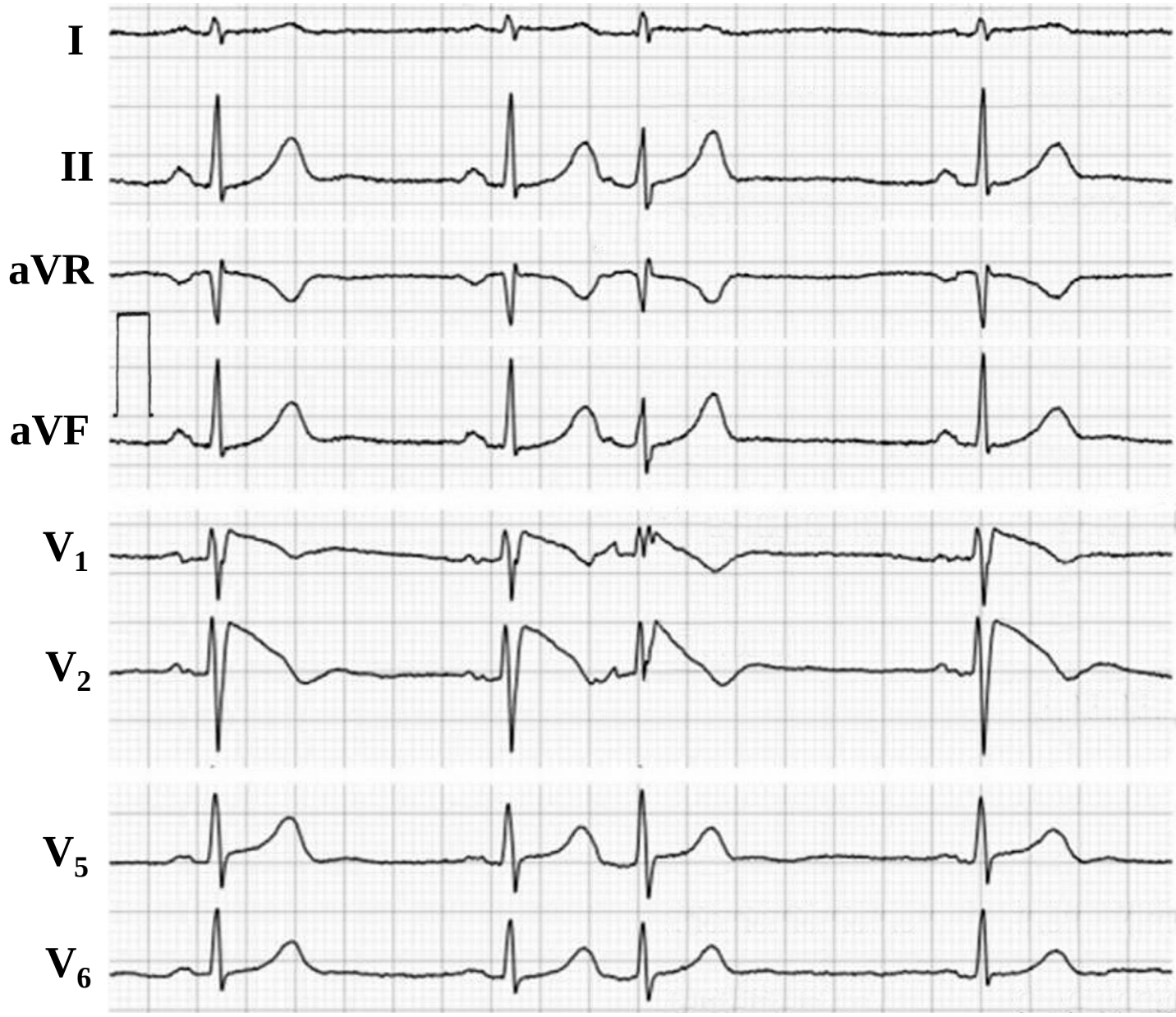
ECG Challenge

Eight-lead ECG with Brugada syndrome in a young adult Asian male

How does the fourth beat assist in the prognosis?

Note: Tracing from the literature


Elementary, My Dear Watson

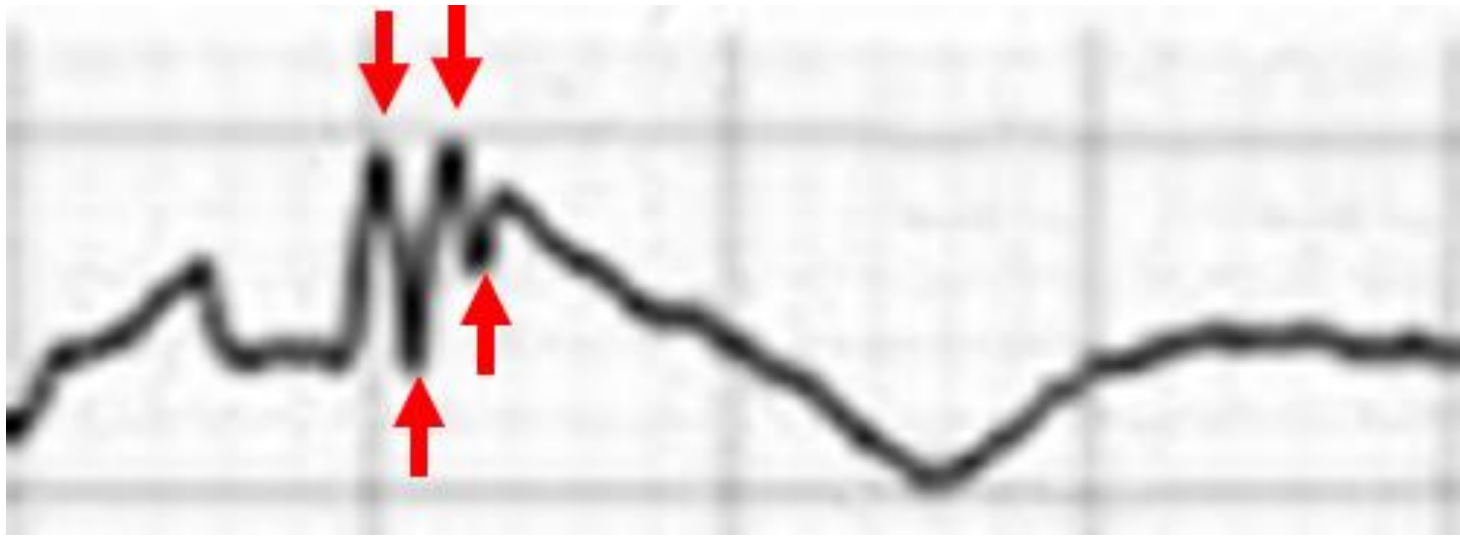

I
II
aVR
aVF
V1
V2
V5
V6

We are waiting for your valuable opinions!

Andrés Ricardo Pérez-Riera, Andrés Vinicius Pérez-Riera (my son) and Murilo Pérez-Riera (my grandson)

Colleagues opinions

4rd beat shows fractionated QRS in V1
Melvin Sheinman



Abnormal fQRS Is defined as either ≥4 spikes in 1 lead or >1 notches in the apex or nadir of the R or S wave in 2 consecutive leads.

Brief trajectory Dr. Melvin Scheinman, one of the pioneers of cardiac electrophysiology (the study of the heart's electrical activity), was the first to perform catheter ablation on humans. His team was instrumental in developing radiofrequency energy applications for cardiac arrhythmias. Scheinman and his colleagues also developed techniques for modifying sinus node function (the sinus node sends the electrical impulse that results in a heartbeat) in patients with inappropriate sinus tachycardia – a condition in which resting heart rate is abnormally high – and to cure patients with automatic junctional tachycardia, in which one area of the heart is leading to a too-fast beat.
Scheinman currently directs the cardiac genetic arrhythmia program, which is devoted to discovering new genes related to heart rhythm disorders.
Scheinman grew up in Brooklyn, New York, and earned an undergraduate degree at Johns Hopkins University, where he graduated first in his class. His medical education included Albert Einstein College of Medicine, residency training at the University of North Carolina at Chapel Hill and cardiology training at UCSF Medical Center.

Dear sir
There’s a PAC after the second beat that is early and it conducts with almost no PRprolongation. There’s no slowing through the AV node. Note that the QRS morphology changes with more aberration in the JT junction and loss of S waves on anterior leads. After the pause the forth beat returns to the previous pattern without any worsening in the coved STT. So one can hypothetically states that is Brugada events are bradycardia dependent and with a vagal relation; the fact that this forth beat is not worse may portends a better prognosis.

Cheers from Brazil BR

TIago Luiz Luz Leiria MD PhD
Cardiology - Electrophysiology
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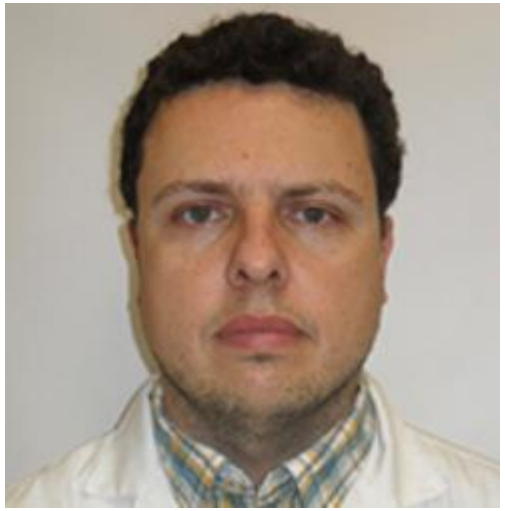


Just a "light weight" opinion. The four beat that is premature atrial contraction make the J point elevation more significant, but more importantly more fractionated that has been associated with increased risk for ventricular arrhythmias

Raul **Weiss MD FHRS, FACC, FAHA**

Director, Electrophysiology Fellowship

Professor of Medicine

Cardiovascular Division

The Ohio State University

Columbus, Ohio. USA

Answer from Andrés Ricardo Pérez-Riera: Your lucid comment is very important. Patients with a very prominent J waves have a worse prognosis: J wave amplitude and the ERP with changes and fluctuation dynamically and dramatically during exercise, taking drugs and rapid atrial pacing (1) Elevated J point amplitude, convex upward J wave, horizontal ST segment, lambda-wave ST shape and left precordial QRS notching pattern (2). In the next slide we shows the main characteristic of the Early Repolarization Syndrome (ERS) from e single center case series The sênior authors is our dear teacher of the theachers professor Melvin " Mel"

1. **Cay S, Cagirci G, Atak R, Balbay Y, Demir AD, Aydogdu S. Heart rate profile during exercise in patients with early repolarization. Chin Med J (Engl). 2010 Sep; 123(17):2305-9**
2. **Pérez-Riera AR, Abreu LC, Yanowitz F, Barros RB, Femenía F, McIntyre WF, Baranchuk A. "Benign" early repolarization versus malignant early abnormalities: clinical-electrocardiographic distinction and genetic basis Cardiol J. 2012; 19(4):337-46.**

Early Repolarization Syndrome (ERS)

Age at diagnosis	30 ± 17
Arrhytmic events curcunstances	At rest 80% with exertion 20%
family history of sudden death	≈10%
Ventricular fibrillation	≈70%
Dynamic early repolarization patterns	≈70%
Polymorphic Ventricular Tachycardia	≈ 30%
Monomorphic Ventricular Tachycardia	≈ 30%
Atrial fibrillation	≈ 30%
atrioventricular block	≈ 20%
Ventricular fibrillation	≈70%
Dynamic early repolarization patterns	≈70%
Uncertain significance on genetic testing	≈ 40%
Quinidine efficacy	Effectively suppressed arrhythmias in 5 of 5 patients but required dose escalation to >1 g/d in 3 of 5 patients.
Ablation	Abnormal epicardial electrograms were recorded over the inferolateral left ventricle in 2 patients who underwent mapping and were successfully ablated. PVC triggers were also targeted for ablation in 3 patients.

1. **Aleksandr Voskoboinik 1, Henry Hsia 2, Joshua Moss 2, Vasanth Vedantham 2, Ronn E Tanel 3, Akash Patel 3, Julianne Wojciak 2, Natalie Downs 2, Melvin M Scheinman 2The many faces of early repolarization syndrome: A single-center case series. Heart Rhythm. 2020 Feb;17(2):273-281. doi: 10.1016/j.hrthm.2019.09.013.**

Buenas tardes Foro!!
Estimado Andrés, que queda una duda, el 4° latido para mi es normal.
Es un ritmo sinusal bradicárdico, con PR de 180 mseg. Onda P parece medir cerca de 120 mseg y es bimodal. El eje del QRS está cercano a +90°. Tiene un patrón de Br tipo 1.
El 3° es una extrasístole auricular (EA) con PR ligeramente mayor (200 mseg) medida en V2. **El QRS de esta EA en V1 da la impresión de tener fragmentación u onda Épsilon. Ambos signos de mal pronóstico.** También mayor onda "s" que el el resto de los latidos, aunque no hay derivacion DIII, y mayor "r" en aVR no alcanzando criterios de malignidad.
Es notable el ancho del QRS en V1 V2 (por método de tangente mide aproximadamente 510 mseg) con respecto al resto de las derivaciones.
Mide lo mismo que el latido anticipado.
A la espera de la opinión de los expertos....
Juan Manzzardo, MD
Mendoza, Argentina

Good afternoon Forum !! Dear Andrés, there is still a doubt, the 4th heartbeat for me is normal.
It is a bradycardic sinus rhythm, with a PR of 180 msec. P wave appears to measure about 120 msec and is bimodal. The QRS axis is close to + 90 °. It has a Br type 1 pattern.
The 3rd is an atrial extrasystole (AE) with slightly higher PR (200 msec) measured in V2. The QRS of this EA in V1 gives the impression of having fragmentation or Epsilon wave. Both signs of poor prognosis. There is also a greater "s" wave than the rest of the beats, although there is no DIII lead, and a greater "r" in aVR, not reaching criteria of malignancy.
The width of the QRS in V1 V2 is remarkable (by tangent method it measures approximately 510 msec) with respect to the rest of the leads. It measures the same as the anticipated heartbeat.
Waiting for expert opinion ....

This is pts with type 1 BrS e PAB originating from Left Superior Pulmonary Vein (LSPV).
Is not uncommon the association of BrS with AF (20%) and PAB.
Best regards

Prof. Carlo Pappone

"Carlo Pappone, the doctor who defeated the Brugada Syndrome" (Carlo Pappone, the doctor who defeated the Brugada Syndrome)

Professor Pappone has recently contributed extraordinarily to the concept of the genesis of this intriguing syndrome. For us it is a great pride and satisfaction to be able to tell such an endorsed opinion.

Main recent publications of Professor Carlo Pappone about BrS.

- van Dam PM, Locati ET, Ciconte G, Borrelli V, Heilbron F, Santinelli V, Vicedomini G, Monasky MM, Micaglio E, Giannelli L, Mecarocci V, Ćalović Ž, Anastasia L, Pappone C. Novel CineECG Derived from Standard 12-Lead ECG Enables Right Ventricle Outflow Tract Localization of Electrical Substrate in Patients with Brugada Syndrome. Circ Arrhythm Electrophysiol. **2020 Jul** 28. doi: 10.1161/CIRCEP.120.008524.
- Pappone C, Monasky MM, Micaglio E, Ciconte G. Right ventricular electromechanical abnormalities in Brugada syndrome: is this a cardiomyopathy? Eur Heart J Suppl**. 2020 Jun;**22(Suppl E):E101-E104. doi: 10.1093/eurheartj/suaa071.
- Pappone C, Mecarocci V, Manguso F, Ciconte G, Vicedomini G, Sturla F, Votta E, Mazza B, Pozzi P, Borrelli V, Anastasia L, Micaglio E, Locati E, Monasky MM, Lombardi M, Calovic Z, Santinelli V. New electromechanical substrate abnormalities in high-risk patients with Brugada syndrome. Heart Rhythm. **2020 Apr**;17(4):637-645. doi: 10.1016/j.hrthm.2019.11.019.
- Monasky MM, Micaglio E, Ciconte G, Pappone C. Brugada Syndrome: Oligogenic or Mendelian Disease? Int J Mol Sci. **2020 Mar** 1;21(5):1687. doi: 10.3390/ijms21051687.
- Monasky MM, Micaglio E, Ciconte G, Borrelli V, Giannelli L, Vicedomini G, Ghiroldi A, Anastasia L, Locati ET, Benedetti S, Di Resta C, Casari G, Pappone C. Novel SCN5A p.V1429M Variant Segregation in a Family with Brugada Syndrome. Int J Mol Sci. 2020 Aug 17;21(16):E5902. doi: 10.3390/ijms21165902.
- Pappone C, Monasky MM, Ciconte G. Epicardial ablation in genetic cardiomyopathies: a new frontier. Eur Heart J Suppl. **2019 Mar**;21(Suppl B):B61-B66. doi: 10.1093/eurheartj/suz028.
- Pappone C, Ciconte G, Manguso F, Vicedomini G, Mecarocci V, Conti M, Giannelli L, Pozzi P, Borrelli V, Menicanti L, Calovic Z, Della Ratta G, Brugada J, Santinelli V. Assessing the Malignant Ventricular Arrhythmic Substrate in Patients With Brugada Syndrome. J Am Coll Cardiol. **2018 Apr** 17;71(15):1631-1646. doi: 10.1016/j.jacc.2018.02.022.
- Pappone C, Brugada J, Vicedomini G, Ciconte G, Manguso F, Saviano M, Vitale R, Cuko A, Giannelli L, Calovic Z, Conti M, Pozzi P, Natalizia A, Crisà S, Borrelli V, Brugada R, Sarquella-Brugada G, Guazzi M, Frigiola A, Menicanti L, Santinelli V. Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome. Circ Arrhythm Electrophysiol. **2017 May**;10(5):e005053. doi: 10.1161/CIRCEP.117.005053.

- Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, Ciconte G, Giannelli L, Santinelli V. Brugada Syndrome Phenotype Elimination by Epicardial Substrate Ablation. Circ Arrhythm Electrophysiol. 2015 Dec;8(6):1373-81. doi: 10.1161/CIRCEP.115.003220.
- Pappone C, Vicedomini G, Petretta A, Giannelli L, Cuko A, Santinelli V. Ventricular fibrillation in lone atrial fibrillation as clinical manifestation of latent Brugada syndrome: Usefulness of flecainide testing. HeartRhythm Case Rep. **2015 Jun** 6;1(5):285-289. doi: 10.1016/j.hrcr.2015.02.013.

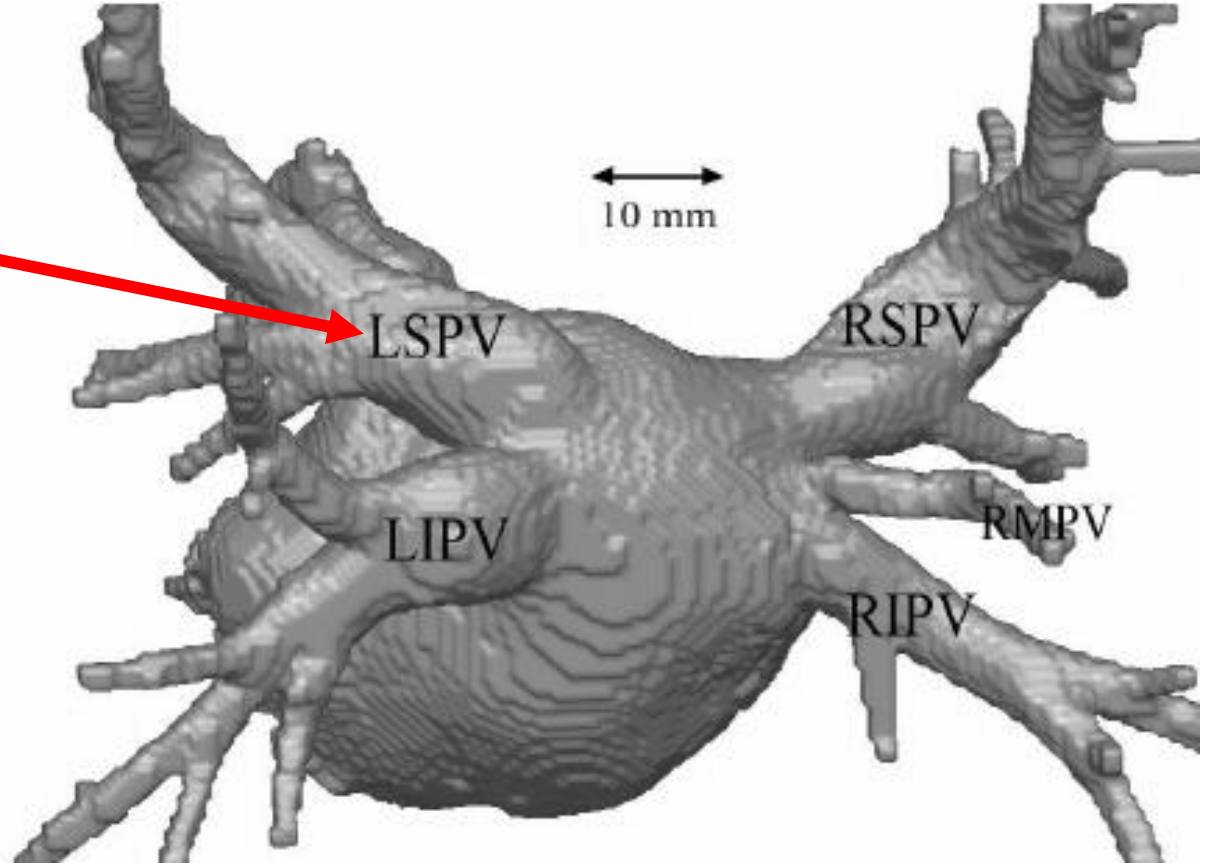
Question from Andrés to Professor Pappone:

How did you identify that premature atrial contractions(PACs) with focus on the Left Superior Pulmonary Vein (LSPV)?

We know that symptomatic, frequent, and drug-refractory PACs can be successfully ablated. Second, the pulmonary veins (PVs), CS, superior vena cava (SVC), annulus, and NCC are the most common origin sites. Third, a significant difference in origins was noted between PACs that induced AF and those that did not induce AF. PACs that trigger AF typically originate from PVs.

Thank you in advance.

Andrés Ricardo **Pérez-Rier**a



LA inner surface extracted from CT data by watershed segmentation and isosurfacing (LSPV, LIPV, RSPV, RMPV, RIPV: left superior and inferior, right superior, middle and inferior pulmonary veins respectively).

Dear Andres,
The short 8-lead ECG tracing with type 1 Brugada pattern shows normal sinus rhythm with one slightly aberrant PAC with an incomplete compensatory pause. The criteria for a +aVR sign are not met, but in lead V1 the fractionated QRS of the PAC suggests an increased vulnerability for malignant ventricular arrhythmias.
I hope you're staying safe. I loved seeing three generations of your family!
Regards,
Frank Yanowitz, MD FACC

Brief scientific trajectory
Education
Baccalaureate Degree: BA (Mathematics), 1961, Cornell University, Ithaca, N.Y.
Medical Degree: M.D., 1966, State University of New York Upstate Medical School, Syracuse, N.Y.
Internship: Straight Medical, 1966-67, University of Chicago Hospitals, Chicago, Illinois
Residency: Internal Medicine, 1967-69, University of Chicago Hospitals, Chicago, Illinois
Fellowship: Cardiology, 1969-71, University of Chicago Hospitals, Chicago, Illinois

Present position and address
Academic Rank: Professor (Clinical), University of Utah School of Medicine, (Retired)
Medical Director, IHC ECG Services Medical Director, Cardiac Rehabilitation, Intermountain Medical Center Professional
Address: 1575 E. Stablewood Circle, Salt Lake City, Utah 84117 Cell Phone: 801-718-9811
E-Mail Address: fyanow@mac.com
Andrés Pérez-Riera comments: Frank is one of the most brilliant electrocardiographers that I have met around the world.
I always learn a lot from him. We have great friendship without having known personally Only viritally !!! These are modern times.

