Delay + **High J-wave amplitude, horizontal/descending ST segment elevation in lateral leads I and aVL.**

Lateral leads I and aVL End-QRS slurring J-wave, lambda like wave or Gussak wave (Gussak I 2004)

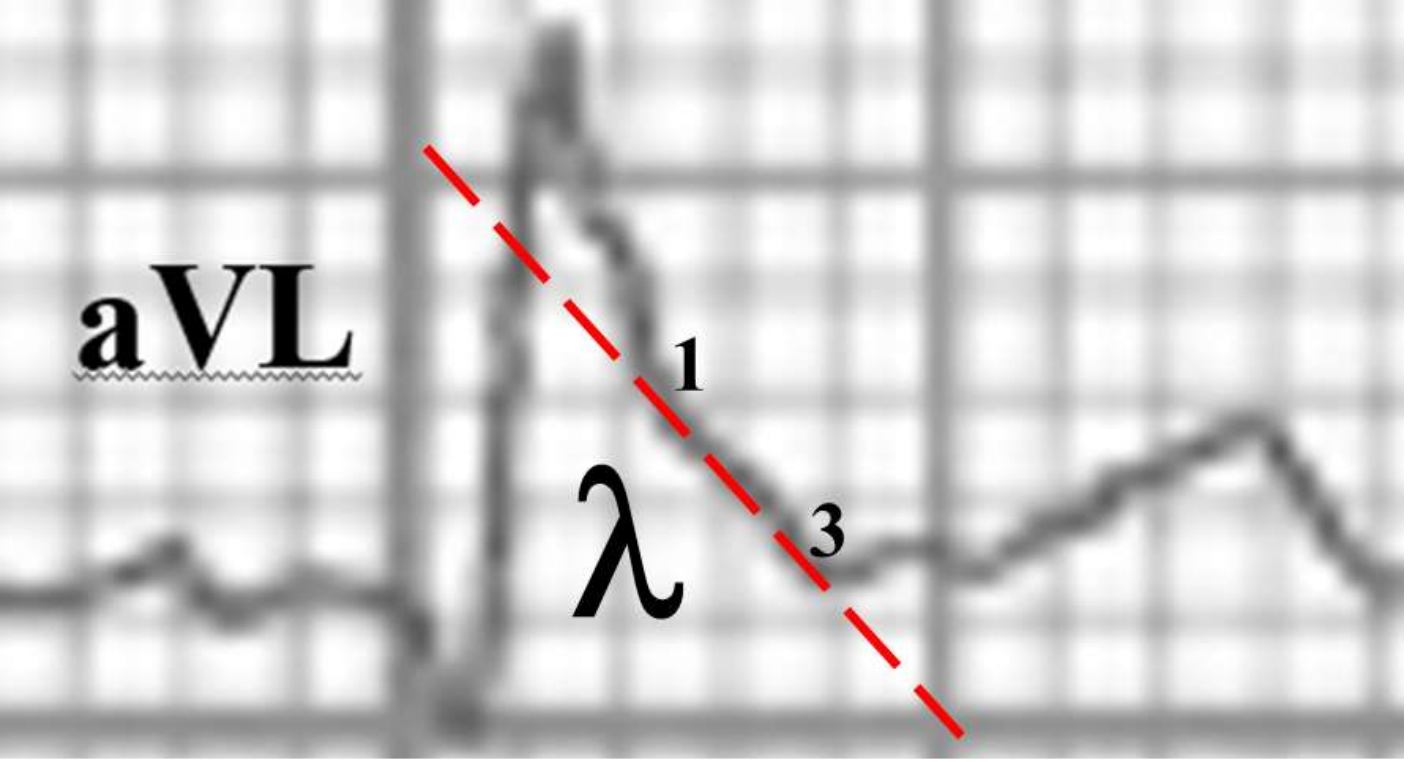


Abrupt change in the slope of the terminal forces of the QRS.

ECD: End Conduction Delay + **High J-wave amplitude, horizontal/descending ST segment+ SCD positive familial background= High risk**

It is necessary EPS

1: **J-peak (Jp); 3: J-$_t$ termination (Macfarlane PW, et al. 2015)**

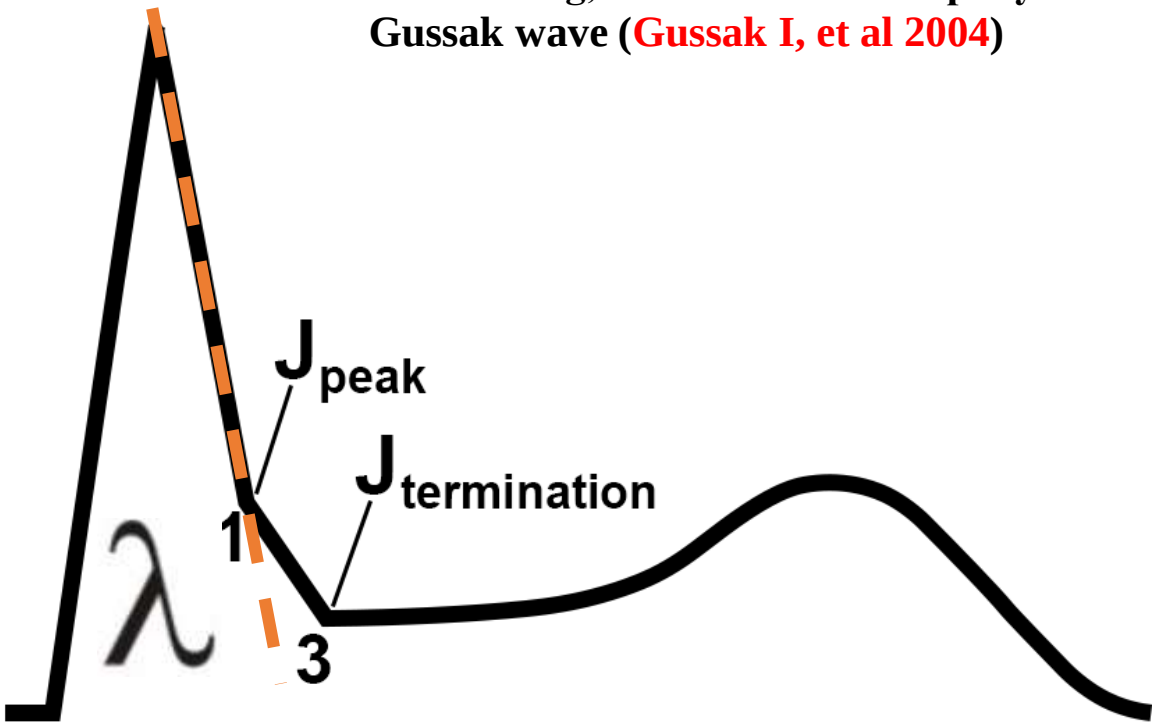


J-wave slurring or “lambda” wave (Gussak I 2004)

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

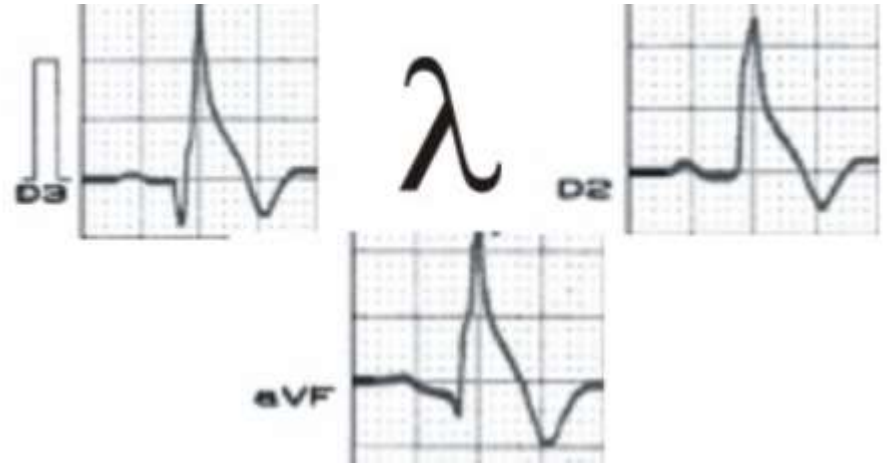
High J-wave amplitude, horizontal/descending ST segment. In the presence of a strong family history of juvenile unexplained sudden death with or without a pathogenic mutation.(Class IIB) this is a currently case (**Priori SG, et al. 2013 Europace and Priori SG, et al. 2013 Heart Rhythm**).

J-wave slurring, “lambda” or the eponym Gussak wave (Gussak I, et al 2004)



1. Tangent line or J-peak = J-point

1 (J- wave onset) and 3 (J-wave termination).



The variations in the ECG patterns of J-point elevations, and the complex of J-points and J-waves in early repolarization (ER)

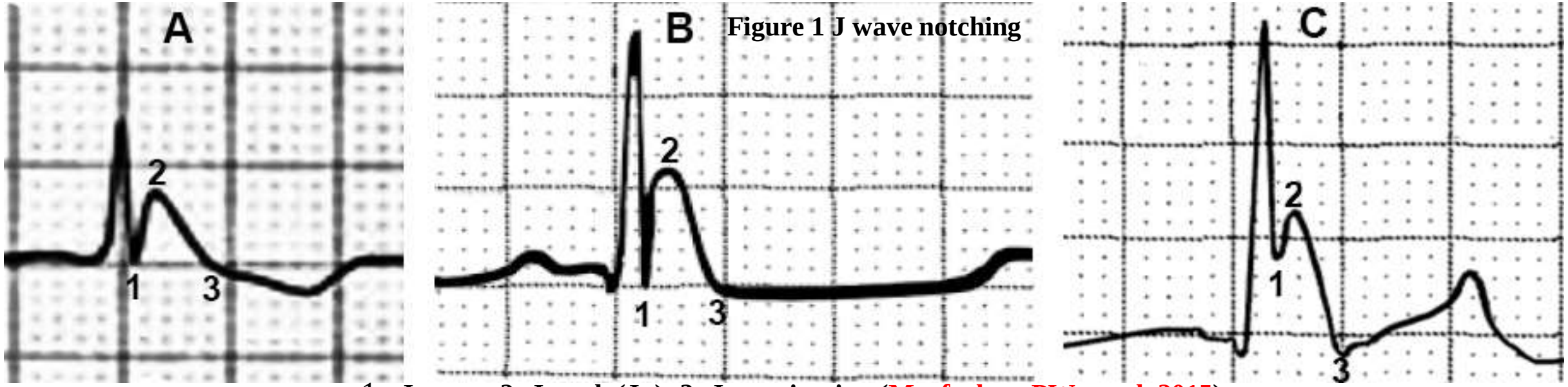
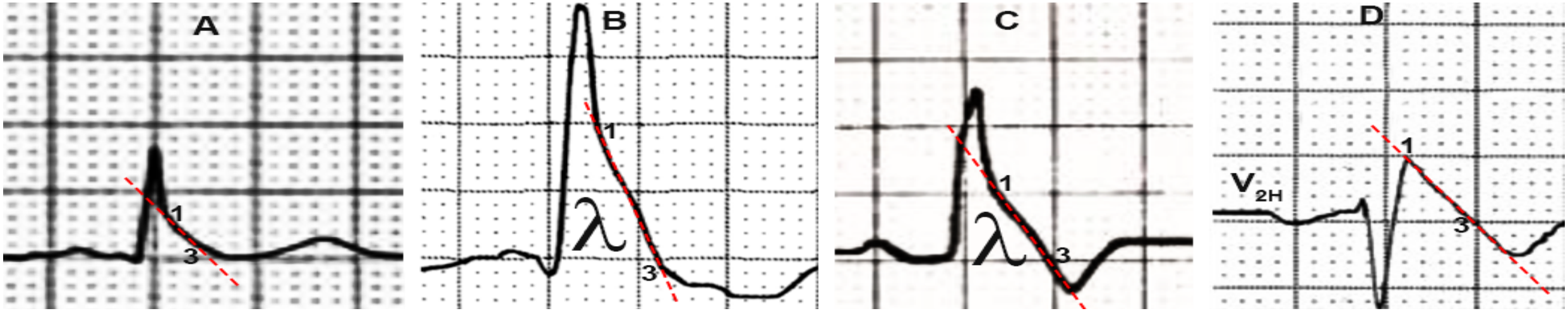


Figure 1 J wave notching

1: **J-onset; 2: J-peak (Jp); 3: J-termination (Macfarlane PW,. et al. 2015).**

Figure 2 J wave slurring, lambda or "Gussak wave" (Gussak I. et al. 2004)

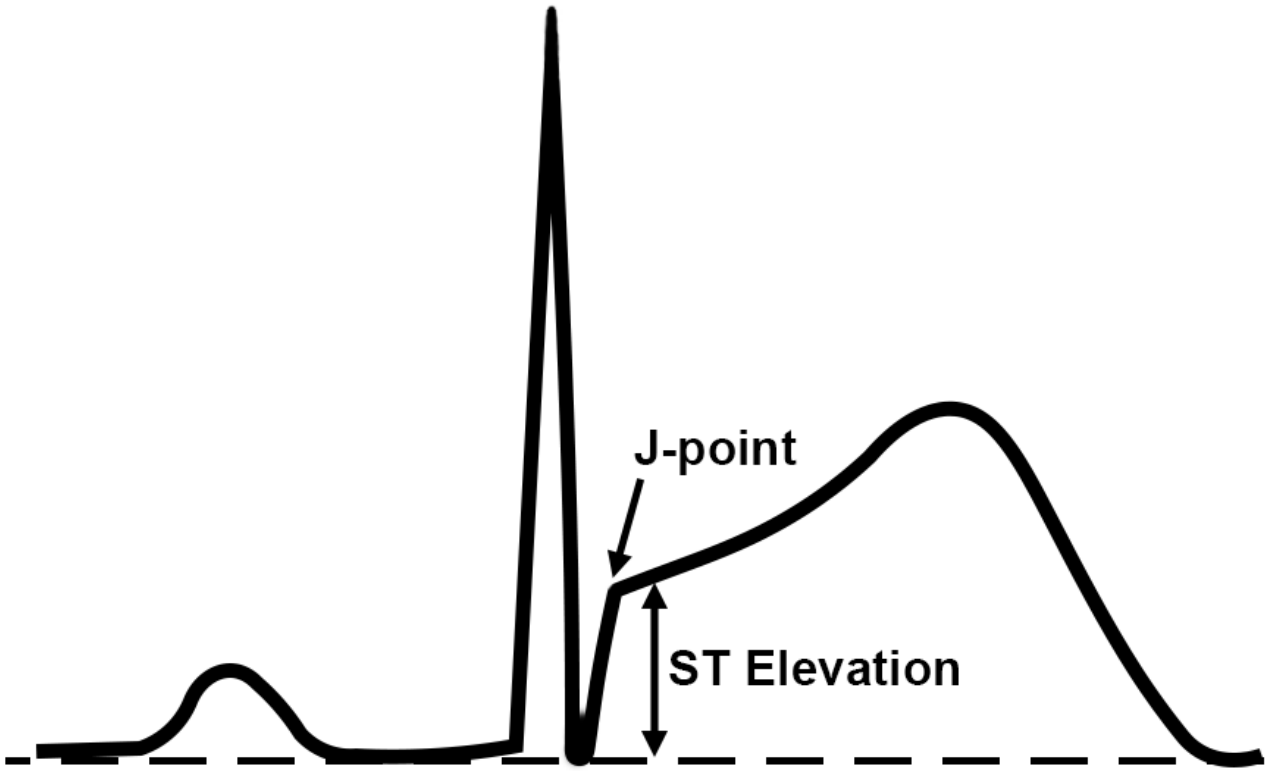


In this variant we have only two points: 1 (J- wave onset) and 3 (J-wave termination). A: With positive T wave; B: With negative ST and T wave; C: With negative symmetrical T wave; D: With negative symmetrical T wave only in right precordial leads: type 1 Brugada ECG pattern.

Features that suggest Benign patterns of early repolarization

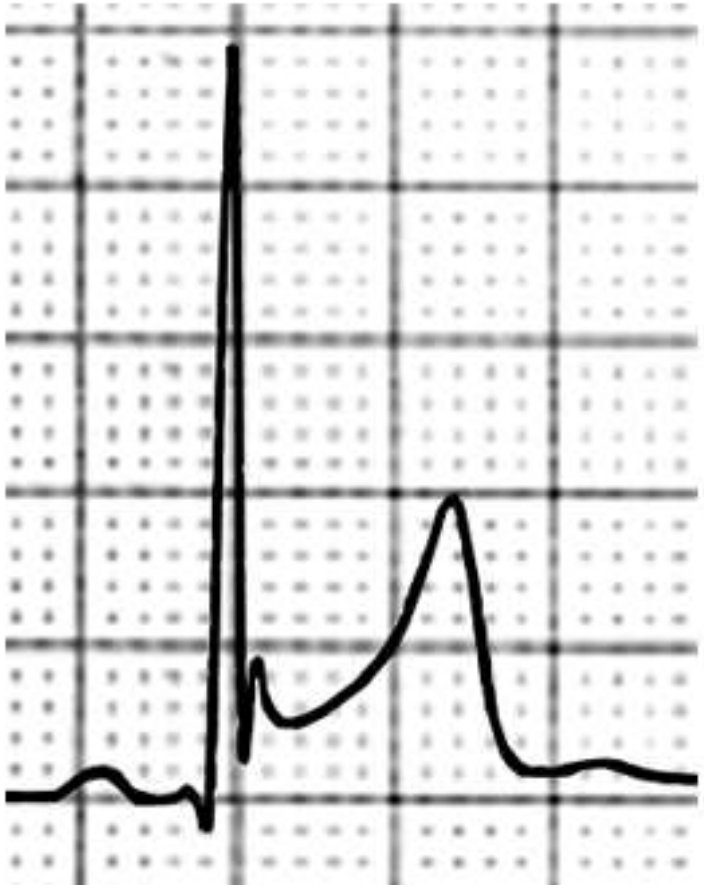
1. Most commonly seen in young healthy male subjects, athletes and afro descendants or afro-Caribbean (**Junttila MJ, et al. 2012**).
2. HR: frequent characteristic sinus bradycardia
3. Frequent respiratory sinus arrhythmia (RSA) or heart rate response to deep breathing. Normally, heart rate varies from beat to beat, primarily due to changes in vagal activity. The most noticeable variation is that which is synchronous with the respiratory cycle (respiratory sinus arrhythmia). Heart rate increases during inspiration and decreases during expiration. Sinus arrhythmia is present when the P-wave morphology is normal and consistent and the P-P intervals vary by more than 160 milliseconds(> 3 small square). Nonrespiratory sinus arrhythmia, in which phasic changes in sinus rate are not related to the respiratory cycle, may be accentuated by the use of vagal agents such as digitalis and morphine; its mechanism is unknown. Patients with nonrespiratory sinus arrhythmia are likely to be older and to have underlying cardiac disease, although the arrhythmia is not a marker for structural heart disease. None of the sinus arrythmias (respiratory or nonrespiratory) indicates SND. Additionally, respiratory variation in the sinus P wave contour can be seen in the inferior leads and should not be confused with wandering atrial pacemaker(WAP), which is unrelated to breathing and therefore is not phasic. The common characteristic of WAP and Multifocal Ectopic Atrial Tachycardia (MEAT) rhythms is variation in the shape or morphology of the P wave in a single ECG lead. The terms WAP and MEAT are not interchangeable: WAP occurs in less-ill individuals, so it is worthwhile to clarify these designations. Critical care and acute care nurses occasionally see both rhythms in practice (**Hannibal GB, 2015**.).
4. The prognostic significance of ER was first comprehensively studied in a general population, in which subjects with J-point elevation in any lead, including anterior leads, was the only inclusion criterion.(**Klatsky AL, et al. 2003**.) The presence of J-waves was not required. In this study, ER was not found to be associated with increased mortality risk. Thus, it appears that J-point elevation or ST-segment elevation itself is

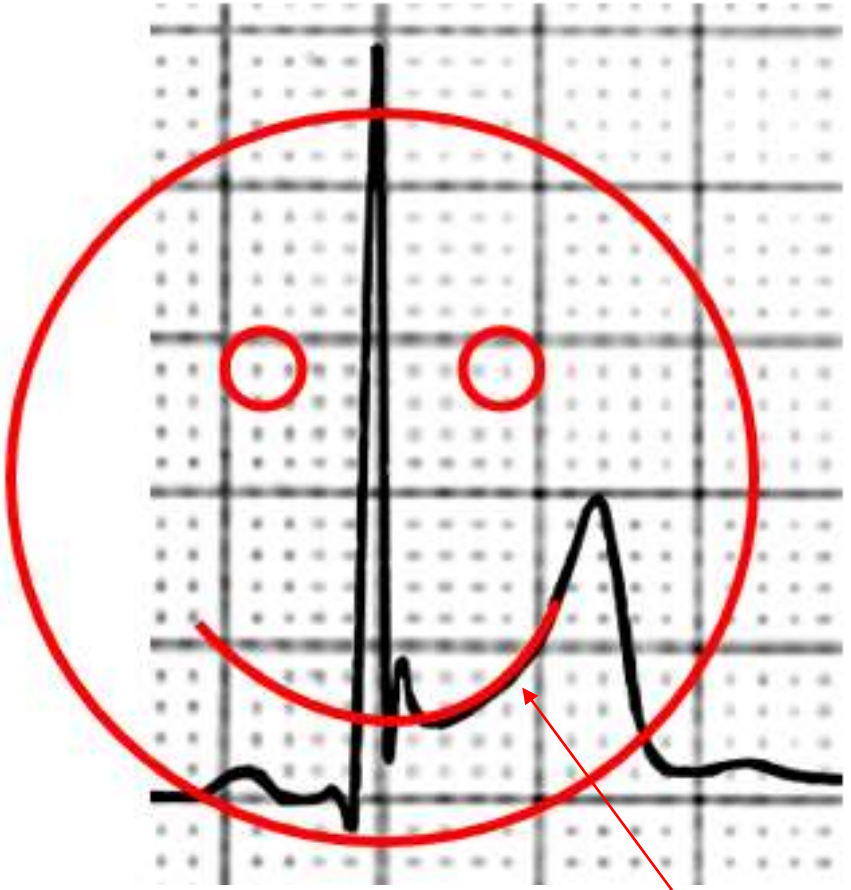
4. not a mortality risk factor in the absence of notching and/or slurring of the terminal portion of QRS or the formation of apparent J-waves. Among the inferolateral ER pattern carriers, ascending ST-segment was not associated with increased mortality risk, as mentioned before.48 Similarly in BrS ECGs, the pattern of the ST-segment morphology plays a role in risk assessment. Several general population-based studies have shown that Type II Brugada ECG finding in a routine ECG screening in otherwise healthy individual without personal or family history of SCD or life-threatening arrhythmias is a benign finding.(**Junttila MJ, et al 2008**.)(**Junttila MJ, et al. 2012**). Currently, early repolarization without J-wave is not considered a pathological feature J-point elevation or ST-segment elevation itself is not a mortality risk factor in the absence of notching and/or slurring of the terminal portion of QRS or the formation of apparent J-waves. Figure below

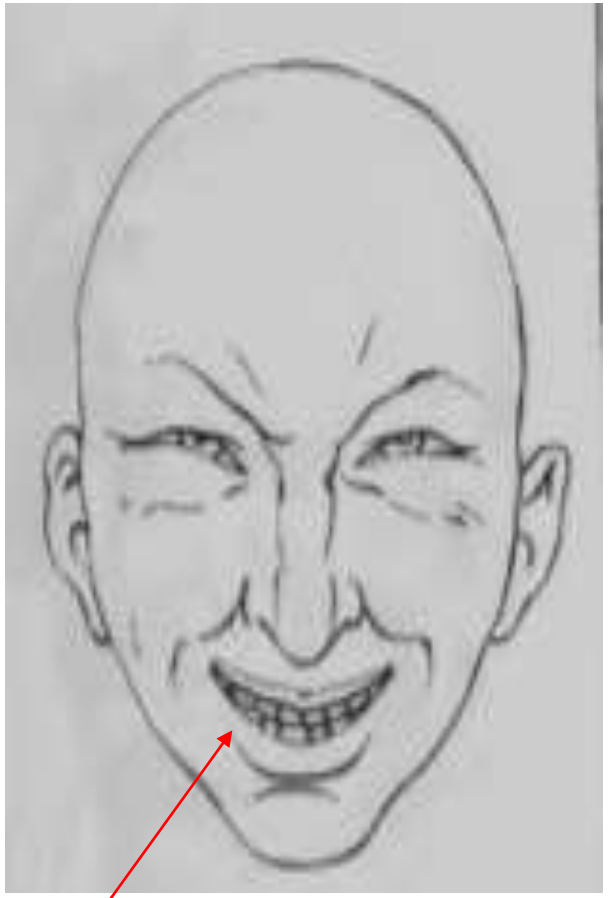


5. Notch or slurring of R wave descending branch (J-wave) is possible but not obligatory;
6. Axes of QRS, ST segment and T wave, oriented in the same direction in the frontal plane;
7. Deep and narrow Q waves followed by R wave of great voltage in left precordial leads;
8. Frequent transition area in the precordial leads of sudden occurrence. Precordial transition refers to the lead where R and S waves are of equal amplitude, and this normally occurs between V3 and V4. Early transition occurs when the R wave is greater than the S wave in lead V1 or V2 and delayed when transition occurs in V5-V6. Poor R-wave progression(PRWP) is a common ECG finding that is often inconclusively interpreted as suggestive, but not diagnostic, of anterior myocardial infarction (AMI). Studies have shown that poor R-wave progression has the following four distinct major causes: AMI, left ventricular hypertrophy, right ventricular hypertrophy, and a variant of normal with diminished anterior forces. Standard ECG criteria that identify and distinguish these causes have been developed. An interpretive approach to the ECG with PRWP is presented that has clinical relevance in the daily treatment of patients. The incidence and mechanism of true PRWP were analyzed by retrospective analysis of ECGs and records of 100 individuals with normal findings, and 50 additional individuals with mitral valve prolapse, at cardiac catheterization with coronary angiography. PRWP occurred in 8% (8/100) of normals and was not related to age, sex, height, weight, body surface area, ponderal index, thoracic skeletal abnormalities, ECG frontal axis, serum cholesterol, arterial blood pressure or mitral valve prolapse. In view of the voltage changes produced by alteration of lead placement, one tail of a normal distribution of null planes may account for PRWP in subjects without disease.
9. Possible reduction in J point and ST segment elevation by sympathetic action and sympathomimetic drugs;

10. J point and ST segment elevation, usually < 2 mm (exceptionally it may be > 5 mm) of superior concavity in middle and/or left precordial leads and possibly in inferior leads. The figure shows V4 precordial lead with STSE concave to the top followed by large positive T wave that resembles a "smA face that laughsiling face".





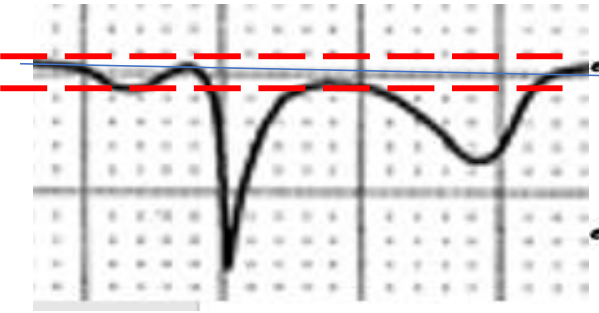


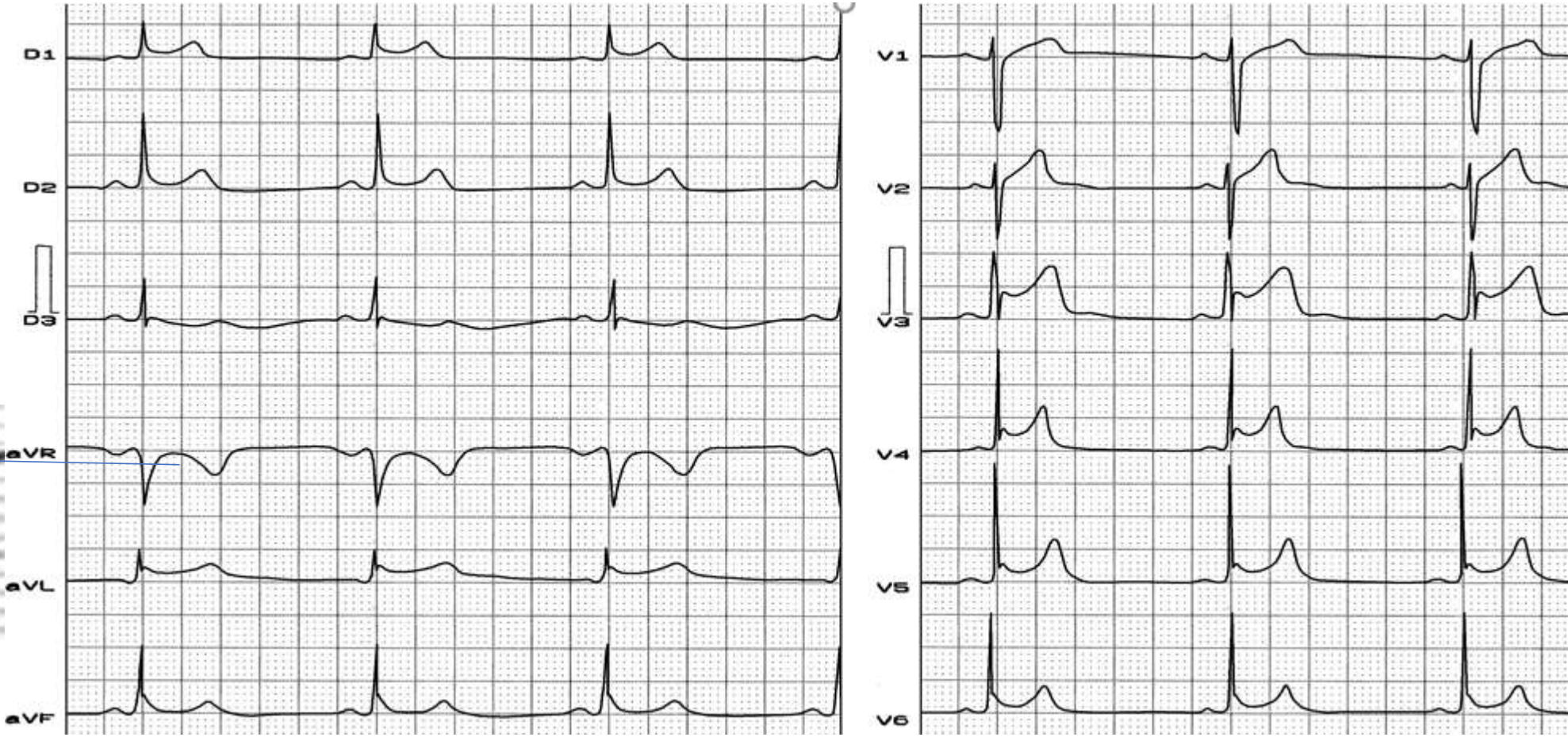
A face that laughs

11. Symmetrical or pseudo symmetrical T waves, with great width and polarity matching QRS;
12. Absence of reciprocal changes or mirror image (with exception in VR lead) On the other hand BrS and IVF have frequent reciprocal changes is multiple lead Figure below

Typical ECG of early repolarization pattern in an black professional basketball player athlete with bradycardia

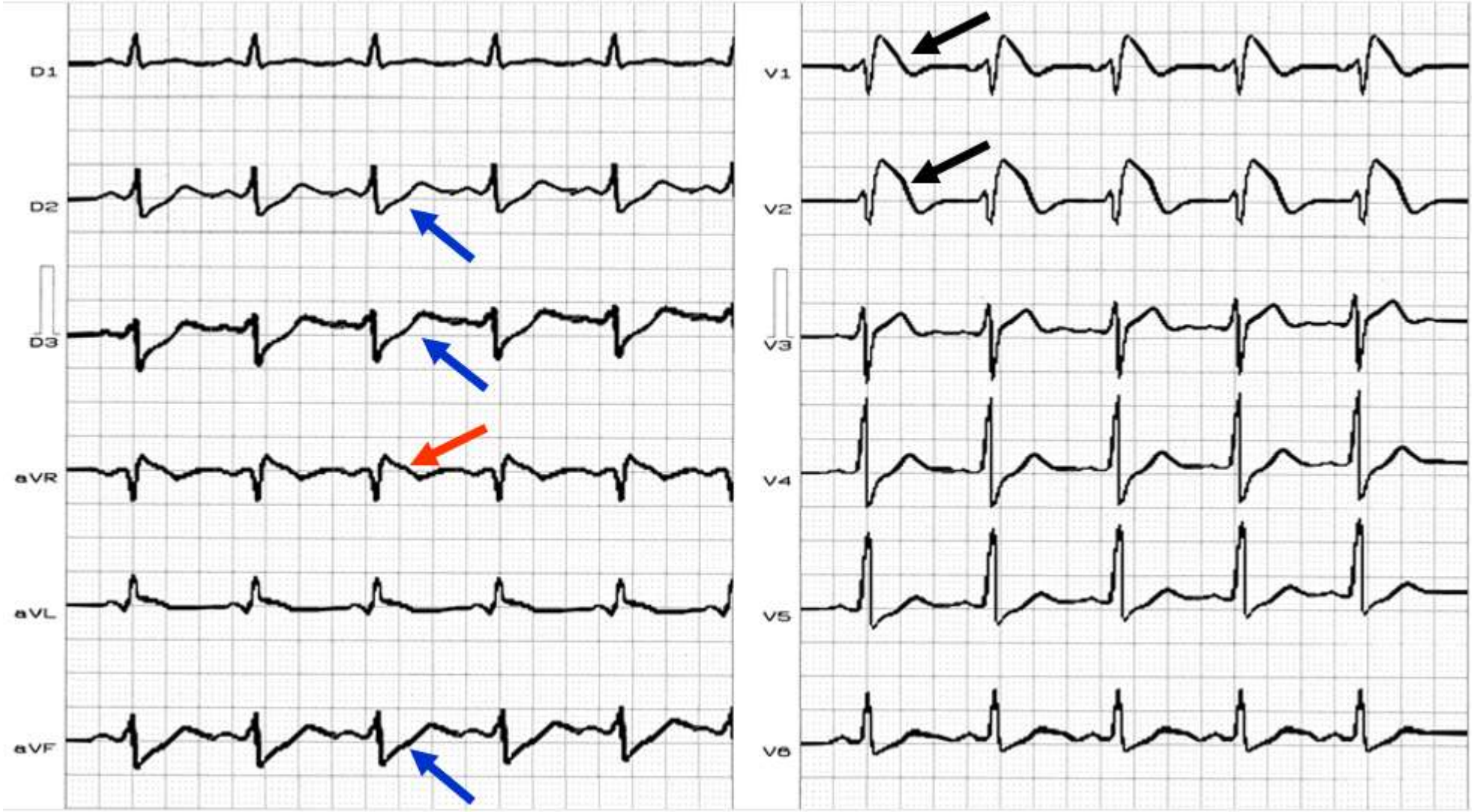
Reciprocal (mirror) image only in aVR lead





ECG diagnosis: sinus bradycardia, (HR 50 bpm). J point and ST segment with elevation > 4 mm in precordial leads from V_3-v_5 of superior concavity. Notch or slurring of terminal portion of the QRS complex (J point). ST segment elevation > 4mm in precordial leads V_3, V_4 and V_5.
Conclusion: sinus bradycardia, early repolarization pattern. .

Typical ECG of Brugada Type 1 pattern in a patient with BrS and reciprocal or mirror image in the inferior leads



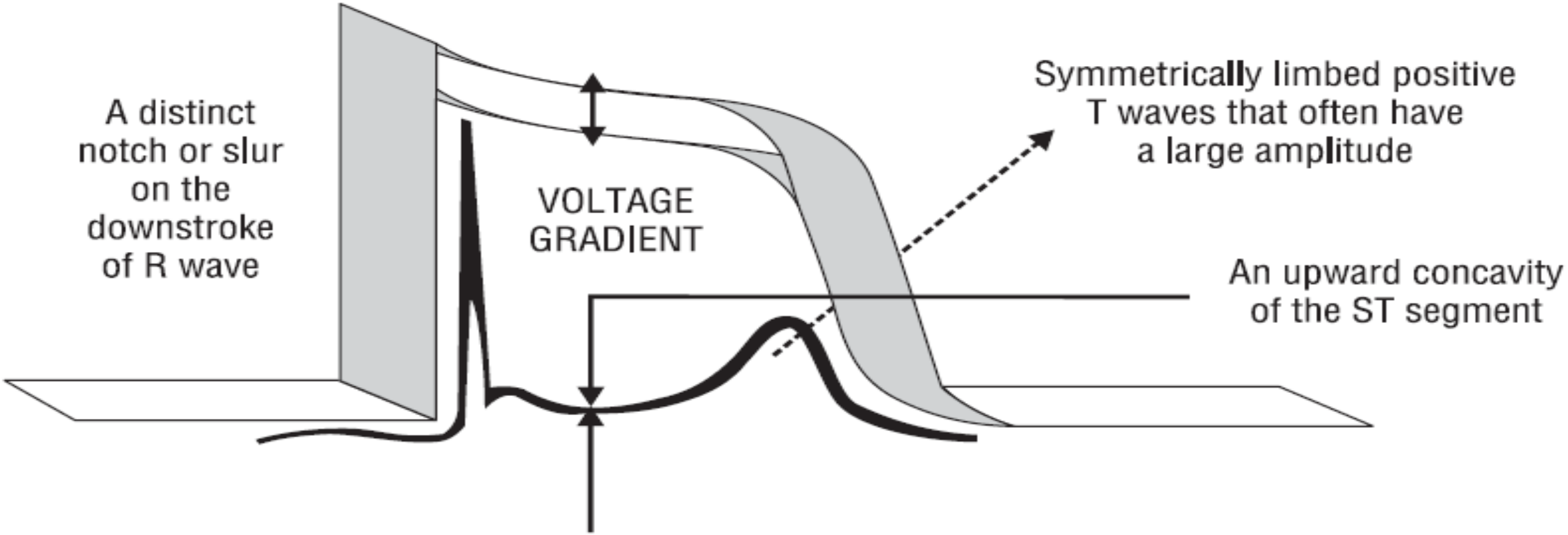
J point and ST segment elevation, convex to the top, ST segment in right precordial leads from V_1 through V_2 (black arrows): Brugada sign or idiopathic J wave. Unipolar aVR lead that heads toward the RV epicardium above the outflow tract, which shows subtle ST segment and J point elevation (red arrows). Inferior leads show reciprocal change or mirror image (blue arrows). Note how the ST segment elevation in aVR and aVL is an mirror image of lead II –III -aVF. This reciprocal change occurs because these inferior leads are approximately opposite to higher (-150°. (-30° and -150°).

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

Reciprocal change is a very important ECG finding, not only supporting the diagnosis of STEMI but also indicating a high-risk patient. Reciprocal change is defined as ST-segment depression occurring on an ECG which also has ST-segment elevation in at least 2 leads in a single anatomic segment. Note how the ST segment morphology in aVL is an exact mirror image of lead III. This reciprocal change occurs because these two leads are approximately opposite to one another (150°).

Theoretical electrophysiological explanation for ST segment elevation in ECGs in athletes

In early repolarization, there is a voltage gradient, however, no dispersion of duration of action potentials in ventricular wall thickness. For this reason, these patients showed ST segment elevation with no tendency to develop arrhythmias (**Pérez-Riera AR et al 2012.**)



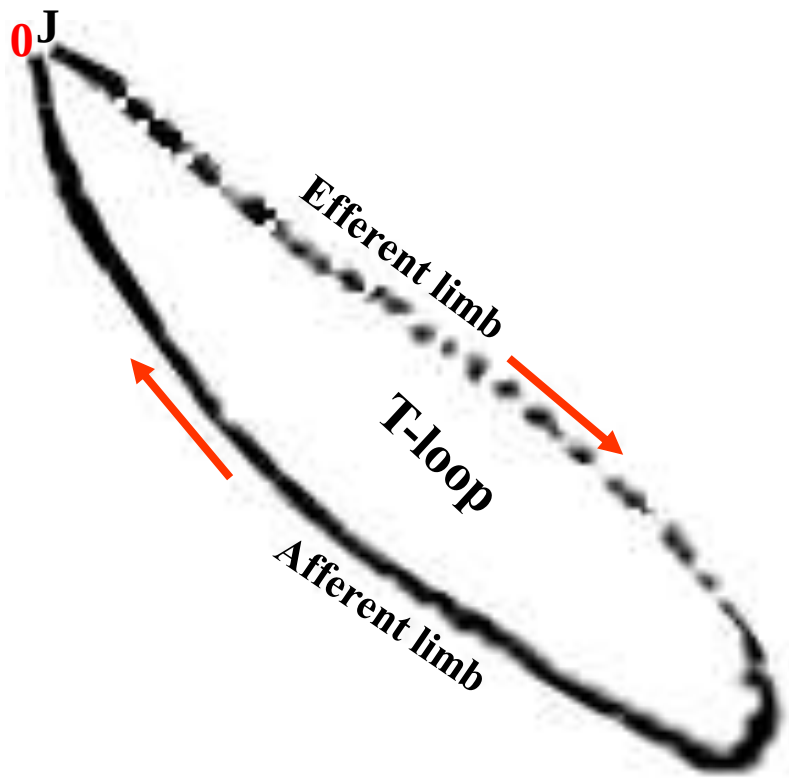
Comparison of ECG changes associated with early repolarization variant (ERV), acute pericarditis, acute myocardial infarction (AMI) and Brugada syndrome (BrS).

	Early Repol. Variant	Acute pericarditis	AMI	BrS type 1
ST segment appearance	Concave to the top	Concave to the top	Concave to the top	Convex to the top
Pathological Q waves	Absent	Absent	Present	Absent
Mirror image changes	Only in aVR	Absent	Present	Possible
Leads involved	Limb and precordial	Limbs and precordial	Segmentary pattern	Right precordial
R voltage	Normal or minimally augmented	Normal	Lost	Normal
PR interval	Not affected	Possible depression	Variable	50% prolongation
ST/T ratio in lead V6	< 0.25	> 0.25	Not applicable	Not applicable

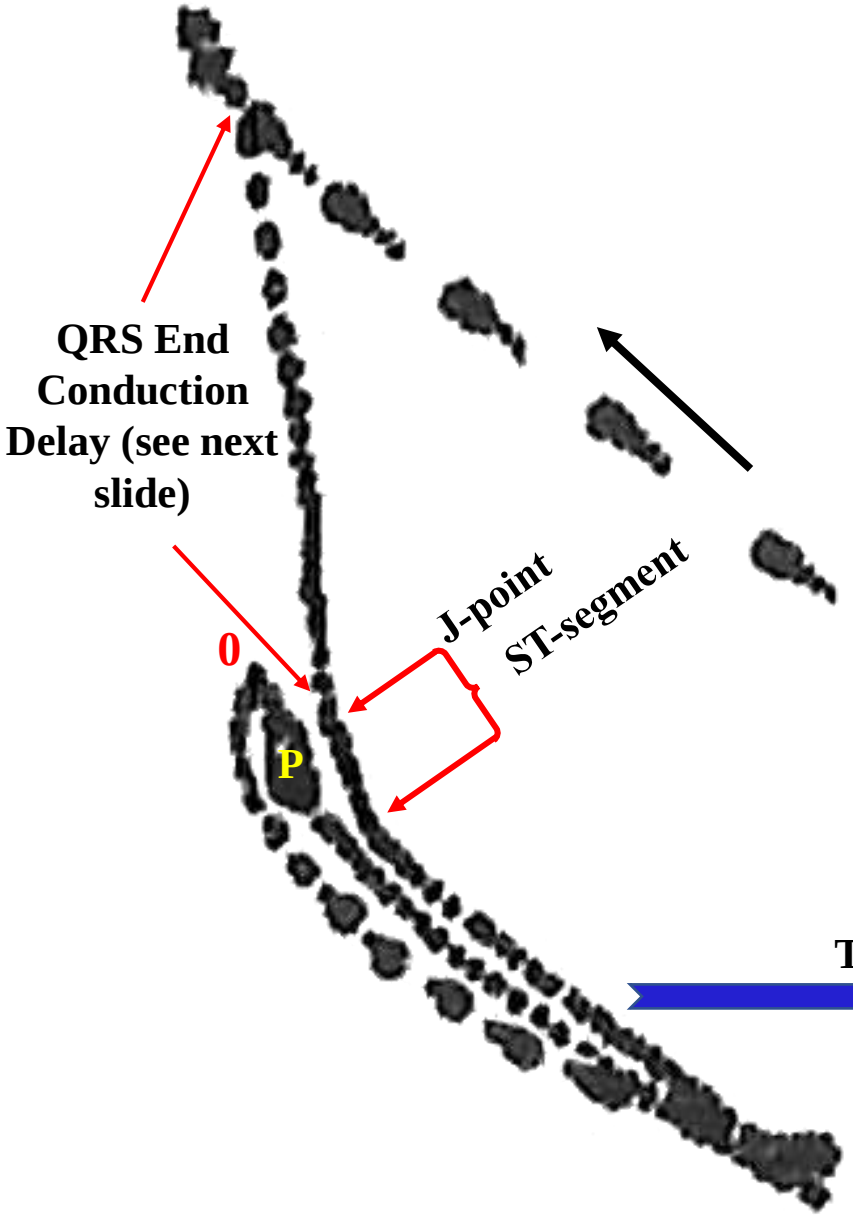
(Riera AR, et al 2008).

Normal T loop

0 &J points are coincident



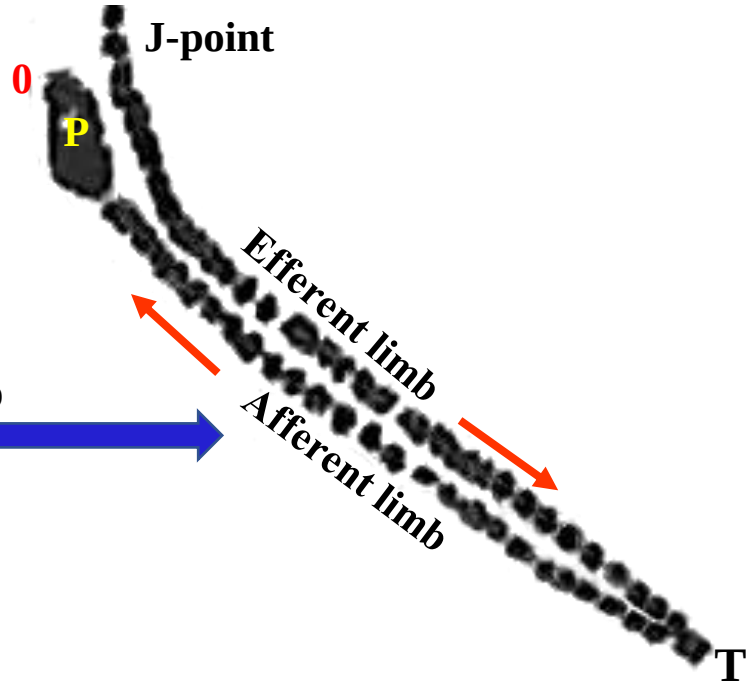
In the present case the T-loop is normal:



Why?

Because

1. The velocity of the efferent limb is smaller than that of the afferent one;
2. The 0 point and J-point are near coincident, they are not distant.(≥ 2mm) Consequently, there is no or minimal the repolarization mechanism.

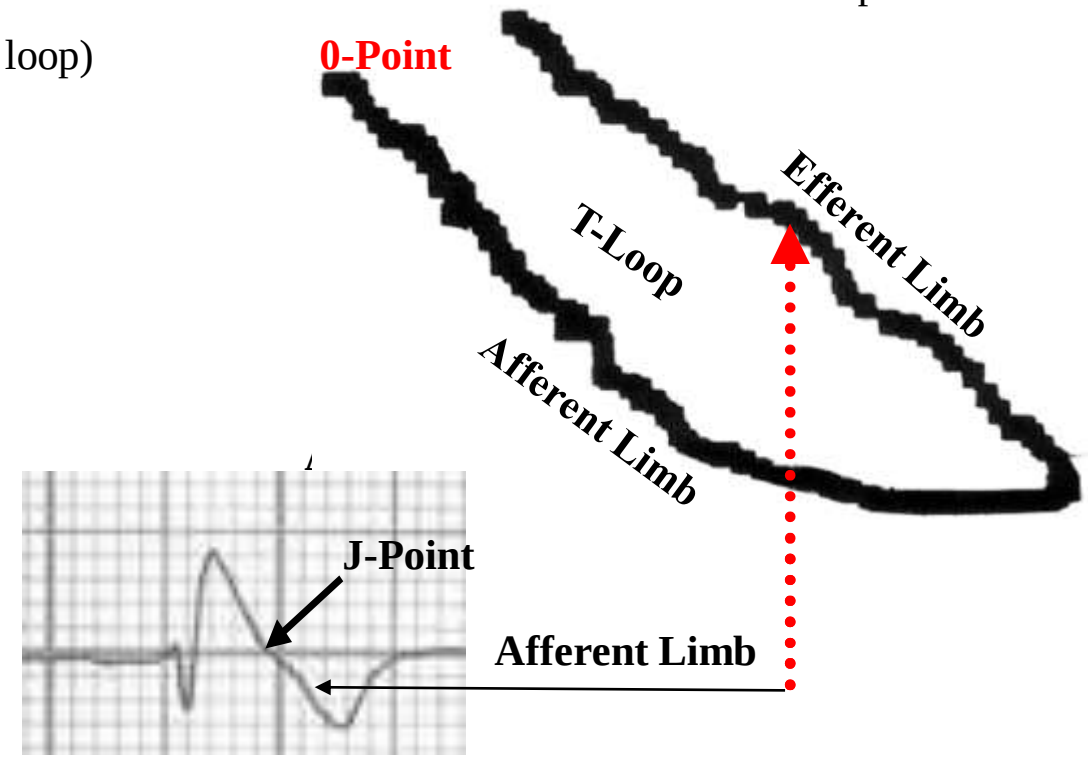


T-Loop showing presence of repolarization mechanism: Meaning of the distance between the 0 and J points of the T loop.

The distance between the 0 and J points is directly proportional to the degree of ST segment elevation

J-Point: T wave/loop onset

The end of ventricular repolarization (T loop)



Conclusion: the greater the distance between the two points, the greater the elevation or depression of the ST segment.

In vectorcardiography there are 3 basic points:

1. **E point**: it constitutes the zero point of VCG and it remains stationary before the onset of the P loop. It corresponds to the isoelectric line between the T wave and the P wave of ECG. The E letter corresponds to the cardiac dipole. E point: it indicates the onset of heart activation in the right atrium. In this point, the intersection of three orthogonal leads occurs (X, Z and Y).

2. **0 point:** it corresponds to the end of biatrial chamber activation, QRS loop onset (because PR segment does not exist, it is only a point) and the end of ventricular repolarization (T loop).

3. **J point:** it corresponds to 3 elements: end of ventricular depolarization (QRS-loop/ QRS complex); beginning of repolarization (ST segment) when it does not present depression or elevation, and T wave onset. In situations where there is depression or elevation of the ST segment, the J point does not coincide with the **0 point**, and the greater or lesser distance between both points indicate the greater or lesser ST segment elevation or depression. The phenomenon is observed in early repolarization, acute phase of infarction, ventricular aneurism, variant angina variant angina or Prinzmetal's angina,(**Maruyama M, et al. 2002**.) acute aortic dissection, acute pericarditis, type 1 Brugada pattern, Brugada phenocopy, Early repolarization syndrome, J-waves syndromes, canceled forms of arrhythmogenic cardiomyopathy (AC) (new nomenclature), raised intracranial pressure, left ventricular hypertrophy, left bundle branch block, Ventricular Paced Rhythm, hypercalcemia, Pulmonary embolism, Takotsubo Cardiomyopathy, following electrical cardioversion, tumors, myocarditis, gallbladder disease and pancreas disease etc.

Meaning according to the location of the conduction delay on QRS-loop

Initial conduction delay on QRS loop = *Preexcitation, WPW syndrome/ delta wave.*

Middle and End conduction delay = *Complete Left Bundle Branch Block.*

End Conduction Delay on QRS loop = *Complete or incomplete Right Bundle Branch Block and right fascicular block on RV free wall .*

Uniform Conduction Delay = *Hypercalemia; quinidine effect; intra-infarction, intramural*

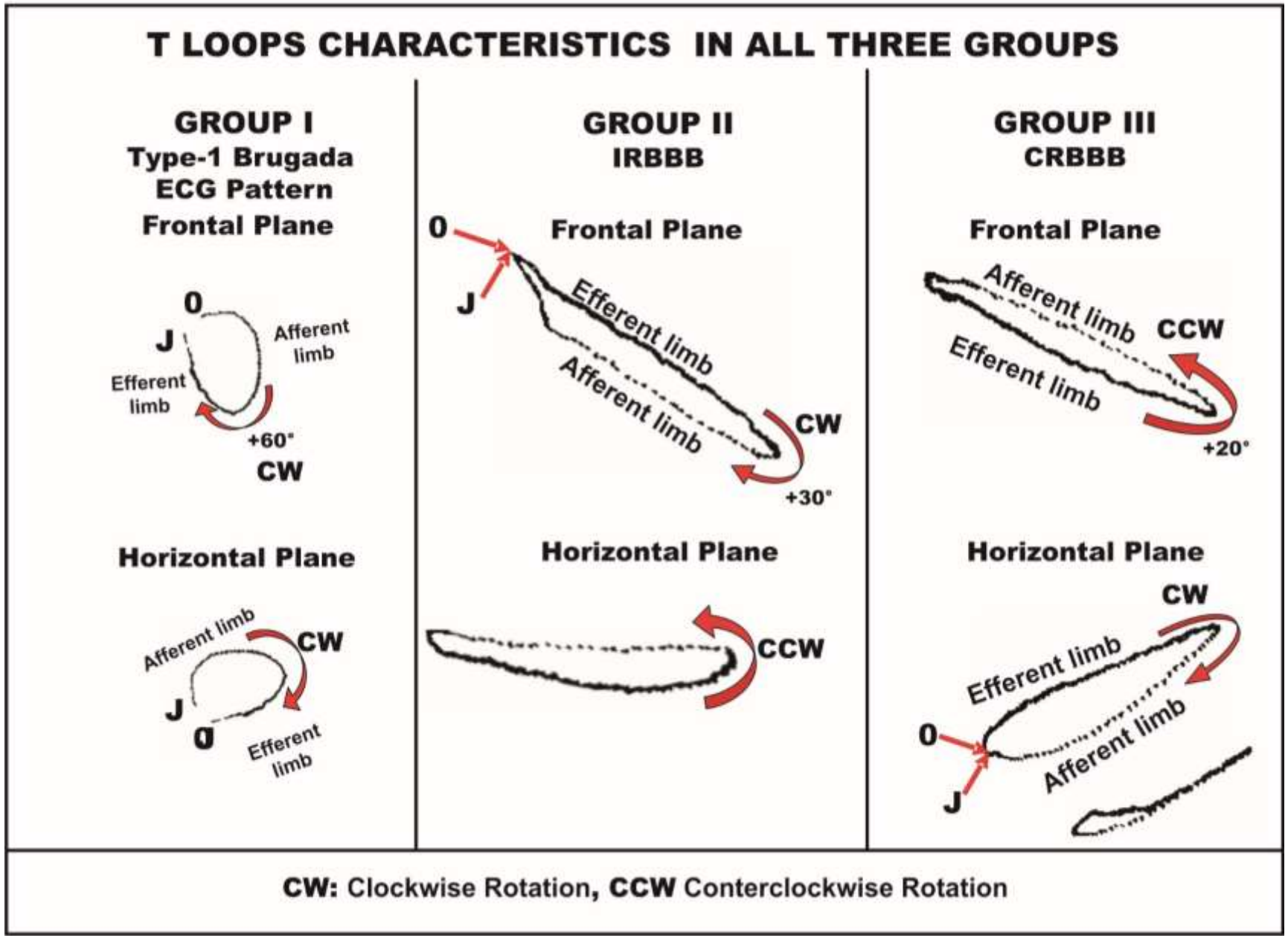
Each dash, comet or "tear" represents a time of 2 ms or 2.5 ms, depending on the calibration of the device.

The “head of the dash” points the direction of the rotation

The greater or the lesser distance between dashes indicates the greater or the lesser conduction velocity in the area. Thus, when they are very close to each other, it indicates the presence of **Conduction Delay**. To consider the phenomenon as true, it is necessary for it to be evident in at least 2 planes.

Comets distant from each other signal a greater speed of conduction of the stimulus or greater dromotropism:

Comets very close to each other indicate slower conduction velocity of the stimulus or conduction delay:



Peréz-Riera AR, Ferreira Filho C, de Abreu LC, Ferreira C, Yanowitz FG, Femenia F, Brugada P, Baranchuk A; International VCG Investigators Group.Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study.Europace. 2012 Jun;14(6):889-97. doi: 10.1093/europace/eur395

Effect of ECG filter settings on J-waves

Nakagawa et al. (**Nakagawa 2004**) performed a systematic study on the association between ECG filter settings and the J-wave morphology. The incidence of J-waves was significantly different among different low-pass filter settings. J-waves appeared more frequently with higher cutoff of low-pass filters (150- and 100-Hz) while at a cutoff of 25- or 35 Hz the J-waves were attenuated or eliminated. The amplitude of the J-waves was compared at all filter settings in patients with notch-type J-waves because the J-wave amplitude can be determined more correctly in notch than slur-type J-waves. The amplitude of J-waves was significantly lower with 25- and 35-Hz filters than 75-, 100-, and 150-Hz filters. The apex of the notch was duller and the amplitude was decreased when low cutoff low-pass filters were applied, which resulted in the disappearance of the J-waves. They evaluated the incidence of J-waves using different low-pass filters. When we considered both notching and slurring as J-waves, their incidence decreased from 16.8% with 150-Hz to 9.5% with 25-Hz filtering. The incidence of notch-type J-waves decreased from 10.7% with 150-Hz to 3.2% with 25-Hz filtering. Low-pass filters with low cutoff frequencies may hide clinically important signals such as J waves and affect the diagnosis. In addition, the J-waves of the shorter duration more frequently disappeared with the low cutoff of low-pass filter settings.

J-waves are usually defined as notching or slurring with an amplitude greater than 0.1 mV at the terminal QRS complex **(Haïssaguerre 2008**). Their reported incidence ranged widely from 5% to 24% (**Haïssaguerre 2008; Rosso 2008; Tikkanen 2009; Haruta 2011**). This may reflect age-, sex-, and race differences in the earlier study populations and differences in the definition of J-waves. Kligfield and García-Niebla findings suggest that the ECG filter setting is an important consideration in attempts to understand differences in the reported incidence of J-waves. ECG filtering is important for the interpretation and comparison of ECG signals. As low-pass filters allow the passage of low-frequency bioelectric signals but attenuate high-frequency signals such as muscle noise (**Kligfield 2007a; García-Niebla 2009a**), the latter must be filtered adequately without the loss of clinically important information. The 2007 guidelines of the AHA recommended a standard low-pass filter of 150 Hz for

adolescents and adults and 250 Hz for children (**Kligfield 2007a**). The inappropriate application of low-pass filters with a low cutoff eliminates most of the muscle noise but also attenuates or eliminates the high frequency component in the ECG signals such as the R-wave voltage, the notch within the QRS complex, and spikes elicited by pacemakers (**Kligfield 2007b; García-Niebla 2009a,b; García-Niebla 2010**).

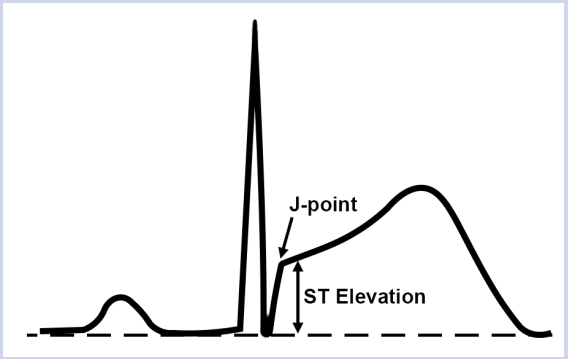
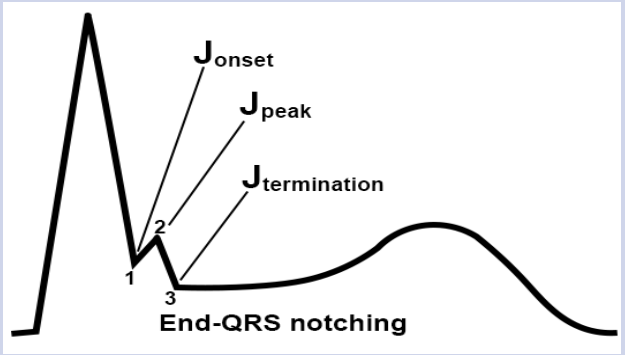
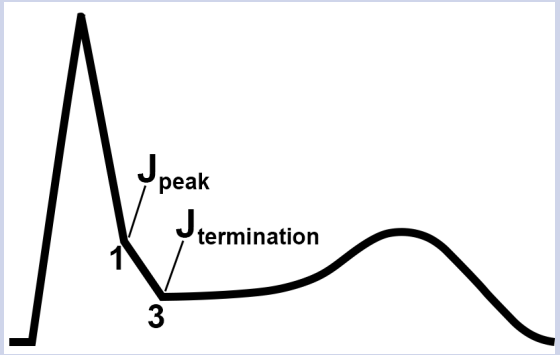
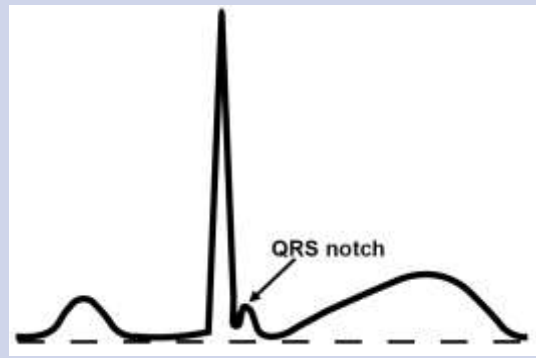
Current ECG recorders allow changes in the high- and low-pass filter settings. Kligfield and Okin (**Kligfield 2007b**) reported that the ECG filter settings were inappropriate in 75% of ECGs obtained within a single American medical community. García-Niebla et al. showed that QRS notching, clearly present with lowpass filters at 150- and 100 Hz, changed to slurring at 40 Hz in a patient manifesting J-waves, cautioned to use an appropriate ECG filter setting. (**García-Niebla 2010**). Their study has some limitations. The mechanisms underlying the genesis of J-waves recorded in patients with organic heart diseases, for example in patients in the acute phase of myocardial infarction (**Naruse 2012; Tikkanen 2012**) may be different in healthy populations. However, patients with coronary artery diseases were in the stable chronic phase of previous myocardial infarction or angina pectoris. In addition, in the sole patient with idiopathic ventricular fibrillation the J-wave changes seen at the different filter settings are similar to those seen in the other patients. Studies are underway to confirm the relevance of this findings for the manifestation of J-waves in patients with idiopathic ventricular fibrillation (**Nakagawa 2014**).

"Benign" early repolarization versus malignant early abnormalities: clinical-electrocardiographic distinction and genetic basis (Pérez-Riera AR, et al. Cardiol J. 2012)

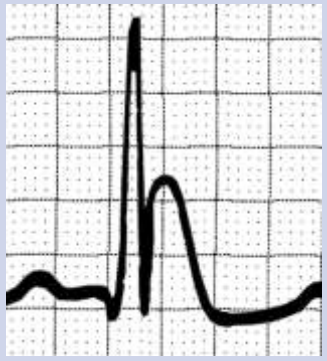
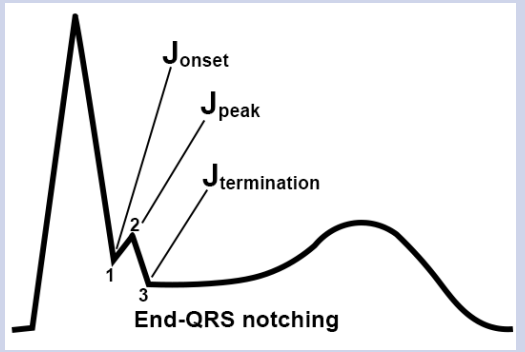
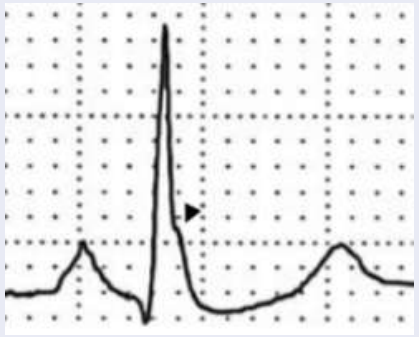
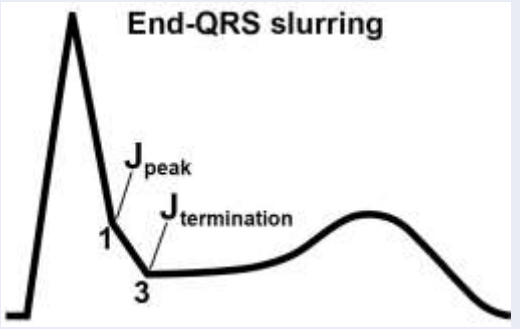
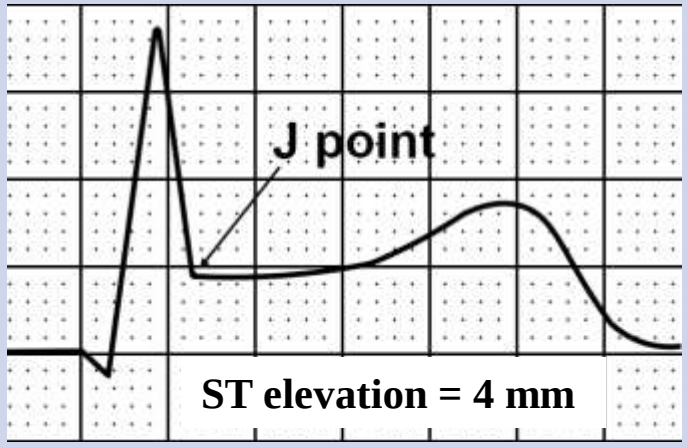
Early Repolarization Syndrome(ERS) and Early Repolarization pattern(ERP) definitions:

1. ERS 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 polymorphic VT/VF. ERS is a condition characterized by an ERP in the ECG and VF in the absence of structural heart disease. Additionally, ERS is associated with lone AF (**Hasegawa 2019**).
2. ERS can be diagnosed in an SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG.
3. ER pattern (ERP) can be diagnosed in the presence of J-point elevation ≥1 mm in ≥2 contiguous inferior and/or lateral leads of a standard 12-lead ECG. Also ERP is defined as an end-QRS notch or slur on the downslope of a prominent R-wave with a J point ≥0.1 mV in ≥2 contiguous leads of the 12-lead ECG, excluding V1 to V3. or 1) Presence of an end-QRS notch or slur lying entirely above the baseline, on the downslope of a prominent R-wave; 2) J peak (peak of notch or slur) is ≥0.1 mV in ≥ 2 contiguous leads of the 12-lead ECG, excluding leads V1 to V3; and 3) QRS duration < 120ms (**Sugrue A, et al. Clin Electrophysiol. 2018**).(**Macfarlane PW, Antzelevitch C, Haissaguerre M. et al. 2015**) (**Patton KK, et al. 2016**).

