Evaluation of baseline ECG in patients undergoing Oral Flecainide Challenge test for suspected Brugada Syndrome: An analysis of lead II

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ABSTRACT

Background and Objectives: We analyzed Lead II in patients undergoing an Oral Flecainide Challenge test (FCT), to identify any pointers that could predict a positive FCT and thereby help in recognition of latent BS.

Methods: The following parameters in lead II were retrospectively analyzed from the pre-test ECG in 62 patients undergoing FCT for suspected BS: The presence or absence of S waves, S wave amplitude, duration and upslope duration; J point parameters- Early repolarization, QRS notch, and QRS Slur; ST segment parameters-lack of isoelectric ST segment, ST duration and QT interval.

Results: 48 had positive FCT (Group-1) while 14 were negative for FCT(Group-2). Lack of an isoelectric ST segment (50% vs 14.29%, p = 0.018) and slurring of QRS (33.33% vs 0%, p = 0.014) was more common in Group-1 than Group-2. Group-1 had shorter ST segment duration (median 81.5 (IQR 64—103.5) vs 110 (IQR 90—132), p = 0.002) and shorter ST: QT ratio (median 0.28 (IQR 0.22−0.35) vs 0.23 (0.18−0.27), p = 0.007). QRS notch/depressed J point (87.5%), QRS slur (100%), and lack of isoelectric ST segment (92.31%) had high sensitivity for predicting an inducible Type 1 Brugada pattern. Combining two parameters- ST: QT ratio<0.24 and lack of isoelectric ST segment-considerably improved the specificity (73.3%), and the positive predictive value of the test to 76%. The results remained accurate when validated in a small prospective cohort.

Conclusion: Shortened ST segment in Lead II, lack of isoelectric ST segment, slurred QRS and ST/QT ratio <0.24 are predictive of underlying Brugada pattern in baseline ECG.

1. Introduction

Brugada Syndrome (BS) is a channelopathy that is responsible for 20% of the Sudden deaths in patients without a structural heart disease [1] [2]. The disease is said to have a prevalence of 1 in 2000 but is often under-recognized because of the dynamic nature of the ST-segment elevation that is characteristic of the condition [3] [4] [5]. The diagnostic ECG pattern in BS has been described as an atypical Right Bundle Branch Block (RBBB) like pattern with coved ST elevation in electrocardiographic (ECG) leads V1-3 [6]. Although Type I pattern is diagnostic, its dynamic nature results in under-diagnosis of the condition [7]. Hence, provocative tests with Na$^+$ channel blockers are widely used to unmask latent BS in suspected individuals [7] [8]. Flecainide, Ajmaline, and Procainamide, all have been used for drug provocation with the highest yield reported with Ajmaline [9]. However, the use of Ajmaline, in many parts of the world is limited by its availability. In this current study, on suspected BS patients undergoing provocation with oral Flecainide, we explore the likelihood of precordial ST changes being "mirrored" in inferior leads (Lead II) in such patients. We aim to evaluate Lead II in the baseline ECGs of patients undergoing oral Flecainide

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Abbreviations

BS   Brugada Syndrome
FCT   Flecainide Challenge Test

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challenge test (FCT), to see if there are any pointers which could predict the positivity of Flecainide challenge and hence the diagnosis of Brugada Syndrome. This may, to some extent, overcome the limitations of the provocative drugs on the positive yield.

2. Aims and objectives

The present study aimed to analyze and compare differences in QRS complex and ST segment in the Lead II in patients with a positive and negative oral Flecainide challenge test (FCT); and to identify pointers in lead II in the baseline ECG, that are predictive of a positive FCT.

3. Methods

This was a retrospective analysis of patients undergoing Oral FCT with a single dose of 400 mg of oral Flecainide for suspected BS [10]. The study was conducted across 3 tertiary referral centers in South India. Patients were identified from a registry of arrhythmic disorders, and the data was collected from the medical records of the respective hospitals. The concerned ethical committees of these institutions had approved this study.

4. Patient population

Consecutive patients who underwent Flecainide challenge test for suspected Brugada Syndrome between 2012 and 16 were included in the analysis. The pre-test (baseline ECG) taken before oral Flecainide challenge was used for analysis and a comparison of ECG findings in Lead II was done in patients with a positive (Group 1) and negative FCT (Group 2). Positive FCT was characterized by coved type I ST elevation of ≥2-mm in ≥1 lead from V1 to V3 [11]. Patients were excluded from the study if they had previously documented spontaneous type 1 Brugada pattern any time in the past.

