



Computerized automated algorithm-based analyses of digitized paper ECGs in Brugada syndrome

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ARTICLE INFO

Article history:

Received 31 May 2021

revised 2 September 2021

accepted 7 September 2021

Keywords:

Brugada syndrome

ECG

Computerized analysis

Digitization

ABSTRACT

Background: Brugada syndrome is a rare inherited arrhythmic syndrome with a coved type 1 ST-segment elevation on ECG and an increased risk of sudden death. Many studies have evaluated risk stratification performance based on ECG-derived parameters. However, since historical Brugada patient cohorts included mostly paper ECGs, most studies have been based on manual ECG parameter measurements.

We hypothesized that it would be possible to run automated algorithm-based analysis of paper ECGs.

We aimed: 1) to validate the digitization process for paper ECGs in Brugada patients; and 2) to quantify the acute class I antiarrhythmic drug effect on relevant ECG parameters in Brugada syndrome.

Methods: A total of 176 patients (30% female, 43 ± 13 years old) with induced type 1 Brugada syndrome ECG were included in the study. All of the patients had paper ECGs before and during class I antiarrhythmic drug challenge. Twenty patients also had a digital ECG, in whom printouts were used to validate the digitization process. Paper ECGs were scanned and then digitized using ECGScan software, version 3.4.0 (AMPS, LLC, New York, NY, USA) to obtain FDA HL7 XML format ECGs. Measurements were automatically performed using the Bravo (AMPS, LLC, New York, NY, USA) and Glasgow algorithms.

Results: ECG parameters obtained from digital and digitized ECGs were closely correlated ($r = 0.96 \pm 0.07$, $R^2 = 0.93 \pm 0.12$). Class I antiarrhythmic drugs significantly increased the global QRS duration (from 113 ± 20 to 138 ± 23 , $p < 0.0001$). On lead V2, class I antiarrhythmic drugs increased ST-segment elevation (from 110 ± 84 to $338 \pm 227 \mu\text{V}$, $p < 0.0001$), decreased the ST slope (from 14.9 ± 23.3 to -27.4 ± 28.5 , $p < 0.0001$) and increased the TpTe interval (from 88 ± 18 to 104 ± 33 , $p < 0.0001$).

Conclusions: Automated algorithm-based measurements of depolarization and repolarization parameters from digitized paper ECGs are reliable and could quantify the acute effects of class I antiarrhythmic drug challenge in Brugada patients. Our results support using computerized automated algorithm-based analyses from digitized paper ECGs to establish risk stratification decision trees in Brugada syndrome.

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Introduction

Brugada syndrome (BS) is a rare inherited arrhythmic syndrome with a coved type 1 ST-segment elevation on the ECG precordial leads and an increased risk of sudden cardiac death (SCD) [1,2].

While the majority of affected Brugada patients are asymptomatic, the syndrome is the cause of a significant proportion of SCDs without structural heart disease, usually in young and otherwise healthy subjects [2].

Previous SCD, syncope, familial history, the presence of a spontaneous type 1 pattern, a positive EP study and sinus node dysfunction have been described as risk factors for severe arrhythmic events during follow-up [2,3]. In survivors of cardiac arrest and in Brugada patients with cardiac syncope, prevention of SCD is based on implantable cardioverter defibrillators (ICDs) [2]. However, the decision to implant an ICD in asymptomatic patients can be problematic, as indicated by the low level of evidence [2–4] and disappointing predictive scores in low- and intermediate-risk Brugada patients [5].

Although the mechanism of arrhythmias in BS is still debated, it is accepted that ECG abnormalities reflect the underlying arrhythmic substrate [6], thus supporting the hypothesis that ECG parameters could improve risk stratification in BS. Accordingly, many studies have evaluated the risk stratification performance of ECG-derived parameters [3,7].

