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ORIGINAL ARTICLE

Electrocardiographic variables associated with underlying Brugada syndrome or drug-induced Type 1 Brugada pattern in patients with slow/fast atrioventricular nodal reentrant tachycardia

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Abstract

Background: The coexistence of clinical atrioventricular nodal reentrant tachycardia (AVNRT) and drug-induced type 1 Brugada pattern (DI-Type 1 BrP) has been previously reported. The present study was designed to determine the 12-lead ECG characteristics at baseline and during AVNRT and to identify a subset of 12-lead ECG variables of benefit associated with underlying Brugada syndrome (BrS)/DI-Type 1 BrP among patients with slow/fast AVNRT.

Methods: A total of 40 (11 numerical/29 categorical) 12-lead ECG parameters were analyzed and compared between patients with ($n = 69$) and without ($n = 104$) BrS/DI-Type1-BrP matched for age, female gender, body mass index, left ventricular ejection fraction and comorbid conditions. Five distinct types of ECG pattern (Type A/B/C/D/E) in V1–V2 leads during AVNRT were defined.

Results: A total of nine electrocardiographic variables, four at baseline, and five during AVNRT were identified. At baseline, patients with BrS/DI-Type 1 BrP had higher prevalence of interatrial block, leftward shift of frontal plane QRS axis, the absence of normal QRS pattern (the presence of rSr' pattern or type 2/3 Brugada pattern) in V1–V2 and QRS fragmentation in inferior leads compared to patients without BrS/DI-Type 1 BrP. During AVNRT, patients with BrS/DI-Type 1 BrP had higher prevalence of Type A ECG pattern ("coved-type" ST-segment elevation) in V1–V2, Type C ECG pattern (pseudo-r' deflection in V_1 and "RBBB-like" pattern in V_2), pseudo-r' deflection in V_1, QRS fragmentation in inferior leads and "isolated" QRS fragmentation/notching/slurring in aVL compared to patients without BrS/DI-Type 1 BrP.

Conclusions: We identify several electrocardiographic variables that point to an underlying type 1 BrP among patients with slow/fast AVNRT.

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KEYWORDS
atrioventricular nodal reentrant tachycardia, ECG, electrocardiography, J wave syndromes, supraventricular tachycardia

1 | INTRODUCTION

Brugada syndrome (BrS) is an inherited cardiac arrhythmia syndrome characterized by a distinct ST-segment elevation in the right precordial leads in the absence of structural heart disease.[1] Type 1 ("coved type") ST-segment elevation is considered diagnostic of BrS. It can be present either spontaneously or induced by fever or by sodium channel blockers.[1] BrS and drug-induced type 1 Brugada ECG pattern (DI-Type 1 BrP) has been shown to be associated with atrial arrhythmias, atrial fibrillation, atrioventricular nodal reentrant tachycardia (AVNRT), and atrioventricular accessory pathways in particular.[2–4]

AVNRT is the most common form of paroxysmal supraventricular tachycardia. The coexistence of clinical AVNRT and DI-Type 1 BrP has been previously reported.[3] The identification of coexisting BrS/DI-Type 1 BrP among patients with AVNRT has electrophysiologic implications from a mechanistic point of view and clinical relevance that will allow physicians to treat their patients more effectively without exposing them to concealed drug cardiotoxicities.[1] The present study was designed to determine the 12-lead ECG characteristics at baseline and during AVNRT and to identify ECG parameters and other variables that may be helpful in identifying the presence of concealed BrS/DI-Type 1 BrP among patients with slow/fast AVNRT.

2 | METHODS

2.1 | Study population

Three hundred thirty-six consecutive, unrelated patients undergoing electrophysiologic study and catheter ablation for symptomatic, drug-resistant AVNRT were retrospectively included in a case–control observational study between July 2011 and November 2019. All patients underwent ajmaline challenge test (ACT). A type 1 BrP ECG was uncovered in 84 of 336 (25%) patients. One hundred sixty-three patients (with BrS/DI-Type 1 BrP [$n = 15$] and without BrS/DI-Type 1 BrP [$n = 148$]) were excluded owing to the following reasons: the presence of structural heart disease ($n = 101$) including coronary artery disease (≥70% stenosis of any major epicardial vessel), hypertensive heart disease, rheumatic heart disease, congenital heart disease, primary cardiomyopathies, and premature ventricular contraction (PVC)-induced cardiomyopathy, the presence of functional/fixed bundle branch block ($n = 24$), slow/slow ($n = 11$), fast/slow ($n = 1$), and left variant AVNRT ($n = 1$), current use of medications known to affect cardiac depolarization and/or repolarization ($n = 4$), severe COPD ($n = 4$), subclinical hypothyroidism ($n = 1$), and lack of clinical AVNRT ECGs ($n = 16$). The remaining 173 patients (125 women/48 men; mean age 43 ± 14.2 years; range 18 to 69) with slow/fast AVNRT and without overt structural heart disease formed the patient population. All patients were in normal sinus rhythm. Twelve-lead ECG characteristics at baseline (resting in the supine position) and during AVNRT were analyzed. All study subjects were of Turkish (Anatolian Caucasian) descent. Study protocol was approved by the Ethics Committee of Ege University School of Medicine. All patients agreed to participate in the study and gave written informed consent.

