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Flecainide challenge test: Predictors of unmasking of type 1 Brugada ECG pattern among those with non-type 1 Brugada ECG pattern

Srinivasa Prasad, Narayanan Namboodiri*, Anees Thajudheen, Gurbhej Singh, Mukund A. Prabhu, S.P. Abhilash, Krishnakumar Mohanan Nair, Aamir Rashid, V.K. Ajit Kumar, Jaganmohan A. Tharakan

Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, India

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ABSTRACT

Background: Many subjects in community have non-type 1 Brugada pattern ECG with atypical symptoms, relevance of which is not clear. Provocative tests to unmask type 1 Brugada pattern in these patients would help in diagnosing Brugada Syndrome. However sensitivity and specificity of provocating drugs are variable.

Methods: We studied 29 patients referred to our institute with clinical presentation suggestive but not diagnostic of Brugada or with non-Type 1 Brugada pattern ECG. Flecainide Challenge Test (FCT) was done in these patients (IV Flecainide test in 4 patients and Oral Flecainide in 25 patients). Resting 12-lead ECG with standard precordial leads and ECG with precordial leads placed 1 Intercostal space above were performed after flecainide administration every 5 min for first 30 min and every 30 min thereafter until ECG became normal or upto 6 h. The positivity was defined as inducible Type 1 Brugada pattern in atleast 2 right sided leads.

Result: Median age was 35(range = 5–65) years. In 16 (55%) patients the Type 1 Brugada pattern was unmasked. There were no episodes of major AV block, atrial or ventricular tachyarrhythmia. Three groups were considered for analysis: Group 1(n = 9) – FCT Positive among patients with non-type 1 Brugada ECG pattern, Group 2(n = 4) – FCT Negative among the patients with non-type 1 Brugada ECG pattern, and Group 3(n = 7) – FCT Positive among patients with no spontaneous Brugada ECG pattern. Binary logistic regression analysis found that family h/o SCD was predictive of FCT positivity in Group 1 (Odd's ratio 21, 95% Confidence interval 1.04 to 698.83, p = 0.004).

Conclusion: Oral flecainide is useful and safe for unmasking of Type I Brugada pattern. In our study, among the many variables studied, family history of sudden cardiac death was the only predictor of flecainide test positivity among those with non-Type 1 Brugada pattern.

1. Introduction

Brugada Syndrome(BrS) is known for its catastrophic course with heightened risk of sudden death in seemingly healthy patients. Diagnosis of BrS in patients with suggestive history is established either by spontaneously occurring Type 1 Brugada ECG pattern or by inducible Type 1 Brugada ECG pattern [1]. Non-Type 1 Brugada ECG pattern (Type 2 and Type 3 Brugada ECG patterns), though are suggestive, are not diagnostic.

Drug challenge with sodium channel blockers is commonly employed to unmask Type 1 Brugada pattern among those without Type 1 Brugada ECG pattern. Studies [2–7] support the importance of this type of tests for the appropriate evaluation of patients with suspicious BrS and syncope of unknown etiology. However, their sensitivity and specificity are variable and is better with ajmaline compared to other agents [3–7]. Usage of these drugs, (either the drug or the form of drug; example – intravenous form of flecainide), are limited in many countries given their nonavailability. Given its limited utility, ajmaline is not easily available in all electrophysiology laboratories. And non-availability of intravenous flecainide and procainamide in many countries has made many laboratories to employ, freely available oral flecainide, to unmask Type 1 Brugada pattern, and

* Corresponding author.
E-mail address: drbvsp@gmail.com (N. Namboodiri).
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has been reported as case studies [8,9]. However a systematic analysis of such data is limited.

On the other hand, many patients in community have non-type 1 Brugada pattern ECG with atypical symptoms, relevance of which is not clear. Unmasking of type 1 Brugada pattern in these patients would help in diagnosing BrS which has significant impact on prognosis and treatment options.

Though some studies [10,11] suggest repeating the test to improve sensitivity, given the prevalence of the condition, more so in eastern part of world, it may not be prudent to repeat the test in all patients with negative result. Determining the predictors of positive challenge would improve our understanding and facilitate appropriate usage of these challenge tests.