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In early studies, Brugada patient cohorts mainly included paper ECGs, and most studies were consequently based on manual measurements evaluating one or a few ECG parameters [8–13]. These manual measurements are often difficult and time consuming and have poor accuracy and reproducibility. Conversely, automatic measurements from digital ECG can provide a more comprehensive and reproducible set of parameters. Unfortunately, Brugada syndrome is a rare disease with a low incidence of events, and gathering large digital ECG cohorts with adequate follow-up could take years, if not decades.

Converting paper ECGs into digital forms (digitization) has been proposed as a means to automatically analyze paper ECGs in different clinical settings [14,15] and could be a viable solution.

In the present study, we hypothesized that paper ECGs acquired from Brugada patients are suitable for digital quantitative analysis.

We aimed: 1) to validate the digitization process for paper ECGs; and 2) to quantify the acute class I antiarrhythmic drug effects on relevant ECG parameters in Brugada syndrome.

Methods

ECG selection and processing

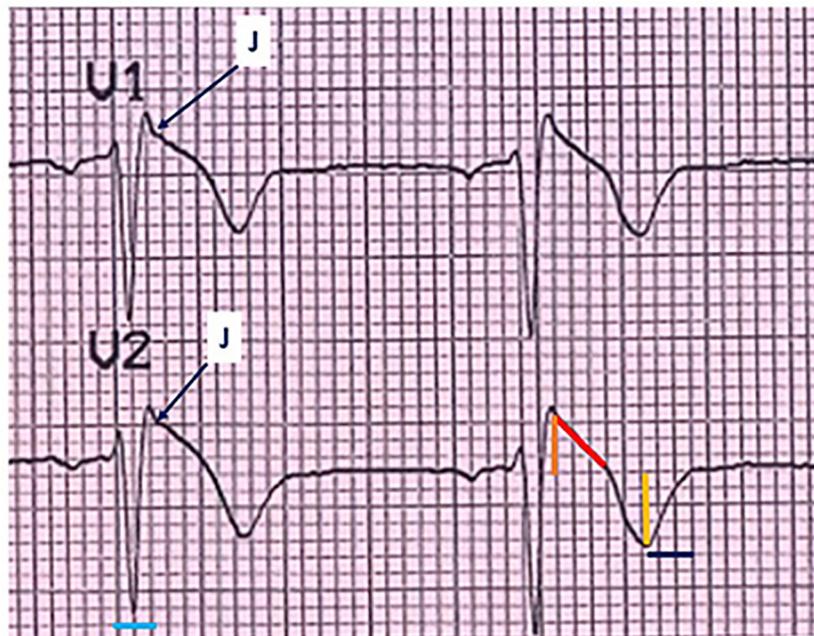
From our reference center BS cohort, we retrieved paper ECGs of patients presenting with at least one type 1 BS pattern ECG (either spontaneous or drug induced).

Paper ECG printouts (in 12×1 , 6×2 or 4×3 display format presenting with a visible grid) were scanned (600 dpi resolution) and then digitized using ECGScan software, version 3.4.0 (AMPS, LLC, New York, NY, USA) to obtain FDA HL7 XML format ECGs [15]. The full 10-s 12-lead ECG was subsequently reconstructed by replicating the average beat of each lead computed from available digitized data.

A subset of 20 patients who also had digitally recorded ECG were used for a validation analysis. These digital ECGs were printed and subsequently digitized. These 20 digital and digitized ECGs were used for digitization process validation. ECGs from BS patients with both spontaneous nontype 1 BS ECGs (baseline) and drug-induced type 1 BS ECGs were used to quantify the acute class I antiarrhythmic drug effects on ECG parameters.

ECG parameters and automated measurements

Automated measurements were obtained combining the outputs from the Bravo and Glasgow algorithms, which are embedded in CalECG software, version 4.1.0 (AMPS, LLC, New York, NY, USA). The protocols of both algorithms are based on the representative beats of each lead, which are computed by CalECG on the reconstructed 10-s 12-lead ECG. The analysis is thus performed on the same waveforms without data selection bias. The rationale for using a combined analysis was to cover the widest spectrum of Brugada-related sensitive parameters.



