Journal of Electrocardiology 92 (2025) 154081

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

Baseline quantitative ECG parameters do not fully predict class 1 antiarrhythmic effect in Brugada patient: Drug-induced ECG changes in Brugada patients

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ARTICLE INFO

Keywords:
Brugada syndrome
ECG digitalization
Automatic measurement
Ajmaline characterization
Multi-parametric ECG quantification

ABSTRACT

Background: Drug challenge is useful to identify patients with Brugada syndrome (BS) without spontaneous ECG type 1 pattern. Effect of class I antiarrhythmic challenge is difficult to anticipate and potentially associated with complications.
Objective: Assess the response to class I antiarrhythmic challenge.
Methods: We included patients from the French multicenter MUTAVIT registry with a drug induced BS. Using digitized ECG, we automatically quantified 12-lead ECG parameters on lead V1-V3.
Results: Among 157 patients (72 % males, mean age 43 ± 13 years), baseline ECG did not show a type 2 or 3 BS pattern in 58 %. Drug infusion induced a QRS prolongation from 96 ± 20 to 117 ± 25 ms and an increase of ST amplitude from 107 ± 82 to 345 ± 231 μV (lead V2).
Amplitude of drug-challenge effect was associated with homogeneous response across groups (with and without baseline BS pattern). Baseline ST elevation correlated with a pronounced response to the induction test (on V1: $r = 0.697$ (0.568; 0.792), $p < 0.001$, $R^2 = 0.486$). Conversely, on-drug QRS duration was poorly correlated with baseline QRS duration (on V2: $r = 0.215$ (0.0527; 0.366), $p < 0.05$, $R^2 = 0.046$). SCN5A variant carriers had longer QRS duration at baseline but not during drug challenge. Male patients had prolonged baseline QRS and baseline and post-induction ST amplitude.
Conclusion: Amplitude of sodium blockade effect on ST elevation was correlated with baseline ST amplitude but dugs effect on QRS duration was only slightly correlated with baseline QRS duration. Presence of (likely) pathogenic *SCN5A* variant was associated with different baseline ECG characteristics and response to sodium channel blockade.

Introduction

Brugada syndrome (BS), initially described in 1992 [1], is marked by a distinctive electrocardiographic pattern, increased risk for ventricular arrhythmias, and sudden cardiac death (SCD) [2]. It primarily affects young individuals and SCD can potentially be prevented by implantable cardioverter-defibrillators (ICD) [3], but ICDs may lead to severe complications. This electrocardiographic pattern is known to be variable [4,5] but since 1996, it has been demonstrated that the use of pharmacological agents can unmask the BS pattern [6–8]. The use of these

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https://doi.org/10.1016/j.jelectrocard.2025.154081

Available online 25 July 2025

pharmacological agents was subsequently popularized for diagnostic purposes [9–11]. The pharmacological challenge test in Brugada syndrome is recommended in the absence of spontaneous type 1 ECG patterns since 2013 [3,12–14] but its effects remain difficult to predict [11,15]. Indeed, some patients with ambiguous baseline ECGs may not exhibit the "coved-type" pattern, whereas others with normal baseline ECGs may be diagnosed with Brugada syndrome after the test. Moreover, this test is not devoid of risk, as it can be pro-arrhythmic [16,17], with a risk of ventricular fibrillation ranging from 0.3 % to 10 % (mean 1.3 %) in adults according to studies [9,15,18–20]. It can also cause hemodynamic instability due to its negative inotropic effect combined with QRS widening. We hypothesized that the electrocardiographic characteristics observed in Brugada syndrome reflect the arrhythmogenic substrate of the pathology and that the pharmacological provocation test proportionally amplifies the ECG abnormalities. Analyzing these abnormalities observed on the baseline ECG could potentially allow for anticipating the response to the pharmacological provocation test.

The objective of this study was to characterize and quantify the pre-test ECGs and the response to the pharmacological induction test in patients with drug-induced Brugada syndrome.

Methods

Study design and population

We conducted a prospective 4-center (Paris, Toulouse, Amiens, Lille) observational study. The study based on the MUTAVIT registry (Clinical Hospital Research Financing Program n° AOR04070 P040411) intended to follow-up patients with a history of ventricular fibrillation (VF) or being at risk of life-threatening ventricular arrhythmia in the absence of structural heart disease.

The patients provided written informed consent after clear and fair information. The protocol was accepted by the advisory committee for the protection of individuals in biomedical clinical research, Paris Saint-Louis.