Dear Dr. Andrés Ricardo Pérez-Riera, MD PhD

Its fragmented QRS which increased the risk of major arrhythmic event **up to three** fold.
Best,

Pat

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Cardiovascular Fellow
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————————————————————————

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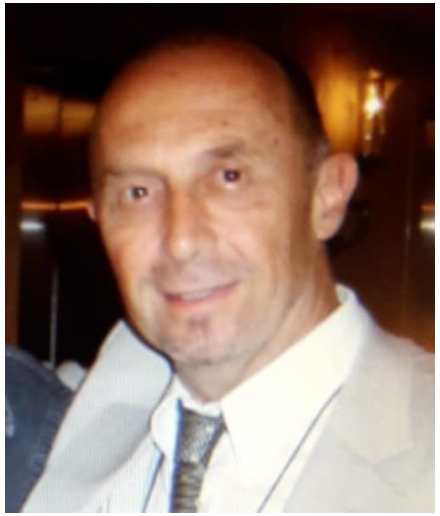
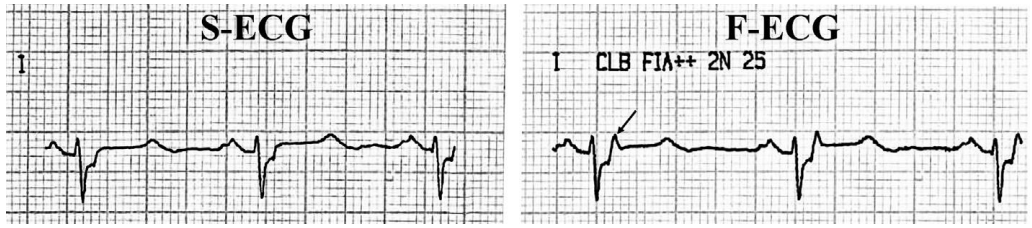
Pattara Rattanawong, MD

Spanish Seria Interesante investigar el Triángulo de la displasia de ventrículo derecho con la derivación bipolar de precordiales de Guy Fontaine para ver mejor la onda épsilon y evaluar el pronóstico ya que es sustrato donde subyacen mecanismos de reentrada para arritmias de mal pronóstico. Por ello lo de MIOCARDIOPATIA ARRITMOGENICA DE VENTRÍCULO DERECHO.

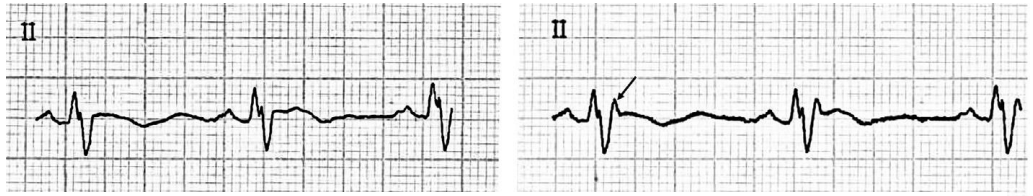
Juan Jose Sirena, MD
Santiago del Estero, Argentina

It would be interesting to investigate the Triangle of Arrithmogenic Cardiomyopathy with the Guy Fontaine precordial bipolar (**F-ECG**) shunt to better see the epsilon wave and evaluate the prognosis since it is the substrate where reentry mechanisms for poor prognosis arrhythmias lie. For this reason, the Arrithmogenic Cardiomyopathy.

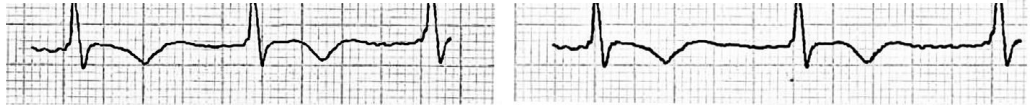


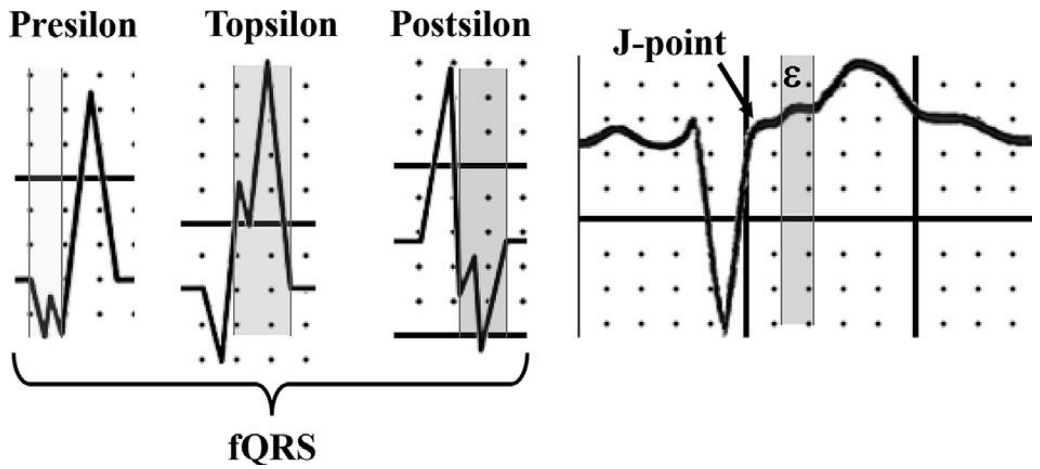


Leads I, II and III with S-ECG and F-ECG. Typical example of AC with LV involvement. Note the ε wave (arrows) observed only with F-ECG in the left (I) and inferior leads (II, III).



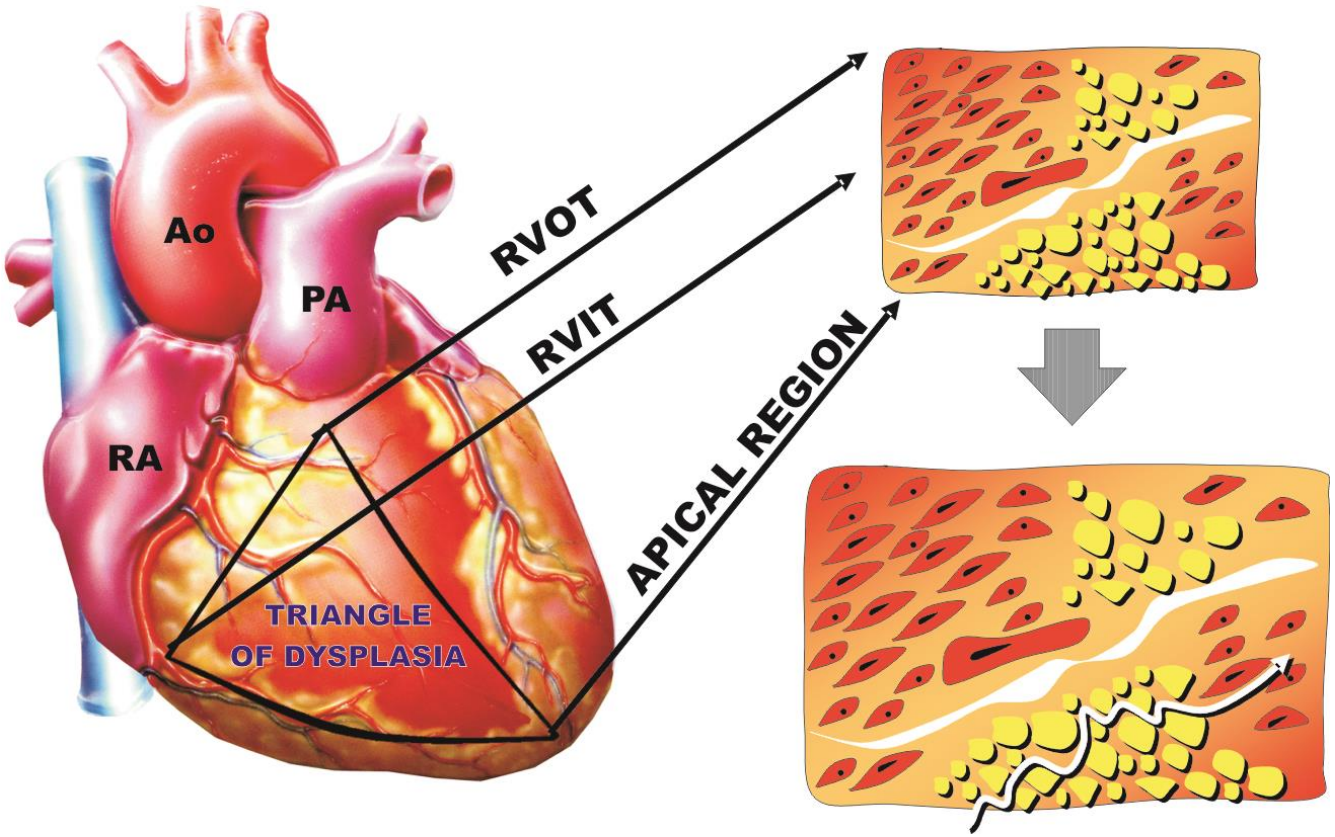
Pérez-Riera AR, Barbosa-Barros R, Daminello-Raimundo R, de Abreu LC, García-Niebla J, de Deus Morais MJ, Nikus K, Marcus FI. Epsilon wave: A review of historical aspects. Indian Pacing Electrophysiol J. 2019 Mar-Apr;19(2):63-67. doi: 10.1016/j.ipej.2019.02.003.





The figure shows the three possibilities of fragmented QRS in AC: at the beginning (presilon), in the middle (topsilon) and at the end (postsilon) of the QRS complex, and when the ε wave is located after the J-point and the beginning of the ST segment. Although the ε wave is a depolarization abnormality (late potential), it is recorded at the beginning of repolarization.

Comments by Andrés Ricardo Pérez-Riera

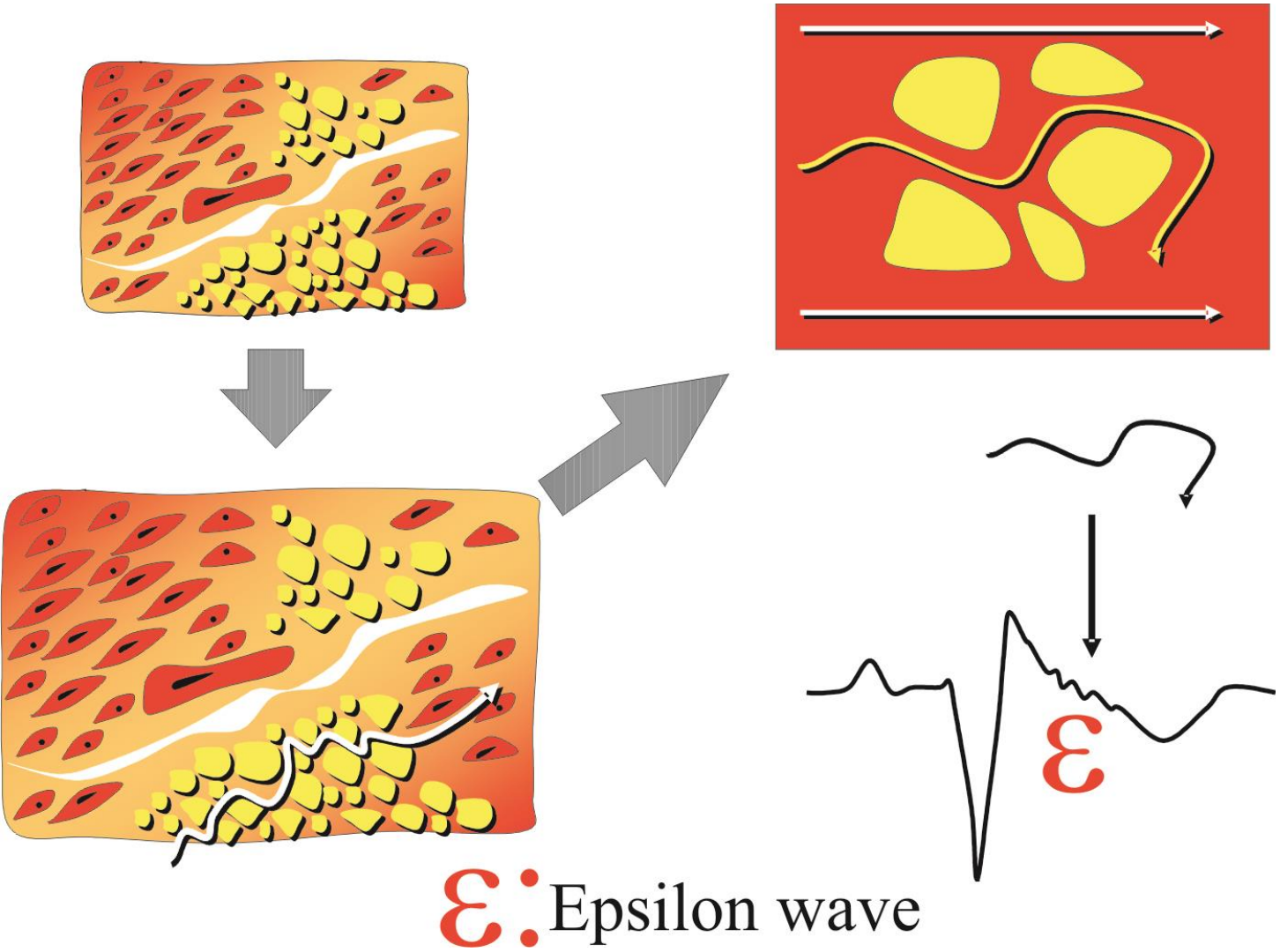


The figure shows the so-called triangle of dysplasia on right ventricle free wall. The vertices or corners of the triangle are made up by:

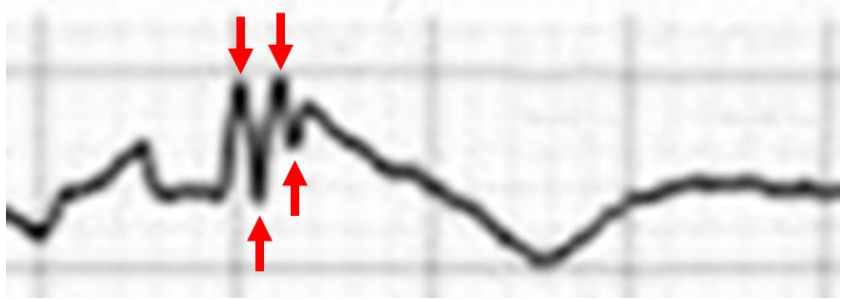
- **The RVOT**
- **Right ventricular apex**
- **The Right Ventricular Inflow Tract(RVIT)**

Dysplasia in this region usually leads to dilatations or aneurysms having paradoxical systolic motion (expansion with systole instead of contraction).

Comments by Andrés Ricardo Pérez-Riera



The present case

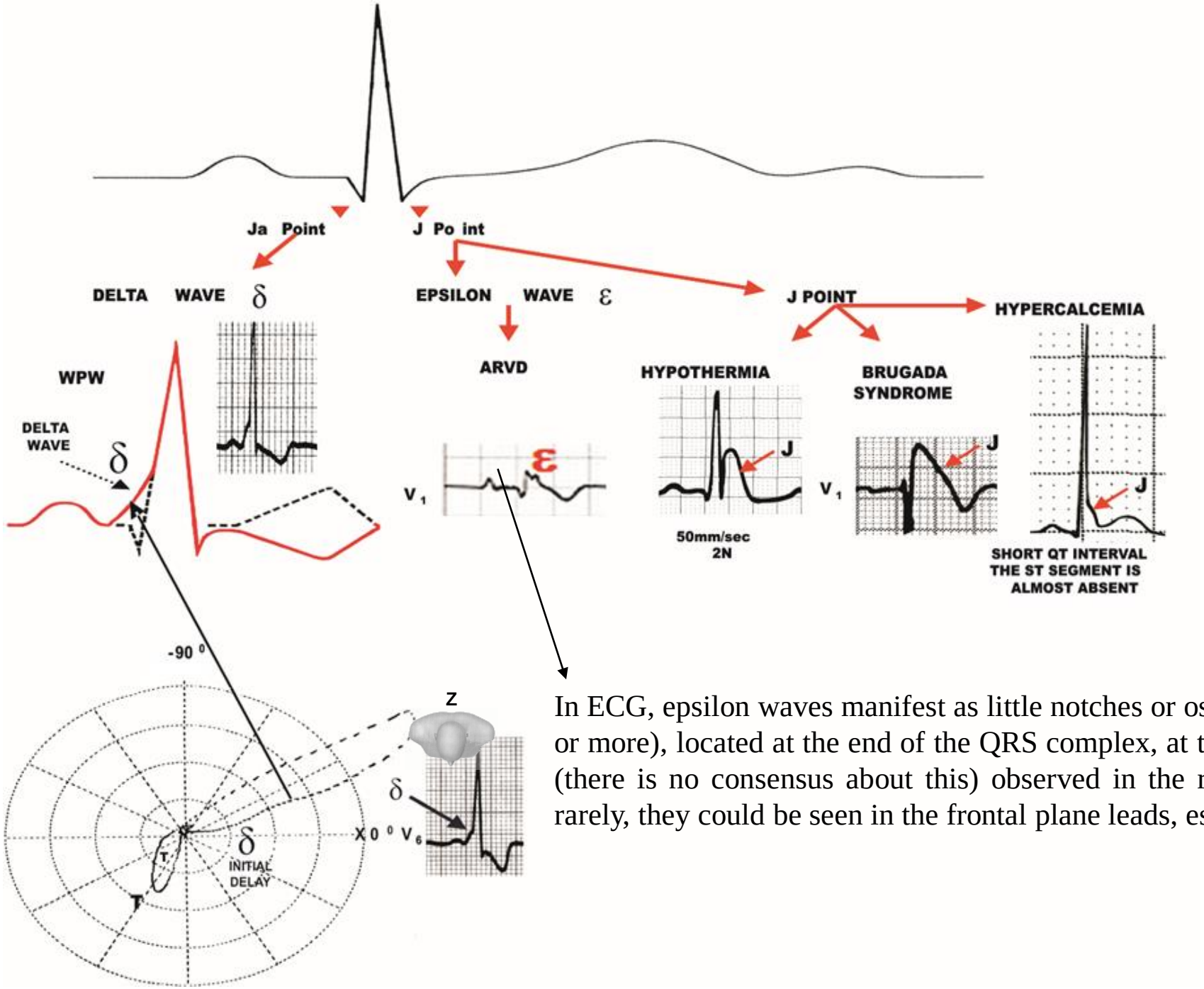


Abnormal fQRS Is defined as either ≥4 spikes in 1 lead or >1 notches in the apex or nadir of the R or S wave in 2 consecutive leads. Conclusion: fragmented QRS is located inside of the QRS complex. On the other hand, epsilon wave is located after the J-point. It is important to comment that epsilon wave is rarely observed in BrS, sometimes induced by ajmaline (1).

1. Aras D, Ozeke O, Cay S, Ozcan F, Acar B, Topaloglu S. Ajmaline-induced epsilon wave: as a potential interim risk factor between the spontaneous- and drug-induced type 1 Brugada electrogram? Europace. 2018 Jul 1;20(7):1225-1226. doi: 10.1093/europace/euy071.

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) [1]. Because the ε wave is of low amplitude, it may be affected by ECG filter settings. At the recommended 150-Hz cutoff frequency the ε wave is best detected in the right precordial leads. Currently ECG guidelines recommend a cutoff of 150 Hz for adolescents and adults and 250 Hz for children [2]. The ECG acquisition is often accompanied by high-frequency electromyographic noise. The noise is difficult to filter due to considerable overlapping of its frequency spectrum with the frequency spectrum of the ECG. In clinical practice a 40-Hz cutoff frequency may be used to reduce muscle noise and improve the appearance of the tracing. This approach results in the loss of important information, which was demonstrated in a case report, where ε waves were masked by excessive low-pass filtering in a patient with AC [3]. Therefore, it is possible that the prevalence of the ε wave in AC patients may be underestimated.

1. **Fontaine G.H., Duthoit G., Li G., Andreoletti L., Gandjbakhch E., Frank R. Epsilon wave on an electronic loop in a case of arrhythmogenic right ventricular dysplasia with myocarditis: an updated definition of the Epsilon wave. Europace. 2017;19:1084–1090. [PubMed] [Google Scholar]**
2. **Kligfield P., Gettes L.S., Bailey J.J. Recommendations for the standardization and interpretation of the electrocardiogram: part I: the electrocardiogram and its technology a scientific statement from the American heart association electrocardiography and arrhythmias committee, council on clinical cardiology; the American college of cardiology foundation; and the heart rhythm society endorsed by the international society for computerized electrocardiology. J Am Coll Cardiol. 2007;49:1109–1127. [PubMed] [Google Scholar]**
3. **Garcia-Niebla J., Baranchuk A., Bayes de Luna A. Epsilon wave in the 12-lead electrocardiogram: is its frequency underestimated? Rev Esp Cardiol (Engl Ed). 2016;69:438. [PubMed] [Google Scholar]**



In ECG, epsilon waves manifest as little notches or oscillations, varying in number (1, 2, 3, or more), located at the end of the QRS complex, at the J point or onset of the ST segment (there is no consensus about this) observed in the right precordial leads; however more rarely, they could be seen in the frontal plane leads, especially in the inferior leads.

Dear Andrés Ricardo Pérez-Riera, MD PhD

Thank for an interesting ECG. My interpretation is the patient is Brugada syndrome with type 1 ECG. In the conducted premature atrial beat, The typical ECG pattern was attenuated. This can be a reverse of a bradycardia-dependent augmentation: a tachycardia-dependent attenuation of cove type.

In the beat following the conducted APB, the RR interval seems prolonged and augmentation of coved type is likely.

In this case, Ito-mediated mechanism must be involved for type 1 ECG.