2.2 | Definition of Brugada syndrome and Drug-Induced type 1 Brugada ECG pattern

BrS was defined according to the J-Wave syndromes expert consensus conference report.[1] Diagnosis of probable and/or definite BrS, possible BrS, or a nondiagnostic score were assigned scores of ≥3.5, 2 to 3, and <2 points, respectively.[1] Type 1 BrP in at least one right precordial lead during ACT with an assigned score of zero was defined as DI-Type 1 BrP.

2.3 | Definition of electrocardiographic characteristics

All subjects had a baseline 12-lead ECG with leads in the standard lead position. Twelve-lead ECG recordings were performed by a standard electrocardiograph (ECG-9132K, Nihon Kohden Corporation) with standard settings (paper speed of 25 mm/s and a gain setting of 10 mm/mV) and summary report (showing median P-QRS-T complexes for each lead) in all subjects. Standard filter settings of 75, 100, and 150 Hz were used. We evaluated the digital ECGs at 400% size on a PC monitor and measured each parameter as well as fragmentation of the QRS complex. A total of 40 12-lead ECG parameters (numerical, $n = 11$) and other variables (categorical, $n = 29$) were analyzed in the study. P-wave indices including P-wave duration, P-wave axis, the presence of interatrial block (partial or advanced), and the presence of abnormal (≥0.04 mm/s) P-wave terminal force in lead V_1 were measured and defined according to previously described criteria.[5–7] PQ and QTc intervals and QRS duration were measured manually in lead II at baseline. Baseline heart rate, P-wave, QRS, and T-wave axis were automatically analyzed. Type 1/2/3 Brugada patterns, rSr' pattern (QRS duration <110 ms) in V1–V2, early repolarization patterns, QRS fragmentation, and mean frontal plane QRS axis were defined according to previously described criteria.[1,8–13]

Every patient had 12-lead ECG during their index clinical arrhythmia. Twelve-lead ECGs were analyzed for the rate of spontaneous

AVNRT, the presence of pseudo-r' deflection in lead V_1, pseudo-S wave in inferior leads, P-in-QRS pattern (the absence of pseudo-r' deflection in lead V_1 and pseudo-S wave in inferior leads), QRS fragmentation, QRS alternans (≥3 s in duration), the presence of any ST-segment elevation (measured 80 ms after the J-point) in leads V1–V2, highest ST-segment elevation amplitude in leads V1–V2 and the presence and location of horizontal/downsloping ST-segment depression (≥0.1 mV persisting 80 ms after the J-point) in at least two consecutive leads. The presence of "isolated" QRS fragmentation and notching or slurring in lead aVL was analyzed similar to previously described single lead prognostic ECG findings among patients with BrS.[14,15]

Five distinct types of ECG pattern in V1–V2 leads during AVNRT based on ST-segment elevation pattern, QRS morphology, and the presence of pseudo-r' deflection were defined (Figure 1): Type A is characterized by "coved-type" ST-segment elevation (≥0.1 to <0.2 mV) in V_1 and/or V_2 lead. Type B is characterized by "saddleback type" ST-segment elevation (≥0.05 to <0.2 mV) in V_1 and/or V_2 lead. Type C is characterized by the presence of pseudo-r' deflection in V_1 with no or minimal (<0.05 mV) ST-segment elevation and "right bundle branch block (RBBB)-like" pattern in V_2. Type D is characterized by pseudo-r' deflection in V_1 without ST-segment elevation. Type E is characterized by P-in-QRS pattern in V_1 and V_2 without ST-segment elevation.

2.4 | Acquisition of Data

The presence of additional spontaneous and/or inducible AVNRT with 2:1 response, atrial (focal atrial tachycardia, atrial fibrillation and frequent [>10/hour] premature atrial contractions) and ventricular arrhythmias (frequent [>10/hour], monomorphic PVCs and/or ventricular tachycardia [VT]) was obtained in all patients.

All study subjects underwent transthoracic echocardiography for the evaluation of valves, right and left ventricular size and function. All patients underwent electrophysiologic study and catheter ablation. None of the patients underwent programmed ventricular stimulation for inducible ventricular arrhythmia. The diagnosis of AVNRT was made based on previously described criteria.[16]

ACT (Gilurytmal®, CARINOPHARM GmbH) was performed according to the J-Wave syndromes expert consensus conference report.[1]