For the present study we included only patients with a drug-induced BS (i.e. baseline ECG showing no spontaneous type 1 pattern and type 1 pattern after the administration of a sodium channel blocker). Brugada pattern was assessed according to established guidelines [3,14] (ST segment elevation of $\geq$2 mm in one or more precordial leads V1 or V2, positioned in the second, third, or fourth intercostal space) and confirmed by two senior cardiologists.

Patient data, clinical history, and ECG were collected at inclusion. Echocardiography was performed, genetic analysis offered, and programmed ventricular stimulation (PVS) conducted at the treating physician's discretion. Inclusion of patients occurred from January 2005 to January 2022.

PVS was performed in patients with specific clinical contexts, namely risk factors for ventricular arrhythmia (history of sudden cardiac death, recurrent arrhythmic syncope, or first-degree family history of sudden death). Up to three ventricular extrastimuli were applied from two sites (apex and right ventricular outflow tract) at two pacing cycle lengths (600 ms and 400 ms). Extrastimuli were delivered in 10-ms decrements to the shortest coupling interval allowing capture, without going below 200 ms. PVS was considered positive if it induced sustained ventricular arrhythmias, including VF or polymorphic VT lasting more than 30 s or requiring emergency intervention.

ECG selection and digitization

For each patient, two paper ECG were retrieved, one baseline without type 1 BS pattern and one during the pharmacological challenge test at the time of maximum recorded type 1 BS pattern. All paper ECGs were de-identified, digitized via ECGScan software (AMPS-llc, NY, USA) [4,21] and stored in a digital format (HL7-XML). Automated measurements were finally obtained applying the BRAVO algorithm (AMPS-llc, NY, USA) and Glasgow ECG Analysis Program (University of Glasgow, UK) on the digitized ECGs [4,22,23].

Qualitative visual analysis allowed us to categorize the baseline ECGs into four groups:

Group 1: ECGs with a "coved-type" pattern but lacking the type 1 criterion (J-point elevation <200 μV).
Group 2: ECGs with a "saddle-back" pattern (whatever STE).
Group 3: ECGs with QRS widening (Bundle Branch Block or Non Specific IntraVentricular Conduction Defect) without a "coved-type" or "saddle-back" pattern.
Group 4: Normal ECGs.

The ECG measurements consisted of the following "global parameters" (i.e., computed on the 12-lead median beat): RR intervals (ms), heart rate (beats per minute (bpm)), PR, QRS, QT intervals, Bazett and Fridericia corrected QTc intervals and ST segment, P wave, and T wave durations (ms), and the QRS frontal axis (degrees). The automated positions of the fiducial cursors (QRS onset and end and T-wave end) were visually checked and manually adjusted, when necessary, by a trained operator.

The parameters analyzed in the V1, V2, and V3 leads were as follows: QRS duration (QRS duration, ms) and ST segment elevation at the J-point (ST amplitude, μV).

Quantitative parameters were measured on both the baseline ECG and the ECG during the pharmacological challenge test. We then calculated a Delta ECG (Δ = post-induction value – Baseline value).

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as numbers and percentages. Statistical tests, including *t*-tests, Mann-Whitney tests, 1-factor ANOVA, Tukey's test, and Kruskall-Wallis test, were used for comparisons based on variable types. A 95 % Spearman or Pearson correlation coefficient, as appropriate, was calculated for comparisons between continuous variables.

The Oldham transformation and the approach proposed by *MacGregor* et al. [24] were used for comparisons of a continuous variable with pre- and post-pharmacological challenge measurements. Specifically, the delta (post-induction value – pre-induction value) is mathematically related to the pre-induction value. Therefore, we analyzed the delta (post-induction value – pre-induction value) relative to the average of pre- and post-induction values [(post-induction value + pre-induction value) / 2].

All tests were two-tailed, and significance was set at $p < 0.05$. RStudio software (Version 4.3.3, 2009–2024 RStudio©, PBC) was used for all statistical analyses.

Results

Clinical data

Among 548 patients in the MUTAVIT registry, 157 met the inclusion criteria.

The clinical characteristics of the study population are presented in Table 1.

Mean age at diagnosis was 43 ± 13 years, there were 121 (77 %) probands patients and 45 female patients (28 %). A history of sudden death was reported in 9 patients (6 %), while 31 (20 %) experienced an arrhythmic syncope, and 19 (12 %) patients had a vasovagal syncope.

Genetic analysis was available for 133 patients, with 18 (14 %) having a SCN5A pathogenic or likely pathogenic (P/LP) variant. Cardiac ultrasound results were available for 130 patients, with 119 (92 %) showing normal results (3 patients had non-severe valvular disease, 4

Table 1
: Clinical characteristics.

