Clinical research

**Decreased nocturnal standard deviation of averaged NN intervals**

An independent marker to identify patients at risk in the Brugada Syndrome

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**Aims**

Risk-stratification of asymptomatic Brugada Syndrome (BS) patients remains a key-issue. A typical spontaneous BS-ECG pattern and ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility are two recognized risk markers. The aim of the study was to identify additional risk markers in asymptomatic BS.

**Methods and results**

We have compared Holter recordings in symptomatic and in asymptomatic patients with BS. Heart rate variability (HRV), QT-interval rate-dependence and ST-segment elevation (ST-SE) were analysed. The study population included 47 BS patients (M=36, mean age=45±13 years) with a malignant ventricular arrhythmia in 11 cases, an unexplained syncope in 10 cases and no symptoms in the remaining 26 cases. A typical spontaneous BS-ECG was present in 21 cases and a drug-induced BS-ECG in 26 cases. A downward trend of the time domain variables of HRV was observed. During the nocturnal period, standard deviation (SD) of the 5 min averaged NN intervals (SDANN) (46±13 vs 57±18 ms, \( P = 0.02 \)) and ultra low frequency component (3287±2312 vs 5030±3270 ms², \( P = 0.04 \)) were significantly lower in symptomatic versus asymptomatic patients. In contrast, no difference was found in QT-interval rate dependence and in ST-SE. At multivariate logistic regression, VT/VF inducibility, typical spontaneous BS-ECG and a decreased nocturnal SDANN were associated with arrhythmic events (\( P = 0.003 \)).

**Conclusion**

A decreased nocturnal SDANN was an independent marker of arrhythmic events in these BS patients.

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**KEYWORDS**

Arrhythmia; Genetics; Sudden death; Prevention

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Brugada syndrome (BS) is an inherited disease characterized by an ST-segment elevation (ST-SE) in leads V1, V2, V3 and a high risk of sudden cardiac death due to ventricular fibrillation (VF). The proposed mechanism of the arrhythmia and ST-SE involves imbalance between the inward (\( I_{Na} \) and \( I_{Ca} \)) and outward currents (\( I_{to} \), \( I_{K,ATP} \), \( I_{Kr} \), \( I_{Cl(Ca)} \)) at the end of phase 1 of the epicardial action potential. The result may be an all-or-none repolarization phenomenon and a phase two reentry leading to...
ventricular arrhythmia. The ST-SE is influenced by the autonomic system and could be increased by an increased vagal tone before the arrhythmic event. Nocturnal predominance of the arrhythmic events and a possible presynaptic sympathetic denervation are also clues in favour of a role of the autonomic nervous system in the BS.

Patients with BS rescued from sudden cardiac death have a high risk of recurrence. A new arrhythmic event occurs in 62% of the subjects. The high recurrence rate justifies the use of automatic implantable defibrillators as no effective drug therapy has been found. Identification of BS in growing number of asymptomatic patients or relatives becomes critical. Risk-stratification includes typical spontaneous BS-ECG and ventricular tachycardia (VT)/ventricular fibrillation (VF) inducibility. According to Brugada, 17% of asymptomatic patients with such markers will have an arrhythmic event during a mean follow-up of 27 months and should be preventively implanted with a defibrillator. However, the potential benefit of such treatment is not clearly demonstrated in asymptomatic patients. Improvement of the risk-stratification in asymptomatic patients appears key-issue.

To identify additional risk markers in asymptomatic BS, we conducted a study comparing Holter monitoring between symptomatic and asymptomatic patients. Heart rate variability (HRV), QT-interval rate-dependence and dispersion as well as the extent and magnitude of ST-SE were investigated with a special concern on the diurnal and nocturnal periods of the recordings.

**Method**

**Study population (Table 1)**

The BS population followed in our institutions (CHU d’Amiens and Hôpital Lariboisière, Paris) includes 106 patients. Symptomatic VT/VFs were documented in 13 cases and unexplained syncpe in 13. Among the 80 asymptomatic patients, an electrophysiological study was performed in 68 cases. A VT/VF was inducible in 40 and not inducible in 28 patients.