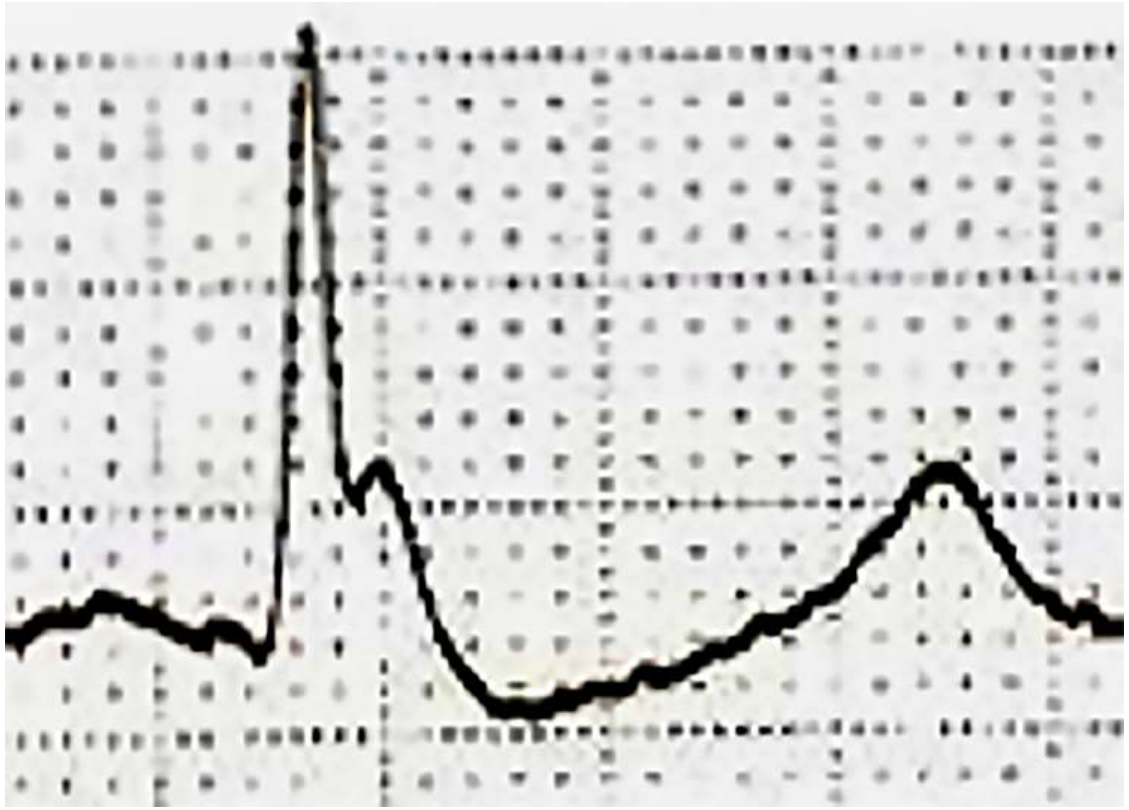
Examples of Early Repolarization

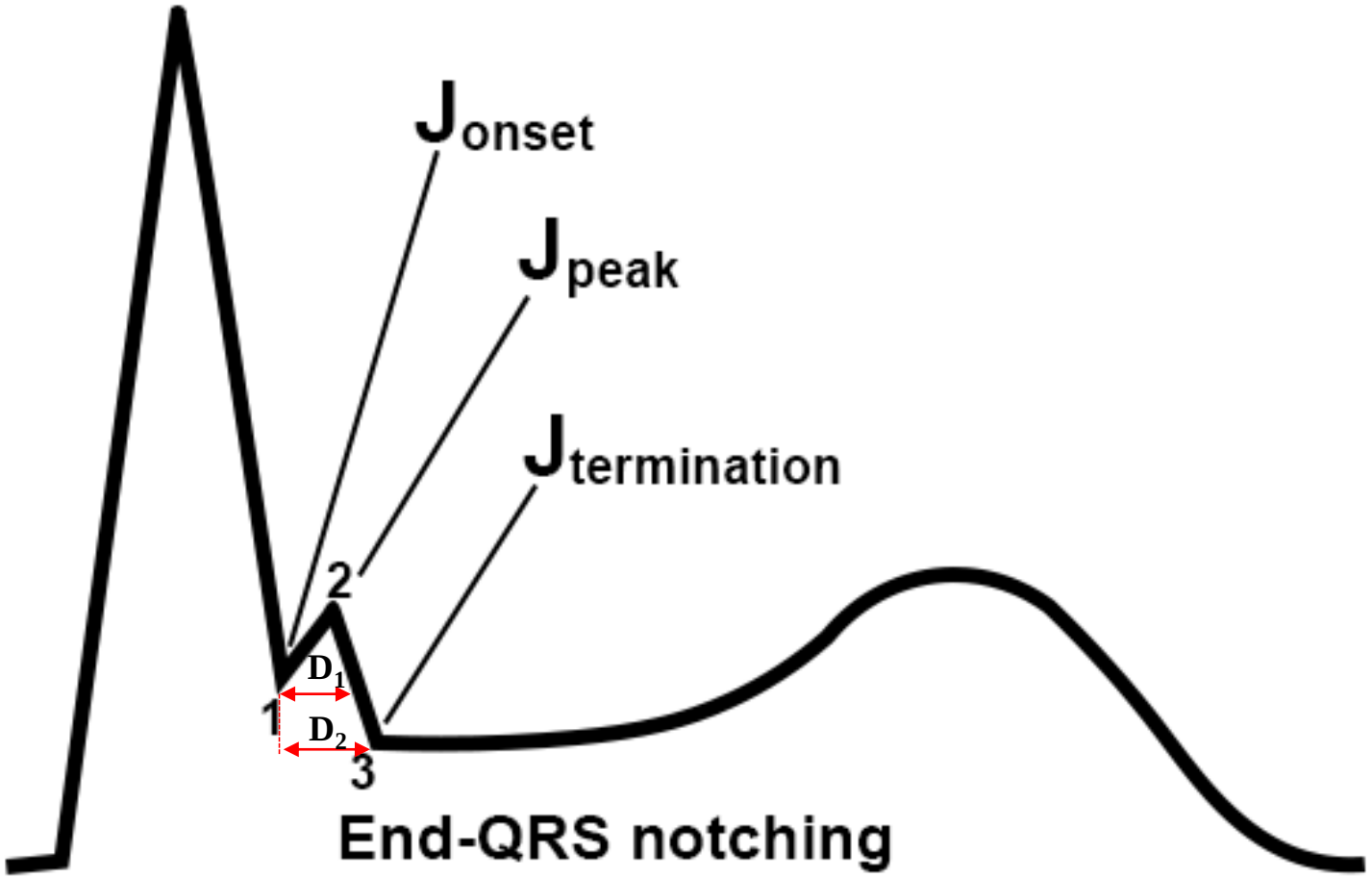
Early repolarization with ST elevation		Early repolarization with terminal QRS notch/slur	
			

Examples of early repolarization and other electrocardiographic repolarization patterns. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

Early repolarization Patterns	Descriptions	Example
Terminal QRS notching or End-QRS notching, A spike-and-dome configuration, or Notch J-wave variant	Low QRS defection at the end of QRS	 
Terminal QRS Slurring or End-QRS slurring	Abrupt change in the slope of the terminal forces of the QRS.	 
ST elevation Without J-wave Currently, this pattern is not considered ERP, The use of the term ER by some groups to refer to the J wave pattern, might explain some of the discordance between the studies in detecting this risk.(**Sallam K, et al 2013**.)	Elevation of the ST segment above the isoelectric baseline. Early repolarization (ER) was initially defined as ST segment elevation not associated with CAD or pericarditis occurring in healthy individuals.(**Grant RP, et al.1951**.) The finding is considered benign and commonly seen in younger age groups, athletes, African Americans and bradycardic individuals. (**Klatsky AL, et al. 2003**.)	

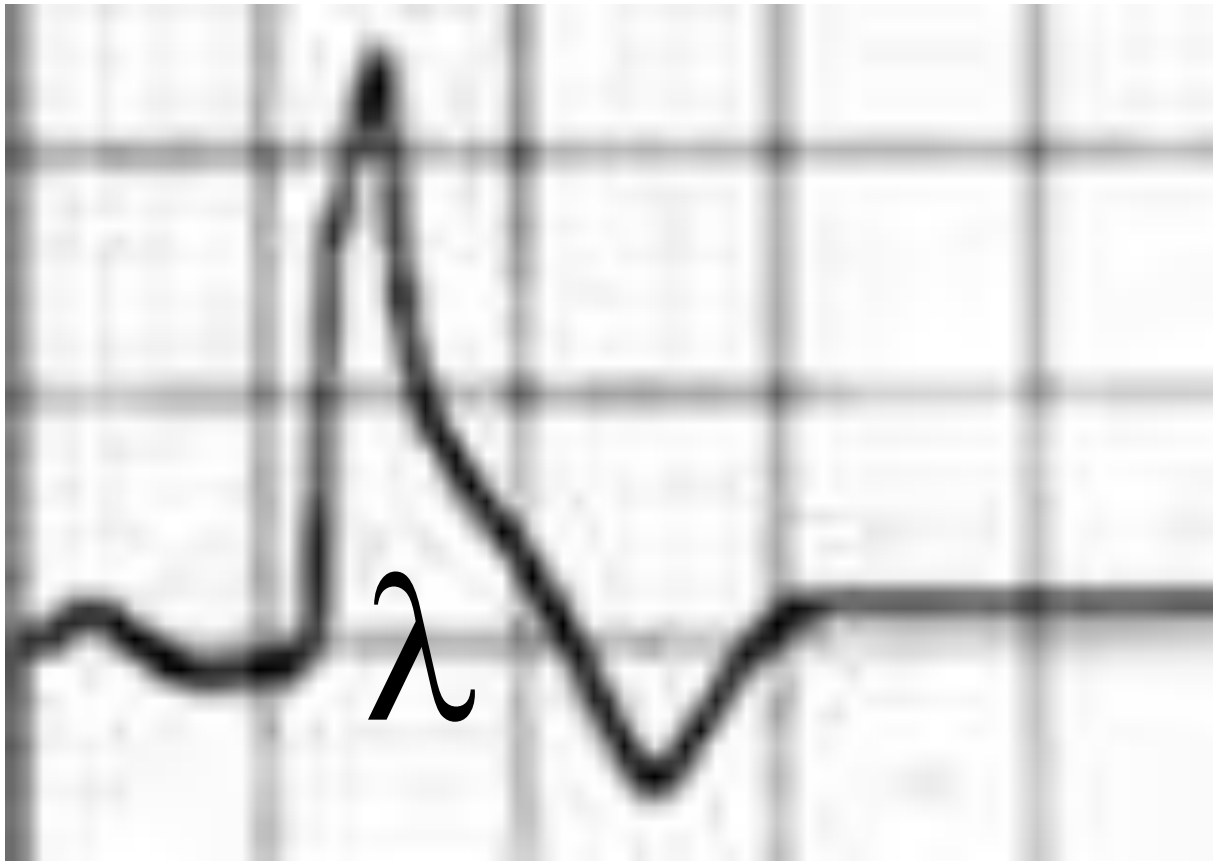
A spike-and-dome configuration, End-QRS notching or Notch J-wave variant

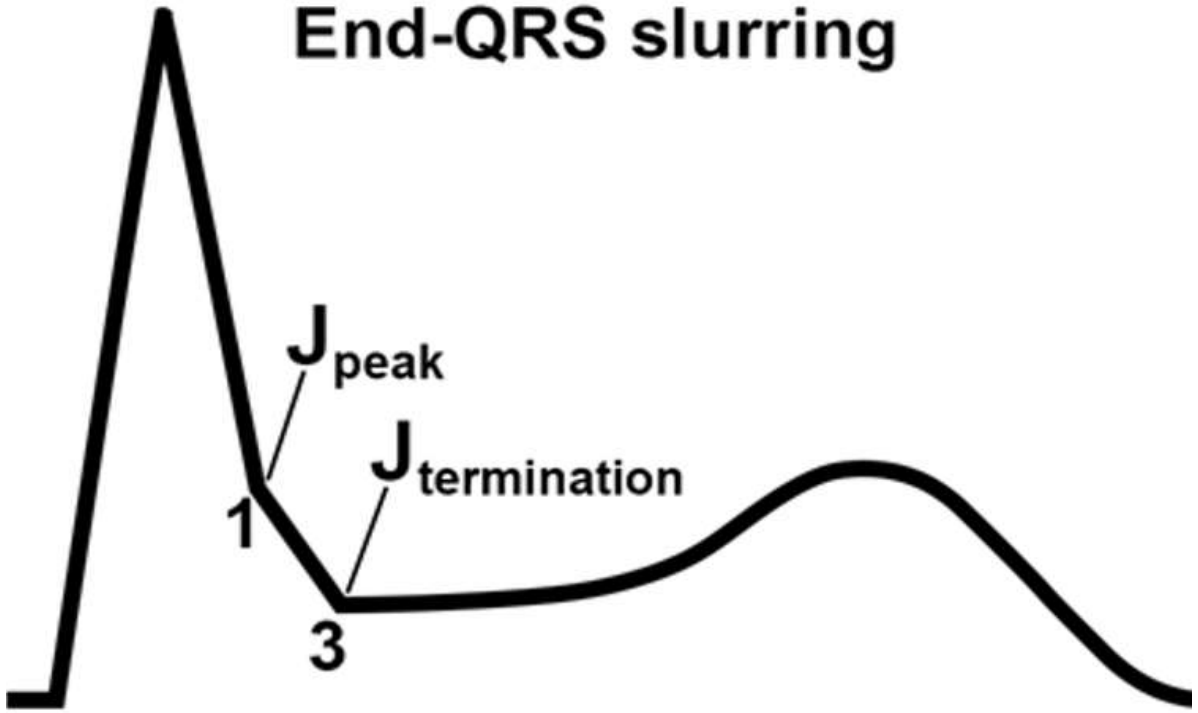


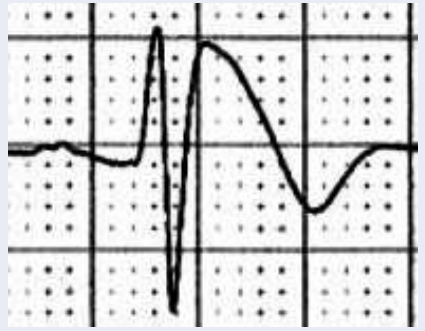
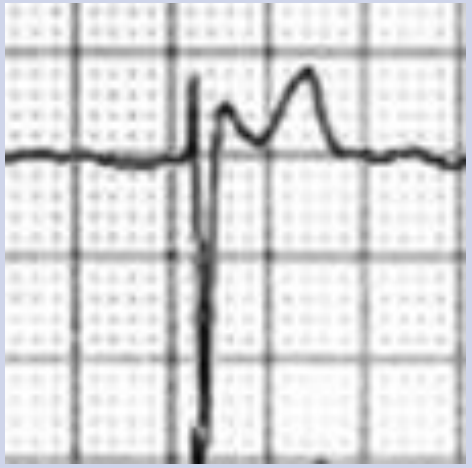
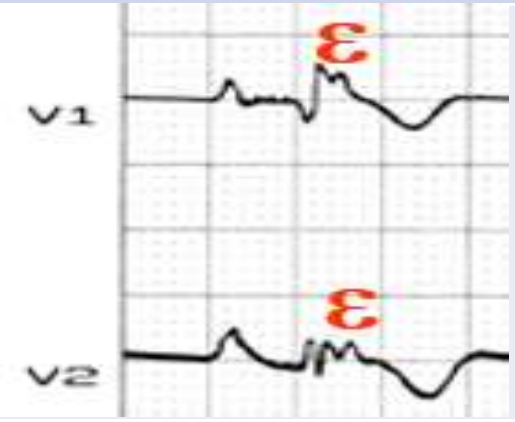


a. The amplitude at the onset of the notch **(J_o)**
b. The amplitude at the peak of the notch **(J_p)**
c. The amplitude at the end(termination) of the notch **(J_t)**
d. The duration from J_o to J_p **(D_1)** and
e. The duration from J_o to J_t **(D_2).**

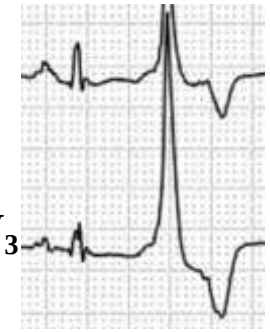
End-QRS slurring J-wave, lambda like wave or Gussak wave (Gussak I 2004)



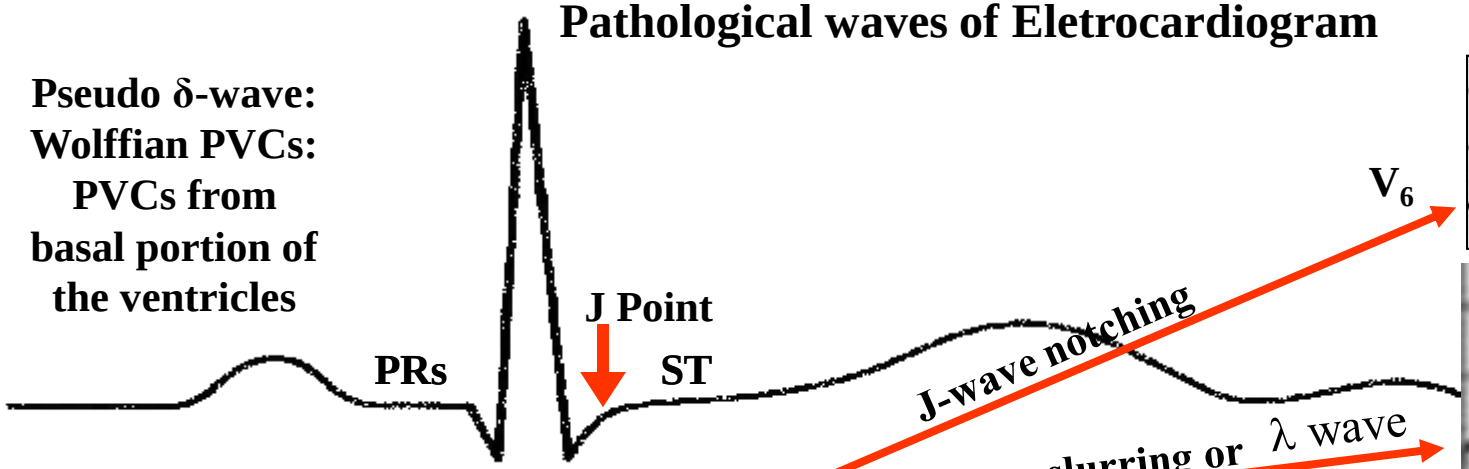


Early repolarization Patterns	Descriptions	Example
Other repolarization patterns	**Description**	**Example**
Type 1Brugada Pattern	J point and ST segment elevation ≥2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on the right precordial leads (V_1-V_2 or from V_1 through V_3) and/or high right precordial leads V_{1H}, V_{2H} and V_{3H}.	
Type 2 Brugada Pattern	A type 2 pattern raises the suspicion of BrS, but the diagnosis depends on the emergence of a type 1 pattern with a drug challenge.(**Sieira J, et al.2017**).	
Epsilon wave *"Fontaine discovered and named the epsilon waves. He chose the epsilon because it follows delta in the Greek alphabet and is the mathematical symbol for smallness" (**Hurst JW, 1998**)*. They are not pathognomonic of AC.	Epsilon waves are located at the end of QRS in the J point or onset of ST segment and observed in ≈ 15-30% of cases with 12-lead ECG. This percentage increases if we use the ECG with the modified protocol and High resolution ECG. Considered to be a major criterion for diagnosis by the Task Force for ARVC/D diagnosis.	

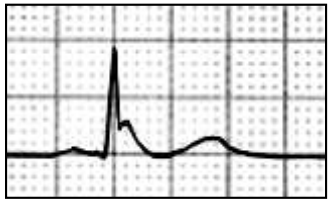
Pathological waves of Eletrocardiogram



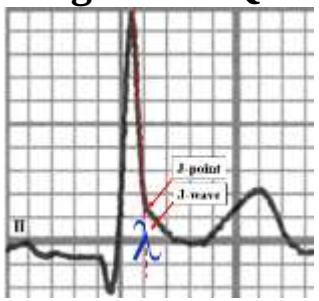
Pseudo δ-wave:
Wolffian PVCs:
PVCs from basal portion of the ventricles



Idiopathic VF



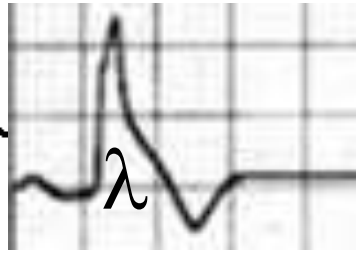
Congenital SQTS



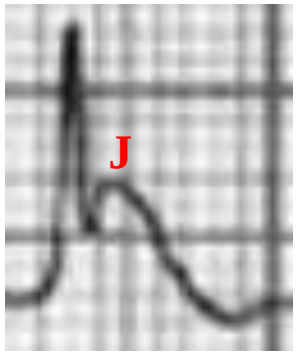
Brain injury

J-wave notching

J-wave slurring or λ wave

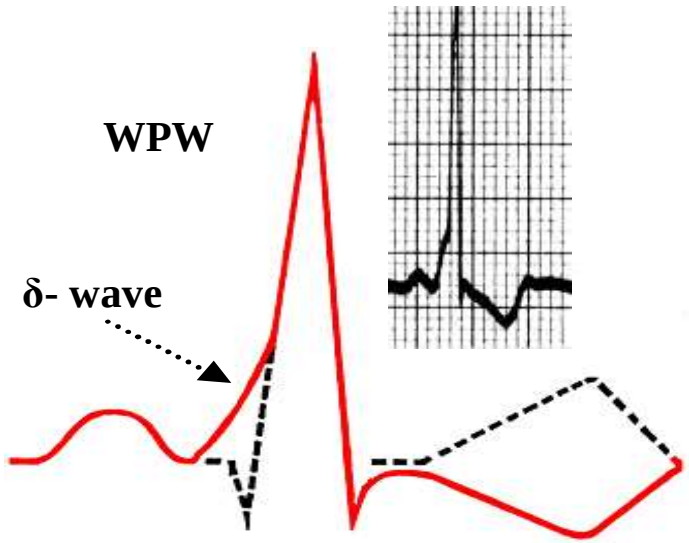


J-wave slurring, lambda (λ) or Gussak wave



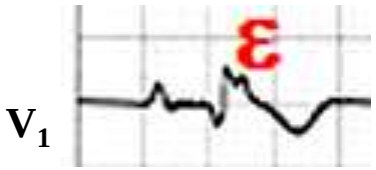
Prinzmetal

δ-wave and pseudo δ-wave

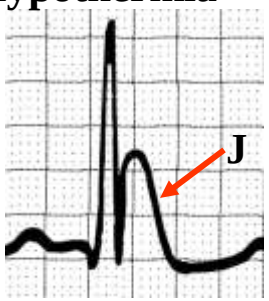


Epsilon wave

ARVC/D



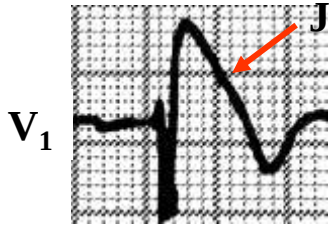
Hypothermia



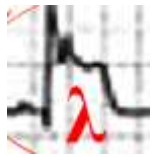
50mm/sec
2N
J-wave notching

Hypercalcemia

Brugada syndrome



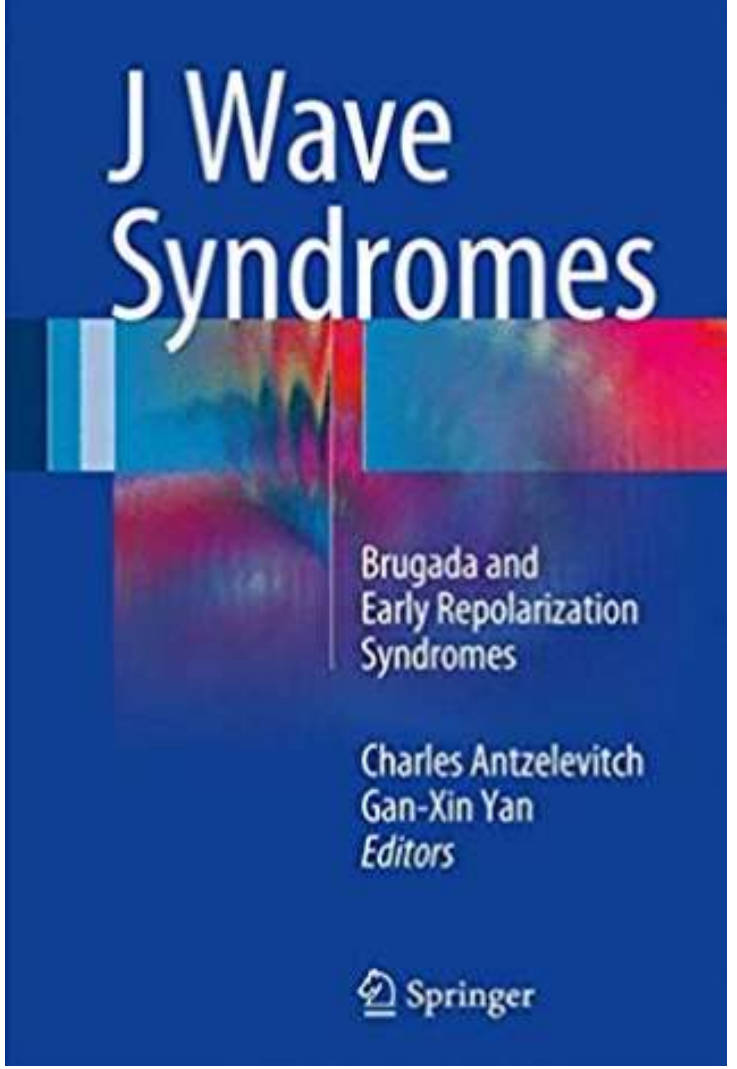
Short QT interval
The ST segment is almost absent



CAD

Ja Point: end of ST segment and beginning of QRS complex
J Point: end of QRS complex and beginning of ST segment

Gan-Xin Yan, MD, PHD



Charles Antezelevitz PhD

They are the pioneers in the clarification of cellular basis for the electrocardiographic J wave.

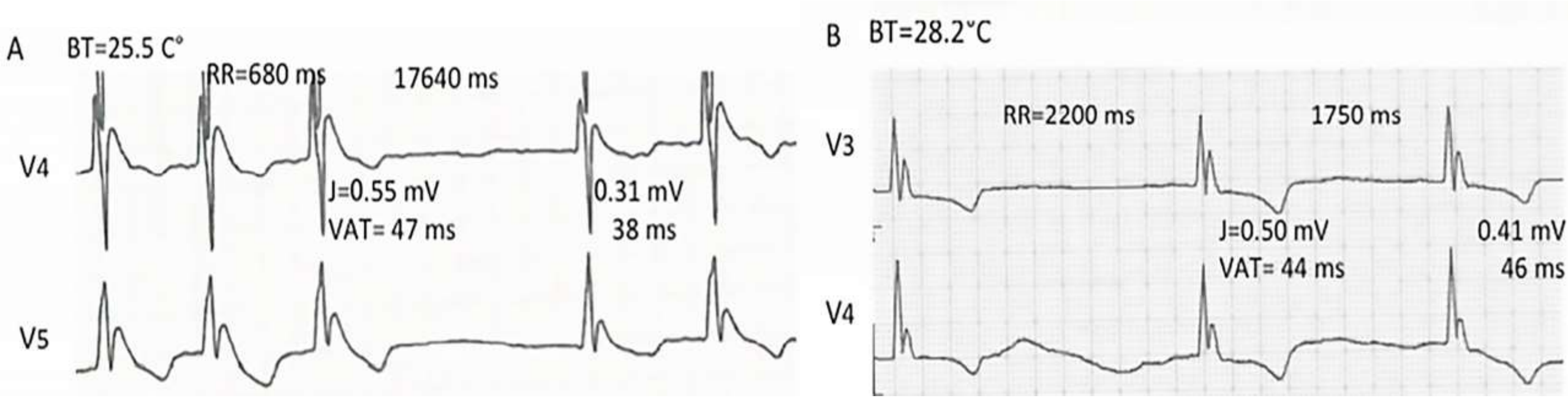
Their results provide the first direct evidence in support of the hypothesis that heterogeneous distribution of a transient outward current-mediated spike-and-dome morphology of the action potential across the ventricular wall underlies the manifestation of the electrocardiographic J wave. The presence of a prominent action potential notch in epicardium but not endocardium is shown to provide a voltage gradient that manifests as a J (Osborn) wave or elevated J-point in the ECG. (**Yan GX, Antzelevitch C. 1996.**).

Qi D, Gao Y, Yan GX. Electrocardiographic J wave: Early repolarization, Brugada wave, and conduction delay. Heart Rhythm. 2019 Jan;16(1):81-82. doi: 10.1016/j.hrthm.2018.08.007. We literally copy this important paper Dr Yan was the senior author

J wave is a deflection between the QRS and ST segment of which polarity is commonly in the same major direction of the QRS complex. J wave may stand as a distinct delta wave following the QRS, or be partially buried inside of the QRS as QRS notching or slurring (**Yan GX, et al. 1996; Badri M, 2015; Liu T, et al. 2016**). Since J wave occurs at the junction that marks completion of ventricular depolarization and beginning of ventricular repolarization, it can be part of either conduction delay or early repolarization. In other words, J wave is simply an ECG definition that does not clearly tell us whether it belongs to ventricular depolarization or repolarization. This then raises two key questions: 1) *What would be the mechanism underlying for J wave if it is part of ventricular repolarization? . 2) How can J wave from repolarization be distinguished from J wave from depolarization clinically?* A spike-and-dome configuration (notch J-wave) of action potential (AP) at phase 1 in ventricular epicardium mediated by a prominent transient outward current (Ito) is responsible for J wave on ECG with ventricular activation from endocardium to epicardium (**Yan GX, et al. 1996**). The behaviors of Ito-mediated J wave are therefore determined by Ito and its interaction with other currents active in AP phase 1 such as INa and ICa,L. Since recovery of Ito from inactivation is relatively slow, Ito-mediated AP notch and resultant J wave on ECG is rate-dependent: i.e. the size of the notch and J wave is commonly larger during bradycardia and smaller during tachycardia (**Yan GX, et al. 1996; Badri M, et al. 2015; Liu T, et al. 2016**). This feature can, therefore, be helpful in distinguishing Ito-mediated J waves from those of depolarization abnormalities which often become larger in size during tachycardia (**Liu T, et al. 2016**). An example derived from it was recognition of the underlying mechanisms for the BrS in 1996 when Yan pointed out that the so-called “right bundle branch block” in cases of VF reported by Brugada brothers in 1992 (**Brugada P, et al. 1992**), which is accentuated during bradycardia or after a pause, was in fact a prominent Ito-mediated J wave (**Yan GX, 1996**). Quinidine, despite a fact that it as an INa blocker can cause conduction delay, was shortly afterwards identified as a specific pharmacotherapeutic agent for the BrS because inhibits Ito in addition to blockade of INa (**Yan GX, 1999**).

Aizawa et al, reported a finding that hypothermia-induced J waves, which was previously demonstrated to be Ito-mediated (**Yan GX, et al. 1996**), were augmented following shorter RR intervals in some patients but decreased in others (**Aizawa Y, et al 2019**). Does it make sense that augmentation of J wave following shorter RR intervals in hypothermia. Similar observation was reported by Takahiro (**Takahiro T et al. 2015**) could be simply due to conduction delay? Hypothermia can slow down ventricular conduction globally. But such globally decreased ventricular conduction velocity, for examples in hyperkalemia or with use of sodium channel blockers, often manifests as QRS widening instead of J wave. In addition, such tachycardia-induced augmentation of J waves in hypothermia could be abolished by isoproterenol (**Takahiro T et al. 2015**). This is striking evidence that rules out conduction delay as the cause for tachycardia-induced augmentation of J wave in hypothermia because isoproterenol abolishes Ito-mediated J wave exclusively via enhancing ICa,L and making Ito more opposed (**Yan GX, et al. 1999**). The question now is: why can Ito-mediated J wave in hypothermia in humans become larger in response to a rate increase? To answer this question, Qi et al. (**Qi et al. 2019**) firstly need to understand pathophysiology of hypothermia. Firstly, hypothermia influences not only Ito but also other ionic currents active for generation of ventricular action potential; secondly, hypothermia can reduce ventricular conduction velocity. These factors plus others such as activation vectors and individual differences in kinetics of ionic channels may influence manifestations of J wave in hypothermia. Although Ito is an dominant ionic current for the AC notch at phase 1, inward currents like INa and ICa,L can influence the amplitude and width of the notch (**Yan GX, 1996; Badri M, 2015; Yan GX, 1999**). Compared with that of canine, ventricular Ito of humans exhibits relatively faster recovery from its inactivated state (**You T 2015**). This indicates that human ventricular Ito in healthy individuals may be less rate-dependent within the range of physiological heart rates. Because of differences in Q10 in activation and recovery between Ito and inward currents particularly ICa,L, ICa,L in hypothermia may be more rate-dependent and, therefore, reduce more significantly than Ito during tachycardia, leaving Ito less opposed and resulting in accentuation of Ito-mediated action potential notch and J wave. The effect of temperature on the balance between Ito and inward currents and eventually on Ito-mediated action can induce Brugada wave under different pathophysiological conditions.

Individual differences in kinetics of Ito and inward currents may be also present. If recovery of Ito from inactivation is slowed sufficiently and becomes more rate-dependent in some patients in hypothermia, bradycardia or pause may amplify their hypothermia-induced J wave. Another important factor that influences J wave manifestation is ventricular conduction. Previous studies have shown that slowing of ventricular transmural conduction allows the J wave to more completely move out the QRS and results in an increase in J wave amplitude (**Yan GX, et al. 1996; Liu T, et al. 2016**). This appears to be the case as seen in the study of Aizawa et al (**Aizawa Y, et al 2019**) in Figure below panel A, augmentation of J wave following shorter RR intervals was accompanied by QRS widening; in panel B, when there was no rate-dependent change in QRS duration, shorter RR intervals were associated with smaller J waves.



BT: Body Temperature

Finally, ventricular activation vector also contributes importantly to J wave manifestation on ECG. Unfortunately, this has been largely ignored in studies for J wave and J wave syndromes. For example, hypothermia can theoretically induce J wave in all of ECG leads. However, J wave in the leads of V1 (perhaps also V2) and aVR in hypothermia is rarely reported and discussed. Hypothermia can in fact produce two types of J wave in leads of V1 and aVR: Brugada wave which exhibits a polarity opposite to that of QRS (**Ansari E, et al. 2003**) and an inverted J wave, as seen in Figure next slide from the reference (**Takahiro T et al. 2015**) and Figure below in the study of Aizawa et al. (**Aizawa Y, et al 2019**). In the regions where the leads of V1 and aVR represent, ventricular activation occurs likely from the epicardium toward the endocardium.

Figure from Aizawa Y et al , 2019

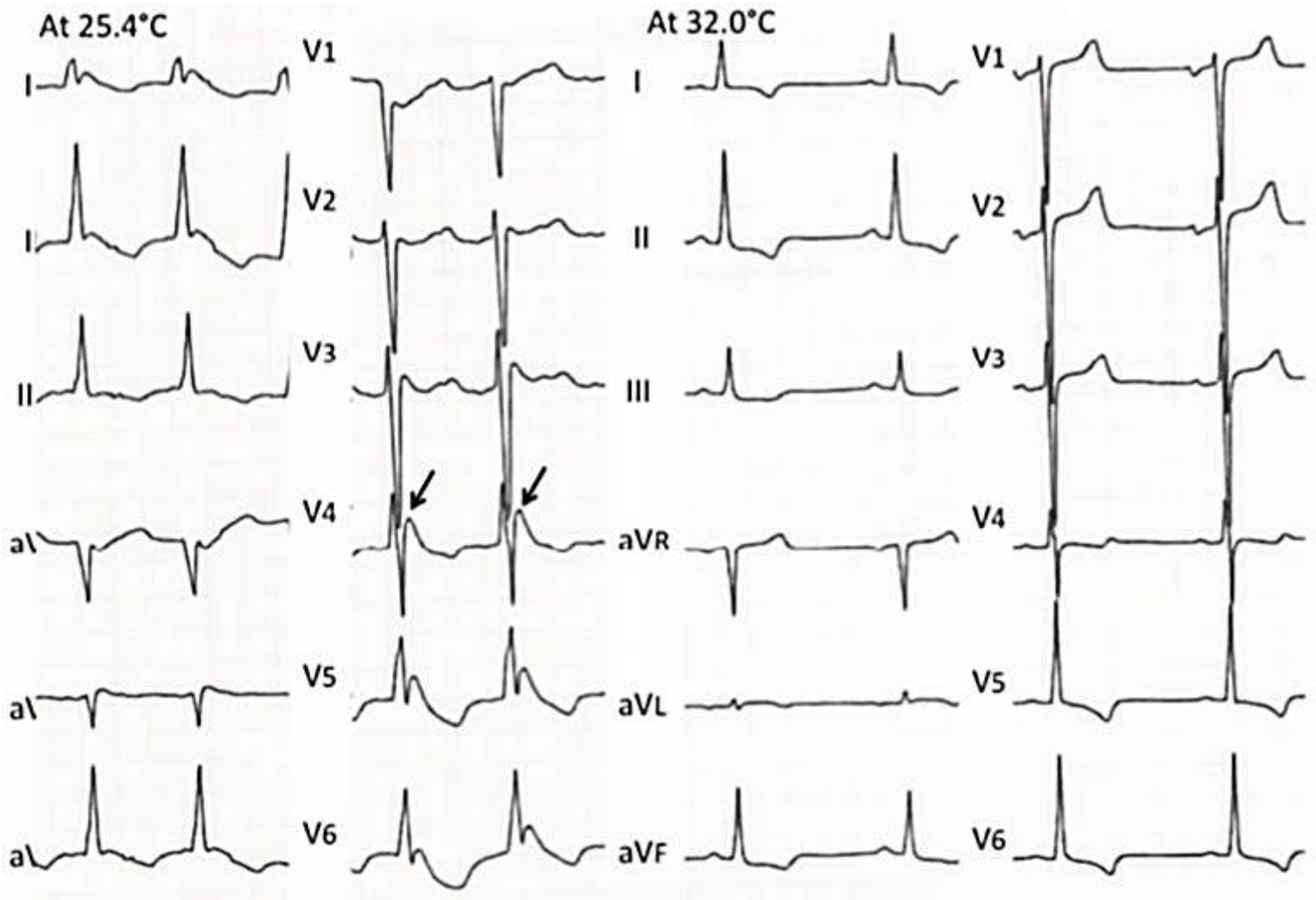
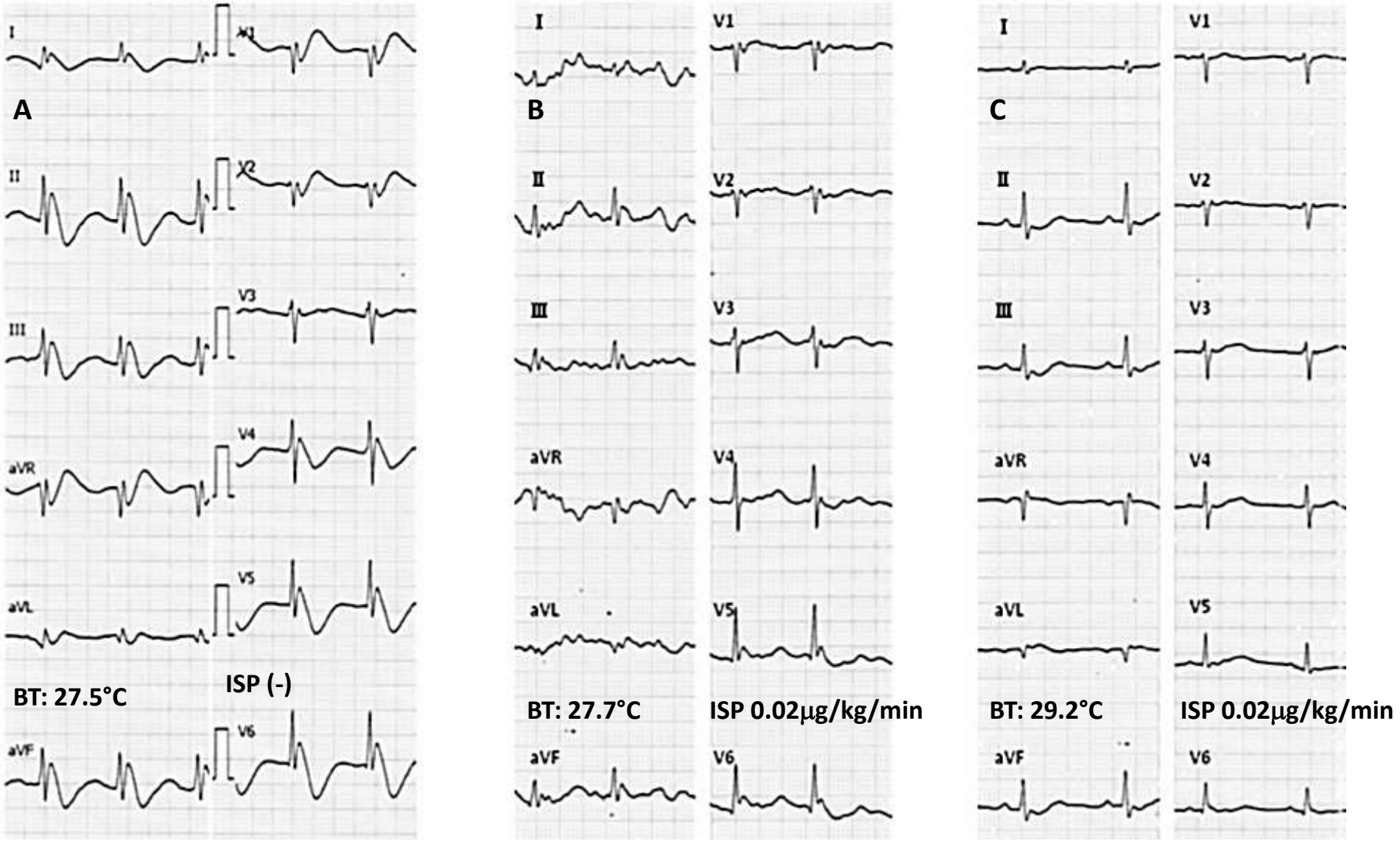


Figure from Takahiro T et al. 2015



A: ECG on arrival to the ED, when the patient's core body temperature (BT) was 27.51C. There are significant J waves extending in all leads, followed by a down sloping ST elevation with a negative T wave. B: ECG about 10 minutes after initiation of isoproterenol (ISP) infusion, when the patient's BT was 27.71C. The magnitude of the J wave is significantly decreased in all leads. C: ECG after rewarming. When the patient's BT reached 29.21C, the J wave almost disappeared.

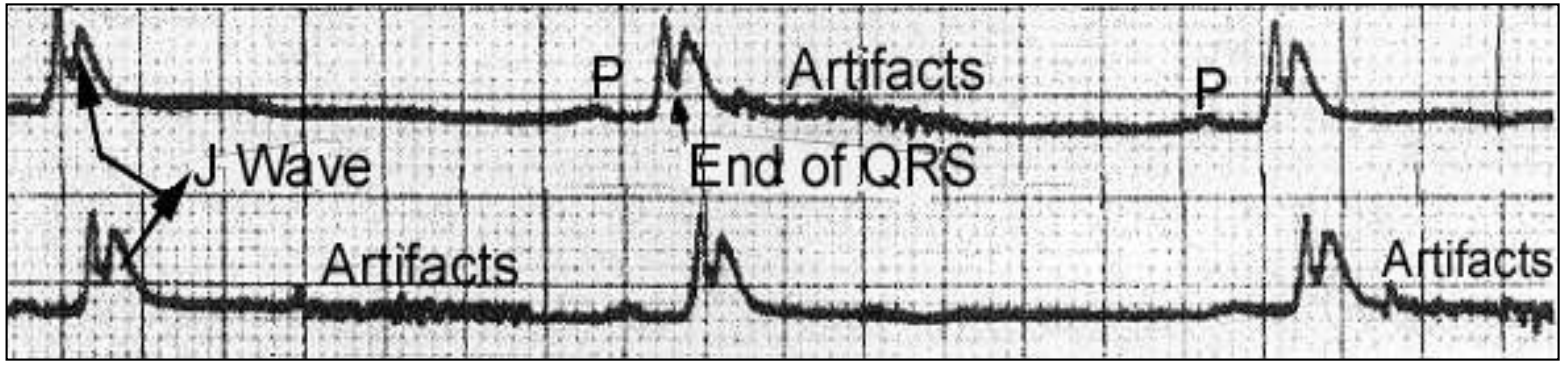
With this ventricular activation sequence, J wave produced by the Ito-mediated epicardial AP notch in RV is completely buried inside the QRS under physiological conditions. Mild to moderate hypothermia is, therefore, unable to bring this J wave out of the QRS. Only severe hypothermia, which potential notch can explain why both hypothermia (**Ansari E et al. 2003**) and fever (**Antzelevitch C et al. 2002**) likely causes complete loss of epicardial action potential dome, can produce a giant J wave, i.e. Brugada wave, capable of standing out the QRS. If hypothermia fails to produce Brugada wave from the epicardium, a relatively small and inverted J wave resulting from action potential notch in the endocardium1 can be commonly seen in V1 or aVR. What we have learnt from the studies of Aizawa et al (**Aizawa Y, et al 2019**) and others is: Ito-mediated action potential notch can manifest as J wave or Brugada wave that can be induced by hypothermia or fever and amplified by bradycardia or tachycardia. Although these diversified manifestations of Ito mediated J wave are largely determined by features of Ito, they are also influenced by ventricular conduction, activation vectors and pathophysiological conditions that alter the balance between Ito and other ionic currents.

1. Hypothermic J- wave or Osborn wave ECG features

Concept: hypothermia is defined as the condition where central temperature (rectal, esophageal or tympanic) is below 35ºC. Hypothermia may be accidental, metabolic, or therapeutic. Accidental hypothermia is more frequent in countries with cold weather, during winter season. The hypothermal state is characterized by drop in basal metabolism, decrease in O_2 consumption and greater production of CO_2.

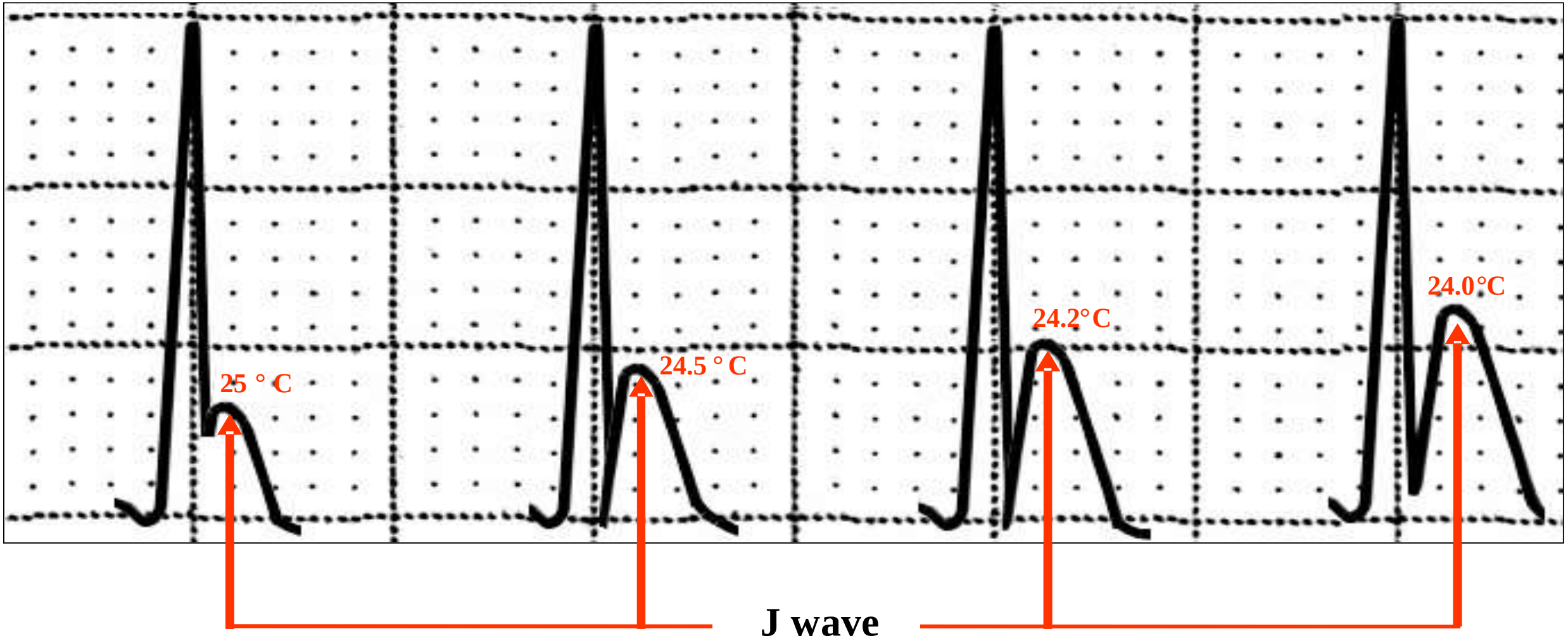
During hypothermia, a gradual decrease of heart rate is observed and systolic volume, with progressive drop of blood pressure later, which becomes significant when central temperature values close to 23ºC are reached.

- **Sinus bradycardia**, but in the initial phase tachycardia by release of adrenaline
- **Atrial fibrillation** (50% of cases), temperature < 32ºC.
- **Artifacts:** fluctuation in the baseline caused by the muscular trembling. Only in the initial phase (of struggle), when body temperature is between 36 and 32ºC.
- **PR interval** prolongation
- **QRS complex:** decrease in voltage and increase in duration.
- **QT and QTc intervals:** marked prolongation.
- Both supraventricular and ventricular arrhythmias
- Very characteristic extra wave, called J wave between the end of QRS complex and ST segment onset, not pathognomonic (may be observed in normothermic conditions, positive and prominent in V_5 and V_6. Inverse correlation between J wave voltage (mm) and central temperature



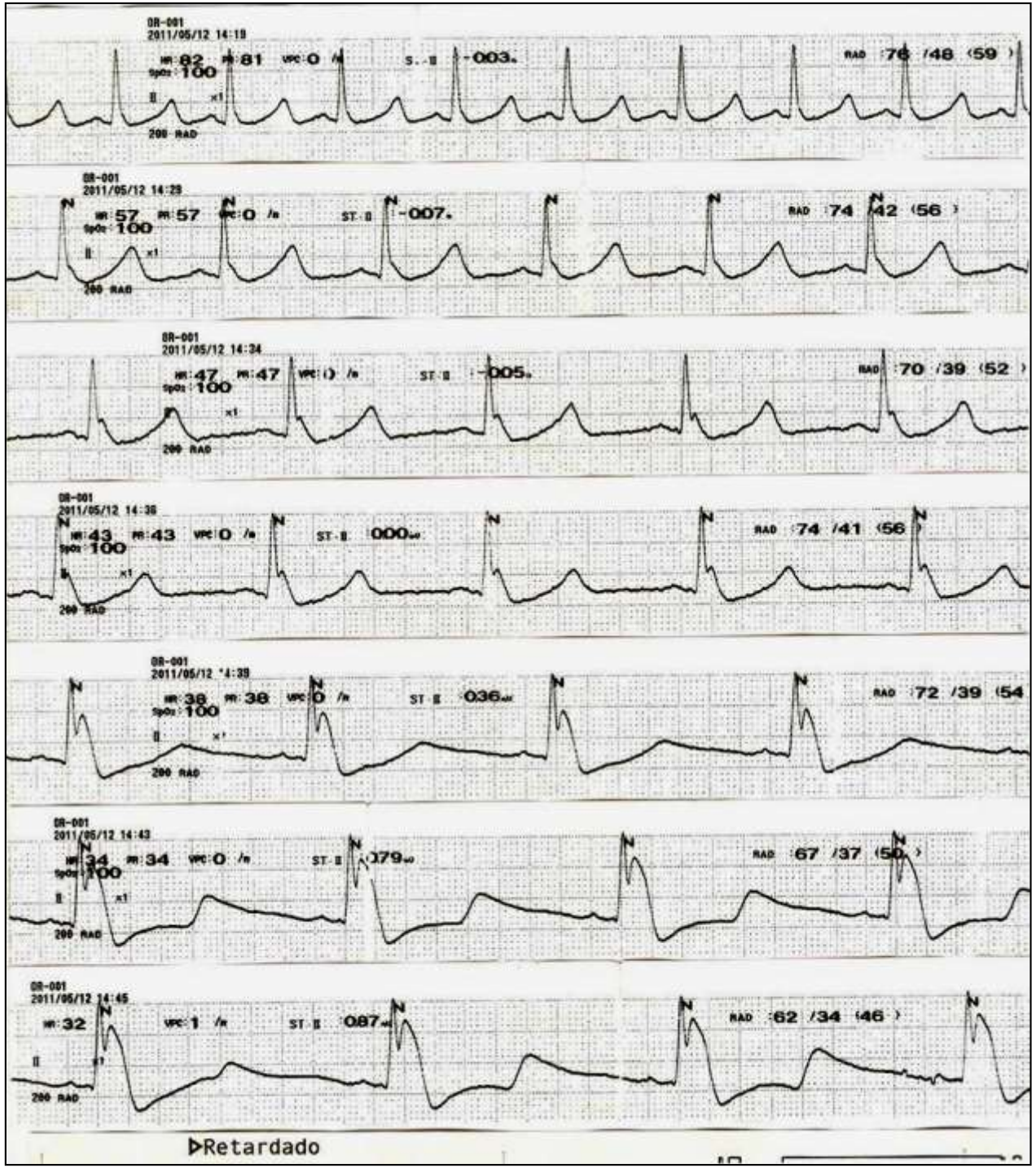
Synonymous: Osborn wave (**Osborn JJ. et al. 1953**.), camel-hump sign (**Abbott JA, et al.1976**.), late delta wave, hathook junction, hypothermic wave, K wave, H wave or current of injury. (**Antzelevitch C, et al.. 2009**)

Inverse and significant correlation between J wave voltage (mm) and central body temperature (BT) in hypothermia



A spike-and-dome configuration, End-QRS notching or Notch J-wave variant

de Souza D, Riera AR, Bombig MT, Francisco YA, Brollo L, Filho BL, Dubner S, Schapachnik E, Povoa R. Electrocardiographic changes by accidental hypothermia in an urban and a tropical region.J Electrocardiol. 2007 Jan;40(1):47-52DOI: 10.1016/j.jelectrocard.2006.08.094



The tracing was obtained during cooling of the blood before a surgical procedure of the heart.

Although the ECG obtained was somewhat expected, what was striking is that the progressive development and augmentation of the J wave was recorded.

Most of the hypothermia cases are published in the moment when the patient is rescued and after recovery. On the other hand, in this case we can see the time course of changes up to the simulation of a monophasic action potential.

Additionally, significant bradycardia is observed and the QT interval was too prolonged, something that usually is not given much attention in the published cases.

Courtesy from Prof. Dr. Raimundo Puerta from Cuba

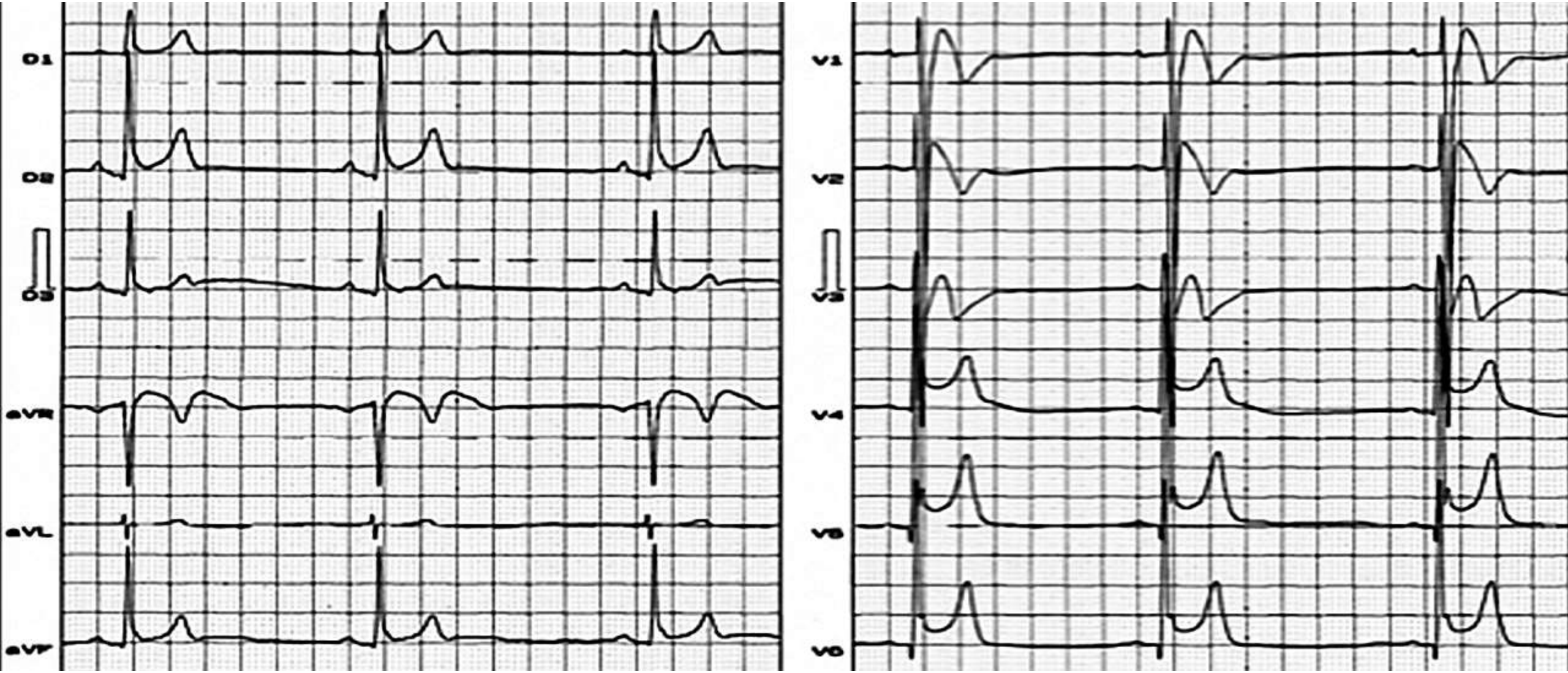
2. Normothermic states

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

J-wave syndromes

- **BrS:** J-wave in the right precordial leads V1-V3. BrS is the right ventricular variant of hereditary J wave syndromes, mainly in RVOT.
- **ERS:** Recent meta-analysis suggests that the ERP is associated with a high risk of arrhythmic events in patients with BrS. In particular, BrS patients with inferolateral
  I. **ERP Type 1:** in lhe lateral lead. Lower risk
  II. **Type 2: ERP:** in the inferior (II, III, aVF) or inferolateral leads (II, III, aVF, V5-V6). Intermediate risk.
  III. **ERP: Type 3 or global ERP:** (inferior, lateral, and right precordial leads: Highest risk. arrhythmic risk.(**Georgopoulos S, et al 2018**). The risk for development of VT/VF is dictated in large part by the ER subtype (Type I, II or III),
- **Overlapping BrS+ ERS:** J-wave syndrome
- **Idiopathic Ventricular Fibrillation(IVF)** Atrial pacing induced an attenuation of J waves on ECGs. On the other hand atrial pacing induced augmentation in non-IVF patients. This findings suggest that the different rate dependence of J-wave amplitude may be because of different mechanisms underlying the genesis of the J waves: *I*to-mediated differences in transmural repolarization—in the IVF patients versus delayed conduction in the non-IVF subjects. in IVF patients higher rate attenuate J-wave . (**Aizawa Y, et al. 2017**).
- **SQTS**
- **LQTS:** Although ERP is common in LQTS, the presence of concomitant ERP does not correlate with either those with a history of LQTS-triggered events prior to diagnosis or those with subsequent breakthrough cardiac events from their treated LQTS substrate. (**Sugrue A, et al. 2018**).
- **Sudden infant death syndrome (SIDS)** (**Kanter RJ, et al, 2012; Antzelevitch C. et al. 2001**.)

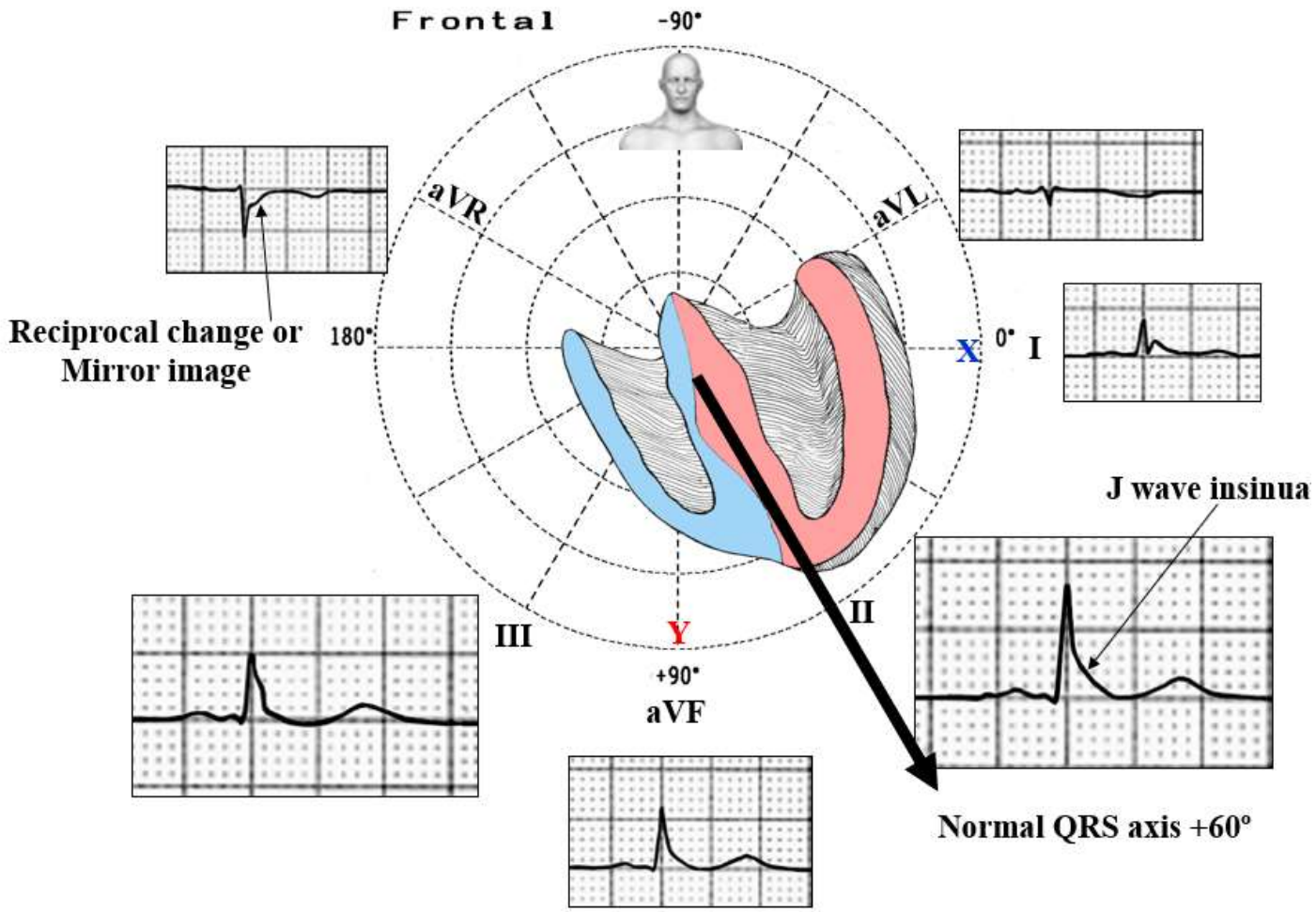
Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities.
(McIntyre WF, Pérez-Riera AR, et al. 2012 J Electrocardiol.)

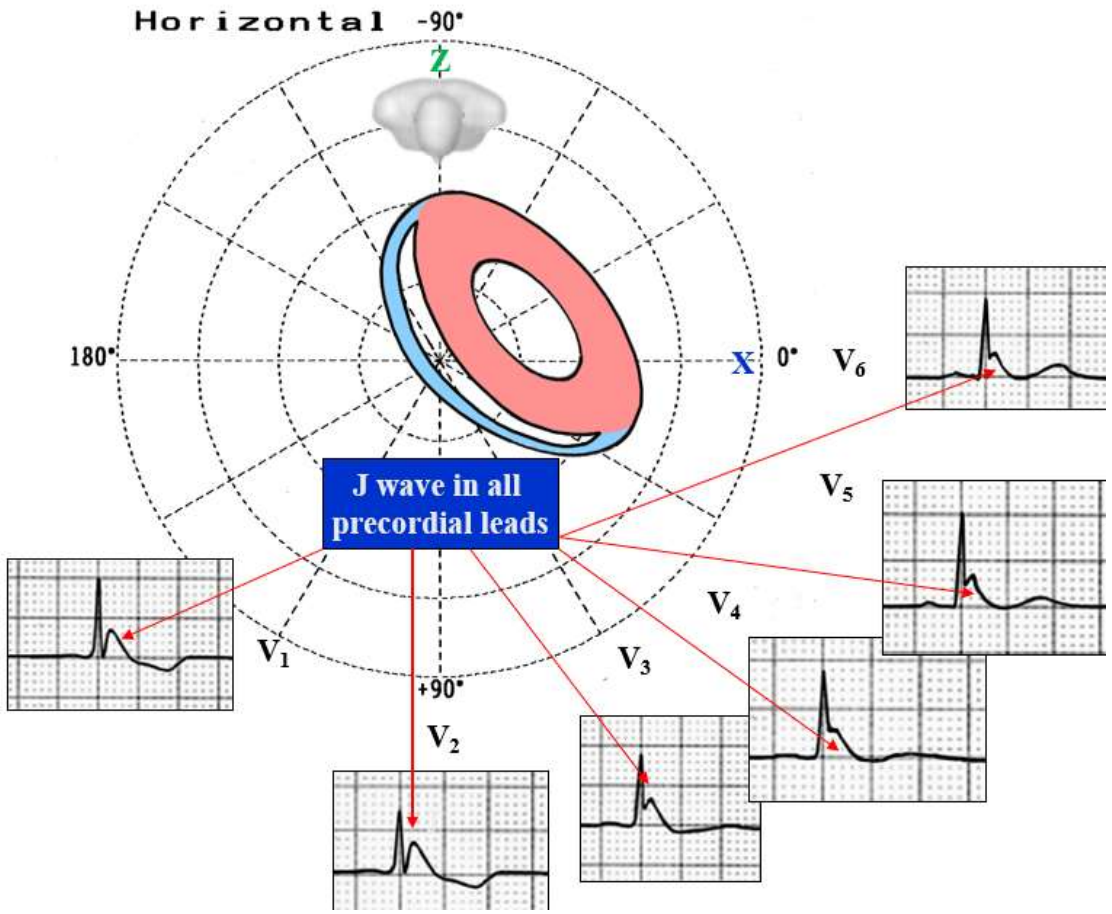


Twelve-lead ECG from the same 20-year-old man, recorded 72 hours later. The ERP persists, and there is now sinus bradycardia with a Brugada type 1 ECG pattern (coved type) in leads V1 to V3. The ST-segment elevation seen in lead aVR has been identified as a potential high-risk marker for ventricular arrhythmia in patients with BrS.

BrS and ERS. differ with respect to the magnitude and lead location of abnormal J waves and are thought to represent a continuous spectrum of phenotypic expression termed J-wave syndromes. Risk stratification and the approach to therapy of these 2 inherited cardiac arrhythmia syndromes are still undergoing rapid evolution. These 2 fascinating syndromes that have captured the interest and attention of the cardiology community in the las two decades.

