Efficacy and safety of dextrose-insulin in unmasking non-diagnostic Brugada ECG patterns

Enrique Velázquez-Rodríguez, MD,* Horacio Rodríguez-Piña, MD,⁎ Alex Pacheco-Bouthillier, MD,⁎ Marcelo Paz Jiménez-Cruz, MD⁎

Servicio de Electrofisiología, Hospital de Cardiología del Centro Médico Nacional Siglo XXI, División de Cardiología, Unidad Médica de Alta Especialidad, Instituto Mexicano del Seguro Social, Universidad Nacional Autónoma de México, Ciudad de México, México

Abstract

Background: Typical diagnostic, coved-type 1, Brugada ECG patterns fluctuate spontaneously over time with a high proportion of non-diagnostic ECG patterns. Insulin modulates ion transport mechanisms and causes hyperpolarization of the resting potential. We report our experience with unmasking J-ST changes in response to a dextrose–insulin test.

Methods: Nine patients, mean age 40.5 ± 19.4 years (range: 15–65 years), presented initially with a non-diagnostic ECG pattern, which was suggestive of Brugada syndrome (group I). They were compared with 10 patients with normal ECG patterns (group II). Participants received an infusion of 50 g of 50% dextrose, followed by 10 IU of intravenous regular insulin. Positive changes were defined by conversion to a diagnostic ECG pattern.

Results: The dextrose–insulin test was positive in six of seven (85.7%) patients (kappa 0.79, p = 0.02) that was confirmed with a pharmacologic test (kappa 1, p = 0.003). One had an inconclusive test, and two with a negative test had an early repolarization ECG pattern. All subjects in group II had a negative test (p < 0.01). The maximum changes of the J-ST segment were observed 41.3 ± 31.4 minutes (range 3–90 minutes) after dextrose–insulin infusion. One patient had monomorphic ventricular bigeminy without spontaneous or induced ventricular fibrillation.

Conclusion: Changes in J-ST segment in the Brugada syndrome are influenced by glucose–insulin, and this report reproduces and supports the efficacy and safety of this metabolic test in the differential diagnosis of patients with non-diagnostic ECG patterns.

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Keywords: Brugada syndrome; ST elevation; Drug-challenge test; Brugada ECG patterns; Autonomic imbalance; Sodium-channel blocker

Introduction

Brugada syndrome (BrS) is a cardiac disorder characterized by a typical J–ST-segment elevation in right precordial leads, affecting young patients with structurally normal hearts, and is associated with risk of sudden cardiac death (SCD) [1].

According to the 2013 expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, BrS is definitively diagnosed when present spontaneously or after a sodium-channel blocker challenge test shows the typical type-1 ECG pattern (i.e., coved pattern: ≥2 mm ST segment elevation, slowly descending and convex with respect to the isoelectric baseline and negative symmetric T wave in at least one right precordial lead V1 or V2) in either 4th, 3rd, or 2nd intercostal space [2].

However, the level and morphology of the J-ST segment can fluctuate spontaneously over time and even day-to-day; then, the typical diagnostic, coved-type 1 ECG pattern does not show stable expression and is often concealed with a high proportion of transiently diagnostic and non-diagnostic ECG patterns. According to the 2012 consensus report on current ECG criteria for diagnosis of Brugada pattern [3], the types 2 and 3 from the previous consensus [4] were joined and unified in only one: the type-2 ECG pattern (i.e., saddleback pattern: ≥2 mm J point elevation, ≥0.5 mm ST segment slowly descending and concave with respect to the isoelectric baseline and positive or flat T wave in V2 and variable in V1).

This non-diagnostic type-2 ECG pattern is considered to be suggestive but not confirmatory of the disease; then, in these cases, a pharmacologic test is required with a sodium-channel blocker to disclose the typical coved-type 1 ECG pattern [2].
In a prospective study, the prevalence of fluctuations between diagnostic and non-diagnostic ECGs in patients with BrS was high (51%); a significant number (47%) did not show a spontaneous diagnostic basal ECG during the follow-up, and only 2% of patients had a continuous typical diagnostic coved-type 1 ECG pattern [5]. The dynamic changes of J-ST are influenced by several factors, notably the modulatory effects of the autonomic nervous system [6–8].

