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Transient ascending ST-segment depression and widening of the S wave in 3-channel Holter monitoring—A sign of dromotropic disturbance in the right ventricular outflow tract in the Brugada syndrome: A report of five cases

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Abstract

Background: Brugada syndrome (BrS) is somewhat a challenging diagnosis, due to its dynamic pattern. One of the aspects of this disease is a significant conduction disorder located in the right ventricular outflow tract (RVOT), which can be explained as a consequence of low expression of Connexin-43. This decreased conduction speed is responsible for the typical electrocardiographic pattern. Opposite leads located preferably in inferior leads of the electrocardiogram may show a deep and widened S wave associated with ascending ST segment depression. Holter monitoring electrocardiographic (ECG) aspects is still a new frontier of knowledge in BrS, especially in intermittent clinical presentations.

Methods: We describe, as an exploratory analysis, five case series of intermittent type 1 BrS to demonstrate the appearance of ascending ST segment depression and widening of the S wave, during 3-channel 24h-Holter monitoring (C1, C2 and C3) with bipolar leads.

Results: In the five cases described, the ST segment depression was observed mainly in C2, but in some cases also in C1 and C3. Only case 1 presented concomitant intermittent elevation of the ST segment in C1. All cases were intermittent.

Conclusion: The recognition of an ECG pattern with ascending ST-segment depression and widening of the S wave in 3-channel Holter described in this case series should raise a suspicion of the BrS and suggests the counterpart of a dromotropic disturbance registered in the RVOT and/or reciprocal changes.

KEYWORDS
Brugada syndrome, Dromotropic disturbance in the right ventricular outflow tract, Holter monitoring, S wave, ST-segment depression

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1 | INTRODUCTION

Brugada syndrome (BrS) is an inherited arrhythmia disorder characterized by an increased risk of unexplained syncope and/or sudden cardiac death (SCD), without macroscopic structural heart disease. Currently, two electrocardiographic (ECG) patterns are recognized as follows: type 1 (coved) and type 2 (saddleback), although only the type 1 has a definitive diagnostic value, whether spontaneous or induced by sodium channel blockers. The type 1 is characterized by J-point ST-segment elevation ≥2 mm of superior convexity or rectilinear descent followed by a negative symmetrical T wave in at least one right precordial lead in conventional position or in the second or third intercostal space (ICS) (Priori et al., 2013).

Due to their dynamic nature, these ECG patterns can be transient or augmented by multiple factors such as precordial electrode positions, variation in autonomic tone or body temperature, or multiple drugs (Brugada et al., 2018).

ST-segment depression in the limb leads was already described as one of the ECG characteristics of BrS related to reciprocal changes or mirror image of the ST-segment elevation in the right precordial leads, and when transient in 3-channel Holter, these ECG changes may help to identify the intermittent type 1 Brugada pattern and a dromotropic disturbance in the right ventricular outflow tract (RVOT) (Crea et al., 2015).

2 | CASE REPORTS

In this series of cases, Holter with three channels and four electrodes placed on the chest was used, as shown in Figure 1a. According to the manufacturer, channel 1 (C1) corresponds to modified leads V1-2, channel 2 (C2) to modified V4-5 while channel 3 (C3) has no specific correspondence to ECG leads.

2.1 | Case 1

A 72-year-old man with brown skin color had no cardiovascular comorbidities or family history of sudden death. He underwent a colonoscopy procedure complicated by colon perforation. During surgical correction, he had an episode of atrial fibrillation detected in the rhythm monitor. At the end of the procedure, an ECG was performed and showed elevation of the ST segment in the right precordial leads (Figure 2c). He was transferred to our hospital, where he underwent coronary angiography that did not show a significant luminal reduction. An echocardiogram was performed, and no structural changes were observed. Holter monitoring displayed elevation of the ST segment in C1 and concomitant ascending depression of the ST segment in channels C2 and C3 in a straight line. The ST changes were evident for most of the recording and disappeared only during periods of higher heart rate (Figure 2a,b).

