Type 1 electrocardiographic burden is increased in symptomatic patients with Brugada syndrome☆

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Abstract

Background: Spontaneous type 1 electrocardiographic (ECG) is a risk factor for arrhythmic events in Brugada patients but the importance of the proportion of time with a type 1 ECG is unknown.

Patients and Methods: Thirty-four Brugada patients (15 symptomatic) underwent a 24-hour 12-lead ECG recording. One-minute averaged waveforms displaying ST-segment elevation above 200 μV, with descending ST-segment and negative T-wave polarity on leads V1-V3 were considered as type 1 Brugada ECG. The burden was defined as the percentage of type 1 Brugada waveforms.

Results: Type 1 ECG on lead V2 was more frequent in symptomatic patients (median 80.6% [15.7–96.7] vs 12.4% [0.0–69.7], P = .05). Patients with a permanent type 1 pattern on lead V2 were more likely to be symptomatic (5/6) than patients without type 1 ECG during a 24-hour period (2/9) (P < .05).

Conclusion: Type 1 pattern is more prevalent across a 24-hour period in symptomatic Brugada patients.

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Introduction

Since the first description of the Brugada syndrome in 1992,1 sum of knowledge has been accumulated.2 Nevertheless, risk stratification and decision of defibrillator implantation (ICD) remain major and highly controversial clinical issues. According to the Second Consensus Conference most Brugada patients with a history of sudden cardiac death or syncope and without any other etiology will be referred for an ICD implantation.3 In asymptomatic Brugada patients, large differences in cardiac event rates are observed during follow-up,4-7 thus leading to different management strategies across centers. The ECG pattern, result of programmed electrophysiological study, and familial history have been identified as risk factors3 although not accepted by everybody.

The presence of a spontaneous type 1 Brugada ECG pattern,4,5 as opposed to a drug-induced pattern, is the most widely established risk factor. It is well known that the ECG Brugada pattern may change over time in a given patient,3,8 and a spontaneous type 1 may be intermittent, that is, a non-type-1 ECG at a given visit does not exclude spontaneous type 1 at other time points. Noticeably, no rule has been proposed to classify a given patient as having a spontaneous type 1 or not. The probability of recording a type 1 ECG is likely to be related to the number of ECG samples collected and the patient specific proportion of time with a type 1 pattern. These considerations and the analogy with atrial fibrillation burden9 have led to the concept of Brugada burden. Veltmann et al have shown that inducibility of ventricular tachycardia or fibrillation during electrophysiological study was significantly higher in patients presenting during follow up with more than 50% type 1 ECGs.10 In a retrospective study of Brugada patients implanted with an ICD, Richter et al showed that patients receiving appropriate shocks had a higher proportion of type 1 ECGs.11 These studies raised the hypothesis that the burden of type 1 Brugada ECG pattern could be of added value to the crude spontaneous type 1 criteria for risk stratification.

In a previous study using 12-lead digital Holter technologies, we could demonstrate that the level of ST-segment elevation was highly variable over a 24-hour period.
in Brugada patients. Beyond ST elevation, we made the hypothesis that 12-lead 24-hour recordings are suitable to detect type 1 Brugada pattern and are an adequate time frame to observe spontaneous fluctuations in Brugada ECG type.

In this study, we aim to quantify and to compare the burden of type 1 Brugada ECG pattern during a 24-hour period in control subjects and symptomatic and asymptomatic Brugada patients.

Methods

Patients

In this case control study, the patient population consisted of 34 patients with a Brugada syndrome or a typical type 1 ECG pattern referred to our Cardiology Center (30 males, mean age 46.4 ± 11.4 years). The ECG diagnosis of Brugada syndrome/pattern was defined as an ST-segment elevation on right precordial leads greater than 200 μV in conjunction with the presence of type 1 morphology (3) recorded either spontaneously or after a class I antiarrhythmic drug challenge (intravenous ajmaline, 1 mg/kg body weight per 5 minutes).

A patient was considered as having a “spontaneous” type 1 Brugada ECG when at least one standard 12-lead ECG recorded before the Holter recording showed a type 1 pattern.

All patients had a structurally normal heart as assessed by trans-thoracic echocardiography and underwent an electrophysiological study. The programmed ventricular stimulation protocol included 2 basic cycle lengths (600 and 400 ms) with up to 3 extra stimuli delivered at the right ventricle apex and outflow tract with a shortest RR interval of 200 ms.

A group of 32 healthy volunteers (16 men; mean age, 50.3 ± 21.6) served as a control group. All control subjects had a normal clinical examination including normal blood pressure and ECG. None of them had past clinical history of disease.