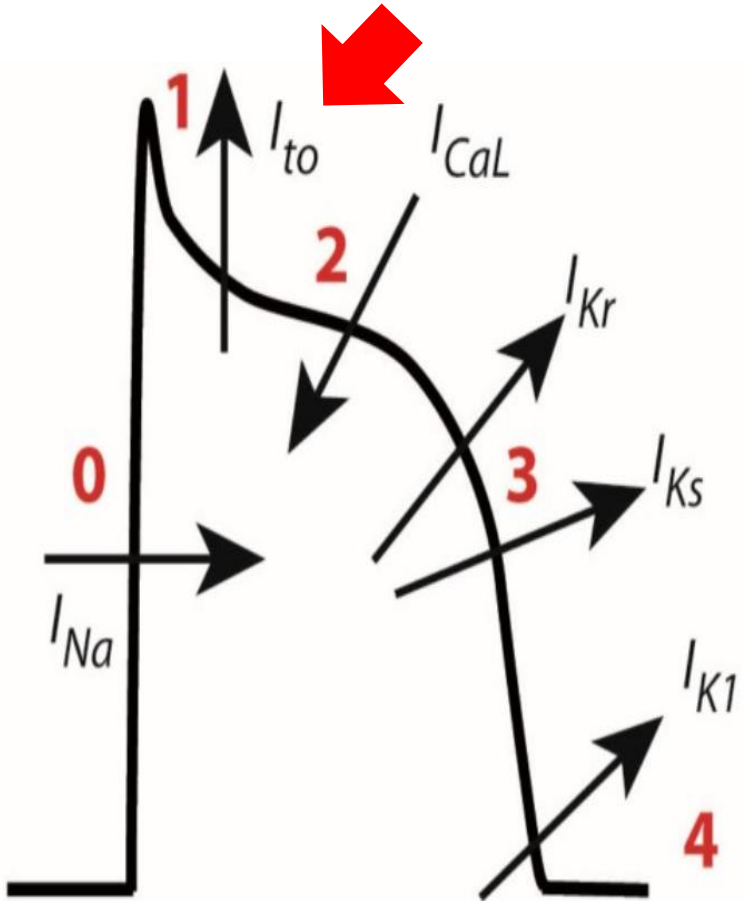
Yoshifusa Aizawa MD PhD

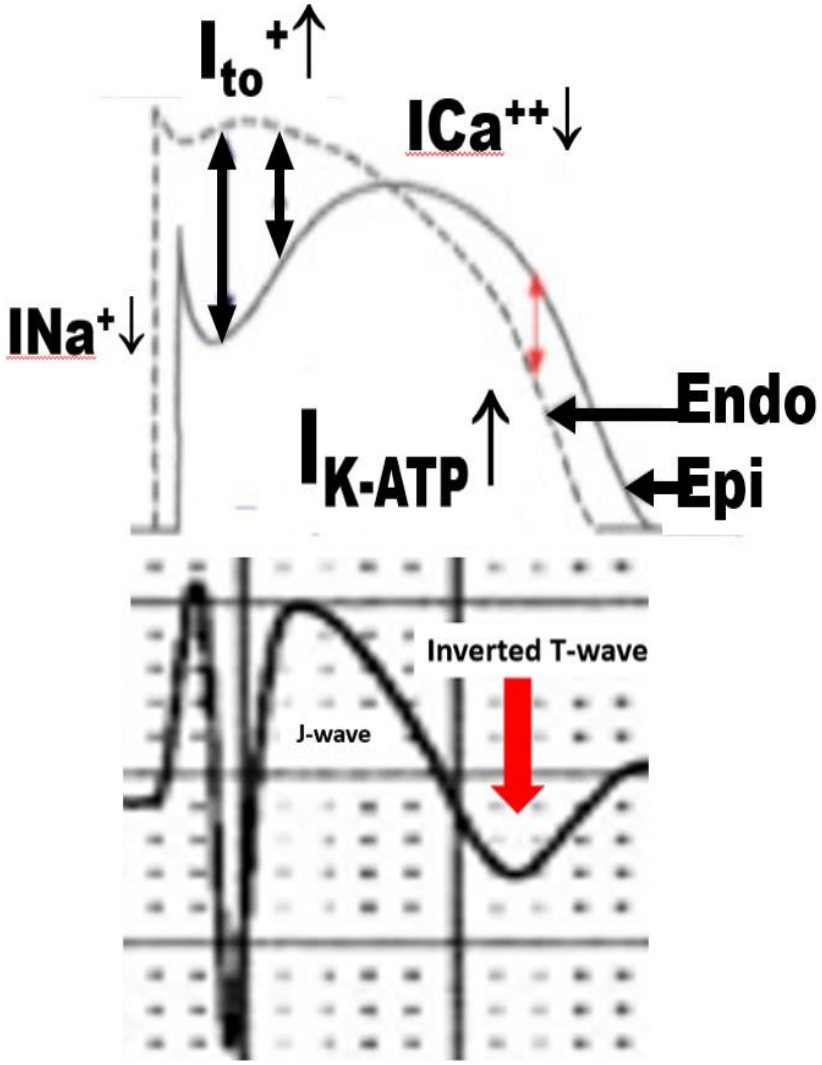
Department of Research and Development, Tachikawa Medical Center, Kanda 3-2-11, Kanda-cho. Nagaoka, Niigata, Japan Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences. Niigata University,Nagaoka and Niigata,JapaN.

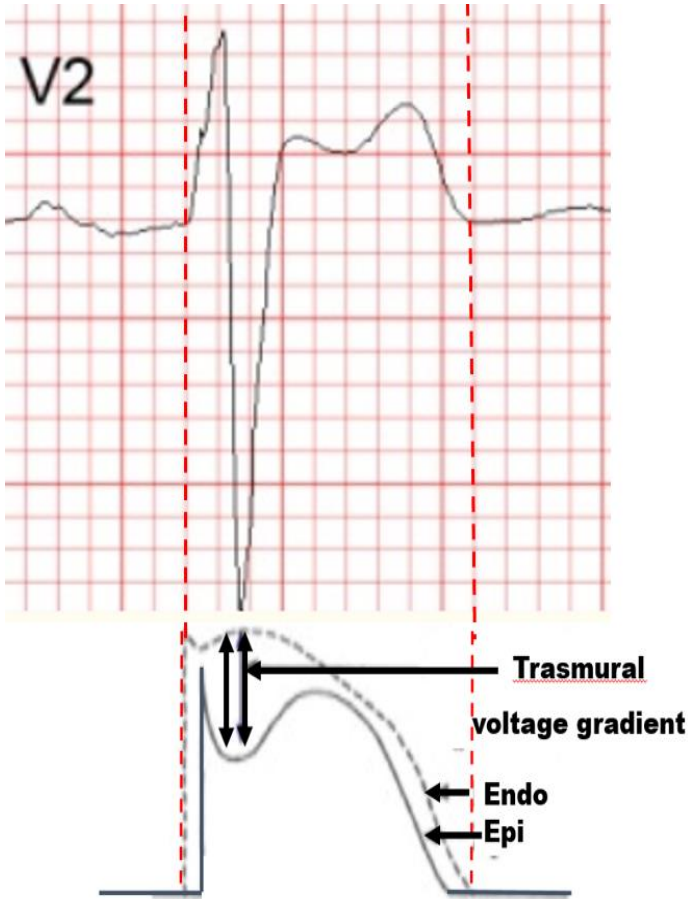
Dear Doctor Aizawa,

I agree with you related I_{to} mediated mechanism in BrS ECG patterns. In this case, the mutation is located in the KCNE3 gene (BrS6), locus: 11q13-14; OMIM: 604433. (**Delpon E, Cordeiro JM, Nunez L, Thomsen PE, Guerchicoff A, Pollevick GD, Wu Y, Kanters JK, Larsen CT, Hofman-Bang J, Burashnikov E, Christiansen M, Antzelevitch C.. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. Circulation Arrhythmia and electrophysiology. 2008;1(3):209-18.doi: 10.1161/CIRCEP.107.748103**). Please see our explanation in the next slide. Andrés

Monophasic Action Potentials correlation Type 1 and 2 ECG Brugada patterns







H.u.S.Peters@t-online.de

Dear Andrès,

After a supraventricular extrasystole with QRS fragmentation in lead V1 and right precordial ST elevation the fourth beat demonstrates in my opinion a typical example of Brugada syndrome with right precordial ST-elevation and T-wave inversion.

Have you any other suggestions ?

Best regards
Stefan Peters
Professur für Friedensforschung
Prof. Dr. Stefan Peters
Licher Str. 76
35394 Gießen
Student Population:
Over 26,000 students, 10% being international students
Language Pre-requisite:
No, but a limited number of classes are taught in English
Primary Instruction Language:
German
Important Dates
Summer Semester: April-September
Winter Semester: October- March

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

Final comments by
Andrés Ricardo Pérez-Riera M.D.PhD.

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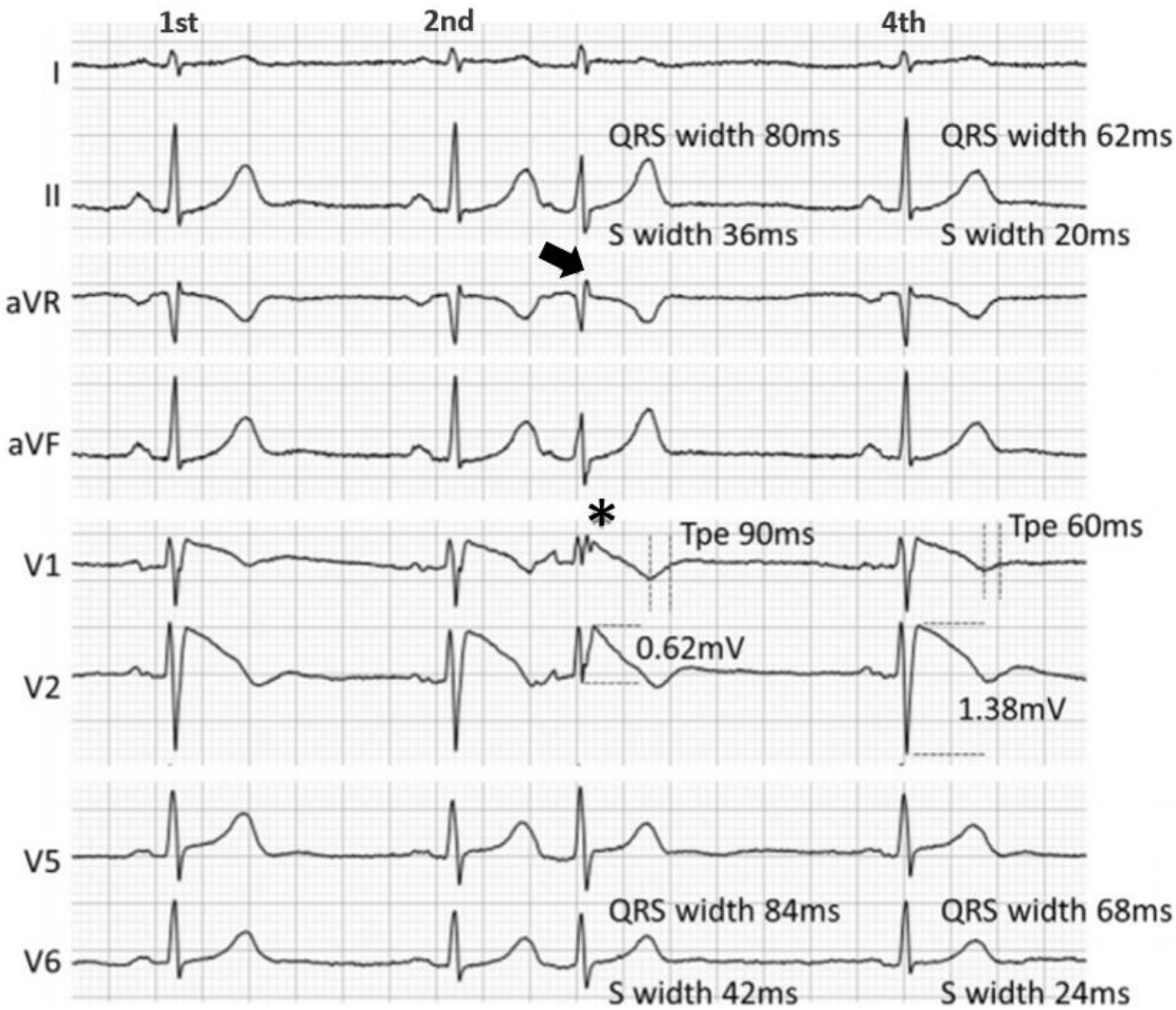


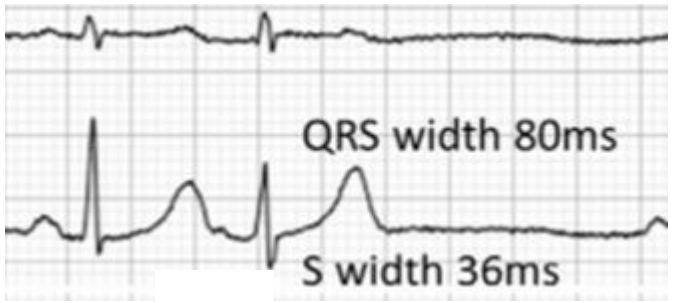
ECG of a patient with BrS. The first, second, and fourth QRS complexes show normal sinus rhythm. Premature atrial contraction causes third QRS complex via normal conduction system with premature excitation and exacerbated conduction of ventricle. This complex shows longer QRS and S width in leads II, aVF, V5, and V6 and lower QRS amplitude in leads V1 and V2 compared with other complexes. The amplitude of R wave in lead aVR is also larger (arrow). Fragmented QRS also appears in lead V1 (*). These features should indicate a close relationship between ventricular conduction delay and specific ECG features. Interestingly, third QRS complex also shows longer Tpeak-Tend interval (Tpe) in leads V1 and V2 compared with others.

Summary of the ECG findings predictors of sudden cardiac death

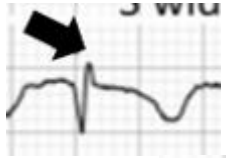
1. **Spontaneous type 1 Brugada ECG pattern.**

2. **Fragmented QRS complex (fQRS).**

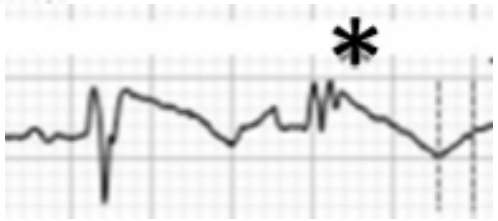
3. **Caló sign in lead I: prominent S-wave in this lead).**



4. **Almost aVR sign.**



5. **Broader QRS duration.**

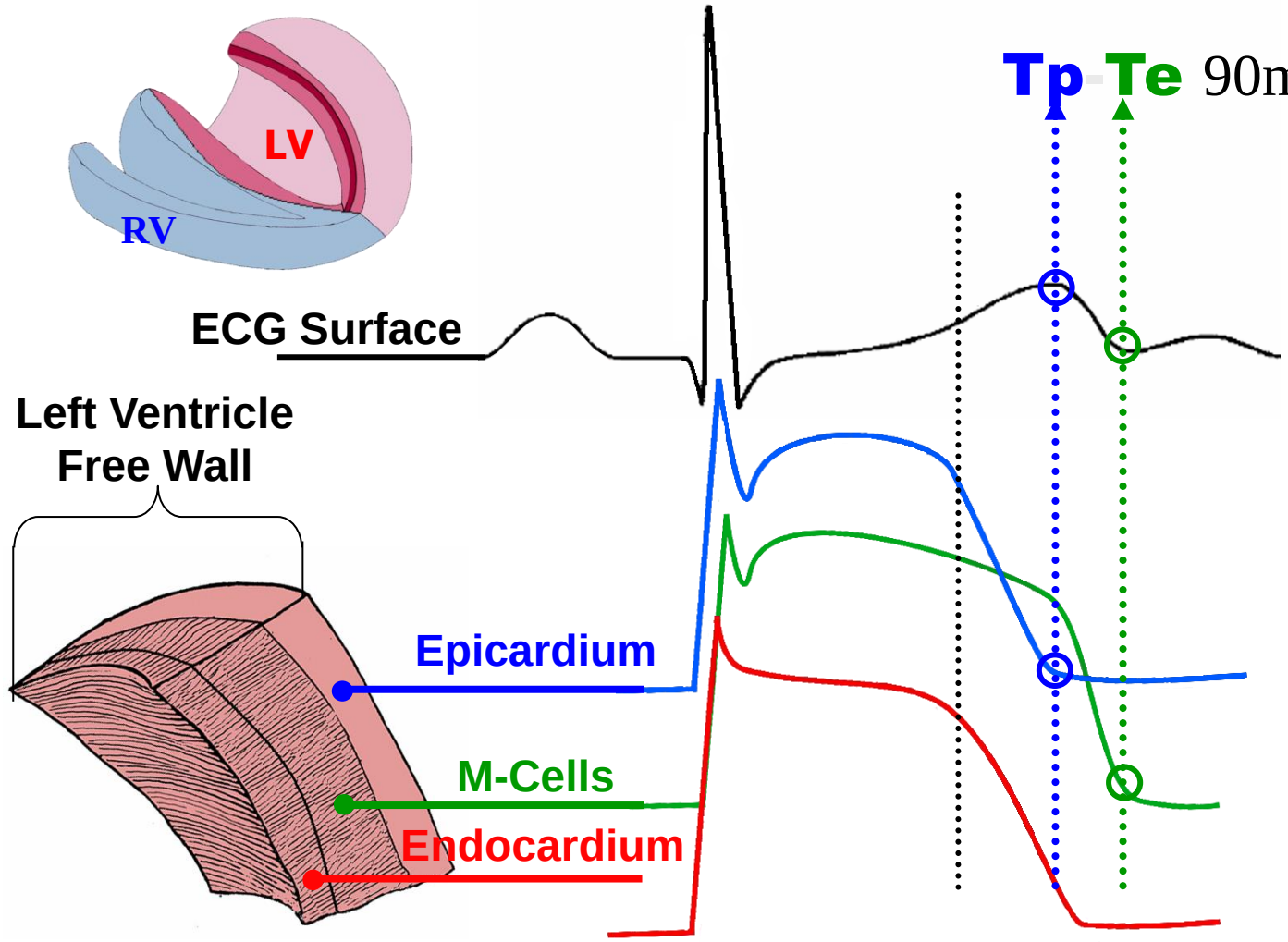


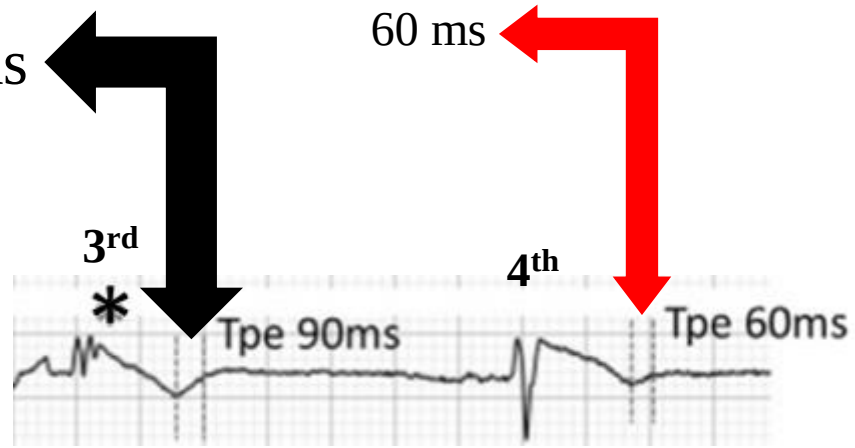
6. **Lesser QRS amplitude.**

7. **The 3rd QRS complex shows longer Tpeak-Tend interval (Tpe) in leads V1 and V2 compared with others.**

8. **Two type 1 Brugada patterns (See explanation in next slide)…….**

T-peak to T-end interval (TpTe: Tpe)



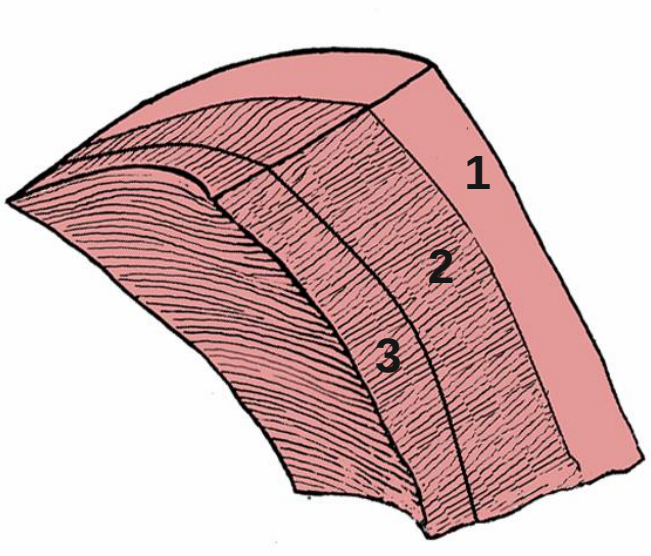


The 3rd QRS complex shows longer Tpeak-Tend interval (Tpe) in leads V1 and V2 compared with others.

Distance between the T-peak/T-end Normal value ≤ 90ms It is prolonged from 90 to 130ms in the global transmural dispersion cases. In this circumstance is observed:

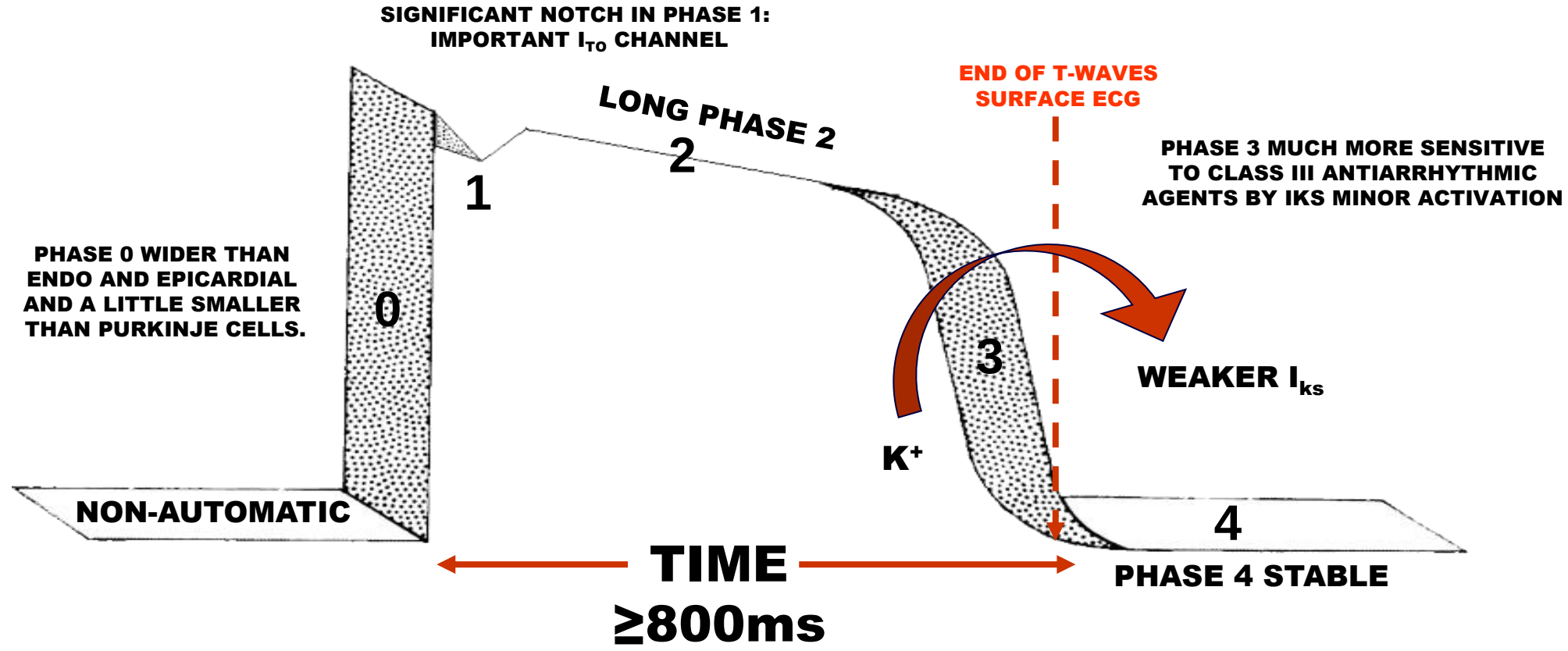
- *QT interval prolongation from 350 to 450 milliseconds*
- *T-peak to T-end interval (TpTe) prolongation*
- *T-wave notches appeared in very limited precordial leads.*

Electrophysiological characteristics of ventricular myocardial cells
Transmural dispersion of repolarization



	Epicardium (1)	Mid-myocardium (2): Transitional cells	Endocardium (3)
AP duration	300ms.	**800ms.**	300ms.
Phase 1: notch	I_{to} channel very abundant, responsible for prominent notch in phase 1.	Abundant I_{to} channel	I_{to} channel absent. There is no phase 1 with notch.