5. Electrocardiographic analysis

The standard 12 lead ECG was recorded at a speed of 25 mm/s and a gain of 1 mV/cm. The scanned and magnified ($\times$10) pre-test ECGs were used for analysis and all ECG intervals and durations were analyzed using online calipers (Eepee calipers, Tomorsoft). The following parameters in lead II were analyzed:

The presence or absence of S wave in lead II, S wave amplitude, duration, and upslope duration was analyzed. J point abnormalities in lead II like Early repolarization pattern, depressed J point or QRS notch and QRS slur were also included. ST segment parameters like ST segment duration and a lack of isoelectric ST segment, and the QT interval and corrected QT interval in Lead II (as calculated by the Bazett's formula) were also included in the analysis.

6. Definitions

Early repolarization pattern was defined as an elevation of the J-point of at least 1 mm above the baseline in >2 consecutive inferior leads while a **QRS notch** was defined as a J point below the level of the T-P segment [12] [13].

QRS slur was defined as an absent J point with the sloped transition of S wave into the ST segment.

ST segment duration referred to the duration between J point and beginning of T wave (point where a tangent drawn along the ascending limb of the T wave intersects the horizontal ST segment) while a **lack of isoelectric ST segment** was defined as an upsloping ST segment with deviation > 1 mm above baseline.

7. Consistency and reproducibility

The measurement of each parameter was obtained by averaging three consecutive beats. Two investigators (MRK and MAP) independently obtained the measurements of each of the anonymized ECGs blinded to patient data and FCT response. Each observer recorded the measurement twice on two different occasions. The consistency of measurement (inter-observer agreement) and its reproducibility (intra-observer agreement) were both analyzed.

8. Statistical analysis

Categorical variables were expressed as proportions and numerical data was expressed as median with interquartile ranges (IQR). Fisher exact test was used for comparison between groups for categorical variables, whereas comparison of quantitative data was carried out by Mann-Whitney test. Receiver-operating characteristics (ROC) curve analysis was used to assess the usefulness of the relevant electrocardiographic parameters in predicting a positive FCT. With an optimal cutoff value derived from ROC curve analysis, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Statistical significance was determined by a p-value $\leq$ 0.05. All analyses were performed with the SPSS 17.0 statistical package (SPSS, Inc., Chicago, Illinois).

9. Results

During the study period, 62 patients underwent FCT for suspected Brugada syndrome. Forty -eight patients who had an inducible type I pattern formed the Group1, whereas 14 in whom a type I pattern was not inducible constituted Group2. The baseline characteristics of the two groups are presented in Table 1. Thirty-seven of the 48 (77.1%) patients in Group 1 were asymptomatic and were suspected on the basis of a Type2 or 3 patterns on an incidental ECG, or during a screening of family members of a documented case of BS. Three (6.25%) patients presented with aborted cardiac arrest, while 5(10.42%) were suspected to have BS during evaluation of palpitations and the remaining 3 (6.25%) during evaluation of syncope. The two groups were comparable with respect to age, sex and clinical presentation (Table 1).

Table 1
Baseline characteristics.

	Group 1 (N-48)	Group 2 (N-14)	P
Age yrs (range)	53 (22—64)	39 (26—55)	0.18
Sex	M- 35(72.91%)	M- 8(57.14%)	0.33
	F- 13(27.07%)	F- 6(42.86%)	
Asymptomatic	37(77.08%)	11(78.57%)	1
Palpitations	5(10.42%)	3(21.43%)	0.36
Syncope	3(6.25%)	0(0%)	1
Seizures	3(6.25%)	3(21.43%)	0.12
Aborted SCA	3(6.25%)	0(0%)	1
Family h/o SCD	0(0%)	0(0%)	1
Family member with Type 1 pattern	24(50%)	8(57.14%)	0.76

10. Electrocardiographic analysis of lead II

The Electrocardiographic comparison between the two groups is depicted in Table 2. The proportion of patients having baseline type2, type 3 or non-distinct electrocardiographic pattern was comparable between the two groups. The intra-class coefficients assessing inter-observer agreement were between 0.89 and 0.95 for all the ECG parameters and the kappa statistic for classification agreement was 0.863 (p < 0.001). The intra-observer reproducibility for each parameter was >0.95 (p < 0.001).

