The ajmaline challenge in Brugada syndrome: Diagnostic impact, safety, and recommended protocol


Hospital of the Westfälische Wilhelms-University, Department of Cardiology and Angiology, Institute for Arteriosclerosis Research, Münster, Germany

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Aims The diagnostic ECG pattern in Brugada syndrome (BS) can transiently normalize and may be unmasked by sodium channel blockers such as ajmaline. Proarrhythmic effects of the drug have been well documented in the literature. A detailed protocol for the ajmaline challenge in Brugada syndrome has not yet been described. Therefore, we prospectively studied the risks of a standardized ajmaline test.

Methods and results During a period of 60 months, 158 patients underwent the ajmaline test in our institution. Ajmaline was given intravenously in fractions (10 mg every two minutes) up to a target dose of 1 mg/kg. In 37 patients (23%) the typical coved-type ECG pattern of BS was unmasked. During the test, symptomatic VT appeared in 2 patients (1.3%). In all other patients, the drug challenge did not induce VT if the target dose, QRS prolongation >30%, presence/appearance of the typical ECG, or the occurrence of premature ventricular ectopy were considered as end points of the test. A positive response to ajmaline was induced in 2 of 94 patients (2%) with a normal baseline ECG, who underwent evaluation solely for syncope of unknown origin.

Conclusion The ajmaline challenge using a protocol with fractionated drug administration is a safe method to diagnose BS. Because of the potential induction of VT, it should be performed under continuous medical surveillance with advanced life-support facilities. Due to the prognostic importance all patients with aborted sudden death or unexplained syncope without demonstrable structural heart disease and family members of affected individuals should presently undergo drug testing for unmasking BS.

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KEYWORDS
Brugada syndrome; Ajmaline challenge; Test protocol; Proarrhythmia; Safety

Introduction
Sudden cardiac death (SCD) frequently is the consequence of ventricular tachycardia/fibrillation (VT/VF) due to an acute ischemic event. It may also occur in patients with various forms of structural heart disease without a triggering ischemic event. In approximately 5–10% of sudden cardiac deaths, no overt structural heart disease can be demonstrated. In 1992, Brugada et al. described a subgroup of patients with a distinct ECG pattern consisting of atypical right bundle branch block and
right precordial ST-elevation, later referred to as ‘Brugada syndrome’. It is now understood as a genetically determined channelopathy with an autosomal dominant pattern of transmission. Several mutations of the gene encoding for the α-subunit of the human cardiac SCN5A sodium channel located on chromosome 3 causing a loss of function of the sodium channel have been described.

Available multicenter data have confirmed the malignant character of this syndrome showing that it is associated with a high recurrence rate in survivors of cardiac arrest and in patients after a syncopal episode. Due to the absence of therapeutic alternatives, the implantation of a cardioverter-defibrillator (ICD) is recommended in symptomatic patients. However, conflicting evidence exists on the prognosis of previously asymptomatic individuals. Brugada et al. recommend ICD implantation in asymptomatic patients with a spontaneously abnormal ECG, if sustained arrhythmia is inducible during electrophysiological study, whereas Priori et al. demonstrated an increased risk of death in patients with a spontaneously abnormal ECG, particularly if they have a history of syncope.

Since its first description, the identification of patients with Brugada syndrome is increasing exponentially. Affected individuals may present with intermittent electrocardiographic manifestations. Additionally, the ECG can be modulated by many factors including body temperature, autonomic tone, and drugs affecting ion channel function. Class IC and IA antiarrhythmic drugs (flecainide, propafenone, ajmaline, disopyramide, procainamide) accentuate ST-segment elevation and are capable of unmasking concealed forms of the disease. Class IC antiarrhythmic drugs tend to induce ST-segment changes in Brugada syndrome more reliably than class IA drugs. Ajmaline, which is available only for intravenous application due to its poor oral bioavailability, seems to be the best drug to unmask Brugada syndrome, possibly because of its kinetics and strength of rate-dependent sodium channel blocking effects. Additionally, a short half-life and the brief duration of its electrophysiological effects (minutes) render it superior to other antiarrhythmic drugs.