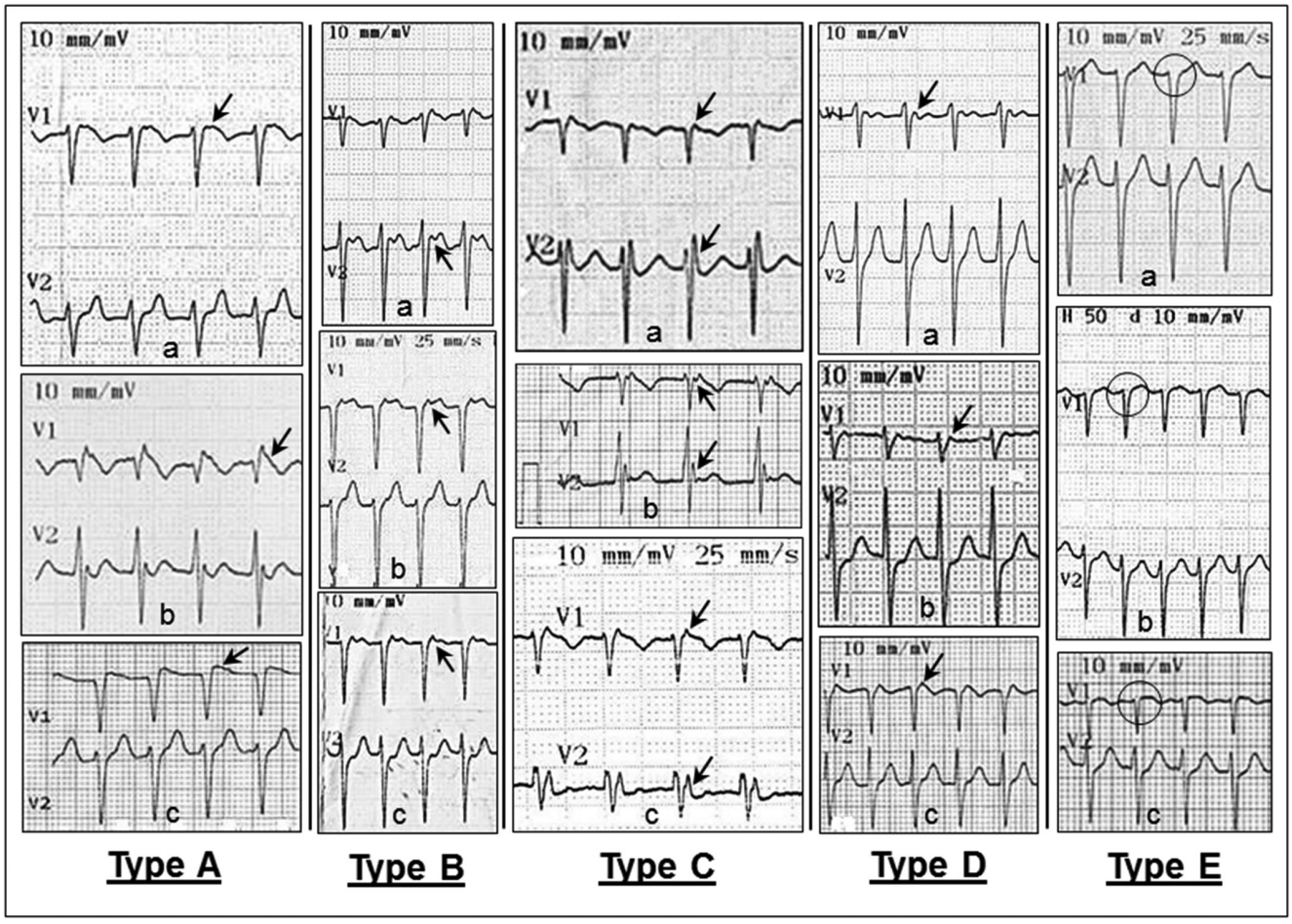

FIGURE 1 Types of electrocardiographic patterns in V1–V2 leads during atrioventricular nodal reentrant tachycardia. Three representative examples (a/b/c) are presented for each type. Arrows and circles indicate the site of interest. All electrocardiograms were recorded at a paper speed of 25 mm/s and a gain setting of 10 mm/mV

2.5 | Statistical analysis

Normally distributed variables were presented as mean ± standard deviation and compared using Student's *t*-test. Non-normally distributed variables were presented as median and compared using Mann–Whitney *U* test. Categorical variables were compared using Pearson's chi-squared and Fisher's exact test. A value of $p < 0.05$ (two-sided) was considered statistically significant.

3 | RESULTS

3.1 | Demographic and clinical characteristics

There were 69 patients with BrS/DI-Type 1 BrP (probable and/or definite BrS [$n = 1$], possible BrS [$n = 10$], nondiagnostic BrS [$n = 4$] and DI-Type 1 BrP [$n = 54$]) and 104 patients without BrS/DI-Type 1 BrP in the patient population. Patients with BrS/DI-Type 1 BrP were matched to patients without BrS/DI-Type 1 BrP in terms of mean age, female gender, mean body mass index, the presence of diabetes mellitus, systemic hypertension, and mean left ventricular ejection fraction (Table 1). Patients with BrS/DI-Type 1 BrP presented with a higher prevalence of chest pain compared to patients without BrS/DI-Type 1 BrP (33.3% vs. 15.4%, $p = 0.006$, respectively).

Seven (10.1%) patients developed monomorphic PVCs only ($n = 5$) and monomorphic PVCs and nonsustained VT ($n = 2$) during ACT among patients with BrS/DI-Type 1 BrP. None of the patients without BrS/DI-Type 1 BrP developed any type of ventricular arrhythmia during ACT.

One patient (54-year-old male) with possible BrS with a Shanghai score of 3 presented with one episode of unexplained syncope along with episodes of reflex syncope. He underwent single chamber defibrillator implantation. He received one appropriate shock for sustained monomorphic VT associated with presyncope within 2 years of implantation. The remaining 10 patients with probable and/or definite or possible BrS were followed closely without any diagnostic and/or therapeutic interventions. None of the patients had history of cardiac arrest.

3.2 | Electrocardiographic characteristics at baseline and during AVNRT

Electrocardiographic characteristics at baseline and during AVNRT in patients with and without BrS/DI-Type 1 BrP are presented in Table 2.

Mean frontal plane QRS axis at baseline as a numerical variable arbitrarily divided into three groups as <0°, 0 to 61° and >61° was observed in 31.9% versus 13.5%, 60.9% versus 65.4% and 7.2% versus 21.2% ($p = 0.002$) of patients with and without BrS/DI-Type 1 BrP, respectively.

