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Multiple serial ECGs aid with the diagnosis and prognosis of Brugada syndrome

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ABSTRACT

Background: A spontaneous coved-type ST segment elevation in the electrocardiogram (ECG) has long been recognized as a risk stratification tool in patients with Brugada syndrome (BrS). This Type-I ST segment elevation is known to exhibit high dynamicity, fluctuating between coved-type and non-coved ST segment elevation. Our objectives in this study were to: 1) Compare ECG parameters in patients with spontaneous coved-type (Type-I) vs. non-coved-type ST segment ECGs; 2) Determine the variability of these ECG parameters with repeated measurements; and 3) Assess the predictive value of ECG parameters in these two groups during follow-up.
Methods: Forty-two consecutive patients with BrS and implanted ICD were studied between 2000 and 2017. Serial ECGs and clinical characteristics were obtained over a period of 199 months.
Results: QT-interval, QTc-interval, QRS duration, Tp-e interval and Tp-e dispersion were all significantly longer in spontaneous Type I vs. non-Type 1 ECGs and all ECG parameters displayed significant variability during serial recording obtained throughout the follow-up period. Patients with a spontaneous Type I ECG during the 114 ± 56 months follow-up period were at a much higher risk for VT/VF than those without a Type I ECG ($p = 0.016$). Moreover, the risk for development of life-threatening ventricular arrhythmias was directly related to the fraction of ECGs displaying a spontaneous Type I pattern during follow-up.
Conclusion: Our study illustrates the need for multiple ECGs to aid with both the diagnosis and prognosis of BrS. Serial ECGs can assist with risk stratification based on the fraction of ECGs that display a spontaneous Type-I BrS ECG.

1. Introduction

A spontaneous coved-type ST segment elevation in the electrocardiogram (ECG) has long been recognized as a risk stratification tool in patients with Brugada syndrome (BrS), particularly in asymptomatic cases or following syncope of doubtful arrhythmic cause [1–3]. Type I ST segment elevation is known to exhibit high dynamicity, fluctuating between coved and non-coved ST segment elevation secondary to pharmacological and autonomic influences and changes in heart rate [4].

The pathophysiological mechanism underlying BrS has been ascribed to ventricular repolarization and/or depolarization abnormalities; the extent to which each contributes to the pathophysiology of the disease remains a matter of debate [1,5]. In addition to prominent J waves, which are responsible for the ST segment elevation in BrS, other electrocardiographic characteristics including a fragmented QRS, early repolarization pattern, prolonged Tpeak-Tend (Tp-e) interval and increased Tp-e dispersion have been associated with increased risk for development of life-threatening arrhythmias [6–9].

The principal objectives of the present study were: 1) To compare ECG parameters in patients with spontaneous coved-type (Type I) vs. non-coved-type ST segment ECGs; 2) To determine the variability of these ECG parameters with repeated measurements; and 3) To assess the predictive value of ECG parameters in these two groups during follow-up of BrS patients with an implanted cardioverter-defibrillator (ICD).

2. Methods

We analyzed ECGs obtained in ambulatory care of the Arrhythmia Unit of the Cardiovascular Surgery and Cardiology Institute between June 2000 and January 2017, from 42 consecutive patients with BrS and an implanted ICD. The defibrillators were implanted in patients with aborted cardiac sudden death, in cases with syncope due to possible arrhythmic cause based on the clinical symptoms and in asymptomatic patients with family

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history of sudden cardiac death or induced with programmed electrical stimulation. Clinical diagnosis was established in all patients based on criteria of consensus reports [10,11]. Patients were followed one and three months after the implant and every 6 months thereafter. At each visit, a standard 12-lead ECG was recorded and device check was performed. In all cases, if a coved ECG was not observed, leads V1 and V2 were raised to the 2nd and 3rd intercostal spaces. All 12-lead ECGs were recorded at a paper speed of 25 mm/s and amplitude of 10 mm/mV. QT interval, QTc interval, QRS width, Tp-e interval and Tp-e dispersion were measured and the presence of Type I or non-coved type pattern, fragmentation and early repolarization in the infero-lateral leads was evaluated by two blinded experts. Measurements on serial electrocardiograms were performed using previously described methods [7]. Patients with <3 ECGs were excluded.

