Case report from Dr. Josheph. Shaffu, et al

Case report

A 37-year-old man was admitted after syncope at rest with facial trauma.

He had been examined for bradycardia 6 years earlier, had a known complete right bundle branch block (RBBB) without apparent structural heart disease.

Familial background: His 2 brothers both had ECG patterns typical for Brugada syndrome, his mother had drug-induced Brugada syndrome. His father was from East Asian descent.

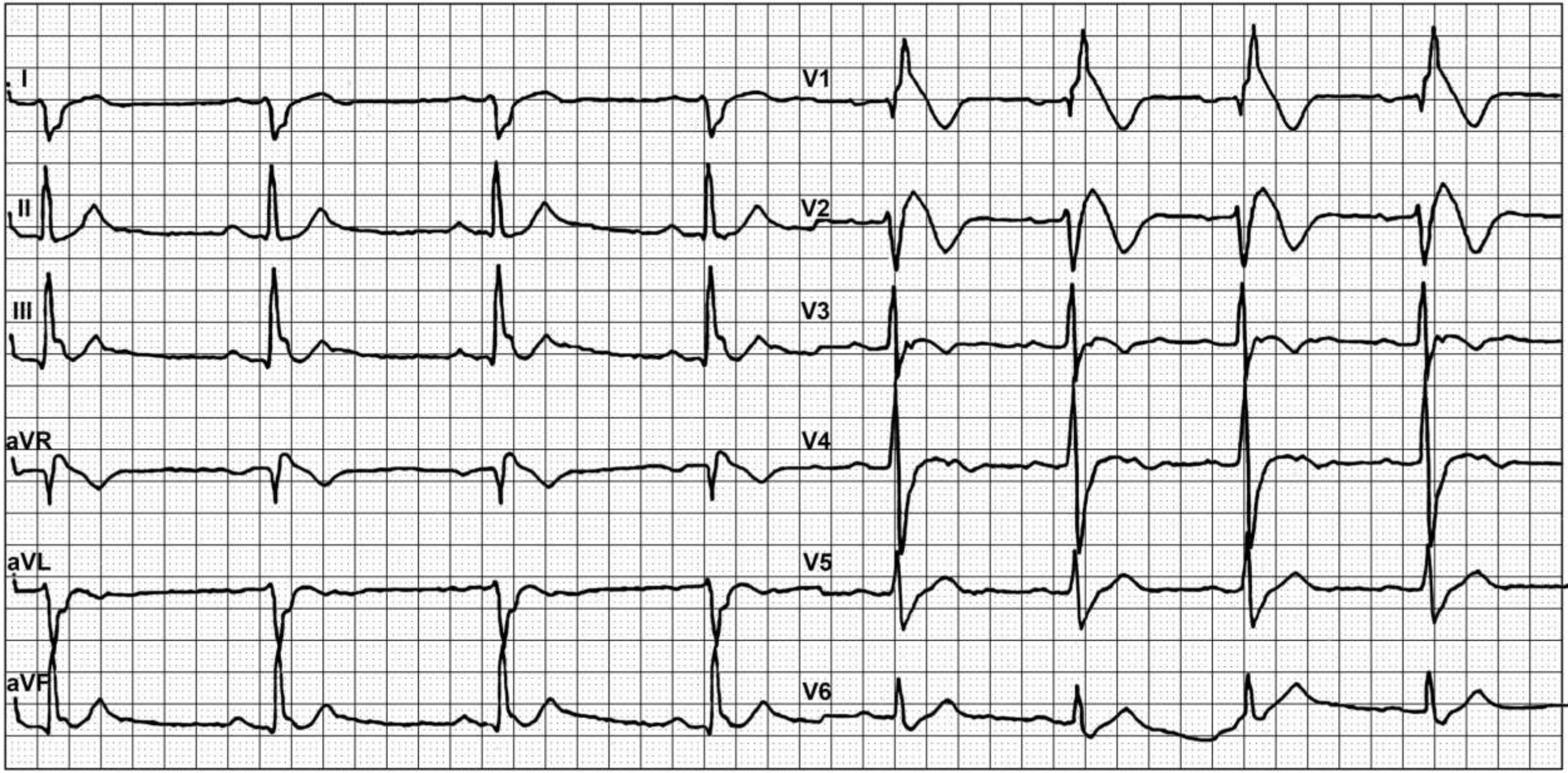
Electrocardiography (ECG) findings (next slide).

Echo: The left ventricular ejection fraction was 57%; the right ventricle had normal wall thickness, without dilatation,

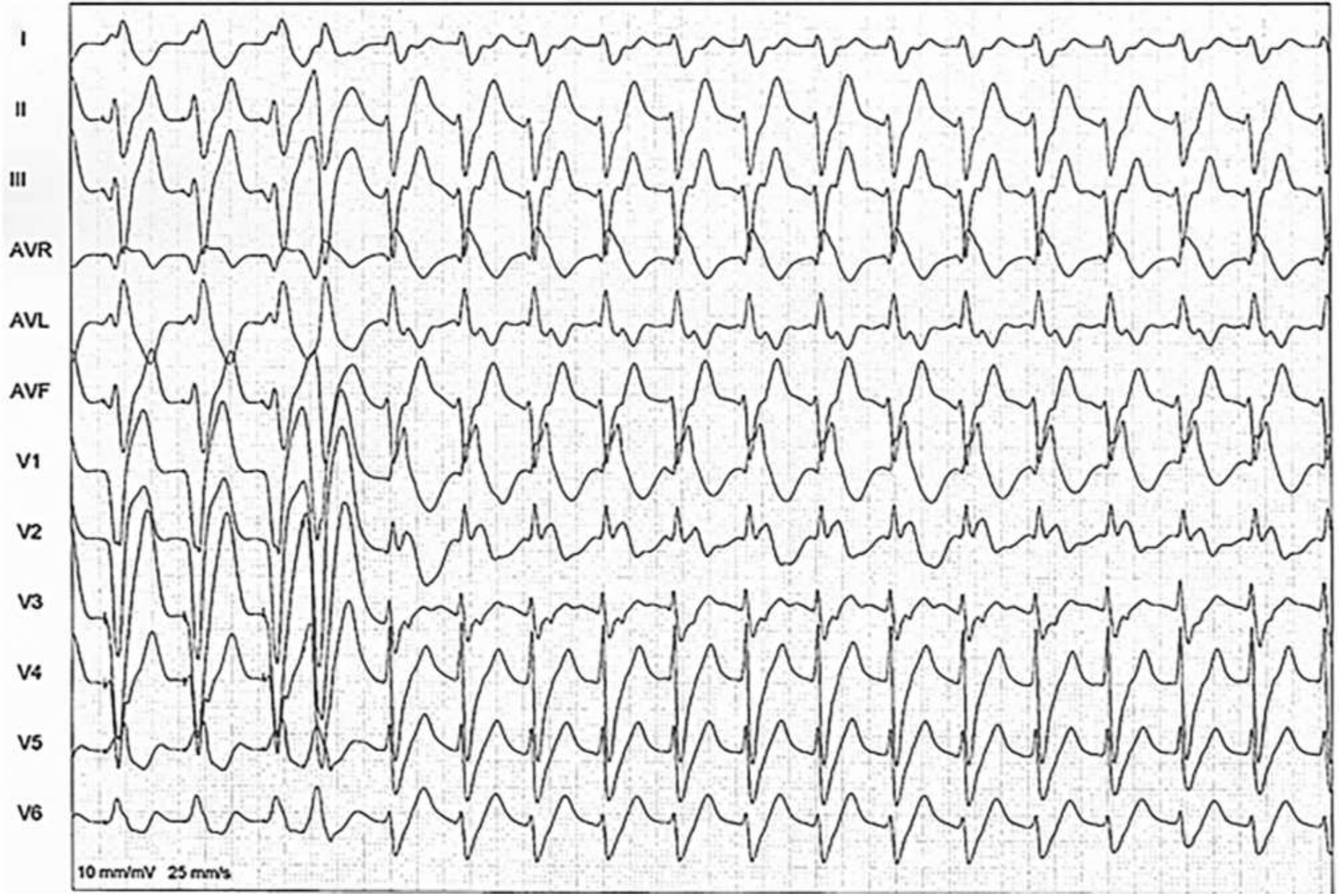
Cardiac magnetic resonance imaging (MRI) was entirely normal..

EEP: A monomorphic ventricular tachycardia was induced (second trace). Induction of symptomatic, sustained wide complex monomorphic tachycardia (cycle length 540ms) with one ventricular extra-stimulus, on a drive train of 600ms. The QRS width is 180ms, with left axis and positive complexes in V1 and V2 (*ECG* electrocardiography, *RBBB*) The tachycardia was a left sided posterior fascicular tachycardia and was easily ablated on a site with a Purkinje potential

A dual-chamber implantable cardioverter defibrillator was implanted, given the bradycardia and conduction disease. Genetic analysis showed 2 missense variants in the SCN5A gene, and one TMEM43 variant, all with unclear relation to his disease, given his East Asian roots. His gene belongs to the TMEM43 family.



Resting ECG Which is the diagnosis ?



Induction of symptomatic, sustained wide complex monomorphic tachycardia (cycle length 540ms) with one ventricular extra-stimulus, on a drive train of 600ms. The QRS width is 180ms, with left axis and positive complexes in V1 and V2 (*ECG* electrocardiography, *RBBB* right bundle branch block)

Questions:

1. **How to guide us with the mutations found ?: 2 missense variants in the SCN5A gene, and one TMEM43 variant,**
2. **Which is the clinical diagnosis?**
3. **Which is the ECG diagnosis ?**
4. **Is this ECG compatible with Brugada syndrome?**
5. **Are the anomalies in the right precordial leads a sign of another disease?**
6. **Is the ventricular arrhythmia related to Brugada syndrome?** A sustained induced monomorphic ventricular tachycardia (second trace). Induction of symptomatic, sustained wide complex monomorphic tachycardia (cycle length 540ms) with one ventricular extra-stimulus, on a drive train of 600ms. The QRS width is 180ms, with left axis and positive complexes in V1 and V2 (*ECG* electrocardiography, *RBBB*) The tachycardia was a left sided posterior fascicular tachycardia and was easily ablated on a site with a Purkinje potential

Colleagues opinions

Thanks for the interesting case. Baseline ECG shows Brugada pattern especially in V2.in addition there are J waves in the inferior leads which point to a higher risk for arrhythmias. In addition tall R in V1 and right axis deviation is noteworthy suggestive of additional fascicular disease ie left septal block and Left posterior fascicular block. The VT is certainly compatible with a left posterior fascicular focus.

To try and put this all together a SCN5A mutation might explain the Brugada pattern as well as conduction delay in the fascicles leading to reentrant fascicular tachycardias. We have described this in patients with bundle to bundle reentry and am aware of a case reported from Canada with SCN5A mutation and fascicular tachycardia

Professor Melvin M. Sheinman

https://www.youtube.com/watch?v=Fm3SwORdBS4

https://www.youtube.com/watch?v=j9w86h7QvJw

The past, present, and future of ablation with Dr. Melvin Scheinman

Dr Melvin A. Scheinman is Professor of Medicine and holds the Walter H. Shorenstein Endowed Chair in Cardiology at the University of California, San Francisco. He has received awards including the Paul Dudley White Award for Excellence in Teaching by the American Heart Association and the Distinguished Science Award of the American College of Cardiology. He grew up in Brooklyn, New York, and took his undergraduate degree at Johns Hopkins University, where he graduated first in his class. Postgraduate medical education included the Albert Einstein College of Medicine, residency training at the University of North Carolina (Chapel Hill), and cardiology training at the University of California, San Francisco Medical Center.

Dear Andrés : Prof Melvin Scheinman brought very interesting comments.

Actually his group (1) described SCN5A mutations in patients with idiopathic bundle branch reentry VT; however none of the BBR-VT cases was suggestive of the “Belhassen VT” type.

In addition I do not find trace of the case from Canada with SCN5A mutation and fascicular VT. Can you ask him to provide this reference.

Thanks.

Bernard Belahsen

1. **Roberts JD, Gollob MH, Young C, Connors SP, Gray C, Wilton SB, Green MS, Zhu DW, Hodgkinson KA, Poon A, Li Q, Orr N, Tang AS, Klein GJ, Wojciak J, Campagna J, Olgin JE, Badhwar N, Vedantham V, Marcus GM, Kwok PY, Deo RC, Scheinman MM. Bundle Branch Re-Entrant Ventricular Tachycardia: Novel Genetic Mechanisms in a Life-Threatening Arrhythmia.JACC Clin Electrophysiol. 2017 Mar;3(3):276-288. doi: 10.1016/j.jacep.2016.09.019.**

Very interesting and infrequent case

With Brugada pattern in V2, early repolarization in inferior leads, wide QRS complex, very tall R´ wave in V1 and epsilon wave in V3
In this case is important to rule out arrhythmogenic cardiomyopathy with important abnormalities in despolarization and repolarization, is possible to the MRI is currently negative because is an early stage of the myocardiopathy or it only presents with electrical abnormalities and not with fibrofatty infiltration which is a rare presentation and it has been associated with PKP2 mutation
The genetic findings and the left ventricle VT are more associated with LV involvement of arrhythmogenic cardiomyopathy

Thanks for sharing

Humberto Rodriguez -Reyes MD, FACC, AHA y HRS Member • Instructor RCP Básico, Avanzado y Avanzado para Expertos (BLS, ACLS, ACLS-EP) de la AHA • Presidente Sociedad Cardiovascular y del Metabolismo Presidente SOMEEC 2013-2014 • Coordinador del capítulo de Reanimación Cardio Pulmonar del Consejo de la Alianza contra la Muerte Súbita de la SIAC.
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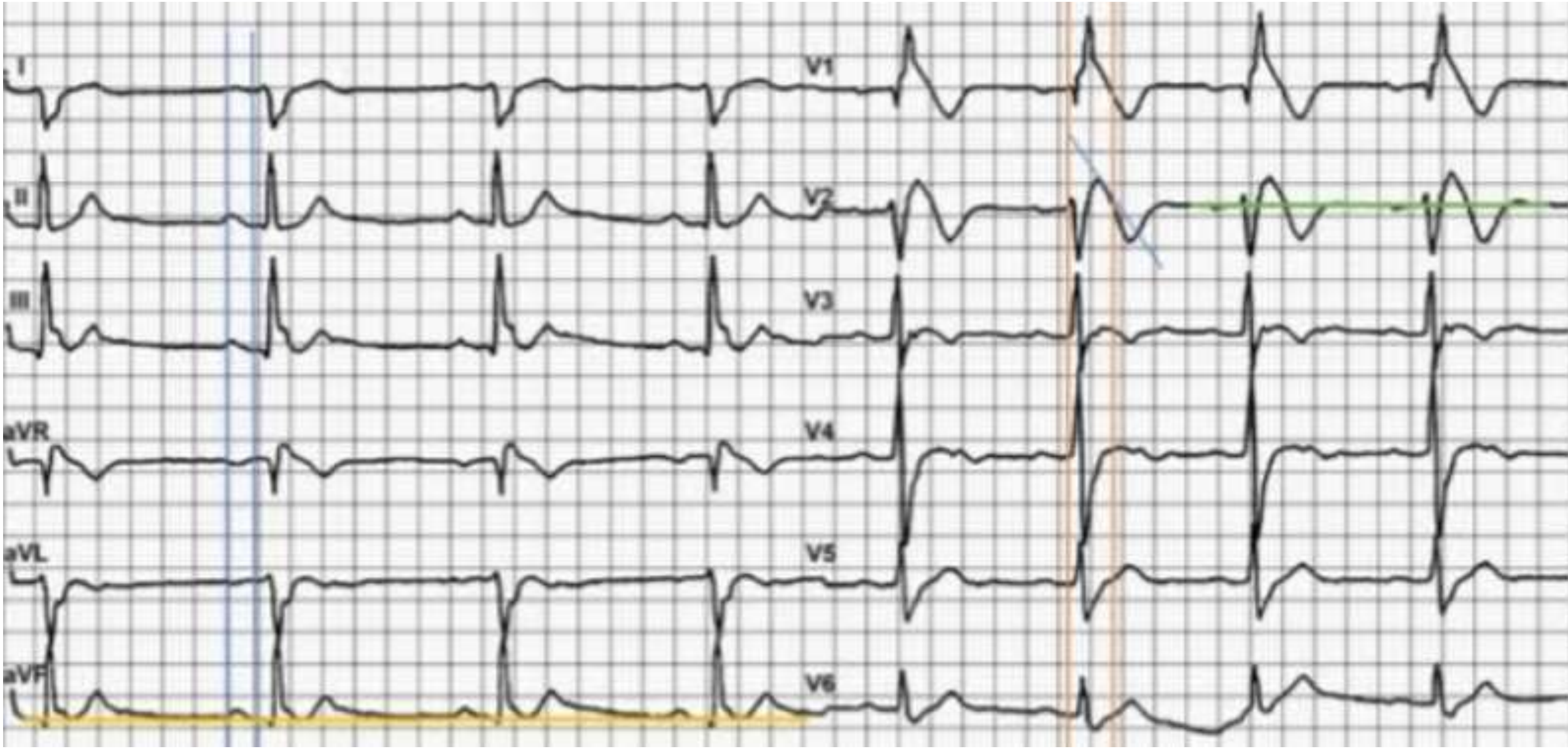
Aguas Calientes México

Buenas noches estimado Andrés! Good evening dear Andrés!

Spanish: Se trata de un paciente masculino, joven, con herencia y étnica positiva para síndrome de Brugada, que desarrolla síncope en reposo por probable TV -FV.. Su ECG muestra ritmo sinusal bradicárdico, bloqueo AV de 1° grado, probable bloqueo interauricular parcial, eje a la derecha alrededor de 110 °, QRS ancho con imagen de BRD like (bifascicular ? BRD +BFPS) en V2 es característico de patrón de Brugada tipo 1. En V1 hay onda R alta y ondas S en precordiales izquierdas, pero en las derechas en más ancho. El QTc es normal. No veo desniveles del ST en derivaciones inferiores ni ondas J, si un ST rápidamente ascendente. La onda R de aVR mide > 0.3 mV. Tampoco veo fQRS como otros signos de peor pronóstico para TV-FV. La TV inducida con un extra estímulo es monomórfica. Habitualmente las TV del BrS son polimorfas. Aunque hay descriptas mono morfas (Shimada y col. 1996). Me permito adjuntar un breve e improvisado diagrama sobre el ECG original.
Esta descripto el gen autosómico recesivo TRPM4 en el BrS (Janin y col. 2018) y el TRPM4 asociado al SCN5A en este síndrome (Gualandi y col. 2017). El siguiente comentario lo planteo como interrogante: pensando en BRD like, y habiendo hecho el estudio electrofisiológico, se podría haber intentado la "Maniobra del Dr Pablo Chiale" y así desenmascarar al todo el BRD y el patrón de Brugada?
Saludos respetuosos y muy cordiales estimado Profesor, esperemos las opiniones de quienes de verdad saben mucho y desde luego su acostumbrada resolución final.
Dr Juan Carlos **Manzzardo,** Mendoza-Argentina

Enghish: This is a male patient, young, with positive ethnicity and inheritance for BrS, who develops syncope at rest due to probable TV-FV. His ECG shows sinus rhythm, bradycardic 1st degree AV block, probable partial interatrial block, QRS axis around +110°, QRS width with RBBB image like (bifascicular? RBBB+ LSFB) in V2 is characteristic of Brugada type 1 pattern. In V1 there is high R wave and S waves in left precordial, but in the right in more width. The QTc is normal. I do not see ST differences in inferior derivations or J waves, if a rapidly rising ST. The R wave of aVR measures> 0.3 mV. Nor do I see fQRS as other signs of worse prognosis for TV-FV. TV induced with extra stimulation is monomorphic. Usually the TVs of the BrS are polymorphic. Although there are described morphorphic (**Shimada M1, Miyazaki T, Miyoshi S, Soejima K, Hori S, Mitamura H, Ogawa S.Sustained monomorphic ventricular tachycardia in a patient with Brugada syndrome.Jpn Circ J. 1996 Jun;60(6):364-70**). I allow myself to attach a brief and improvised diagram about the original ECG.(see next slide) The autosomal recessive TRPM4 gene in BrS (Janin et al 2018) and TRPM4 associated with SCN5A in this syndrome (Gualandi et al 2017) are described. The following comment I pose as a question: thinking of RBBB like, and having done the EPS, could have tried the "Chiale manouver" and thus unmask the whole RBBB and the Brugada pattern?
Regards respectful and very cordial esteemed Professor, let's hope the opinions of those who really know a lot and of course their usual final resolution


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

English

Dear Juan Carlos Thank you for your lucid analysis As always denoting your intelligent mind. Your analysis of the case seemed very complete to me. I will only make a few observations to see if you agree You commented that the electric axis of the QRS is around +110° The QRS pattern in aVR is of type QR with the Q discretely deeper than the height of the R that follows it, however the latter is much wider than the Q in virtue of the CRBBB that causes terminal conduction delay located forward and to the right just in the area of the RVOT faced by aVR, therefore, the area of the final R is greater than the area of the initial Q consequently I think that the axis is minimally to the right of +120 °. Not discreetly to the left (+ 110 °,) I observed with increase the voltage of the R of aVR and I had the impression that it does not exceed 2mm, consequently, I think it is not present the aVR sign, (**Babai Bigi MA, et al., Heart Rhythm, 2007**). For those who do not know or do not remember these authors show the existence of a significant correlation between a prominent R wave in aVR (aVR sign) and the risk of development of arrhythmic events in BrS. In the presence of BrS, the prominent R wave in primary aVR may further reflect a delay in right ventricular conduction of the RVOT and, subsequently, greater electrical heterogeneity, which in turn is responsible for an increased of arrhythmia´s risk. The aVR sign was defined as R wave **≥ 0.3 mV or R / q> / = 0.75 in the aVR** lead. In other words, this sign is based on the depolarization theory of the BrS where there is a final disturbance conduction on RVOT because of the minor expression of the connexin 43 contracted by Naademanee et al .(**Nademanee K, et al Journal of the American College of Cardiology. 2015**.) You comment that the recessive TRPM4 gene in the BrS is described, but you got confused because the mutation found is TMEM43 and not TRPM4. Please, look well in the description of the story.

Regarding your question, if it will not be interesting to perform “Chiale maneuver”, I answer that it is not necessary because in this case the CRBBB does not eclipse the Type 1 Brugada pattern as seen in V2. The definition of the type 1 pattern currently does not require that it be present in two or more right precordial leads, as long as it has one for the diagnosis of the syndrome (**Priori SG1 et al., Heart Rhythm, 2013**).

An affectionate hug and thanks for your opinion. Andrés.

Spanish

Querido Juan Carlos Gracias por tu lucido análisis Como siempre denotando tu mente inteligente. Tu análisis del caso me pareció bien completo Apenas haré mínimas observaciones para ver si concuerdas

1. Dices que el eje eléctrico del QRS está por vuelta de los 110° El patrón en aVR es de tipo QR con la Q discretamente más profunda que la altura de la R que le sigue, no obstante esta última es mucho más ancha que la Q en virtud del BCRD que ocasiona retardo final de conducción localizado adelante y a la derecha justamente en el área del RVOT enfrentada por aVR, por lo tanto, el área de la R final es mayor de que el área de la Q inicial consecuentemente pienso que el eje está mínimamente a la derecha de +120°. Y no discretamente a la izquierda(+110°,)
2. Observé con aumento el voltaje de la R de aVR y tuve la impresión que no pasa de 2mm, consequetemte pienso que no está presente o signo de Babai Bigi MA, (**Babai Bigi MA, et al. Heart Rhythm. 2007**). Para los que no saben o no se recuerda estos autores muestran la existencia de una correlación significativa entre una onda R prominente en aVR (signo aVR) y el riesgo de desarrollo de eventos arrítmicos en el síndrome de Brugada. En presencia de BrS, la onda R prominente en aVR principal puede reflejar más un retraso en la conducción ventricular derecha del tracto de salida y, posteriormente, una mayor heterogeneidad eléctrica, que a su vez es responsable de un mayor riesgo de arritmia. El signo aVR se definió como onda R ≥ 0,3 mV o R / q> / = 0,75 en la derivación aVR. En otras palabras este signo se basa en la teoría de la despolarización del Brugada donde existe un disturbio final de conducción justamente por la menor expresión de la conexiona 43 en contrada por Naademee .
3. Tu comentas que está descripto el gen TRPM4 recesivo en el Brugada más te confundiste porque la mutación encontrada es TMEM43 y no TRPM4 fijate bien en la descripción de la historia.
4. En relación a tu pregunta si no será interesante tentar la maniobra de Chiale te respondo que no es necesario porque en este caso el BRD no eclipsa el patrón Brugada como se ve en V2. La definición del patrón tipo 1 actualmente no exige que esté presente en dos o más derivaciones precordiales derechas basta que tenga una para el diagnóstico del síndrome (**Priori SG1 et al. Heart Rhythm. 2013).** Tu dices “QRS ancho con imagen de BRD like (bifascicular ? BRD +BFPS)” Me parece que si tiene bloqueo AV de primer grado deberías decir “QRS ancho con imagen de BRD like (trifascicular ? BRD +BFPS)”

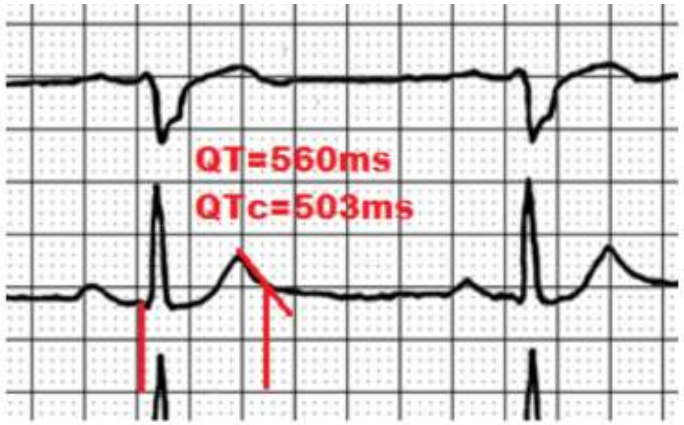
Un abrazo afectuoso y gracias por opinar
Potro/Andrés.

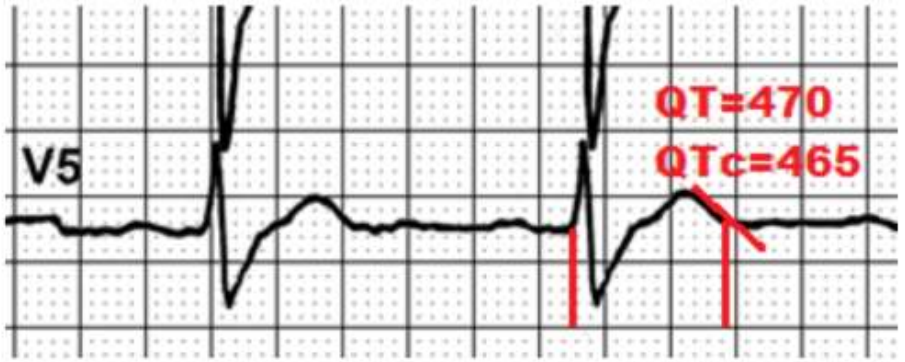
Answer to questions from Adail Paixão Almeida MD

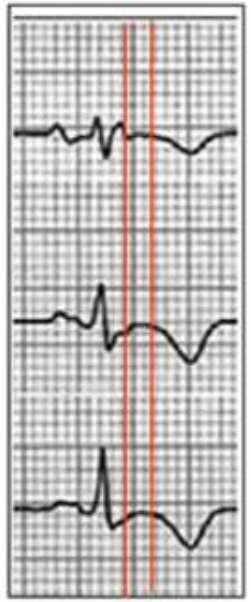
a. Which is the clinical diagnosis? A: **Unexplained syncope at rest We don't know the subjacent cause. Possible VT**
b. Which is the clinical diagnosis? **Syncope episode of unknow origin**
c. Which is the ECG diagnosis? **Complete right bundle branch block, spontaneous Type 1 Brugada pattern with "Lambda shape" in V1 and typical in V2, parietal block, presence of epsilon wave in V3, possible long QT interval,** (1-3)
d. EPS: **Monomorphic sustained ventricular tachycardia type idiopathic fascicular ventricular tachycardia**
e. Are the anomalies compatible with Brugada syndrome? **Yes see next slide**
f. Are the anomalies in the right precordial leads compatible with Brugada syndrome? **Yes**
g. Are the abnomalities in the right precordial leads compatible with another entity? **Maybe ARVC/D Gene TMEM43 mutation SCN5A BrS**
h. Is the arrhythmia compatible with BrS? **Not frequently. In BrS the typical VT is polymorphic VT/VF. The event of SMVT is observed in ARVC but with LBBB pattern**

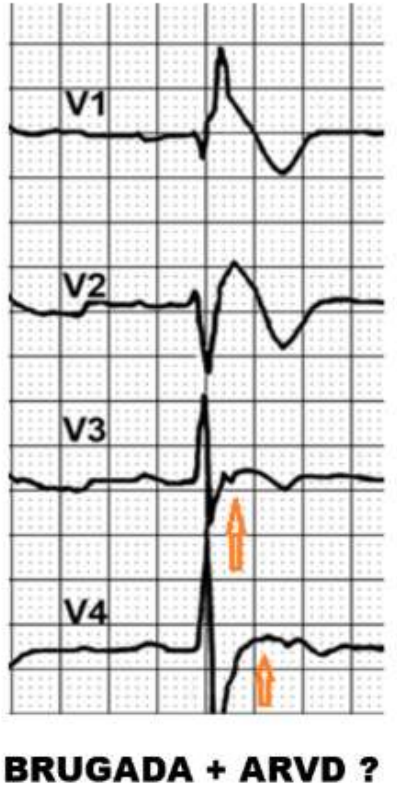
Adail Paixão Almeida

1. Martini B, Cannas S, Nava A. Brugada by any other name? Eur Heart J. 2001 Oct;22(19):1835-6.
2. Pérez Riera AR, Antzelevitch C, Schapacknik E, Dubner S, Ferreira C.Is there an overlap between Brugada syndrome and arrhythmogenic right ventricular cardiomyopathy/dysplasia?J Electrocardiol. 2005 Jul;38(3):260-3.
3. Hoogendijk MG1.Diagnostic dilemmas: overlapping features of brugada syndrome and arrhythmogenic right ventricular cardiomyopathy.Front Physiol. 2012 May 23;3:144. doi: 10.3389/fphys.2012.00144.









Adail Paixão Almeida MD Vitoria da Conquista Bahia Brazil Nick name "Painho" (Mean: Caring way of Bahians and Northeastern call their parents. His electrophysiologist son calls Adail Painho.

He holds a medical degree from the Federal University of Ceará (1974). He is currently an enrolled physician of the Regional Council of Medicine of the Bahia State. Has experience in the area of Cardiology with Specialization in Clinical Cardiology and Ergometry. Titled by the Brazilian Society of Cardiology. Registration in Internal Medicine in CFM and Intensivist. Lecture and regular speaker at state and regional events of SBC / Ba and AMB / ABM / Ba. Professional Member of the American Heart Association

Final comment by Andrés Ricardo Pérez-Riera, MD, PhD

Laboratório de Delineamento de Estudos e Escrita Científica da Faculdade de Medicina do ABC, Santo André, SP, Brazil

Laboratory of Study Design and Scientific Writing of the Faculty of Medicine of ABC, Santo André, SP, Brazil

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

https://ekgvcg.wordpress.com/

Gene	Protein	Frequency in ARVC	Structure	Mutation Type	Inheritance	Phenotype	OMIM Entry	Genotype/ Phenotype
TMEM43	LUMA	<1%	Nuclear envelop. Intecalated disk, sarcolemma	Missense Splice-site	AD	ARVC EDMD Emery-Dreifuss muscular dystrophy-related myopathy 7 (5)	ARVC5	Involvement, High risk SXD and HF, Poor R wave progression on ECG

(1. Gandjbakhch E. et al. J Am Coll Cardiol 2018; 2. Merner ND, et al. Am J Hum Genet 2008; 3. Hodgkinson, et al. Clin Genet 2013.4; 4. Christensen, et al. Clin Genet 2011.5; 5. Liang WC, et al. Ann Neurol 2011; 6. Haywood AF, et al. Eur Heart J. 2013)

This gene belongs to the TMEM43 family. Defects in this gene are the cause of familial arrhythmogenic right ventricular dysplasia type 5 (ARVD5), also known as arrhythmogenic right ventricular cardiomyopathy type 5 (ARVC5). Arrhythmogenic right ventricular dysplasia is an inherited disorder, often involving both ventricles, and is characterized by MVT, with LBBB patternm heart failure, SCD, and fibrofatty replacement of cardiomyocytes. This gene contains a response element for PPAR gamma (an adipogenic transcription factor), which may explain the fibrofatty replacement of the myocardium, a characteristic pathological finding in AC. May have an important role in maintaining nuclear envelope structure by organizing protein complexes at the inner nuclear membrane. Required for retaining emerin at the inner nuclear membrane (By similarity). Emery-Dreifuss muscular dystrophy 7, autosomal ARVC, type 5

From Emery-Dreifuss muscular dystrophy 7, autosomal dominant (EDMD7): A form of Emery-Dreifuss muscular dystrophy, a degenerative myopathy characterized by weakness and atrophy of muscle without involvement of the nervous system, early contractures of the elbows, achilles tendons and spine, and cardiomyopathy associated with cardiac conduction defects. [MIM:614302] **(Liang WC, et al. Ann Neurol 2011).**

ARVD, familial, 5 (ARVD5): A congenital heart disease characterized by infiltration of adipose and fibrous tissue into the RV and loss of myocardial cells, resulting in ventricular and supraventricular arrhythmias. [MIM:604400] Cytogenetic Location: 3p25.1, which is the short (p) arm of chromosome 3 at position 25.1

Other names for this gene

ARVC5: In 83 affected individuals with ARCD-5 (604400) from 15 unrelated Newfoundland families (**Merner et al. Am J Hum Genet 2008**), identified heterozygosity for a missense mutation (S358L; 612048.0001) in the TMEM43 gene that was not found in 47 spouses or 161 controls. In an analysis of the TMEM43 gene in 55 Danish probands who fulfilled the criteria for ARVD and 10 patients with only some features of ARVD, Christensen et al. (**Christensen AH, et al J Med Genet 2010**) identified 1 woman fulfilling the criteria who carried the S358L variant. In DNA samples from 195 unrelated individuals with suspected ARVD, Baskin et al. (**Baskin B, et al.Hum Genet. 2013**) identified 6 patients who carried the S358L 'Newfoundland' mutation in TMEM43, including a 43-year-old New Zealand man who was not of Newfoundland descent. In addition, 5 patients carried 5 different rare sequence variants in the TMEM43 (see, e.g., 612048.0004), 2 of whom also carried a variant in the PKP2 and DSP genes, respectively. **EDMD7:** Based on the putative role for TMEM43 in the nuclear envelope, Liang et al. (**Liang WCC et al. Ann Neurol. 2011**) analyzed the TMEM43 gene in 41 patients with Emery-Dreifuss muscular dystrophy (EDMD) who were negative for mutations in known EDMD-related genes and identified different heterozygous missense mutations in 2 unrelated individuals LUMA

Gene Function (Bengtsson and Otto (2008) found that TMEM43 binds A- (LMNA; 150330) and B- (LMNB1; 150340) type lamins and depends on A-type lamins for its inner nuclear membrane localization. The TMEM43 protein was also shown to interact with emerin (EMD; 300384). Downregulation of TMEM43 and overexpression of dominant-negative acting TMEM43 caused redistribution of emerin. The findings suggested that TMEM43 functions as a nuclear membrane organizer (**Liang WCC et al. Ann Neurol. 2011**) demonstrated that TMEM43 interacts with SUN2 (613569), another inner nuclear membrane protein.

Main Alternative Diagnosis and/or Potential ACM Mimicking Diseases
Brugada syndrome
Sarcoidosis
Dilated cardiomyopathy
Athlete's heart
Idiopathic infundibular PVC/VT
Myocarditis
Uhl's disease
Other causes of RV dilatation and/or dysfunction
Ebstein's anomaly
Left to right shunt: interatrial septal defect, anomalous pulmonary venous return
Tricuspid regurgitation
Inferior infarct with RV extension

Main nomenclatures used in the literature

1) **Arrhythmogenic right ventricular cardiomyopathy (ARVC)**
2) **Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)**
3) **Arrhythmogenic cardiomyopathy (AC). Important: In this presentation we will use AC nomenclature**

Arrhythmogenic cardiomyopathy (AC), is a hereditary disease characterized by ventricular arrhythmias, right ventricular and/or left ventricular dysfunction, and fibrofatty replacement of cardiomyocytes. Patients with AC typically present between the second and the fourth decade of life with ventricular tachycardias. However, sudden cardiac death (SCD) may be the first manifestation, often at young age in the concealed stage of disease. AC is diagnosed by a set of clinically applicable criteria defined by an international

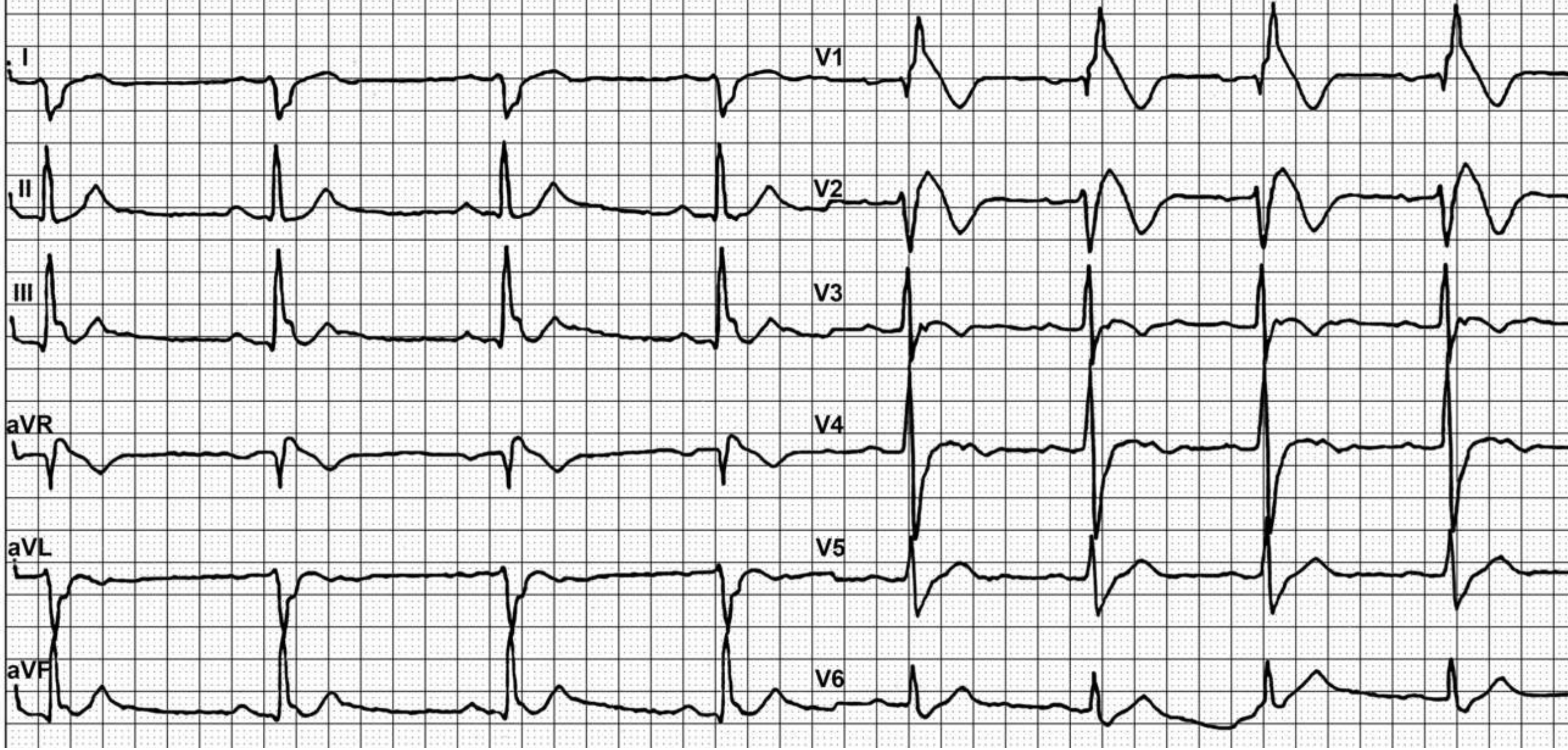
Task Force. The current Task Force Criteria are the essential standard for a correct diagnosis in individuals suspected of AC. The genetic substrate for AC is predominantly identified in genes encoding desmosomal proteins.