	Total ($n = 157$)
Proband	121 (77)
Female	45 (28)
Age at diagnosis	43 ± 13
Sudden cardiac death	9 (6)
Arrythmic syncope	31 (20)
Vagal syncope	19 (12)
Lypothimy	9 (6)
Coronary artery disease	4 (3)
Hypertension	16 (10)
Diabetes	2 (1)
Dyslipidémia	19 (12)
Psychiatric disease	7 (4)
Familial sudden death	41 (26)
Familial sudden death < 45 years	11 (7)
SCN5A pathogenic mutation ($n = 133$)	18 (14)
Positive programmed ventricular stimulation ($n = 48$)	17 (35)

had moderate impairment of systolic function (LVEF = 45–50 %)). PVS was performed in 48 patients, with 17 (35 %) testing positive (4 positive PVS in Group 1, 2 in Group 2, 4 in Group 3, and 6 in Group 4), with no significant difference between the groups.

The type of provocation test used was ajmaline in 143 patients (91 %), flecaïnide in 6 patients (4 %), and procainamide in 2 patients (1 %). For the remaining 6 patients, the specific test used was not identified.

Pre-test ECG

Fig. 1 shows the distribution of baseline ECGs into the four qualitative classes. 42 % of patients had baseline ECG suggestive of BS (coved type <200 uV or saddleback pattern) but 58 % did not (group 3 and 4).

Table 2 presents the electrocardiographic characteristics of patients according to their ECG group, at baseline, after induction, and changes (delta). On baseline ECGs, QRS duration in V1 was prolonged in group 2 compared to group 4. The J-point amplitude was higher in group 2 compared to group 1, 3 and 4 in lead V2 and compared to group 4 in lead V3. There was no difference in the parameters of global QRS duration, PR interval, or QT interval.

Post-test ECG

As expected, Supplemental data Table 1 shows that the pharmacological test (sodium channel blockade) significantly prolongs the global (12 lead) duration of depolarization and repolarization parameters (PR, QRS, and QT intervals, $p < 0.001$). Table 2 shows the data for global and right precordial leads measurements according to the 4 baseline ECG classification categories. The table illustrates that there was no statistically significant difference in electrocardiographic parameters between the four ECG groups in post-test ECGs or in delta ECGs.

Determinants of drug-challenge effect on ECG parameters

Baseline ST amplitude was slightly correlated with post-induction ST amplitude in leads V1, V2 and V3 but strongly correlated with delta ST amplitude (Table 3). An adjusted R^2 of 0.51 was obtained for the association between baseline ST amplitude in V1 and delta ST amplitude in V1 (with a classical R^2 of 0.486) (Fig. 2).

Baseline QRS duration was positively correlated with post-induction QRS duration and delta QRS duration in the three right precordial leads (V1–V3), although the coefficients of correlation (R) were low. R^2 values were calculated to evaluate the association between baseline QRS duration and delta QRS duration, yielding the following results: $R^2 = 0.123$ in V1, $R^2 = 0.046$ in V2, and $R^2 = 0.125$ in V3. In addition, baseline QRS duration was positively correlated with post-induction ST amplitude and delta ST amplitude in lead V2 but not in leads V1 and V3 (Table 3).

The presence of an SCN5A P/LP variant was associated with a statistically significant prolongation of global QRS duration on the baseline ECG. On drug, a similar trend was observed but did not reach statistical significance. Conversely, drug-induced QRS changes were not different according to the genetic status but showed a non-significant trend toward a reduced effect in SCN5A P/LP variant carriers (Table 4).

Table 4 shows a significant prolongation of baseline and post-induction QRS duration in lead V1 in males when compared to females. There was also a prolongation of global QRS duration post-induction in males compared to females. Baseline and post-induction