2.2 | Case 2

A 46-year-old male farmer with brown skin color was admitted to the hospital in September 2019, due to palpitation, acute precordial pain, and dizziness while he was working. He denied syncopal episodes, but his wife reported that 2 weeks before the admission, she found her husband unconscious on his bed with noisy breathing, drooling over, and with tonic movements. The initial ECG showed a coved ST-segment elevation in the right precordial leads (Figure 2f). The echocardiogram did not show any structural changes, and coronary artery computed tomography (CT) was normal. Holter monitoring showed a straight ascending ST-segment depression in C2 and a concave ST-segment depression in C3 for most of the recording time with no changes in C1 (Figure 2d,e). An electrophysiological study (EPS) was also performed, but no ventricular arrhythmia

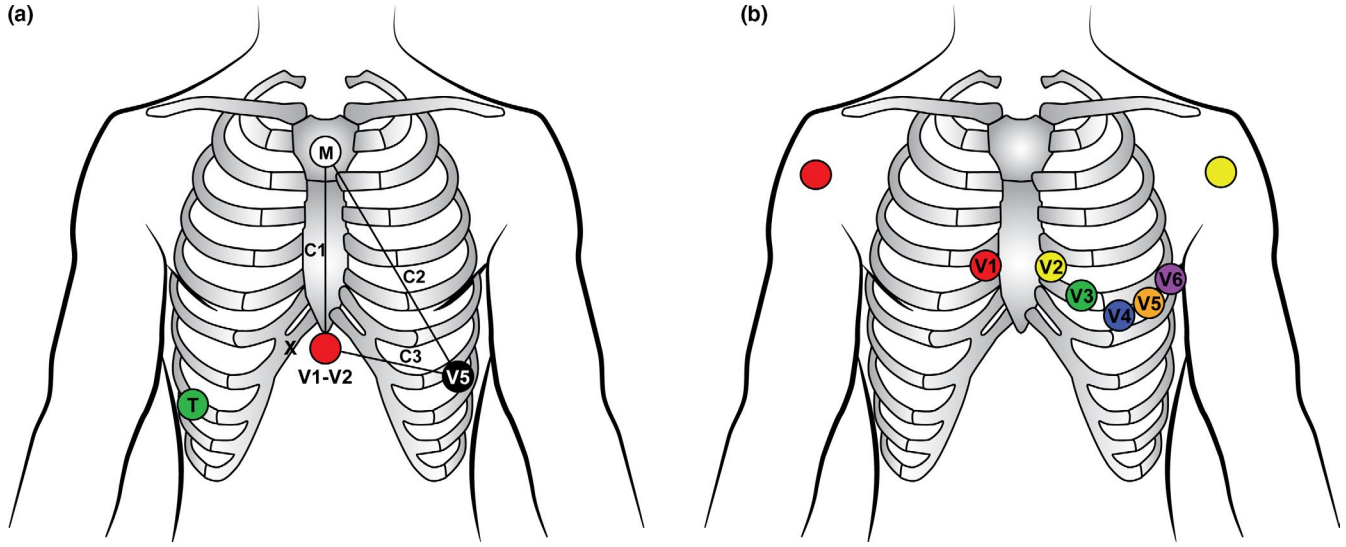


FIGURE 1 (a) Scheme for positioning the Holter electrodes using four electrodes and three bipolar leads. (b) Diagram for positioning the precordial electrodes of conventional ECG using six unipolar leads

FIGURE 2 Holter monitoring and 12-lead ECG of the five cases. (a, d, g, j, and m) show time points with no ST-segment depression, while (b, e, h, k, and n) illustrate the observed type of ST-segment depression. (c, f, i, l, and o) show the corresponding 12-lead ECGs in V1 and V2

could be induced. The event reported by the wife was interpreted as "nocturnal agonal breathing" secondary to a probable arrhythmic event, which was considered as an indication for an implantable cardioverter-defibrillator (ICD).

2.3 | Case 3

A 33-year-old man with brown skin color and no history of comorbidities was admitted to the emergency department in April 2016, with palpitations associated with dyspnea and precordial pain. During admission, he had an episode of ventricular fibrillation, which was reverted. In sinus rhythm, he presented an ST-segment elevation with coved morphology and negative T wave in the right precordial leads (Figure 2i). Coronary angiography did not show any stenosis. The echocardiogram was also normal. Holter monitoring showed a slightly concave ST-segment depression in C2, concave ST-segment depression in C3, and for most of the time no changes in C1 (Figure 2g,h). The patient was subsequently referred for ICD implantation.

