Left Axis Deviation in Brugada Syndrome patients during ajmaline challenge

Dear Arthur: We have been reading with interest the recent work of Martijn H van der Ree et al. where you are coauthor (**Martijn H van der Ree Vendrik, J., Kors, J. A., Amin, A. S., Wilde, A. A. M., Tan, H. L. & Postema, P. G., 2 et al. Left Axis Deviation in Brugada Syndrome: Vectorcardiographic Evaluation during Ajmaline Provocation Testing Reveals Additional Depolarization Abnormalities. Int J Mol Sci. 2021 Jan 6; 22 (2): 484. doi: 10.3390 / ijms2202048**).

The authors observed in a large cohort of 1430 Brugada Syndrome (BrS) patients undergoing the ajmaline test - using the VCG in which the authors found that 18% of the patients during the positive ajmaline challenge developed QRS axis deviation to the left: "LAD" Left Axis Deviation in the frontal plane (QRS-axis> 30°). **In electrocardiography, LAD is an ECG pattern where frontal plane QRS axis is between −30° and −90°.** This is reflected by a QRS complex positive in lead I and negative in leads aVF and II. It is not clear if they considered this detour as being a left anterior fascicular block (LAFB). The authors analyzed the depolarization and repolarization parameters using the VCG loop and compared patients with and without LAD> -30°. Thus, they found that the prevalence of LAD during the ajmaline challenge was 18% and that this (LAD -30 °) was not explained by a Terminal Conduction Delay (TCD) in RVOT, but was associated with a proximal conduction delay (first QRS-quartile of QRS loop). Additionally, there was no significant heterogeneity of action potential morphology (i.e. absence of transmural ventricular gradient across ventricular wall thickness?), but the presence of LAD resulted in discordant repolarization: obtuse (wide spatial QRS-T angle: 122° for those with LAD proximal conduction delay (first QRS-quartile of QRS loop) versus 44° for those who don't.).

The ECG / VCG of type 1 BrS is characterized by a TCD corresponding to the RVOT (**Peréz-Riera AR, et al; International VCG Investigators Group. Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study. Europace. 2012 Jun; 14 (6): 889-97. Doi: 10.1093 / europace / eur395**.), BrS patients who developed LAD after ajmaline challenge have additional proximal conduction slowing, which is associated with discordant repolarization. The authors comment that it has yet to be determined whether

this has implications for risk stratification. (obtuse wide spatial QRS-T angle: 122° for those with LAD versus 44 ° for those without).

Commentaries:

Patients with a wide QRS-T angle have a 40% risk of death from any cause and a 71% risk of dying from the heart compared with those with a normal QRS-T angle (**Zhang et al., (Xinlin Zhang et al. Spatial/Frontal QRS-T Angle Predicts All-Cause Mortality and Cardiac Mortality: A Meta-Analysis PLoS One. 2015 Aug 18;10(8):e0136174. doi: 10.1371/journal.pone.0136174**.). Most likely this indicates progressive disease of the His conduction system characteristic of BrS, as mentioned by Pedro and Josep in their original work where they observed HV interval prolongation, intra-hisian block and in some cases Split His, within, or distal to the His bundle, with the use of the His bundle recording technique. (**Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992 Nov 15;20(6):1391-6. doi: 10.1016/0735-1097(92)90253-j.**). Intra-hisian AV block is a rare phenomenon, but it is important for the development of advanced or complete AV block. Seung Pyo Hong et al observed a 77-year-old female patient with the 2:1 AV block due to an intra-hisian block. In this case the authors tried to detect the block site, but an alternating pattern of the AH conduction was noted on the His-electrogram in the EPS. The cause of the confusing finding might have been the instability of the catheter to record a His potential. They could detect a splitting of the His-electrogram with an intra-hisian block after minimal manipulation of the catheter. The authors' observations suggest that catheter stability is important for a precise recording in the EPS and radiofrequency catheter ablation procedure (**Seung Pyo Hong 1, Yon Woong Park 1, Young Soo Lee 1Intra-His bundle block in 2:1 atrioventricular blockWorld J Cardiol. 2015 Oct 26;7(10):700-2. doi: 10.4330/wjc.v7.i10.70**).

The prolonged PR interval in BrS is considered a risk marker (**Federico Migliore et al. First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: a long-term follow-up study from the Veneto region of Northeastern Italy. Europace. 2019 Feb 1;21(2):322-331. doi: 10.1093/europace/euy144**.) because it is due to low Hisian and not high prolongation in the AV node.

PR prolongation as a consequence of His-ventricle (HV) split or HV prolongation. Besides a history of cardiac arrest or syncope, first-degree AV block on basal ECG is an independent predictor of malignant arrhythmic event (MAEs) and a stronger marker of arrhythmic risk than a spontaneous 'coved-type' ECG pattern in patients with BrS. (**Migliore F, Testolina M, Zorzi A, *et al.* First-degree atrioventricular block on basal electrocardiogram predicts future arrhythmic events in patients with Brugada syndrome: a long-term follow-up study from the Veneto region of Northeastern Italy. Europace. 2019;21:322-33**) First-degree AV block is associated with more frequent major arrhythmic events in BrS patients. PR interval seemed to be prolonged but is yet to be determined whether the PR interval association is still significant if it did not cross the first-degree AV block threshold(**Pranata R, Yonas E, Chintya V, *et al.* Association between PR Interval, First-degree atrioventricular block and major arrhythmic events in patients with Brugada syndrome - Systematic review and meta-analysis. J Arrhythm. 2019;35:584-590**) A history of syncope or cardiac arrest, first-degree AV block on basal ECG is an independent predictor of MAEs and a stronger marker of arrhythmic risk than a spontaneous type 1 ECG pattern in patients with BrS. Factors associated with PR prolongation and their clinical significance (Figure 1).

