# Usefulness of patient's history and non-invasive electrocardiographic parameters in prediction of ajmaline test results in patients with suspected Brugada syndrome

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## Abstract

**Introduction:** The aim of the work was to assess the usefulness of patient's history and non-invasive electrocardiographic parameters in the prediction of ajmaline test results in patients with suspected Brugada syndrome.
**Material and methods:** The study involved a group of 59 patients (37 men) at average age of 31.6 ±12.2 years with suspected concealed form of Brugada syndrome. Pharmacological provocation with intravenous ajmaline administration was performed. The patients were divided into two groups depending on ajmaline test results. Individual and total predictive value for ajmaline test was based on the analysis of medical anamnesis and non-invasive electrocardiographic examination.
**Results:** The analysis carried out within the work indicated a special predictive value of 2 parameters which constituted the study inclusion criteria – family history of Brugada syndrome (28.6% vs. 3.8%; $p = 0.0477$) and occurrence of saddleback electrocardiographic changes in ECG curve (42.9% vs. 0.0%; $p = 0.0002$). Non-invasive electrocardiographic parameters which showed significant predictive value for ajmaline test were as follows: dispersion of QTc interval (prior to the provocation test 54.43 ±24.77 ms vs. 32.70 ±12.98 ms; $p = 0.0005$ and during daytime activity 46.81 ±27.16 ms vs. 32.07 ±13.19 ms; $p = 0.0198$), corrected QT intervals, Tpeak-Tend intervals in particular leads, QTpeak intervals, dispersion of Tpeak-Tend interval assessed from precordial leads (V1–V6) (42.86 ±13.80 ms vs. 26.54 ±11.70 ms; $p = 0.001$) and J-point elevation in V2 and V3 leads.
**Conclusions:** Both interview and non-invasive electrocardiographic parameters which reflect cardiomyocyte repolarization disorders are of high predictive value in anticipating ajmaline pharmacological provocation results in patients with suspected Brugada syndrome.

**Key words:** Brugada syndrome, non-invasive predictors, ajmaline challenge.

## Introduction

Brugada syndrome (BS) is a genetic, electrical heart disorder which may lead to sudden cardiac death. It is found all over the world, yet countries of south-east Asia are the place of its endemic occurrence. The symptoms

might occur at any age but it affects mostly young people. Average age of developing clinical symptoms is 40 years of age. The disease is manifested by blackouts and/or sudden cardiac death in a mechanism of ventricular fibrillation. The diagnosis is based on electrocardiographic criteria as well as clinical manifestation. Typical BS electrocardiographic changes occur as a result of ion function disorders in the heart which are caused by genetic changes and provoke disturbances of repolarization processes in cardiomyocytes. Electrocardiographic features of the syndrome are dynamic and the ECG curve is periodically normal – typical BS characteristics disappear, which makes BS diagnosis difficult. Because of the concealed form of BS a great number of people remain undiagnosed [1]. Specific pharmacological provocation tests with class I drugs are critical in revealing concealed electrocardiographic features of BS. Test with administration of this medicine carries a risk of life-threatening ventricular arrhythmia due to its known pro-arrhythmic action. Concurrently, lack of patient's consent to perform the test in case of undiagnosed concealed form of the syndrome may also be life-threatening. Therefore, finding non-invasive test parameters which would allow for prediction of pharmacological provocation results and thus considerably decrease the number of people exposed to potential complications connected with the test is a matter of great importance. To date, there are only a few reports assessing the role of electrocardiographic parameters in prediction of pharmacological provocation results in patients with suspected BS. Those works do not allow for establishing clear parameters useful in clinical practice.

Therefore, the aim of the study was to assess the usefulness of patient's history and non-invasive electrocardiographic parameters in prediction of ajmaline test results in patients with suspected BS.

## Material and methods

### Patient population

The study involved a group of 59 Polish patients (37 men) with suspected concealed BS based on specific electrocardiographic and/or clinical criteria (Table I): complete and incomplete right bundle branch block (RBBB) in ECG, suspected but non-diagnostic ECG (type 2 and 3), history of sudden cardiac arrest (SCA), unexplained syncopes, sudden cardiac death (SCD) amongst family members under 45, family history of BS.

The specific exclusion criteria were: electrolyte disorders, neurological syncopes, e.g. epilepsy, organic heart disease, history of allergic reaction to ajmaline.

No patient had used antiarrhythmic drugs or had electrolyte disturbances at the time of ECG findings.

The protocol of the study has been approved by the Commission for Bioethics of the Military Institute of Medicine in Warsaw. Written informed consent was obtained from all the patients.

The patients underwent all the following examinations: interview, physical examination, basic laboratory tests, 12-lead electrocardiography at rest, echocardiography, and 12-lead 24-hour Holter ECG monitoring. Subsequent pharmacological provocation with intravenous ajmaline administration dosed 1 mg/kg body weight during 5 min was performed in safe conditions during 12-lead 24-hour Holter ECG monitoring.

### Twelve-lead 24-hour Holter ECG monitoring

A twelve-lead Holter monitoring system (Mortara Instruments H-Scribe 2) at the sweep speed of 25 mm/s was employed. The PQ interval, QRS duration, QT intervals, corrected QT intervals (QTc), dispersion of QTc interval (QTd), J-point elevation in V1, V2 and V3 leads at J point and at 80 ms after

**Table I.** Distribution of the examined population depending on inclusion criteria

| Inclusion criteria | Number of included patients |
|---|---|
| RBBB in ECG (complete and incomplete) | 35 patients (59.32%): |
| | • RBBB complete – 8 patients (13.6%) |
| | • RBBB incomplete – 27 patients (45.76%) |
| History of SCA | 7 patients (11.8%) |
| Unexplained syncopes | 31 patients (52.5%) |
| SCD amongst family members under 45 | 5 patients (8.5%) |
| Family history of BS | 4 patients (6.8%) |
| Suspected but non-diagnostic ECG (type 2 and 3) | 16 patients (27.11%): |
| | • type 2 – 4 patients (6.78%) |
| | • type 3 – 12 patients (20.33%) |

J point, Tpeak-Tend intervals in particular leads (TpTe), and dispersion of Tpeak-Tend interval assessed from precordial leads (V1–V6) (Tp-Te d6) were manually measured during a single beat.

These parameters were measured manually in particular parts of Holter recording: during daytime (between 7 AM and 11 PM) when heart rate (HR) 90 ≥ HR ≤ 120/min, during nighttime (between 11 PM and 7 AM) when HR ≤ 60/min and a few minutes (≤ 5 min) before the ajmaline challenge test (independently from HR).

PQ interval was measured in lead II. QRS duration was measured in leads II, V1, V2 and V3.

