JACC: CASE REPORTS VOL. 2, NO. 14, 2020


MINI-FOCUS ISSUE: ELECTROPHYSIOLOGY

ADVANCED

CASE REPORT: CLINICAL CASE

# Electrocardiographic "Northwest QRS Axis" in the Brugada Syndrome

## A Potential Marker to Predict Poor Outcome

Andrés Ricardo Pérez-Riera, MD, PhD,[a] Frank Yanowitz, MD,[b] Raimundo Barbosa-Barros, MD,[c] Rodrigo Daminello-Raimundo, PhD,[a] Luiz Carlos de Abreu, PhD,[a,d] Kjell Nikus, MD, PhD,[e] Pedro Brugada, MD, PhD[f]

**ABSTRACT**

Conduction delay in the right ventricular outflow tract as manifested in the electrocardiogram constitutes a high-risk predictor of ventricular arrhythmias in patients with Brugada syndrome. We present a case with a right QRS axis between -90° and ±180°. This feature has never been reported in the context of Brugada syndrome. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:2230–4) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

A 28-year-old man, descendent from an Asian father and a Caucasian mother, consulted for complaint of repeated unexplained syncope at rest and during sleep in the previous month. Agonal breathing also was evident on several nocturnal occasions.

### LEARNING OBJECTIVES

- To show potential multiple phenotypes of heterozygous mutations in the *SCN5A* gene.
- To highlight the clinical significance of the QRS electrical axis in the upper-right quadrant "northwest QRS axis" in the frontal plane in Brugada syndrome.

### MEDICAL HISTORY

His father had a permanent pacemaker implanted at 37 years of age because of "genetic sick sinus syndrome (SSS)." The patient has an identical twin brother, who was hospitalized 1 year before for paroxysmal atrial flutter, apparently caused by Brugada syndrome (BrS). The electrocardiogram (ECG) from that episode is shown in **Figure 1**. A heterozygous mutation in the *SCN5A* gene (p.G400R and p.T1461S) was found in the father and twin brothers. Curiously, the ECG phenotypes of both twin brothers are extremely similar. Nothing noteworthy was revealed in the physical examination. Heart rate was 56 beats/min, blood pressure was 110/60 mm Hg, temperature was 36.5°C, and respiratory rate was 15 breaths/min.

From the [a]Laboratório de Metodologia de Pesquisa e Escrita Científica, Centro Universitário Saúde ABC, Santo André, São Paulo, Brazil; [b]Intermountain Medical Center, Intermountain Heart Institute, Department of Internal Medicine, The University of Utah, Salt Lake City, Utah; [c]Coronary Center of the Hospital de Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza, Ceará, Brazil; [d]Graduate Entry Medical School, University of Limerick, Limerick, Ireland; [e]Heart Center, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; and the [f]Cardiovascular Division, Free University of Brussels (UZ Brussel) VUB, Brussels, Belgium.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received June 4, 2020; revised manuscript received July 13, 2020, accepted July 22, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.07.037

## DIFFERENTIAL DIAGNOSIS

The patient presented repetitive syncope at rest or during sleep with urinary incontinence at night, agonal respiration, a strong family history suggestive of BrS in his twin brother, and SSS in the young father as well as mutation in the *SCN5A* gene. His father is from Philippines, where BrS is endemic.

## INVESTIGATIONS

An ECG (**Figure 2A**), serum electrolytes measurement, transthoracic echocardiogram, cardiac magnetic resonance imaging scan, and electrophysiological study (EPS) were requested. All results were normal except for the ECG. EPS was performed from the right ventricular apex, with a minimum of 3 ventricular extra stimuli at 3 different pacing rates. There was no induction of ventricular arrhythmia, and ventricular effective refractory period was >200 ms.

