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## Sodium-channel blocker challenge in the familial screening of Brugada syndrome: safety and predictors of positivity

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1 **ABSTRACT**

2 **Background:** Sodium channel blocker challenge (SCBC) is frequently performed to unmask  
3 Brugada syndrome (BrS).

4 **Objectives:** We aim to identify, predictors of positivity and complications of SCBC, in the  
5 setting of familial screening.

6 **Methods:** All consecutive patients from 2000 to 2014 who benefit from a SBC and belong to  
7 a family with at least 2 subjects affected by the syndrome were enrolled and followed  
8 prospectively. Data were reviewed by 2 physicians blinded to the clinical and genetic status.

9 **Results:** Among 672 SCBC performed in 137 families, 337(50%) were positive. Multivariate  
10 analysis identified ajmaline (OR 2.98 (1.65-4.91), a significant S wave in DII (OR=3.11  
11 (2.12-4.58), DIII (OR= 2.75 (1.78-4.25) or V5 lead (OR= 3.71 (2.54-5.44), as predictors of a  
12 positive SCBC ( $P < 0.0001$ ). Eleven (1.6%) patients presented complications (10 ventricular  
13 arrhythmia, 1 atrial flutter) but no deaths occurred. A familial history of complications (OR =  
14 41 [10; 203];  $P < 0.0001$ ), young age ( $P = 0.04$ ) and decreased conduction ECG parameters at  
15 baseline ( $p = 0.04$ ) were predictors of complication. QRS enlargement during SCBC was not  
16 associated with complications.

17 During a median follow-up of 106 [54-143] months, 11 life-threatening arrhythmia occurred.

18 **Conclusions:** SCBC in the screening of familial Brs is safe. The risk of complication is  
19 considerably increased in case of familial history of complicated SCBC, in very young  
20 patients and in the presence of decreased ECG conduction parameters. However, QRS  
21 enlargement during the test is not directly related to complications and should not be used to  
22 prematurely stop the test unless leading to false negative results.

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24 **Key words:** Brugada syndrome; Sodium Channel Blockers Challenge; Ajmaline; Flecainide;  
25 Complication.

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## 1 Introduction

2

3 Brugada syndrome (BrS) is responsible for sudden cardiac death (SCD) due to  
4 ventricular fibrillation (VF) which typically occurs at rest and could be the first manifestation  
5 of the disease<sup>1</sup>. Diagnosis is based on a specific ECG pattern – type 1 ST segment elevation in  
6 the right precordial leads as defined in the recent guidelines<sup>2</sup>. Owing to the variability of this  
7 ECG pattern, its prevalence in the general population remains unclear but has been estimated  
8 to range between 0.05% and 0.2%<sup>3-5</sup>. In subjects without spontaneous type 1 ECG aspect,  
9 sodium channel blocker challenge (SCBC) is commonly used to unmask the ECG pattern<sup>2,6</sup>.  
10 Ajmaline and flecainide are the most commonly used drugs while Procainamide is considered  
11 as less efficient<sup>6</sup>.

12 While this test is widely used, its safety remains a matter to debate<sup>7-11</sup>. Indeed, last  
13 guidelines consider as a stopping criteria, a QRS enlargement of more than 30%<sup>2</sup>.  
14 Challenging this criteria, Batchvarov et al have suggested that it can lead to underdiagnose  
15 BrS while the risk of complications in this situation appears to be low<sup>7</sup>.

16 The aim of this study was to evaluate, aside from QRS enlargement stopping criteria,  
17 the safety and predictors of a positive SCBC, during familial screening of Brs.

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## 1 **Methods**

### 2 ***Study Population and design***

3 All consecutive patients undergoing SCBC during familial screening of Brs, in 10  
4 French university hospitals from 2000 to 2014, were included. This study was conducted  
5 according to European guidelines for clinical and genetic research. Informed written consent  
6 was obtained from each patient who agreed to participate in the clinical and genetic study.