2.4 | Case 4

A 35-year-old man with brown skin color, referred to the hospital in July 2019 for a preoperative consultation before planned rhinoplasty because of ST-segment elevation in the right precordial leads (Figure 2l). He denied cardiovascular symptoms but reported a history of sudden death of his older brother at the age of 30. The transthoracic echocardiogram was normal, and an exercise stress test showed good functional capacity and no symptoms, but an accentuated type 1 Brugada pattern in the immediate post-effort was observed. Holter monitoring showed an ascending ST-segment depression in C1 and C2, in a straight line, which disappeared only during periods of higher heart rate. C3 did not show any significant changes (Figure 2j,k). During the planned surgical procedure, it was recommended to use continuous rhythm monitoring, immediate treatment of possible hyperthermia and we provided a list of drugs to be avoided (http://brugadadrugs.org). He returned for an EPS after the procedure; an episode of ventricular fibrillation was induced. A joint decision recommended ICD implantation for primary prevention of SCD.

2.5 | Case 5

A 64-year-old Caucasian woman was referred for exercise testing due to complaints of atypical chest pain in October 2020. During the test, she remained asymptomatic but had transient ST-segment elevation with convex morphology consistent with the type 1 Brugada pattern in the recovery phase (Figure 2o). The echocardiogram showed no structural heart disease. Holter monitoring showed transient ascending ST-segment depression, in a straight line, in C1 and C2 around noon and during a short period in the afternoon. C3 did not show any significant changes in the ST segment (Figure 2m,n). The patient has undergone follow-up without invasive procedures.

3 | DISCUSSION

In the five cases described, the ST-segment depression was observed mainly in C2, but in some cases also in C1 and C3. Only case 1 presented concomitant intermittent elevation of the ST segment in C1. All cases were intermittent. They were preceded by a broad-based S wave with a slowly ascending morphology in a straight or slightly concave line, followed by a positive T wave, resulting in QRS broadening—it was difficult to determine the end of the QRS and the beginning of the T wave. In Figure 2b, e, h, k, and n we can see a ramp signal, represented by a straight line between the nadir of the S wave and the peak of the T wave representing the loss of transition between the QRS and the T wave.

Figure 3 shows the ST-segment depression of the five cases and their reverse image showing an upward convex or rectilinear ST-segment elevation that would meet the criteria for a type 1 pattern in the right precordial leads, suggesting that it corresponds to a mirror image.

Bipolar leads used in the chest were directed downwards and/or to the left (Figure 1a), resulting, particularly in C2, in a vector that opposes the vector of RVOT (Figure 4). The widening of the S wave, occurring mainly in periods of lower heart rate, can also be explained by a dromotropic disturbance registered in RVOT, due to interstitial fibrosis and reduced gap junction expression (connexin-43).

In line with our Holter findings, a wide S wave in lead I in the ECG has previously been described as a risk marker for ventricular fibrillation and/or sudden cardiac death in the BrS (Calò et al., 2016). The foundation of this ECG finding is similar to that of the aVR sign (R wave ≥0.3 mV or R/q ≥0.75) in the BrS (Babai Bigi et al., 2007) and the Northwest QRS axis sign, recently described by our group, in which only lead aVR is predominantly positive in the frontal plane, as the QRS axis is located between −90° and ±180 (Pérez-Riera et al., 2020).

Depression of the ST segment in the inferior leads was already described as one of the ECG aspects of the BrS representing reciprocal changes or mirror image of the ST-segment elevation in the right precordial leads. Crea et al. highlighted the role of limb leads in this setting. In a population of 87 patients with the spontaneous type 1 pattern, 47% of the patients showed an ascending ST-segment depression in the inferior leads (≥0.1 mV deep, ≥80 ms in duration) (Crea et al., 2015).