From this cohort, 47 patients had both a drug-free Holter recording and a programmed ventricular stimulation. They form the basis of this study (Male=36, mean age=45±13 years). Symptomatic patients (n=21) were defined as those having a history of cardiac events including cardiac arrests, malignant ventricular arrhythmias and syncpe. Cardiac arrest or malignant ventricular arrhythmia occurred in 11 patients and unexplained syncpe in 10 patients. Symptoms appeared during the diurnal period in 12 cases and in the nocturnal period in nine patients. The 26 asymptomatic BS were relatives of patients or had been diagnosed by chance. Patients had typical spontaneous BS-ECGs in 21 cases and drug-induced BS-ECGs in 26 cases. SCN5A mutations were identified in 12 out of the 21 patients who were genotyped.

Brugada Syndrome was diagnosed in accordance with the current diagnosis criteria. In symptomatic patients or subjects with a familial history of BS, diagnosis was based on a coved-type ST-SE in more than one right precordial lead (V1–V3) in the presence or absence of a Na channel blocker. In asymptomatic patients with saddle-type ECG, a >0.2 mV drug-induced coved ST-SE in right precordial leads was required. The absence of structural heart disease was verified by non invasive and invasive investigations including 2D echocardiography, magnetic resonance imagining (MRI) and coronary angiography with right and left ventricular angiography when appropriate. A typical spontaneous BS-ECG was defined by the presence of, at least, one coved-type ECG recording. Na channel blockade challenge was carried out in the other cases with intravenous infusion of ajmaline (1 mg/kg/s) to confirm the diagnosis of BS. During the tests, ECGs were monitored on a computerized electrophysiological system and stored on optical disks. Na channel blockade challenge was regarded as positive if a >0.2 mV down-sloping ST-SE measured 20 ms after the end of the QRS was detected in the right precordial lead including V1 and V2 recorded in the 2nd intercostal space.

**Holter monitoring**

Digital Holter ECGs were recorded on PCMCIA flash cards and analysed with the SyneTec software (ELA medical, F-Le Plessis-Robinson). The A/D sampling rate of the Holter system is 200 Hz.
with an 8-bit resolution. Extrasystoles and artefacts were removed from analysis.

Heart rate variability
The following HRV parameters were measured: standard deviation of all the NN intervals (SDNN), standard deviation of 5 min averaged NN intervals: (SDANN), root mean squared of successive difference of NN intervals: (rMSSD), percentage of NN intervals over 50 ms: (pNN50) in time domain and, high frequency: 0.15–0.40 Hz (HF), low frequency: 0.04–0.15 Hz (LF) and very low frequency: 0.003–0.04 (VLF) components in frequency domain. Heart rate variability frequency domain was computed using a fast Fourier transform on 256 s periods. A Hanning window was used to limit border effects. Ultra low frequency component was calculated because the software is designed to perform spectral analysis on frequencies occurring every 5 min to every 24 h was not measured directly.

QT-interval analysis
A mean complex waveform based on 30 s of ECG was calculated by the software by synchronizing the onset of the QRS. The peak of the T wave was individualized using the parabola method (QT apex). The end of the T wave was determined by the intersection between the maximum decreasing tangent and the isoelectric line (QT end). The accuracy of the apex and end of T wave location was verified visually before data computing. Corrected QT apex (QTac) and corrected QT end (Q Tec) were calculated with the Bazett formula. As well, QTa/RR slopes, QTe/RR slopes and QT-interval dispersions between the recorded leads were automatically computed for the 24 hours and for the diurnal and nocturnal periods. By default, the diurnal and nocturnal periods were set between 8:00–21:00h and 23:00–06:00h. Adjustments with sleeping periods were performed when necessary according to the patient’s diary.

ST-SE analysis
ST-segment elevation was investigated over the 24 h. The isoelectric line 25 ms before the onset of QRS was chosen as a reference. Presence of a ST-SE episode was defined as at least >1 min BS-ECG episode. ST-segment elevation was measured 20 ms after the end of the QRS. Relative duration of ST-SE over the length of the recording was quantified for the levels of >0.2 mV and >0.1 mV. All the ST-SE episodes were controlled visually. Permanent ST-SE was arbitrarily defined as the presence of a >0.1 mV ST-SE during more than 80% of the total Holter monitoring length.

Electrophysiologic study
Electrophysiologic study was carried out with a standardized protocol including a driving cycle length of 600 and 400 ms, up to three extra stimuli and with a shortest coupling interval of 200 ms. Both right ventricular apex and outflow tract were paced at twice the right ventricular diastolic threshold. Ventricular tachycardia/ventricular fibrillation inducibility was defined as induction of monomorphic or polymorphic ventricular tachycardia lasting >20 s or degenerating into ventricular fibrillation.

