A prospective study on spontaneous fluctuations between diagnostic and non-diagnostic ECGs in Brugada syndrome: implications for correct phenotyping and risk stratification

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Aims Fluctuations between the diagnostic ECG pattern and non-diagnostic ECGs in patients with Brugada syndrome are known, but systematic studies are lacking. The purpose of this study was to prospectively evaluate the spontaneous ECG changes between diagnostic and non-diagnostic ECG patterns in patients diagnosed with Brugada syndrome.

Methods and results In 43 patients with Brugada syndrome (27 males; mean age 45 ± 11 years), 310 resting ECGs were obtained during a median follow-up of 17.7 months. The ECGs were analysed for the presence of coved type, saddle-back type or no, respectively unspecific, changes. A coved-type ECG pattern with more than 2 mm ST-segment elevation in at least two right precordial leads was defined as diagnostic. The patients were compared for different clinical characteristics with respect to the pattern of fluctuations. Out of a total of 310 ECGs, 102 (33%) revealed a coved type, 91 (29%) a saddle-back type, and 117 (38%) a normal ECG. Fifteen patients (35%) initially presented with a diagnostic coved-type ECG. Fourteen patients (33%) with an initially coved-type ECG exhibited intermit- tently non-diagnostic ECGs during follow-up. Only one patient (2%) presented constantly with a coved-type ECG. Out of 28 patients (65%) with an initially non-diagnostic ECG, eight (19%) patients developed a diagnostic coved-type ECG during follow-up. Twenty patients (47%) revealed a coved-type ECG during ajmaline challenge, but never had a baseline coved-type ECG recorded. No significant differences were found in gender and clinical characteristics among patients with or without fluctuations between diagnostic and non-diagnostic basal ECGs. The rate of inducible ventricular fibrillation was significantly higher in patients with more than 50% coved-type ECGs than in patients with less than 50% diagnostic ECGs.

Conclusion The prevalence of fluctuations between diagnostic and non-diagnostic ECGs in patients with Brugada syndrome is high and may have an implication on the correct phenotyping and on the risk stratification in patients diagnosed with Brugada syndrome without aborted sudden cardiac death. For correct phenotyping and risk stratification, repetitive ECG recordings seem to be mandatory.

KEYWORDS
Brugada syndrome; Risk stratification; ECG; ECG fluctuation; Sudden cardiac death

Introduction

The Brugada syndrome is characterized by typical coved-type ST-segment elevations in the right precordial leads and a high risk of sudden cardiac death (SCD) in individuals with a structurally normal heart.1-4 Currently, risk stratification is based on the basal ECG, the history of syncope or SCD, the pharmacological challenge with sodium channel blockers, and the inducibility of ventricular tachyarrhythmias during programmed ventricular stimulation. The presence of a basal abnormal electrocardiogram, i.e. coved-type ECG pattern with an ST-segment elevation of more than 0.2 mV in at least two right precordial leads, has been described to be a strong predictor for the occurrence of spontaneous ventricular tachyarrhythmias.2,4 A non-diagnostic basal ECG seems to be associated with a lower risk of ventricular tachyarrhythmias during follow-up.2,4,5 However, it is well known that the ECG pattern compatible with a Brugada ECG may only be transiently diagnostic.4,6,7 Possible fluctuations between diagnostic and non-diagnostic ECGs have major implications for correct phenotyping and for the risk stratification of patients diagnosed with a Brugada syndrome. In the present prospective study,
we have assessed the prevalence of ECG fluctuations in patients with the diagnosis of Brugada syndrome.