We hypothesized that certain clinical & electrophysiological characteristics of patients like aborted sudden cardiac death (SCD), spontaneously occurring ventricular arrhythmia, inducible ventricular arrhythmia or family history of BrS could help predict positive flecainide challenge test (FCT) and thereby in identification of patients with Type 1 Brugada pattern – which would help us in better risk stratification of these non-type 1 Brugada pattern patients.

1.1. Study aims and objectives

We aimed to study the clinical and electrophysiological profile of patients who underwent flecainide challenge test with the objective to study and compare the clinical, genetic and electrophysiological profile of patients with positive and negative FCT in patients without Type 1 Brugada ECG pattern.

2. Materials and methods

This study is a part of prospective registry, involving all consecutive patients who underwent FCT for suspected BrS or to look for inducibility of ECG pattern in non-Type 1 Brugada pattern at Sree chitra Institute of Medical Sciences and Technology, Trivandrum, India between January 2008 to April 2015.

2.1. Inclusion criteria

- Patients suspected to have Brugada by
- ECG – Non Type 1 Brugada pattern (Type 2 or Type 3 Brugada pattern).
- F/h/o Brugada Syndrome.
- Patients for whom FCT was contemplated as a part of workup to rule out Brugada syndrome.
- H/o aborted SCD.
- Unexplained Syncope/Pre-syncope.
- Documented ventricular arrhythmia.

2.2. Exclusion criteria

- Evidence of structural heart disease that explains their symptoms.
- Spontaneous Type 1 Brugada Pattern.
- Contraindication to Flecainide.
- Patient who did not give their consent.

2.3. Flecainide challenge test and ECG criteria

- Flecainide Dose [1,9].

IV: 2 mg/Kg for 10 min as infusion, max 150 mg.

Oral: 400 mg stat.

- ECG monitoring: (apart from continuous bed side telemetry).
  - Normally placed 12 lead ECG and one space above right sided leads (V1, V2, V3R, V4 R).
  - *For IV protocol*: ECGs every minute for 10 min & every 5 min thereafter till 30 min or till ECG abnormalities revert.
  - *For Oral Protocol*: ECGs every 5 min for first 30 min, and then at 30 min interval till 6 h or till abnormalities revert.
- Positivity: Inducible Type 1 Brugada pattern in atleast 2 right sided leads were considered as positive FCT.
  - Type 1 Brugada pattern is characterized by
    - a coved ST-segment elevation 2 mm (0.2 mV) followed by a negative T wave.
  - Type 2 ST-segment elevation has a
    - saddleback appearance with a high takeoff ST-segment elevation of 2 mm, a trough displaying <1 mm ST elevation, and then either a positive or biphasic T wave.
  - Type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm.

Medical records of all patients were reviewed to extract information on clinical, laboratory, ECG characteristics, details of flecainide challenge test, electrophysiological findings and other relevant data.

Of the study population, 3 groups were considered for further analysis for predicting positive response of FCT: Group 1 – FCT Positive among patients with non-type 1 Brugada ECG pattern, Group 2 – FCT Negative among the patients with non-type 1 Brugada ECG pattern, and Group 3 – FCT Positive among patients with no spontaneous Brugada ECG pattern.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, Illinois). Data are expressed as mean or median (range). A Fischer's Exact test was performed to test for statistical significance between categorical data and percentage frequencies. Binary logistic regression with a forward stepwise model was utilized to find the predictors of a positive response to the drug challenge test. The Hosmer and Lemeshow test was used to check for model fitness. A p value < 0.05 was considered to be statistically significant.

3. Results

Thirty two patients were considered for FCT; M = 27 (M:F: 84%: 16%). 1 patient developed Type 1 Brugada Pattern just prior to starting flecainide, considered as spontaneous Type 1 Brugada pattern and was excluded from analysis. 2 patients did not undergo tests (technical or patient did not consent). Hence 29 patients underwent FCT.

Of 29 subjects, 24 (83%) were male.13 (44.8%) had Type 2 or Type 3 Brugada pattern (non-Type 1 Brugada pattern). Other 16 did not have any type of Brugada pattern at the time of drug challenge, but were considered for the challenge in view of their strongly suspicious clinical profile like family h/o BrS, aborted SCD, documented ventricular arrhythmia, unexplained syncope (Table 1). 4 patients had IV flecainide challenge test and 25 patients had oral FCT. Choice of IV or oral flecainide was based only on availability of the intravenous form at that point of time (Fig. 1).