The presence of ST-segment elevation in V_1 and/or V_2 leads during AVNRT in the entire study population was correlated with the presence of abnormal P-wave terminal force in lead V_1 ($p = 0.021$), shorter

TABLE 1 Comparison of demographic and clinical characteristics of patients with and without Brugada syndrome/drug-induced Type 1 Brugada ECG pattern

Variable	Patients with BrS/DI-Type 1 BrP ($n = 69$)	Patients without BrS/DI-Type 1 BrP ($n = 104$)	*p*-value
Age (years)	43.2 ± 13.1	43.1 ± 14.9	0.975
Age of onset of AVNRT (years)	29.6 ± 13.4	31.5 ± 15.3	0.418
Female gender	51 (73.9)	74 (71.2)	0.691
Presenting symptoms			
Palpitations	68 (98.6)	104 (100)	0.399
Chest pain	23 (33.3)	16 (15.4)	0.006
Syncope	18 (26.1)	21 (20.2)	0.364
Reflex syncope	13 (18.8)	14 (13.5)	0.340
AVNRT-related syncope	5 (7.2)	7 (6.7)	0.896
Unexplained syncope	1 (1.45)	0	1.000
Presence of systemic hypertension	16 (23.2)	32 (30.8)	0.276
Presence of diabetes mellitus	9 (13)	18 (17.3)	0.449
Body mass index (kg/m^2)	27.2 ± 5.5	26.9 ± 6.8	0.747
Left ventricular ejection fraction (%)	64.7 ± 4.5	63.9 ± 3.9	0.286

Note: Data are given as mean ± SD, number of patients and percentages. $p < 0.05$ considered to be significant.

Abbreviations: AVNRT, atrioventricular nodal reentrant tachycardia; BrS, Brugada syndrome; DI-Type 1 BrP, drug-induced Type 1 Brugada ECG pattern.

TABLE 2 Comparison of electrocardiographic characteristics of patients with and without Brugada syndrome/drug-induced Type 1 Brugada ECG pattern at baseline and during atrioventricular nodal reentrant tachycardia

Variable	Patients with BrS/DI-type 1 BrP (*n* = 69)	Patients without BrS/DI-type 1 BrP (*n* = 104)	*p*-value
12-lead ECG characteristics at baseline			
Heart rate (bpm)	76.7 ± 13.6	75.2 ± 13.6	0.487
P-wave indices			
P-wave duration (ms)	106.9 ± 15.3	104.2 ± 12.8	0.207
P-wave axis (°)[a]	41 (9 to 90)	45.5 (−53 to 81)	0.655
Interatrial block	21 (30.4)	18 (17.3)	0.043
Abnormal P-wave terminal force in V_1	19 (27.5)	18 (17.3)	0.108
PQ interval (ms)	151.1 ± 22.2	144.7 ± 19.4	0.053
QTc interval (ms)	422.4 ± 23	420.9 ± 23.2	0.671
QRS duration (ms)	91.2 ± 9.6	86.3 ± 8.7	0.001
Frontal plane QRS axis (°)[a]	21 (−69 to 88)	36.5 (−38 to 95)	0.001
Left axis deviation	6 (8.7)	1 (1.0)	0.017
Left anterior fascicular block	4 (5.8)	0	0.024
Left posterior fascicular block	0	1 (1.0)	1.000
Low QRS voltage	5 (7.2)	12 (11.5)	0.353
T-wave Axis (°)[a]	34 (−21 to 90)	34 (−30 to 90)	0.231
Normal QRS pattern in V1–$V_{2/4^{th}\ ICS}$	53 (76.8)	102 (98.1)	<0.0001
rSr' pattern in V1–$V_{2/4^{th}\ ICS}$	11 (15.9)	1 (1.0)	0.005
Type 2/3 Brugada pattern in V1–$V_{2/4^{th}\ ICS}$	5 (7.2)	1 (1.0)	0.038
QRS fragmentation in inferior leads	55 (79.7)	62 (59.6)	0.006
QRS fragmentation in lateral leads	13 (18.8)	18 (17.3)	0.797
QRS fragmentation in V_{1-5}	22 (31.9)	30 (28.8)	0.670
Isolated QRS fragmentation in aVL	34 (49.3)	55 (52.9)	0.642
Early repolarization pattern in inferior leads	6 (8.7)	32 (30.8)	0.001
Early repolarization pattern in lateral leads	22 (31.9)	34 (32.7)	0.911
Isolated QRS notching/slurring in aVL	32 (46.4)	39 (37.5)	0.245
12-lead ECG characteristics during AVNRT			
Spontaneous AVNRT rate (cycle length/ms)	345 ± 36	337 ± 49	0.228
Pseudo-r' deflection in V_1	65 (94.2)	76 (73.1)	0.001
Pseudo-S wave in inferior leads	50 (72.5)	63 (60.6)	0.108
P-in-QRS pattern in V_1 and inferior leads	2 (2.9)	21 (20.2)	0.001
QRS Alternans	27 (39.1)	27 (26.0)	0.067
QRS fragmentation in inferior leads	31 (44.9)	25 (24.0)	0.004
QRS fragmentation in lateral leads	1 (1.4)	3 (2.9)	0.538
QRS fragmentation in V_{1-5}	3 (4.3)	0	0.032
Isolated QRS fragmentation in aVL	23 (33.3)	19 (18.3)	0.024
Isolated QRS notching/slurring in aVL	52 (75.4)	62 (59.6)	0.032
ST-segment depression in inferolateral leads	32 (46.4)	49 (47.1)	0.924
ST-segment Elevation in V1–V2	33 (47.8)	41 (39.4)	0.274
Highest ST-segment elevation amplitude in V1–V2 (mV)[a]	0.094 (0.024 to 0.169)	0.075 (0.024 to 0.172)	0.479
Type of ECG pattern in V1–V2			
Type A	8 (11.6)	1 (1.0)	0.002
Type B	9 (13.0)	24 (23.1)	0.100