Patients and methods

Between 2000 and 2005, 44 patients were diagnosed with Brugada syndrome at the University Hospital Mannheim. A total of 43 consecutive unrelated patients (27 males, 16 females) diagnosed with Brugada syndrome were included in this prospective study. One patient was excluded from the analysis due to a familiar relationship in order to guarantee independence of the data points. No patient was lost in follow-up. Mean age at the time of diagnosis was 45 ± 11 years. Structural heart disease was excluded in all patients. All patients underwent pharmacological challenge with either intravenous ajmaline (1 mg/kg body weight) or flecainide (2 mg/kg body weight). A test was considered positive if a baseline type II or III or normal ECG converted to a coved-type ECG with an ST-segment elevation of more than 0.2 mV in more than one right precordial lead. Programmed ventricular stimulation was performed in 42/43 patients with up to three extrastimuli at three different driving cycle lengths at two right ventricular sites: the right ventricular apex and the right ventricular outflow tract, until refractoriness. The diagnosis of Brugada syndrome was based on coved-type ECG pattern with >2 mm ST-segment elevation in at least two right precordial leads and a clinical symptom according to the criteria of the Brugada syndrome consensus conference.8

Surface electrocardiogram

The intention was to obtain basal ECGs at the first presentation (index ECG) after one week and at each scheduled 3-months follow-up visit. To control also for incidental fluctuations and short-term changes, all available ECGs, which were recorded at each outpatient clinic visit during in-hospital stay and during unscheduled visits or routine ICD follow-up visits, were also included into the analysis. ECG recordings were performed in the absence of anti-arrhythmic drugs or any medication that influences cardiac repolarization and at normal electrolyte levels. All ECGs were recorded in a supine position at normal body temperatures. Recording speed was 25 and 50 mm/s. The right precordial leads (V1 and V2) were placed in the fourth intercostal space parasternally. Similar position of the right precordial leads in the different surface ECGs were assured by the intension to obtain basal ECGs at the first presentation and the diagnosis of the ECGs obtained during follow-up. To control also for incidental fluctuations and short-term changes as non-diagnostic. All ECGs were analysed by three experienced physicians blinded to patient and diagnosis.

ECG analysis

Heart rate, PQ interval, QRS duration, and QT interval were measured. The QT interval was corrected using Bazett’s formula. The maximal ST-elevation of all right precordial leads was determined. Additionally, each ECG was classified as Brugada-coved type, type II or III following the criteria of the Brugada consensus conference 2002.9 A coved-type Brugada ECG was determined as diagnostic for Brugada syndrome, type II, III or unspecified changes as non-diagnostic. All ECGs were analysed by three experienced physicians blinded to patient and diagnosis.

Comparison of the clinical characteristics

Patients were divided into four subgroups according to their initial ECG at first presentation and the diagnosis of the ECGs obtained during follow-up. In group A, patients were summarized, who presented with a coved-type ECG and revealed non-diagnostic ECGs during follow-up. Group B contained patients with permanently diagnostic ECGs. Patients who presented with a non-diagnostic ECG and showed diagnostic ECGs during follow-up were categorized in group C, and patients without any spontaneous basal ECG were allocated to group D. Clinical characteristics and electrocardiographical parameters of patients with non-diagnostic index ECG and diagnostic index ECG were compared concerning fluctuation to a diagnostic or non-diagnostic basal ECG during follow-up. Further, patients were divided into two groups using an arbitrary cut-off of more than 50% and less than 50% diagnostic ECGs of all ECG tracings obtained within the individual patient. Furthermore, data were also analysed with respect to gender.

Statistics

Data were given as means ± standard deviation or medians with interquartile range. Continuous variables between the different subgroups were analysed by the two-sided paired or unpaired Student’s t-test. The χ² test and the Fisher’s exact test were used to evaluate differences in categorical variables between the subgroups. A value of P < 0.05 was considered statistically significant.

Results

Basal ECGs

During a median follow-up of 17.7 months (interquartile range 22 months), a total of 329 12-lead surface electrocardiograms were recorded. In the final analysis, 310 ECGs were included. Nineteen ECGs (6%) had to be excluded because of deviation of the R-wave amplitude in the right precordial leads of more than 0.1 mV. At least three ECGs were obtained per patient. Minimal time interval between two ECGs was one day and the maximal interval was three months. There was no discrepancy in the diagnosis among the three blinded physicians who analysed the ECGs. The median number of ECGs per patient was seven, ranging from three to 19 ECGs. The mean interval between two consecutive ECGs was 16 days. A total of 102 ECGs (33%) were classified as diagnostic (coved type). A saddle-back type (type II and III) occurred in 29% (91 ECGs) and 117 ECGs (38%) were classified as neither coved type nor type II nor III (Figure 1). Mean PQ interval was 177 ± 23 ms, mean QRS duration was 97 ± 14 ms, and QTc interval was 413 ± 31 ms. The mean maximal ST-segment elevation was 0.25 ± 0.28 mV.