A spontaneous J–ST-segment change on an ECG is usually seen after meals. This may reflect changes of autonomic modulation by a full stomach (i.e., an increase of vagal activity) [9]. In addition, high vagal tone plays an important role in the occurrence of ventricular tachyarrhythmias in BrS [10,11].

Some investigators have reported that a glucose load can influence J–ST-segment elevation and unmask a coved-type 1 ECG pattern. After the first reports by Watanabe et al. [12] and Nishizaki et al. [13] that high insulin secretion plays a functional role in QT dispersion in both healthy volunteers and patients with congenital long QT syndrome, they also demonstrated that oral glucose load-induced high insulin levels were associated with an increase and morphologic changes in the J-ST segment; this is one of the contributing factors that would explain the dynamic changes of J-ST in patients with BrS [14]. At the same time, Nogami et al. [15] demonstrated a significant accentuation of the abnormal J-ST configuration observed in six patients with BrS with persistent or transient J–ST-segment elevation after glucose and insulin intravenous infusion tests.

Our objective is to report our experience in unmasking the changes in the J-ST segment in response to a metabolic challenge with dextrose–insulin intravenous infusion in a group of patients with non-diagnostic ECG patterns that are suggestive of BrS.

Methods

Study patients

Nine consecutive patients were referred to the arrhythmia clinic between September 2006 and September 2013, with a mean age of 40.5 ± 19.4 years (range: 15–65 years). All nine had a non-diagnostic ECG index pattern (group I). These patients were compared with 10 healthy subjects, mean age 43 ± 11 years (range: 20–60 years), with similar demographic characteristics and normal resting ECG, as a control group (group II). No genetic analysis was performed on any patient.

Metabolic test

Informed consent was obtained from all patients, and metabolic challenge was made in a fasting state with the Nogami et al. [15] modified protocol: 50 g of 50% dextrose solution was infused over 30 minutes through an intravenous catheter, followed by 10 IU of intravenous regular insulin. An ECG was continuously monitored at bedside during 180 minutes, and 12-lead ECGs were recorded at a filter bandwidth of 0.08 Hz and 40 Hz at 10 mm/mV of amplitude and paper speed of 25 and 50 mm/s at the basal state and at anytime, if obvious modifications in the J-ST segment were observed at the bedside monitor. Blood samples were obtained for measurement of serum glucose and potassium at baseline, 60, 120, and 180 minutes after the dextrose–insulin load.

The dextrose–insulin test was considered positive with ≥1 mm J–ST-segment elevation and morphologic changes from non-diagnostic ECG patterns to a typical coved-type 1 ECG pattern. At least two observers who were unaware of the clinical cases reviewed each ECG. No insulin analysis was performed on any patient.

Pharmacologic test

To confirm the effects of the metabolic test, a class IC sodium-channel blocker agent was used in eight of nine patients in group I. The pharmacologic test was made 24 to 48 hours after the dextrose–insulin test. A single oral load dose of 600 mg of propafenone (five subjects) or 2 mg/kg of intravenous propafenone (two subjects) and a single oral load dose of 200 mg of flecainide (one subject) were administered. Bedside ECG monitoring and 12-lead ECGs were recorded with the same protocol as the metabolic challenge group, and a positive pharmacologic test was made according to the expert consensus statement [2,3].

Electrophysiologic study

Before and after dextrose–insulin infusion test, eight patients (89%) in group I underwent electrophysiologic (EP) study that included programmed, high right atrial and right ventricular apex and outflow tract stimulation with a protocol at three drive cycle lengths of 600, 500, and 400 msec, with up to three extrastimuli limited to 200 msec. Only two subjects in group II with unexplained syncope underwent an EP study.

Statistical analysis

Data are expressed as mean ± standard deviation, and the unpaired t-test was used to compare the mean value between the two groups. A p value <0.05 was considered significant. Kappa coefficient test was used to assess the degree of concordance.