Type I ECG was defined as a coved ST-segment elevation of ≥2 mm (0.2 mV) followed by a negative T wave in at least two right precordial leads [11]. We defined early repolarization pattern as a prominent (≥1 mm above basal ECG line) J wave or slurring in at least two consecutives leads in the basal ECG, with or without ST segment elevation, excluding V1–V3 leads [12]. Fragmentation was diagnosed when abnormal fragmentation of the QRS complex was apparent with ≥4 spikes in one or ≥8 spikes in all right precordial leads [6]. The study was approved by the ethical committee of the Cardiovascular Surgery and Cardiology Institute, Havana, Cuba.

2.1. Statistics

Group differences were analyzed by one-way ANOVA followed by Scheffé's multiple comparison test. Numeric variables were compared using dependent-samples *t*-test. To examine prognostic value from percentage of ECGs showing a type I ECG on the follow-up and determine cutoff values, analysis of receiver operating characteristic (ROC) curves was made. Kaplan-Meier survival curves were plotted, and log rank test was used to compare the curves. Data are expressed as mean ± SD. A value of $p < 0.05$ was considered statistically significant.

3. Results

We studied a high-risk group; the majority of the patients had a spontaneous Type 1 ECG at time of diagnosis and >80% were symptomatic (33% had suffered aborted sudden cardiac death and 52% syncope). Fifty percent had documented life-threatening ventricular arrhythmias: 6 suffered aborted sudden cardiac death at time of diagnosis but had no recurrences, whereas 15 developed ventricular arrhythmias during follow-up (Table S1). Two hundred and eighty five ECGs were evaluated, 132 (46%) with Type I ECG and 153 non-coved type ECG. Thirty patients (71%) displayed a spontaneous Type I coved-type ECG at least once during follow-up and 12 patients (29%) did not display this pattern during follow-up. Two patients failed to display a spontaneous Type I ECG at time of diagnosis; one exhibited a Type I ECG but with J point <2 mm and the other one with saddle back morphology. These 2 were diagnosed as BrS with a positive ajmaline challenge, inducing a Type I ECG; one (JC) had aborted sudden cardiac death and in the other (GM) VF was induced with programmed electrical stimulation. Table S2 summarizes the characteristics of the patients included in the study. At follow-up (114 ± 56 months), 15 patients received appropriate therapy by the device (35.7%), 8 with aborted sudden cardiac death, 6 with syncope and one was asymptomatic.

Six patients were asymptomatic, five with spontaneous Type I ECG at baseline, five of these were inducible with programmed electrical stimulation and two had a family history of sudden cardiac death. At follow-up, three failed to display a spontaneous Type I ECG (16 ECGs), one displayed a Type I ECG 75% of the time (8 ECGs) and two displayed a Type I ECG 100% of the time (8 ECGs). One patient suffered appropriate ICD therapy; he displayed a spontaneous Type I ECG at baseline and 100% of the time during the follow-up period; he was also inducible using programmed electrical stimulation.

Only 3 patients (1%) displayed an ECG diagnostic of early repolarization and none presented with a fragmented QRS.

The majority of patients displayed a spontaneous Type I ECG during the follow-up period, 19 exhibited 3 or more Type I ECGs (142 ECGs), 5 displayed 2 Type I ECGs (35 ECGs), 6 displayed only one Type I ECG (36 ECGs) and 12 never displayed a coved ECG (72 ECGs) at follow-up.

QT interval, QTc interval, QRS duration, Tp-e interval and Tp-e dispersion were all statistically significantly longer in Type I vs. non-coved-type ECGs (Table 1A) and all ECG measurements displayed significant variability during serial recording obtained throughout the follow-up period. (Table 1B). Figs. 1 and 2 illustrate the variability observed in two patients.