An important characteristic of the BrS is the dynamic nature of the ECG manifestations. Strategies, such as placing electrodes superiorly in the second or third ICSs, seem to increase the sensitivity of the diagnosis (Nakazawa et al., 2004). The pattern is related to the autonomic tone and is more prevalent in periods of vagal predominance, such as during sleep or in the postprandial period. Fever can unmask the type 1 pattern and is associated with the risk of triggering an arrhythmic event (Brugada et al., 2018). The appearance or worsening of the pattern in the recovery phase of an exercise test

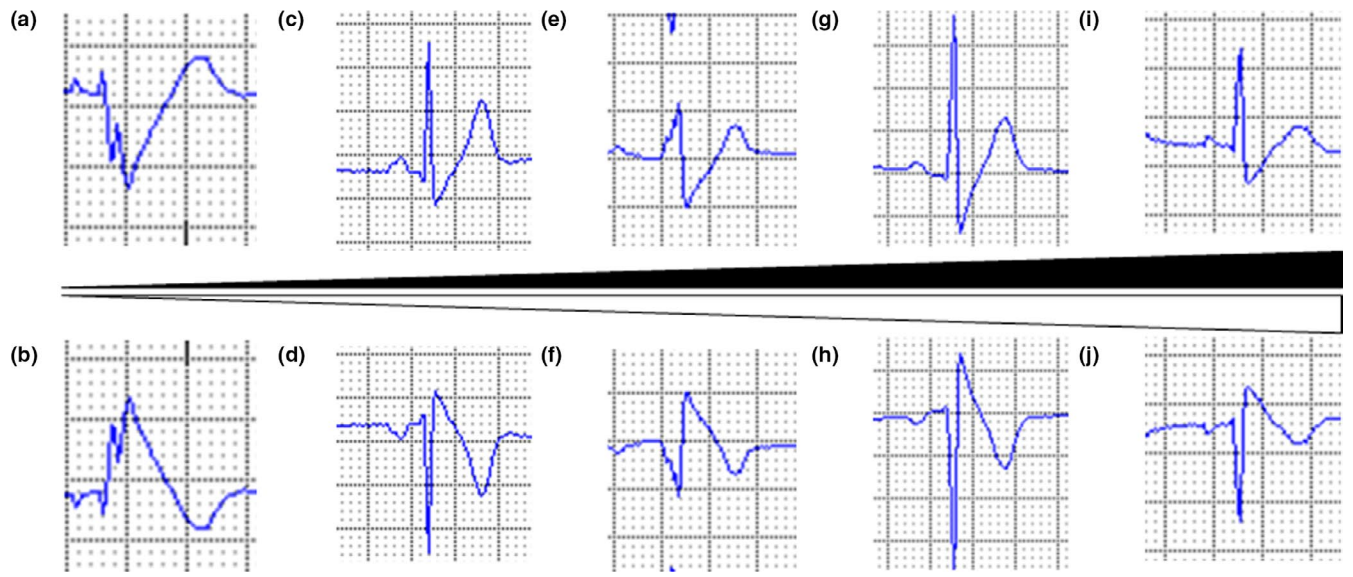
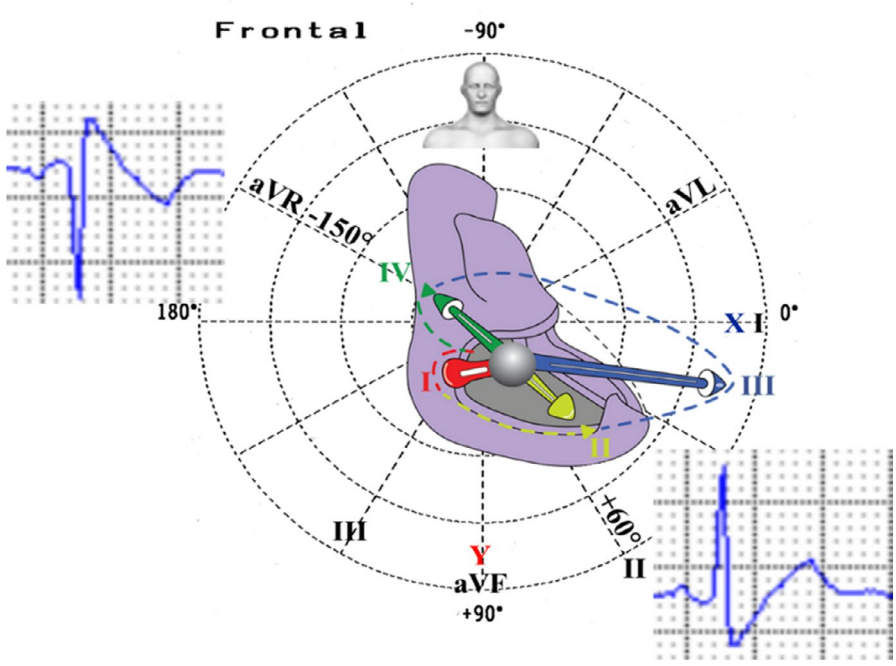