Lack of an isoelectric ST segment was significantly more common in Group-1 than Group-2 (50% vs 14.29% respectively, p = 0.018). Similarly, slurring of QRS was also more common in the Group- 1 than Group-2(33.33% vs 0% respectively, p = 0.014). The ST segment duration was significantly shorter in Group 1 than Group 2 (median 81.5 (IQR 64–103.5) vs 110 (IQR 90–132), p = 0.002). The ST: QTc segment ratio also significantly differed between the two groups (median 0.23 (0.18–0.27) in Group 1 vs 0.28 (IQR 0.22–0.35) in Group 2, p = 0.007). There was no significant difference between other parameters (Table 2). For maximum predictive accuracy, the best ST: QTc cut-off was 0.24 using the ROC curve, with a sensitivity of 73% and specificity of 64% (AUC = 0.73, 95% CI 0.70–0.88, 0 = 0.008).

11. The accuracy of the parameters

The sensitivity, specificity, and predictive values of these parameters are shown in Table 3. While QRS notch/depressed J point (87.5%), QRS slur (100%), and lack of isoelectric ST segment (92.31%) had a high sensitivity for predicting an inducible Type 1 Brugada pattern, none of the parameters had a high specificity. Combining the two parameters- ST: QTc ratio<0.24 and lack of isoelectric ST segment-considerably improved the specificity (73.3%), and the positive predictive value of the test to 76% (Table 3).

12. Prospective validation of the parameters

Prospective validation of these findings was done by predicting the possible response to FCT from the basal ECG by the blinded investigator. The ECGs of 8 consecutive patients with suspected Brugada syndrome who had a non-type I ECG pattern were analyzed for the predictive parameters. Seven (87.5%) of these had incidentally detected Type II Brugada pattern, whereas one (12.5%) had syncope. The response to FCT could be accurately predicted in seven of these. The combined parameters had a sensitivity of 100%, specificity of 75%, a positive predictive value of 80%, and a negative predictive value of 100% for accurately predicting the FCT response.

13. Discussion

The classic Brugada pattern in the ECG is characterized by dome-shaped ST elevation in V1-3, either present spontaneously or after provocation with a Na^+ channel blocker like Flecainide or Ajamaline [11] [14]. While the characteristic Type I pattern is unmistakable, the less obvious Type II and Type III patterns (that would benefit from provocation) are under-recognized resulting in under diagnosis of BS [15]. Also, several investigators have suggested that the ST Elevation in BS is dynamic, varies with the autonomic tone and that Type 1–3 patterns, as well as unremarkable ECGs, may be evident in the same individual at different times [16] [17] [18]. Even in our study, of the 48 FCT positive patients, 19 (39.58%) had a non-distinct ECG at baseline (Fig. 1). Subjecting cases only on the basis of type 2 or 3 patterns in baseline ECG to FCT will result in underestimation of the disease prevalence.

Chevallier et al., described alpha and beta angles, between the upslope of S wave and r^1 in V1 and V2, to predict the outcome of provocative tests in suspected Brugada Syndrome [19]. We, in this study, looked at the inferior lead (lead II) in the baseline ECG of patients undergoing an FCT to see if any set of findings was consistent with a positive test. We compared the lead II findings in the "most normal ECG" or the pre -flecainide challenge test ECG in 48 patients with a positive provocation test with 14 patients with a negative provocation test and found the following:

1. Univariate analysis showed the following 5 ECG parameters to significantly differ in patients with a positive FCT: Lack of

Table 2
Comparison of ECG parameters between the two groups.