7 Except for QRS enlargement stopping criteria, SCBCs were performed according to  
8 the second consensus conference (Ajmaline: 1 mg/kg; Flecainide: 2 mg/kg)<sup>6</sup>. Complications  
9 were defined as occurrence of ventricular arrhythmias (VF) and sustained or non-sustained  
10 ventricular tachycardia (VT), atrial arrhythmias or atrioventricular block.

11 The diagnosis of BrS was based on 2013 criteria<sup>2</sup> with the presence of a typical type 1  
12 ECG pattern, either spontaneous or pharmacologically induced, in at least one right precordial  
13 lead including (V1, V2, V3) in the 2<sup>nd</sup>, 3<sup>rd</sup> or 4<sup>th</sup> intercostal space. Type 1 ST segment  
14 elevation was defined as a J-wave elevation higher than 0.2mV, followed by a coved type ST  
15 segment elevation and ended with a negative T wave.

16 Clinical follow-up was collected prospectively from either the referring  
17 cardiologists or directly from the patients.

18

### 19 ***ECG data***

20 Two physicians blinded to the clinical and genetic status reviewed baseline ECG, first  
21 diagnosis ECG during SCBC or ECG at the end of the test in case of negative test.

22 P wave, PQ interval, QRS, QT peak, QTend, QTc duration (corrected by Bazett's  
23 formula) and Tpeak-Tend interval (TPE, time interval between the peak and the end of the T  
24 wave) were measured in V1. Additional parameters were measured in DII (terminal S wave

1 duration and amplitude), DIII (terminal S wave duration and amplitude), V5 (terminal S wave  
2 duration and amplitude) and aVR (terminal R wave duration and amplitude).

3 All measurements were performed using Image J software (National Institutes of  
4 Health, Bethesda, Maryland, <http://rsb.info.nih.gov/ij>).

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## 6 ***Genetic analysis***

7 The *SCN5A* gene was screened in each proband. Relatives were screened for familial  
8 mutations according to the genetic status of the proband.

9 Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28  
10 exons of *SCN5A* were amplified by polymerase chain reaction (PCR) utilizing intronic primers. PCR  
11 products were screened for *SCN5A* mutations using denaturing high performance liquid  
12 chromatography (dHPLC)-DNA sequencing or High Resolution Melting (HRM). The description of  
13 mutations is based on cDNA reference sequence GenBank NM\_198056.

14 This study was conducted according to European guidelines for clinical and genetic research.  
15 Institutional ethical committees approved clinical and genetic database. Informed written consent was  
16 obtained from each patient who agreed to participate in the clinical and genetic study.

## 17 ***Statistical Analysis***

18 Data were analysed with the SPSS and SAS packages (SPSS Inc version 23,0,  
19 Chicago, Ill; SAS Institute Inc version 9,4, Cary, NC).

20 Continuous variables were reported as mean  $\pm$  SD or median (lower quartile, upper  
21 quartile), as appropriate. Continuous variables were analysed by Student's unpaired *t*-test or  
22 the Wilcoxon test, as appropriate. The  $\chi^2$  test and Fisher's exact test were used for  
23 comparison of categorical variables.

24 Multivariate logistic regression models were used to identify provider-related factors  
25 associated with positive tests.

1 All tests were 2 tailed and a  $P$  value under 0.05 was considered as statistically  
2 significant.

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## 1 **Results**

### 2 ***Population***

3           The study population consist of 672 consecutive patients from 137 families (median  
4 age  $40 \pm 17$  years). Three hundred and twenty-eight patients were male (49%). Three hundred  
5 and thirty-seven patients (50%) presented a positive SCBC with an induced type 1 ECG  
6 pattern. The molecule used was ajmaline in 497 (74%) and flecainide in 175 (26%) SCBC.  
7 *SCN5A* mutation was identified in 43/136 (31%) probands and in 120/268 (45%) of their  
8 relatives. Population characteristics are summarized in *Table 1*.