Sixteen (55%) patients were found to be positive on FCT (Fig. 2). Of which 8 (50%) patients had Type 2 brugada pattern, 1 (6%) patient had Type 3 Brugada pattern, and 7 (44%) patients had no spontaneous Brugada pattern. Median time to positivity was

Table 1
Baseline clinical profile.

	Non type 1 Brugada pattern	No spontaneous Brugada pattern
Number of patients	13 (44.8%)	16 (55.2%)
Mean age (years)	38 (15–65)	34.3 (5–58)
M:F	12:1	12:4
Structurally normal heart	13	15
Asymptomatic	2 (15%)	2 (12.5%)
Pre-syncope	3 (23%)	4 (25%)
Syncope	7 (53%)	9 (56.2%)
Palpitations	2 (15%)	2 (12.5%)
History of aborted SCD	1 (7.6%)	3 (18.7%)
Family history of SCD	7 (53%)	6 (37.5%)
Family history of Brugada	2 (15%)	1 (6.2%)
Documented ventricular arrhythmia	2 (15%)	2 (12.5%)
Sinus Node dysfunction	1 (7.6%)	2 (12.5%)
Prominent or wide S wave in Lead I	9 (69%)	3 (18.7%)
Fragmented QRS	3 (23%)	0
Early repolarisation in inferolateral leads	5 (33%)	2 (12.5%)

SCD: sudden cardiac death.

150 min (range = 90–180 min). Recording the ECG by placing the leads one space above improved sensitivity of the test by detecting the induced Brugada pattern in 6 patients (37%) in whom test would have been considered negative otherwise. PR interval, QRS duration and QTc median difference compared to baseline was 23 ms (range = −4 to +54), 23 ms (range = 0 to +59) and 36 ms (range = −11 to +77), respectively. There were no episodes of major AV block, atrial or ventricular tachyarrhythmia.

FCT was positive in 55% (Fig. 2a), of which 50% had Type 2 Brugada pattern in resting ECG and 44% had no evidence of any Brugada pattern in their resting ECG (Fig. 2b). 2 of 4 patients tested with IV FCT was positive and 14 of 25 patients tested with oral FCT was positive (Fig. 2c). Median time for positivity was 150 min on Oral FCT (n = 14) (Fig. 2d).

Of the study population, 3 groups were considered for further analysis: Group 1 – FCT Positive among patients with non-type 1 Brugada ECG pattern, Group 2 – FCT Negative among the patients with non-type 1 Brugada ECG pattern, and Group 3 – FCT Positive among patients with no spontaneous Brugada ECG pattern.

Multiple clinical factors and electrophysiological characteristics – syncope/presyncope, arrhythmic symptoms, family history of SCD, history of aborted SCD, family h/o Brugada, documented ventricular arrhythmia on ILR/Holter/ECG, presence of sinus node dysfunction and ECG characteristics like S in lead I, fragmentation of QRS & early repolarisation pattern in inferolateral leads-were considered for analysis of predicting the FCT response. Genetic analysis of SCN5A mutations was not considered since it was not available for all patients. Univariate analysis and binary logistic regression (Tables 2 and 3) found that family h/o SCD was independently predictive of FCT positivity (Odd's ratio 21, 95% Confidence interval 1.04 to 698.83, p = 0.004) among those with Type 2 or Type 3 Brugada pattern.