In a minority of patients a non-desmosomal mutation predisposes to the phenotype.

Risk stratification in AC is imperfect at present.

Genotype-phenotype correlation analysis may provide more insight into risk profiles of index patients and family members.

In addition to symptomatic treatment, prevention of SCD is the most important therapeutic goal in AC. Therapeutic options in symptomatic patients include antiarrhythmic drugs, catheter ablation, and ICD implantation. Furthermore, patients with AC and also all pathogenic mutation carriers should be advised against practising competitive and endurance sports.

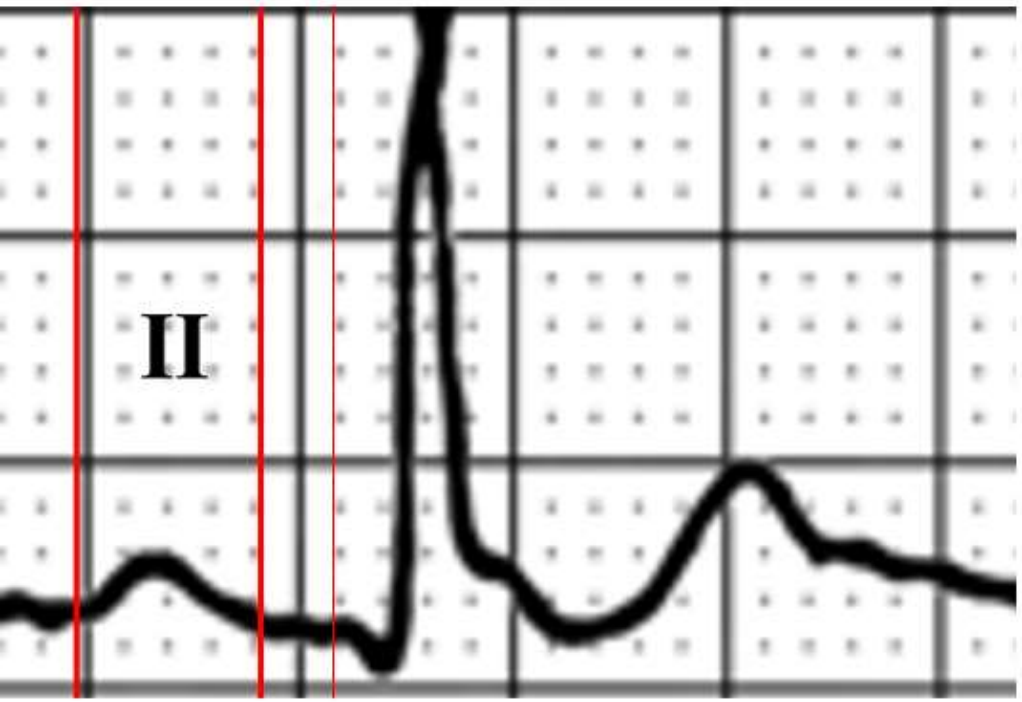


ECG diagnosis: Sinus bradycardia, HR 53bpm, P-axis(SÂP) + 60°, P-duration 160ms in II and 120ms in V1, P-wave dispersion, first degree interatrial block and/or left atrial enlargement, PR interval 195ms, right axis deviation (SÂQRS +124°), wide QRS duration=160ms, left posterior fascicular block, complete RBBB, type 1 Brugada pattern in V2, epsilon wave, right parietal block, very prolonged R-wave peak time in V1, presence of the "Elf sigh" in V1 leads "Caló sign" in I.

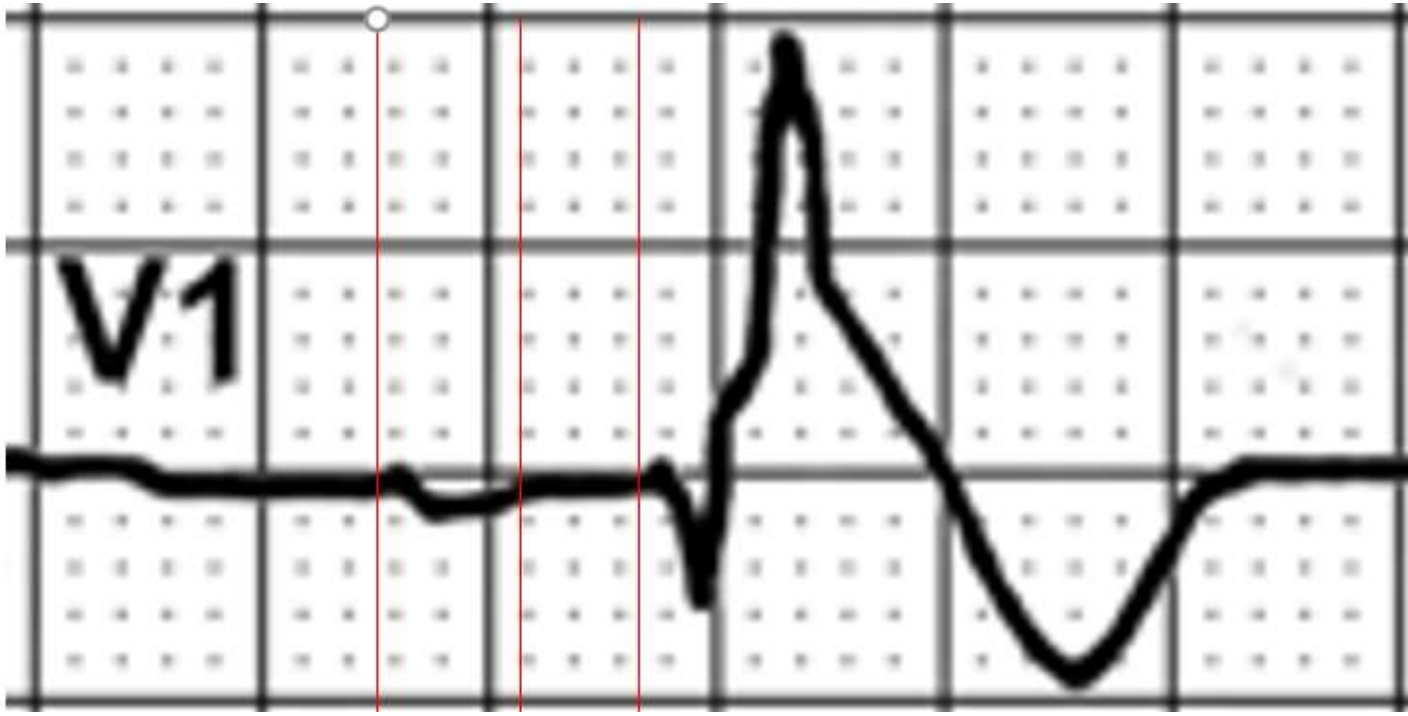
Main Electrocardiographic abnormalities observed in AC

- **Eventual Right atrial , left atrial or biatrial enlargement and interatrial block, P-wave dispersion**
- **Eventual PR interval prolongation**
- **Prolongation of QRS duration (QRSd) in the right precordial leads**
- **QT prolongation in right precordial leads**
- **Delayed S wave upstroke on right precordial leads (right parietal block)**
- **Ratio of the QRSd in leads $^{V1+V2+V3}/_{V4+V5+V6} \geq 1.2$**
- **Delayed S wave upstroke(right parietal block)≥ 55ms**
- **Ratio of the QRSd in leads $^{V1+V2+V3}/_{V4+V5+V6} \geq 1.2$**
- **Fragmented QRS (f-QRS)**
- **QRS dispersion**
- **T wave inversion in the right precordial leads in patients > 14 years of age in the absence of CRBBB. It is considered a minor criteria in the revised Task Force criteria. Negative T wave in lateral leads and positive in aVR suggest LV involvement.**
- **Presence of epsilon waves, epsilon potentials, or Fontaine waves (considered a mayor criteria in the revised Task Force criteria)**
- **Low-QRS voltage in the limb leads; are <5 mm because of loss of viable myocardium.**
- **Frequently premature ventricular contractions with LBBB pattern.**
- **Eventual sustained monomorphic VT with superior QRS axis. (considered a mayor criteria in the revised Task Force criteria)**
- **Eventual sustained monomorphic VT with inferior QRS axis. (considered a minor criteria in the revised Task Force criteria)**
- **Frequently supraventricular arrhythmias: FA, Flutter atrial.**
- **Incomplete RBBB or complete RBBB**

Prolonged PR or PQ interval



P-duration=160ms in II, PR segment only 75 ms; PR interval 195ms



P-duration=120ms in V1, PR segment only 75 ms, PR interval 195ms

PR interval 195ms: Conclusion: Pronged P-wave consequence of first degree interatrial block(1) and/or left atrial enlargement? Dynamic P-wave duration from 160ms in II lead to 120ms I V1. In this case, we observe a significant P wave dispersion (160/120 ms). P-wave dispersion (PWD) is a noninvasive ECG marker for atrial remodeling and predictor for atrial fibrillation. PWD is defined as the difference between the widest and the narrowest P-wave duration recorded from the 12 ECG leads **(Pérez-Riera AR, et al., Indian Pacing Electrophysiology Journal 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5197451/ ; Bayés de Luna et al. J Electrocardiol. 2012)**

See figure in the next slide

Some studies report visualizing P-wave onset and offset in a minimum of 8 to 9 leads as an inclusion criterion, although a minimum of three leads has been used to determine P- dispersion (Pd) (**Agarwal, *et al.* Am J Cardiol. 2003**). P-wave indices are manually calculated with calipers or with digitized images. Manual measurement uses paper speed at 50 mm/s and the voltage 1 to 2 mV/cm (**Aytemir, *et al.* Pacing Clin Electrophysiol. 2000**) with additional magnification. Manual measurements have less accuracy compared with digital measurements.

Interatrial blocks (IABs)

Prolonged PWD, is a marker of LAE and/or interatrial block, both associated with myocardial fibrosis, AF tendency, ischemic stroke, heart failure, sudden cardiac death (SCD) in the general population, and all-cause death. This association is independent of AF and is only partially mediated by shared cardiovascular risk factors (**Maheshwari, et al. Am J Cardiol. 2017**). IAB, the Bayes´ syndrome, is considered partial (P-IAB) when the P-wave is ≥120 ms, and advanced (A-IAB) when the P-wave in the inferior leads II, III and aVF is biphasic (+/-) in addition to prolonged PWD (**Martin-Demiguel, et al. Am J Cardiol. 2019**). Biphasic (+/-) plus-minus P-wave in A-IAB is due to retrograde caudo-cranial activation of the LA induced by the presence of fibrosis in the BR in the LA ceiling. This was confirmed in humans by electro-anatomic mapping (**Holmqvist, et al. Heart Rhythm. 2008**) and with advanced CMR techniques and in post-mortem specimens (**Baranchuk A. 2017**).

IAB is a prevailing cardiac conduction abnormality that is under-recognized in clinical practice.

Prolonged PWD with a cutoff of >120 ms to >150 ms in sinus rhythm before ablation may be associated with AF recurrence after pulmonary vein isolation (PVI) regardless of age, gender, left atrial size, and the presence of structural heart disease (**Pranata et al. Ann Noninvasive Electrocardiol. 2019**). The term left atrial abnormalities was coined and widely used to encompass both atrial enlargement and IAB (**Lee, et al. Am J Cardiol. 2007**). Established ECG criteria for LAE do not reliably reflect anatomical LAE and lack sufficient predictive value to be useful clinically. P-wave abnormalities should be noted as nonspecific LA abnormalities. The presence of at least one ECG criterion for LAE is sensitive but not specific for anatomical LAE. Individual criteria for LAE, including P mitrale, P-wave axis ≤30°, or NPTF- V1 > 0.04 s.mm are highly specific, though not sensitive. ECG is highly specific but insensitive for RAE. Individual ECG P-wave changes do not reliably predict anatomical atrial enlargement (**Tsao, et al. J Cardiovasc Magn Reson. 2008**).

Bayes syndrome is an under-recognized arrhythmic syndrome characterized by the association of A-IAB with significant cardiogenic and neurogenic implications such as atrial arrhythmia, more specifically atrial fibrillation (**Conde, et al. Arch Cardiol Mex. 2014**), vascular dementia, non-lacunar cardioembolic ischemic stroke and a possible cryptogenic stroke (as cerebral ischemia of obscure or unknown origin) (**Arboix, et al.**

World J Clin Cases. 2017). Recently, Bayés et al classified IABs in typical and atypical ("atypical A-IAB"). Atypical A-IAB is present when the sinus P-wave depicts a terminal negative component in lead aVF; indicating that final part of the P-wave/P-loop is located in the negative hemifield of aVF (upwards the orthogonal X lead/I lead 0°/±180°), and therefore, a retrograde caudo-cranial activation of the LA is present.

There are three morphologically atypical patterns of A-IAB: Type I: The terminal component of the P-wave in lead II is equiphasic; Type II: The terminal component of the P-wave in lead II is biphasic "minus-plus" (-/+) and Type III: P-waves in III and aVF are totally negative and biphasic in II. These cases must be differentiated from ectopic atrial rhythm, where there are negative P-waves in leads III and aVF (**de Luna AB, et al. J Electrocardiol. 2019**). Table below shows the new classification of IABs (**Bayes de Luna, et al. J Electrocardiol. 2018**).

Electrocardiographic classification of interatrial blocks (IABs)
1.Typical IAB: 1.a. Partial interatrial blocks (P-IABs) a. First degree PWD ≥120 ms without negative terminal component in the inferior leads b. Second degree AV block: when transient or intermittent (aberrancy). 1.b. Advanced interatrial block or third degree (A-IAB) P-wave ≥ 120 ms with biphasic "plus-minus" P-wave in the inferior leads II, III and aVF.
2. Atypical IAB (A-IAB) (I): Morphological criteria Type I: P-wave ≥ 120ms with biphasic morphology in leads III and aVF and the final component of the P-wave in lead II is equiphasic (isodiphasic). Type II: P-wave ≥ 120 ms with biphasic morphology in leads III and aVF and the final component of the P-wave in lead II is biphasic (-/+). Type III: P-wave ≥ 120 ms with the first component of the P-wave equiphasic in leads III and aVF. (II) Duration criteria 1) P-wave <120 ms with typical morphology (biphasic (±) 2) P-wave in the inferior leads II, III, and aVF.

Interatrial block: classification and identification

Definition: It is a transient pattern of partial or advanced IAB, or atrial aberrancy; in other words deviating from the proper or expected course of stimulus inside the atrium. Atrial aberrancy is also possible when PACs or premature parasystolic atrial beats are present.(**Bayés de Luna A, et al .J Electrocardiol. 1978; Julia J Rev. Esp. Cardiol. 1978; Breall WS, et al. Br Heart J. 1972).** Atrial aberrancy may also be present as a transient bizarre P wave without the morphology of first or third degree IAB. These changes in P wave morphology are caused by variations in the atrial path of the sinus impulse through the atria. They should be differentiated from changes induced by breathing, atrial fusion beats, and artefacts, including diaphragmatic contraction.

Classification

1. ***First Degree Interatrial Block,***
2. ***Second degree or transient Interatrial Block(atrial Aberrancy) and***
3. ***Third Degree Interatrial Block, Complete or Advanced Interatrial Block***

Differential diagnosis

Aberrant atrial conduction must be differentiated from:Immediatly after atrial premature contractions (60% of cases of atrial aberrancy); A wandering atrial pacemaker; aberrancy after AV junctional escape beats or AV junctional premature contraction, coexisting multifocal premature beats; aberrrant atrial conduction after parasystolic beats, mainly interpolated atrial parasystolic beat and several artifacts**.**

1. ***First Degree Interatrial Block (IAB)***

Electrocardiographic characterization

P-wave duration ≥120 ms (Platonov PG. Cardiol J. 2008). P-wave duration is generally accepted as the most reliable non-invasive marker of atrial conduction and its prolongation is associated with AF. However, patients with paroxysmal AF without structural heart disease may not have P-wave prolongation, thus suggesting that the global conduction slowing is not an obligatory requirement for development of AF. (**Ariyarajah V, et al. J Electrocardiol. 2006**).

The widest P wave defining the degree of block could be found in any leads

2) Bifid P waves

Finally, the prevalence of first-degree interatrial block in the general population is very high, and their relation with AF and an increased risk for global and cardiovascular mortality has been shown.(**Bayés de Luna A, et al. J Electrocardiol. 2012**)

Second-degree or transient interatrial block (atrial aberrancy)

Definition: It is a transient pattern of partial or advanced IAB, or atrial aberrancy; in other words deviating from the proper or expected course of stimulus inside the atrium. Atrial aberrancy is also possible when premature atrial contractions or premature parasystolic atrial beats are present (**Bayes De Luna A, et al. Rev Esp Cardiol. 1978; Julia J. Rev. Esp. Cardiol. 1978; Breall WS, et al. Br Heart J. 1972**).

Atrial aberrancy may also be present as a transient bizarre P wave without the morphology of first or third degree IAB. In the figures of the next 2 slides, an example of second degree IAB may be seen.

These changes in P wave morphology are caused by variations in the atrial path of the sinus impulse through the atria. They should be differentiated from changes induced by breathing, atrial fusion beats, and artifacts, including diaphragmatic contraction. Second degree of IAB can be induced by atrial or ventricular premature complexes, which appear and disappear suddenly and transiently in one ECG and show a P wave that changes morphology transiently in successive ECGs, leading to misdiagnosis.

Differential diagnosis

Aberrant atrial conduction must be differentiated from:

1.Immediatly after atrial premature contractions (60% of cases of atrial aberrancy)

2.A wandering atrial pacemaker;

3.Aberrancy after AV junctional escape beats or AV junctional premature contraction

4.Coexisting multifocal premature beats;

5.Aberrrant atrial conduction after parasystolic beats, mainly interpolated atrial parasystolic beat.

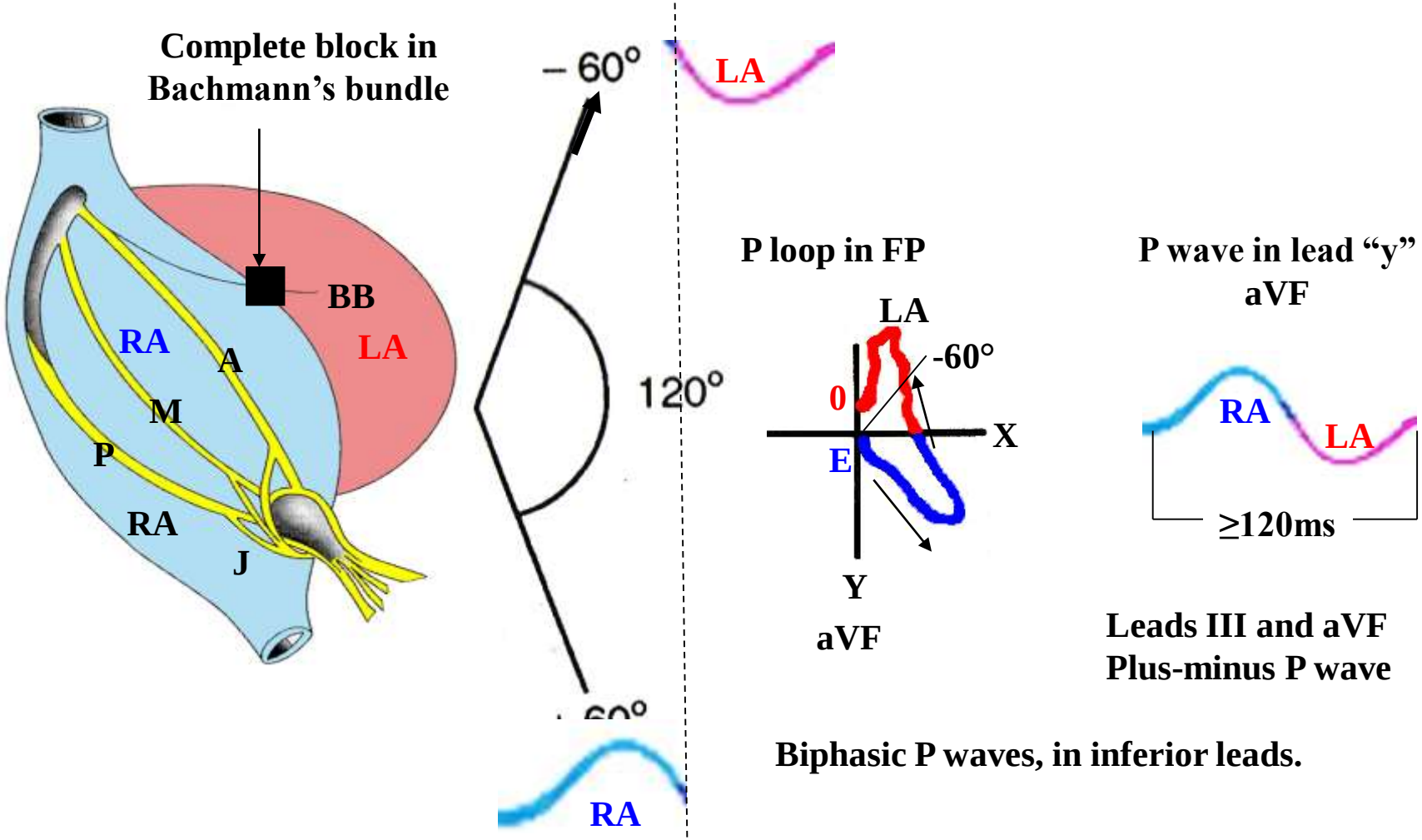
6.Several artifacts**.**

Third degree, complete or advanced interatrial block

Definition: In these cases the stimulus is blocked in the Bachmann region and LA is activated retrogradely with a P wave duration ≥120 ms and plus-minus(+/-) ± P wave in inferior leads II, III and aVF. There is an open angle ≥90° between the vector of the first part and of the second part of the P wave in the inferior leads. Orthogonal Y lead plus-minus with a negative mode >40 ms appear with notches and slurring in the last part of the P loop. IAB is associated in most of cases with LAE (90° of cases) and dysfunction, decreased left ventricular (LV) filling, a propensity for LA appendage thrombosis, reduced atrial natriuretic peptide levels, and is a predictor of paroxysmal supraventricular tachyarrhythmias such as AF, atrial flutter as well as an exacerbation of the LV failure. The prevalence of first degree IAB is much higher than advanced or complete IAB. Really the ECG pattern of advanced IAB is an extremely strong marker of supraventricular tachyarrhythmia in a short period of time, much more so than the presence of first degree or partial Interatrial block. Bayés de Luna A et al.(**Bayés de Luna A, et al. Eur Heart J. 1988**) studied 16 patients with ECG evidence of advanced IAB with retrograde activation of the left atrium (**LA**): P duration ≥120 ms, and plus-minus (+/-) biphasic P waves in inferior leads II, III, and aVF. Eight patients had valvular heart disease, four had dilated cardiomyopathy and four had other forms of heart disease. Patients with valvular heart disease and cardiomyopathy were compared with a control group of 22 patients with similar clinical and echo characteristics, but without IAB. Patients with advanced IAB and retrograde activation of the **LA** had a much higher incidence of paroxysmal AF (93.7%) during follow-up than did the control group. Eleven of 16 patients (68.7%) with advanced IAB and retrograde activation of **LA** had atrial flutter (atypical in seven cases, typical in two cases, and with two or more morphologies in two cases). *Six patients* from the control group (27.7%) had sustained atrial tachyarrhythmias (five AF and one typical atrial flutter). The atrial tachyarrhythmias were due more to advanced IAB and retrograde PACs than to left atrial enlargement, because the control group with a **LA** of the same size, but without advanced IAB and retrograde activation of **LA** and with less inactivation of LA and frequent PACs, had a much lower incidence of paroxysmal tachycardia.

Bayés de Luna et al.(**Bayés de Luna A, et al. Int J Cardiol. 1989**) demonstrated the value of preventive antiarrhythmic treatment in patients with advanced interatrial block. In this population LAE is present in 90% of cases. Using drugs (amiodarone, quinidine or verapamil) this percentage was greatly lowered (25%). From 81,000 ECGs, Bayes de Luna et al (**Bayes de Luna A. J Electrocardiol. 1985**) collected 83 cases that fulfilled the criteria of Interatrial Conduction Disturbances with Left Atrial Retrograde Activation (IACD-LARA) (P +/- in II, III and VF with P width ≥120 ms). The authors present the detailed study of 35 cases with surface ECG and VCG and 29 cases with orthogonal ECG leads. The results are then compared against two control groups: with heart disease (30 cases) and without heart disease (25 cases). The prevalence of IACD-LARA was nearly 1% globally, and 2% among patients with valvular heart disease. Arrhythmias such as AF and atrial flutter in advanced IAB is observed in > 90% of cases. Diagnosis criteria of advanced interatrial block and retrograde activation of the LA (**Bayés de Luna A. et al 1977;1988; Bayés de Luna A, et al. J Electrocardiol. 2012**): Biphasic, bifid, or notched "plus-minus" P waves, in inferior leads II, III and aVF of ECG and Y orthogonal lead of VCG, P duration ≥120 ms, angle between the first portion (RA) and end portion (**LA**) >90º, orthogonal Y lead plus-minus with the final negative portion ≥40 ms, ≥40 ms final portion of P loop of upstart orthogonal X and Z leads, final portion of P loop delayed, notches and slurring in the last part of the P loop, high Esophageal lead with positive P wave polarity and delayed, low Esophageal lead with plus-minus P wave polarity and delayed, intracavitary ECG with P wave craniocaudal activation inside the RA, intracavitary ECG with P wave caudal-cranial activation inside LA.This clinical-electro-vectorcardiographic manifestation of advanced IAB should be considered a syndrome : Bayés syndrome (**Hernandez-Betancor I, et al. Curr Cardiol Rev. 2017**).

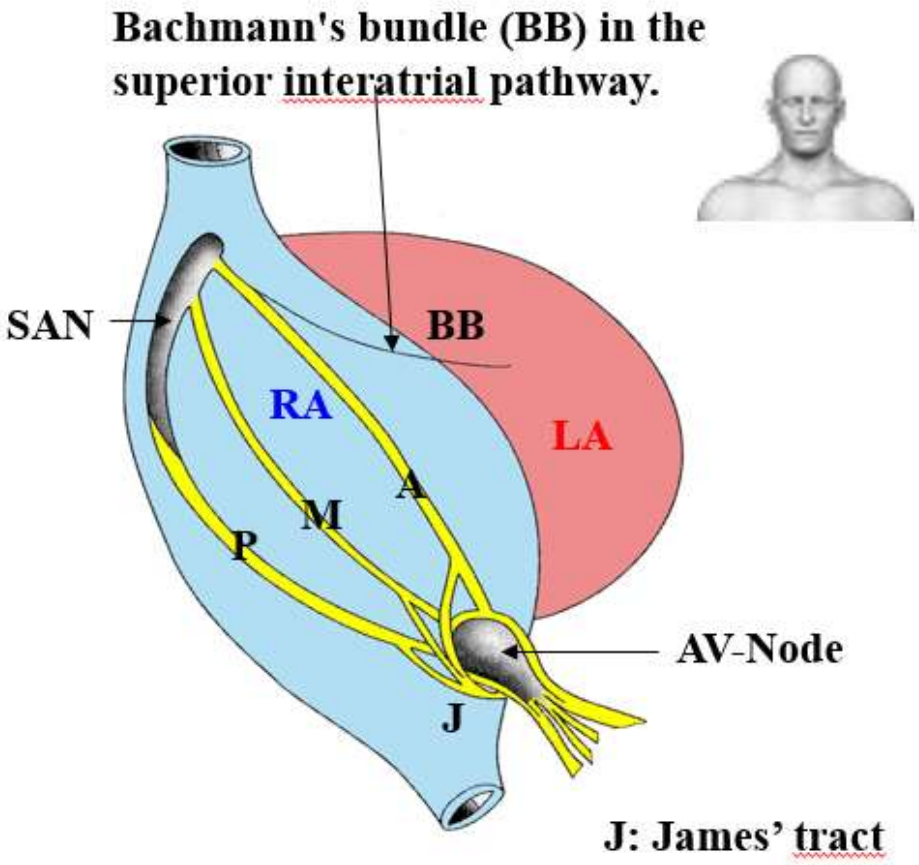
Third degree block, complete or advanced interatrial block

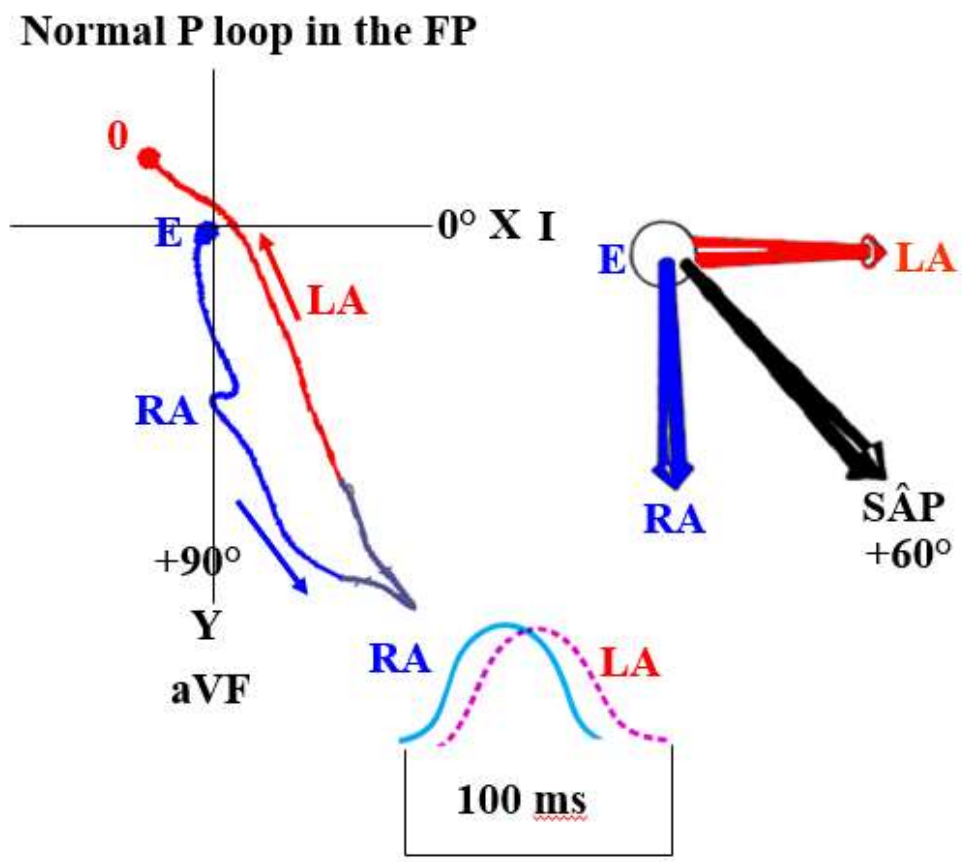


Third Degree (Advanced or complete IAB)

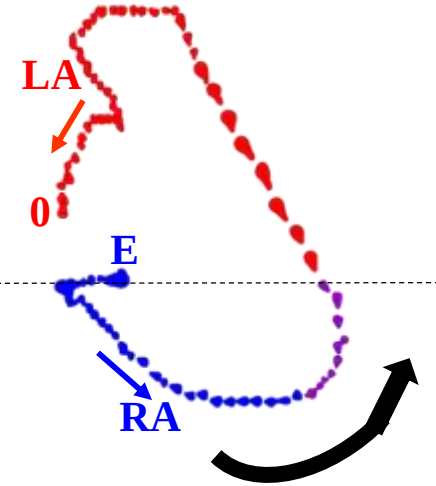
Electrical impulse is blocked/delayed in Bachmann's muscular interatrial bundle (BB), but retrograde left atrial activation usually occurs (**Ariyarajah V, et al. Chest. 2005**). Note the existence of an open angle between the vector of the first portion of P wave (RA) and the last portion (**LA**). Electrophysiological study demonstrates retrograde activation of the LA. Consequently P loop/wave in orthogonal lead "Y", aVF and III is biphasic plus-minus ±. **LA** activation occurs by an alternate route rather than proceeding from right to left via the BB (**Spodick DH. J Electrocardiol. 2008**).

Normal P-loop/ wave on frontal plane

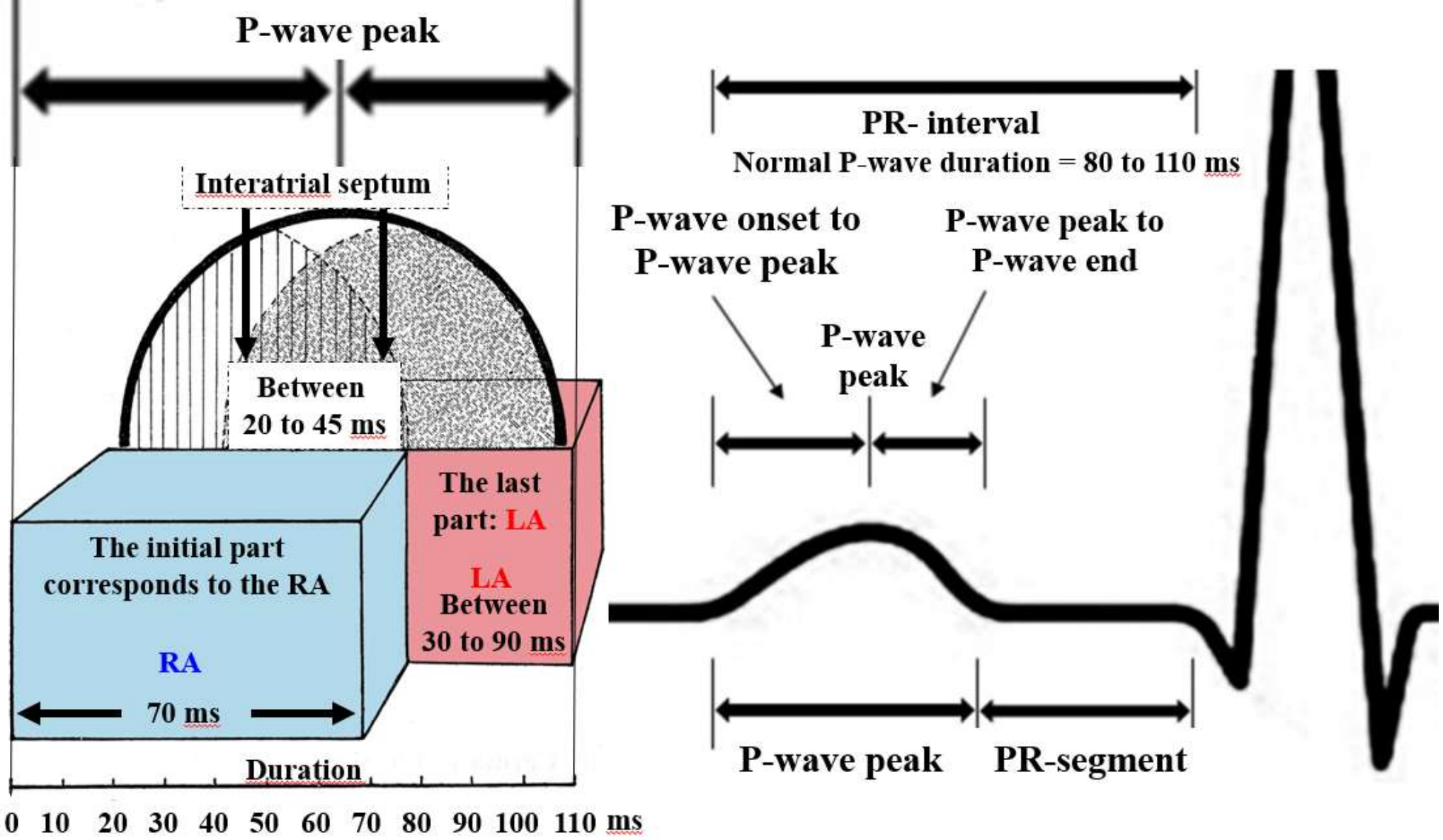




Magnified P-loop (32x)
P-loop VCG in advanced IAB



Caudo-cranial activation of the left atrium (LA)



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 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 The presence of AF in BrS is a known risk marker.

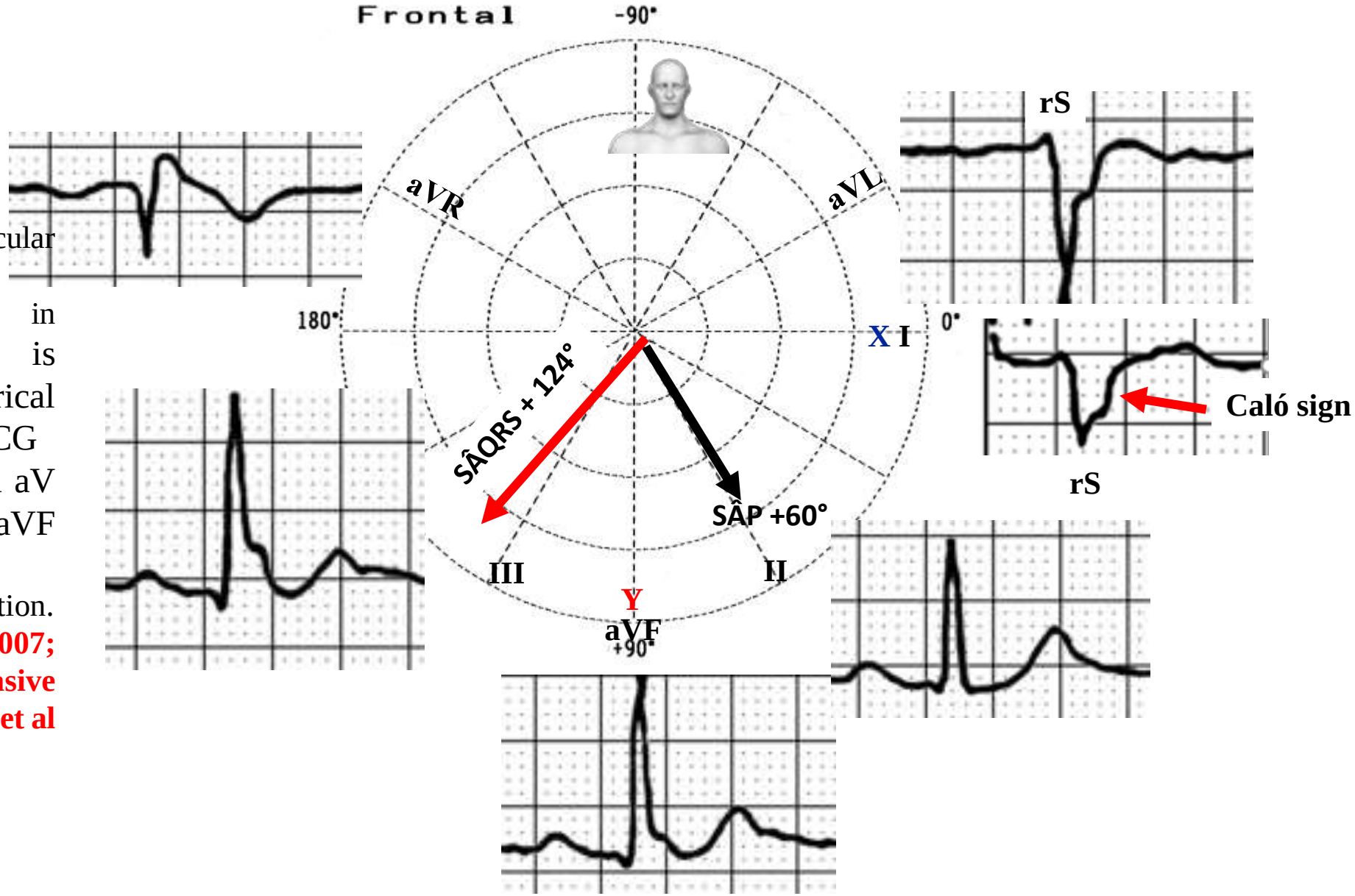
Without considering the contribution of each component, inconsistent associations between the PR-interval and AF are inevitable. So, some studies showing non-significant associations (**Aro et al., 2014**), on the other hand others showing a stronger (**Alonso et al., 2013**). A possible explanation 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, Cammarata, & Li, 2014**). The components of the PR-interval are not strongly correlated, and the magnitude of the association with AF will vary by each component (**Smith et al., 2017**).

