CLINICAL RESEARCH

Ajmaline challenge for the diagnosis of Brugada syndrome: Which protocol?

Test à l’ajmaline pour le diagnostic du syndrome de Brugada: quel protocole?

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Received 21 April 2010; received in revised form 6 October 2010; accepted 7 October 2010

KEYWORDS
Brugada syndrome; Ajmaline challenge; Ventricular arrhythmia; Isoproterenol

Summary
Background. — Ajmaline challenge is commonly used for the diagnosis of Brugada syndrome. A slow infusion rate has been recommended in view of the proarrhythmic risk, but the diagnostic value of various infusion rates has not been investigated.

Aims. — To compare rapid and slow ajmaline infusion rates and to assess the proarrhythmic risk.

Methods. — The first part of this study prospectively compared rapid and slow infusion rates in terms of results and ventricular arrhythmias. Thirty-two patients (mean age 41 ± 12 years; 26 men) received the two ajmaline challenges on different days. According to randomization, ajmaline (1 mg/kg) was infused at 1 mg/sec or over 10 minutes. The second part of the study retrospectively assessed the prevalence of ventricular arrhythmia during 386 challenges performed at a rapid infusion rate.

Results. — No differences were observed between rapid and slow tests. All patients diagnosed as positive or negative with one test obtained the same result with the other test. Ventricular premature beats were observed in five of 32 patients during the slow challenge and in four of 32 patients during the rapid challenge. No sustained ventricular arrhythmias were observed. Analysis of the 386 tests revealed four episodes of ventricular arrhythmia (two complex ventricular premature beats, one non-sustained ventricular tachycardia and one ventricular fibrillation).

Abbreviations: BS, Brugada syndrome; ECG, electrocardiogram; NSVT, non-sustained ventricular tachycardia; VA, ventricular arrhythmia; VF, ventricular fibrillation; VPB, ventricular premature beat; VT, ventricular tachycardia.

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doi:10.1016/j.acvd.2010.10.007
**Background**

BS is associated with a risk of sudden death due to VF [1]. ECG abnormalities include J point elevation by at least 0.2 mV and a coved pattern of the ST segment with a negative T wave in the right precordial leads. Right bundle branch block can also be associated with the syndrome [2]. These signs are sometimes intermittent. In 1996, Miyasaki et al. showed that ST elevation can be revealed by the use of sodium channel blocking agents [3]. Ajmaline and flecainide have been used in Europe, procainamide in the USA and pilsicainide in Japan. The various drugs have been compared, and ajmaline has the highest sensitivity for detection of BS [4]. However, ajmaline may have proarrhythmic effects and different infusion rates have been recommended [2,5–8]. Administration of 1 mg/kg at the rate of 10 mg/min was proposed at the first consensus conference [2]. Ajmaline challenge stopping criteria were defined in 2003 in order to avoid proarrhythmic effects. Fractionated administration of a dose of 10 mg every 2 minutes to reach a total dose of 1 mg/kg was proposed [8]. In 2005, the second consensus conference recommended a dose of 1 mg/kg over 5 minutes [9]. Other teams have reported their experience with protocols used to study conduction disorders, i.e. 1 mg/kg at a rate of 1 mg/sec [10,11]. Finally, other authors (such as Wolpert et al.) use 1 mg/kg over 10 minutes [4]. No randomized study has compared the sensitivity/specificity and risks associated with the various ajmaline administration protocols. Ajmaline induces concentration-dependent, frequency-independent and voltage-dependent sodium channel blockade [12], and concentration-dependent and frequency-independent inhibition of the transient outward potassium current [13]. The rate of administration of ajmaline, by modifying the peak plasma concentration, can alter potassium channel inactivation and reactivation kinetics and modulate the intensity and duration of sodium channel blockade. Furthermore, as the time to onset of action of ajmaline is 2 to 3 minutes, rapid injection of ajmaline (1 mg/sec for a dose of 1 mg/kg) induces higher cardiac concentrations than the same dose injected over 10 minutes. Rapid injection could accentuate J point elevation during the first minutes to the detriment of the specificity of the test. Inversely, the dose injected over 10 minutes could reduce the sensitivity of the test. The objective of this study was to compare the electrocardiographic effects of two rates of administration of ajmaline and to determine whether the diagnostic contribution is modified by the ajmaline administration rate. Retrospective evaluation of the prevalence of VA in a series of 386 tests performed with injection of 1 mg/sec was designed to estimate the proarrhythmic risk during rapid injection of ajmaline.
Methods