## DISCUSSION

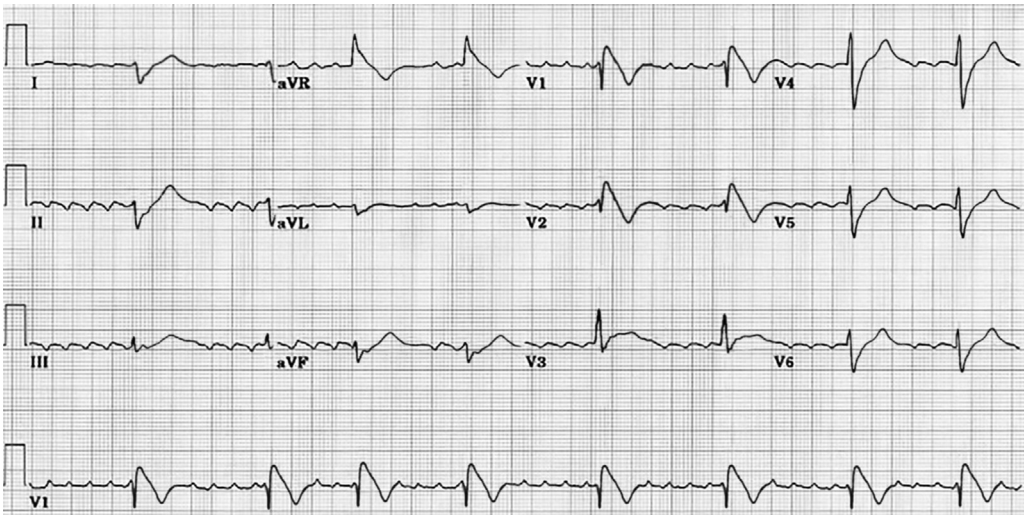
Extreme QRS right-axis deviation is a rare ECG finding that occurs when the QRS axis is between -90° and ±180°. The normal QRS axis is between -30° and +90°. **Table 1** shows clinical scenarios associated with extreme right-axis deviation (1,2).

Symptomatic BrS with "northwest QRS axis" indicates pronounced conduction delay in the right ventricular outflow tract (RVOT). A prominent final R wave, as a sign of increased risk for spontaneous ventricular tachyarrhythmia (VTA) in patients with BrS, was described by Babai Bigi et al. (3). Ragab et al. (4) evaluated the significance of high R-wave voltage in lead aVR as a predictor for VTA in 132 patients with BrS. A positive R-wave sign in lead aVR was observed in 31%, and it was more frequently observed in patients who experienced VTA before the initial diagnosis, during EPS, or during follow-up. The positive R-wave sign occurred more frequently in symptomatic patients with histories of out-of-hospital cardiac arrest, VTA, or syncope than in asymptomatic patients. During the follow-up, this sign was more frequently detected in patients who developed either de novo or recurrent VTA. In a multivariable regression analysis, the R-wave sign was an independent risk marker (4). Calò et al. (5) analyzed data from 347 patients with a type 1 Brugada ECG pattern but with no histories of cardiac arrest; 4% of the patients had syncope, 5.2% had previous atrial fibrillation (AF), and 91.1% were asymptomatic at presentation. ECG characteristics at the first clinic visit were analyzed to predict

### ABBREVIATIONS AND ACRONYMS

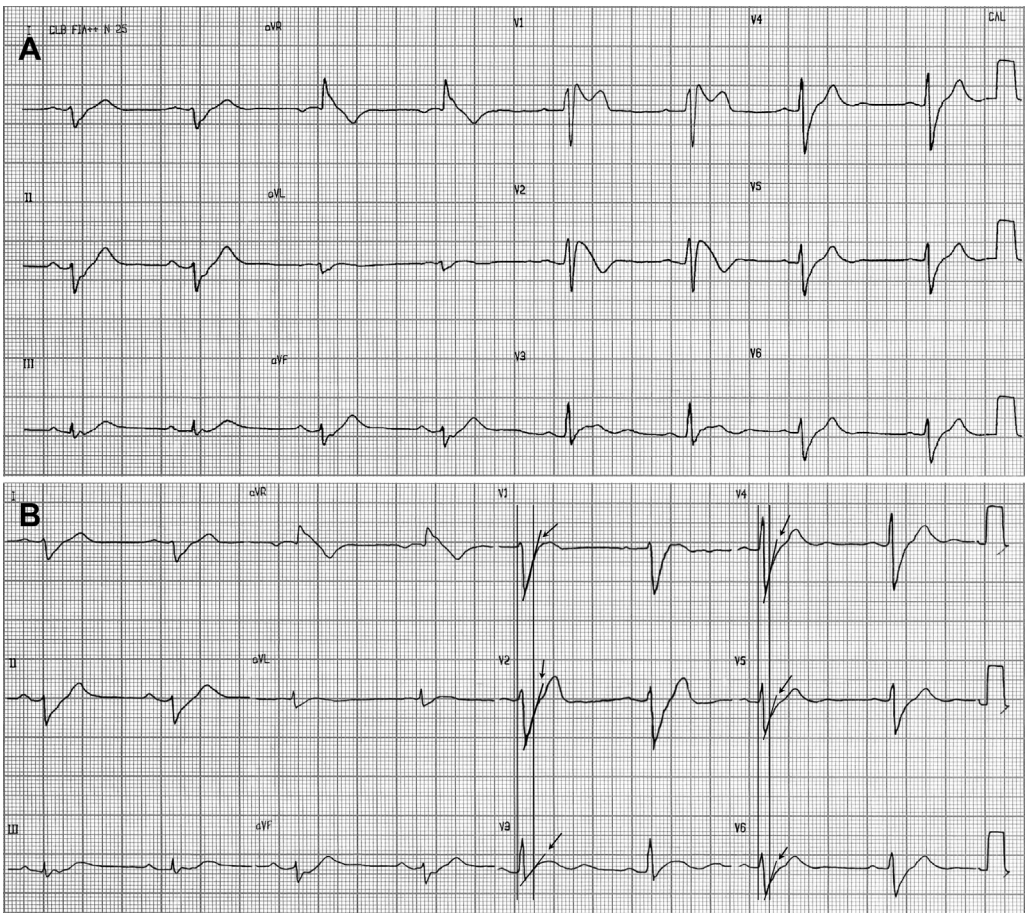
**AF** = atrial fibrillation
**BrS** = Brugada syndrome
**ECG** = electrocardiogram
**EPS** = electrophysiological study
**ICD** = implantable cardioverter defibrillator
**RVOT** = right ventricular outflow tract
**SCD** = sudden cardiac death
**SSS** = sick sinus syndrome
**VF** = ventricular fibrillation
**VTA** = ventricular tachyarrhythmia