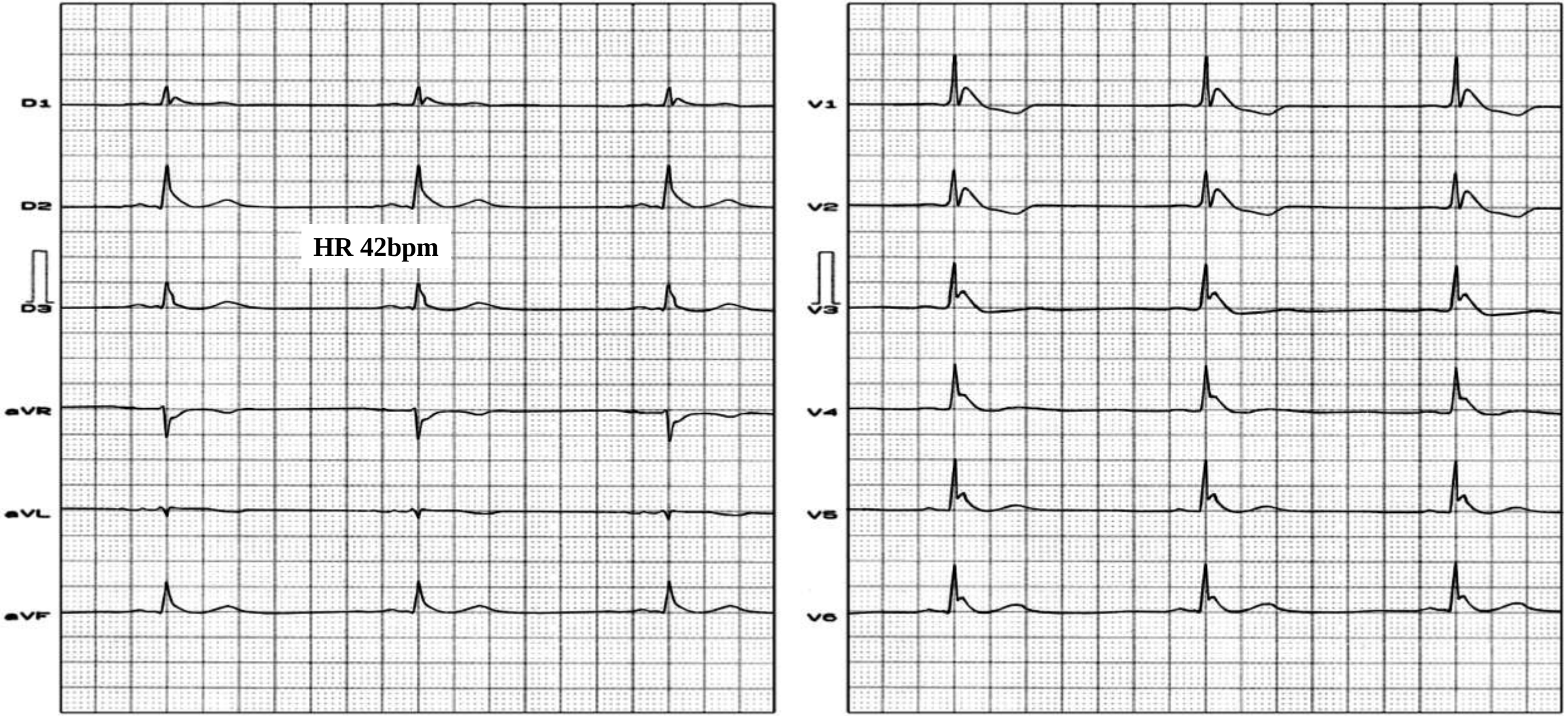
Classical case of ERS Type 3 severe prognosis



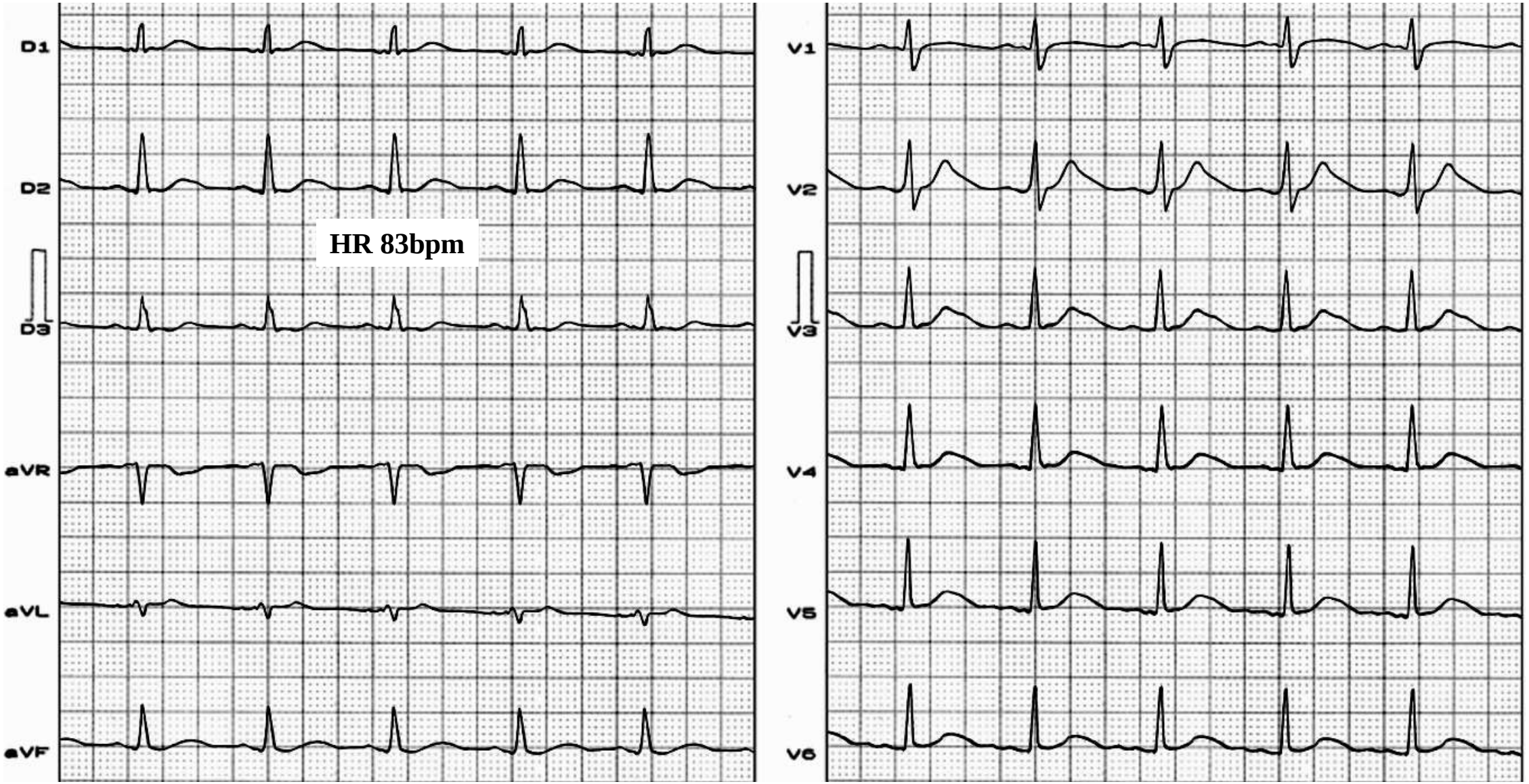


A: Basal tracing. We observe J-wave across all precordial and inferior leads.

Example of idiopathic ventricular fibrillation with “malignant” Early Repolarization Syndrome type 3



B: ECG after two days after oral quinidine 1500 mg/day



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

Similarities and differences between BrS and ERSs and possible underlying mechanisms (Antzelevitch.et al.2017)

	BrS	ERSs	Posible Mechanism(s)
Similarities between BrS and ERS			
Male predominance	Yes (71 to 80%) in Caucasian 94%-96% in Japanese	Yes (80%)	Testosterone modulation of ion currents underlying the epicardial AP notch
Average age of first event	30–50	30–50	
Associated with mutations or rare variants in KCNJ8, CACNA1C, CACNB2, CACNA2D, SCN5A, ABCC9, SCN10A	Yes	Yes	Gain of function in outward currents (IK-ATP) or loss of function in inward currents (ICa or INa)
Relatively short QT intervals in subjects with Ca channel mutations	Yes	Yes	Loss of function of ICa
Dynamics changes of ECG	High	High	Autonomic modulation of ion channel currents underlying early phases of the epicardial AP
VF often occurs during sleep or at a low level of physical activity	Yes	Yes	Higher level of vagal tone and higher levels of Ito at the slower heart rates
VT/VF trigger	Short-coupled PVC	Short-coupled PVC	Phase 2 reentry
Ameliorative response to quinidine and bepridil	Yes	Yes	Inhibition of Ito and possible vagolytic effect

	BrS	ERSs	Posible Mechanism(s)
Similarities between BrS and ERS (continuation)			
Ameliorative response to isoproterenol denopamine and milrinone	Yes	Yes	Increased ICa and faster heart rate
Ameliorative response to cilostazol	Yes	Yes	Increased ICa, reduced Ito and faster heart rate
Ameliorative response to pacing	Yes	Yes	Reduced availability of Ito due to slow recovery from inactivation
Vagally mediated accentuation of ECG pattern	Yes	Yes	Direct effect to inhibit ICa and indirect effect to increase Ito (due to slowing of heart rate)
Effect of sodium channel blockers on unipolar epicardial electrogram	Augmented J waves	Augmented J waves	Outward shift of balance of current in the early phases of the epicardial AP
Fever	Augmented J waves	Augmented J waves (rare)	Accelerated inactivation of INa and accelerated recovery of Ito from inactivation.
Hypothermia	Augmented J waves mimicking BrS	Augmented J waves	Slowed activation of ICa, leaving Ito unopposed. Increased phase 2 reentry but reduced pVT due to prolongation of APD (**Morita H, et al. 2007**)

	BrS	ERSs	Posible Mechanism(s)
Differences between BrS and ERS (continuation)			
Region most involved	RVOT	Inferior-lateral LV wall	Higher levels of Ito and/or differences in conduction
Leads affected	Right precordial leads	II, II a, VF, V4, V5, V6; I, aVL, Both: inferolateral wall	
Regional difference in prevalence	Asia: BrS>ERS	Europe: BrS = ERS	
Incidence of late potential in signal- averaged ECG	Higher	Lower	
Prevalence of atrial fibrillation	Higher	Lower. However ERS is associated with lone AF (**Hasegawa Y et al. 2019**)	
Effect of sodium channel blockers on surface ECG	Increased J-wave manifestation	Reduced J-wave manifestation	Reduction of J wave in the setting of ER is thought to be due largely to prolongation of QRS. Accentuation of repolarization defects predominates in BrS, whereas accentuation of depolarization defects predominates in ERS.
Structural changes, including mild fibrosis and reduced expression of Cx43 in RVOT or fibrofatty infiltration in cases of ARVC. Imaging studies have also revealed wall motion abnormalities and mild dilation in the region of the RVOT.	Higher in some forms of the syndrome	Unknown	Some investigators have hypothesized that some of these changes may be the result of, rather than the cause of the BrS substrate, which may create a hibernation-like state due to loss of contractility in the RVOT secondary to loss of the AP dome.

Proposed Shanghai Score System for diagnosis of early repolarization syndrome (Antzelevitch.et al. 2017)	Points
A. Unexplained cardiac arrest, documented VF or polymorphic VT	3
B. Suspected arrhythmic syncope	2
C. Syncope of unclear mechanism/unclear etiology	1
*Only award points once for highest score within this category	
II. Twelve-Lead ECG	
A. ER ≥0.2 mV in ≥2 inferior and/or lateral ECG leads with horizontal/descending ST segment	2
B. Dynamic changes in J-point elevation (≥0.1 mV) in ≥2 inferior and/or lateral ECG leads	1.5
C. ≥0.1 mV J-point elevation in at least 2 inferior and/or lateral ECG leads	1
*Only award points once for highest score within this category	
III. Ambulatory ECG Monitoring	
A. Short-coupled PVCs with R on ascending limb or peak of T wave	2
IV. Family History	
A. Relative with definite ERS	2
B. ≥2 first-degree relatives with a II.A. ECG pattern	2
C. First-degree relative with a II.A. ECG pattern	1
D. Unexplained sudden cardiac death ,< 45 years in a first- or second-degree relative	0.5
*Only award points once for highest score within this category	
V. Genetic Test Result A. Probable pathogenic ERS susceptibility mutation	O.5

Score (requires at least 1 ECG finding) ≥5 points: Probable/definite ERS; 3–4.5 points: Possible ERS; ,3 points: Nondiagnostic

Other causes of early repolarization pattern include the following: (Antzelevitch C et al. 2017)

• Juvenile ST pattern	• Hypocalcemia
• Pericardial disease (pericarditis, pericardial cyst, pericardial tumor)	• Hyperpotassemia
• Hypothermia	• Thymoma
• Hyperthermia	• Aortic dissection
• Myocardial tumor (lipoma)	• Arrhythmogenic right ventricular cardiomyopathy
• Hypertensive heart disease	• Takotsubo cardiomyopathy
• Athlete’s heart	• Neurologic causes (intracerebral bleeding, acute brain injury)
• Myocardial ischemia	• Myocarditis
• STEMI (i.e., anteroseptal myocardial infarction	• Chagas disease
• Fragmented QRS (terminal notching)	• Cocaine use

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Gene defects associated with the Early Repolarization (ERS) and Brugada (BrS) syndromes

Genetic Defects Associated wih ERS

	Locus	Gene/Protein	Ion Channel	% of Probands
ERS1	12p11.23	*KCNJ8, Kir6.1*	↑$I_{K\text{-}ATP}$	
ERS2	12p13.3	*CACNA1C, Cav1.2*	↓ I_{Ca}	4.1%
ERS3	10p12.33	*CACNB2b, Cavβ32b*	↓ I_{Ca}	8.3%
ERS4	7q21.11	*CACNA2D1, Cavá2ä*	↓ I_{Ca}	4.1%
ERS5	12p12.1	*ABCC9, SUR2A*	↑ $I_{K\text{-}ATP}$	Rare
ERS6	3p21	*SCN5A, Nav1.5*	↓ I_{Na}	Rare
ERS7	3p22.2	*SCN10A, Nav1.8*	↓ I_{Na}	3p22.2

Brugada syndrome

Concept

Clinical and electrocardiographic entity (without apparent structural heart disease) hereditary heterogeneous pattern with autosomal dominant transmission (33% of cases) or sporadic (67%), mainly caused by mutation in the SCN5A gene encoding the α subunit of Na^+ channel (Na (v) 1.5) located on the short arm of chromosome 3 (locus: 3p21). Until present date, 20 types of genes affected are known.

Clinically manifested by a tendency to syncope and/or sudden death in 60-80% of cases during night rest, with great male predominance (8:1), endemic in Southeast Asia (Thailand, Philippines) and Japan, predominantly in productive life time (young adult).

Brugada syndrome (BrS) is a clinical-inherited autosomal dominant familial/hereditary (≈37%) or sporadic (≈63% of cases) with incomplete penetrance arrhythmogenic-electrocardiographic channelopathy associated with an increased risk for dizziness, agonal respiration, syncope or resuscitated sudden cardiac death(SCD)/ sudden cardiac arrest (SCA) consequence of developing malignant polymorphic ventricular tachyarrhythmia (PVT)/ ventricular fibrillation (VF) precipitated by vagotonia often occurring during sleep or at rest especially after a large meal or in the presence of fever as trigger, mainly in children with male predominance in apparently healthy adults, in their third to fourth decade of life, less frequently in children or in the elderly, with minor structural abnormalities in the right ventricular outflow tract (RVOT) (**Gray et al., 2018**) and whose obligatory electrocardiographic pattern for the diagnosis is the so-called type 1 ECG Brugada pattern, Brugada sign (**Tomcsanyi, J, et al. 2018**) or coved-type ST segment elevation characterized by rSr' or rSR' pattern, J-point and ST segment elevation ≥ 2 mm convex to the top or rectilinear oblique descendent followed by negative symmetric T wave in at least one right precordial lead (≥1 right precordial lead) positioned in the second 2nd, third 3rd, or 4th intercostal space (ICS) (**Priori SG, et al. 2013**), spontaneously or unmasked by

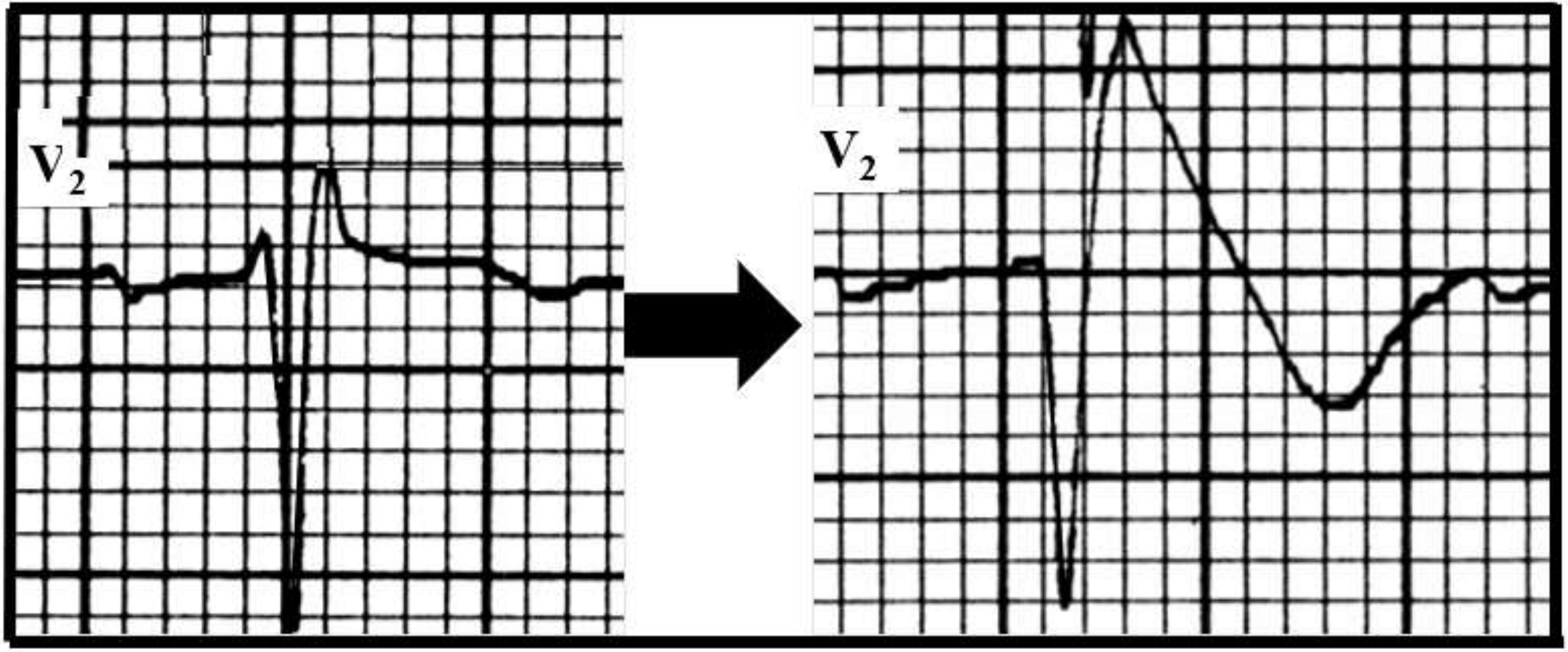
class Ia sodium channel blockers (i.e. ajmaline and pilsicainide, procainamide, disopyramide, or propafenone have been used for the drug challenge test in BrS). Table 1 (**Priori SG, et al., 2015**). 12-lead surface ECG has represented the primary source of information for diagnosis and prognosis, but the specificity and accuracy (Brugada phenocopies) of the abnormal ECG pattern are relatively low (**Antzelevitch et al., 2016**). Day-by-day fluctuations are frequent in the ECG pattern may occur in the same patient, including a concealed Brugada ECG (normal pattern) (**Richter et al., 2009**). Serial ECGs can assist with risk stratification based on the fraction of ECGs that display a spontaneous type 1 Brugada ECG pattern (**Castro Hevia et al., 2019**).

The table below shows the Sodium channel blockers used for the drug challenge test in Brugada syndrome.

Ajmaline Class 1a	**≤1mg/kg IV over 5 min. False-positive responses is possible with >1mg/kg. (*(Sun AY. 2019) Sung AY 2019*)**
Flecainide Class/Subclass 1c	2mg/kg IV over 10min
Flecainide Class/Subclass 1c	Oral at single dose of 400 mg (**Dubner S et al 2013**)
Pilsicainide Class/Subclass 1c	1mg/IV over 10 min
Procainamide Class /Subclass 1c	10mg/kg IV over 10 min

The outcome of the sodium-channel blocker challenge was significantly affected by the drug used, with ajmaline more likely to provoke a type 1 Brugada electrocardiographic pattern compared with procainamide. Patients undergoing the sodium-channel blocker challenge may have contrasting results depending on the drug used, with potential clinical, psychosocial, and socioeconomic implications.(**Cheung CC, et al. 2019.**).

Examples of positive test after intravenous ajmaline injection



Before ajmaline injection **After ajmaline injection**

Additionally. a positive ajmaline response was observed in a large proportion of unexplained cardiac arrest (UCA) or sudden unexplained death (SUD). families. Ajmaline has potential for confounding possibly false-positive responses in this population, particularly at high doses, which could possibly lead to a misdiagnosis. Clinicians should consider all alternative causes in UCA/SUD and avoid ajmaline doses >1 mg/kg. Ajmaline provocation testing appears to be safe and feasible in the pediatric population when performed in an appropriate setting by an experienced team. A positive response is more common in patients with a family history of BrS in a first-degree relative, and there may be an age-related penetrance to the test. (**McMillan MR, et al. 2014**). Ajmaline challenge to rule out the presence of BrS should be considered prior to propafenone "Pill-in-the-pocket" (PIP) treatment with type IC drugs for cardioversion of recent-onset AF. PIP therapy in AF patients who are identified to have SCN5A R1193Q polymorphism. (**Li L, et al. 2019**)

Class 1 Antiarrhythmic Drugs classification (Lei M, et al. 2018.)

I. **Class: Ia; Subclass:** Nav1.5 open state; intermediate ($\tau \approx 1–10$ seconds) dissociation kinetics; often concomitant K^+ channel block; **Pharmacological Target:** Reduction in peak INa, AP generation, and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant IK block increasing APD and ERP; increase in QT intervals; **Electrophysiological effects:** Reduction in peak INa, AP generation, and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant IK block increasing APD and ERP; increase in QT intervals; **Examples of drug:** Quinidine, Ajmaline and Disopyramide; **Major Clinical Applications:** Supraventricular tachyarrhythmias, particularly recurrent AF; VT, VF (including SQTS and BrS). for the drug challenge test in BrS (Ajmaline) and treatment (Quinidine);

II. **Class:1; Subclass:** 1b; **Pharmacological Target:** Nav1.5 open state; rapid dissociation (τ≈0.1–1 second); INa; window current; **Electrophysiological effects:** Reduction in peak INa, AP generation and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; shortening of APD and ERP in normal ventricular and Purkinje myocytes; prolongation of ERP and post repolarization refractoriness with reduced window current in ischemic, partially depolarized cells Relatively little electrocardiographic effect; slight QTc shortening(.**Gillis A, et al 2004**); **Examples of drug:** Lidocaine, mexiletine; **Major Clinical Applications:** Ventricular tachyarrhythmias (VT, VF), particularly after myocardial infarction **National Institute of Health Care Excellence. Arrhythmias. 2014. https://bnf.nice. org.uk/treatment-summary/arrhythmias.html. Accessed September 21, 2018**.)(**Al-Khatib SM. et al. 2017**)

III. **Class: I; Subclass: Ic; Pharmacological Target:** Nav1.5 open state; rapid dissociation (τ≈0.1–1 second); INa; window current; **Electrophysiological effects:** Reduction in peak INa, AP generation and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; reduced overall excitability; prolongation of APD at high heart rates; increase in QRS duration(.**Salvage SC, et al. 2018**); **Examples of drug:** Propafenone, flecainide and Pilsicainide. **Major Clinical Applications:** Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, AF, and tachycardias involving accessory pathways) VTs resistant to other treatment in the absence of structural heart disease, premature ventricular contraction (PVC), catecholaminergic polymorphic ventricular tachycardia (CPVT). (**Page RL, et al. 2016**).

Ajmaline test — suggested standardized protocol (Poli et al., 2018; Rolf , et al., 2003.)

Indication	**Aborted SCD in patients without apparent structural heart disease. Syncope of unknown origin in patients without structural heart disease. Polymorphic VT in patients without structural heart disease. Family history of BrS, SCD and/or recurrent syncope of unknown origin. Suspicious ECG (saddle-back ST-segment elevation)**
Environment	Patient in fasting, resting and drug-free state. Presence of physician with experience in intensive-care medicine. Advanced cardiopulmonary life-support facilities available including external defibrillator, intubation set and drugs (atropine, isoproterenole). Safe venous access. 12 lead standard ECG. Blood pressure monitoring.
Performance	Fractionated IV ajmaline application (10 mg every 2 min) up to target dose of 1 mg/kg. Continuous ECG documentation at paper speed of 10 mm/s (one strip at 50 mm/s every 2 min). Patient and ECG supervision until normalization of ECG
Interruption criteria	Reached target ajmaline dose. Occurrence of J-point elevation or ST-segment elevation ≥2 mm in at least one right precordial lead. Occurrence of frequent short-coupled premature ventricular contractions, or complex ventricular arrhythmias, VT, sinus dysfunction/ arrest or AV-block (Type II or III) (**Gandjbakhch, E, et al. 2014**). QRS widening (>130%) or interrupt the test when the QRS broadens to ≥150% in patients without baseline intraventricular conduction anomalies and when the QRS broadens to ≥125% in patients with baseline intraventricular conduction prolongation (**Batchvarov VN, et al, 2009/2009**).
Life-threatening ventricular arrhythmias	I. Firth approach: oral quinidine or IV isoproterenol to treat electrical storms II. Treatment of Na^+ channel blockers-induced cardiotoxicity with cardiac arrest, widening of QRS complex and hypotension refractory to intravenous fluid therapy: sodium bicarbonate as an antidote, the QRS duration narrows with possible normalization of the ECG III. Peripheral extracorporeal membrane oxygenation (RCMO) (**Chang CH, et al. 2016**).
Indication	Aborted SCD in patients without apparent structural heart disease. Syncope of unknown origin in patients without structural heart disease. Polymorphic VT in patients without structural heart disease. Family history of BrS, SCD and/or recurrent syncope of unknown origin. Suspicious ECG (saddle-back ST-segment elevation)

Brugada syndrome Genetic background

The first genetic association with BrS discovered was a loss-of-function mutation in the cardiac voltage-gated Na+ channel gene SCN5A in 1998 (**Chen et al., 1998**). It is thought to be found in 15-30% of BrS cases. There is increasing evidence that BrS is an oligogenetic disease (**Le Scouarnec et al., 2015**), with involvement of more than one genetic factor with different effect sizes (**Bezzina CR, et al., 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, et al. 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, et al., 2009**). There might be some role for genetic testing in risk stratification (**Yamagata K, et al., 2017**).

BrS types, locus, OMIM, gene, channels affected and percentage

1. BrS-1 (**Chen Q, et al 1998.**): Locus: 3p21-23; OMIM: 601144; Gene: SCN5A; Ion channel and effect: INa+ loss-of-function; Protein: NaV1.5 - α subunit of the cardiac sodium channel carrying the sodium current INa+; % of probands: 11-28%. Amin et al (**Amin AS, et al. 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. (Continuation…..)Studies have revealed significant overlap between aberrant rhythm phenotypes, and single mutations have been identified

I. that evoke multiple rhythm disorders with common gating lesions (**Pérez-Riera AR, et al. 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 phenotypes. More than 400 mutations have been identified in the SCN5A gene. Although the mechanisms of SCN5A mutations leading to a variety of channelopathies can be classified according to the alteration of INa-P and INa-L as gain-of-function, loss-of-function and both, (**Han D, et al 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 AP with ST segment prolongation and late T occurrence. Among the mutations in SCN5A associated with LQT3 is 1795insD, which is characterized by the insertion of 3 nucleotides (TGA) at position 5537 C-terminal domain of the NaV1.5 protein (**Bezzina CR, et al 1999**). Carriers of this mutation may not only present with LQT3, but also with ECG features of sinus bradycardia, PCCD, and BrS, thus creating the first described arrhythmic 'overlap syndrome' (**Remme CA., et al.**). 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, PCCD, and BrS Additionally, and multifocal ectopic premature Purkinje-related complexes; 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 loss- and gain-of-function mutations may cause dilated cardiomyopathy and/or AF. (**Wilde AAM, et al. 2018**). On ECG PR interval prolongation is the only parameter that predicted the presence of a SCN5A mutation in BrS, additionally, late potentials on SAECG LP were more frequently observed in SCN5A mutation carriers(**Robyns T, et al. 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, et al 2018 .**)

II. BrS-2 (**London B, et al. 2007**): Locus: 12p13.3; OMIM: 911778; Gene: GPDIL; Ion channel and effect: INa+ loss-of-function; Protein: Glycerol-3phosphate dehydrogenase like peptide-reduced GPD1-L activity leads to phosphorylation of Nav1.5 and decreased INa^{+}; % probands: Rare. Defects in this gene are also a cause of SIDS. This is the SCD of an infant <1 year that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of clinical history.

III. BrS-3 (**Antzelevitch C, et al. 2007.**): Locus: 12p13.3; OMIM: 114205; Gene: CACNA1C, Cav1.2; Ion channel and effect: ICa loss-of-function; Protein: e: Cav1.2- □-subunit of the voltage-gated calcium channel carrying the L-type calcium current ICa(L); % probands: 6.6%. Chromosomal location: 12p13.33, which is the short (p) arm of chromosome 12 at position 13.33. Shared with Timothy syndrome. SN5A and CACNA1C: complex BrS (**Beziau DM, et al. 2014.**).

IV. BrS-4 (**Antzelevitch C, et al. 2007.**): Locus: 10p12.33; OMIM: 600003; Gene: CACNB2b, Cavβ2b; Ion channel and effect: ICa loss-of-function; Protein: Cavβ2B- β-2 subunit of the voltage-gated calcium channel carrying the L-type calcium current ICaL.(LTCC) regulates calcium entry into cardiomyocytes. CACNB2 (β2) LTCC auxiliary subunits traffic the pore-forming CACNA subunit to the membrane and modulate channel kinetics. β2 is a membrane associated guanylate kinase (MAGUK) protein. A major role of MAGUK proteins is to scaffold cellular junctions and multiprotein complexes. β2.1 may also function in the heart as a MAGUK scaffolding unit to maintain N-cadherin-based adherens junctions and heart tube integrity (**Chernyavskaya Y, et al.2012.**); % probands: 4.8%.

V. BrS-5 (**Watanabe H, et al. 2008**.): Locus: 19q13,1; OMIM: 600235; Gene: SCN1B, Naβ1; Ion channel and effect: INa+ loss-of-function; Protein: Nav β 1-subunit of the Na^{+} channel carrying the sodium current: INa+; % probands: 1.1%. Loss-of-function mutations in the β-subunits (encoded by C) have also been described for AF (**Watanabe H, et al.**). # 612838 A number sign (#) is used with this entry because of evidence that BrS-5 and a nonspecific cardiac conduction defect are caused by heterozygous mutation in the SCN1B gene 19q13,1.

VI. BrS-6. (**Delpon E, et al. 2008**.): Locus: 11q13-14; OMIM: 604433; Gene: KCNE3, MiRP2; Ion channel and affect: Ito gain-of-function; Protein: MiRP2- β subunit to voltage potassium channels. Modulates the transient outward potassium current Ito; % probands: Rare. # 613119 A number sign (#) is used with this entry because of evidence that BrS-6 is caused by heterozygous mutation in the KCNE3 gene on chromosome 11q13.

VII. BrS7 (**Hu D, et al.2009.**): Locus: 11q23.3; OMIM: 6081214; Gene: SCN3B; Ion channel and affected: INa+ loss-of-function; Note: Nav□-3 subunit of the cardiac sodium channel carrying the sodium current INa+; % probands: Rare. # 613120 A number sign (#) is used with this entry because of evidence that BrS-7and AF-16 (18, 19) are caused by heterozygous mutation in the SCN3B gene on chromosome 11q24. BrS8: Locus: 12q11.23; OMIM: 600935; Gene: KCNJ8, Kir6.1; Ion channel and effect: Ik-ATP gain-of-function; Protein: Kir6., carries the inward rectifier potassium current Ikr; % probands: 2%. # 613123A number sign (#) is used with this entry because of evidence that BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q24 (**Ueda K, et al. 2009.**).

VIII. BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q24 (**Ueda K, et al. 2009**). Locus: 12q11.23; OMIM: 600935; Gene: KCNJ8, Kir6.1; Ion channel and effect: Ik-ATP gain-of-function; Protein: Kir6., carries the inward rectifier potassium current Ikr; % probands: 2%. # 613123A number sign (#) is used with this entry because of evidence that BrS-8 is caused by heterozygous mutation in the HCN4 gene on chromosome 15q24 (**Ueda K, et al. 2009**).

IX. BrS9: Locus: 7q21.11; OMIM: 114204; Gene: CACNA2D1, Ca, α2δ; Ion channel and effect: ICa loss-of-function; Protein: α2δ subunit of the voltage-gated calcium channel carrying the L-type calcium current ICa(L); % probands: 1.8%. Rare.# 616399 A number sign (#) is used with this entry because of evidence that BrS-9 is caused by heterozygous mutation in the KCND3 gene on chromosome 1p13 (**Giudicessi JR, et al. 2011.**).

X. BrS10: Locus:1p13.2; OMIM:605411; Gene: KCND3, Kv4.3; Ion channel and effect: Ito gain-of-function; Protein: Kv4.3, α-subunit of the transient outward potassium channel Ito; % probands: Rare. The prominent role of the Ito in BrS pathogenesis, the rare gain-of-function mutations in KCND3 serve as a pathogenic substrate for BrS. Giudicessi et al provided the first molecular and functional evidence implicating novel KCND3 gain-of-function mutations in the pathogenesis and phenotypic expression of BrS, with the potential for a lethal arrhythmia being precipitated by a genetically enhanced I(to) current gradient within the right ventricle where KCND3 expression is the highest (**Giudicessi JR, et al. 2011**.).

XI. BrS11 (**Olesen MS, et al. 2011**): Locus: 17p13.1; OMIM: 607954; Gene: RANGRF; Ion channel and effect: INa+ loss-of-function; Protein: Encodes MOG1 – influences trafficking of Nav 1.5. The protein MOG1 is a cofactor of the cardiac sodium channel, Nav1.5. Overexpression of MOG1 in Nav1.5-expressing cells increases sodium current markedly. Mutations in the genes encoding Nav1.5 and its accessory proteins have been associated with cardiac arrhythmias of significant clinical impact; % Probands: Rare (**Campuzano O, et al 2014.**). Olesen et al. screening of Nav1.5 cofactor MOG1 uncovered a novel nonsense variant that appeared to be present at a higher frequency among patients than in control subjects.

XII. BrS12 (**Ishikawa T, et al. 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; % Probands: Rare. 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.

XIII. BrS13: Locus (**Barajas-Martinez H, et al. 2012**): 12p12.1; OMIM: 601439; Gene: ABCC9 SUR2A; Ion channel and effect: Ik(ATP) gain-of-function; Protein: SUR2A, the adenosine triphosphate (ATP) binding cassette transporter of the Ik(ATP) channel.; % Probands: Rare. The ABCC9 is an ion channels/ion channel-related AF. Adenosine triphosphate (ATP)-sensitive potassium cardiac channels consist of inward-rectifying channel subunits Kir6.1 or Kir6.2 (encoded by KCNJ8 or KCNJ11) and the sulfonylurea receptor subunits SUR2A (encoded by ABCC9). KCNJ8 is a susceptibility gene for BrS and early repolarization syndrome (ERS and point to S422L as a possible hotspot mutation. The S422L-induced gain of function in ATP-sensitive potassium channel current is due to reduced sensitivity to intracellular ATP. ABCC9 has ERS and BrS susceptibility genes. A gain-of-function in IK-ATP when coupled with a loss-of-function in SCN5A may underlie type 3 ERS, which is associated with a severe arrhythmic phenotype (**Hu D, et al. 2014.**).

XIV. BrS14 (**Riuro H, et al. 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; % 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.

XV. BrS15: Locus: 12p11; OMIM: 602861; Gene: PKP2, Plakophillin-2; Ion channel and effect: INa+ loss-of-function; Protein: Plakophillin-2 – interacts with INa+; % probands: Rare. Plakophilin-2 (PKP2) variants could produce a BrS phenotype, which is the same allelic disorder as some sudden unexplained nocturnal death syndromes (SUNDS). All coding regions of PKP2 gene in 119 SUNDS victims were genetically

XV. screened using PCR and direct Sanger sequencing methods. Three novel mutations (p.Ala159Thr, p.Val200Val, and p.Gly265Glu), one novel rare polymorphism (p.Thr723Thr), and 8 polymorphisms were identified.A compound mutation (p.Ala159Thr and p.Gly265Glu) and a rare polymorphism (p.Thr723Thr) were found in one SUNDS case with absence of the apparent structural heart disease. The detected compound mutation identified in this first investigation of PKP2 genetic phenotype in SUNDS is regarded as the plausible genetic cause of this SUNDS case. The rare incidence of PKP2 mutation in SUNDS (1%) supports the previous viewpoint that SUNDS is most likely an allelic disorder as BrS (**Huang L et al. 2016.**). Mutations in proteins of the desmosome are associated with arrhythmogenic cardiomyopathy (AC). Life-threatening ventricular arrhythmias (VAs) often occur in the concealed forms/phase of the AC before the onset of structural changes. Evidence indicating that loss of desmosomal integrity (including mutations or loss of expression of plakophilin-2; PKP2) leads to reduced sodium current, the PKP2-INa relation could be partly consequent to the fact that PKP2 facilitates proper trafficking of proteins to the intercalated disc, and, PKP2 mutations can be present in XV patients diagnosed with BrS, thus supporting the previously proposed notion that AC and BrS are not two completely separate entities (**Cerrone M, et al.2014.**). Mutations on PKP2 account for the majority of AC cases, a disease characterized by high incidence of VAs and a progressive cardiomyopathy with fibrofatty infiltration involving predominantly the right ventricle. Although BrS was initially described as a purely electric condition in intact hearts, it is now recognized that structural changes occur mainly at the right ventricular outflow tract (RVOT) **(Papavassiliu T, et al. 2004.**). These findings support the hypothesis, suggested in the past by some clinicians, that the two conditions could be at the bookends of a phenotypical common spectrum. PKP2 is a structural protein of the desmosome whose principal role is to maintain tissue integrity and cell-to-cell stability. However, data from cellular and mouse models demonstrated that loss of PKP2 could facilitate arrhythmias by decreasing sodium current (**Cerrone M, et al.2012.**), thus through an electrophysiological effect. Indeed, in vitro characterization of the PKP2 mutations detected in patients with a BrS phenotype showed a

XV. decreased sodium current, consistent with the clinical phenotype. Super-resolution microscopy data showed that loss of PKP2 could affect proper trafficking of the sodium channel at the membrane, thus supporting the concept that proteins could have accessory roles aside from the primary one ascribed to them. The role of the cardiac intercalated disc as a functional unit with both structural and electric regulatory functions has been opening new paths of investigations on the possible arrhythmogenic substrate in BrS (**Nademanee K, et al. 2015**).

XVI. BrS-16 (**Wang C, et al.201**): Locus: 3q28; OMIM: 601513; Gene: FGF12, FHAF1; Ion channel and effect: INa+ loss-of-function; Protein: Fibroblast growth factor homologues1. factor-1- mutation decreases INa+; Cytogenetic location: 3q28-q29; % Probands: Rare. Multilevel investigations strongly suggest that Q7R-FGF12 is a disease-associated BrS mutation. FHF effects on Na(+) and Ca(2+) channels are separable. Most significantly, the Hennessey study establishes a new method to analyze effects of human arrhythmogenic mutations on cardiac ionic currents. On the basis of the recent demonstration that FGF homologous factors (FHFs; FGF11-FGF14) regulate cardiac Na(+) and Ca(2+) channel currents, FHFs are candidate BrS loci (**Hennessey JA et al. 2013.**). Mutation FGF12 also causes neonatal-onset epilepsy.

XVII. BrS-17 (**Hu D, et al. 2014.):** Locus: 3p22.22; OMIM: 604427; Gene: SCN10A, Nav1.8; Ion channel and effect: INa+ loss-of-function; Protein: Nav1.8-αsubunit of the neural sodium channel.; % Probands: 16.7%. Hu et al identified SCN10A as a major susceptibility gene for BrS, thus greatly enhancing our ability to genotype and risk stratify probands and family members. The SCN10A SNP V1073 is strongly associated with BrS. Rare variants in the screened QRS-associated genes (including SCN10A) are not responsible for a significant proportion of SCN5A mutation negative BrS. The common SNP SCN10A V1073 was strongly associated with BrS and demonstrated loss of NaV1.8 function, as did rare variants in isolated patients (**Behr ER. et al. 2015.**).

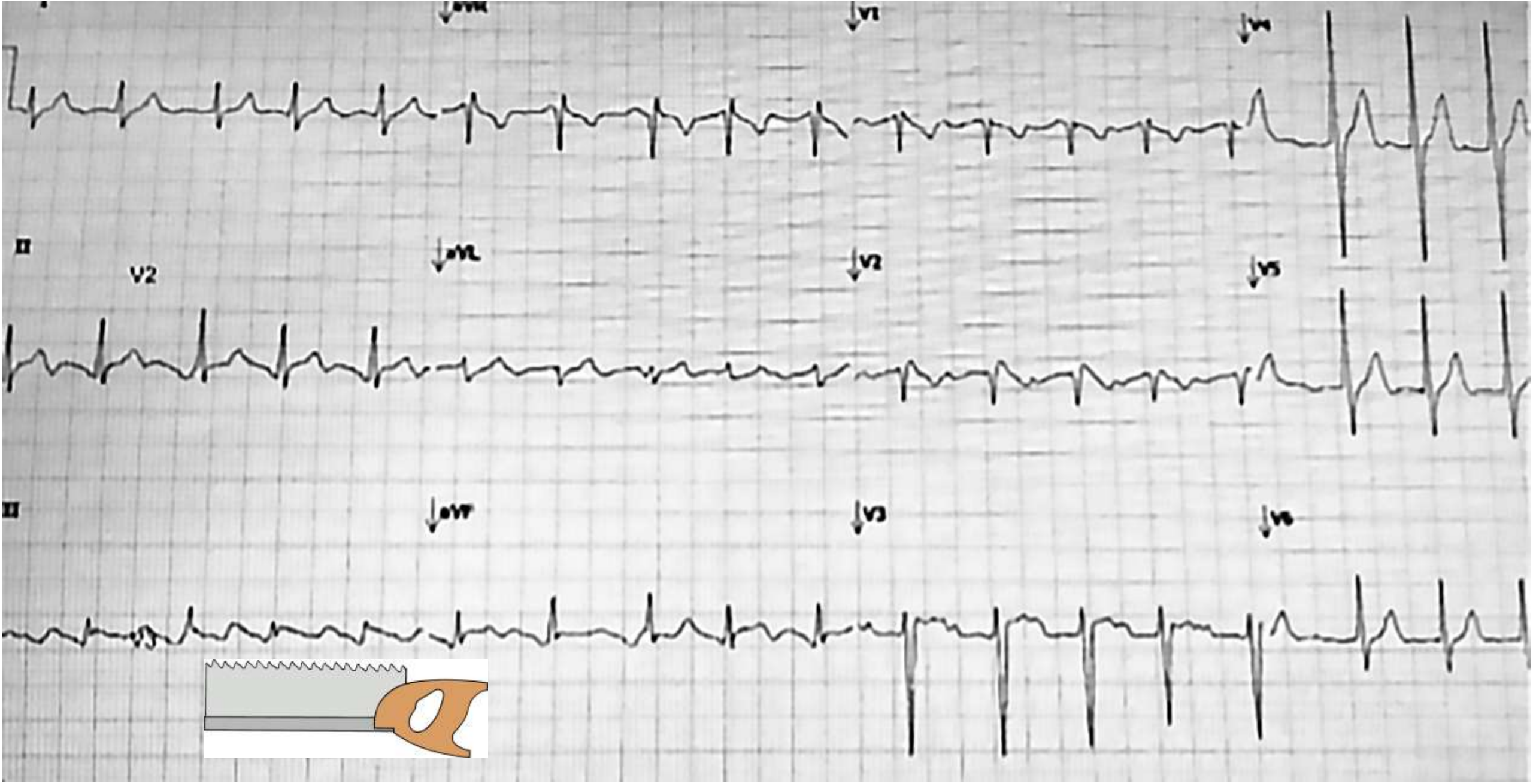
XVII.The expression of sodium channel Nav1.8 in cardiac nervous systems has been identified, and variants of SCN10A that encodes Nav1.8 contribute to the development of BrS by modifying the function of Nav1.5 or directly reducing the Na+ current. Fukuyama et al screened for the SCN10A gene using a high-resolution melting method and direct sequencing. and compared the clinical characteristics among the probands with gene mutations in SCN10A, 6 probands with CACNA1C and 17 probands with SCN5A. They identified six SCN10A variant carriers (2.5%): W189R, R844H (in two unrelated probands), N1328K, R1380Q, and R1863Q. Five were male. Four were symptomatic: one died following SCD age 35, one suffered ventricular fibrillation, and two had recurrent syncope. Compared with BrS patients carrying SCN5A or CACNA1C mutations, although there were no significant differences among them, symptomatic patients in the SCN10A group tended to be older than those in the other gene groups (**Fukuyama M, et al.2016.**).

XVIII.BrS-18 (**Bezzina CR, et al. 2013.**)**:** Locus: 6q; OMIM: 604674; Gene: HEY2 (transcriptional factor); Ion channel and effect: INa+ loss-of-function; Protein: Transcription factor identified in GWAS; % Probands: Rare. The association signals at SCN5A-SCN10A demonstrate that genetic polymorphisms modulating cardiac conduction can also influence susceptibility to cardiac arrhythmia. The implication of association with HEY2, supported by new evidence that Hey2 regulates cardiac electrical activity, shows that BrS may originate from altered transcriptional programming during cardiac development. . Recently, Trujillo-Quintero et al(**Trujillo-Quintero JP, et al. 2019**) identified a familial BrS associated with a complete deletion of the SCN5A and SCN10A Genes.

XIX.BrS-19 (**Boczek NJ, et al. 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

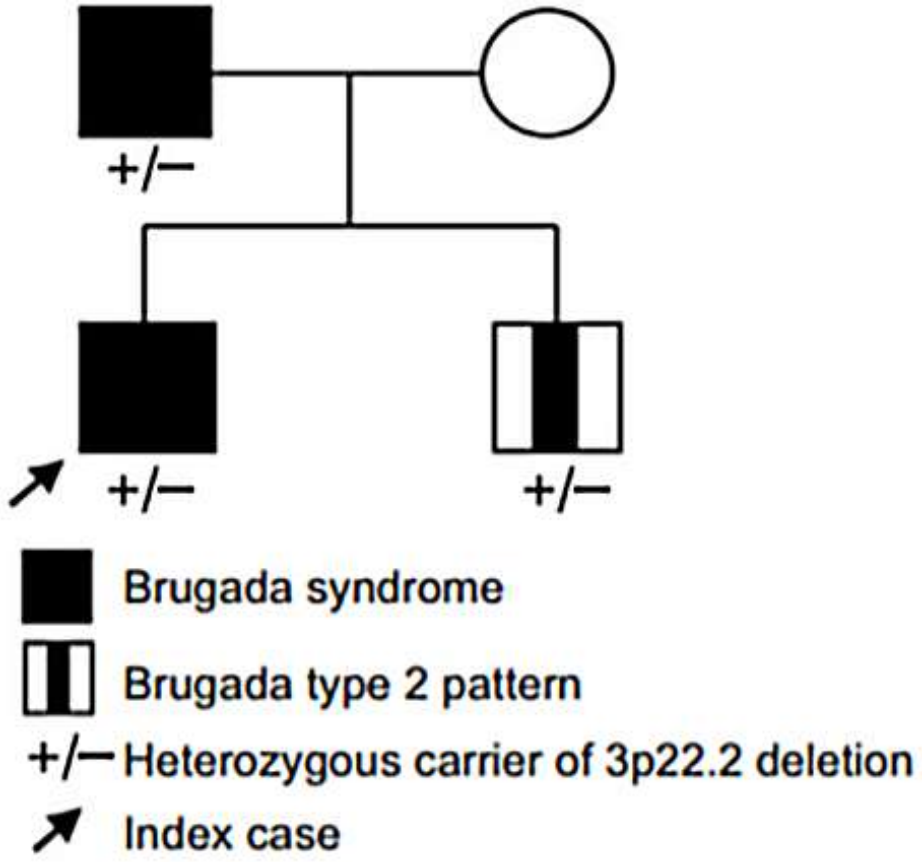
Trujillo-Quintero et al(**Trujillo-Quintero JP et al. 2019**) identified a familial BrS associated with a complete deletion of the SCN5A and SCN10A Genes. The main gene implicated in BrS is the sodium channel gene, SNC5A, but other genes may make a smaller contribution. For a genetic study to be considered complete, in addition to examining all these genes, copy number variations (CNV), such as large deletions or duplications, should be ruled out, as a small percentage of BrS cases may be due to these variants. Trujillo-Quintero et al. presented the case of a family with BrS, whose genetic study by massive next-generation sequencing (NGS) enabled identification of the etiology. The proband, a 13-year-old boy, was hospitalized for palpitations after intense exercise. He had experienced no previous symptoms and was not receiving drug therapy. Before this event, he had undergone monitoring by the arrhythmia unit with yearly ECG testing because his father had been diagnosed with BrS with spontaneous type 1 ECG pattern and induced VF on EPS and was treated with ICD implantation. On admission, ECG testing showed an atrial flutter associated with a Brugada type 1 pattern. Genetic study using an NGS panel identified complete deletion of the SCN5A and SCN10A genes. Confirmation using another, more specific molecular technique for CNV study (SNP-array) enabled characterization of the deletion, which included 8 genes. Only 3 of these genes have been associated with the disease: SCN5A and SCN10A (BrS), and ACVR2B (complex congenital heart defects). Genetic study of the family (by SNP-array, low-cost and accurate) identified the same deletion in the affected father and asymptomatic brother. The deletion had not been described previously. A similar deletion is recorded in the DECIPHER database, but only 3 of the genes identified are involved (EXOG, SCN5A and SCN10A); it is considered pathogenic and was found in a male without a described phenotype. Several studies have reported large partial deletions in the SCN5A gene in BrS patients. In all these cases, multiplex ligation-dependent probe amplification (MLPA) was used after a previous genetic study had yielded negative results . Lastly, the authors mention the coexistence of atrial flutter and type 1 BrP in the proband. (See ECG in the next slide)

SCN5A has an important pathophysiological role in sinus node automatism.

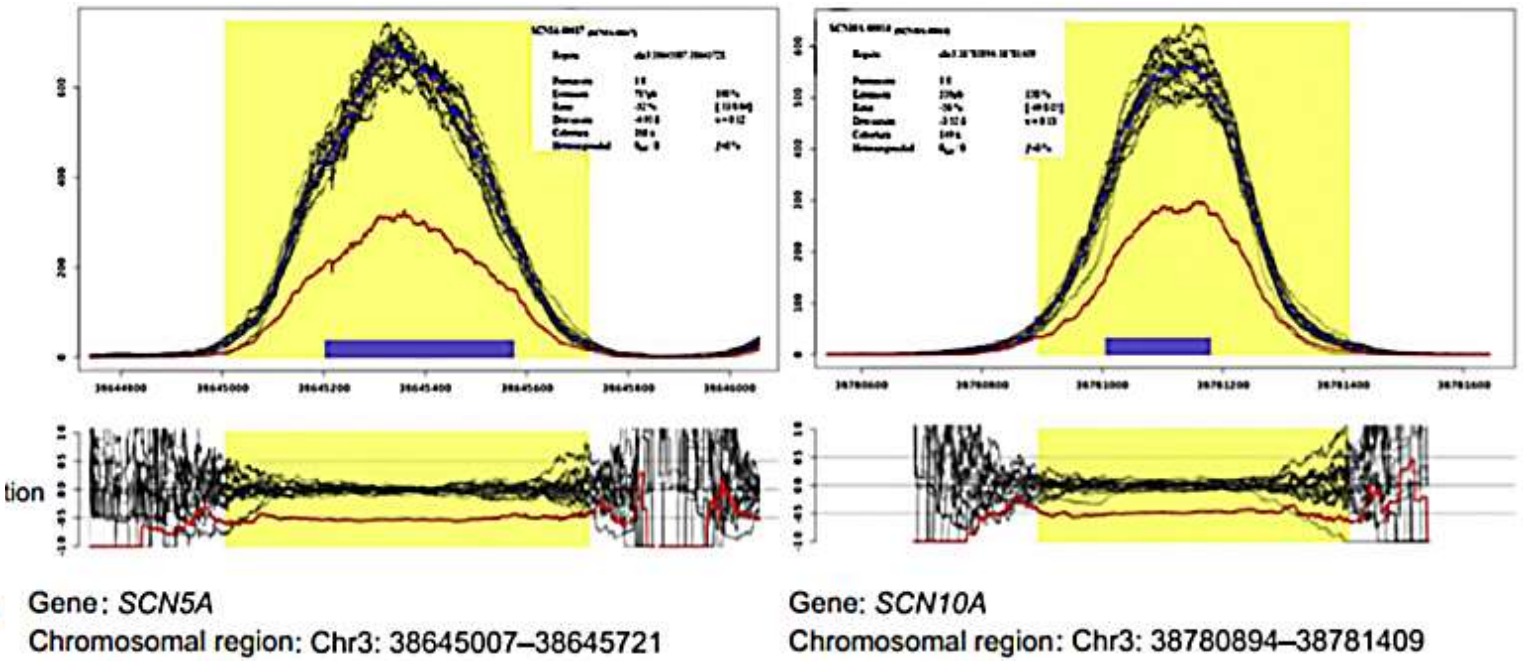


Electrocardiogram of the proband case: Heart rate between 111 and 136bpm, atrial flutter (**Sawtooth appearance)**with variable AV conduction and spontaneous type 1 BrP

1. Family pedigree; familial genetic study (SNP-array).



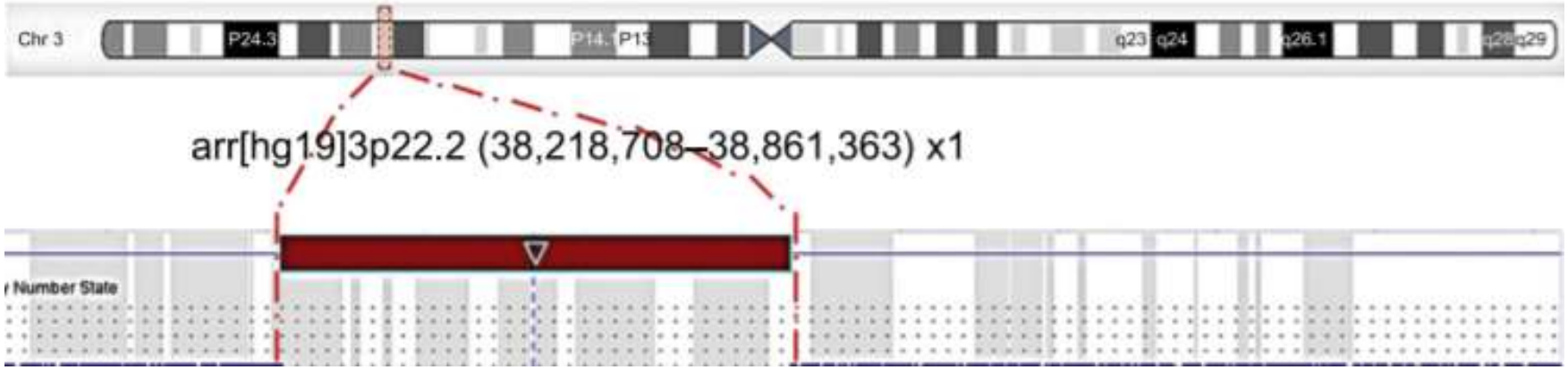
Analysis of NGS coverage shows a deletion in heterozygosis; abscissa axis, genomic region; ordinate axis, sequence coverage (number of reads); each black line represents 1 single case; the blue line, the median of all cases, and the red line, the index case.



Gene: *SCN5A*
Chromosomal region: Chr3: 38645007–38645721

Gene: *SCN10A*
Chromosomal region: Chr3: 38780894–38781409

3p22.2 deletion, characterized by SNP-array; the graph shows a signal decrease in this region. NGS, massive next-generation sequencing.



III. Family history	Points
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first-or second-degree relative	1
C. Unexplained SCD	0.5
IV. Genetic test result	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5

*One item from this category must apply. †Only award points once for highest score within this category. Score (requires at least 1 electrocardiographic (ECG) finding): >3.5 points: probable and/or definite BrS; 2 to 3 points: possible BrS: < 2 points nondiagnostic. SCD=sudden cardiac death; VF =ventricular fibrillation; VT = ventricular tachycardia. PVT= Polymorphic Ventricular Tachycardia

Observation: Kawada et al provided validation for the use of the Shanghai Score System for the diagnosis and risk stratification of patients with BrS (**Kawada S, et al., 2018**).

Type 1 Brugada ECG pattern is the keystone in the diagnosis of BrS. Spontaneous coved-type or type I pattern is considered a noninvasive electrocardiographic risk marker in BrS without requiring any further evidence of malignant arrhythmias. However, when the type 1 Brugada ECG pattern is unmasked by drugs, additional clinical criteria are required for the diagnosis (**Antzelevitch C. et al., 2017**). In a large percentage of patients, the ECG findings are normal or inconclusive, and a drug challenge is required to confirm the condition. This may also occur with members of the patients' families (**Trujillo-Quintero JP, et al., 2019**).

BrS diagnosis criteria from the Second Consensus (Antezelevitz C, et al 2005)

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

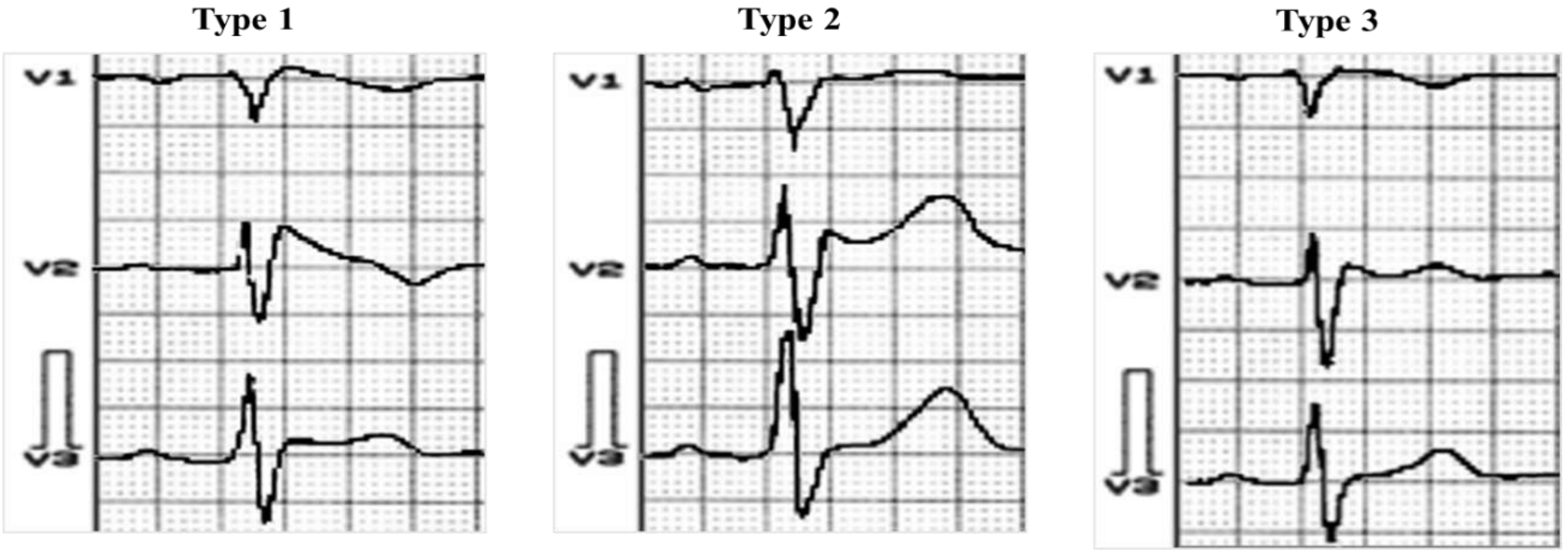
Shanghai Score System for Diagnosis of BrS	Points
I. ECG* (12-lead/ambulatory)	
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 Brugada ECG pattern that converts with provocative drug challenge	2
II. Clinical history†	
A. Unexplained cardiac arrest or documented PVT/VF	3
B. Nocturnal agonal respirations	
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	2
E. Atrial flutter/fibrillation in patients	1

There are three kind of clinical criteria for the diagnosis of BrS:

1. Data from the family history: SCD in a family member younger than 45 years
2. ECG type 1 in family members.
3. Arrhythmia-related symptoms: Syncope; Seizures;
4. Agonal respiration, gasping respiration or agonal breathing (it is an abnormal pattern of breathing and brainstem reflex characterized by gasping, labored breathing, accompanied by strange vocalizations and myoclonus);
5. Resuscitated sudden cardiac death (SCD).
6. Documented ventricular arrhythmias: Polymorphic ventricular tachycardia (PVT), Ventricular fibrillation (VF), Premature Ventricular Contractions(PVCs) with short coupled, LBBB pattern and inferior axis.
7. Inducibility of VT/VF

BrS is definitely diagnosed when the patient presents 1) a type 1 ECG (either spontaneously or elicited by class I AADs, and 2) at least one of the above-mentioned clinical criteria. If a type 1 ECG is observed in the absence of any clinical criteria, this should be referred to as “idiopathic Brugada ECG pattern” or Brugada phenocopy. Key findings that support the suspicion of Brugada phenocopies include the presence of an identifiable underlying condition, disappearance of the pattern with resolution of the condition, absence of family history of sudden death or type 1 BrS pattern in first-degree relatives, absence of symptoms such as syncope, seizures or nocturnal agonal respiration, and a negative sodium channel blocker challenge test. Currently, Brugada pattern on ECG can manifest as type 1 (coved pattern) and type 2 (saddleback pattern with day-to-day variation). The appearance of type 1 Brugada pattern is required for the diagnosis of BrS (**Bayes de Luna A. et al., 2012**). From 2002 to 2012 three types were considered: (**Wilde AA. et al., 200**2) (Figure next slide):

Brugada electrocardiographic types from the first consensus (Wilde AA 2002)



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

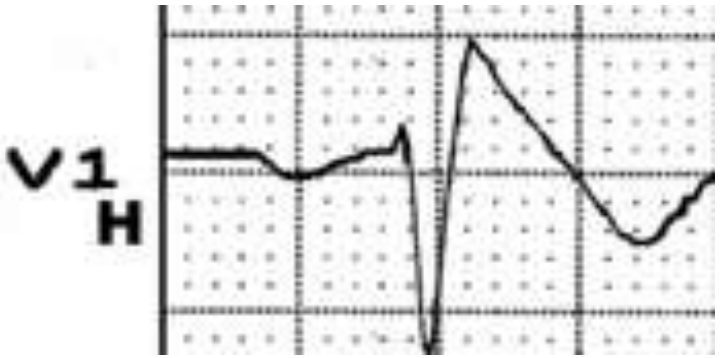
Type 2: J point and ST segment elevation ≥2 mm (0,2 mV) with saddleback appearance, and remains at least 1 mm above the isoelectric line, followed by positive or biphasic T wave.

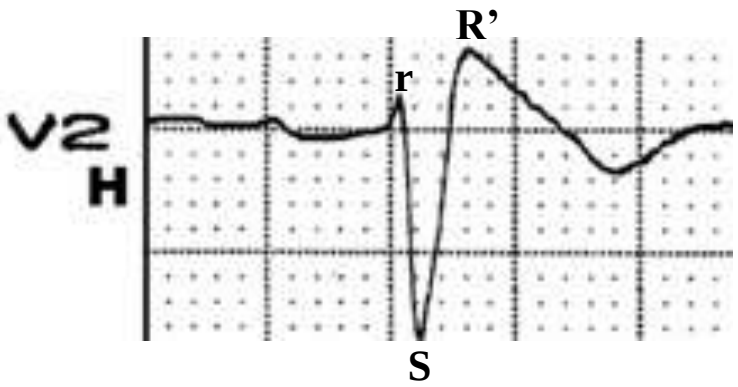
Type 3: J point and ST segment elevation <1 mm and with variable shape: whether coved type or saddleback appearance. In type 3, the terminal section of the ST segment never exceeds 1 mm above the isoelectric line.

Note that type 2 and 3 patterns are characterized by the same general shape of the J-ST-T wave, but the ST segment elevation in type 3 pattern is slightly <0.1 mV. The Brugada ECG pattern can be dynamic and is sometimes concealed.

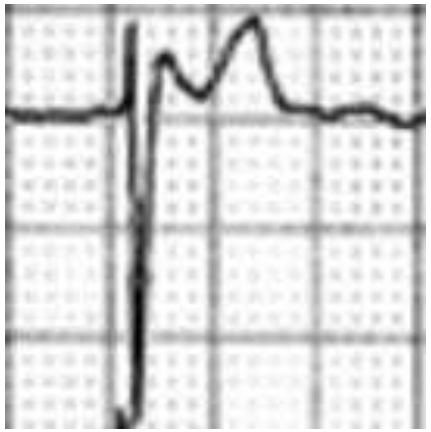
New ECG classification

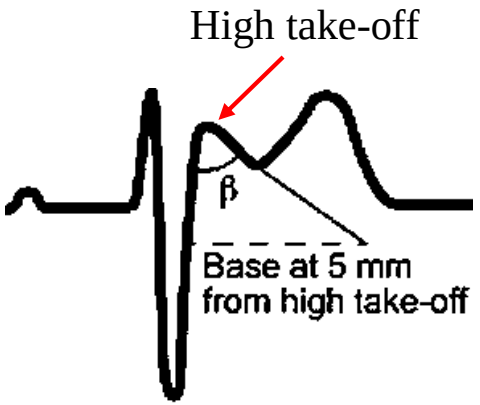
Type 1 Brugada pattern: J point and ST segment elevation ≥2 mm, with upper convexity or descending oblique rectilinear followed by negative T wave on the right precordial leads (V_1-V_2 or from V_1 through V_3) and/or high right precordial leads V_{1H}, V_{2H} and V_{3H}.





Type 2 Brugada pattern: it has ST segment elevation with saddleback shape, high take-off angle broad, β angle always >36° and the base of the triangle from high take-off of 5 mm. In the new ECG criteria, only 2 ECG patterns are considered: pattern 1 identical to classic type 1 of other consensus (coved pattern) and pattern 2 that joins patterns 2 and 3 of the first consensus (saddle-back pattern) (**Bayés de Luna A. et al. 2012**).