Table 1A
Electrocardiographic parameters in patients with and without a Type I ST segment elevation.

ECG measurements	Coved-type pattern (mean ± S.D.)	Non-coved pattern (mean ± S.D.)	p value
QTc (msec)	434 ± 42 n = 132	408 ± 29 n = 153	<0.001
QT (msec)	401 ± 37 n = 132	364 ± 29 n = 153	<0.001
QRS width (msec)	102 ± 19 n = 132	96 ± 20 n = 153	=0.0067
Tp-e (msec)	105 ± 18 n = 132	93 ± 14 n = 153	<0.001
Tp-e dispersion (msec)	37 ± 17 n = 124	30 ± 14 n = 146	<0.001

All patients receiving appropriate ICD therapy displayed a spontaneous Type I ECG at time of initial diagnosis. The Kaplan-Meier curves shown in Fig. 3A and Table 1C illustrate that patients displaying a higher % of Type I ECGs during follow-up have a greater risk for developing life-threatening arrhythmic events. Of the 8 patients who displayed a coved-type ECG in 100% of serial ECGs recorded during follow-up, 62.5% received an appropriate shock. Of the 12 patients who never displayed a coved-type ECG at follow-up, only 8.3% received an appropriate shock during follow-up.

Patients in the four groups were similar with respect to presenting symptoms at the time of diagnosis. Three patients in Group A suffered aborted sudden cardiac death, 4 from Group B, 4 from Group C and 3 from Group D. Six patients from Group A presented with syncope, 6 from Group B, 7 from Group C and 3 from Group D. Three from Group A were asymptomatic, 1 from Group C and 2 from Group D.

The area under the ROC curve for % of Type I ECGs during follow-up was 0.716; indicating that this variable is a relatively good discriminator of patients likely to develop life-threatening arrhythmic events (sensitivity: 86%, specificity: 56%). As indicated by the Kaplan-Meier curves displaying cumulative event-free survival, patients presenting with Type I ECG 33% or more often during follow-up were much more likely to have arrhythmic events than those exhibiting a Type I ECG less often than 33% during follow-up ($p = 0.004$), Fig. 3B.

4. Discussion

Variability in the manifestation of a Type I ECG pattern in patients with suspected BrS presents a challenge for the diagnosis of the syndrome. In our cohort of 42 patients diagnosed with BrS, 29% failed to exhibit a Type I ECG during at least one of multiple serial ECG recording obtained during a follow-up period of 114 ± 56 months. In our cohort, 22 patients (52%) displayed variations of the pattern of ST segment elevation during follow-up, only 8 (19%) displayed at Type I pattern in all follow-up ECG, and 12 (29%) displayed a Type I ECG in none of the ECGs recorded at follow-up.

Previous studies report diverse results. Richter et al. [13] reported the results of a multicenter trial involving 89 BrS patients implanted with an ICD (72% symptomatic). A spontaneous Type I ECG was recorded in 64% at time of implant and 38% displayed a Type I ECG

Table 1B
Variability of electrocardiographic measurements (n = 42).

ECG measurements	Mean of maximum values ± S.D.	Mean of minimum values ± S.D.	p value
QTc (msec)	448 ± 44	394 ± 30	<0.001
QT (msec)	411 ± 41	363 ± 32	<0.001
QRS width (msec)	109 ± 21	93 ± 19	<0.001
Tp-e (msec)	115 ± 17	87 ± 14	<0.001
Tp-e dispersion (msec)	53 ± 19	22 ± 8	<0.001