ECG parameters:

QRS duration: QRS onset to J point (J) (blue line)

ST amplitude at J point (orange line)

ST slope (slope between the J point and $3/8^{\text{th}}$ of the ST-T segment) (red line)

T maximum amplitude (yellow line)

Tpeak-Tend interval (TpTe) (dark blue line)

Fig. 1. Example of the “Brugada relevant” ECG parameters measured in the study.

The complete list of ECG measurements obtained with the Bravo and Glasgow algorithms is provided in the supplemental data.

The following global parameters were considered: RR, PR, QRS, QT intervals, Bazett's and Fridericia's QTc, ST and T duration, and QRS frontal axis.

The lead-specific parameters for leads V1, V2 and V3 were: QRS duration, QRS area, total area of repolarization after the J point (A Tot J), its positive and negative components (A Tot + J and A Tot - J), ST amplitude at J point, ST-segment duration, ST slope (slope between the J point and 3/8 of the ST-T segment), T maximum positive amplitude (T + Amp), T maximum negative amplitude (T- Amp), total area of repolarization of the T-wave (A Tot T), its positive and negative components (A Tot + T and A Tot - T), and Tpeak-Tend interval (TpTe) (Fig. 1).

Statistical analysis

Categorical variables are expressed as percentages, and continuous variables as means ± SDs for normal distributions and medians with interquartile ranges (IQRs) for nonnormal distributions. The measurement agreement between digital and digitized ECGs was evaluated

with correlations and Bland and Altman plots. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the paired samples *t*-test or the Kruskal Wallis test, as appropriate. A *p* value <0.05 was considered significant.

Results

Study population

A type 1 BS pattern paper ECG was available in 353 patients. The type 1 pattern was spontaneous in 149 patients and drug induced in 204. Spontaneous type 1 ECGs were not used in the present study.

Of the 408 paper ECGs (1 baseline and 1 on-drug ECG for 204 patients), quality was not sufficient for digitization in 28 cases (7% of the 408 paper ECGs; 10/204 baseline ECGs and 18/204 drug-induced type 1 ECGs).

Consequently, 176 patients (30% females, mean age 43 ± 13 years old, range 16–75) had digitized ECGs both at baseline and with a drug-induced type 1 BS pattern. Ajmaline (1 mg/kg IV in 3 min) was

