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

Dylan THERASSE[1], MD, Frederic SACHER[2], MD, Bertrand PETIT[3], MD, Dominique BABUTY[4], MD, PhD, Philippe MABO[5], MD, PhD, Raphael MARTINS[5], MD, PhD, Laurence JESEL[6], MD, Philippe MAURY[7], MD, PhD, Jean Luc PASQUIE[8], MD, PhD, Jacques MANSOURATI[9], MD, PhD, Jean Marc DUPUIS[10], MD, Florence KYNDT[1, 11], PharmaD, PhD, Aurélie THOLLET[1], PharmaD, PhD, Beatrice GUYOMARCH[1], Julien BARC[12], PhD, Jean Jacques SCHOTT[1], PhD, Herve LE MAREC[1], MD, PhD, Richard REDON[1], PhD, Vincent PROBST[1], MD, PhD, Jean-Baptiste GOURRAUD[1], MD, PhD.

[1] l'institut du thorax, INSERM, CNRS, UNIV Nantes, CHU Nantes, Nantes, France; [2] CHU Bordeaux, Hôpital cardiologique, Bordeaux, France; [3] CHR La Réunion, Service de Cardiologie, Saint Pierre, France; [4] CHU Tours, Service de cardiologie, Tours, France; [5] CHU Rennes, Service de cardiologie, Rennes, France; [6] CHU Strasbourg, Service de cardiologie, Strasbourg, France; [7] CHU Toulouse, Service de cardiologie, Toulouse, France; [8] CHU Montpellier, Service de cardiologie, Montpellier, France; [9] CHU Brest, Service de cardiologie, Brest, France; [10] CHU Angers, Service de cardiologie, Angers, France; [11] CHU Nantes, Service de Génétique Médicale, Nantes, F-44000 France ; [12] l'institut du thorax, INSERM, CNRS, UNIV Nantes, Nantes, France.

Short title: **S**odium channel blockers test in familial Brugada syndrome

Corresponding author : Jean-baptiste Gourraud, Service de cardiologie, CHU de Nantes, Hôpital Nord Laennec, boulevard Jacques Monod, 44093 Nantes cedex, France; tel: +33-240-165-009; fax: +33-240-165-024 ; e-mail: jeanbaptiste.gourraud@chu-nantes.fr

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ABSTRACT

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

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

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

Results: Among 672 SCBC performed in 137 families, 337(50%) were positive. Multivariate analysis identified ajmaline (OR 2.98 (1.65-4.91), a significant S wave in DII (OR=3.11 (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 positive SCBC (*P* <0.0001). Eleven (1.6%) patients presented complications (10 ventricular arrhythmia, 1 atrial flutter) but no deaths occurred. A familial history of complications (OR = 41 [10; 203]; *P*<0.0001), young age (*P* =0.04) and decreased conduction ECG parameters at baseline (p=0.04) were predictors of complication. QRS enlargement during SCBC was not associated with complications.

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

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

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

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Introduction

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

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

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

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Methods

Study Population and design

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

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

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

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

ECG data

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

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

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

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

Genetic analysis

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

Genomic DNA was extracted from peripheral blood leukocytes using standard protocols. All 28 exons of *SCN5A* were amplified by polymerase chain reaction (PCR) utilizing intronic primers. PCR products were screened for *SCN5A* mutations using denaturing high performance liquid chromatography (dHPLC)-DNA sequencing or High Resolution Melting (HRM). The description of mutations is based on cDNA reference sequence GenBank NM_198056.

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

Statistical Analysis

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

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

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

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

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Results

Population

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

Characteristics of positive SCBC

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

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

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

Complications

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

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

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

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

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Clinical Follow-up

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

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Discussion

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

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

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

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

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

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

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

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

<u>Study limitations:</u>

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

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Conclusion

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

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

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Tables

Table 1: description of the population

SCBC: sodium channel blocker challenge

SCD: sudden cardiac death

		Groups		Total	p value
		Positive SCBC	Negative SCBC		
Total		337 (50%)	335 (50%)	672	
Age (years)		41 +/- 16	36 +/- 17	40 +/- 17	0.004
Sex: male (n (%))		154 (46%)	174 (52%)	328 (49%)	NS
Syncope (n (%))		82 (9%)	18 (2%)	11 (1,6%)	NS
Familial history of SCD (n (%))		142 (42%)	123 (37%)	265 (39%)	NS
number of affected relatives (median)		4	4	4	NS
***SCN5A* mutation in family (n, %)**		93 (79%)	27 (28%)	120 (45%)	<0.001
Molecule used	Ajmaline	272 (81%)	225 (67%)	497 (74%)	<0.001
	Flecainide	65 (19%)	110 (33%)	175 (26%)	