Patients

The study was approved by the local ethics committee. Each subject signed an informed consent form. Between 2005 and 2008, 32 consecutive subjects with type 2 or 3 BS were prospectively included in the first phase of the study. In this population, ECG changes were disclosed after the onset of symptoms, incidentally or in the context of family screening. Exclusion criteria were contraindications to ajmaline (previous myocardial infarction, heart failure or impaired left ventricular ejection fraction, complete left bundle branch block, bifascicular block, second- or third-degree atrioventricular block, use of a class I antiarrhythmic agent, pregnancy or breastfeeding, children under the age of 15 years).

The second phase of the study consisted of retrospective evaluation of ajmaline challenges performed with the rapid injection protocol between January 2002 and July 2009. This phase comprised 386 subjects in whom the test was performed for family screening of BS or sudden death, unexplained syncope, discovery of type 2 or 3 ECG, or resuscitated cardiac arrest. ECG recordings were reviewed specifically for the analysis of VAs. Single VPBs, complex VPBs (frequent VPBs, polymorphic VPBs, bigeminy, couplets), NSVT and VF were notified.

Ajmaline challenges

Ajmaline challenges were conducted in the electrophysiology laboratory, in the presence of a cardiologist. Each patient underwent two ajmaline challenges, and the order was determined by randomization, with a crossover design. The two tests were performed on different days, < 1 month apart. All tests were performed at the same time of the day, in the late morning. Tests were preceded by echocardiography and β-human chorionic gonadotropin if necessary. The ajmaline injection was performed at a dose of 1 mg/kg, either at an infusion rate of 1 mg/sec or over 10 minutes.

Continuous 12-lead ECG monitoring, including leads V1 and V2 in the second intercostal space, was performed on a computerized electrophysiology system (EP Med Systems, NJ, USA). Measurements were performed with the software callipers, at a time-scale of 200 mm/sec at T0 (0 minutes), T3 (T0 + 3 minutes), T5 (T0 + 5 minutes) and T10 (T0 + 10 minutes) after the end of injection for the two protocols, and at T0, T3 and T5 after the beginning of injection for the slow test. ECGs were printed on paper at these different times and recorded continuously on optical disk. The presence of any arrhythmias was recorded. At the end of administration of ajmaline, the ECG recording continued until the reading returned to normal. The test results were evaluated by two independent, blinded observers. The test was considered positive if more than one lead exhibited coved type with a J point elevation > 0.2 mV [2].

Statistics

Variables are expressed as means and standard deviations. Comparisons between groups were performed by analysis of variance or by using the Wilcoxon test for paired samples. A paired Student’s t test was used to compare paired variables. Tests were considered to be significant for p < 0.05. Statistical analysis was performed with SPSS software Version 11 (SPSS Inc., Chicago, IL, USA).

Results

Part I

Study population

Subjects had a mean age of 40.9 ± 12 years (range 19–69); the sex ratio was 4.3 (81.2% men). Patients had a type 2 ECG in 22 (68.8%) cases and a type 3 ECG in 10 (31.2%) cases. Symptoms consisted of syncope (n = 5), faintness (n = 2) or palpitations (n = 11). The other subjects were asymptomatic (n = 14) and their ECG abnormality was found during a family screening (n = 7) or fortuitously (n = 7).

