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Clinical Research

Automatized quantitative electrocardiography from digitized paper electrocardiograms: A new avenue for risk stratification in patients with Brugada syndrome

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ABSTRACT

Background. – Arrhythmic risk stratification is a major challenge in Brugada syndrome. Studies have evaluated risk stratification based on manually measured electrocardiogram (ECG) parameters at baseline and/or after drug challenge.
Aim. – To assess the predictive value of multiple ECG parameters measured automatically from digitized paper ECGs.
Methods. – During a prospective, multicentre cohort study that included patients with Brugada syndrome with type 1 ECG (spontaneously or drug-induced), paper ECGs were digitized and analysed. Major events were sudden cardiac death, aborted cardiac arrest and appropriate implantable cardioverter-defibrillator (ICD) therapy in the ventricular fibrillation (VF) zone. The predictive value of clinical and ECG parameters was assessed using univariable and multivariable Cox models.
Results. – ECGs from 301 patients (74% male, mean age 43.1 ± 13.3 years, mean follow-up 7.1 ± 5.6 years) were analysed. Major events occurred in 6% of patients before diagnosis and 8% during follow-up. Two baseline ECG parameters were independently associated with major events: QRS prolongation in lead V1 > 113 ms (hazard ratio [HR] 3.49, 95% confidence interval [CI] 1.72–7.09; $P < 0.001$) and S duration on DI > 33.5 ms (HR 3.56, 95% CI 1.52–8.31; $P < 0.01$). In drug-induced patients, changes in the Tpeak-Tend interval on V2 were associated with major events (HR 4.69, 95% CI 1.21–18.17; $P = 0.014$).
Conclusion. – Paper ECG datasets could be used for automatic quantitative ECG measurements. We confirmed the association of previously described parameters with events and identified useful new parameters. Multi-parametric ECG quantification may be used to assess risk in patients with Brugada syndrome.

1. Abbreviations

ANOVA	analysis of variance
ECG	electrocardiogram
ICD	implantable cardioverter-defibrillator
ROC	receiver operating characteristic
RVOT	right ventricular outflow tract
VF	ventricular fibrillation

2. Background

Brugada syndrome, initially described in 1992 [1], is marked by a distinctive electrocardiographic pattern and increased risk of ventricular arrhythmias and sudden cardiac death [2]. It pri-

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marily affects young individuals and can potentially be prevented by implantable cardioverter-defibrillators (ICDs) [3], although ICDs may lead to severe complications. Risk scores have been proposed to improve arrhythmic risk stratification (e.g. Sieira score [4], Shanghai score [2]), but have been shown to perform poorly in patients with an intermediate risk [5] and the predictive value of positive ventricular stimulation remains debated [6–8].

Several studies have assessed risk stratification in Brugada syndrome using electrocardiogram (ECG)-derived parameters [8–13], but manual measurements are challenging, time-consuming and exhibit poor accuracy and reproducibility. Automatic measurements from digital ECGs offer greater precision. In a previous study, we showed that automated algorithm-based measurements of depolarization and repolarization parameters from digitized paper ECGs are reliable [14]. In the current study, we aimed to automatically measure multiple ECG parameters from digitized paper ECGs to assess their association with arrhythmic events in Brugada syndrome.

3. Methods

3.1. Study design and population

We conducted a prospective four-centre (Paris, Toulouse, Amiens, Lille) observational study. The study, based on the MUTAVIT registry (Clinical Hospital Research Financing Program No. AOR04070 P040411), intended to follow up patients with a history of ventricular fibrillation (VF) or at risk of life-threatening ventricular arrhythmia in the absence of structural heart disease.

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

The inclusion criterion was an ECG showing a type 1 Brugada pattern [3], confirmed by two senior cardiologists. Exclusion criteria included contraindications to sodium channel blockers, pregnancy, breastfeeding and age < 15 years for patients requiring a challenge test.

Patient data, clinical history and ECGs were collected at inclusion. Echocardiography was performed, genetic analysis offered, and programmed ventricular stimulation conducted at the treating physician's discretion. Follow-up occurred from January 2005 to November 2021, with major events including sudden cardiac death, aborted cardiac arrest and ICD therapy in the VF zone. Cardiac events also included syncope deemed to be of cardiac cause.

3.2. ECG selection and digitization

For each patient, a baseline paper ECG was retrieved. If the baseline ECG did not display a type 1 Brugada syndrome pattern, another paper ECG showing the pattern obtained during a drug challenge was considered. All paper ECGs were de-identified, digitized [14] and stored in a digital format (HL7-XML). Automated measurements were finally obtained by applying the Bravo and Glasgow algorithms to the digital ECGs [14–16].

The ECG measurements consisted of the following 'global parameters' (i.e. computed on the 12-lead median beats): RR intervals (ms); heart rate (bpm); PR, QRS, QT intervals and Bazett and Fridericia corrected QTc intervals (ms); Tpeak-Tend (TpTe) interval (ms); 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. Some specific parameters from the Bravo and Glasgow algorithms were also automatically measured on leads V1, V2 and V3 (Table 1). A complete list of ECG measurements is provided in Text A.1 and A.2. Parameters derived from previous studies and associated with relevant outcomes were also considered. These included spontaneous type 1, T/R ratio in DII and V5, R-wave amplitude in AVR (μV), S-wave duration in DI and V1 (ms) and the presence of early inferolateral repolarization (R notch on inferior leads) [7,9–12,17–20]. Finally, all baseline and drug-induced ECGs were analysed, and when both visits were available, the drug-induced versus baseline differences of each parameter were computed.