SÂQRS + 124°: Right axis deviation

For the diagnosis of LPFB is necessary

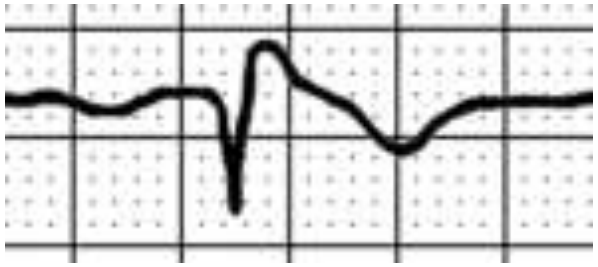
1. No evidence of right ventricular hypertrophy
2. No evidence of vertical heart in slendersubjects. This is a cardiac electrical position, recognized in the ECG when the QRS complex in lead aV L resembles V_1 while that in aVF resembles V_6. and
3. No evidence of a large lateral infarction.

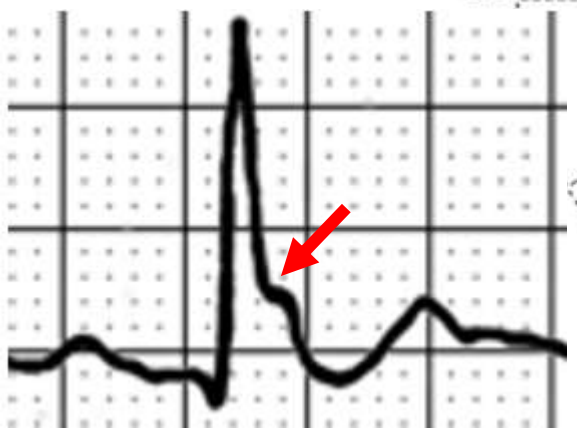
(**Elizari Mval . et Circulation 2007; Pérez-Riera AR et al Annals Non Invasive Electrocardiol. 2015; Pérez-Riera AR et al Indian Pacing Electrophysiol. 2018**)

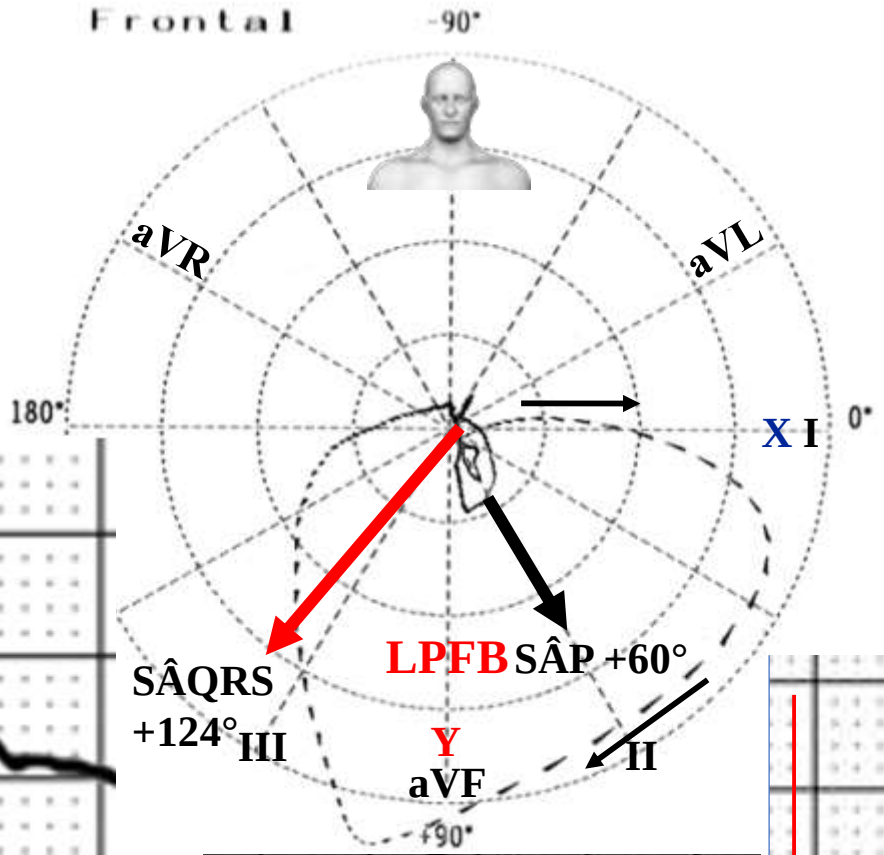


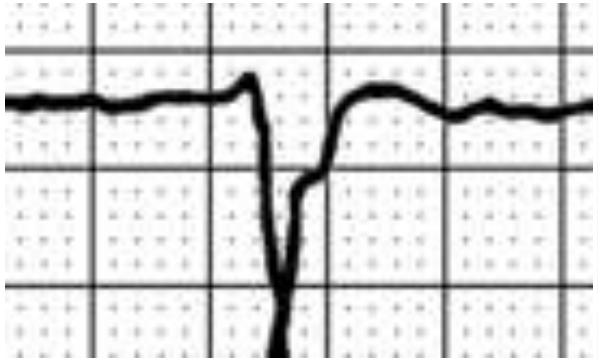
Positive Caló sign reflects terminal right end conduction delay (**RECD**) in the right ventricular outflow tract (RVOT) and subsequently more electrical heterogeneity in the ventricular wall thickness (**Calò L, et al. J Am Coll Cardiol. 2016**).

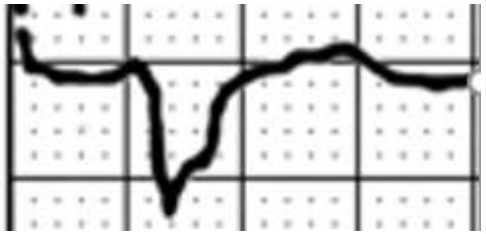
Hypothetical ECG/VCG correlation on the Frontal Plane



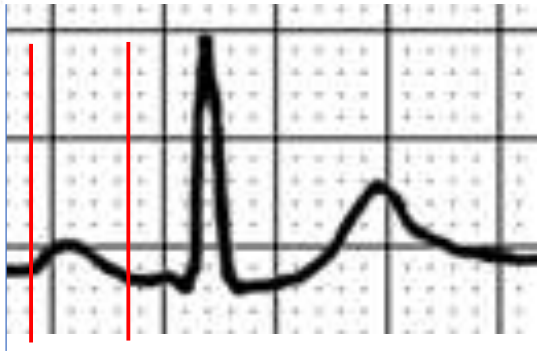




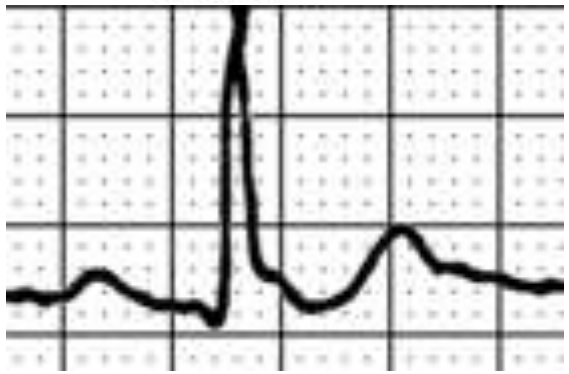




rS pattern in leads I and aVL



P-wave duration =160ms: PR segment 75ms; PR interval 195ms



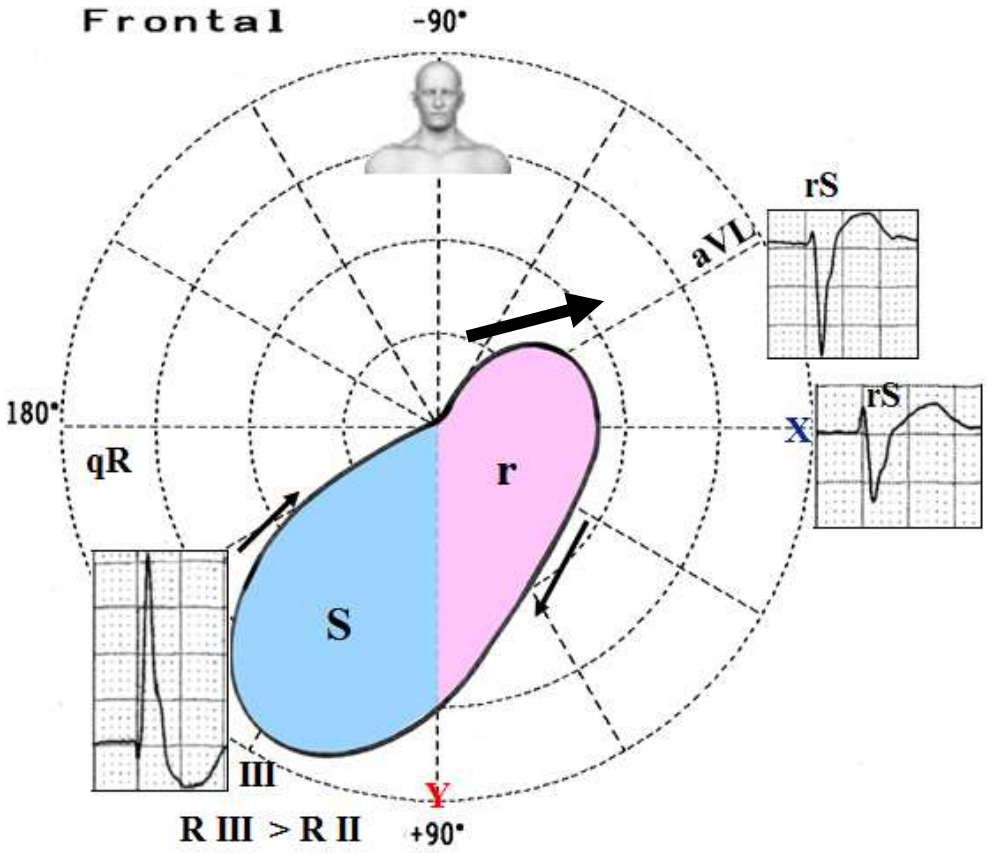
Notch in the descending limb of the R wave in III: middle-final notch(red arrow). This is an hallmark of LPFB, and R-III>RII

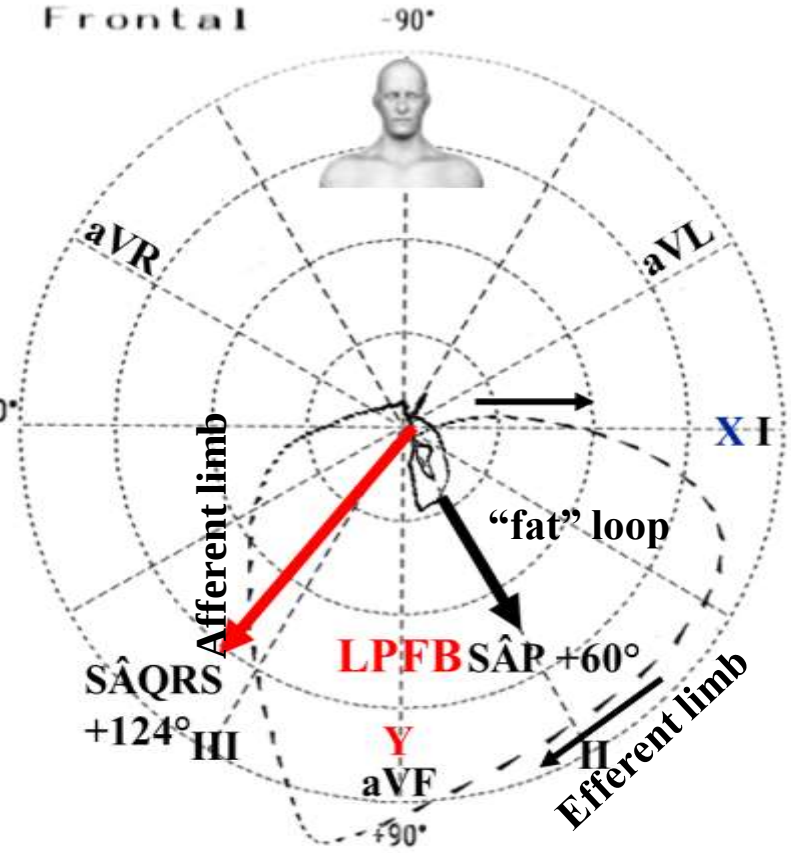
SÂQRS + 124°: Right axis deviation

Ventricular activation time, R-wave peak time or intrinsicoid deflection (ID) in aVF≥35 ms.

The interatrial blocks, by analogy with other types of block, (sinoatrial, atrioventricular, and/or bundle-branch block at the ventricular level), may be of first (partial), second (transient interatrial block is part of atrial aberrancy second degree), or third degree (advanced). The P wave has a normal electrical axis.

Vectorcardiographic criteria of LPFB in the Frontal Plane



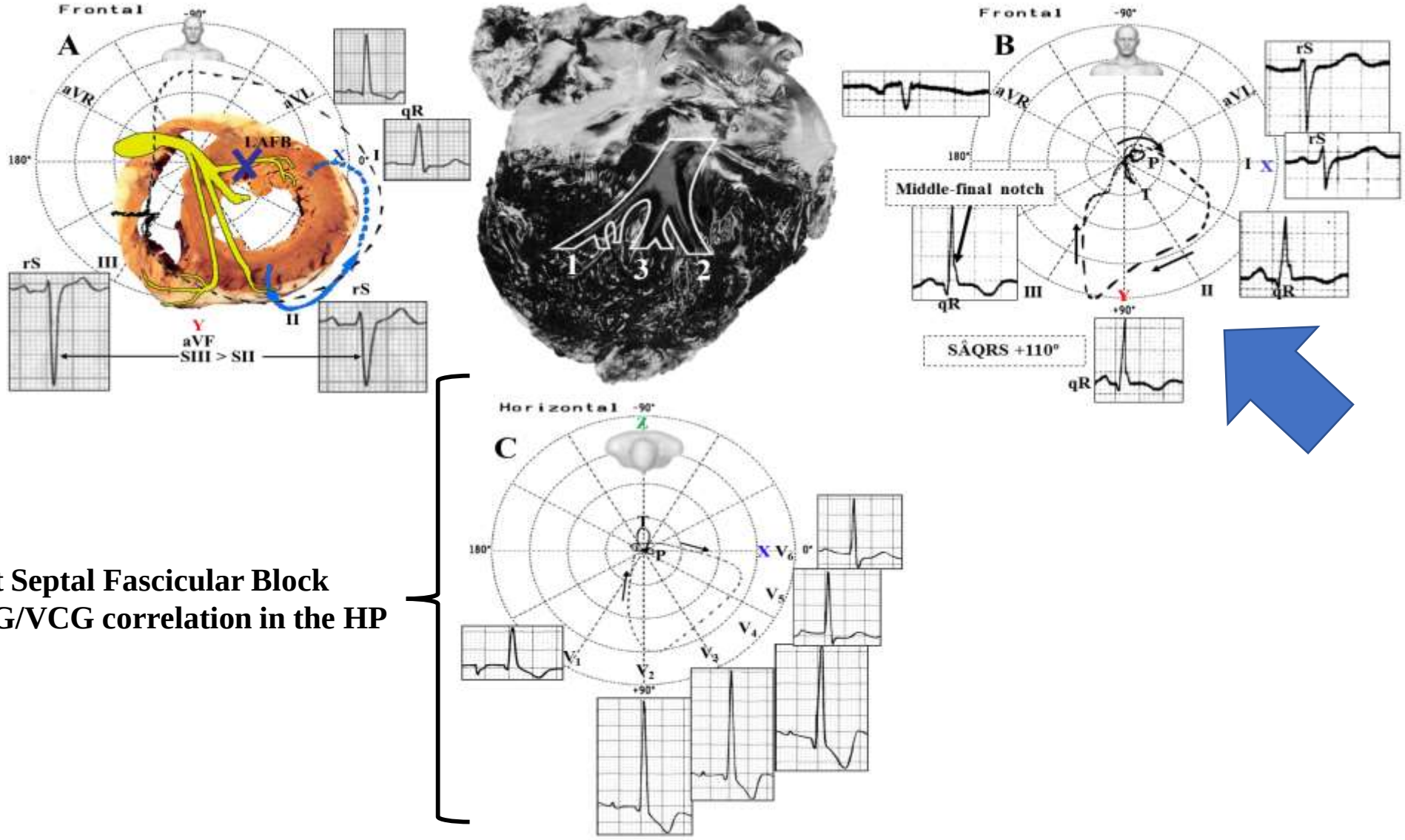


1. QRS axis between +90°-180° in adults;
2. rS pattern in leads I and aVL
3. qR pattern in III, aVF and II: Q wave is always present in III and may be small or absent in II or aVF.
4. Notch in the descending limb of the R wave in III (middle-final notch);
5. RIII > RII: SÂQRS closer to +120º (III) than +60º (II), when closer to the latter, it would indicate an incomplete form of LPFB.
6. The q wave in III is always greater than the q wave in II and aVF. If there is association with inferior infarction, the Q wave > 40 ms.
7. QRS duration less than 120 ms if isolated (without RBBB)
8. Ventricular activation time, R-wave peak time (in aVF≥35 ms.

Characterization of QRS loop in the frontal plane: Initial vector 20 ms vector heading above and to the left; efferent limb to the left; clockwise rotation (CWR); greater area of QRS loop located in the right inferior quadrant; maximal vector heading below and to the right near +110º (from +80º to +140º); QRS loop of "broad" aspect (“fat” loop”); afferent limb located in the right inferior quadrant. Typical QRS loop in the frontal plane that explains the rS pattern in I and aVL and the qR pattern in III with notch in the descending limb of the R wave and R wave in III > R in II. Notch in the descending limb of the R wave in III (middle-final notch).

Left Anterior Fascicular Block ECG/VCG correlation in the FP

Left Posterior Fascicular Block ECG/VCG correlation in the FP



Left Septal Fascicular Block ECG/VCG correlation in the HP

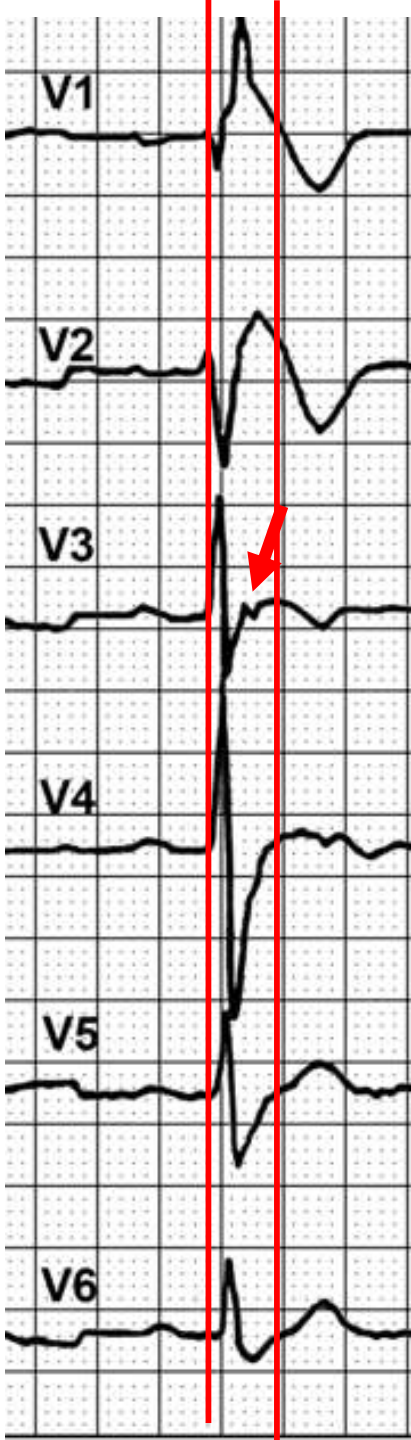
LAFB (A) causes left axis deviation in the frontal plane (usually between -45º and -90º); LPFB (B) causes right axis deviation in the frontal plane (QRS axis ≈+120º, between +80 to +140º); while left septal fascicular block (C) causes prominent anterior QRS forces in the horizontal plane.

Parietal block

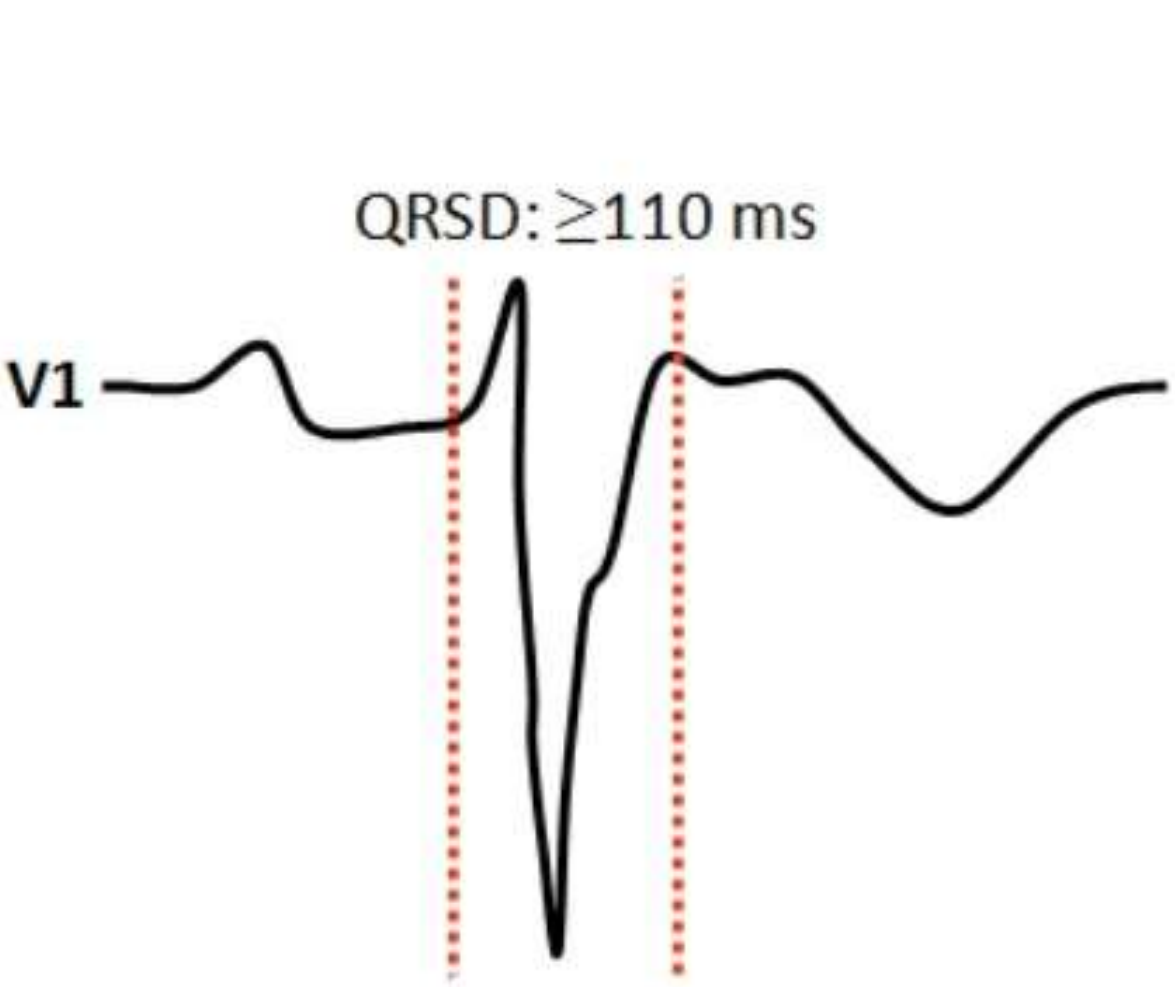
QRSD of $^{V1+V2+V3}$ / $_{V4,\ V5\ and\ V6}$ ≥ 1.2 in approximately 65% of cases. QRS prolongation located in the right precordial leads (**Nasir K. Circulation. 2004**).

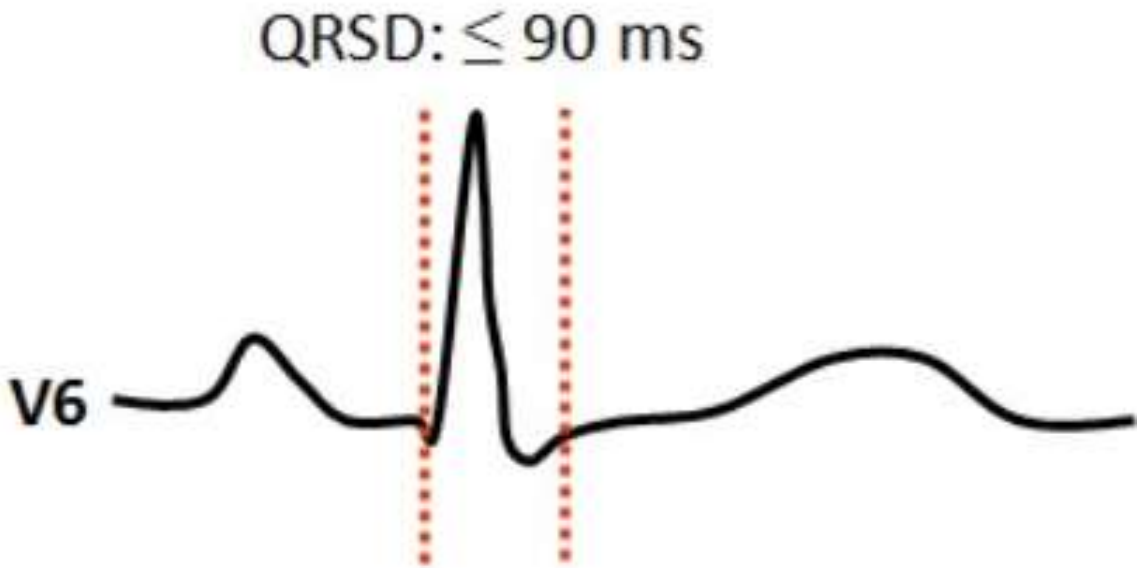
QRSD ≥ from V1 to V3 with 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVC/D (**Nasir K. Pacing Clin Electrophysiol. 2003**).

The mechanism of the right conduction defects is not disease of the bundle branch itself but a distal block probably situated in the RV wall. This hypothesis is supported by the histological appearances of the dysplastic zones (**Fontaine G, et al. Arch Mal Coeur Vaiss. 1984**). Located prolongation has been described for QRSd interval from V1 to V3, related to V1 + V2 + V3 / V4 + V5 + V6 >1.2 in 97% of the cases of ARVC/D, and it is related with the amount of fibrotic tissue in patients with VT that originate in the RV. The sensitivity of this criterion is not known in other entities and it speaks in favor of slow RV conduction. Recent studies show that the sign is not specific, since it is found in Brugada syndrome with QT interval prolongation only from V1 to V3 (**Pitzalis MV, et al. J Am Coll Cardiol. 2003**). If QT interval prolongation occurs only from V1 to V3, it is clear that this is due to depolarization time prolongation. If we admit that in Brugada syndrome there is some degree of RBBB, this QT interval prolongation may be partially due to this fact. QT interval constitutes a classical measurement for ventricular repolarization; however, it includes depolarization (QRS), which represents the so-called “electrical systole”, which includes ventricular depolarization and repolarization. In these cases of branch block and WPW, it is better to measure the JT interval and not QT (next slide).



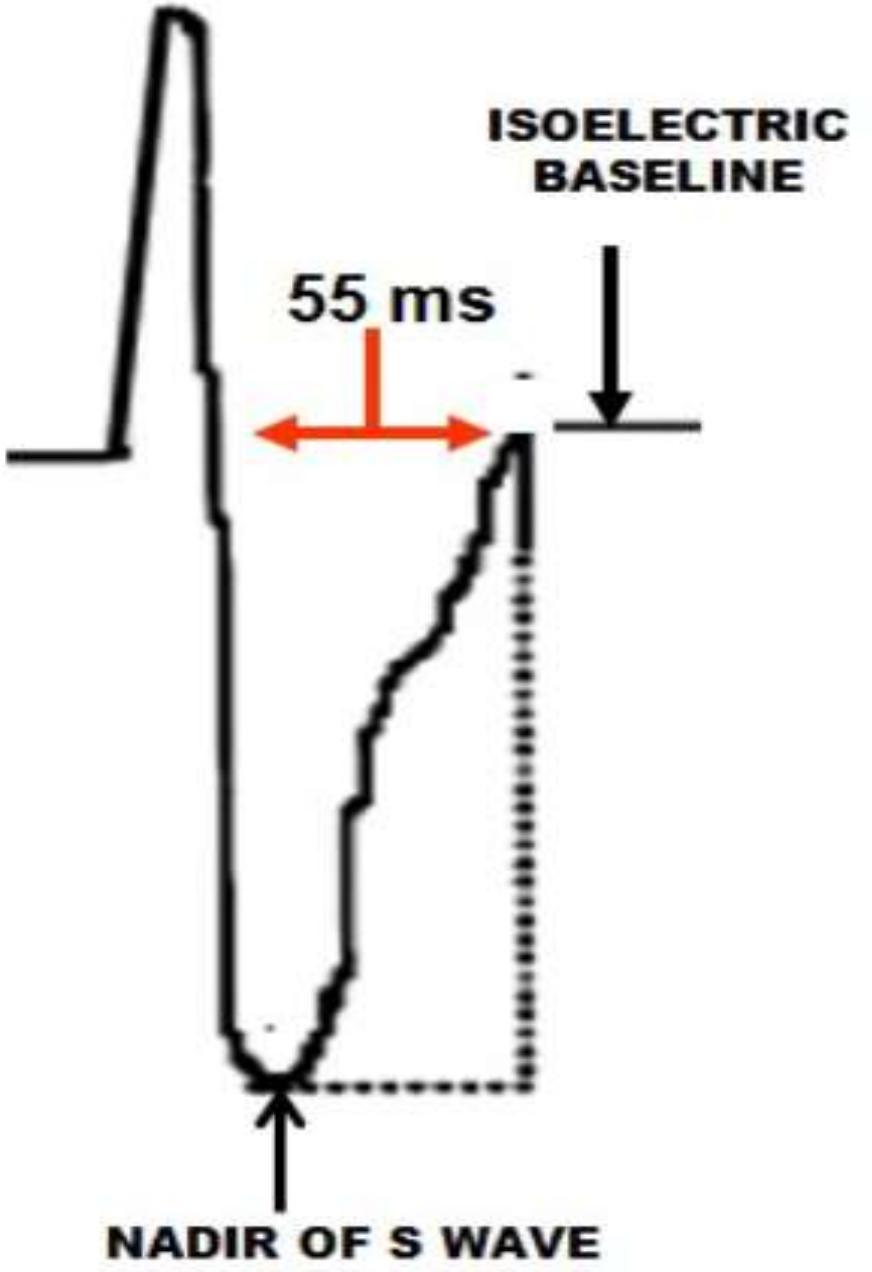
Parietal block: selective dromotropic disturbance on right precordial leads

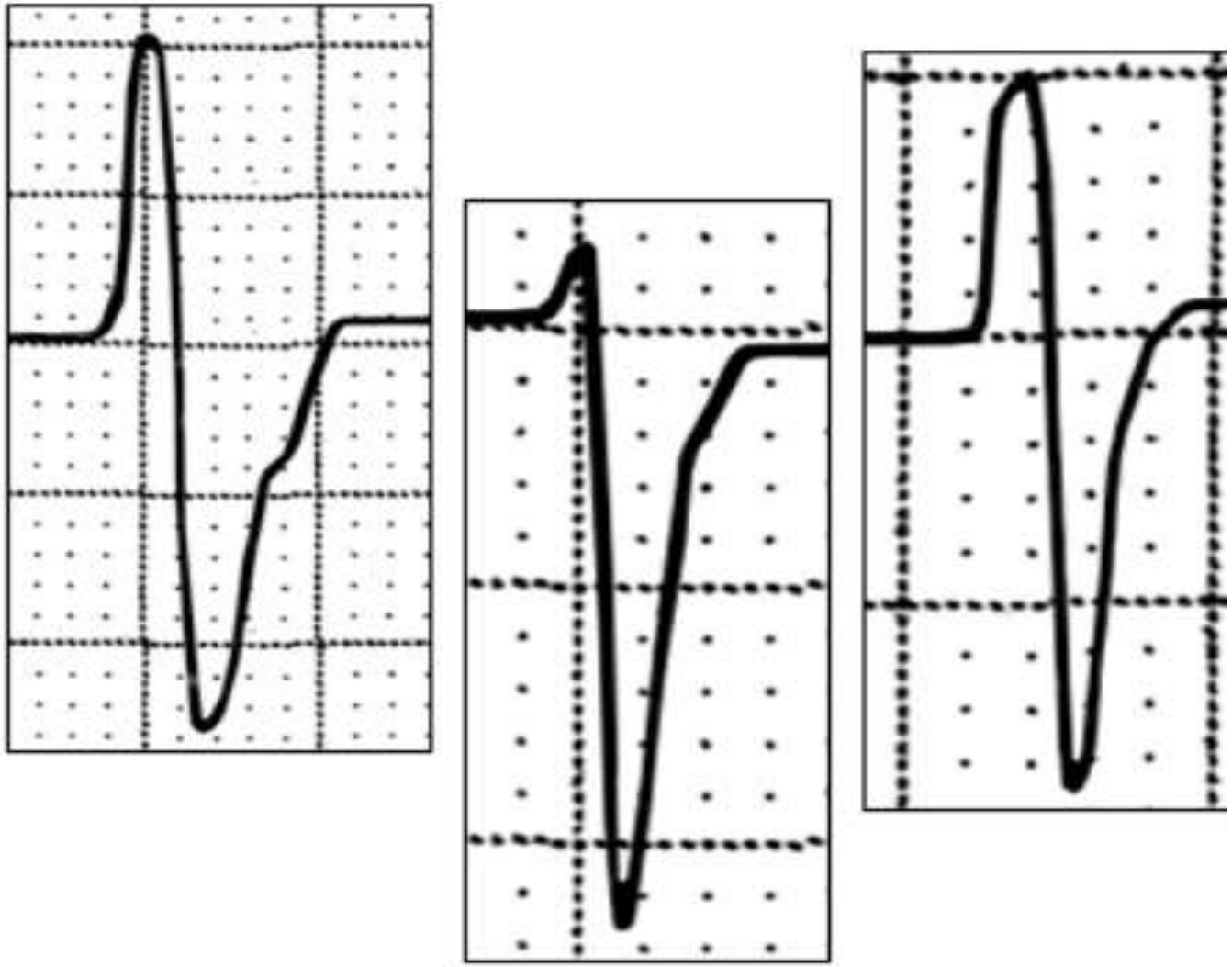




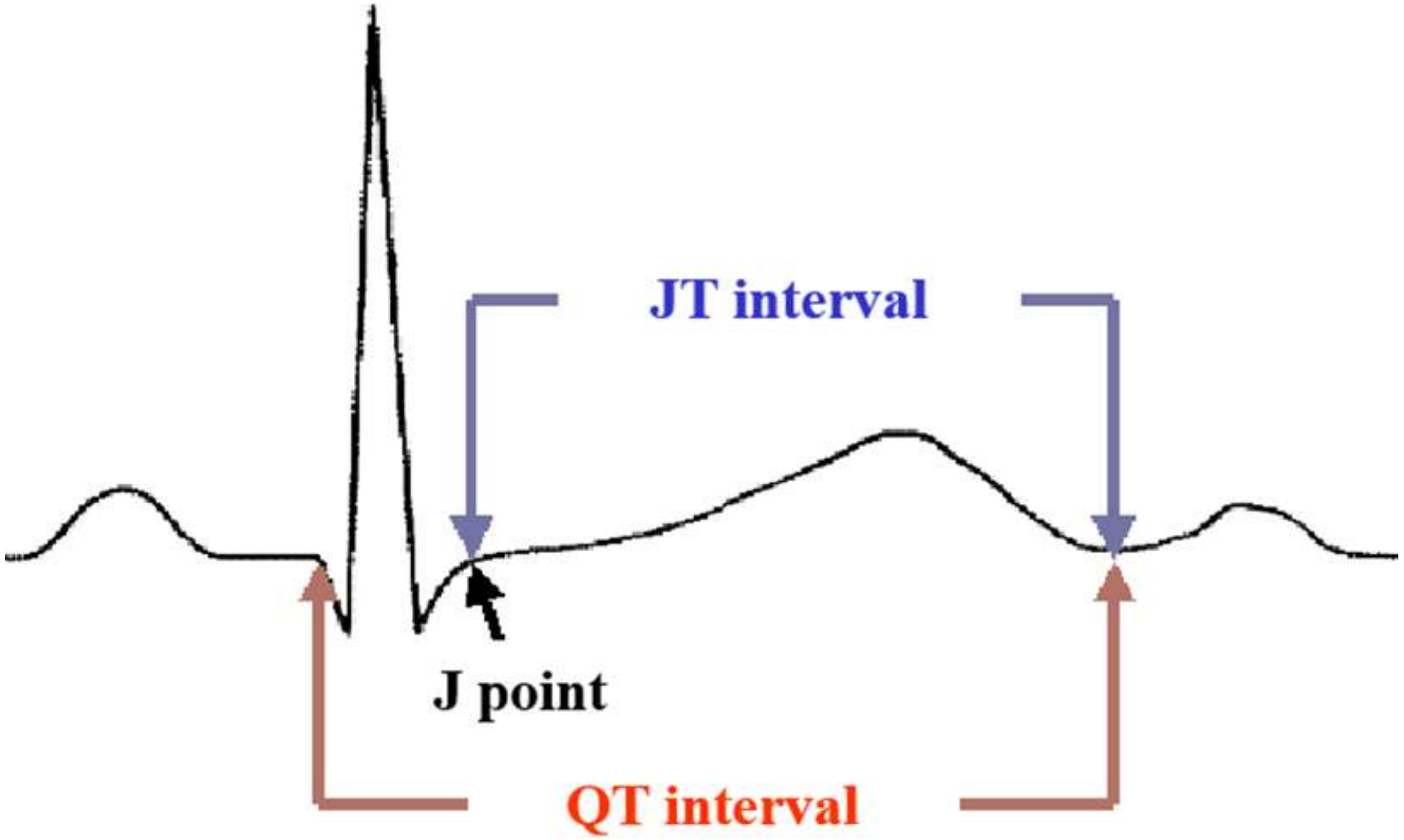
QRSD of $^{V1+V2+V3}$ / $_{V4,\ V5\ and\ V6}$ ≥ 1.2 in approximately 65% of cases. QRS prolongation located in the right precordial leads (**Nasir K. Circulation. 2004**).