The QT was measured from the beginning of the QRS to the end of T-wave, defined as the intersection of the tangent to the downslope of the T-wave and the isoelectric line. T waves smaller than 1.5 mm in amplitude were not measured.

The QT duration was corrected for heart rate according to Bazzet's formula if the HR was between 60 and 120/min [2] (daytime and pre-test recording) and according to the Hodges formula if HR ≤ 60/min [3] (night time recording).

QTd was defined as the difference between the maximum and minimum QTc ($QTc_{max} - QTc_{min}$) of the 12 leads.

The ST-segment elevation was measured at the J point (the point where the QRS complex joins the ST segment) and at 0.08 s from the J point in leads V1 to V3.

The Tp-Te interval was measured in each precordial lead and obtained from the difference between QT and QTpeak interval (QTp), measured from the beginning of the QRS until the peak of the T-wave. In the case of negative or biphasic T wave, QTp was measured to the nadir of the T-wave. In the case of biphasic T wave the peak of the deeper deflection was considered as the end of QTp. T waves smaller than 1.5 mm in amplitude were not measured.

Tp-Te d was defined as the difference between the maximum and minimum Tp-e in the precordial leads V1 to V6 during a single beat.

### The ajmaline challenge test

The pharmacological challenge test with intravenous ajmaline administration dosed 1 mg/kg body weight during 5 min was performed in safe conditions, during 12-lead 24-hour Holter ECG monitoring.

Drug administration was terminated when diagnostic type 1 Brugada ECG developed; premature ventricular beats, ventricular tachycardia or atrioventricular block (second or third degree) developed; QRS ≥ 130% of baseline.

Occurrence of type 1 electrocardiographic patterns or conversion of types 2 or 3 to the diagnostic type 1 pattern after ajmaline administration was considered as a positive test result [3]. Occurrence of type 2 or 3 ST segment elevation was considered as a negative test result.

### Statistical analysis

The first stage of the study included two standard procedures for determining the relation between the ajmaline test result and other variables. Independence $\chi^2$ test was applied for qualitative variables. As regards quantitative variables, mean values were determined for every examined variable with division into negative and positive test results. Also the comparison of these variables with *t* test was performed. In both cases the value of $p < 0.05$ was considered statistically significant.

The next stage was the selection of significant features that have an influence on the syndrome prediction. The following strategies were applied:

- The choice of features with small number of missing values (1 missing value was accepted in the positive test result group, while 26 missing values were accepted in the negative test result group).
- The choice of features for which *p*-value in $\chi^2$ test of the greatest reliability for qualitative variables and Student *t*-test for quantitative variables was relatively low.
- The choice of the most important features with the use of Random Forest with consideration of the following criteria: mean decrease in accuracy and mean decrease in Gini. Final selection of significant features involved verification based on background knowledge and clinical practice.

Following the initial selection the decision tree technique was applied for construction of decision models. The Gini index was responsible for node division in the decision tree and also only trees of maximally 3 depth levels were used. The following elements were used for qualitative evaluation of the obtained classifiers: accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Both database and calculations at the first stage of the work were performed with the use of Statistica 6.0 software, while the process of selecting features of predictive significance and structure of decision trees were carried out using the R statistical package.

## Results

### Patient demographics

Study inclusion criteria were met by 59 patients (22 women and 37 men). Mean age of the group was 31.6 ±12.2 years, from 16 to 62 years. Mean age for women was 29.68 ±10.9 years while for men it was 32.8 ±12.9 years. The majority of patients (72.8%) were under 40 years of age.

All the patients had echocardiography which revealed no significant organic heart disease.

### Clinical characteristics of the group with positive result of pharmacological challenge test

Every patient underwent the pharmacological challenge test. No significant adverse effects were observed. None of the patients met the criteria of discontinuation before the scheduled end of the study.

A positive test result – type 1 ST segment elevation (Figure 1) – which was considered as diagnostic for BS – was obtained in 7 individuals (11.86%). The other 52 patients (88.14%) had a negative provocation test result.

The group of 7 patients with type 1 ST segment elevation diagnostic for BS following ajmaline administration consisted of 6 men (85.7%) and 1 woman (14.3%). Mean age of this group was 36.5 ±15.2, from 16 to 52 years. The group of patients with a negative test result included 31 men (59.6%) and 21 women (40.4%). Mean age of this group was 30.9 ±11.7, from 18 to 62 years. No statistically significant dependency between gender, age and body mass and ajmaline test was observed.

As regards the group of 7 individuals with a positive provocation test result, 2 patients had a his-