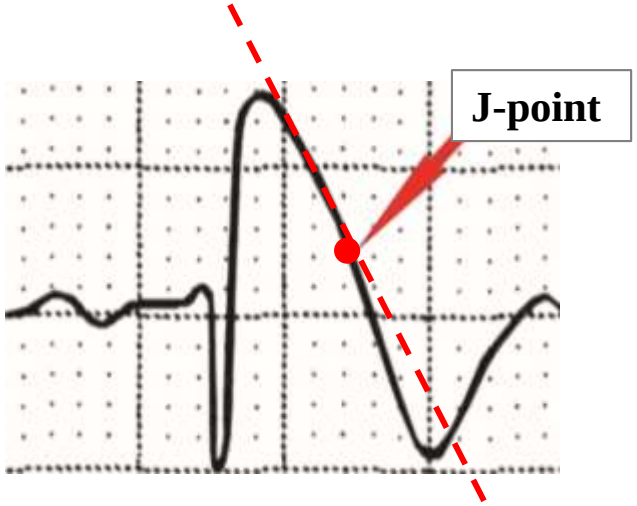
Proposal of classification of type 1 Brugada pattern

STSE convex upward

STSE rectilinear oblique and downward

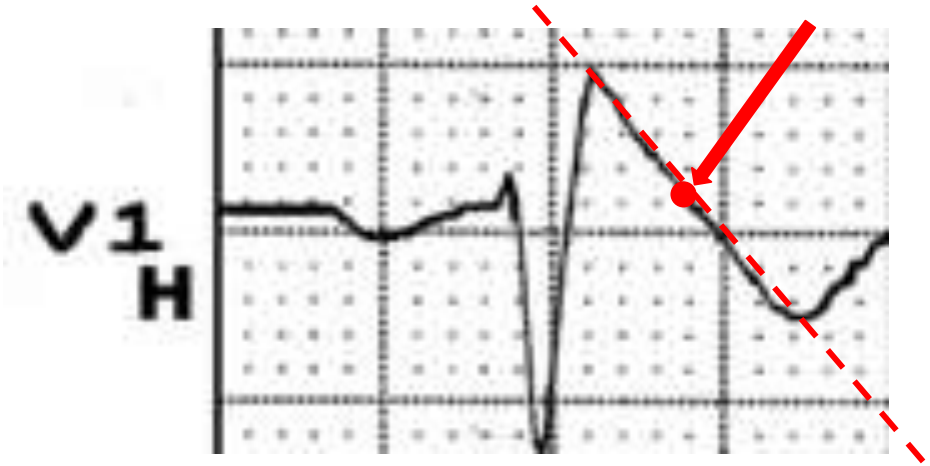
Right precordial leads

Subtype 1A



The dotted line is the tangent line

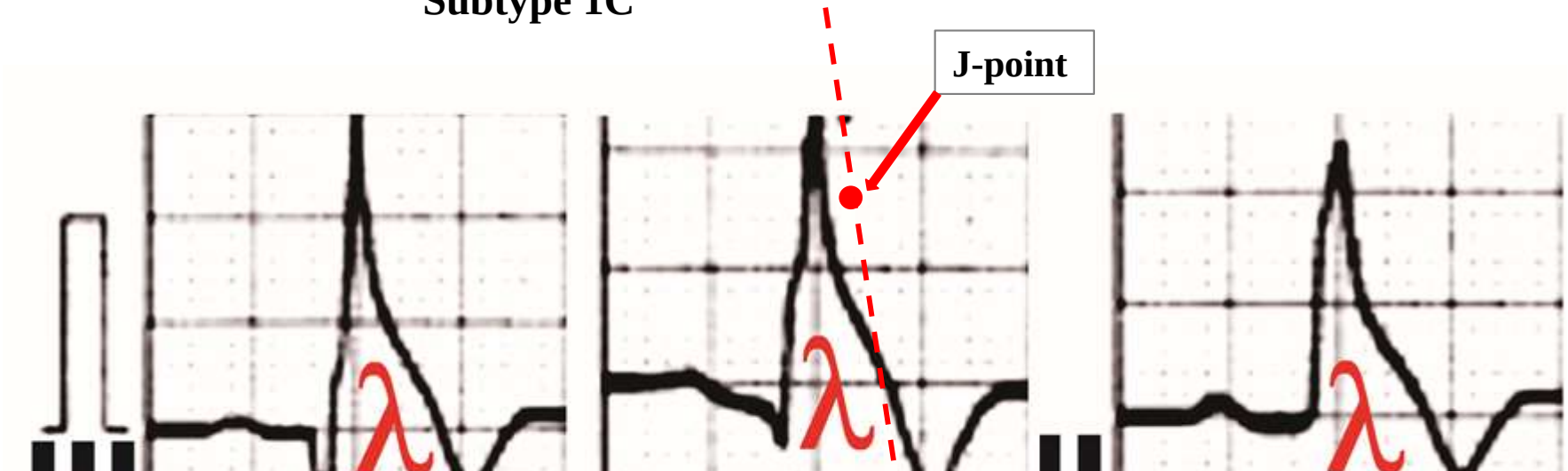
Subtype 1B



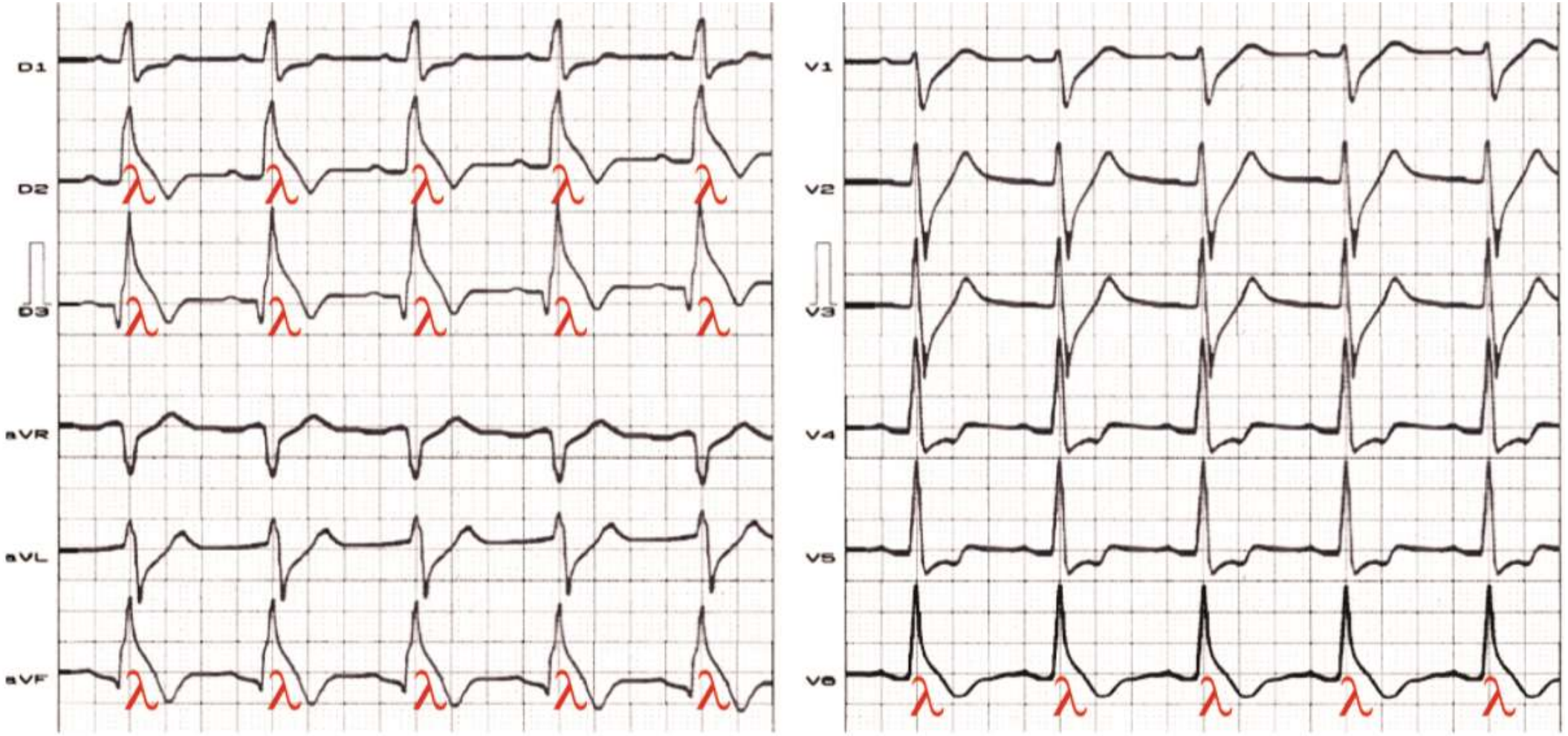
The dotted line is the tangent line

Inferior leads BrS + ERP in inferolateral leas

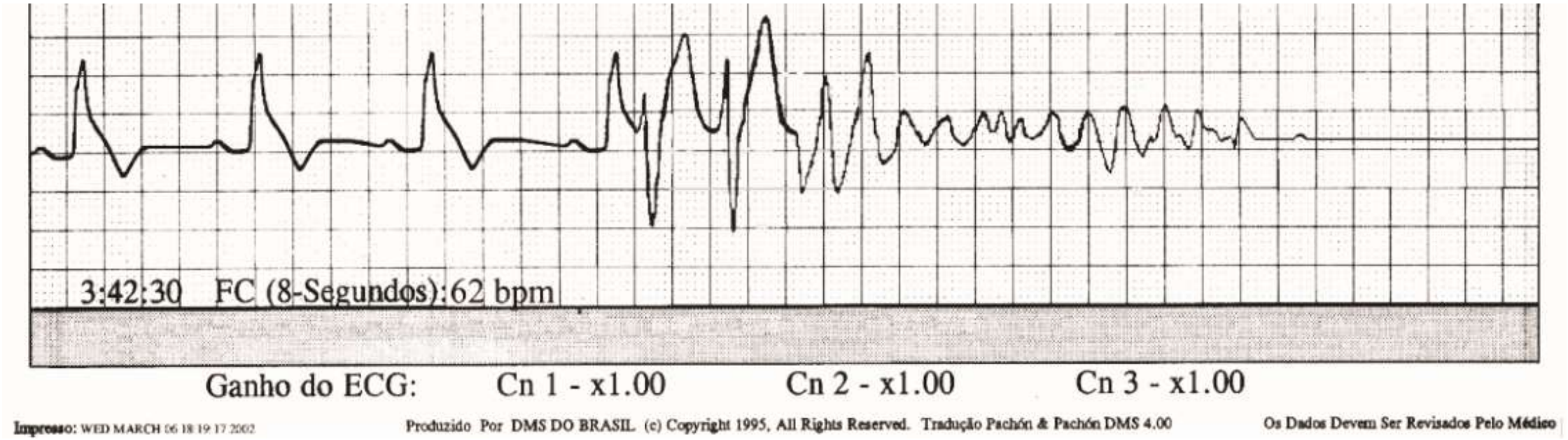
Subtype 1C



Example of subtype 1C ECG Brugada pattern

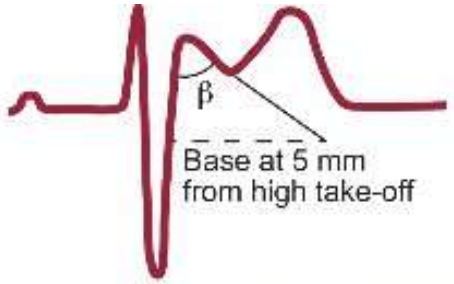


The ECG shows persistent ST segment elevation in the inferior and apical leads, associated to concomitant reciprocal or mirror image in the anterior wall that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia. (*Riera AR,et al. 2004*)



Holter monitoring recorded the final event, manifest by PVT episode with initial short-coupling ventricular premature contractions (R on T) that ended quickly in VF and asystole.

Pattern 1C of repolarization has been observed in acute myocardial infarction by Kukla et al (**Kukla P et al. 2007**). These authors raised the hypothesis that the "Lambda-like ST" could be a new marker of risk of acute infarction with ST segment elevation.



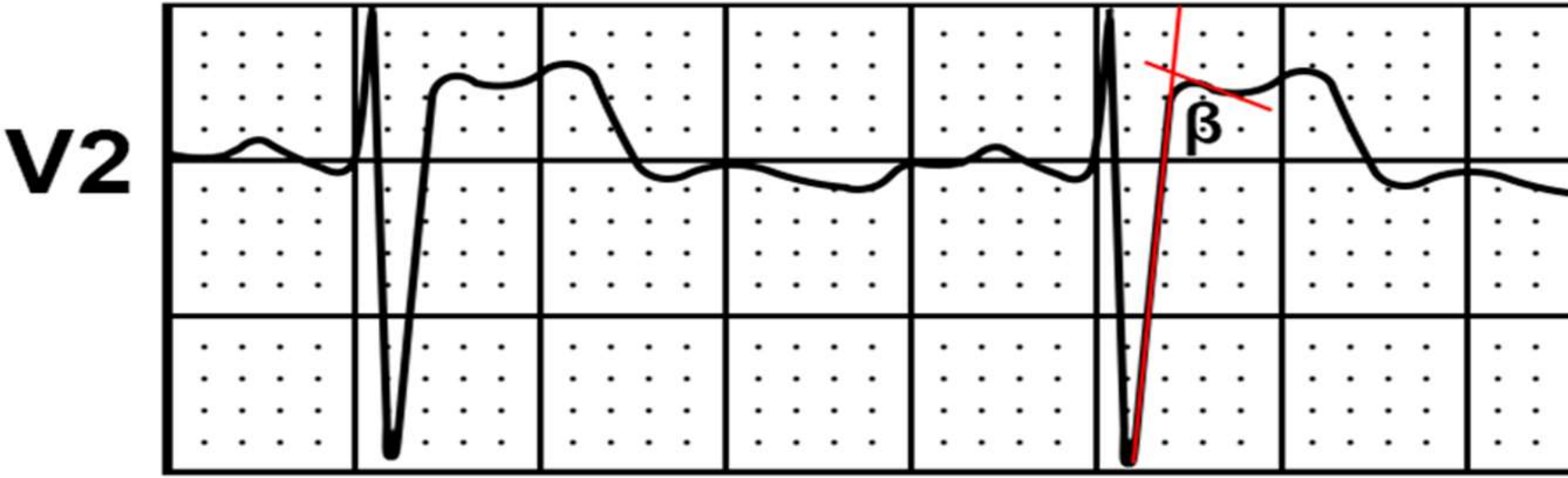
Type 1 Brugada pattern in V1-V2:

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

Type 2 Brugada pattern in V1-V2:

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

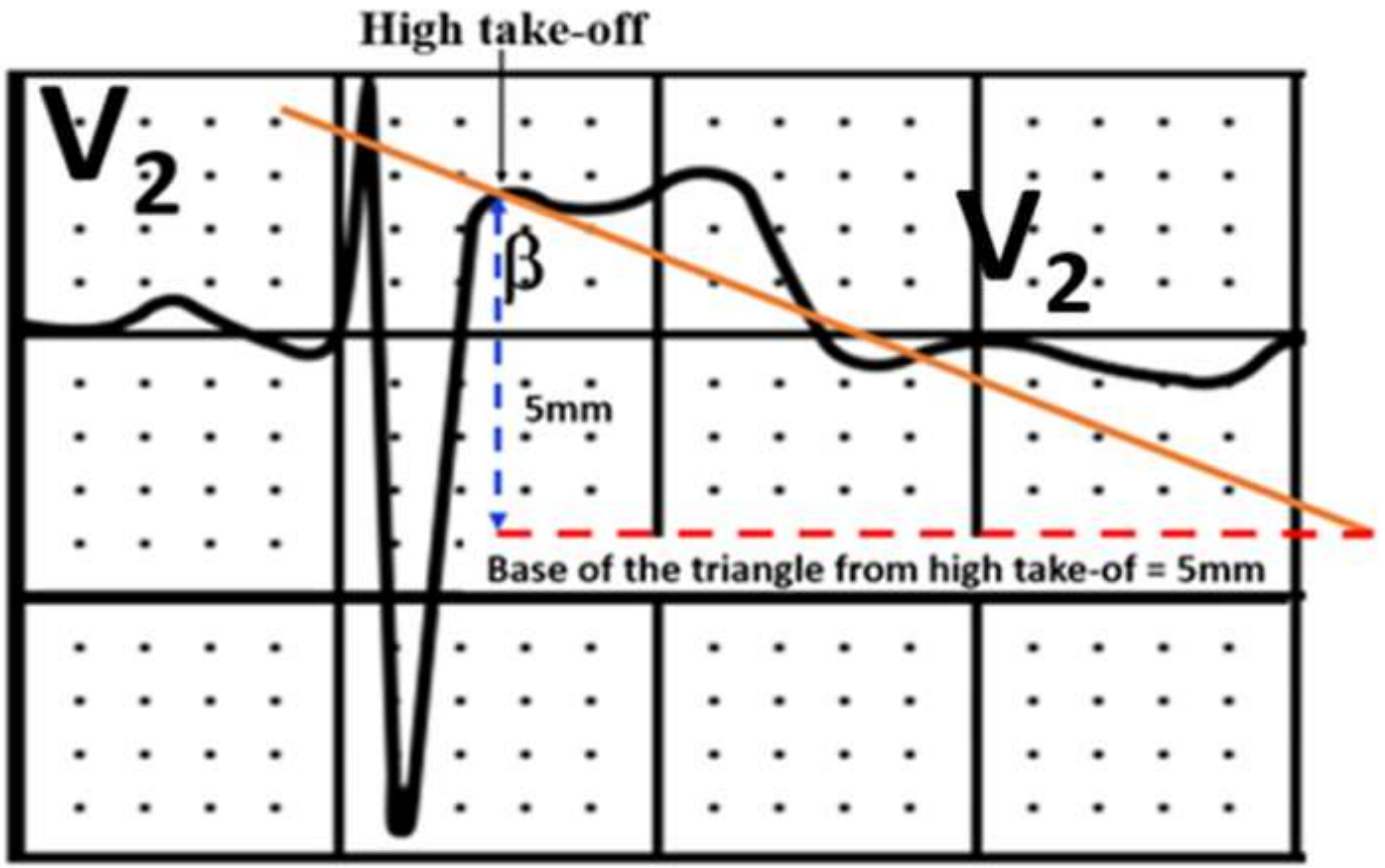
Type 2 Brugada pattern



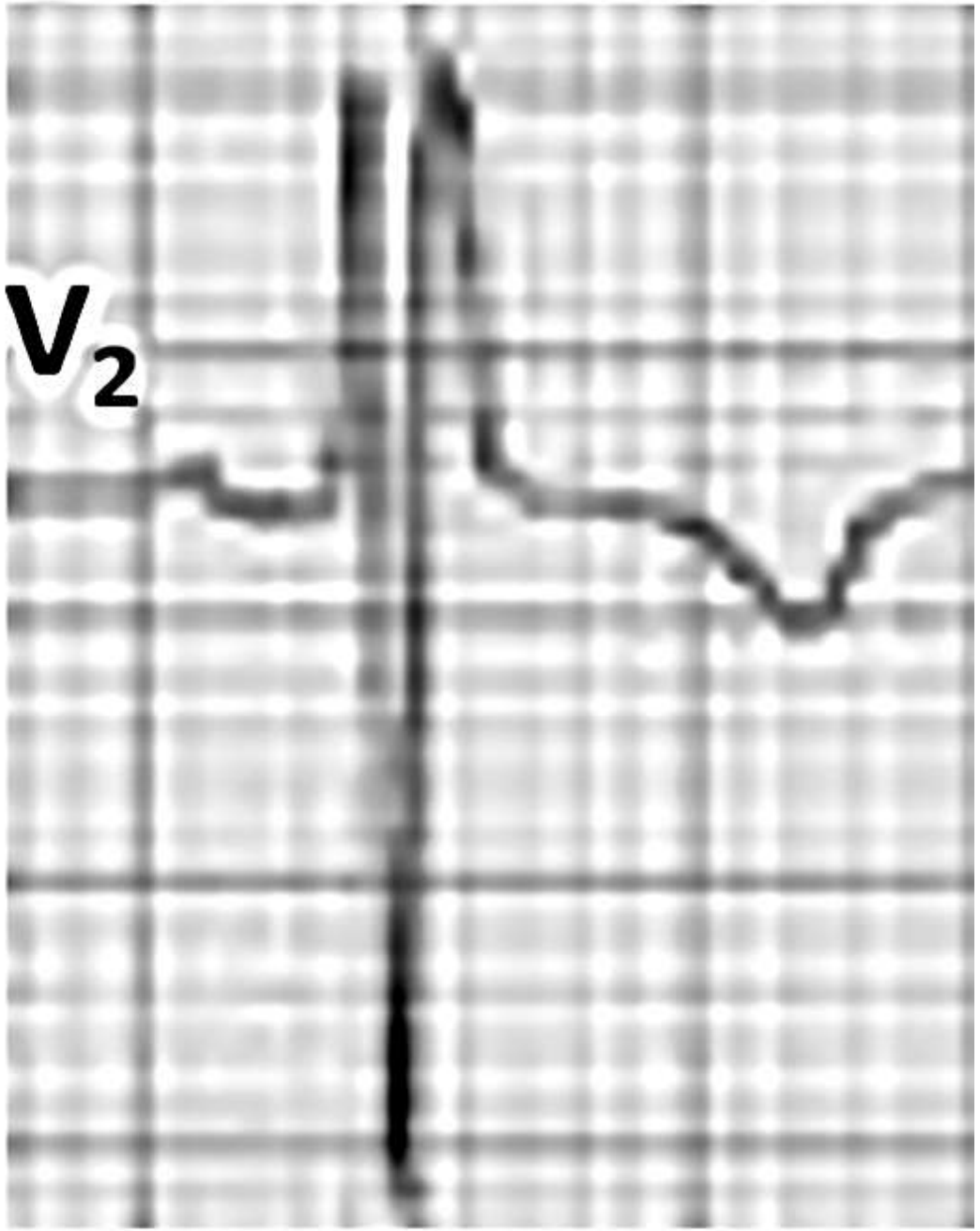
Type 2: It has triphasic pattern in right precordial leads rSr' or rSR' pattern ≥2 mm J-point an ST segment elevation with saddleback appearance trough that is still ≥1 mm ST-segment elevation and, followed by a positive or biphasic T-wave, and broad β- angle. A β-angle (≥58°) and base of the triangle in type 2 Brugada ECG pattern may distinct a true Brugada ECG from "innocent" incomplete RBBB with high sensitivity and specificity. The β-angle is calculated by measuring the angle between the upslope of the S-wave and the downslope of the r′-wave.

The base of the triangle is calculated by measuring duration of the base of the triangle between the upslope of S wave and the downslope of the r′-wave at 0.5 mV (or 5mm) from the high take-off. *A base of the triangle in lead V2 ≥ 4mm suggests BrS pattern*. Figure

A



B

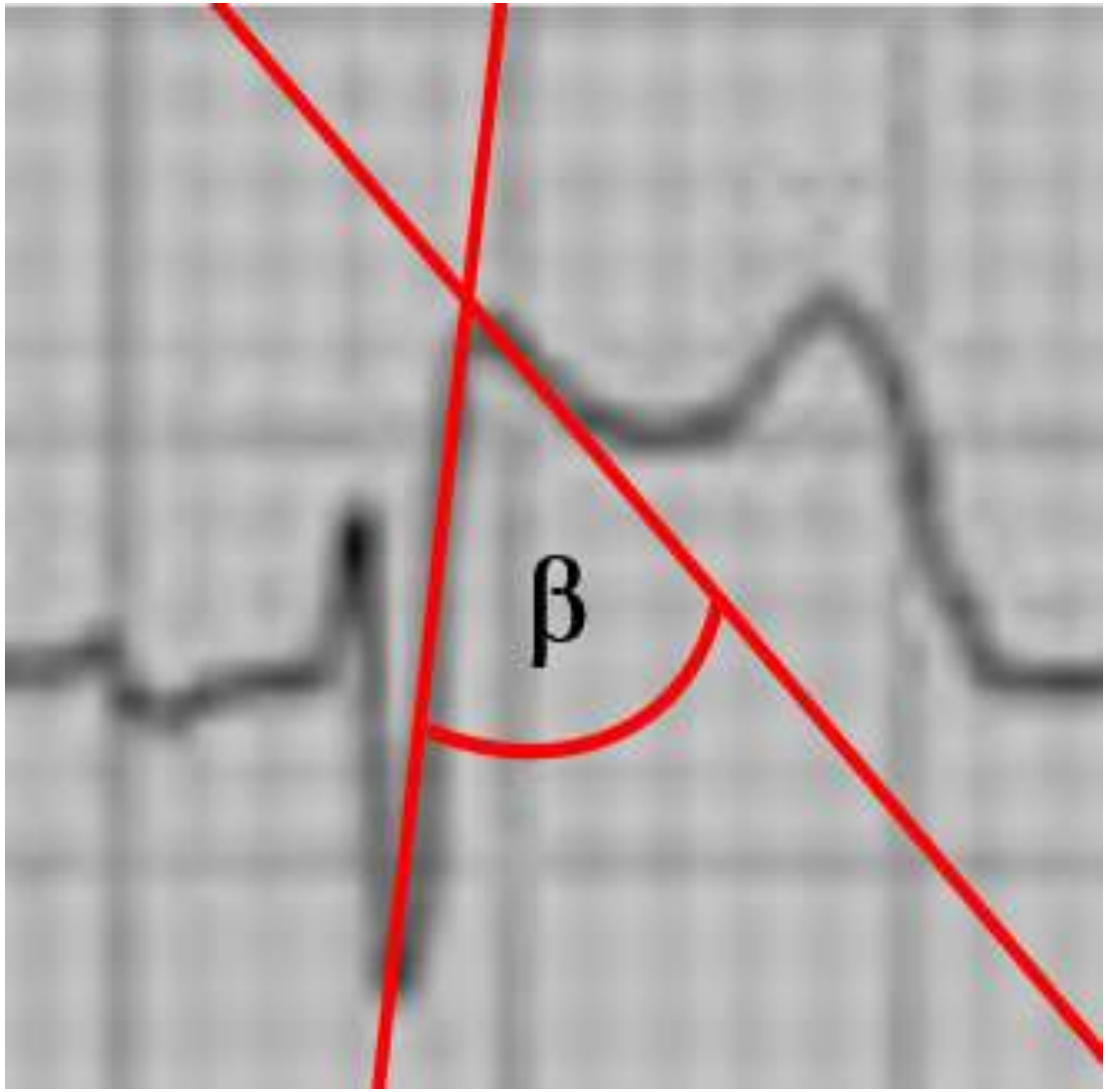


A Type 2 Brugada pattern in V1-V2

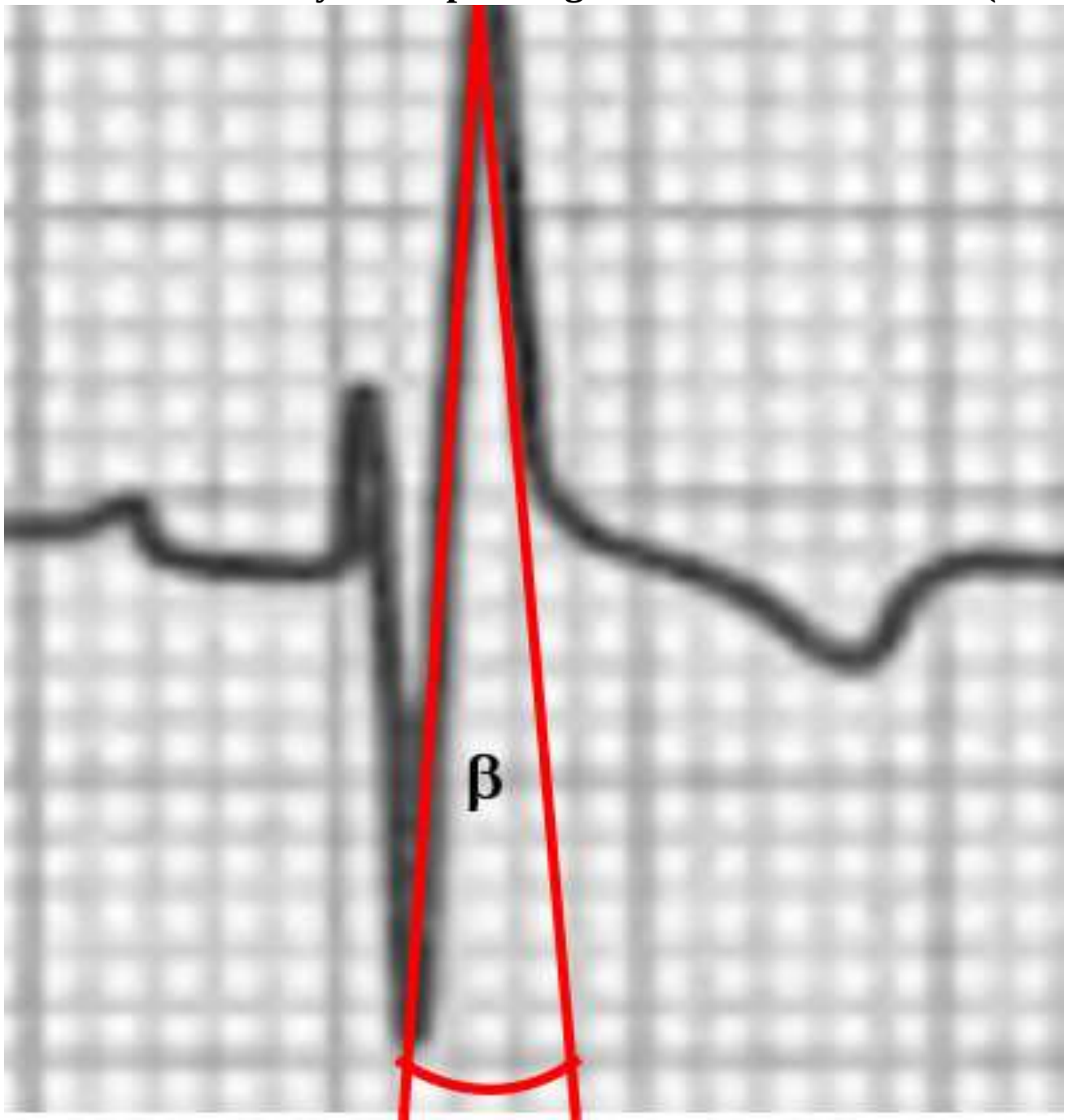
versus

B Innocent or ordinary incomplete right bundle branch block (IRBBB)

Type 2 Brugada pattern in V1-V2



Innocent or ordinary incomplete right bundle branch block (IRBBB)



	Type 2 Brugada pattern	Innocent IRBBB
β-angle Optimal cut off 54°	Broad 54° 62 ± 20°	Acute 13° mean 36 ± 20° (16-56°)
Duration of the base of the triangle	≥3,5mm	<3,5mm
High take-of	Wide	Acute
T-wave polarity	Positive or plane	Negative
β-angle Optimal cut off 54°	Broad 54° 62 ± 20°	Acute 13° mean 36 ± 20° (16-56°)

(**Chevallier et al., 2011; Gottschalk BH, et al. 2016; Ohkubo, et al., 2011**)

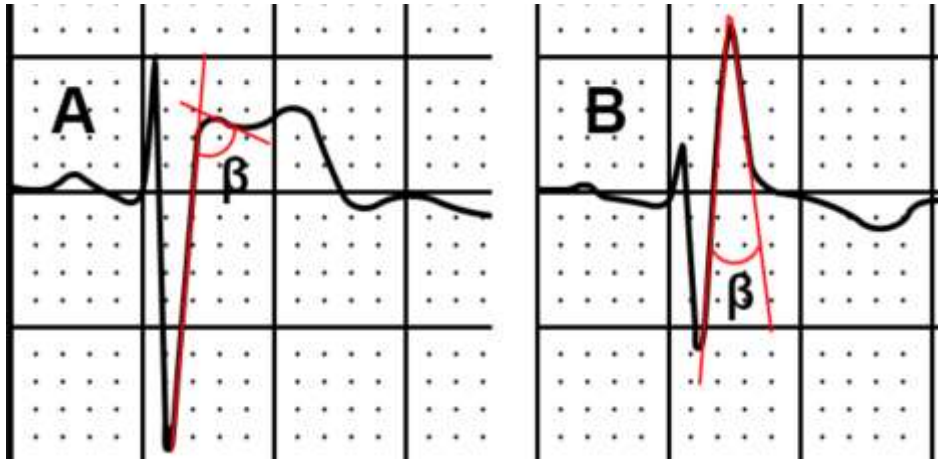
Causes of triphasic pattern in right precordial leads with QRS duration >100 ms and <120 ms in adults: incomplete right bundle branch block Differential diagnosis with type 2 Brugada pattern

As a normal variant, ordinary or "innocent" IRBB.

It is 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. et al., 2018**). The QRS duration must be >100 ms and <120 ms (if <100 ms normal variant predominates), there should be a terminal R' wave in lead V1

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 incomplete RBBB 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 et al 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 et al. 2013**). Men with IRBBB had a significantly greater likelihood of developing complete RBBB. In cases of genuine “innocent” IRBBB, the angle formed by the ascending and descending ramp of r’/R’ is acute with an average of 12° (between 8° to 20°) (**Ohkubo K, et al. . 2011.**). On the other hand, in type 2 Brugada ECG pattern this angle is broader.

β angle in type 2 Brugada ECG pattern (A) and “innocent” incomplete RBBB



A. Type 2 Brugada ECG pattern has characteristic broad β angle Broad 62° ± 20° and

B. “Innocent” incomplete RBBB acute angle (12° in mean).

Vectorcardiograms in patients with Brugada type 1 ECG pattern have distinctive characteristics compared with healthy individuals with incomplete or 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 (**Perez-Riera et al., 2012**).

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 (RV) cavity size and/or remodeling (structural cardiac adaptations) right ventricle with slowing of conduction from exercise-induced RVH (**La Gerche et al. 2011; 2012**). 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. Both CRBBB and IRBBB appear to be noninvasive markers of a training-related triad characterized by RV enlargement, a relatively reduced RV systolic function at rest, and interventricular dyssynchrony. This triad reflects a degree of RV hibernation that confers more potential for augmentation during exercise or, alternatively, a form of subclinical RV pathologic features related to intense training, requires additional investigation. CRBBB/IRBBB might serve as an important selection criterion for future studies. Because CRBBB is relatively rare among athletes, the long-term clinical significance remains unknown. Among trained athletes, appear to be markers of a structural and physiological cardiac remodeling triad characterized by RV dilation, a relative reduction in the RV systolic function at rest, and interventricular dyssynchrony (**Kim JH et al, 2011**). 12-lead ECG at rest is not substantially affected by training in children, despite a physiological increase in cavity size.

Thus, in preadolescent athletes, 12-lead ECG at rest does not reflect exercise-induced morphologic remodeling and seems to be influenced more by sexual maturation than by training. At baseline, athletes had lower heart rate at rest compared with controls and a further decrease was observed after training.An IRBBB was found in 19% of athletes and 15% of controls with no changes after training. Although none of the athletes showed negative T waves from V1 to V3, 6% of controls at baseline had T-wave inversion V1 to V3 with a decrease to 3% after 5 months. The early repolarization pattern did not differ between athletes and controls. (**D´Ascenzi F et al., 2017**). Common, conditionally benign and training related ECG changes are sinus bradycardia and sinus arrhythmia, first degree atrioventricular block IRBBB, benign early repolarization pattern, and isolated QRS voltage criteria for LVH. Uncommon ECG changes, unrelated to training, and some specific syndromes are ST segment depression and/or ≥ 2 mm T wave inversion in ≥2 adjacent leads, intraventricular conduction disturbance, Wolf-Parkinson-White syndrome, long QT syndrome, short QT interval syndrome, CPVT, monomorphic ventricular extrasystoles and benign ventricular tachycardia.

III) 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 and qr pattern in V1 (the right auricular chamber, being located exactly underneath the exploratory electrode of V1, would allow 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 in the horizontal plane, and negative T waves in V1 in 100% of cases (**Martins De Oliveira J, et al.1958.**)

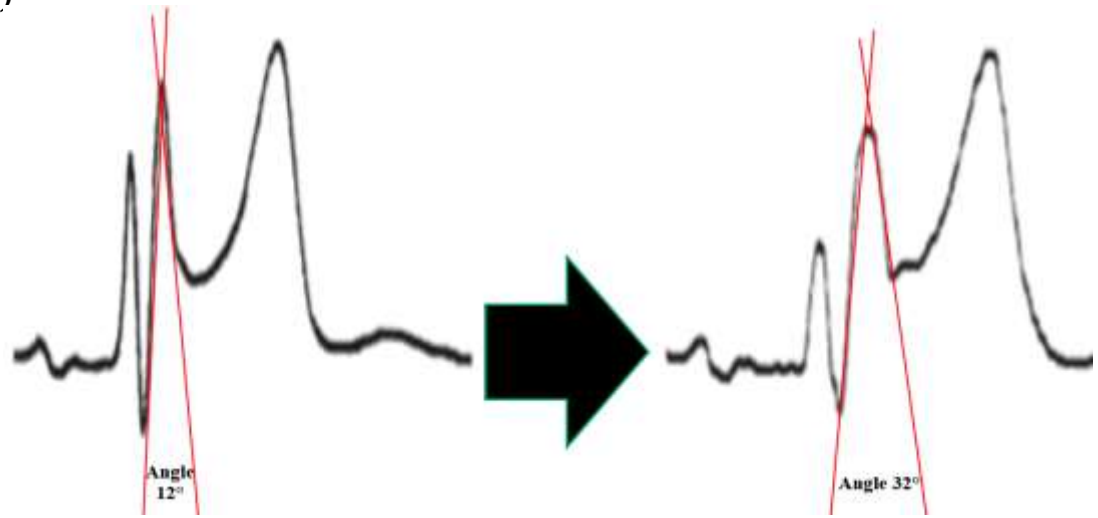
IV) Straight-back syndrome

- 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, et al. 2009**).

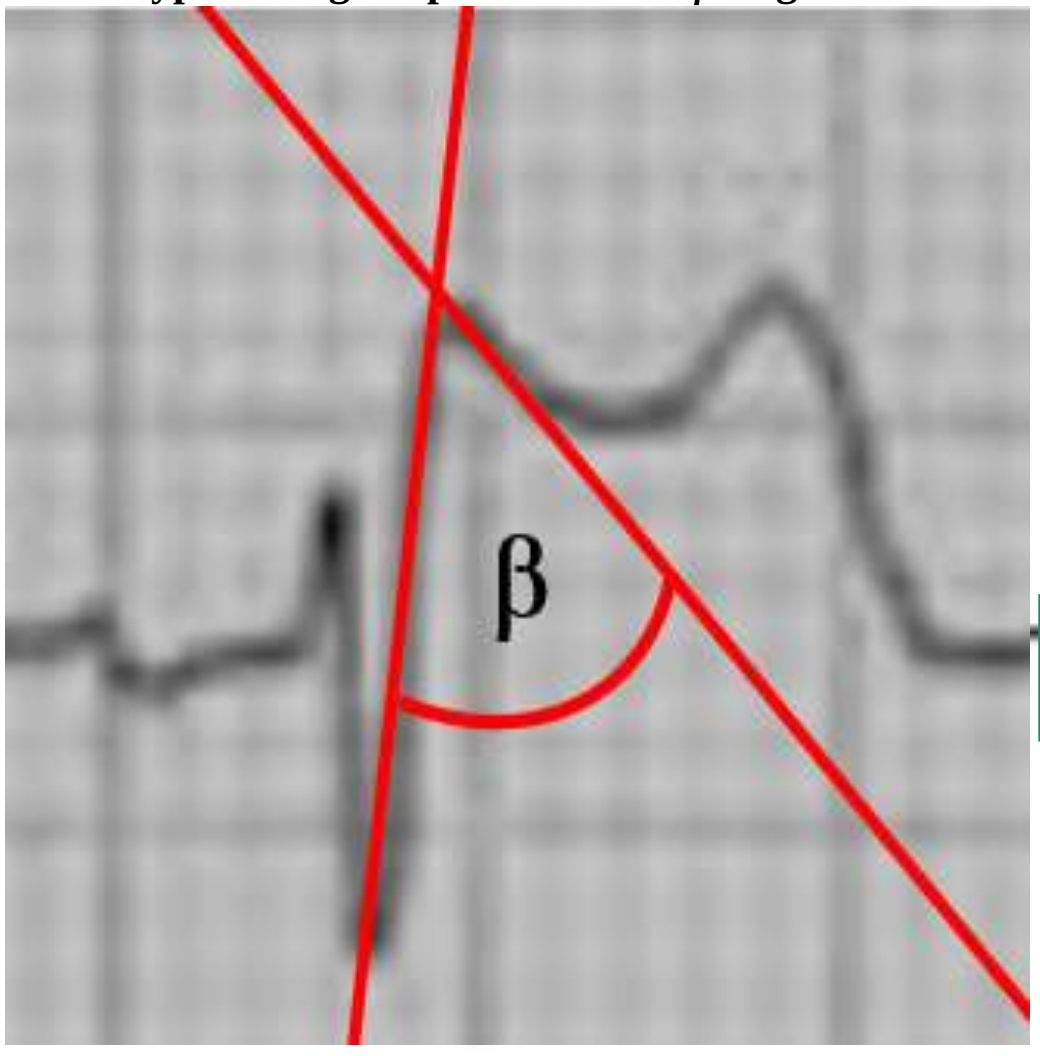
V) Atrial Septal Defect Ostium Secundum (ASD-OS):

- An 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 volumetric/diastolic overload of the right atrium and right ventricle. Children are rarely symptomatic, but long-term complications after age 20-year-old 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, et al. 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, et al. 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

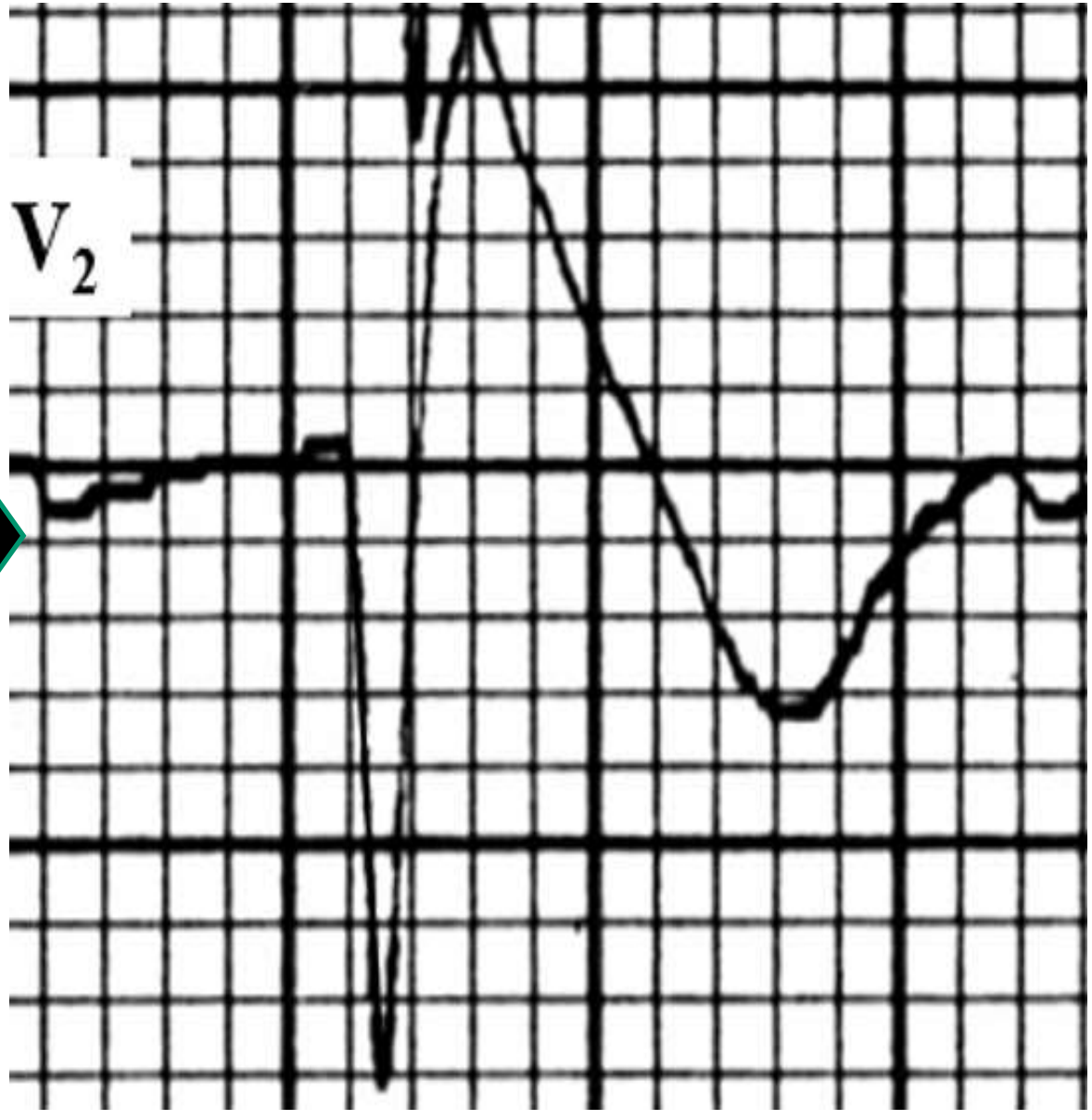
- although the RBBB pattern persisted. A crochetage pattern of the R wave in inferior limb leads is frequent in patients with ASD, correlates with shunt severity and is independent of the RBBB pattern. Sensitivity and specificity of this sign are remarkably The type 1 ECG pattern is necessary for the diagnostic of BrS; types 2 and 3 require antiarrhythmic drug challenge to confirm its presence. Ohkubo et al evaluated a 12-lead ECG-based criterion to differentiate between ordinary incomplete right bundle branch block (iRBBB) and true type 2 and 3 patterns that evolve toward type 1 during drug challenge. The authors studied 22 patients (21 men, 1 woman; mean age, 46.8 ± 13.2 years) referred for drug challenge (1 mg/kg IV pilsicainide). In magnified ECG lead V1 and/or V2 with an iRBBB pattern, the baseline angle defined as the cross section of the upslope of the r' wave with the downslope of the r' wave was measured and compared between patients responding negatively versus positively to drug challenge, and was found to be significantly smaller in patients responding negatively (20.9 ± 12.9°, n = 6, versus 38.7 ± 16.5°, n = 13; P = 0.009). This ECG-based method successfully discriminates between the ordinary iRBBB pattern and drug-induced evolution toward a type 1 Brugada ECG.
- Measuring the terminal QRS angle. The angle between of th upslope of the S wave an that of the downslope o the r` wave is measured on the baseline ECG(**Ohkubo K, et al. 2011**)



Type 2 Brugada pattern broad β-angle



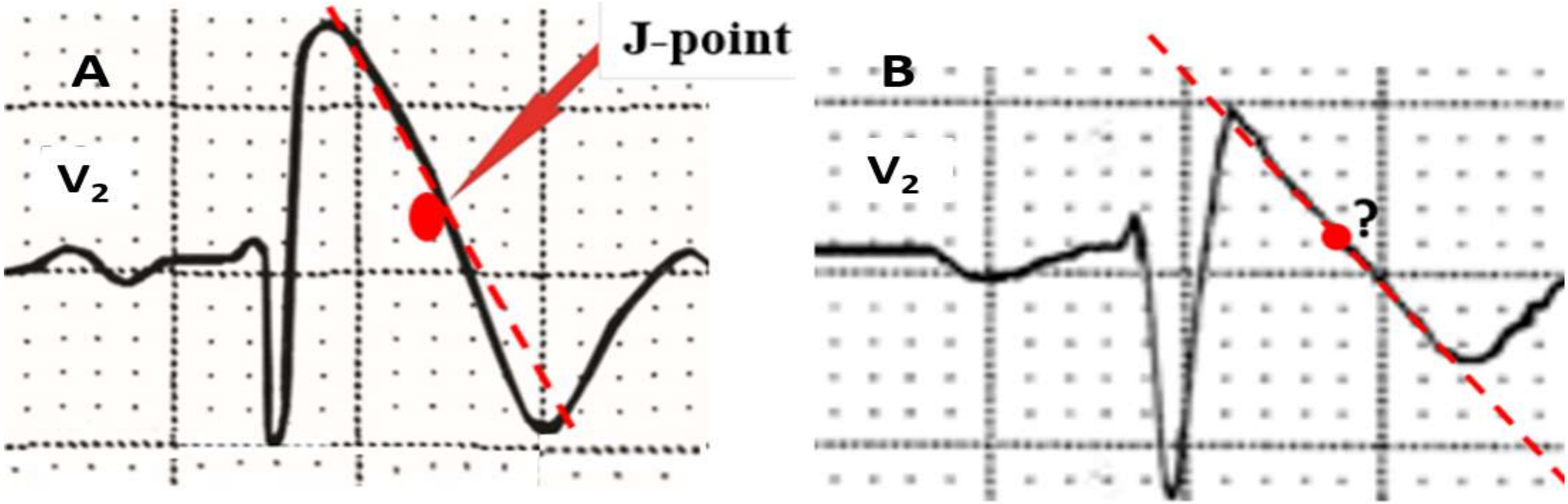
Type 1 Brugada pattern



Brugada phenocopies are ECG patterns indistinguishable from Brugada pattern that may appear and disappear in relation with multiple causes but are not related with BrS (Figure).

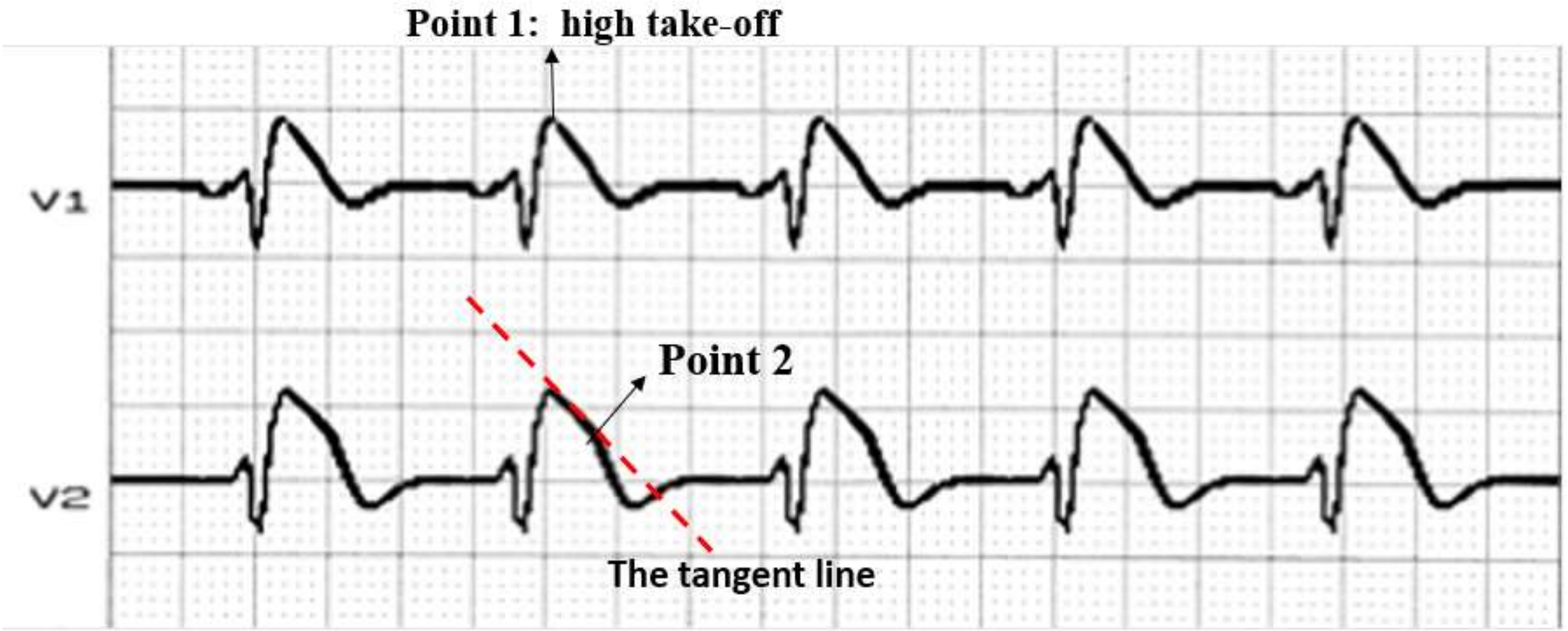
Figure Type 1 Brugada ECG pattern in the right precordial leads

Sub-typo A **Sub-type B**



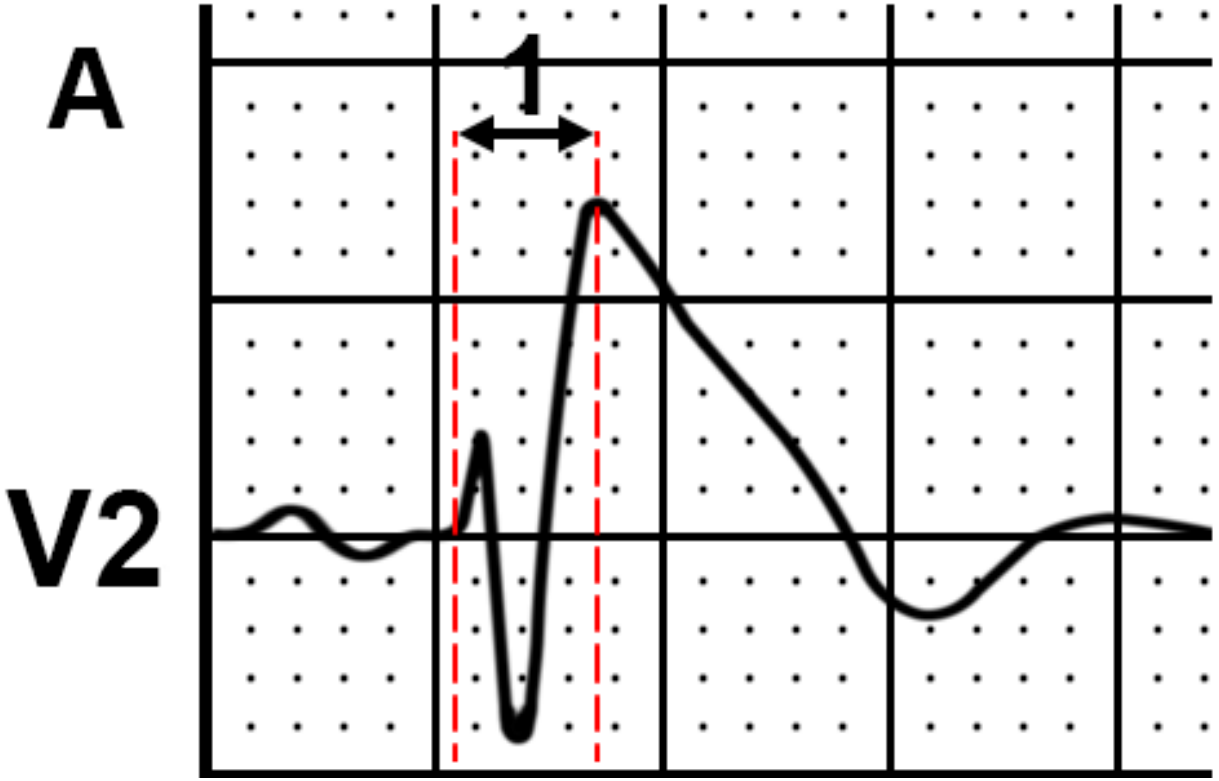
The ST segment can be of superior convexity (A) or descending rectilinear (B). To determine the location of point J (end of QRS) we use the tangent line method that accompanies the descending ramp of R' (dotted line). It is considered that the point J is located at the moment that the tangent line separates 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 duration of the QRS. This value is important because a QRS duration ≥120 ms in V2 and ≥ 90 ms in V6, are a markers of event risk.

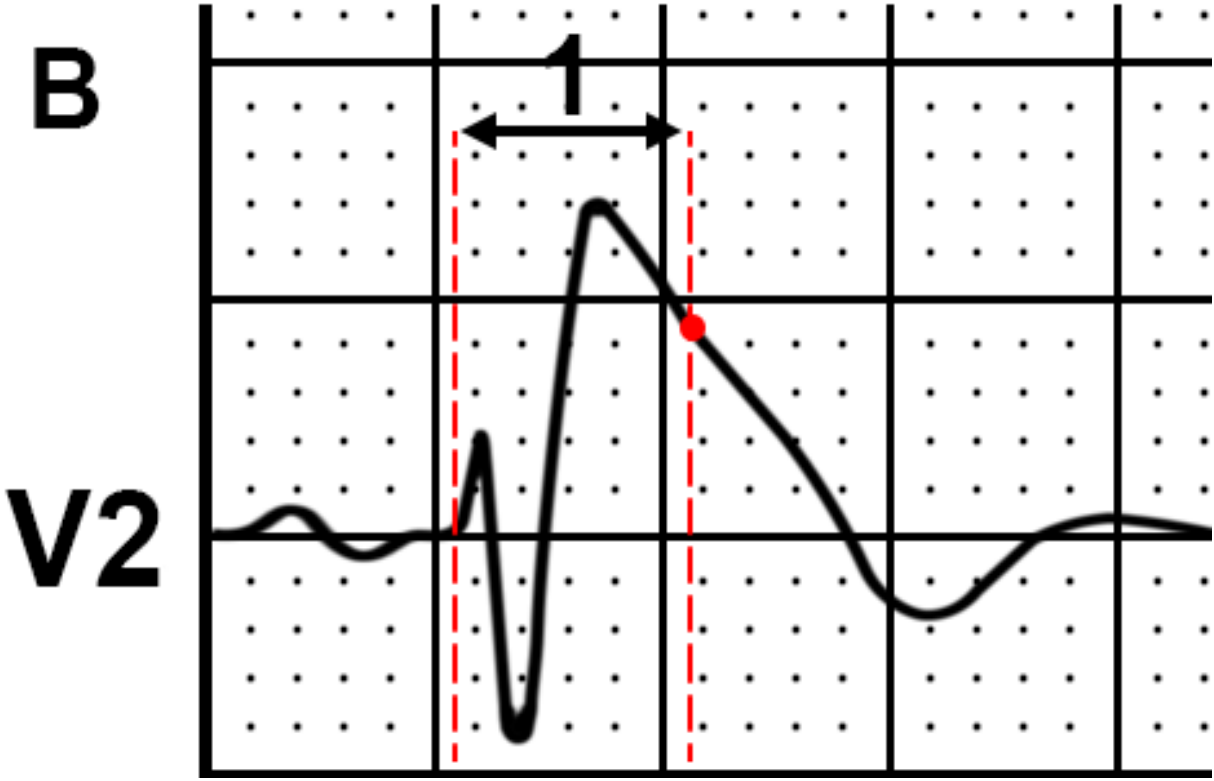
Where is the location of the end of the QRS complex (the J-point)? In point 1 or 2?



Answer: the correct answer is **i**n point 2. Point 1 corresponds to the highest point (high take-off) and point 2 to J point, that is the end of the QRS and beginning of ventricular repolarization.

r-J interval definition: This interval elapsed from QRS onset to J point in V_1 or V_2.

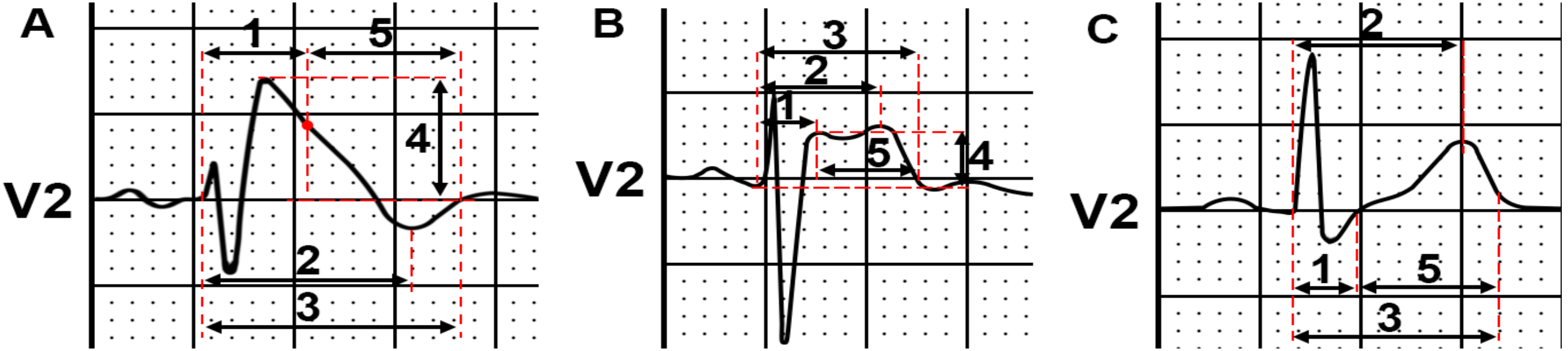




A. This measurement is wrong because it extends from the onset of the QRS to the high take-off. When this measurement in lead V2 ≥90 ms is predictors of cardiac events recurrence in symptomatic patients (Takagi et al., 2007).

B. is correct because it extends from onset of QRS to true J point determined by tangent line.

.



(2) **r-T peak interval (rTp): interval from QRS onset to the peak of T wave.**

(3) **r-T end interval (rTe): interval from QRS onset to the end of T wave.**

(4) **J point amplitude.**

(5) **J-T end interval (JTe): interval from J point to the end of T wave.**

Repolarization versus depolarization mechanism and abnormal expression of cardiac neural crest cells in heart development

I. Ventricular repolarization components on the electrocardiogram

- ❖ J-wave
- ❖ ST-segment
- ❖ T-wave
- ❖ U-wave

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

II) Ventricular depolarization components on the electrocardiogram

1. **QRS fragmentation (fQRS)**
2. **QRS duration ≥120 ms in V2 and II**
3. **Epsilon wave**
4. **Right End Conduction Delay**
5. **Parietal block**
6. **QT peak**
7. **QT end**
8. **r-J interval**
9. **Late potentials (LPs)**

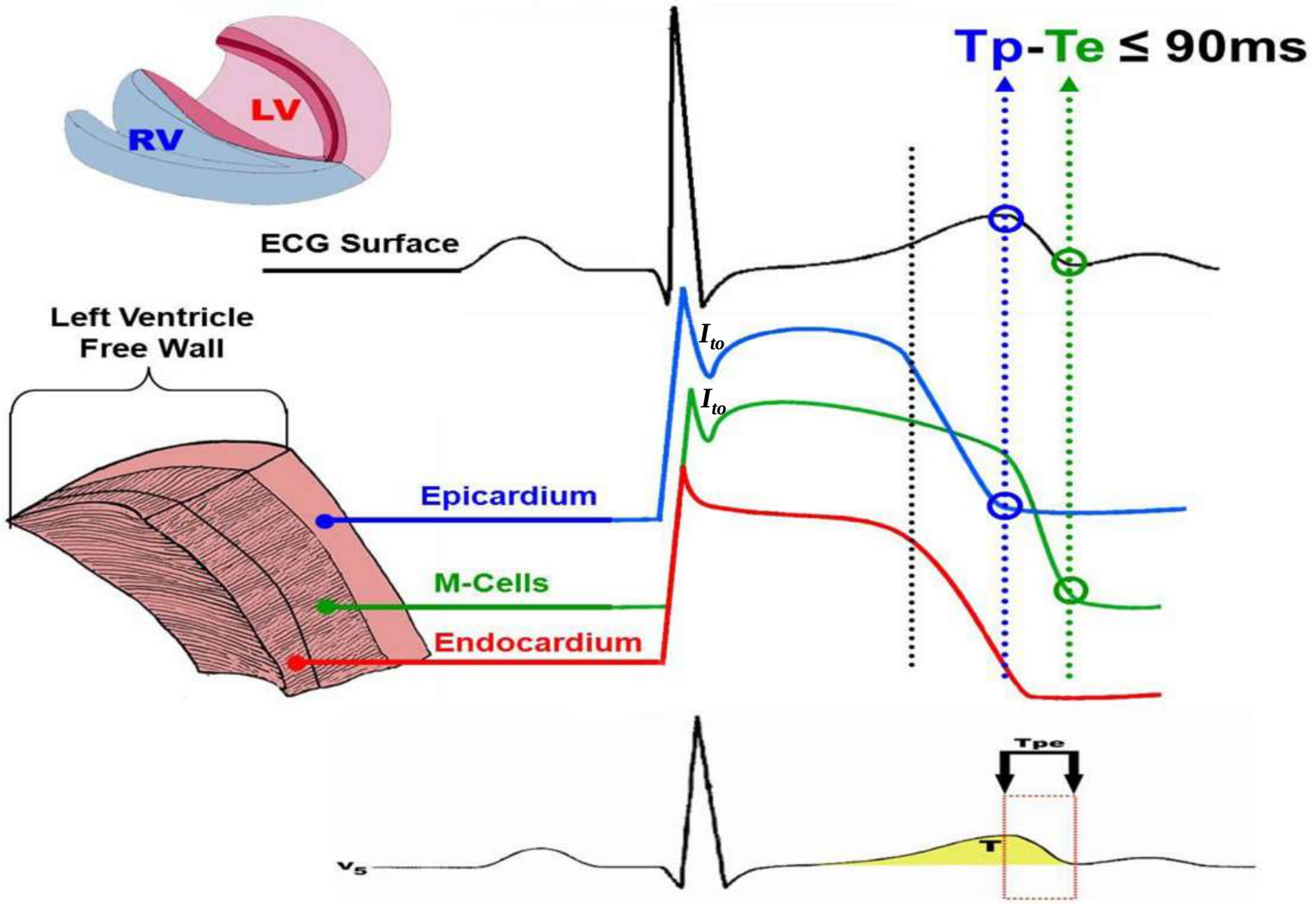
Three pathophysiological mechanisms have been postulated to explain the type 1 Brugada pattern:

(1) late activation of the right ventricle causes ST-segment elevation and repolarization of the same myocardium causes the negative T-wave. Diminished subepicardial connexin43 expression with intercellular uncoupling can amplify APD gradients between epicardial and midmyocardial layers (**Poelzing S1, et al. 2005.**), explaining why M cells are more readily detectable under pathologic conditions such as the BrS,

(2) Excitation failure at the right ventricular epicardium causes ST-segment elevation and moderate activation delay at neighboring sites causes the negative T-wave.

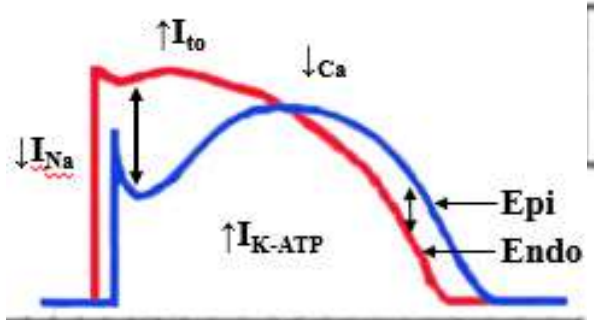
(3) Loss of the Na^+ current action potential dome at the right ventricular epicardium but not the endocardium in the right ventricular outflow tract, resulting in “unopposed” transmural dispersion in action potential duration (**Skinner JR, et al. 2019**).

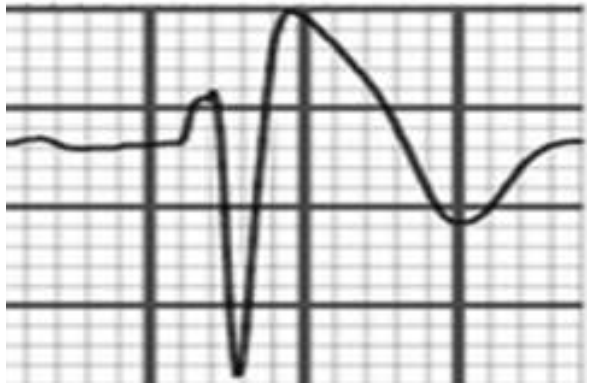
Transmembrane APs from epicardium, endocardium and midmyocardium (M cells): repolarization mechanism



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

Early repolarization mechanism in Brugada syndrome repolarization mechanism





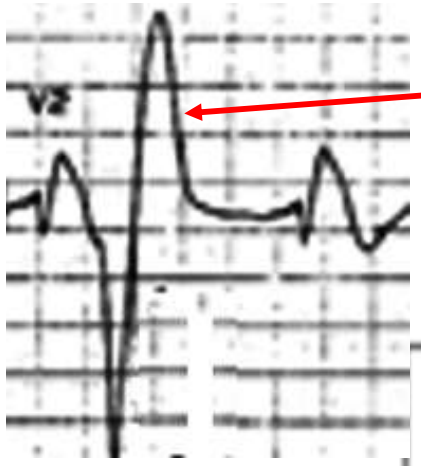
Gene mutations SCN5A and other

↓I_{Na}; ↓I_{Ca}

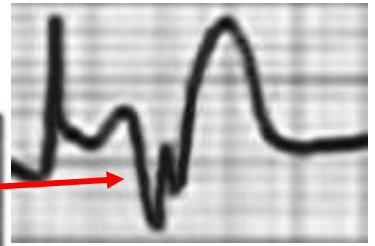
I_{to}; ↑I_{K-ATP}

Fever
Ischaemia
Multiple Drugs
Cocaine
Alcohol
Hypokalaemia
Hypothermia

Type 1 Brugada Pattern

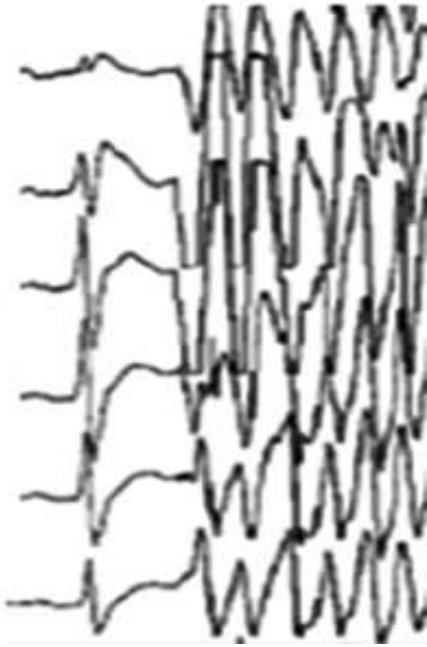


Short-coupled PVCs/ Polymorphic VT
Phase 2 reentry VT



Self-terminating VT/VF

Sustained VF



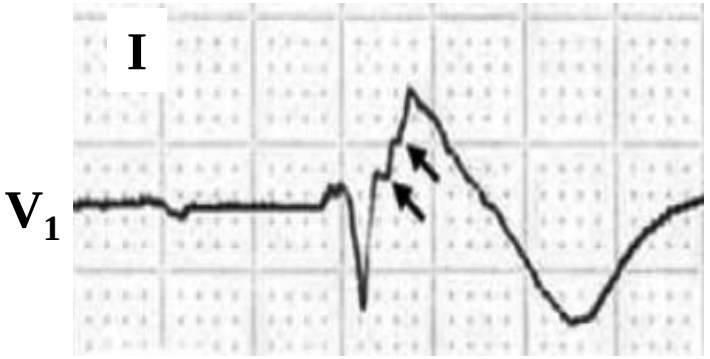
Depolarization mechanism

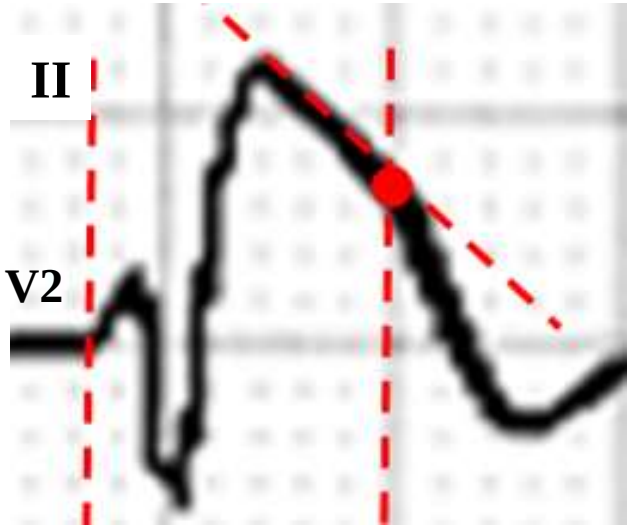
I. QRS fragmentation or fragmented QRS complex (fQRS): defined as ≥ 2 notches of the R wave or in the nadir of the S wave in at least 2 consecutive leads.