Table 1
Analysed electrocardiographic parameters.

Known parameters	
TpTe	Interval between T wave peak and T wave end
T/R II or V5	T/R ratio in DII or V5
R amp AVR	R amplitude in aVR (aVR sign)
Inferior R notch	Early inferolateral repolarization
S dur I	S duration in DI
QRS dur	QRS duration
Other parameters	
QRS area	QRS surface
QRS int	QRS integral
JTp	Interval duration from J wave to T wave apex
JTpArea	Interval area from J wave to T wave apex
ST slope	Slope between J point and 3/8 of ST-T segment
STamp	Maximum ST segment amplitude
L slope Val Fr J	T wave coefficient of upward slope (from J)
L slope Pos Fr J	T wave max upward slope position (from J)
R slope Val Fr J	T wave coefficient of downward slope (from J)
R slope Pos Fr J	T wave max downward slope position (from J)
SymArea Fr J	Ratio of the area of the T wave (from J) before and after its peak
T– amp	Maximum negative amplitude of T wave
QT int	QT integral

3.3. Statistical analysis

Continuous variables are presented as means ± standard deviations. Categorical variables are expressed as numbers and percentages. Statistical tests, including *t*-tests, Mann-Whitney tests, Pearson's Chi-square test, Fisher's Exact test, 1-factor analysis of variance (ANOVA), Tukey's test, and Kruskall-Wallis test, were used for comparisons based on variable types.

The occurrence of events was assessed from birth to the end of follow-up, referred to as 'lifetime events'. Risk factors for arrhythmic events were evaluated using univariate and multivariable Cox models. In the multivariable analysis, variables with $P \leq 0.1$ were included, and a stepwise selection algorithm determined the most relevant variables associated with the outcome. Pertinent hazard ratios (HRs) and 95% confidence intervals (CIs) > 0.995 and < 1 are reported as 0.999 while those > 1 and < 1.005 are reported as 1.001.

All tests were two-tailed, and significance was set at $P < 0.05$. RStudio software (Version 4.1.2, 2009-2022 RStudio©, PBC) was used for all statistical analyses.

4. Results

4.1. Clinical data

Among 548 patients in the MUTAVIT registry, 352 met the inclusion criteria and follow-up was available for 301 patients. The clinical characteristics of the study population are presented in Table 2. Mean age at diagnosis was 43.1 ± 13.3 years, 26% were female and 82% were probands. Overall, 25% of patients had a family history of sudden death, of which 27% occurred before the age of 45 years.

Genetic analysis was available for 282 patients, of whom 26% had pathogenic or likely pathogenic mutations. Cardiac ultrasound results were available for 236 patients, of whom 94% showed normal results (seven patients had non-severe valvular disease, five

Table 2
Clinical characteristics of the patients.

	All patients ($n=301$)	Asymptomatic ($n=217$)	Cardiac syncope ($n=51$)	Major events ($n=33$)	ANOVA	*P*
Age at diagnosis (years)	43.1 ± 13.3	43.7 ± 13.0	43.8 ± 14.2	38.0 ± 13.5	0.065	
Follow-up duration (years)	7.1 ± 5.6	6.5 ± 5.2	7.5 ± 5.2	11.0 ± 6.7*,**	**0.0072**	
Age at end of follow-up (years)	50.2 ± 13.9	50.0 ± 13.6	51.2 ± 13.9	49.3 ± 16.2	0.80	
Female sex	77 (26)	62 (29)	14 (27)	1 (3)*,**	**0.0044**	
Proband	248 (82)	173 (80)	45 (88)	30 (91)	0.14	
Near syncope	53 (18)	36 (17)	11 (22)	6 (18)	0.70	
Non-cardiac syncope	44 (15)	21 (10)**	17 (33)**	6 (18)	**<0.001**	
Family history of sudden death	74 (25)	55 (25)	11 (22)	8 (24)	0.85	
Sudden family death < 45 years	20 (7)	13 (6)	2 (4)	5 (15)	0.093	
Family history of syncope	13 (4)	6 (3)	5 (10)**	2 (6)	**0.041**	
Ischaemic heart disease	5 (2)	3 (1)	1 (2)	1 (3)	0.43	
Diabetes	3 (1)	3 (1)	0 (0)	0 (0)	–	
Dyslipidaemia	37 (12)	26 (12)	7 (14)	4 (12)	0.96	
Hypertension	38 (13)	28 (13)	8 (16)	2 (6)	0.42	
Psychiatric disease	13 (4)	7 (3)	3 (6)	3 (9)	0.15	
SCN5A mutation ($n=282$)	63 (22)	45 (23)	8 (17)	10 (31)	0.25	
Positive programmed ventricular stimulation ($n=131$)	68 (52)	41 (51)	14 (43)	13 (68)	0.23	
SVT	13 (4)	5 (2)**	3 (6)	5 (15)**	**0.0027**	
Age at ICD implantation (years) ($n=85$)	41.5 ± 13.4	43.7 ± 11.8	43.6 ± 14.0	38.1 ± 13.5	0.18	

ANOVA: analysis of variance; ICD: implantable cardioverter-defibrillator; SVT: supraventricular tachycardia. Characters in bold are *P* values that have reached the significant treshold < 0.005.
* $P<0.05$ versus asymptomatic patients.
** $P<0.05$ versus patients with cardiac syncope.

had moderate impairment of systolic function [left ventricular ejection fraction 45–50%] and one had left ventricular hypertrophy [hypertensive patient]). Programmed ventricular stimulation was performed in 131 patients, of whom 52% tested positive.