Test results

The concordance between rapid tests and slow tests was 100%. All patients diagnosed as positive or negative with one test obtained the same result with the other test. No difference in the results was observed between the two tests according to readings by the two observers (Fig. 1). The positive ajmaline challenge rate was 46.9% (15/32). Ajmaline challenges were more often positive for type 2 ECGs than for type 3 ECGs (p < 0.001). No significant difference in the VPB rate was observed according to the protocol used (p = 0.51). VPBs occurred in three subjects during positive tests and in five subjects during negative tests. No runs of VPBs were observed during the 64 tests; ECG changes were identical for the two protocols (Table 1) and for both positive and negative tests, except for the QTc interval (Table 2). The maximum variation of the amplitude of J point was observed in lead V2 for the two tests, in 75 and 69% of cases, respectively. The peak changes in J point elevation, PR, RR, QRS and QTc interval were observed 3 minutes after injection, except in RR in the slow test (Figs. 2 and 3).

Part II

Study population

Subjects had a mean age of 42 ± 15 years (range 15–81); 55% were men. Tests were performed for family screening in 290 (75%) cases. Sixteen (4.2%) patients had a history of syncope and two (0.6%) had a history of resuscitated sudden death. Fifty-five (14%) patients had a family history of sudden death. The ECG was normal in 264 (68%) cases, transient type 1 in 38 (10%) cases and type 2 or 3 in 84 (22%) cases.

Results and complications of ajmaline challenge

The ajmaline challenge was positive in 183 (47%) patients. Two (0.5%) of the 386 patients presented runs of monomorphic VT (a triplet of VPBs and a triplet of VPBs followed by a doublet), with no recurrence during subsequent ECG monitoring. Another two (0.5%) patients presented serious VAs. The first patient, a 29-year-old woman, presented polymorphic NSVT of 15 complexes over 7 s, occurring 1 minute after the onset of a type 1 appearance on the ECG, i.e. 2 minutes after the end of the injection of the entire dose.
of ajmaline. Widening of the QRS and J point elevation was observed before the run (Fig. 4). The test was performed in the context of BS screening in a family of 15 cases of BS. The ECG before the test was normal. The second case occurred in an asymptomatic 21-year-old woman also consulting in the context of family screening. The ECG before the test was normal. Three minutes after the end of the injection, a type 1 ECG pattern on lead V1 was observed, with widening of the QRS > 130%, followed by VF. Sinus rhythm was restored after 30 minutes of resuscitation, without neurological repercussion (Fig. 5). Resuscitation included repeated electrical shocks, infusion of sodium bicarbonate, a bolus of adrenaline and isoproterenol. Intravenous isoproterenol was administered as a continuous infusion of 0.06 mg/min for 15 minutes, and stopped a few minutes after sinus rhythm, without recurrence of ventricular event. A Scarpa surgical approach was done in preparation for circulatory support, without recurrence of ventricular event. A Scarpa surgical approach was done in preparation for circulatory support, without recurrence of ventricular event. A Scarpa surgical approach was done in preparation for circulatory support, without recurrence of ventricular event.

**Discussion**

No significant difference was observed between the slow test and the rapid test in terms of diagnostic performance, variation in ECG variables or the frequency of isolated VPBs. The development of isolated VPBs was not correlated with a positive ajmaline challenge. In contrast, runs of polymorphic VT were preceded by ECG changes typical of BS. The risk of potentially fatal arrhythmias was 0.5% during the rapid test.

No studies evaluating the diagnostic performances of the ajmaline challenge as a function of injection rates in BS have been published in the literature. Independently of injection rate, the lengthening of QRS, PR and QTc intervals observed in this study was identical to that observed in previous studies [14,15], including in studies performed in BS patients [5,8,16]. All ajmaline tests were performed at the same time of the day to avoid spontaneous nycthemeral ECG fluctuations [17].