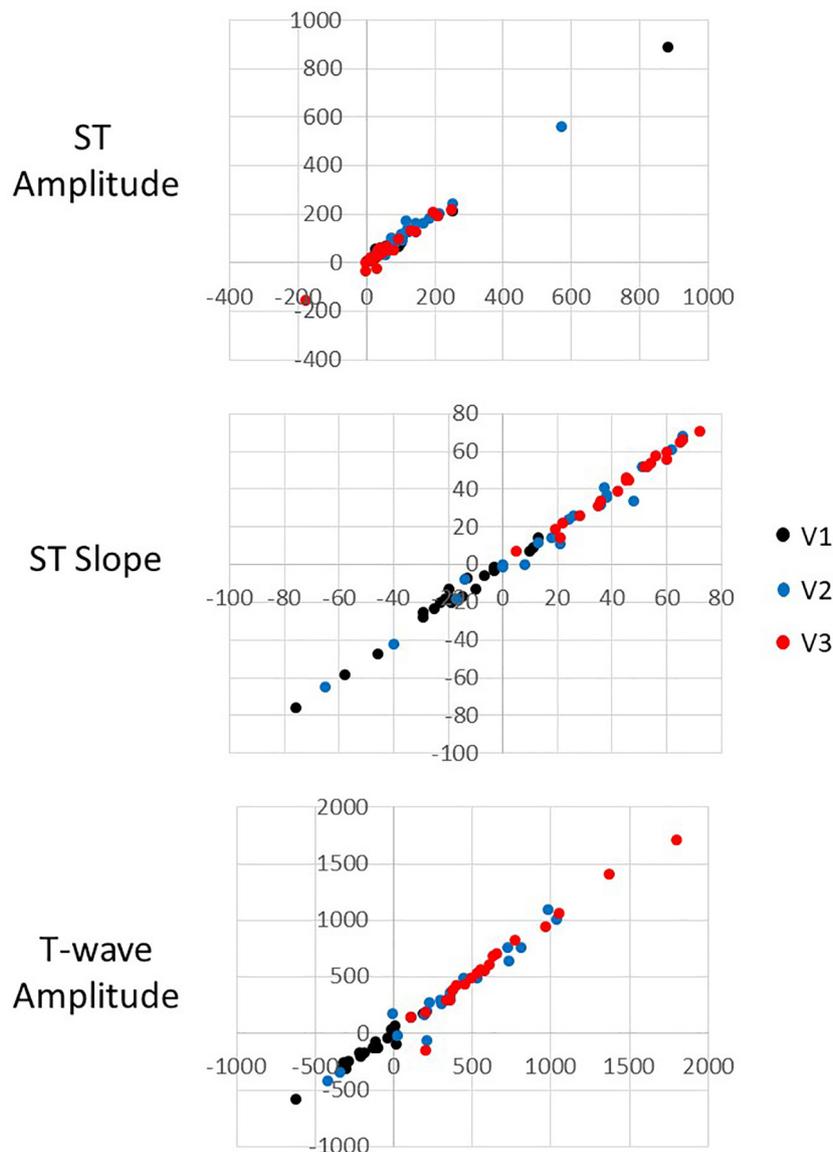


Fig. 2. Relationship between ECG parameters automatically measured from digital (X-axis) and digitized ECG (Y-axis) on leads V1 (black dots), V2 (blue dots) and V3 (red dots).

Table 1
Global ECG parameters measured at baseline and on class I antiarrhythmic drugs.

Parameter	Baseline ECG	ECG on class I antiarrhythmic drug	P value
RR interval (ms)	872 ± 172	763 ± 144	<0.0001
PR interval (ms)	154 ± 33	183 ± 44	<0.0001
QRS interval (ms)	113 ± 20	138 ± 23	<0.0001
QRS frontal axis	41 IQR(2; 65)	22 IQR (-27; 74)	0.09
QT interval (ms)	393 ± 36	405 ± 43	<0.001
QTcB (ms)	424 ± 34	465 ± 34	<0.0001
QTcF (ms)	413 ± 28	446 ± 32	<0.0001
ST duration (ms)	75 ± 31	41 ± 27	<0.0001
T duration (ms)	206 ± 35	226 ± 44	<0.0001

used to induce a type 1 pattern in all but 5 patients, in whom flecainide (2 mg/kg IV in 10 min) was used.

Digitization process validation

ECG parameters obtained from digital and digitized ECGs were closely correlated ($r = 0.96 \pm 0.07$, $R^2 = 0.93 \pm 0.12$).

The Bland and Altman bias and $1.96 \times SD$ were 0.1 ± 0.9 beats per minute for heart rate, -3.3 ± 14.3 ms for global QRS and 0.4 ± 10.3 ms for global QT duration.

Fig. 2 shows the correlations between ECG parameters automatically measured from digital and digitized ECG on leads V1, V2 and V3.

The Bland and Altman bias $\pm 1.96 \times SD$ was $-0.9 \pm 2.8 \mu V$ for ST amplitude, 0.6 ± 8.3 for ST slope and $3.7 \pm 6.9 \mu V$ for T-wave amplitude.

Class I antiarrhythmic drug effects on relevant ECG parameters

Global parameters measured at baseline and upon drug challenge are shown Table 1. Class I antiarrhythmic drugs significantly shortened the RR interval and prolonged the PR, QRS and QT intervals.