However, it is marketed only in selected European countries and not available in the U.S. A potential proarrhythmic effect of class I drugs has been reported in a series reported by Brugada et al., one of 45 Brugada patients developed spontaneous VF after pharmacological provocation. In addition, a case report of a 13-year-old survivor of cardiac arrest with an intermittent Brugada-ECG who developed incessant hemodynamically tolerable monomorphic VT after ajmaline administration has been reported. Ventricular premature complexes occurring in Brugada patients displaying a marked ST-elevation when exposed to class I drugs were reported by others. Additionally, marked Brugada-type ECG changes preceding or following premature ventricular contractions, VT or VF have been described in the literature. This may suggest a link between the effect of antiarrhythmic agents on the ECG abnormalities and their potential proarhythmic effects.

In order to quantify VT/VF occurrence during the ajmaline challenge and to identify factors associated with it, we prospectively analysed the ajmaline challenges performed at our institution. We intended to outline an ajmaline test protocol, which is safe without loss of power with regard to diagnostic purposes.

**Methods**

**Patient characteristics**

The study population consisted of 158 consecutive Caucasian patients, mean age 42 (11–89) years, with one or more of the following clinical presentations (Table 1): (1) aborted cardiac arrest (n=21), (2) syncope of unknown origin (n=95), (3) documented VT (n=18), (4) asymptomatic individuals with a family history of sudden cardiac death, syncope (n=47) or Brugada syndrome (n=9) or with (5) a suspicious but not diagnostic ECG (incomplete/complete bundle branch block pattern, ‘saddle-type’ ECG with ST-segment elevation less than 0.2 mV) during routine examination (n=64). Structural heart disease was excluded by clinical history and noninvasive and invasive methods.

**Twelve-lead ECG acquisition, data analysis and drug administration**

The ECG was defined as typical ‘coved-type’ if displaying a right bundle branch block (RBBB) pattern with a terminal r wave and a J-point elevation...
of at least 0.2 mV with a slowly descending ST-segment in continuation with a flat or negative T wave in leads V1 to V3 (Fig. 1) either spontaneously or after the administration of ajmaline. Heart rate, PQ, QRS and QTc (Bazett formula) duration on ECG were measured before, during and after drug administration in all patients (Table 2). We administered the drug in fractions of 10 mg every two minutes up to a target dose of 1 mg/kg.

**End points**

The test was considered positive if the abnormal coved-type ECG pattern appeared in more than one right precordial lead (V1–V3; Fig. 1). We initially terminated the ajmaline challenge before reaching the target dose only if QRS prolongation exceeded 30% compared to baseline interval. After the performance of 32 tests, we also stopped ajmaline administration before reaching the target dose when a typical Brugada-type ECG or premature ventricular beats occurred. This was because major side effects had occurred (see results).

**Statistical analysis**

Data were analysed with the SPSS package for paired and unpaired data. The student’s t-test for unpaired data was used to compare differences between patients with positive and negative ajmaline test. A value of p<0.05 (p<0.001 where specified) was considered statistically significant. Quantitative data are presented as mean±SD.

### Results

#### ST-segment changes during ajmaline test

The ST segment pattern was worsened (further elevation >2 mm) in 28 of 58 patients (48%) with suspicious ECG abnormalities who initially had not met the criteria of a typical ‘coved-type’ ECG pattern (n=6 had an initially coved-type ECG). Of those, n=17 patients were previously symptomatic (SCD (n=6) or syncope (n=11)) with or without a family history of Brugada syndrome (n=2), SCD or syncope of unknown origin (n=3). In the group of asymptomatic patients with nondiagnostic ECG abnormalities (n=11), VT had been documented in n=2 patients and the family history was remarkable of Brugada syndrome in n=3 patients and of SCD or syncope of unknown origin in n=3 patients.

A diagnostic coved-type ECG pattern was induced in 3 of 94 patients (3%) with a normal baseline ECG. Two of these patients solely underwent

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**Table 1** Clinical characteristics and test results of patients undergoing the ajmaline challenge