CHARACTERISTICS OF AP OF "M" CELLS OF VENTRICULAR MIDMYOCARDIUM



Counterpoint about the transmural dispersion of repolarization time

Dispersion in repolarization is important for the genesis of the T wave, and for the induction of reentrant arrhythmias. Because the T wave differs across species Opthof et al reviewed the epicardial, endocardial and transmural repolarization patterns contributing to repolarization in whole hearts from man, dog and pig. transmural repolarization time gradients are small and are directed from endocardium (early) to epicardium (late) in dog and human and from epicardium to endocardium in pig; the RV tends to repolarize before the LV and this difference is larger in dog than in pig; a negative relation between the activation times and the repolarization times is rare in man, and absent in dog and pig. Given the above, a large dispersion in repolarization between two myocardial areas **does not lead to arrhythmias without a premature beat.** Moreover, an arrhythmic substrate can be identified by a metric composed of activation times and repolarization times, the reentry vulnerability index, RVI.(1) The concept that the interval between the peak (T(peak)) and the end (T(end)) of the T wave (T(p-e)) is a measure of transmural dispersion of repolarization time is widely accepted but has not been tested rigorously by transmural mapping of the intact heart. Opthof et al tested the relationship of T(p-e) to transmural dispersion of repolarization by correlating local repolarization times at endocardial, midmural, and epicardial sites in the left and right ventricles with the T wave of the ECG.(2) Local activation times, activation-recovery intervals, and repolarization times were measured at 98 epicardial sites and up to 120 midmural and endocardial sites in eight open-chest dogs. In four of the dogs, long-term cardiac memory was induced by 3 weeks of ventricular pacing at 130 bpm because previous data suggest that, in this setting, delayed epicardial repolarization increases transmural dispersion. The other four dogs were sham operated.

1. **Tobias Opthof , Michiel J Janse , Veronique M F Meijborg , Juan Cinca , Michael R Rosen, Ruben Coronel. Dispersion in ventricular repolarization in the human, canine and porcine heart. Prog Biophys Mol Biol. 2016 Jan;120(1-3):222-35. doi: 10.1016/j.pbiomolbio.2016.01.007.**

In sham dogs, T(p-e) was 41 +/- 2.2 ms, whereas the transmural dispersion of repolarization time was not significant between endocardium and epicardium. Cardiac memory was associated with evolution of a transmural gradient of 14.5 +/- 1.9 ms (P <.02), with epicardium repolarizing later than endocardium. The corresponding T(p-e) was 43 +/- 2.3 ms (not different from sham). In combined sham and memory dogs, T(p-e) intervals did not correlate with transmural dispersion of repolarization times. In contrast, dispersion of repolarization of the whole heart (measured as the difference between the earliest and the latest moment of repolarization from all left and right ventricular, endocardial, intramural, and epicardial recording sites) did correlate with T(p-e), although the latter underestimated total repolarization time by approximately 35%. The explanation for this finding is that parts of the heart fully repolarize before the moment of T(peak). The authors concluded that T(p-e) does not correlate with transmural dispersion of repolarization but is an index of total dispersion of repolarization.(1)

1. Tp-e does not correlate with transmural dispersion of repolarization times.
2. There is no midmural zone of latest repolarization in normal hearts and those paced into cardiac memory.
3. Left ventricular epicardial repolarization occurs later, not earlier, than left ventricular endocardial repolarization. Moreover, Tp-e appears to be an index of total dispersion of repolarization.

1. **Tobias Opthof 1, Ruben Coronel, Francien J G Wilms-Schopman, Alexei N Plotnikov, Iryna N Shlapakova, Peter Danilo Jr, Michael R Rosen, Michiel J Janse. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm. 2007 Mar;4(3):341-8. doi: 10.1016/j.hrthm.2006.11.022.**

In the intact canine heart. Two variables have been proposed as relevant for assessing transmural dispersion of repolarization.

(1) Tp-e interval recorded from the ECG is a parameter that has made its way to clinical application(**1;2;3**) even though it has been validated primarily in the ventricular wedge preparation.(4) Only one study has assessed the Tp-e interval in the intact heart.(5)

(2) Dispersion in QT or QTc intervals is based on the differences between the end of the QT interval on the standard 12-lead ECG. The Tobias Opthof et al. study (6) bears on both concepts, each of which has been applied clinically despite incomplete understanding of its relevance

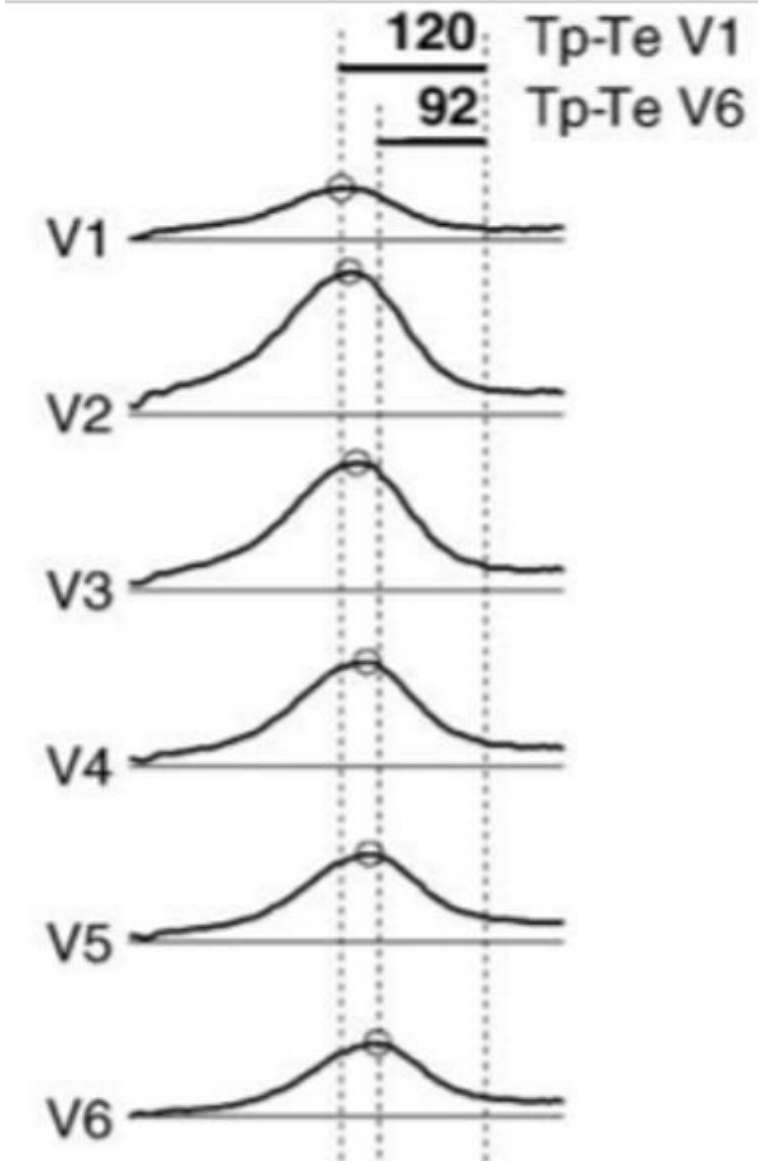
1. **Haraguchi Y, Yoshinaga M, Sarantuya J, Shimago A, Nishi J, Kono Y, Nomura Y, Kubo R, Egushi T, Tanaka S, Yanagi S, Fukushige T, Maruyama I, Kawano Y. Interval representative of transmural dispersion of repolarization in children and young adolescents with congenital long QT syndrome. Circ J 2005;69: 78–82.**
2. **Tanabe Y, Inagaki M, Kurita T, Nagaya N, Taguchi A, Suyama K, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Shimizu W. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. J Am Coll Cardiol 2001;37:911–919.**
3. **Lubinski A, Kornacewicz-Jach Z, Wnuk-Wojnar AM, Adams J, Kempka M, Krolak T, Lewicka-Nowak E, Radomski M, Swiatecka G. The terminal portion of T wave: a new electrocardiographic marker of ris**
4. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. Circulation 1998;98: 1928–1936.
5. Bai R, Lü J, Pu J, Liu N, Zhou Q, Ruan Y, Niu H, Zhang C, Wang L, Kam R. Left ventricular epicardial activation increases transmural dispersion of repolarization in healthy, long QT, and dilated cardiomyopathy dogs. Pacing Clin Electrophysiol 2005;28:1098–1106.
6. **Tobias Opthof 1, Ruben Coronel, Francien J G Wilms-Schopman, Alexei N Plotnikov, Iryna N Shlapakova, Peter Danilo Jr, Michael R Rosen, Michiel J Janse. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Heart Rhythm. 2007 Mar;4(3):341-8. doi: 10.1016/j.hrthm.2006.11.022.**

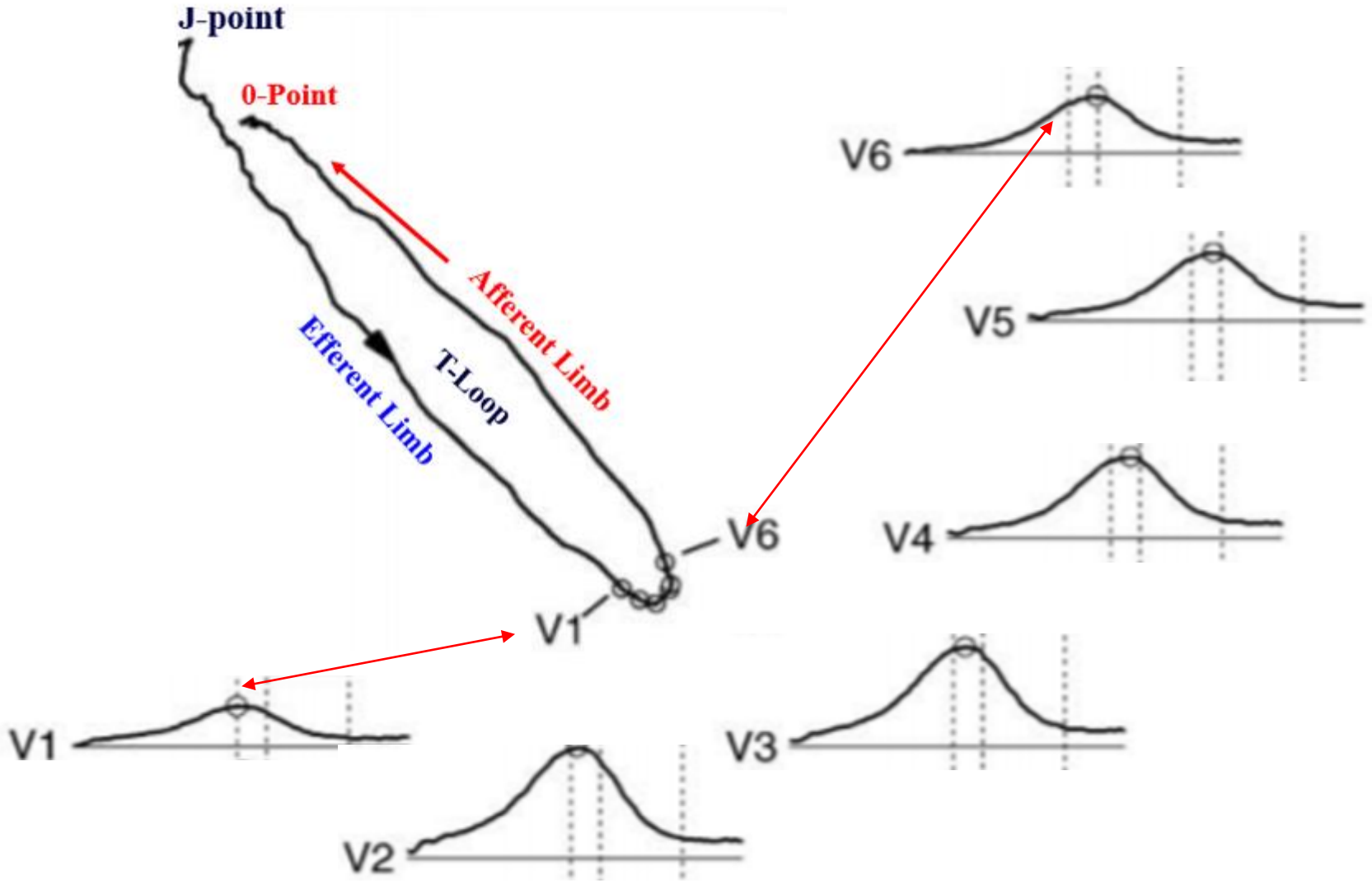
The interval between T peak (Tp) and T end (Te) has been proposed as a measure of transmural dispersion of repolarization, but experimental and clinical studies to validate Tp-Te have given conflicting results.

Kors et al have investigated the meaning of Tp-Te and its diagnostic potential using a digital model of the left ventricular wall to simulate the effect of varying action potential durations on the timing of Tp and Te. Furthermore, they used the vectorcardiogram to explain the relationships between Tp locations in the precordial electrocardiogram leads.

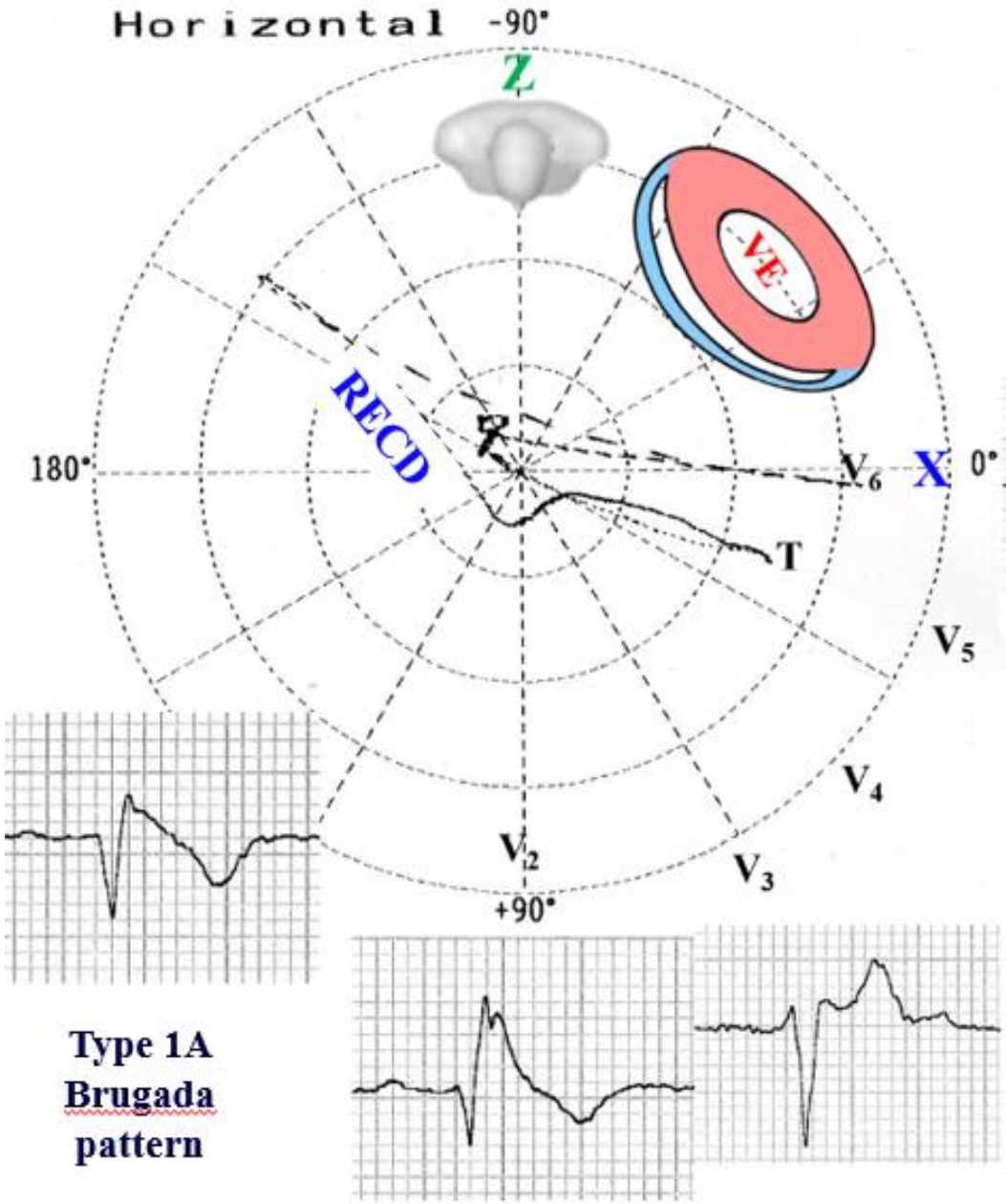
Prolongation or ischemic shortening of action potentials in their model did not result in substantial Tp shifts. The phase relationships revealed by the vectorcardiogram showed that Tp-Te in the precordial leads is a derivative of T loop morphology. The authors concluded that Tp-Te is the resultant of the global distribution of the repolarization process and is a surrogate diagnostic parameter.

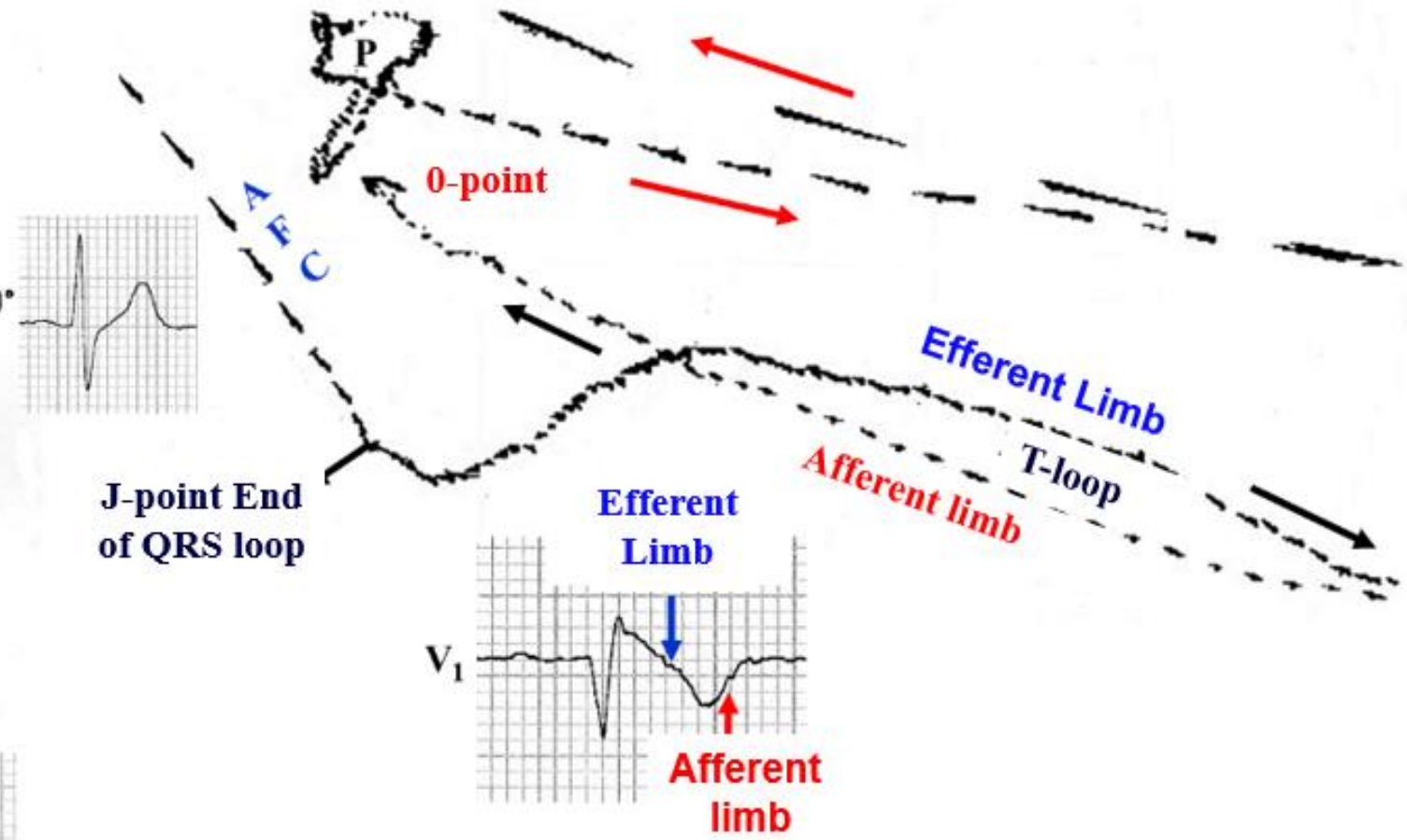
1. **Jan A.KorsPhDHenk J.Ritsema van EckMD, PhDGerardvan HerpenMD, PhD. The meaning of the Tp-Te interval and its diagnostic value.Journal of Electrocardiology Volume 41, Issue 6, November–December 2008, Pages 575-580 https://doi.org/10.1016/j.jelectrocard.2008.07.030**


120 Tp-Te V1
92 Tp-Te V6
V1
V2
V3
V4
V5
V6


J-point
0-Point
Afferent Limb
Efferent Limb
T-Loop
V6
V1
V1
V2
V6
V5
V4
V3

Electrovetorcardiographic correlation of type I Brugada pattern in Horizontal Plane



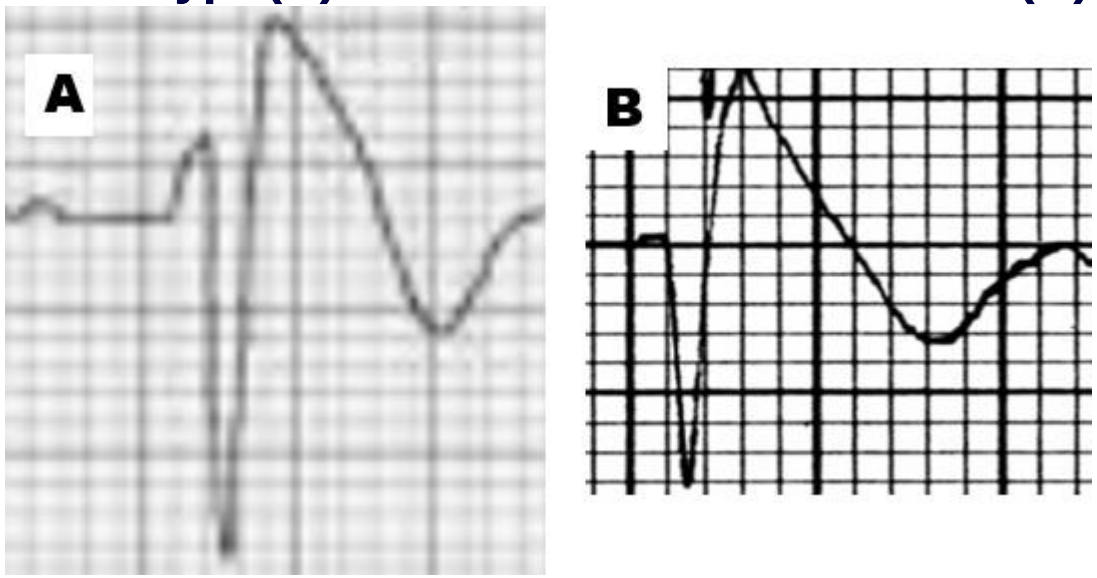


RECD; Right End Conduction Delay On right posterior quadrant

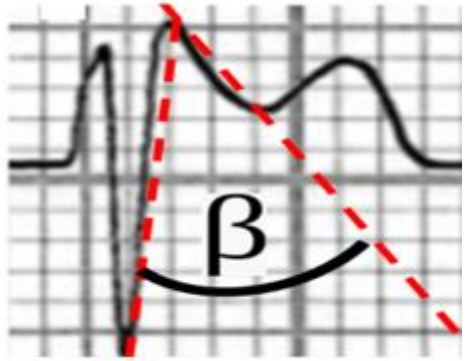
Electrocardiographic criteria for diagnosis of Brugada pattern Consensus 2012 modified the ECG criteria (1)

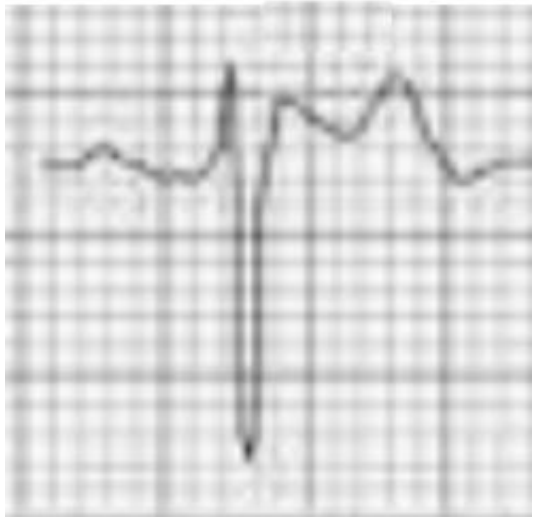
In this ECG consensus were considered only 2 ECG patterns: pattern 1 identical to classic type 1 of previous 2002 and 2005 consensus (coved pattern) and pattern 2 that joins patterns 2 and 3 of (saddle-back pattern). This consensus document describes the most important characteristics of two patterns and also the differential diagnosis with right bundle-branch block, athletes, pectus excavatum, and arrhythmogenic right ventricular cardiomyopathy. Also discussed is the concept of Brugada phenocopies.