Parameter	Group 1 (n = 48)	Group 2 (n = 14)	P
Type 2	14 (29.17%)	2 (14.29%)	0.32
Type 3	15(31.25%)	3(21.42%)	0.53
Non-distinct	19 (39.58%)	9 (64.29%)	0.15
S in LII	45	12	0.38
S-LII< 2 mm	36	8	0.21
S-LII>2 mm	9	4	0.48
Lack of isoelectric ST segment	24 (50%)	2 (14.29%)	**0.018**
Early Repolarization	5 (10.4%)	1(7.48%)	1
J depression (QRS notching)	7 (14.58%)	1(7.48%)	0.42
QRS slur	16 (33.33%)	0(0%)	**0.014**
Varying S amplitude	3(6.25%)	0(0%)	1
QT LII (ms)	372.62 ± 39.47 374.5(344.75–394.75)	398.2 ± 31.36 400 (368–419)	**0.09**
S duration (ms)	50.84 ± 22.11 55 IQR (43–63.25)	43.60 ± 25.88, 51 IQR(32–64)	0.56
ST duration (ms)	84.88 ± 27.79 81.5 (64–103.5)	113.67 ± 33.32 110 (90–132)	**0.002**
S upslope duration (ms)	35.46 ± 17.67 35.5 (25–50)	26.53 ± 15.5 32 (20–38)	**0.11**
RR interval (ms)	837.93 ± 148.25 841 (745.5–925.75)	850.13 ± 174.03 800(750–928)	0.24
ST/QT ratio	0.23 ± 0.06 0.23 (0.18–0.27)	0.28 ± 0.07 0.28 (0.22–0.35)	**0.007**
ST/RR ratio	0.45 ± 0.06 0.45(0.41–0.49)	0.48 ± 0.09 0.48 (0.44–0.52)	0.357

Table 3
Sensitivity, specificity and Predictive values of various parameters.

Parameter	Sensitivity (%, 95%CI)	Specificity(%, 95%CI)	PPV(%, 95%CI)	NPV(%, 95%CI)
Depressed J point/QRS notch	87.5 (46.67–99.34)	24.56 (14.53–38.04)	48(33.67–62.58)	86.67 (59.54–98.34)
QRS slur	100 (75.6–100)	32(19.52–46.7)	30.6 (18.25–46.4)	100(79.4–100)
Lack on an Isoelectric ST segment	92.31 (73.4–98.67)	33.33 (19.57–50.31)	48(33.88–62.42)	86.67(59.4–98.34)
ST:QT ratio <0.24	73 (46.8–80.83)	64 (53.96–79.14)	42(28.49–56.73)	26.67(8.91–55.17)
Lack of isoelectric ST/ST:QT ratio <0.24	72 (60–85.23)	73.3(52.51–83.55)	76(60.51–86.4)	13.33(2.3–41.61)
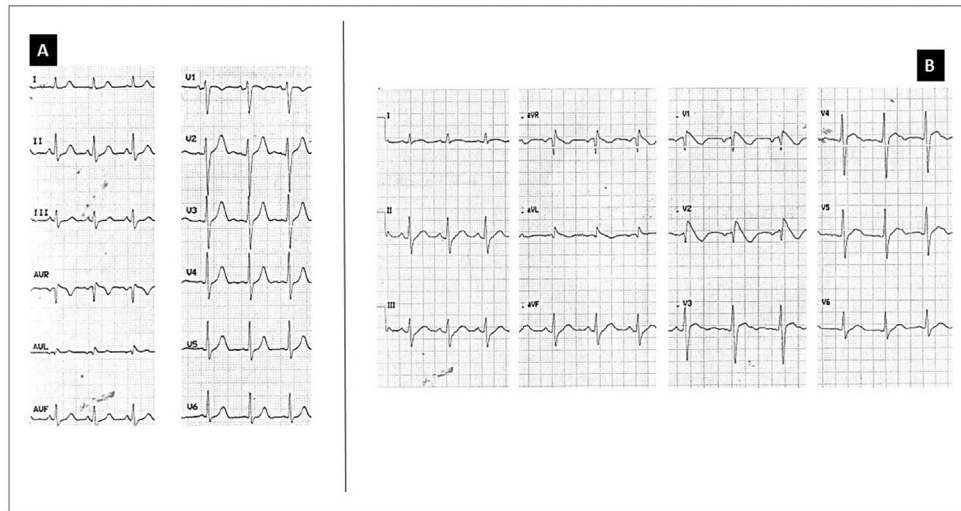
Fig. 1. A) Pre FCT ECG without any obvious Type 2 or Type 3 Brugada pattern. **B)** Post FCT ECG in the same patient showing classic Brugada Pattern in V1-V3. Note that Lead II in pre-FCT ECG shows small S waves with a short ST segment.
FCT- Flecainide Challenge Test.

isoelectric segment, slurred QRS, short ST segment in LII, ST: QT ratio, and a longer S-wave duration.

2. The presence of an upsloping ST segment or ST/QT ratio <0.24 had a sensitivity of 73% and specificity of 73.3% in predicting a positive FCT.
3. A QRS notch or QRS slur was highly sensitive (>90% sensitivity) but had low specificity in predicting a positive Flecainide challenge test.