4. Discussion

This study is first of its kind from India to the best of our knowledge. In this article we describe series of consecutive patients with suspected BrS, and non-Type 1 Brugada pattern in whom flecainide was used to unmask the disease. Major results of our study were: 1) family history of SCD predicted positivity of flecainide challenge test among those with Type 2 or Type 3 Brugada pattern. 2) Oral FCT is safer and 3) increased sensitivity of detecting

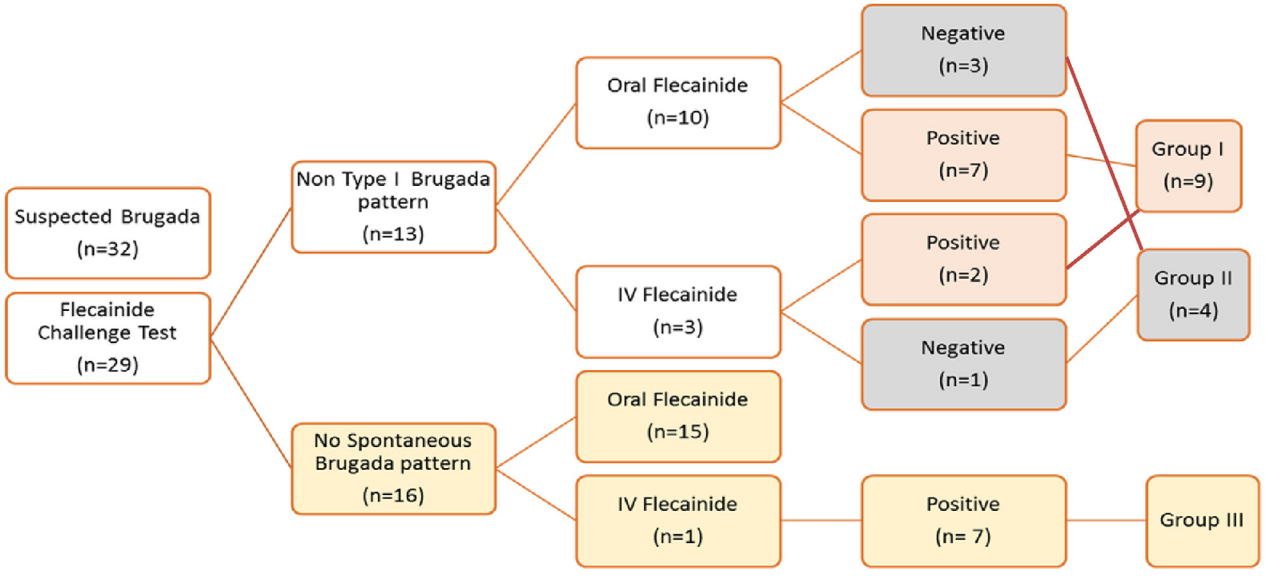

Fig. 1. Study flow.

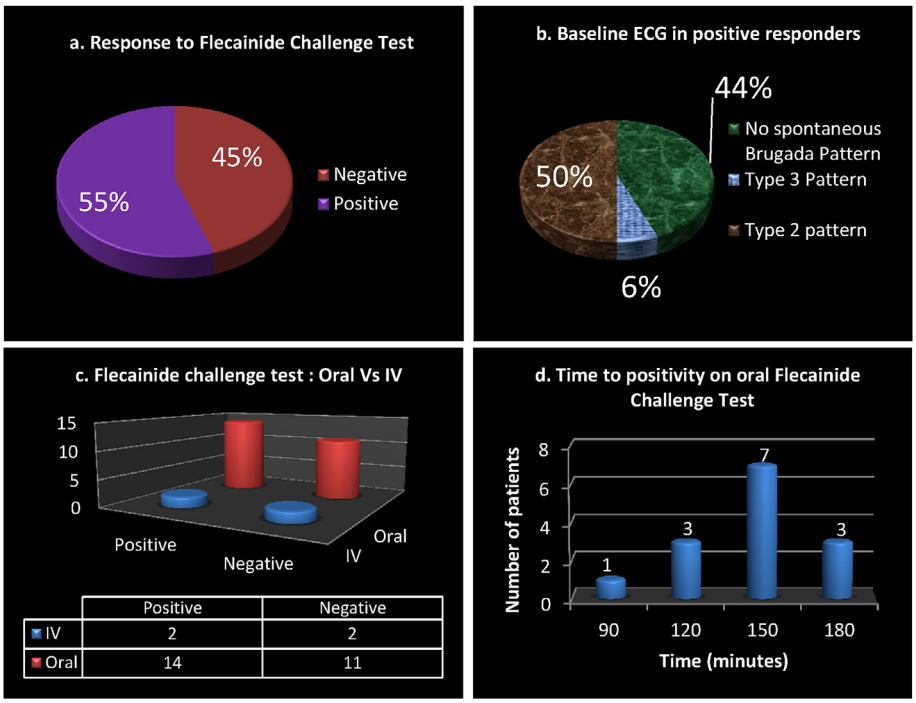

Fig. 2. Flecainide challenge test – characteristics.