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

SCBC+: positive sodium channel blocker challenge

SCBC-: negative sodium channel blocker challenge

	Baseline			End of the test		
	SCBC + (n=326)	SCBC - (n=328)	p value	SCBC + (n=328)	SCBC - (n=329)	p value
DII (ms)						
QRS	92 ± 19	82 ± 16	< 0.0001	123 ± 24	101 ± 20	< 0.0001
V1 (ms)						
P	68 ± 19	62 ± 17	< 0.0001	83 ± 22	72 ± 19	< 0.0001
PQ	156 ± 31	146 ± 27	< 0.0001	201 ± 40	178 ± 35	< 0.0001
QRS	94 ± 17	91 ± 15	0.06	112 ± 26	103 ± 20	< 0.0001
QT peak	299 ± 34	299 ± 34	0.99	317 ± 37	298 ± 36	< 0.0001
QTc	407 ± 39	394 ± 36	< 0.0001	468 ± 51	420 ± 38	< 0.0001
TPE	71 ± 25	68 ± 17	0.0005	90 ± 27	75 ± 22	< 0.0001
S duration (ms)						
DII	35 ± 24	23 ± 21	< 0.0001	58 ± 27	35 ± 24	< 0.0001
DIII	33 ± 28	20 ± 24	< 0.0001	47 ± 36	28 ± 28	< 0.0001
V5	42 ± 19	28 ± 18	< 0.0001	67 ± 21	50 ± 16	< 0.0001
R duration (ms)						
aVR	32 ± 22	25 ± 20	< 0.0001	52 ± 25	35 ± 22	< 0.0001
S amplitude (mV)						
DII	1.72 ± 1.7	1.2 ±1.5	< 0.0001	3 ± 2.2	2.2 ± 2.8	< 0.0001
DIII	2 ± 2.8	1.3 ± 2.5	< 0.0001	2.5 ± 2.9	1.8 ± 2.6	< 0.0001
V5	3.5 ± 3	2.6 ± 2.9	< 0.0001	7 ± 4.8	5 ± 3.5	0.0003
R amplitude (mV)						
aVR	1.5 ± 2.1	1.1 ± 1.78	< 0.0001	2.4 ± 1.5	1.9 ± 2.6	< 0.0001

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Figures legend

Figure 1: Example of a positive SCBC.