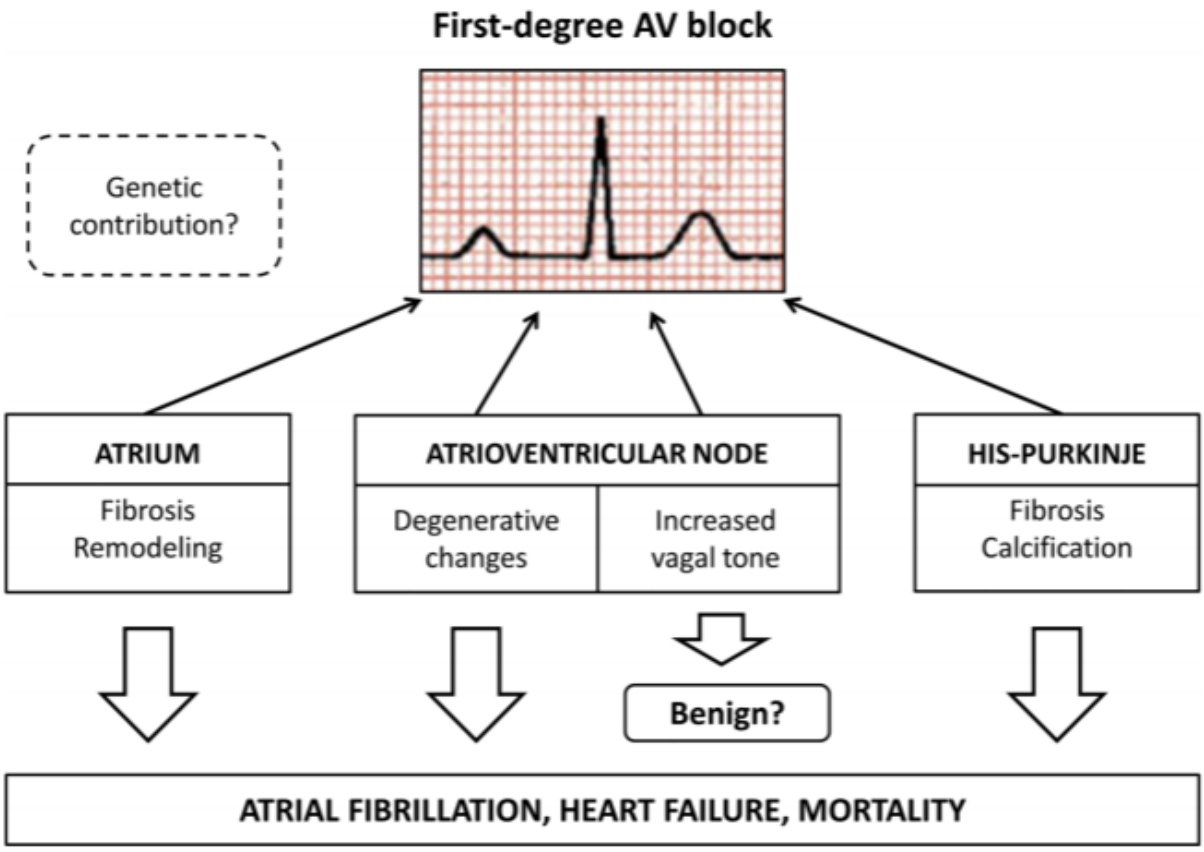

Figure 1

First degree AV block and left-axis deviation of the QRS as I think you remember, I have shown the differences between the LAD consequence of **"TCD"** and that dependent on LAFB. Figure 2

ECG/VCG correlation in the horizontal plane TCD (Terminal Conduction Delay or Right End Conduction Delay(RECD) in Type 1 Brugada ECG pattern versus truly RBBB