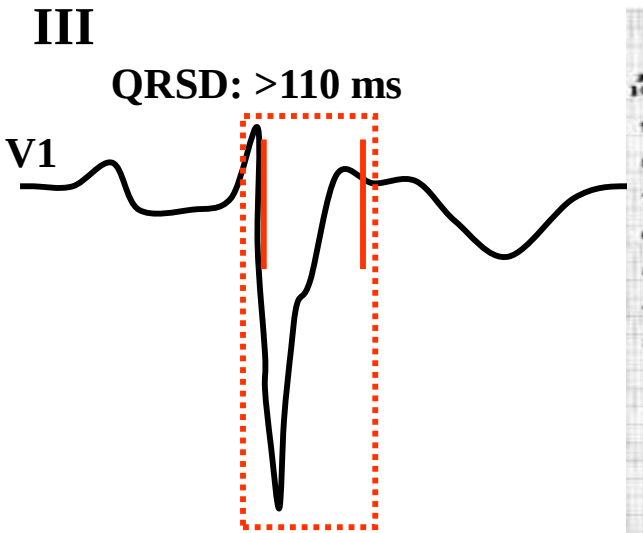
II. QRS duration ≥120 ms in V2 and II, f-QRS are powerful depolarization marker for VF/SCD is a significant S-wave (≥0.1 mV and/or ≥40 ms) in lead I in patients with BrS (**Calò 2016**)

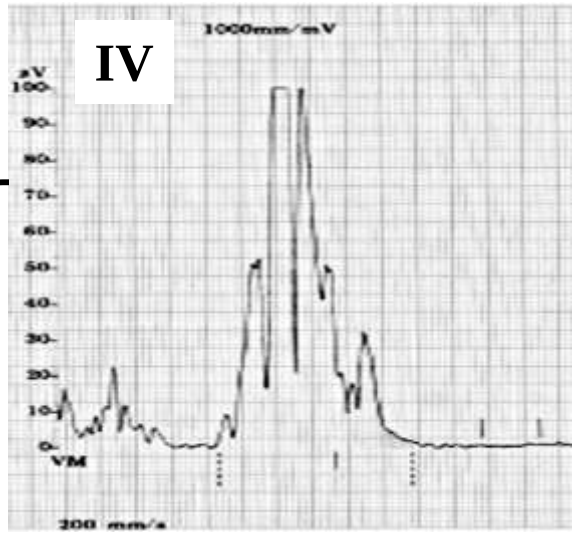
III. QT-interval prolongation in right precordial leads (**Pitzalis MV, et al. 2003.**). Presence of LPs on SAECG: 1) Total filtered QRS duration (f-QRS) ≥114 ms; 2) Root Mean Square voltage (RMS40

IV.) of the terminal 40 ms of the f-QRS complexes ≥20 μV; and 3) Duration of low-amplitude signals 40 μV of the f-QRS complexes (LAS_{40}) ≥38 ms. LP is identified when 2 of the criteria are satisfied. 5) Right End Conduction Delay on VCG

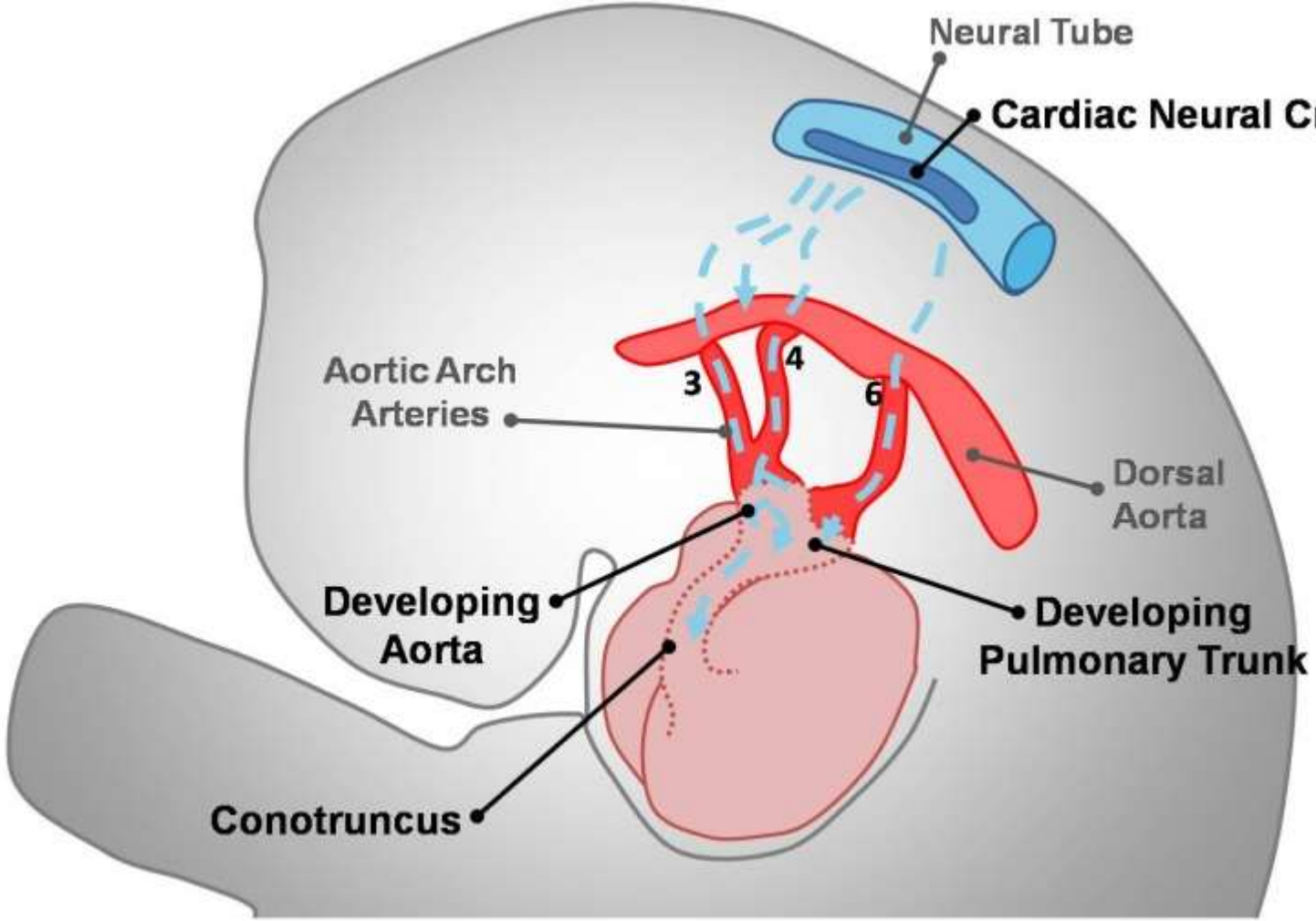






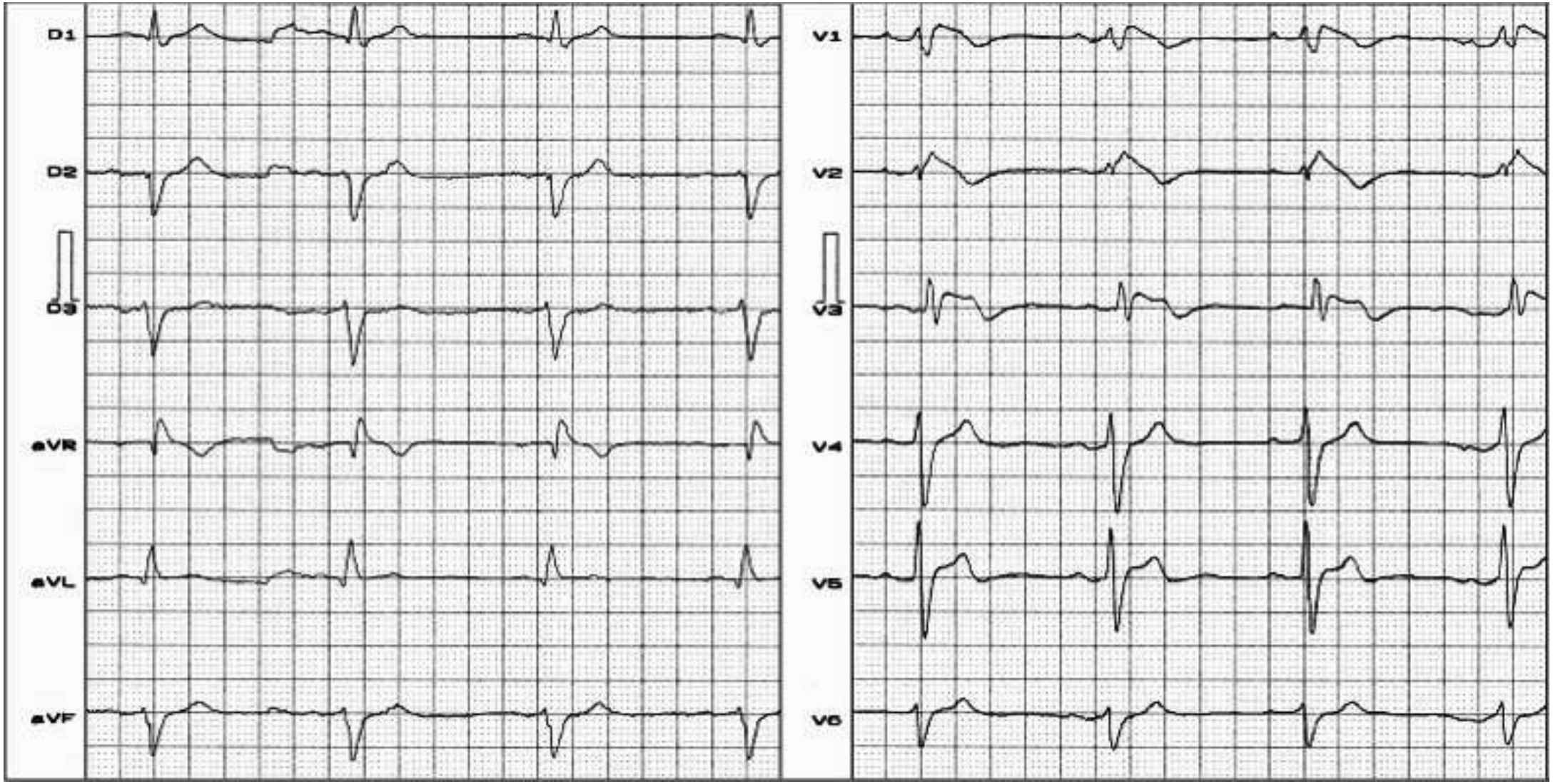


Abnormal expression of cardiac neural crest cells in heart development (**Elizari 2007**) in fact this theory is also eclectic because it admits both mechanisms: depolarization and repolarization. The cardiac neural crest(CNC) cells are a subpopulation of cranial neural crest discovered nearly 33 years ago by ablation of premigratory neural crest. The CNC cells are necessary for normal cardiovascular development.



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

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

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

➢ Genetic forms

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

- Without apparent structural heart disease

J-wave Syndromes

- BrS: J-wave in the right precordial leads V1-V3
- Overlapping between BrS and ERS**(McIntyre WF, Pérez-Riera AR, et al. 2012 J Electrocardiol.)(Pérez-Riera AR, et al. 2017) (Kalla H, et al. 2000.)(Riera AR, et al 2004)**
- IVF
- SQTS; LQTS
- With structural heart disease

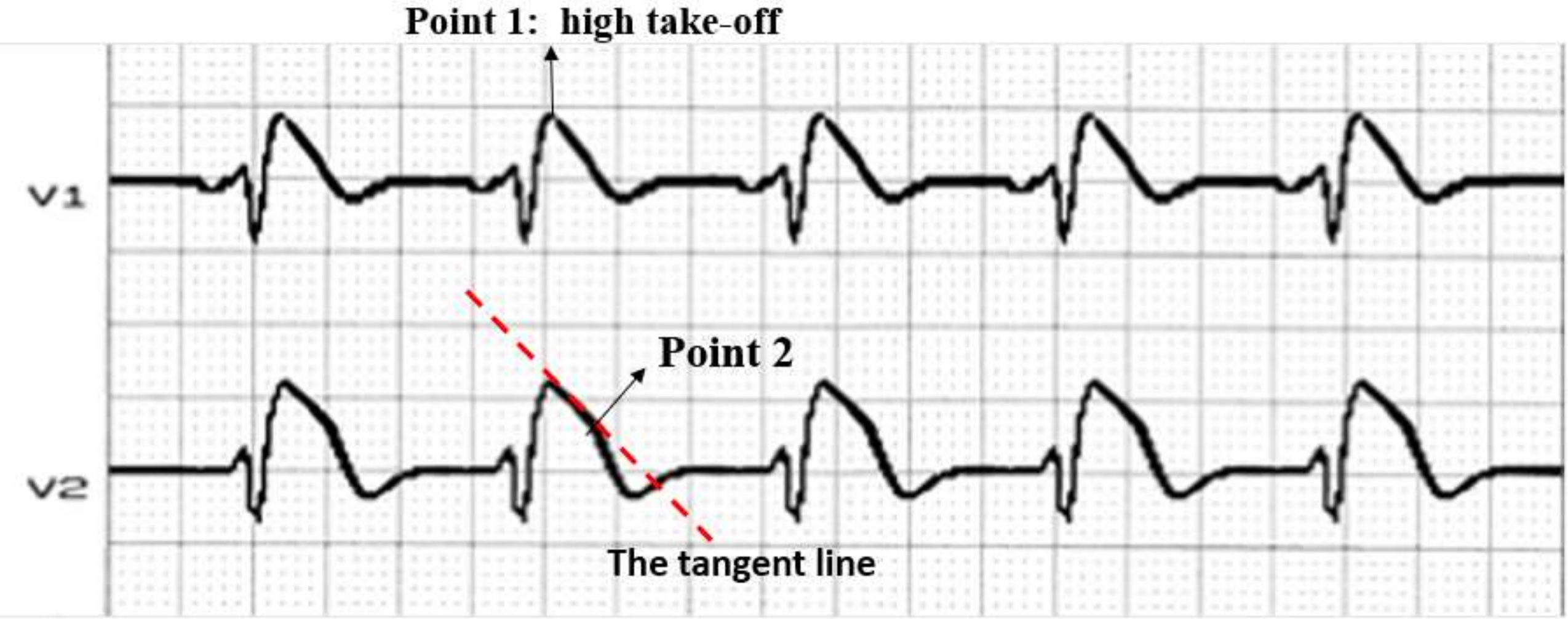
- Concealed forms of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D) (**Nava 1988**)

➢ Acquired forms

- Ischemia- mediated VT/VF: Vasospastic angina, (**Maruyama M, et al. 2002**.) Prinzmetal J waves/ Ischemic J-Waves (**Shinohara T. et al. 2018**)(**Fumimoto T, et al, 2017**.)
- Miscellaneous
  - ✓ Hypercalcemia(**Sridharan MR, et al. 1984**.)(**Otero J, et al. 2000**.)(**Jenkins JK, et al 1987**.)
  - ✓ Brain injury(**Hersch C. 1961**.)
    - ❖ Subarachnoid hemorrhage(**De Sweit J. et al. 1972.**.)
    - ❖ Acute intracranial hypertension
    - ❖ Transient postictal hemiplegia (Todd's paralysis) (**O'Connell E, et al. 2013**)
  - ✓ Damage to sympathetic nerves in the neck: or spinal cord injury leading to loss of sympathetic tone
  - ✓ Cardiopulmonary arrest from over sedation **(Shinde R, et al. 2007.)** or after resuscitation from cardiac arrest(**Jain U, et al. 1990**.)
  - ✓ Accessory third papillary muscle with a prominent J-wave
  - ✓ Hypervagotonia.

Modified from Yan GX, et al. J wave and J wave syndromes (in Chinese) **Chin J Card Arrhythm. 2004;8:360–5**.

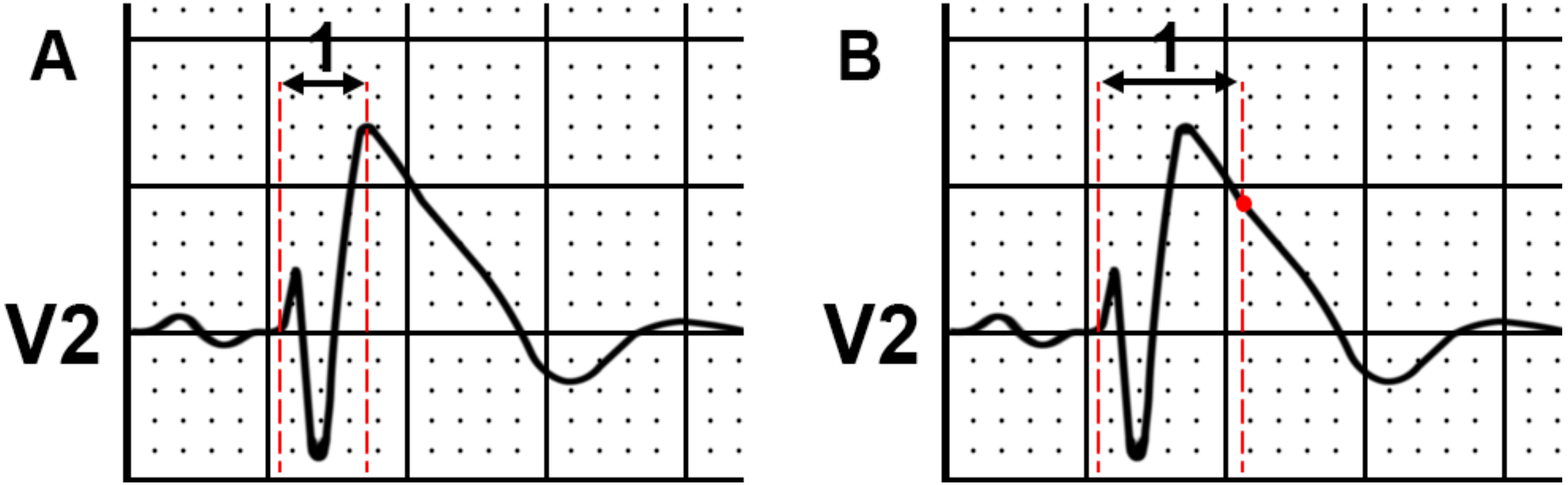
Where is the location of the end of the QRS complex (the J-point)? In point 1 or 2?



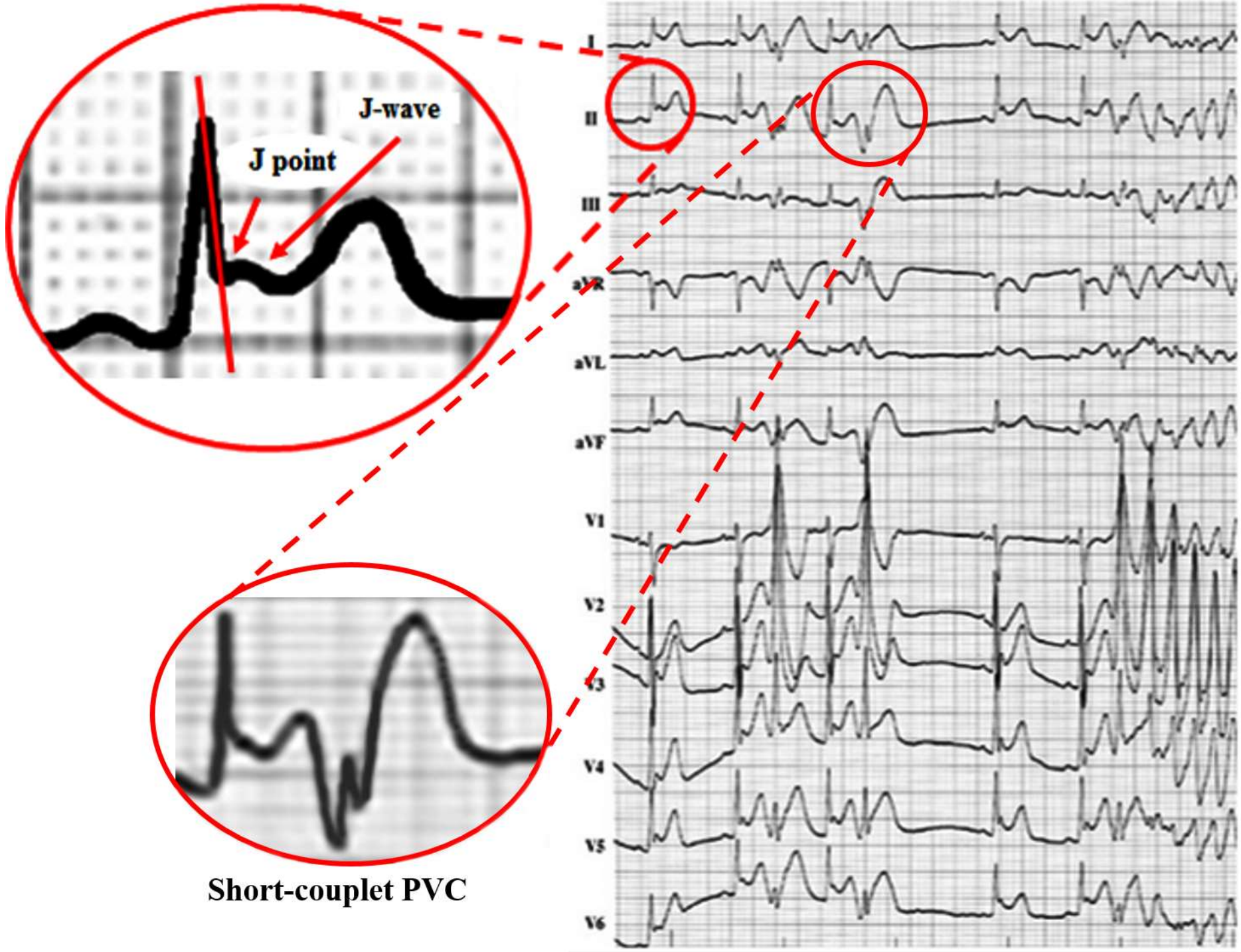
Answer: the correct answer is **i**n point 2. Point 1 corresponds to the highest point (high take-off) and point 2 to J point, that is the end of the QRS and beginning of ventricular repolarization.

r–J interval, defined as the time between the earliest deflection of the QRS complex and J wave

Wrong (A) and correct (B) measurements of the r-J interval



r-J interval: from QRS onset to J point in V1 or V2.
A is wrong because it extends from the onset of the QRS to the high take-off. When this measurement in lead V2 ≥90 ms is predictors of cardiac events recurrence in symptomatic patients (**Takagi et al., 2007**).



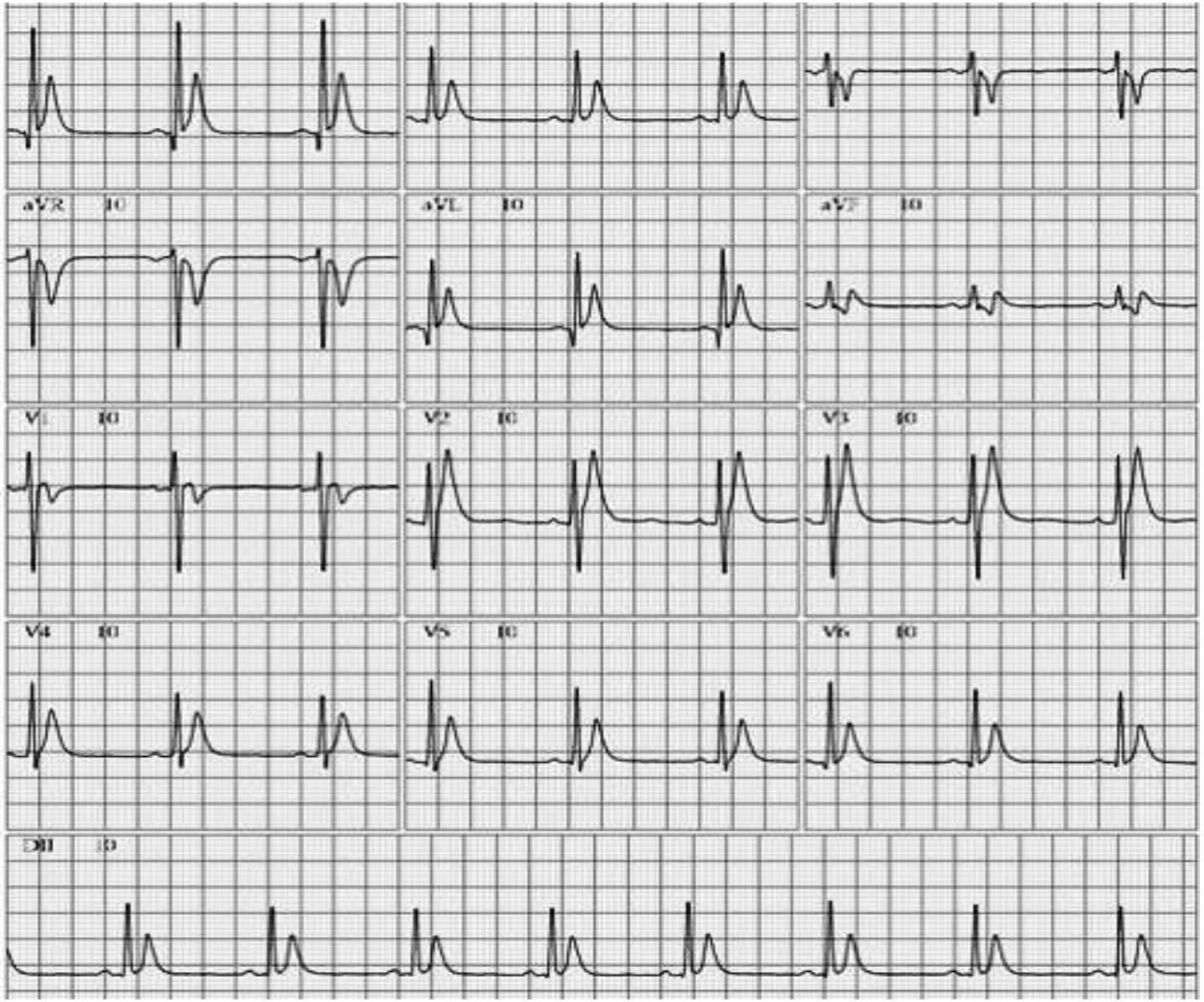
Short-couplet PVC

Short QT syndrome with early repolarization

The main features of congenital SQTS are:

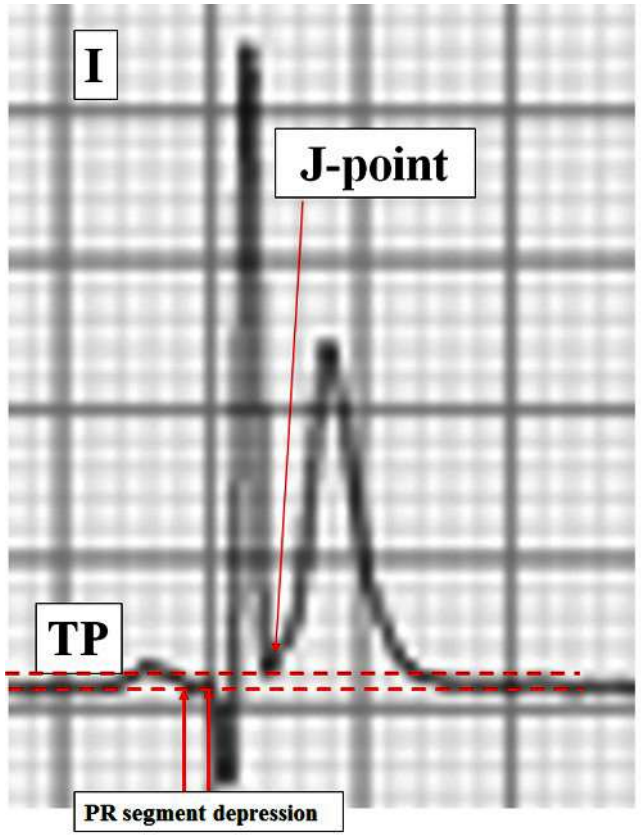
- Absence of structural heart disease
- Familial clinical-electrocardiographic entity
- Autosomal dominant inheritance or sporadic, and genetically heterogeneous
- Constant and uniform very short QT and QTc intervals (QTc interval ≤330 ms)
- Positive family history for sudden cardiac death (SCD)
- Manifested by syncope, sudden death, dizziness and high tendency to appearance of episodes of paroxysmal runs of atrial fibrillation (AF)
- The response to exercise testing is a slight reduction of the QT interval during the increase in heart rate.
- Short refractory periods and tendency for inducible AF and VF were seen in electrophysiology studies (EPSs).
- Autopsy did not reveal any structural heart disease

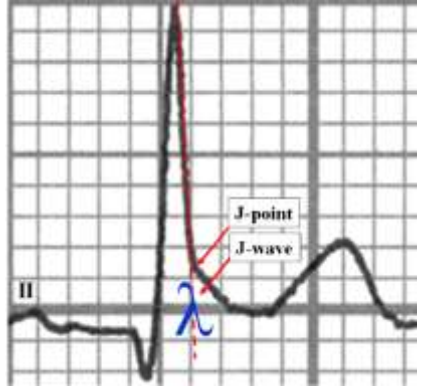
Name: MTC; **Sex**: F; **Age**: 54 y/o; **Date**: March 20, 2014; **Ethnic group**: Caucasian. ECG of one sister of the proband.



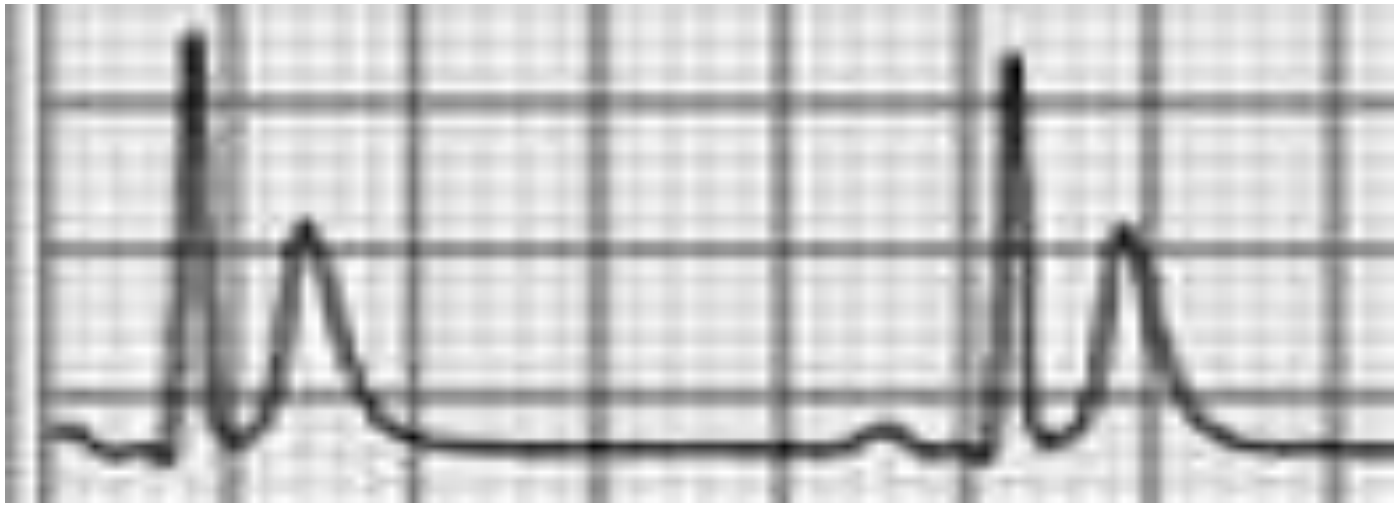
Clinical diagnosis: Congenital short QT syndrome with mutation in Caveolin-3 (SQT7).

ECG diagnosis: Sinus rhythm, HR = 68 bpm; P wave: ; SÂP + 32º, PR interval duration: 120 ms, PR segment depression (>0.5 mm) in II and V5, absence of ST segment, positive-negative T wave or “minus-plus T wave sign” in aVF, and QT = 280 ms; QTc = 295 ms.





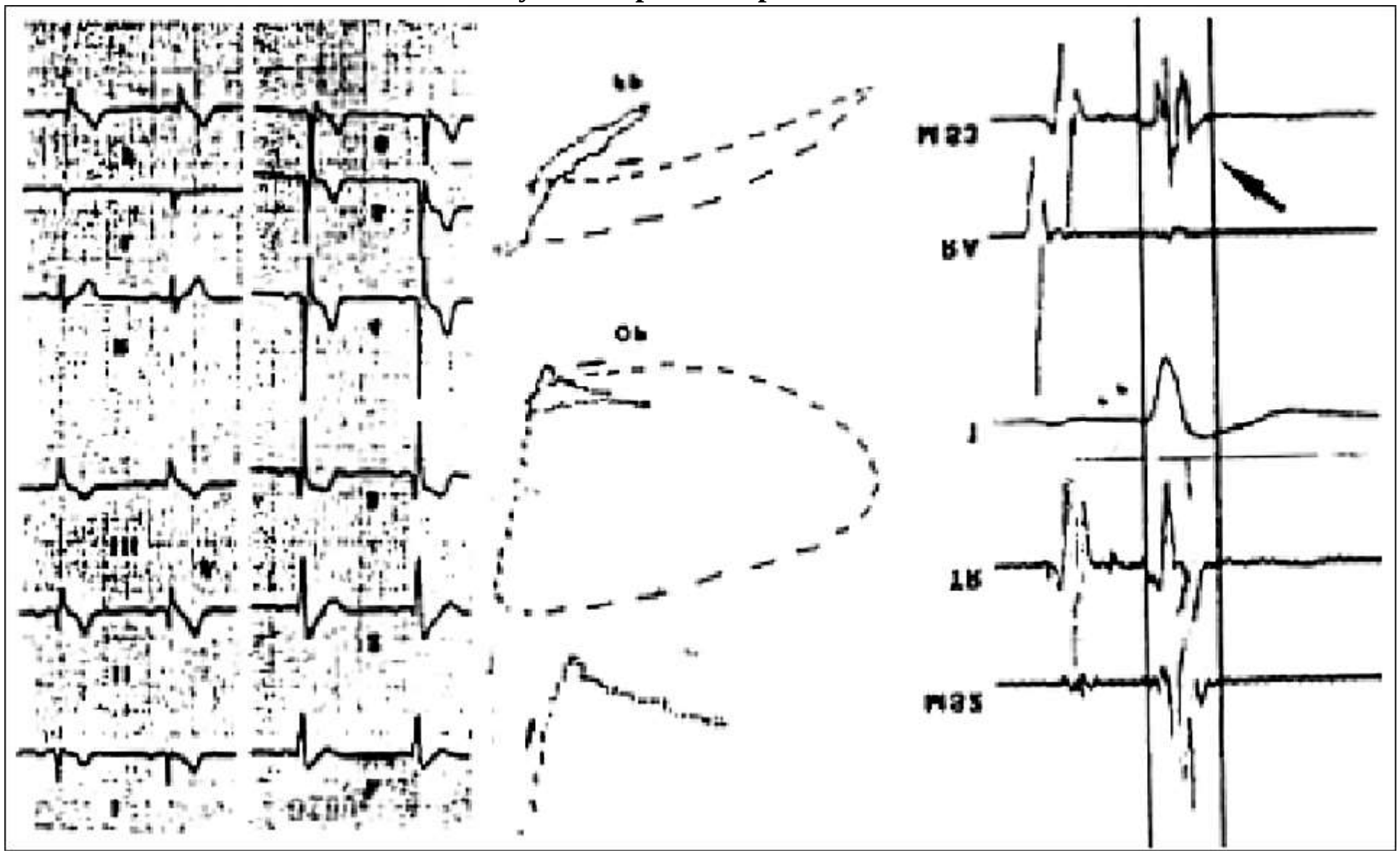
El primer punto de inflexión de la rampa descendente de la onda R es considerado el punto J real. En estos casos el método de la “línea tangente” es ideal. Elevación del segmento ST = 0,8 mm. Consideramos una variante tipo C atípica de patrón de repolarización precoz. El aspecto de lambda es un marcador de arritmias fatales.



J-wave syndrome with structural heart disease

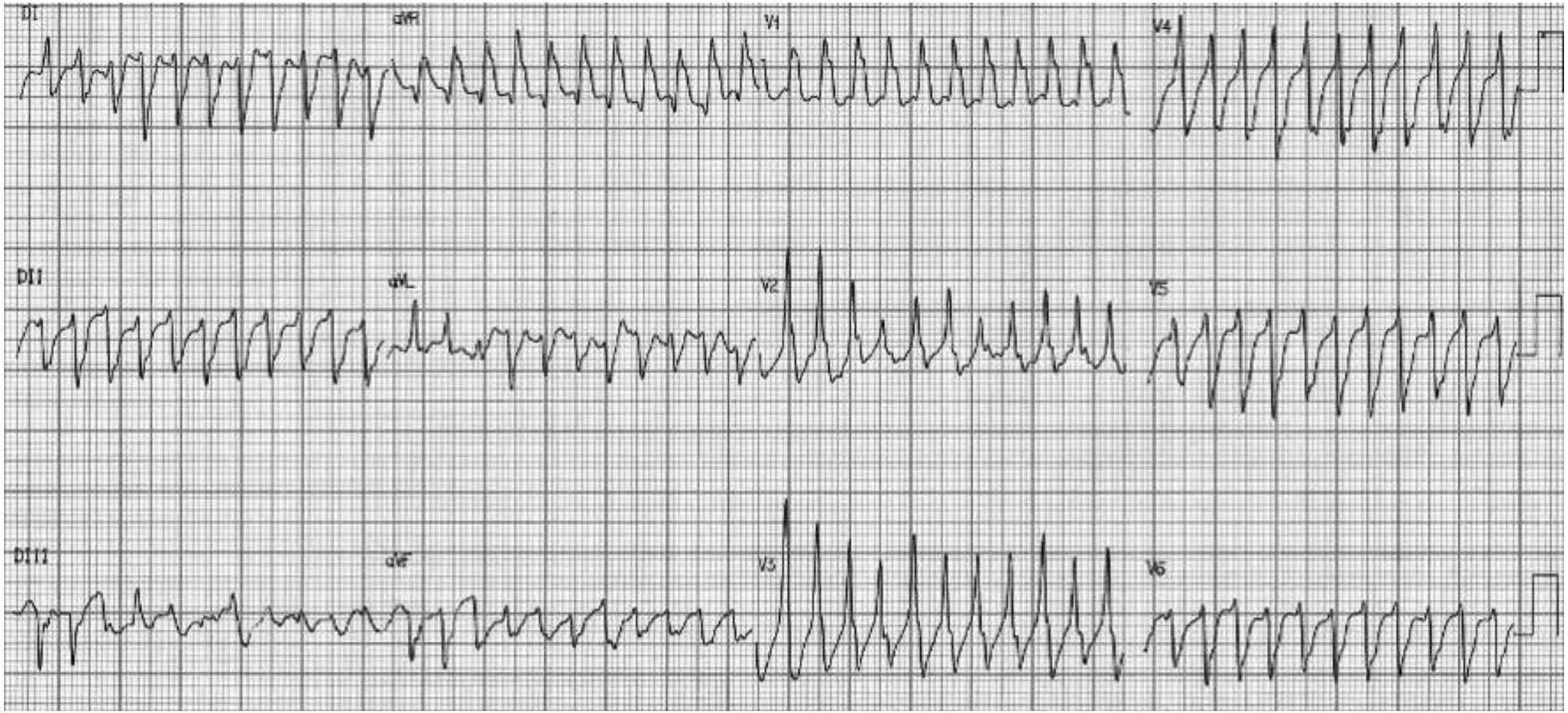
1. Concealed forms of arrhythmogenic dysplasia of the right ventricle

36-year-old patient, episode of VF



The authors interpreted this tracing as early repolarization pattern. Today we know that this is the typical type 1 ECG Brugada pattern, which from the vectorcardiographic point of view is diagnosed as RECD by one of the RB fascicles of the RBB (**Nava A, et al. 1988**).

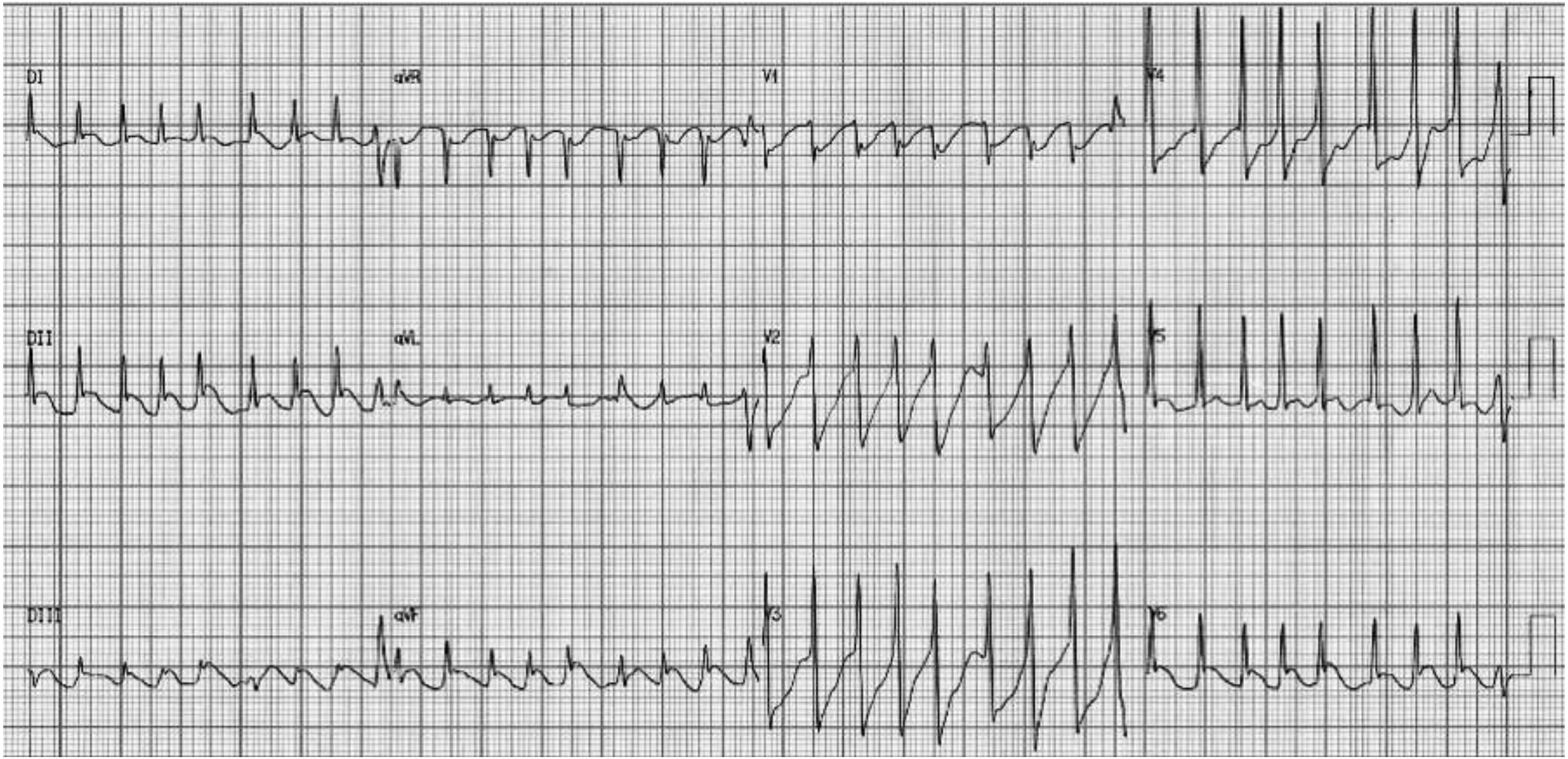
2. Brain injury - ECG at admission (08:32 A.M.) - Massive J-waves in the context of intracranial hemorrhage



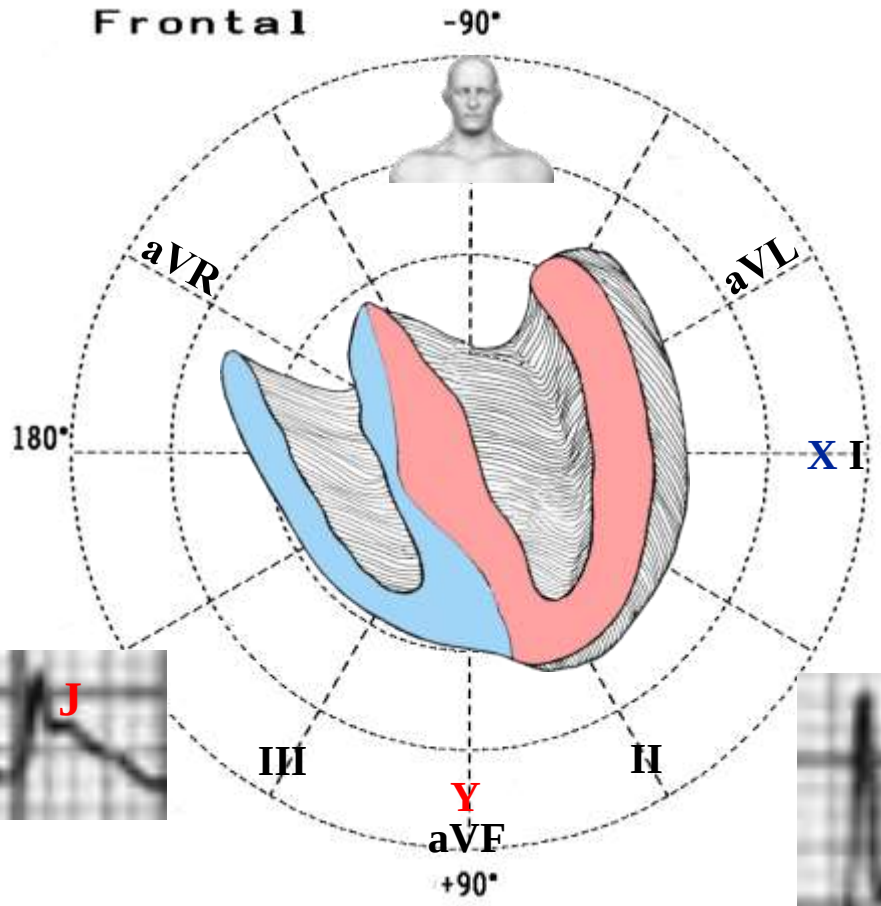
Clinical diagnosis: 56-year-old female who presented to the emergency department with a decreased level of consciousness following intensification of a two-week long worsening headache. The patient's past medical history was significant for hypertension for which she was on no medication. On physical exam, she was unconscious (Glasgow Coma Scale (GCS) 6).

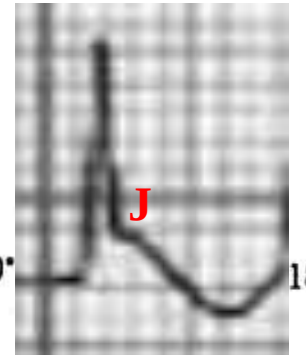
ECG diagnosis: Wide-complex QRS VT (160 ms) at a rate of 294 bpm with visible fusion and capture beats. Monophasic R-waves in leads V1–V2 indicated left ventricular origin.

ECG performed at 08:40 A.M. – after cardioversion

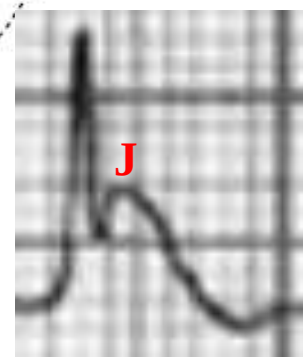


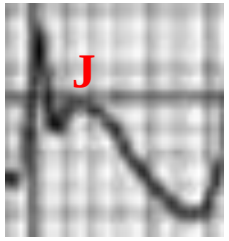
ECG diagnosis: The patient was electrically cardioverted and a second ECG performed after 8 minutes demonstrated rapid AF at 188 bpm and massive J-waves (maximal amplitude: 0.47 mV in lead II) with ST-segment elevation in the inferolateral leads and ST-segment depression in the anterior leads (V1–V4).

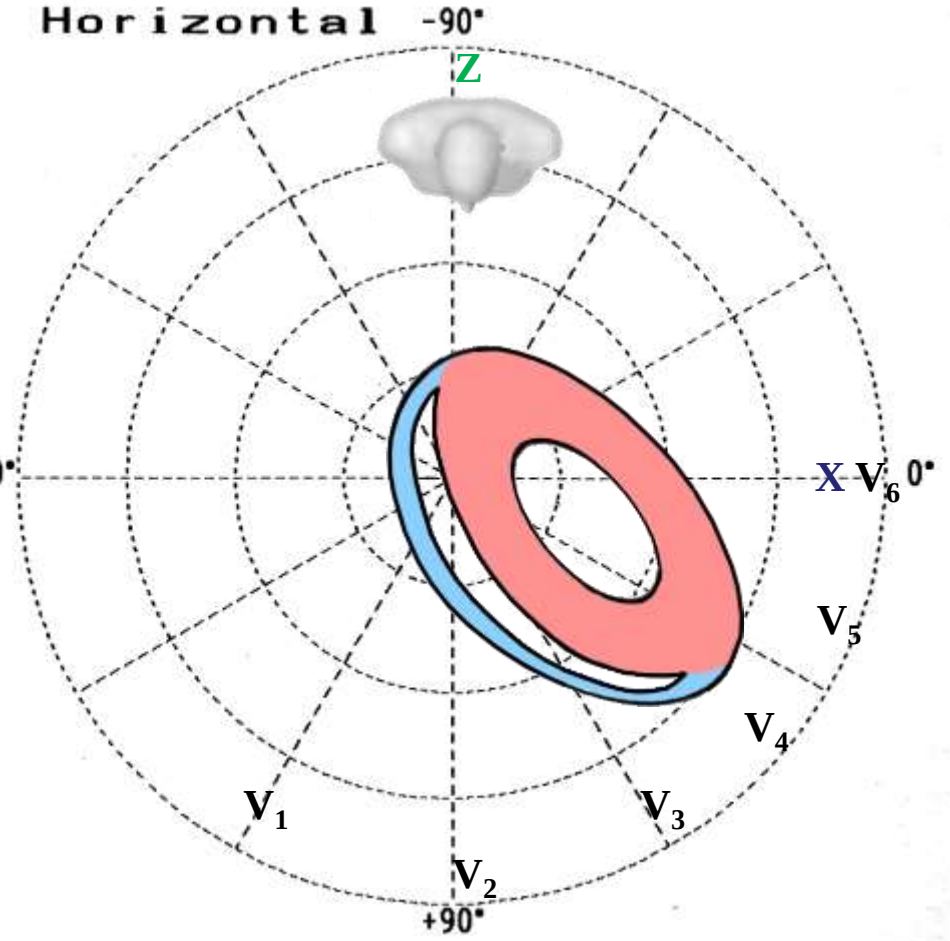

Frontal
-90°
aVR
aVL
180°
X I
0°
III
II
Y
aVF
+90°

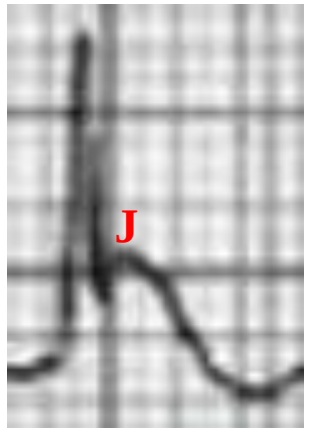

J

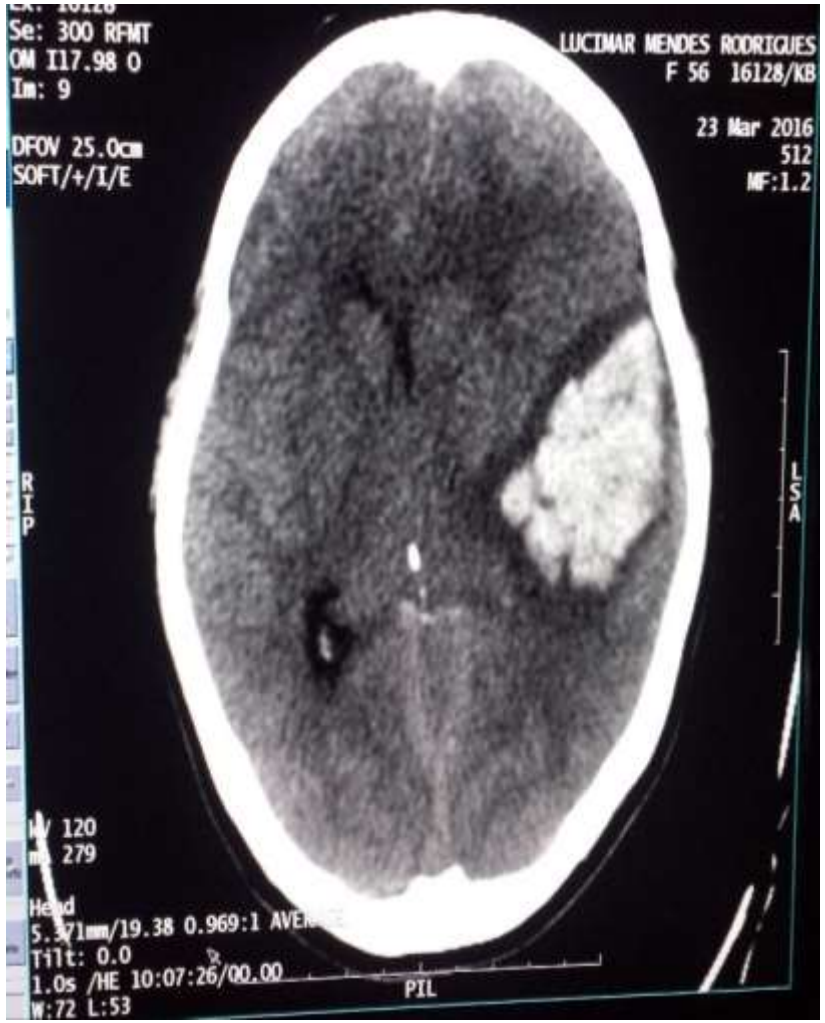
J

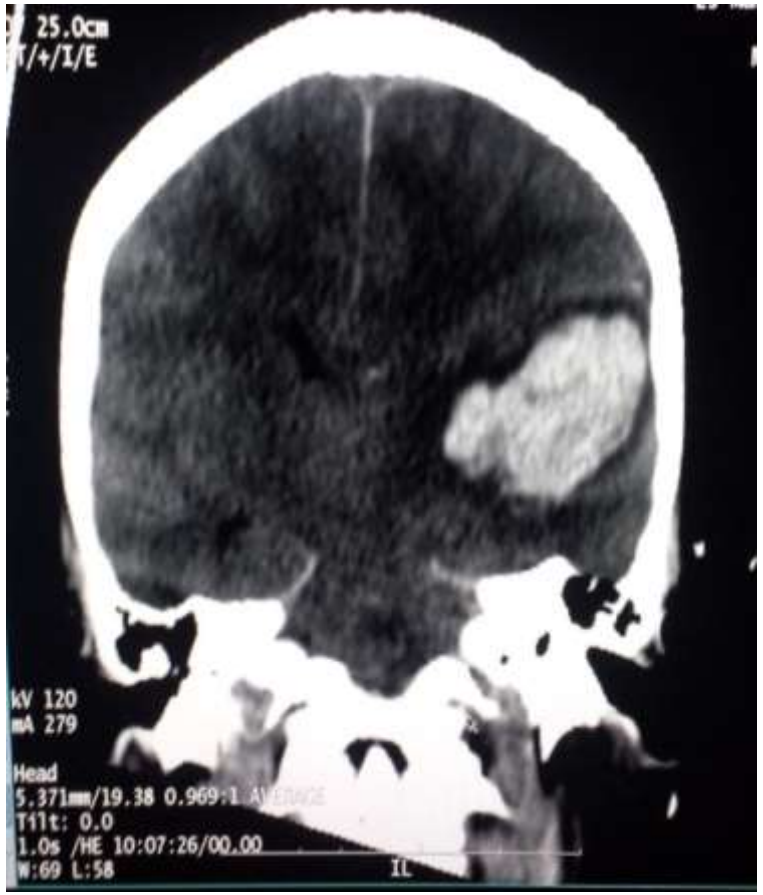

J

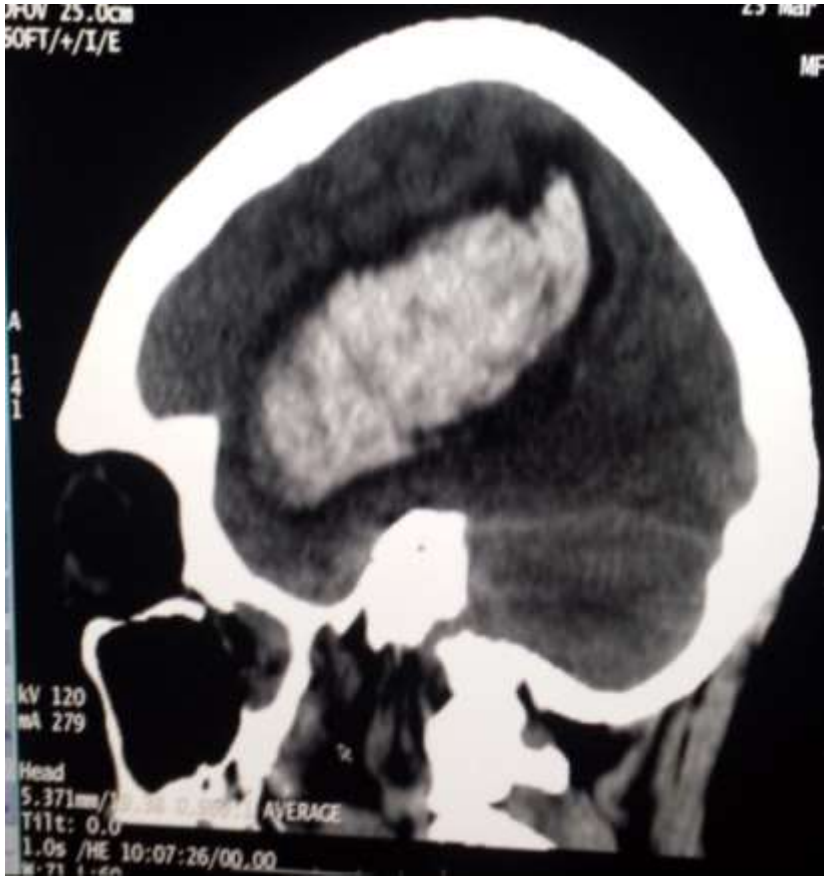

J


Horizontal
-90°
Z
180°
X V6
0°
V5
V4
V1
V3
V2
+90°

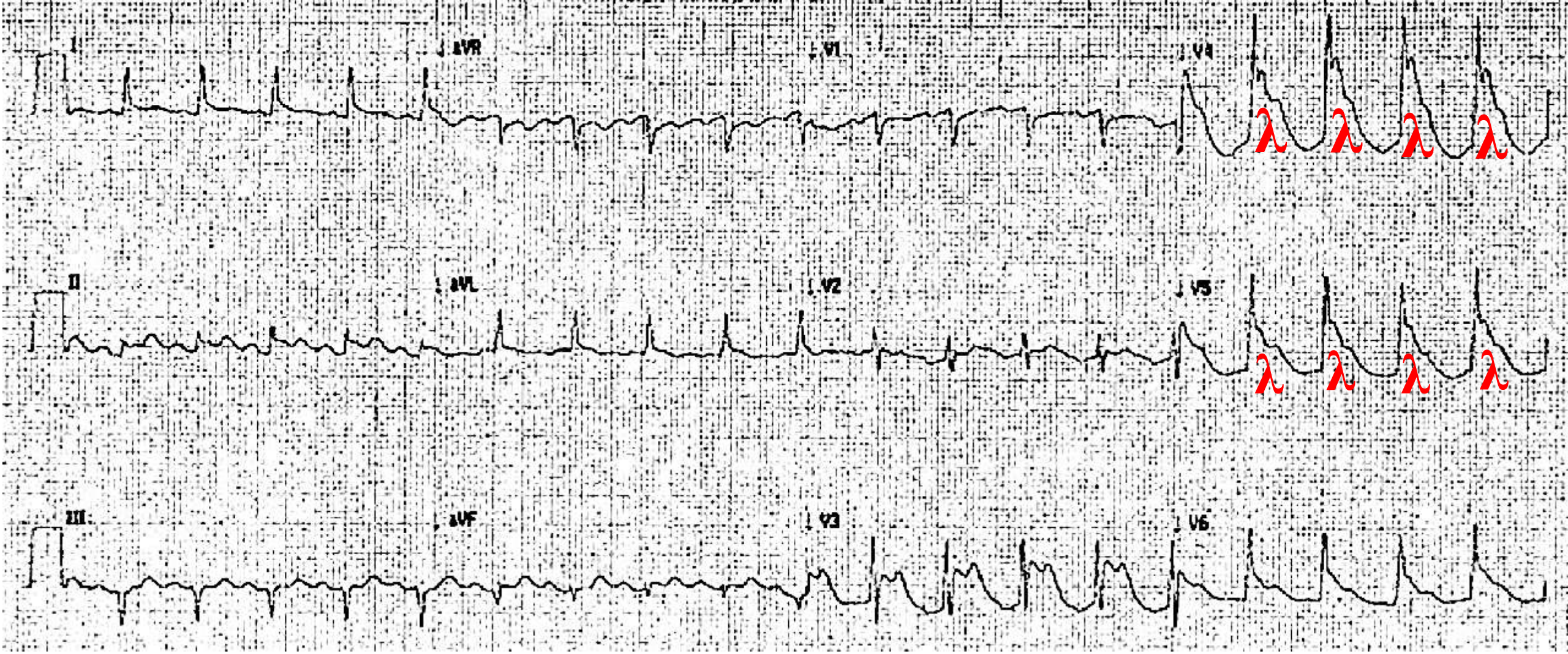

J







Computed tomography of the brain showing a massive intraparenchymal hematoma.



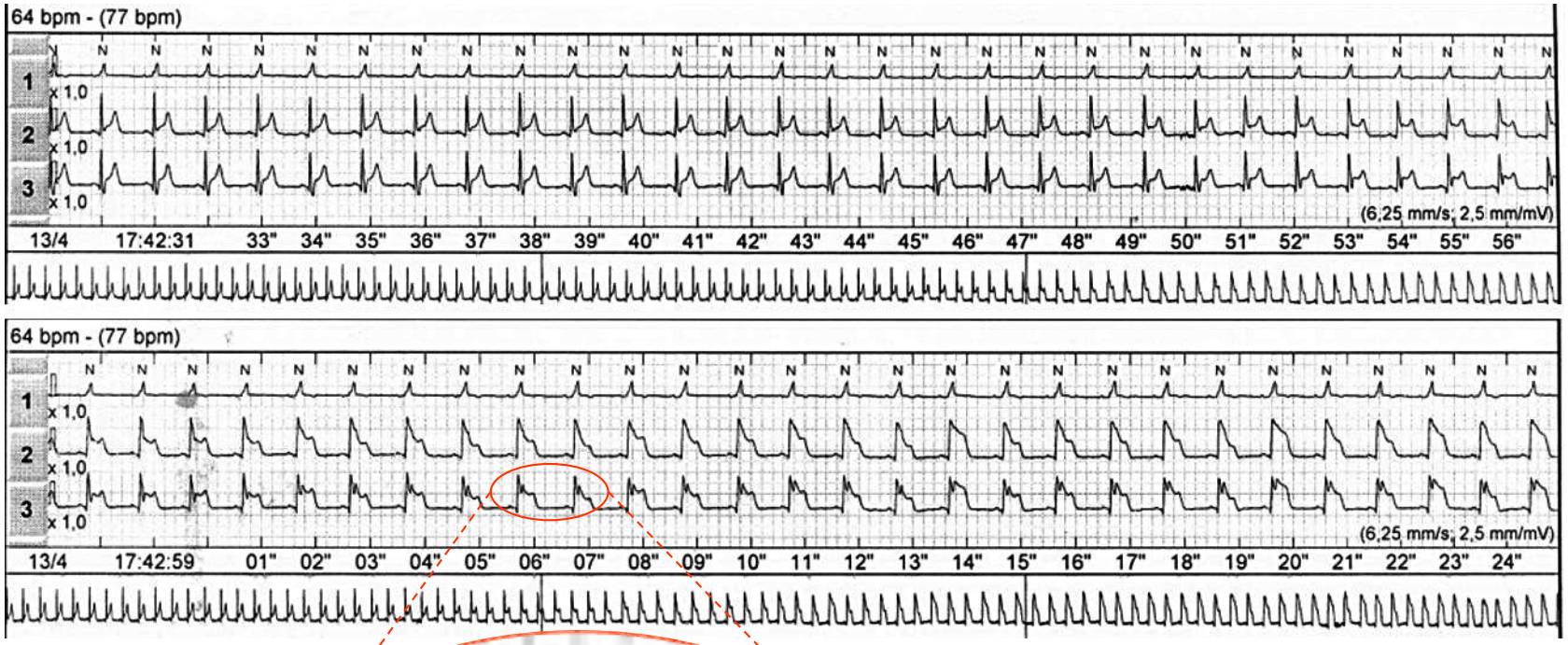
Clinical diagnosis: ECG performed subsequent postictal confusion/hemiplegia with left-sided upper and lower extremity hemiparesis: cerebral and cardiac hypoperfusion (ischemia) following a postictal event with an increase in sympathetic tone.

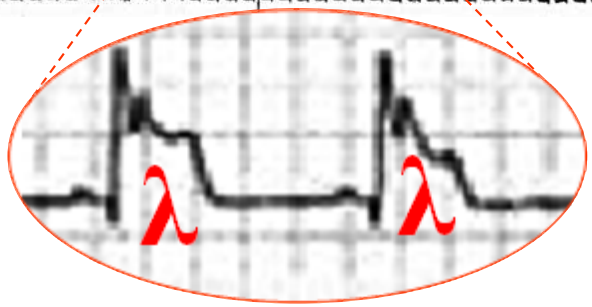
ECG diagnosis: Lambda waves in the setting of cerebral injury such as trauma or hemorrhage; however, ECG evidence of a dynamically displaced J-point has not been previously described in the setting of postictal hemiplegia.

3. Ischemia- mediated VT/VF: 3-A) Vasospastic angina, Prinzmetal J waves/ Ischemic J-Waves

During myocardial ischemia in patients with Prinzmetal vasospastic angina. J-wave augmentations caused by myocardial ischemia during coronary spasms has lambda wave morphology. The presence and augmentation of J waves, especially prominent J waves with the characteristic ST-elevation patterns, were associated with VF (**Sato A, et al. 2012**).

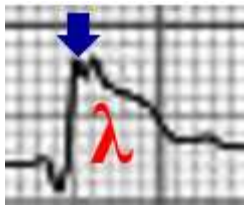
We show a continuous Holter monitoring below belonging to a man who had coronary revascularization a time ago, during an episode of angina and concomitant ST segment elevation and ischemic giant J-wave "lambda-like type" associated with Premature Ventricular Contractions with Bigeminy sequence and very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



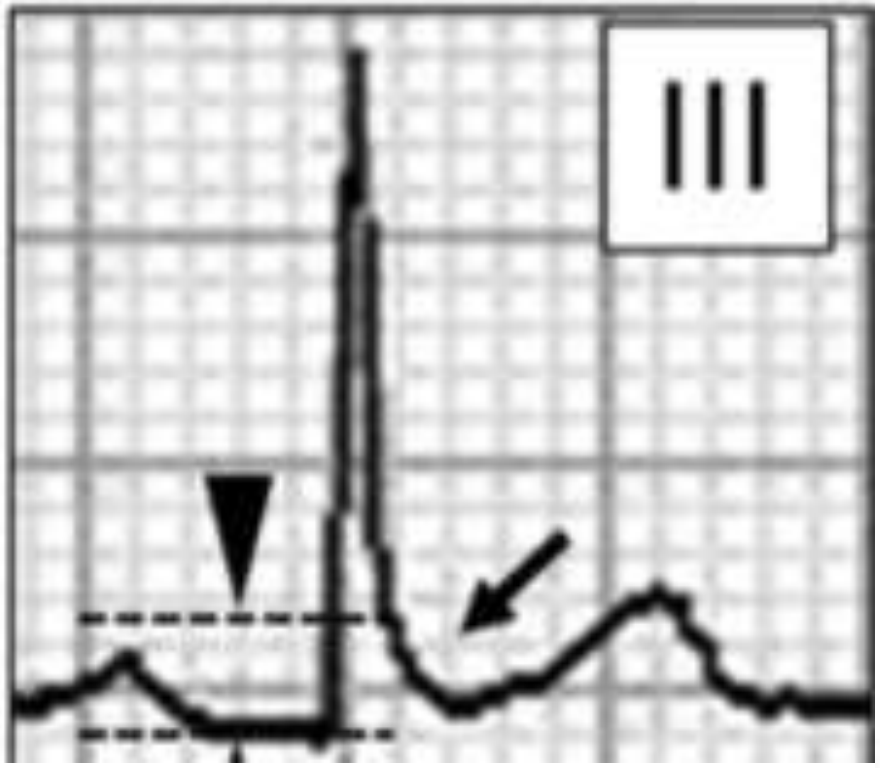


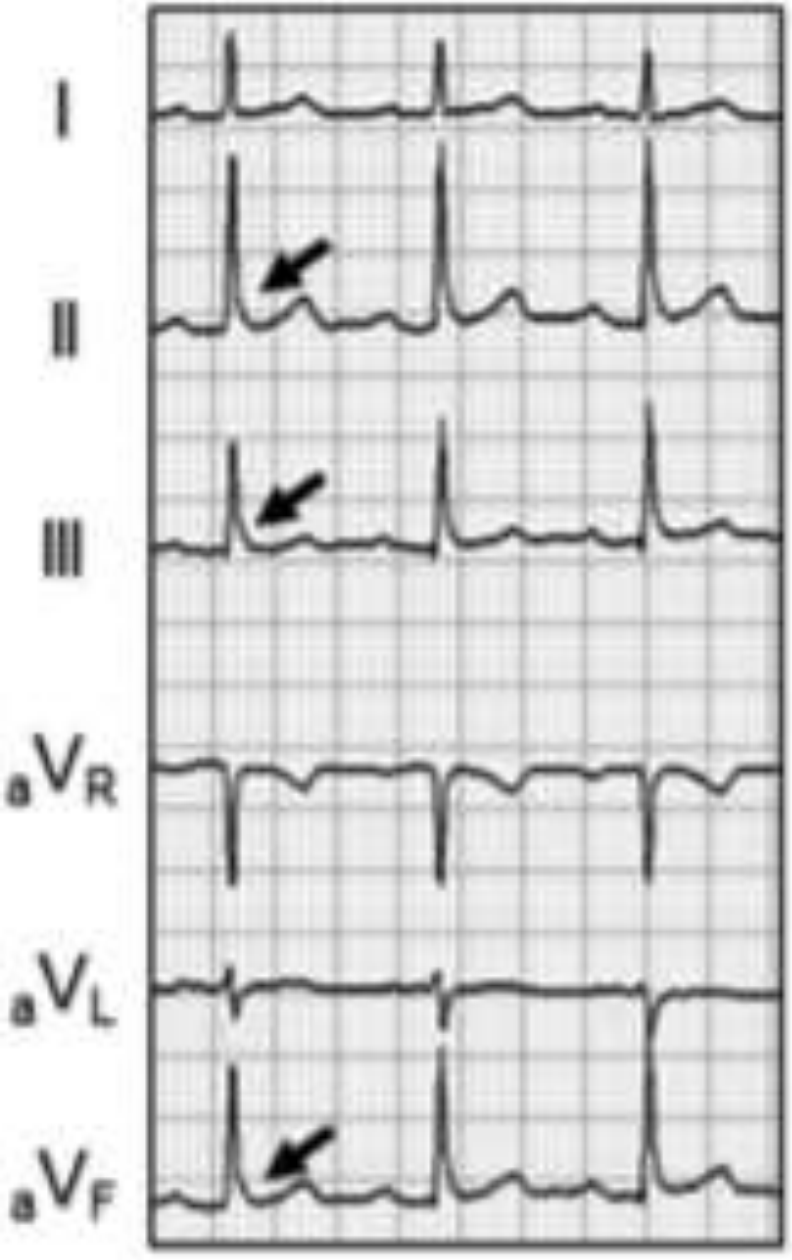
Observation: the pattern is very similar with ECG-2 from the present case because we have f-QRS + lambda wave.