Coved-type ECGs

A total of 102 ECGs were classified as coved-type ECG. Mean PQ interval of the coved-type ECGs was 191 ± 21 ms and mean QTc interval was 420 ± 31 ms. Both parameters were significantly longer than in non-coved-type ECGs (P = 0.001). The mean maximal ST-elevation in coved-type ECGs was 0.38 ± 0.24 mV and significantly higher than in the non-diagnostic ECGs (P = 0.01). No significant difference was found in QRS duration between diagnostic coved-type and saddle-back type ECGs (99 ± 10 vs. 98 ± 13 ms, P = 0.55).

Non-diagnostic ECGs

A total of 208 non-diagnostic ECGs for Brugada syndrome were obtained: 91 were classified as saddle-back (type II and III) ECGs and 117 ECGs as neither coved type nor type II nor III. The mean PQ interval of the saddle-back ECGs was significantly longer with 180 ± 25 ms as compared with normal ECGs (162 ± 23 ms, P < 0.001). The QRS duration was significantly higher in saddle-back ECGs (97 ± 14 vs.
91 ± 16 ms, P < 0.0001). No significant difference was found for the QT interval.

Index ECGs

Fifteen out of 43 patients (35%) presented with a diagnostic coved-type index ECG; 12 out of 43 patients (28%) were classified as type II ECG; seven (16%) as type III, and nine ECGs (21%) were found to be neither coved type nor type II nor III (Figure 1).

Transitions between diagnostic and non-diagnostic ECGs during follow-up

Group A
Out of 15 patients with a diagnostic index ECG (35%), 14 (10 males; mean age 49.3 ± 8.8 years) revealed at least one non-diagnostic ECG during the median follow-up of 29 months (interquartile range 32.4). Out of a total of 107 follow-up ECGs, 61 (57%) were classified as diagnostic coved-type ECGs, 20 (19%) as saddle-back type (type II and III), and 26 (24%) as neither coved type nor II nor III. In Figure 2, the ECGs of a patient with an initially diagnostic and non-diagnostic ECGs during follow-up are displayed.

Group B
Group B consisted of only one patient (2%). This male patient diagnosed at the age of 44 was the only patient, who persistently showed coved-type ECGs, recorded (n = 6) during a follow-up of 11 months. He had no history of syncope or familial SCD. During programmed ventricular stimulation, ventricular fibrillation was inducible.

Group C
Eight out of 43 patients (19%; 48.4 ± 11.2 years; 5 males) presented initially with a non-diagnostic index ECG and showed intermittently diagnostic ECGs during the median follow-up of 29.5 months (interquartile range 11.8). In these eight patients, a total of 67 ECGs were obtained during follow-up, of which 35 (52%) were diagnosed as coved-type ECGs, 30 (45%) as type II or III, and two (3%) as neither coved-type nor II nor III. Figure 3 shows fluctuations from non-diagnostic to diagnostic ECGs.

Group D
Twenty out of 43 patients (47%; 41 ± 12 years; 11 males) presented with a non-diagnostic index ECG and never had a spontaneous diagnostic coved-type ECG recorded during a median follow-up of 14.2 months (interquartile range 12.4 months). All of these patients revealed a coved-type ECG during pharmacologic challenge with a class I anti-arrhythmic drug. A total of 130 ECGs were obtained in this group. Forty-one ECGs were classified as saddle-back type and 92 ECGs were neither coved type nor saddle-back type. An example of a patient with constantly non-diagnostic ECGs but positive response to ajmaline challenge is illustrated in Figure 4.