In the studies by Batchvarov et al. [5] and Veltmann et al. [16], only lengthening of the QTc interval (but not heart rate, PR interval or QRS width) was slightly greater on positive tests. These data are in line with those reported with the rapid test in the first part of this study and confirm the good ECG tolerance of this protocol.

**Table 1  ECG variables: rapid vs slow infusion.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable</th>
<th>Baseline</th>
<th>3 minutes</th>
<th>Δ (%)</th>
<th>Baseline</th>
<th>10 minutes</th>
<th>Δ (%)</th>
<th>p¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR (ms)</td>
<td>Rapid</td>
<td>167 ± 28</td>
<td>219 ± 3.6</td>
<td>32.5</td>
<td>166 ± 32</td>
<td>217 ± 33</td>
<td>32.8</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>103 ± 14</td>
<td>134 ± 18</td>
<td>31.7</td>
<td>100 ± 13</td>
<td>132 ± 17</td>
<td>33.6</td>
<td>0.8</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>Rapid</td>
<td>425 ± 37</td>
<td>481 ± 32</td>
<td>13.7</td>
<td>403 ± 24</td>
<td>470 ± 39</td>
<td>16.7</td>
<td>0.2</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>Rapid</td>
<td>847 ± 78</td>
<td>740 ± 10</td>
<td>−11.1</td>
<td>902 ± 133</td>
<td>754 ± 87</td>
<td>−15.5</td>
<td>0.06</td>
</tr>
<tr>
<td>J wave (mV)</td>
<td>Rapid</td>
<td>0.28 ± 0.1</td>
<td>0.51 ± 0.17</td>
<td>95.0</td>
<td>0.26 ± 0.1</td>
<td>0.51 ± 0.22</td>
<td>96.8</td>
<td>0.5</td>
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</tbody>
</table>

¹ Comparison between infusion protocols.

of the day to avoid spontaneous nycthemeral ECG fluctuations [17].

**Table 2  ECG variables: positive vs negative test.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infusion rate</th>
<th>Positive test (n = 15)</th>
<th>Negative test (n = 17)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Rapid</td>
<td>58 ± 31</td>
<td>48 ± 24</td>
<td>0.3</td>
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<tr>
<td></td>
<td>Slow</td>
<td>48 ± 20</td>
<td>54 ± 29</td>
<td>0.3</td>
</tr>
<tr>
<td>QRS</td>
<td>Rapid</td>
<td>34 ± 16</td>
<td>29 ± 15</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>33 ± 18</td>
<td>32 ± 14</td>
<td>0.3</td>
</tr>
<tr>
<td>QTc</td>
<td>Rapid</td>
<td>69 ± 37</td>
<td>45 ± 28</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>70 ± 42</td>
<td>64 ± 31</td>
<td>0.4</td>
</tr>
<tr>
<td>RR</td>
<td>Rapid</td>
<td>−121 ± 109</td>
<td>−94 ± 86</td>
<td>0.5</td>
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<tr>
<td></td>
<td>Slow</td>
<td>−125 ± 72</td>
<td>−167 ± 124</td>
<td>0.2</td>
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</table>

In the studies by Batchvarov et al. [5] and Veltmann et al. [16], only lengthening of the QTc interval (but not heart rate, PR interval or QRS width) was slightly greater on positive tests. These data are in line with those reported with the rapid test in the first part of this study and confirm the good ECG tolerance of this protocol.

**Literature reports of the risk of VA during sodium channel blockade challenge in BS are summarized in Table 3.** Studies in which the presence of type 1 ECG was most frequent reported the highest rates of proarrhythmias. This appears to be true regardless of the type of sodium channel blocking agent used. However, it should be noted that a risk of VF was also observed when the ECG was strictly normal before the injection (Fig. 5), and when the injection was performed over 5 minutes [16]. In view of the risk of fatal arrhythmias, as recommended by Rolf et al. [8], the injection of ajmaline should therefore be performed over 10 minutes and should be stopped in the case of significant J point elevation or widening of the QRS by more than 130%. Ajmaline has the advantage of a shorter half-life and a briefer blocking effect on transient outward potassium channel blockade.
### Table 3  Ventricular arrhythmias during sodium channel blockade challenge.