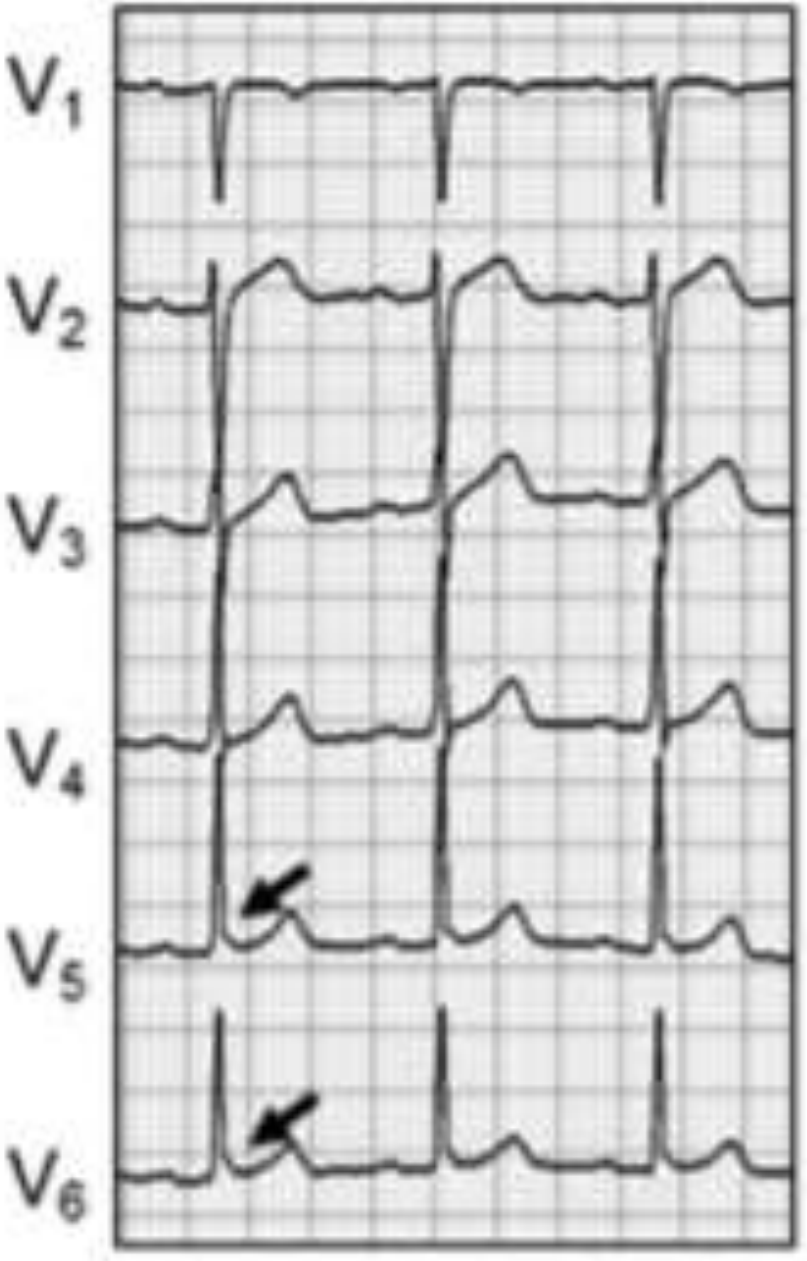
ECG-2



ECG-12 lead of a patient with Prinzmental angina at rest. J-wave slurring variant



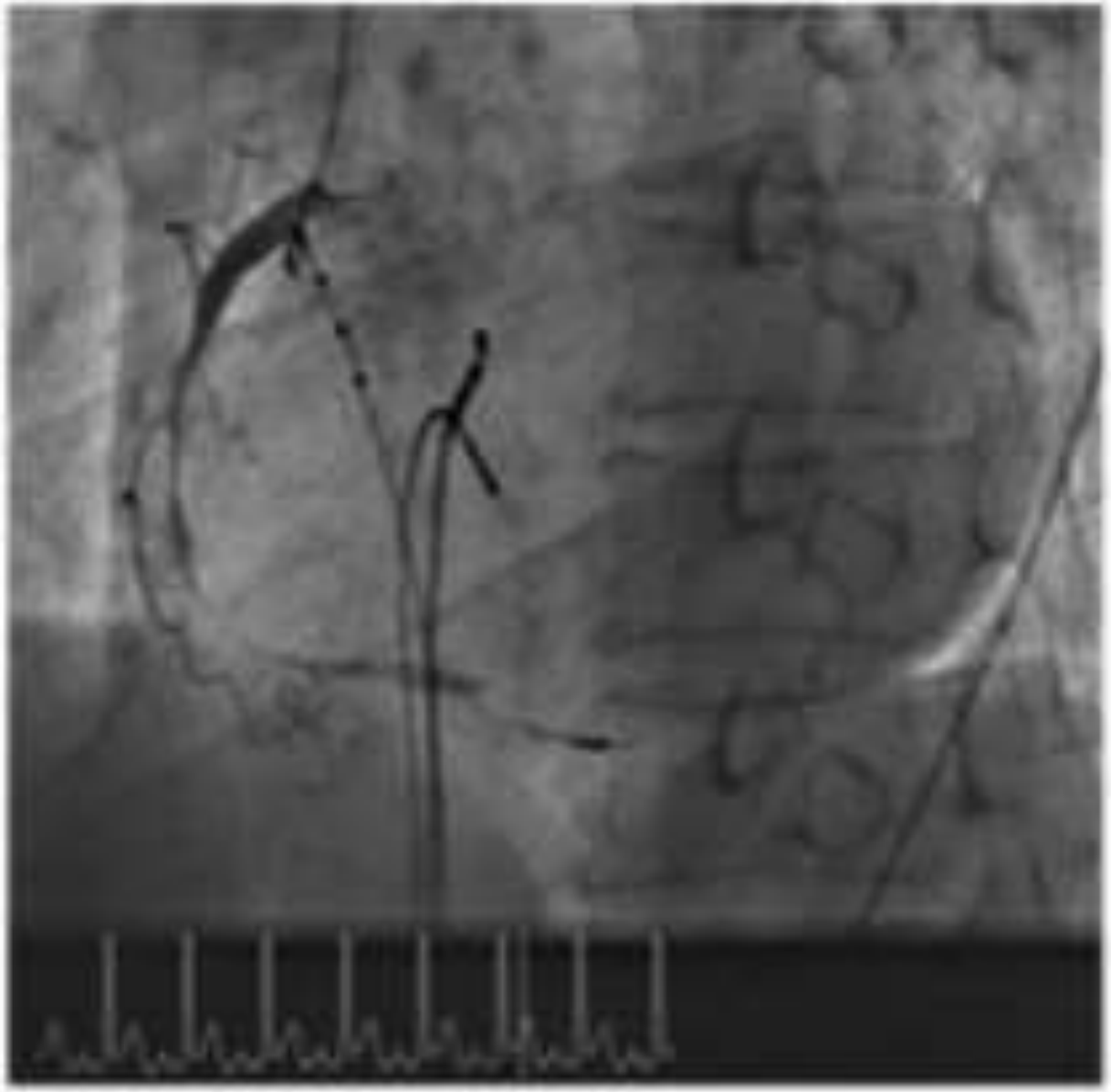




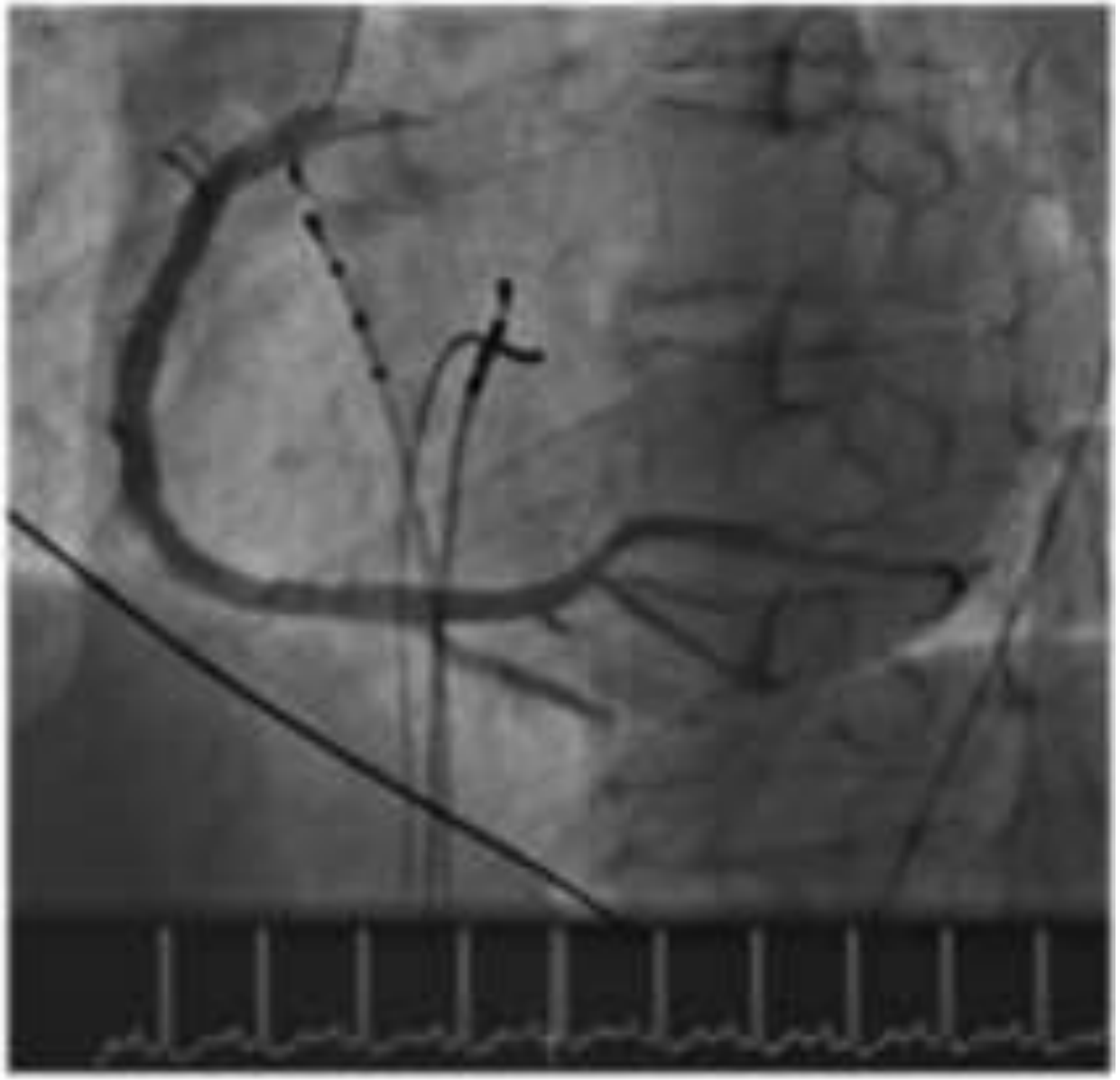
The 12-lead ECG showing a prominent J-point elevation in II, III, aVF (inferior leads), and V5, V6 (lateral leads).

The J-wave amplitude in III was 0.28 mV. The existence of J waves, especially in the inferior leads, might be a risk factor for VF in vasospastic angina patients.(**Fumimoto T, et al 2017**)

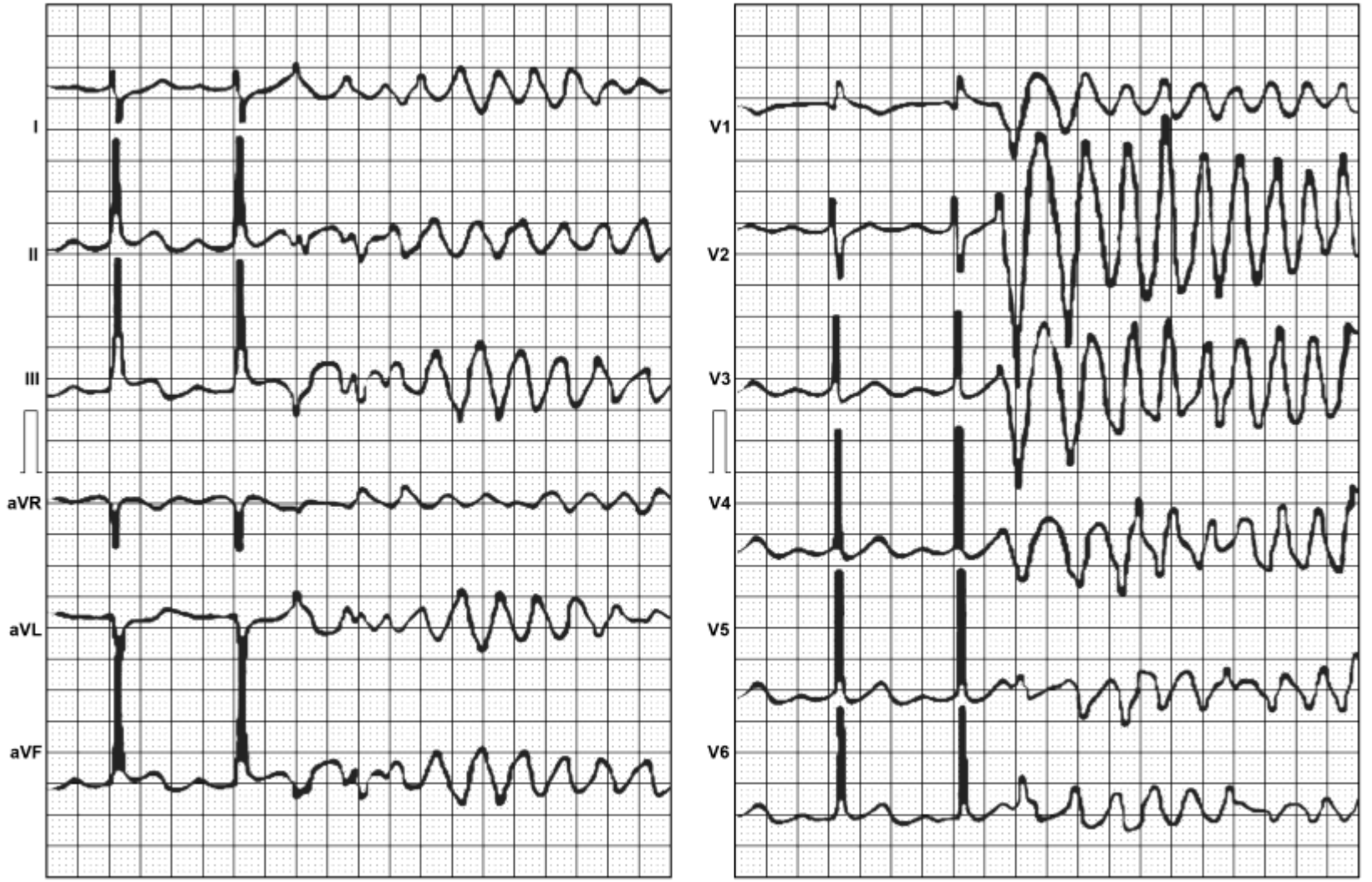
See next sled

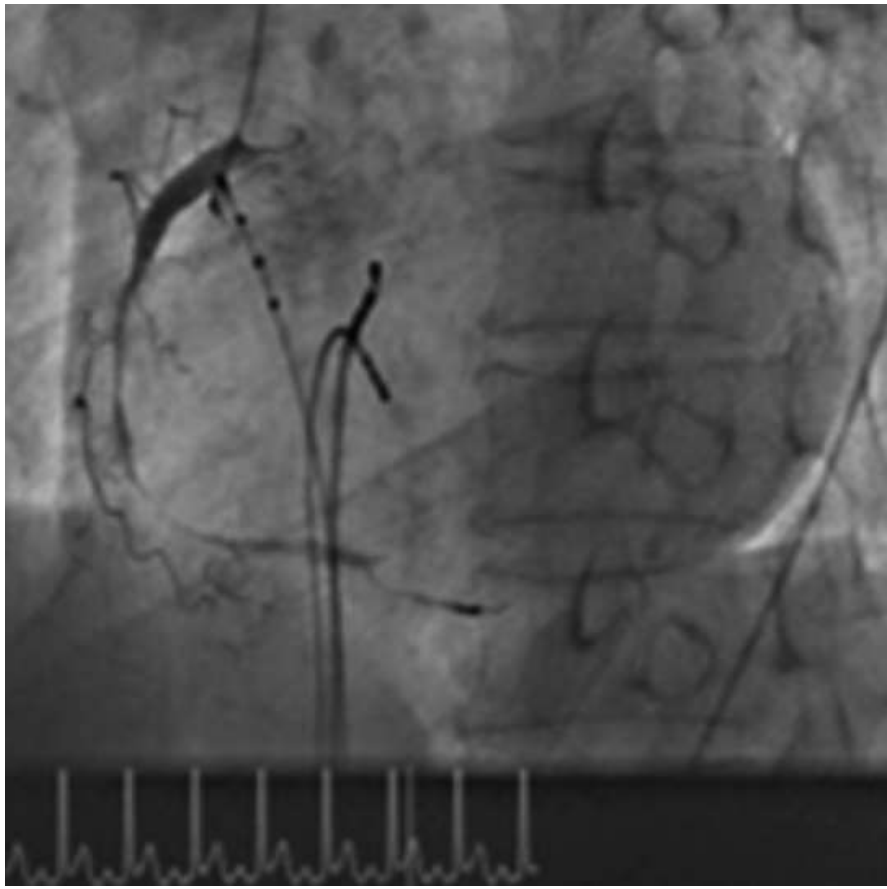


Provocation test with ergonovine induced total occlusion of the right coronary artery



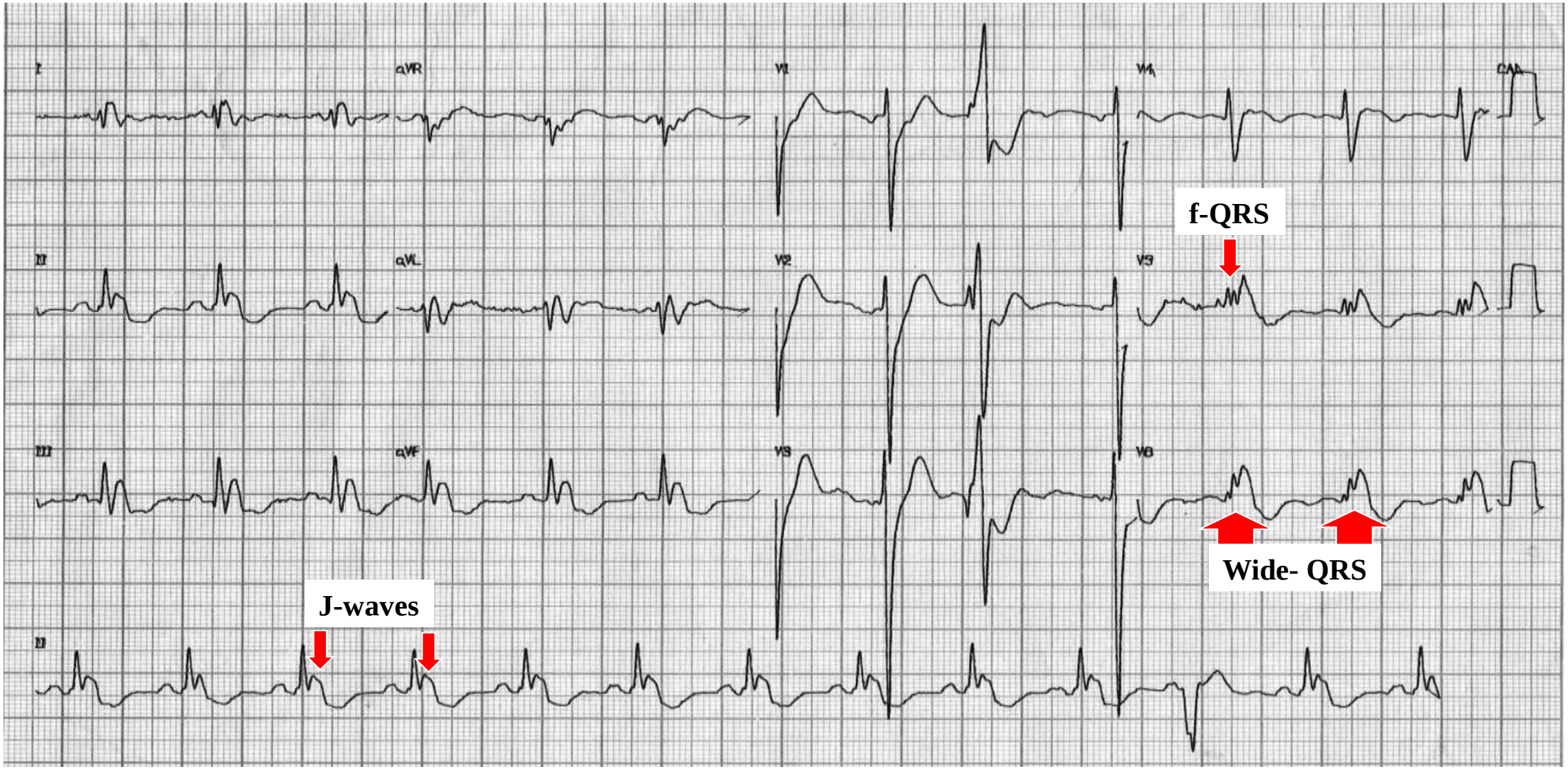
A stenotic lesion was not observed after infusion of isosorbide dinitrate





VF was induced during total occlusion of a right coronary artery. ECG = electrocardiogram; VF = ventricular fibrillation

3-B) Severe coronary artery disease

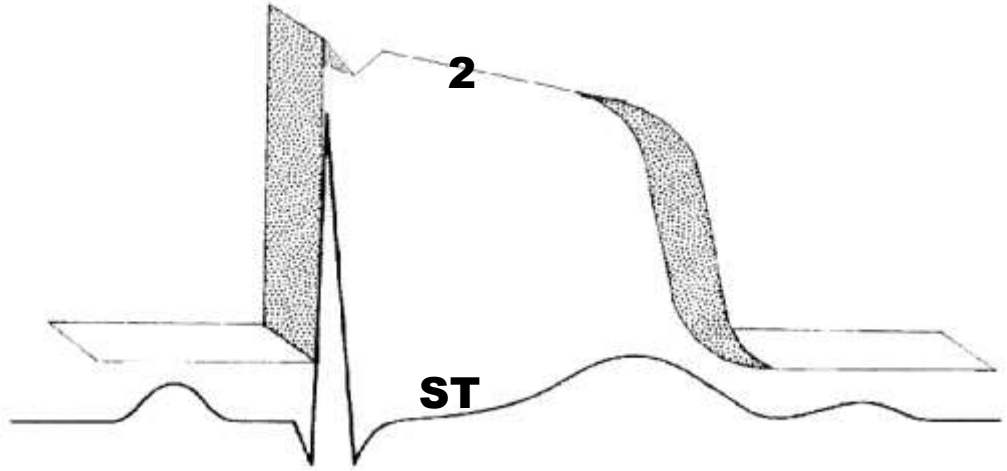


Association of f-QRS in at least two contiguous leads on the 12-lead ECG + Wide QRS complexes + J-waves ≥0.1 mV combined with a descending/horizontal ST segment constitute a malignant ER pattern (**Misuzawa Y, et al. 2014**). Identifying patients with higher risk of fatal arrhythmias after CABG surgery. All are components of multifactorial risk for increased morbidity and mortality, sudden cardiac death and recurrent cardiovascular events.

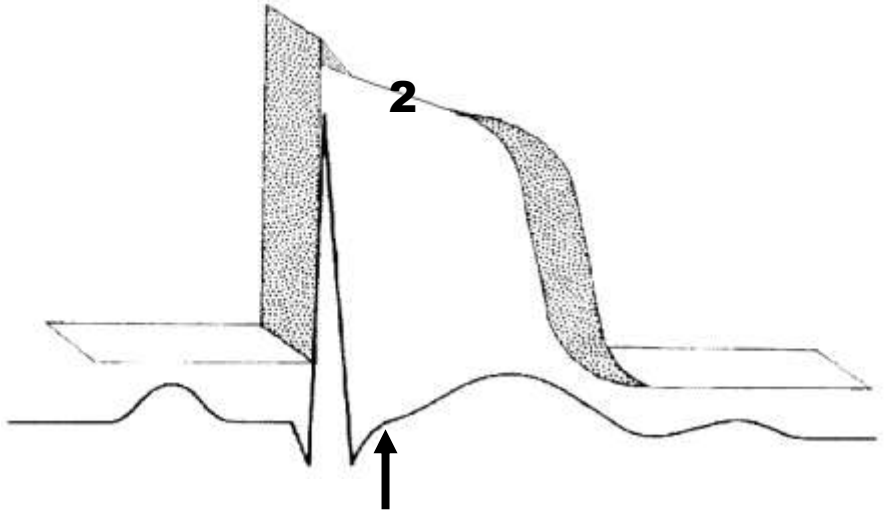
4. Hypercalcemia

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

Normal

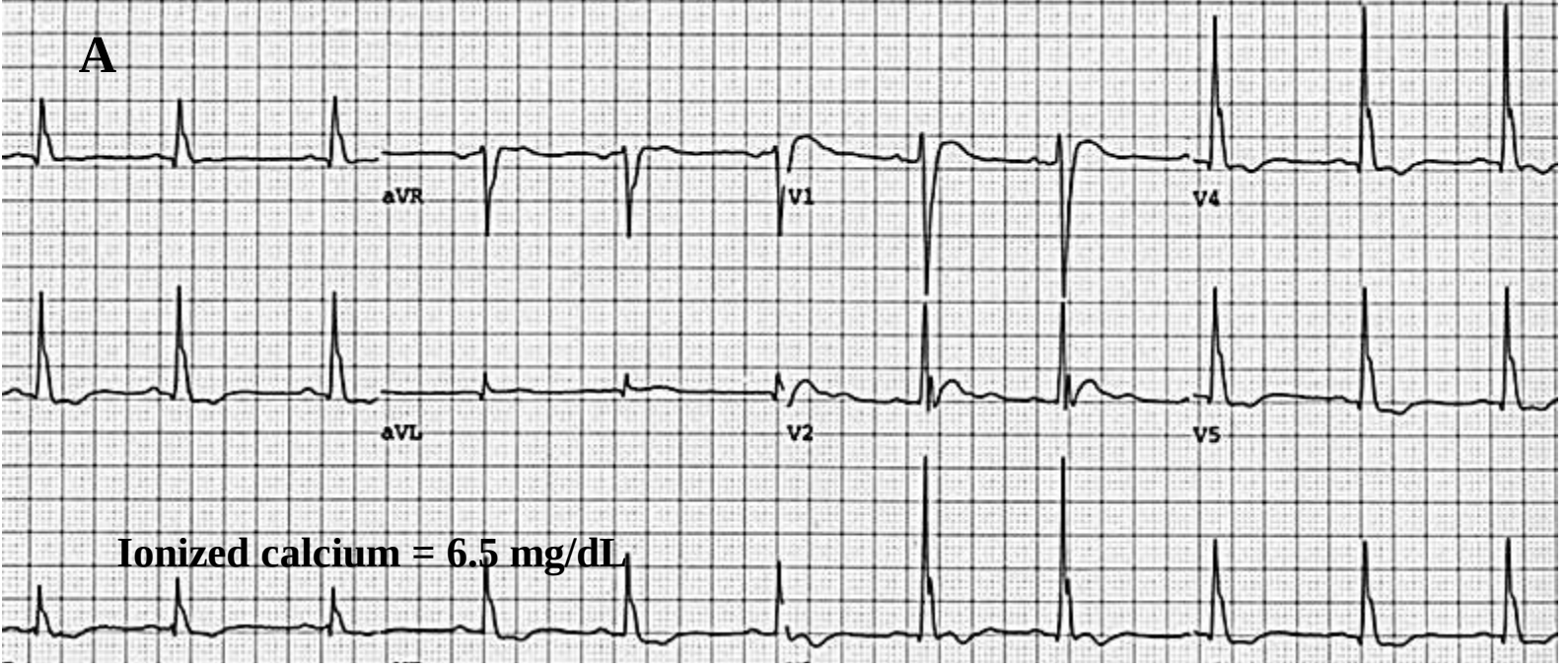


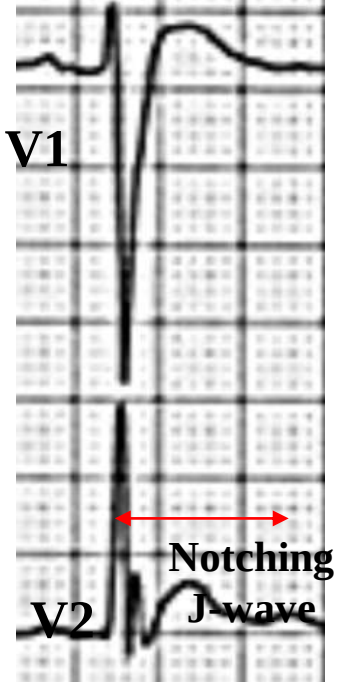
Hypercalcemia

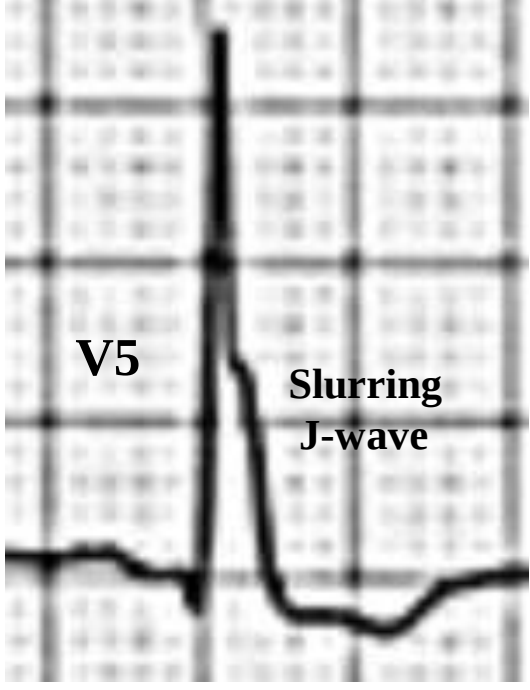


Almost absent ST segment

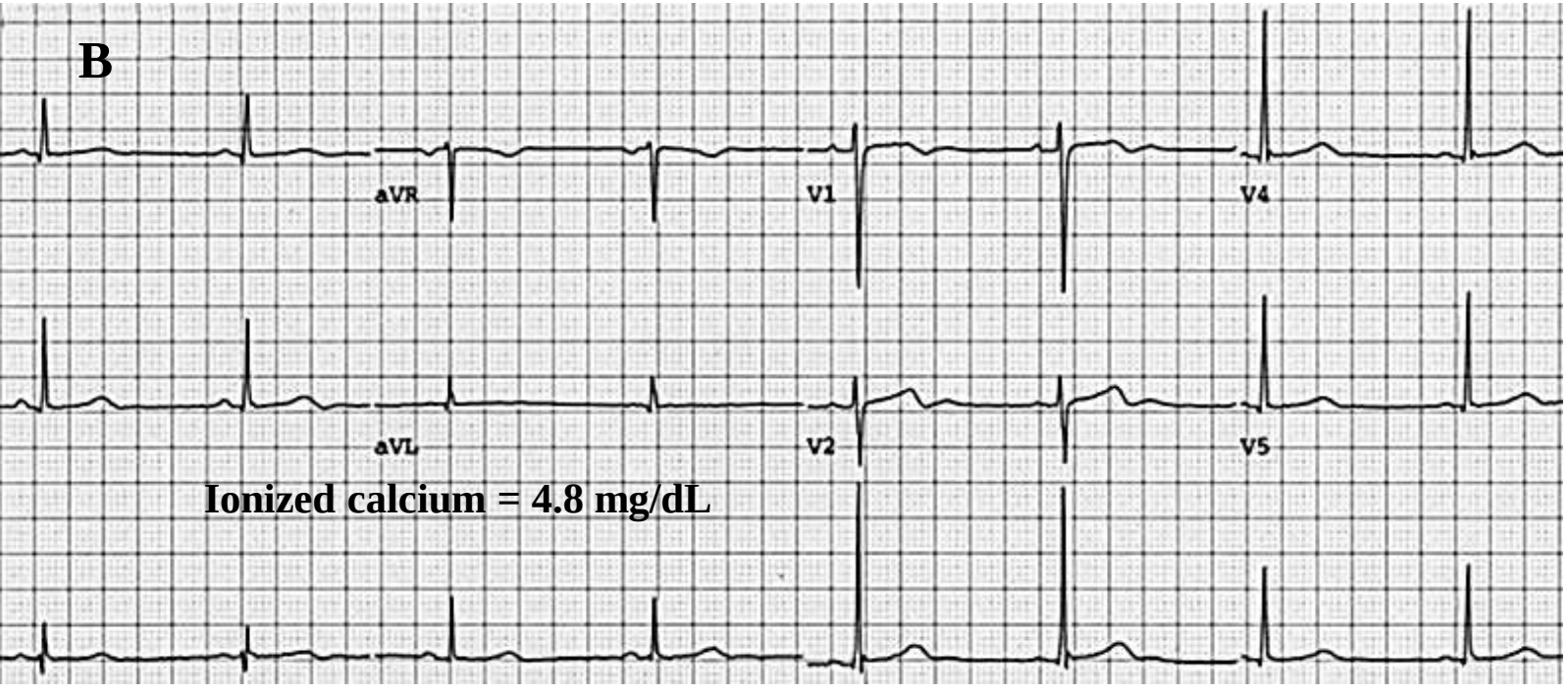
QTc interval shortening, Q-oTc interval shortening: interval from Q wave onset to T wave onset corrected according to HR.
Q-aT interval decrease: interval between QRS onset to T wave apex. Values below 270 ms are diagnostic.





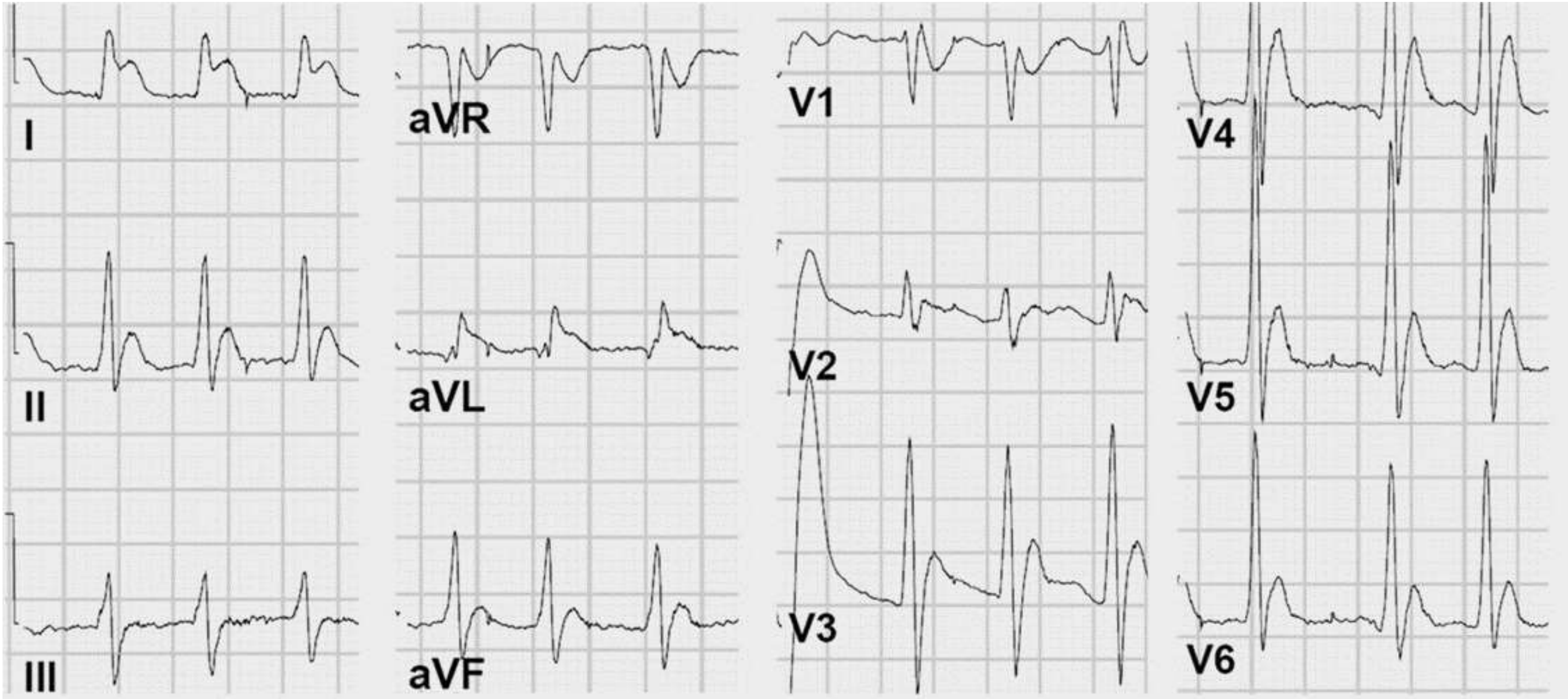


A) Electrocardiogram show the J-wave, minimal ST-segment (short QT interval) in a patient with severe hypercalcemia. For HR=68 bpm, the normal QTc mean value is 361 ms. The lower limit is 317 ms and upper limit is 404 ms. QTc is normal using Framingham study (**Sagie A et al, 1992**).



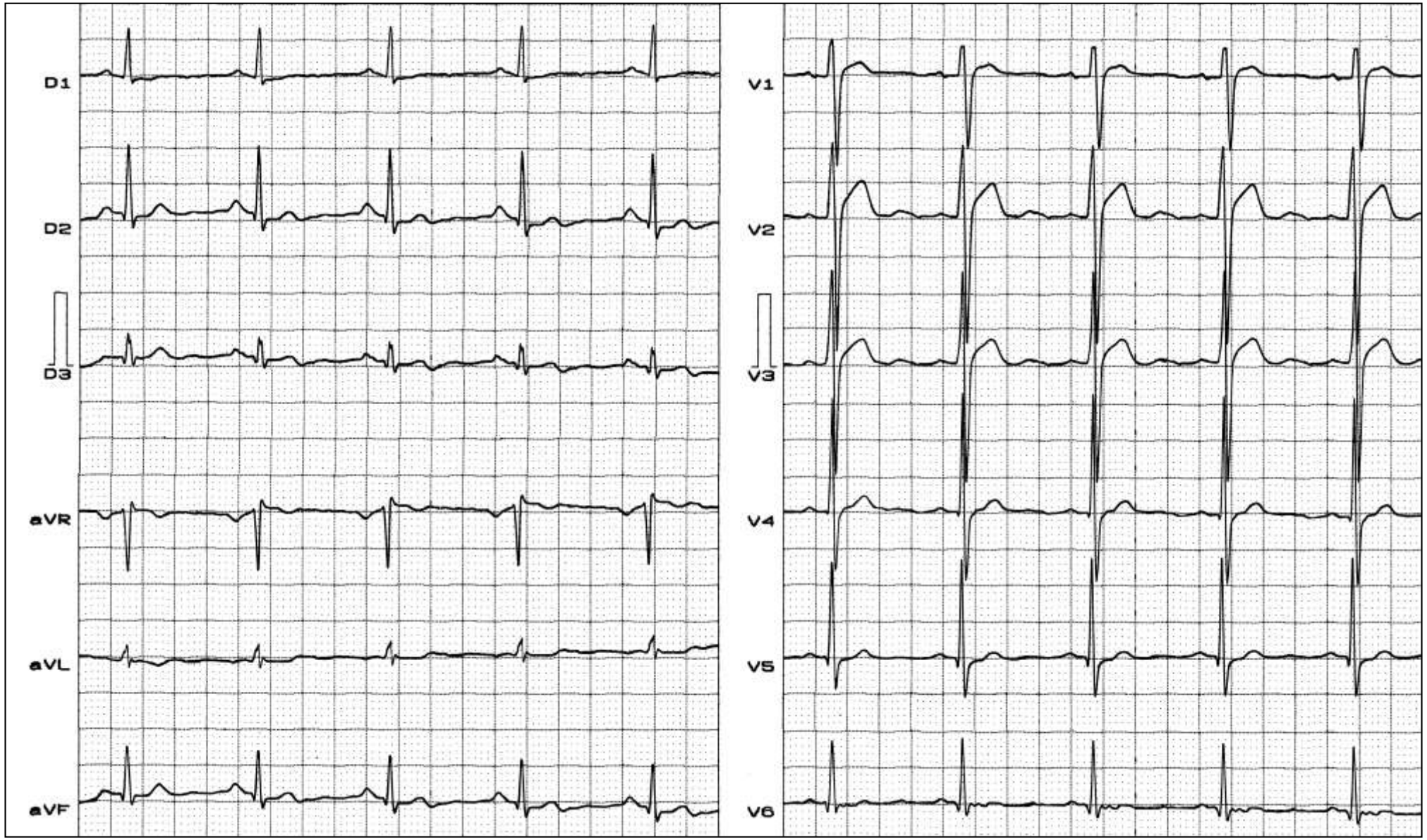
B) After correction of the hypercalcemia, the electrocardiogram has only sinus bradycardia: 50 bpm.

Typical ECG of hypercalcemia: Short QT interval and J-wave



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

Typical ECG of a patient during hypercalcemia



Clinical diagnosis: 16-year-old teenager with osteosarcoma. High ionized serum calcium: 3.5 mEq/l (normal: 2.2 to 2.7 mEq/l).
ECG diagnosis: sinus rhythm, HR: 75 bpm, QTc interval: 346 ms, short Q-oTc and Q-aT, almost non-existent ST segment, T wave follows immediately after QRS complex.

Asymptomatic Spontaneous Type 1 Brugada pattern

This topic is polemic. Individuals displaying type 1 ECG pattern of BrS were initially considered at high risk of SCD, but recent studies have demonstrated that at least the asymptomatic subjects have a very low risk of arrhythmic events (**Brugada J 2002; Probst V, et al. 2010**). The risk stratification and the best treatment approach of asymptomatic subjects with type 1 ECG pattern of BrS still remain controversial. The long-term prognosis of asymptomatic individuals with spontaneous or drug-induced type 1 ECG phenotype of BrS.

Letsas et al. studied asymptomatic individuals with spontaneous or drug-induced type 1 ECG phenotype of BrS display a benign course during long-term follow-up. In addition, the follow-up period of this study is one of the longest published in the literature. On the other hand, early studies have shown a high incidence of ventricular events or SCD in previously asymptomatic subjects with BrS.

Brugada et al have initially reported that 8% of asymptomatic subjects with BrS ECG phenotype had the first arrhythmic event during follow-up period (27 ± 29 months), an occurrence of a life-threatening event of 3.5% per year. However, the subgroup of asymptomatic individuals with drug-induced ECG phenotype had no events during follow-up (**Brugada J 2002**). The same group of investigators has later demonstrated that 6% of asymptomatic patients displayed a malignant event during follow-up (42 ± 42 months), corresponding to an event rate of 1.7% per year (**Brugada P 2005**).

Delise et al. (**Delise P, et al. 2011**) have reported that major arrhythmic events occurred in 2.8% of asymptomatic subjects during a median follow-up period of 40 months, an occurrence of a life-threatening event of 0.8% per year.

Eckardt et al. (**Eckardt 2005**) demonstrated that only 0.8% of patients without previous cardiac arrest or syncope had SCD and documented VF during a follow-up period of 40 ±50 months, corresponding to an event rate of 0.24% per year. In 3 Japanese studies, the annual incidence of SCD in previously asymptomatic individuals with BrS ECG phenotype was only 0.4% to 0.5% (**Atarashi 2003; Hong 2004; Yokokawa 2007**). The annual incidence of arrhythmic events in asymptomatic individuals in an Italian registry was very low (0.48%) (**Giustetto 2009**). In Champagne et al. study, no malignant events occurred in asymptomatic BrS population during a mean follow-up of 36 ± 18 months (**Champagne 2007**). In FINGER registry, the incidence of ventricular arrhythmic events in asymptomatic individuals was 0.5% per year (**Probst V, et al. 2010**). In a subpopulation of this registry with the longest average follow-up period published so far (66 months), 4.5% of the asymptomatic individuals experienced an arrhythmic event, corresponding to an annual event rate of 0.8% (**Probst V, et al. 2010**). Atrial tachyarrhythmias, mainly atrial fibrillation, are commonly seen in BrS. Letsas et al. (**Letsas 2009**) demonstrated a high incidence of atrial arrhythmias in asymptomatic individuals with type 1 ECG pattern of BrS (21.2%). In this cohort, none of them reported syncopal episodes. Conflicting evidence exists on the prognostic value of EPS in asymptomatic subjects with BrS. Brugada et al (**Brugada P 2005**) have shown that EPS exhibited a high negative predictive value (99%) as a tool of risk stratification. Other investigators, including 2 meta-analyses, did not support the use of programed ventricular stimulation (PVS) in risk stratification (**Probst V et al. 2010; Delise P, et al. 2011; Paul 2007; Gehi 2006**). In Letsas series, PVS induced VT/VF in 56.3% of asymptomatic subjects. None of them had syncope or ventricular arrhythmic event during follow-up.However, this heterogeneity regarding the use of EPS in risk stratification may be related to methodological differences in stimulation protocols and/or criteria for positive EPS. The only effective treatment of SCD associated with BrS is ICD implantation (**Benito 2008; AntzelevitchC, et al. 2005**). However, primary prevention for asymptomatic individuals still remains a contentious issue. The recommendations of the second consensus conference on BrS, asymptomatic individuals with spontaneous type 1 ECG pattern or asymptomatic individuals with a drug-induced type 1 ECG pattern and a family history of SCD should undergo EPS to

guide the selection of patients for ICD implantation (**Antzelevitch 2005**). This approach may lead to a large number of EPS, which in turn leads to a high number of ICD implantations. This strategy may expose asymptomatic individuals to ICD-related complications (**Sacher 2006; Sarkozy 2007**).

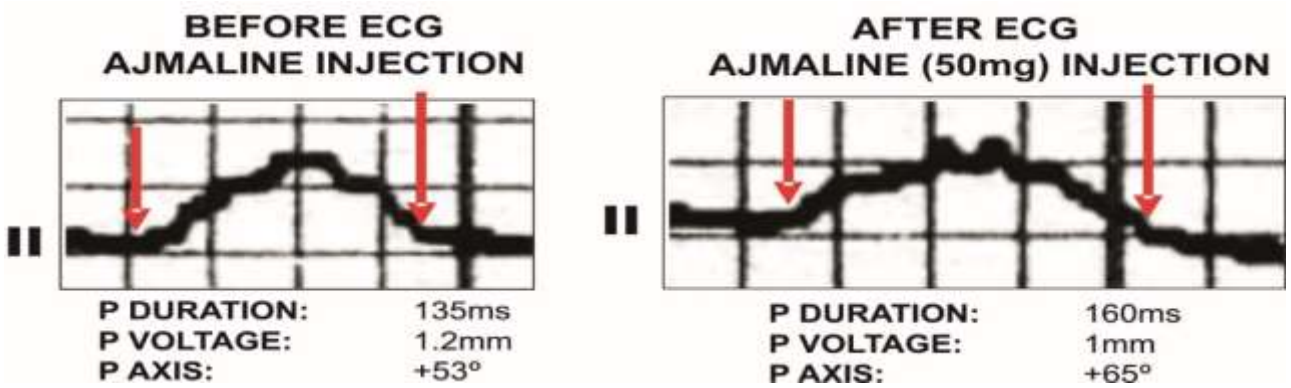
In a large BrS population, Sacher et al. (**Sacher 2006**) have demonstrated a low incidence of ventricular arrhythmic events in asymptomatic individuals (4%) during a mean follow-up of 31 months, in addition to a significant risk of device-related complications (31%), mainly inappropriate shocks.

Some researchers think that asymptomatic individuals with spontaneous or drug-induced type 1 ECG phenotype of BrS display a benign clinical course during long-term follow-up (**Letsas 2011**).

Priori et al. (**Priori SG, et al. 2005**) reported an annual incidence of arrhythmic events in asymptomatic individuals of 0.4%.

Risk stratifies of patients with the J wave Syndromes (BrS and ERS)

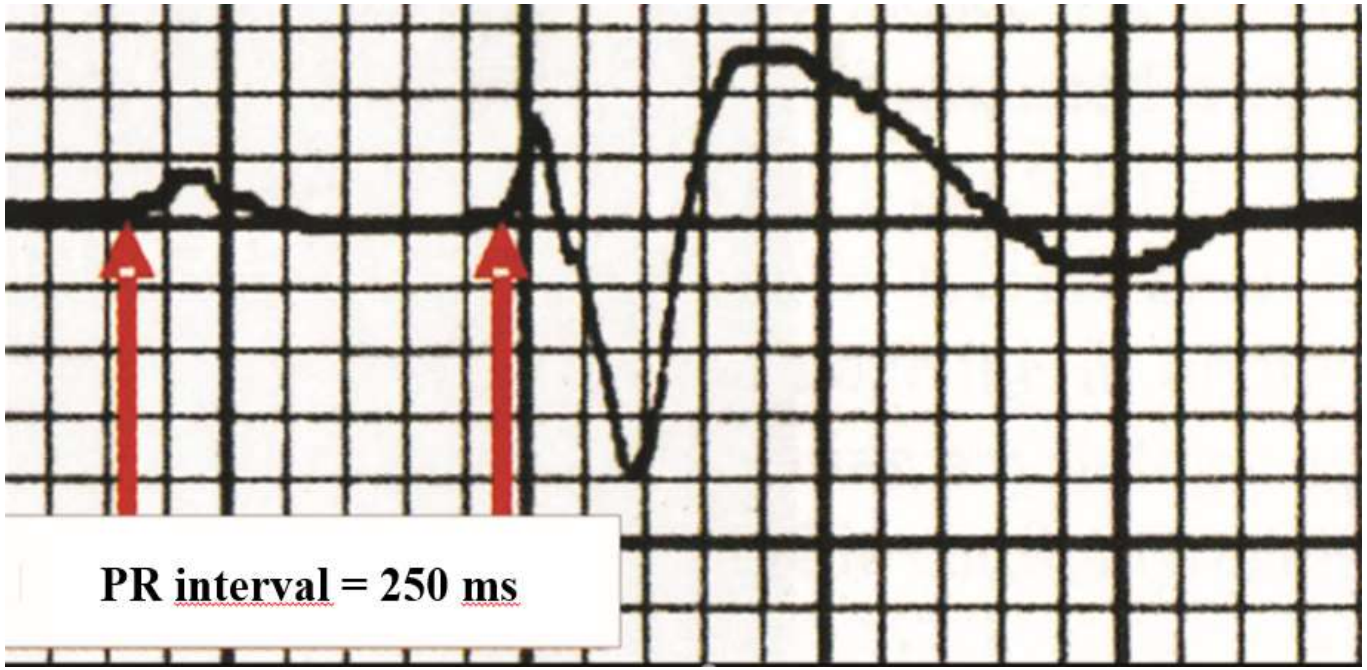
1. Association of ER or BrS pattern with SCD, unexplained syncope, or unexplained family history of SCD (**Priori SG, et al, 2002**).
2. History of cardiac events or syncope likely due to VT/VF (**Morita H, 2008; Priori SG, 2013; Probst V, et al, 2010; Delise P, et al. 2011**).
3. Nocturnal agonal respiration (**Antzelevitch C, et al Circulation 2005; Antzelevitch C, et al Heart Rhytm 2005**).
4. P-wave prolongation: BrS patients with SCN5A mutations exhibit more conduction abnormalities on ECG such as longer P-wave, PR/PQ interval, and QRS interval in comparison with probands without mutations (SCN5A (-), and have higher risk for cardiac events. Multivariate analysis indicated that only SCN5A mutation and history of aborted CA were significant predictors of cardiac events (SCN5A (+) versus SCN5A (-): hazard ratio, 2.0 and P=0.045; history of aborted cardiac arrest versus no such history: hazard ratio, 6.5 and P<0.001) (**Yamagata K. et al., 2017**). Figure



The tracing shows the P-wave in a patient with BrS and positive SNC5A mutation, performed before and immediately after ajmaline test (1 mg/kg). P wave duration (Pd) before the injection is prolonged (Pd=135 ms). After drug administration Pd wave increases more (Pd=162 ms). These atrial dromotropic disorders could be the substrate for reentrant atrial tachycardias such as AF.

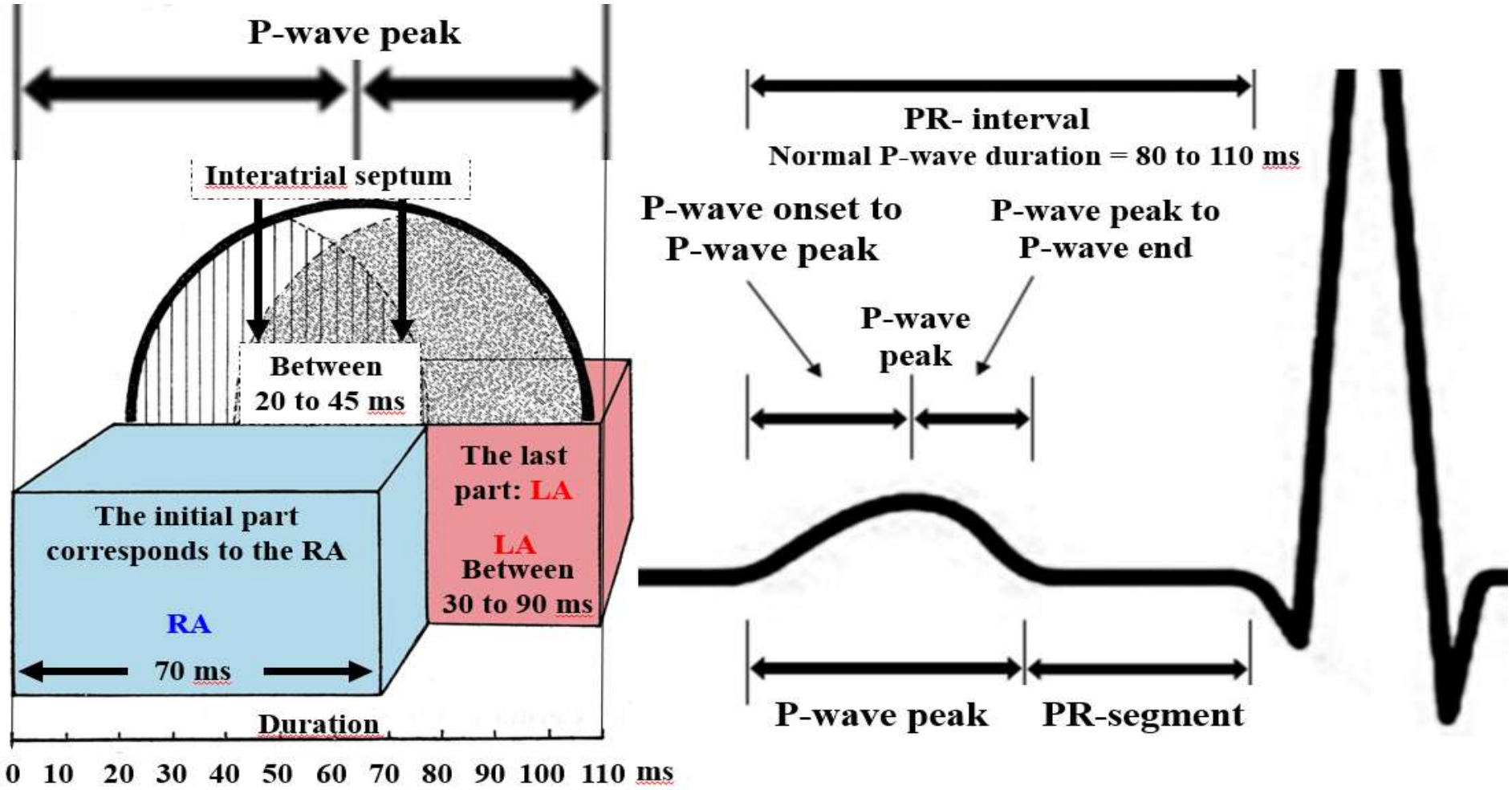
5. Prolonged PR or PQ interval

Risk of syncope is associated with longer PR interval in males. In females in whom cardiac events occurred have a significant prolongation of PR and HV intervals. PR interval prolongation is an ECG risk marker (**Berthome P, et al., 2019**). PR interval prolongation consequence of prolonged HV split or HV is a marker of events and bad prognosis (**Miyamoto A. et al., 2011**). In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes 100 ms (**Yokokawa M, et al. 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 prolonged HV interval is possible in His bundle electrogram by the existence of intra-His or infra-His block. Figure



The figure shows a tracing of a symptomatic patient with BrS after intravenous ajmaline injection. First-degree atrioventricular block (PR interval = 216 ms) and type 1 Brugada ECG pattern in V_1 lead (positive test).

The PR-interval represents a composite of distinct three components (P-wave onset to P-wave peak duration, P-wave peak to P-wave end duration, and PR-segment). These three parameters are not uniformly associated with AF. Figure



The presence of AF in BrS is a known risk marker. Without considering the contribution of each component, inconsistent associations between the PR-interval and AF are inevitable. So, some studies showing non-significant associations (**Aro AL, et al., 2014**), on the other hand others showing a stronger (**Alonso A, et al.2013.**).

A possible explanation for these inconsistencies relates to the distinct components of the PR-interval: time from P-wave onset to peak P-wave (conduction within the right atrium), time from peak P-wave to the end of P-wave (conduction within the left atrium), and the PR-segment (atrioventricular (AV) conduction). P-duration contribution to the length of PR interval ranged from 30% to 90% (median 70%). PR-interval associations with outcomes are dictated by the level of contribution of P duration to its length, a contribution that has a wide range and is expected to vary across populations. These findings could explain the inconsistent reports of PR-interval associations in different studies and call for caution when using PR interval in risk prediction models (**Soliman EZ, et al. 2013.**). The components of the PR-interval are not strongly correlated, and the magnitude of the association with AF will vary by each component (**Smith JW et al., 2017**). Human cardiomyopathy-associated 1 (XIRP1) and 3 (XIRP2) are intercalated disc-associated, Xin repeats-containing proteins. Mouse Xirp1 is necessary for the integrity of intercalated disc and for the surface expression of Ito and delayed rectifier K+ channels, whereas mouse Xirp2 is required for Xirp1 intercalated disc localization. Thus, XIRP1 and xin actin binding repeat containing 2 (XIRP2) may be potentially causal genes for SUNDS and BrS. Analyzing available Xirp2 knockout mice, Huang et al. further found that mouse hearts without Xirp2 exhibited prolonged PR and QT intervals, slow conduction velocity, atrioventricular conduction block, and an abnormal infranodal ventricular conduction system. Whole-cell patch-clamp detected altered ionic currents in Xirp2-/- cardiomyocytes , consistent with the observed

association between Xirp2 and Nav1.5/Kv1.5 in co-immunoprecipitation. 16 XIRP rare variants (6 were in silico predicted as deleterious) were identified in SUNDS victims, and 4 XIRP rare variants (2 were in silico predicted as deleterious) were detected in BrS patients **(Huang H, et al., 2018**). 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 M1, et al 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 prolonged 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 A, et al 2011.**).

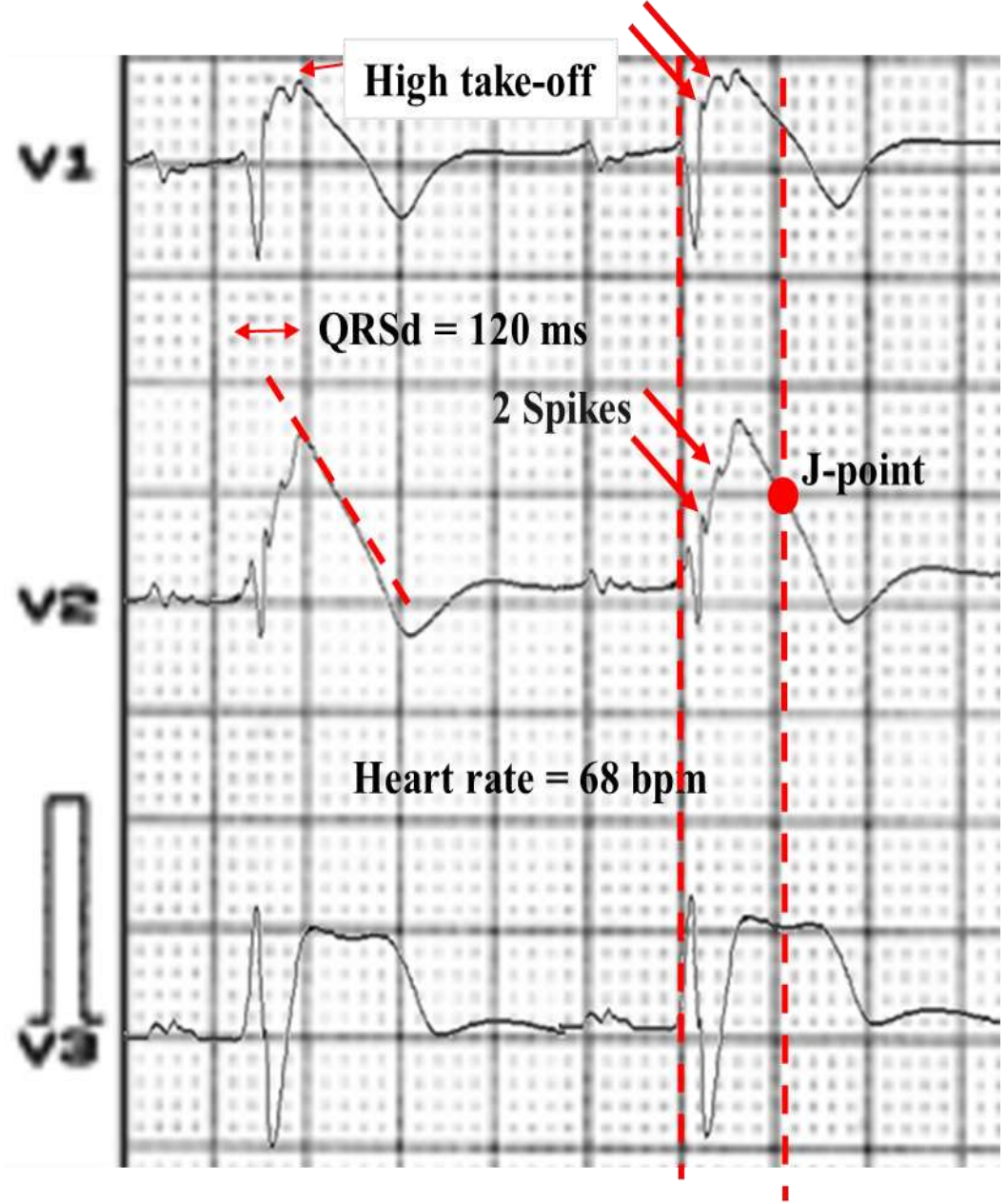
6. **Prolonged QRS duration:** Multivariable analysis showed that QRS interval ≥120 ms were independent predictors of cardiac events in females. A QRS duration ≥120 ms in V2 (**Junttila MJ et al., 2008**) and ≥90 ms in V6 (**Takagi M, et al. 2007.)** are a markers of event risk. Prolonged QRS duration measured from QRS onset to the J point in leads II and V2 on a standard 12-lead ECG is associated with ventricular arrhythmia and could serve as a simple noninvasive marker of vulnerability to life-threatening cardiac events in patients with BrS. The QRS interval was measured from QRS onset to the J point in leads II and V2. (**Ohkubo K, et al 2011.**). The QRS interval is necessary measured from QRS onset to the J point in leads II and V2. A QRS interval in lead V2 ≥ 120 ms was found to be a possible predictor of a life-threatening ventricular arrhythmia and/or syncope. Prolonged QRSd as measured on an ECG is associated with ventricular arrhythmia and could serve as a simple noninvasive marker of vulnerability to life-threatening cardiac events in patients with BrS (**Ohkubo K, et al 2011.**). QT prolongation in the setting of QRS ≥120 ms is believed to be triggered by prolonged depolarization rather than repolarization. Hence, JT interval is suggested as an alternative to QT interval when QRS duration is prolonged. In individuals with QRS ≥120 ms and participants with QRS duration <120 ms, prolonged QT and JT were equally predictive of all-cause mortality. Similar patterns

were observed with shortened QT and JT intervals. Although both QT and JT intervals are predictive of mortality, JT is more predictive in the setting of QRS duration ≥120 ms (complete RBBB and LBBB, ventricular pre-excitation and non-specific intraventricular conduction disturbances) supporting the use of JT interval in patients with prolonged QRS (**Zulqarnain MA, et al, 2015**).

7. **Fragmented QRS** (**Morita H. et al, 2008; Priori SG, et al 2012; Rollin et al, 2012; Merchant et al, 2009**). Fragmented QRS (fQRS) defined as ≥4 spikes in one lead or ≥8 spikes in all leads V1-V3 (**Morita H et al., 2008**) is a convenient marker of myocardial scar evaluated by 12-lead ECG recording. In recent meta-analysis Meng et al. showed that BrS patients with fQRS are at high risk for future arrhythmic events. The presence of fQRS is associated with a 3-fold increased risk of future arrhythmic events in patients with BrS, and the presence of fQRS confers a 3- and 2-fold increase for VF and SCD events, respectively (Meng et al., 2017).The presence of fQRS warrants prospective evaluation as valid arrhythmogenic risk marker in BrS. fQRS is defined as additional spikes within the QRS complex in at least two contiguous leads. In patients with CAD, fQRS was associated with myocardial scar detected by single photon emission tomography and was a predictor of cardiac events. fQRS was also a predictor of mortality and arrhythmic events in patients with reduced LVEF. fQRSs, which include various RSR' patterns, without a typical BBB are markers of altered ventricular depolarization owing to a prior myocardial scar. fQRS improve the ability to detect a prior MI compared with Q waves alone by ECG. fQRS is a marker of a prior MI, defined by regional perfusion abnormalities, which has a substantially higher sensitivity and negative predictive value compared with the Q wave. fQRS is an independent predictor of cardiac events in patients with CAD. It is associated with significantly lower event-free survival for a cardiac event on long-term follow-up (**Das MK, et al. 2007.**). fQRS, T-wave inversion, and ST depression are independent predictors of mortality during a mean follow-up period of 34 +/- 16 months. In conclusion, fQRS on ECG is a moderately sensitive but highly specific sign for ST elevation MI and NSTEMI. fQRS is an independent predictor of mortality in patients with ACS.

- Entities where fQRS is used as a non-invasive marker of events (**Das MK, et al. 2009**).

1. Coronary artery disease (**Das MK et al., 2010**) where it represents a conduction delay of the stimulus and is associated to an increase in mortality and arrhythmic events in these patients.
2. Non-ischemic cardiomyopathies (**Das MK, et al. 2010**). In non-ischemic dilated cardiomyopathy with narrow QRS to predict dyssynchrony (**Tigen K, et al 2009**).
3. Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (**Peters S, et al 2008**).
4. Cardiac sarcoidosis (**Homsi M, et al. 2009**).
5. Congenital heart diseases (**Moss AJ.et al. 2010**).
6. Acquired LQTS (**Haraoka K,et al. 2010**). The existence of fQRS plays an important role in the appearance of Torsades de Pointes (TdP) in patients with acquired long QT interval. Severe mitral stenosis with pulmonary hypertension) (**Yuce M, et al 2010**).