<table>
<thead>
<tr>
<th></th>
<th>Positive ajmaline challenge total (n)</th>
<th>Suspicious baseline ECG (n)</th>
<th>Positive ajmaline challenge and suspicious baseline ECG (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>9 (13%)</td>
<td>22 (33%)</td>
<td>7</td>
</tr>
<tr>
<td>Family history</td>
<td>3 (13%)</td>
<td>9 (38%)</td>
<td>3</td>
</tr>
<tr>
<td>Syncope and family history</td>
<td>4 (25%)</td>
<td>6 (40%)</td>
<td>4</td>
</tr>
<tr>
<td>Aborted SCD*</td>
<td>5 (45%)</td>
<td>7 (64%)</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>5 (45%)</td>
<td>6 (55%)</td>
<td>5</td>
</tr>
<tr>
<td>BS family</td>
<td>3 (60%)</td>
<td>4 (80%)</td>
<td>3</td>
</tr>
<tr>
<td>Documented VT</td>
<td>2 (40%)</td>
<td>2 (40%)</td>
<td>2</td>
</tr>
<tr>
<td>Documented VT and family history</td>
<td>1 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope and documented VT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aborted SCD, syncope and documented VT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aborted SCD and syncope</td>
<td>1 (50%)</td>
<td>2(100%)</td>
<td>1</td>
</tr>
<tr>
<td>Syncope and BS family</td>
<td>2 (100%)</td>
<td>2(100%)</td>
<td>2</td>
</tr>
<tr>
<td>Aborted SCD, syncope, documented VT and family history</td>
<td>1</td>
<td>1(100%)</td>
<td></td>
</tr>
<tr>
<td>Aborted SCD, syncope and family history</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Aborted SCD, documented VT and family history</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Aborted SCD and BS family</td>
<td>1 (100%)</td>
<td>1(100%)</td>
<td>1</td>
</tr>
<tr>
<td>Aborted SCD and family history</td>
<td>1 (100%)</td>
<td>1(100%)</td>
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</tr>
<tr>
<td>Aborted SCD and documented VT</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Syncope, documented VT and BS family</td>
<td>1 (100%)</td>
<td>—</td>
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</tr>
</tbody>
</table>

158 (100%) 37 (23%) 64 (41%) 34

*SCD: sudden cardiac death; BS: Brugada syndrome; VT: ventricular tachycardia; family history: family history of SCD and/or syncope; BS family: family history of Brugada syndrome; other: recurrent presyncope of unknown origin, frequent polymorphic ventricular extrasystoles.
evaluation for syncope of unknown origin, the other underwent family screening for Brugada syndrome and had additionally experienced syncope and documented VT.

The test was negative in 30 of the 64 patients (47%) with suspicious baseline ECG and in n=91 of 94 patients (97%) without ECG abnormalities before the test. QRS duration was prolonged in all patients

**Fig. 1** Surface ECG (leads V1-6) shows the right precordial ECG changes during the fractionated application of ajmaline in one of our first patients with Brugada syndrome. A ‘saddle-type’ ECG at baseline dynamically changes into the typical ECG pattern of right bundle-branch block and ST-segment elevation of the ‘coved-type’. Note that the drug challenge could have been stopped after 20–30 mg of ajmaline without loss of diagnostic power to reduce the potential risk of VT.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A: ECG parameters before and after the ajmaline challenge (n=158 total patients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (/min)</td>
<td>69±15</td>
<td>78±13</td>
<td>8±10</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PQ (ms)</td>
<td>160±29</td>
<td>195±31</td>
<td>35±19</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>96±16</td>
<td>116±18</td>
<td>21±11</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>415±28</td>
<td>442±32</td>
<td>28±23</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>B: ECG parameters before and after the ajmaline challenge (n=37 patients with positive ajmaline challenge)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (/min)</td>
<td>74±15*</td>
<td>83±15*</td>
<td>7±10</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PQ (ms)</td>
<td>175±36†</td>
<td>212±32†</td>
<td>38±14</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>99±15</td>
<td>125±16*</td>
<td>27±14†</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>419±34</td>
<td>467±36†</td>
<td>47±24†</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>C: ECG parameters before and after the ajmaline challenge (n=121 patients with negative ajmaline challenge)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (/min)</td>
<td>68±14*</td>
<td>76±12*</td>
<td>8±9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PQ (ms)</td>
<td>156±25†</td>
<td>191±29†</td>
<td>35±20</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>96±16</td>
<td>114±18†</td>
<td>19±9†</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>414±26</td>
<td>445±27†</td>
<td>23±21†</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

* p<0.05 (B vs. C).
† p<0.001 (B vs C); mean value±standard deviation.
Mean QRS (PQ) prolongation was 21±11 (35±19) ms vs. baseline (Table 2). QTc intervals did not increase more than 12% in any patient (including n=4 patients with suspected Long QT syndrome). Patients with a positive ajmaline test result had an additional prolongation of the QTc interval (27 ms QRS prolongation vs 47 ms QTc prolongation). Heart rate before and after the test (pre test 74 vs 68/min, post test 83 vs 76/min, p<0.05) and PQ interval (pre test 175 vs 156 ms, post test 212 vs 191 ms, p<0.001) and increase in QRS (27 vs 19 ms, p<0.001) and QTc (47 vs 23 ms, p<0.001) intervals were significantly greater in patients with positive reaction to ajmaline. Following discontinuation of the drug, the ECG changes returned to baseline within 20–30 min.