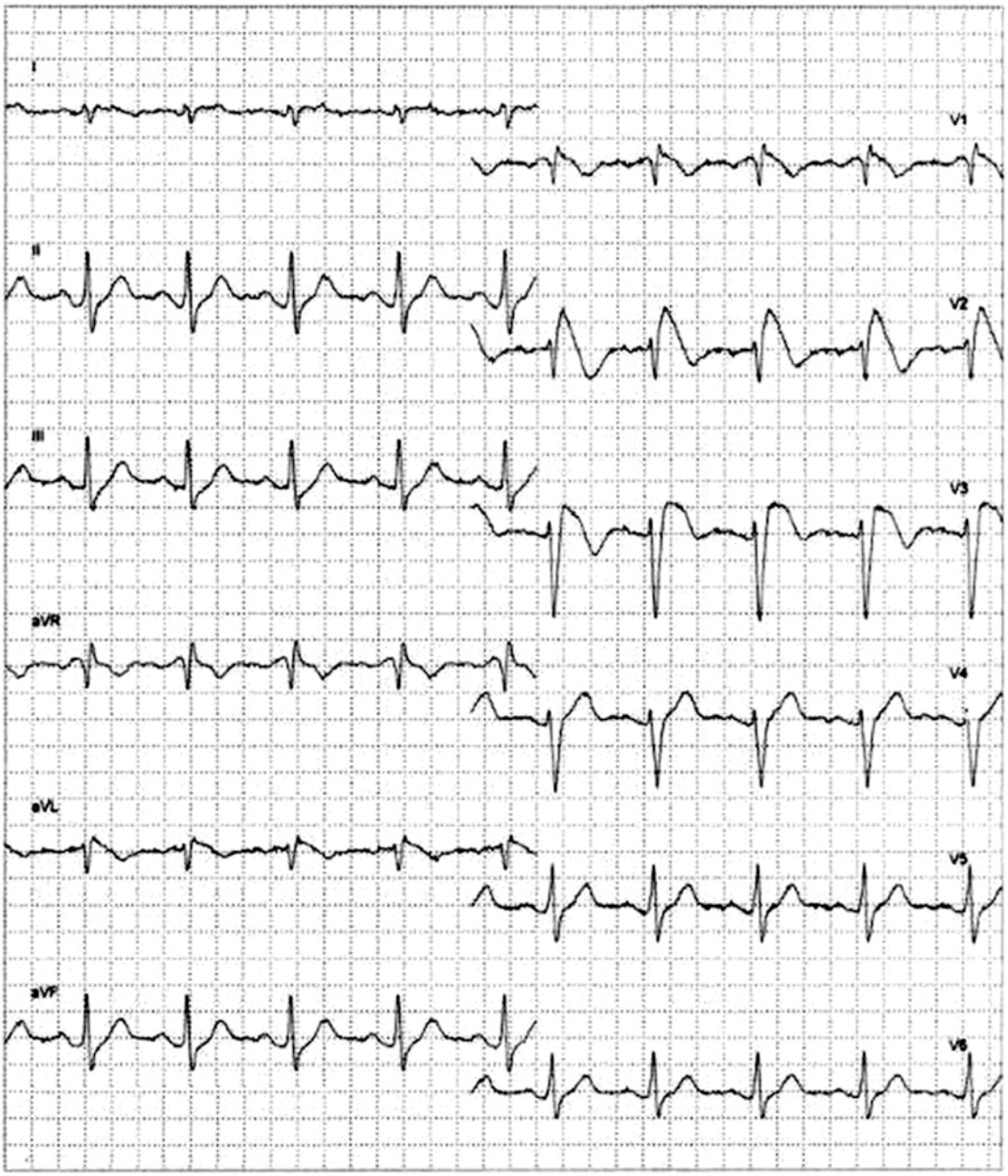



**Figure 1.** Twelve-lead ECG from a patient with positive test results. The configuration of the ST-segment elevation in leads V1 to V3 is a coved type

tory of SCA (men), among whom in 1 person the diagnosed SCA mechanism was ventricular fibrillation. The SCA mechanism in the second individual remains unknown. Both patients had a cardioverter-defibrillator implanted. In the group of the other 5 patients, initially considered as asymptomatic, syncopes occurred 16 months after the challenge test in 1 person (woman), which was an indication for implanting a cardioverter-defibrillator. The other 4 individuals remained asymptomatic during the observation lasting from 39 to 60 months.

## Predictive value of parameters which constituted study inclusion criteria

### Predictive value of medical interview

The dependency between family history of BS and ajmaline test result was statistically significant. Diagnosis of BS in the family was observed only in 2 individuals with a negative test result (3.8%) and in 2 patients with a positive test result (28.6%) (Table II).

Also, a statistically significant dependency between unexplained syncopes and ajmaline test result were observed. Unexplained syncopes were noted in over 50% of patients with a negative test result (57.7%) and only in 1 individual with a positive test result (14.3%) (Table III).

No dependency between SCA occurrence in patient's history and family history for SCD and ajmaline test result was observed. History of SCA was observed in a small number of cases of both a negative test result (5 patients, 9.6%) and a positive test result (2 patients, 28.6%). Family history of SCD was noted only in 5 patients (9.6%) with a negative test result, while no such cases were observed in patients with a positive test result.

### Predictive value of non-invasive electrocardiographic parameters

No statistically significant dependency between complete or incomplete RBBB occurrence and ajmaline test result was observed. Complete RBBB was

**Table II.** Family history of BS and ajmaline test result

| | | | Test result | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | | Negative | | Positive | | | |
| Family history of BS | $p = 0.0477$ | No | 50 | 96.20% | 5 | 71.40% | 55 | 93.20% |
| | | Yes | 2 | 3.80% | 2 | 28.60% | 4 | 6.80% |
| | Total | | 52 | 100% | 7 | 100% | 59 | 100% |

**Table III.** Unexplained syncopes and ajmaline test result

| | | | Test result | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | | Negative | | Positive | | | |
| Unexplained syncopes | $p = 0.0010$ | No | 22 | 42.30% | 6 | 85.70% | 28 | 47.50% |
| | | Yes | 30 | 57.70% | 0 | 0.00% | 30 | 50.80% |
| | | Yes (after the test) | 0 | 0.00% | 1 | 14.30% | 1 | 1.70% |
| | Total | | 52 | 100.00% | 7 | 100.00% | 59 | 100.00% |

**Table IV.** Elevation of type 2 and/or 3 ST segment and ajmaline test result

| | | | Test result | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | | | Negative | | Positive | | | |
| Suspected but non-diagnostic ECG (type 2 and 3) | $p = 0.0085$ | No | 41 | 78.80% | 2 | 28.60% | 43 | 72.90% |
| | | Yes | 11 | 21.20% | 5 | 71.40% | 16 | 27.10% |
| Suspected but non-diagnostic ECG (type 2) | $p = 0.0002$ | No | 52 | 100% | 4 | 57.10% | 56 | 94.90% |
| | | Yes | 0 | 0% | 3 | 42.90% | 3 | 5.10% |
| Suspected but non-diagnostic ECG (type 3) | $p = 0.6652$ | No | 41 | 78.80% | 5 | 71.40% | 46 | 78.00% |
| | | Yes | 11 | 21.20% | 2 | 28.60% | 13 | 22.00% |
| | Total | | 52 | 100% | 7 | 100% | 59 | 100% |

observed only in a small number of patients with a negative test result (15.4%), while no such cases were observed in patients with a positive test result. Incomplete RBBB was noted in 48.1% of patients with a negative test result and in 28.6% of patients with a positive test result ($p$ = 0.3219).

In the case of suspected but non-diagnostic ECG recording, statistical significance was shown with reference to saddleback ECG, which is type 2 and 3 together and type 2 ECG evaluated separately (Table IV). Elevation of type 2 ST segment significantly increased the probability of obtaining a positive result. Elevation of type 2 ST segment was observed in none of the patients with a negative test result and in 3 individuals with a positive test result, which amounted to 42.9% of the patients. Such dependency was not observed with regard to elevation of type 3 ST segment. Elevation of type 3 ST segment was observed in 21.2% of patients with a negative test result and almost the same percentage of patients with a positive test result, 28.6% ($p$ = 0.6652).

### Predictive value of electrocardiographic parameters evaluated from 12-lead 24-hour Holter ECG monitoring

Statistical analysis of individual electrocardiographic parameters evaluated from 12-lead ECG at 3 times of the day – prior to the ajmaline test, during daytime activity, and at night – showed a number of differences between mean values described in the study method of electrocardiographic parameters between the groups with positive and negative test results.

Non-invasive electrocardiographic parameters which showed significant predictive value of the ajmaline test result were: QTd, QTc intervals, Tp-Te intervals in particular leads, QTp intervals, Tp-Te d6 and J-point elevation in V2 and V3 leads (statistically significant results are presented collectively in Table V).