FIGURE 3 Traces of all 5 Holter cases and its inverted image, by flipping the trace vertically. (a) C3 of case 1; (b) Inverted C3 image of case 1; (c) C2 of case 2; (d) Inverted C2 image of case 1; (e) C2 of case 3; (f) Inverted image of inverted C2 of case 3; (g) C2 of case 4; (h) Inverted C2 image of case 4; (i) C2 of case 5; (j) Inverted C2 image of case 5

FIGURE 4 Outline showing the four vectors of ventricular depolarization: *Vector I* (left middle-septal vector), *Vector II* (low-septal vector), *Vector III* (vector resulting from the activation of the free walls of both ventricles), and *Vector IV* (final ventricular depolarization located in the RVOT area) pointing to the right shoulder near aVR (−150°) and concomitantly moving away from channel 2 (near +60°). Note a deep/broad S wave in the C2/II lead, and an opposite pattern in aVR



can be a diagnostic tool and even correlate with a worse arrhythmic prognosis (Makimoto et al., 2010). For this reason, continuous ambulatory recording with Holter monitoring can be an important tool, since it is capable of unraveling intermittent patterns.

The usefulness of the 12-lead Holter to detect Brugada pattern fluctuations was demonstrated by Cerrado et al. who published a study with 251 patients with spontaneous or drug-induced BrS, who underwent a 12-lead 24h Holter. In the group initially classified as drug-induced, 20% of the patients had an intermittent type 1 pattern during Holter monitoring, allowing them to be reclassified as representing the spontaneous form, with a worse prognosis (Cerrato et al., 2015).

In another study with 12-lead Holter monitoring, Gray et al found that patients with cardiac events may have a significantly higher temporal burden of type 1 ST-segment elevation in the 24 h monitoring period (Gray et al., 2017).

Unfortunately, 12-lead Holter monitoring is not easily available in the clinical setting, so it is useful to observe other signs that might raise the suspicion of BrS pattern. Although curve morphologies observed in 3-channel Holter are similar to those in conventional ECG leads, this is not the case for V1 and V2, since they are unipolar leads, and this can lead to misinterpretations. Therefore, many patients with the spontaneous type 1 pattern undergo Holter monitoring without showing any significant ST-segment elevation. However,

they can present with an ascending ST-segment depression and widening of the S wave.

4 | CONCLUSION

The conventional 3-channel Holter monitoring is a widely used diagnostic method in the investigation of syncope and arrhythmias. The recognition of an ECG pattern with ascending ST-segment depression and widening of the S wave described in this case series should raise a suspicion of the BrS. Further studies are needed to confirm the sensitivity and specificity of this finding, as well as to determine whether it has a prognostic value in risk stratification.

CONFLICT OF INTEREST

None declared.

ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Hospital de Messejana, Dr. Carlos Alberto Studart Gomes.

AUTHOR CONTRIBUTIONS

Conception and design of the research: Antonio Thomaz de Andrade, Raimundo Barbosa-Barros and Andrés Ricardo Pérez-Riera. *Data collection and writing the initial manuscript*: Antonio Thomaz de Andrade. *Critical revision of the manuscript for intellectual content*: Kjell Nikus, Rodrigo Daminello Raimundo, Luiz Carlos de Abreu, Sacilotto L, Darrieux F, Yanowitz FG, Brugada P and Pérez-Riera AR. All contributions critically revised the final manuscript.

DATA AVAILABILITY STATEMENT

All data are available and can be provided if requested.

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