Comparison of the clinical characteristics according to ECG presentation

The clinical characteristics according to the initial ECG presentation are outlined in Table 1. Comparing patients with a diagnostic index ECG (group A and B), the only parameter which was significantly different was a longer QRS duration in the patient with constant diagnostic ECGs (P = 0.04). In patients with non-diagnostic index ECGs (group C and D), significant differences were found for age and PQ interval. PQ intervals were shorter and patients were younger at the time of diagnosis in group D. The number of ECGs per patient over the whole follow-up was smaller in group D,
but within the first three months no significant differences in the number of ECGs per patient were observed.

**Time to fluctuation**

For patients with a diagnostic index ECG (group A and B) and for patients with a non-diagnostic index ECG (group C and D), the time to the first non-diagnostic and the first diagnostic ECG, respectively, were analysed. Figure 5 displays the cumulative time to the first diagnostic and non-diagnostic ECG, respectively. The median time to first non-diagnostic ECG for group A was 12 days (interquartile range 26 days). After 103 days of follow-up, all patients of group A showed at least once one non-diagnostic ECG. Within this time, a mean of $5.5 \pm 1.7$ ECGs per patient were obtained with a mean time interval of $18 \pm 13$ days between the two ECGs.

In patients with non-diagnostic ECGs and fluctuations to diagnostic ECGs (group C), after 66 days of follow-up in all patients, the first diagnostic ECG was obtained. The median time to the diagnostic ECG was 16 days (interquartile range 29 days). Within the first 66 days of follow-up, the mean number of ECGs per patient was $5.3 \pm 1.9$ for group D and $5.2 \pm 1.9$ for group C, respectively. Mean time interval between two ECGs was also not significantly different ($17 \pm 13$ days for group D and $19 \pm 10$ days for group C, respectively).

**Comparison of patients with more or less than a 50% proportion of diagnostic ECGs**

Each patient in groups A, B, and C ($n = 23$) had at least one coved-type ECG recorded either at first presentation (index ECG) or during follow-up. In 14 out of 23 patients (61%), more than 50% of all recorded ECGs were coved-type ECGs, whereas the remaining nine patients showed in less than half of the ECGs a coved-type ECG. The clinical characteristics are given in Table 2. Significant differences between these two groups were found concerning inducibility of ventricular tachyarrhythmias and PQ interval, QRS width, and mean maximal ST-segment elevation. The inducibility of VT/VF was significantly higher (92%) in patients with more than 50% coved-type ECGs ($P = 0.02$). The PQ interval and the QRS width were significantly longer in patients in whom more frequently coved-type ECGs were recorded ($190 \pm 22$ vs. $172 \pm 20$ ms and $98 \pm 12$ vs. $93 \pm 16$ ms, respectively, $P = 0.02$). The mean maximal ST-segment elevation in patients with >50% coved-type ECGs was significantly higher compared with patients with less than 50% coved-type ECGs ($0.31 \pm 0.14$ vs. $0.19 \pm 0.18$ mV, $P < 0.0001$, Table 2).

**Comparison of ECG parameter and clinical characteristics according to gender**

This population of patients with Brugada syndrome consisted of 27 male and 16 female patients. A total of 182 ECGs was obtained among the males ($6.7 \pm 2.9$ ECGs/patient) and 128 among the females ($8 \pm 4.2$ ECGs/patient, $P = 0.23$). No significant difference were found between males and females in this population concerning age, history of syncope or aborted SCD, family history of SCD, or a coved-type index ECG. The inducibility of ventricular tachyarrhythmias was higher in males (85%) than in female patients (56%), but did not reach the level of significance ($P = 0.07$). PQ interval, QRS width, and mean maximal ST-elevation were significantly higher in males ($P < 0.0001$). Coved-type ECGs were significantly more often recorded in males than in females ($P < 0.0001$), whereas the amount of non-diagnostic ECGs was significantly higher among the female patients ($P < 0.0001$).