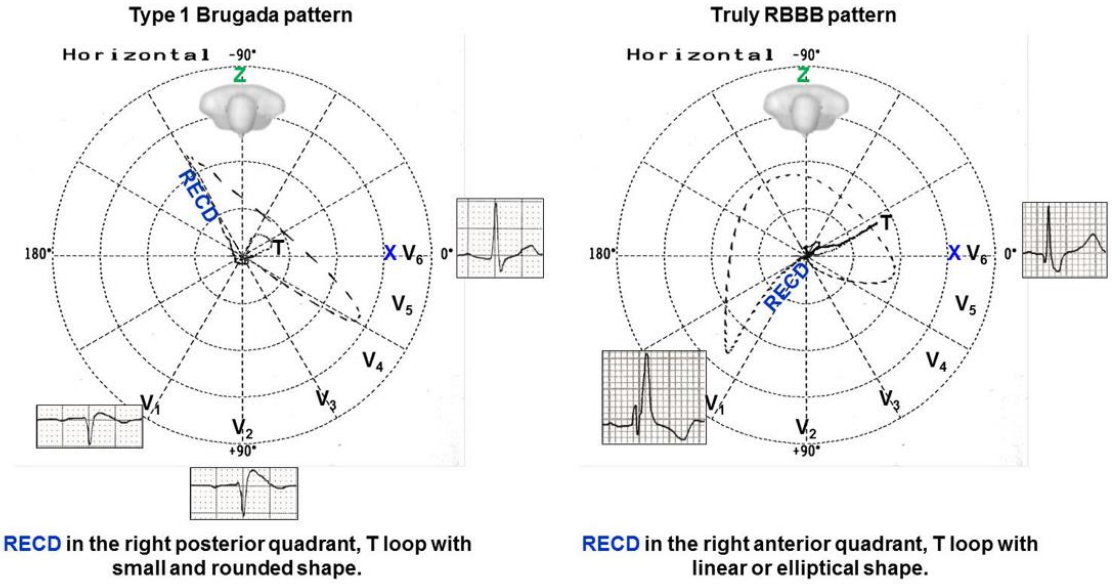

Figure 2. VCG types in Complete RBBB Horizontal Plane

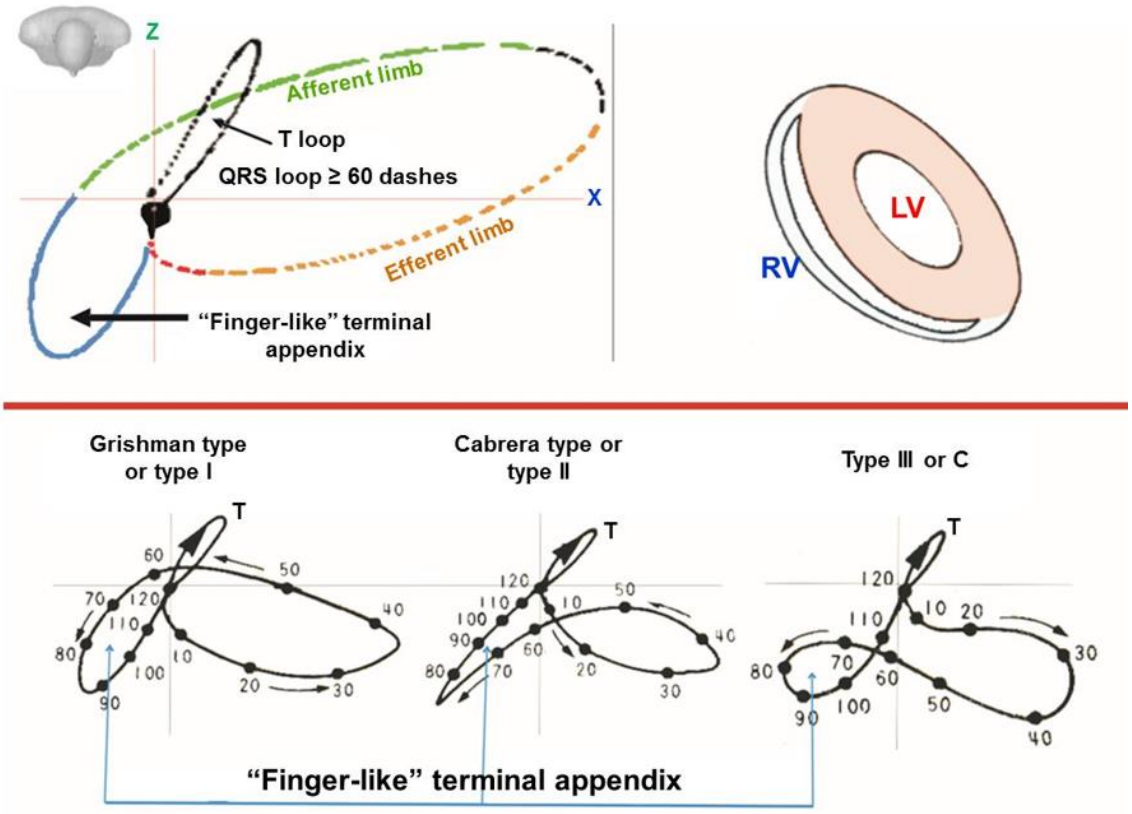

Figure 3. Truly CRBBB vectorcardiogram variants in the horizontal plane

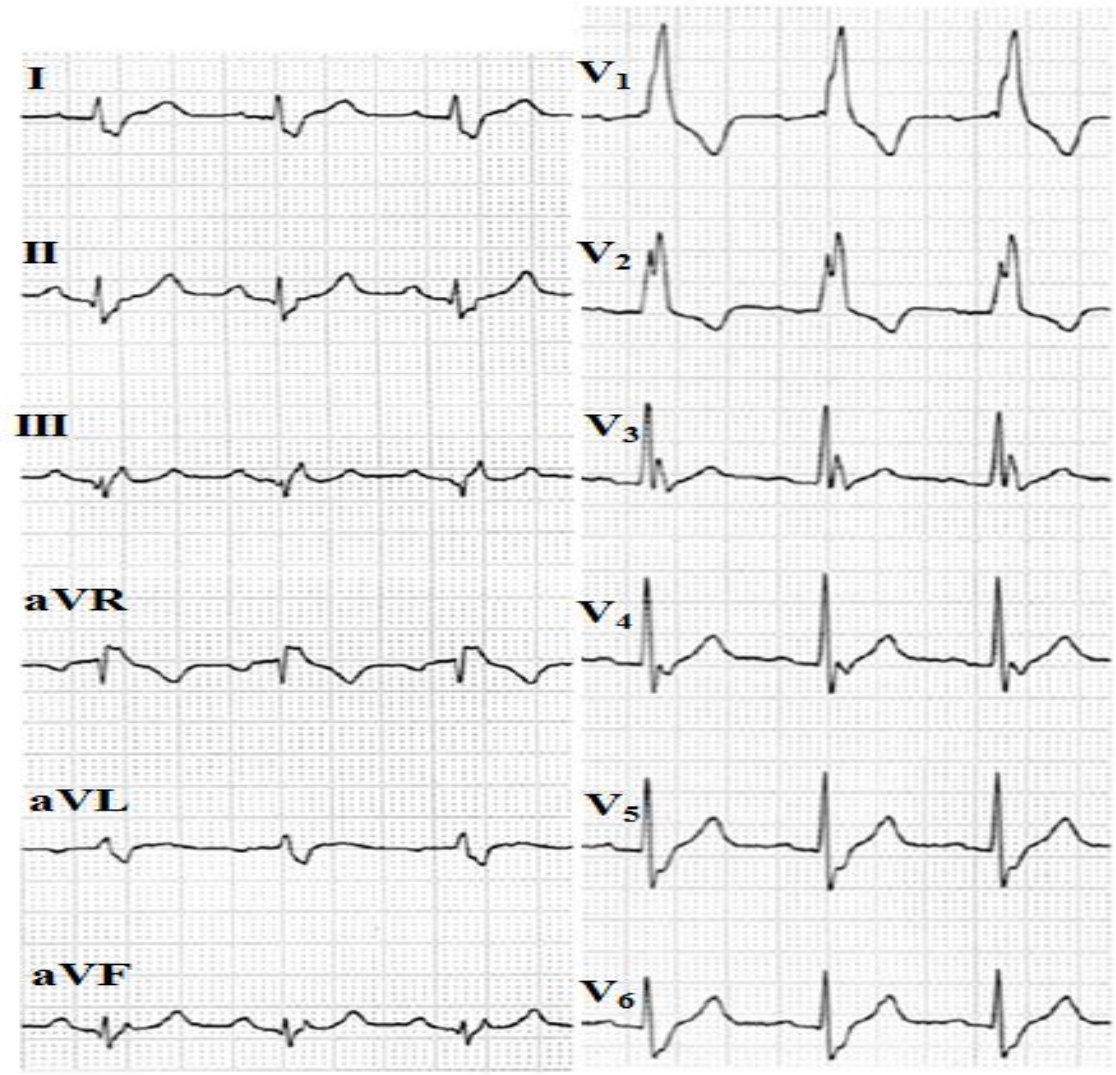

Figure 4 12-lead ECG showed CRBBB pattern: QRSD 140 ms, late R in V_1, final broad R wave in aVR, and wide terminal S in left leads. The QRS duration = 140 ms