### 9 ***Characteristics of positive SCBC***

10           Among the 672 SCBC, a positive result was associated with age ( $41 \pm 16$  vs  $36 \pm 17$   
11 y;  $p=0.004$ ), the presence of a *SCN5A* mutation in the family (93 (79%) vs 27 (28%);  
12  $p<0.001$ ) and the use of ajmaline (272 (54%) of positive SCBC vs 65 (37%) for flecainide;  
13  $p<0.001$ ) (figure 1).

14           Patients with a positive SCBC additionally presented at baseline a longer P wave ( $68 \pm$   
15  $19$  ms vs  $62 \pm 17$  ms;  $P <0.001$ ), PR ( $156 \pm 31$  ms vs  $146 \pm 27$  ms;  $P <0.001$ ) and QTc  
16 interval ( $407 \pm 39$  ms vs  $394 \pm 36$  ms;  $P <0.001$ ) in V1 lead and a longer QRS interval ( $92 \pm$   
17  $19$  ms vs  $82 \pm 16$  ms;  $P <0.001$ ) in DII lead. Both duration and amplitude of the terminal S  
18 wave in DII, DIII and V5 leads and the terminal R wave in aVR were also associated with a  
19 positive SCBC ( $P <0.0001$ ). Similar results were observed at the end of the SCBC (*Table 2*).

20           In multivariate analysis, the drug used (ajmaline vs flecainide) was the best predictor  
21 of a positive SCBC (OR 2.98 (1.65-4.91);  $P <0.0001$ ). A significant S wave (e.g., amplitude >  
22 1 mV and duration > 40 ms) in DII (OR=3.11 (2.12-4.58),  $P <0.0001$ , DIII (OR= 2.75 (1.78-  
23 4.25),  $P <0.0001$ ) and V5 lead (OR= 3.71 (2.54-5.44),  $P <0.0001$ ) or a significant terminal R  
24 wave in aVR (OR= 2.22 (1.51-3.26),  $P <0.0001$ ) were also associated with a positive SCBC  
25 (*Figure 1*).



## 1 **Complications**

2        Among the 672 SCBC performed, complications occurred in 11 (1.6%) including 9  
3 sustained VT, one VF and one atrial flutter. Four of these patients required external DC  
4 shock. There were neither high-grade conduction disorders, nor deaths caused by SCBC.  
5 Three families presented complications during SCBC in several (2 to 3) family members.  
6 SCN5A variant segregating with the phenotype has been identified in those three families.  
7 The (c.2254G>A) has been previously described as a mutation.<sup>12,13</sup> The two others  
8 (c.2998C>T and c.5417\_5420del) are frameshift or non-sense variant whose one has been  
9 previously described<sup>14</sup>.

10        The main clinical risk factor for complications was familial history of complicated  
11 SCBC (OR = 41 [10; 203];  $P < 0.0001$ ) and younger age (median age  $21 \pm 18$  v  $42 \pm 16$  years;  
12  $P = 0.04$ ). There was a non-significant trend to a higher risk of complications with the use of  
13 ajmaline (11 complications /497 SCBCs for ajmaline vs 0/175 for flecainide;  $P = 0.07$ ).

14        Complications were also associated with a longer P wave ( $114 \pm 16$  vs  $92 \pm 18$  ms;  $P$   
15  $= 0.004$ ) and PR interval ( $192 \pm 27$  ms vs  $162 \pm 28$  ms;  $P = 0.004$ ) at baseline. The terminal S  
16 wave in lead DII ( $65 \pm 25$  ms vs  $32 \pm 23$  ms;  $P < 0.0001$ ), DIII ( $57 \pm 30$  ms vs  $25 \pm 27$  ms;  $P$   
17  $< 0.0001$ ) and the terminal R wave in aVR ( $50 \pm 16$  ms vs  $30 \pm 21$  ms;  $P < 0.0001$ ) duration  
18 were also significantly larger in complicated SCBC.