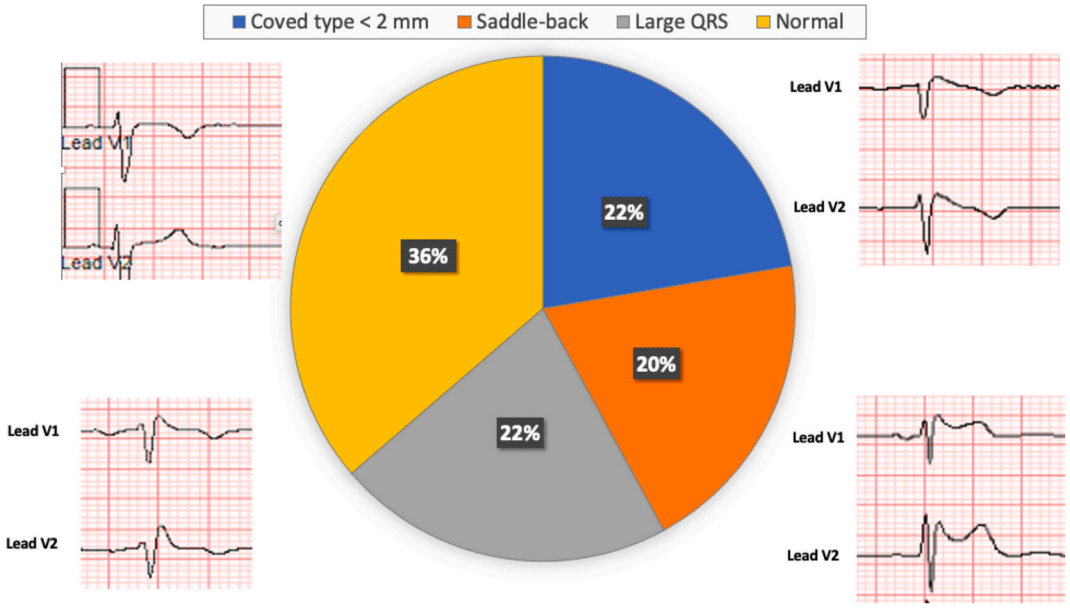

Fig. 1. Distribution of patients by their ECG group.

Table 2
: Electrocardiographic characteristics according to ECG group.

		All (n = 157)	Coved type Groupe 1 (*n* = 35)	Saddle back Groupe 2 (*n* = 31)	Large QRS Groupe 3 (*n* = 34)	Normal Groupe 4 (*n* = 57)	ANOVA *P* value
Baseline	QRS Dur V1	92 ± 20	94 ± 29	96 ± 22	99 ± 17	85 ± 12	**< 0.01** †¥
	QRS Dur V2	96 ± 20	99 ± 29	100 ± 19	99 ± 19	90 ± 14	0.09
	QRS Dur V3	96 ± 16	101 ± 19	89 ± 19	100 ± 15	93 ± 12	**0.02** *§¥
	QRS GBL Duration	112 ± 19	115 ± 23	115 ± 22	114 ± 16	107 ± 15	0.10
	PR interval	151 ± 30	154 ± 29	151 ± 29	150 ± 27	150 ± 34	0.93
	QT interval	392 ± 36	403 ± 49	391 ± 31	387 ± 32	390 ± 31	0.3
	ST Amp V1	41 ± 45	49 ± 39	51 ± 50	22 ± 43	42 ± 46	0.08
	ST Amp V2	107 ± 82	111 ± 79	157 ± 90	84 ± 73	95 ± 75	**< 0.01** *§†
	ST Amp V3	96 ± 74	103 ± 80	126 ± 81	92 ± 65	76 ± 67	**< 0.01** †
Post induction	QRS Dur V1	112 ± 29	116 ± 30	113 ± 31	113 ± 31	113 ± 31	0.81
	QRS Dur V2	117 ± 25	119 ± 21	116 ± 32	122 ± 24	122 ± 24	0.19
	QRS Dur V3	119 ± 254	124 ± 28	121 ± 27	121 ± 20	121 ± 20	0.25
	QRS GBL Duration	138 ± 22	143 ± 22	137 ± 23	139 ± 20	139 ± 20	0.2
	PR interval	183 ± 44	189 ± 53	177 ± 42	182 ± 50	185 ± 37	0.72
	QT interval	407 ± 43	414 ± 58	407 ± 50	408 ± 33	401 ± 34	0.37
	ST Amp V1	142 ± 119	159 ± 109	128 ± 142	142 ± 147	142 ± 147	0.78
	ST Amp V2	345 ± 231	339 ± 300	396 ± 242	362 ± 238	362 ± 238	0.08
	ST Amp V3	162 ± 184	167 ± 150	171 ± 196	168 ± 236	168 ± 236	0.52
Delta	QRS Dur V1	18 ± 42	23 ± 34	16 ± 37	14 ± 27	24 ± 27	0.67
	QRS Dur V2	19 ± 38	20 ± 30	16 ± 35	24 ± 24	21 ± 29	0.67
	QRS Dur V3	20 ± 38	24 ± 29	30 ± 29	21 ± 23	22 ± 22	0.48
	QRS GBL Duration	22 ± 26	29 ± 24	23 ± 33	26 ± 22	27 ± 23	0.80
	PR interval	44 ± 42	49 ± 46	47 ± 43	50 ± 38	36 ± 40	0.32
	QT interval	14 ± 44	11 ± 61	16 ± 55	18 ± 36	12 ± 29	0.52
	ST Amp V1	96 ± 124	106 ± 106	70 ± 148	126 ± 138	99 ± 102	0.62
	ST Amp V2	225 ± 248	226 ± 301	218 ± 264	279 ± 234	214 ± 174	0.56
	ST Amp V3	60 ± 178	63 ± 154	53 ± 178	76 ± 233	80 ± 148	0.98