(Continues)

TABLE 2 (Continued)

Variable	Patients with BrS/DI-type 1 BrP (*n* = 69)	Patients without BrS/DI-type 1 BrP (*n* = 104)	*p*-value
Type C	14 (20.3)	5 (4.8)	0.001
Type D	35 (50.7)	47 (45.2)	0.475
Type E	3 (4.3)	27 (26.0)	0.001
Coexisting arrhythmias			
Spontaneous/inducible AVNRT with 2:1 response	4 (5.8)	4 (3.8)	0.550
Spontaneous atrial arrhythmias (focal AT/AF/PACs)	1 (1.4)	6 (5.8)	0.158
Spontaneous ventricular arrhythmias (PVC and/or VT)	7 (10.1)	8 (7.7)	0.575

Note: Data are given as mean ± SD, number of patients and percentages. [a]Data are given as median and range. $p < 0.05$ considered to be significant.
Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; PAC, premature atrial contraction; PVC, premature ventricular contraction; VT, ventricular tachycardia.

tachycardia cycle length (330.6 ± 38.5 vs. 347.7 ± 47.5 ms, $p = 0.012$), the presence of pseudo-r' deflection in lead V_1 ($p < 0.0001$), and ST-segment depression in inferolateral leads ($p < 0.0001$) among all the demographic and electrocardiographic characteristics.

At baseline, patients with BrS/DI-Type 1 BrP had higher prevalence of interatrial block, leftward shift of frontal plane QRS axis, the absence of normal QRS pattern (the presence of rSr' pattern or type 2/3 Brugada pattern) in V1–V2 and QRS fragmentation in inferior leads compared to patients without BrS/DI-Type 1 BrP (Table 2). During AVNRT, patients with BrS/DI-Type 1 BrP had higher prevalence of Type A ECG pattern ("coved-type" ST-segment elevation) in V1–V2, Type C ECG pattern (pseudo-r' deflection in V_1 and "RBBB-like" pattern in V_2), pseudo-r' deflection in V_1, QRS fragmentation in inferior leads and "isolated" QRS fragmentation/notching/slurring in aVL compared to patients without BrS/DI-Type 1 BrP (Table 2).

Representative examples of the above-mentioned electrocardiographic characteristics in patients with DI-Type 1 BrP are illustrated in Figure 2.

4 | DISCUSSION

Clinical, spontaneous AVNRT frequently coexists with DI-Type 1 BrP.[3] The identification of coexisting BrS/DI-Type 1 BrP among patients with AVNRT has important epidemiologic, electrophysiologic and clinical implications.[1] In this study, we identified nine electrocardiographic parameters and other variables at baseline and during slow/fast AVNRT that point to an underlying type 1 BrP.

4.1 | Electrocardiographic variables associated with underlying BrS/DI-Type 1 BrP

The world-wide prevalence of a Brugada ECG pattern (type 1, 2, and 3) in the general population is estimated to be 0.5 to 1.6 per 1000.[1] An rSr' pattern in the right precordial leads is a relatively common electrocardiographic finding.[8] The prevalence of incomplete RBBB (QRS duration between 110 and 120 ms) in general population is 3.5%.[17] The prevalence of rSr' pattern in V1–V2 with a normal QRS duration (<110 ms) in adult population is currently unknown. In our study population, the prevalence of rSr' pattern in V1–V2 with a normal QRS duration and type 2/3 BrP in V1–V2 at baseline were more common in patients with BrS/DI-Type 1 BrP compared to patients without BrS/DI-Type 1 BrP. The absence of normal QRS pattern (either the presence of rSr' pattern or type 2/3 Brugada pattern) in V1–V2 at baseline was a strong electrocardiographic variable associated with underlying BrS/DI-Type 1 BrP.

Interatrial block is a distinct electrocardiographic pattern describing the conduction delay between the right and left atria through Bachmann's bundle.[18] Histologic studies have identified atrial fibrosis as the pathological substrate of interatrial block.[18] Advanced age, systemic hypertension, coronary artery disease, obstructive sleep apnea, cardiac amyloid and catheter ablation along with genetic susceptibility are known risk factors for interatrial blocks.[18] Underlying BrS/DI-Type 1 BrP may be an additional contributing factor for interatrial block and generation of reentrant circuits in AVNRT.

Left axis deviation is a common finding in patients with BrS with a prevalence of 9.5%.[19] It is believed to be caused by conduction slowing in the more proximal conduction system rather than conduction slowing in the right ventricular outflow tract.[20] In our study population, the prevalence of left axis deviation was more common in patients with BrS/DI-Type 1 BrP ($n = 6$, [BrS = 1] and [DI-Type 1 BrP = 5]) compared to patients without BrS/DI-Type 1 BrP ($n = 1$). Leftward shift of baseline frontal plane QRS axis was a strong electrocardiographic parameter associated with underlying BrS/DI-Type 1 BrP.