19        QRS duration during SCBC was not associated with complications ( $133 \pm 21$  ms vs  
20  $134 \pm 35$  ms;  $P = 0.9$ ) (figure 2). However, among the 11 patients with complications, 6  
21 (54%) does not achieve the drug challenge leading to decrease the median dose of sodium  
22 channel blocker to 0.25 (0.2-0.5) mg/kg. Additionally, median QRS enlargement during the  
23 test trend to be higher in the presence of complication ( $133\% \pm 22$  vs  $127\% \pm 31$ ;  $p = 0.06$ ).  
24 Fifty-seven percent of patient with positive tests and 39% of patients with negative tests had a  
25 QRS enlargement higher than 30% in DII lead.

1 ***Clinical Follow-up***

2           After a median follow-up of 106 [54-143] months, 11 patients (73% male; mean age:  
3 38 ± 18 y) experienced life-threatening arrhythmia including 1 SCD, 1 aborted SCD and 9  
4 appropriate shocks. These nine patients who experienced appropriated shock had positive  
5 SCBC.

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## 1 Discussion

2 SCBC is the corner stone of Brs screening as it allows unmasking the diagnostic  
3 Brugada ECG pattern particularly during familial screening. Considering the doubt about  
4 SCBC safety and a low risk of arrhythmia in asymptomatic relatives with undiagnosed  
5 baseline ECG, some argues this familial screening should be restricted<sup>15</sup>. However, diagnosis  
6 in such patients can allow to introduce general lifestyle changes preventing arrhythmia  
7 occurrence and to carry on with the familial screening in descendant, which can present a  
8 higher risk of arrhythmia<sup>16</sup>.

9 Overall, our study demonstrated that SCBC is safe. The complication rate was only  
10 1.6%, confirming the safety of this test when performed in an appropriate environment<sup>8</sup>. We  
11 identified that family history of adverse events during the SCBC represents the stronger risk  
12 factor for the occurrence of arrhythmia during the test. Indeed, 63% of the complications  
13 (7/11) in our study involved 3 out of the 137 families studied. This data suggests that these  
14 families have an increased susceptibility to the occurrence of complications probably due to a  
15 particular genotype. Of note, a *SCN5A* mutation was found in these three families. Those  
16 families presented with segregation of a *SCN5A* variant, whose one has been previously  
17 described as a mutation<sup>12,13</sup> and the two others are frameshift or non sense mutation that may  
18 lead to a decreased Na current and an increased effect of sodium channel blockers<sup>14</sup>.  
19 However, the phenotype we observed has never been described in previous studies of patients  
20 carrying the same mutation.

21 Patients with complications were also younger (median age:  $21 \pm 18$  years). As  
22 recently described by Conte<sup>17</sup>, the risk of complications is increased in children. In our study,  
23 8 patients were under 16 years of age at the time of the SCBC and 3 (37.5%) presented a  
24 complication during the test that is from far higher than in the rest of the population. There is  
25 currently no clear explanation for this increased rate. In children, because of the absence of

1 fibrosis of the his bundle and its branches, there is a good security factor allowing a normal or  
2 subnormal propagation of the cardiac influx even in case of decrease of the sodium current,  
3 such with SCN5A mutation<sup>18</sup>. This may explain the rarity of the Brugada syndrome in  
4 children<sup>19,20</sup>. However, although Brs is relatively rare in children, it appears to be associated  
5 with an increased rate of conduction disturbance at baseline<sup>17,19-21</sup>. Then, SCN5A mutation  
6 are from far more frequent in children with Brs than in adult<sup>20</sup> that confirm the importance of  
7 a decreased sodium current to unmask the Brugada syndrome in children. This suggests that  
8 the presence of conduction abnormalities (even minor) in children is in fact in relation with a  
9 strong decrease of the ability of the cardiac influx to propagate into the conduction tissue. In  
10 this situation, the addition of a sodium cardiac blocker could lead to a dramatic decrease of  
11 the conduction and then to severe complications. This is in line with the fact that, in our study,  
12 conduction disturbance at baseline is associated with complication occurrence. Notably, the  
13 presence of a terminal S wave in DII, DIII and V5 or a terminal R wave in aVR, which can  
14 represent enhanced conduction delay in the right ventricular outflow tract (RVOT)<sup>22</sup>, depict  
15 patients at higher risk of complications during the test.