Figure 5 The first and second beats show CRBBB. The third beat without CRBBB (spontaneous transient or intermittent RBBB) shows type 1 Brugada pattern a loss of CRBBB and the normalized QRS complex. Spontaneous resolution of the CRBBB unmasks the type 1 Brugada pattern.

TCD or Right End Conduction Delay (RECD) in the Frontal.

In BrS TCD is observed only group I in the FP

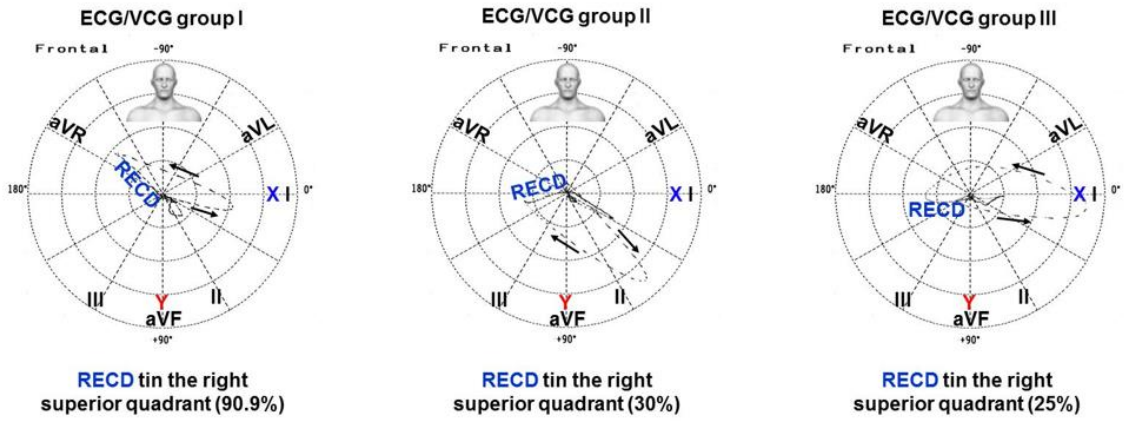

Figure 6. VCG.