Parietal block: selective dromotropic disturbance on right precordial leads



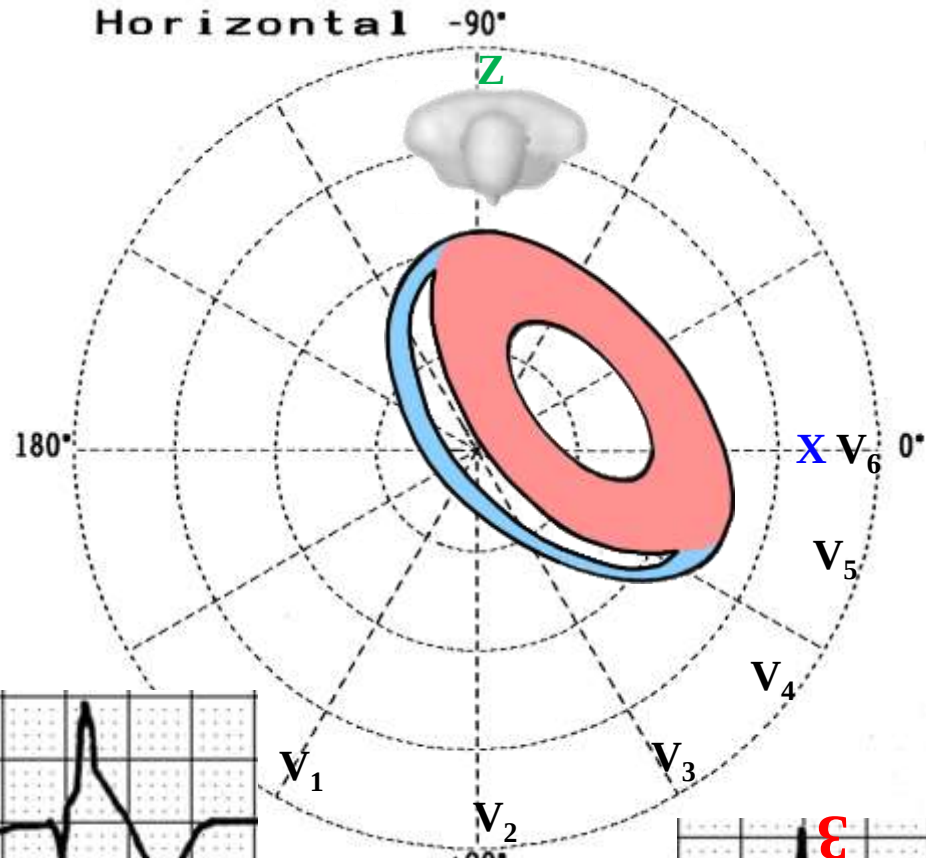


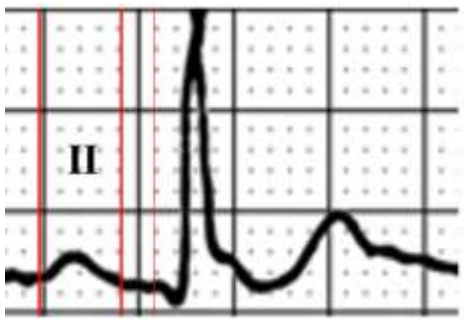
The JT interval value and its limits



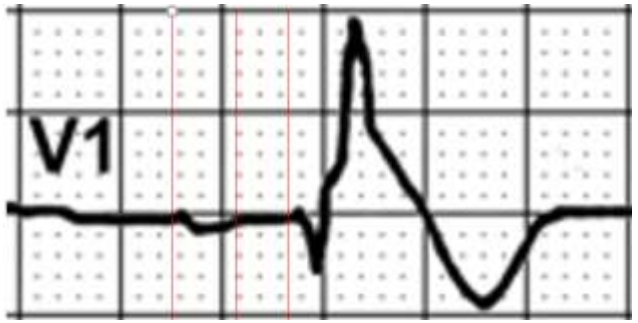
QT interval is used to measure ventricular repolarization; nevertheless, this parameter includes ventricular depolarization (QRS) and represents the so-called electrical systole, which is the addition of ventricular depolarization (QRS) and repolarization (ST/T = JT interval).

If branch block or WPW type ventricular pre-excitation occurs, the QTc interval does not express ventricular repolarization correctly. In these cases, JT interval measurement is more reliable (JT = QT - QRSd) than QT interval, because the parameter excludes depolarization that is prolonged, as a consequence of sequential activation of the biventricular chamber (normally this activation is simultaneous).

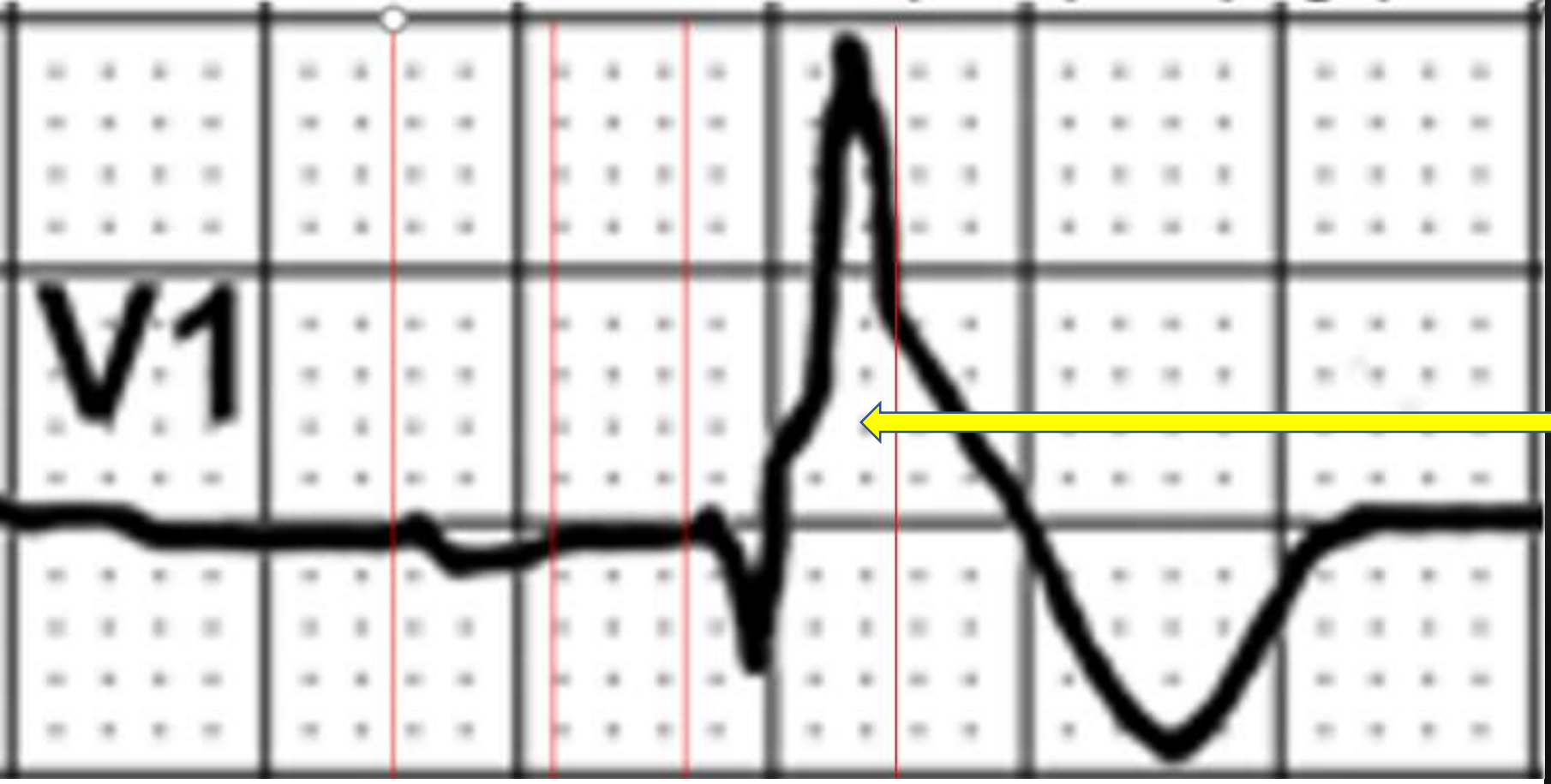




II P-wave duration =160ms: first degre interatrial block

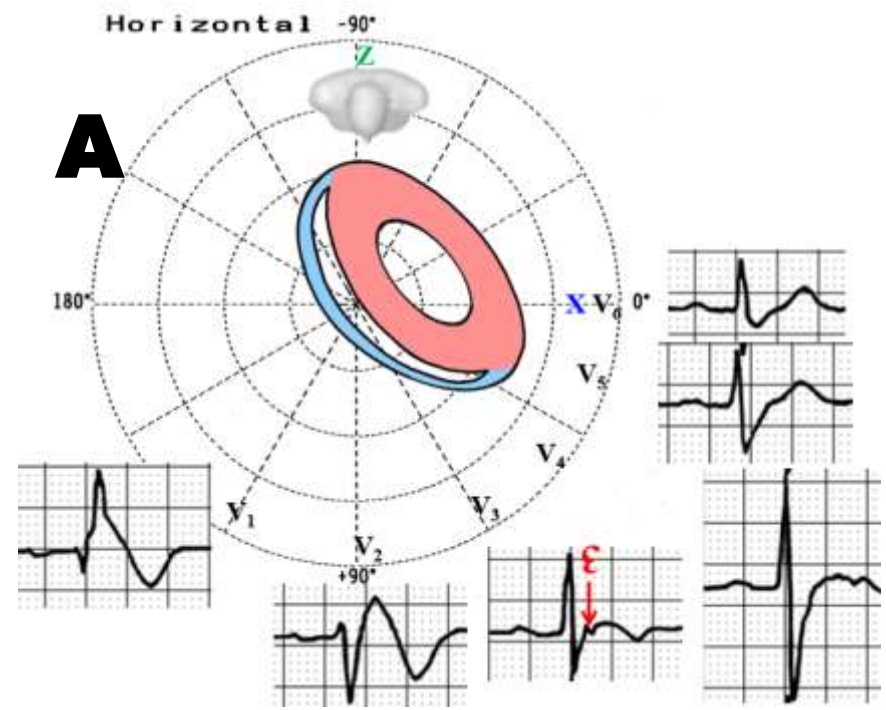


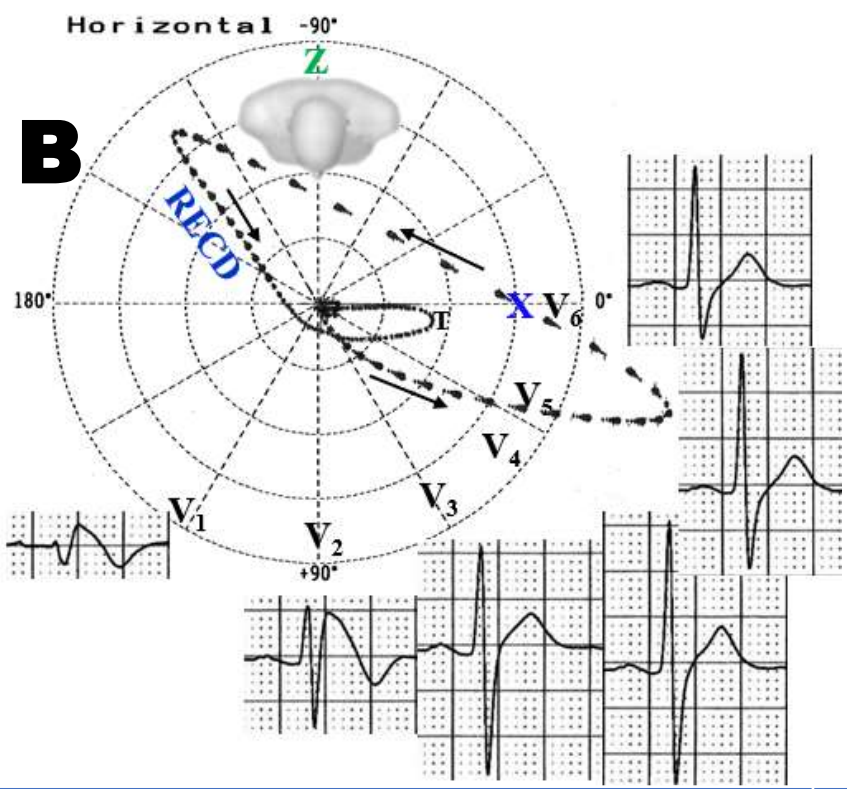
P-duration=120ms in V1, PR segment only 75 ms, PR interval 195ms

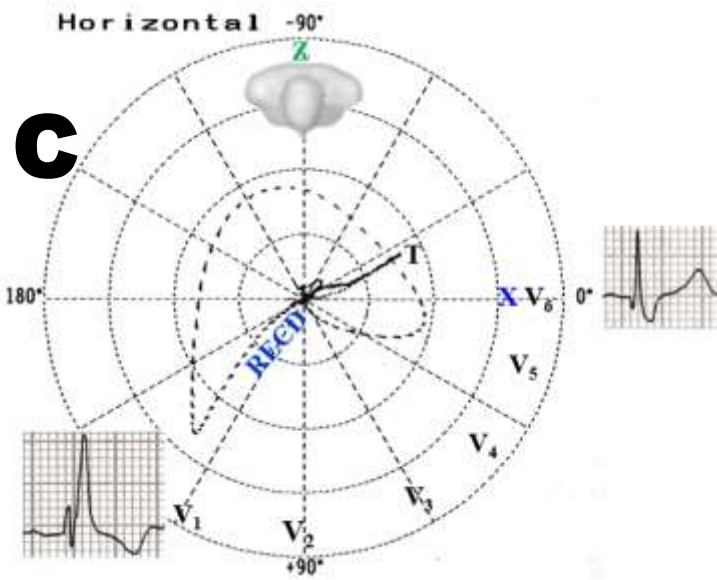


P-duration=120ms in V1, PR segment only 75 ms, PR interval 195ms, broad QRS duration (160ms) triphasic pattern rsR′(CRBBB) extreme prolongation of ventricular activation time until R′ wave apex very similar to lambda wave shape of J-wave. The QRS interval is necessary measured from QRS onset to the J 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 QRS duration as measured 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 **(Ohkubo K, et al, Int Heart J. 2011).**

The "Elf sign" in V1 lead means severe dromotropic disturbance across the RVOT at the middle , and the end of the QRS complex. J-wave with Lambda like shape.

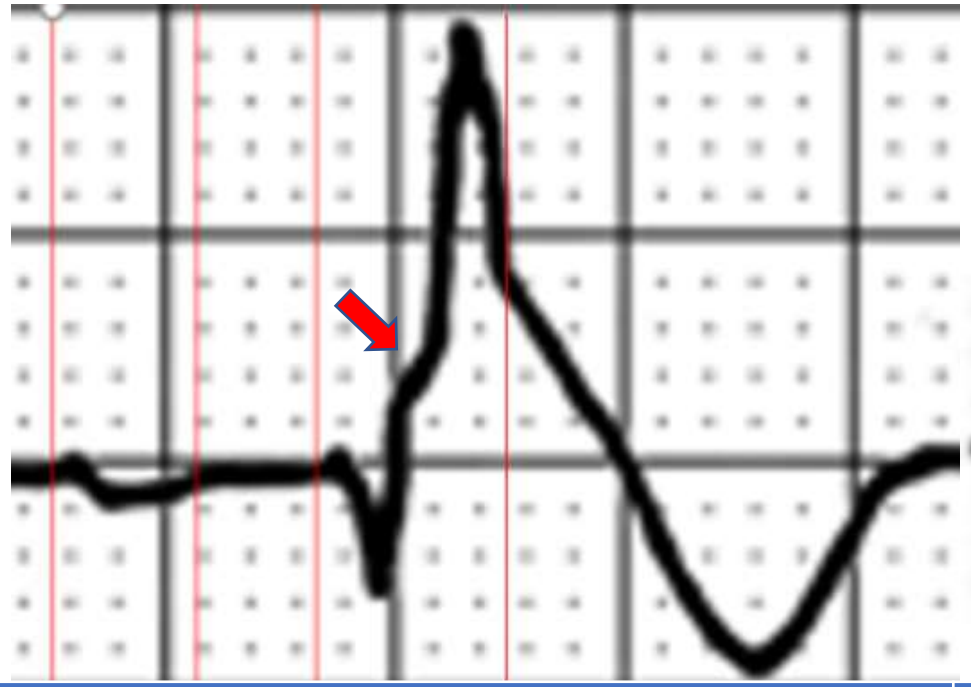


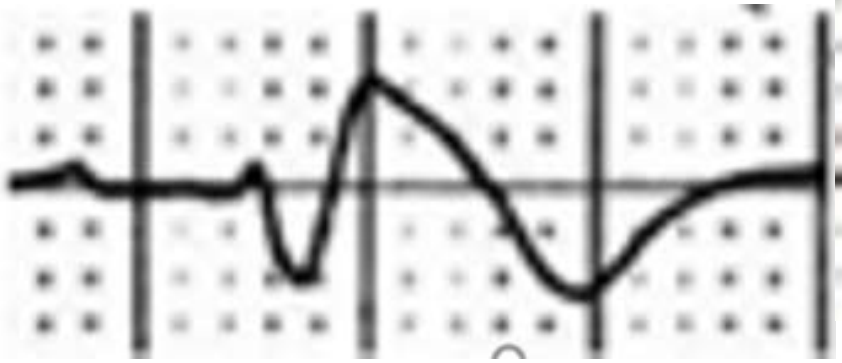


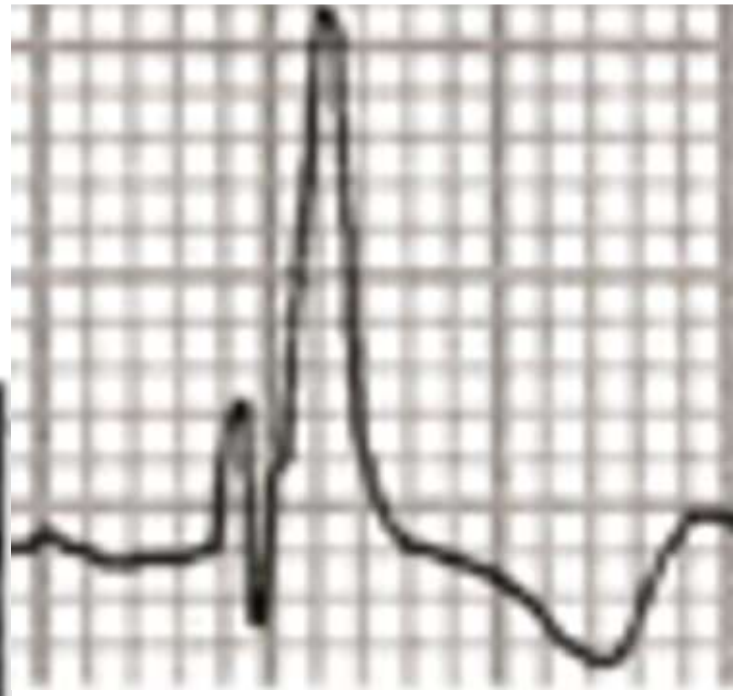


	HP in the present case CRBBB+ Type 1 BrP + "Elf sigh in V1" probable overlapping BrS + ARC	ECG/ VCG correlation in the Horizontal Plane in isolated type 1 Brugada ECG pattern	ECG/VCG in truly CRBBB
A	rSR´ in V1 followed by negative T wave	rSR´ in V1 followed by negative T wave	rSR´ in V1 followed by negative T wave
B	Unfortunately, we do not have the VCG	Right End Conduction Delay (RECD) in the posterior right quadrant. T-loop has finger shape pointed to leftward and efferent limb with slower velocity related afferent limb	RECD in the anterior right quadrant. T-loop has linear shape directed to back and leftward and efferent limb with slower velocity related afferent limb.
C	R`-wave in V1 with a notch in the ascending ramp: middle-end conduction delay. The "Elf sigh" in the right precordial leads means	R`-wave in V1 with oblique ascending ramp without notching	Classical triphasic QRS pattern rSR´ with broad final R´ wave

V1 the present case "Elf sign in V1" Probable overlapping BrS + AC	V1 type 1 Brugada pattern	V1 complete RBBB

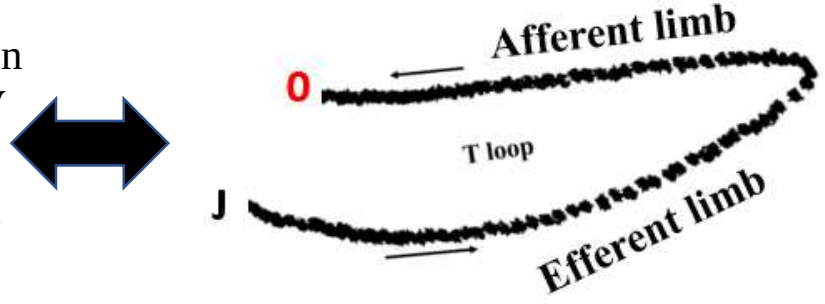


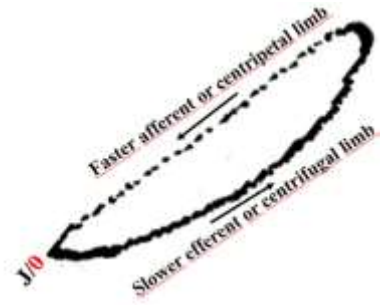




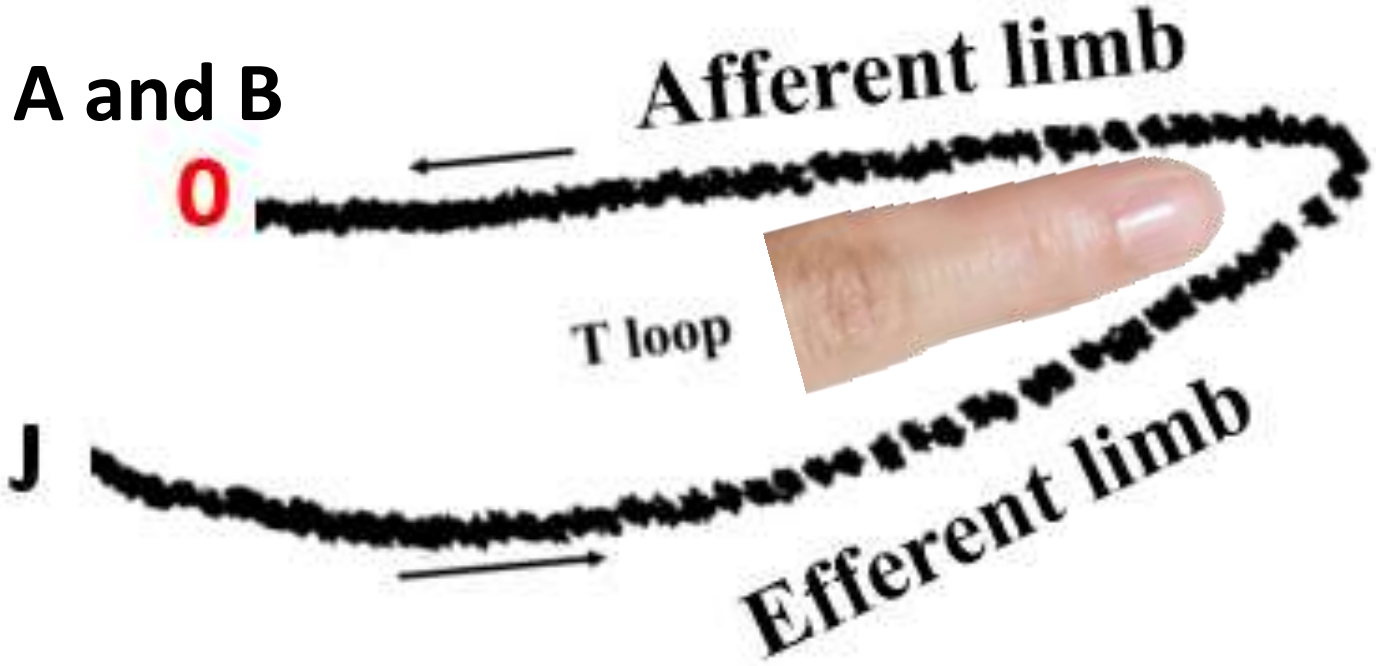
Ascending R` wave with notch (red arrow) followed by negative symmetrical T-wave	Ascending R`wave without notch and oblique ascendant followed by negative symmetrical T-wave	With less oblique ascendant followed by negative asymmetrical T-wave

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



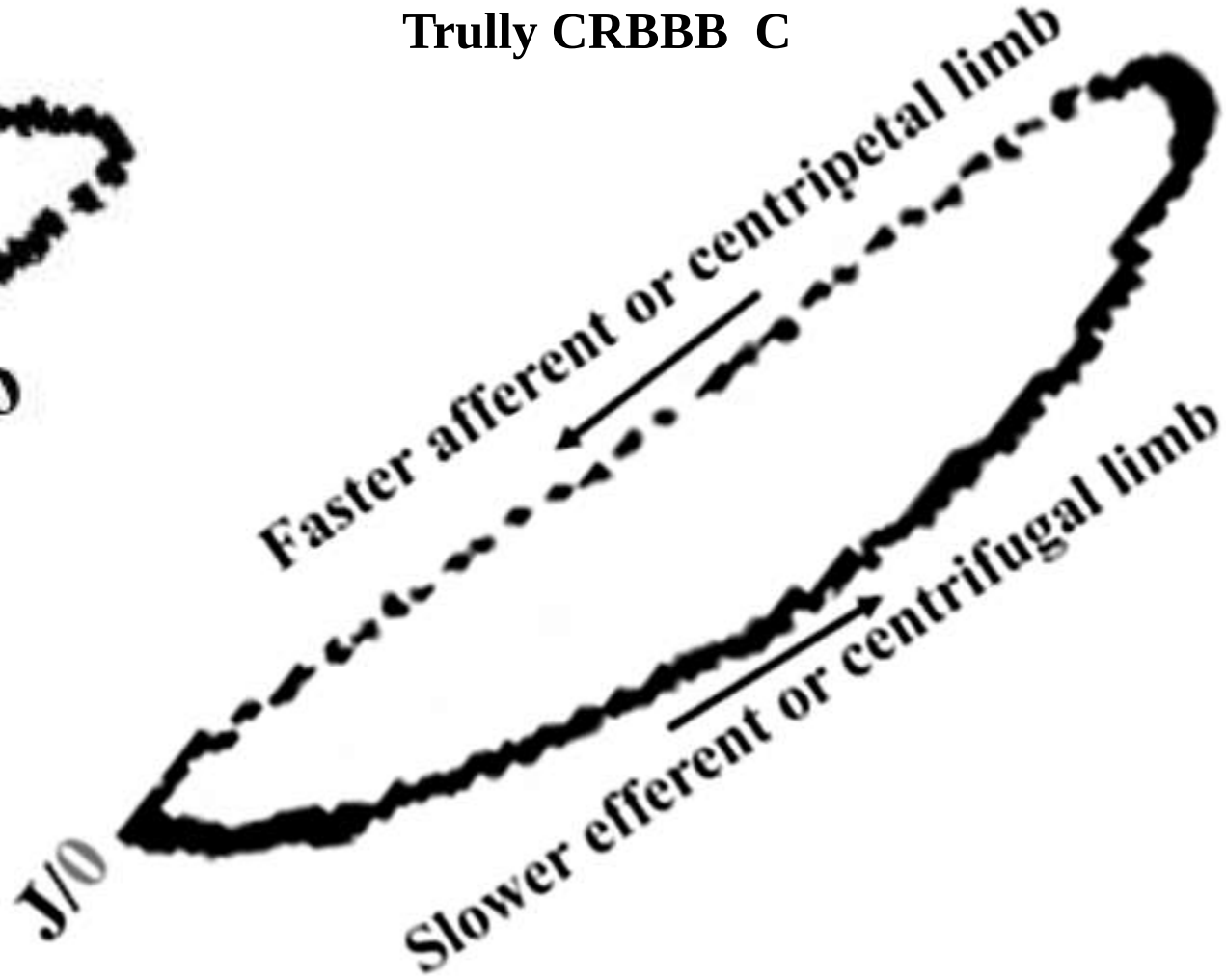


A and B



Points 0 and J are distant (>0.1 mV), indicating in ECG, J point and ST segment elevation ≥0.2 mV (2 mm).Efferent and afferent limbs with similar conduction velocities: repolarization mechanism present. Points J and 0 are separated ≥2 mm, indicating J point and ST segment elevation. When both points are distant >1 mm it indicates ST segment elevation, which is not observed in VCG. This may be indicative of early repolarization pattern, Brugada syndrome with types 1 and 2 pattern, idiopathic ventricular fibrillation, congenital short QT syndrome, ST-segment elevation acute coronary syndrome, Prinzmetal variant angina, acute pericarditis in phase 1, left ventricular aneurysm of anterior wall. Both the afferent and efferent limbs present slow inscription, dashes very close to one another. Shape: elliptic or with "finger" shape. Direction: to the left, around +5°. Rotation: counterclockwise. Magnitude: 0.34 mV. QRS/T angle: 7

Trully CRBBB C

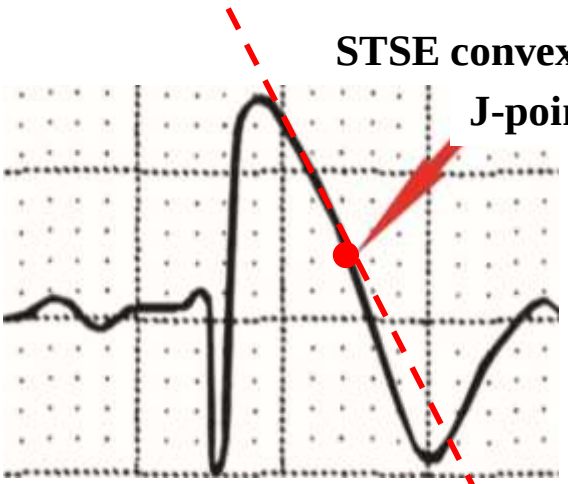


Points J and 0 together. Shape: elongated, elliptic or linear. Direction: to the left and front, around 23° (-14° to +45°). Efferent limb of slower inscription than the afferent one. Rotation: nearly always counterclockwise, except for the linear morphology. Magnitude: mean 0.34 mV (0.15 to 0.60 mV).QRS/T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

Proposal of classification of type 1 Brugada pattern

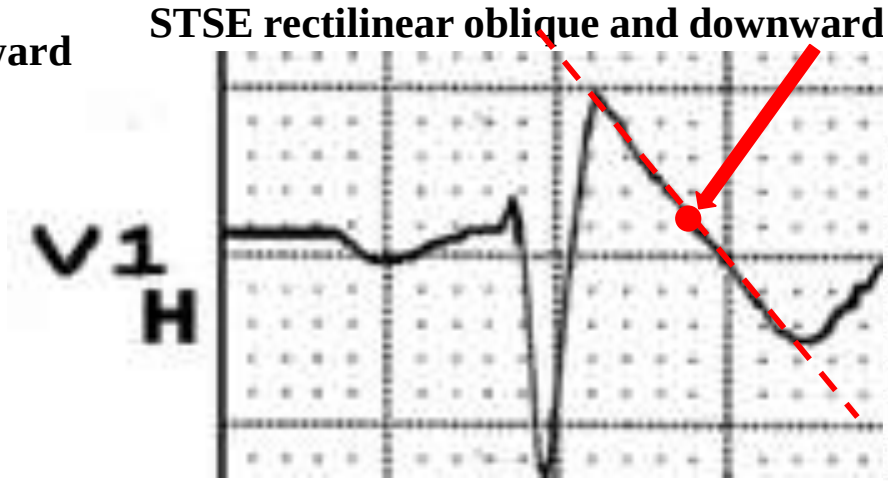
Right precordial leads

Subtype 1A

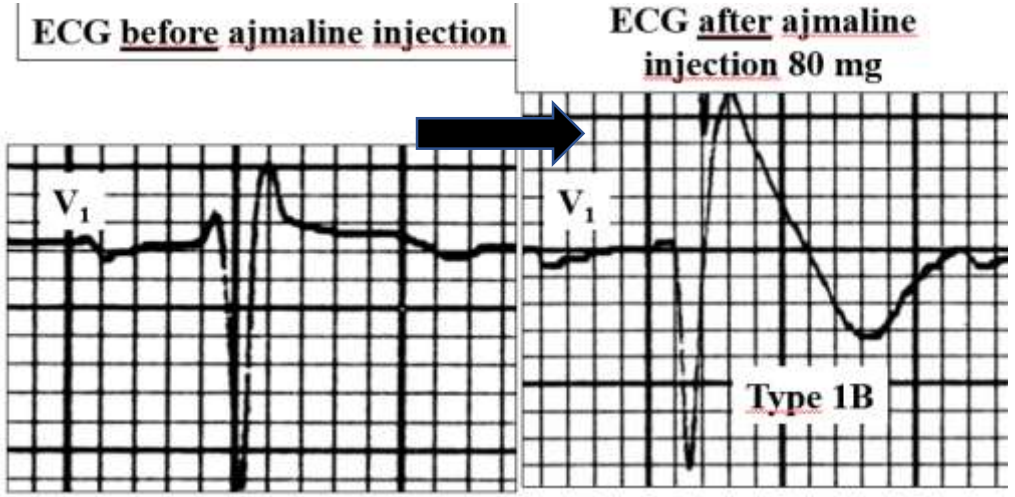


The dotted line is the tangent line

Subtype 1B

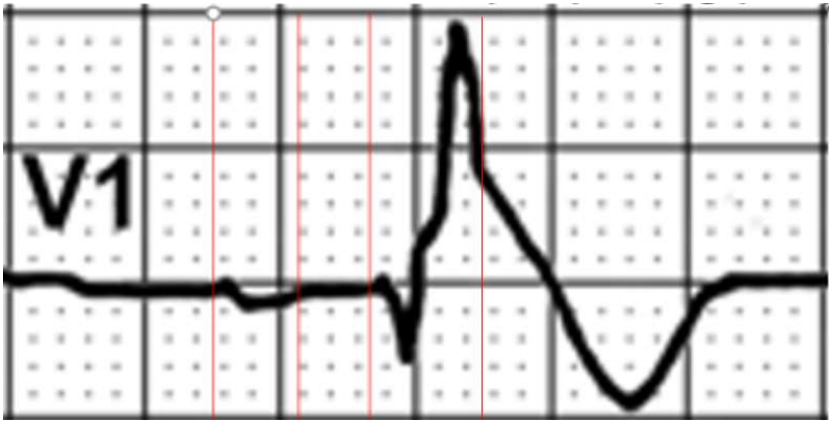


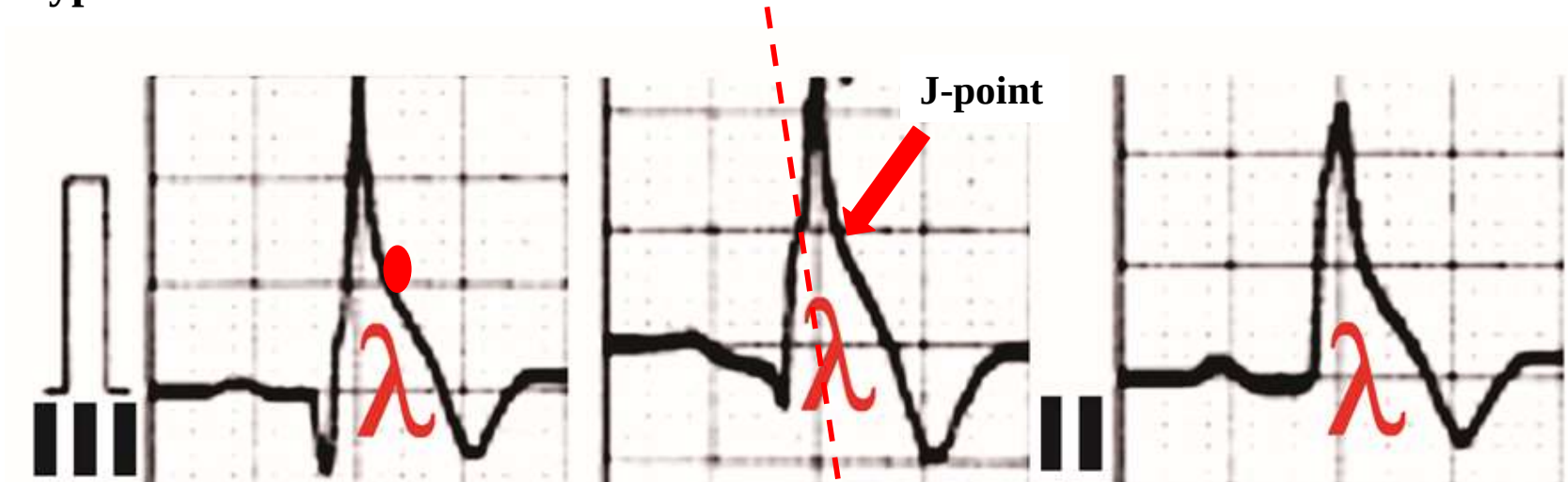
The dotted line is the tangent line



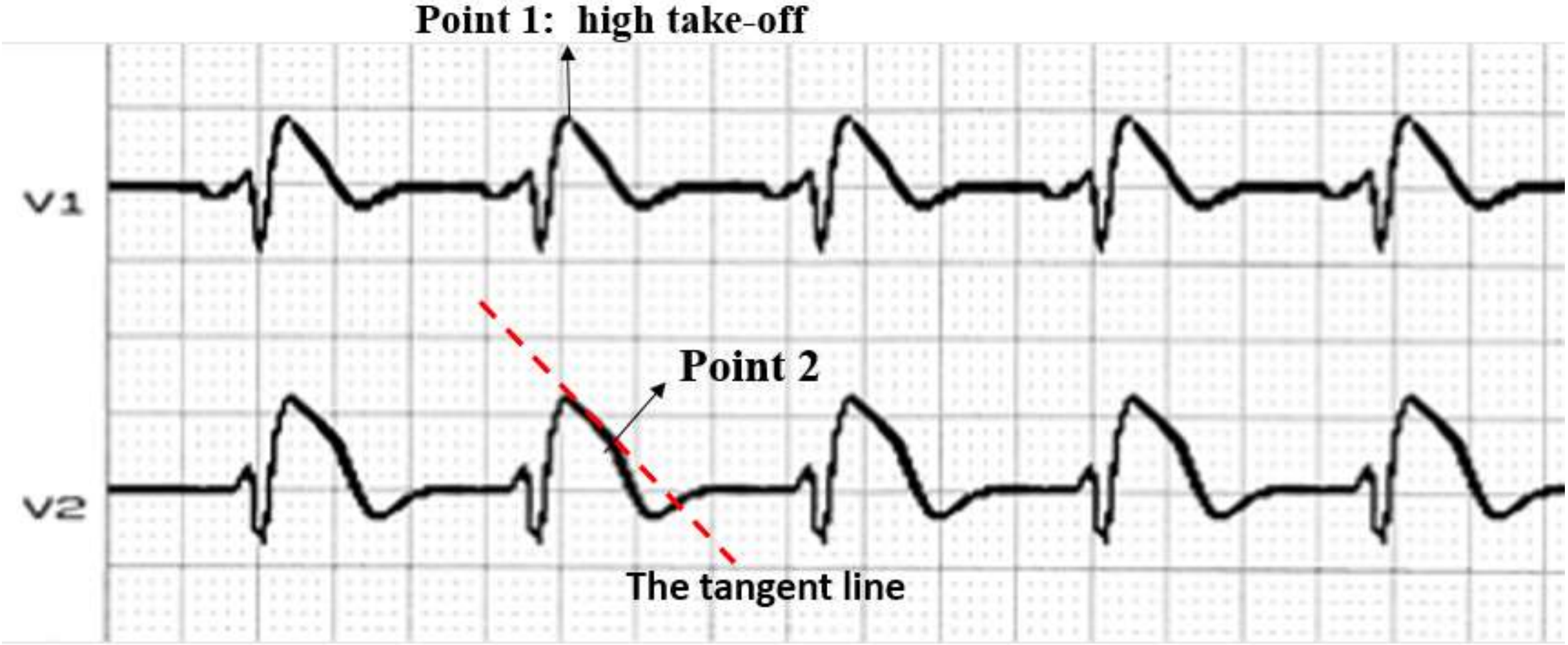
Inferior leads

Subtype 1C



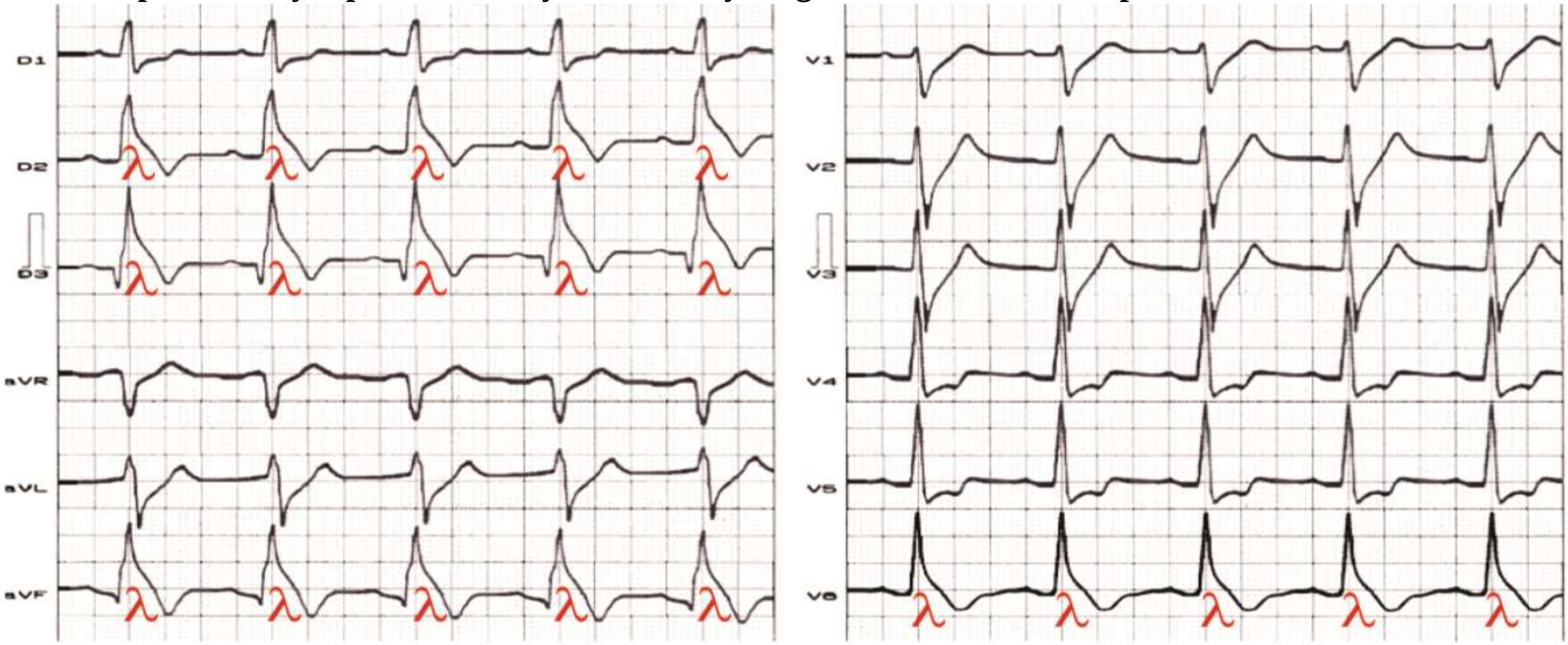


Where is the end of the QRS complex: the J point?