Results

The clinical characteristics of patients in group I are listed in Table 1. At the time of the first presentation, no patient had spontaneous coved-type 1 ECG pattern in right precordial lead V1 or V2 in either 2nd, 3rd, or 4th intercostal space; therefore, all nine patients presented initially with a non-diagnostic index ECG. Four of nine patients (44.4%) had a continuous, fixed, typical saddleback-type 2 ECG pattern, and five (55.5%) had a spontaneous J–ST-segment change from typical saddleback-type 2 to barely recognizable ECG (J point amplitude <2 mm, ST elevation <0.5 mm) on different days, and one patient of this subgroup sometimes even had a normal ECG. Both groups of patients had no evidence of structural heart disease based on physical...
examination and echocardiogram, as well as no evidence of diabetes mellitus, renal disorders, metabolic electrolyte imbalance, drug-induced inhibition of the $I_{Na}$ and $I_{Ca}$, or any other underlying clinical conditions; thus, Brugada phenocopy was ruled out [16].

Previous clinical events and family history

As shown in Table 1, six of nine patients in group I were symptomatic (66.6%): three due to recurrent syncope; one of them (patient 1) had aborted SCD due to documented polymorphic ventricular tachycardia degenerated into ventricular fibrillation (VF) and one pre-syncope due to sinus node dysfunction (SND). Only two patients sought medical attention for sustained or intermittent palpitations. Two patients in group II had unexplained syncope with previous negative head-up tilt test.

Four cases had a family history of sudden unexplained death (patients 1 and 9; fathers at unknown and 40 years of age, respectively) and aborted SCD with permanent neurological sequelae (siblings 3 and 4; father at 45 years of age) (Table 1).

Effects of dextrose–insulin test

The dextrose–insulin test was positive in six of nine (66.6%) patients of the group I (Figs. 1 to 4). Only one case (patient 6) was classified with an inconclusive test,
due to <1 mm J–ST-segment elevation (Figs. 5A), (Table 2). The two cases (patients 7 and 8) with a negative test were classified as variants of an early repolarization pattern, according to new electrocardiographic criteria [3] (Fig. 6).

Therefore, in six of seven (85.7%) patients who were converting to a diagnostic coved-type 1 ECG pattern, the diagnosis of BrS was confirmed (kappa 0.79, p = 0.02).
Three of four (75%) patients who initially presented with a fixed saddleback-type 2 ECG pattern changed to diagnostic typical, coved-type 1 ECG pattern (Figs. 1 and 2), and three of five (60%) patients with spontaneous changes between saddleback-type 2 to barely recognizable index ECGs developed a diagnostic coved-type 1 ECG pattern (Figs. 3 and 4). Compared with the group I, all subjects in the control group II had a negative test ($p < 0.01$).

A maximum J-ST elevation with coved-type 1 pattern was observed 41.3 ± 31.4 minutes (range: 3–90 minutes) after the onset of dextrose–insulin load infusion; in the same way, the maximum QTc interval showed a tendency to increase but without statistical significance (QTc 422 ± 27 ms to 435 ± 20 ms, $p \text{NS}$).

Regarding the induction of arrhythmias, only one case in group I (patient 1) developed long-lasting monomorphic PVCs in bigeminy rhythm, suggesting RVOT origin simultaneously with elevation of the J-ST segment (Fig. 1B). There were no direct relationships between the time of the maximum J-ST changes and glucose and potassium plasma levels. Impaired glucose tolerance was not documented in either group. One patient in the control group II had asymptomatic hypoglycemia (68 mg/dL).

Effects of pharmacologic test

All patients with a positive dextrose–insulin test were also positive for the sodium-channel blocker test, in addition to the case (patient 6) with a dextrose–insulin test not conclusive that was unmasked by oral propafenone ($kappa$ 1, $p < 0.003$) (Fig. 5B). Therefore, the pharmacologic test was positive in seven of seven cases (100%) with definitive diagnosis of BrS (Table 2). One case with a negative dextrose–insulin test (patient 8) was excluded from the pharmacologic test by history of rate-dependent left bundle branch block (documented by Holter, treadmill exercise test and EP study) and was classified as early repolarization pattern.

We observed a non-significant tendency to a faster positive response and higher ST segment elevation ($p = \text{NS}$) but a significant wider QRS complex with class IC sodium-channel blocker agents versus dextrose–insulin test (108 ± 8 ms vs. 116 ± 7 ms, $p < 0.05$) (Fig. 3). No subject in the control group II underwent pharmacologic challenge test.