The morphology of the QRS complex and the T-wave in any lead reflects the instantaneous summation of opposing electrical vector dipoles during depolarization or repolarization of the ventricles. In Myocardial infarction, ST elevation in the infarcted segment is accompanied by reciprocal ST depression in opposing leads which are believed to "mirror" the changes of the infarct-related ST elevation [20]. On the basis of this concept of "mirror image" electrical changes in opposing leads we selected lead II to see if there were any characteristics that were consistent with a latent Brugada pattern.

13.1. Changes in the QRS complex and the J-point

Although most of the ECG description in BS has centered on the anterior precordial leads, a few investigators have reported inferior lead changes in BS. Rollin et al. reported associated Type 1 ST elevation (in addition to anterior precordial leads) in either aVR,V6 or inferior leads in upto 10% of patients with BS [21]. Occasional cases of Brugada-type ST elevation in isolated inferior and lateral precordial leads have also been reported [22–28]. While the exact mechanism of this finding has not been elicited, a novel mutation in

sodium channel gene was suggested in one of the reports [26]. The most common inferior lead finding in BS is the presence of early repolarization in about 11% of the patients as reported by Sarkosy et al. [22]. Early repolarization in inferior leads has also been found to correlate with arrhythmic events in these patients [22] [27]. We found similar Early repolarization pattern in the inferior leads in 5/48 (10.4%) of our cohort of patients with BS. In addition, we found a depressed J point (that appeared as a notch (QRS notch) in the terminal S wave) in 7/48 (14.58%) and a slurred QRS complex (with a non-distinct J point and a smooth continuation of the S wave as the ST segment) in 24% of the patients who had latent BS (as unmasked by Flecainide) (Fig. 2). These two 'J point' abnormalities have not been previously reported in BS. Both these findings had high sensitivity (>90%) but low specificity in predicting a positive FCT. Our findings suggest that the presence of a depressed J point or a slurred QRS complex in lead II in a non-distinct ECG could indicate the presence of a latent BS. Whether this new J point abnormalities further bridge the gap between early repolarization and BS or suggest the opposite and merely reflect the slowed terminal conduction and delayed depolarization along the diseased RVOT remains to be debated.

Recently, Calo et al., supporting the 'depolarization hypothesis', suggested the presence of a large/wide S wave in lead I to be a powerful predictor of life-threatening ventricular arrhythmias in patients with Brugada Syndrome [29]. According to the study by Calo et al., delayed activation of the RVOT in Brugada syndrome resulted in S wave in Lead I akin to patients with RBBB who also have S wave in Lead I. In a normal ECG, The S wave represents the terminal portion of the QRS vector which is determined by activation of the basal portions of the two ventricles and the RVOT. A
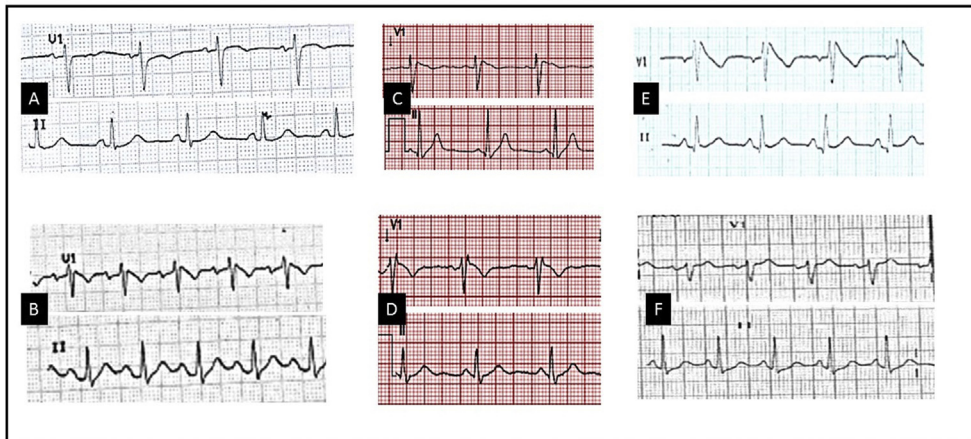
Fig. 2. Lead II findings in Brugada Syndrome. **A)** The varying amplitude of S waves, **B)** Lack of Isoelectric ST segment and a shortened ST segment, **C)** QRS Slur, **D)** Short ST segment, **E)** Early repolarization and **F)** Depressed J point (QRS Notch).

considerable delay in activation of the RVOT should result in the formation of small S wave in left directed leads like Lead I and possibly Lead II. In our study S wave in lead II was evident in 90% of the baseline ECGs of patients who eventually were diagnosed as BS after drug provocation. The majority of these patients had a small (<2 mm) S wave in Lead II. However, a similar prevalence and duration of S wave even in patients with a negative FCT questions the significance of this finding.