ANOVA P value: represents the p-value among the four groups: saddle-back, coved-type, QRS widening, and normal.
* denotes a p-value < 0.05 for the test comparing the saddle-back group to the coved-type group.
§ denotes a p-value < 0.05 for the test comparing the saddle-back group to the QRS widening group.
† denotes a p-value < 0.05 for the test comparing the saddle-back group to the normal group.
ž denotes a p-value < 0.05 for the test comparing the coved-type group to the QRS widening group.
‡ denotes a p-value < 0.05 for the test comparing the coved-type group to the normal group.
¥ denotes a p-value < 0.05 for the test comparing the QRS widening group to the normal group.

Table 3
: Baseline J-point amplitude and QRS duration correlation coefficients.

		Post induction ST Amp	Delta ST Amp	Post induction QRS Dur	Delta QRS dur
Baseline ST Amp	V1	0.263 (0.096; 0.424) **	0.697 (0.568; 0.792) ***†		
	V2	0.219 (0.055; 0.371) **	0.778 (0.703; 0.836) ***†		
	V3	0.249 (0.085; 0.400) **	0.672 (0.569; 0.755) ***†		
Baseline QRS dur	V1	0.089 (−0.081; 0.264)	0.136 (−0.0305; 0.295)	0.240 (0.078; 0.389) **	0.350 (0.198; 0.486) ***†
	V2	0.334 (0.178; 0.474) ***	0.324 (0.167; 0.465) ***	0.223 (0.062; 0.373) **	0.215 (0.0527; 0.366) **†
	V3	−0.150 (−0.309; 0.018)	−0.082 (−0.250; 0.080)	0.240 (0.078; 0.389) **	0.353 (0.200; 0.489) ***†

* p < 0,05, ** p < 0,01, *** p < 0,001.
† denotes correlations conducted after transformation by Oldham.

ST amplitude were higher in males than in females in leads V2 and V3 (post-induction ST amplitude in V2: 274 ± 148 for females; 388 ± 212 for males, $p < 0.001$).

Discussion

The objective of this prospective observational study was to characterize the response to the pharmacological induction test in patients with induced Brugada syndrome across four French centers. We studied 157 patients and digitized at least one ECG per patient after pharmacological provocation. To our knowledge, this is one of the few studies evaluating the response to pharmacological induction testing in Brugada syndrome based on parameters obtained through ECG digitization and automatic electrocardiographic measurement analysis.

We observed that the magnitude of the sodium channel blockade effect on the ST segment was strongly correlated with baseline ST amplitude. However, approximately one-third of patients (36 %) had a normal baseline ECG, and fewer than half exhibited baseline ST segment abnormalities. Baseline electrocardiographic differences between ECG qualitative groups were no longer apparent during the pharmacological challenge. A moderate correlation was also found between baseline QRS duration and its prolongation after pharmacological induction, although the explained variance (R^2) barely exceeded 10 %. Finally, we noted that the presence of a pathogenic SCN5A mutation was associated with distinct ECG features and a differential response to sodium channel blockade.

Profile of patients

The profile of our patients appears comparable to the populations in major Brugada syndrome registries [18,25,26]. Indeed, our study includes 72 % males, with a mean age at diagnosis of 43 ± 13 years. In addition, it features a significant number of symptomatic patients at diagnosis, with 6 % experiencing recovered sudden cardiac death and 11 % having suffered a syncopal episode due to arrhythmia. A P/LP variant was found in 14 % of our patients, with 11 % involving the SCN5A gene. This is lower than the known proportion of patients with Brugada syndrome, which is around 20–25 %, but consistent with the