According to the study, dispersion of QTc was larger in the group of patients with a positive test result compared to the group with a negative test result. This dependency was maintained at all the measurement points, while statistical significance was obtained in the measurement prior to the provocation test (mean 54.43 ±24.77 ms for patients with a positive result and 32.70 ±12.98 ms for patients with a negative result; $p$ = 0.0005) and during the greatest daytime activity (mean 46.81 ±27.16 ms for patients with a positive result and 32.07 ±13.19 ms for patients with a negative result; $p$ = 0.0198). As regards the measurement at night, the difference was not statistically significant but the values of QTd in the group with a positive result were higher compared to the group with a negative result (mean 40.00 ±16.33 ms for patients with a positive result and 30.59 ±11.56 ms for patients with a negative result; $p$ = 0.0600).

Analysis of QTc intervals measured at night showed their shorter mean values in all the 12 leads in patients with a positive ajmaline test result compared to a negative result, while in the aVL lead and all the precordial leads (V1–V6) the differences were statistically significant.

Analogical measurements performed during daytime activity revealed shorted mean QTc values for all the 12 leads observed in patients with a positive test result, yet the differences were not statistically significant. The results of QTc measurement prior to the ajmaline test were comparable in both groups. All the mean values of QTc for each of the 12 leads in both groups were within values considered as normal. The comparison of mean values of QTc between day and night in the group with positive and negative ajmaline test results presented an interesting phenomenon. Mean QTc in particular leads were shortened at night. Moreover, this shortening was clearly greater in precordial leads, especially in patients with a positive test result. These differences were statistically significant in leads V1 and V4.

Tp-Te d6 was an independent predictive factor for a positive ajmaline test result (mean 42.86 ±13.8 ms for the group with a positive result and 26.54 ±11.7 ms for the group with a negative test result; $p$ = 0.0013). In the measurement of Tp-Te interval at different times of the day, the difference was not statistically significant but Tp-Te d6 values remained higher in the group with a positive result compared to the negative result group. The obtained results were caused by longer Tp-Te intervals in patients with a positive provocation result compared to the measurement in the negative result group.

Elongated Tp-Te interval resulted from shortening of the QTp interval (which is shortening of repolarization time in subepicardial cells), which was greater is the group with a positive test result. In nighttime measurement mean QTp in all the leads except for I were statistically significantly shorter in patients with a positive provocation test result (the QTp in lead I was also shorter in positive result patients but the difference was not statistically significant). A similar tendency occurred in all the leads in measurements performed prior to the ajmaline test but the differences were not statistically significant.

The comparison of mean QTp and Tp-Te intervals in particular leads between day and night (Table VI) for both groups provided further interesting results. All the mean values of QTp were higher during nighttime compared to daytime in all the 12 leads and the increase in these values was significantly lower in patients with a positive ajma-

**Table V.** Collective presentation of non-invasive electrocardiographic parameters which showed significant predictive value for ajmaline test

| Parameter | Before test | Day | Night |
|---|---|---|---|
| QT d | 54.43 ±24.77 ms vs. 32.7 ±12.98 ms; $p = 0.0005$ | 46.81 ±27.16 ms vs. 32.07 ±13.19 ms; $p = 0.02$ | NS ($p = 0.06$) |
| QTc | NS | NS | I (NS); II (NS); III (NS); aVR (NS) |
| | | | aVL (355.85 ±6.84 ms vs. 390.98 ±28.21 ms; $p = 0.01$) |
| | | | aVF (NS) |
| | | | V1 (362.33 ±10.66 ms vs. 386.47 ±24.21 ms; $p = 0.02$) |
| | | | V2 (360.11 ±15.26 ms vs. 383.72 ±29.23 ms; $p = 0.04$) |
| | | | V3 (354.39 ±24.07 ms vs. 386.18 ±26.27 ms; $p = 0.004$) |
| | | | V4 (365.82 ±20.33 ms vs. 392.27 ±24.89 ms; $p = 0.009$) |
| | | | V5 (368.68 ±6.82 ms vs. 390.86 ±24.63 ms; $p = 0.02$) |
| | | | V6 (368.68 ±8.06 ms vs. 387.91 ±24.27 ms; $p = 0.04$) |
| QTp | NS | NS | I (NS) |
| | | | II (317.14 ±21.38 ms vs. 348.46 ±26.67 ms; $p = 0.004$) |
| | | | III (320.00 ±25.82 ms vs. 346.92 ±30.13 ms; $p = 0.03$) |
| | | | aVR (311.43 ±15.74 ms vs. 344.23 ±25.46 ms; $p = 0.002$) |
| | | | aVL (308.00 ±17.89 ms vs. 346.67 ±29.88 ms; $p = 0.01$) |
| | | | aVF (314.29 ±19.02 ms vs. 346.54 ±27.36 ms; $p = 0.004$) |
| | | | V1 (316.67 ±26.58 ms vs. 346.00 ±27.48 ms; $p = 0.02$) |
| | | | V2 (302.86 ±29.28 ms vs. 338.00 ±32.60 ms; $p = 0.01$) |
| | | | V3 (288.57 ±19.52 ms vs. 328.57 ±30.00 ms; $p = 0.001$) |
| | | | V4 (294.29 ±15.12 ms vs. 334.62 ±29.93 ms; $p = 0.001$) |
| | | | V5 (302.86 ±17.99 ms vs. 338.43 ±26.79 ms; $p = 0.001$) |
| | | | V6 (311.43 ±10.69 ms vs. 342.40 ±25.76 ms; $p = 0.003$) |
| Tp-Te | I (NS) | NS | I (NS) |
| | II (91.43 ±25.45 ms vs. 74.23 ±13.91 ms; $p = 0.008$) | | II (91.43 ±15.74 ms vs. 71.92 ±14.42 ms; $p = 0.002$) |
| | III (82.86 ±21.38 ms vs. 68.70 ±15.58 ms; $p = 0.04$) | | III (85.71 ±15.12 ms vs. 71.54 ±16.01 ms; $p = 0.03$) |
| | aVR (80.00 ±23.09 ms vs. 64.23 ±12.73 ms; $p = 0.008$) | | aVR (88.57 ±22.68 ms vs. 68.46 ±13.92 ms; $p = 0.002$) |
| | aVL (NS) | | aVL (NS) |
| | aVF (88.57 ±27.95 ms vs. 70.98 ±14.60 ms; $p = 0.01$) | | aVF (88.57 ±15.74 ms vs. 73.46 ±16.67 ms; $p = 0.03$) |
| | V1 (NS) | | V1 (NS) |
| | V2 (NS) | | V2 (NS) |
| | V3 (93.33 ±16.33 ms vs. 77.14 ±15.81 ms; $p = 0.02$) | | V3 (NS) |
| | V4 (91.43 ±19.52 ms vs. 78.43 ±14.88 ms; $p = 0.04$) | | V4 (94.29 ±15.12 ms vs. 80.00 ±17.26 ms; $p = 0.04$) |
| | V5 (88.57 ±10.69 ms vs. 73.46 ±12.97 ms; $p = 0.005$) | | V5 (88.57 ±10.69 ms vs. 74.90 ±14.33 ms; $p = 0.02$) |
| | V6 (82.86 ±17.99 ms vs. 68.46 ±12.74 ms; $p = 0.01$) | | V6 (80.00 ±11.55 ms vs. 68.40 ±10.76 ms; $p = 0.01$) |
| Tp-Te d6 (V1–V6) | NS | NS | 42.86 ±13.80 ms vs. 26.54 ±11.70 ms; $p = 0.001$ |
| ↑J in V1 | NS | NS | NS |
| ↑J in V2 | 0.08 ±0.07 mV vs. 0.03 ±0.04 mV; $p = 0.002$ | NS | NS |
| ↑J in V3 | 0.09 ±0.05 mV vs. 0.05 ±0.05 mV; $p = 0.04$ | NS | NS |