Adverse events during the ajmaline challenge

The most remarkable events observed during ajmaline challenge were symptomatic VT which occurred in two of our first 32 patients (6%). Both had a coved-type ECG after ajmaline injection.

The first patient was a 53-year old sister of a patient with Brugada syndrome who had been asymptomatic prior to testing. Her baseline ECG showed a J-point elevation less than 0.1 mV in the right precordial leads. Following the fractionated application of 40 mg ajmaline, further J-point elevation in the right precordial leads which switched over to the typical coved-type ECG in a beat-to-beat fashion was observed (Fig. 2). Subsequently short-coupled ventricular extrasystoles occurred. Two more injections of ajmaline were given and hemodynamically relevant repetitive nonsustained polymorphic VT developed. These VT finally degenerated in a monomorphic VT with RBBB configuration (Fig. 2). No significant QRS prolongation was seen before VT initiation. The VT cluster terminated within 5 min. The second patient was a 40-year-old male survivor of sudden cardiac arrest and a positive family history of syncope with a classic coved-type ECG before the test. He underwent an ajmaline challenge and received 80 mg in a fractionated and dose-limited manner. His baseline coved-type ECG was aggravated and premature ventricular contractions occurred after 50 mg ajmaline. VT runs up to six consecutive beats were seen after the full dose. A few days later a body surface potential map was performed at rest and after administration of ajmaline.17 Before the target dose was reached, short-coupled premature ventricular contractions preceded the sudden onset of sustained polymorphic VT (Fig. 3). Multiple defibrillations were required to terminate the arrhythmia. In these two patients, the diagnostic ECG pattern was already overt when drug administration was continued and the formation of premature ventricular contractions preceded the
occurrence of VT. Since then, we adapted our protocol (see methods). The end points were not only the full target dose or significant QRS prolongation, but now included the unmasking of the typical ECG pattern during the test and the occurrence of ventricular extrasystoles (Table 3). We performed 126 ajmaline tests with this altered protocol without any further induction of tachyarrhythmias.

Using this standardized protocol, PQ-, QRS- and QTc-intervals were always prolonged without clinical relevance. After administration of the full ajmaline dosage, neither second/third degree SA/AV-block nor polymorphic VT of the torsade de pointes type were observed. The ECG changes entirely resolved within a time period of 30 min after the test. Only few patients (n=7) reported minor complaints such as nausea or headache.

**Discussion**

The present study underlines the ability of ajmaline to confirm an ECG pattern compatible with Brugada syndrome in individuals in whom the disease is suspected due to a positive family history of Brugada syndrome, syncope or sudden cardiac death, previous syncope, documented VT or a suspicious but not diagnostic ECG. We were able to demonstrate that the fractionated application of ajmaline in otherwise healthy patients was safe if certain criteria for test termination were fulfilled (Table 3). These criteria comprised QRS prolongation exceeding 30% compared to baseline interval, the occurrence of a classic coved-type ECG or the occurrence of premature ventricular contractions. The low degree of proarrhythmia...
may be explained by the fractionated drug application which is likely to be superior to bolus administration.

**Electrocardiographic features of Brugada syndrome**

In Brugada syndrome, two different electrocardiographic patterns exist: the ‘coved-type’ ECG and the ‘saddle-like’ ECG. Transition between the two types has been described in some patients with Brugada syndrome. According to current literature, the diagnosis of Brugada syndrome requires a ‘coved-type’ ECG pattern either spontaneously or drug-induced in more than one right precordial lead. Although affected Brugada patients – as proven by genetic testing may not show the typical ECG spontaneously or after the ajmaline challenge, no false positive drug challenge has been reported so far. We consider an ECG compatible with Brugada syndrome if a ‘coved-type’ pattern with ST-segment elevation of at least 2 mm is expressed. Since we studied a selected patient population, we did not aim at proving sensitivity or specificity of the drug test in the diagnosis of Brugada syndrome.