Type 1 Brugada pattern coved type(A) or rectilinear descendent (B)



Type 2 Brugada pattern or Saddle back

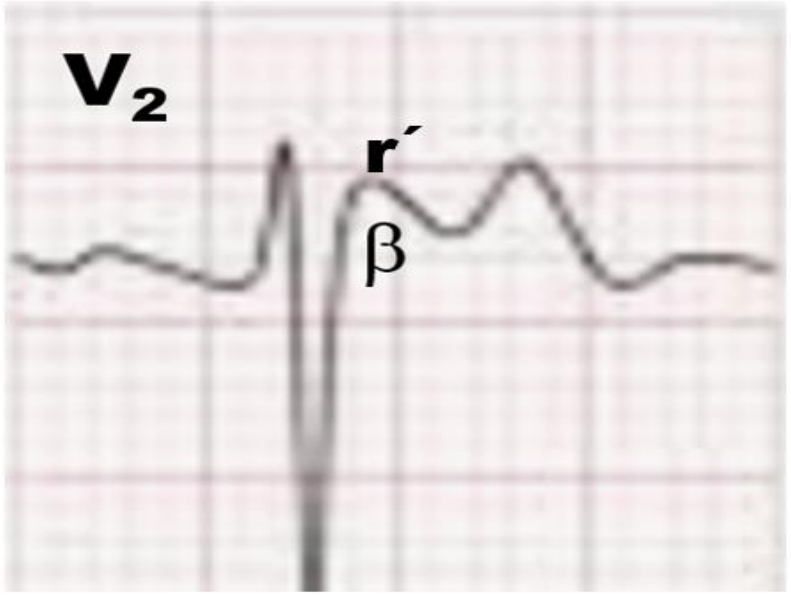


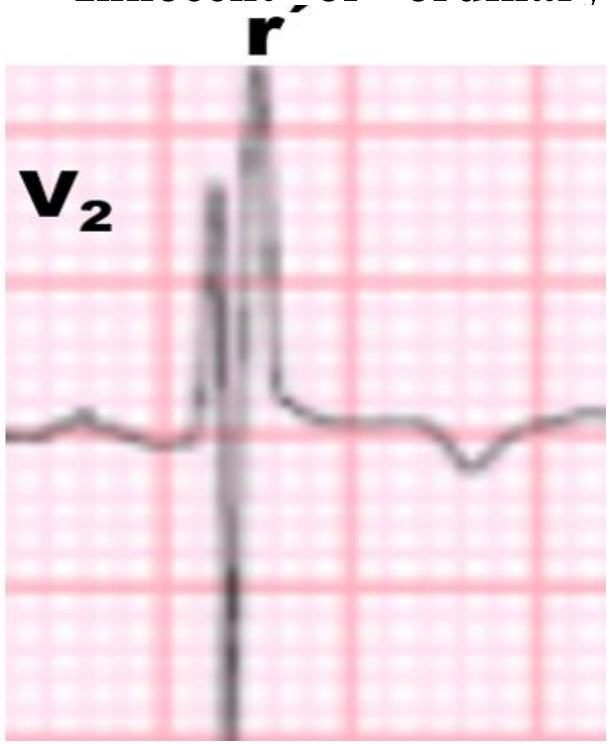


In BrS the β-angle (mean 53°) of the r'-wave is broad, rounded and generally of low voltage, with a slow descent.

1. Antonio Bayés de Luna 1, Josep Brugada. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012 Sep;45(5):433-42. doi: 10.1016/j.jelectrocard.2012.06.004

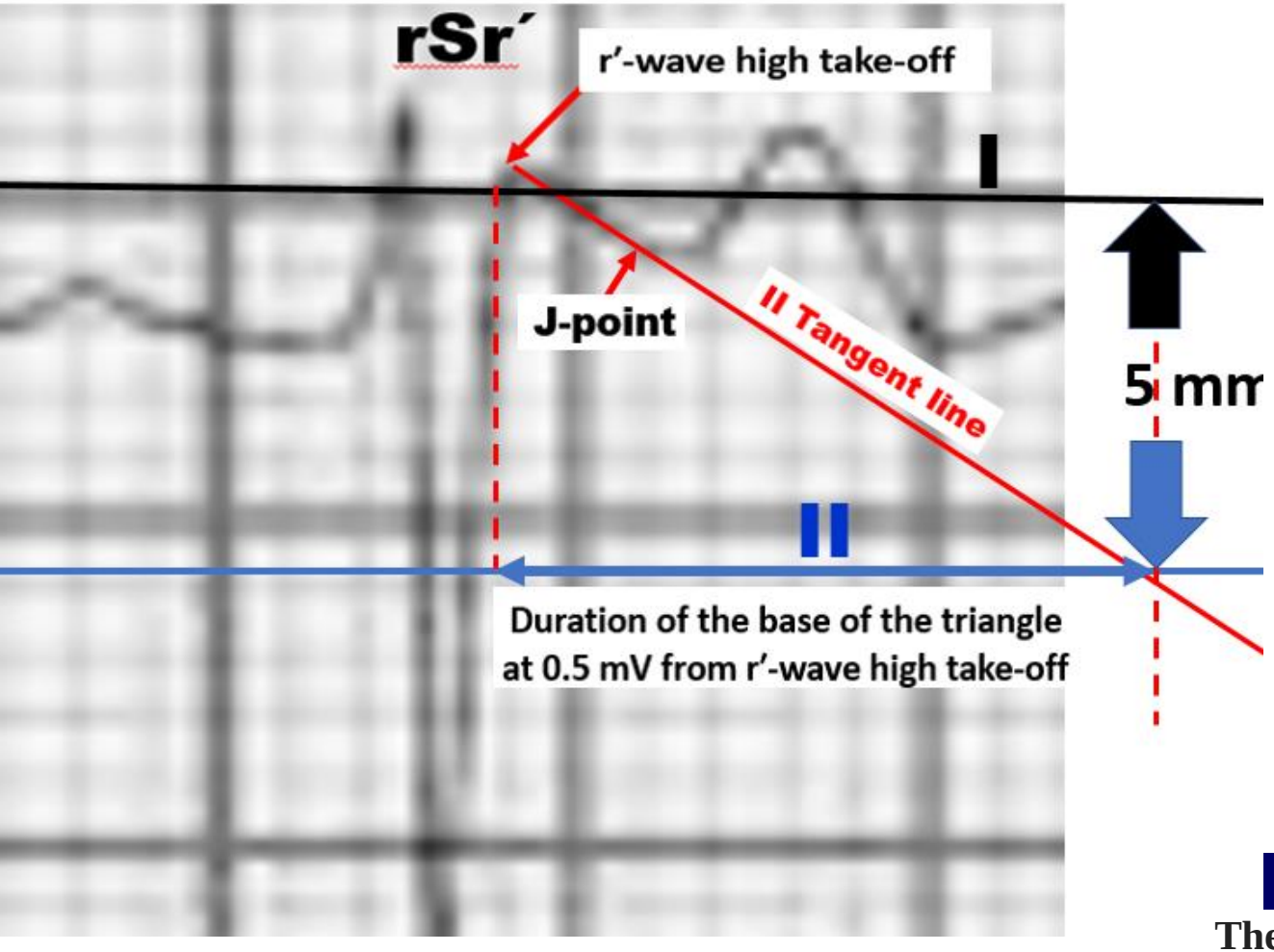
Type 2 Brugada ECG pattern Versus "Innocent" or "ordinary" incomplete RBBB



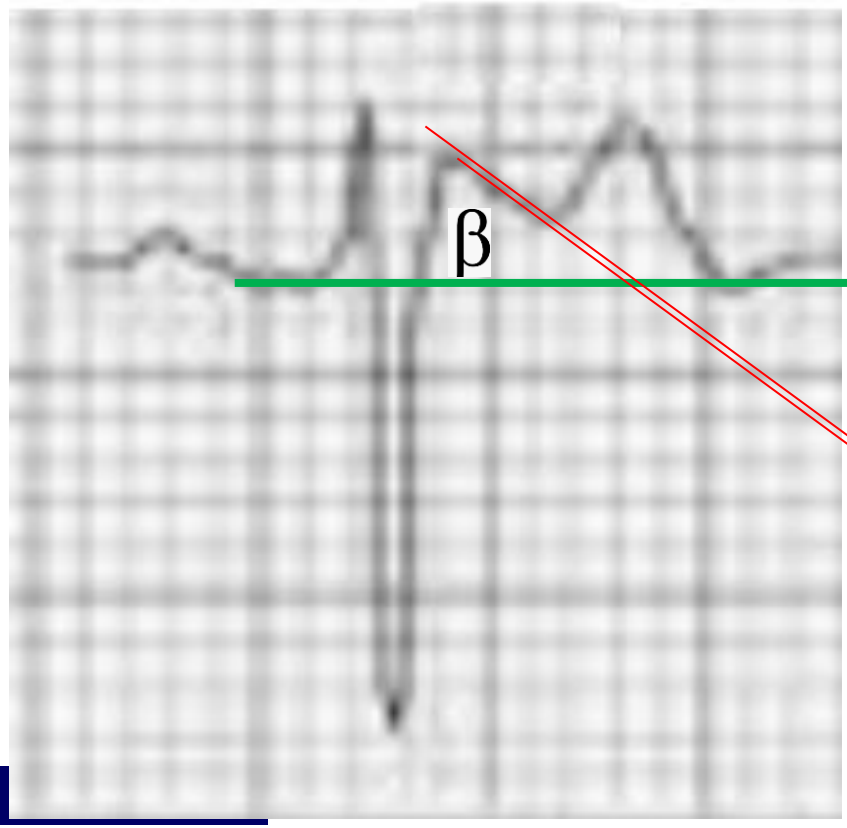


1. Stéphane Chevallier, Andrei Forclaz, Joanna Tenkorang, Yannis Ahmad, Mohamed Faouzi, Denis Graf, Juerg Schlaepfer, Etienne PruvotJ. New electrocardiographic criteria for discriminating between Brugada types 2 and 3 patterns and incomplete right bundle branch block Am Coll Cardiol. 2011 Nov 22;58(22):2290-8. doi: 10.1016/j.jacc.2011.08.039.

	Type 2 Brugada ECG pattern	"Innocent" or "ordinary" incomplete RBBB
β-angle	Broader ≈ 58°	Narrow about 12°
Shape	Rounded	Pointed
r´ wave voltage	usually lower than R	usually taler than R
Descendent r´ wave ramp	Slow	Fast



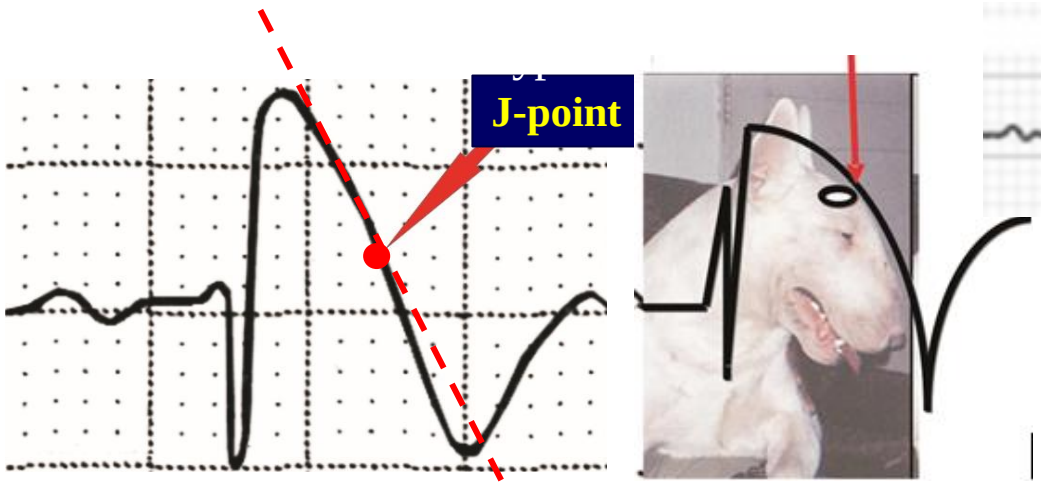
The duration of the base of the triangle at the isoelectric line ≥60

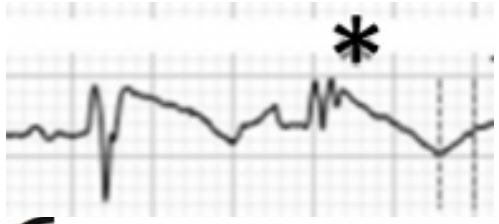


The β-angle ("Chevallier Angle") has a higher sensitivity and specificity for BrS, and is preferred over the α-angle. β-angle >58° suggests Brugada pattern.

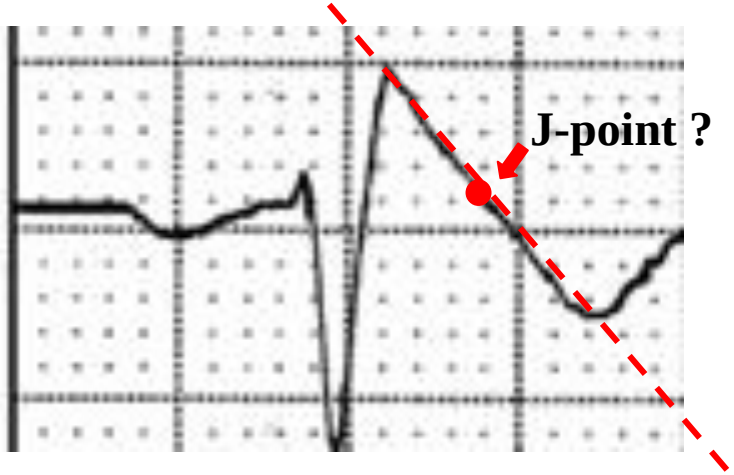
I. **Draw a horizontal line from top or high take-off of r' wave (black line I)**
II. **Draw a horizontal line 5 mm below this (blue line II)**
III. Tangent line: Extend the downsloping r'-ST segment (**Red** line until it intersects the blue line

New proposal of classification of type 1 Brugada pattern/Right precordial leads or high right precordial leads





Subtype 1B



ST segment elevation convex upward The dotted line is the tangent line. Sub-Type 1A: J point and ST segment elevation ≥2 mm, with superior convexity, followed by negative T wave.

“Bull-terrier sub-type” The English Bull Terrier characteristically has a long head, strong and deep until the end of the muzzle. Observed from his right profile, he has a convexity to the top and to the left from the top of the cranium to the muzzle. “Bull Terrier pattern”.

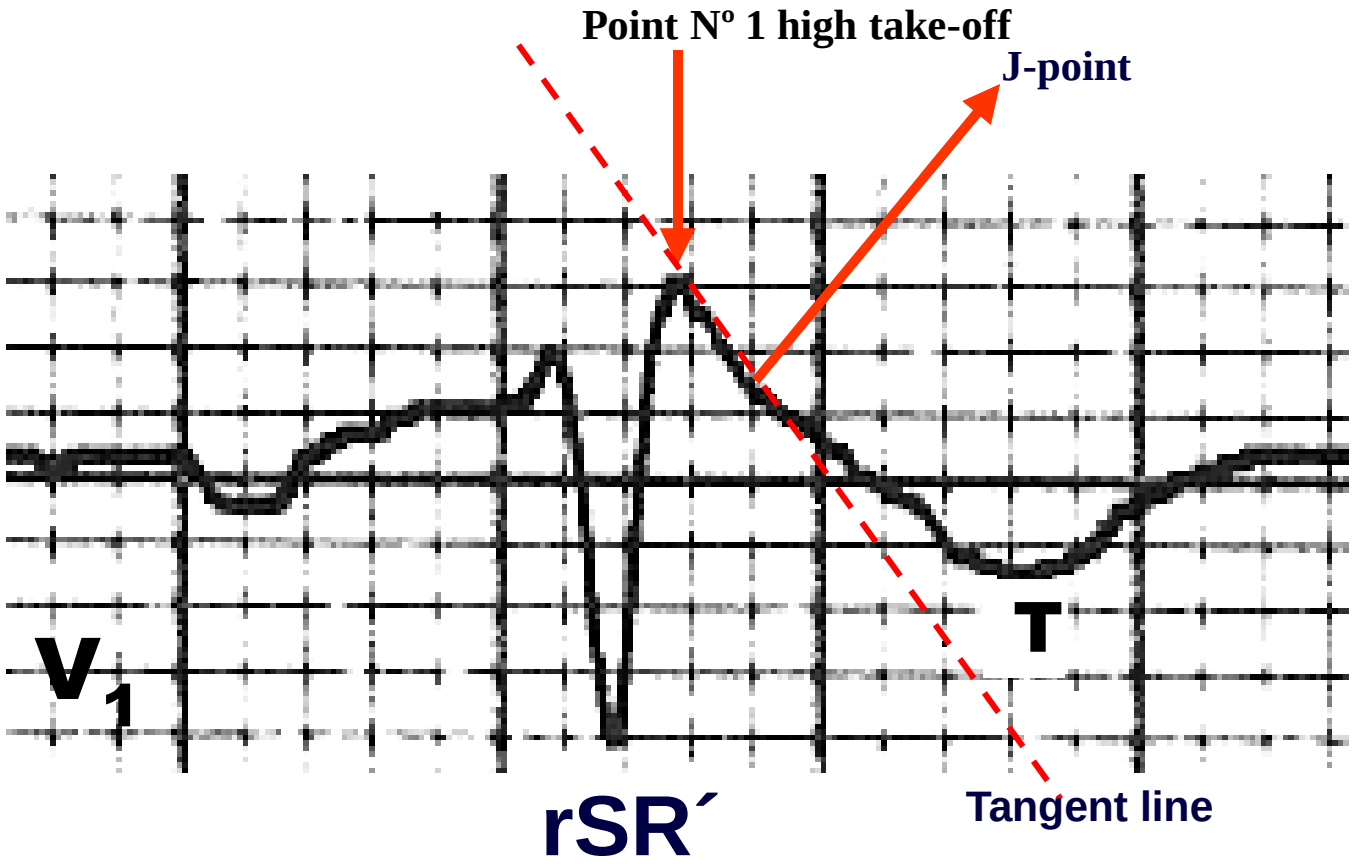
ST segment elevation rectilinear oblique and downward

The dotted line is the tangent line

The diagnosis of the syndrome is based only on the presence of an electrocardiographic pattern characterized by elevation of the J point of the ST segment of ≥2 mm of superior convexity "coved type" (Subtype 1A) or descending rectilinear (Subtype 1B) followed by negative T wave symmetric (type 1 pattern) in ≥1 right precordial leads

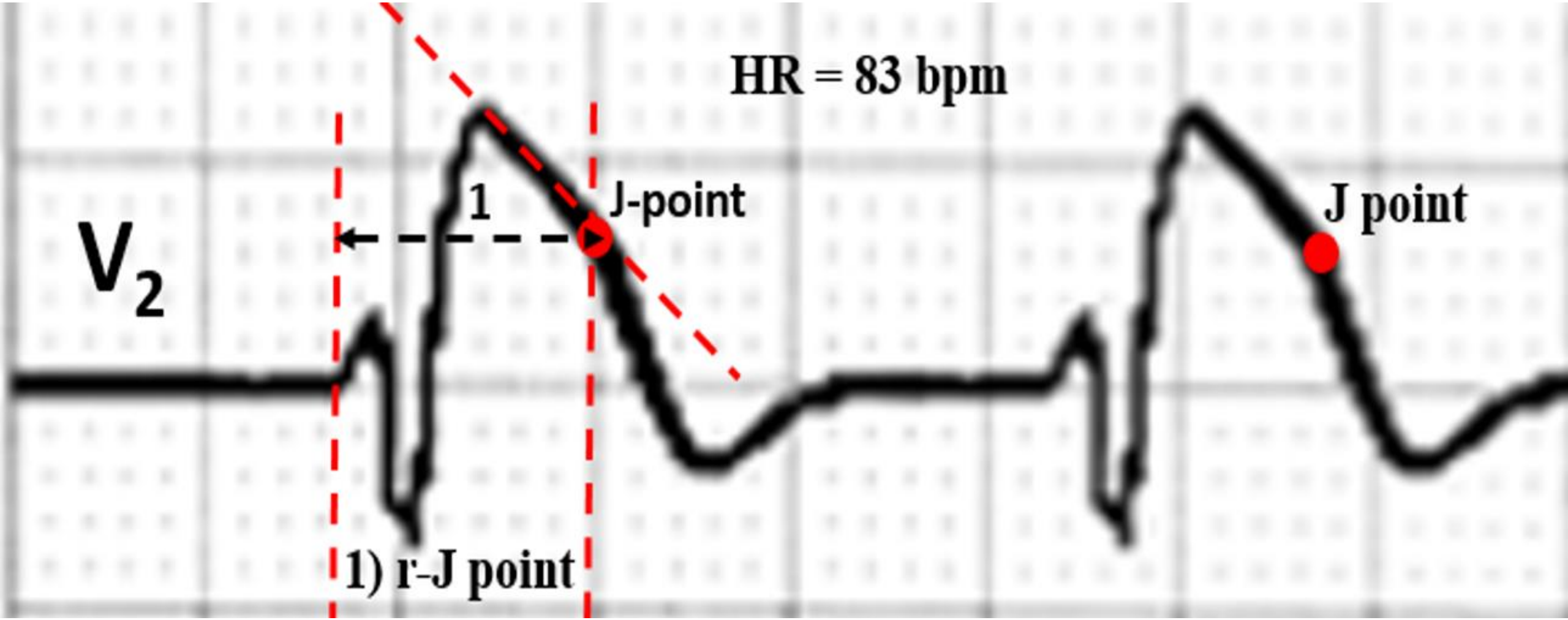
In the **type 1B it is not possible to accurately determine where depolarization ends and repolarization begins**.