16 QRS enlargement during the test was previously related to a high risk of  
17 complications<sup>6</sup>. As previously suggested by Batchvarov<sup>7</sup>, our study demonstrates that a  
18 significant number of patients have an enlargement of the QRS over 30% before the end of  
19 the test. In fact, 57% of patient with positive tests had a QRS enlargement higher than 30%  
20 meaning that if we had strictly followed the guidelines, the sensitivity of the test will have  
21 been dramatically decreased while the risk of complications in this situation appears to be  
22 low. Then, our results suggest changing the guidelines, as stopping prematurely the test for  
23 QRS enlargement of more than 30% will lead to an unacceptable number of patients  
24 undiagnosed without significantly decreasing the risk of complications. However, as  
25 demonstrated in several case reports<sup>9,23,24</sup>, management of such QRS enlargement could

1 require specific attention. Indeed, in the complicated group, the QRS enlargement appears to  
2 be faster despite a lower dosage of SCN5A channel blockers. Although we are not able to  
3 identify stopping criteria according to the QRS enlargement kinetic, a fast enlargement during  
4 the test may sensitize the physician about the risk of complication. As a consequence, SCBC  
5 should always be performed in experienced center.

### 7 **ECG criteria to detect patients at high risk of a positive test**

8 We demonstrated that significant S wave in inferolateral leads and terminal R wave in  
9 aVR lead at baseline were associated with a positive response to SCBC. These results confirm  
10 previous study<sup>25</sup> and can help to select patients who need the test to confirm the diagnosis of  
11 BrS. It also provides interesting findings in BrS pathogenesis. The third vector of cardiac  
12 depolarization, generating both such wave exhibits the depolarization of basal myocardium  
13 and in particular, the right ventricular outflow tract (RVOT)<sup>22,26</sup>. Baseline conduction  
14 disturbances, especially axial deviation with prominent S wave in inferior or lateral leads,  
15 highlight the role of conduction delay in the RVOT<sup>27,28</sup>. This was recently emphasized by  
16 Calò who suggests the prognostic value of RVOT conduction delay using S wave in DI lead<sup>22</sup>.  
17 Our results reinforce the importance of conduction disturbance in the RVOT that appear to be  
18 essential both in the diagnosis and prognosis of BS patients.

### 19 Study limitations:

20 This study was a retrospective and multicentric study. Then, SCBC procedures are different  
21 with particular differences in the administration of drugs (continuous intravenous or bolus  
22 injection). However identical diagnostic performances have been demonstrated on suspected  
23 Brugada electrocardiograms<sup>29</sup>.

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1 **Conclusion**

2 We demonstrated that SCBC appears to be safe. The risk of complication is  
3 considerably increased in patients with a familial history of complicated SCBC and in very  
4 young patients. Specific ECG markers should also be used to detect patients at higher risk.  
5 Notably, a fast enlargement during the test may sensitize the physician about the risk of  
6 complication.

7 Although conduction disturbance appears efficient to predict a positive test, QRS  
8 enlargement is not significantly related to complications in our study. It should not be used to  
9 prematurely stop the test unless leading to false negative results. However,

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8  
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22

1 **Tables**

2

3 **Table 1:** description of the population

4 SCBC: sodium channel blocker challenge

5 SCD: sudden cardiac death

	Groups		Total	p value
	Positive SCBC	Negative SCBC		
<b>Total</b>	337 (50%)	335 (50%)	672	
<b>Age (years)</b>	41 +/- 16	36 +/- 17	40 +/- 17	0.004
<b>Sex: male (n (%))</b>	154 (46%)	174 (52%)	328 (49%)	NS
<b>Syncope (n (%))</b>	82 (9%)	18 (2%)	11 (1,6%)	NS
<b>Familial history of SCD (n (%))</b>	142 (42%)	123 (37%)	265 (39%)	NS
<b>number of affected relatives (median)</b>	4	4	4	NS
<b>SCN5A mutation in family (n, %)</b>	93 (79%)	27 (28%)	120 (45%)	<0.001
<b>Molecule used</b>	Ajmaline	272 (81%)	225 (67%)	<0.001
	Flecainide	65 (19%)	110 (33%)	