Table 2
Characteristics of patients with respect to response to FCT and baseline ECG pattern – univariate and multivariate analysis.

	Gp I	Gp II	Gp III	Gp I vs Gp II				Gp I vs Gp III			
				Fischer's exact	Logistic regression			Fischer's exact	Logistic regression		
					OR	95% *CI*	*p* value		*OR*	95% *CI*	*p* value
Sample size	9/13 (69.2%)	4/13 (30.8%)	7/16 (43.7%)								
Mean Age (years)	41 (15–65)	29.25 (17–38)	36.4 (5–58)								
M:F	9:0	3:1	7:0	0.307				1.000			
Structurally Normal Heart	9	4	7								
Presyncope	1 (11.1%)	2 (50%)	1 (14.2%)	0.210	0.12	0.007–2.17	0.546	0.700	0.75	0.03–14.57	0.849
Syncope	5 (55.5%)	1 (25%)	2 (28.5%)	0.187	7.5	0.73–76.77	0.153	0.437	3.125,	0.38–25.56	0.288
Palpitations	1 (11.1%)	1 (25%)	0	0.530	0.37	0.01–8.1	0.531	0.562	2.64	0.09–75.29	0.568
H/O Aborted SCD	1 (11.1%)	0	2 (28.5%)	0.690	1.58	0.05–47.51	0.789	0.400	0.31	0.02–4.41	0.389
F/h/o SCD	7 (77.7%)	0	3 (42.8%)	**0.021**	21	1.04–698.8	**0.004**	0.302	4.66	0.53–40.8	0.164
F/h/o Brugada	1 (11.1%)	1 (25%)	0	0.530	0.37	0.01–8.1	0.531	0.562	2.64	0.09–75.29	0.568
Documented V arrhythmia	2 (22.2%)	0	2 (28.5%)	1.000	0.28	0.06–102.3	0.120	1.000	0.71	0.07–6.92	0.07
Sinus Node dysfunction	1 (11.1%)	0	1 (14.2%)	0.690	1.58	0.05–47.51	0.789	0.700	0.75	0.03–14.57	0.849
Prominent or wide S wave in Lead I	8 (88.8%)	1 (25%)	3 (43%)	0.051	24	1.11–518.6	0.64	0.105	10.6	0.82–138.2	0.742
Fragmented QRS	3 (33.3%)	0	0	0.496	0.0	0.13–0.82	0.62	0.212	0.0	0.13–0.83	0.63
Early repolarisation in inferolateral leads	4 (44.4%)	1 (25%)	2 (28.5%)	1.000	2.4	0.17–32.8	0.18	0.632	0.8	0.07–8.47	0.105
EPS done	4	2	6								
Inducible VT on EPS	2	0	2	0.400	5.0	0.15–166.6	0.368	0.547	2.0	0.14–26.73	0.600

SCD: sudden cardiac death; F/h/o: family history of; H/O: history of; VA: Ventricular arrhythmias; ILR:Implantable loop recorder; EPS: Electrophysiological Study. **Gp I**: Type 2/3 Brugada Pattern patients – Positive FCT; **Gp II:** Type 2/3 Brugada Pattern patients – Negative FCT; **Gp III:** No spontaneous Brugada pattern patients – Positive FCT.

FCT positivity with regular recording of superior placed ECG lead.

4.1. Clinical predictors of positive response to drug challenge test

a) Family history of SCD.

In the present study, 14 (48.2%) out 29 patients who underwent FCT had positive family history of SCD. Of which 10 patients (7 with Type 2 or Type 3 brugada pattern and 3 with normal ECG) were tested negative. Remaining 4, who had negative FCT had normal resting ECG. Interestingly, all 7 who had family history of SCD with baseline Type 2 or type 3 Brugada pattern were tested positive. In univariate and binary logistic regression analysis, family history of SCD was identified as independent predictor of positive FCT.