Arrhythmias during electrophysiologic study

In the cases (patients 3 and 6) with spontaneous and intermittent SND, this was confirmed by abnormal corrected sinus node recovery time. No patients had inducible, ventricular, life-threatening arrhythmias at the baseline state. Programmed right atrial stimulation triggered reproducible sustained typical atioventricular nodal reentrant tachycardia and sustained atrial tachycardia (patients 3 and 4, respectively); both never had a history of palpitations and/or ECG-documented tachycardias. The case with history of spontaneous typical atrial flutter (patient 6) was non-inducible. EP testing was negative in the two patients in group II with unexplained syncope (Table 2).

After the dextrose–insulin test, programmed ventricular stimulation triggered polymorphic ventricular tachycardia that degenerated into VF in only one case (patient 2). It is noteworthy that this patient was in the asymptomatic group. One case (patient 6 with Stokes–Adams syncope) had reproducible nonsustained polymorphic ventricular tachycardia.

Follow-up

Four of seven (57%) patients with a non-diagnostic index ECG remained unchanged, one had intermittent normal ECG, and two patients (28.5%) showed evidence of intermittent typical coved-type 1 ECG pattern (by 12-lead ECG or 24-hour Holter monitoring) (Fig. 5C). An implantable cardioverter defibrillator was indicated in three patients (1, 2, and 6) (Table 2) with no evidence of therapeutic shocks during a mean follow-up of 36 months (range: 24–48 months). Only one
Fig. 5. A: Left. Non-diagnostic ECG index pattern (V1 and V2 at 3rd intercostal space). Right: Inconclusive dextrose–insulin test (≤1 mm J–ST-segment elevation). B: Non-diagnostic ECG index pattern (V1 and V2 at 4th intercostal space). Previous case with inconclusive dextrose–insulin test. The pharmacologic test with an oral load dose of propafenone (600 mg) unmasked the typical coved-type 1 Brugada pattern. C: Spontaneous ECG pattern (Holter). (Patient 6).

Table 2
Test response, electrophysiologic findings, and treatment.

<table>
<thead>
<tr>
<th>Test response, electrophysiologic findings, and treatment.</th>
<th>Metabolic test</th>
<th>Pharmacologic test</th>
<th>Class IC drug</th>
<th>EPS findings</th>
<th>VAI post</th>
<th>Definitive diagnosis</th>
<th>Treatment</th>
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<tr>
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<td>+</td>
<td>Flecainide</td>
<td>Normal</td>
<td>Brugada</td>
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<td>ICD class I Evidence A</td>
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<td>+</td>
<td>Propafenone</td>
<td>Normal</td>
<td>VF</td>
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<td>ICD class Ila Evidence C</td>
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<tr>
<td></td>
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<td>+</td>
<td>IV Propafenone</td>
<td>AVNRT</td>
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AT, atrial tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; EPS, baseline electrophysiologic study; ERP, early repolarization pattern; ICD, automatic implantable cardioverter-defibrillator; IV, intravenous; LBBB, rate-dependent left bundle branch block; NSPVT, nonsustained polymorphic ventricular tachycardia; SND, sinus node dysfunction; VAI post, ventricular arrhythmia induction post dextrose–insulin; VF, ventricular fibrillation; (+), positive response; (−), negative response; (±), inconclusive test.
(patient 3, with SND), who refused a pacemaker, received oral orciprenaline that was effective and well tolerated. The cases with inducible supraventricular tachyarrhythmias during EP studies (patients 3 and 4) did not undergo radiofrequency catheter modulation/ablation. Both remained completely asymptomatic and free of spontaneous tachycardias during 5 years of follow-up.

Discussion

We evaluated the efficacy and safety of dextrose–insulin load infusion in a group of nine patients with non-diagnostic ECG index patterns that were suggestive of BrS. J-ST wave morphology changed after dextrose–insulin in 85.7% of our cases with a definitive diagnosis of BrS, but not in the control group, and without side effects and no significant arrhythmias.

Spontaneous changes between diagnostic and non-diagnostic ECGs

We emphasize that in our patients, the ECG varied over time; 42.8% changed between non-diagnostic and diagnostic ECG pattern and even a temporarily normal ECG. Therefore, the diagnosis and risk stratification can be hampered by the dynamic nature of Brugada ECG patterns. In a study by Richter et al. [17], 1161 ECGs (13 ± 8 ECGs/patient) were analyzed from 89 Brugada patients implanted with an ICD, during a mean follow-up of 48 ± 35 months. Only 24% of the ECGs/patient were coved-type 1, and notably 76% were non-diagnostic (25% saddleback-type 2 or 3 of previous consensus [4] and 51% normal). 96.4% of the coved-type 1 Brugada ECG pattern had transient normalization and/or conversion to non-diagnostic saddleback-type 2 ECGs patterns; thus, in patients with a spontaneous coved-type 1 Brugada pattern, only every third ECG is diagnostic and every third ECG is normal.