13.2. Changes in the ST segment

Another interesting finding in our study is with respect to the ST segment in lead II. The ST segment in normal individuals is an isoelectric segment representing the time between the end of depolarization and the beginning of repolarization [30]. Our results show that patients with an upsloping ST segment and a shorter ST segment duration at baseline are more likely to be positive for drug provocation. Lack of isoelectric ST segment was noted in 48% of patients with a positive FCT while the average ST segment duration was 85 ms in this group (vs 113 ms in patients with negative FCT). The upsloping ST segment and a shorter ST segment duration likely indicate an overlap between depolarization and repolarization in patients with Brugada Syndrome. Whether this overlap is secondary to a delay in depolarization or an earlier repolarization remains speculative. Both, a 'Repolarization hypothesis' suggesting a shortening of the dome of phase 2 action potential in the epicardium, and, a 'Depolarization hypothesis' favoring a delay in conduction and depolarization in the RVOT secondary to sodium channel abnormality have been proposed to explain the arrhythmogenesis in BS [31] [32] [33]. Further research is needed to understand the effects of the altered depolarization/repolarization on the ST and QTC interval when the full-fledged Brugada type I pattern is not manifest.

13.3. Changes in the QT interval

Abnormalities in QT interval have been reported in BS. Pitzalis et al. reported QTc prolongation in right but not left precordial leads in patients with BS [34]. Studies have aslo reported an association between QTc prolongation, transmural dispersion of repolarization and the presence of events in BS [35] [36]. However, these studies measured the QTc interval in manifest rather than latent Brugada pattern. In contrast to earlier reports, we found a shortened QTc in Lead II to be suggestive of a latent Brugada pattern. The shortened

QT interval is likely secondary to the finding of a shortened ST segment, which in our study was found more often in patients with a latent Brugada pattern ECG. The dynamicity of the ST segment is well known, but the corresponding values in the latent BS electrocardiogram needs to be further studied and the present study suggests that subtle changes in ST interval do exists.

The present study suggests that depressed J point, QRS slurring, and lack of an isoelectric ST segment in Lead II are excellent parameters for screening patients with high likelihood of an inducible Type 1 Brugada pattern with FCT, in view of their high sensitivity. Combining the lack of an isoelectric ST segment and the ST: QT ratio <0.24 significantly increases the positive predictive value and the specificity in identifying patients harboring a Brugada type I pattern.

14. Conclusion

One of the first study analyzing a frontal ECG lead in non-manifest BS, the present report suggests that the ST segment in lead II has several pointers that are predictive of a latent Brugada pattern on the ECG. A shortened ST segment in Lead II, a lack of isoelectric ST segment, slurred QRS and ST/QT ratio <0.24 were all predictive of an underlying Brugada pattern in a baseline ECG.

15. Clinical implications

These ECG parameters can be a simple, risk-free, bed-side, screening tool in evaluating patients with suspected arrhythmic syncope in whom an FCT can be planned.

16. Limitations

The retrospective nature of the study and the small cohort size especially in Group 2 are limiting factors which could affect the interpretation of the observations and the results of the study. However, the prospective validation of the findings adds to the strength of the study. Only Flecainide was used as a provocative drug, and the yield of a Type I pattern could have been theoretically different if other drugs were used. Prospective studies with larger patient groups, and using other provocative drugs are required to confirm the findings of the study.

Conflict of interest

None.