**Table VI.** Results – predictive value of ECG parameters (differences between day and night values)

| Differences between ECG parameters | Patients with negative test result | | | Patients with positive test result | | | Value of *p* for mean test | *F* test value for standard deviation (SD) |
|---|---|---|---|---|---|---|---|---|
| | *n* | Mean | SD | *n* | Mean | SD | | |
| QTc in V1 (night (Hodges) – day (Bazett)) [ms] | 46 | –42.57 | 25.89 | 6 | –66.44 | 26.91 | 0.0394 | 0.7679 |
| QTc in V4 (night (Hodges) – day (Bazett)) [ms] | 50 | –43.12 | 27.60 | 7 | –68.81 | 41.43 | 0.0348 | 0.1068 |
| QTp in aVR [ms] | 52 | 62.31 | 30.85 | 7 | 37.14 | 13.80 | 0.0386 | 0.0496 |
| QTp in V2 [ms] | 32 | 54.38 | 33.79 | 5 | 8.00 | 17.89 | 0.0052 | 0.2231 |
| QTp in V4 [ms] | 49 | 58.78 | 31.99 | 7 | 28.57 | 38.05 | 0.0263 | 0.4573 |
| QTp in V5 [ms] | 49 | 66.94 | 28.74 | 7 | 28.57 | 30.24 | 0.0018 | 0.7444 |
| QTp in V6 [ms] | 49 | 67.35 | 29.63 | 7 | 37.14 | 17.99 | 0.0115 | 0.2096 |
| Tp-Te in II [ms] | 50 | 4.40 | 1950 | 7 | 31.43 | 22.68 | 0.0014 | 0.5051 |
| Tp-Te in III [ms] | 45 | 7.56 | 20.13 | 7 | 25.71 | 19.02 | 0.0299 | 0.9833 |
| Tp-Te in aVR [ms] | 50 | 5.20 | 17.98 | 7 | 31.43 | 30.24 | 0.0017 | 0.0384 |
| Tp-Te in V2 [ms] | 30 | 4.00 | 16.94 | 5 | 32.00 | 36.33 | 0.0074 | 0.0107 |
| Tp-Te in V5 [ms] | 49 | 5.31 | 14.59 | 7 | 22.86 | 13.80 | 0.0041 | 0.9869 |
| Tp-Te in V6 [ms] | 48 | 1.67 | 14.19 | 7 | 20.00 | 16.33 | 0.0028 | 0.5308 |

line test result (statistically significant differences for leads aVR, V2, V4, V5 and V6). As a result, mean Tp-Te showed a considerably greater increase in the values at night in the positive result group compared to patients with a negative result. This dependency was observed in all the leads (except for V1) while statistical significance was noted in the following leads: II, III, aVR, V2, V5 and V6.

The presented study does not confirm the values suggested in the literature on other predictive parameters of the ajmaline test, such as elongated PQ interval or widened QRS complex. Mean values of PQ interval and duration of QRS complex were comparable in both groups at all three measurement points.

### Predictive models

The analysis of the single parameters presented above was used to carry out statistical analysis and select parameters that have a significant influence on prediction of the ajmaline test result.

The 28 most significant features were selected (out of 418) by means of random laser technique using the following conjunction conditions: number of missing data in the 'positive test' group $\leq 1$; number of missing data in the 'negative test' group $\leq 26$; mean decrease of accuracy $\geq 0.44$; mean decrease of Gini $\geq 0.07$.

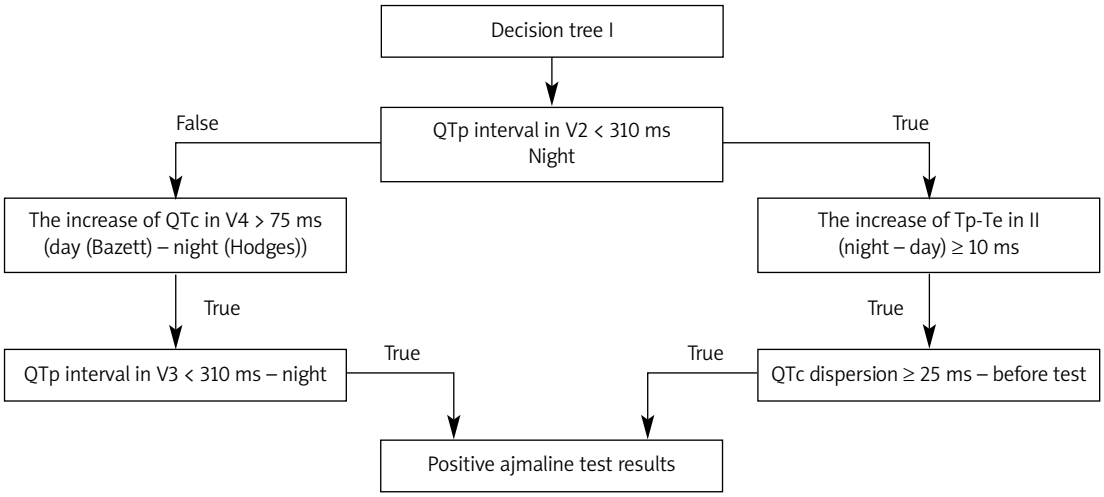
Ten decision models for predicting the ajmaline test result were formed with the use of precisely selected parameters. Following quantitative evaluation of predictive value of particular models with consideration of their accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), 3 models of the greatest decision power (100%) were chosen (Figures 2–4).