QRS fragmentation in inferior leads has been reported among patients with BrS with a prevalence of 29.6%.[21] It most likely reflects global involvement of the heart outside of the right ventricular

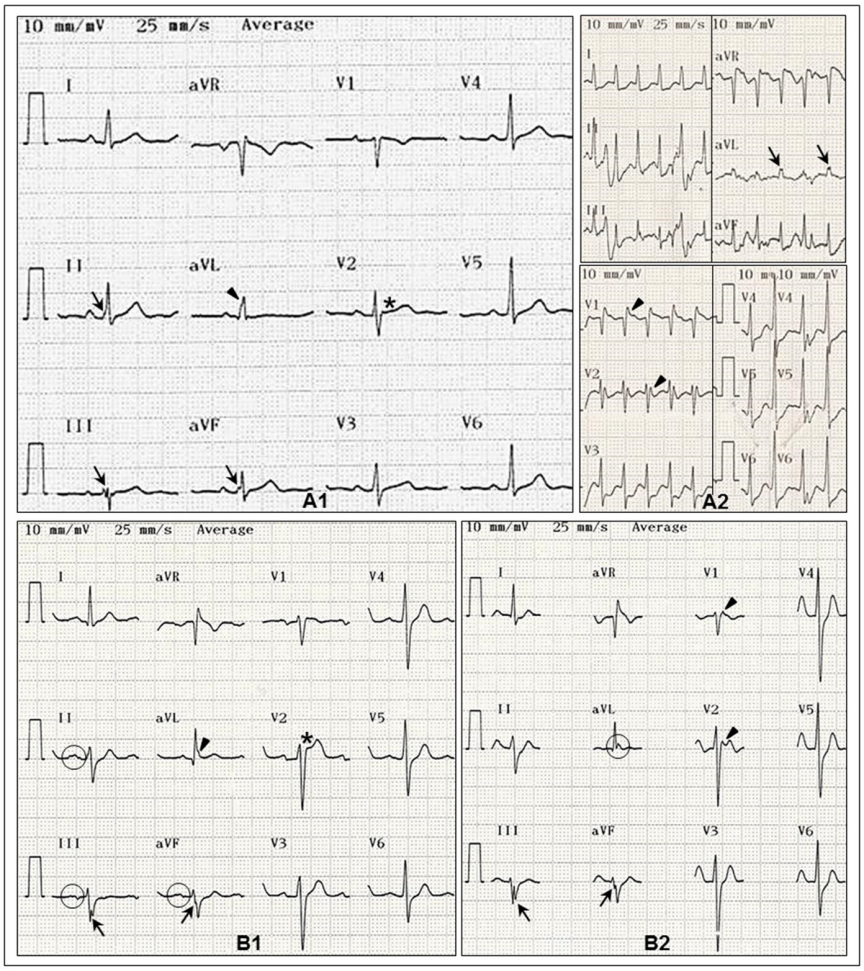

FIGURE 2 Twelve-lead electrocardiograms at baseline (A1/B1) and during atrioventricular nodal reentrant tachycardia (AVNRT) (A2/B2) in two patients with underlying drug-induced type 1 Brugada pattern. A1- patient was a 30-year-old female with a body mass index of 21.3 who presented with a 1-year history of paroxysmal supraventricular tachycardia. She had structurally normal heart with a left ventricular ejection fraction of 65%. She had type 3 Brugada pattern in V_2 (asterisk), QRS fragmentation in lead aVL (arrowhead) and inferior leads (arrows) and frontal plane QRS axis of 34°at baseline. Electrophysiologic study revealed slow/fast AVNRT. A2- she had Type C pattern in V1–V2 (arrowheads), QRS fragmentation in aVL (arrows) and QRS alternans in all precordial leads during AVNRT. B1- patient was a 59-year-old male with a body mass index of 29.4 who presented with a 15-year history of paroxysmal supraventricular tachycardia. He had structurally normal heart with a left ventricular ejection fraction of 68%. He had type 2 Brugada pattern in V_2 (asterisk), QRS notching/slurring in lead aVL (arrowhead), QRS fragmentation in inferior leads (arrows), advanced interatrial block with a P-wave duration of 145 ms (circles) and frontal plane QRS axis of −45°at baseline. Electrophysiologic study revealed slow/fast AVNRT. B2- he had Type B pattern in V1–V2 (arrowheads), QRS notching/slurring in aVL (circle), and QRS fragmentation in inferior leads (arrows) during AVNRT

outflow tract in patients with BrS. Higher prevalence of QRS fragmentation among patients with BrS/DI-Type 1 BrP in our study can be because of different definitions, different clinical characteristics of cohorts (BrS vs. DI-Type 1 BrP) and dynamic nature of QRS fragmentation.

Dynamic nature of J-point and ST-segment elevations at baseline, during exercise test and recovery phase have been studied in patients with BrS and compared with control subjects.[22,23] At baseline, the peak J-point amplitude in V1–V2 was higher in patients with BrS than in control subjects. The peak J-point amplitude increased during exercise test in patients with BrS and control subjects but resulted in a coved-type pattern only in patients with BrS. During recovery, the peak J-point amplitude in V1–V2 increased further in patients with BrS but returned to baseline levels in control subjects. In accordance with these studies, a coved-type pattern (Type A ECG pattern in our study) in V1–V2 during AVNRT was more common in patients with BrS/DI-Type 1 BrP compared to patients without BrS/DI-Type 1 BrP and found to be one of the electrocardiographic findings associated with underlying BrS/DI-Type 1 BrP. We did not find any difference in the frequency and degree of ST-segment elevation in V1–V2 during AVNRT between patients with and without BrS/DI-Type 1 BrP. This lack of difference may be because of higher number of patients with Type B ECG pattern (associated with ST-segment elevation in V1–V2) in patients without BrS/DI-Type 1 BrP and contributing role of potential variables other than faster heart rate for ST-segment elevation in V1–V2 during AVNRT such as the presence