Table 2 shows automated measurements of parameters of the QRS, the ST-T and the T-wave on the 3 right precordial leads. Class I antiarrhythmic drug significantly increased global QRS duration and area, ST-segment elevation (ST Amp), and the area of the ST-T segment after the J-point (A tot J), decreased the ST slope toward more negative values, and increased the area of the negative component of the T wave and the Tpeak-Tend interval (TpTe) (Table 2).

Fig. 3 shows the individual changes in ST amplitude and ST slope on lead V2.

The mean increase in ST amplitude and decrease in ST slope were observed, but interindividual variability was present. The ECG tracings of the 2 outliers for ST amplitude on lead V2 showed that the algorithm could correctly identify the J point position and measure an accurate ST elevation amplitude (Fig. 3).

Discussion

The goal of this work was to assess the feasibility of automated analysis of digitized ECGs from Brugada patients. We performed a 2-step validation.

First, we found that automated measurement of depolarization and repolarization ECG parameters from digital and subsequently digitized paper ECGs from Brugada patients can be reliably assessed. We then showed that the effects of a class I AA drug challenge on ECG parameters relevant for BS diagnosis could be automatically quantified.

Digitization

Digitization and subsequent analysis of paper ECGs is frequently used in the context of pharma thorough QT studies as a bridge before using only digitally recorded ECGs [14–16]. Accordingly, analyses have focused mainly on standard ECG parameters (RR, PR, QRS and QT

Table 2
Automated measurements of parameters on the 3 right precordial leads.

Parameter	Lead	Baseline ECG	ECG on class I antiarrhythmic drug	P value
QRS duration	V1	93 ± 21	112 ± 30	<0.0001
	V2	97 ± 21	118 ± 26	<0.0001
	V3	96 ± 17	119 ± 25	<0.0001
QRS Area	V1	-13,044 ± 11,840	-4177 ± 16,941	<0.0001
	V2	-9107 ± 18,985	5541 ± 26,289	<0.0001
	V3	-1662 ± 22,065	70,068 ± 43,882	<0.0001
A Tot J	V1	18,146 ± 9380	34,092 ± 19,486	<0.0001
	V2	47,039 ± 32,049	59,562 ± 35,310	<0.01
	V3	68,751 ± 43,579	69,010 ± 46,196	NS
A Tot + J	V1	8307 ± 9065	13,791 ± 11,192	<0.0001
	V2	45,307 ± 33,416	43,904 ± 37,435	NS
	V3	68,454 ± 43,846	64,379 ± 48,150	NS
A Tot - J	V1	-9834 ± 10,388	-20,294 ± 17,120	<0.0001
	V2	-1729 ± 6664	-15,651 ± 22,269	<0.0001
	V3	-294 ± 881	-4626 ± 15,095	<0.01
ST amp	V1	42 ± 46	142 ± 119	<0.0001
	V2	110 ± 84	338 ± 227	<0.0001
	V3	98 ± 77	174 ± 180	<0.0001
ST dur	V1	105 ± 38	65 ± 34	<0.0001
	V2	92 ± 35	60 ± 36	<0.0001
	V3	93 ± 28	61 ± 33	<0.0001
ST Slope	V1	-8.7 ± 12.2	-33.6 ± 16.4	<0.0001
	V2	14.9 ± 23.3	-27.4 ± 28.5	<0.0001
	V3	33.7 ± 19.1	23.1 ± 29.9	<0.0001
T+ Amp	V1	39 ± 62	119 ± 121	<0.0001
	V2	312 ± 247	329 ± 221	NS
	V3	487 ± 287	416 ± 300	<0.01
T- Amp	V1	-109 ± 90	-173 ± 119	<0.0001
	V2	-20 ± 65	-122 ± 148	<0.0001
	V3	-8 ± 80	-25 ± 85	NS
A Tot T	V1	12,025 ± 9206	18,590 ± 14,342	<0.0001
	V2	36,963 ± 29,441	25,624 ± 23,920	<0.01
	V3	59,484 ± 38,910	43,415 ± 37,558	<0.0001
A Tot + T	V1	2657 ± 5845	2039 ± 4518	NS
	V2	35,340 ± 30,555	14,029 ± 24,316	<0.0001
	V3	59,291 ± 39,107	41,009 ± 39,201	<0.0001
A Tot - T	V1	-9362 ± 9825	-16,545 ± 14,608	<0.0001
	V2	-1622 ± 6426	-11,590 ± 15,829	<0.0001
	V3	-192 ± 803	-2403 ± 7310	<0.01
TpTe	V1	81 ± 20	104 ± 29	<0.0001
	V2	88 ± 18	104 ± 33	<0.0001
	V3	93 ± 18	104 ± 28	<0.001