Many previous studies [12–15] have shown that family history of SCD does not predict increased event rate or inducible ventricular arrhythmia or positive drug challenge test among BrS (all types included). However none of them have analyzed the data for differential risk between Type 1 and non Type 1 Brugada pattern.

Our study, by its nature, addresses this major clinical issue of

Table 3
Predictor of positive flecainide challenge test by multivariate analysis by binary logistic regression with a forward stepwise model.

	B	Exp(B)	95.0% C.I.for EXP(B)		*p*-value
			Lower	Upper	
Family history of SCD	21.896	3.231	1.040	698.812	0.004

risk stratification among Type 2 or Type 3 BrS patients. Prognosis of inducible Type 1 Brugada pattern is known to be poor compared to those with negative drug challenge test. Therefore sodium channel blocker challenge test can be considered in all patients with family history of SCD in patients with baseline ECG showing Type 2 or Type 3 Brugada pattern.

b) H/o Syncope.

Seventeen (58.6%) of 29 patients had presyncope (n = 7) or Syncope (n = 10), of which 09 were tested FCT positive (6 with Type 2 or Type 3 Brugada pattern and other 3 had normal baseline ECG). History of Syncope predicted the FCT positivity with an Odd's ratio of 7.5 between group 1 and group 2, though statistically insignificant. Unlike other arrhythmic risk predicting studies [2,3,12–15], our study did not find the history of syncope to be useful for predicting positive response of drug challenge test. This possibly could be because of our inclusion criteria of including all unexplained syncope and conscious exclusion of definitive cases of Type 1 Brugada pattern and any other structural heart disease. Also likely that the etiology of syncope need not be arrhythmic in this unselected group.

c) Family history of Brugada.

In this study, 3 (10.3%) of 29 patients had family history of BrS, of which 2 had Type 2 or Type 3 Brugada pattern (1 was FCT positive) and other had normal baseline ECG (FCT was negative). Neither univariate nor binary logistic regression, found this to be predictor of FCT positivity among non-Type 1 Brugada pattern. This finding extends the general notion [16] of limited usefulness of family history of Brugada syndrome in predicting further clinical events among BrS patients (all put together) to subgroup of non-Type 1 brugada patients also.

In our study, family history of SCD has the strongest prediction with odds ratio of 21 (p = 0.04). The anticipated genetic association was more than that noted with symptomatic status with syncope. This could be due to various reasons. First, the disease prevalence in the family may be more than anticipated and many may be asymptomatic. Second, syncope need not be arrhythmic. Third, various biophysical factors affecting ionic channels and other genetic moderators might be playing their role in determining the nature of symptoms. A study by priori et al. [13], had shown that upto 90% of family members of affected pro-bands could be asymptomatic, more than half of them had negative phenotype (silent mutation carriers) or had diagnostic ECG only after provocative challenge test. These results suggest the need of aggressive approach towards family members of victims of SCD, more so in those who have Type 2 or Type 3 Brugada pattern in resting ECG.

Long-term follow-up of patients diagnosed with BrS from the FINGER registry [17] have shown that event rates in asymptomatic patients is low (0.5% per year) and bigger in patients with aborted SCD (7.7% per year) or syncope (1.9% per year). Our study, which included largely symptomatic patients, and hence at higher risk, portrays – family h/o SCD, as a strong predictor of unmasking of Type 1 Brugada pattern with flecainide challenge test. None of the asymptomatic patients in our study had any clinical event on followup.

4.2. ECG predictors of positive response to drug challenge test

a)Prominent or Wide S in lead I.

Prominent S wave was defined as >1 mm in depth and wide S wave was defined as > 1 mm in width on a ECG recorded with standard speed of 25 mm per sec and 10 mV/mm voltage. Twelve of 29 patients had prominent or wide S wave in lead I, of which 9 patients had Type 2 or Type 3 Brugada pattern (8 had positive FCT) and 3 had normal baseline ECG (all 3 were positive for FCT). On univariate analysis, this parameter failed to achieve statistical significance (p = 0.057), though there was a trend towards increased incidence among FCT positive patients.