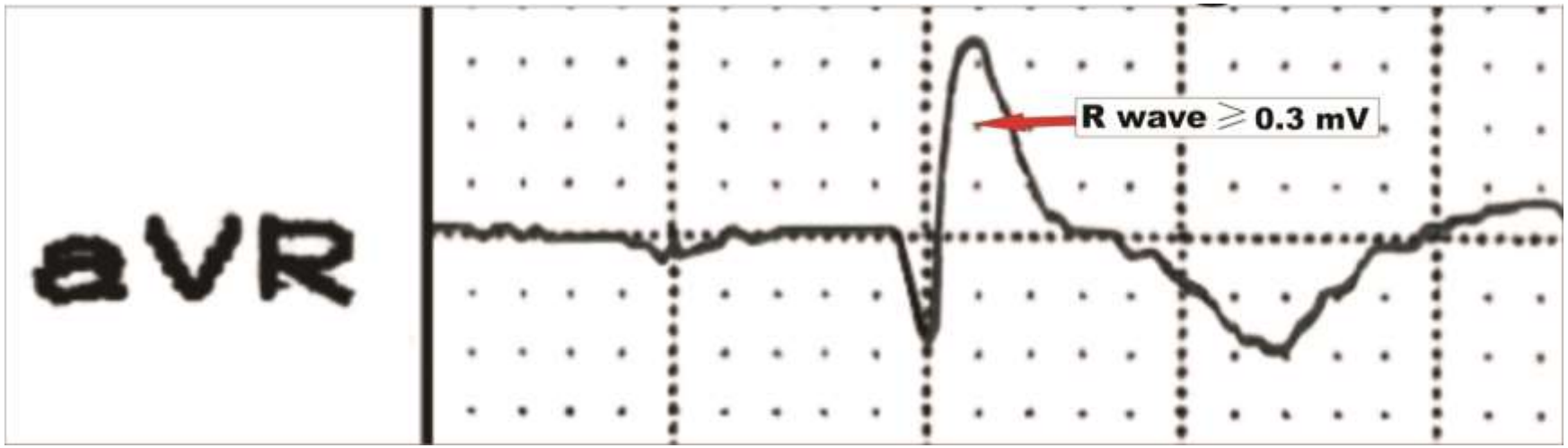


Dotted lines show onset and termination of the QRS complex. Two spikes are observed at the upstroke of the S wave in leads V1 and V2. Fragmented wide QRS complex in a 35-year-old Asian male patient with BrS. f-QRS appears to be a marker for the substrate for spontaneous VF in BrS and predicts patients at high risk of syncope. It is a conduction abnormality within the QRS complex (**Morita H, et al., 2008**).

8. **Atrial Fibrillation:** The presence of atrial fibrillation(AF). Spontaneous AF and VF are closely linked clinically and electrophysiologically in BrS patients. Patients with spontaneous AF have more severe clinical backgrounds in BrS. SCN5A mutation is associated with electrical abnormality but not disease severity. (**Kusano KF et al. 2008**). In BrS sinus rhythm is the rule but sinus node dysfunction (SND) and atrial fibrillation (AF) are considered risk markers in BrS. AF can be the first manifestation of latent BrS. Rodrigues-Mañero et al studied the prevalence of AF as the first clinical diagnosis in patients with BrS and their characteristics and diagnosis management in a large cohort. The universe consisted of 611 patients with BrS. The data from those with a diagnosis of AF previous to the identification of BrS were analyzed (n = 35). 11 cases were unmasked after the initiation of a class I antiarrhythmic drug and one during general anesthesia. In the remaining, BrS was diagnosed using an ajmaline test performed mainly because of younger age in patients with lone AF (n = 13), previous syncope or SCD (n = 3), or a clinical history of SCD in the family (n = 5). 14 had a family history of SCD, 15 had had previous syncope, and 4 had survived CA. Concomitant electrical disorder was found in 13 patients. Remarkably, 21 patients had normal findings on the baseline ECG. AF could be one of the first clinical manifestations of latent BrS in a considerable number of patients. This identification is crucial because the treatment of these patients is subject to relevant changes. The ajmaline test as an important role, mainly in young patients with a family history of SCD, despite having normal findings on ECG (**Rodriguez-Mañero M, et al., 2013**).The incidence of cardioembolic stroke in patients with BrS and AF is near 14% (unexpectedly high). The cerebrovascular accidents are often the presenting clinical manifestation and are significantly associated with asymptomatic AF and older age. CHADS2 and CHA2DS2Vasc scores did not predict the unexpectedly high risk of thromboembolic events in this group of patients. BrS patients with transient ischemic attack/stroke are more frequently asymptomatic. The use of more invasive diagnostic tools might be useful in order to increase the rate of AF detection (**de Asmundis C. et al., 2019**).

9. **Spontaneous Type I BrP ECG** (**Priori SG, et al 2012; Priori SG, et al, 2012; Antzelevitch C, et al Heart Rhytm 2005**). Of the different markers, only a spontaneous type 1 ECG pattern has clearly shown a sufficiently high predictive value (**Asvestas D et al., 2018; Delise P, et al., 2011**). in BrS patients, a spontaneous Type-1 ECG is an independent risk factor for SCD in males, but not in females. A spontaneous Type-1 BrS is associated with a worse prognosis when combined with positive EPS (**Li X, et al. 2019**). The majority of BrS patients with previous aborted SCA events did not have a spontaneous type I and/or prior history of syncope. Conventional and newer markers of risk appear to only have limited ability to predict SCA (**Leong KMW, et al. 2019**).

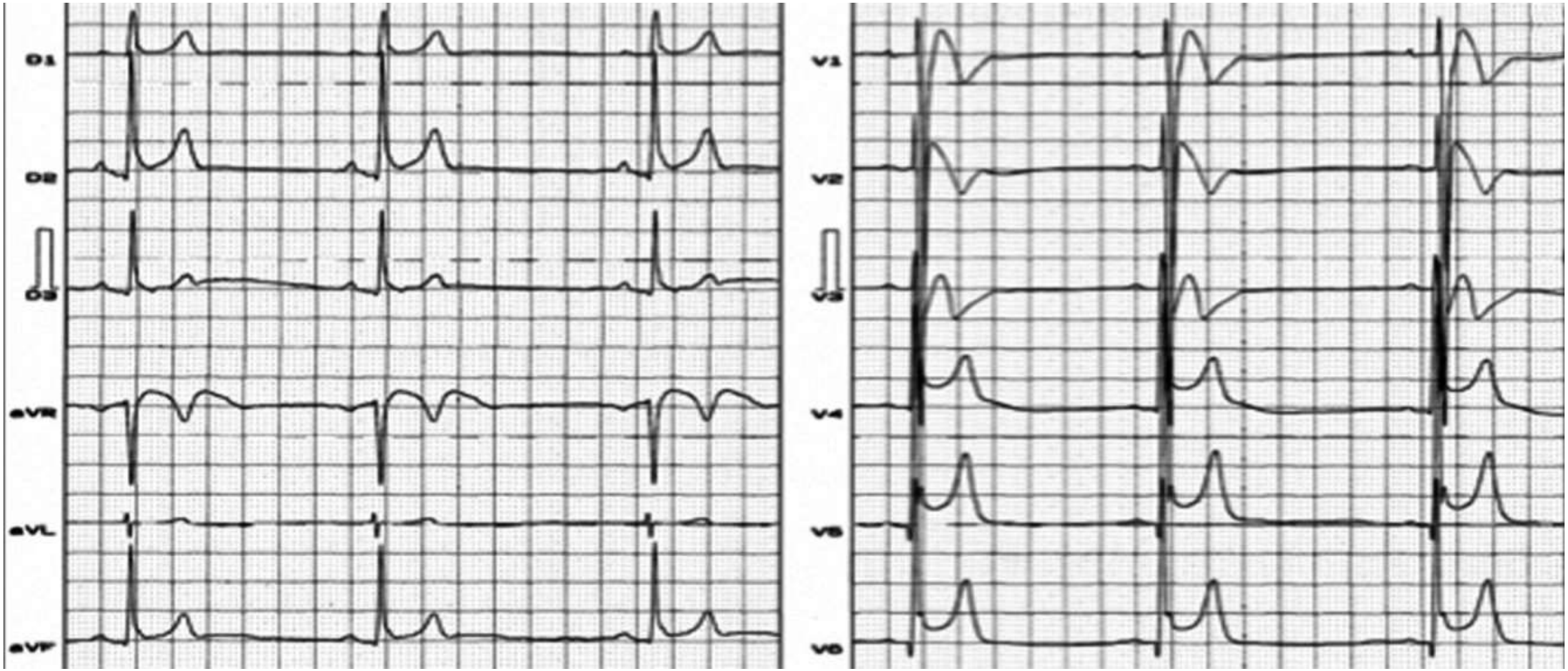
10. **Prominent final R wave on aVR lead; R wave ≥3 mm or R/q ≥0.75 in lead aVR (Babai Bigi MA, et al. 2007**). Babai Bigi et al demonstrated a significant correlation between a prominent R wave in lead aVR (aVR sign) and risk for development of arrhythmic events in BrS. In the presence of BrS, prominent R wave in lead aVR may reflect more right ventricular conduction delay and subsequently more electrical heterogeneity, which in turn is responsible for a higher risk of arrhythmia.



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). Slow conduction at the RVOT may contribute to the induction of VF by PVS.

11. Coexistence of early repolarization pattern (notching or slurring with J-wave ≥ 1 mm at the end of QRS) in inferolateral leads and type 1 Brugada pattern

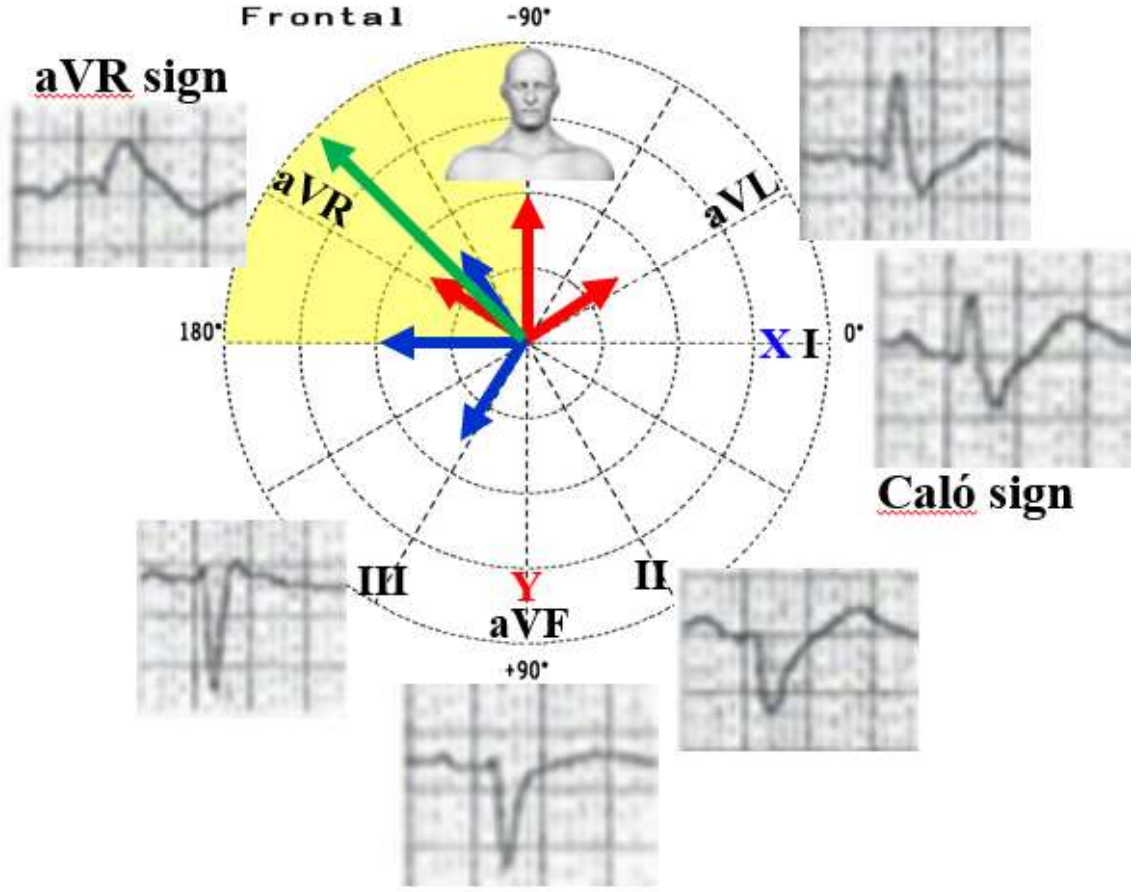
Coexisting early repolarization pattern and Brugada syndrome: recognition of potentially overlapping entities (McIntyre WF, Pérez-Riera AR, et al. 2012)



Twelve-lead ECG from the same 20-year-old man, recorded 72 hours later. The ERP persists, and there is now sinus bradycardia with a Brugada type 1 ECG pattern (coved type) in leads V1 to V3. The ST-segment elevation seen in lead aVR has been identified as a potential high-risk marker for ventricular arrhythmia in patients with BrS.

12. **Significant S wave in lead I (Calò L, et al., 2016);** The presence of a wide and/or large S-wave in lead I was a powerful predictor of life-threatening ventricular arrhythmias in patients with BrS and no history of cardiac arrest at presentation. However, the prognostic value of a significant S-wave in lead I should be confirmed by larger studies and by an independent confirmation cohort of healthy subjects. Explaining the rationale behind this study, Calò and colleagues note that "The so-called third vector, which is directed upward and somewhat to the right and backward, generates the S-wave in lead I. This vector is determined by electrical activation of the basal region of both ventricles and by depolarization of the RVOT. A prominent S-wave in lead I is typically present in cases of congenital heart disease, valvular heart disease, and *cor pulmonale* that cause right ventricular enlargement and fibrosis. Thus, Caló et al. hypothesized that a deep and/ or large S-wave in lead I in BrS would reveal a conduction delay over the RVOT and could be used to identify high-risk patients." The study analysed data from 347 consecutive patients (78.4% male; mean age 45±13.1 years) at four Italian centers with spontaneous type I BrP on ECG but with no history of cardiac arrest (including 91.1% asymptomatic at presentation, 5.2% with a history of AF, and 4% with syncope). Electrocardiographic characteristics at the first clinic visit were analyzed to predict VF or SCD during a follow-up. (48±38 months), 276 (79.5%) patients remained asymptomatic, 39 (11.2%) developed syncope, and 32 (9.2%) developed VF or SCD. Patients who developed VF or SCD had a lower prevalence of SCN5A gene mutations and a higher prevalence of positive EPS results ($p<0.0001$), a family history of SCD and AF. The most powerful marker for VF or SCD was a significant S-wave (≥0.1mV and/or ≥40ms) in lead I,. "In the multivariate analysis, the duration of S-wave in lead I ≥40ms and AF were

independent predictors of VF or SCD during follow-up. Electroanatomic mapping in 12 patients showed an endocardial activation time significantly longer in patients with an S-wave in lead I, which Calò *et al* attribute to a significant delay in the anterolateral RVOT. The presence of a wide and/or large S wave in lead I in BrS, expression of a delayed activation in the RVOT, can be used as a potential novel marker of SCD risk stratification.



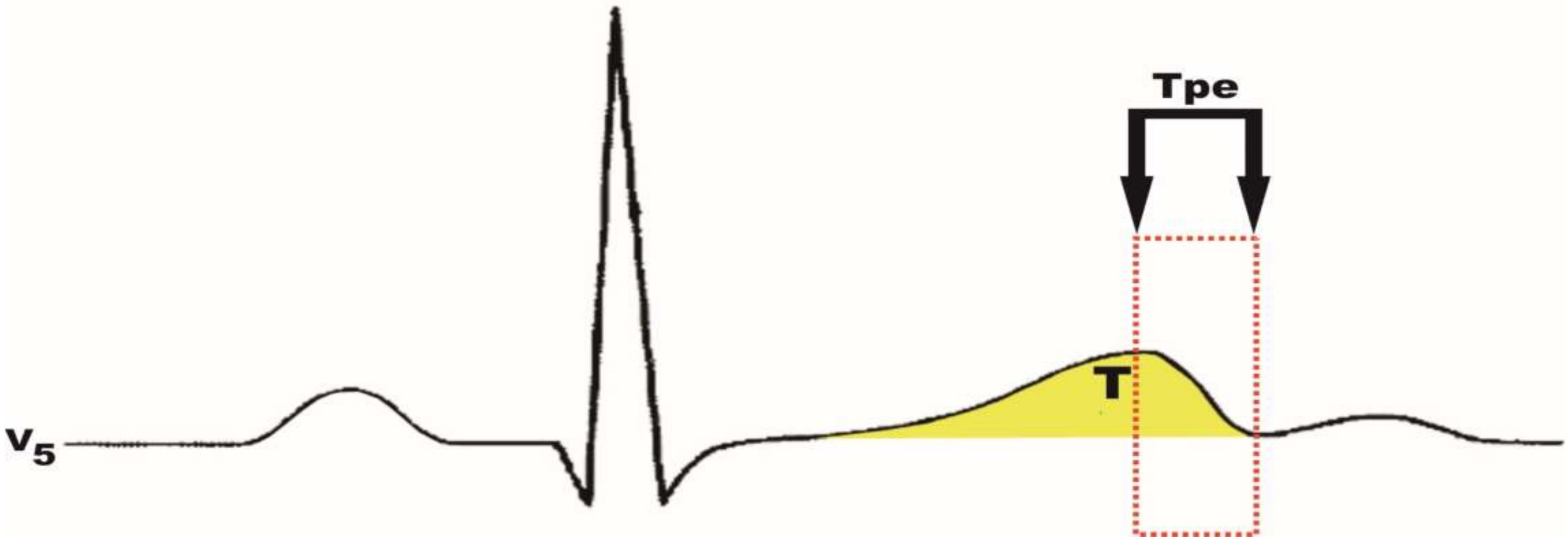
Patient with electrocardiographic pattern Brugada type 1 in the precordial leads. In the frontal plane both signals are present aVR sign (prominent final R wave on aVR lead; R wave ≥3 mm or R/q ≥0.75) and Caló sign (wide and/or large S-wave in lead I). Both signals, reflect terminal o right end conduction delay (RECD) in the in the RVOT and subsequently more electrical heterogeneity, which in turn is responsible for a higher risk of arrhythmia.

13. **Deep SI, SII >SIII pattern. not only electrocardiographic signs indicative of RVOT conduction delay but also QRS Vector Magnitude (QRSvm) can be used as a predictor for ventricular tachyarrhythmia(VTA) events in BrS patients (Ragab AAY, et al. 2019.)**

Multivariate regression analysis showed that Voltage dependent QRS 3-dimensional vector magnitude (QRSvm) and RVOT signs are independent predictors for VTA in BrS patients (QRS vector magnitude: odds ratio 3.68, 95% CI 2.4 to 6.2, p = 0.001; RVOT: odds ratio 2.6, 95% CI 1.4 to 4.9, p = 0.001). Not only ECG signs indicative of RVOT conduction delay but also QRSvm can be used as a predictor for VTA events in BrS patients. The QRSvm is a promising parameter for predicting VTA in patients with tetralogy of Fallot (ToF) (**Cortez D, et al, 2017.**)

14. Prolonged Tpeak –Tend interval $T_{peak} - T_{end}$ prolongation and $T_{peak} - T_{end}$ dispersion (Tpe)

$T_{peak} - T_{end}$ is the interval elapsed from the apex to the end of T wave (Tpeak-Tend interval or Tpe). Tpe may correspond to transmural dispersion of repolarization and consequently, the amplification of this interval is associated to malignant ventricular arrhythmias. The normal value of Tpeak/Tend interval (Tpe) is 94 ms in men and 92 in women when measured in the V_5 lead. Tpe prolongation to values ≥120 ms is associated to a greater number of events in patients carriers of BrS(**Castro Hevia J et al, 2006**.). Recent research concluded that TpTe was not significantly prolonged in those patients with type 1 BrP presenting with unexplained syncope or malignant arrhythmic events during follow-up. (**Mugnai G, et al. 2017.**)



15. T-wave alternans during night time as a predictor for ventricular fibrillation in patients with Brugada syndrome. (**Sakamoto S, et al. .)**Sakamoto et al assessed TWA for risk stratification using 24-h multichannel Holter electrocardiogram (24-M-ECG) in BrS. They enrolled 129 patients with BrS grouped according to histories of VF, n = 16; syncope, n = 10; or asymptomatic, n = 103 and 11 controls. Precordial electrodes were attached to the third (3L-V1, 3L-V2) and fourth (4L-V1, 4L-V2 and 4L-V5) intercostal spaces. The authors measured the values of maximum TWA (max-TWA) during the night time (12 a.m.-6 a.m.) and the day time (12 p.m.-6 p.m.) and calculated parameters of HRV. Compared to the asymptomatic and control groups, the VF and syncope groups showed significantly greater 3L-V2 max-TWA during the night time. The cutoff value for the 3L-V2 max-TWA during the night time was determined as 20 μV (sensitivity 94 % and specificity 48 %). Multivariate analysis revealed that 3L-V2 max-TWA during the night time ≥20 μV and previous VF episodes were independent predictors of future VF episodes. During a mean follow-up period of 68 ± 37 months, 16 patients experienced VF episodes. The incidence of VF episodes was the highest during the night time. The 3L-V2 max-TWA during the night time may be a useful predictor for VF episodes in patients with BrS.
16. J point or ST segment elevation of ≥0.2 mV in right precordial leads in the case of BrS, or inferior and inferolateral leads or global leads in the case of ERS.(**Takagi M et al, 2013; Kawata et al, 2013**).
17. Horizontal or downsloping ST segment following the J wave in cases of ERS (**Tikkanen JT, et al 2011; Rosso et al, 2012; Takagi M et al, 2013; Adler et al, 2013**).
18. Appearance of distinct and prominent J waves (**Badri M, et al. 2015**).

19) Association of BrS or ER pattern with abbreviated QT intervals (**Burashnikov E, et al. 2010; Watanabe H et al, 2010**).

20) Short-coupled premature ventricular contractions (**Kalla H, et al, 2000; Gang ES et al, 2004; Viskin S et al, 2005**).

21) Transient J wave augmentation or fluctuation of J wave portends a high risk for VF in patients with ER (**Aizawa Y et al, 2012**)

22) Augmentation of the ST segment elevation during the early recovery phase of exercise test in patients with BrS (**Makimoto H et al. 2010**).

23) Pause-dependent augmentation of J waves that is accompanied by T wave inversion (**Aizawa Y et al, 2012; Qi X et al, 2004**).

24) Association of ER with Horizontal or Descending ST segment (**Tikkanen JT, et al 2011**).

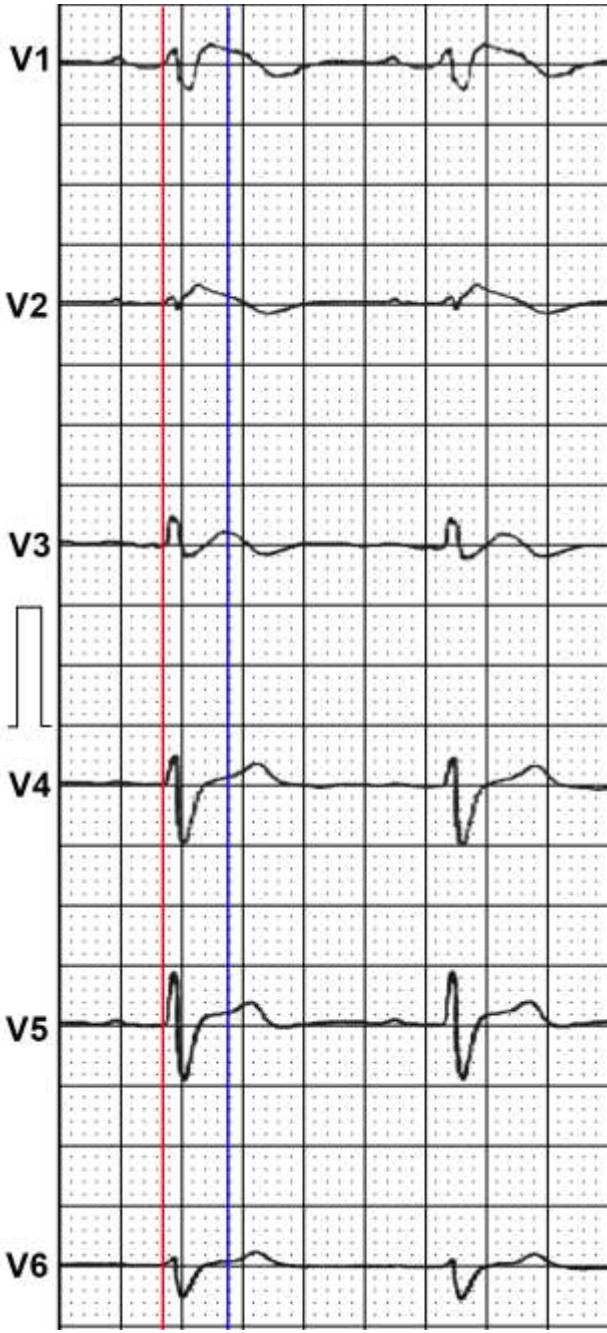
25) T wave amplitude variability (**Yoshioka K, et al, 2013**)

26) The presence of late potentials (LPs) on signal-averaged ECG(SAECG). It is defined as ≥1 out of the following 3 criteria: filtered QRS duration >114 ms, terminal (last 40 ms) QRS root mean square <20 μV or low amplitude signal (under 40 μV) duration >38 ms (**Marcus FI et al., 2010**). LPs in a SAECG are often found in BrS (**Ikeda T, et al., 2005; Yoshioka et al., 2013**), but the predictive value is considered limited. LPs on epicardial bipolar electrogram or SAECG (**Nademanee K et al, 2011; Ikeda T et al, 2011; Yoshioka et al, 2013; Aizawa et al, 2008; Furushima H, et al, 2007; Nagase S, et al, 2002; Huang et al, 2009**). LPs are a noninvasive risk stratifier in patients with BrS. These results may support the idea that conduction disturbance per se is arrhythmogenic. (**Ikeda T et al. 2001**). LPs characteristics detected by the Holter-based SAECG system over 24 hours differ between BrS and ARVC patients. Dynamic daily variations of LPs were seen only in BrS patients. This may imply that mechanisms of lethal ventricular arrhythmia in BrS may be more correlated with autonomic abnormality than that of ARVC.(**Abe A et al. 2012**).

27) Short ventricular refractory period (VRP < 200 ms) in BrS during EPS (**Priori SG, et al 2012**).

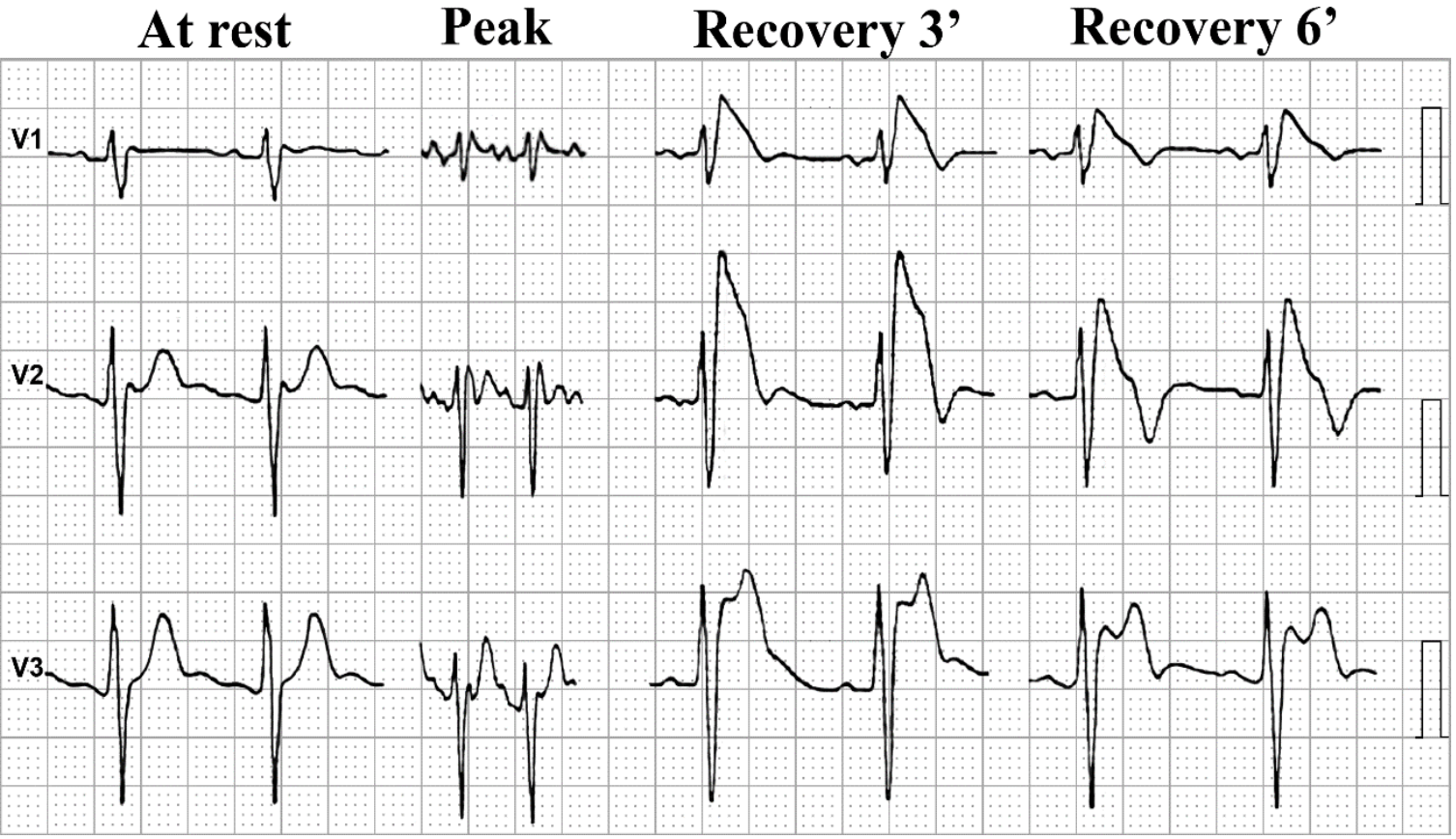
28. Increase in the duration of QRS complexes only in the right precordial leads (from V1 to V3), being normal in the left leads (V4 to V6) in the absence of right bundle branch block: Parietal block

Pitzalis et al identified the selective prolongation of QT interval duration in the right precordial leads (V1 to V3) in comparison to the left ones (V4 to V6). In other words, lengthening of QT intervals in the right precordial leads. QRSD of V1+V2+V3 /V4, V5, V6 > 1.2. This feature is considered typical of ARVC/D, but it is also observed in BrS (**Pitzalis MV, et al. 2003.**).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 V1 to V3, being normal or lesser from V4 to V6, it is clear that this increase may be due to prolongation of ventricular depolarization and/or by ST/T prolongation (repolarization). If we admit that in BrS there is some degree of BBB, 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, and therefore represents the so-called electric systole, which includes depolarization (QRS) and ventricular repolarization (ST/T = JT interval). Side figure: The figure shows that the QRS duration complexes and QT intervals of the right precordial leads (V_1-V_2-V_3) is greater than in the left precordial leads (V_4-V_5-V_6) and that QT ratio $^{V1+V2+V3}/_{V4+V5+V6}$ is ≥1.2



29. ST-segment augmentation (≥0.05 mV in V1 to V3 leads) at the early recovery phase (1 to 4 min at recovery) after treadmill exercise testing:

Current guidelines (**Priori SG, et al., 2013**) support as well exercise ECG testing in first-degree relatives of patients with idiopathic VF and SUDS and BrS The analysis of recovery phase QTc, repolarization dynamics, and augmentation of ST-elevation during recovery represent promising parameters for risk stratification of SCD but they need validation in other studies with a larger study population (**Refaat MM, et al. 2014.**). Augmentation of ST-segment elevation during recovery from exercise testing was specific in patients with BrS, and can be a predictor of poor prognosis, especially for patients with syncope alone and for asymptomatic patients (**Makimoto H, et al. 2010**).



At rest: Brugada patient showing type 2 ST-segment elevation in lead V2(saddle-back)

Peak: ST-segment amplitude slightly decreased,

Recovery 3' and 6': Type 1 and 2 Brugada pattern with point J and ST segment elevation augmentation. Positive electrophysiology study for ventricular arrhythmia inducibility or ventricular effective refractory period less than 200 ms. Positive late potentials recorded in the signal-averaged electrocardiogram (SAECG). Family history of SCA was previously reported as not predictive of future arrhythmic events.

30. Risk score in BrS patients aged ≤19 years

Gonzalez Corcia et al. Analyzed a consecutive cohort of 128 young BrS patients (≤25 years old at diagnosis). Symptomatic BrS occurring during a young age is a rare but malignant condition related to a very high risk of future arrhythmic events and SCD. Symptomatic patients showed significantly abnormal baseline electrical characteristics when compared with the asymptomatic cohort, including: spontaneous type I ECG, SND, prolonged PR interval, intraventricular conduction delay and atrial arrhythmias. EPSs resulted positive more frequently in symptomatic patients, but no risk association for future events could be determined. During the follow-up period (mean: 65 months), 10 arrhythmic events occurred in nine symptomatic patients (event rate: 4.5% per year). No events occurred in the asymptomatic group. Variables significantly associated with arrhythmic events during follow-up were presence of symptoms at diagnosis and spontaneous type I ECG. The presence of atrial arrhythmias and conduction abnormalities was also associated with the risk of arrhythmic events during follow-up (**Gonzalez Corcia MC, et al. 2017; Gonzalez Corcia MC, et al. 2017**). Concomitant epicardial RVOT ablation and ICD implantation with epicardial leads can be a safe, feasible, and effective approach for symptomatic child BrS patients (**de Asmundis C, et al. 2018**).

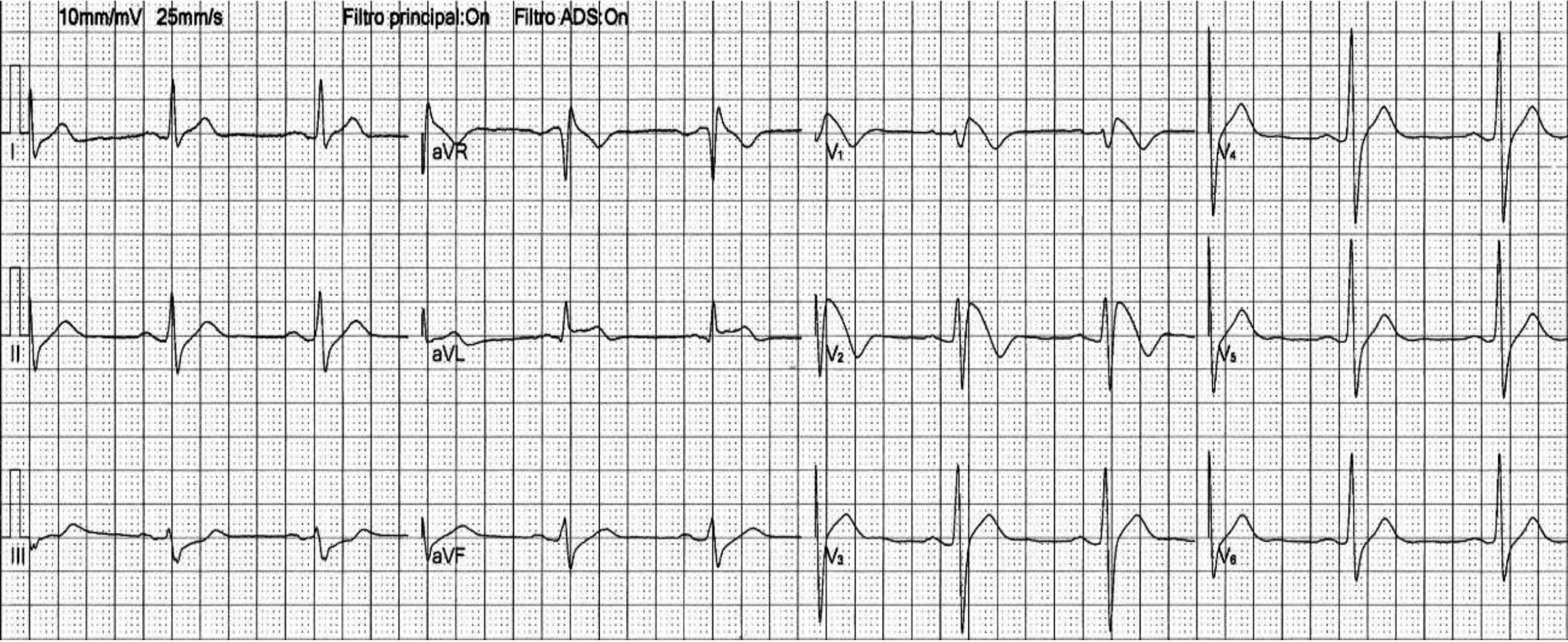
31. The value of the vectorcardiogram in Brugada syndrome

Introduction

In the initial description of BrS by the Brugada brothers (**Brugada P, et al. 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, et al., 2013**) found right bundle branch block (RBBB) only in 28% of BrS patients (**Alonso A, et al.2013**). In addition, several patients with BrS and type 1 electrocardiographic Brugada pattern did not meet criteria of 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 CRBBB (QRS duration ≥120 ms in adults, >100 ms in children ages 4 to 16 years, and >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 >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 (**Surawicz B, et al., 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 (**Antzelevitch, C., et al. 2016**).

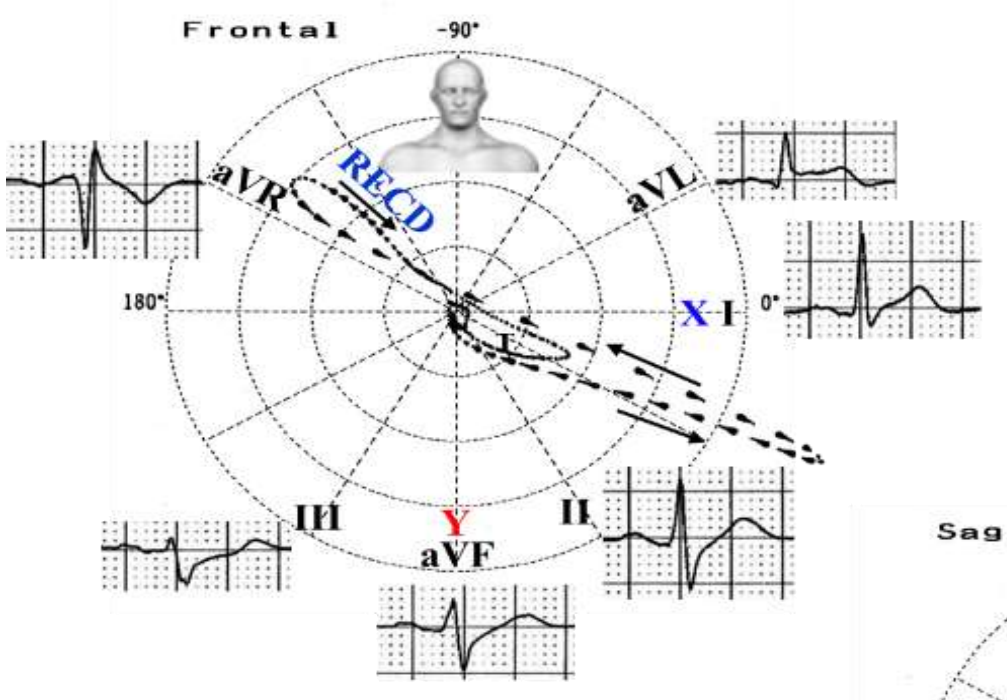
We will show the main vectorcardiographic features of type 1 ECG Brugada pattern.

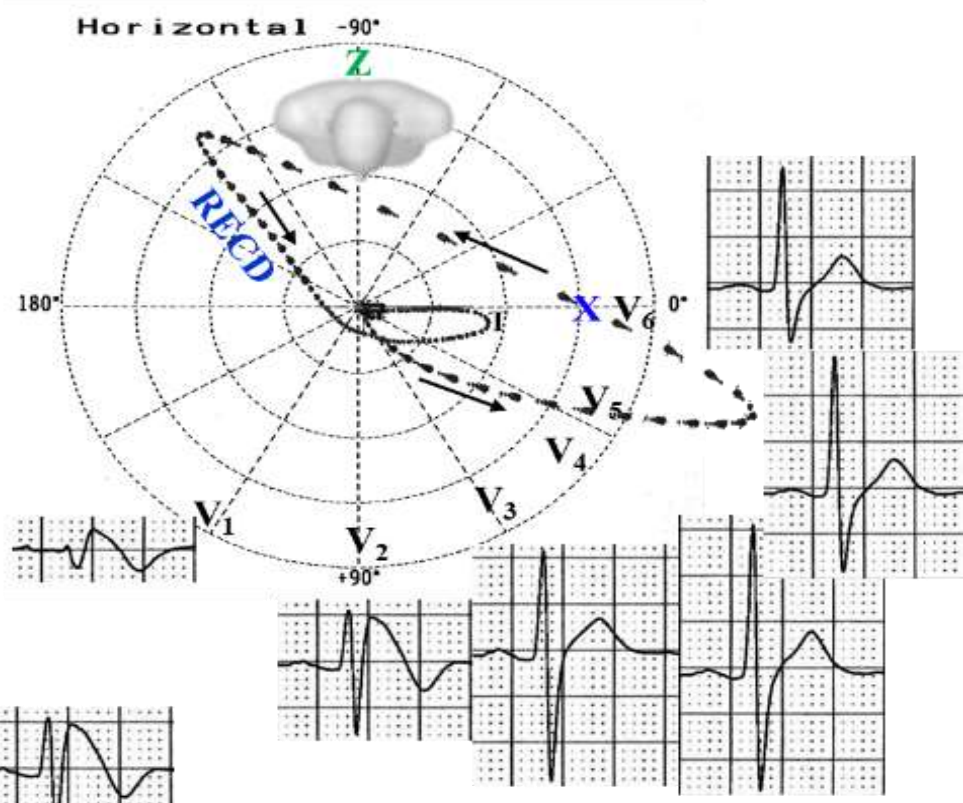
We carefully analyzed an extensive series of 121 ECGs/VCGs from BrS patients with spontaneous or induced by provocative test. From the total sample, 102 ECG/VCGs came from the Department of Clinical and Experimental Cardiology, Academic Medical Center, Amsterdam, The Netherlands; and 19 ECG/VCGs came from our series (total of 121 ECG/VCGs).

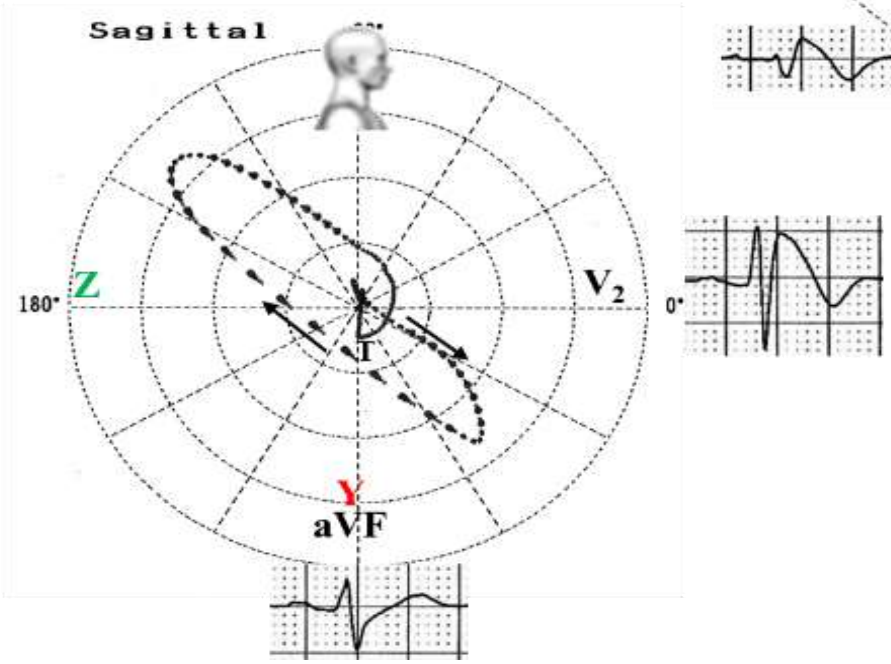


Sinus rhythm, HR 58 bpm, P axis +50°, prolonged P-wave duration 150 ms, PR interval 200 ms, P voltage 1 mm, QRS axis -20°, final R wave in aVR typical of spontaneous type 1 Brugada pattern. The increase in P-wave duration in the general population is a risk marker for sudden cardiac death and AF (**Maheshwari A, et al., 2017**). Patients carriers of BrS with SCN5A mutations display more conduction abnormalities in ECG (P wave, PR and QRS 460). **Conclusion:** prolonged P wave + type 1 Brugada 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

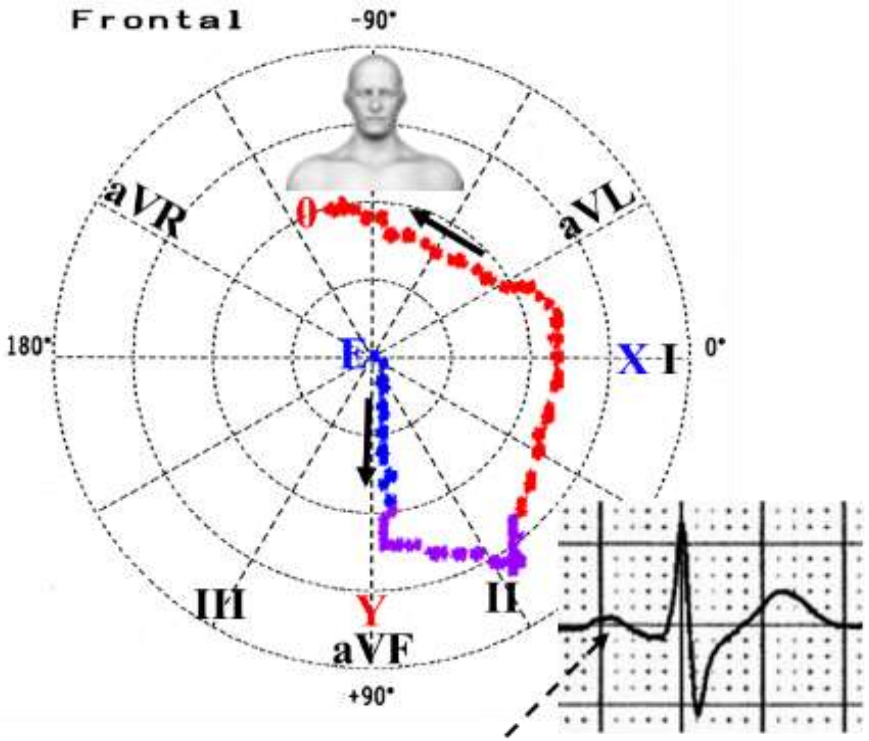


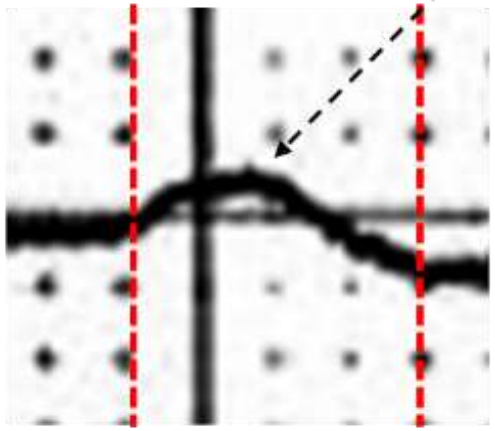


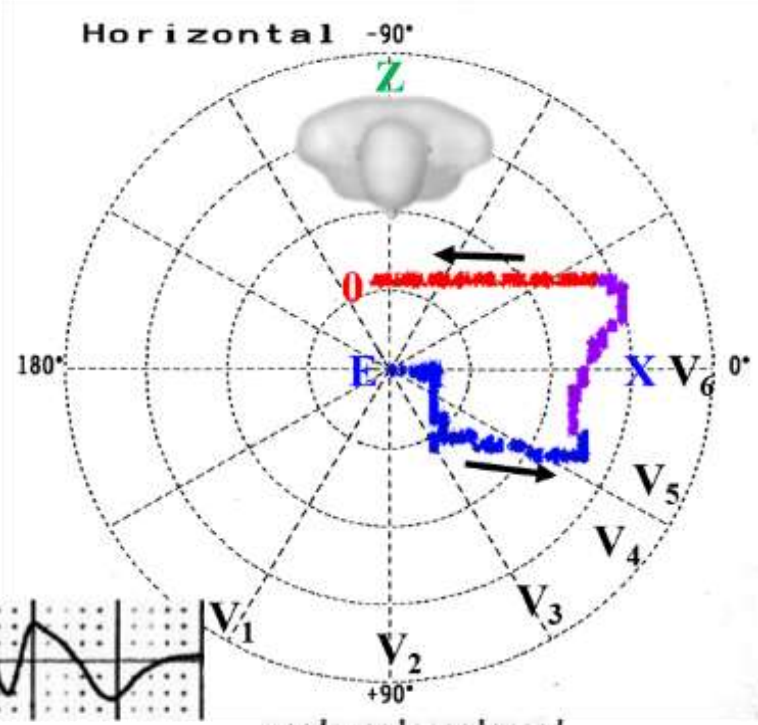


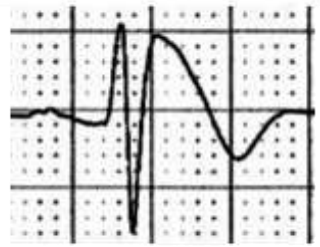
FP: Typical right end conduction delay (RECD) through the superior or subpulmonary fascicle of the right bundle branch. This delay is near aVR lead, corresponding to the RV outflow tract, which explains the final R of aVR. Our classification of right end conduction delays through the superior fascicle 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. HP: RECD in the posterior right quadrant: depolarization mechanism.

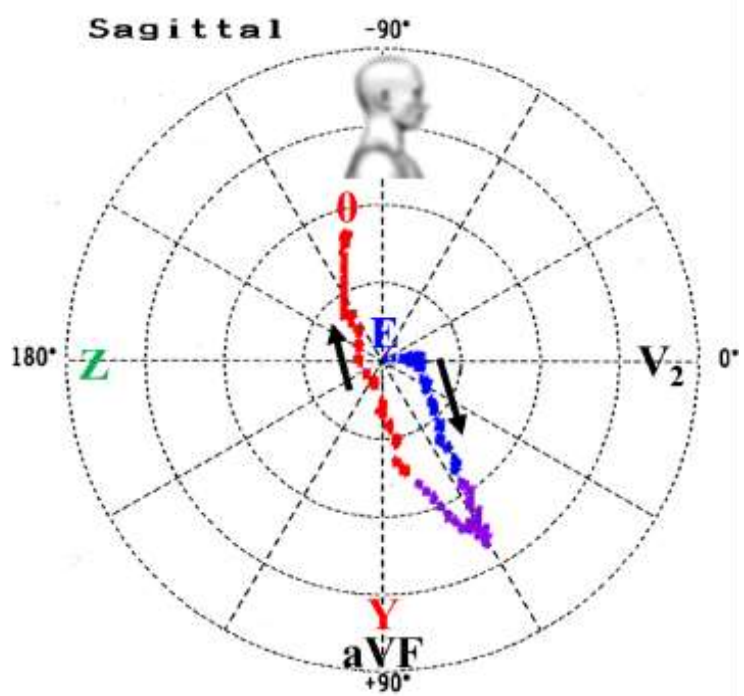
Increased P loop(32 x) and wave in the three planes

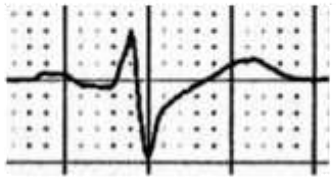






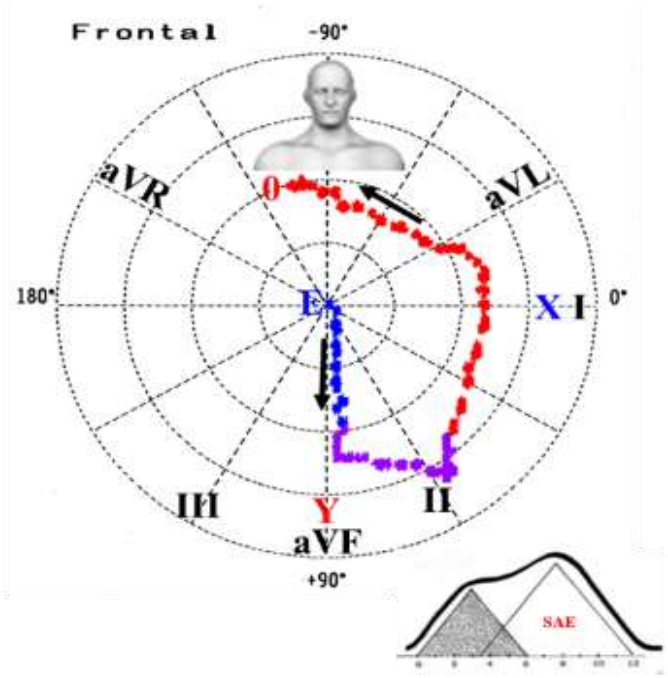


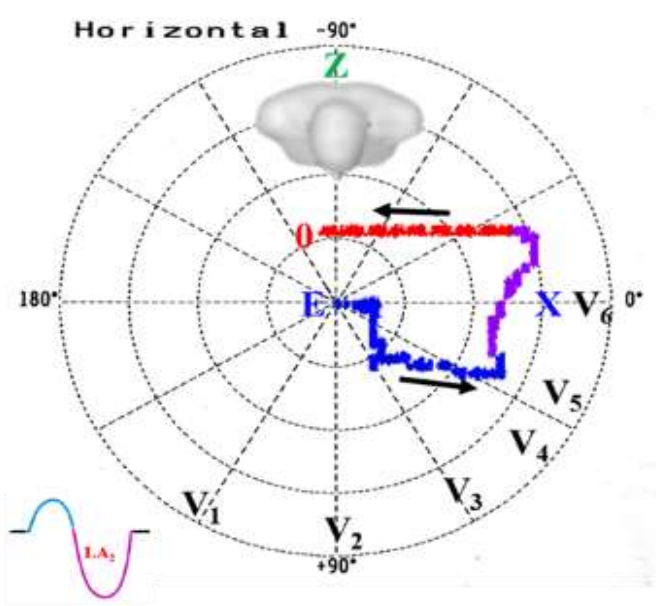


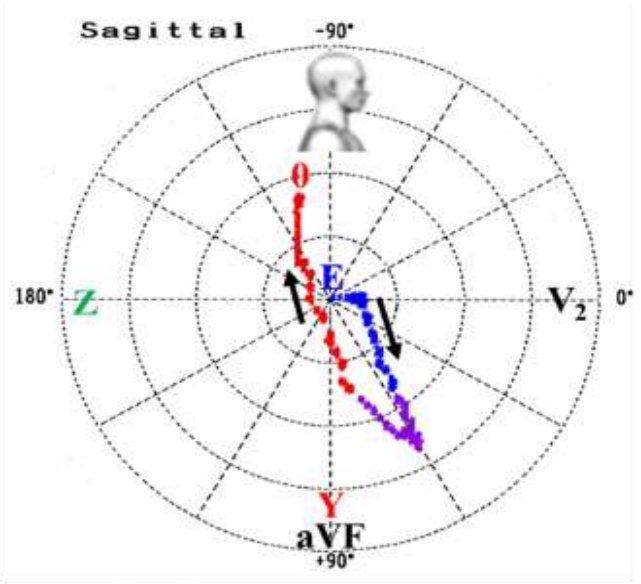


Prolonged P wave (150 mm = LAE)

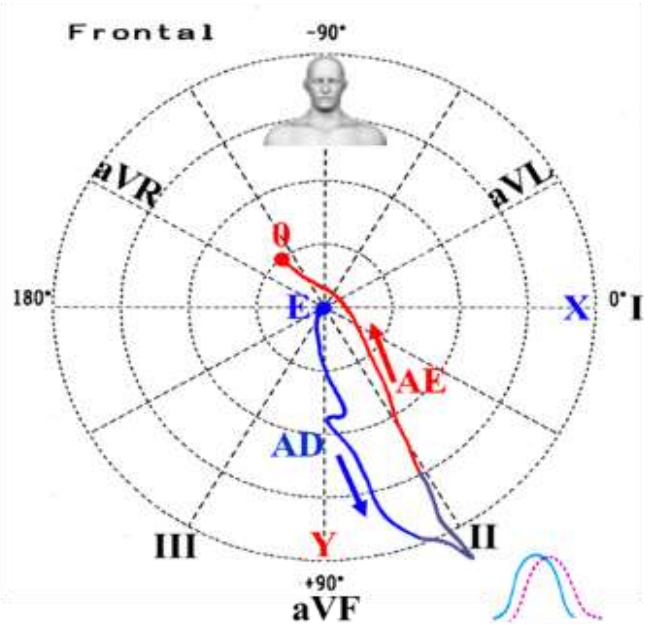
Enhanced P loop in the three planes in this particular case

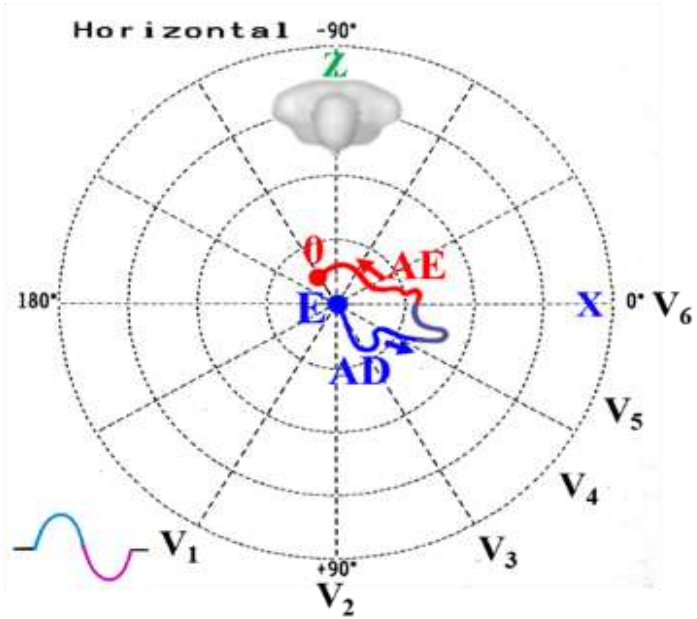


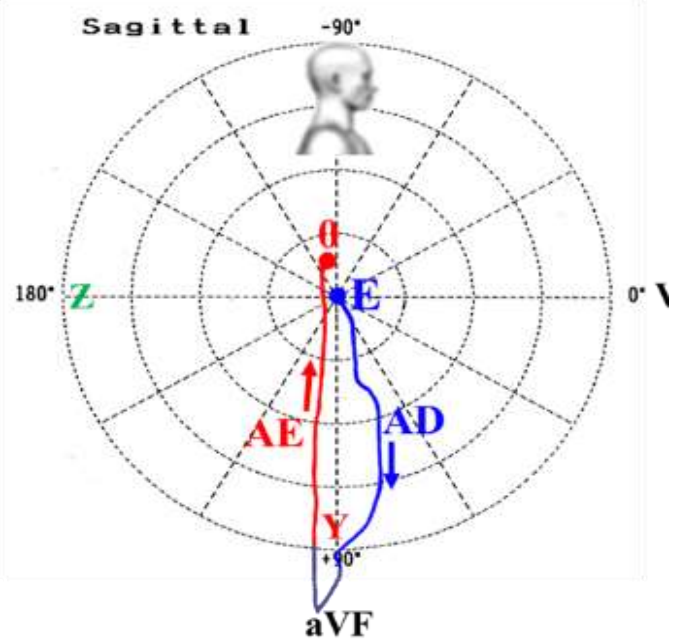




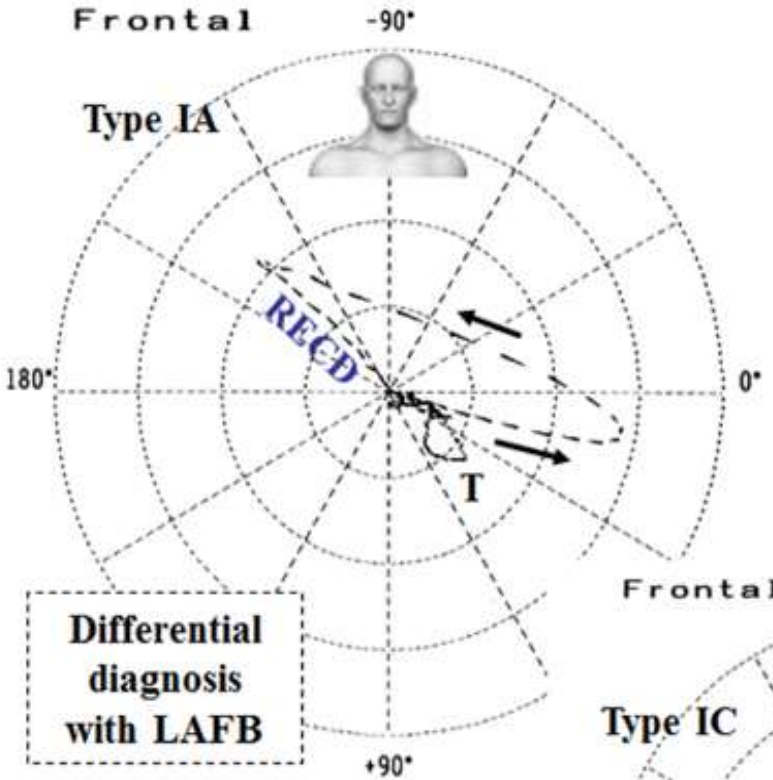
Normal P loop in the three planes



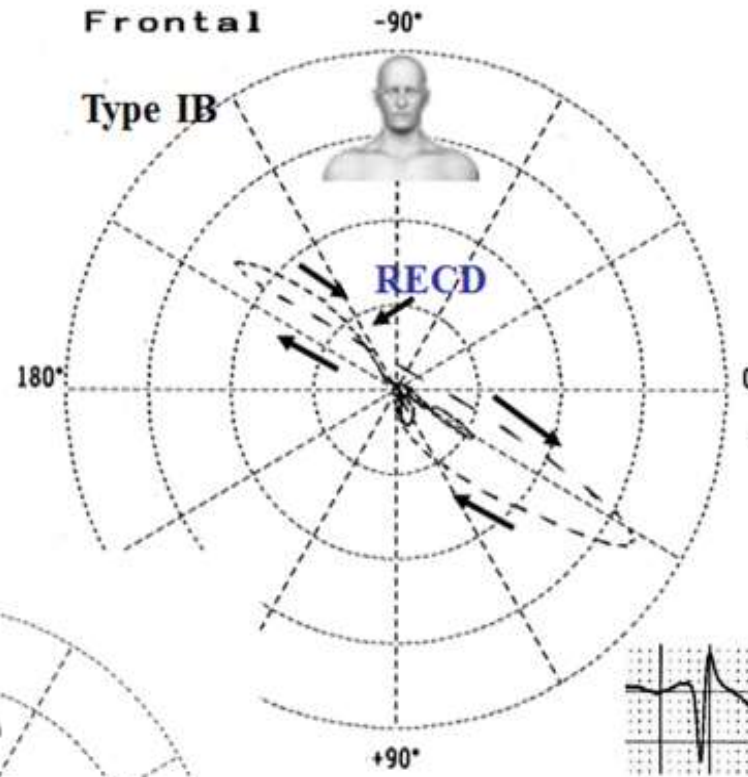


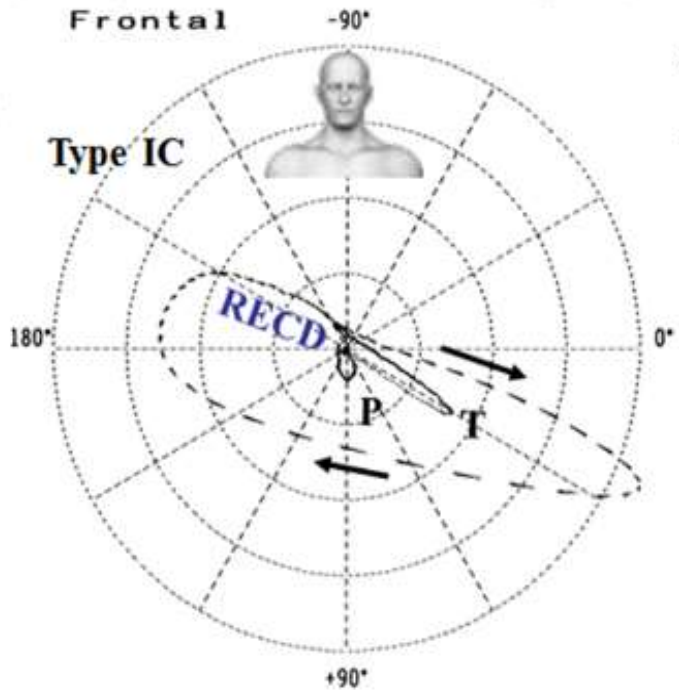


The 3 VCG types of right end conduction delays through the superior fascicle of the right bundle branch

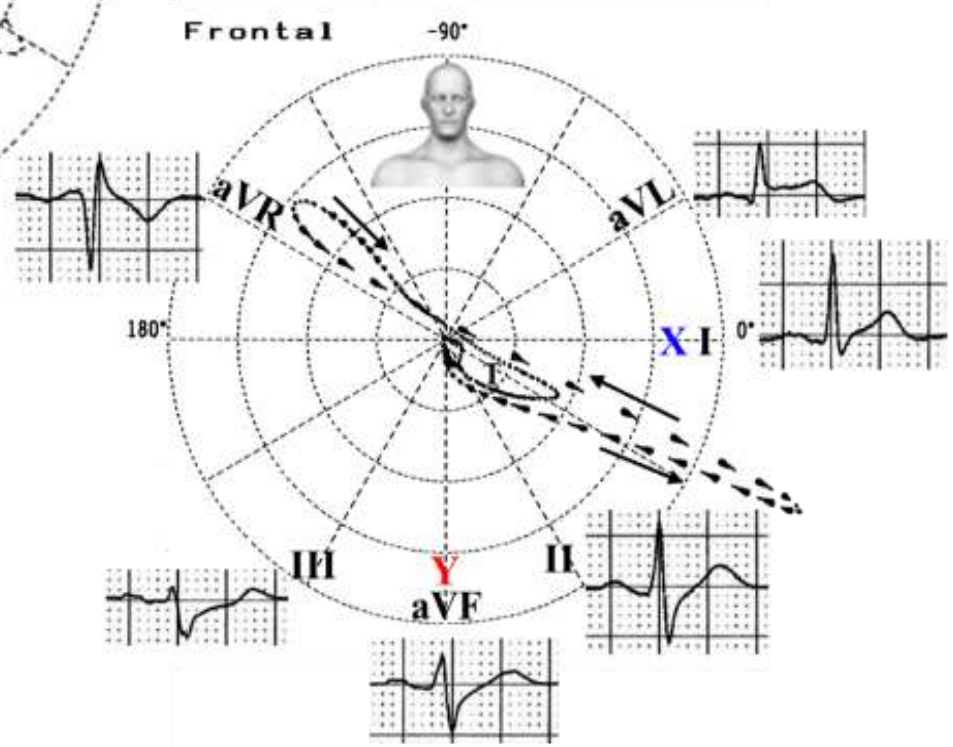


Differential diagnosis with LAFB

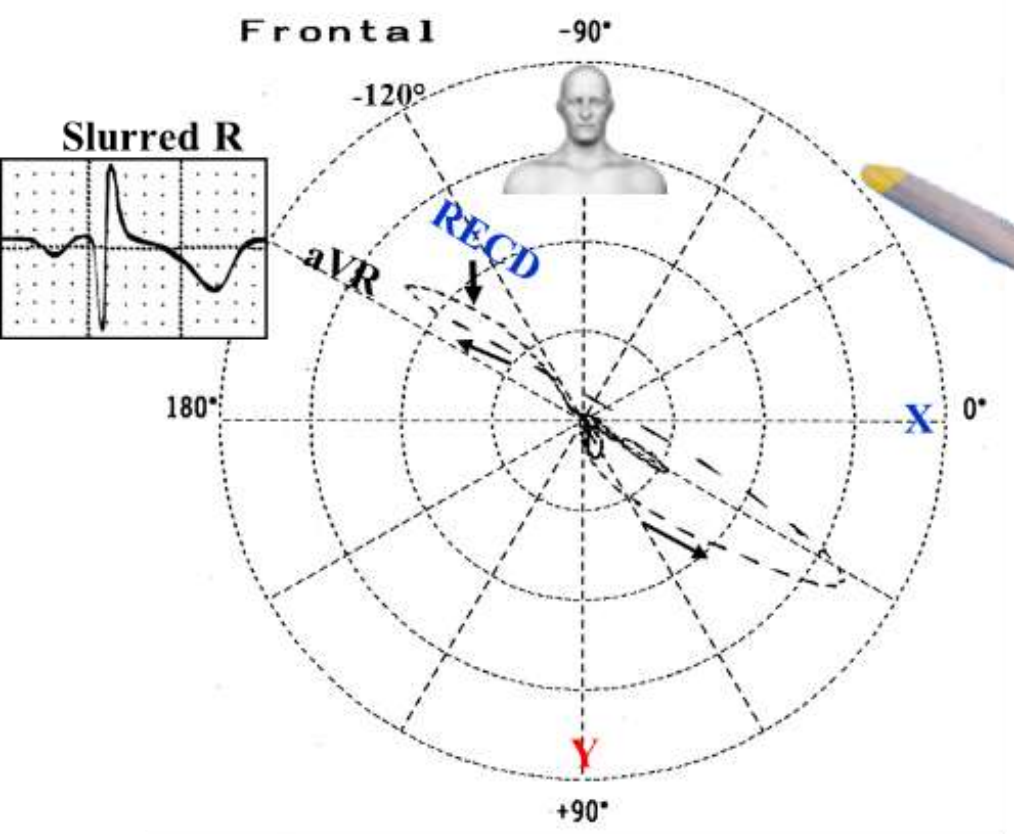


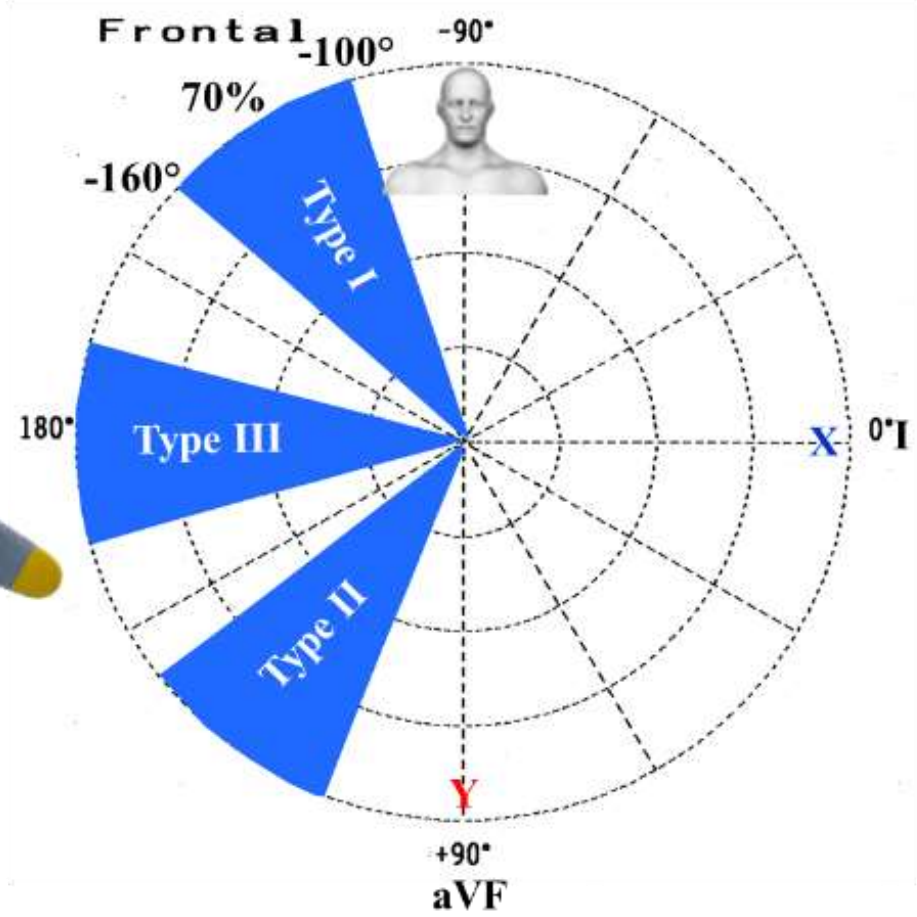


QRS loop with eight shape and its final part located in the right upper quadrant close to aVR with very close dashes (RECD). This type resembles the propellers of a single-engine plane.