References

[1] Antzelevitch C, Brugada P, Brugada J, et al. Brugada syndrome: from cell to bedside. Curr Probl Cardiol 2005;30(1):9–54.
[2] Juang JM, Huang SK. Brugada syndrome-an under-recognized electrical disease in patients with sudden cardiac death. Cardiology 2004;101(4):157–69.
[3] Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol 2006;29:1130–59.
[4] Brugada R, Campuzano O, Sarquella-Brugada G, et al. Brugada syndrome. Methodist Debakey Cardiovasc J 2014;10:25–8.
[5] Shimizu W. The Brugada syndrome—an update. Intern Med 2005;44:1224–31.
[6] 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.
[7] Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the heart rhythm society and the european heart rhythm association. Circulation 2005;111(5):659–70.
[8] Brugada R, Brugada J, Antzelevitch C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000;101(5):510–5.
[9] Wolpert C, Echternach C, Veltmann C, et al. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. Heart Rhythm 2005;2(3):254–60.
[10] Dubner S, Azocar D, Gallino S, et al. Single oral flecainide dose to unmask type 1 Brugada syndrome electrocardiographic pattern. Ann Noninvasive Electrocardiol 2013;18(3):256–61.
[11] Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106(19):2514–9.
[12] Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm 2010;7(4):549–58.
[13] Haïssaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358(19):2016–23.
[14] Bayés de Luna A, Brugada J, Baranchuk A, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol 2012;45(5):433–42.
[15] Juang JM, Huang SK. Brugada syndrome—an under-recognized electrical disease in patients with sudden cardiac death. Cardiology 2004;101(4):157–69.
[16] Take Y, Morita H, Wu J, et al. Spontaneous electrocardiogram alterations predict ventricular fibrillation in Brugada syndrome. Heart Rhythm 2011;8(7):1014–21.
[17] Veltmann C, Schimpf R, Echternach C, et al. A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification. Eur Hear J 2006;27(21):2544–52.
[18] WadaT Morita H. Clinical outcome and risk stratification in Brugada syndrome. JOA 2013;29:100–9.
[19] Chevallier S, Forclaz A, Tenkorang J, et al. New electrocardiographic criteria for discriminating between brugada types 2 and 3 patterns and incomplete right bundle branch block. J Am Coll Cardiol 2011;58:2290–8.
[20] Morris F, Brady WJ. ABC of clinical electrocardiography: acute myocardial infarction-Part I. BMJ 2002;324(7341):831–4.
[21] Rollin A, Sacher F, Gourraud JB, et al. Prevalence, characteristics, and prognosis role of type 1 ST elevation in the peripheral ECG leads in patients with Brugada syndrome. Heart Rhythm 2013;10:1012–8.
[22] Sarkozy A, Chierchia GB, Paparella G, et al. Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome. Circ Arrhythm Electrophysiol 2009;2(2):154–61.
[23] Potet F, Mabo P, Le Coq G, et al. Novel brugada SCN5A mutation leading to ST segment elevation in the inferior or the right precordial leads. J Cardiovasc Electrophysiol 2003;14(2):200–3.
[24] Ogawa M, Kumagai K, Yamanouchi Y, et al. Spontaneous onset of ventricular fibrillation in Brugada syndrome with J wave and ST-segment elevation in the inferior leads. Heart Rhythm 2005;2(1):97–9.
[25] Van den Berg MP, Wiesfeld AC. Brugada syndrome with ST-segment elevation in the lateral leads. J Cardiovasc Electrophysiol 2006;17(9):1035.
[26] Lombardi F, Potenza S, Beltrami A, et al. Simultaneous ST-segment elevation in the right precordial and inferior leads in Brugada Syndrome. Cardiovasc Med 2007;8(3):201–4.
[27] Kamakura S1, Ohe T, Nakazawa K, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol 2009;2(5):495–503.
[28] Letsas KP, Sacher F, Probst V, et al. Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome. Heart Rhythm 2008;5(12):1685–9.
[29] Calò 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(12):1427–40.
[30] Hurst JW. Abnormalities of the S-T segment—Part I. Clin Cardiol 1997;20(6):511–20.
[31] Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation 1999;100(15):1660–6.
[32] Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? Cardiovasc Res 2005;67(3):367–78.
[33] Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm Electrophysiol 2012;5(3):606–16.
[34] Pitzalis MV, Anaclerio M, Iacoviello M, et al. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. J Am Coll Cardiol 2003;42(9):1632–7.
[35] Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, et al. Tpeak-tend and tpeak-tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the brugada syndrome. J Am Coll Cardiol 2006;47(9):1828–34.
[36] Maury P, Sacher F, Gourraud JB, et al. Increased Tpeak-Tend interval is highly and independently related to arrhythmic events in Brugada syndrome. Heart Rhythm 2015 Dec;12(12):2469–76.