A recent article by Calo et al. [18], had shown that prominent or wide S in lead I was useful predictor of sudden death among Brugada patients. Our study, though showed the trend of increased incidence of prominent S in lead I among Type 2 or Type 3 Brugada pattern with FCT positivity with a high odd's ratio of 24, it was not statistically significant on either univariate or binary logistic regression. This could be because of the study design with a conscious exclusion of all definitive BrS patients who would be at higher risk of SCD and also can be affected by smaller sample size. Other ECG parameters like fragmentation of QRS and early repolarisation pattern were not found to be significant in our study, unlike other studies which report variable degree of significance.

4.3. Oral FCT

Oral FCT though considered as alternative to Ajmaline provocation test, due to its nonavailability, the FCT protocol is not yet standardised. Bioavailability of oral flecainide in its standard dose averages 70% (range 60–86%), and higher bioavailability is achieved by higher doses. Thus, in consistent with other studies [7,11], we used single dose of 400 mg Flecainide tablets as the challenge dose for oral FCT.

In this study, we observe that maximum time to positivity was 3 h and maximum time to subsequent normalization was 6 h. We suggest, that there is no need to observe beyond 6 h.

4.4. Safety of oral FCT

Shahrzad et al. [15] observed some clinical and electrocardiographic predictors of positive response to the intravenous sodium channel blockers in patients suspected of the BrS. During test, a transient episode of a second-degree atrioventricular block and isolated ventricular ectopics, a QRS prolongation ≥30%, baseline QRS duration in V1 ≥110 ms and a ST-segment elevation ≥0.17 mV in V2 had a good sensitivity and specificity for a positive response. However, our study showed only an insignificant prolongation of the QTc, QRS and PR intervals after drug administration. There were neither 2nd nor 3rd degree AV block in our patients. Thereby providing evidences for safety of oral FCT, nevertheless, we suggest monitoring for ECG changes, arrhythmias and hemodynamic parameters as with any other drug challenge test.

4.5. Electrophysiological Study (EPS) – role in risk stratification

Risk stratification aimed at the identification of patients at risk for sudden death is an important goal of research teams worldwide. The inducibility of Ventricular tachycardia (VT)/fibrillation (VF) during EPS may forecast risk, although some studies [12,14,19] failed to find an association between inducibility and recurrence

of VT/VF among both asymptomatic and symptomatic patients with BrS. The role of EPS is still a controversial topic in patients with BrS; Priori et al.in their PRELUDE study (PRogrammed ELectrical stimUlation preDictive valuE) [12] showed that EPS was unable to identify high-risk patients. In this study high proportion of patients underwent EP study compared to other studies, but like other studies failed to find an association with FCT.

However given the variable sensitivity of provocating drugs, Type 1 pattern may not be unmasked on some of the occasions. Studies [10,11] have shown that repeating the test improves sensitivity albeit with a warning of increased incidence of drug adverse events. With the conflicting evidence of utility of repeating FCT to improve sensitivity, coupled with the potential danger of inducing malignant arrhythmia and associated mortality, we suggest that, decision of repeating the test should be based on highly suspicious clinical profile. And in this regard, among those with non-Type 1 Brugada pattern, a family h/o SCD could serve as a clinical indicator to repeat the test on a different day in case of initial negativity.

4.6. Study limitations

Our study has few limitations. First, small sample size is our study's major limitation. Second, we did not use other sodium channel blocking drugs for challenge for comparison. Also we did not intend to prove efficacy and safety comparison between intravenous and oral FCT. Third, repetition of the FCT in negative patients was not done. Given the variable sensitivity of provocating drugs, Type 1 pattern may not be unmasked on some of the occasions. Few studies [10,11] have shown increased sensitivity on repeating the test, but with potential risk of serious drug adverse events. These studies had often used intravenous form of sodium channel blocking drugs. However in our study, we did not have any serious drug adverse events. Finally, though we screened for sodium channel mutation in few of patients, non-sodium channel mutations were never screened for.

5. Conclusion

We conclude that oral flecainide is useful and safe for unmasking of Type 1 Brugada pattern. In our study, Family history of sudden cardiac death was a major predictor of flecainide test positivity among those with non-Type 1 Brugada pattern.

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