**Discussion**

After the description of the Brugada syndrome by Brugada et al.\(^1\) in 1992, the number of patients diagnosed with
Brugada syndrome is steadily increasing. Patients with aborted SCD and the typical Brugada ECG pattern are recommended to receive an implantable cardioverter defibrillator. However, risk stratification in patients with Brugada syndrome without previous SCD is currently based on the ECG, the history of syncope, and/or the inducibility of ventricular tachyarrhythmias during the programmed ventricular stimulation.2,4,5

Non-systematic studies and single case reports have presented fluctuations between diagnostic and non-diagnostic ECG pattern in the right precordial leads in patients with Brugada syndrome.6,7 The present study investigated prospectively the prevalence of fluctuations of the typical ECG pattern of Brugada syndrome in patients diagnosed with Brugada syndrome.

Prevalence of diagnostic ECGs

The main findings of the present prospective study are as follows.

- The overall percentage of diagnostic coved-type basal ECGs during short to midterm follow-up is 33%.
- 51% of the patients diagnosed with Brugada syndrome presented fluctuations between diagnostic and non-diagnostic ECGs.
- A significant number of patients (47%) with a Brugada syndrome does not reveal a spontaneous diagnostic basal ECG during follow-up.
- Only one out of 43 patients presents with a continuously diagnostic coved-type ECG.

Time to fluctuation

There have been several anecdotal reports on fluctuations of ECGs in patients with a Brugada syndrome. As mentioned above, there are numerous factors which may induce changes or normalizations of the ECG in Brugada syndrome. Furthermore, there is the observation that the ECG changes may more often occur later in life around the fifth decade, although it is not yet known why the ECGs develop in this way, in contrast, for example, to the short or long QT-syndrome. From our study, no statement with respect to onset of a diagnostic ECG can be made as all ECGs were recorded after the time of diagnosis. However, we observed significant fluctuations for 29% with a non-diagnostic index ECG to diagnostic basal ECG within 66

### Table 1  Clinical characteristics of the four subgroups according to the index ECG and the ECGs during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>P-value (A vs. B)</th>
<th>Group C</th>
<th>Group D</th>
<th>P-value (C vs. D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14 (32%)</td>
<td>1 (2%)</td>
<td>Not applicable</td>
<td>8 (18%)</td>
<td>20 (47%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Males</td>
<td>10 (71%)</td>
<td>1</td>
<td>1.0</td>
<td>5 (62%)</td>
<td>11 (55%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean age</td>
<td>49.3 ± 8.8</td>
<td>44.1</td>
<td>Not applicable</td>
<td>48.4 ± 11.2</td>
<td>42.8 ± 11.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (36%)</td>
<td>0</td>
<td>1.0</td>
<td>4 (50%)</td>
<td>9 (45%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Aborted SCD</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
<td>2 (10%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Family history SCD</td>
<td>3 (21%)</td>
<td>0</td>
<td>1.0</td>
<td>1 (13%)</td>
<td>3 (15%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ajmaline challenge positive</td>
<td>14/14 (100%)</td>
<td>1 (100%)</td>
<td>1.0</td>
<td>8/8 (100%)</td>
<td>20/20 (100%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Flecaïnide challenge done</td>
<td>7 (64%)</td>
<td>1</td>
<td>1.0</td>
<td>7 (100%)</td>
<td>11 (55%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Flecaïnide challenge positive</td>
<td>5/7 (71%)</td>
<td>1</td>
<td>1.0</td>
<td>5/7 (71%)</td>
<td>4/11 (36%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Inducible VT/VF</td>
<td>10/13 (77%)</td>
<td>1</td>
<td>1.0</td>
<td>5/8 (62%)</td>
<td>15/20 (75%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Total ECGs</td>
<td>107 (35%)</td>
<td>6 (2%)</td>
<td>Not applicable</td>
<td>67 (22%)</td>
<td>130 (42%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>ECGs/patient</td>
<td>7.6 ± 3.9</td>
<td>6</td>
<td>Not applicable</td>
<td>8.4 ± 2.9</td>
<td>6.5 ± 2.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ECGs/patient in first 3 months</td>
<td>5.5 ± 1.7</td>
<td>5</td>
<td>Not applicable</td>
<td>5.3 ± 1.9</td>
<td>5.2 ± 1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean coved-type ECG/patient</td>
<td>60%</td>
<td>100%</td>
<td>Not applicable</td>
<td>43%</td>
<td>0%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Coved-type ECGs (n)</td>
<td>61 (57%)</td>
<td>6 (100%)</td>
<td>Not applicable</td>
<td>35 (52%)</td>
<td>0 (0%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Saddle-back ECGs (n)</td>
<td>20 (19%)</td>
<td>0 (0%)</td>
<td>Not applicable</td>
<td>30 (45%)</td>
<td>41 (32%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Normal ECGs (n)</td>
<td>26 (24%)</td>
<td>0 (0%)</td>
<td>Not applicable</td>
<td>2 (3%)</td>
<td>89 (68%)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mean PQ interval (ms)</td>
<td>191 ± 19</td>
<td>180 ± 32</td>
<td>0.18</td>
<td>182 ± 22</td>
<td>162 ± 26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean QRS duration (ms)</td>
<td>98 ± 13</td>
<td>107 ± 8</td>
<td>0.04</td>
<td>97 ± 11</td>
<td>95 ± 14</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean QTc interval (ms)</td>
<td>410 ± 26</td>
<td>421 ± 17</td>
<td>0.19</td>
<td>413 ± 32</td>
<td>405 ± 27</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean max. ST-elevation</td>
<td>0.30 ± 0.18</td>
<td>0.38 ± 0.09</td>
<td>Not applicable</td>
<td>0.26 ± 0.1</td>
<td>0.1 ± 0.1</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