Furthermore, according to Roos et al. [18], Brugada probands had syncope as the first manifestation of the disease (36.9%). Of these, 55% had a non-diagnostic ECG at first presentation of syncope (36% normal ECGs and 19% saddleback-type 2 ECG pattern). All our patients with recurrent syncope and positive dextrose–insulin test had a non-diagnostic ECG pattern at first presentation; therefore, most patients have a non-diagnostic or even a normal ECG at the time of the presentation of syncope.

Unmasking Brugada syndrome by dextrose–insulin test

Our results are similar to Nogami et al. [15]. In a group of seven patients (mean age: 45 ± 10 years), four of five patients (80%) with non-diagnostic, saddleback-type 2 and type 3 patterns (by the previous consensus) [4] converted to diagnostic coved-type 1 ECG pattern after glucose–insulin infusion. Only two of five patients (40%) accentuated the J–ST-segment elevation after only glucose infusion. Nishizaki et al. [14] studied a group of 20 patients (mean age: 50 ± 10 years) who received an oral glucose load (75 g in 200 mL of water). Augmentation of ST elevation (>1 mm) was observed in 15 of 20 cases (75%) in patients with BrS but in none of the control group. Patients who showed a coved-type 1 pattern before the glucose load exhibited more positive ECG changes than patients with saddleback-type 2 or transiently normalized ST segment, 8 of 8 cases (100%) versus 7 of 12 cases (58%) (p < 0.05). However, only 3 of 12 cases (25%) converted from a saddleback-type 2 to coved-type 1 ECG pattern, and additional positive changes including negative or biphasic T wave were present in 60% of saddleback-type 2 ECG pattern. Therefore, our results reproduced and confirmed the reports of previous authors.
It is noteworthy that the application of the criteria established in the last consensus statement (βangle duration, slower downslope of J-ST, and duration of the base triangle in leads V1–V2) had very high reliability to predict a positive test result and allowed us to discriminate non-diagnostic ECGs that will turn into a diagnostic covered type-1 ECG [3,19–21].

Possible mechanism of J-ST changes induced by glucose–insulin

A number of factors modulate the electrocardiographic and arrhythmic manifestations of the BrS. Autonomic tone and the influence of certain hormones can likewise modulate ST segment elevation. Nishizaki et al. [14] evaluated the possible role of insulin in ST segment elevation in patients with BrS. Positive ST segment/ST-T wave changes were observed in response to an abrupt increase in insulin level during oral glucose test but not in normal control subjects. In a covered-type 1 pattern, the maximum ST elevation was observed at the same time as the peak plasma insulin level after glucose load in 54% of cases, whereas maximum ST elevation was observed at the same time as peak plasma glucose level in 31% of cases. Changes returned to baseline in most cases, with concomitant return of insulin levels. They assumed that the plasma insulin level rather than glucose level might be causally associated with ST segment/ST-T wave changes because the plasma glucose level was kept within limits of daily food intake. Nogami et al. [15] found no relationship between ECG changes and blood glucose or serum potassium concentrations.

At the cellular level, insulin modulates ion transport mechanisms in cardiac muscle, causing hyperpolarization of the membrane resting potential [22]. It has been speculated that a possible mechanism is a balance between the modulation of the Na⁺/K⁺ pump current mediated by insulin receptors and additional influences on other channels and/or regional differences of its effects on repolarizing current [13,23]. Although there is no agreement on the cellular mechanism, the consensus is that glucose intake and insulin secretion are associated with the dynamic manifestation of a Brugada-type ECG.

Relationship between vagal tone and meals with changes in J-ST

Autonomic nerve modulation, particularly high vagal tone, can likewise modulate ST segment elevation and may explain the greater frequency of dynamic variations over time and day-to-day, as well as occurrence of arrhythmias in particular conditions. Kasanuki et al. [24] found that increased vagal activity, as measured by heart rate variability analysis, promotes a typical Brugada ECG.