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Drug used</th>
<th>N</th>
<th>Type 1 ECG (%)</th>
<th>SCD or syncope (%)</th>
<th>Testpositivity (%)</th>
<th>VPB (%)</th>
<th>VA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugada et al., 2000</td>
<td>Ajmaline 5 min</td>
<td>106</td>
<td>32</td>
<td>&gt; 32</td>
<td>42</td>
<td>Frequent VPBs: 4.7</td>
<td>VF: 1.3 with ajmaline</td>
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<td></td>
<td>Flecainide</td>
<td></td>
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<td></td>
<td>Procainamide</td>
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<td></td>
<td>Ajmaline 10 mg/2 min</td>
<td>158</td>
<td>3.8</td>
<td>SCD: 13.3 Syncope: 60.1</td>
<td>23.4</td>
<td>Not reported</td>
<td>VT: 1.3 but 0 after protocol change</td>
</tr>
<tr>
<td>Rolf et al., 2003</td>
<td>Ajmaline</td>
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<td>10 mg/2 min</td>
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<tr>
<td>Gasparini et al., 2003</td>
<td>Flecainide</td>
<td>22(41 tests)</td>
<td>86.4</td>
<td>SCD: 9.1 Syncope: 36.4</td>
<td>100</td>
<td>Not reported</td>
<td>VT: 7.3</td>
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<tr>
<td></td>
<td>Pilsicainide</td>
<td>65</td>
<td>100</td>
<td>SCD: 10.6 Syncope: 18.1</td>
<td>40</td>
<td>Single VPBs: 6</td>
<td>VT: 6.2</td>
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<td>Morita et al., 2003</td>
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<td>28</td>
<td>64.3</td>
<td>SCD: 10.7 Syncope: 42.9</td>
<td>100</td>
<td>Single VPBs: 6</td>
<td>VT: 11</td>
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<tr>
<td>Batchvarov et al., 2009</td>
<td>Ajmaline 5 min</td>
<td>148</td>
<td>No</td>
<td>SCD: 12.8 Syncope: 27.0</td>
<td>20.3</td>
<td>Single VPBs: 8.1 Complex VPBs: 4.7</td>
<td>NSTV: 2</td>
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<tr>
<td>Veltmann et al., 2009</td>
<td>Ajmaline 5 min</td>
<td>677</td>
<td>No</td>
<td>SCD: 1.8 Syncope: 25.7</td>
<td>39</td>
<td>VPB: 1.2</td>
<td>NSTVL 0.30</td>
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<td></td>
<td>Ajmaline 1 mg/sec</td>
<td>386</td>
<td>9.8</td>
<td>SCD: 0.6 Syncope: 4.2</td>
<td>47.3</td>
<td>Single VPBs: 14.1 Complex VPBs: 0.26</td>
<td>NSTV: 0.8</td>
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<td>Our study, part II</td>
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ECG: electrocardiogram; NSVT: non-sustained ventricular tachycardia; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VPB: ventricular premature beat; VT: ventricular tachycardia.
Figure 1. Bland and Altman plots of J wave amplitude (JWA) changes with the two infusion protocols, at 0 minutes (T0), 3 minutes (T3), 5 minutes (T5) and 10 minutes (T10) after the end of injection. The mean of J point elevation is represented by the abscissa (x-axis) value, and the difference between J point elevation by the ordinate (y-axis) value. The graph showed good agreement between the two protocols.