Mean follow-up was 7.1 ± 5.6 years and the mean age at the end of follow-up was 50.2 ± 13.9 years. ICDs were implanted in 28% of patients and 10% had an implantable loop recorder. Overall, 18% of patients were treated with hydroquinidine and three patients underwent an ablation procedure for arrhythmic storms.

There were 102 symptomatic events (69 before diagnosis and 33 during follow-up, of which 12 were recurrences), including 43 major events (18 before diagnosis and 25 during follow-up, of which 10 were recurrences) and 59 cardiac syncope (51 before diagnosis and eight during follow-up, of which two were recurrences) (Fig. 1).

Six patients had both a cardiac syncope and a major event during follow-up and were considered as patients with major cardiac events. Overall, 84 patients had cardiac events: 33 patients with a major event at a mean age of 39.0 ± 15.7 years, and 51 patients with a cardiac syncope at a mean age of 35.0 ± 17.3 years. Among 301 patients with follow-up, seven (2.3%) died. The causes of death varied, including extracardiac causes and endocarditis on ICD leads.

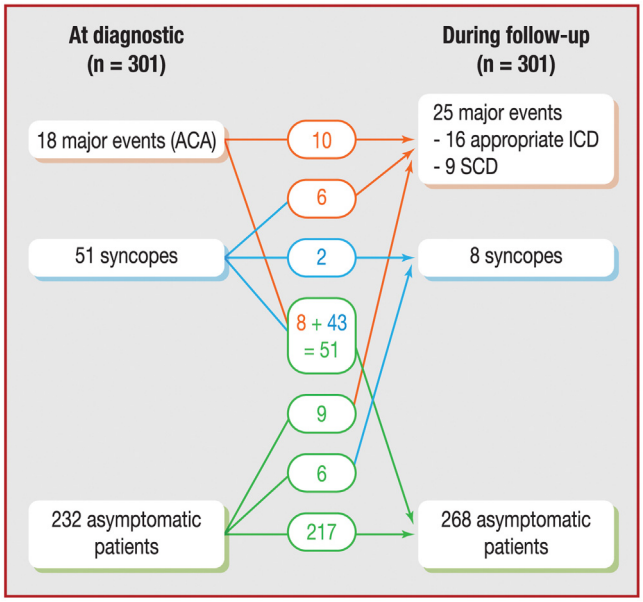


Fig. 1. Events before and after diagnosis. ACA: aborted cardiac arrest; ICD: implantable cardioverter-defibrillator; SCD: sudden cardiac death.

4.2. ECG data

Overall, 458 digitized ECGs were analysed (294 baseline and 164 during drug challenge). A total of 158 patients had both baseline and drug-challenge ECGs, 136 had a spontaneous type 1 ECG pattern and seven patients had only drug-challenge ECGs.

Baseline 12-lead ECG parameters are presented in Table A.1. Patients with major events had a prolonged mean QRS duration (133 ± 26 vs 115 ± 19 ms; $P<0.001$) and a shortened mean ST-segment duration (48 ± 27 vs 65 ± 32 ms; $P<0.01$) compared to asymptomatic patients. They also had longer mean RR interval (924 ± 193 vs 818 ± 158 ms; $P=0.032$), longer mean QRS duration (133 ± 26 vs 114 ± 22 ms; $P<0.01$), but shorter mean ST-segment duration (48 ± 27 vs 69 ± 31 ms; $P<0.01$) compared to patients with cardiac syncope.

Parameters associated with events in previous studies are also provided in Table A.1. Patients with major events showed a prolonged mean TpTe interval in V1 (102 ± 33 vs 87 ± 20 ms; $P=0.041$) and a prolonged mean S-wave duration in DI (45 ± 32 vs 22 ± 23 ms; $P<0.01$) compared to asymptomatic patients. They also had prolonged mean TpTe on V1 (102 ± 33 vs 80 ± 17 ms; $P=0.014$) and a prolonged mean S-wave duration on DI compared to patients with cardiac syncope (45 ± 32 vs 24 ± 21 ms; $P=0.011$).

ECG parameters during the drug challenge and drug-induced changes were similar across symptomatic status groups (Tables A.2 and A.3).

Table 3
Univariate and multivariable Cox models predictive of major event[a].