Where is the end of QRS complex and the beginning of the ventricular repolarization (J point)?



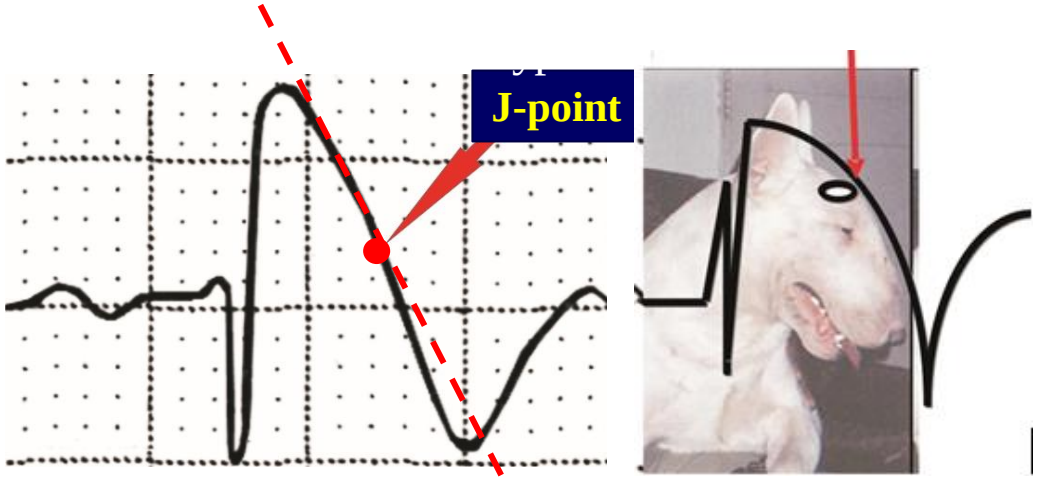
In Brugada syndrome with type 1 ECG pattern and early-stage of "concealed" forms arrhythmogenic cardiomyopathy sometimes is difficult to determine precisely when the QRS complex ends and repolarization begins In other words, it is difficult to precisely determine the location of the J point. This point is located is where the tangent line separates from the descending ramp of R' wave.

Prolonged QRS duration measured from precordial lead V2 ≥120 ms



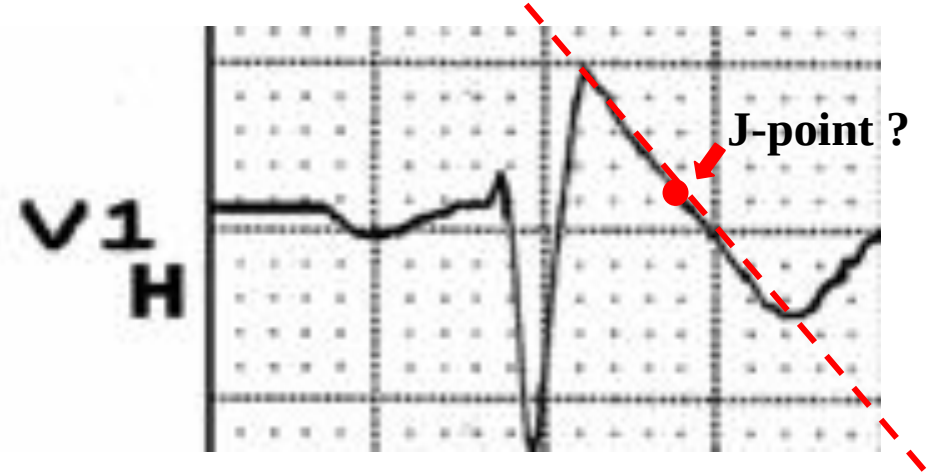
Vertical dotted lines show onset and termination of the QRS complex in V2. In this case QRSd = 165 ms. Wide QRS duration is an ECG marker of events in BrS patients.

New proposal of classification of type 1 Brugada pattern/Right precordial leads or high right precordial leads



ST segment elevation convex upwardThe dotted line is the tangent line.

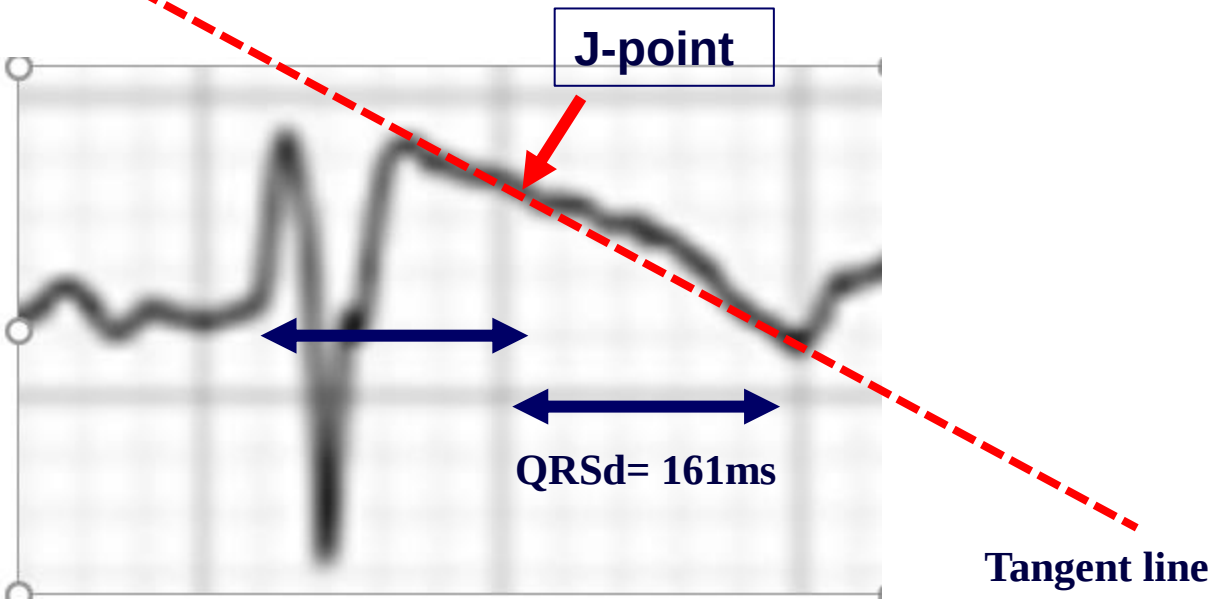
Subtype 1B

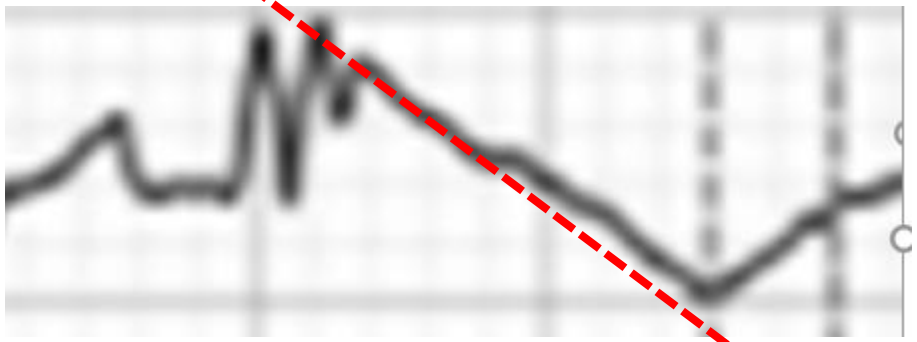


ST segment elevation rectilinear oblique and downward

The dotted line is the tangent line

The present case: very broad QRSd





Clinical Importance of the New Proposed Classification of the Type 1 Brugada Pattern into Three Subtypes

The importance of differentiating subtype IA from IB is that in type IB it is difficult to determine the exact location of the J point, that is, the end of depolarization and the beginning of ventricular repolarization. Recently, Rattanawong et al.(1) demonstrated in a systematic review of 22 studies that a wide QRS complex (≥ 120ms) is associated with a 1.55-fold increased risk of major arrhythmic events (MAE) in BrS patients. A wide QRS complex (≥120) such as the present case is an independent predictor of major arrhythmic events (MAE) in patients with BrS, especially when implantable cardioverter-defibrillator placement is considered in asymptomatic patients. Additionally, the presence of an early repolarization pattern in the inferior wall (II-III and aVF) or inferolateral (II-III = aVF, I, aVL, V5-6) in patients with BrS (Subtype III) indicates worse evolution and has the characteristics mentioned in the table follows. The QRS interval is the intraventricular conduction time, and is represented by QRS complex duration. This QRS complex is made up by a set of deflections or waves that represent ventricular depolarization. The ventricular depolarization duration is influenced by:

I. **Age** (0 to 5 years: up to a maximal 80 ms; from 5 to 14 years, from 40 to 90 ms; and in teenagers from 14 years and adults from 60 to 100 ms) (only 2% of normal adults have a QRS>100 ms),
II. **Race** (shorter in African-American people),
III. **Heart rate:** (inversely proportional)

This duration is somehow increased in BrS with a median duration estimated in 110 ms (+/-2 ms) to 130 ms. The only significant difference between symptomatic and asymptomatic carriers of BrS was the QRS interval duration measured in the II lead or in V_2.

1. **Pattara Rattanawong, MD, et al., Wide QRS complex and the risk of major arrhythmic events in Brugada syndrome patients: A systematic review and meta-analysis. J Arrhythm. 2020 Feb; 36(1): 143–152.Published online 2019 Dec 27. doi: 10.1002/joa3.12290**

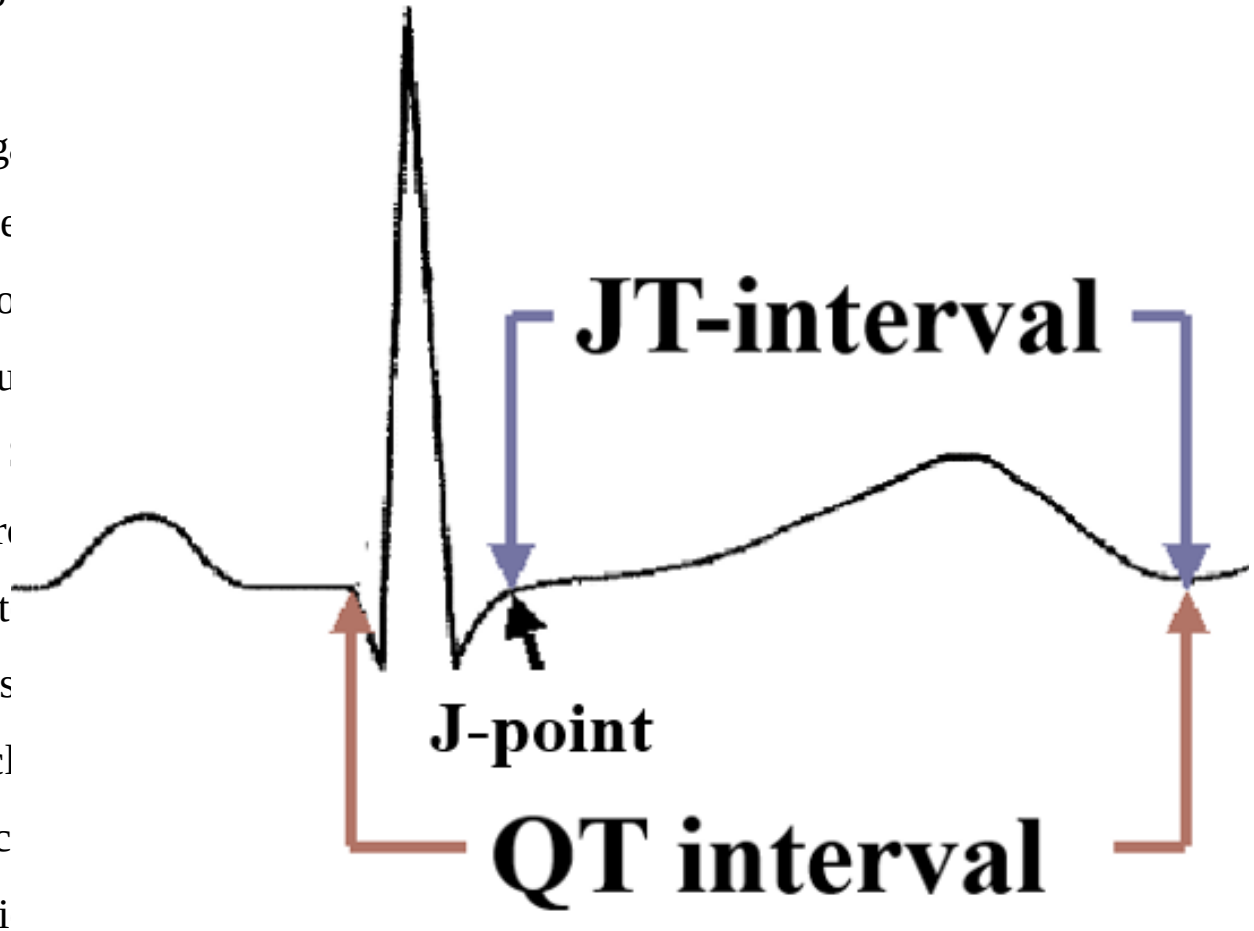
The median QRS interval in V_2 was 115+/-26 ms in symptomatic versus 104+/-19 ms in asymptomatic patients ($p<0.001$), QRS interval duration prolongation measured from the standard 12-lead ECG, is associated with symptoms and could serve as a simple non-invasive risk marker of vulnerability to dangerous ventricular arrhythmias in BrS

Ohkubo et al studied PR, QRS, and QT intervals duration in BrS patients (10 symptomatic and 25 asymptomatic). QRS was measured in V_2 from the onset of QRS until the J point. A ≥120 ms value turned out to be a predictor of arrhythmias and was the only parameter that differentiated symptomatic from asymptomatic patients. (1)

1. **Kimie Ohkubo 1, Ichiro Watanabe, Yasuo Okumura, Sonoko Ashino, Masayoshi Kofune, Koichi Nagashima, Tatsuya Kofune, Toshiko Nakai, Satoshi Kunimoto, Yuji Kasamaki, Atsushi Hirayama. Prolonged QRS duration in lead V2 and risk of life-threatening ventricular Arrhythmia in patients with Brugada syndrome. Int Heart J. 2011;52(2):98-102. doi: 10.1536/ihj.52.98.**

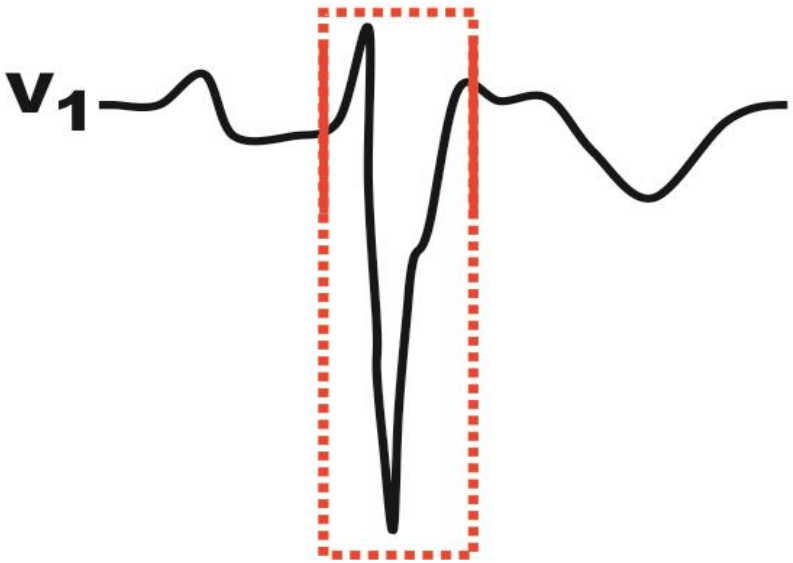
QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome

Pitzalis et al (1) identified the selective prolongation of QT interval duration in the right precordial leads (V_1 to V_3) in comparison to the left ones (V4 to V6). As the QT interval is made up by ventricular depolarization (QRS) ventricular repolarization (ST/T). Probalby this selective prolong represents a certain degree of parietal block in the RVOT, as the one obse in ARVC/D. If the QT interval is prolonged only from V1 to V3, being nc or lesser from V4 to V6, it is clear that this increase may be du prolongation of ventricular depolarization (QRS complex) and/or by prolongation (repolarization). If we admit that in BrS there is some degr QRS prolongation on right precordial lead, clearly the QT int prolongation is due partly to this. The QTc interval constitutes the clas measurement for ventricular repolarization; however, this parameter incl ventricular depolarization (QRS), and therefore represents the so-c electric systole, which includes depolarization (QRS) and ventri repolarization (ST/T = JT interval).

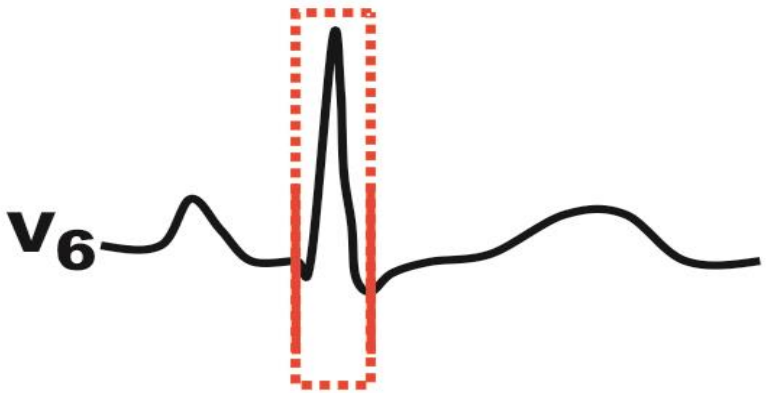


1. Maria Vittoria Pitzalis 1, Matteo Anaclerio, Massimo Iacoviello, Cinzia Forleo, Pietro Guida, Rossella Troccoli, Francesco Massari, Filippo Mastropasqua, Sandro Sorrentino, Andrea Manghisi, Paolo Rizzon. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42(9):1632-7. doi: 10.1016/j.jacc.2003.07.005