### Fluctuations of basal ECGs

In this study, we could find a high proportion of patients with Brugada syndrome who present transiently with diagnostic and non-diagnostic ECGs. In 22 out of 43 patients (51%) in this population, fluctuation between the diagnostic and non-diagnostic ECG pattern of Brugada syndrome occurred. Several factors are known to have an impact on the ECG pattern of Brugada syndrome. The vagal tone, body temperature, antiarrhythmic and non-cardiovascular drugs, or hormonal status could be shown to have an influence on the occurrence of the typical ECG pattern of Brugada syndrome.7,10–22 Fever and an extreme vagal tone can be excluded in our patients. All ECGs were recorded at normal body temperatures and in resting position. There was also no concurrent medication that potentially may provoke typical Brugada ST-segment elevations.
The only parameter, which was significantly different between patients with and without the mutation was the PQ interval. However, no analysis according to gender, age, or other clinical characteristics was performed.

In the population presented in this paper, patients were divided in different subgroups concerning the ECG at first presentation and fluctuations between diagnostic and non-diagnostic ECGs during prospective ECG recording after the diagnosis of Brugada syndrome was made. Between groups A and B, the only ECG parameter significantly different was the QRS duration. This analysis has to be evaluated carefully because group B consisted only of one patient. Between groups C and D, the PQ interval was significantly longer in patients with intermittent diagnostic ECGs (group C). Prolonged AV-conduction is known in coved-type ECGs that may count for this finding. Further analysis of the patients with spontaneous coved-type ECGs revealed that patients with more than 50% coved-type ECGs of all ECG traces recorded had significantly prolonged PQ and QRS interval, whereas QTc interval was not significantly different.

In males, PQ and QRS intervals were significantly longer as compared with females. Furthermore, the prevalence of a coved-type ECG and the mean maximal ST-segment elevation was significantly higher in males. These findings stand in line with the higher incidence of the Brugada syndrome in males.9,21 Experimental studies suggested that a more prominent transient outward current in males is responsible for these findings.24,25 Hong et al.26 described a family with a female predominance of the manifestation of Brugada syndrome. This family had the same mutation as a family with SUDS and a male predominance of phenotype and symptoms. Experimental studies could show a reduced Ito due to increased estrogen levels. These studies consider that probably not only the gender, but also individual hormonal levels are responsible for the gender-specific findings in Brugada syndrome.