Statistical analysis
Variables were expressed as mean±standard deviation. Comparisons between groups were performed with the chi-squared test and with the Mann–Whitney U non-parametric test. Repeated values were compared with paired t tests. Correlations between qualitative variables were estimated by the contingency coefficient. A bilateral P value under 0.05 was considered as significant.

A binary logistic regression model was used in order to estimate the Holter variables which influenced the symptomatic condition in BS. The two usual risk-markers of symptomatic BS (VT/VF inducibility and presence of a typical spontaneous B5-ECG) and Holter data which were significantly different between symptomatic and asymptomatic BS patients in univariate analysis were included into the binary logistic regression. Data were included when the P value was <0.1. A forward stepwise (Wald) procedure was used. All the statistical analyses were performed with the SPSS software 9.0.

Results
Asymptomatic and symptomatic groups were comparable in clinical variables including age, sex ratio, body mass indexes, mean Holter duration and condition of recording. The amount of familial BS was higher in asymptomatic patients (Table 1).

HRV (Table 2 and Table 3)
Mean 24 h RR-interval, diurnal and nocturnal RR-intervals were similar in symptomatic and asymptomatic patients. A downward trend of all the time domain variables of HRV, especially during the nocturnal period and a significant reduction of the nocturnal SDANN (46±13 vs 57±18 ms vs P=0.02) were found in symptomatic vs. asymptomatic patients. Ultra low frequency was significantly lower during the night in symptomatic versus asymptomatic patients(3287±2312 vs 5030±3270 ms², P=0.04) while LF/HF ratio and VLF were not different between the two groups.

QT-interval rate-dependence and dispersion
A loss of the normal circadian modulation of QT rate-dependence was evidenced with disappearance of the normal difference between diurnal and nocturnal values of the QTa/RR or QTe/RR slopes in the two groups of patients (Table 4). Comparison between the group of symptomatic and asymptomatic BS did not disclose significant differences in QTa/RR or QTe/RR slopes, in corrected QTa-intervals (313±26 vs 312±30 ms) and corrected QTe-intervals (39±32 vs 39±37 ms), or in QTa dispersion (10±7 vs 13±15 ms) and QTe dispersion (12±6 vs 20±23 ms).

Characteristics of ST-SE (Table 5)
Holter including at least one right precordial lead for appropriate ST-segment analysis were available in 87% (41/47) of the patients. The presence of ST-SE as well as its >0.2 mV or >0.1 mV relative extent over the 24 h were
not different between the symptomatic and the asymptomatic patients. ST-segment elevation episodes were more frequent during nocturnal period (Fig. 1) than during diurnal period (22/32, 69% vs 10/32, 31%, P=0.03) without any difference between the two groups of patients. There was no correlation between the timing of the clinical events and the nyctemeral distribution of the ST-SE or between the permanent feature of the ST-SE and the presence of a typical spontaneous BS-ECG.

Permanent ST-SE was observed in 23.8% of the typical spontaneous BS-ECG and in 15.4% of the cases of Brugada-compatible ECG (NS).

Risk markers for cardiac events in BS

Ventricular tachycardia/ventricular fibrillation inducibility and presence of a typical spontaneous BS-ECG were associated with cardiac events. Ventricular tachycardia/ventricular fibrillation inducibility was observed in 90% (19/21) of the symptomatic patients with BS (RR=4.4, [95% CI: 1.2–16]) and in 50% (13/26) of the asymptomatic patients (RR=0.47, [0.24–0.87]) (P=0.003). A typical spontaneous BS-ECG was present in 67% (14/21) of the symptomatic patient (RR=2.5, [1.2–5.0]) and in 27% (7/26) of the asymptomatic patients (RR=0.45, [0.29–0.76]), (P=0.006). Age and sex were not predictor of cardiac events.