intervals), and to the best of our knowledge, digitization has seldom been used in the context of Brugada syndrome.

Digitization of ECGs from our Brugada syndrome clinical cohort with long follow-up was successfully performed for >90% of ECGs. The reasons for unsuccessful digitization were in most cases fading of the grid, preventing calibration. Drifting of the baseline and individual lead signals crossing each other could explain other failures to digitize paper ECGs.

Paper printouts do not always display a full 10 s of all acquired leads. Since many automated algorithms use 10-s recordings, this fact could be a problem for analyzing digitized ECGs. Therefore, we reconstructed a 10-s ECG by replicating available ECG data. This method could be difficult to apply in cases of poor-quality ECG and/or baseline drifting. It could also falsely minimize beat-to-beat variability and might be associated with the loss of the noise reduction obtained by the beat averaging process.

To validate the digitization process on ECGs recorded in Brugada patients, we first performed a benchmark validation on identical ECGs digitally recorded and subsequently printed, scanned, and digitized. The correlations and Bland and Altman plot results can be considered acceptable in relation to the values of the ECG parameters. In addition, ECG parameters relevant for Brugada ECG pattern description were also closely correlated (Fig. 2). It is noteworthy that the validation was fully automated, without visual validation or caliper position manual changes.

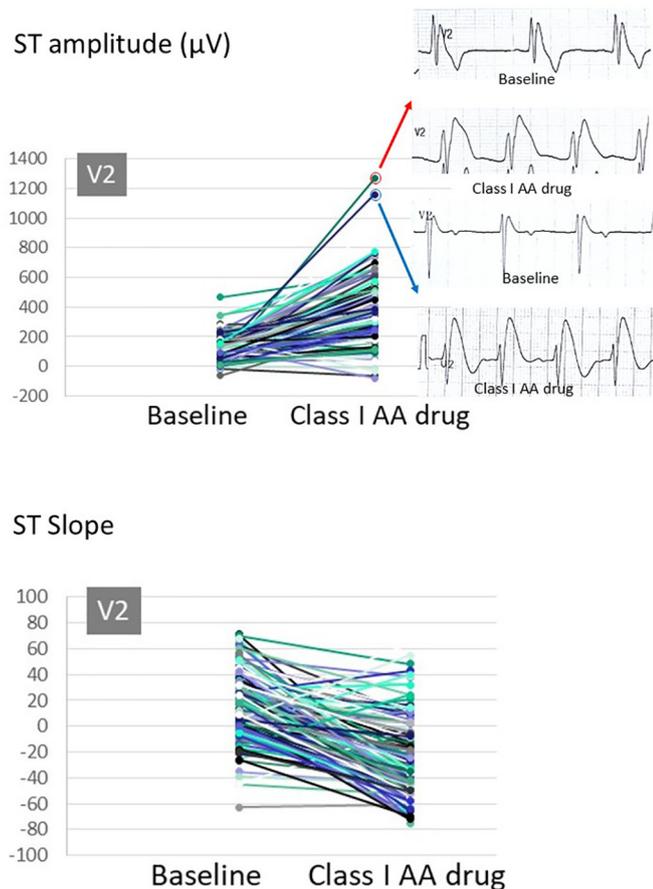


Fig. 3. Individual changes in ST amplitude and ST slope on lead V2. The upper right insert shows the ECG tracings of the 2 outliers for ST amplitude on lead V2.