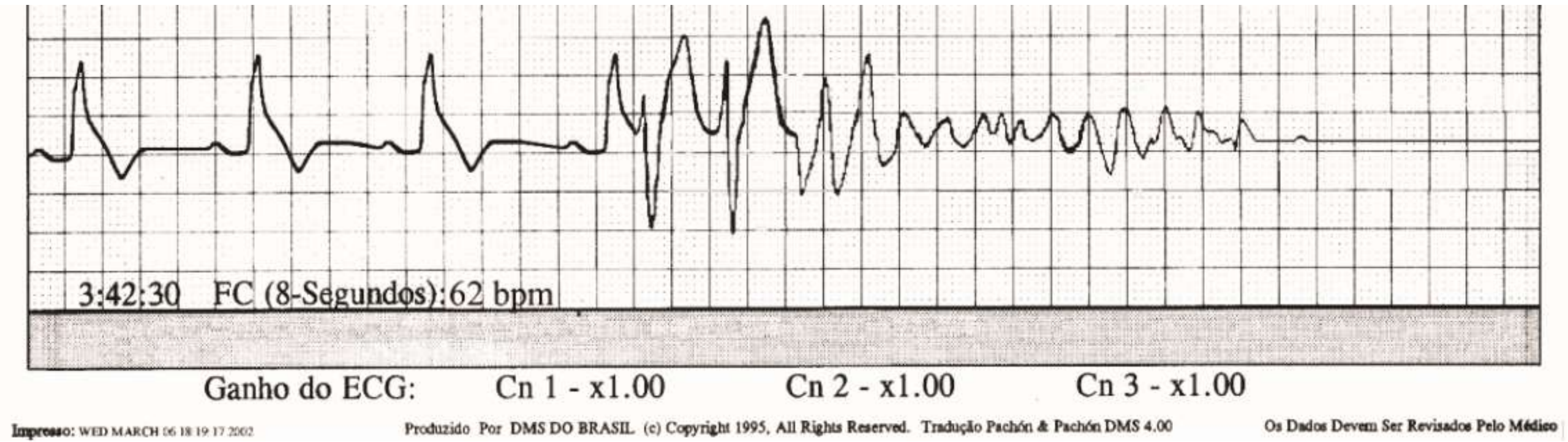
Answer: Point 2. Point 1 corresponds to high take-off and point 2 indicates the end of the QRS complex

Example of early repolarization syndrome in young Thailand man with episode of cardiac arrest



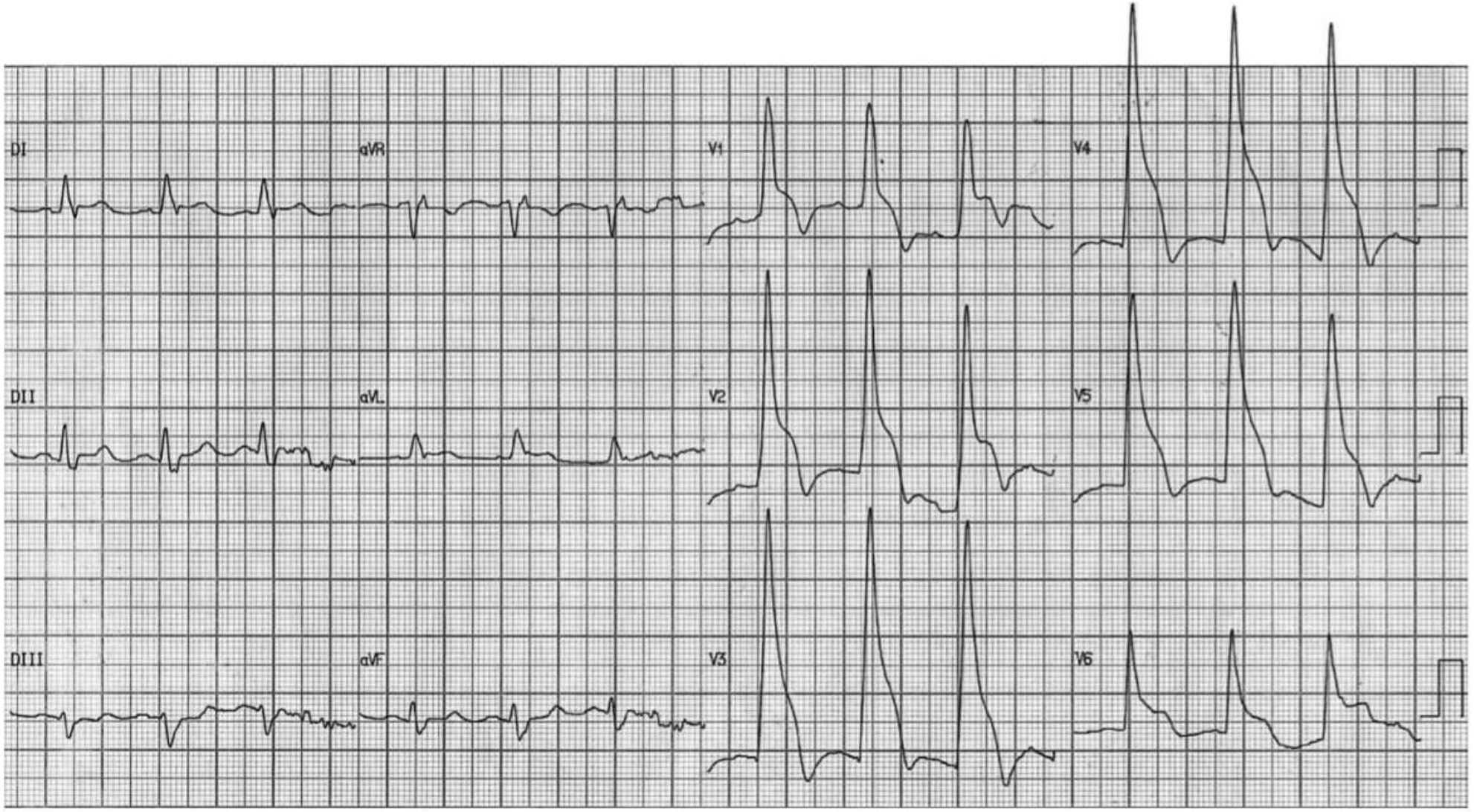
The ECG shows persistent ST segment elevation in the inferior and apical leads J-wave slurring or Lambda wave , associated to concomitant reciprocal or mirror image in the anterior wall that was not modified with the use of sublingual nitrate in absence of hypothermia, electrolyte imbalance or ischemia.

Riera AR, et al. J Electrocardiol. 2004.

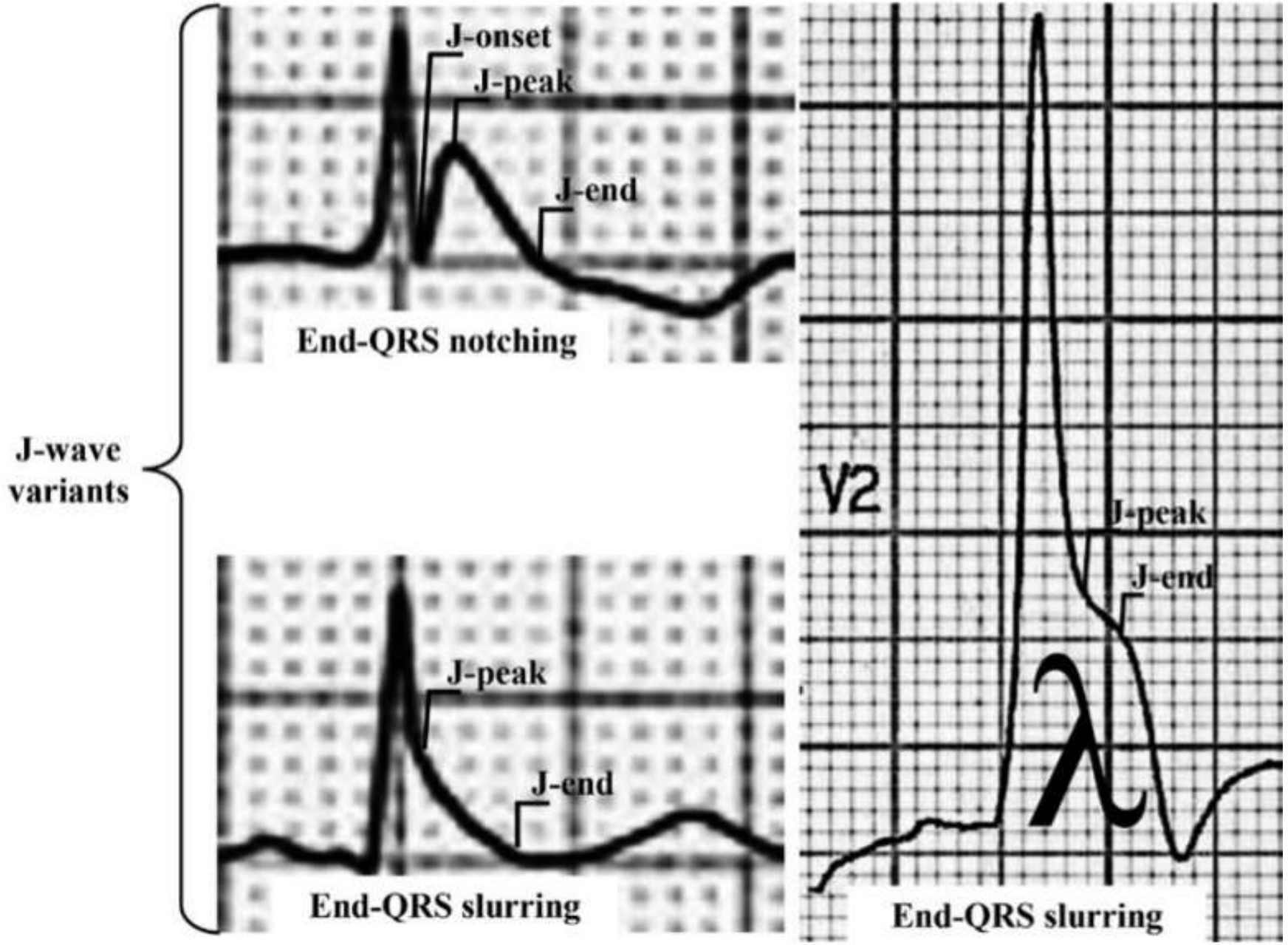


Holter monitoring recorded the final event, manifest by PVT episode with initial short-coupling ventricular premature contractions (R on T) that ended quickly in VF and asystole. Pattern 1C of repolarization has been observed in acute myocardial infarction by Kukla et al (Kukla 2007). These authors raised the hypothesis that the "Lambda-like ST" could be a new marker of risk of acute infarction with ST segment elevation. The lambda-like J wave could be caused by ischemia although the mechanism has not been fully elucidated (**Tomcsányi J, et al. J Electrocardiol. 2019**). Yagi et al reported a case of AMI that showed discrepancy between ST-T elevation with lambda-like ischemic J wave in a broad area and coronary angiographical finding of diagonal branch occlusion (**Yagi S et al. J Med Invest. 2019**). A special form of this lambda-like ST segment elevation accompanied by a QRS (R wave) of more than 10 mm has also been described. This was termed a "triangular QRS-ST-T waveform" pattern (**Ciprinai A, et al. J Electrocardiol. 2018**). It is also known that this unique ECG sign does only occur in occlusive CAD (**Tarantino N, et al. J Electrocardiol. 2018**). The lambda-like ST-elevation ECG pattern is extremely rare in patients with type 2 myocardial

infarction (T2MI) triggered by variant angina or coronary spasm. When this ECG pattern appears, sudden cardiac death (SCD) caused by lethal ventricular arrhythmia may occur because clinicians do not pay sufficient attention to this phenomenon. The lambda-like ST-elevation pattern is identified with other ST-elevation patterns by geometry and may be a new risk predictor for lethal ventricular arrhythmia on ECG. When this pattern is identified, clinicians should adopt aggressive therapeutic strategies, including ICD implantation and etiological treatment (**Wang G, et al. Medicine (Baltimore). 2018**). Recently we described a case of ACS with transient prominent anterior QRS forces (PAF) caused by proximal subocclusion of the LAD coronary artery before the first septal perforator branch. The ECG change indicates left septal fascicular block (LSFB) with associated slurring-type giant J-wave. Currently, this J-wave variant is considered as a lambda-like wave or QRS-ST-T "triangulation". Its presence is indicative of poor prognosis because of the risk for cardiac arrest as a consequence of VT/VF. See figure next slide.

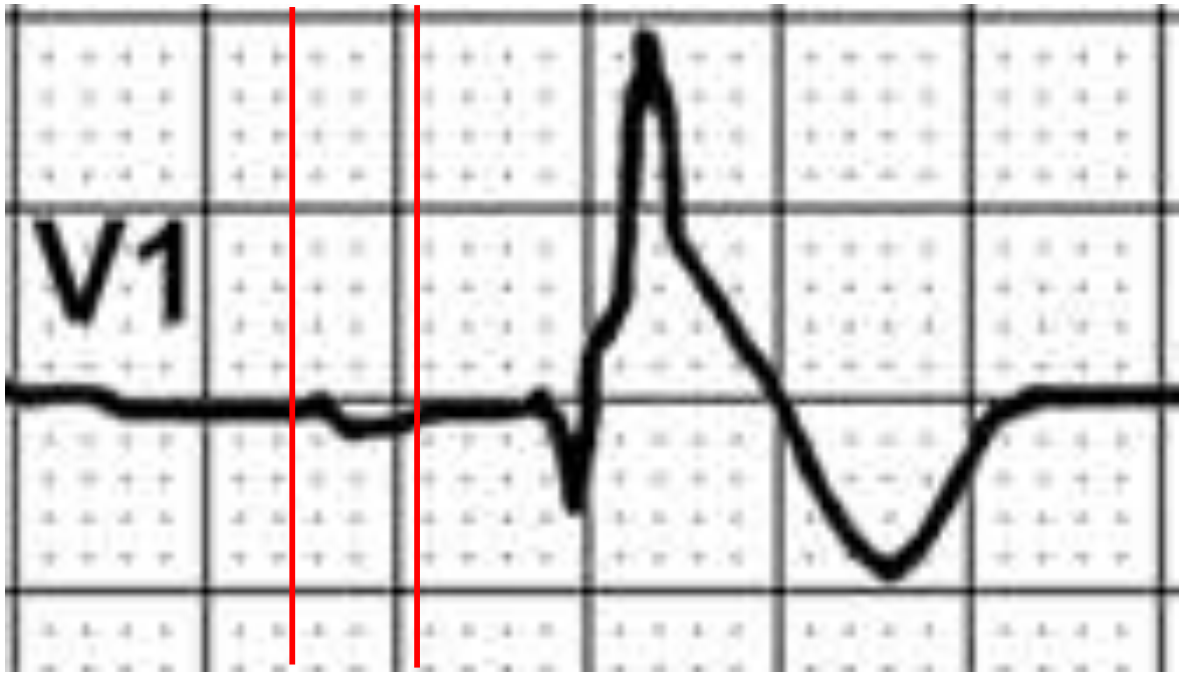


Sinus rhythm, heart rate 88 bpm, P-wave duration 120 ms, P axis +55°, PR interval 160 ms, prolonged R-wave peak time (RWPT) in V1–V2, QRS-axis-10°, QRS duration 120 ms. No clear distinction between the end of QRS and the beginning of ST (QRS–ST–T "triangulation"), embryonic q wave in V3–V4, PAF: R-wave "in crescendo" from V1 to V4 and decreasing in V5–V6, very high J-wave of end-QRS slurring type across all precordial leads, and prolonged QT/QTc interval (500/588 ms). Note: J-wave end-QRS slurring with lambda-like/ Gussak-wave (**Gussak, I. J Electrocardiol. 2004**) or triangular QRS-ST-T waveform. Conclusion: Left atrial enlargement, LSFB (**Perez-Riera, de Abreu, Barbosa-Barros, Nikus, & Baranchuk. 2016**), and giant slurring variant J-wave end-QRS.

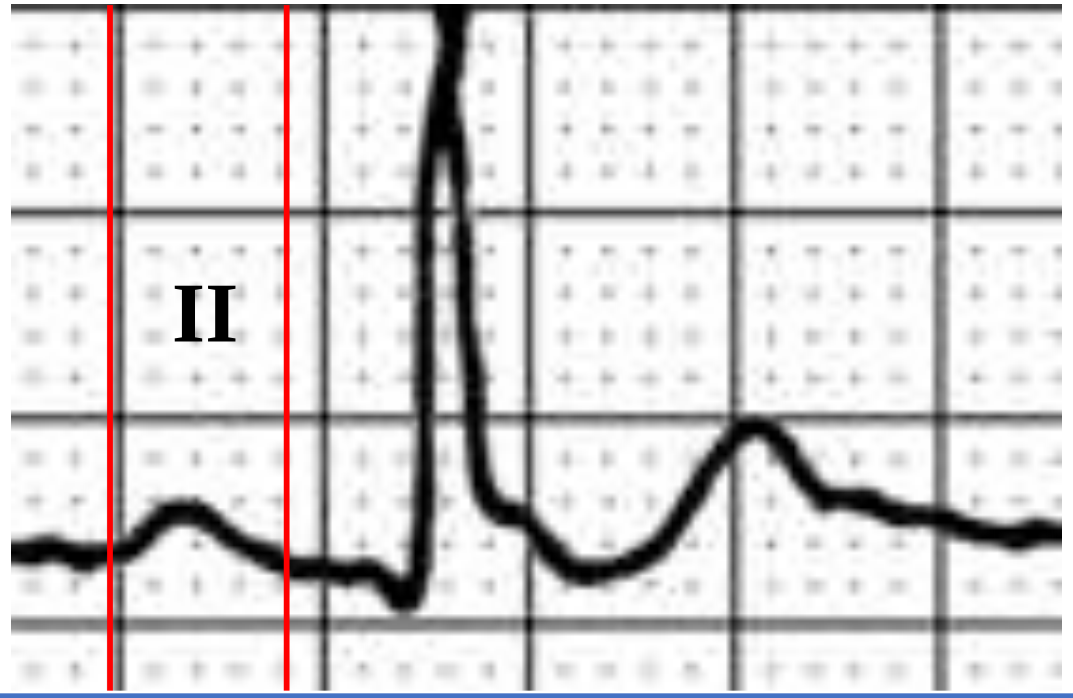


Schematic figure of J-wave variants: end-QRS notching, end-QRS slurring represented by the present case. Early repolarization with or without ST-segment elevation is characterized by end-QRS notching or slurring (the present case).

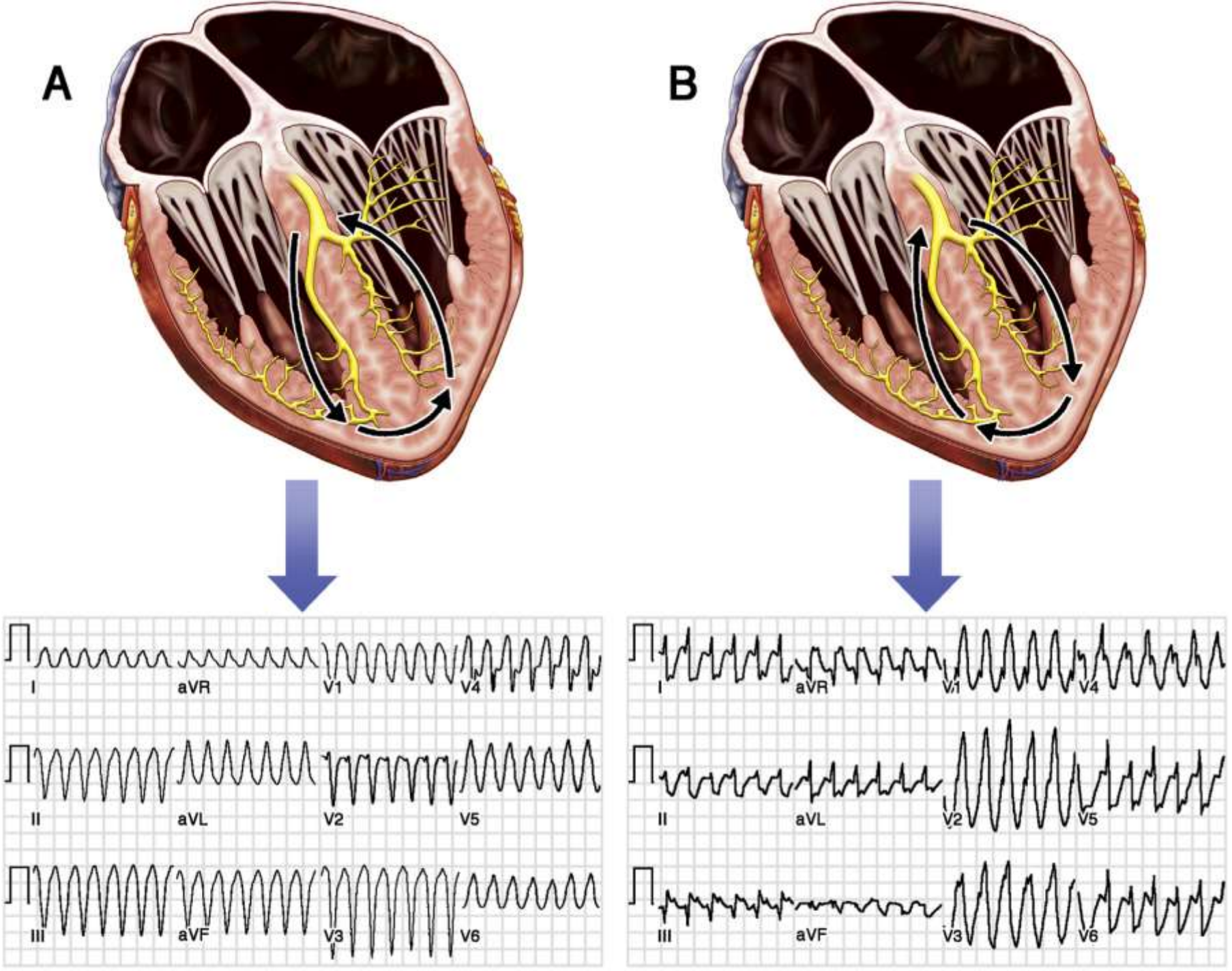
Significant P-wave dispersion (= 40 ms)



V1 P-wave duration =120ms

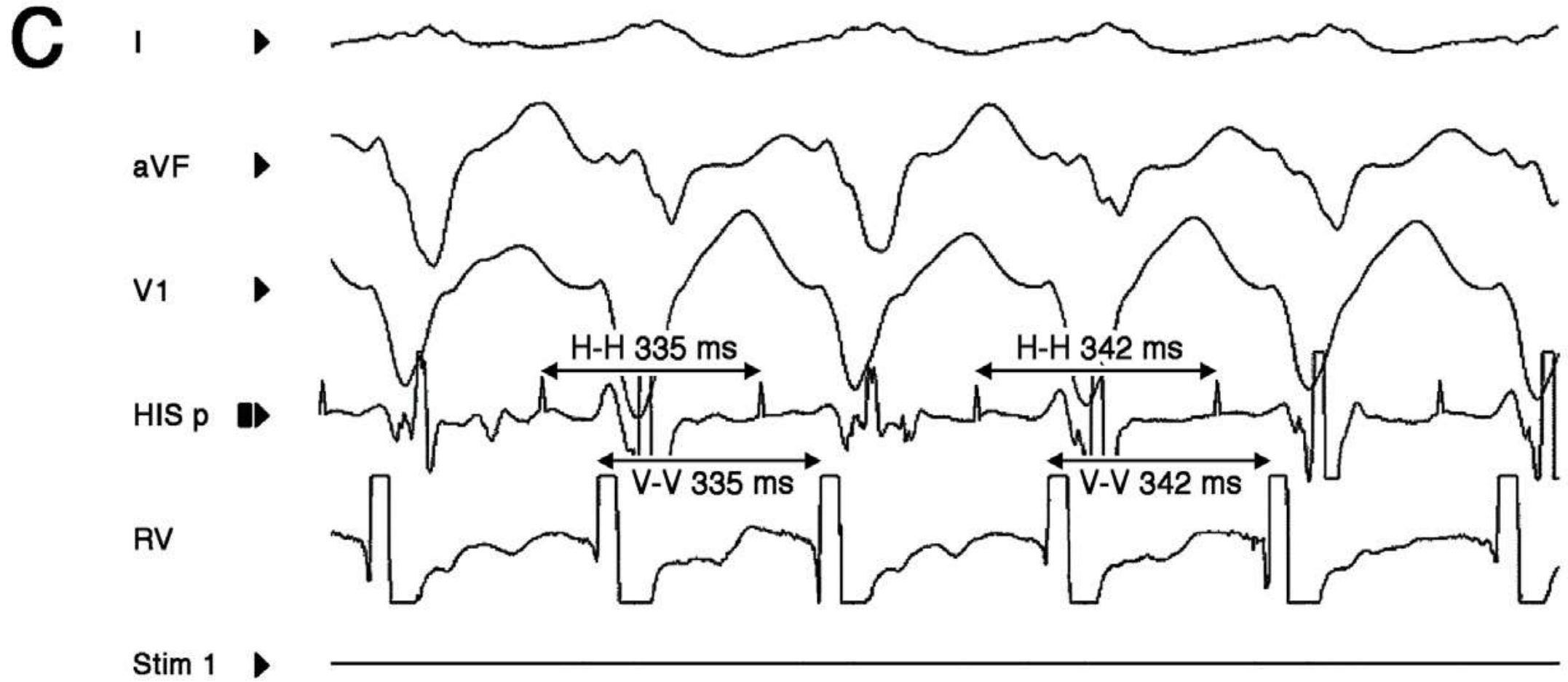


II P-wave duration =160ms: first degree interatrial block



(A) BBRVT antegrade conduction down the RBB and retrograde conduction along the LBB resulting in an ECG with a LBBB morphology.

(B) BBRVT circuit with antegrade conduction down the LBB and retrograde conduction along the RBB resulting in an ECG with a RBBB morphology.



C. Intracardiac tracing of BBRVT revealing the H-H interval preceding and predicting the subsequent ventricular-ventricular interval. BBRVT ¼ bundle branch re-entrant ventricular tachycardia; H ¼ His; V ¼ ventricular.

Summary of ECG diagnosis

1. **Sinus bradycardia.; 2. first degree interatrial interatrial block and /or Left atrial enlargement.; 3. P-wave dispersion; 4. left posterior fascicular block (LPFB).; 5. Complete Right Bundle Branch Block.; 6. Parietal block; 7. "elf sign"; 8. Lambda shape or J-slurring wave; 9. Epsilon wave; 10. Negative T wave from V1 to V4 and; 11. Induced idiopathic bundle branch re-entrant ventricular tachycardia (BBRVT) with an underlying genetic etiology.** Recently, Prof. Melvin Scheinman group, studying apparent idiopathic BBRVT, identified the first genetic culprits for this life-threatening arrhythmia, providing further insight into its underlying pathophysiology and emphasizing a potential role for genetic testing in this condition. Their findings also highlight BBRVT as a novel genetic etiology of unexplained SCD that can be definitely treated with RFCA. The authors studied cases of BBRVT with normal biventricular size and function recruited from 6 North American centers. Enrollment required a clinically documented wide complex tachycardia and BBRVT proven during EPS. Study participants were screened for mutations within genes associated with cardiac conduction system disease. Pathogenicity of identified mutations was evaluated using in silico phylogenetic and physicochemical analyses and in vitro biophysical studies. Among 6 cases of idiopathic BBRVT, each presented with hemodynamic compromise and 2 suffered cardiac arrests requiring resuscitation. Putative culprit mutations were identified in 3 of 6 cases, including 2 in SCN5A (Ala1905Gly [novel] and c.4719C>T [splice site mutation]) and 1 in LMNA (Leu327Val [novel]). Biophysical analysis of mutant Ala1905Gly Nav1.5 channels in tsA201 cells revealed significantly reduced peak current density and positive shifts in the voltage-dependence of activation, consistent with a loss-of-function. The SCN5A c.4719C>T splice site mutation has previously been reported as disease-causing in 3 cases of BrS, whereas the novel LMNA Leu327Val mutation was associated with a classic laminopathy phenotype. Following catheter ablation, BBRVT was noninducible in all cases and none experienced a clinical recurrence during follow-up. See figure next slide.

Definitive etiologic diagnosis: BrS, ARC, or both overlapping? (Hoogendijk MG Front Physiol. 2012.)

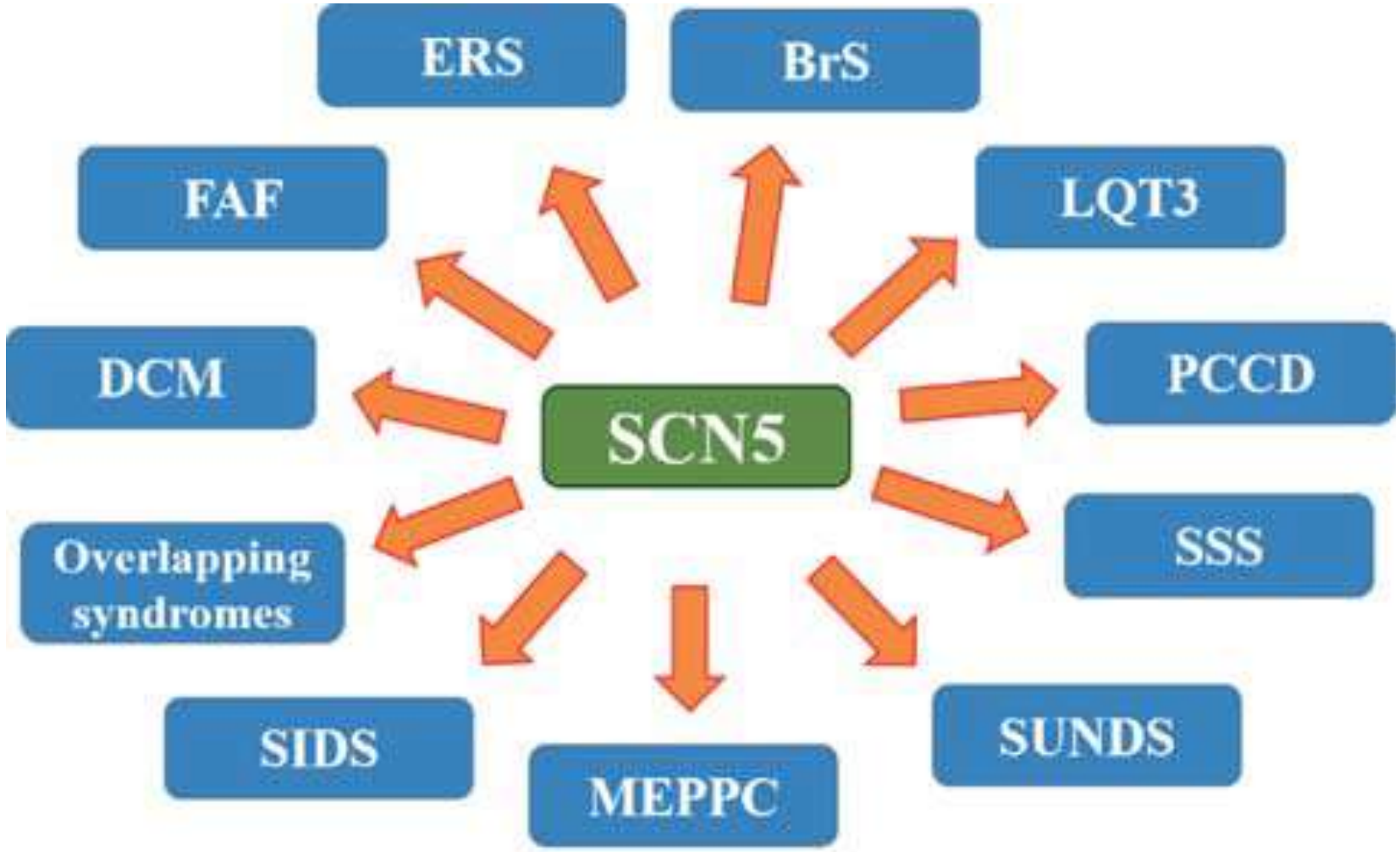
	Factors that suggest BrS	Factors that suggest ARC	Factors that suggest Overlapping
Family history	+ Paternal line East Asian descent. His 2 brothers both had ECG patterns typical for BrS, his mother had drug-induced BrS.		
Dromotropic disturbance	+ He had been examined for bradycardia 6 years earlier	Possible	Suggestive
Genetic mutation SCN5A gene, and one TMEM43	SCN5A	TMEM43	Suggestive
Normal echo and CMRI	+ Normal	Possible ant early stage	
ECG with Epsilon wave	It is possible though rare (**Letsas KP et al. Heart Rhythm. 2011**)	+ Considered a Mayor depolarization/conduction abnormalities criteria (**Marcus FI, et al. Circulation 2010**)	Suggestive
Spontaneous Type 1 Brugada	+ Risk marker	Corrado et al described in canceled forms. It was found in 14% of young sudden death victims (**Corrado D. Circulation. 2001**)	Yes
EPS with induction of monomorphic VT	Possible but unusual	Suggestive	Possible
EPS left sided posterior fascicular tachycardia	Recently observed by (**Roberts JD, et al. JACC Clin Electrophysiol. 2017**)	?	?

Conclusion: Phenotypic overlap between AC and BrS

The clinical features of BrS and AC are frequently in patients. The first epicardial electrograms underlying the Brugada ECG pattern support the notion that conduction disturbances in structural discontinuous myocardium underlie the BrS (**Holmqvist F, Heart Rhythm. 2008) :** (**Nademanee K, et al. Journal of the American College of Cardiology. 2015**). The structural RV abnormalities in ARVC therefore most likely predispose patients to develop the Brugada ECG pattern and the associated ventricular arrhythmias. The strict exclusion of structural heart disease in the BrS as advocated in the 2005 consensus repor appear arbitrary. These conclusions plead for a broadening of the diagnostic criteria by making a distinction in patients with the Brugada features in the presence and absence of identifiable underlying structural heart disease. This patients group is heterogeneous and incorporates various underlying cardiac conditions besides ARC : the Brugada ECG pattern can also occur in the setting of Chagas' disease (**Chiale PA,et al.Am J Cardiol. 1982; Brito MR, et al. Europace. 2010**). Thus far, prospective data are available of only 17 ARVC patients with drug-induced Brugada ECG (**Peters S. et al. Europace 2008**) which is associated with a low arrhythmogenic risk in the setting of BrS (Probst et al. Only one monomorphic VT was recorded during follow-up. Secondly, the myocardial condition and arrhythmogenic substrate that facilitates the Brugada features may change over time in patients with and underlying cardiomyopathy. In the ARC follow-up study by Peters, the reproducibility of drug-induced Brugada ECG pattern was four out of eight. Until the arrhythmogenic risk in patients with the Brugada ECG pattern in the setting of structural heart disease has been assessed, it appears reasonable to avoid or treat known triggers arrhythmias in BrS patients such as certain pharmacological agents (**Postema PG, et al. J. Am. Coll. Cardiol.**) and fever The literature demonstrates scientific evidence that features of both ARVC and BrS may occur in some patients.

Previous clinical studies demonstrated a phenotypic overlap between the AC and BrS. In 1986, Martini et al(**Martini B, Am Heart J. 1989**) described six patients who experienced ventricular fibrillation and had clinical evidence of underlying structural abnormalities of the right ventricle; three of them exhibited a Brugada-like ECG pattern. Tada et al. reported right ventricular morpho-functional abnormalities and/or histologic abnormalities consistent with ARVC in 5 out of 6 Japanese men with a clinical and ECG diagnosis of BrS (**Tada H, et al. Am J Cardiol. 1998**). Corrado et al. reported an Italian family with Brugada-like ST-segment elevation, RV cardiomyopathic changes at echocardiography and diagnostic morphologic features of AC at histopathologic investigation of the heart specimen of the proband with SCD (**Corrado D, et al. J Am Coll Cardiol. 1996**).