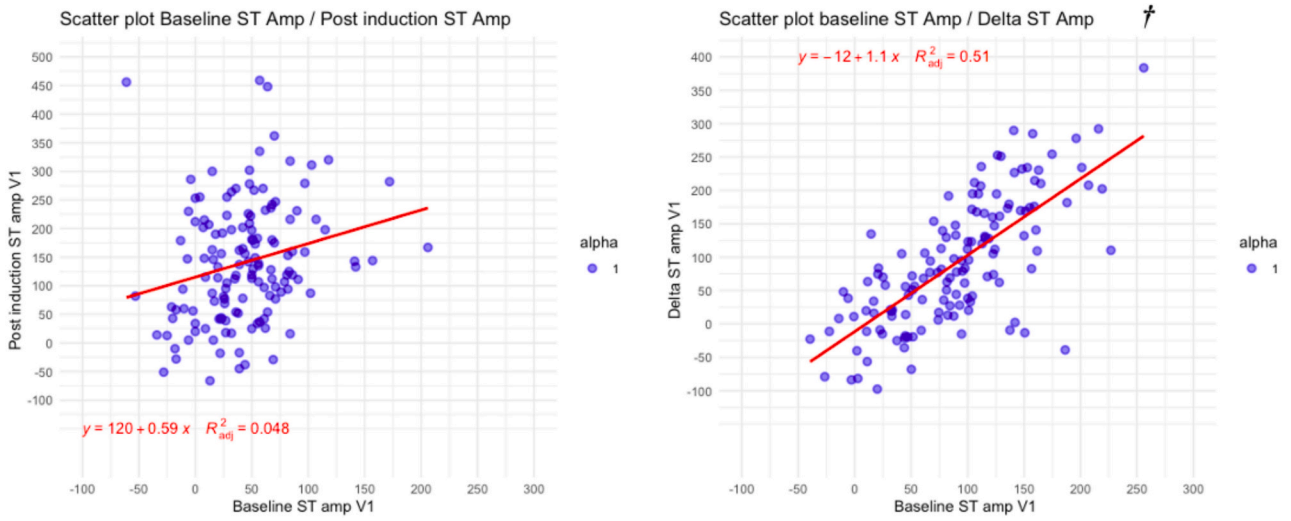

Fig. 2. ST amplitude scatter plots.
† denotes correlations conducted after transformation by Oldham.

Table 4
: Electrocardiographic characteristics based on SCN5A mutation and sexe status.

		SCN5A − (n = 115)	SCN5A + (n = 18)	NA (n = 24)	ANOVA P value	Male (n = 112)	Female (n = 45)	p
QRS Dur V1	baseline	91 ± 18	106 ± 34	90 ± 17	**< 0.05** *§	95 ± 22	86 ± 15	**<0.01**
	induction	110 ± 29	119 ± 35	116 ± 25	0.38	117 ± 29	101 ± 27	**<0.01**
	delta	20 ± 31	16 ± 37	25 ± 26	0.64	23 ± 31	15 ± 32	0.15
QRS Dur V2	baseline	93 ± 16	117 ± 35	95 ± 17	**< 0.05** *§	97 ± 21	93 ± 18	0.23
	induction	115 ± 24	124 ± 31	119 ± 28	0.1	119 ± 25	112 ± 25	0.11
	delta	22 ± 26	9 ± 43	25 ± 25	0.55	22 ± 31	20 ± 23	0.79
QRS Dur V3	baseline	94 ± 14	114 ± 24	92 ± 13	**<0.001** *§	97 ± 17	93 ± 13	0.2
	induction	118 ± 22	135 ± 31	114 ± 20	**< 0.05** *§	121 ± 22	115 ± 27	0.19
	delta	25 ± 25	19 ± 32	22 ± 21	0.59	24 ± 23	22 ± 29	0.66
QRS GBL Duration	baseline	110 ± 17	127 ± 29	108 ± 15	**<0.01** *§	113 ± 25	109 ± 29	0.2
	induction	136 ± 20	150 ± 29	137 ± 22	0.06	141 ± 25	131 ± 24	**0.014**
	delta	21 ± 26	21 ± 24	27 ± 21	0.20	23 ± 22	18 ± 24	0.24
ST Amp V1	baseline	41 ± 47	29 ± 30	50 ± 45	0.24	46 ± 41	29 ± 53	0.07
	induction	153 ± 108	127 ± 94	93 ± 91	0.05	152 ± 107	116 ± 100	0.06
	delta	109 ± 111	92 ± 85	53 ± 90	0.10	106 ± 106	85 ± 109	0.31
ST Amp V2	baseline	106 ± 79	105 ± 73	117 ± 102	1	127 ± 85	59 ± 47	**<0.001**
	induction	356 ± 181	461 ± 349	278 ± 128	0.07	388 ± 212	274 ± 148	**<0.01**
	delta	251 ± 177	361 ± 361	173 ± 140	0.064	267 ± 220	207 ± 139	0.06
ST Amp V3	baseline	94 ± 71	96 ± 101	104 ± 70	0.63	113 ± 77	53 ± 45	**<0.001**
	induction	187 ± 150	98 ± 184	175 ± 175	0.17	204 ± 157	113 ± 145	**<0.01**
	delta	95 ± 141	0,8 ± 209	75 ± 190	0.16	91 ± 162	64 ± 144	0.34

P_ANOVA represents the p-value among the three groups: Non-mutated, SCN5A, and NA.
* denotes a p-value < 0.05 from the test comparing the SCN5A - group versus the SCN5A + group.
§ denotes a p-value < 0.05 from the test comparing the SCN5A + group versus the NA group.
p represents the p-value between males and females.

induced nature of the condition [27].