Typical spontaneous BS-ECG, VT/VF inducibility, nocturnal SDANN, nocturnal Ultra low frequency and nocturnal SDNN were entered into a binary logistic regression model using a stepwise procedure. Ventricular tachycardia/ventricular fibrillation inducibility, a typical spontaneous BS-ECG and a low nocturnal SDANN were independently associated with cardiac events. The

### Table 2  Time-domain heart rate variability in symptomatic versus asymptomatic patients with Brugada Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic BS (21 patients)</th>
<th>Asymptomatic BS (26 patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24h RR interval (ms)</td>
<td>868±1088</td>
<td>852±114</td>
<td>0.43</td>
</tr>
<tr>
<td>Diurnal RR interval</td>
<td>812±109</td>
<td>790±116</td>
<td>0.33</td>
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<tr>
<td>Nocturnal RR interval</td>
<td>978±119</td>
<td>976±116</td>
<td>0.75</td>
</tr>
<tr>
<td>24 h SDNN (ms)</td>
<td>123±33</td>
<td>134±33</td>
<td>0.33</td>
</tr>
<tr>
<td>Diurnal SDNN</td>
<td>95±28</td>
<td>99±26</td>
<td>0.96</td>
</tr>
<tr>
<td>Nocturnal SDNN</td>
<td>81±27</td>
<td>95±28</td>
<td>0.07</td>
</tr>
<tr>
<td>24 h SDANN (ms)</td>
<td>103±29</td>
<td>112±33</td>
<td>0.40</td>
</tr>
<tr>
<td>Diurnal SDANN</td>
<td>76±26</td>
<td>77±23</td>
<td>0.96</td>
</tr>
<tr>
<td>Nocturnal SDANN</td>
<td>46±13</td>
<td>57±18</td>
<td>0.02</td>
</tr>
<tr>
<td>24 h pNN50 (%)</td>
<td>9±8</td>
<td>11±10</td>
<td>0.50</td>
</tr>
<tr>
<td>Diurnal pNN50</td>
<td>7±6</td>
<td>9±7</td>
<td>0.56</td>
</tr>
<tr>
<td>Nocturnal pNN50</td>
<td>14±15</td>
<td>17±17</td>
<td>0.48</td>
</tr>
<tr>
<td>24 h rMSSD (ms)</td>
<td>31±16</td>
<td>36±22</td>
<td>0.49</td>
</tr>
<tr>
<td>Diurnal rMSSD</td>
<td>27±12</td>
<td>30±16</td>
<td>0.54</td>
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<tr>
<td>Nocturnal rMSSD</td>
<td>39±25</td>
<td>46±36</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*BS: Brugada Syndrome; pNN50: percentage of NN intervals over 50 ms; rMSSD: root mean squared of successive difference in NN intervals; SDNN: standard deviation of all the NN intervals; SDANN: standard deviation of 5 min averaged NN intervals

### Table 3  Frequency domain heart rate variability in symptomatic versus asymptomatic patients with Brugada Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic BS (21 patients)</th>
<th>Asymptomatic BS (26 patients)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h HF (ms²)</td>
<td>296±569</td>
<td>423±608</td>
<td>0.39</td>
</tr>
<tr>
<td>Diurnal HF</td>
<td>210±238</td>
<td>289±337</td>
<td>0.37</td>
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<tr>
<td>Nocturnal HF</td>
<td>425±562</td>
<td>657±1103</td>
<td>0.38</td>
</tr>
<tr>
<td>24 h LF (ms²)</td>
<td>955±674</td>
<td>1146±679</td>
<td>0.34</td>
</tr>
<tr>
<td>Diurnal LF</td>
<td>812±569</td>
<td>891±551</td>
<td>0.63</td>
</tr>
<tr>
<td>Nocturnal LF</td>
<td>1091±928</td>
<td>1291±893</td>
<td>0.45</td>
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<tr>
<td>24 h LF/HF (%)</td>
<td>5.4±4.5</td>
<td>4.7±2.5</td>
<td>0.51</td>
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<tr>
<td>Diurnal LF/HF</td>
<td>8.6±11.2</td>
<td>5.2±3.2</td>
<td>0.58</td>
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<tr>
<td>Nocturnal LF/HF</td>
<td>5.2±5.4</td>
<td>3.9±2.5</td>
<td>0.46</td>
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<tr>
<td>24 h VLF (ms²)</td>
<td>2154±1478</td>
<td>2342±1130</td>
<td>0.62</td>
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<tr>
<td>Diurnal VLF</td>
<td>1823±1168</td>
<td>1888±924</td>
<td>0.83</td>
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<tr>
<td>Nocturnal VLF</td>
<td>2450±1874</td>
<td>2905±1675</td>
<td>0.35</td>
</tr>
<tr>
<td>24 h ULF (ms²)</td>
<td>12619±6825</td>
<td>14955±7964</td>
<td>0.29</td>
</tr>
<tr>
<td>Diurnal ULF</td>
<td>7062±5190</td>
<td>7364±3905</td>
<td>0.82</td>
</tr>
<tr>
<td>Nocturnal ULF</td>
<td>3287±2312</td>
<td>5030±3270</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*HF: high frequency component of the spectral analysis; LF: low frequency component; LF/HF: ratio of LF on HF components; VLF: very low frequency component; ULF: ultra low frequency component.
Overall model was significant at the 0.003 level according to the model chi-square statistic. The odds ratio of cardiac events increased by 65% each time the SDANN decreased by 10 ms, assuming that inducibility and ECG pattern are held constant (Table 6). Combining a SDANN <50 ms to a spontaneous BS-ECG and VT/VF inducibility increases specificity from 85% to 96% with a sensitivity of 52%; the positive and negative predictive values varying respectively from 78% to 92% and from 76% to 71%.