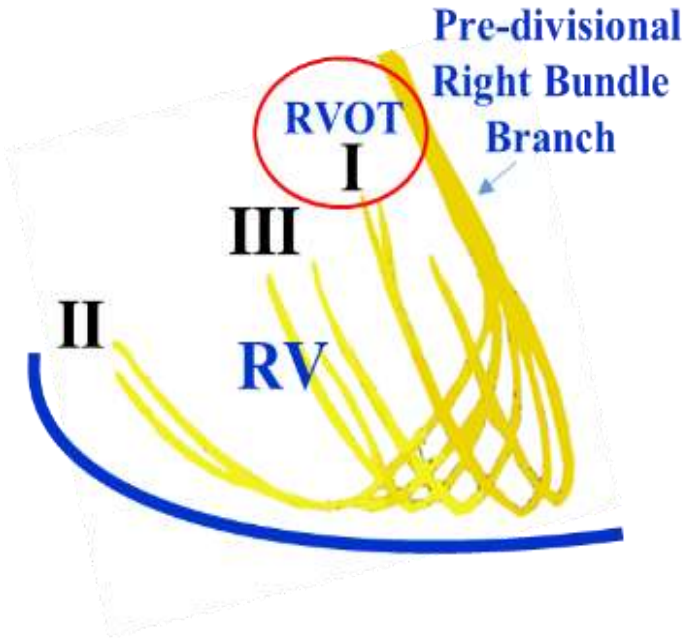
RECD subtype 1B

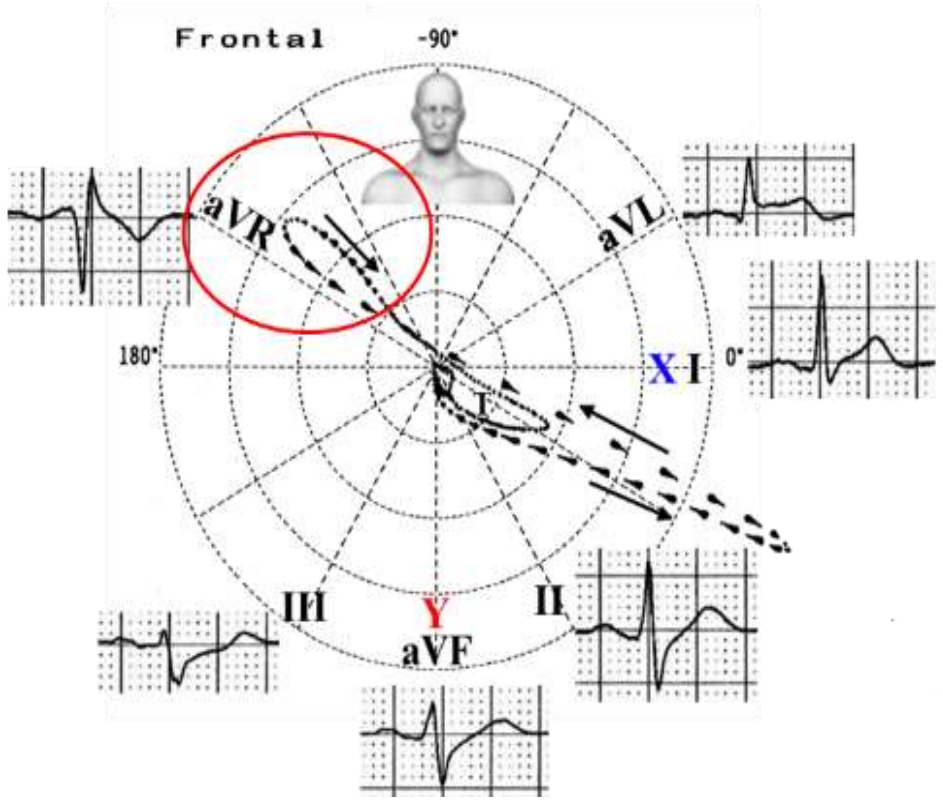


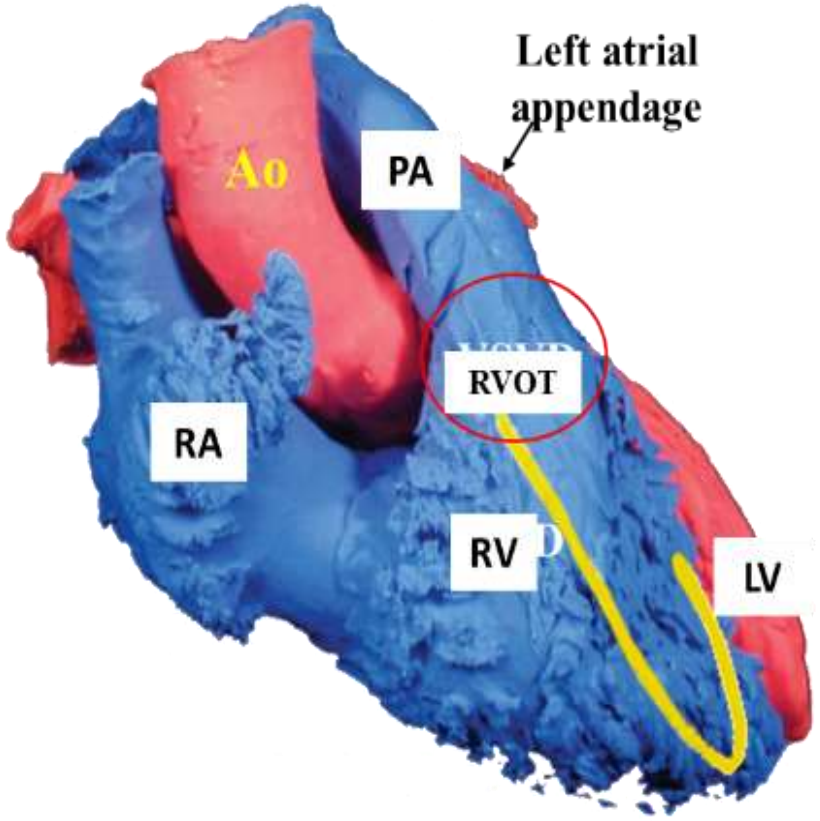


This type resembles the propellers of a single-engine plane.

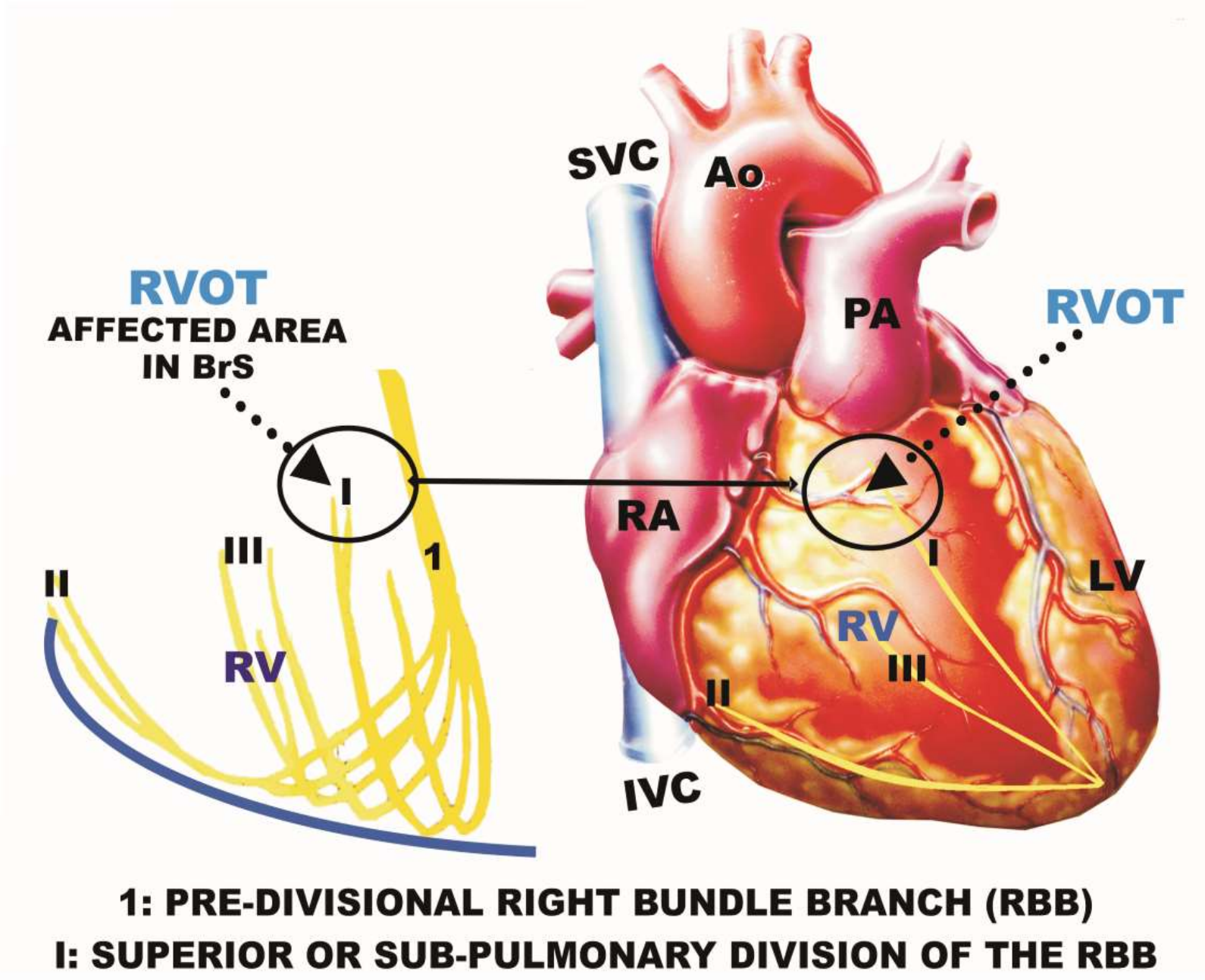
Distribution of the three fascicles of the His bundle right branch in the RV free wall





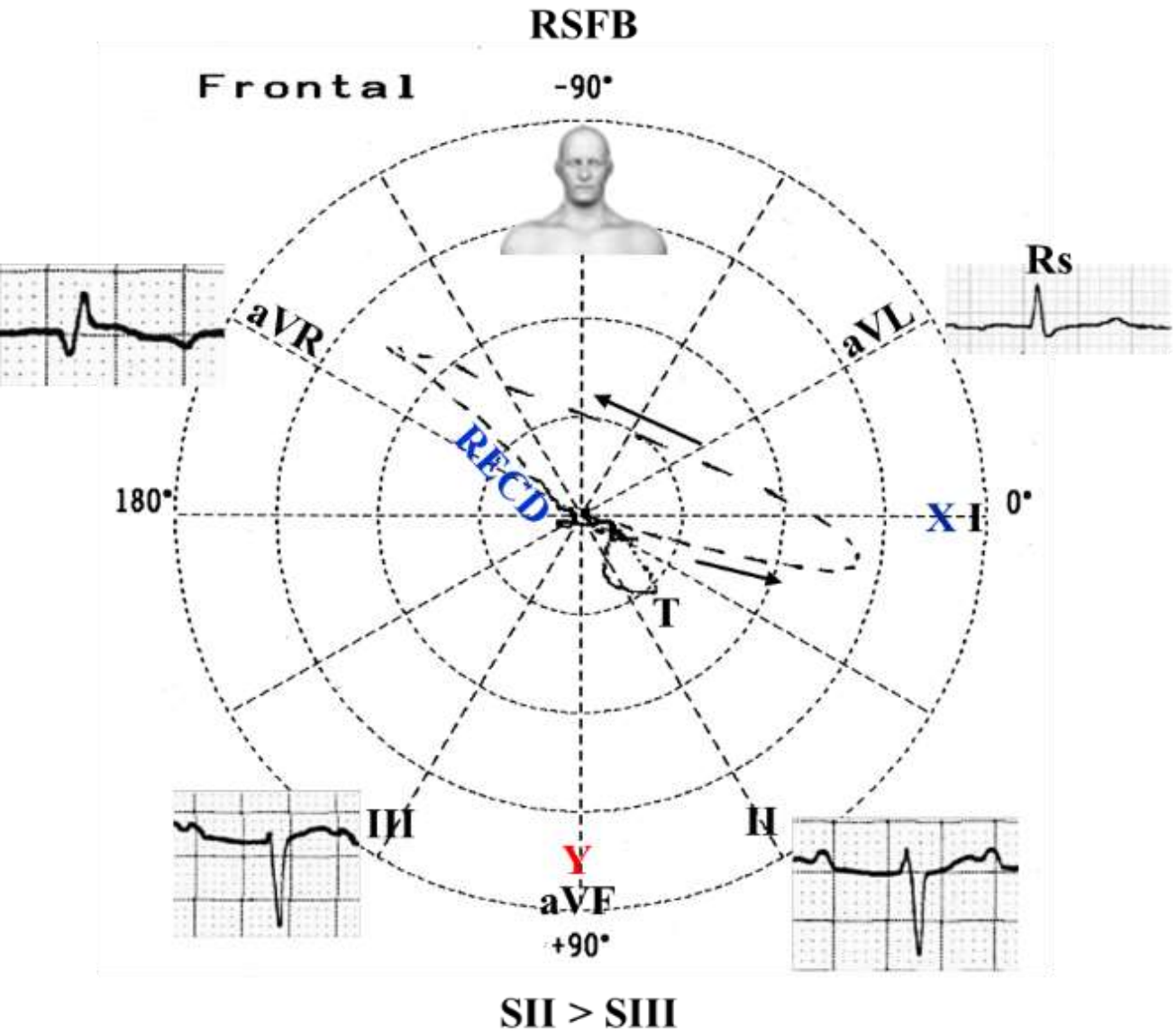


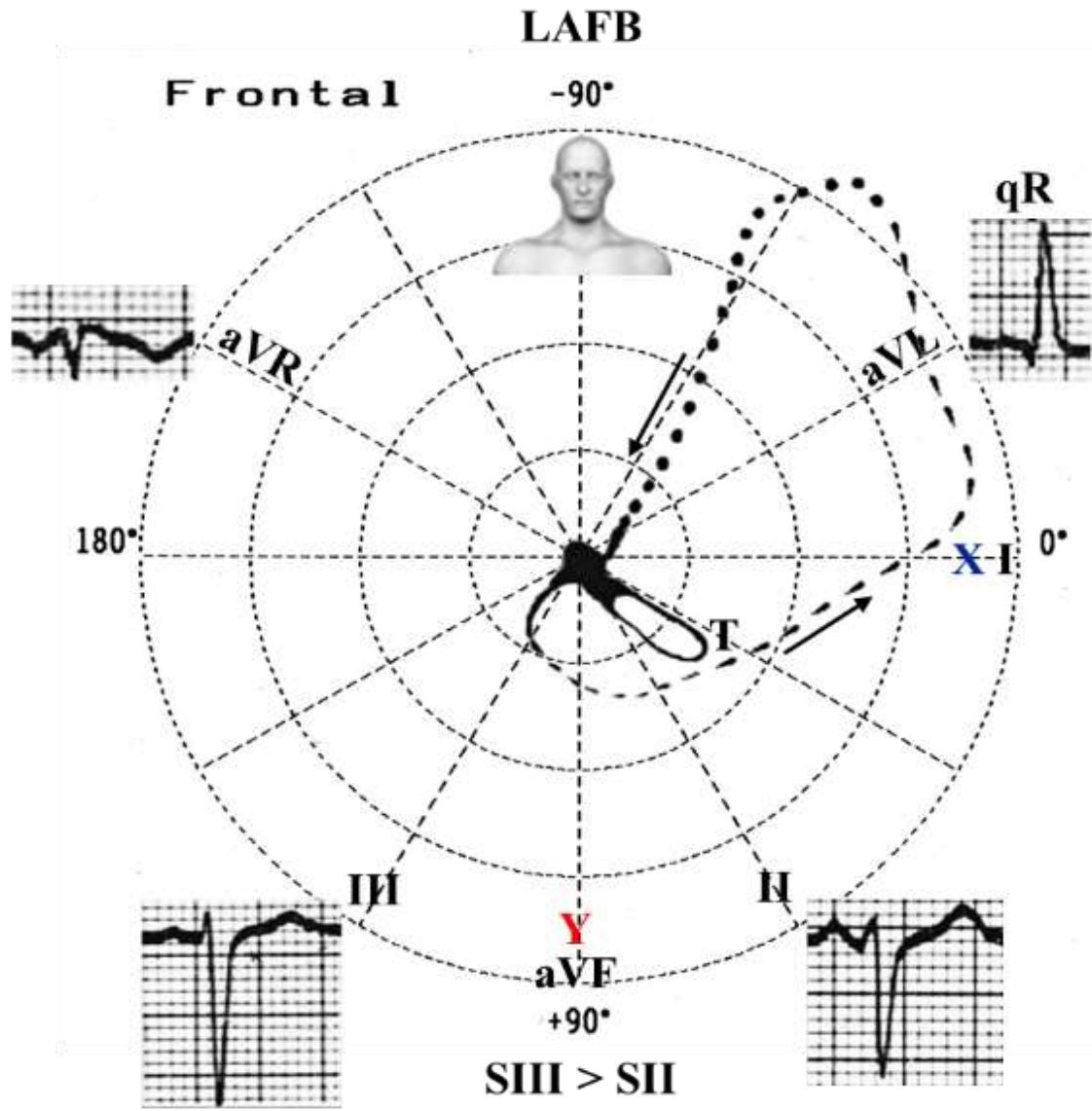
I – Superior or subpulmonary fascicle territory; II – Inferior or posterior-inferior fascicle territory; III – Middle fascicle territory Structural epicardial alterations in the right ventricular outflow tract (RVOT) are the substrate for the conduction anomalies in BrS. Electroanatomic mapping of endocardial 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 et al., 2018). 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, et al., 2015**).



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 Hisian system affected in BrS: “Right Superior Fascicular Block” (depolarization mechanism).

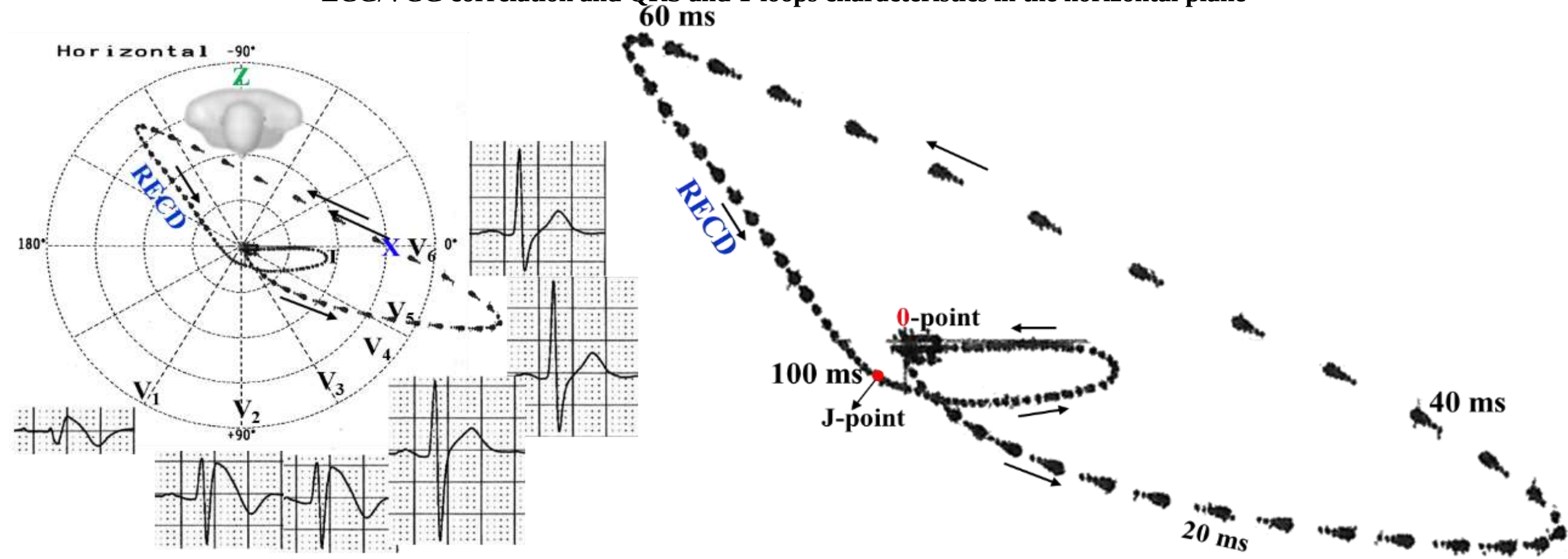
ECG/VCG differential diagnosis between right superior fascicular block (RSFB) and left anterior fascicular block (LAFB) (Pérez-Riera AR, et al. 2005)





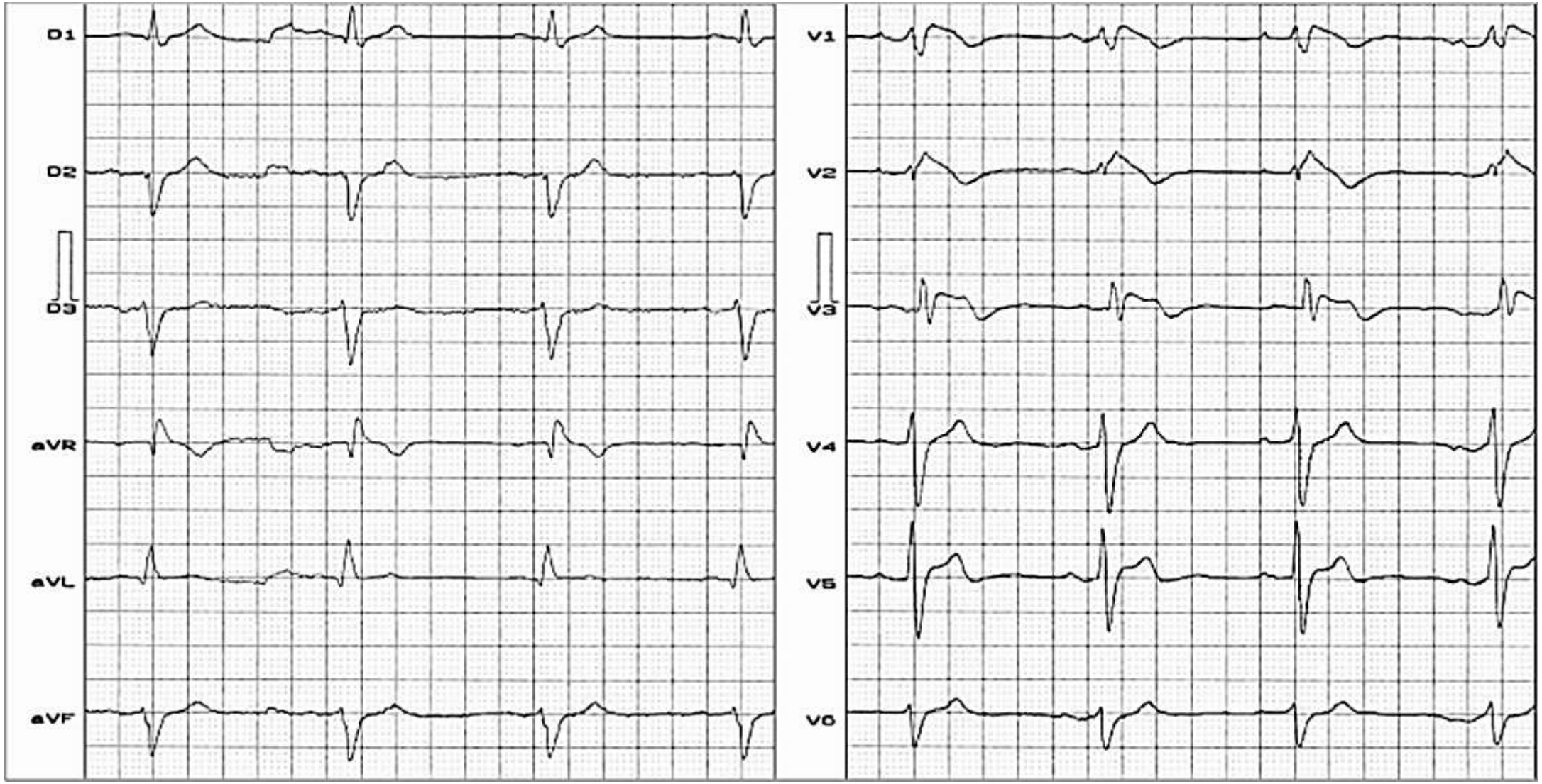
	LAFB	RSFB
Initial 10 ms vector of QRS loop	Heading downward and to the right	Heading downward and to the left
QRS morphology in I & aVL	qR pattern	Rs
SII/SIII ratio	SIII>SII	SII>SIII
Location of end conduction delay (ECD)	In the left superior quadrant when present	In the right superior quadrant (**Pastore CA et al. 1983**)
Prominent R wave in aVR (R-wave ≥ 0.3 mV)	Absent	It could be present and it is called aVR sign (**Babai Bigi MA, et al. 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 B, et al. 1989**).

ECG/VCG correlation and QRS and T loops characteristics in the horizontal plane



Initial 20 ms forces directed to front and leftward, rapid passage from left to right between 40ms to 60ms and the final 40ms with RECD in the posterior right quadrant (depolarization mechanism). The underlying electrophysiological mechanism in patients with BrS is delayed depolarization over the anterior aspect of the RVOT epicardium. 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 type 1 Brugada pattern. The QRS loop remembers the type C right ventricular overload typical of chronic obstructive pulmonary disease (COPD) or emphysema (**Luna filho B, et al. 1989**). Finally, the T-loop pointing left as a finger, with both efferent and afferent limbs with slow and similar speed inscription.

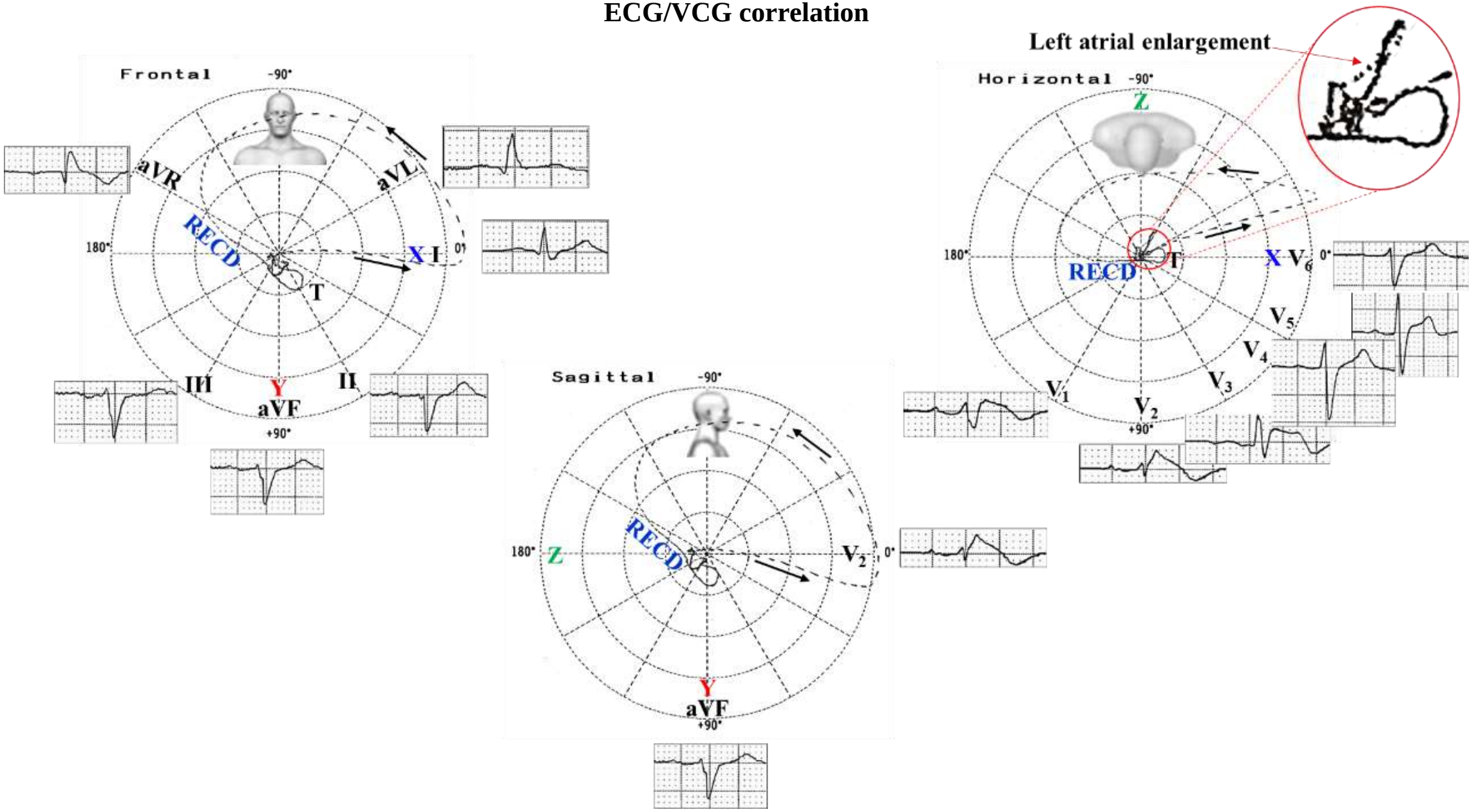
Name: MK; Age: 38 y/o; Gender: Male; Ethnic Group: Asian; Weight: 68 kg; Height: 1.70 m



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

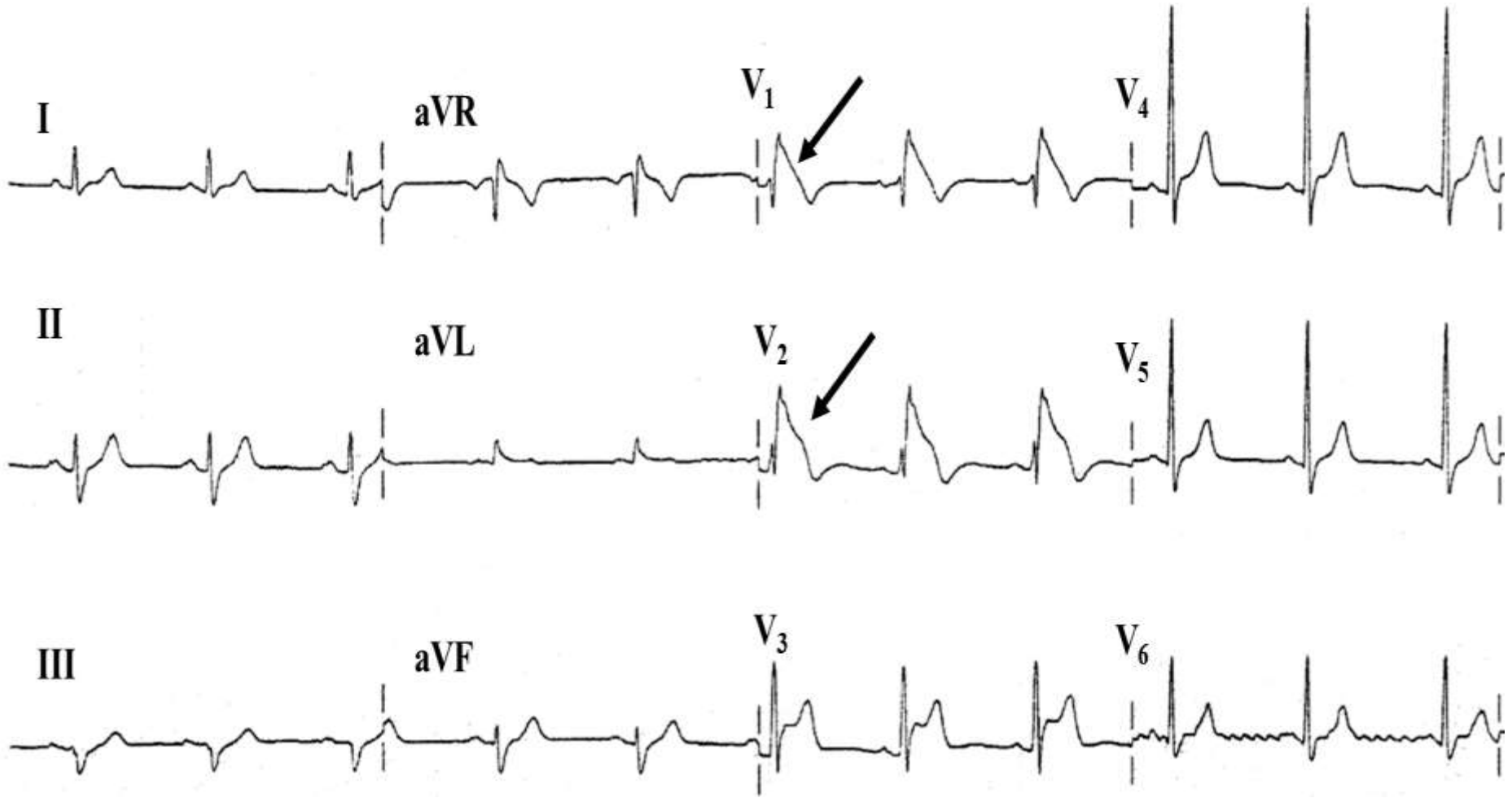
ECG diagnosis: Sinus bradycardia (HR <60 bpm), type 1 Brugada ECG pattern, prolonged QRS duration, aVR signal: final R wave of aVR lead >3 mm, fQRS in V1-V2. Extreme left axis deviation: Left anterior fascicular block? or Right superior fascicular block?

ECG/VCG correlation



FP: 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.

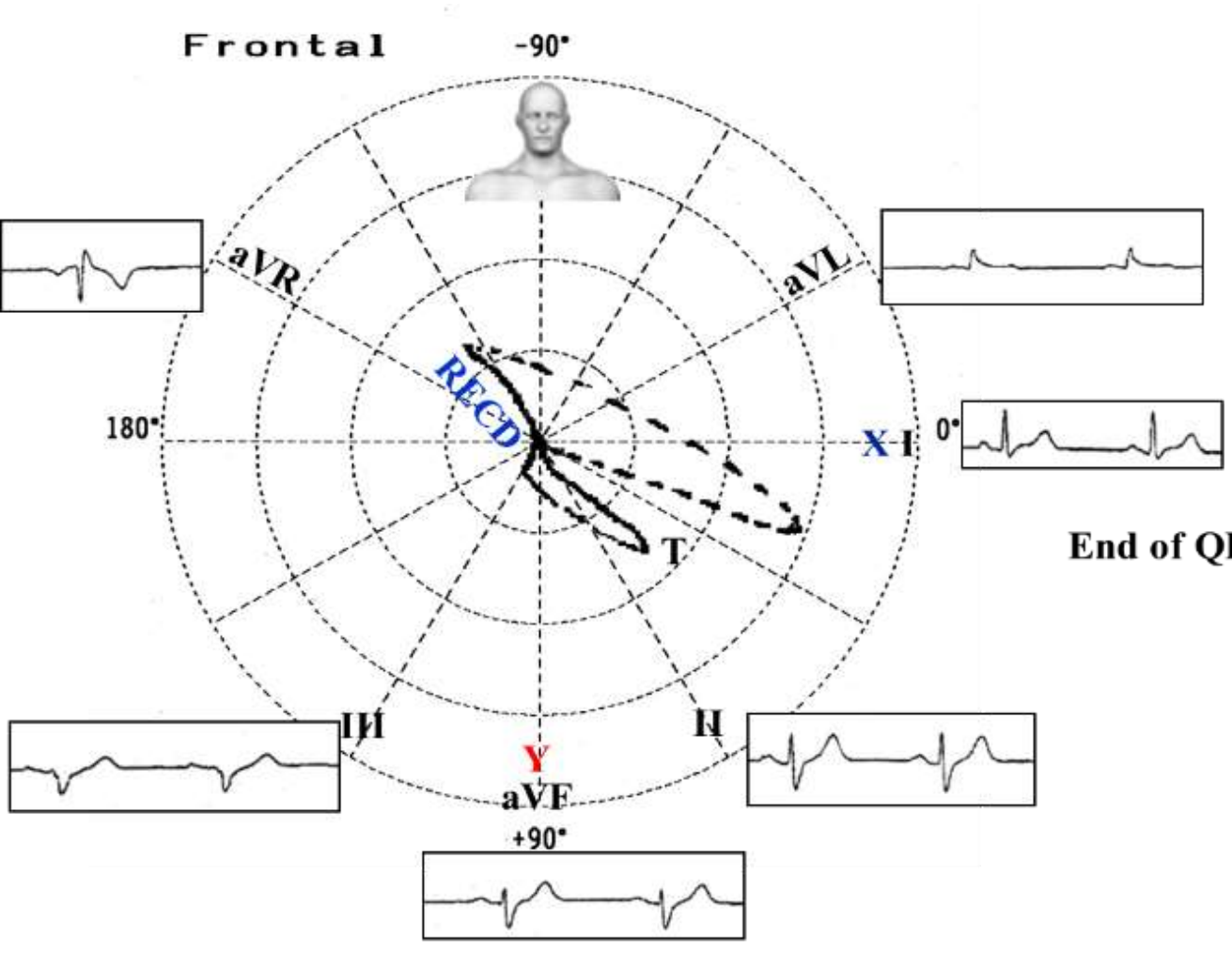
ECG with typical type 1 Brugada pattern and final part broadening by superior fascicle block of RBBB Male, 56-year-old patient (03/16/2002). He complained of atypical precordial pain

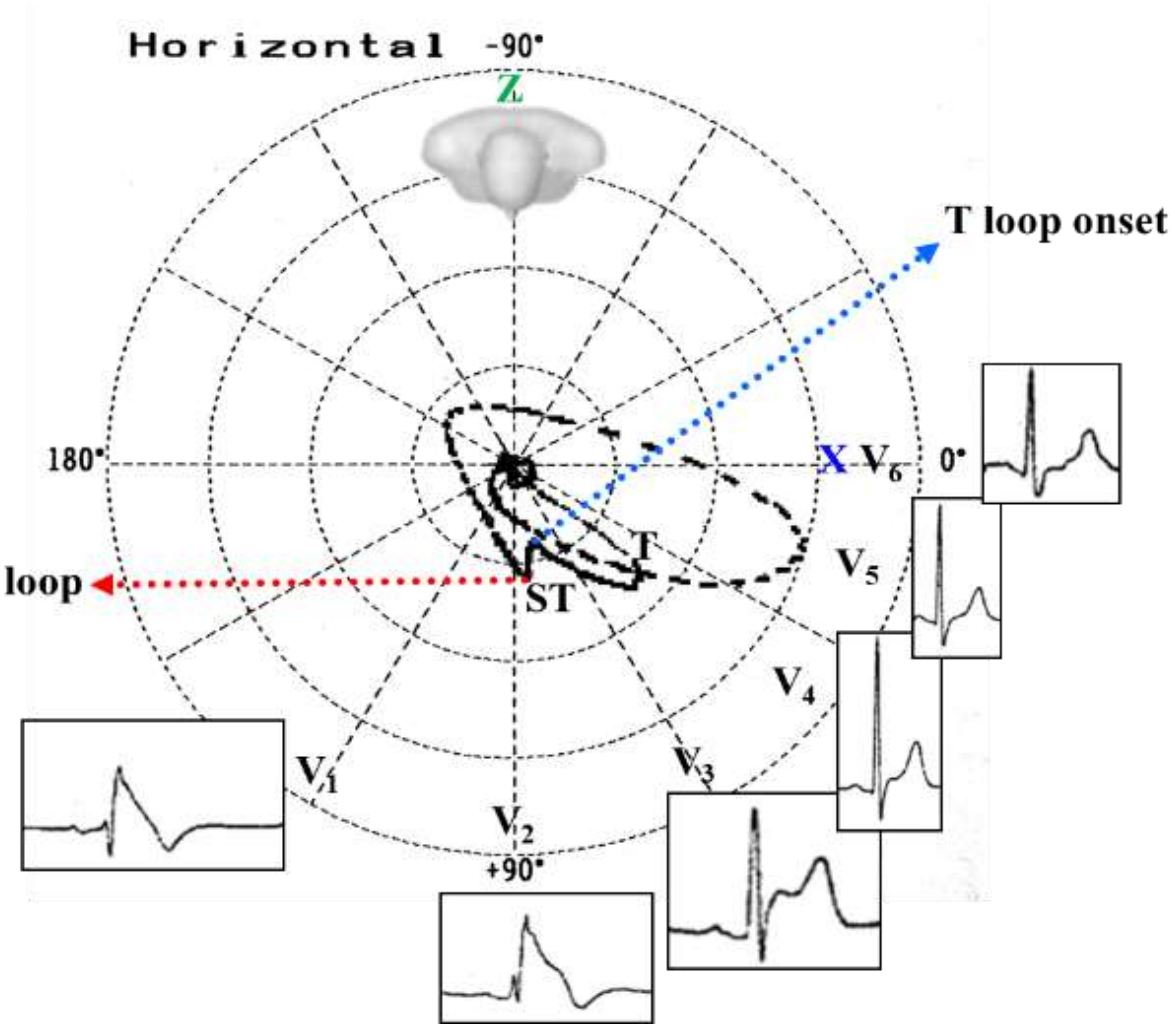


Final part widening by the superior, anterosuperior or subpulmonary fascicle of the RBB, type I according to our classification. Extreme shift of SAQRS to the left in the left superior quadrant –45º. ST segment and J point elevation with convex to the top morphology in V1 and V2 and saddle type in V3. aVR with D wave broadening: “crista delay” or RV outflow tract widening. S waves in left precordial leads V5-V6. 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.

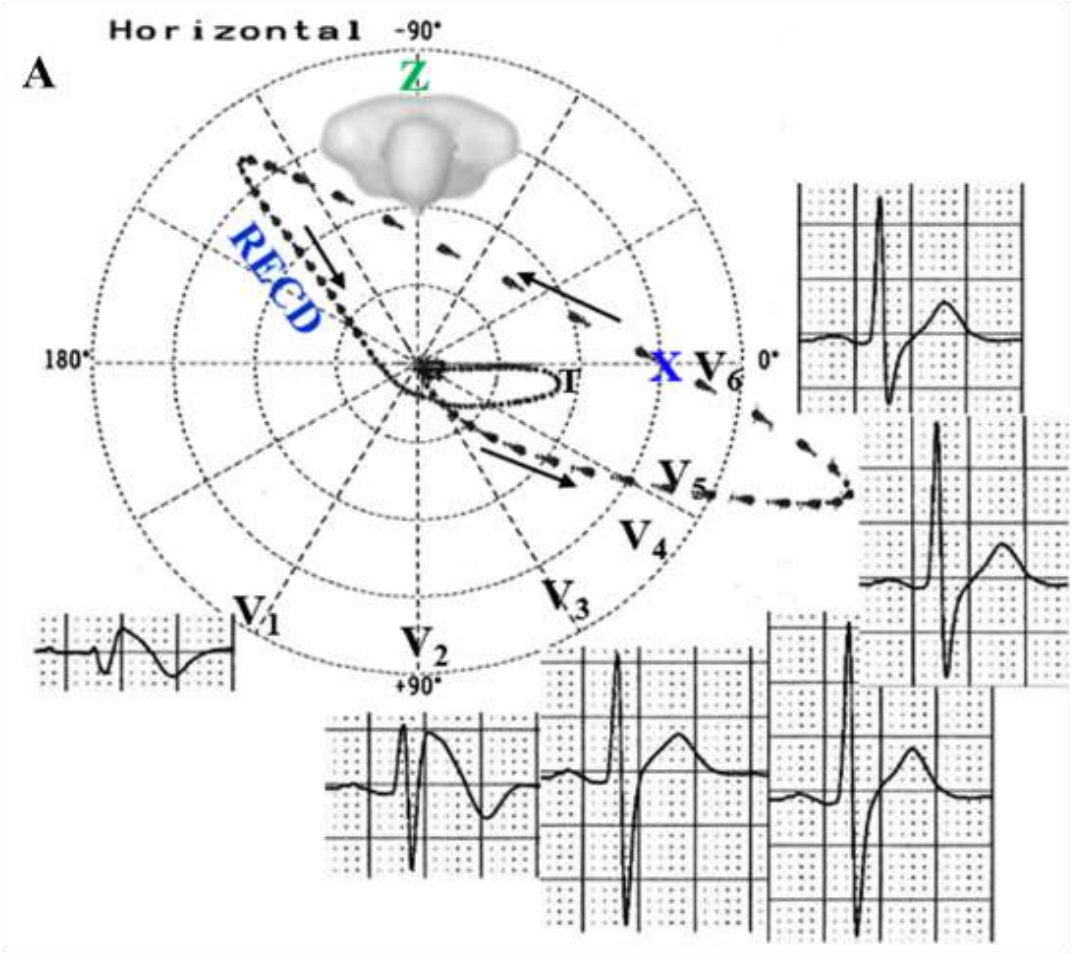
ECG/VCG correlation of BrS in the frontal and horizontal planes of the same patient



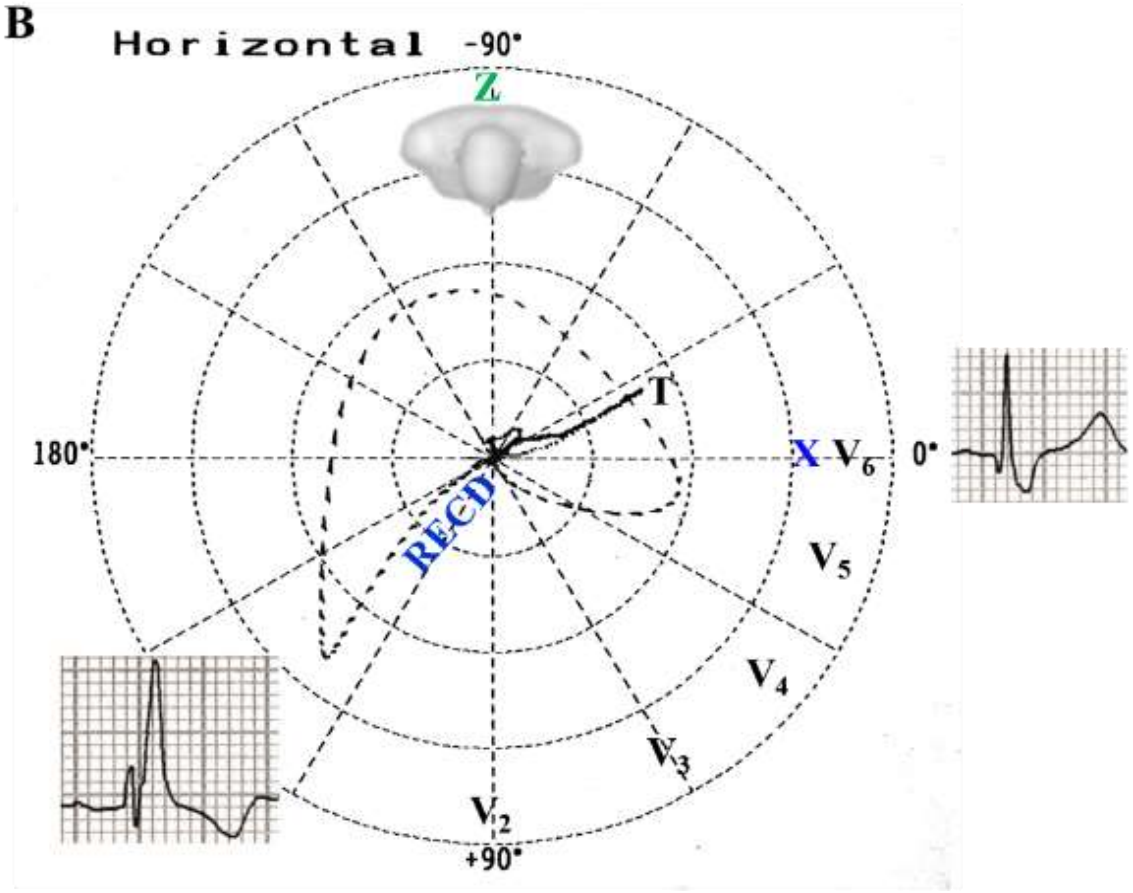


FP: Conclusion: it is the first VCG of Brugada syndrome shown in world literature. End conduction delay (ECD) by superior fascicle of the RBB. **Type IA of our classification.**

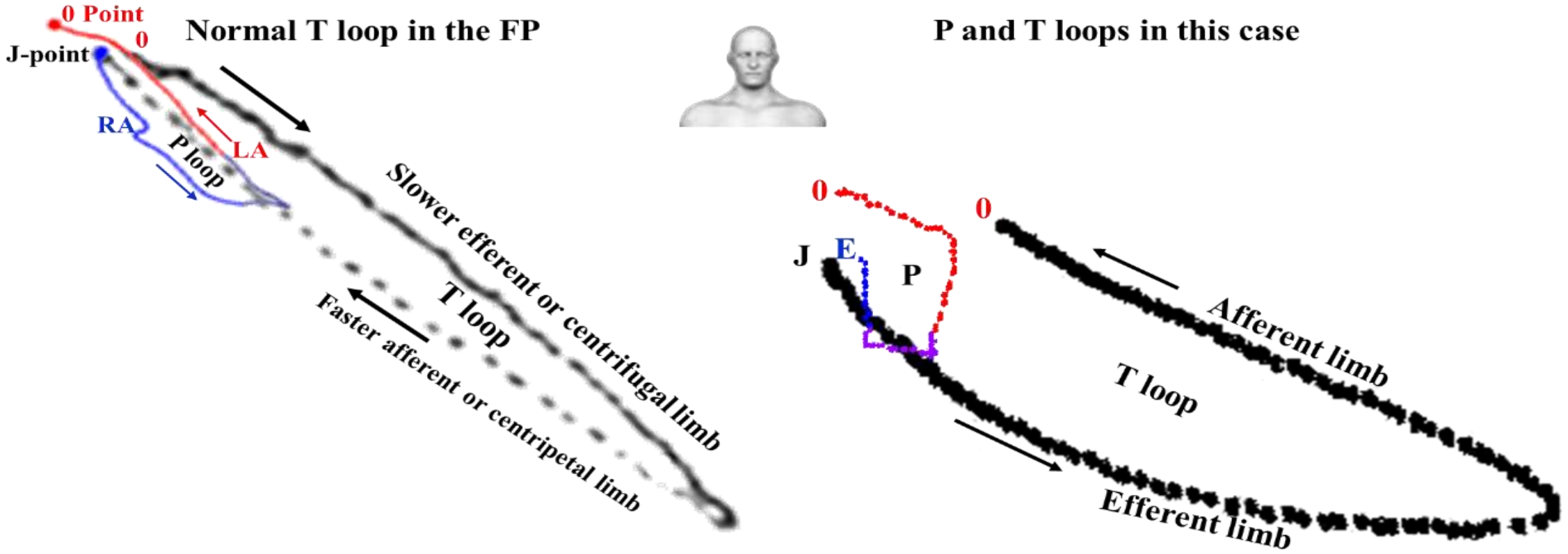
HP: The end of QRS loop does not coincide with T loop onset (as it occurs in normal conditions) since there is elevation both in the J point and the ST segment.



Truly RBBB pattern in the HP ECG/VCG correlation



A. Right End Conduction Delay (RECD) in the right posterior quadrant: depolarization mechanism. Sometimes T-loop is small, with rounded shape, efferent and afferent limbs with similar velocities.
B. Right End Conduction Delay (RECD) in the right anterior quadrant. T-loop has linear shape directed to back and leftward, and efferent limb with slower velocity related afferent limb.



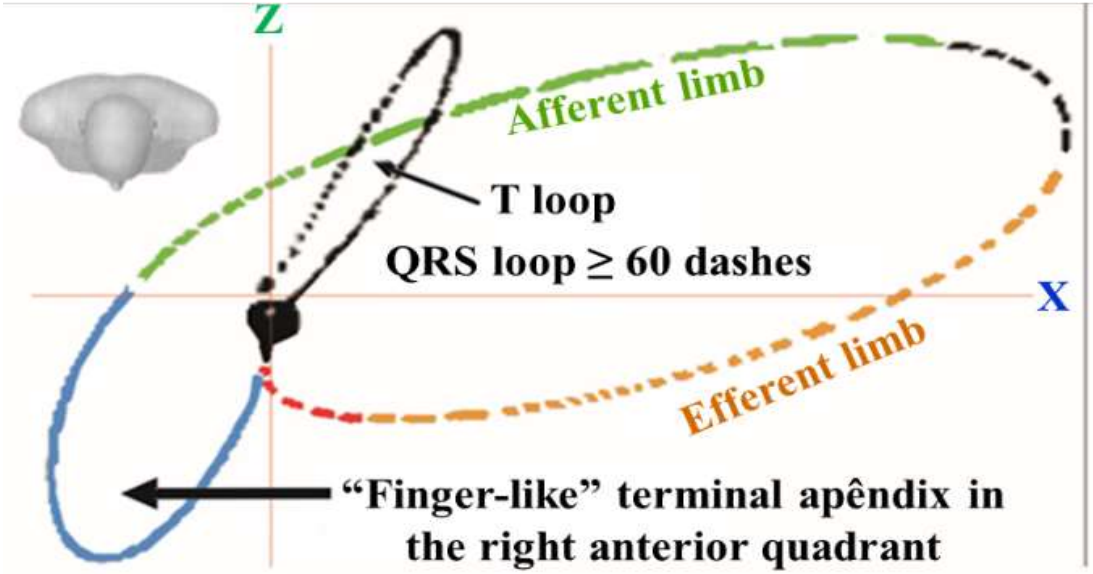
Normal T loop: J Point corresponds to the onset of T loop; **0 Point** corresponds to the end of T loop. Usually, the distance between both points is **≤0.1 mV.**

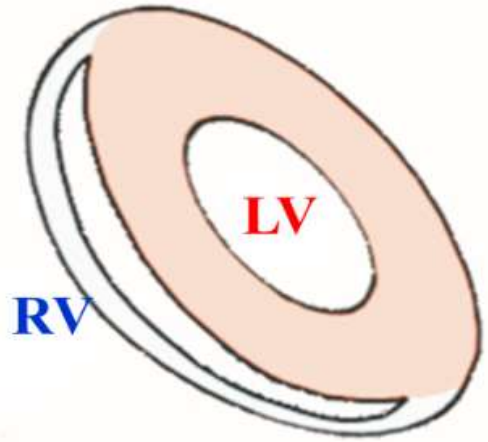
Morphology: elongated, elliptic or almost linear.
Direction: to the left or below around +36° (10° to 70°).
Magnitude: 0.35 mV (0.15 to 0.63 mV).
Rotation: clockwise or counterclockwise.
QRS/T angle: ≤36°.

This case: 0 and J points are distant each other (>0.1 mV), indicating in ECG, J point and ST segment elevation ≥0.2 mV (2 mm).

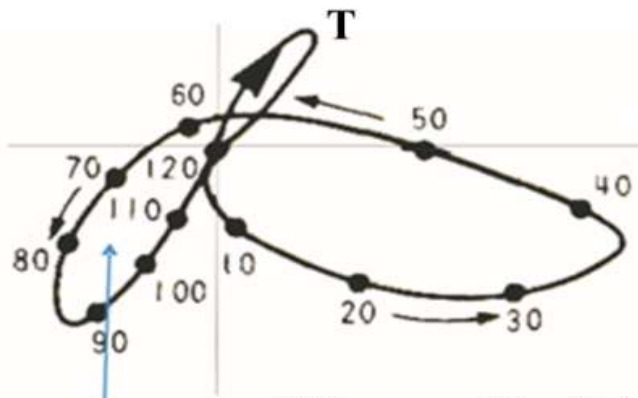
Efferent and afferent limbs with similar conduction velocities: repolarization mechanism present.

RBBB vectorcardiographic types in the horizontal plane

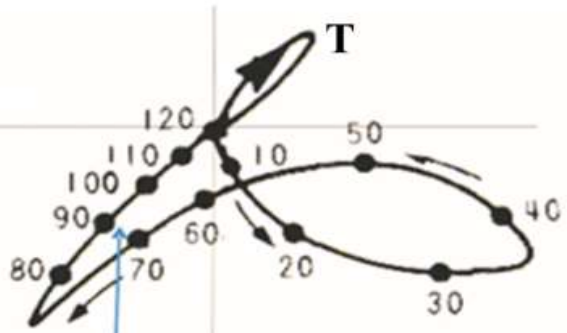




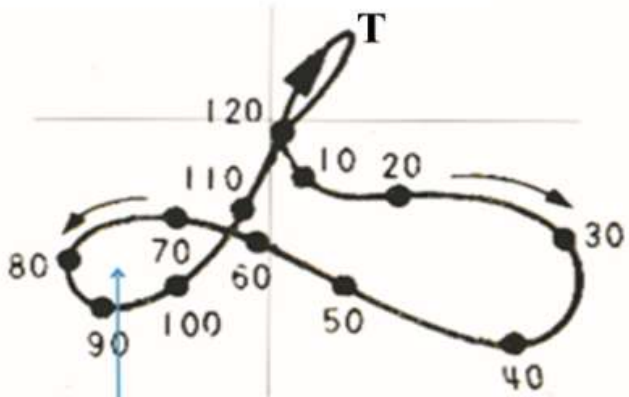
Grishman type
or type I



Cabrera type
or type II

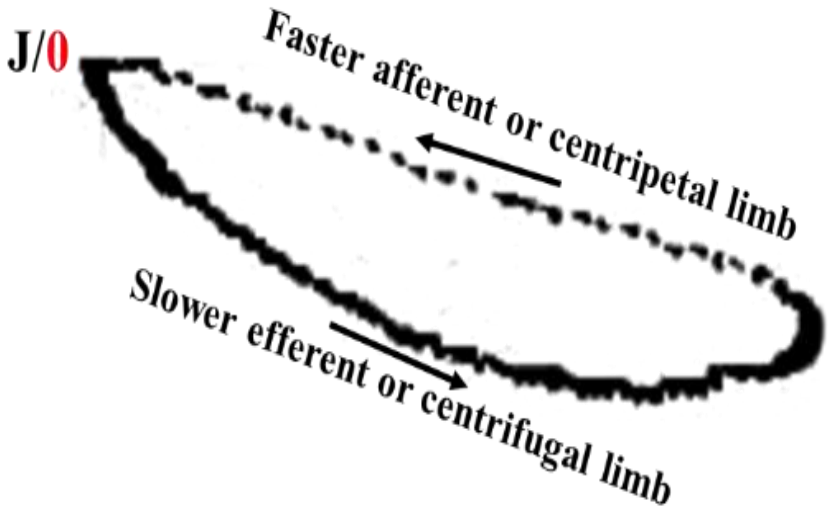


Type III or C



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

Normal T loop in the HP



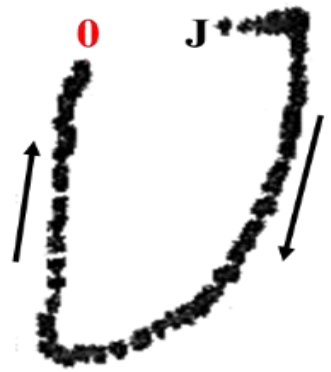
Normal T loop: J and 0 points are coincident.
Shape: elongated, elliptic or linear.
Direction: to the left and front, around 23° (-14° to +45°).
Efferent limb of slower inscription than the afferent one.
Rotation: nearly always counterclockwise, except for the linear morphology.
Magnitude: mean 0.34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

T loop in type 1 Brugada pattern

T loop in type 1 Brugada pattern
J and 0 points 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, BrS 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 type 1 Brugada 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**

Conclusions BrS is a clinical-electrocardiographic entity. Type 1 Brugada ECG pattern is the keystone in the diagnosis of BrS. Spontaneous coved-type is considered a noninvasive risk marker in BrS without requiring any further evidence of malignant arrhythmias.

Approach in this case

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 (**Postema PG, et al. 2009**).(www.brugadadrugs.org)

b) Avoidance of excessive alcohol intake.

c) Immediate treatment of fever with antipyretic drugs.

d) Quinidine may be considered in asymptomatic patients with a diagnosis of BrS with a spontaneous type I ECG(Class 2B). 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 SG, et al. 2013 Europace; Priori SG, et al. 2013 Heart Rhythm**).

e) 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 IIB) this is a currently case. On the other hand, following the proposed Shanghai Score System for diagnosis of ERS This patient is nondiagnostic because has only 2,5 points: ER ≥0.2 mV in ≥2 inferior and/or lateral ECG leads with horizontal/descending ST segment = 2 point+ Unexplained sudden cardiac death ,< 45 years in a first- or second-degree relative=0.5 point We proposed an electrophysiological study to this patient to decide if it is positive to implant a CDI. Then the patient disappeared.

Yan GX approach to early repolarization syndrome

When a patient with ER is seen, one must obtain detailed medical information, including age, gender, and past medical and family history. It is also important to pay attention specifically to the following high-risk ER patterns:

- ***J wave or J-point elevation amplitude ≥0.2 mV in inferior leads;***
- ***Bradycardia or pause-dependent J-wave augmentation;***
- ***Pause-dependent horizontal or down-sloping ST segment followed by flatten or inverted T waves***
- ***Short-coupled extrasystoles interrupting T wave peak; and***
- ***Short QTc interval.***

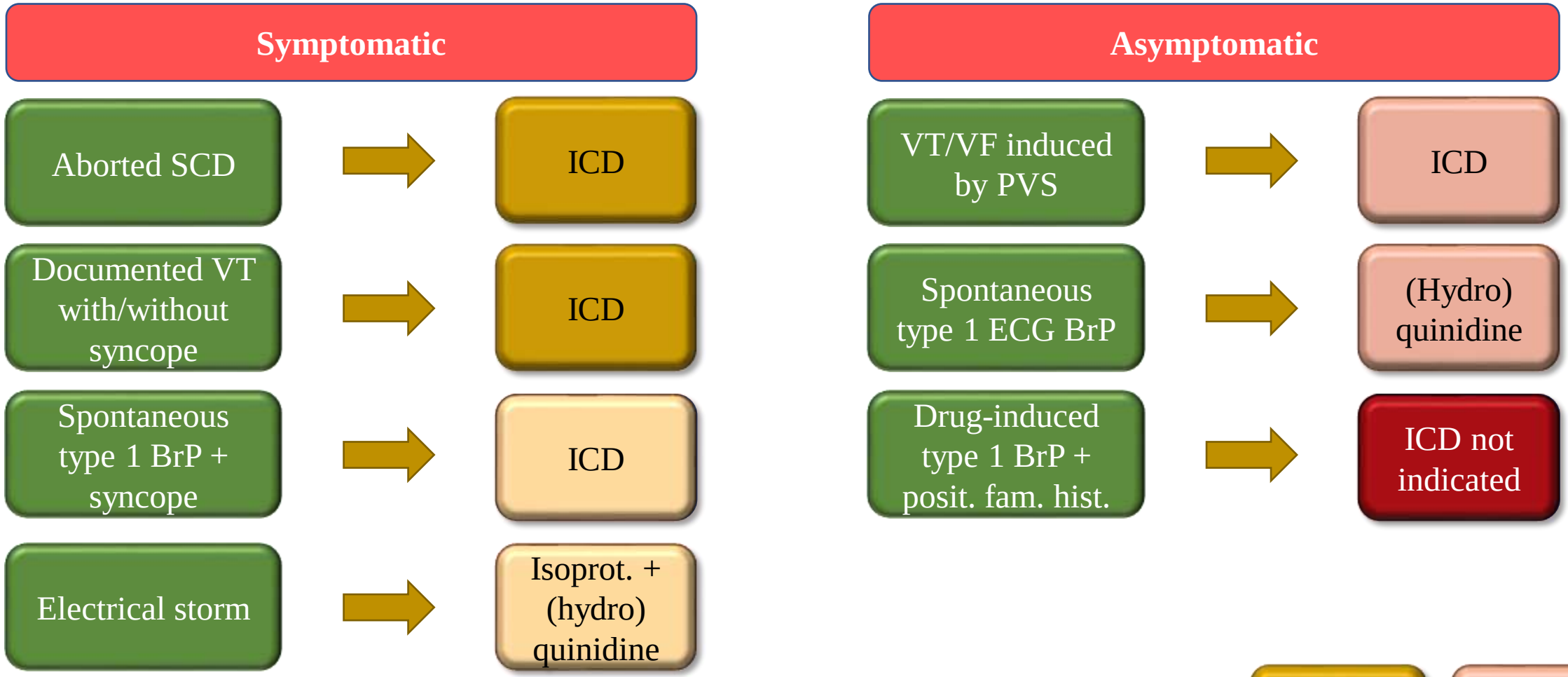
An asymptomatic patient Observation this patient has not ERS He/she has ERP

a. *Without a family history of unexpected SCD at age ≤45 years, do nothing.*
b. *With a strong family history for juvenile SCD, an implantable cardioverter defibrillator (ICD) may be considered if ER exhibits at least two of the high-risk patterns.*
c. *Otherwise, an implantable loop recorder and/or genetic testing is then considered. A syncope patient Vasovagal syncope is not uncommon in patients with "benign" ER patterns like tall R waves with upwardly concave ST elevation in left precordial leads.*
d. *If there is an absence of the high-risk ER patterns, do nothing.*
e. *If the syncope is highly suspected to be from malignant arrhythmias without other identifiable causes, ICD may be considered in the patient with a strong family history for SCD.*
f. *If the syncope is equivocal or there is absence of a strong family history for SCD, an implantable loop recorder and/or genetic testing should*

- *be* considered. Mutations in genes coding major cardiac ionic channels like sodium and calcium channels support early repolarization syndrome diagnosis. A patient with aborted SCD or documented polymorphic VT/VF.
- ICD is indicated if other reversible causes for SCD or documented sustained polymorphic VT/VF with or without syncope cannot be identified.
- For patients with early repolarization syndrome, class Ia and Ic sodium channel blockers, except quinidine and L-type calcium channel blockers, should be avoided.
- When ICD is indicated, quinidine, due to its additional property of inhibiting transient outward current (Ito), can substitute for ICD if the patient refuses ICD or ICD implantation is contraindicated. If quinidine is not available, cilostazol may be considered.
- Isoproterenol infusion can be useful in suppressing VT/VF storms in patients with ERS.

The key point in Yang approach to ER is to stratify the patient for SCD risk (**Yan GX, et al. 2016**).

Algorithm for diagnosis, risk stratification, and treatment of Brugada syndrome



Definitive diagnosis

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

General treatment measures

- Avoid drugs (brugadadrugs.org)
- Reduce fever immediately (paracetamol)
- Avoid excessive alcohol consumption

Class I | **Class IIb**

Class IIa | **Class III**

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