Ajmaline effect

In addition to the above-described bench validation, we decided to further validate the digitization process by quantifying the effects of sodium channel blockade on ECG parameters in Brugada patients. This validation was used as a surrogate to manually measure all ECG depolarization and repolarization parameters, which would have been almost impossible for the >100 ECG parameters automatically measured in 352 ECGs. Our aim was hence to validate the ability of fully automated measures from digitized ECGs to detect a pathophysiological effect.

We used 2 available ECG algorithms (Bravo AMPS LLC and Glasgow) that include measurements of J-point and ventricular repolarization-related parameters. However, digitized ECGs could also have been analyzed using other commercially available devices. It is also conceivable to analyze digitized ECGs with customized algorithms to better characterize the Brugada ECG pattern, for instance, without assumptions about the J-wave position [17].

We were able to quantify drug-induced PR, QRS and QT interval prolongation on the overlap median, as well as on the right precordial leads, and the effect of sodium channel blockade on relevant parameters in BS, such as ST amplitude at the J-point, ST slope and T-wave amplitude. Therefore, automated measurements from digitized ECGs appropriately recapitulated the expected effects of sodium channel blockade on the depolarization-repolarization process on ECG parameters from BS patients [18].

Usefulness and perspective

Scanning an image of a paper ECG could be sufficient to avoid historical paper ECGs from fading in patients' files. Digitization could be

further used to secure ECG tracing in a format allowing physicians and/or researchers to run automated computerized quantitative ECG analyses with high reproducibility and high output.

This method could be applied to the backlog of paper ECG historical databases in Brugada syndrome and in other channelopathies or rare diseases to validate previous risk stratification studies [7–13] and to look for and test multiparameter models for risk stratification [19]. In addition, digitized ECGs would be easy to share for collaborative studies and could greatly increase opportunities for any type of computerized ECG signal analysis (time domain, frequency domain, vectocardiographic approaches, CineECG, artificial intelligence, etc.).

Limitations

Some limitations should be acknowledged. First, the limitations of digitization have been well identified [20], digitization is not possible for 100% ECG, and part of the process is not automated and is time consuming.

Second, we did not manually measure on the paper ECGs all of the parameters that have been automatically measured from digitized ECGs. Such a validation would, however, have been technically challenging for “complex” parameters, such as areas, slopes, and derived parameters. Even for simpler parameters, such as intervals, measurement of ECG parameters would have been very difficult to perform with acceptable precision and reproducibility for tenths of parameters on hundreds of ECGs. However, in clinical settings for diagnostic purposes, it might be warranted to indicate measured relevant values on the ECG output to allow for visual qualitative validation.

Third, the selection of analyzed ECGs by an expert physician in inherited arrhythmic syndromes could have introduced a systematic bias. However, this bias was probably minimized by the study design, which included both type 1 and non-type 1 Brugada pattern ECGs, as well as by the intrinsically blind automated computerized analyses.

Finally, risk stratification based on parameters automatically measured from digitized ECGs will need to be validated in prospective BS patient cohorts.

Conclusion

In conclusion, automated algorithm-based measurements of depolarization and repolarization parameters from digitized paper ECGs are reliable and could quantify the acute effects of class 1 antiarrhythmic drug challenge in Brugada patients. Historical cohorts with only paper ECG recordings could be used in the search for prognostic ECG parameters in Brugada syndrome.

Acknowledgment

We are thankful to Professor Peter W. Macfarlane for his help with the Glasgow algorithm.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jelectrocard.2021.09.009>.

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