Implication for risk stratification

Different groups have presented data on the outcome of patients diagnosed with Brugada syndrome.2–5 In all reports concerning risk stratification of patients with Brugada syndrome, the diagnostic index ECG is one of the important parameters in predicting SCD. The history of syncope is another major parameter in risk stratification. The predictive value of the inducibility of ventricular tachyarrhythmias is discussed controversially.2,4,5

In 2001, Brugada et al. published the follow-up data of 334 patients diagnosed with Brugada syndrome with a diagnostic index ECG. A total of 14% of the asymptomatic patients with a diagnostic ECG experienced a malignant ventricular arrhythmia within a follow-up of 27 ± 29 months. Symptomatic patients with a history of syncope or aborted SCD were estimated to have a mean recurrence rate of 11% per year.3 In the recent publication by Brugada et al., follow-up data of 547 patients without previous SCD were presented. It could be shown that a diagnostic, i.e. coved-type, index ECG predicts a higher risk in experiencing SCD within the mean follow-up of 24 ± 32 months than a non-diagnostic ECG that converted into diagnostic by pharmacological challenge with a class I antiarrhythmic drugs independently of a history of syncope or inducible ventricular tachyarrhythmias. A positive history of syncope and
The risk of SCD. The male gender was another risk factor for a spontaneous arrhythmic event.\textsuperscript{23} In our population of patients with Brugada syndrome, 22 out of 43 (51\%) showed fluctuations between diagnostic and non-diagnostic ECGs. Application of these findings on risk stratification by Brugada et al. would cause a potential underdiagnosis or incorrect risk stratification in 22/43 patients in our population. Eight out of these 22 patients presented with an initially non-diagnostic basal ECG which would result in a lower risk for an SCD according to Brugada et al. Due to repetitive ECG recordings, diagnostic coved-type ECGs could be obtained in these patients and consecutively the potential risk of SCD increased. Considering the fact that two out of these eight patients had a previous syncope and inducible ventricular tachyarrhythmias, the risk of these two patients with an initially non-diagnostic ECG increased from 9.7\% within approximately 2 years to a highest risk of 27.2\%. Furthermore, two patients presented with syncope and in another four asymptomatic patients, ventricular tachyarrhythmias were inducible, which results in an important increase of risk from 1.2 to 4.1\% and 4.5 to 14\%, respectively. The repetitive recording of further ECGs would have an impact on the treatment of at least these eight patients who presented with an initially non-diagnostic ECG and showed diagnostic ECGs during follow-up. Only one single ECG could have led the physician to an incorrect prognosis and treatment of the individual patient.

Priori et al. presented the data of 200 patients diagnosed with Brugada syndrome. They investigated ECG pattern, history of syncope, inducibility of ventricular arrhythmias, SCN5A mutation, family history for SCD, and the gender in predicting the occurrence of cardiac arrest in patients with Brugada syndrome. They found that only the association of a diagnostic ECG and the history of syncope demonstrated a significant increase of the risk of SCD with a hazard ratio of 6.4. Patients with a spontaneous diagnostic ECG for Brugada syndrome were classified as ‘intermediate risk’ for SCD with a hazard ratio of 2.1. Patients with a non-diagnostic ECG in the presence or absence of a syncope were meant to be at low risk.\textsuperscript{23}

Applying this risk stratification on the population presented in this paper, five out of 43 patients were classified as high risk because of an initially diagnostic ECG and a history of syncope. However, during follow-up, all five patients showed intermittently a non-diagnostic ECG and could potentially be classified as low risk according to this risk stratification. Out of 28 patients who presented with a non-diagnostic ECG, in eight patients a diagnostic ECG for Brugada syndrome could be obtained during follow-up. Four out of these eight patients presented due to previous syncope. The risk of all eight patients increased during follow-up: in four patients from lowest risk (negative ECG with or without syncope) to high risk (positive ECG and history of syncope), the remaining four patients changed risk group from low to intermediate because of the diagnostic ECG obtained. Twenty out of 28 patients with initially non-diagnostic ECGs remain in the low-risk group during follow-up because of continuously non-diagnostic basal ECGs.