The three possible types of QRS loop rotations in TCD (or RECD) in the frontal plane.

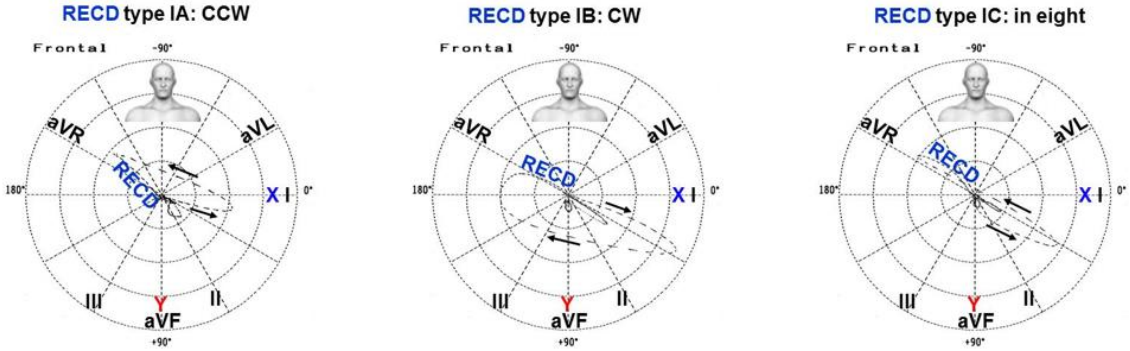

Figure 7. The figure shows the three possible types of QRS loop rotations in BrS patients in the frontal plane. Type IA - QRS loop with counterclockwise rotation (CCW) and extreme superior QRS axis deviation: Right Superior Fascicular Block with Right End Conduction Delay(**RECD**).

Note: >90% of the Brugada patients shows **RECD** (or terminal conduction delay TCD) in the right superior quadrant near aVR (RVOT). Differential diagnosis with LAFB.

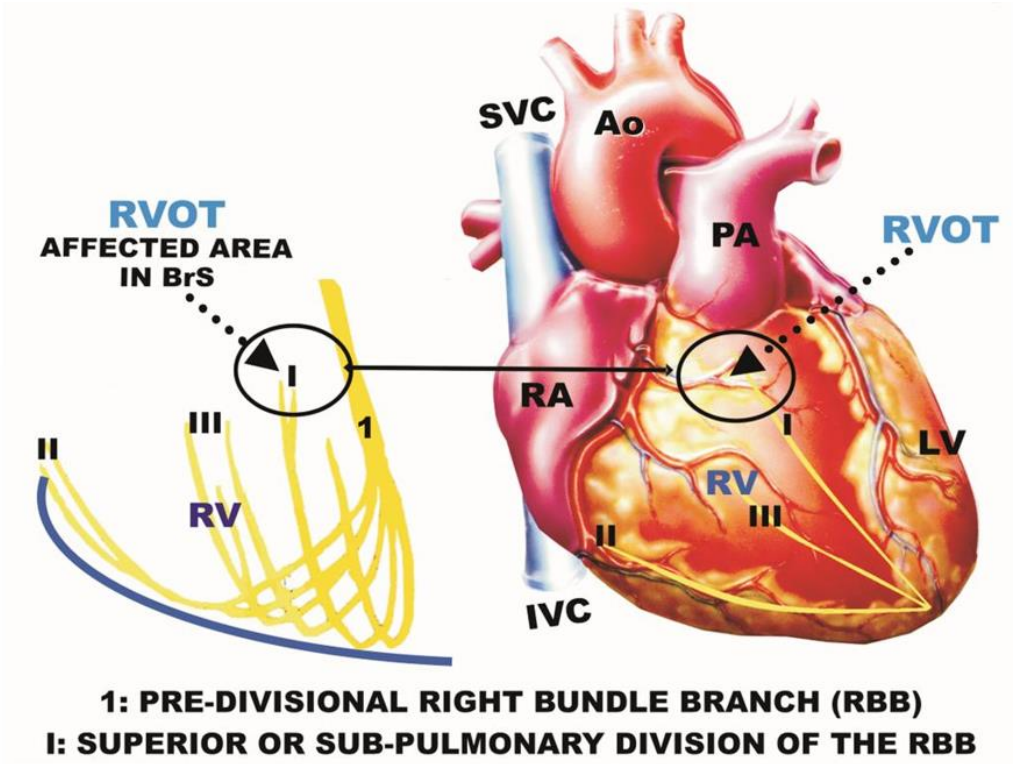

Figure 8. The figure shows the three hypothetical clusters of fibers (I, II and II) on the free wall of the right ventricle, and the partial superior right Hissian system affected in BrS: "Right Superior Fascicular Block" (depolarization mechanism).