The cardiac sodium channel its mutations and their spectrum arrhythmia phenotypes

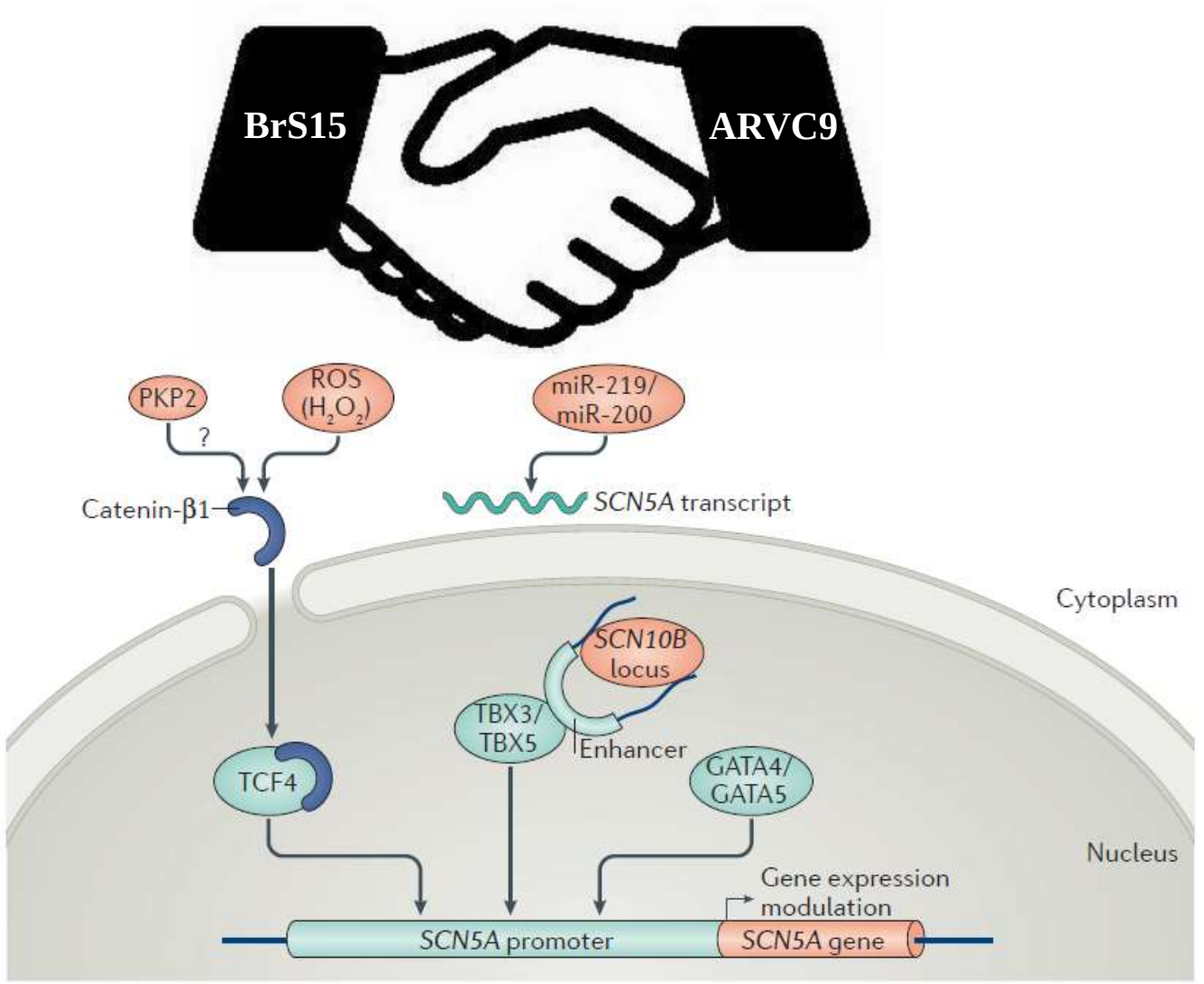


http://www.revistas.usp.br/jhgd/article/view/122759 (Pérez-Riera, et al. J Human Growth and development 2016)

Representation of numerous phenotypes consequence of SCN5A gene mutations: Early repolarization syndrome (ERS); Brugada syndrome (BrS); Congenital long QT syndome variant 3 (LQT3); Progressive Cardiac Conduction Disease (PCCD) or Lenègre disease; Sick Sinus Syndrome (SSS); Sudden Unexplained Nocturnal Death Syndrome (SUNDS); Multifocal Ectopic Purkinje-related Premature Contractions (MEPPC); Sudden Infant Death Syndrome (SIDS); Overlapping syndromes; Dilated Cardiomyopathy (DCM); and Familial Atrial Fibrillation (FAF).

BrS15

ARVC9



Moncayo-Arlandi J, Brugada R. Nat Rev Cardiol. 2017

Factors modulating *SCN5A* gene expression. H2O2 (and possibly plakophilin 2; PKP2) promotes the nuclear translocation of catenin-β1. Transcription factor 4 (TCF4) and catenin-β1 form a complex that interacts with a promoter region of *SCN5A*, suppressing the expression of this gene. The microRNAs miR-219 and miR-200 regulate the post-transcriptional expression of *SCN5A*. The T-box transcription factors TBX3 and TBX5 interact with an enhancer region in *SCN10A* and *SCN5A* loci, and regulate the expression of both genes. The transcription factors GATA4 and GATA5 synergistically activate the expression of *SCN5A* through promoter binding sites. ROS, reactive oxygen species.

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 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, Tang S, Peng L, Chen Y, Cheng J. Molecular Autopsy of Desmosomal Protein Plakophilin-2 in Sudden Unexplained Nocturnal Death Syndrome. Journal of forensic sciences. 2016;61(3):687-91). 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, Delmar M. Desmosomes and the sodium channel complex: implications for arrhythmogenic cardiomyopathy and Brugada syndrome. Trends in cardiovascular medicine. 2014;24(5):184-90). 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, Wolpert C, Fluchter S, Schimpf R, Neff W, Haase KK, et al. Magnetic resonance imaging findings in patients with Brugada syndrome. Journal of cardiovascular electrophysiology. 2004;15(10):1133-8). 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, Noorman M, Lin X, Chkourko H, Liang FX, van der Nagel R, et al. Sodium current deficit and arrhythmogenesis in a murine model of plakophilin-2 haploinsufficiency. Cardiovascular research. 2012;95(4):460-8), thus through an electrophysiological effect. Indeed, in vitro characterization of the PKP2 mutations detected in patients with a BrS phenotype showed a 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, Raju H, de Noronha SV, Papadakis M, Robinson L, Rothery S, et al. Fibrosis, Connexin-43, and Conduction Abnormalities in the Brugada Syndrome. Journal of the American College of Cardiology. 2015;66(18):1976-86).

ARVC9

Gene	Protein	Frequency in ACM	Structure	Mutation type	Inheritance	Phenotype AR/compound heterozygous	OMIM Entry	Genotye/Phenotype Studies
PKP2	Plakophilin-2	20%-45%	Desmosome	Non-missence ++(splice-site, nonsense, ins/del, large del) Missense	AD+++. AC DCM	AD+++. AC DCM	ARVC9	Conventional ARVC phenotype

(Quarta G, Circulation 2011; Christensen AH, J Med Genet 2010; Kapplinger JD, J Am Coll Cardiol 2011; Xu T, J Am Coll Cardiol 2010; Gerull B, Nat Genet 2004)

Differential diagnosis between AC and BrS

	AC	BrS
Age of presentation (yrs)	15–30	30–40
Gender	M>F (3:1)	M>F (8:1)
Distribution	World-wide (Italy endemic in Veneto region)	World-wide (Southeast Asia)
Inheritance	AD (AR)	AD
Predominant pathogenetic genes	Desmossomal genes 60%	SCN5A gene 20-30%
Typical symptoms	Palpitations, syncope, cardiac arrest	Syncope, cardiac arrest
Imaging	Structural RV (and LV) abnormalities	Normal or subtle
Biopsy	Fibrofatty replacement	Normal minimal
ECG: repolarization	Right precordial TWI	Right precordial high take-off ST elevation and TWI
ECG depolarization	Right precordial QRS prolongation, ε waves	RBBB/LAD
AV conduction times	Normal	Prolonged PR/HV interval
ECG changes	Fixed	Dynamic
Ventricular arrhythmias	Monomorphic VT, VF with a left bundle branch block pattern, most likely	Polymorphic VT, VF

Typical mechanism of VT	**Scar- related reentry** resulting from a macro-reentry around fibrofatty tissue Monomorphic	**Phase 2 reentry** **Polymorphic very fast with short coupled interval the first VPC**
Natural history	Sudden death, heart failure	Sudden death
Event triggered	Catecholamines and mostly occur during or immediately after exercise	Enhanced by vagotonic agents or β-adrenergic blockers, nocturnal vagotony, fever
Biventricular heart failure	Possible	No
Endomyocardial biopsy		The histopathologic finding of fatty infiltration of the myocardium (non-diagnostic for ARVC) was observed by Ohkubo et al. (**Ohkubo K. Int Heart J. 2010**) in 20% (5 of 25) and by Zumhagen et al. (**Zumhagen S, Circ Arrhythm Electrophysiol. 2009**) in 19% (4 of 21) of BrS patients undergoing RV endomyocardial biopsy. However, a lower prevalence of typical fibrofatty myocardial replacement suggestive of ARVC was reported both in the series of Frustaci et al. (**Frustaci A. Circulation. 2005**) and Zumhagen et al. (**Zumhagen S. Circ Arrhythm Electrophysiol. 2009**).

AD = autosomal dominant; AR = autosomal recessive; AV = atrioventricular; LAD = left axis deviation; LV = left ventricle, RBBB = right bundle branch block; RV = right ventricle; TWI = T-waves inversion; VF = ventricular fibrillation; VT = ventricular tachycardia

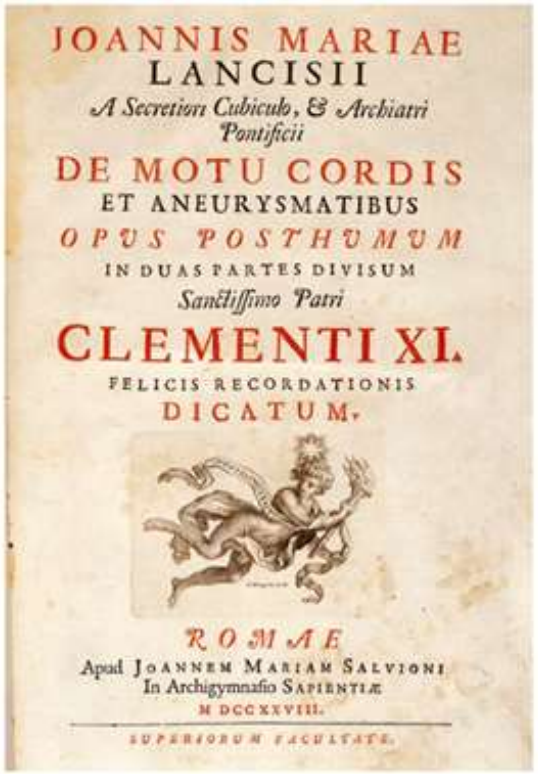
Differential diagnosis between AC and BrS

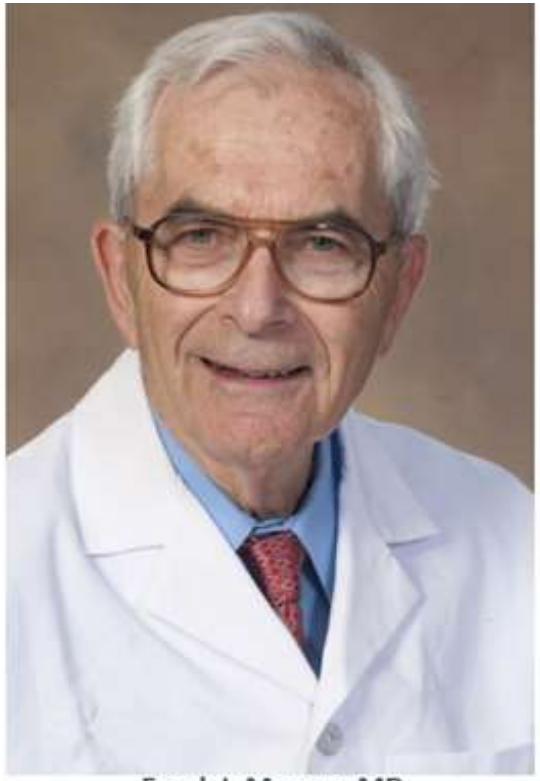
- **Age of presentation (yrs)**
  - **AC** 15–30
  - **BrS** 30-40
- **Gender**
  - **AC:** Men are more frequently affected than women with an approximate ratio of 3:1.
  - **BrS: M>F (8:1)**
- **Inheritance**
  - **AC:** Arrhythmogenic cardiomyopathy is typically inherited as an autosomal dominant(AD) pattern with variable penetrance and incomplete expression. Approximately 40% to 50% of AC patients have a mutation in genes encoding a desmosome protein. The gene is on the chromosome 14q23-q24.[3]There is an autosomal recessive(AR) trait variant associated with palmoplantar keratosis and wooly hair named Naxos disease and the Carvajal syndrome
  - **BrS** AD (≈ 25%) or sporadic Cerrone et al screened by direct sequencing the *PKP2* gene in a cohort of 200 patients with clinical diagnosis of BrS and no mutations on the most prevalent genes. Cerrone et al discovered five single amino acid substitutions in five unrelated patients (**Cerrone M, et al. Circulation. 2014**). This is the first systematic retrospective analysis of a patient group to define the coexistence of sodium channelopathy and genetic PKP2 variations. PKP2 mutations may be a molecular substrate leading to the diagnosis of BrS. In order to assess if this missense variant in PKP2 could affect the cardiac I_{Na}, we used an HL-1 cell line, stably silenced for the endogenous PKP2. In the absence of PKP2, these cells showed a decrease in the native I_{Na}. Cells transiently transfected

- with each one of the PKP2 mutants associated with the BrS phenotype showed significantly decreased I_{Na}, when compared with cells transfected with wild type PKP2. Similar results were obtained when they used a line of human iPSC-derived cardiomyocytes from a patient lacking PKP2 at the cell membrane.(**Kim C. Nature. 2013; Awad MM. Human mutation. 2006**). In these cells, I_{Na} increased upon transfection with wild type PKP2. Transfection with one of the PKP2 mutants associated with BrS was not able to restore normal I_{Na}. These data represent the first evidence that missense mutations in PKP2 can cause a decrease in cardiac sodium channel I_{Na} and facilitate arrhythmias, even in the absence of a structural cardiomyopathy. They propose that PKP2 mutations provide at least part of the molecular substrate of BrS. The inclusion of PKP2 as part of routine BrS genetic testing remains premature; yet, the possibility that some patients showing signs of disease may harbor PKP2 variants should be considered when the genotype is negative for other genes associated with 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 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, 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 notion that AC and BrS are not two completely separate entities (**Cerrone M, Trends in cardiovascular medicine. 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, it is now recognized that structural changes occur mainly at the RVOT (**Papavassiliu T, 2004**). These findings support the hypothesis, 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 Na^+ current (**Cerrone M, Cardiovascular research. 2012**), thus through an electrophysiological effect. Indeed, in vitro characterization of the PKP2 mutations detected in patients with a BrS phenotype showed a decreased Na^+ current, consistent with the clinical phenotype. Super-resolution microscopy data showed that loss of PKP2 could affect proper trafficking of the Na^+ channel at the sarcolemma, 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, Journal of the American College of Cardiology. 2015**)

- **History**
  - **AC:** first described by the Pope's physician, Giovanni Maria Lancisi{1654-1720}, in his book entitled *De Motu Cordis et Aneurysmatibus,* (**Lancisi 1736**). The first comprehensive clinical description of the disease was reported by Frank Marcus et al in 1982, when he reported 24 adult cases with ventricular tachyarrhythmias with LBBB pattern (**Marcus FI Circulation 1982**). He described a a family who had experienced pathologic RV, heart failure and SCD in four generations. Marcus et al. () published a case series that for the first time captured the clinical profile of ARVC. In 24 patients, they described the fibro-fatty replacement, the ventricular tachyarrhythmias, and premature ventricular complexes with left bundle branch block morphology, the repolarization abnormalities in the form of inversed T-waves in the right precordial leads, delayed activation on standard or signal averaged ECGs, the morphological features of increased dimensions and wall motion abnormalities of the right ventricle and the familial occurrence of this disorder. The causative mechanism was unknown and was speculated to lie in the development of the right ventricle hence it was termed "arrhythmogenic right ventricular dysplasia" [7] The electrocardiographic features of the disease were first described, including the epsilon wave in 1984 (**Fontaine G et al. Arch Mal Coeur Vaiss. 1984**).


JOANNIS MARIAE
LANCISII
A Secretiis Cubiculo, & Archiatri Pontificii
DE MOTU CORDIS
ET ANEURYSMATIBUS
OPUS POSTHUMUM
IN DUAS PARTES DIVISUM
Sanctissimo Patri
CLEMENTI XI.
FELICIS RECORDATIONIS
DICATUM.
ROMAE
Apud JOANNEM MARIAM SALVIONI
In Archigymnasio SAPIENTIÆ
M DCCXXVIII.
SUPERIORUM FACULTATE.

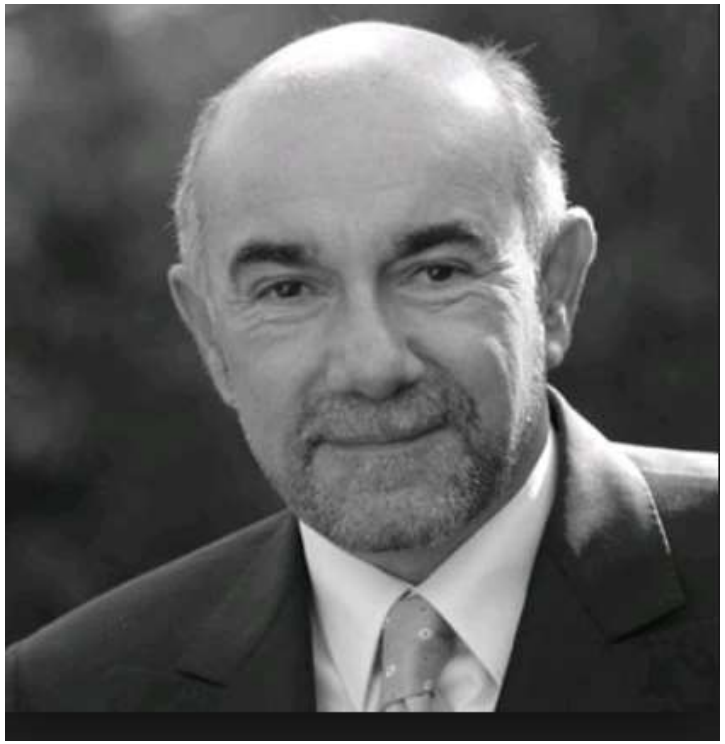

Frank I. Marcus, MD


Guy Fontaine

➢ **BrS**

- **1953:** Halfway through the 20th century (1953), Osher and Woff noticed the right bundle branch block (RBBB) electrocardiographic pattern, associated to ST segment elevation in the right precordial leads. These were considered at the time as normal variants, not having been related to sudden cardiac death (SCD) (**Osher HL, Wolff L. J Med Sci. 1953**).
- **1975**, Calo (**Calo AA. et al. G Ital Cardiol. 1975**) reported an electrocardiographic triad that consisted of: R' wave, ST segment elevation and negative T wave in right precordial leads, which coincide with the characteristics of the electrocardiographic pattern currently known as Brugada-type, being considered a normal variant at the time.
- **1984:** A similar ECG pattern, this time associated with na aborted SD and occuring in a 42-years-old male on the 2nd October 1984, was seen in Padua, Italy
- During the 80s, the Center for Disease Control in Atlanta observed an abnormally high incidence of SCD in Asian refugees who immigrated to USA from the northeast of Thailand. This form of SCD is known in this country as Lai Tai (death during sleep). Approximately two decades later, the conclusion was reached that the entity known as "Sudden Unexplained Nocturnal Death Syndrome" (SUNDS) originates in an allele belonging to the same gene (SCN5A) as Brugada Disease (**Vatta M, et al. Hum Mol Genet. 2002**).
- In 1986, Prof. Pedro Brugada received his first patient with typical ECG, a Polish Caucasian child, who suffered several episodes of syncope. The boy presented as family background his sister's SCD, even though she had been treated with association of pacemaker implantation and amiodarone. In 1989, a patient with characteristic ECG was described as being a carrier of early repolarization syndrome (**Brugada P, Brugada J. (abstr) PACE. 1991**).

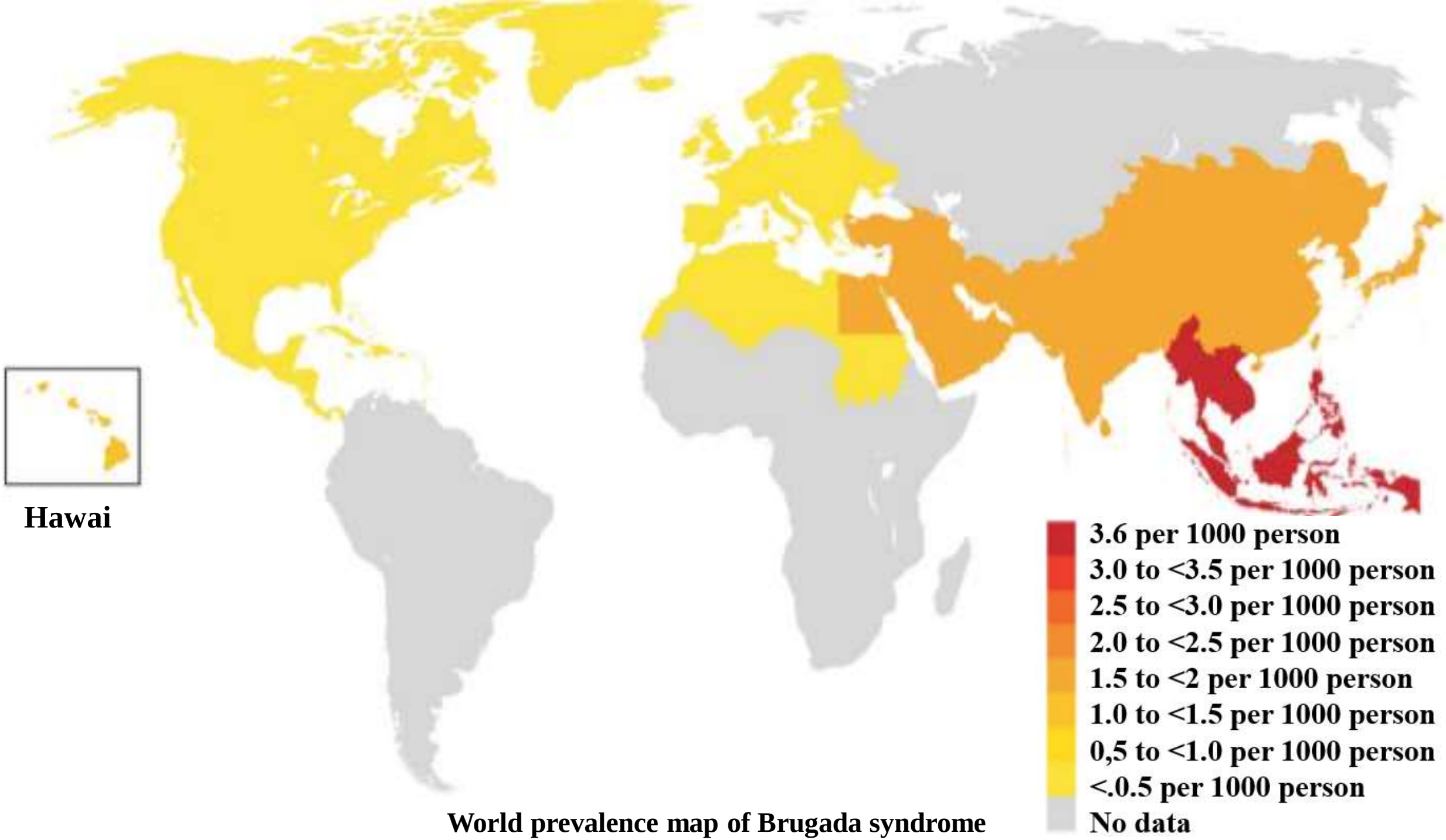
- **1987** Martini B et al described six patients with apparently idiopathic VF, 3 of them had upsloping WT segment elevation, RBBB and inverted T-waves. They documented subtle structural abnormalities in the RV (**Martini B, et al. Am Heart J. 1987**).
- **1992:** Pedro and Josep Brugada, adding 2 more cases, presented as an abstract in the NASPE meeting, a new clinical-cardiologic syndrome, typified by the association of RBBB, persistent ST segment elevation, normal QT interval and SCD. The Brothers described 8 cases and introduced the term Right Bundle Branch Block, ST segment elevation and Sudden death syndrome The first patient in their series with this syndrome was seen in 1986. The patient was a three years old boy from Poland, With multiple episode of loss of consciousness and the child´s sister had died suddenly at age two after multiple episodes of aborted sudden death, both had the characteristic ECG (**Brugada P, et al. J Am Coll Cardiol. 1992**).



Prof. Em. Dr. Pedro Brugada

Prof. Dr. Josep Brugada

- **Prevalence**
  - **AC**: It is estimated as 1/5000. **(Czarnowska E et al. Kardiol Pol. 2003 2003**). The prevalence is dependent on geographic circumstance**s (Hagenah 2004**). The estimated prevalence of familial AC in the general population ranges from 1 in 2,000 to 1 in 5,000 people Cause SCD in youth 5%(US) and 25% (Italy) One of the most common cause of SD athletes. AC can be sporadic or inherited, usually transmitted with an AD pattern with incomplete penetrance and variable expression, or rarely as an AR pattern. The AR is frequently associated with palmoplantar keratoderma, wooly hair, and dystrophic nails. Naxos disease and Israeli Desmoplakin-Recesssive are observed in Arabic populations. These cardio-cutaneous syndromes have been reported in the literature from Greece, Italy, India, Ecuador, Israel and Turkey **(Heidbuchel H, et al. *Br J Sports Med* 2012**).
  - BrS: worldwide pooled prevalence of BrS is 0.5 per 1,000. The highest prevalence was reported in Southeast Asia (3.7 per 1,000,). the prevalence of BrS in Thailand was over 146 times more common than in North America and 37 times more common than in Europe. BrS and Type-2/3 BrP were also more common in males than in females (**Vutthikraivit W, et al. Acta Cardiol Sin. 2018**). BrS: The prevalence in Japan is 0.1%-0.2% (**Macfarlane PW, et al. J Electrocardiol. 2013**). From 44 unrelated index patients and family members, Schulze-Bahr et al (**Schulze-Bahr E, et al. Hum Mutat. 2003**) performed a complete genetic analysis of SCN5A in BrS. The authors concluded that: The sporadic cases are predominant: 63% against 37% of familiar cases; Disease penetrance (disease absence in some individuals with disease gene), is complete in the SCN5A+ adult patients, but incomplete in SCN5A+ children (17%); Genetic testing of SCN5A is especially useful in familial disease to identify individuals at cardiac risk; In sporadic cases, a genetic basis and the value of mutation screening has to be further determined.

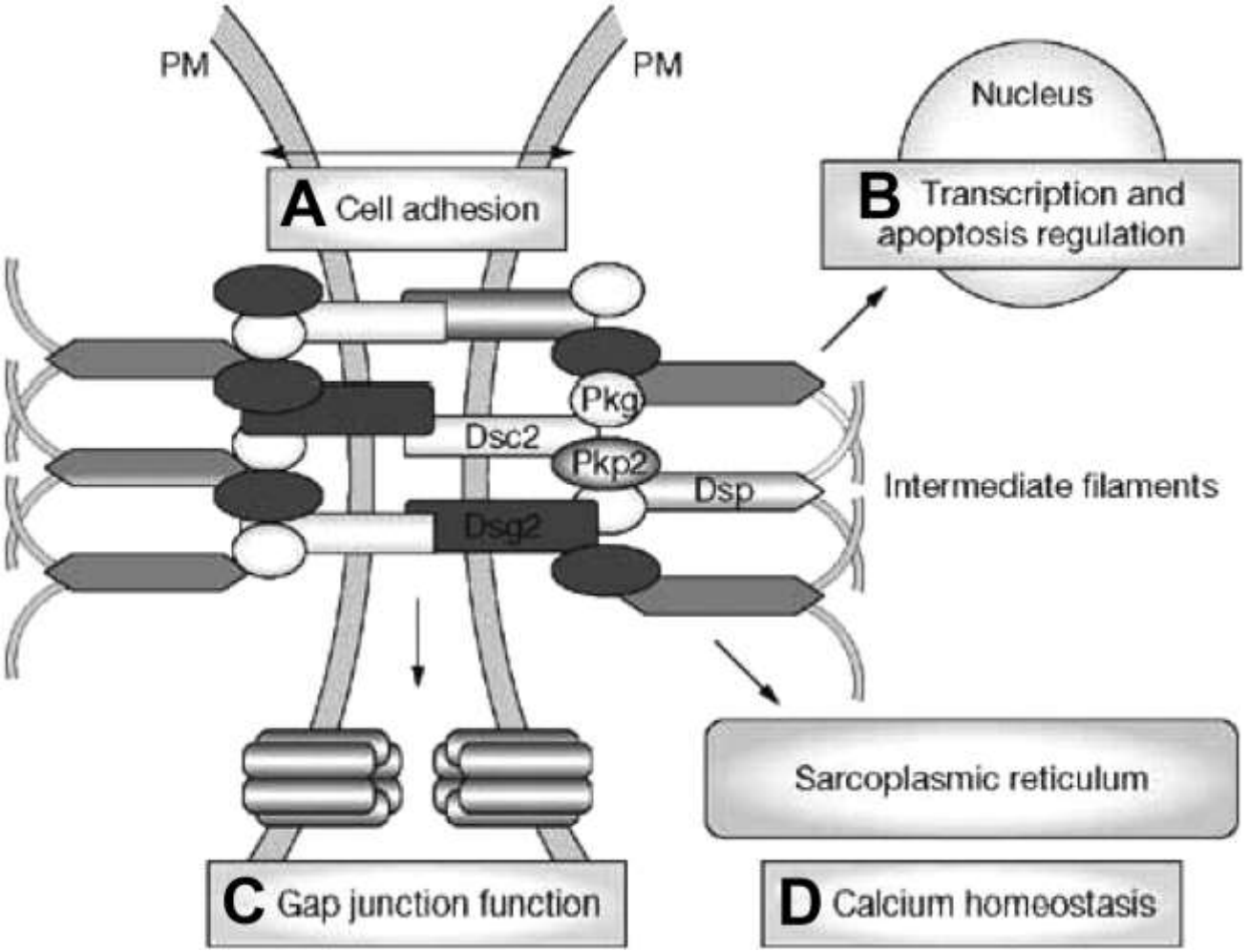


World prevalence map of Brugada syndrome

- **Endemic áreas**
  - **AC:** Véneto area Italy, Naxos Ilhas Grece.
  - **BrS:** World-wide (Southeast Asia) Thailand, Japan, Fillipines
- **Manifestations**
  - **ARC: Typical** Palpitations, syncope, cardiac arrest
  - **BrS:** sincope, sudden cardiac death, agonal respiration
- Typical symptoms
- **Event triggered**
  - **AC:** Effort (adrenergic stimulus)
  - **BrS:** at rest, during nocturnal sleep (vagotony) The characteristic Brugada ECG pattern is dynamic and can even disappear temporarily (**Brugada J. et al. J Cardiovasc Electrophysiol. 1997**). Prior to the initiation of VF however, the Brugada ECG pattern reappears in these patients (**Kasanuki H., et al. Circulation 1995**). The Brugada ECG pattern is most pronounced at night or at rest (**Mizumaki K, et al. 2004**), during febrile illness (**Amin AS, et al. Ann Intern Med. 2008**), and after consumption of a copious meal (**Ikeda T., et al.. J. Cardiovasc. Electrophysiol. 2006)** which also are known triggers of VT and SCD in BrS patients. Sodium channel blockers are known to augment or provoke the Brugada ECG pattern (**Miyazaki T, et al. J. Am. Coll. Cardiol 1996**). Other drugs can ameliorate the Brugada ECG pattern such as isoproterenol and quinidine (**Alings M., et al. Pacing Clin. Electrophysiol. 2001**) and have been used to prevent arrhythmias in observational studies and case reports (**Belhassen B. et al, Circulation 2004; Belhassen B. et al. Heart Rhythm. 2017**).

- **Race**
  - **AC:** Caucasian predominance
  - **BrS:** Asian predominance. in Asians was nine times more common than in Caucasians and 36 times more common than in Hispanics.
- **Physical examination**
  - **AC:** Eventual heart failure.
  - **BrS:** Normal, eventual atrial fibrillation
- **Natural history**
  - **AC:** syncope, sudden cardiac death, heart failure
  - **BrS:** syncope, sudden cardiac death
- **Biventricular heart failure**
  - **AC:** LV involvement was found in 76% of hearts with AC, was age dependent and was associated with clinical arrhythmic events, more severe cardiomegaly, inflammatory infiltrates and heart failure. ARVC can no longer be regarded as an isolated disease of the right ventricle.(**Corrado D. J Am Coll Cardiol. 1997**).
  - **BrS: No**

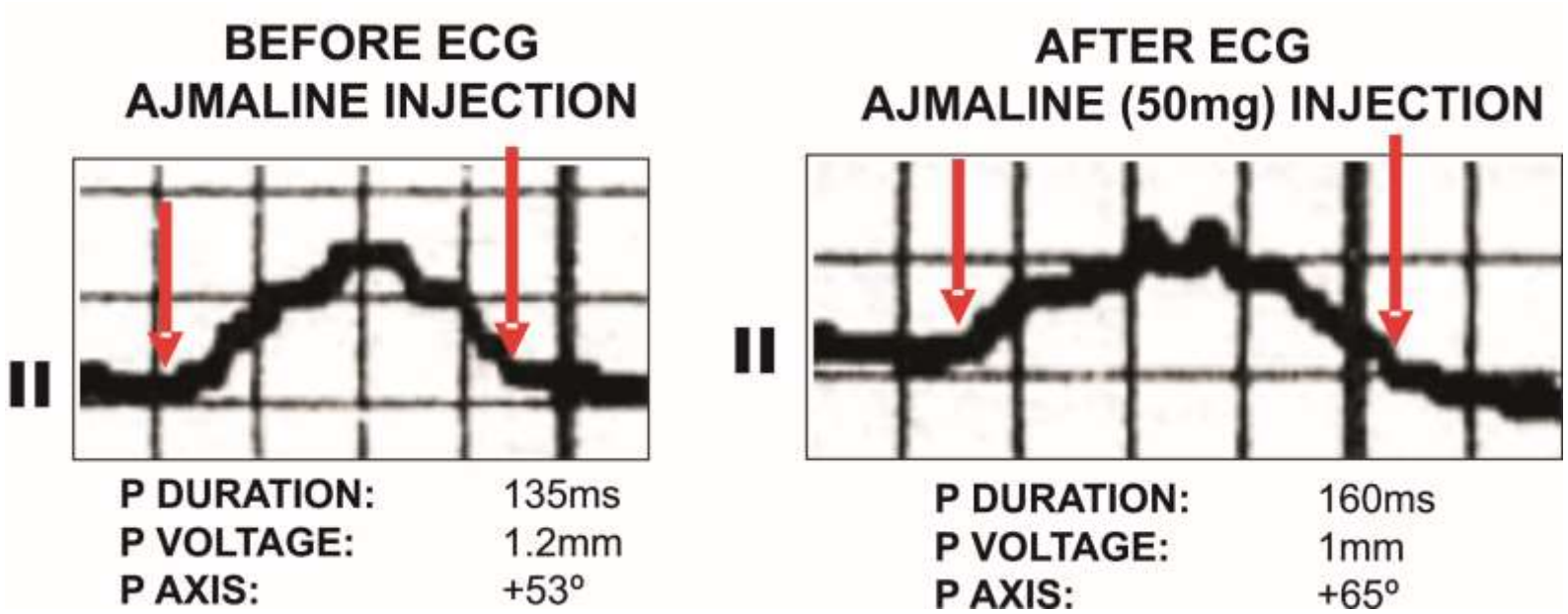
- **Predominant pathogenic gene**
  - **AC: Desmossomal 60% of cases.** The cardiac desmosome and proposed roles of the desmosome in (A) supporting structural stability through cell–cell adhesion, (B) regulating transcription of genes involved in adipogenesis and apoptosis, and maintaining proper electrical conductivity through regulation of (C) gap junctions and (D) calcium homeostasis. Dsc2 indicates desmocollin-2; Dsg2, desmoglein-2; Dsp, desmoplakin; Pkg, plakoglobin; Pkp2, plakophilin-2; and PM, plasma membrane.



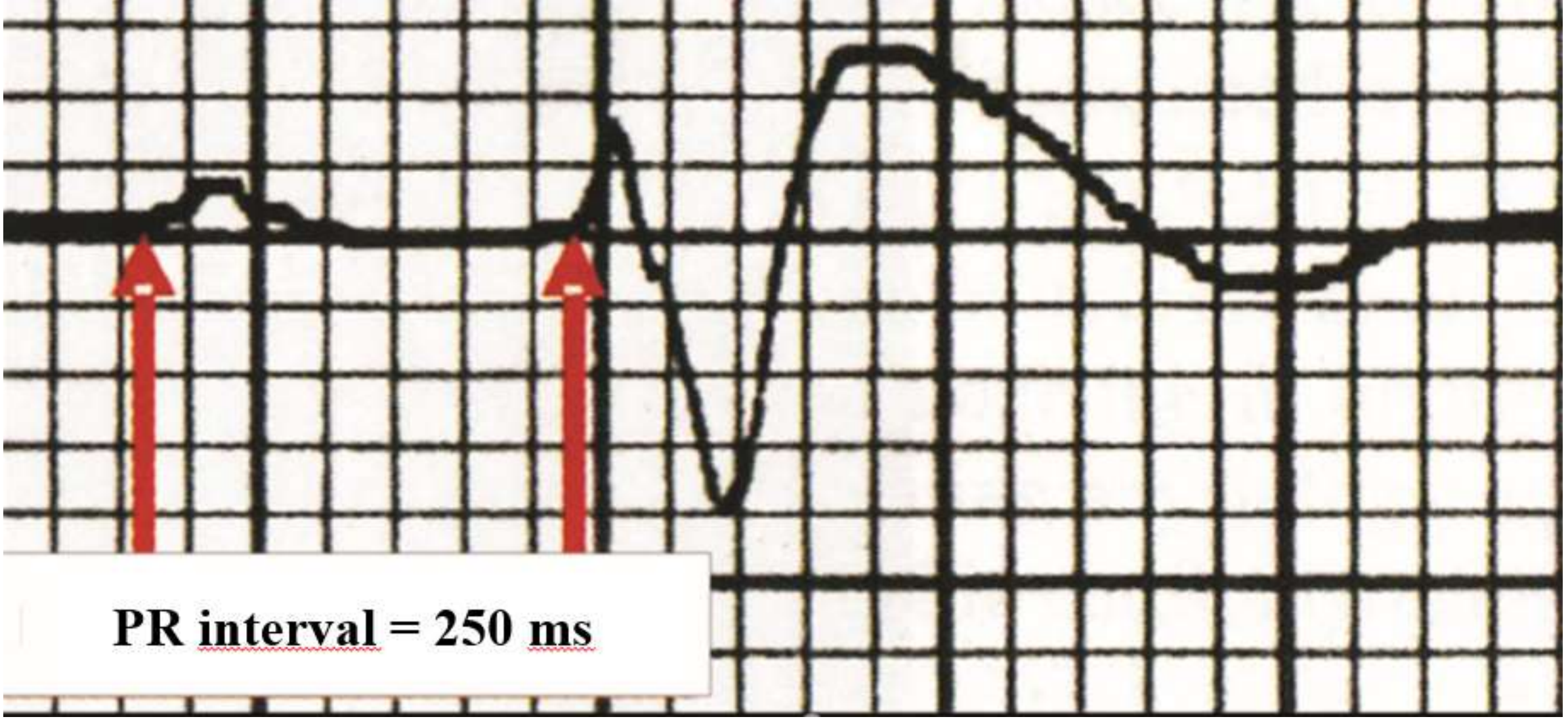
- **BrS: SC5A:** The first genetic association with BrS discovered was a loss-of-function mutation in the cardiac voltage-gated Na^+ channel gene SCN5A in 1998 (**Chen Q., et al .** ***Nature, 1998***). It is thought to be found in 15-30% of BrS cases. There is increasing evidence that BrS is an oligogenetic disease (**Le Scouarnec S, et al.** ***Hum Mol Genet, 2015***), with involvement of more than one genetic factor with different effect sizes (**Bezzina CR, et al.** ***Nat Genet.*** **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.** ***Hum Mutat.*** **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.** ***Circ Cardiovasc Genet.*** **2009**). There might be some role for genetic testing in risk stratification (**Yamagata, et al. Circulation 2017**).