The exact electrophysiologic mechanism of this syndrome has not yet been fully elucidated. Three mechanisms are proposed for ST segment elevation in Brugada syndrome: local conduction abnormality, local ventricular depolarization and early repolarization abnormality. The latter hypothesis postulates an accentuation of the action potential notch in the right ventricular epicardium carried by the transient outward current (Ito) via reduction of the fast sodium inward current (INa). A genetic sodium channel defect, which may lead to such reduction of the sodium current has been linked to the Brugada syndrome.3 The resulting transmural voltage gradient, normally responsible for the inscription of the J wave, may give rise to a saddleback-form of ST-segment elevation if the epicardial repolarization precedes repolarization in mid- and endocardial regions. Further accentuation of the notch accompanied by a prolongation of the epicardial action potential may lead to the development of a coved-type ST-segment elevation. Ultimately, a loss of the action potential dome at some epicardial sites may result. As a consequence, marked intramural dispersion of repolarization may be responsible for local re-excitation via phase 2 re-entry. Through this mechanism very closely coupled extrasystoles capable of initiating circus movement reentry arrhythmias can be triggered.9,20 The use of agents that primarily block INa but not Ito (flecainide, ajmaline and procainamide) can further diminish sodium current already reduced by Brugada mutations. This hypothesis may explain the potential of sodium channel blockers to unmask concealed forms of the Brugada syndrome and the potential proarrhythmic adverse effects.7,8,11,16 Further evidence for this hypothesis is yielded by the observation of marked ST-segment elevation just prior or following the onset of polymorphic VT in Brugada syndrome. In addition, we have recently demonstrated that the body surface area of ST elevation without drug provocation correlated to the inducibility of VT in Brugada syndrome. Due to the dynamic nature of the ECG changes concern may raise about the significance of negative test results. It has been shown in studies utilizing high-resolution body surface potential mapping, that recordings outside the positions of the standard ECG leads—high right precordial leads in the second or third intercostal space—may show more pronounced ECG changes typical of Brugada syndrome compared to the standard right precordial leads in the fourth intercostals space.21,22 The present study underlines the potential of ajmaline to induce the above mentioned ST segment changes in the right precordial leads in Brugada syndrome.

Of note, one patient required five defibrillation shocks until sustained polymorphic VT was terminated. This is compatible with reports in the literature that termination of VT might be rendered more difficult after administration of class I drugs. Possibly due to conduction slowing, sodium channel blockers can provoke incessant VT/VF, which are difficult or impossible to terminate.23 Additionally, blocking cardiac sodium channels in animals is reported to increase the amount of energy required to defibrillate a fibrillating heart.24 In parallel to previous observations, the PQ interval challenge was significantly increased in patients with a positive ajmaline test, presumably reflecting the presence of a HV-conduction delay.

**Clinical implications of the ajmaline challenge**

Due to prognostic implication for the affected individual, it is important to recognize the suspect ECG pattern which is the cornerstone for the diagnosis of Brugada syndrome. However, there are certain circumstances mimicking the Brugada-ECG, that should be ruled out carefully.20 Transient normalization of the ECG signature of this syndrome may lead to failed recognition. This could have negative consequences on the management of these patients.
at high risk for recurrence of lethal arrhythmias. In this regard, inspection of previous ECGs and performing a baseline and a follow-up ECG in all patients to whom class I antiarrhythmic drugs are prescribed and carefully reviewing it for appearance of the typical pattern of right bundle branch block and ST elevation seems good clinical practice, as it could unmask the disease in patients with occult or borderline ECG patterns. Furthermore, pharmacological interventions may facilitate development of polymorphic VT/VF. A correct diagnosis of a suspicious ECG pattern is of great importance to save a patient’s life and to avoid medico-legal consequences. Suspicion of Brugada syndrome should therefore lead to the performance of a pharmacological challenge.\(^3,20\)

In patients with a typical Brugada like ECG pattern either spontaneously or after administration of ajmaline we recommend programmed electrical stimulation at two ventricular sites with up to three premature beats\(^2^6\) and genetic testing.

**Conclusion**

At present, the provocative tests are not utilized routinely and a standardized protocol has not been published yet. Especially institutions without experience with the drug challenge may be cautious because of the suspected likelihood of VT induction and difficulty of VT termination. Brugada et al.\(^7\) already emphasized the need to perform administration of ajmaline for diagnostic or investigational purposes in an appropriate environment under strict medical surveillance with advanced life-support facilities available. The present study demonstrated, that the acute proarrhythmic effect of ajmaline in Brugada syndrome can be controlled if the proposed requirements are fulfilled during the drug challenge (Table 3).

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**References**