	Univariate		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Baseline ECG				
Global RR	1.001 (1.001–1.01)	**0.022**	1.01 (1.001–1.02)	**0.001**
TpTe V1	1.02 (1.01–1.03)	**0.004**	1.03 (0.99–1.06)	0.12
SymArea Fr J V1	0.99 (0.98–0.999)	0.083	0.98 (0.97–0.99)	**0.006**
QRS dur V1	1.03 (1.01–1.04)	**<0.001**	1.05 (1.01–1.10)	**0.011**
QT int V1	1.01 (1.001–1.02)	**0.025**	0.96 (0.94–0.99)	**0.005**
R amp aVR	1.001 (1.001–1.01)	0.089	0.99 (0.98–0.999)	**0.027**
S dur I	1.02 (1.01–1.04)	**<0.001**	1.04 (1.01–1.08)	**0.023**
Female sex	0.08 (0.01–0.61)	**0.015**	0.00 (0.00–infinity)	1.00
SVT	4.09 (1.57–10.65)	**0.004**	4.59 (0.73–28.94)	0.11
Post-induction ECG				
TpTe V2	0.98 (0.95–1.001)	0.093	0.34 (0.00–3.35)	0.99
JTpArea V2	1.001 (1.001–1.001)	**0.018**	1.00 (0.80–1.26)	0.97
ST amp V1	1.01 (1.001–1.01)	0.075	0.62 (0.00–infinity)	0.97
ST slope V3	1.05 (1.01–1.08)	**0.012**	4.65 (0.00–2.80)	0.98
LSlope Val Fr J V1	0.62 (0.44–0.89)	**0.010**	0.00 (0.00–infinity)	0.96
Delta ECG				
TpTe V2	0.99 (0.98–0.999)	0.080	0.99 (0.97–0.999)	**0.049**
R amp V3	1.001 (1.001–1.001)	0.092	1.001 (1.001–1.001)	**0.033**
ST Amp V3	0.999 (0.99–0.999)	**0.026**	0.999 (0.99–0.999)	**0.008**
LSlope Val Fr J V1	0.86 (0.73–1.01)	0.070	0.83 (0.70–0.99)	**0.041**

amp: amplitude; CI: confidence interval; dur: duration; ECG: electrocardiogram; HR: hazard ratio; int: integral; TpTe: Tpeak-Tend. Please see Table 1 for further definitions.
[a] Pertinent HRs and 95% CIs > 0.995 and < 1 are reported as 0.999 while those > 1 and < 1.005 are reported as 1.001.

4.3. Predictive factors

Table 3 shows the key results of the univariate and multivariable analyses for baseline ECGs, while results for all parameters are presented in Table A.4. RR interval duration (HR 1.01, 95% CI 1.001–1.02; *P* = 0.001), SymArea from J to V1 (HR 0.98, 95% CI 0.97–0.99; *P* = 0.006), QRS duration in V1 (HR 1.05, 95% CI 1.01–1.10; *P* = 0.011), integral QT in V1 (HR 0.96, 95% CI 0.94–0.99; *P* = 0.005), R Amp AVR (HR 0.99, 95% CI 0.98–0.999; *P* = 0.027) and S duration in DI (HR 1.04, 95% CI 1.01–1.08; *P* = 0.023) were independently associated with the risk of a major event.

For QRS duration on V1, the area under the receiver operating characteristic (ROC) curve was 0.69 (95% CI 0.58–0.80) and the optimal cut-off value of 113 ms had a sensitivity of 0.55 and a specificity of 0.77 (Fig. 2A). The cumulative incidence curve of major events according to QRS duration in V1 (> or < 113 ms) as a function of age is shown Fig. 2B. The univariate HR of the binary qualitative variable 'QRS V1 > or < to 113 ms' was 3.49 (95% CI 1.72–7.09; *P* = 0.00022) (Fig. 2B).

For S duration on DI, the area under the ROC was 0.70 (95% CI 0.58–0.82) and the optimal cut-off value of 33.5 ms had a sensitivity of 0.67 and a specificity of 0.67 (Fig. 3A). The cumulative incidence curve of major events according to S duration in DI (> or < 33.5 ms) as a function of age is shown in Fig. 3B. The univariate HR of the binary qualitative variable 'S dur DI > or < 33.5 ms' was 3.56 (95% CI 1.52–8.31; *P* = 0.0018) (Fig. 3B). No discriminant cut-off values could be found for the other parameters.

Table 3 also shows the results of the univariate and multivariable analyses for ECGs during drug challenge. All analysed parameters are presented in Table A.5. There were no statistically significant variables in the multivariable analysis.

Table 3 also shows the results of the univariate and multivariable analyses for the changes in ECG parameters induced by drug challenge. All analysed parameters are presented in Table A.6. The delta of TpTe in V2 (HR 0.99, 95% CI 0.97–0.999; *P* = 0.049), the delta of R Amp in V3 (HR 1.001, 95% CI 1.001–1.001; *P* = 0.033), the delta of ST Amp in V3 (HR 0.999, 95% CI 0.99–0.999; *P* = 0.008) and the delta of LSlope value in V1 (HR 0.83, 95% CI 0.70–0.99; *P* = 0.041) were independently associated with the risk of a major event.

For the delta of TpTe in V2, the area under the ROC was 0.68 (95% CI 0.51–0.85) and the optimal cut-off value of −1 ms had a sensitivity of 0.71 and a specificity of 0.7 (Fig. 4A). The cumulative incidence curve of major events according to the delta of TpTe in V2 (> or < −1 ms) as a function of age is shown in Fig. 4B. The univariate HR of the binary qualitative variable 'delta of TpTe V2 > or < −1 ms' was 4.69 (95% CI 1.21–18.17; *P* = 0.014) (Fig. 4B). No discriminant cut-off values could be found for the other parameters.

5. Discussion

We report the automatic quantitative multiparameter ECG evaluation obtained from digitized paper ECGs from a cohort of 301 patients with Brugada syndrome. We found that many ECG parameters (both new and previously described) were independently associated with the occurrence of major events. Our results show that: (1) retrospective paper ECG databases could be used for automatic measurements and (2) multi-parametric ECG quantification may improve risk stratification in patients with Brugada syndrome.