- **Chacteristic of ECG changes**
- **ECG depolarization**
  - **AC:** Right precordial QRS prolongation (parietal block), epsilon waves. This wave represent right ventricular late potentials, can be brought out by recording the ECG at double speed (50mm/s), double amplitude (20mm/mV), and a 40 Hz filter. Here, epsilon waves are evident as small, notched deflections just after the QRS in lead V1. Signal averaged ECG in the absence of QRSD >110 ms. fQRS duration >114 ms or Duration of terminal QRS <40 μV ≥38 ms orRoot-mean-square voltage of terminal 40 ms ≤20 μV. Terminal activation delay ≥55 ms

- **BrS:** P-wave prolongation: A647D mitigates the lethal LQT3 phenotype seen with P1332L, it also reduces mexilitine sensitivity and decreases INa density. These explain proband's mild repolarization abnormality and prominent conduction defect in the atria and ventricles, and the expression of P1332L with A647D yields a novel disease phenotype for which mexiletine pharmacotherapy is no longer suitable (**Liu J. PLoS One. 2018**). Augmented P-wave duration in lead II, P-wave dispersion (**Letsas KP, et al. Pacing Clin Electrophysiol. 2009**), PR interval prolongation, peripheric conduction delay HV prolongation, split-His, LAFB, f-QRS**.** end conduction delay on RV The presence of atrial fibrillation (**Kusano KF et al. J Am Coll Cardiol. 2008**). OT territory. Prolonged QRS duration measured from lead II or lead V2 ≥120 ms (**Junttila 2008**). Also in right precordial QRS prolongation (parietal block) QTc interval more than 460 ms in lead V2 (**Take 2011**) and QT-interval prolongation in right precordial leads (Pitzalis 2003). increase in QRS complex duration (>110º) in the right precordial leads, in absence of CRBBB: parietal block (**Pitzalis MV, et al. J Am Coll Cardiol. 2003**), $T_{peak} - T_{end}$ prolongation and $T_{peak} - T_{end}$ dispersion (**Castro Hevia 2006**), baseline fQRS increased major arrhythmic events up to 3-fold. fQRS could be an important tool for risk assessment in patients with BrS (**Rattanawong. Ann Noninvasive Electrocardiol. 2018; Morita H, et al. Circ Arrhythm Electrophysiol. 2017**).

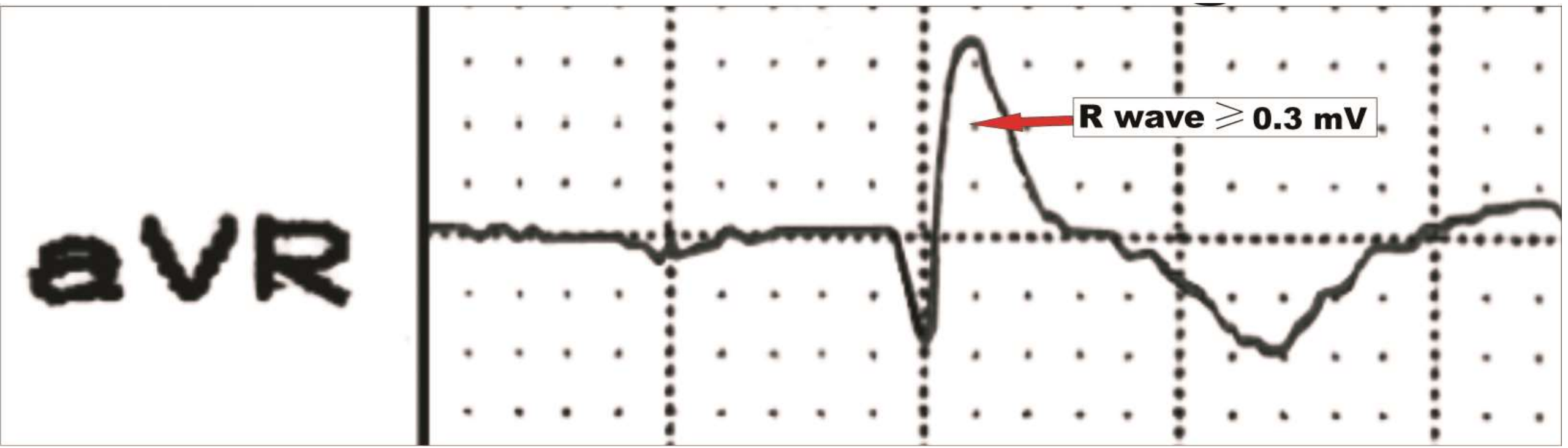


The tracing shows the P wave in a patient with BrS and positive SNC5A mutation, performed before and immediately after ajmaline test (1 mg/kg).P wave duration (Pd) before the injection is prolonged (Pd=135 ms). After drug administration Pd wave increases more (Pd=162 ms). These atrial dromotropic disorders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



The figure shows a tracing of a symptomatic patient with Brugada syndrome after intravenous ajmaline injection. First-degree atrioventricular block (PR interval = 216 ms) and Brugada type-1 ECG pattern in V_1 lead (positive test). In BrS the PR interval of ECG and the His bundle electrogram in approximately 50% of the cases are prolonged, even reaching sometimes figures of 100 ms (**Yokokawa 2007**). This prolongation of the PR interval is observed predominantly in cases where the SCN5A gene mutation can be proven (carriers). The presence of a prolongued HV interval is possible in HBE by the existence of intra-His or infra-His block. PR prolongation consequence of HV split or HV prolongation is considered another ECG risk marker (**Miyamoto A. et al. Circ J. 2011**).

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 (**Babai Bigi MA. Heart Rhythm. 2007**).

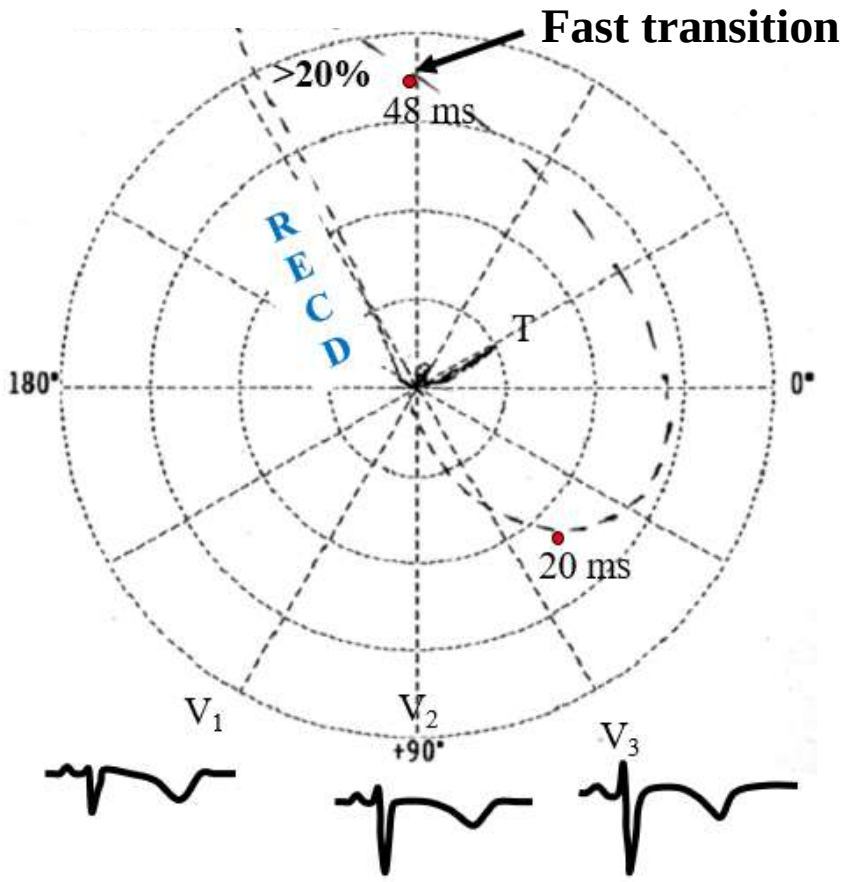


The aVR sign: Presence of prominent final R wave on aVR lead; R wave ≥3 mm or R/q ≥0.75 in lead aVR (aVR sign). Slow conduction at the RVOT may contribute to the induction of VF by PVS.

- AC: Epsilon wave The epsilon wave of the ECG together with fragmented QRS (fQRS), the terminal conduction delay, incomplete rIRBBB) and complete/advanced RBBB (CRBBB) of peripheral origin are part of a spectrum of ventricular depolarization abnormalities AC. Although the epsilon wave is considered a major diagnostic criterion for AC since 2010 (AC Task Force Criteria), its diagnostic value is limited because it is a sign of the later stage of the disease. It would be more appropriate to say that the epsilon wave is a "hallmark" of AC, but is of low diagnostic sensitivity. Although the epsilon wave has high specificity for AC, it can be present in other pathological conditions (**Pérez-Riera AR, et al. Indian Pacing Electrophysiol J. 2019**). The epsilon (ε) wave can be defined as an electric signal of depolarization observed between the end of the QRS complex and the beginning of the T wave. The ε wave is found in the right precordial leads, where the QRS complex is broader than the in the left precordial leads (difference ≥25 ms) in arrhythmogenic cardiomyopathy (AC). In patients with AC, who have left ventricular (LV) involvement, the ε wave can be registered in the left and/or inferior leads. The ε wave represents delayed potentials resulting from slow intraventricular conduction due to islands of surviving myocardium interspersed with fatty and fibrous tissue. This ventricular post-excitation wave consists of a slurring at the end of the QRS complex or an independent potential/s after the return to the isoelectric line. The depolarization abnormality is hardly detectable by the standard 12-lead ECG (S-12-ECG). Possible causes of ε waves in the ECG In a study with elite endurance athletes (190 senior and 157 junior athletes), an ε wave was found in 3/190 senior athletes (1.57%) and in 1/189 individuals from a sedentary control group 31–40 years of age . CMRI showed AC findings in one of the senior athletes. Pathological ε waves in patients other than in AC: **CAD:** the ε wave has been observed in one case of acute inferior myocardial infarction (MI) associated with RV myocardial infarction. **Uhl's anomaly or "parchment heart":** is an unusual myocardial abnormality first described by Henry Uhl in 1952. It is characterized by partial or complete absence of the RV myocardium, with severe RV systolic and diastolic impairment. Patients with Uhl's anomaly, who survive to adulthood, may develop right-sided heart failure or arrhythmias.

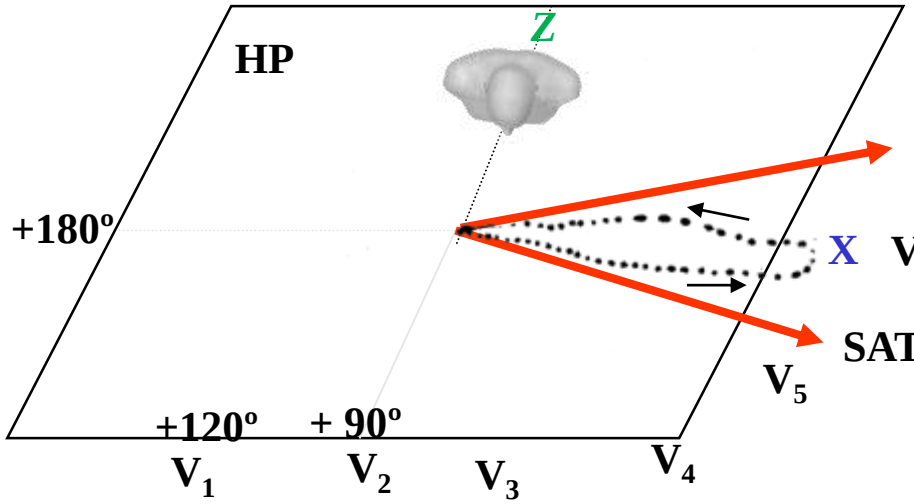
- The ECG shows tall and wide P waves, right axis deviation, frequent RBBB, prominent ε waves in all QRS complexes, and signs of severe dilatation of the RV and right atrium. **After repair of Fallot's tetralogy :** a case report described a patient with tetralogy of Fallot, who showed all features of the familial form of RV, including an ε wave. The patient had heart transplantation because of numerous episodes of ventricular tachycardia, and chronic heart failure, and he had a right ventricular outflow patch aneurysm. **Infiltrative diseases:** cardiac sarcoidosis may cause the pathological substrate required for production of ε waves. Therefore, differentiating AC from cardiac sarcoidosis is of clinical importance **Sickle cell anemia**: JW Hurst briefly mentions a probably unpublished observation of epsilon waves in a patient with sickle cell disease with RV hypertrophy due to pulmonary arterial hypertension
- **Brugada syndrome (BrS):** it is believed that BrS and AC are different clinical entities with respect to the clinical presentation and the genetic predisposition. The coexistence of these two relatively rare clinical entities has been reported (**Hoogendijk MG. Front Physiol. 2012**). There may be cases where the differential diagnosis is not clear (**Ozeke O, et al. Int J Cardiol. 2018**). ε waves appear to be rare in BrS, and were found in 2 of 47 patients by Letsas et al. (**Letsas KP, et al. Heart Rhythm. 2011**), and in 1 of a total of 12 unrelated index BrS cases included in the study by Yu et al. (**Yu J, et al. Herz. 2014**).

- **ECG repolarization**
  - **AC:** Right precordial. T-wave inversion (TWI) in right precordial leads V1, V2, and V3 in individuals over the age of 14 years. And without CRBBB is considered a major criteria (**Marcus FI, et al. Circulation 2010**).



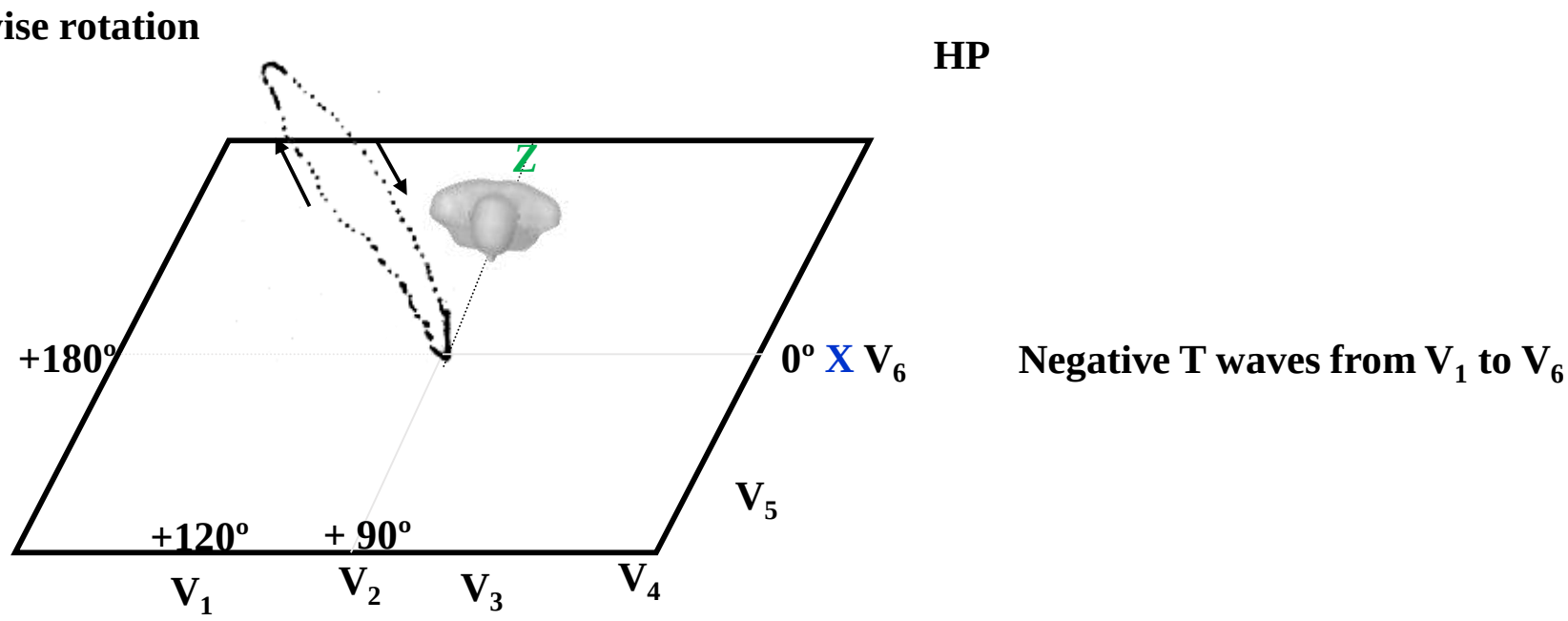
RECD – Right End Conduction Delay; T-loop directed to back and leftward

T loop behavior in AC and its relationship with RV end diastolic volume



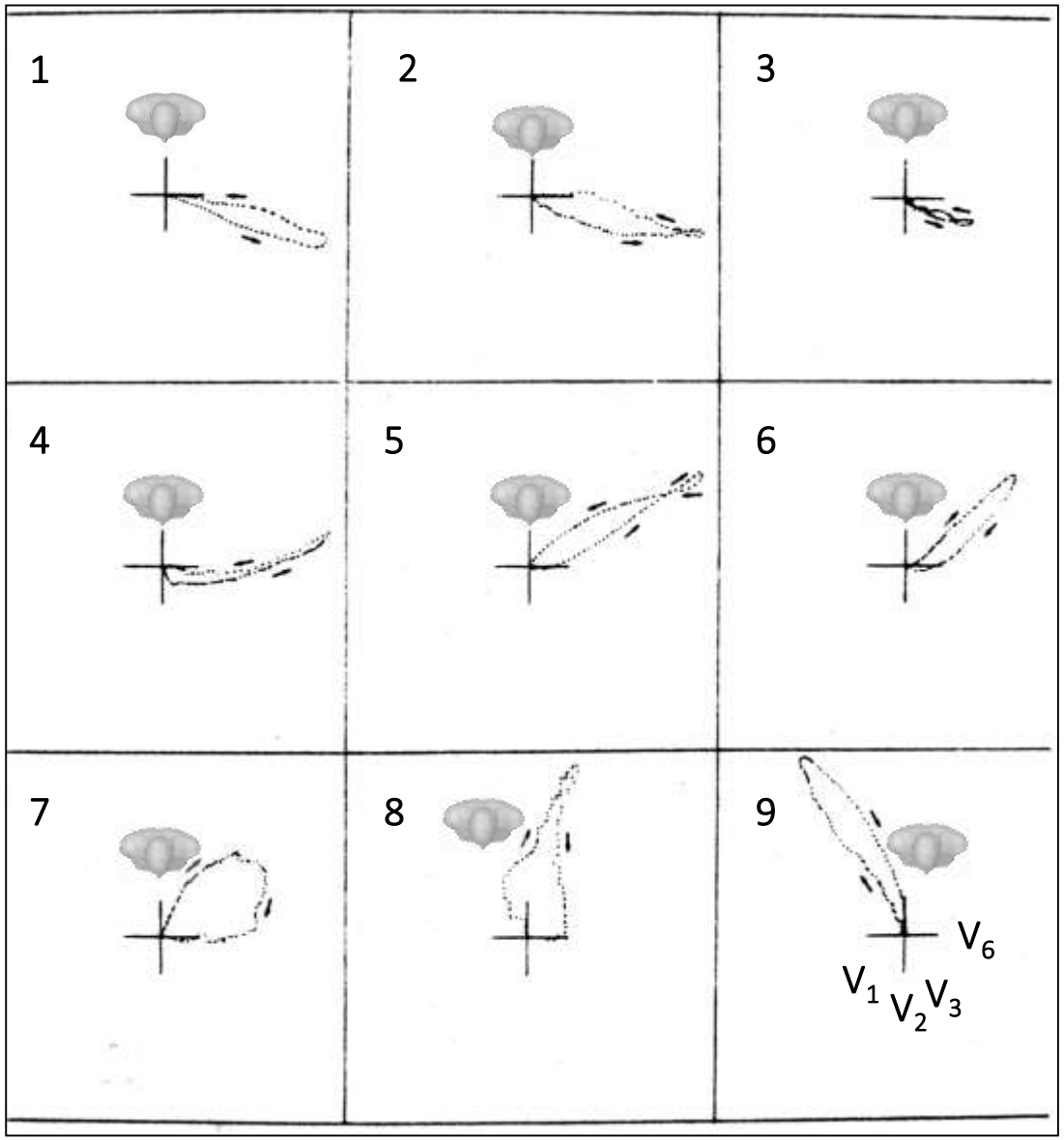
When the RV end diastolic volume is not very increased (in average 100 ml/m^2). The T loop presents counterclockwise rotation in the HP and axis between +15º and –10º (average +5º).

T loop behavior in AC and its relationship with RV end diastolic volume



When the RV end diastolic volume is large (in average 320 ml/m^2), the T loop displays clockwise rotation in the HP and is located in the right posterior quadrant, which justifies the negative T wave in all precordial leads Note: the presence of T loop of clockwise rotation, indicates the presence of underlying heart disease. When T-wave is negative in lateral leads I, aVL, V5-V6 and positive in aVR it is indictive of LV involvement.

T loop behavior in AC and its relationship with RV end diastolic volume



Negative T waves from V_1 to V_6

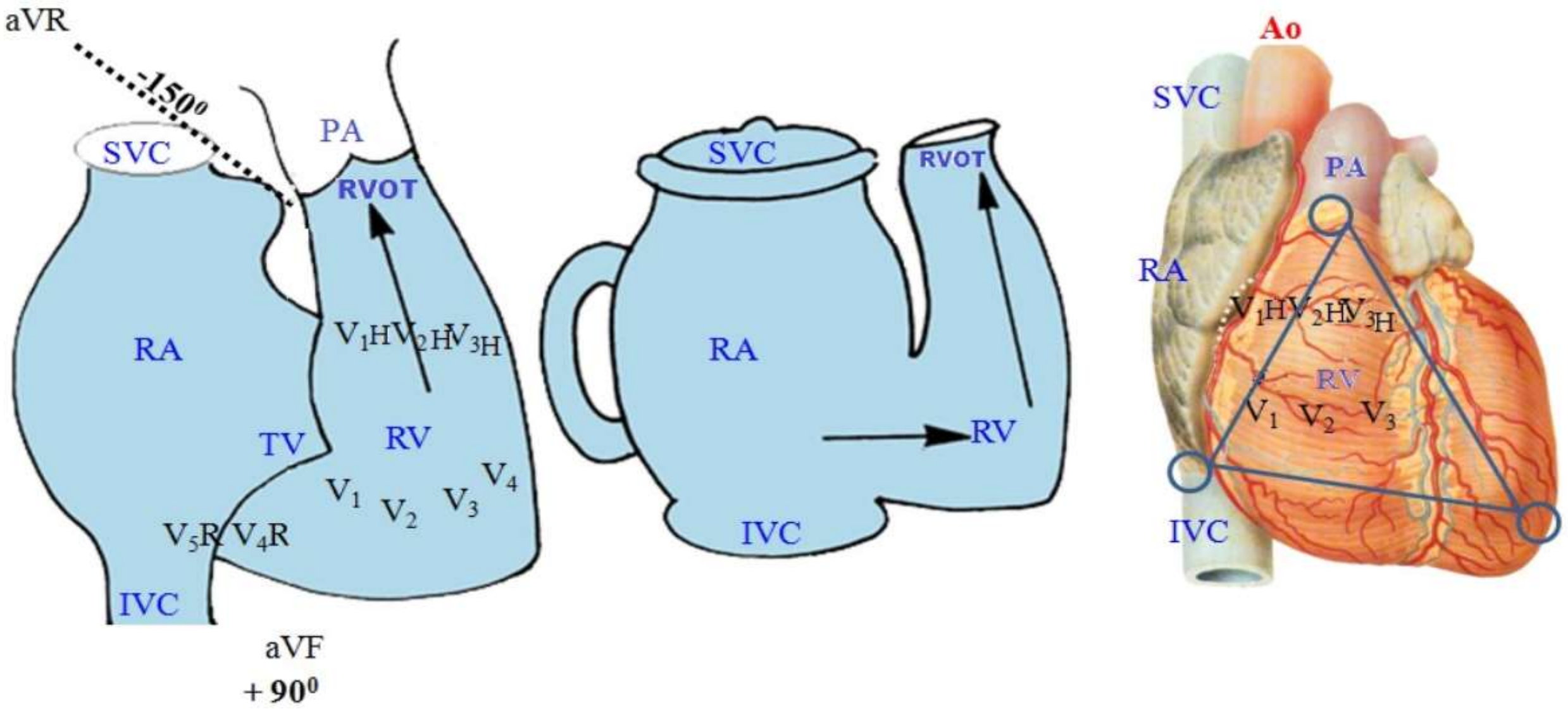
T loop in 9 patients in the HP, carriers of AC. T loops are arranged on the basis of progressive RVH.

T loop (nº 1) has a RV end diastolic volume of 100 ml/m^2 and the last loop (nº 9) has 320 ml/m^2 (Nava A et al. J of Electrocardiol. 1988).

Note the progressive alteration of the T loop from 1 to 9.

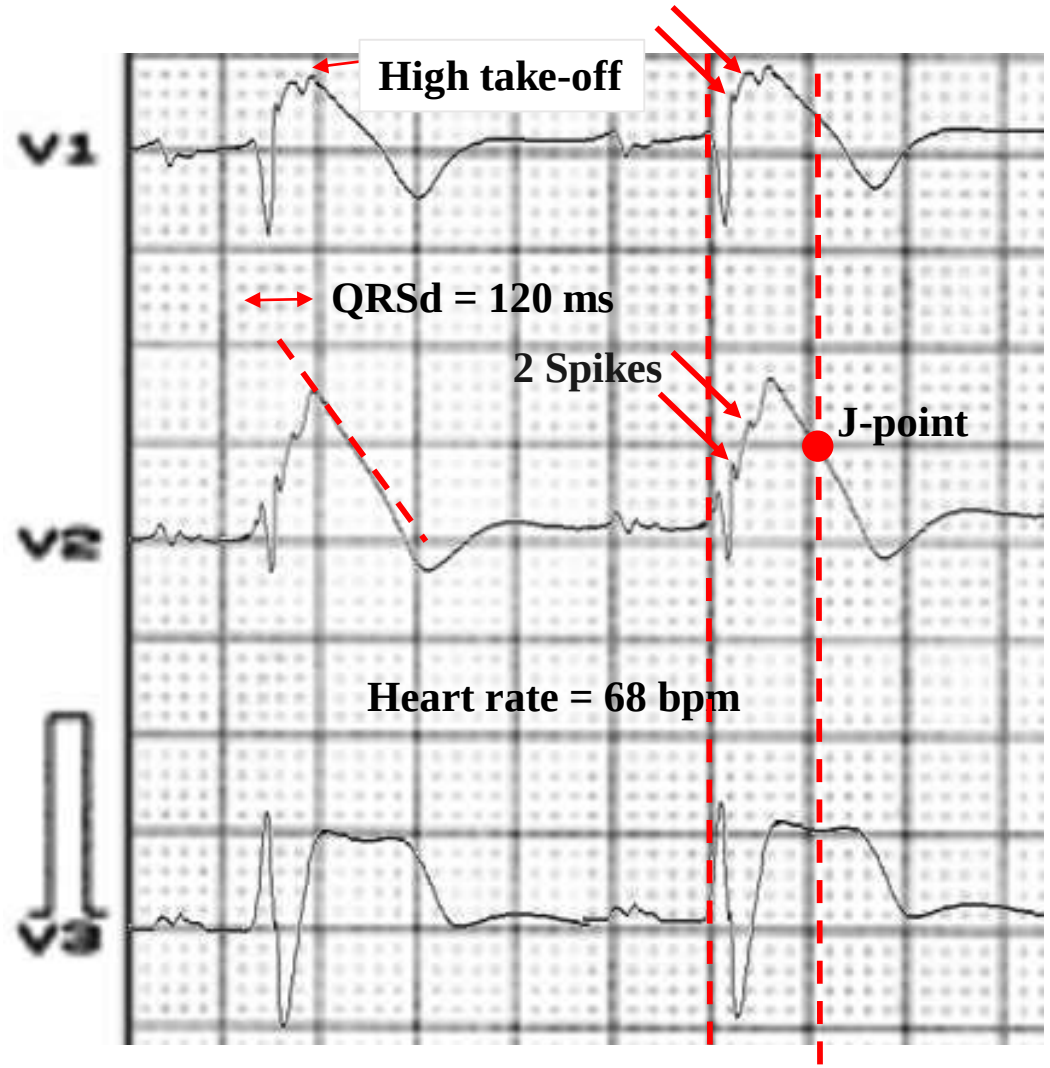
➢ BrS ECG repolarization alterations

1. The presence of horizontal (as opposed to rapidly ascending) ST segment after the J point (**Takagi M, et al. Heart Rhythm. 2013**). The presence of a J wave in multiple leads and horizontal ST-segment morphology after J wave may indicate a highly arrhythmogenic substrate in patients with BrS.
2. Augmentation of the ST segment elevation during the early recovery phase of exercise test is 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. J Am Coll Cardiol. 2010**).
3. Multivariate analysis revealed that a PQ interval ≥170 ms and T-wave amplitude <105 μV in lead V(1) were independent risk stratifiers of life-threatening events. Survival analysis (mean follow-up, 78.6±81.8 months) showed that the PQ interval and a negative T-wave in lead V(1) were significantly associated with poor prognosis (**Miyamoto A, et al. Circ J. 2011**).
4. The presence of atrial fibrillation (**Kusano KF, et al.J Am Coll Cardiol. 2008**).
5. The presence of late potentials (LPs) LPs are a noninvasive risk stratified in patients with BrS. These results may support the idea that conduction disturbance per se is arrhythmogenic (**Ikeda T. et al..J Am Coll Cardiol. 2001**).
6. A spontaneous change in ST segment is associated with the highest risk for subsequent events in subjects with a Brugada-type ECG. The presence of syncopal episodes, a history of familial sudden death, and/or LP may increase its value (**Ikeda T, et al. Ann Noninvasive Electrocardiol. 2005**).



The BrS affects predominantly the right ventricle in the right ventricle outflow tract (RVOT) epicardium (**Doi A, et al. J Cardiovasc Electrophysiol. 2010**). The larger part of clinical evidence supports the presence of right end conduction delay (RECD) as part of the process of BrS pathophysiology in the RVOT, as a consequence of structural abnormalities in the heart as part of BrS (**Coronel R et al Circulation 2005; Pérez-Riera AR Europace 2012**). On the other hand, in the concealed forms of AC, the RECD pattern can also be observed showing type-1 ECG pattern. This pattern was shown many years ago by Guy Fontaine.

Fragmented QRS in Brugada Syndrome



Two spikes are observed at the upstroke of the S wave in leads V_1 and V_2.

Dotted lines show onset and termination of the QRS complex

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. Circulation 2008**).

Presence of a “notch” within a non-wide QRS complex in two adjacent leads (V_1-V_2.): f-QRS. It is a non-invasive marker of events (**Das MK, Heart Rhythm. 2009**).

- ischemic and nonischemic cardiomyopathy.(**Das MK, et al. Heart Rhythm. 2010**) where it represents a conduction delay of the stimulus and is associated to an increase in mortality and arrhythmic events in these patients.
- Non-ischemic cardiomyopathies (**Das MK. Heart Rhythm. 2010**). In non-ischemic dilated cardiomyopathy with narrow QRS to predict (**Tigen K, et al. Can J Cardiol. 2009**).
- Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) (**Peters 2008**).
- Cardiac sarcoidosis (**Homsi M, et al. Ann Noninvasive Electrocardiol. 2009**)
- Acquired long QT syndrome. The existence of fQRS plays an important role in the appearance of Torsades de Pointes (TdP) in patients with acquired long QT interval. (**Moss AJ. Heart Rhythm. 2010; Haraoka K, et al. Heart Rhythm. 2010**).
- Myocardial dysfunction, pulmonary hypertension and severity in mitral stenosis.(**Yuce M, et al. Tohoku J Exp Med. 2010**).

- **Atrial arrhytmias**

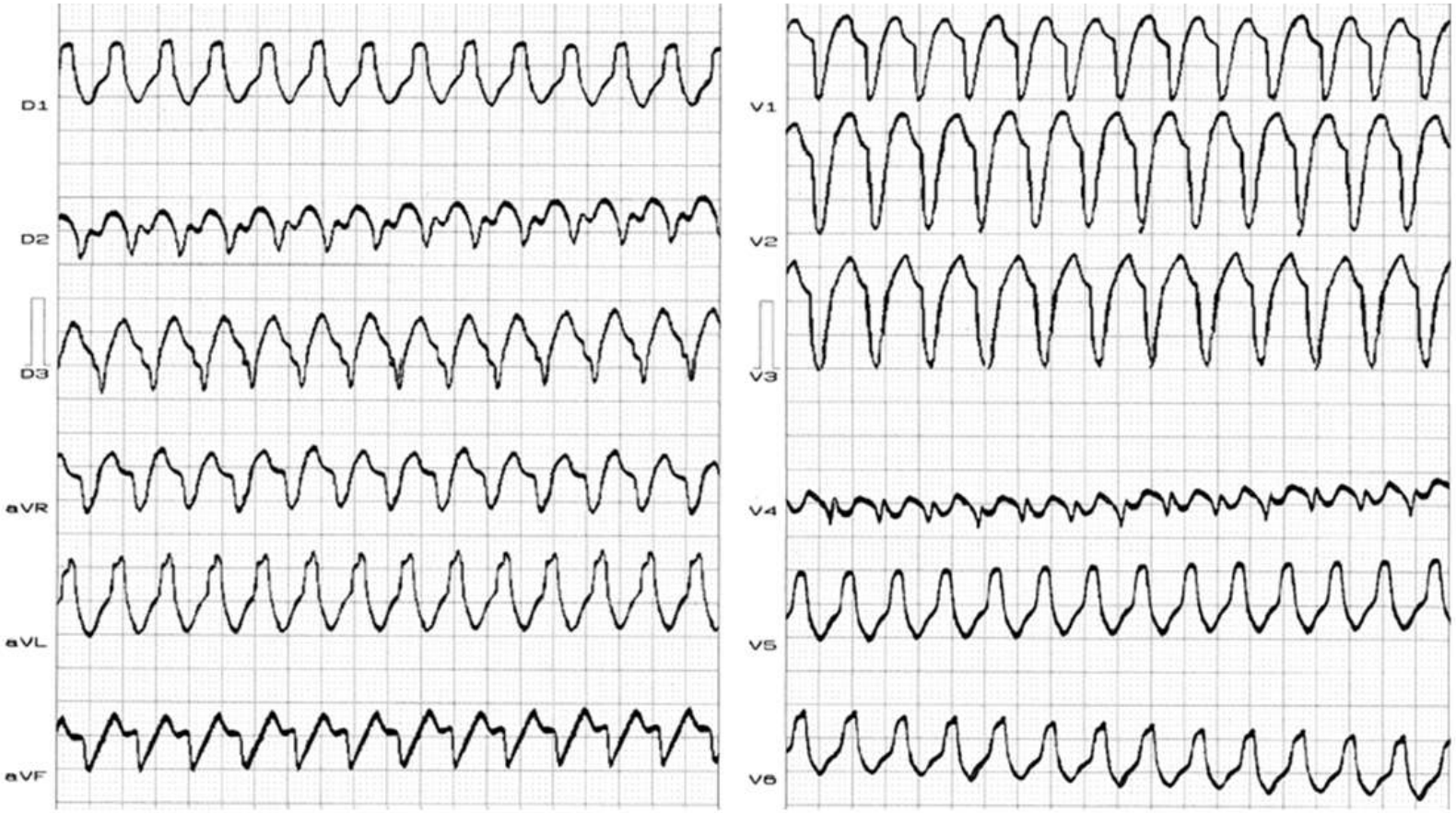
  - **AC: late (secondary):** Less is known about atrial remodeling and atrial tachyarrhythmias (ATa) in AC; Wu et al performed a cross-sectional study aimed to determine the prevalence, characterization, and predictors of atrial remodeling and ATa in a large series of patients with AC. From February 2004 to September 2014, 294 consecutive patients who met the task force criteria for AC were enrolled. The prevalence, characterization, and predictors of atrial dilation and ATa were investigated. RA dilation was identified in 160 patients (54.4%) and LA dilation in 66 patients (22.4%). Both RA and LA dilation were found in 44 patients (15.0%). Twenty-five patients (8.5%) had AF, whereas 19 patients (6.5%) had atrial flutter (AFL). Of which, 7 patients (2.4%) had both AF and AFL. Multivariate analysis showed that AFL, hypertension, and RA dilation were associated with increased risk for AF. AF increased the risk of AFL. In conclusion, atrial remodeling and ATa were common in patients with AC (**Wu et al. Am J Cardiol. 2016**).

- increased risk of paroxysmal atrial fibrillation. Atrial fibrillation can be the first manifestation of latent BrS. The ajmaline test plays an essential role, mainly in young patients with a family history of SD, despite having normal finding on a base line ECG (**Rodrígues-Mañero 2013**) BrS is frequently associated with atrial arrhythmias, AF being the most frequent. Amin et al (**Amin AS, et al. Europace. 2011**) verified that patient carriers of BrS have an increased risk of developing AF because Na^+ channel involvement facilitates the appearance of AF by causing intra-atrial conduction delay and inducing structural remodeling. Moreover, they showed that the basal duration of the P wave is greater in patients with BrS with the mutation, compared to those without. Intraatrial conduction slowing could be the substrate to maintain AF. On the contrary, the presence of mutation may decrease AF by suppressing PACs. PACs are more frequent in patients with BrS without the mutation than in those with. The reduction of PACs may inhibit the triggering mechanism to initiate AF. Kofune et al (**Kofune M, et al. Int Heart J. 2010**) studied the atrial vulnerability in patients with BrS. The authors compared 18 patients with BrS with 11 normal individuals with similar ages without AF (control group). PES was carried out from the RA , from where the following was studied: *The refractory period of the RA(ERP-RA): This parameter was similar in both groups. interatrial conduction time (IACT): It was significantly higher in the group of patients with BrS. Monophasic APs of the high RA (MAPs) AF inducibility with duration of >30 seconds: AF was induced in all the patients with BrS with 1 or 2 extrastimuli and in none of the controls. The maximal slope of the restitution curve, MAPD(80) (repolarization), was significantly higher in the group with BrS than in the control group.* VF induction occurred with PVS in all the patients of the group of BrS carriers. The authors concluded that both abnormal interatrial conduction (depolarization) and the maximal slope of the restitution curve, MAPD(80) (repolarization), may contribute to BrS arrhythmogenicity.

- **Atrial arrhytmias**

  - **BrS:early (primary)** Sinus rhythm is present in approximately 80% of cases, but there may be a tendency for other rhythms, because electrophysiological alterations are not just confined to the ventricles. Accordingly the genetic mutations could involve both the sinoatrial node (SA node) and atrial tissue. Experimental and computational analyses of the E161K mutation in the sodium channel suggest that a loss of function in this channel is not only associated with BrS and conduction disorders, but also with SA node dysfunction (**Smits JP, et al. J Mol Cell Cardiol. 2005**.). Sumiyoshi et al (**Sumiyoshi M, et al. Circ J. 2005**) studied 5 symptomatic patients carriers of BrS (4 with spontaneous episodes of VF and one with syncope) of which 3 had documented sinus pauses of >3 sec. The electrophysiological study showed a prolonged recovery time of the SA node in two patients. Fazelifar et al (**Fazelifar AF, et al. Pacing Clin Electrophysiol. 2006**) presented the case of a 23-year-old man referred for ablation of atrial flutter in whom SA node dysfunction was observed following the procedure that persisted after stopping the drugs and ruling out other causes such as organic heart disease and electrolytic disorders. The ECG showed type-1 BrS pattern with the flecainide provocative test. The case clearly shows the association of BrS with SA node disease.