Figure 2. Kinetics of J point amplitude during slow and rapid tests, at 0 minutes (T0), 3 minutes (T3), 5 minutes (T5) and 10 minutes (T10) after the end of injection (means ± standard deviations).

current than other sodium channel blocking agents, and is therefore more rapidly reversible [13,22]. Predictive factors for the development of arrhythmia during sodium channel blockade challenge performed for the detection of BS are difficult to define because of the rarity of these events. According to Chinushi et al., the frequency of VPBs is higher in the presence of marked ST elevation before the test, but identical whether or not patients are symptomatic [21]. Batchvarov et al. emphasized the higher incidence of VAs during positive tests compared with negative tests [5], suggesting that the test should be stopped as soon as a positive response is observed.

In our study, the two cases of severe polymorphic arrhythmia occurred in female patients with no personal or family history of sudden death and with a strictly normal baseline ECG. The risk of arrhythmia was assumed to be low. A G1743R mutation was demonstrated in one patient. This mutation, responsible for a marked reduction of the density of sodium current channels, has been previously reported by Valdivia et al. [23]. The other patient was not screened for SCN5A mutations. In view of the different morphology of the VPBs, Morita et al. [24] also proposed a different origin of the arrhythmia between subjects with or without SCN5A mutations, which could therefore explain the increased proarrhythmic risk in patients presenting such a mutation. A high rate of VA (43%) was reported during flecainide challenge in the presence of an SCN5A mutation in the studies by Gasparini et al. [19]. The presence of an SCN5A mutation may therefore be predictive of the development of proarrhythmia.

Isoprenaline efficiency had been described in the context of electrical storm in patients with BS [25—28], and in cases of VA induced by drugs such as procainamide and pilsicainide [29,30]. It also seems to be effective in VA generated by ajmaline. Isoproterenol is known to restore the dome of epicardial action potential and to normalize the ST segment by increasing the inward calcium current [31]. Its beta-adrenergic stimulation has been added in our clinical
Figure 3. Kinetics of PR, QRS, QTc and RR intervals during slow and rapid tests, at 0 minutes (T0), 3 minutes (T3) and 5 minutes (T5) after the end of injection (means ± standard deviations).

Figure 4. Development of polymorphic non-sustained ventricular tachycardia at the third minute of a rapid ajmaline challenge.
Development of ventricular fibrillation 3 minutes after rapid intravenous administration of 60 mg of ajmaline in a 20-year-old woman. Panel A: 12-lead electrocardiogram before the test; no ST elevation in the right precordial leads. Panels B and C: progressive increase in the QRS duration and appearance of features of right bundle branch block with J point elevation (type 1 pattern) on lead V1. Panel D: polymorphic ventricular tachycardia then intractable ventricular fibrillation for 30 minutes despite 10 electrical shocks and intravenous administration of isoproterenol. Panel E: restoration of effective sinus rhythm after the 11th shock.

Case to an increased sympathetic activity due to adrenaline injection. The isoproterenol concentrations that we used (0.06 mg/min) were larger than those usually described in the electrical storms (0.1 to 1 μg/min) [25, 26, 28, 30, 32]. The irreducible character of VF, despite electrical shocks, justifies this high dose. Ablation of the triggering ventricular ectopies has been described in electrical storms in case of failure of therapeutic options [33]. Our therapeutic option was cardiopulmonary “bypass” because of the emergency. Heart transplantation has already been described as a last resort [34].

One limitation is related to the power of the first part of our study. After a post-hoc calculation, a cohort of at least 80 patients would have been necessary to prove with a probability of 80% the absence of difference between the two tests.

Clinical implications

The analysis of 386 ajmaline challenge tests showed that rapid administration of ajmaline is associated with a risk of severe VA, even in asymptomatic patients with normal baseline ECG. The sensitivity of the test was not decreased by slowing the rate of administration of ajmaline over 10 minutes. The 10-minute ajmaline challenge is therefore recommended.

Conflict of interest statement

None. Funding: This study was supported by a grant from the Amiens-Picardie University Hospital.

Acknowledgments

The authors would like to thank Ms Beatrice Desachy and Christele Denturk for their technical contribution to the ajmaline challenge, and Mr Momar Diouf for his contribution to statistical analysis.

References