6

7

1 **Table 2:** ECG parameters according to sodium channel blocker challenge results

2 SCBC+: positive sodium channel blocker challenge

3 SCBC-: negative sodium channel blocker challenge

4

	Baseline			End of the test		
	SCBC + (n=326)	SCBC - (n=328)	p value	SCBC + (n=328)	SCBC - (n=329)	p value
<b>DII (ms)</b>						
<b>QRS</b>	92 ± 19	82 ± 16	< 0.0001	123 ± 24	101 ± 20	< 0.0001
<b>VI (ms)</b>						
<b>P</b>	68 ± 19	62 ± 17	< 0.0001	83 ± 22	72 ± 19	< 0.0001
<b>PQ</b>	156 ± 31	146 ± 27	< 0.0001	201 ± 40	178 ± 35	< 0.0001
<b>QRS</b>	94 ± 17	91 ± 15	0.06	112 ± 26	103 ± 20	< 0.0001
<b>QT peak</b>	299 ± 34	299 ± 34	0.99	317 ± 37	298 ± 36	< 0.0001
<b>QTc</b>	407 ± 39	394 ± 36	< 0.0001	468 ± 51	420 ± 38	< 0.0001
<b>TPE</b>	71 ± 25	68 ± 17	0.0005	90 ± 27	75 ± 22	< 0.0001
<b>S duration (ms)</b>						
<b>DII</b>	35 ± 24	23 ± 21	< 0.0001	58 ± 27	35 ± 24	< 0.0001
<b>DIII</b>	33 ± 28	20 ± 24	< 0.0001	47 ± 36	28 ± 28	< 0.0001
<b>V5</b>	42 ± 19	28 ± 18	< 0.0001	67 ± 21	50 ± 16	< 0.0001
<b>R duration (ms)</b>						
<b>aVR</b>	32 ± 22	25 ± 20	< 0.0001	52 ± 25	35 ± 22	< 0.0001
<b>S amplitude (mV)</b>						
<b>DII</b>	1.72 ± 1.7	1.2 ± 1.5	< 0.0001	3 ± 2.2	2.2 ± 2.8	< 0.0001
<b>DIII</b>	2 ± 2.8	1.3 ± 2.5	< 0.0001	2.5 ± 2.9	1.8 ± 2.6	< 0.0001
<b>V5</b>	3.5 ± 3	2.6 ± 2.9	< 0.0001	7 ± 4.8	5 ± 3.5	0.0003
<b>R amplitude (mV)</b>						
<b>aVR</b>	1.5 ± 2.1	1.1 ± 1.78	< 0.0001	2.4 ± 1.5	1.9 ± 2.6	< 0.0001

5

1 **Figures legend**

2

3 **Figure 1:** Example of a positive SCBC.

4 The test (ajmaline 1mg/kg over 10 min) was performed in an asymptomatic 18 yo woman  
5 after the identification of a symptomatic BrS in her father.

6 Please note the S wave in DII and DIII on baseline ECG and the QRS fragmentation in  
7 precordial leads.

8 Measurement performed in 3 consecutive beats reveal a significant increased in the PR  
9 interval (from 268 ms to 304 ms), the QRS interval (from 81 ms to 143 ms) and the QT  
10 interval (from 381 ms to 420 ms) during the test. All ECG was performed with a 25 mm/s  
11 speed and a 10 mm/mV amplitude. No complication occurred during the test.

12

13 **Figure 2:** Proportion of positive and complicated SCBC according to QRS enlargement

14 Percentage of positive SCBC according to QRS enlargement is represented in blue.

15 Percentage of complicated SCBC according to QRS enlargement is represented in red.

16