- **Ventricular arrhytmiasVentricular tachycardia**
  - **ARC:** Monomorphic VT, VF with a left bundle branch block pattern, most likely Catecholamines and mostly occur during or immediately after exercise. Scar- related reentry resulting from a macro-reentry around fibrofatty tissue. Non-sustained or sustained VT with LBBB pattern with superior axis is considered a Major criteria. And Non-sustained or sustained VT with LBBB pattern with inferior or unknown axis or >500 PVCs/24 h are considered minors criteria.



SMVT with LBBB morphology and SÂQRS with extreme deviation to the left: the focus is localized in the right ventricle inflow tract, the apex or the inferior wall of the RV. Heart rate: 214 bpm. VT with LBBB morphology and SÂQRS to the left nearly always suggest structural heart disease.

- **BrS:** Polymorphic VT with circadian pattern of presentation. Enhanced by vagotonic agents or β-adrenergic blockers, nocturnal vagotony, fever. Of all the arrhythmic events, 93% occurred at night or early in the morning, and 92% had pronounced ST-segment elevation. These results suggest that Bru-ECG may be associated not only with an increased risk of ventricular tachyarrhythmias but also with an increased risk of paroxysmal AF, and that the arrhythmogenesis may be related to the pronounced ST-segment elevation. The PVT is characterized by a very high rate (between 260 to 352 bpm) and very short coupling of the first ventricular premature contraction (333±60 ms), that may evolve into self-terminating or sustained ventricular fibrillation (VF).

High resolution ECG in AC

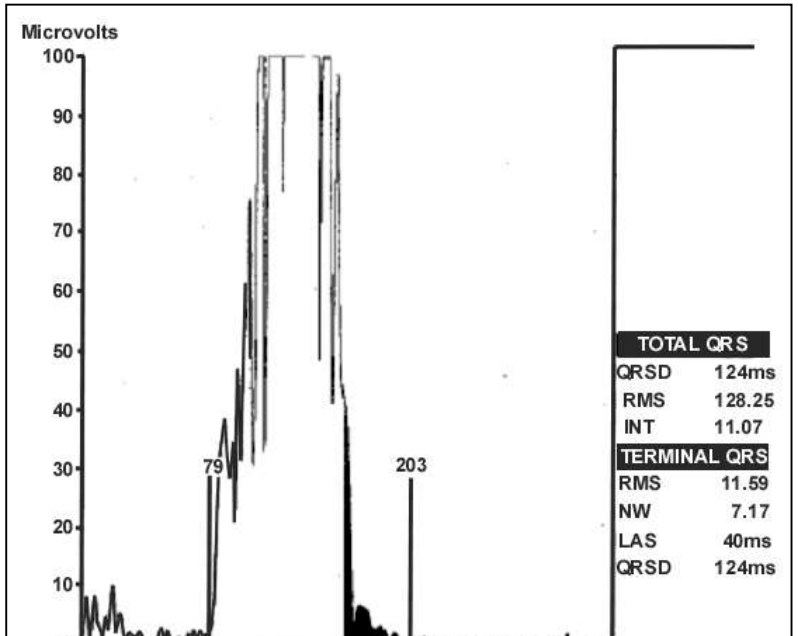
- In AC, high resolution ECG is frequently associated to late potentials (LP).
- The ε wave may be observed in surface ECG; however, it is seen much more frequently in high resolution ECG (**Gregor P. Vnitr Lek. 2003**).
- High resolution ECG is used to detect late potentials (LP) and ε waves in AC carriers.
- Patients with positive high resolution ECG (presence of LP) have statistically significant increase of S-VT and/or SCD in comparison to those with normal high resolution ECG or branch block.
- High resolution ECG with LP constitutes a marker of arrhythmic events in patients with non-ischemic dilated cardiomyopathies. On the contrary, patients with dilated cardiomyopathies with normal high resolution ECG, display worsening only if they develop progressive CHF (**Mancini DM, et al. Circulation. 1993**).
- Fibro-fatty substitution of the myocardium is the substrate of slow and fragmented activation, responsible for the presence of LP.
- Abnormal high resolution ECG seems to correlate with the severity of the disease.
- High resolution ECG does not seem a sensitive resource in the minor or concealed forms of the disease, since in these patients there is no proper information with this method (**Oselladore L, et al. Am J Cardiol. 1995**).
- The combination of the analysis of time domain and frequency domain of high resolution ECG may be useful for screening patients carriers of AC. This combination of both domains increases sensitivity without reducing specificity.
- Use of filters with a range between 20 and 250 Hz (substituting the classical ranges between 40 and 250 Hz) (**Kinoshita O, et al.Circulation. 1995**).

- The presence of LP in AC is found in 70% to 80% of cases. These LP may identify patients with a tendency to develop VT runs in little apparent or restricted forms, and it serves to differentiate them from benign RVOT idiopathic VT, with no underlying structural disease. In these cases, high resolution ECG has LP in 0% to 5% of the cases as in normal patients.
- When there is structural heart disease, LPs are found in 20% to 40% of cases. In doubtful cases, invasive studies are necessary to rule out a limited form of cardiomyopathy (**Fauchier JP, et al. Pacing Clin Electrophysiol. 1996**).
- In absence of branch block, the presence of LP in high resolution ECG is proportional to the size of the RV cavity, and thus is parallel to RV dysfunction (**Mehta D, et al. J Am Coll Cardiol. 1996**).
- In order to study the differences between benign repetitive MVT that originate in the RV and the VT from ARVC/D, ECG during the event and high resolution ECG may be helpful.
- ECG during VT and high resolution ECG may be useful to differentiate both entities. In the case of ARVC/D, VT presents QS in V1 and QRSD related to the amount of fibrous tissue existing in the RV (**Kazmierczak J, et al Heart. 1998**).
- There are significant differences for filtered and non-filtered QRS, low duration sign and square root. In absence of CLBBB, these differences become non significant for filtered or non-filtered QRS (**Kazmierczak 1998**).
- There is a narrow correlation between the result from high resolution ECG and the extension of the disease, with the presence of VT.
- High resolution ECG is not a valuable resource in minor forms of the disease, but as this is a noninvasive method, it may be useful to assess the progression of the disease (**Nava 2000**).
- In comparison to 12-lead ECG, high resolution ECG detects abnormalities at higher rates in patients carriers of ARVC/D (57% vs. 86%). High resolution ECG is more sensitive as screening test than 12-lead ECG to detect patients carriers of ARVC/D (**Sekiguchi 2001**).
- The anatomopathological process of ARVC/D also considers late ventricular potentials, which when they are registered as LP in high resolution ECG, indicate electrical stability worsening associated to rapid progression of high resolution ECG, while clinical parameters remain unchanged. This fact suggests that progression parameters in high resolution ECG are markers of electrical instability increase (**Bauce 2002**).
- Sensitivity, specificity, predictive value and accuracy of the different criteria of high resolution ECG were estimated in comparison to SMVT inducibility. Filtered QRS duration (fQRS) in high resolution ECG is considered as predictive for the result of the electrophysiological study and ARVC/D evolution (**Nasir 2003**).

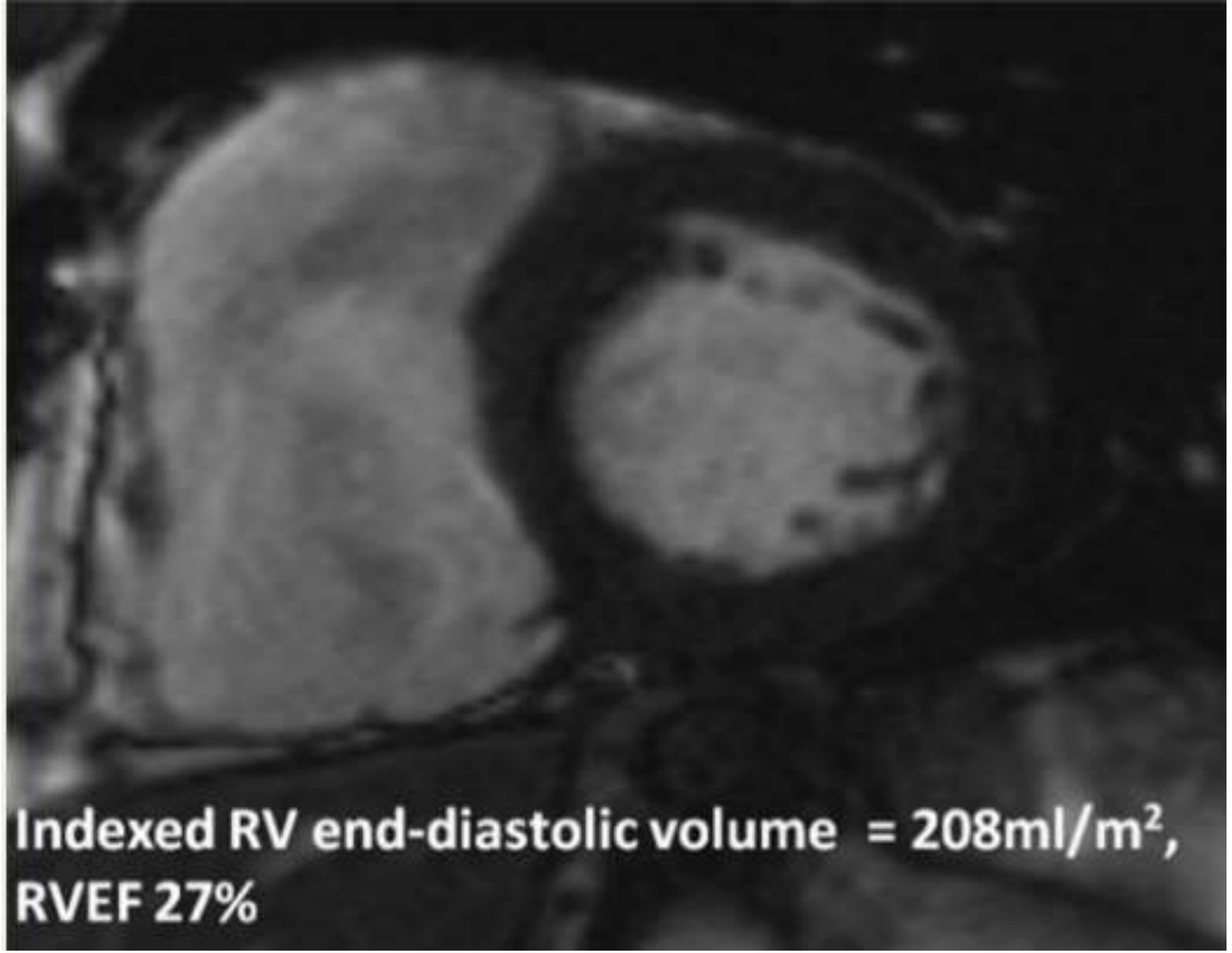
- The average of presence of late potentials in AC is between 70-80%, with extreme values of 47-100%. The latter percentage is observed in severe forms and with documented spontaneous VT.
- High resolution ECG is a very useful resource to follow the evolution of the disease.
- In relatives of patients, high resolution ECG presents a positivity of LP between 4-16%.
- Detecting posterior potentials improves by using 25 Hz filters and specificity is better observed in the orthogonal lead Z.
- High resolution ECG should be considered a standard test in the study of patients with suspicion or carriers of AC;
- Future research is necessary to confirm the value of high resolution ECG as predictor of arrhythmic risk and determining factor of progression of the disease, as well as to study the prevalence of high resolution ECG in relatives of patients, thus allowing early detection;
- Multidisciplinary continuing studies on AC will help to answer some of these questions (**Nasir K, et al. Ann Noninvasive Electrocardiol. 2003**).

High resolution criteria

1. **Filtered QRS duration ≥114 ms**
2. **Duration of terminal QRS , 40 mV: ≥ 38 ms**
3. **Root-mean-square voltage of terminal 40 ms: ≤20 mV**

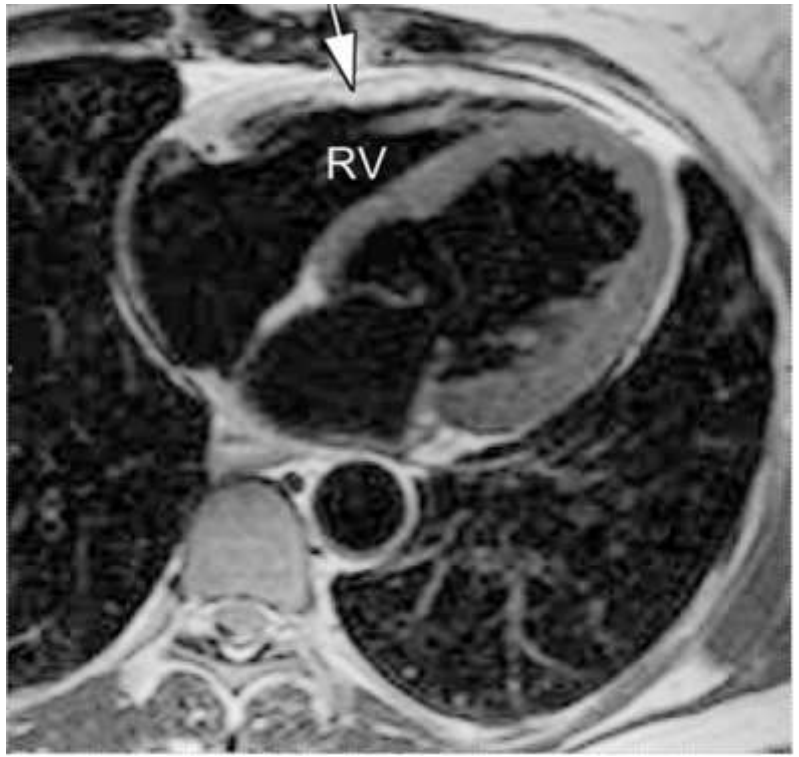


High resolution ECG with LP (QRSD: 124 ms, LAS: 40 ms, RMS: 11,59 μV)

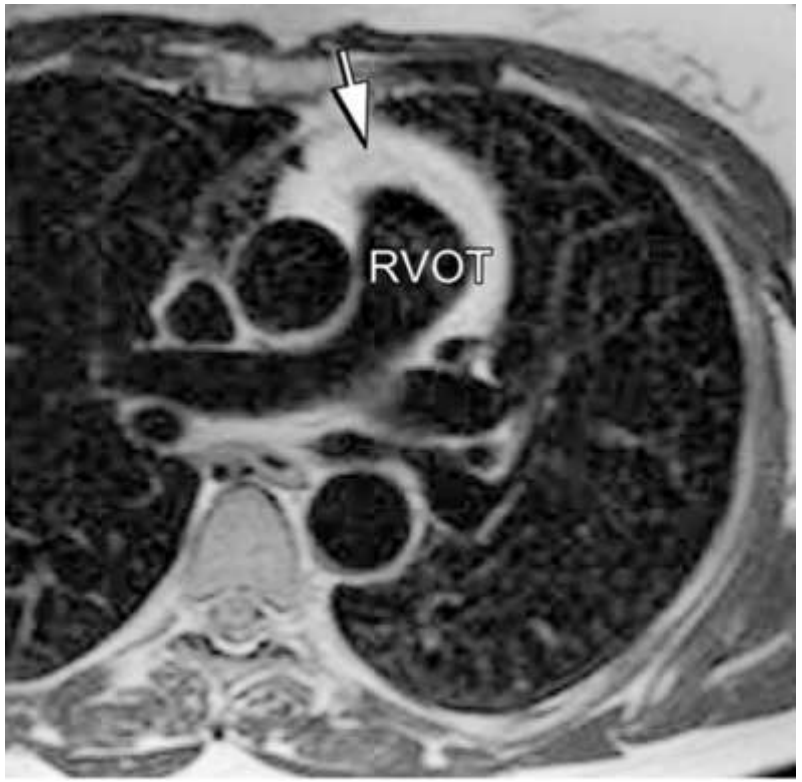


Cardiac magnetic resonance imaging in a patient with AC. The figure shows enlarged right ventricular volume and decreased right ventricular ejection fraction by cardiac magnetic resonance. AC, arrhythmogenic cardiomyopathy; RV, right ventricle; RVEF, right ventricular ejection fraction.

- **Image**
  - **ARC:** As underlying heart diseases of right VTs, ARC causes wall-motion abnormalities based on fibrofatty myocardial degeneration



Axial T1-weighted black blood spin-echo images show extensive transmural fatty replacement of the right ventricular myocardium (*RV*) (arrow)



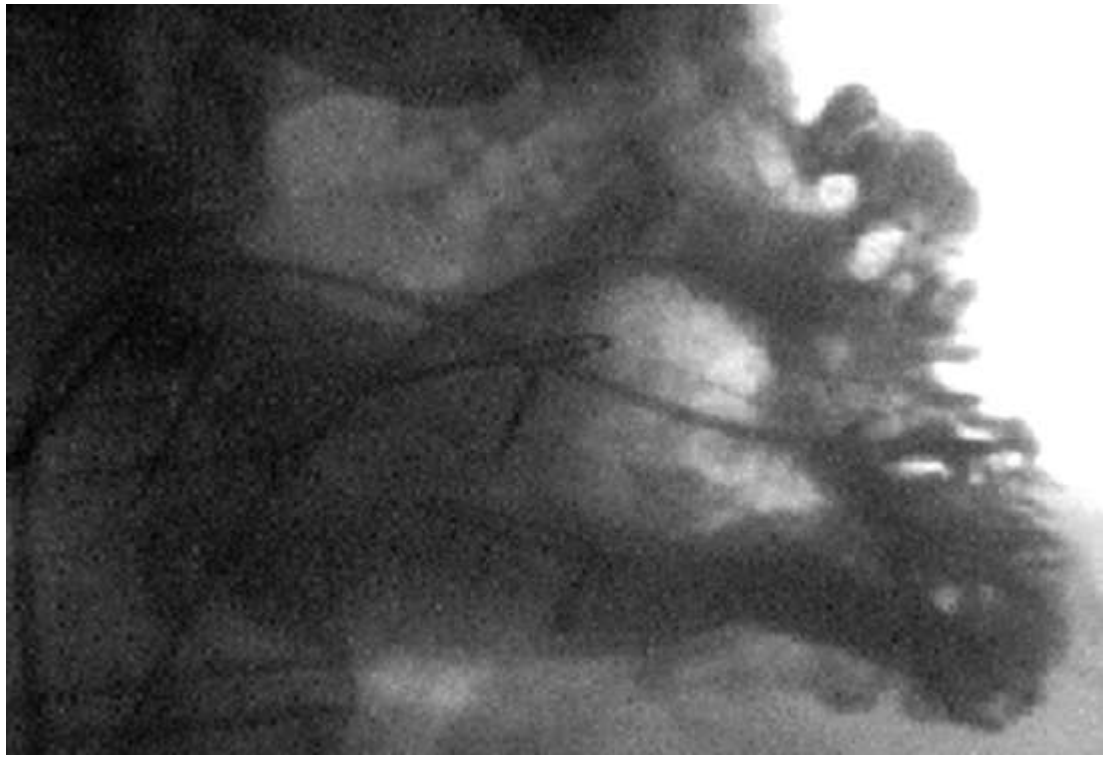
The right ventricular outflow tract (*RVOT*) (arrow), which is a major criterion for the diagnosis of ARC.

➢ BrS image on cardiac magnetic resonance (CMR) feature tracking (FT) compared with ARC, RVOT-VT and healthy volunteers (HV)

As underlying heart diseases of right ventricular tachyarrhythmias, ARC causes wall-motion abnormalities based on fibrofatty myocardial degeneration, while RVOT-VT and BrS are thought to lack phenotypic cardiac magnetic resonance (CMR) characteristics. To examine whether CMR feature tracking (FT) in addition to ARC objectively facilitates detection of myocardial functional impairments in RVOT-VT and BrS.

Cine CMR datasets of four retrospectively enrolled, age-matched study groups (n = 65; 16 ARC, 26 RVOT-VT, 9 BrS, 14 healthy volunteers (HV) were independently assessed by two distinctly experienced investigators regarding myocardial function using CMR-FT. Global strain (%) and strain rate (s^{-1}) in radial and longitudinal orientation were assessed at RVOT as well as for LV and RV at a basal, medial and apical section with the addition of a biventricular circumferential orientation. RV longitudinal and radial basal strain (%) in ARC were significantly impaired compared to RVOT-VT. Synergistically, RVOT endocardial radial strain (%) in ARC was significantly lower than in RVOT-VT For differentiation against BrS, RV basal and medial radial strain values (%)) were significantly reduced when compared to HV even in case of a normal RV EF. The authors concluded that CMR-FT facilitates relevant differentiation in patients with RV tachyarrhythmias: between ARC against RVOT-VT and HV as well as between BrS with even a preserved EF against HV (**Heermann P, et al. Clin Res Cardiol. 2019**).

- **ARC Angiogram**



Conventional angiogram of the RV in a patient with ARC shows heavy trabeculation and aneurysmal bulges of the RVOT.

Ajmaline challenge in AC versus BrS

- **AC:** Provocable coved-type ST-segment elevation in right precordial leads is an observation in approximately 16% of patients with typical AC. The value of this observation should be analyzed in a long-term follow-up of 17 patients identified by systematic ajmaline challenge. Ajmaline challenge in typical AC characterizes a subgroup of elderly, predominantly female patients with the risk of developing conduction disease. Tachycardia-related events are rare. The indication of ICD implantation in recurrent syncope's is critical as the rate of lead-associated complications in a more than 3 years follow-up is high (**Peters S. Europace. 2008**). The ECG. The ECG changes alone or in combination can provide strong evidence for the diagnosis of ARVC/D and helps to differentiate ARVC/D from right ventricular outflow tract (RVOT) tachycardia. The typical pattern of the ECG in the Brugada syndrome is ST segment elevation in the right precordial leads. This abnormality can be dormant and elicited by administration of drugs that cause Na channel blockade, such as ajmaline or type 1A or 1C antiarrhythmic drugs. Individuals who do not have the Brugada ECG findings at baseline but have this pattern induced by antiarrhythmic drugs are also at risk for SCD. Further risk stratification may be obtained in the asymptomatic patients if VF is induced at EPS (**Marcus FI. J Electrocardiol. 2000**).
- **BrS:** 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 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 J, et al Int J Cardiol. 2019**). The table bellow shows the Sodium channel blockers used for the drug challenge test in BrS.

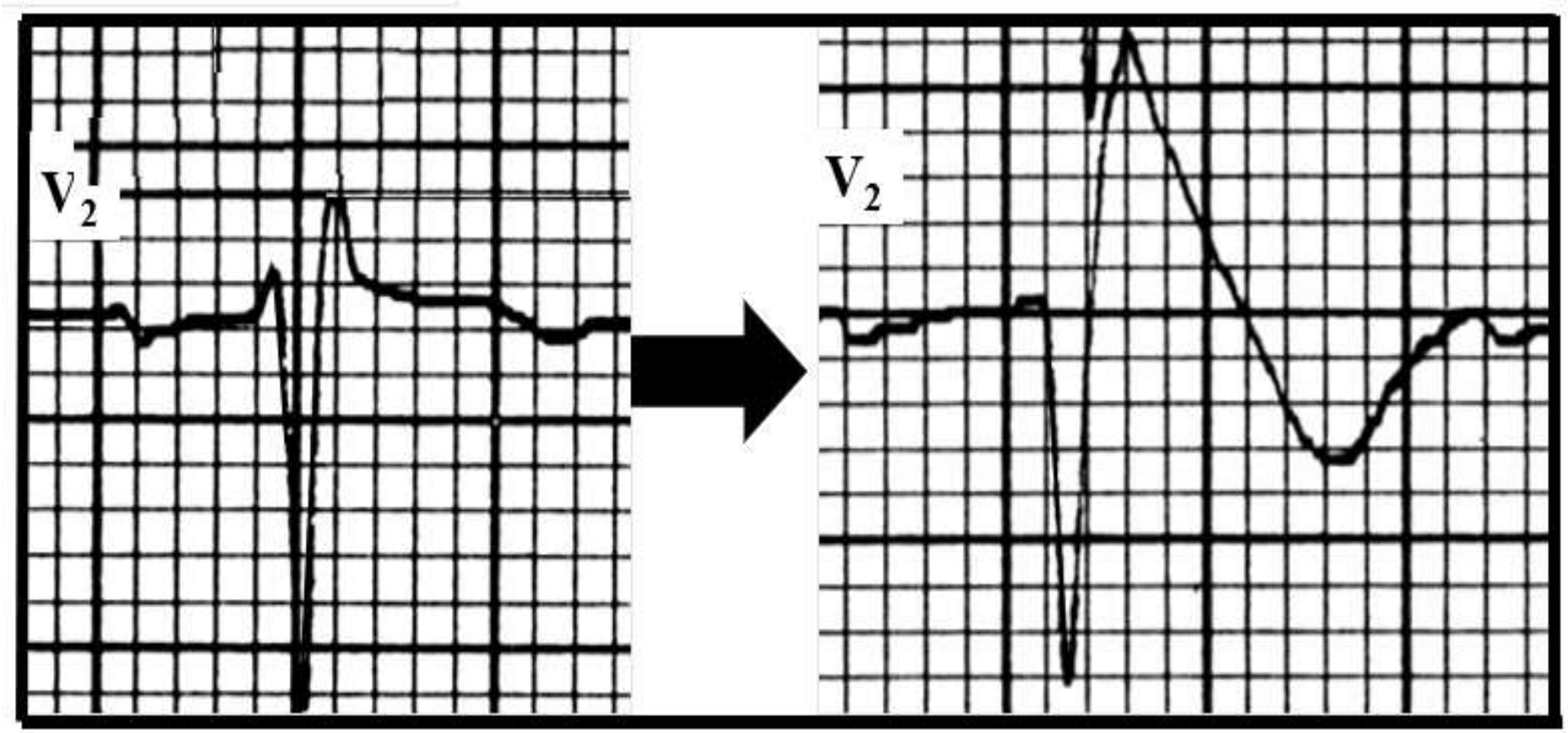
Drug	Doses and administration
Ajmaline Class 1a	≤1mg/kg IV over 5 min. False-positive responses is possible with >1mg/kg. (**Sung AY. JACC Clin Electrophysiol. 2019** *)
Flecainide Class/Subclass 1c	2mg/kg IV over 10min
Flecainide Class/Subclass 1c	Oral at single dose of 400 mg (**Dubner S, et al. Ann NoninvasiveElectrocardiol. 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. JACC Clin Electrophysiol. 2019**). 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. Open Heart. 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. Front Physiol. 2019**).

Examples of positive test after intravenous ajmaline injection

Before ajmaline injection **After ajmaline injection**

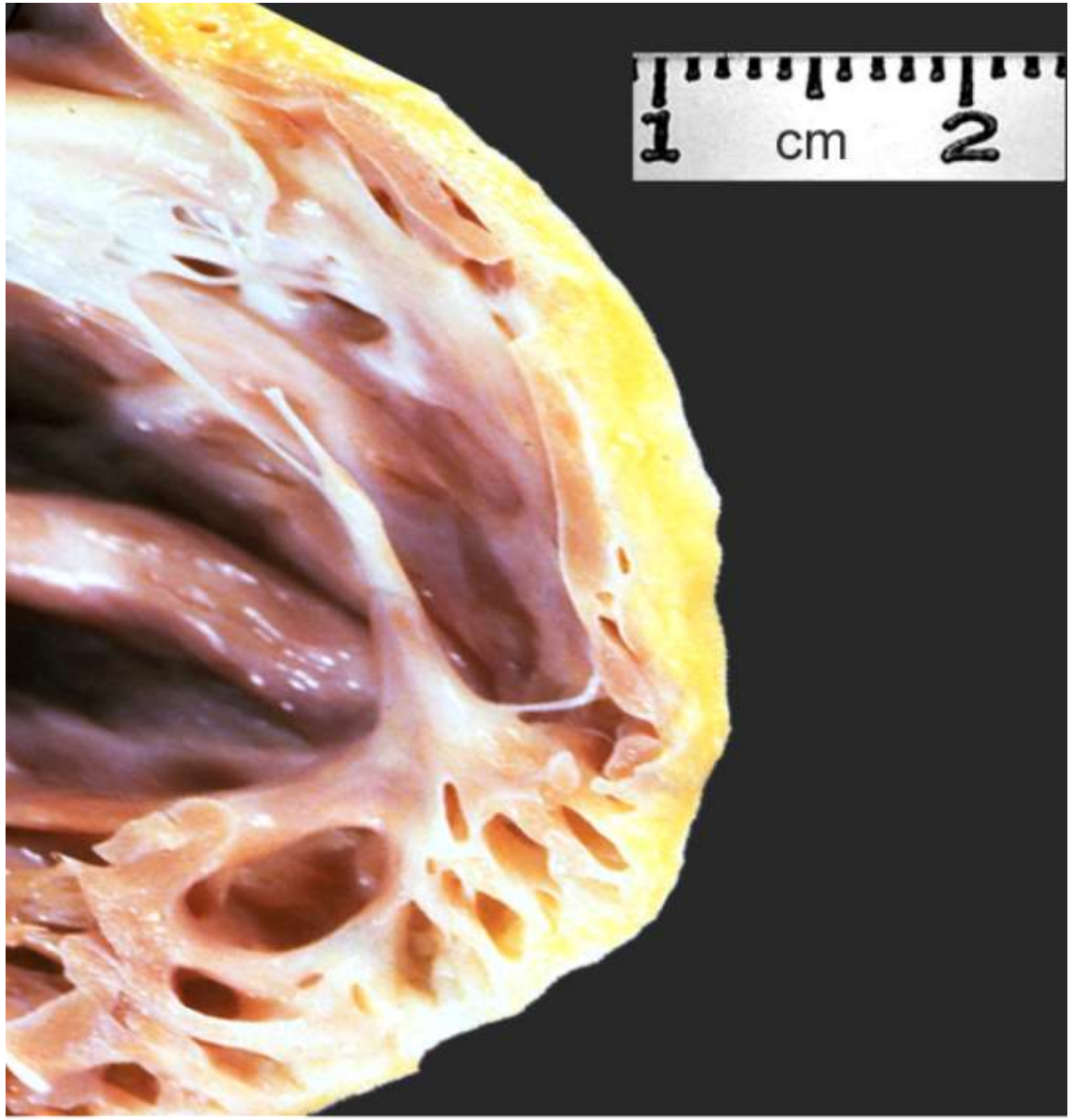


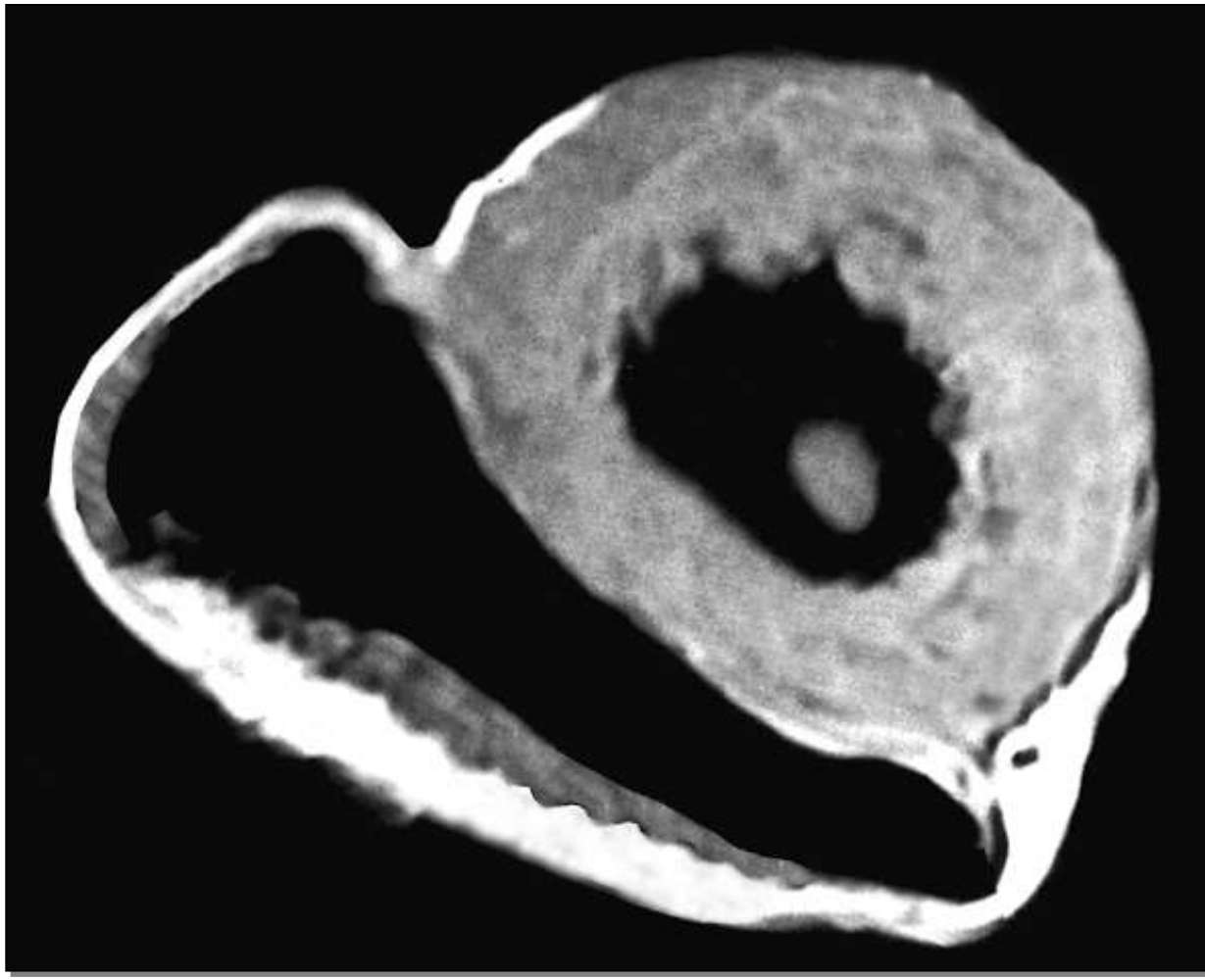
Ajmaline test — suggested standardized protocol (Poli S et al. Europace 2018; Rolf S et al. Eur Heart J. 2003)

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., Int J Cardiol. 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. Heart Rhythm. 2009**).

Life-threatening ventricular arrhythmias	**I. Firth approach: oral quinidine or IV isoproterenol to treat electrical storms** **II. Treatment of Na^+ channel blockers-induced cardiotoxicity56 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 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)**
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, isoproterenol). 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

- **Endomyocardial biopsy**
  - **ARC:** Epicardial fibrofatty replacement





The characteristic found is fibro-fatty replacement of right ventricular myocardium

- **BrS:** The histopathologic finding of fatty infiltration of the myocardium (non-diagnostic for ARC) was observed by Ohkubo et al. (**Ohkubo K, et al. Int Heart J. 2010**) in 20% (5 of 25) and by Zumhagen et al. (**Zumhagen S, et al. Circ Arrhythm Electrophysiol. 2009**) in 19% (4 of 21) of BrS patients undergoing RV endomyocardial biopsy. However, a lower prevalence of typical fibrofatty myocardial replacement suggestive of ARVC was reported both in the series of Frustaci et al (**Frustaci A, et al Circulation. 2005**) and Zumhagen et al. (**Zumhagen S, et al. Circ Arrhythm Electrophysiol. 2009**). Nademanee et al verified that BrS is associated with epicardial surface and interstitial fibrosis and reduced gap junction expression in the RVOT. This collocates to abnormal potentials, and their ablation abolishes the BrS phenotype and life-threatening arrhythmias. BrS is also associated with increased collagen throughout the heart. Abnormal myocardial structure and conduction are therefore responsible for BrS (**Nademanee K, et al. Journal of the American College of Cardiology. 2015**). Prolonged electrograms localized to epicardial RVOT with variable low voltage were identified in all patients with BrS. J-point and ST-segment elevation correlated with greater transmural dispersion of late activation and is independent of total low-voltage area. Despite normalization of spontaneous type 1 pattern in all patients after ablation, recurrence was still observed, suggesting the ICD as the cornerstone therapy for BrS (**Zhang P, et al. Heart Rhythm. 2016**).

The Revised Task Force Criteria for ARVD / ARVC (Marcus FI. Circulation 2010)

I. Global or regional dysfunction and structural alterations* Major/Minor

Major By 2D echo	Minor By 2D echo
Regional RV akinesia, dyskinesia, or aneurysm and 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m2) or fractional area change ≤33%	Regional RV akinesia or dyskinesia and 1 of the following (end diastole): PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m2) PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m2) or fractional area change >33% to ≤40%
By MRI	**By MRI**
Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) • or RV ejection fraction ≤40%	Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female) • or RV ejection fraction >40% to ≤45%
By RV angiography	
Regional RV akinesia, dyskinesia, or aneurysm	

II. Tissue characterization of wall

Major	Minor
Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.	Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.

III. Repolarization abnormalities

Major	Minor
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBB QRS ≥120 ms).	Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6. Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete RBBB

IV. Depolarization/conduction abnormalities

Major	Minor
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
	• Filtered QRS duration (fQRS) ≥114 ms
	• Duration of terminal QRS <40 µV (low-amplitude signal duration) ≥38 ms

	Root-mean-square voltage of terminal 40 ms ≤20 μV
	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block

V) Ventricular Arrhythmias

Major	Minor
Non-sustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	• Non-SVT or S-VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • >500 PVCs per 24 hours (Holter)

VI. Family history

Major	Minor
• AC confirmed in a first-degree relative who meets current Task Force criteria	• History of AC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
• AC confirmed pathologically at autopsy or surgery in a first-degree relative	• Premature sudden death (<35 years of age) due to suspected AC in a first-degree relative
• Identification of a pathogenic mutation† categorized as associated or probably associated with AC in the patient under evaluation	• AC confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.

∗ Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

† A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non–ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree. E.g.: in TMEM43, DSP, PKP2, DSG2, DSC2, JUP.

Source: Cardiomyopathy Association, http://www.cardiomyopathy.org

Three phases have been described in ARVC disease progression (**Sen-Chowdhry S, et al. Circulation 2007; Thiene G, et al. N Engl J Med 1988**). In the early 'concealed phase', individuals are often asymptomatic, but are at risk of ventricular arrhythmias and sudden cardiac death.12,26 (**Sen-Chowdhry S, et al. Annu Rev Med 2010**). In the overt 'electrical phase', individuals present with symptomatic arrhythmias, and RV morphological abnormalities may or may not be detectable by conventional imaging modalities (**Sen-Chowdhry et al. Annu Rev Med 2010**) Diffuse, progressive disease may result in right, left, or biventricular heart failure, often combined with ventricular arrhythmias.

First The early concealed phase	Subtle structural changes within the RV, Usually no symptoms, May have VT. With risk of ventricular arrhythmias and sudden cardiac death
Second Overt electrical phase	Noticeable structural/functional changes within the RV, Symptoms ventricular dysrhythmias, presyncope, syncope, palpitations. Individuals present with symptomatic arrhythmias, and RV morphological abnormalities may or may not be detectable by conventional imaging modalities.
Third Diffuse, progressive disease Weakening of RV	RV dilates and weakens, RV failure symptoms: edema of legs or ankles, abdominal distension, dyspepsia, anorexia
Third Phase of LV	LV dilates and weakens, HF Symptoms: dyspnea on exertion, orthopnea, breathlessness. may result in right, left, or biventricular heart failure, often combined with ventricular arrhythmias.

- **Image**
  - **AC:** As underlying heart diseases of right VTs, ARC causes wall-motion abnormalities based on fibrofatty myocardial degeneration

Major	
	2D Echocardiography
	Regional RV akinesia, dyskinesia, or aneurysm and
	PLAX RVOT >32 mm (or PLAX RVOT >19 mm/m^2) or
	PSAX RVOT >36 mm (or PSAX RVOT >21 mm/m^2) or
	Fractional area change <33%
	MRI
	Regional RV akinesia, dyskinesia, or dyssynchronous RV contraction and
	Ratio of RVEDV to BSA >110 ml/m^2 (male) or >100 ml/m^2 (female) or
Minors	
	2D Echocardiography
	Regional RV akinesia or dyskinesia and
	PLAX RVOT ≥29 to <32 mm (or PLAX RVOT ≥16 to <19 mm/m^2) or
	2D Echocardiography

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