5.1. ECG digitization and automatic measurements

Current medical standards are based on 10-second, 12-lead ECG recordings from paper ECG printouts. Unfortunately, these data are often inaccessible and unsuitable for automated analysis due to the limitations of paper-based storage. Paper printouts are susceptible to issues such as ink evaporation, blurriness, folding and crushing, requiring substantial human resources for tasks such as storage and access. Digitizing raw files demands expensive equipment or manual copying [21].

In our study, paper ECGs were digitized by ECGScan, a software tool known for its versatility in managing the ECG signals [22]. The digitization process requires proper rotation of the image to compensate for tilting effects, cutting leads and grid cancellation by drawing around the signal of interest in order to extract the binarized leads (hence increasing the duration of the process). We selected it due to its previously validated accuracy for measuring ECG parameters relevant to Brugada syndrome, allowing us to automatically assess numerous quantitative ECG parameters [14]. Other algorithms, while available, have several limitations [22].

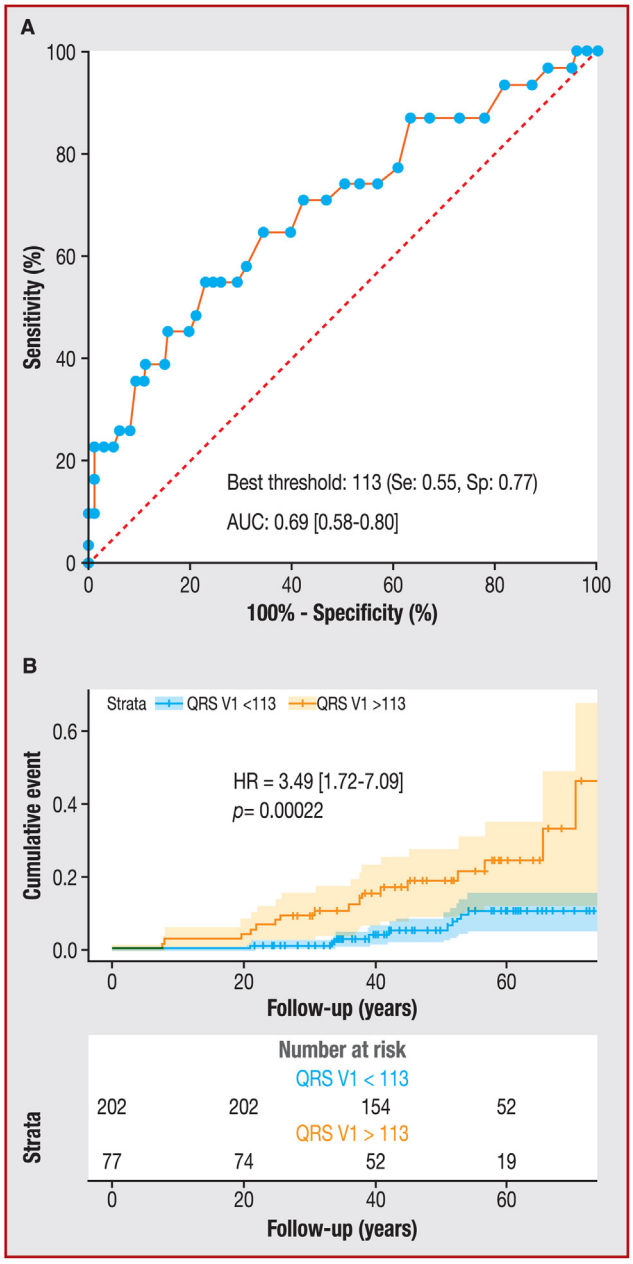


Fig. 2. A. ROC curve of QRS duration in V1 (baseline ECG). B. Cumulative incidence curve of major events according to QRS duration in V1 as a function of age. AUC: area under the curve; CI: confidence interval; ECG: electrocardiogram; HR: hazard ratio; ROC: receiver operating characteristic; Se: sensitivity; Sp: specificity.