ECG recording and analysis

All patients and control subjects underwent a 12-lead (6 limb and 6 precordial leads), 24-hour continuous ECG recording under drug-free conditions (Ela Medical, Sorin group, Le Plessis Robinson, France). Electrocardiographic recordings were carefully edited to ensure that all cardiac beats of sinus origin were accurately identified and that nonsinus beats as well as artifacts had been excluded for quantitative analysis.

A customized version of a software package for quantitative ECG analysis was subsequently applied. The averaging process, alignment, and noise calculation methods have been previously described. One-minute averaged QRS-T complexes were obtained, leading to 1440 ECG waveforms over the 24 hours of the recording for each of the 3 right precordial leads (V1-V3). Each 1-minute waveform was considered as suitable for quantitative ECG measurement only if it was built from a minimum of 20 individual QRS-T complexes of sinus origin and if the level of residual noise was less than 3 μV.

The onset of the QRS complex (Qonset) was defined as the earliest QRS sample across the 12 ECG leads. The baseline was defined as the horizontal line crossing the Q-onset position. The Q onset and the baseline position were automatically determined but visually validated and manually corrected when necessary.

In a previous study, we observed that the maximum ST-segment elevation was on average 110 ms after Q onset and never before Q+80. Thus, for the present study, a “Brugada” window was defined as the time period starting 80 ms and ending 140 ms after the Q onset position. The validity of the window was visually checked in all patients and all waveforms.

Within the Brugada window, quantitative ECG parameters were automatically measured from the 1-minute averaged waveforms:

1. The amplitude of ST segment elevation at each sampling point within the Brugada window.
2. The amplitude of maximum ST elevation within the Brugada window.
3. The ST-segment slope (ascending or descending) within the Brugada window.
4. The T-apex amplitude.

For each of the 3 right precordial leads the 24-hour ECG trends of ST-segment elevation at a given ECG sample within the Brugada window were displayed (Fig. 1).

The diagnosis type 1 Brugada ECG was defined as the association of (1) a maximum ST elevation of above 200 μV, (2) a descending ST segment, and (3) a negative T-wave polarity.

The Brugada burden in a given patient and in a given right precordial lead was defined as the number of ECG waveforms associated with a type 1 Brugada pattern divided by the total number of suitable 1-minute averaged QRS-T complexes of sinus origin during the recording (ie, divided by 1440 for 24 hours of recording) and was expressed as a percentage. Similarly, the burden of maximum ST-segment elevation >200 μV was also calculated.

Separate analysis was conducted on a diurnal period (4 consecutive hours after awakening) and on a nocturnal period (4 consecutive hours with the slowest heart rates within the sleeping period).

Based on the 24-hour type 1 Brugada burden, the following 3 ECG categories were then defined:

- Permanent type 1 corresponding to a type 1 burden of >95%
- Absence of type 1 corresponding to a type 1 burden of <1% and
- Intermittent type 1 occurrence (burden ranging from 1 to 95%)

Statistical analysis

Data are presented as mean ± SD for normally distributed parameters and as median (25th-75th percentiles) otherwise.
Comparisons of burdens between groups were performed by rank sum tests. For the categorical analysis, proportions within groups were compared by a Fisher exact test. Statistical analysis was performed using Statview 5.0 (SAS Institute, Inc, NC).

**Results**

**Clinical data**

On standard resting ECG at bedside, the typical Brugada type 1 pattern was recorded spontaneously in 20 (59%) of the 34 patients and after ajmaline challenge in the remaining 14 patients.

During the electrophysiological study, ventricular fibrillation was induced in 65% of the patients (22/34).

Among the 34 Brugada patients, 19 were classified as asymptomatic (no history of syncope or sudden cardiac death). Among these 19 asymptomatic patients, 3 have been referred because of a familial history including symptomatic probands (1 with sudden cardiac death and 2 with syncope) and the 16 others were fortuitous cases. The asymptomatic group (n = 15) includes 10 patients presenting with syncope, 1 with seizure during hyperthermia, 1 with rapid ventricular tachycardia (ventricular flutter), and 3 patients with a personal history of sudden cardiac arrest.

**Burdens of Maximum ST elevation >200 μV and type 1 Brugada pattern**

A type 1 Brugada ECG was never observed in control subjects.

Type 1 burden on lead V2 was higher in patients with a spontaneous type 1 bedside ECG than in patients in whom type 1 ECG was documented after ajmaline challenge (median time 78.2% [51.0-96.7] versus 5.1% [0.0-27.1], P < .001).

Maximum ST elevation greater than 200 μV alone was more frequently observed in Brugada patients than in control subjects on leads V1 and V2, but no difference was observed between symptomatic and asymptomatic Brugada patients (Table 1).

On lead V1, the type 1 pattern occurrence was similar in asymptomatic and symptomatic Brugada patients (median time: 17.4% [0.1-97.0] vs median time 38.6% [3.8-81.0], respectively).