## Discussion

Brugada syndrome is a serious and still an underestimated cause of sudden cardiac death, especially in young people. The disease should be suspected in the case of any episode of ventricular fibrillation/SCA in a person with no detectable organic cardiac pathology. Today, the pharmacological provocation test is the only method of diagnosing BS in the case of no typical spontaneous electrocardiographic presentation [4, 5]. The question is which patients and what symptoms should constitute indications for additional pharmacological challenge testing.

The pro-arrhythmic effect of antiarrhythmic class I medications is responsible for cases of provoking serious ventricular arrhythmia following drug administration on diagnostic examination described in the literature [6–10]. Comparison of the effectiveness of particular drugs recommended for the provocation test is beneficial for ajmaline [11, 12]. According to previously presented research on ajmaline and flecainide, sensitivity and specificity of ajmaline are higher, which is also confirmed by direct juxtaposition of the medications [11].

Considering the results of the studies carried out so far, ajmaline was used in this study due to the




IF (QTp interval in V2 < 310 ms – at night AND The increase of Tp-Te in II (night – day) ≥ 10 ms AND QTc dispersion ≥ 25 ms – before test)
OR
((Not QTp interval in V2 < 310 ms – at night) AND The increase of QTc in V4 > 75 ms – (day (Bazett) – night (Hodges)) AND QTp interval in V3 < 310 ms – night)
Then → Positive ajmaline test result
Else → Negative ajmaline test result

$\chi^2$ test with Yate correction: $\chi^2 = 48.9598$, $df = 1$, $p = 2.613 \times 10^{-12}$
Test result (negative) False – 51, True – 0
Test result (positive) False – 0, True – 7
Lack of data – 1 in negative result group ($n = 59$)

**Figure 2.** Decision tree I

highest sensitivity and specificity [6, 11, 13, 14], with at the same time a considerably small number of test complications [6, 7, 13]. Another reason for choosing ajmaline was its short half-life (approximately 10 min) [15] which allows for a short time of monitoring after the test and thus provides a safe way to conduct the test during the patient's 1-day stay in the department.

According to current indications [4], occurrence of previously described type 1 electrocardiographic changes was considered as a positive result of the pharmacological provocation test with ajmaline. Although ajmaline sensitivity and specificity are not 100%, no alternative and equally effective method of diagnosing BS can be found. Therefore, it should be assumed that the method of differentiating both groups of patients based on the ajmaline test result that was used in the study is currently fully justified. Also the criteria of test discontinuation prior to the end of drug administration are compliant with recommendations [4]. According to a recently published study [16], establishing the criterion of test discontinuation as widening of QRS complex ≥ 130% of the initial value leads to a false negative result in some cases. In the presented work, this criterion could not have influenced a false result since no test discontinuation prior to administration of the target dose took place. However, it should be noted that widening of the QRS complex occurred totally in 4 patients (2 with positive and 2 with negative provocation test result) up to 140%, 140%, 142% and 146% of the initial value respectively, yet the values were observed in ECG recording assessed during a few subsequent seconds ≤ 1 min following the end of drug administration.

## Population characteristics

In the world, BS is most common in men – they develop the disease 8–10 times more frequently than women [17]. Moreover, prognosis is much worse for men. In South-East Asia, which is considered as a place of endemic disease prevalence, BS is one of the main causes of death in men under 50 years of age [18]. The presented study showed no statistically significant dependency between age and ajmaline test result. Worse prognosis for men is also difficult to assume. As regards the group with a positive test result, only 2 patients with a past history of SCA are men. Although the number of patients defined this way is too small in terms of statistical significance, it is worth noting the tendency described in the literature.