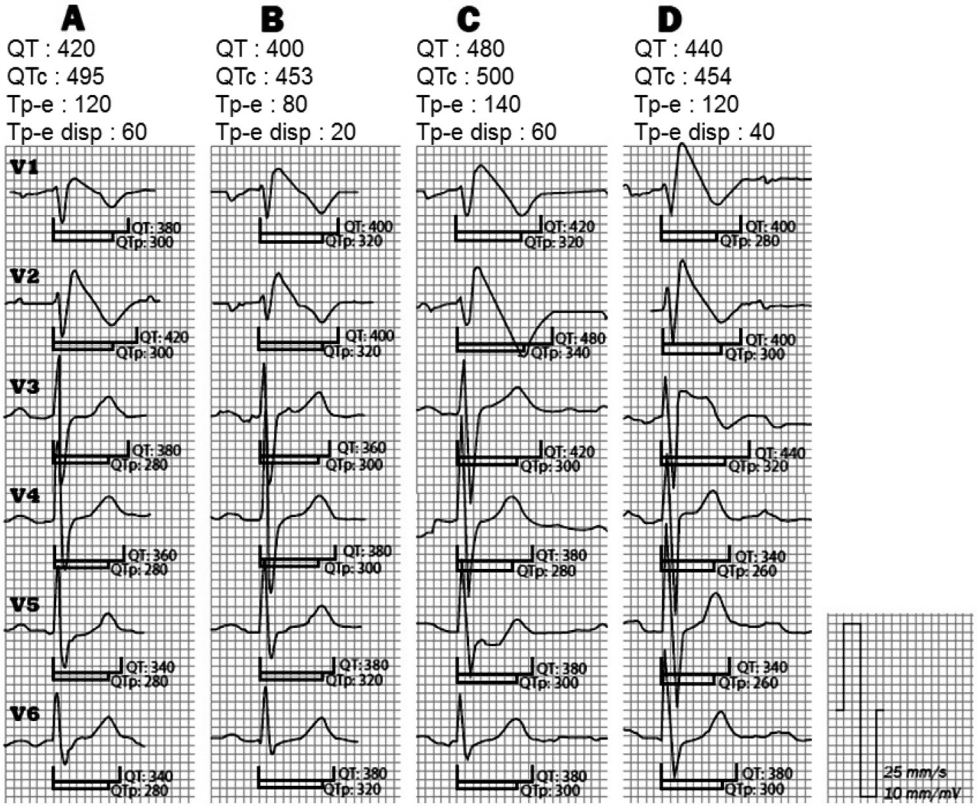


Fig. 1. Serial ECG Recordings obtained from patient #59 (JMM, female, syncope). A, B, C, D, the variability in QT, QTc, Tp-e and Tp-e dispersion values were 80, 47, 60 and 40 ms, respectively.