On lead V2 the type 1 Brugada burden was different according to the symptomatic status. On that lead, symptomatic Brugada patients displayed a type 1 Brugada ECG during a median time of 80.6% (15.7-96.7) of the recording, against a median time of 12.4% (0.0-69.7) in asymptomatic patients (P = .05) (Table 1).

Fig. 2 shows the percentiles of Brugada type 1 burden on lead V2 in symptomatic and asymptomatic Brugada patients.
The area under the receiver operating characteristic curve was 0.695 (95% CI, 0.514-0.840), \( P < .05 \) (Fig. 3). A type 1 Brugada burden ≥80% on lead V2 yielded to a 53% (95% CI, 26.6-78.7) sensitivity and 89.5% (95% CI, 66.9-98.7) specificity for symptom occurrence in Brugada patients.

Type 1 burden did not show circadian pattern. For instance, on lead V2, the Brugada burden was 19.3% (0.0-71.5) during the day vs 14.2% (0.0-72.7) during the night in asymptomatic Brugada patients and 80.2% (8.3-99.9) during the day vs. 89.2% (27.6-97.7) during the night in symptomatic Brugada patients (\( P \) non significant for both subgroups).

Categorical analysis and clinical status

Within individuals, the ECG pattern fluctuated over the 24 hours period with intermittent type 1 detected in more than half of the patients on leads V1 and V2 (Table 2).

Considering the 3 precordial leads all together, only 1 patient had a permanent type 1 ECG pattern during the whole recording. This patient had a history of resuscitated sudden cardiac arrest.

Absence of any type 1 ECGs on any of the 3 precordial leads over the 24 hours of the recording was diagnosed in a group of 6 patients out of 34 (Table 2). In this group, 5 patients were asymptomatic and the other one had experienced seizure during hyperthermia leading to his classification as symptomatic. In addition, the Brugada ECG was evidenced only during pharmacological challenge in 5 out of these 6 patients.

Considering precordial leads separately, type 1 was permanent on at least 1 lead in 11 of the 34 patients. Among them, 5 were symptomatic. The ECG phenotypes are different according to the precordial lead considered.

On lead V1, a permanent type 1 ECG was observed in 7 subjects, 2 of them being symptomatic. Ten patients had no detectable type 1 ECG on lead V1 and among them, 3 were symptomatic (Fisher exact test not significant).

In comparison with lead V1, a permanent type 1 ECG (n = 6) on lead V2 was more often associated with symptoms (5 out of 6 patients: 3 with sudden cardiac death, 1 with ventricular flutter, and 1 with syncope). When there was no type 1 ECG on lead V2 (n = 9), patients mainly were asymptomatic (7 of 9) among these 2 symptomatic patients 1 experienced seizure during hyperthermia and 1 syncope (Fig. 4). Symptomatic status was more often associated with permanent type 1 than with absent type 1 pattern on lead V2 (Fisher exact test \( P < .05 \)).
Among patients with an intermittent type 1 pattern on lead V2 the burden was not significantly different between symptomatic and asymptomatic patients (Fig. 4).

All patients but one with spontaneous type 1 standard ECG had type 1 pattern on the Holter recording. On the other side, 10 out of the 14 patients with no spontaneous type 1 on the standard 12-lead ECG had type 1 pattern on Holter recordings. Thus, the sensitivity of Holter recording in detecting type 1 is not 100% but Holter recording appears more sensitive.

**Discussion**

**Main findings**

Brugada syndrome is mainly defined by its typical ECG pattern which has been long recognized as time variant fingerprint. Both short-15 and long-term changes have been described during prolonged follow-up,3,8 but the 24-hour variability of ST elevation and of Brugada burden had not been fully characterized.

Using a custom ECG algorithm we showed that a 24-hour time period is long enough to detect a switch from type 1 to non-type 1 Brugada ECG pattern in more than three fourths of the patients on the 3 conventional right precordial leads.

Symptomatic Brugada patients were characterized by more prevalent occurrence of type 1 ECG on lead V2 when compared to asymptomatic patients. We also showed that the burden category on lead V2 may be helpful in predicting symptoms. Patients with a permanent type 1 pattern on lead V2 or those with burden higher than 80% were more likely to be symptomatic and to present more severe symptoms. On the opposite, patients with lack of type 1 ECG during a 24-hour period were more often asymptomatic.

**Technical considerations**

In this study, the right precordial leads have been acquired in ambulatory conditions using “true 12 leads” Holter recorders, that is, without any mathematical lead reconstruction other than the Einthoven matrix. It should be acknowledged that the position of the standard electrodes on the limb roots is not strictly identical to a conventional 12 leads ECG (limb extremities). However, this hook up configuration does not impact the precordial ECG signal.