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

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

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

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

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

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

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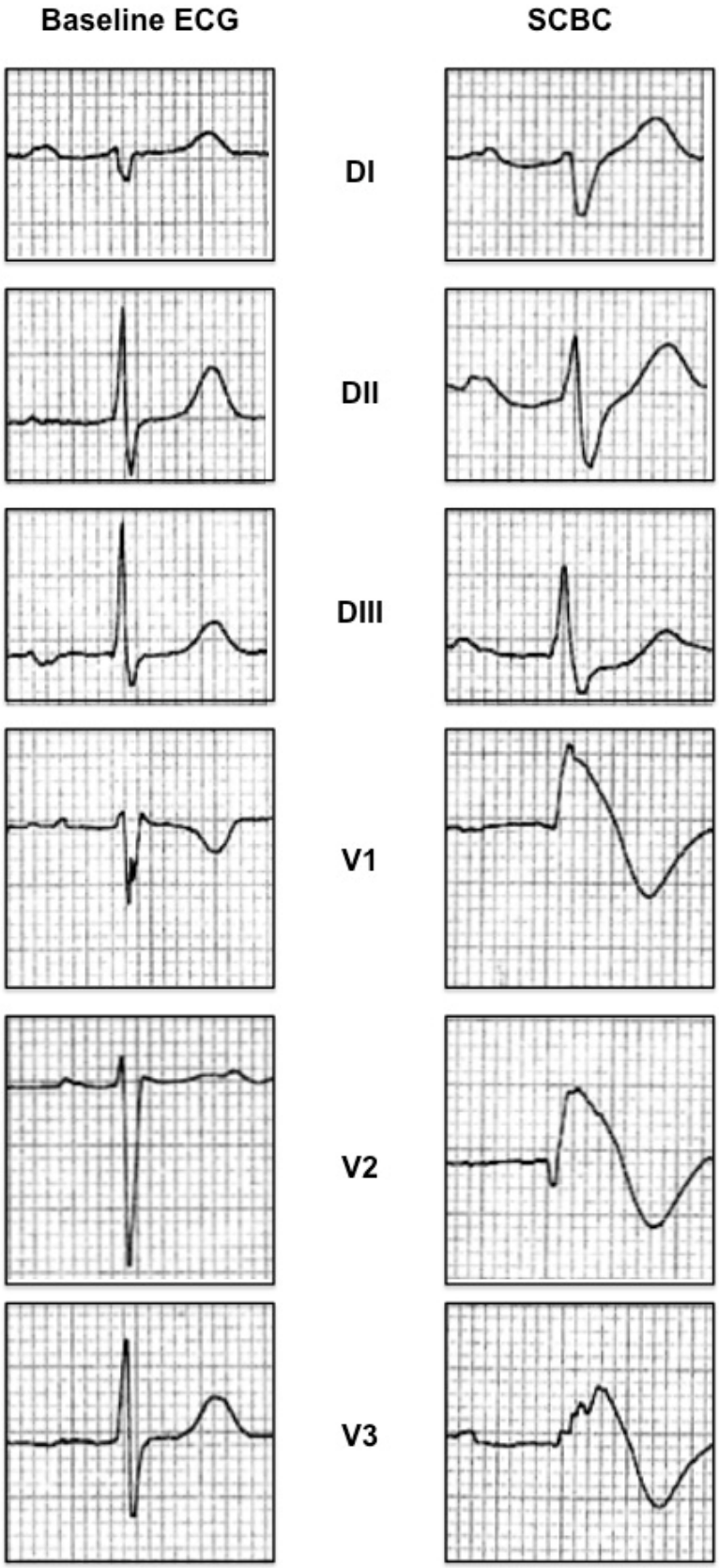

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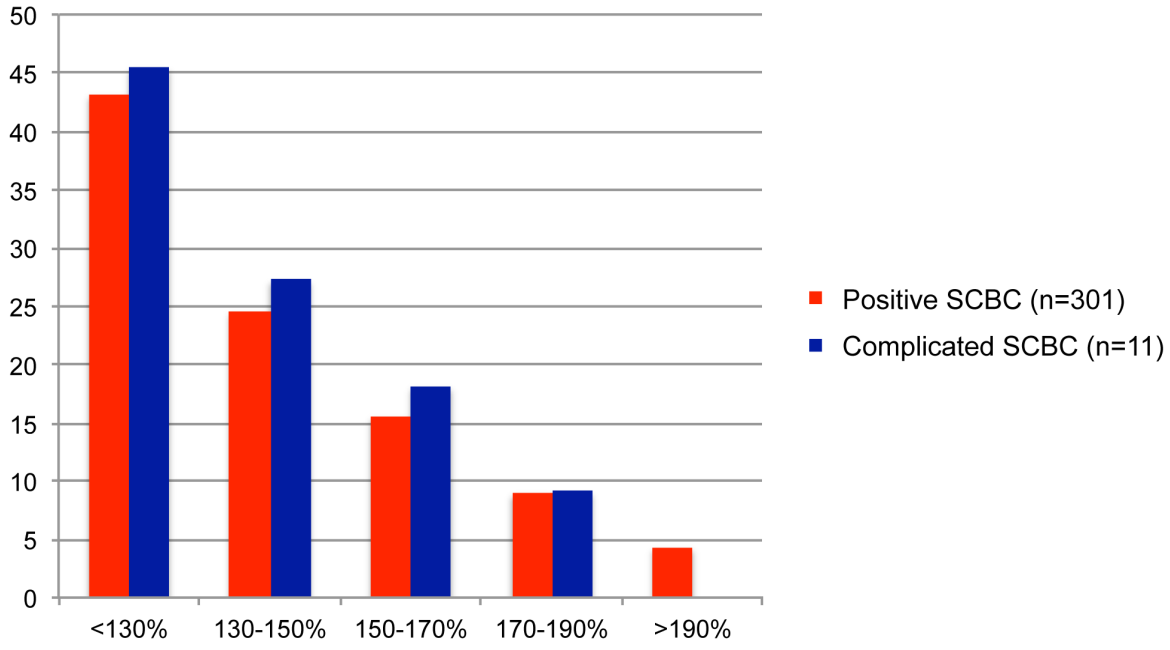

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