Discussion

The main result of this study is identification of a decreased nocturnal SDANN and ULF in patients with symptomatic BS. The decrease in nocturnal SDANN was independent of the two markers used for risk stratification: a typical spontaneous BS-ECG and VT/VF inducibility (Table 6). Combining a SDANN <50 ms to a spontaneous BS-ECG and VT/VF inducibility increases specificity from 85% to 96% with a sensitivity of 52%; the positive and negative predictive values varying respectively from 78% to 92% and from 76% to 71%.

Decreased nocturnal SDANN and nocturnal ULF in symptomatic patients with BS

A defined part of HRV reflects the input of the autonomos nervous system on the sinus node. High frequency component of spectral analysis and time domain indices such as rMSSD and pNN50 measures vagal influences. Low frequency component of the spectral analysis is considered either as a marker of sympathetic activation or of both vagal and sympathetic modulation. The origin of the lower components of HRV is less understood. VLF may represent the influence of the thermoregulatory, the renin-angiotensin systems as well as of physical activity or movement while ULF and SDANN are clearly increased by physical activity or muscular movement. Heart rate variability has been extensively studied in normal and abnormal clinical situations. Decrease of the lowest components of HRV is an independent prognostic factors after acute myocardial infarction. There are few data on HRV values in carriers of channelopathies. Two studies have found differences in autonomic modulation in the congenital long QT syndrome, with a lower sympathetic activity. A third study found no modification in HRV parameters in the different forms of the congenital long QT syndrome. Ultra low frequency was not measured in any of those studies. In idiopathic VF, time domain HRV was not found modified compared to controls. In the BS, HRV has been evaluated in few studies and there are no data available on SDANN or ULF. Unchanged HRV was found in carriers of SCN5A mutation with features of both long QT syndrome and BS (1795insD). An increased sympathetic activity was observed before VF attacks in a patient with an electrical storm. Lastly, an attenuated vagal tone was found in one asymptomatic patient.

In the present work, unlike the study hypothesis, we have not found differences in the HRV parameters assessing autonomic nervous system activity between symptomatic versus asymptomatic patient. We have found in symptomatic BS, a nocturnal reduction of the parameters...
Fig. 1  (A) A 42-year-old patient with an asymptomatic Brugada Syndrome presenting with three types of ECG recorded over a 6-month period. (B) From top to bottom: tachograph (bpm), level of ST-segment elevation in mV in lead B, duration of the ST-segment elevation episodes >0.2 mV. Sudden nocturnal episodes of ST-segment elevation independently of heart rate modification. Lack of diurnal ST-segment elevation. 1 and 2: Appearance and disappearance of the J point and ST-segment elevations.
(SDANN and ULF) reflecting the lowest components of HRV.32

Loss of circadian modulation of QT rate-dependence in BS

QT rate-dependence as measured by QT/RR slope is greater during the diurnal period than during the nocturnal period in normal subjects.33 Circadian modulation of the QT rate-dependence is thought to be related to the influence of the autonomic nervous system at the ventricular level. Nevertheless, it has been demonstrated that QT/RR is also under the influence of gender and aging. QT/RR is steeper in female34 and decreases when age increases.35 In normal volunteers close to the forth decade, which is the mean age of the study population, low circadian modulation of the QT rate-dependence is reported.35 Therefore, loss of circadian modulation of QT/RR observed here may be related to a defective ventricular repolarization control but also explained by the mean age of the study population.