**FIGURE 1 Electrocardiogram of the Twin Brother**




Atrial flutter with variable heart rate response, saw-tooth appearance in the inferior leads, heart rate ≈300 beats/min with F-wave axis near -90° and counterclockwise rotation. The "regular irregularity" of the respiratory rate (RR) intervals in the $V_1$ rhythm strips, 2 next largest RR intervals (≈1,200 ms) have 1 6:1, 2 5:1 conduction ratio, and 1 4:1 ratio. The RR intervals in atrial fibrillation are considered to be "irregularly irregular," unless long intervals end with escape beats from the atrioventricular junction. QRS axis -155°, prominent final R-wave in aVR, broad S-wave in I, and type 1 Brugada electrocardiographic pattern.

**FIGURE 2 Electrocardiogram of Our Patient**




**(A)** Sinus bradycardia (heart rate = 49 beats/min), QRS axis in the **top right** quadrant. QRS axis was ≈−160°. There is a prominent R-wave in aVR (8 mm), which may reflect significant conduction delay in the right ventricular outflow tract. This delay is associated with increased arrhythmia risk. The aVR sign is an electrocardiographic (ECG) risk marker for arrhythmic events in patients with Brugada syndrome (3), also, type 2 Brugada ECG pattern in $V_1$ and type 1 Brugada ECG pattern in $V_2$. **(B)** Higher degree of sinus bradycardia (heart rate = 46 beats/min), final R-wave in aVR near 4 mm, wider QRS duration, absence of Brugada ECG pattern in $V_1$ to $V_2$, very prolonged S-wave upstroke in $V_1$ to $V_3$, flattened T waves, and prominent U-wave in $V_3$: quinidine-induced long QTU interval and torsade de pointes may be related to bradycardia-dependent early afterdepolarizations (15). In addition, the QRS duration of $V_1 + V_2 + V_3$ (480 ms) divided by the QRS duration of $V_4 + V_5 + V_6$ (360 ms) is ≥1.2, constituting a sign of high sensitivity for arrhythmogenic right ventricular cardiomyopathy, as it is present in 98% of patients of this cardiomyopathy (16). In the current case, after the use of quinidine, this phenomenon was also observed, indicating that the sign is not specific of arrhythmogenic right ventricular cardiomyopathy. **Arrows** = tangent line to determine the end of QRS.

ventricular fibrillation (VF) and sudden cardiac death (SCD) during follow-up; 79.5% of patients remained asymptomatic, 11.2% developed syncope, and 9.2% developed VF/SCD. This last group had a higher prevalence of positive EPS, family history of SCD, and AF. The most powerful marker for VF/SCD was a deep and broad S-wave ≥1 mm or S-wave duration ≥40 ms in lead I. This sign was an independent predictor of VF/SCD. Electroanatomic mapping showed that the endocardial activation time was significantly longer in patients with S waves in lead I, mostly because of a significant delay in the RVOT (5).