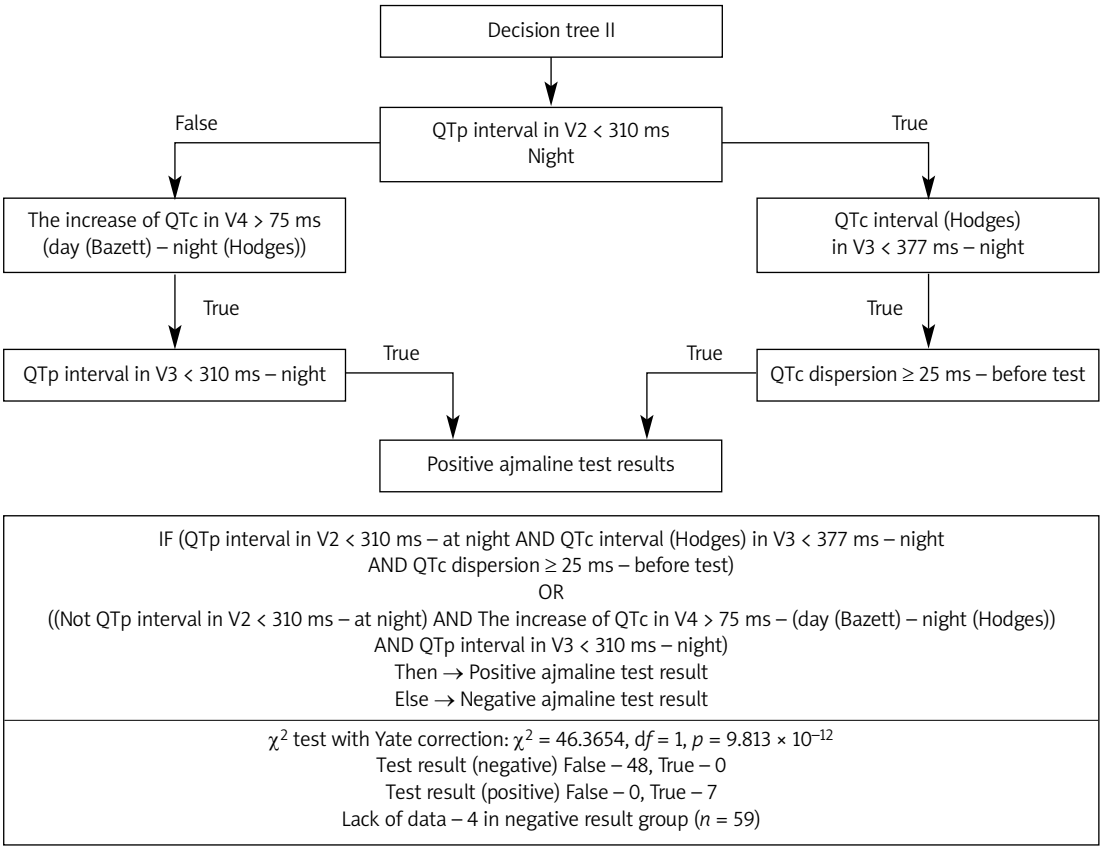



**Figure 3.** Decision tree II

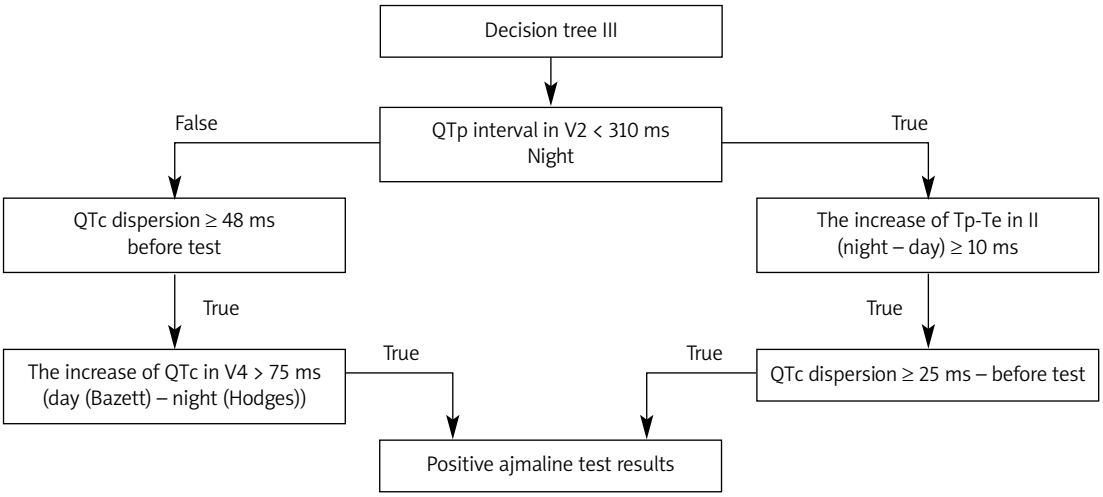
## Assessment of predictive value of parameters that constitute study qualification criteria

The analysis carried out in the study showed a specific predictive value of one criterion from the interview that might indicate BS. The syndrome diagnosed in the family significantly increased the probability of obtaining a positive ajmaline test. As regards the group with a positive result, 28.6% of patients had a positive family history of BS (compared to 3.8% of patients with a negative result; $p = 0.0477$). The obtained result is compliant with literature data [16, 19], which clearly suggest the need for diagnostics of patients' relatives.

Despite strong evidence of the high value of past history of SCA and/or family history of SCD in risk stratification of patients with diagnosed BS, the study did not confirm the value of these parameters in predicting the ajmaline test result. The obtained results may be caused by the fact that BS is a rare cause of SCA and SCD, especially in our region. The BS is much more frequently caused by heart diseases typical of our population – coronary disease and its complications as well as other organic heart diseases like cardiomyopathy and valve disorders.

Interesting results are connected with predictive value of syncope history in predicting the ajmaline test result. Currently, the predictive value of syncopes in patients with diagnosed BS seems to be undoubted. Frequency of syncope occurrence in the general population is high. As regards the causes of the syncopes, both cardiogenic syncopes and those not related to heart diseases should be mentioned. Even if the non-cardiogenic, mainly neurological causes of syncopes as well as diagnosed cardiogenic causes connected with known organic heart disease are excluded, there is still a group of patients with syncopes of unexplained etiology. Prevalence of this type of syncope in European studies amounts to 24% [20, 21]. Patients with undiagnosed BS should be definitely included in this group. The analysis carried out in the study showed that unexplained syncopes occurred much more frequently in patients with a negative ajmaline test result (57.5% vs. 14.3%). It is difficult to provide a clear explanation of the obtained result. As mentioned above, prevalence of syncope in the population is high and epidemiological studies clearly prove that BS constitutes only a small percentage of their causes.

Right bundle branch block (RBBB) was initially considered as one of the criteria for diagnosing BS by the Brugada brothers [22]. However, it soon

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OR
((Not QTp interval in V2 < 310 ms – at night) AND QTc dispersion ≥ 48 ms before test AND The increase of QTc in V4 > 75 ms (day (Bazett) – night (Hodges))
Then → Positive ajmaline test result
Else → Negative ajmaline test result

$\chi^2$ test with Yate correction: $\chi^2 = 48.8243$, $df = 1$, $p = 1.681 \times 10^{-12}$
Test result (negative) False – 52, True – 0
Test result (positive) False – 0, True – 7
Lack of data – 0 ($n = 59$)

**Figure 4.** Decision tree III

became clear that the shape of ST segment elevation and thus formation of the J wave give an impression of R wave formation, which looks like RBBB. Therefore, RBBB as an expression of delayed depolarization of the right ventricular muscle might occur in BS in the case of accompanying intraventricular conduction disturbances but is not a criterion of disease diagnosis [5]. The role of intraventricular conduction disturbances in BS is still a subject of numerous discussions, while its markers were proposed as factors of increased risk of ventricular arrhythmia in BS [23, 24]. According to the study, occurrence of both complete and incomplete RBBB was not connected with a more frequent positive result of the pharmacological provocation test.

The basis for BS diagnosis is electrocardiographic changes known as coved type (type 1). Electrocardiographic changes in the form of changes in ST-T complex shape called saddleback type (type 2 and 3) are an image that does not allow for diagnosing BS but its conversion into type 1 after performing pharmacological provocation test constitutes a BS diagnostic criterion. Frequency of occurrence of saddleback electrocardiographic changes in the population is considerably higher than frequency of spontaneous coved changes. In the presented work saddleback ECG analyzed collectively was significantly related to a positive provocation test (71.4% in the group with a positive result vs. 21.2% in the group with a negative result; $p = 0.0085$). However, it is worth noting that differentiation of saddleback ECG into type 2 and 3 allowed for identification of type 2 ECG as the one that significantly increases frequency of a positive ajmaline test. Type 2 ECG occurred in 3 individuals (42.9%) in the positive result group and in none of the patients with a negative result ($p = 0.0002$). The results obtained in the work indicate a special role of type 2 ECG in prediction of the provocation test result with concurrent lesser meaning of type 3. Therefore, they are a valuable clue in identifying patients who are expected to show a positive response to ajmaline provocation.

## Predictive value of non-invasive electrocardiographic parameters assessed from 12-lead Holter ECG recording

Suggestion of particular electrocardiographic parameters as those increasing the probability of diagnosing BS emerges from their more or less proven role in risk stratification in patients with diagnosed BS.