Holter ST-SE in BS

Relative duration of ST-SE was not longer in symptomatic patients than in asymptomatic patients and was not correlated to the presence of a typical spontaneous BS-ECG. The presence of a typical spontaneous BS-ECG which is recognized as a marker of risk in the BS did not depend on the relative extent of ST-SE during Holter monitoring. Thus patients with typical spontaneous BS-ECG and patients with Brugada-compatible ECG could not be differentiated by the extent of ST-SE. However, from a practical point of view, ST-segment study during Holter monitoring may be useful when revealing the typical pattern in relatives or subjects with suspicious 12-lead ECG (Fig. 2).

Risk markers in BS

A typical spontaneous BS-ECG versus a drug-induced BS-ECG is an accepted marker of arrhythmic event.11,15 The event rate was 14% (16/111) in presence of a typical spontaneous BS-ECG in asymptomatic individuals followed during a 27-month follow-up.13 Accuracy of electrophysiologic study to predict outcome in patients with BS is debated. For Priori15 and Kanda36 programmed ventricular stimulation has low if no value predicting recurrence of arrhythmic events in symptomatic patients with BS. In contrast, in the largest series concerning the specific outcome of asymptomatic patients with BS,37 the overall accuracy was 70.5% and the negative predictive value was 99%. It has been suggested that the differences may result in the number and categories of subjects integrated in each study38 as well as in the various protocols used for the programmed ventricular stimulation.39 No other markers were found in this last study except a trend toward a better outcome in female versus male.11 Recently, attention has been focused on the importance of ventricular late potentials in identifying patients at risk.40 Multivariate regression analysis including late potential, T-wave alternans and QT-interval dispersion showed that the presence of late potential had the most significant correlation with the occurrence of arrhythmic event. However, multivariate analysis did not include programmed ventricular stimulation or the presence of a typical spontaneous BS-ECG.

In the present study, we found as in previous reports, that VT/VF inducibility and a typical spontaneous BS-ECG were markers of risk in BS patients. We noticed that a decreased nocturnal SDANN was independently associated with arrhythmic events and that there was no clear evidence of a defective autonomic nervous activity based on Holter analysis in symptomatic BS patients.

Methodological considerations

This study is a case-control study. Despite the absence of matching, control asymptomatic patients were comparable to symptomatic patients for the main clinical variables. Nevertheless, a difference in the amount of familial BS was evidenced and may have influenced the results.

Due to a large number of testing made in this study, false positive result may have been found. Nevertheless, the fact that concordant results are observed in two variables with similar signification (nocturnal SDANN and nocturnal ULF) argues against such an error-type.

The small number of recurrence of arrhythmic events in symptomatic patients and the short follow-up after Holter recordings were not appropriate for using the Cox regression model. Therefore, the preliminary data reported here should be confirmed in a prospective study with an adequate follow-up.

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Univariate and multivariate analyses of three indices associated with symptomatic Brugada Syndrome</th>
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<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td><strong>Multivariate analysis</strong></td>
</tr>
<tr>
<td><strong>Odds ratio [95%CI]</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>VT/VF inducibility</td>
<td>9.5 [1.8–49]</td>
</tr>
<tr>
<td>Spontaneous BS-ECG</td>
<td>5.4 [1.5–19]</td>
</tr>
<tr>
<td>Nocturnal SDANN (ms)</td>
<td>–</td>
</tr>
</tbody>
</table>

*Each time SDANN decreases by 10 ms, odds ratio increases by 65% (OR=1.65 [1.11; 2.44]) in symptomatic versus asymptomatic patients. SDANN: standard deviation of the 5 min averaged NN intervals.
Fig. 2  (A) A 45-year-old patient with a suspected Brugada Syndrome. Baseline ECG showed a 0.2 mV ST-segment elevation in V2 without saddle-type or coved pattern of Brugada syndrome. (B) During Holter monitoring, several nocturnal episodes of typical coved ST-segment elevation occurred. Progressive J wave elevations are shown in 1 and in 2. C: Na channel blockade challenge confirmed the diagnosis of Brugada Syndrome with a characteristic coved-type ST-segment elevation response. -2V1, -2V2: V1 and V2 recorded in the second intercostal space.
As well, for ST-SE systematic analysis on Holter monitoring, the electrodes should be carefully positioned in order to systematically record suitable right precordial leads.

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