of abnormal P-wave terminal force in lead V_1, shorter tachycardia cycle length, the presence of pseudo-r' deflection in lead V_1, and reciprocal ST-segment depression in inferolateral leads. Faster heart rate has been proposed to produce a potentially arrhythmogenic decrease in the sodium current (I_{Na}) resulting in ST-segment elevation in V1–V2 by oxidant stress, as may occur with fever and ischemia.[24]

Type C ECG pattern during AVNRT can be because of the presence of rSr' pattern during sinus rhythm, higher placement of electrodes in V1–V2, tachycardia-induced functional right bundle branch block, J-point elevation, and retrograde P waves distorting the QRS complex. An rSr' pattern in V1–V2 during sinus rhythm was present in 15.9% and 1.0% of patients with and without BrS/DI-Type 1 BrP, respectively, in our study.

Pseudo-r' deflection in lead V_1 during supraventricular tachycardia is a specific finding for slow/fast type AVNRT, present in 40% to 60% of patients.[25] We have previously reported that patients with DI-Type 1 BrP have higher (92.3% vs. 72.3%) prevalence of pseudo-r' deflection in lead V_1 during AVNRT compared to patients without DI-Type 1 BrP.[3] This finding was explained by longer V-$A_{\text{right atrial appendage}}$ time interval during electrophysiologic study in patients with DI-Type 1 BrP compared to patients without DI-Type 1 BrP.[3] Analysis of the atrial activation sequence during AVNRT in humans revealed that the pseudo-r' deflection in lead V_1 is determined by activation of the superolateral aspect of the right atrium.[26] As a result of this finding, we hypothesize that higher prevalence of pseudo-r' deflection in patients DI-Type 1 BrP may result from the amplified delay in activation of the superolateral aspect of the right atrium.

Several "isolated" QRS complex abnormalities such as a wide and/or large S-wave in lead I or a prominent R-wave in lead aVR have been described as a prognostic risk factor in patients with BrS.[14,15] These ECG characteristics most likely reflect a conduction delay and/or repolarization abnormalities in the right ventricular outflow tract. "Isolated" QRS fragmentation in lead aVL at baseline was a common finding in our study population. We observed a higher prevalence of "isolated" QRS fragmentation in lead aVL during AVNRT in patients with BrS/DI-Type 1 BrP compared to patients without BrS/DI-Type 1 BrP. All patients with "isolated" QRS fragmentation in lead aVL during AVNRT had QRS fragmentation in lead aVL at baseline.

4.2 | Clinical relevance of DI-Type 1 BrP

The coexistence of clinical, spontaneous AVNRT and DI-Type 1 BrP is of potential clinical relevance for the appropriate management of those patients in terms of cautious use of certain antiarrhythmic agents known to exacerbate the Brugada phenotype (Class IC sodium channel blockers, propranolol, and calcium-channel blockers), avoidance of Brugada pattern-inducing noncardiac drugs such as certain selective serotonin reuptake inhibitors and antiepileptic agents, consideration of standard preventative measures such as use of antipyretics during fever, avoidance of unjustified defibrillator implantations, and long-term follow-up of these patients.[1,3]

It has been recently reported that patients with DI-Type 1 BrP have a very low arrhythmic (appropriate defibrillator therapy and sudden cardiac death) risk with an annual incidence of 0.38%.[27] Programmed ventricular stimulation does not help to stratify high-risk patients.[27] Close follow-up without any diagnostic and/or therapeutic interventions is currently recommended in asymptomatic patients with DI-Type 1 BrP.[1,27]

4.3 | Study limitations

Twelve-lead ECGs immediately after termination of AVNRT were not available to determine the dynamic behavior of J-point and ST-segment elevations in V1–V2. The determination of the polarity of P-waves in V_1 during AVNRT is challenging. Therefore, the role of retrograde P-waves in the generation of ST-segment elevation during AVNRT is not conclusive. Number of patients with probable and/or definite BrS was limited.

5 | CONCLUSIONS

Certain electrocardiographic variables such as interatrial block, leftward shift of frontal plane QRS axis, the absence of normal QRS pattern (the presence of rSr' pattern or type 2/3 Brugada pattern) in V1–V2 and QRS fragmentation in inferior leads at baseline and Type A and Type C ECG patterns, pseudo-r' deflection in V_1, QRS fragmentation in inferior leads and "isolated" QRS fragmentation/notching/slurring in aVL during AVNRT can help for identification of coexisting BrS/DI-Type 1 BrP among patients with clinical, spontaneous AVNRT. Larger studies are necessary to validate and improve the electrocardiogram-based detection of our findings particularly with the application of advanced artificial intelligence methods in routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest for this article.