ECG/VCG differential diagnosis between right end conduction delay (RSFB) or TCD and left anterior fascicular block (LAFB)

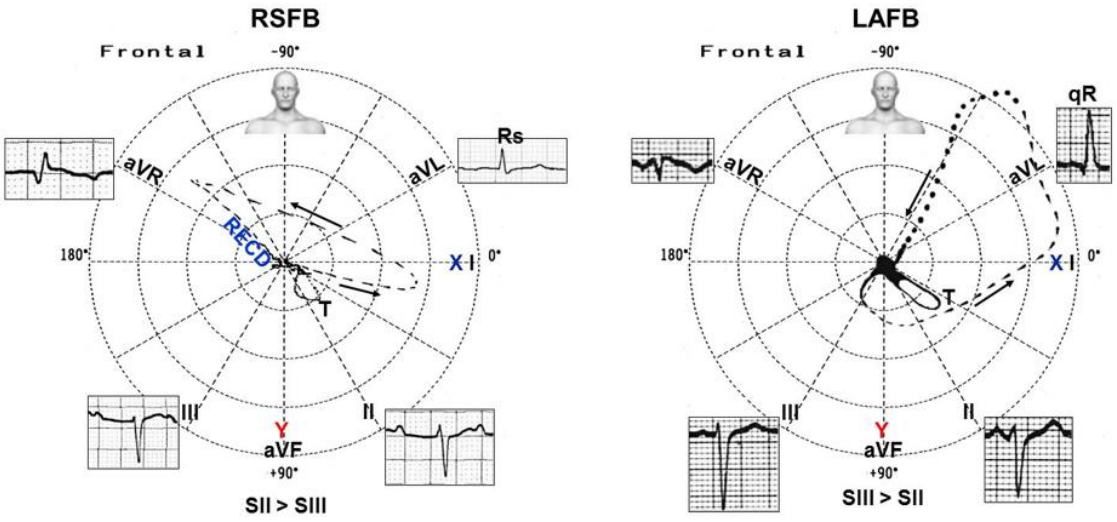

Figure 9. ECG/VCG differential diagnosis between right superior fascicular block (RSFB) or Right End Conduction Delay (**RECD**) and left anterior fascicular block (LAFB).

Table 1 LAFB versus terminal conduction delay (TCD) or RSFB ("Right Superior Fascicular Block" (depolarization mechanism).

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

Example Pseudo LAFB associated with BrS

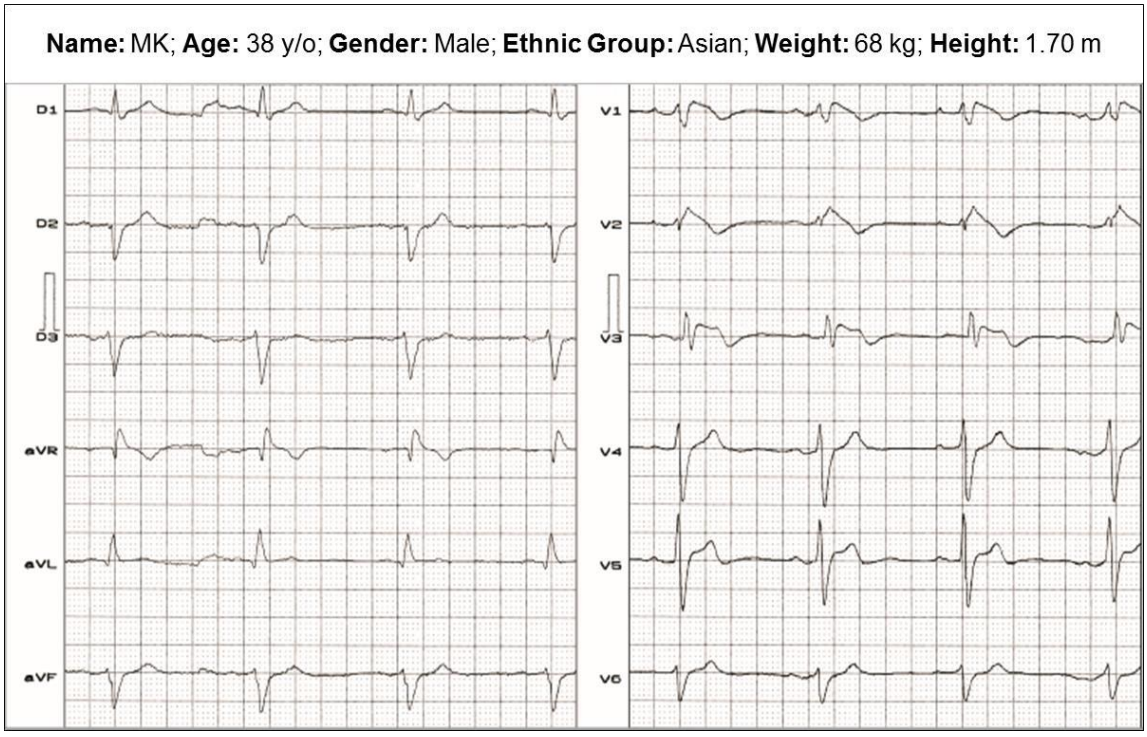

Figure 10. Clinical diagnosis: Syncope. Positive familiar background of sudden death in young (≤35 y/o) first-degree relative. Genetic research performed: negative. ECG diagnosis: Sinus bradychardia (HR <60 bpm), Brugada type 1 ECG pattern, prolonged QRS duration, aVR signal: final R wave of aVR lead >3 mm, fQRS in V1-V2. Extreme left axis deviation: Left anterior fascicular block? or Right superior fascicular block?