The main technical difference between our ECG data set and the conventional bedside ECG recordings is the use of a specific time averaging process on a 60-second time frame. The beat-to-beat fluctuations in repolarization parameters which have been described in the Brugada syndrome are not visible after averaging.15,17 On the other hand, the noise reduction14 is a critical advantage when performing automatic quantitative ECG analysis. In the present study, we chose to average sinus QRS-T complexes every minute as a compromise between time resolution and noise reduction. We could thus obtain hundreds of low-noise averaged ECGs, defined as a residual noise below 3 μV, although obtained in ambulatory conditions.

Results from automatic detection of Brugada patterns have already been reported in resting conditions.18 The ECG features typical of a type 1 pattern might be easier to extract than those of types 2 and 3. The parameters we used for type 1 definition in our model are close to the method proposed by Kaneko et al.18 In their study, the use a 200-μV cutoff for type 1 detection was associated with very good sensitivity and specificity.

Finally, it should be emphasized that our method does not require the identification of the J point which can be notoriously difficult, particularly in the presence of morphological patterns like those associated with Brugada syndrome. In our approach, the transition between the end of the depolarization and the beginning of the repolarization is evaluated as a continuum, without depending from a specific ECG sample.

**Type 1 burden and risk stratification**

The present study is the first to quantify ST changes over 24 hours in a Brugada population. We show that most of our patients display intermittent type 1 pattern, which emphasizes the critical role of the ECG recording duration when trying to define “spontaneous” type 1 Brugada. Intuitively, one can hypothesize that increasing the recording duration shall be associated with a better sensitivity in detecting spontaneous type 1 ECG.

Correct identification of spontaneous type 1 Brugada pattern is not a trivial issue since published reports focusing on prognosis factors in the syndrome have consistently...
identified its presence as a predictor of subsequent arrhythmic events.4,7 Beyond this prognosis value of a spontaneous type 1 ECG, recent data have shown that the higher the proportion of type 1 ECG collected during follow-up, the higher the inducibility rate of ventricular tachycardia or fibrillation10 or the higher the proportion of appropriate shocks by ICD.11 Results from our study are confirmatory but the burden categories are available with a short turn around time.

Our data suggest that type 1 burden on lead V2 might be more helpful in predicting symptoms than data from leads V1 or V3. Previous studies already underlined the importance of lead V2 in risk stratification in Brugada syndrome.19,21 The rationale behind such lead specific information remains unclear.

Body surface mapping has shown that recording high right precordial leads (second and third intercostal spaces) could improve the sensitivity to detect type 1 pattern.22 The diagnosis and prognosis values of type 1 on these high precordial leads remains however to be elucidated.

In light of the nocturnal prevalence of arrhythmic events in Brugada patients,23 and based on the relationship between type 1 burden and clinical symptomatic status, one could expect a nocturnal pattern presenting a more enhanced type 1 burden. This, however, was not observed in our study. According to the Brugada ECG model proposed by Yan et al.,24 increased vagal tone should promote the type 1 electrical substrate. However, it has been long suggested that while being predominant, the absolute level of nocturnal vagal tone might be diminished, a phenomenon described as the adrenergic paradox.25,26 One can also hypothesize that the “pro-arrhythmic” effect of vagal environment may not be directly linked to type 1 ECG burden in humans. Similarly, it has been shown that meal intake was associated with increased ST segment elevation in Brugada patients.27 The time of feeding was not recorded during the Holter recordings in our study; thus, we could not evaluate specifically ST segment elevation during this period. However, our time bin approach would be suitable for such analyses.

The actual link between type 1 burden and arrhythmic risk is not fully understood. In the wedge model preparation, the typical Brugada morphology is related to the epicardial and transmural ventricular repolarisation gradients.24 Increase of the gradients is associated with arrhythmogenicity in experimental conditions.24,28 In humans, one can hypothesize that more prevalent type 1 pattern could reflect more severe ionic channels malfunctions.

Limitations

The number of patients included in our study was relatively small; we thus cannot exclude a lack of statistical power to demonstrate ECG differences between groups and could not perform multivariate analyses. In addition, because of its retrospective nature, our results need to be confirmed by a prospective evaluation of larger cohort of Brugada patients. Finally, despite genetic analyses, the genotype of each of our patients was not known. We cannot exclude gene-specific differences in ECG pattern prognosis value.

Conclusions

Long-term 12-lead ECG recordings increase the probability of detecting spontaneous type 1 ECG pattern that is more prevalent across a 24-hour period in symptomatic patients. The evaluation of long-term type 1 ECG burden may improve both phenotypic characterization as well as risk stratification in Brugada patients. Our study suggests that Holter recordings should be incorporated in regular Brugada workup. Prospective studies are needed to confirm our preliminary data and to demonstrate the potential interest of Brugada burden evaluation in risk stratification and ICD implantation decision.

References