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REFERENCES

1. Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. J Arrhythm. 2016;32:315–39.
2. Eckardt L, Kirchhof P, Loh P, Schulze-Bahr E, Johna R, Wichter T, et al. Brugada syndrome and supraventricular tachyarrhythmias: a novel association? J Cardiovasc Electrophysiol. 2001;12:680–5.
3. Hasdemir C, Payzin S, Kocabas U, Sahin H, Yildirim N, Alp A, et al. High prevalence of concealed Brugada syndrome in patients

with atrioventricular nodal reentrant tachycardia. Heart Rhythm. 2015;12:1584–94.
4. Hasdemir C, Juang JJ, Kose S, Kocabas U, Orman MN, Payzin S, et al. Coexistence of atrioventricular accessory pathways and drug-induced type 1 Brugada pattern. Pacing Clin Electrophysiol. 2018;41:1078–92.
5. Maheshwari A, Norby FL, Roetker NS, Soliman EZ, Koene RJ, Rooney MR, et al. Refining prediction of atrial fibrillation-related stroke using the P_2-CHA_2DS_2-VASc score. Circulation. 2019;139:180–91.
6. Bayés de Luna A, Escobar-Robledo LA, Aristizabal D, Weir Restrepo D, Mendieta G, Massó van Roessel A, et al. Atypical advanced interatrial blocks: definition and electrocardiographic recognition. J Electrocardiol. 2018;51:1091–3.
7. Eranti A, Aro AL, Kerola T, Anttonen O, Rissanen HA, Tikkanen JT, et al. Prevalence and prognostic significance of abnormal P terminal force in lead V1 of the ECG in the general population. Circ Arrhythm Electrophysiol. 2014;7:1116–21.
8. Baranchuk A, Enriquez A, García-Niebla J, Bayés-Genís A, Villuendas R, Bayés de Luna A. Differential diagnosis of rSr' pattern in leads V1–V2. Comprehensive review and proposed algorithm. Ann Noninvasive Electrocardiol. 2015;20:7–17.
9. Macfarlane PW, Antzelevitch C, Haissaguerre M, Huikuri HV, Potse M, Rosso R, et al. The early repolarization pattern: a consensus paper. J Am Coll Cardiol. 2015;66:470–7.
10. Take Y, Morita H. Fragmented QRS: what is the meaning? Indian Pacing Electrophysiol J. 2012;12:213–25.
11. Haukilahti MA, Eranti A, Kenttä T, Huikuri HV. QRS fragmentation patterns representing myocardial scar need to be separated from benign Normal variants: hypotheses and proposal for morphology based classification. Front Physiol. 2016;7:653.
12. Marume K, Noguchi T, Kamakura T, Tateishi E, Morita Y, Miura H, et al. Prognostic impact of multiple fragmented QRS on cardiac events in idiopathic dilated cardiomyopathy. Europace. 2021;23:287–97.
13. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances. J Am Coll Cardiol. 2009;53:976–81.
14. Calò L, Giustetto C, Martino A, Sciarra L, Cerrato N, Marziali M, 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.
15. 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.
16. Nakagawa H, Jackman WM. Catheter ablation of paroxysmal supraventricular tachycardia. Circulation. 2007;116:2465–78.
17. Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City heart study. Eur Heart J. 2013;34:138–46.
18. Power DA, Lampert J, Camaj A, Bienstock SW, Kocovic N, Bayes-Genis A, et al. Cardiovascular complications of interatrial conduction block: JACC state-of-the-art review. J Am Coll Cardiol. 2022;79:1199–211.
19. Atarashi H, Ogawa S, Harumi K, Sugimoto T, Inoue H, Murayama M, et al. Idiopathic ventricular fibrillation investigators. Three-year follow-up of patients with right bundle branch block and ST segment elevation in the right precordial leads: Japanese registry of Brugada syndrome. J Am Coll Cardiol. 2001;37:1916–20.
20. van der Ree MH, Vendrik J, Kors JA, Amin AS, Wilde AAM, Tan HL, et al. Left Axis deviation in Brugada syndrome: Vectorcardiographic evaluation during Ajmaline provocation testing reveals additional depolarization abnormalities. Int J Mol Sci. 2021;22:484.
21. 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;10:e004765.
22. Amin AS, de Groot EA, Ruijter JM, Wilde AA, Tan HL. Exercise-induced ECG changes in Brugada syndrome. Circ Arrhythm Electrophysiol. 2009;2:531–9.
23. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, Noda T, et al. Augmented ST-segment elevation during recovery from exercise predicts cardiac events in patients with Brugada syndrome. J Am Coll Cardiol. 2010;56:1576–84.
24. Aiba T, Farinelli F, Kostecki G, Hesketh GG, Edwards D, Biswas S, et al. A mutation causing Brugada syndrome identifies a mechanism for altered autonomic and oxidant regulation of cardiac sodium currents. Circ Cardiovasc Genet. 2014;7:249–56.
25. Kalbfleisch SJ, el-Atassi R, Calkins H, Langberg JJ, Morady F. Differentiation of paroxysmal narrow QRS complex tachycardias using the 12-lead electrocardiogram. J Am Coll Cardiol. 1993;21:85–9.
26. Kuga K, Li A, Endo M, Niho B, Suzuki A, Enomoto M, et al. Atrial components contributing to pseudo r' deflection in lead V1 in slow/fast atrioventricular nodal reentrant tachycardia: analysis of the atrial activation sequence by basket catheter isochronal mapping. Circ J. 2002;66:236–40.
27. Russo V, Pafundi PC, Caturano A, Dendramis G, Ghidini AO, Santobuono VE, et al. Electrophysiological study prognostic value and long-term outcome in drug-induced type 1 Brugada syndrome: the IBRYD study. JACC Clin Electrophysiol. 2021;7:1264–73.

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