The most frequently used provocation test was ajmaline (91 %), as recommended by the 2022 guidelines on the prevention of sudden cardiac death, with ajmaline being more sensitive than flecainide. [3,14].

Electrocardiographic characteristics by ECG group

We divided the patients into groups based on their baseline electrocardiographic pattern. More than one-third of patients with induced Brugada syndrome had a normal baseline ECG (Group 4, 36 %), and in less than half of cases (42 %) there was an ST-segment abnormality (22 % coved-type, 20 % saddle-back). Our analysis is an observational review of ECGs from patients with induced Brugada syndrome; thus, one should not conclude that a normal baseline ECG implies a high likelihood of induction, but that among those with induced Brugada syndrome, a substantial proportion have a normal baseline ECG.

The global QRS duration of our induced Brugada population (112 ± 19 ms) was prolonged compared to the general population (normal <100 ms), likely reflecting the high proportion of baseline QRS prolongation. Additionally, the saddle-back group had a significantly longer QRS in lead V1 compared to the normal ECG group, suggesting intrinsic sodium channel loss-of-function leading to conduction disturbances. Global QRS duration did not differ significantly among groups and was also prolonged in patients with a normal baseline ECG, likely due to measuring global QRS across 12 leads, extending duration compared to individual leads.

Finally, no differences were found in the post-induction ECG characteristics or delta values among groups, suggesting a homogeneous response to the provocation test. This indicates a pharmacological effect

stronger than baseline loss-of-function, meaning baseline ECG categories cannot predict QRS prolongation or ST elevation during drug challenge.

Electrocardiographic correlations

As previously described, sodium channel blockade induced by the injection of the pharmacological agent used during the induction test leads to a prolongation of PR, QRS, and QT intervals, as well as an elevation of the ST segment amplitude [4].

In the present study, we observed that the amplitude of sodium channel blockade effect on the ST segment strongly correlates with baseline ST amplitude. Specifically, the increase in delta ST amplitude in leads V1-V3 was positively associated with elevated baseline ST amplitude, with correlation coefficients around 0.7. Notably, post-induction J-point amplitude was only weakly correlated with baseline J-point amplitude, with correlation coefficients around 0.2 (in V3: 0.249 (0.085; 0.400), $p < 0.01$). Therefore, baseline J-point amplitude may predict the gradient of J-point elevation but does not accurately predict post-induction values.

Baseline QRS duration in V2 was correlated with increases in post-induction ST amplitude (0.334 (0.178; 0.474)) and delta ST amplitude (0.324 (0.167; 0.465)). However, this was not true for all right precordial leads, as no significant correlation was found between baseline QRS duration and ST amplitude in V1, with even a negative trend between QRS duration and ST amplitude in V3. This may imply that baseline QRS duration predicts a positive pharmacological response, particularly in V2, but the correlation coefficients are low and the explainable variance (R^2) does not exceed 10 %. Thus, there appears to be a de-correlation between pure depolarization parameters (QRS duration) and sodium channel blockade effects on ventricular repolarization (ST elevation).

Baseline QRS duration also predicts post-induction QRS prolongation and global QRS delta increase. Baseline QRS duration in V1-V3 was significantly correlated with delta QRS and post-induction QRS duration in V1-V3, but again, the explainable variance (R^2) barely exceeds 10 %. This suggests that longer baseline QRS durations are more likely to prolong during pharmacological testing, reflecting the extent of intrinsic sodium channel blockade. This should be considered to ensure that the test is conducted with appropriate safety measures (termination when QRS $\geq$ 130 % above baseline value and antagonization by the injection of 8.4 % molar bicarbonate solution [3,14].

SCN5A P/LP variants and sex status

As expected, patients with a pathogenic P/LP variant in the SCN5A gene [3,12], exhibited a prolongation of global QRS duration and in leads V1-V3 compared to patients without identified mutations or non-mutated patients. However, except for post-induction QRS duration in lead V3, there is no difference among the groups regarding post-induction QRS duration or delta (global QRS duration or QRS duration in V1-V3). This likely implies that the effect of sodium channel blockade induced by the pharmacological agent used during the induction test significantly exceeds the effect of the mutation alone with respect to QRS widening. This substantial effect of the sodium channel blocker appears to be confirmed by the homogeneous response observed across the different electrocardiographic groups [1 to 4] in post-induction and delta analyses.