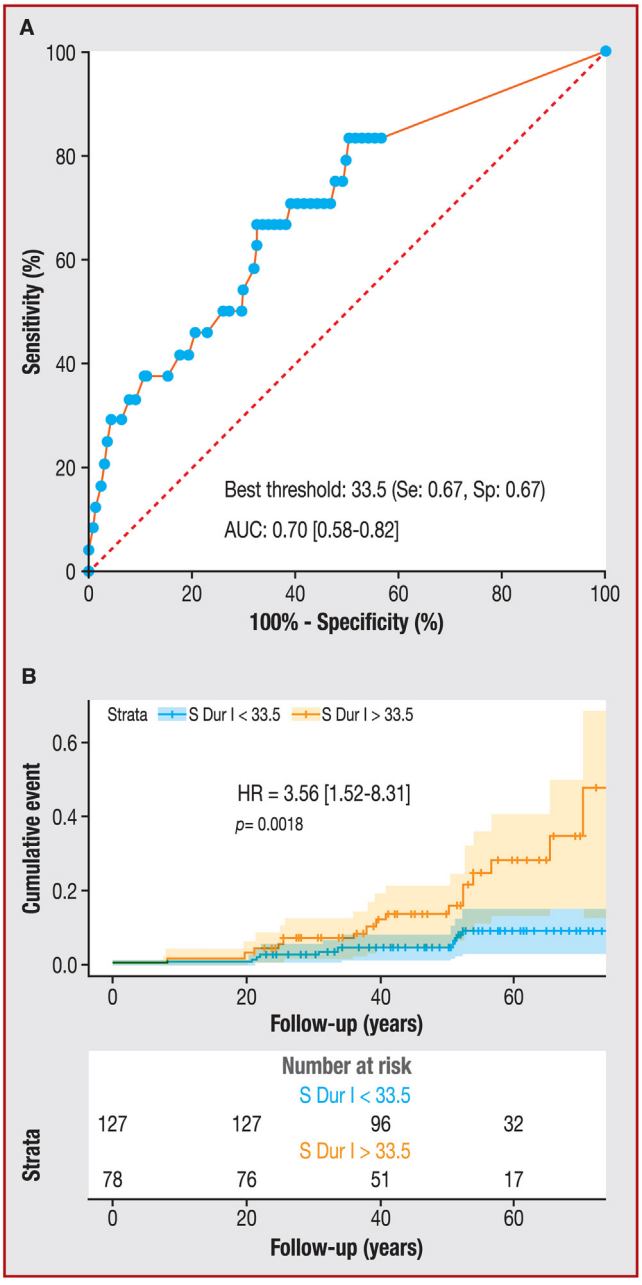


Fig. 3. A. ROC curve of S duration in DI (baseline ECG). B. Cumulative incidence curve of major events according to S duration in DI as a function of age. AUC: area under the curve; CI: confidence interval; ECG: electrocardiogram; HR: hazard ratio; ROC: receiver operating characteristic; Se: sensitivity; Sp: specificity.

5.2. *Patient profiles and outcomes*

In this study, the patient profile was in line with recent large Brugada syndrome registries [7,23,24]. It included mainly (74%) men with a mean diagnosis age of 43.1 ± 13.3 years, of whom 72% are asymptomatic, 11% experienced major events and 17% had rhythmic syncope. We found mutations in 26% of patients who underwent genetic testing, with 22% involving the *SCN5A* gene, consistent with previous studies [23,25].

Brugada syndrome symptoms typically manifest between the ages of 30 and 50 years [26], which is mirrored by our population which had a mean age of 39.0 ± 15.7 years for major events and 35.0 ± 17.3 years for arrhythmic syncope. Most symptomatic patients (93%) experienced their first event between 18 and 65 years of age, with only six outliers, including three patients aged 69 years and three minors.

None of our patients died from ventricular arrhythmia. Among the seven patients who died during follow-up, one succumbed to ICD device infection. Cardiac deaths are infrequent in Brugada syndrome, they mainly relate to ICD complications or arrhythmic storms [7,23]. A personal history of major events significantly increases the risk of ventricular arrhythmias, consistent with the literature [3,7,23]. However, arrhythmic syncope at diagnosis, affecting 17% of our cohort, did not predict more major events during follow-up, aligning with previous studies [23,25] but possibly influenced by reporting bias.

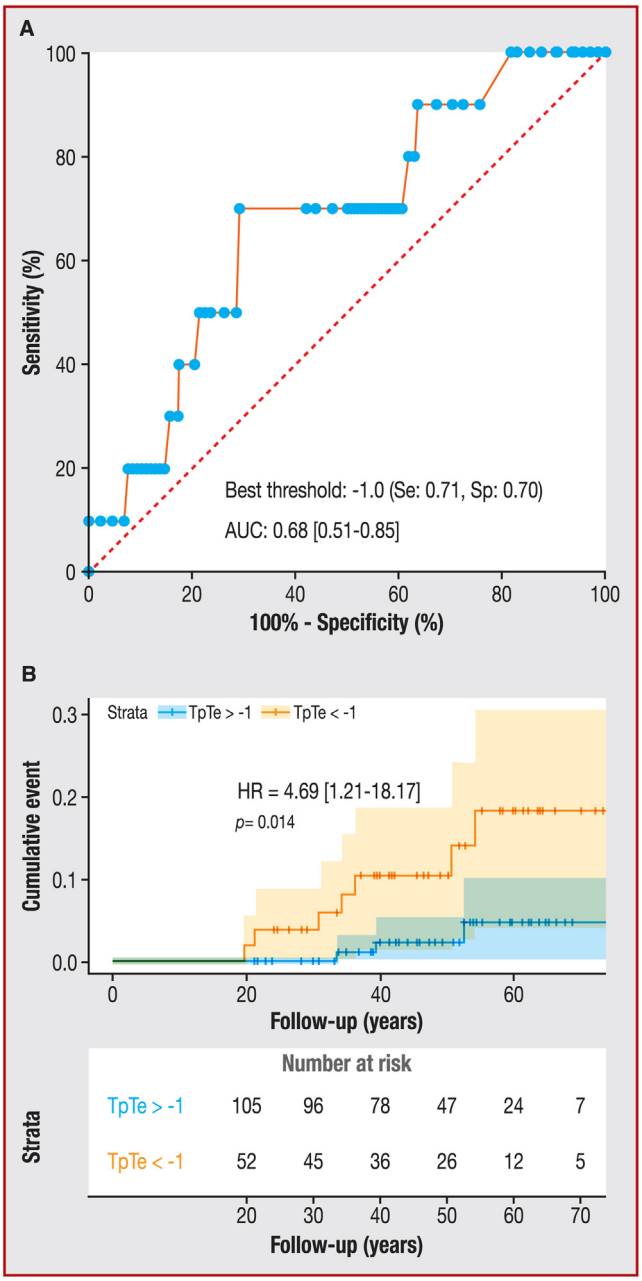


Fig. 4. A. ROC curve of TpTe in V_2 (delta ECG). B. Cumulative incidence curve of major events according to TpTe in V_2 as a function of age. AUC: area under the curve; CI: confidence interval; ECG: electrocardiogram; HR: hazard ratio; ROC: receiver operating characteristic; Se: sensitivity; Sp: specificity; TpTe: Tpeak-Tend.