**THE ASSOCIATION BETWEEN THE aVR SIGN AND THE S-WAVE IN LEAD I SIGN.** Both the aVR sign and the S wave in lead I sign are the reciprocal image of each other because they are located in opposite regions with respect to ventricular depolarization. In patients with these ECG features, the frontal-plane

activation vector goes from left to right and from below upward, pointing to the aVR and moving away from the lead I. This results in a prominent final R-wave in lead aVR and a deep and wide S-wave in lead I (Figure 3).

Based on the ECG findings in the twins presented in this brief report, we speculate that the presence of a QRS axis in the "northwest quadrant" in patients with BrS may suggest a severe degree of conduction disturbance in the RVOT. The voltage of the final R-wave of aVR in both identical twins were ≥5 mm and 8 mm, and according to previous studies, a high R-wave in lead is an ECG marker of higher mortality risk in BrS. However, a prospective study would be preferable to study this association.

Despite the clear causal relationship between *SCN5A* mutations and the BrS phenotype, there is clinical variability of it. Loss-of-function mutations in *SCN5A* have been associated with the BrS, Lenègre disease, LQT3, idiopathic VF, early repolarization syndromes, dilated cardiomyopathy, sinus-node dysfunction, SSS, sudden infant death syndrome, sudden unexplained nocturnal death syndrome, familial AF, multifocal ectopic Purkinje-related premature contractions, and overlapping phenotypes (6). The proband had BrS, his brother an overlapping phenotype, and his father SSS. Only men are affected, suggesting incomplete penetrance (7).

This unusual family case with heterozygous SCN5A mutation, with only male members affected, most probably belongs to a cluster of syndromes described in different countries as the nightmares bangungut/sudden unexpected nocturnal death syndrome (Philippines), lai-tai (Thailand and Laos), and pokkuri (Japan). Monanski et al. reported that the novel NM_198056.2:c.1111C>T (p.Gln371*) heterozygous variant in the SCN5A gene is associated with a severe form of BrS and other phenotypes such as conduction disturbances or SSS. They reported segregation with BrS in a family and evidence of pathogenicity of this heterozygous variant in the *SCN5A* gene (8). These observations together strongly support a pathogenic role for this variant (9).

**TABLE 1 Possible Clinical Scenarios in Which Right-Axis Deviation Can Be Observed**

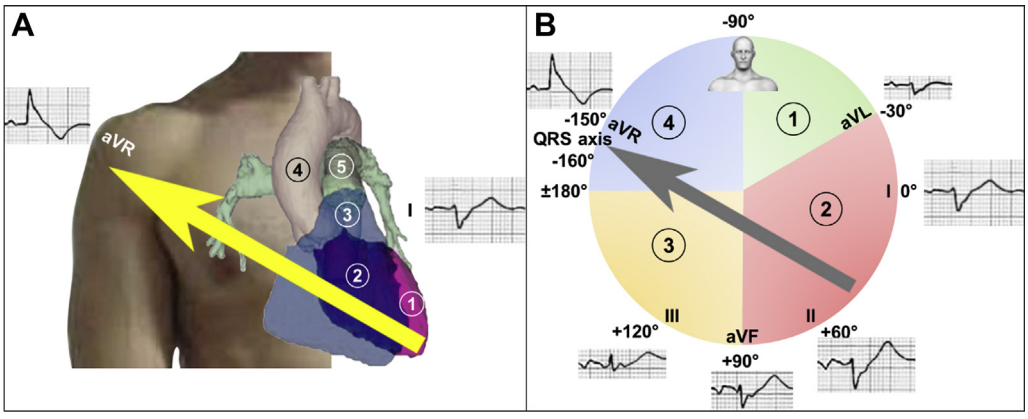
| Clinical Scenario | Details |
|---|---|
| ECG lead misplacement | Reversal of right arm and left leg cables |
| Altered position of the heart in the chest | Dextrocardia |
| Ventricular rhythm | Ventricular tachycardia<br>Accelerated idioventricular rhythm<br>Ventricular escape rhythm |
| Severe hyperkalemia | |
| Drug intoxication | Tricyclic antidepressant, sodium channel blocker |
| Pulmonary emphysema | "Type C" right ventricular hypertrophy |
| Right superior fascicular block* | |

*Previously described in patients with Brugada syndrome (1,2).

## MANAGEMENT

As there was suspicion of BrS, the patient was considered Class IIa (8) for implantable cardioverter defibrillator (ICD) placement because he had a spontaneous type 1 Brugada ECG pattern and a history of

**FIGURE 3 Ventricular Depolarization in the Frontal Plane**




**(A)** 1: Left ventricle; 2: right ventricle; 3: right ventricular outflow tract; 4: Aortic root; 5: pulmonary artery. **(B)** 1: left axis deviation; 2: normal QRS axis; 3: right axis deviation; 4: extreme right axis deviation. **Arrows** = direction of ventricular depolarization.

repetitive syncope. He refused ICD placement; oral quinidine was initiated and clinical orientations, following the Heart Rhythm Society/European Heart Rhythm Association/Asia Pacific Heart Rhythm Society (HRS/EHRA/APHRS) expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes (10).