QRSD: >110ms

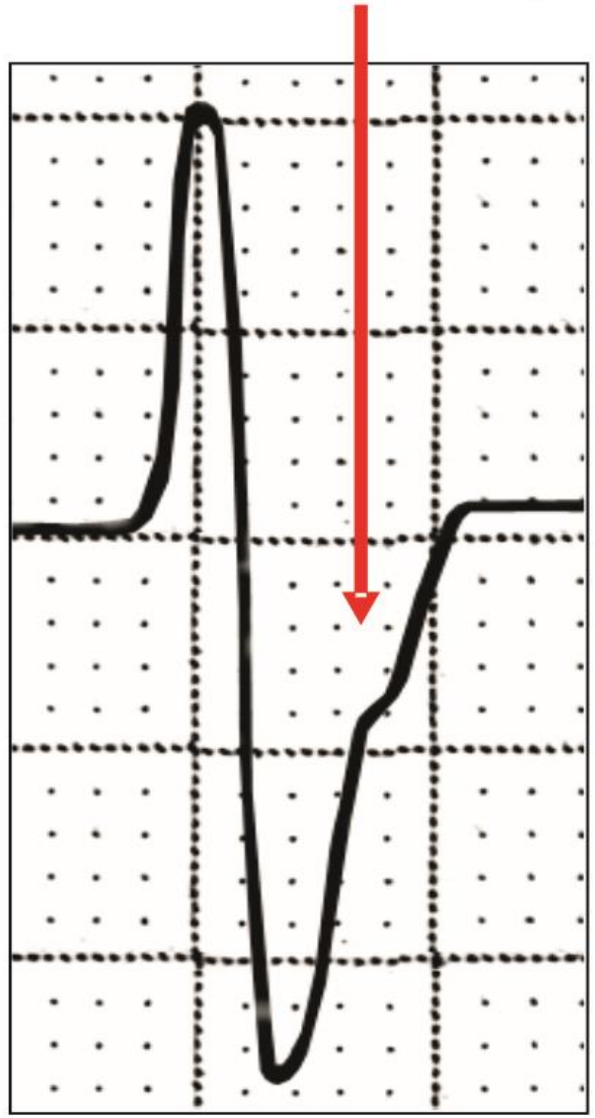


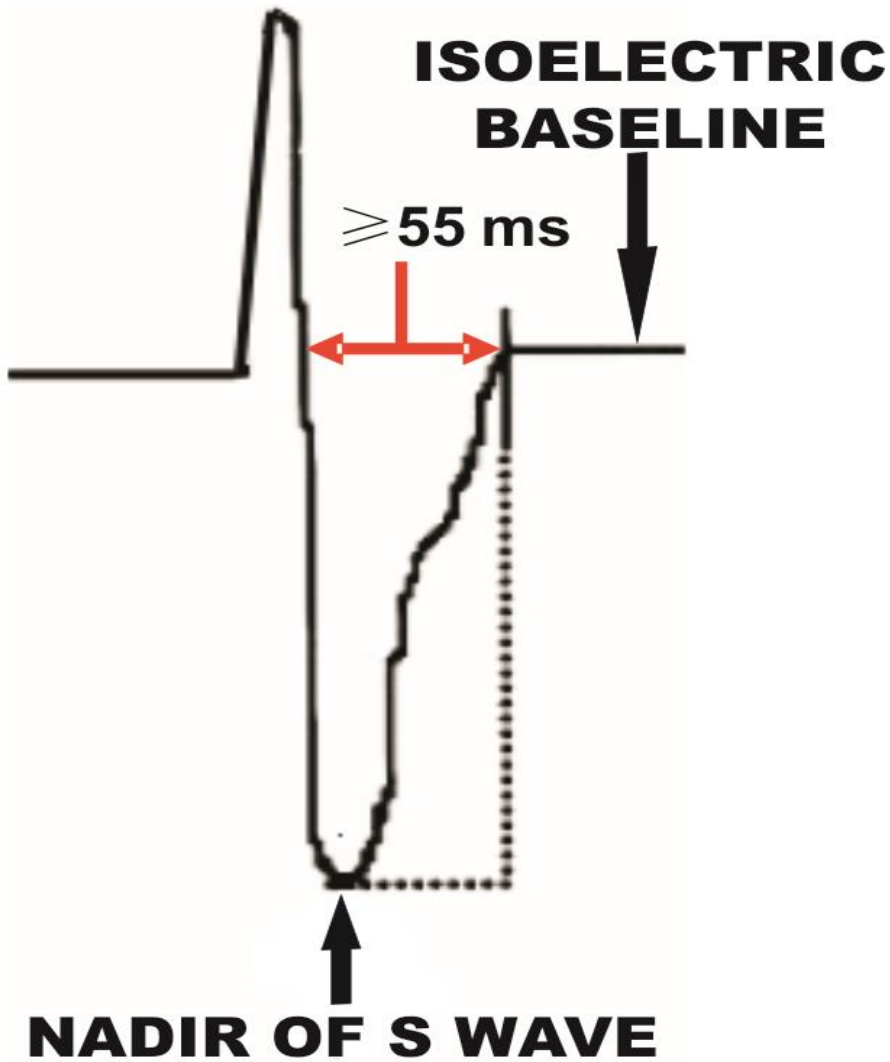
QRSD: 90ms

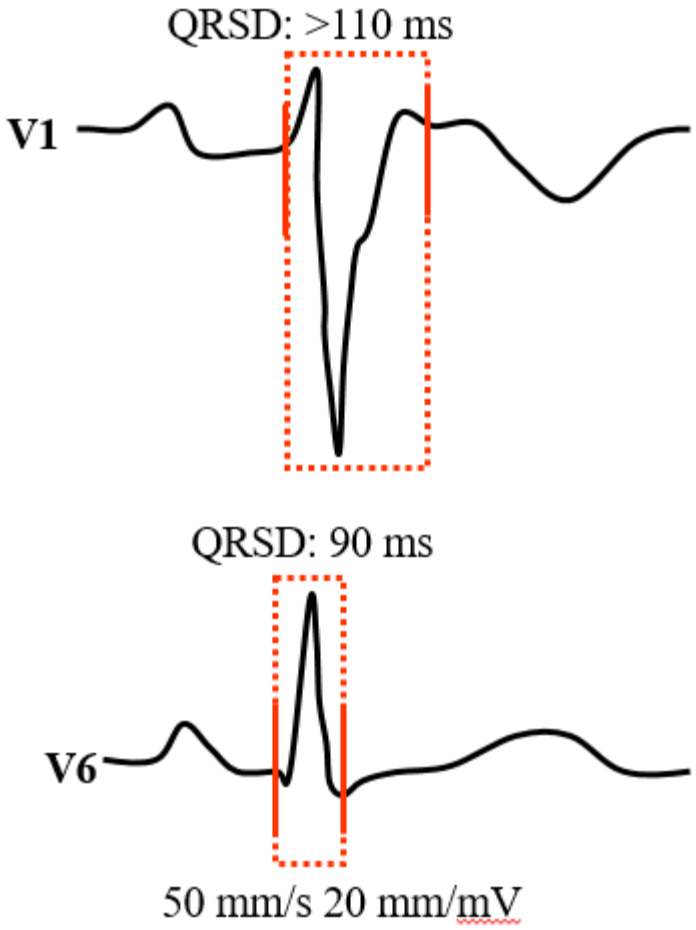


QRSD: QRS Duration

PARIETAL BLOCK







QRSD $^{V1+ V2 + V3}/_{QRSD\ V4, + V5 + V6}$ relationship

QRSD of $^{V1+ V2 + V3}/_{QRSD\ V4, + V5 + V6} \geq 1.2$ in approximately 65% of cases. QRS prolongation located in right precordial leads. QRSD ≥ from V_1 to V_3 with 91% sensitivity, 90% specificity that predicts VT in patients carriers of ARVC/D. (1). BrS may display prolongation in QT interval duration from V_1 to V_3 and subsequently prolongation of QTc interval in right precordial leads.(2)

1. **Khurram Nasir 1, Chandra Bomma, Harikrishna Tandri, Ariel Roguin, Darshan Dalal, Kalpana Prakasa, Crystal Tichnell, Cynthia James, Phillip J Spevak, Frank Marcus, Hugh Calkins, Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria, Circulation. 2004 Sep 21;110(12):1527-34. doi:10.1161/01.CIR.0000142293.60725.18.**
2. **Maria Vittoria Pitzalis 1, Matteo Anaclerio, Massimo Iacoviello, Cinzia Forleo, Pietro Guida, Rossella Troccoli, Francesco Massari, Filippo Mastropasqua, Sandro Sorrentino, Andrea Manghisi, Paolo Rizzon. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol. 2003 Nov 5;42(9):1632-7. doi: 10.1016/j.jacc.2003.07.005..**

	BrS patients with ST-segment elevation in inferolateral leads	BrS patients without ST-segment elevation in inferolateral leads
Phenotype severity	**Greater severity**	**Less severity**
Relative percentage	**15%**	**89%**
Symptoms in the first presentation	**These patients were less likely to be asymptomatic**	**These patients were more likely to be asymptomatic**
PR interval	**Longer**	**Shorter**
Effect of Class I AAD administration	Provokes inferior-lateral coved Brugada pattern in 4.6% of patients or only in inferior leads	**Induce the Brugada type 1 pattern only on right precordial leads**
AAD administration provoked	Induced more QRS interval prolongation	Induced lessser QRS interval prolongation

The manifestation of coved-type ST-segment elevation in inferolateral leads in BrS. Inferior-lateral pattern occurs spontaneously relatively frequently in BrS. These patients have a more severe phenotype. Class I AAD administration provokes inferior-lateral coved Brugada pattern in 4.6% of patients. Sarkozy et al reported for the first time 3 patients in whom the class I AAD-provoked coved Brugada pattern was only observed in the inferior leads.(These autors studied 280 patients (age, 41+/-18 years; 168 males) with BrS were screened for inferior-lateral repolarization abnormalities. The repolarization abnormalities were classified either as ER pattern or coved ≥2-mm Brugada pattern and as spontaneous or class I antiarrhythmic drug (AAD) induced. Thirty-two patients (11%) had inferior-lateral spontaneous ER pattern. These patients were less likely to be asymptomatic at first presentation (13 of 32 versus 156 of 248 patients, P=0.02), and spontaneous type I ECG was more frequent among them . The spontaneous ER pattern occurred more frequently among patients with BrS than in 283 family members not having BrS 6%, P=0.03). Class I AAD administration provoked inferior-lateral coved Brugada pattern in 13 patients with BrS. These patients had longer baseline PR intervals. (

Sarkozy A, et al. Circ Arrhythm Electrophysiol. 2009 Apr;2(2):154-61. doi: 10.1161/CIRCEP.108.795153

Electrocardiographic variables identified as being associated with sudden cardiac death in Brugada syndrome

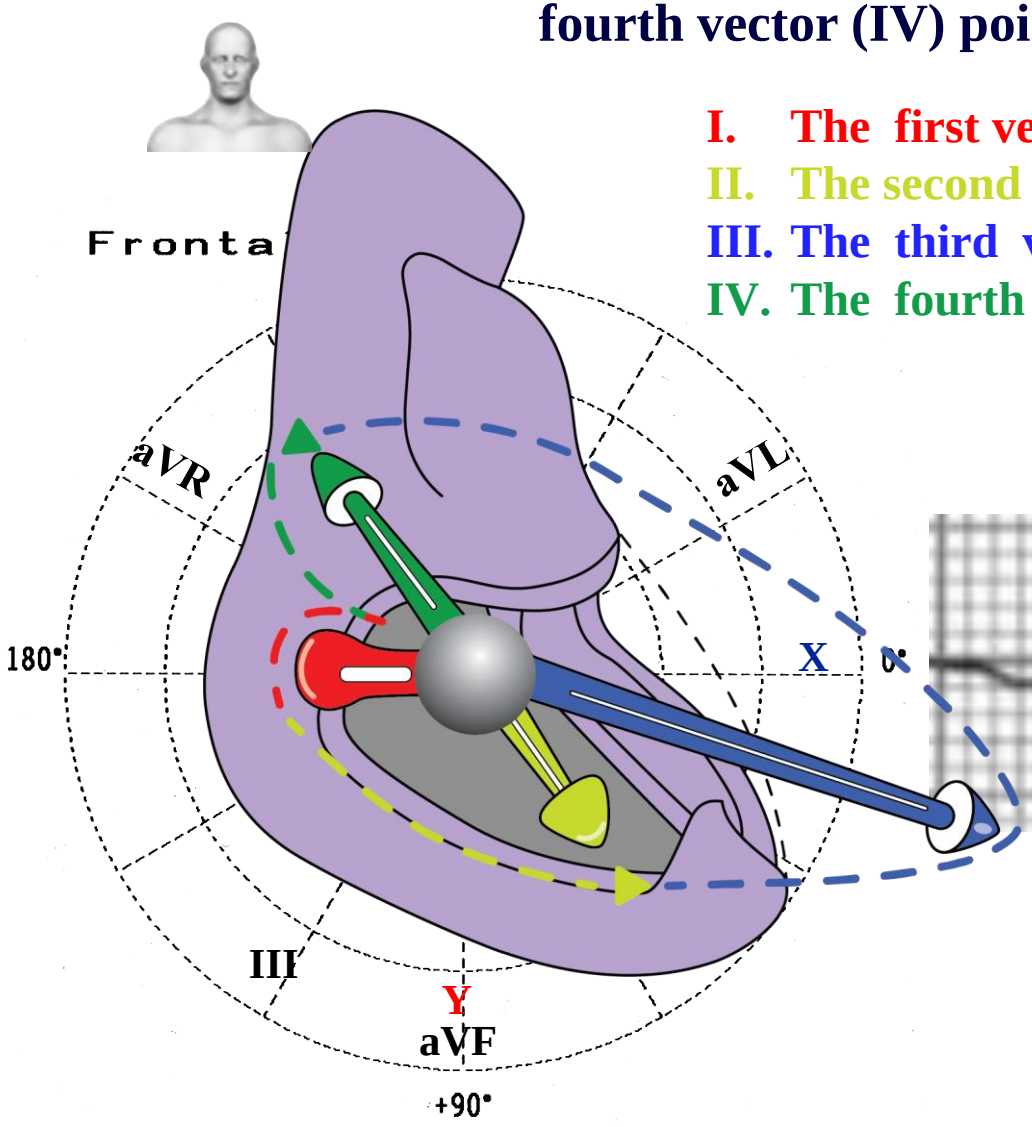
Deep and/ or large S-wave in I > 0.1 mV and/or > 40 ms is a powerful predictor of life-threatening ventricular arrhythmias Calò et al (1) studied 347 consecutives BrS patients with no history of cardiac arrest at presentation. Including 91.1% asymptomatic at presentation, 5.2% with a history of AF, and 4% with a history of arrhythmic syncope. However, the prognostic value of this ECG signal should be confirmed by larger studies and by an independent confirmation cohort of healthy subjects. Electrocardiographic characteristics at the first clinic visit were analyzed to predict VF/SCD during follow-up. (48 ± 38 months), Patients who developed VF/SCD had a lower prevalence of *SCN5A* gene mutations and a higher prevalence of positive EPS.

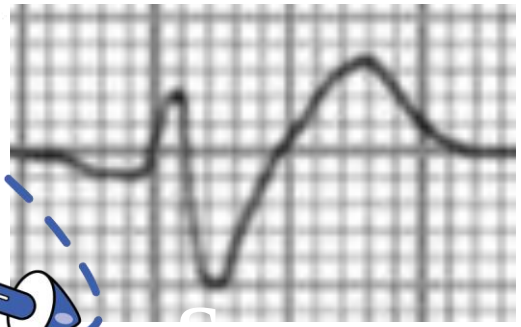
Theoretical basis: The fourth vector of ventricular depolarization, is directed upward and somewhat to the right and backward, generates the S-wave in bipolar lead I of the frontal plane This vector is determined by electrical activation of the basal region of both ventricles and by depolarization of the RVOT. A prominent S-wave in lead I is typically present in cases of congenital heart disease, valvular heart disease, and cor pulmonale that cause RVH.

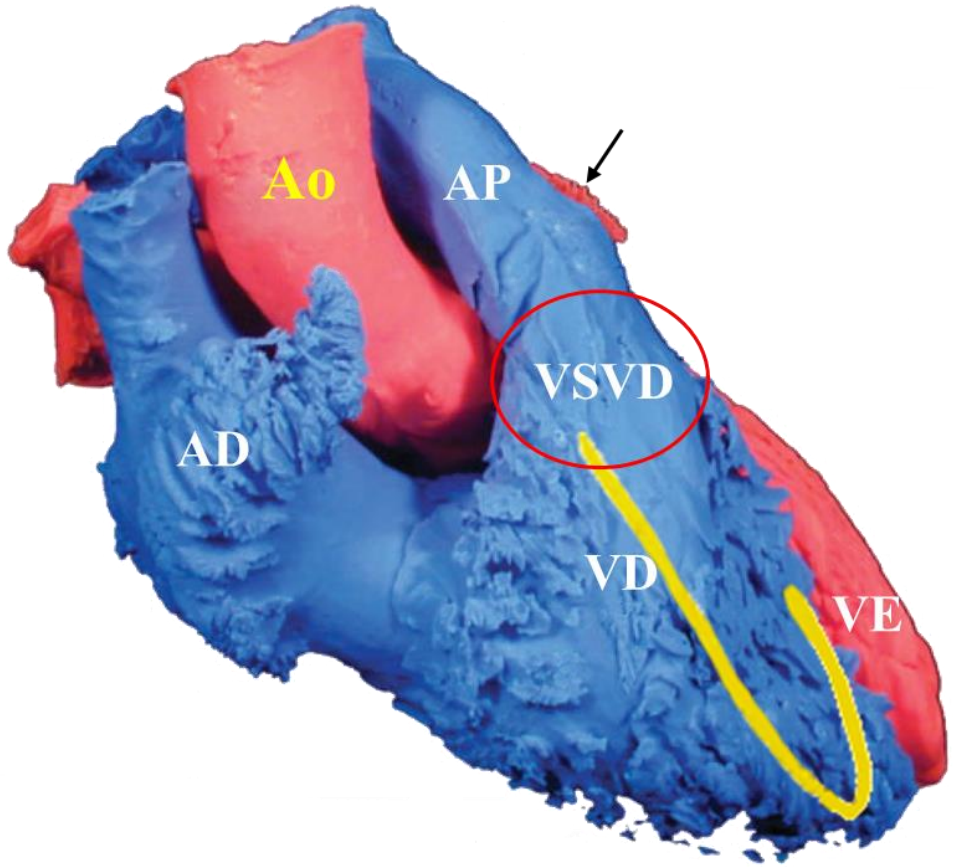
1. **Leonardo Calò, Carla Giustetto, Annamaria Martino, et al. A New Electrocardiographic Marker of Sudden Death in Brugada Syndrome: The S-Wave in Lead I. Randomized Controlled Trial J Am Coll Cardiol . 2016 Mar 29;67(12):1427-1440. doi: 10.1016/j.jacc.2016.01.024.**

fourth vector (IV) pointed to the RVOT and runs away from lead I

I. The first vector
II. The second vector
III. The third vector
IV. The fourth vector





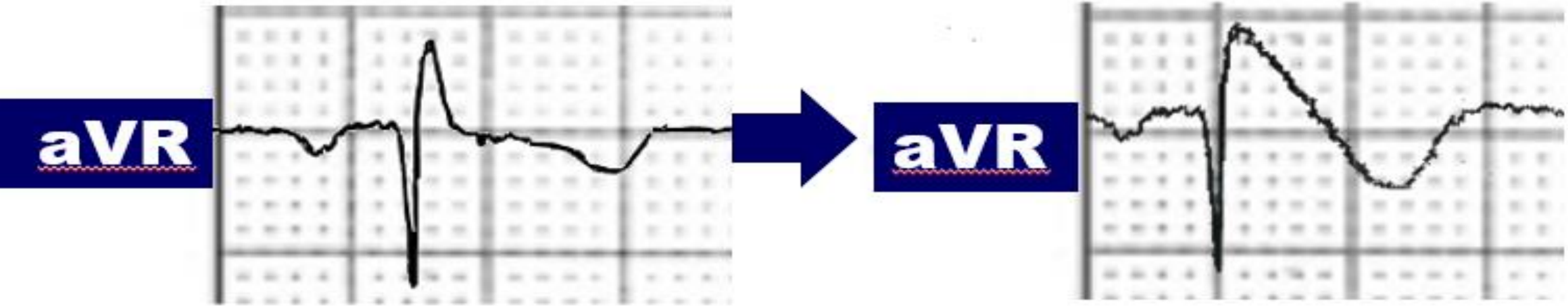


Thus, Caló et al hypothesized that a deep and/ or large S-wave in lead I in BrS would reveal a conduction delay over the RVOT and could be used to identify high-risk patients.

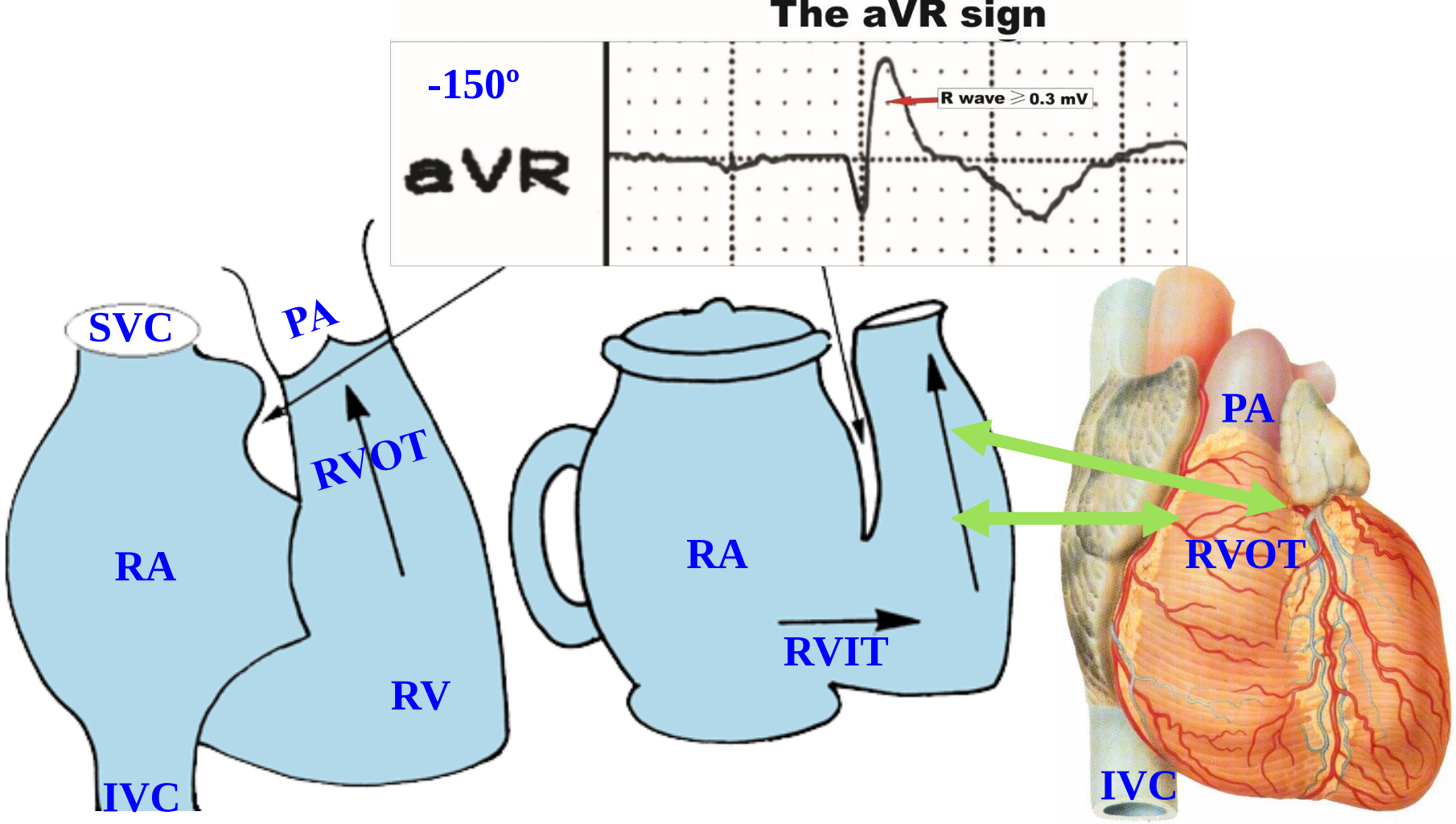
The aVR sign

A **Date:** Friday September 30, 2011.

B **Date:** Tuesday October 4, 2011.



The aVR sign consists of a voltage of the final R wave of aVR> 3mm or 0.3mV or R/q ≥0.75. Presence of prominent final R wave on aVR is indicative of slow conduction at the RVOT may contribute to the induction of VF by EPS. Terminal tall and broad R wave of the QRS complex in lead aVR



The BrS affects predominantly the right ventricle in the right ventricle outflow tract (RVOT) epicardium (Doi 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 2005; Pérez-Riera 2012). On the other hand, in the concealed forms of arrhythmogenic right ventricular cardiomypathy/dysplasia (ARVC/D), the RECD pattern can also be observed showing type-1 ECG pattern. This pattern was shown many years ago by Guy Fontaine et al (Hayashi 2010).

Mohamad Ali Babai Bigi et al studied the importance of aVR sign in patients with BrS.

The authors studied 24 patients all men with a mean age of 32.1 +/- 13.6 years with the BrS ECG pattern and compared them with 24 age- and sex-matched healthy controls. 13 patients were symptomatic.

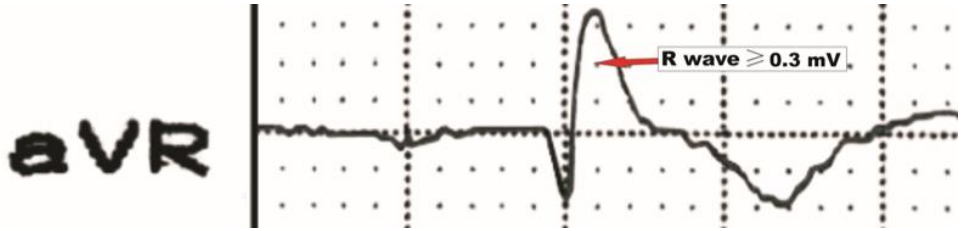
The R wave amplitude or R/q ratio in lead aVR was significantly higher in patients who experienced a recurrence of events compared to those who did not. The aVR sign was defined as R wave ≥ 0.3 mV-3mm or R / q ≥ 0.75 in lead aVR. Most of the recurrences (78%) occurred in those patients who presented the aVR sign; 84% of patients with BrS with the sign of aVR present had events during follow-up. In contrast, only 27% of patients with BrS with absence of aVR sign had events during follow-up.