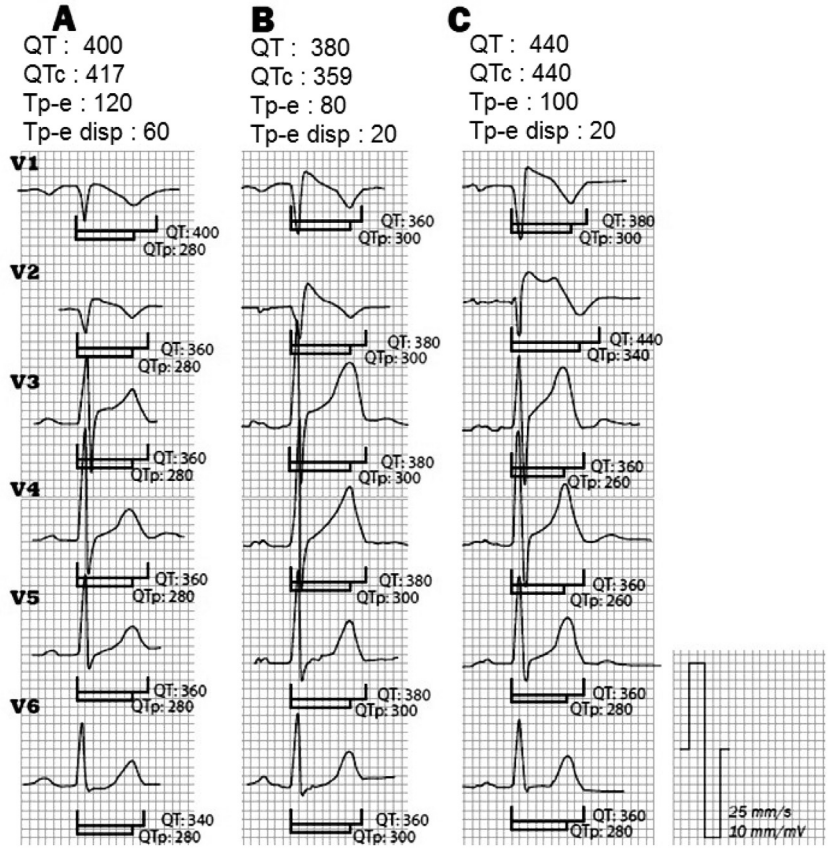
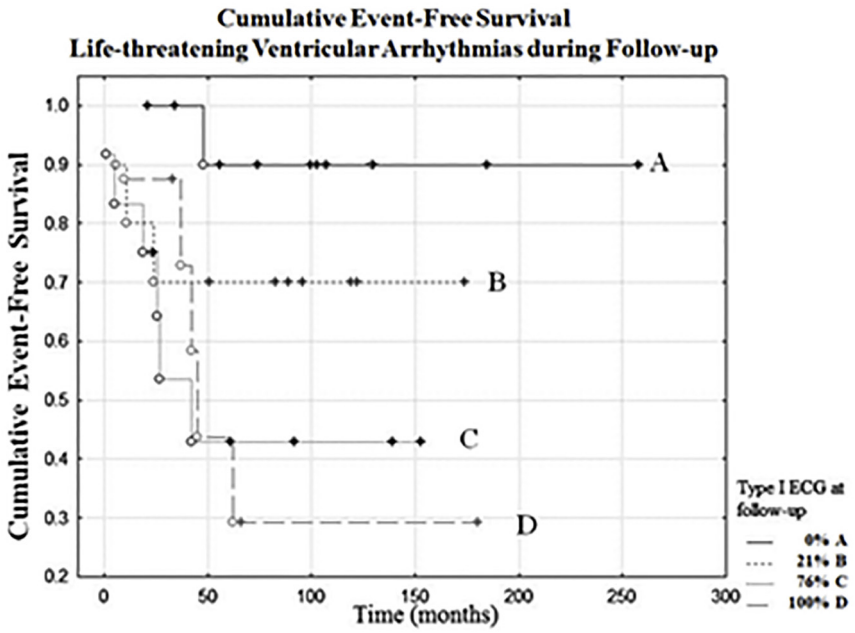


Fig. 2. Serial ECG Recordings obtained from patient #64 (TCT, male, syncope). A, B, C: the variability in QT, QTc, Tp-e and Tp-e dispersion values were 60, 81, 40 and 40 ms respectively.

A



Patients at risk

Groups	Follow-up (months)				
	0	50	100	150	200
A	12	9	6	2	1
B	10	7	3	1	0
C	12	4	2	1	0
D	8	3	1	1	0
Total	42	23	12	5	1

B

Fig. 3. A: Kaplan Meir Curves showing event free survival as a function of % of follow-up ECGs displaying a Type I ECG. Group A represents patients without spontaneous coved ECG at follow-up. Groups B, C and D represent patients displaying a Type I ECG 21%, 76% and 100% of the time during the follow-up period, respectively. Log-rank test yielded a $p = 0.009$ for Group A vs D, $p = 0.015$ for Group A vs C and $p > 0.05$ for Group A vs B, B vs C, B vs D and C vs D. **B**: Kaplan-Meier analysis of arrhythmic events during follow-up depending on percentage of ECGs type I ECG < 33% or ≥33%.

Table 1C
Increased incidence of Type I ECG among serial ECGs recorded during follow-up increases risk for life-threatening ventricular arrhythmias.