Programmed ventricular stimulation was only performed in approximately half of the patients in our cohort and was not included in prediction models.

Male gender and the presence of supraventricular tachycardias were associated with major events in univariate analysis, consistent with other studies [7,12,23,25]. The presence of an *SCN5A* mutation and a family history (sudden death or syncope) did not significantly correlate with cardiac events, in agreement with registry data [7].

5.3. ECG predictors of events

Digitizing paper ECGs enables automated measurement of numerous ECG parameters, enhancing speed and reproducibility. Previous studies often considered only a few ECG parameters due to manual measurement challenges. However, some parameters are interrelated and could be incorporated into multivariable models.

Longer QRS duration on lead V1 and S-wave duration on lead I, which have already been described as prognostic factors [9,20], were confirmed as predictors of events in our study. Prolongation of QRS duration was first described in 2013 [9], was then challenged by Maury et al. [11] before being reintroduced in 2020 by Giustetto et al. [20]. Measurement of QRS duration is not an easy task, especially on right precordial leads in patients with Brugada syndrome in whom coved ST elevation makes the determination of the end of the QRS challenging. Differences in QRS duration measurement might explain part of the discrepancies observed between studies. The automated method we used in our study does not guarantee a real QRS duration assessment but at least it is associated with a reproducible and consistent QRS duration evaluation. Of note, the predictive performance of each of these two predictive factors was not sufficient for accurate risk stratification. Whether their integration into multiparameter prediction models would be beneficial remains to be determined.

Spontaneous type 1 ECG pattern, associated with increased risk in some studies [7,11], did not significantly correlate with events in our cohort. Other parameters such as TpTe, QTc, P duration, T/R ratio, early repolarization pattern, 'AVR sign' (R-wave amplitude in AVR > 0.3 mV) [10,11,13,19,27,28] did not significantly relate to events in our study. Fragmented QRS, late potentials, peripheral type 1 and sinus node dysfunction [4,27,29,30] could not be assessed based on our 12-lead 10-second ECG tracings.

Additionally, automated ECG analysis enabled the measurement of parameters such as areas and symmetry, which cannot be obtained manually. Parameters such as QRS-T integral and T-wave symmetry ratio in V1 were independently associated with the occurrence of severe cardiac events. These parameters have not been described before.

Quantitative measurements facilitated the evaluation of ECG changes induced during drug challenge, suggesting that ECG changes rather than ECG during drug challenge could assist in risk stratification.

5.4. Pathophysiology

While it is tempting to interpret ECG parameters associated with events as supporting either the depolarization or the repolarization theories, the crude quantitative characterization of the ECG does probably not allow us to draw pathophysiological conclusions.

QRS duration prolongation is easily explained by a global slowing of depolarization propagation through the ventricle and is often described in loss-of-function SCN5A carriers [31,32]. Similarly, S duration prolongation suggests a slowed propagation through the right ventricle and its outflow tract. In Brugada syndrome, it is widely agreed that the right ventricular outflow tract (RVOT) is the site of the pathology's substrate and it is understood that the depolarization of the RVOT is physiologically delayed, implying that its electrocardiographic expression is more likely to be found on the last vector of the QRS. It intuitively seems logical that a more pronounced substrate would manifest through a more pronounced slowing of propagation in the RVOT, and thus influence the duration of the S-wave in lead D1.

Increased RR interval was predictive of major events in our study. It can be interpreted as a surrogate for latent sinus dysfunction. Other ECG parameters shown to be associated with cardiac events are considered as descriptors of ventricular repolarization properties (e.g. repolarization area symmetry or QT integral) and could be interpreted in favour of the repolarization theory.

Recently, it has been proposed that both depolarization and repolarization abnormalities could interplay and thereby create

the arrhythmogenic substrate in patients with Brugada syndrome [33]. In addition, we cannot rule out that patients with a similar phenotype classified as Brugada syndrome could have different pathophysiological mechanisms or different relative importance of pathophysiological mechanisms.

Overall, it seems reasonable to evaluate the global ECG signal (i.e. with both its depolarization and repolarization components) when trying to characterize the electrophysiological substrate in patients with Brugada syndrome.

5.5. Limitations

This observational study has some inherent limitations. Our major event definition included ventricular arrhythmias, but some may resolve without an appropriate ICD shock. The relatively small number of major events, especially in asymptomatic patients, may have affected predictive model analysis, but our study was intended to be exploratory. Multiple tests could have increased the alpha risk, although strict statistical methods were applied.