Food intake is also a modulator of vagal activity. Ikeda et al. [10] were the first to attract attention to the spontaneous ST segment changes often observed after meals in patients with BrS. Subsequently, they tested the hypothesis that gastric distention after a large meal is associated with spontaneous ST elevation and with arrhythmogenesis in BrS [11].

These findings were strongly supported by Mizumaki et al. [25] and Nishizaki et al. [26] who evaluated changes of ST segment elevation before and after taking meals. Patients with type-I symptomatic and asymptomatic BrS showed that bradycardia-dependent augmentation of ST elevation was enhanced in the postprandial period. Variations of ST segment elevation were associated with changes in glucose-induced insulin levels after meals, being highest after dinner [26].

Pharmacologic test

The consensus statement establishes the administration of intravenous class I sodium-channel blocker as the standard test to unmask a type-I covered ECG pattern (ajmaline, flecainide, pilscainide, or procainamide) [2,4]. These agents are widely used, although the sensitivity and specificity may vary significantly depending on the sodium-channel blocker used, dose, and the criteria of a positive test; furthermore, the reproducibility, false-positive rate, and safety are still not completely well defined. Finally, these pharmacologic agents may also induce acquired forms of the BrS. It is important to stress that these limitations are characteristics of the current management in clinical practice [27].

Until now, experience with dextrose–insulin challenge is very limited compared with sodium-channel blockers, and because the mechanism of action at the cellular level is not known exactly, it is too early to know whether this metabolic challenge test can eventually overcome the aforementioned limitations of sodium-channel blockers.

Clinical implications

In clinical practice, there are several situations to consider. For example, recording ECGs by placing the right precordial leads at higher intercostal spaces (2nd or 3rd) increases the sensitivity for detecting Brugada-type ECG patterns, but there is also some evidence that a false-positive saddleback-type 2 or RSR’ pattern is obtained and is highly prevalent with high precordial leads compared with standard leads in athlete and non-athlete populations [28,29]. Then, in this group of patients, dextrose challenge test may be useful to avoid a false diagnosis of a Brugada-type ECG.

The European Society of Cardiology recommends ECGs for the screening of SCD in young competitive athletes [30]. The standard 12-lead ECG is performed with the subject in supine position during quiet respiration and then in standing position. Moreover, because a large meal increases serum concentrations of glucose and insulin and is one of the modulators of vagal activity, we believe that it would be useful to perform the ECG between 30 min and 2 h after eating, instead of at a fasting state. The majority of both symptomatic and asymptomatic patients present with a non-diagnostic index ECG; therefore, in addition to obtaining multiple ECG recordings, it is reasonable to perform a diagnostic test, and dextrose–insulin test is a simple, safe, and effective option. Until now, the number of patients in this and other series is limited to suggesting other recommendations from the clinical point of view; therefore, it is evident that further study is required to understand the role that this metabolic challenge test can play.
Study limitations

Our group represents a small number of patients, but the prevalence of the BrS is very low in our region. For the same reason, we did not have a control group with diagnostic coved type-1 ECG pattern to properly assess the predictive value of dextrose–insulin test. We did not perform a measurement of plasma insulin levels. No genetic analysis was performed to evaluate an eventual gene-specific test response to the dextrose–insulin challenge.

There are only isolated case reports with oral or intravenous propafenone [31–34], but this class IC agent has similar pharmacodynamic properties to flecainide (INa, IKr, IKur blockade). Propafenone has slow dissociation kinetics, similar to flecainide and ajmaline, and induces a strong use-dependent block typical of class IC antiarrhythmic drugs. Then, in our cases, we found propafenone to be a useful agent to validate the results with dextrose–insulin test to unmask type-1 coved ECG patterns.

Conclusion

The incidence of fluctuation between diagnostic and non-diagnostic ECGs of patients with suspicion of BrS is high and is because of multiple factors. In this regard, clinical evidence has emerged suggesting that changes in J-ST segment in the BrS are influenced by glucose–insulin, and this report reproduces and supports the efficacy and safety of this metabolic test in the differential diagnosis of patients with non-diagnostic ECG patterns. Although, a large number of patients are needed to know the sensitivity and specificity of this metabolic challenge test and to determine its role as a diagnostic option.

References