## FOLLOW-UP

After 90 days of quinidine administration, the patient remained asymptomatic, and the spontaneous type 1 Brugada ECG pattern disappeared (**Figure 2B**). Quinidine is known to work especially well in preventing arrhythmias that are polymorphic and start with a short coupling interval as in patients with BrS (11,12). This drug inhibits the potassium current Ito in ventricular epicardial cells, thus restoring electrical homogeneity and abolishing phase 2 re-entrant activity (13). Ito inhibition by quinidine is probably the most clinically relevant effect of this drug in BrS (11,14).

## CONCLUSIONS

Heterozygous *SCN5A* mutations seem to lead to severe clinical disease entities with overlapping ECG manifestations. An extreme right QRS axis deviation could be an even more severe expression than the aVR sign and the S-wave in lead I sign. However, further studies are warranted to describe the long-term consequences of harboring compound heterozygous mutations of the *SCN5A*. Additional genetic variation is one of the explanations for the low penetrance and variable clinical phenotypes.

## AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr. Andrés Ricardo Pérez-Riera, Rua Nicolau Barreto, 258, Vila Cordeiro, São Paulo-SP 04583-000, Brazil. E-mail: riera@uol.com.br.

## REFERENCES

**1.** Pérez-Riera AR, Ferreira C, Schapachnik E. Value of 12 lead electrocardiogram and derived methodologies in the diagnosis of Brugada disease. In: Antzelevitch C, Brugada P, Brugada J, et al., editors. The Brugada Syndrome From Bench to Bedside. Hoboken, NJ: Blackwell Futura Publishing, 2005:87–110.

**2.** Pérez-Riera AR, Ferreira Filho C, de Abreu LC, et al. Do patients with electrocardiographic Brugada type 1 pattern have associated right bundle branch block? A comparative vectorcardiographic study. Europace 2012;14:889–97.

**3.** Babai Bigi MA, Aslani A, Shahrzad S. aVR sign as a risk factor for life-threatening arrhythmic events in patients with Brugada syndrome. Heart Rhythm 2007;4:1009–12.

**4.** Ragab AAY, Houck CA, van der Does L, et al. Usefulness of the R-wave sign as a predictor for ventricular tachyarrhythmia in patients with Brugada syndrome. Am J Cardiol 2017;120:428–34.

**5.** Calo L, Giustetto C, Martino A, et al. A new electrocardiographic marker of sudden death in Brugada syndrome: the S-wave in lead I. J Am Coll Cardiol 2016;67:1427–40.

**6.** Pérez-Riera AR, Daminello Raimundo R, Watanabe RA, et al. Cardiac sodium channel, its mutations and their spectrum of arrhythmia phenotypes. J Hum Growth Dev 2016;26:281–96.

**7.** Giudicessi JR, Ackerman MJ. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. Transl Res 2013;161:1–14.

**8.** Herfst LJ, Potet F, Bezzina CR, et al. Na+ channel mutation leading to loss of function and non-progressive cardiac conduction defects. J Mol Cell Cardiol 2003;35:549–57.

**9.** Monasky MM, Micaglio E, Giachino D, et al. Genotype-phenotype correlation in a family with Brugada syndrome harboring the novel p.Gln371* nonsense variant in the SCN5A gene. Int J Mol Sci 2019;20:5522.

**10.** Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–63.

**11.** Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004;110:1731–7.

**12.** Belhassen B, Viskin S, Fish R, et al. Effects of electrophysiologic-guided therapy with class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:1301–12.

**13.** Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol 2001;12:268–72.

**14.** Imaizumi Y, Giles WR. Quinidine-induced inhibition of transient outward current in cardiac muscle. Am J Physiol 1987;253:H704–8.

**15.** el-Sherif N, Bekheit SS, Henkin R. Quinidine-induced long QTU interval and torsade de pointes: role of bradycardia-dependent early afterdepolarizations. J Am Coll Cardiol 1989;14:252–7.

**16.** Nasir K, Bomma C, Tandri H, et al. Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. Circulation 2004;110:1527–34.

**KEY WORDS** peripheral right blocks, right distal blockages, terminal conduction delay, zonal right conduction defect, zonal right blocks