ECG/VCG correlation

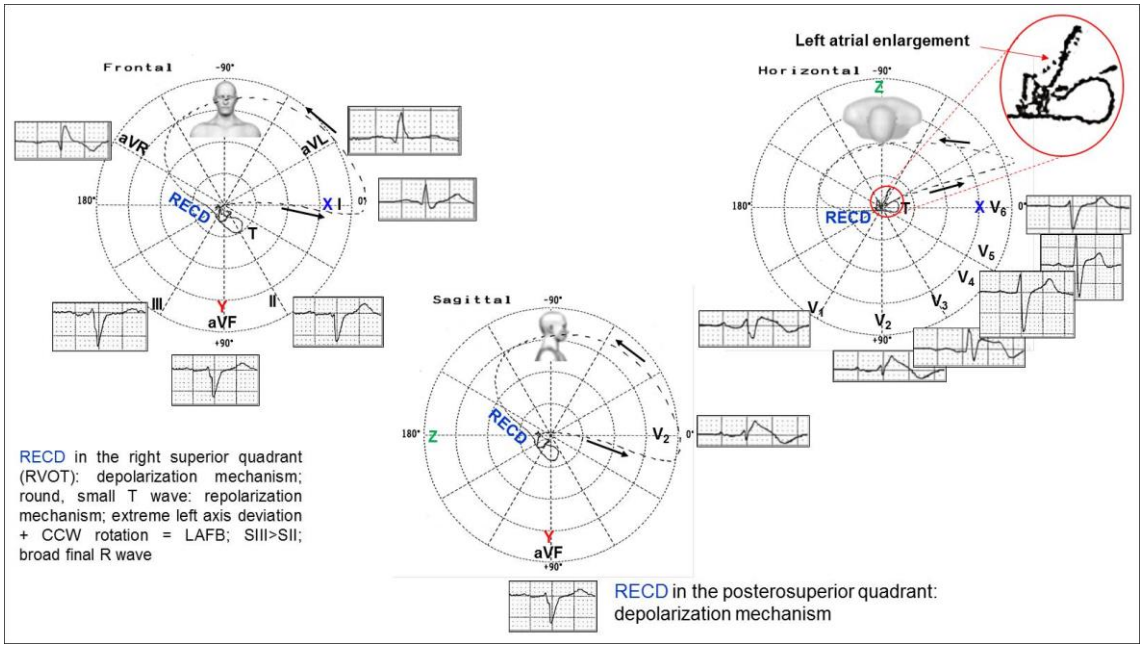

Figure 11. ECG/VCG correlation.

CLINICAL SIGNIFICANCE OF RIGHT END CONDUCTON DELAY (RECD) OR TERMINAL CONDUCTION DELAY (TCD)

Its clinical significance and interest lies in the fact that:

1) They may be confused with left fascicular blocks: Left Anterior Fascicular Block (LAFB) and Left Posterior Fascicular Block (LPFB) Figure 12;

2) They may be confused with myocardial infarctions or electrically inactive areas (pseudo electrically inactive areas) both in the anterior and the interior walls.

3) They may represent the electro-vectorcardiographic pattern of Brugada syndrome and one subpopulation (in early phase) of Arrhythmogenic Right Ventricular Dysplasia (ARVD/C).