	Groups			
	A	B	C	D
# of patients with serial ECGs showing a Type I ST segment elevation	12	10	12	8
% of serial ECGs showing a Type I ST segment elevation	0%	21%	76%	100%
# of patients receiving appropriate ICD therapy	1	3	6	5
% of patients receiving appropriate ICD therapy	8.3%	30%	50%	62.5%

Group A represents patients without spontaneous coved ECG at follow-up. Groups B, C and D represent patients displaying a Type I ECG 21%, 76% and 100% of the time during the follow-up period, respectively.

over a mean 48 ± 35 months follow-up period. Appropriate ICD therapy occurred in only 18% of patients. In our cohort, 81% were symptomatic, 95% displayed a spontaneous Type I ECG and 35.7% received appropriate ICD therapy. Veltman and co-workers (4) studied 43 patients, 15 (35%) displayed a spontaneous Type I ECG at time of diagnosis and 8 displayed a Type I ECG during a follow-up period of 17.7 months.

In our study, the percent of patients developing life-threatening ventricular arrhythmias at follow-up was a direct function of the frequency with which a Type I ECG was observed (Table 1C). Thus, as illustrated in the Kaplan Meier curves (Fig. 3A) patients without a spontaneous Type I ECG at follow-up had a much lower risk than those with a spontaneous Type I ECG, but our study also shows that the level of risk increases as the fraction of Type I ECGs increases among the serial ECGs obtained during follow-up.

The dynamicity of the BrS ECG is well documented [14]. Day to day fluctuations are common. Increases of ST segment elevation predisposing to development of VT/VF have been reported secondary to modulation of autonomic nervous system activity, increased vagal activity in particular [15,16]. Parasympathetic stimulation-mediated ST segment elevation, predisposes to the development of VT/VF at night, and is believed to be due to reduction calcium channel current and augmentation of I_{to} secondary to slowed heart rate, which increases the availability of I_{to} by providing more time for the current to recover from inactivation [17].

Yan and Antzelevitch developed the first experimental model to explain the ionic and cellular basis for the electrocardiographic and arrhythmic manifestation of BrS [18]. An accentuation of the epicardial action potential notch and eventual loss of the epicardial action potential dome was shown to result in ST-segment elevation, phase 2 reentry, and polymorphic ventricular tachycardia/ventricular fibrillation (VT/VF). Diminution of inward currents (I_{Na} and I_{Ca}) or enhancement of outward currents (I_{to}, $I_{K\text{-}ATP}$, I_{Kr}, etc) can result in an accentuation of the epicardial action potential notch, eventually causing an all-or-none repolarization at the end of phase 1. This was shown to lead to the development of phase 2 reentry, which provided a closely-coupled extrasystole capable of precipitating VT/VF. Modulation of any of the above currents by autonomic influences, electrolyte imbalances, hormonal regulation as well as a wide variety of drugs could cause a shift in the balance of currents in the early phases of the epicardial action potential, thus contributing to the dynamicity of the BrS ECG [1,19].

5. Conclusion

Our study illustrates the need for multiple ECGs to aid with both the diagnosis and prognosis of BrS. Serial ECGs can assist with risk stratification based on the fraction of ECGs that display a spontaneous Type I BrS ECG.

6. Limitations

All electrocardiographic measurements were made in a blinded fashion independently by two experts in the field in order to minimize intra- and inter-observer differences which are unavoidable with manual measurements of the ECG [20,21]. An important limitation of the study is the high risk of our patients; the majority had spontaneous type I ECG at time of diagnosis (95%), >80% were symptomatic (33% suffered aborted sudden cardiac death and 52% syncope of probably arrhythmic cause), and 50% had documented life-threatening ventricular arrhythmias. The relatively small number of patients studied is a limitation as well. Accordingly, these relationships should be investigated in studies involving a larger cohort before extrapolating to the general population of patients with BrS.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.089.

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Disclosures

None.

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