The authors concluded that there is a significant correlation between the presence of a prominent R wave in lead aVR (aVR sign) and the risk of developing arrhythmic events in BrS. In the presence of BrS, the prominent R wave in the aVR lead may reflect a greater delay in conduction in the right ventricular outflow tract and, consequently, more electrical heterogeneity, which in turn is responsible for an increased risk of arrhythmia.

1. **Mohamad Ali Babai Bigi 1, Amir Aslani, Shahab Shahrzad. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm. 2007 Aug;4(8):1009-12. doi:10.1016/j.hrthm.2007.04.017.**

The aVR sign and its patterns and clinicals context

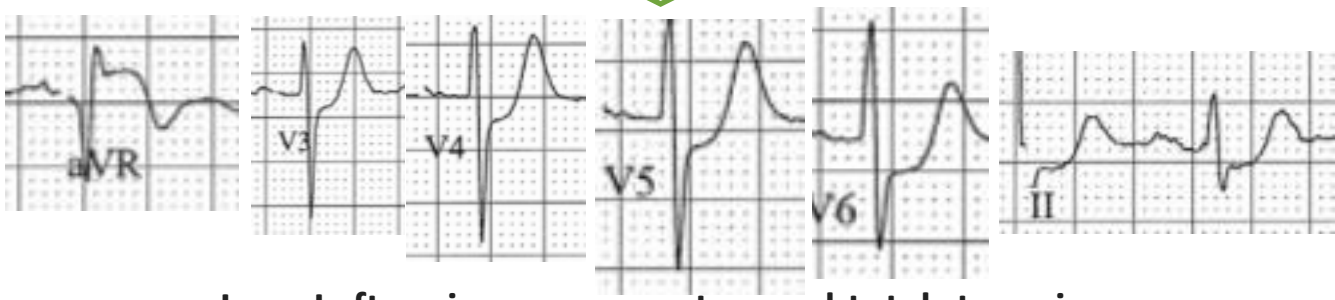
Brugada syndrome



The aVR sign consists of a voltage of the final R wave of aVR> 3mm or 0.3mV or R/q ≥0.75. Presence of prominent final R wave on aVR is indicative of slow conduction at the RVOT may contribute to the induction of VF by EPS. Terminal tall and broad R wave of the QRS complex in lead aVR

Signs and symptoms of an acute coronary syndrome (ACS)

Combination of multilead ST depression and ST elevation in lead aVR



I. **Left main coronary artery subtotal stenosis**

or

II. Non-ACS situations

ST-elevation myocardial infarction (STEMI) equivalent

- Severe left ventricular hypertrophy,
- Acute hemorrhagic shock,
- Massive pulmonary embolism,
- Proximal aortic dissection type A (possibly reflecting involvement of the orifice of the LMCA),
- Myocarditis,
- Following cardiac arrest,
- Paroxysmal supraventricular tachycardia, especially when the HR was excessive

Summary and recommendations

- In the clinical context of BrS the aVR sign consists of a voltage of the final R wave of aVR> 3mm or 0.3mV or R/q ≥0.75. Presence of prominent final R wave on aVR is indicative of slow conduction at the RVOT may contribute to the induction of VF by EPS. Terminal tall and broad R wave of the QRS complex in lead aVR.
- Diffuse ST depression with simultaneous ST elevation in lead aVR is the hallmark of the aVR sign. ST elevation can also be present in V1. The higher the ST elevation, the more severe the prognosis.
- Regardless of its etiology, the electrocardiographic aVR sign usually reflects a high-risk condition that warrants urgent evaluation and management. • If the clinical presentation is suggestive of acute coronary syndrome, the aVR sign can indicate severe left main or multivessel coronary artery stenosis but not acute thrombotic obstruction. Thus, the aVR sign is not a STEMI equivalent.
- If alternative causes have been ruled out, urgent, but not necessarily immediate, cardiac catheterization and reperfusion is warranted. In the absence of contraindication, consideration should be given to the use of intravenous beta-blocker.
- Anchor bias toward STEMI in the setting of aVR sign can be disastrous given alternative causes including severe LVH, hemorrhagic shock, myocarditis, massive PE, type A acute thoracic aortic dissection, and supraventricular tachycardia.
- Physicians need to be educated about the high risk of missing the aVR sign in patients who present with acute chest pain, but also about the fairly wide differential diagnosis of this ECG phenomenon.

Fragmented QRS (fQRS) or QRS fragmentation

- **Abnormal fQRS Is defined as either ≥4 spikes in 1 lead or >1 notches in the** fQRS complexes in the right precordial leads are associated with occurrence of ventricular fibrillation (VF) in BrS patients.
- Epicardial mapping has revealed abnormal electrograms at the right ventricular outflow tract (RVOT) and eventually in the inferior region of the right ventricle. fQRS may reflect the extent of the area of abnormal potentials, but whether the distribution of fQRS has prognostic value is not known. The distribution of fQRS is associated with prognosis in BrS, further supporting the association of fQRS and arrhythmia substrate.
- fQRS appeared in various ventricular region; the frequency of fQRS was highest at the RVOT, followed by the inferior region and RV, and appearance of fQRS in any ventricular region was associated with occurrence of lethal arrhythmic events in patients with and without symptoms.
- Appearance of fQRS in multiple regions was associated with easily induced VF by PES and a marker of early occurrence of lethal arrhythmic events.(1)
- Epicardial mapping and ablation have revealed that the existence of delayed potential on the epicardium of RVOT is a substrate of ECG chanricular arrhythmia in BrS, and it is also recorded outside of RVOT region(1)
- To adequately study QRS fragmentation (fQRS), it is necessary to preform the standard 12-lead ECG with and additional V1–3 leads at the 2nd, 3rd and 4th intercostal space with a 0–150 Hz filter and evaluated ECG parameters at 400% size on a liquid crystal display.
- **apex or nadir of the R or S wave in 2 consecutive leads.**

1. Morita H, Watanabe A, Morimoto Y, Kawada S, Tachibana M, Nakagawa K et al. Distribution and prognostic significance of fragmented QRS in patients with Brugada syndrome. Circ Arrhythm Electrophysiol 2017 Mar;10(3):e004765.doi: 10.1161/CIRCEP.116.004765.

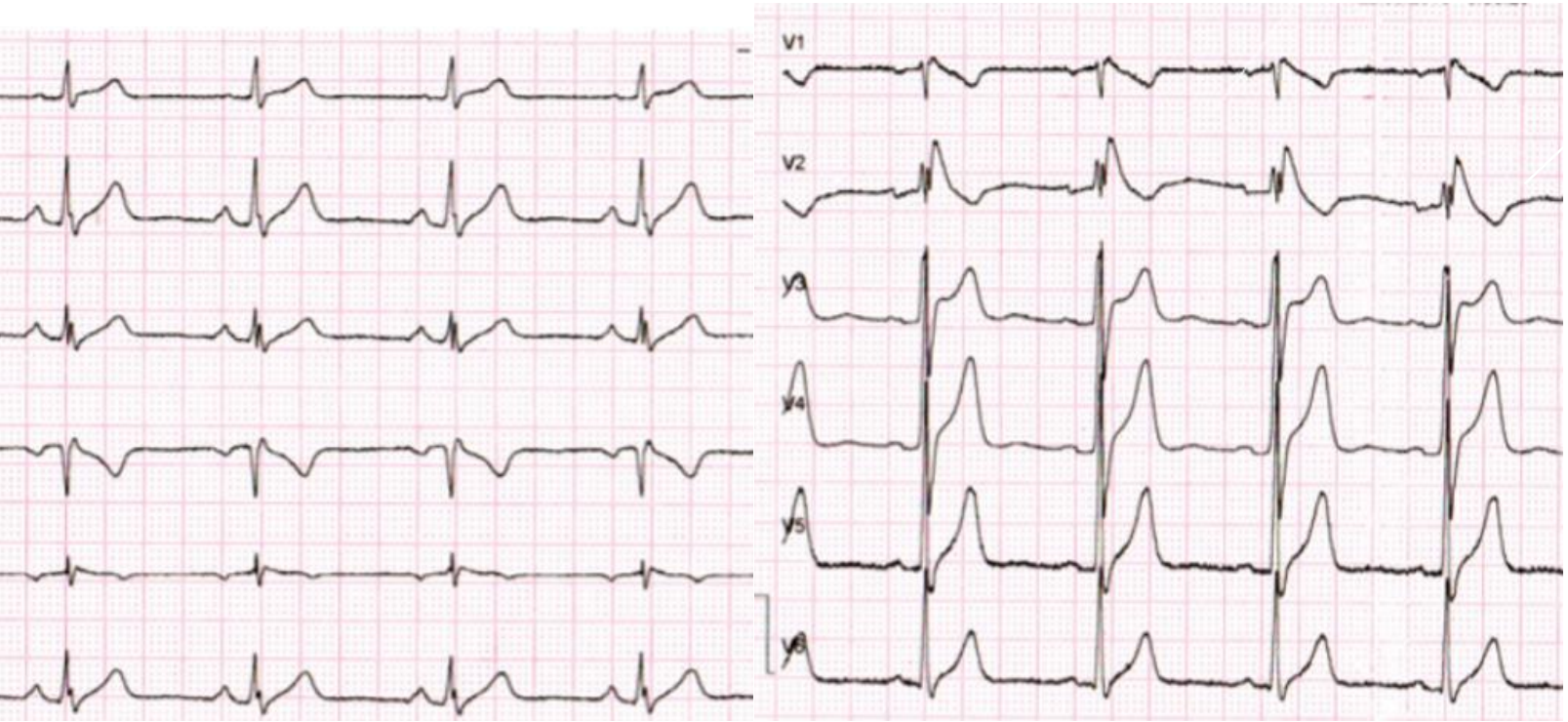
- QRS complex with >2 positive spikes in the R or S wave in two contiguous leads of the right ventricular outflow tract (RVOT, leads V1 and V2 located at the 3rd intercostal space) and/or the inferior region (leads II, III, and aVF) and/or the lateral region of the ventricle (leads I, aVL, V5, and V6. Inferolateral ER was defined as J point elevation with a slur or a notched J wave (≥0.1 mV) in at least two contiguous leads of the inferior leads (II, III, and aVF), lateral leads (I, aVL, and V4–6), or both(1)
- fQRS criteria: ≥4 positive spikes in one of the leads V1 through V3, or ≥8 positive spikes in all of leads V1, V2, and V3, according to a 2008 study[2], when patients had one of these criteria, we considered them positive for fQRS (2008 criterion[2]).
- Patients with both ER pattern associated with f-QRS have a significantly higher f requency of arrhythmic events than patients who have neither ER nor f-QRS[1].
- Fragmented QRS (fQRS) is a marker of myocardial scar or conduction/dromotropic disturbance evaluated by electrocardiography.
- In BrS patient we must to study the number of positive spikes within QRS complex in leads V1 through V3 and inferior/inferolateral leads
- fQRS appeared in leads V1 through V3 in the 3rd intercostal space but not in the 4th intercostal space

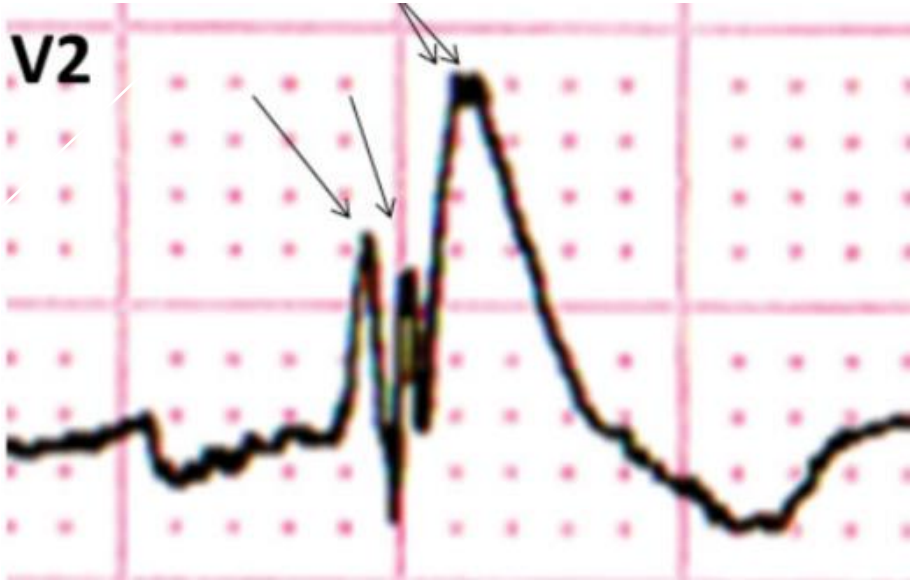
1. **Tokioka K, Kusano KF, Morita H, Miura D, Nishii N, Nagase S et al. Electrocardiographic parameters and fatal arrhythmic events in patients with Brugada syndrome: combination of depolarization and repolarization abnormalities. J Am Coll Cardiol . 2014 May 27;63(20):2131-2138. doi: 10.1016/j.jacc.2014.01.072**
2. **Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, Morita ST, Ohe T, Zipes DP, Wu J. Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome.Circulation. 2008; *118*:1697–1704. doi: 10.1161/CIRCULATIONAHA.108.770917.**

- The PRELUDE study has shown that fQRS was useful for identify candidates for a prophylactic ICD implantation in patients with BrS(1)
- Patients with BrS often had fQRS and it was more frequently observed in the VF group (1)
- fQRS appeared highest at the RVOT, followed by the inferior region and RV, and appearance of fQRS in any ventricular region was associated with occurrence of lethal arrhythmic events in symptomatic and asymptomatic patients.
- Appearance of fQRS in multiple regions was associated with easily induced VF by Programed Ventricular Stimulation(PVS) and a marker of early occurrence of lethal arrhythmic events.
- PVS with a strict protocol(at two sites of the right ventricle with up to three extrastimuli [two pacing cycle lengths and minimum coupling interval of 180 ms) for asymptomatic patients with fQRS and/or long Tpe interval ≥100ms to identify high-risk patients. (3)
- Patients who had fQRS in multiple regions had a shorter time to arrhythmic events than did patients with fQRS in a single region.(2)

1. **Silvia G Priori 1, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. J Am Coll Cardiol. 2012 Jan 3;59(1):37-45. doi: 10.1016/j.jacc.2011.08.06Hiroshi Morita 1, et al. Circulation. 2008 Oct doi: 10.1161/CIRCULATIONAHA.108.770917.**
2. **Hiroshi Morita, MD, PhD et al. Distribution and Prognostic Significance of Fragmented QRS in Patients With Brugada Syndrome. Circ Arrhythm Electrophysiol. 2017;10:e004765. DOI: 10.1161/ CIRCEP.116.004765.**
3. **Saori Asada 1, et al 1Indication and prognostic significance of programmed ventricular stimulation in asymptomatic patients with Brugada syndrome. Europace. 2020 Jun 1;22(6):972-979. doi: 10.1093/europace/euaa003.**

Brugada type 1 ECG pattefrn associated wuit fQRS





Low pass filter: 35 Hz **Low pass filter: 150 Hz**

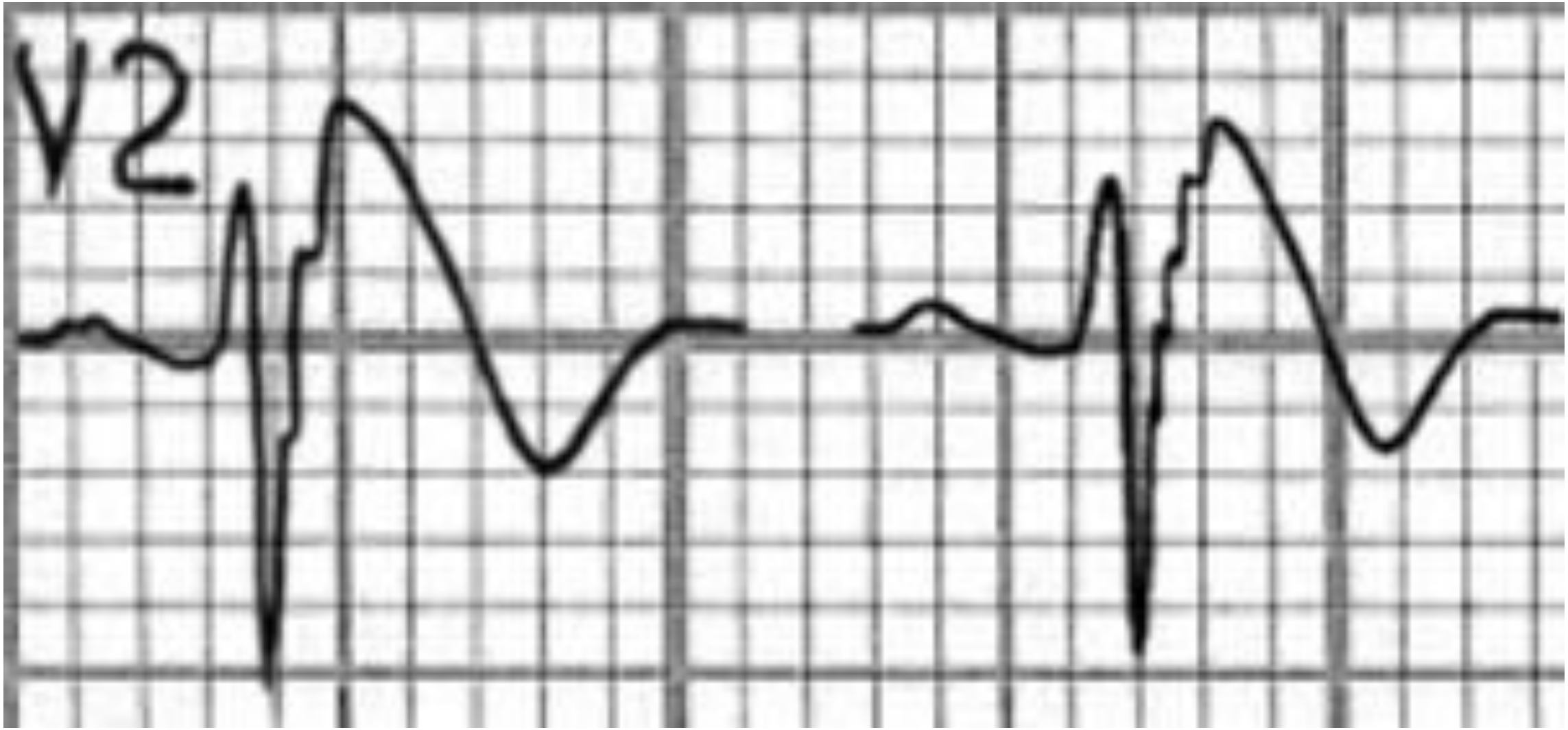
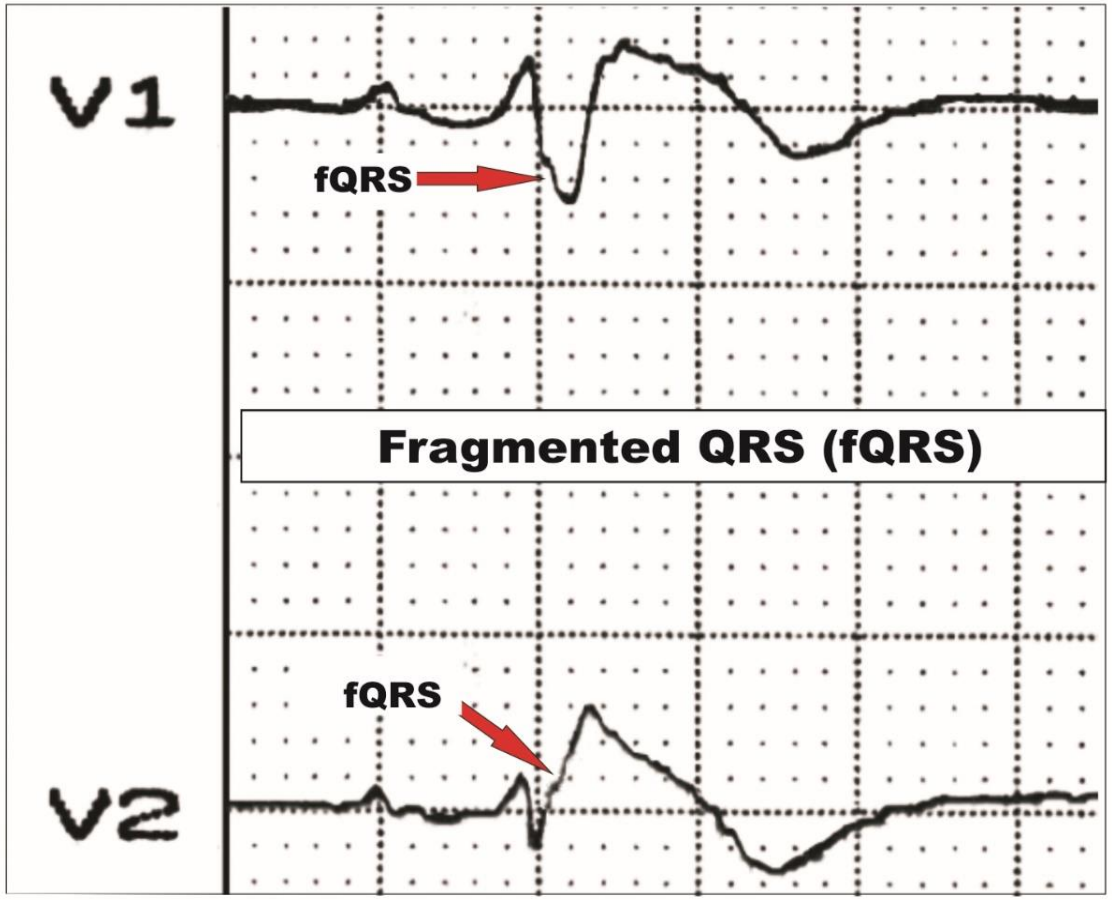


Figure . Effects of low-pass filter. ECG recording with a low-pass filter of 35Hz showed only 2 spikes within the QRS complex (left). Change of the cut-off frequency from 35 to 150 Hz unmasked 2 additional spikes within the QRS complex (right).



Presence of a “notch” within a non-wide QRS complex in two adjacent leads (V1-V2.): f-QRS. It is a non-invasive marker of events (**Das 2009**). In BrS fQRS is defined as ≥4 spikes in 1 or ≥8 spikes within the QRS complex in all of the leads (V1, V2, and V3).83

In BrS, fQRS is caused by RVOT epicardial activation delay and eventually inferolateral aspect of the RV.83 Rattanawong et al. assessed the association between fQRS and major arrhythmic events in BrS by a systematic review and a meta-analysis. The authors concluded that baseline fQRS increased major arrhythmic events (MAE) up to 3-fold. This study suggests that fQRS could be an important tool for risk assessment in BrS patients. fQRS in the right precordial leads are associated with occurrence of VF in BrS. Epicardial mapping has revealed abnormal electrograms at the RVOT and inferior region of the RV. fQRS may reflect the extent of the area of abnormal potentials. The presence of multiple regions of fQRS is associated with worse prognosis.84

Luzia my dear granddaughter