The most recent publication about the long-term prognosis of patients with Brugada syndrome was presented by Eckardt et al. about 212 individuals from four different institutions. During a follow-up of 40 ± 50 months, they found that an aborted SCD or a syncope and a spontaneous type I Brugada ECG were the only predictors for a severe arrhythmic event during follow-up. Asymptomatic patients had a benign outcome during the follow-up with only one first arrhythmic event out of 123 patients.\textsuperscript{3} In our population, 18 out of 43 patients (42\%) presented with a syncope of unknown origin. Five of these patients (26\%) presented with an initially diagnostic type I ECG, but non-diagnostic ECGs during follow-up (group A). Four patients (21\%) with a previous syncope had an initially non-diagnostic ECG and diagnostic ones during follow-up. It follows that nine out of 43 patients may have been classified as low risk with only non-diagnostic ECG and conversion into diagnostic after drug challenge. Of note, one out of these 20 patients presented with syncope had showed only positive response to ajmaline and not to flecainide, which may cause further underdiagnosing of Brugada syndrome.

### Implication for clinical practice

The incidence of fluctuation between diagnostic and non-diagnostic ECGs of patients with Brugada syndrome is high. Fluctuations of the typical ECG pattern have important

| Table 2 | Characteristics of patients with coved-type ECGs. Patients with more than 50\% coved-type ECGs vs. patients with less than 50\% coved-type ECGs of all ECGs recorded within the individual patient were compared |
|---------|-------------------------------------------------|-------------------------------------------------|------------|
| n = 23  | >50\% coved-type ECGs | <50\% coved-type ECGs | P-value    |
| Number of patients | 14 | 9 | Not applicable |
| Males | 11 | 5 | 0.36 |
| Mean age | 46.0 ± 10.3 | 49.9 ± 9.1 | 0.37 |
| Syncope | 5 | 4 | 1.0 |
| Family history SCD | 2 | 2 | 1.0 |
| Flecainide challenge positive | 8/10 | 3/5 | 0.56 |
| Inducible VT/VF | 12/13 | 4/9 | 0.02 |
| Index coved-type ECG | 10 | 5 | 0.65 |
| Mean follow-up | 27.9 ± 12.5 | 21.6 ± 18.2 | 0.33 |
| Total ECGs | 122 | 58 | Not applicable |
| ECGs/patient | 8.7 ± 4.1 | 6.4 ± 3.2 | 0.17 |
| Mean PQ interval (ms) | 190 ± 22 | 172 ± 20 | <0.0001 |
| Mean QRS duration (ms) | 98 ± 12 | 93 ± 16 | 0.02 |
| Mean QTc interval (ms) | 415 ± 31 | 406 ± 23 | 0.05 |
| Mean max. ST-elevation (coved-type) | 0.31 ± 0.14 | 0.19 ± 0.18 | <0.0001 |
influence on risk stratification of individuals with Brugada syndrome without aborted SCD. In case of non-diagnostic index ECGs, multiple ECG-recordings should be performed due to potential considerable changes of risk stratification of the individual patient.

Limitations

There are several limitations in this study. First, this analysis was performed on all available ECGs during follow-up and did not use predefined sampling points, for example every three months. However, we decided to include all available ECGs, so ECGs were also recorded within a short period of time and during unscheduled visits as the causes for fluctuations and especially their temporal behaviour are still quite unclear. Whether basal ECGs in patients with Brugada syndrome evolve diagnostic with advanced age, this study cannot answer due to a too short follow-up for this question. To answer this question, ECGs of patients with Brugada syndrome from all decades of life have to be analysed.

The leads V1 and V2 were placed in the conventional way (fourth intercostal space). Over a follow-up of a median of 17.7 months, an exactly identical position of the right precordial leads cannot be guaranteed. Some minor deviation of the position of the ECG electrodes between the different ECG recordings may have occurred. However, this deviation was aimed to be controlled for by the R-wave amplitudes in the right precordial leads.

Recently, an effect of heavy meal intake on the amplitude and development of the coved-type Brugada ECG was observed.27–29 We did not include the analysis of the influence of meal intake regarding change of the basal ECG. Finally, no conclusions with respect to a prognostic significance of occurrence or degree of fluctuations can be drawn based on this data. Future studies with a longer follow-up and predefined sampling points and number of samples in a large patient population are needed to assess the prognostic significance of fluctuations in Brugada syndrome.

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References