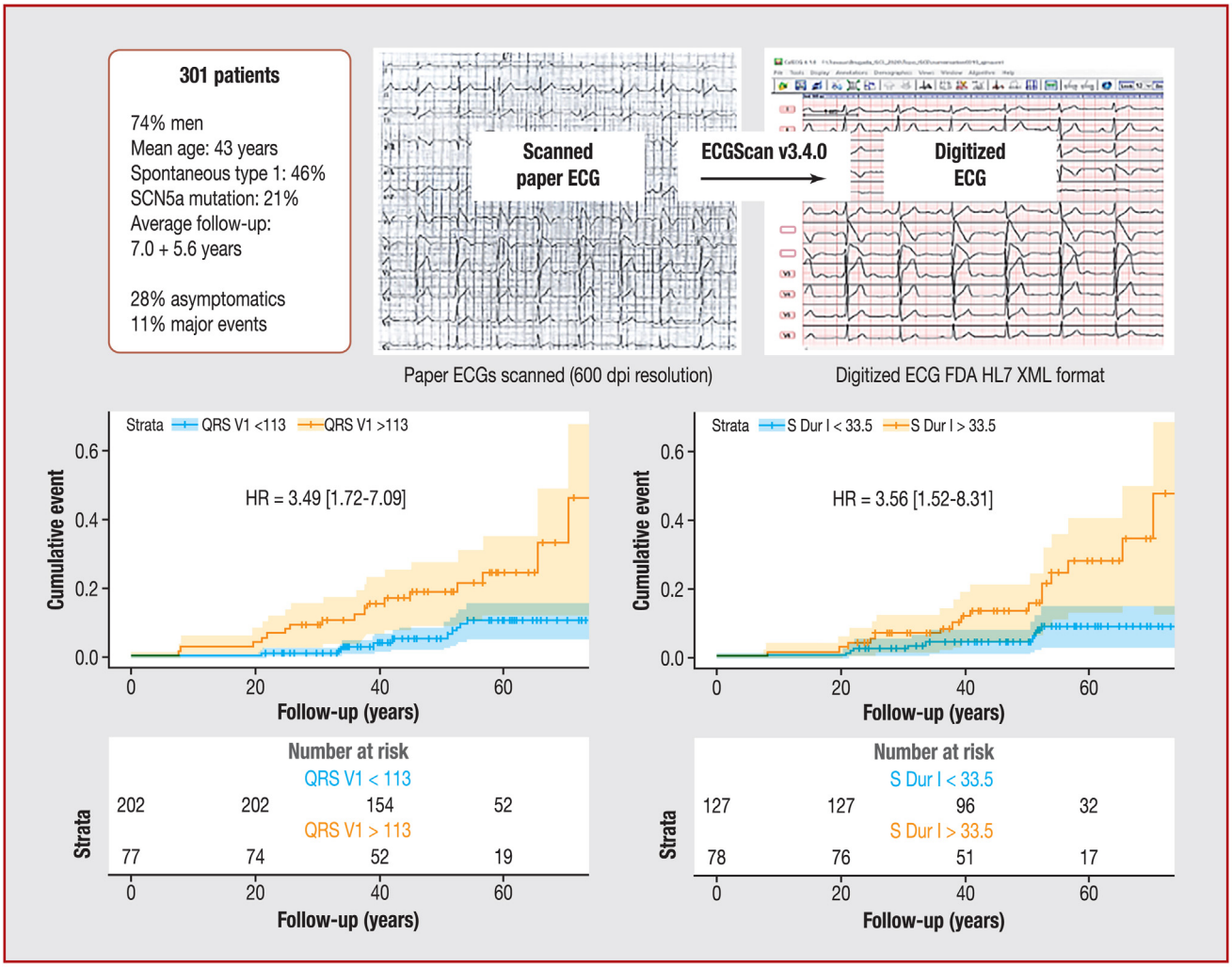
The retrospective diagnosis of syncope is often difficult and subject to an information bias. Assessing the potential cause of syncope (i.e. cardiac versus non-cardiac cause) is even more difficult. Accordingly, correct identification of cardiac syncope is potentially flawed. In the present study, we focused on major events, which are more reliably ascertained.

Accordingly, the main predictors described in our study should be validated in an independent cohort on a larger scale. For example, a new prognostic score was recently proposed by Rattanawong et al. [34] in October 2023, through a pooled analysis involving 7358 patients collected in a systematic review.

Our study highlights cross-correlations among ECG parameters and emphasizes the value of automated ECG analysis in exploring predictive factors for Brugada syndrome events. Recent studies, such as the one by Tse et al. [35] published in 2022, have also used automated ECG analysis in small cohorts, proposing new predictive ECG parameters including QRS duration. Our study serves as a proof-of-concept study for the quantitative assessment of numerous ECG parameters using digitized paper ECGs.

6. Conclusions

Retrospective paper ECG databases could be used after digitization for automatic quantitative ECG measurements. We confirmed the association of some of the previously described parameters and the occurrence of events and describe new potentially useful parameters. Multi-parametric ECG quantification may improve risk stratification in patients with Brugada syndrome, but large collaboration is warranted if we want to perform well-powered studies able to predict events in low- and intermediate-risk patients (Central illustration).



Central illustration. Two parameters that were extracted from digitized paper ECGs were significantly predictive of major events (sudden cardiac death, aborted cardiac arrest and appropriate ICD therapy in the VF zone). CI: confidence interval; DPI: dots per inch; ECG: electrocardiogram; FDA HL7-XML: Food and Drug Administration Health Level 7 Extensible Markup Language; HR: hazard ratio; ICD: implantable cardioverter-defibrillator; QRS V1: QRS duration in V1; S Dur I: S duration in DI; VF: ventricular fibrillation.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.acvd.2024.05.123.

Disclosure of interest

The authors declare that they have no competing interest.

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