We also observed no significant difference in ST amplitude among patients with SCN5A P/LP variants compared to other groups. The amplitude of sodium channel blockade induced by a P/LP SCN5A variant does not translate into a distinct electrocardiographic manifestation of early repolarization at baseline in our population of patients with induced Brugada syndrome.

Our analysis by sex revealed that global QRS duration and QRS duration in lead V1 were prolonged post-induction in men compared to women, and baseline and post-induction ST amplitude were also more pronounced in men in leads V2 and V3. Although there is no reported increased risk of arrhythmia during pharmacological induction testing in men compared to women [15,18], our results suggest that male patients may exhibit greater sensitivity to the effects of sodium channel blockade. This is consistent with the study by *Veltmann* et al. [15], which showed in their multivariate analysis that male sex was a risk factor for a positive response to ajmaline testing.

Based on these results, it may be concluded that the induction test could be more pronounced in men, and careful attention to arrhythmic risk is important. However, this should not undermine the diagnosis in women, who may present with less evocative pre-test ECGs and a less pronounced response.

Advantages and limitations of electrocardiographic digitization

The validation of the practice of digitizing paper ECGs in patients with Brugada syndrome has already been described by our team [4]. Digitization offers key advantages, such as preventing ECG loss or degradation over time and facilitating secure transmission for collaborative studies. This process allows for retrospective analysis of high-quality ECGs, crucial for examining conditions like Brugada syndrome and other channelopathies. The versatility of the ECGscan software, highlighted by *Baeza* et al. [28]. makes it particularly effective for digitizing ECG signals. Despite its benefits, digitization has inherent limitations, especially concerning the quality of the original ECG. To address this, we selected high-quality ECGs with strict criteria. However, this process is time-consuming due to the need for manual adjustments during digitization, which extends the overall procedure duration.

Our study has some limitations, mainly due to its observational design and the small number of symptomatic patients. However, the study's focus was to characterize the response to pharmacological testing in Brugada syndrome, not to identify predictive factors for arrhythmic risk, making an observational approach appropriate. ECG classification into groups [1–4,or] was done by a single observer, which may introduce bias, though based on established criteria [3,12,29], ensuring consistency. While we did not characterize certain qualitative ECG features, we focused on recognized diagnostic criteria, particularly ST segment elevation at the J-point >2 mm.

This is an exploratory study aimed at identifying research targets that could be enhanced with new parameters or techniques such as artificial intelligence. Indeed, a study published in 2023 by *Melo* et al. [30] evaluated the use of deep learning to identify specific electrocardiographic markers of Brugada syndrome in patients with induced SBr, potentially rivaling the use of pharmacological provocation tests (AUC 0.934). Similarly, a study published in May 2024 by *Calburean* et al. [31] developed a deep convolutional neural network capable of predicting the positivity of the ajmaline test with good performance (AUC-ROC 0.805 (0.845–0.736)). Prospective studies with long-term follow-up are needed to determine whether the magnitude of the pharmacological response correlates with arrhythmic risk and to explore the mechanisms underlying the observed sex differences.

Conclusion

This study aimed to better understand the factors influencing the response to pharmacological induction. Our findings highlight the critical value of pharmacological testing in unmasking subtle electrophysiological abnormalities that may not be apparent on baseline ECG. While a strong correlation was observed between the sodium channel blockade effect and baseline ST amplitude, a substantial proportion of patients displayed normal baseline ECGs. Importantly, baseline electrocardiographic differences between groups vanished during drug challenge, and the response to sodium channel blockade varied significantly across subgroups — notably among male patients and SCN5A mutation carriers. These observations call for caution in relying solely on baseline

ECG criteria to predict pharmacological test outcomes, and emphasize the need for a nuanced, individualized approach in clinical evaluation.

The authors have no conflicts of interest to disclose.

CRediT authorship contribution statement

Pierre-Léo Laporte: Writing – review & editing, Writing – original draft. **Martino Vaglio:** Software. **Isabelle Denjoy:** Resources. **Pierre Maison-Blanche:** Methodology. **Philippe Maury:** Resources. **Alexis Hermida:** Resources. **Didier Klug:** Resources. **Alice Maltret:** Resources. **Fabio Badilini:** Software. **Antoine Leenhardt:** Supervision. **Fabrice Extramiana:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no conflicts of interest to disclose related to the content of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2025.154081.

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