Current knowledge includes no parameters from non-invasive studies that could allow for prediction of a pharmacological provocation test result. The

concealed form of the syndrome constitutes a great problem which is an underlying cause of the high percentage of undiagnosed BS cases. Concurrently, occurrence of various forms of ST segment elevation in leads V1–V3 which do not meet the diagnostic criteria for BS is very common. Frequency of occurrence of ST segment elevation ≥ 0.1 mV in leads V1, V2 or V3 is estimated at 0.48–6% in the population considered as healthy [25–27]. It would be difficult to perform a pharmacological provocation test in all those patients considering possible complications. At the same time it is important to diagnose concealed form of the syndrome when the tests indicate comparable risk of fatal arrhythmia in patients with permanent and transient spontaneous changes in ECG [6, 28, 29].

The presented work contains the assessment of numerous electrocardiographic parameters measured within a few minutes prior to the ajmaline test – to reflect measurements independent from HR (i.e. typical resting ECG). Moreover, measurements were made at points of different activity (time of the greatest daytime activity and night rest).

Life-threatening episodes of ventricular arrhythmia that might lead to SCD in BS most commonly occur in early morning hours [30, 31]. This suggests a critical role of the autonomic nervous system in pathogenesis of rhythm disturbances accompanying BS. The studies on patients with diagnosed BS showed significantly greater fluctuations of ST segment elevation during daytime in patients with BS compared to the control group. What is more, the fluctuations indicated a significant relationship with heart rate [32]. The level of ST segment elevation decreased with higher HR. This might be one of the reasons for underestimating diagnoses of concealed BS. When the HR is high, which is frequently observed in young people during daytime activity, the level of ST segment elevation might be insufficient in terms of BS diagnostic criteria. Twelve-lead 24-hour ECG monitoring might significantly increase the chance of diagnosing the syndrome.

A complex of parameters reflecting disturbances in cardiomyocyte repolarization turned out to be non-invasive electrocardiographic parameters that showed significant predictive value of the ajmaline test. This is compliant with currently known pathogenetic mechanisms responsible for electrocardiographic changes observed in BS. Concurrently, these parameters are to a large extent the same as the predictive factors in patients with diagnosed BS reported in the literature.

As regards the electrocardiographic parameters mentioned above, their measurement at night was found to be the most valuable – the greatest number of statistically significant values was observed at this time. The same parameters measured prior to the ajmaline test showed lesser value, while statistical significance of these parameters frequently disappeared during measurement at the maximum daytime activity. The results are compliant with the greater expression of electrocardiographic changes typical of BS at nighttime presented above. It is worth noting that although particular parameters lost their statistical significance, the same tendency in both analyzed groups was maintained (the group with positive vs. negative test results).

Interestingly, the differences between the assessed electrocardiographic parameters that show statistical significance in differentiating patients with positive and negative test results are present not only in the right-side precordial leads. It is not a new phenomenon as the reports on BS form with typical ECG changes in leads of the inferior and/or left lateral ventricular wall can be found. This form of BS is described more and more frequently [33]. Also, the issue of worse prognosis in patients with atypical manifestation of electrocardiographic changes for BS is increasingly common [33]. Moreover, markers of increased risk of ventricular arrhythmia in BS are described in other than right-ventricular leads. It has been shown that R wave amplitude in aVR lead ≥ 3 mm or the ratio of R/q ≥ 0.75 in this lead are connected with an increased risk of ventricular arrhythmia in BS [34].

The level of ST segment elevation is another useful parameter as both a predictive parameter in patients with diagnosed BS and a predictive marker in BS diagnostics. Unfortunately, different authors have different opinions on the optimal point of ST elevation measurement, which suggests that apart from J point measurement also the second point within the ST-T complex that could be critical for BS should be sought. During preparation of the study method, the point of ST segment elevation measurement was established arbitrarily. J point measurement was natural since it is the place of joining the end of the QRS complex with the beginning of the ST segment as recommended in BS diagnostics [4]. Additionally, ST segment elevation was measured at 80 ms after the J point assuming that this measurement is strictly connected with the ST segment. As regards the largest study assessing the predictive value of ST segment elevation in predicting pharmacological provocation results [19], measurements were performed at the J point and the maximal ST elevation at the J point of the right-side precordial leads (V1–V3) was chosen for the analysis. The obtained maximal J point elevation had higher statistical significance in patients with a positive result compared with negative result patients (0.13 ±0.12 mV vs. 0.04 ± 0.07 mV, $p < 0.0001$). Unfortunately, it was not stated in which of the three analyzed leads the ST segment elevation level was the highest. The presented work

showed no predictive value of ST elevation level measured at 80 ms after the J point in the standard position of V1–V3 electrodes. However, the results of other publications presented above do not clearly show the significant role of this parameter in prediction of the provocation test result. Considering measurements performed at the J point, the results did not turn out to be very promising either. Mean J point elevation measured in V2 and V3 leads was higher in patients with a positive provocation test result compared to patients with a negative result at all measurement times. The difference was statistically significant only in measurements taken prior to the ajmaline test.

The results of the presented work proved that the greatest predictive value was shown by parameters that are an electrocardiographic reflection of cardiomyocyte repolarization disturbances. No significant role of ECG changes leading to depolarization disturbance and/or conduction in the heart was confirmed.

The presented thesis was confirmed by the compiled predictive models. All the included parameters reflect repolarization disturbances in both early and final stages. Special attention was paid to the fact of clear differentiation in the results of electrocardiographic measurements that reflect repolarization disturbances between day and night. Therefore, repolarization disturbances in BS patients are aggravated at night. Twenty-four-hour ECG monitoring as well as comparison of particular ECG parameters between day and night appeared to be very important. Thus, due to measurement of standard electrocardiographic parameters from a 12-lead recording and their correlation with clinical data, it is possible to significantly reduce the number of patients with suspected BS who would require pharmacological provocation to make the diagnosis.

Due to the small number of patients with a positive ajmaline test result (7 individuals) the obtained results should be interpreted with a certain dose of carefulness. This number results from a considerably low disease prevalence in the analyzed population (Poland). Statistical analysis with the Random Forest technique which allowed for selecting 3 decision models of 100% decision power increases the practical value of the work. However, due to the small number of patients, validation on a larger group would be required (e.g. in countries with considerably higher prevalence).

In conclusion, the aim of the presented work was to determine parameters from non-invasive tests that would allow for prediction of pharmacological provocation ajmaline test results in patients with suspected concealed form of BS and thus to considerably reduce the number of patients exposed to potential complications connected with the test. According to the analyses, interview and a complex of non-invasive electrocardiographic parameters that reflect cardiomyocyte repolarization disturbances show a high predictive value in predicting pharmacological provocation with ajmaline in patients with suspected Brugada syndrome.

The multi-factor analysis of variables from the interview and non-invasive electrocardiographic test that was performed in the work allowed for establishing predictive models which can predict test results with very high sensitivity and specificity. The use of the developed decision models in clinical practice may lead to a decrease in the number of patients with suspected BS who would require a pharmacological provocation test to establish the diagnosis.

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