Figure 12

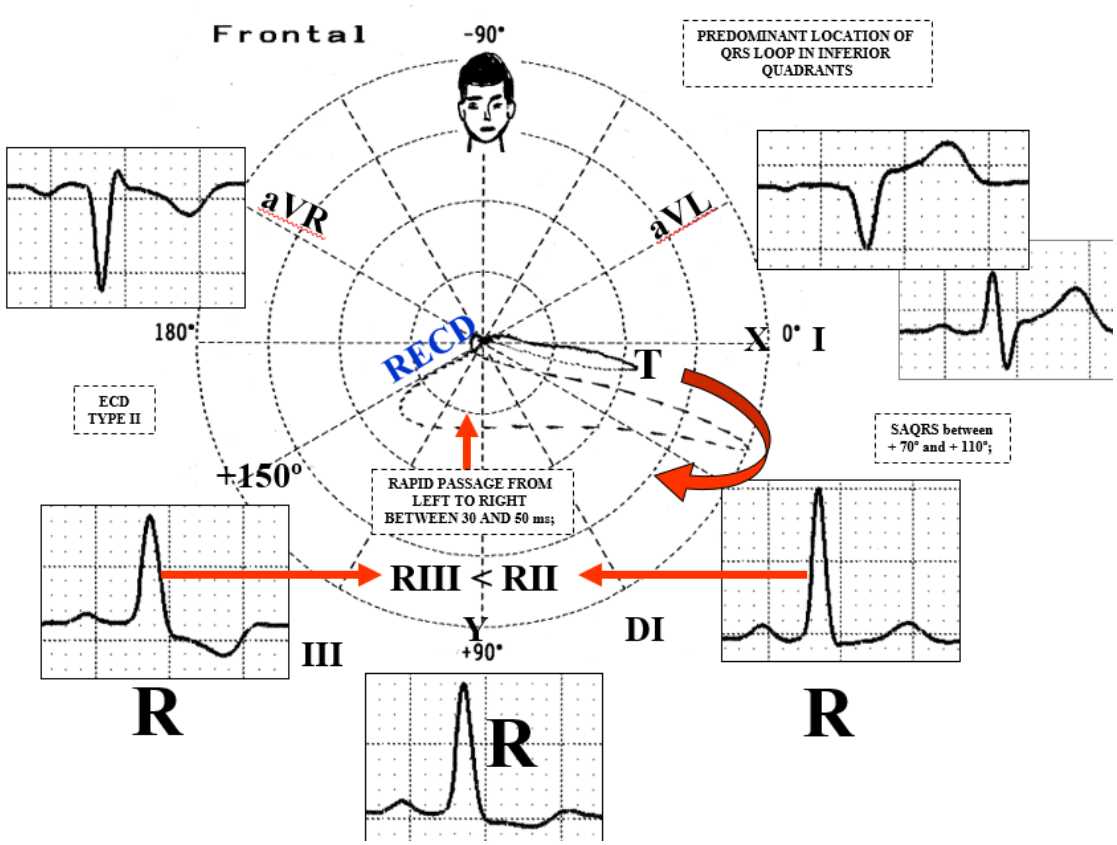

Figure 12 Pseudo LPFB

Inferior **RECD** or TCD confused with Left Posterior Fascicular Block (LPFB)

DIFFERENTIAL DIAGNOSIS BETWEEN RECD TYPE II AND LPFB

	RECD TYPE II	LPFB
R-wave peak time in aVF, V5 and V6:	Normal.	Increased: up to 30 ms.
R-wave peak time in aVL:	Normal.	Decreased: up to 15 ms.
Aspect of QRS loop in the frontal plane:	Clockwise and with characteristic rapid passage from left to right between 30 and 50 ms.	Clockwise, aspect of "fat" loop and maximal vector close to + 120°.
Clinical factors that should be excluded:	Not stated.	Vertical heart, RVH and lateral infarction.

36 YEARS OLD, EPISODE OF VF

Clinical diagnosis ARVC

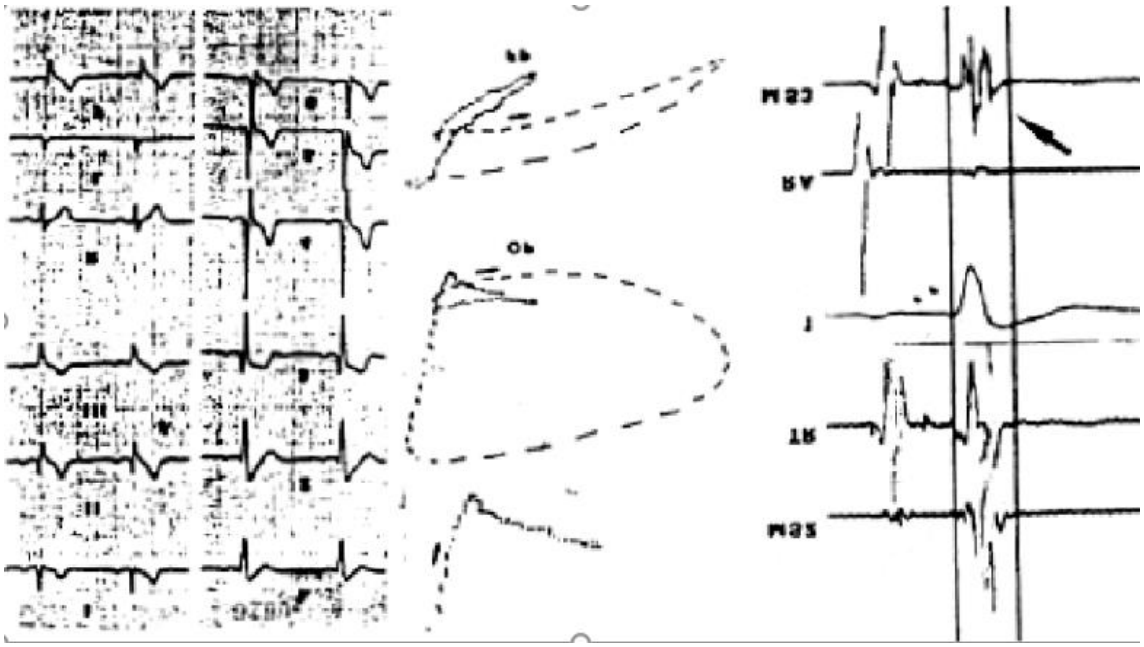

Figure 13 The authors interpreted this tracing as early repolarization. Today we know that this is the typical type 1 Brugada pattern, which from the vectocardiographic point of view is diagnosed as RECD by one of the Right Bundle fascicles.