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REVIEW

Management of untreatable ventricular arrhythmias during pharmacologic challenges with sodium channel blockers for suspected Brugada syndrome

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Pharmacologic challenge with sodium channel blockers is part of the diagnostic workout in patients with suspected Brugada syndrome. The test is overall considered safe but both ajmaline and flecainide detain well known pro-arrhythmic properties. Moreover, the treatment of patients with life-threatening arrhythmias during these diagnostic procedures is not well defined. Current consensus guidelines suggest to adopt cautious protocols interrupting the sodium channel blockers as soon as any ECG alteration appears. Nevertheless, the risk of life-threatening arrhythmias persists, even adopting a safe and cautious protocol and in absence of major arrhythmic risk factors. The authors revise the main published case studies of sodium channel blockers challenge in adults and in children, and summarize three cases of untreatable ventricular arrhythmias discussing their management. In particular, the role of advanced cardiopulmonary resuscitation with extra-corporeal membrane oxygenation is stressed as it can reveal to be the only reliable lifesaving facility in prolonged cardiac arrest.

Keywords Sodium channel blockers challenge • Brugada syndrome • Life-threatening ventricular arrhythmias • Refractory cardiac arrest • Extra-corporeal membrane oxygenation

Introduction

Brugada syndrome (BS) is characterized by specific ST segment and T wave alterations in right precordial leads positioned in the second, third or fourth intercostal space.[1] However, it is well known that these diagnostic features can be concealed or can fluctuate even to the point of complete normalization.[2,3] This is why pharmacologic challenge with sodium channel blockers is part of the diagnostic workout in patients with non-diagnostic ECG alterations, with history of unexplained syncope, who survived sudden death, or with family history of BS.[1]

From a theoretical point of view, different sodium channel blockers are suitable for the pharmacological challenge, but flecainide and ajmaline are the most widely employed. In fact, other class I drugs, such as procainamide, are traditionally considered to be less potent than flecainide and ajmaline at unmasking a Brugada pattern in the ECG; this differences are attributable to a more rapid dissociation of the drug from the sodium channels resulting in a comparatively minor inhibition of Ina currents.[4–6] In comparison to flecainide, ajmaline presents safety advantages related to its faster binding kinetics and more reliable results[7]; it has also been shown to have a higher sensitivity, probably because it inhibits Ito currents less than flecainide.[8]

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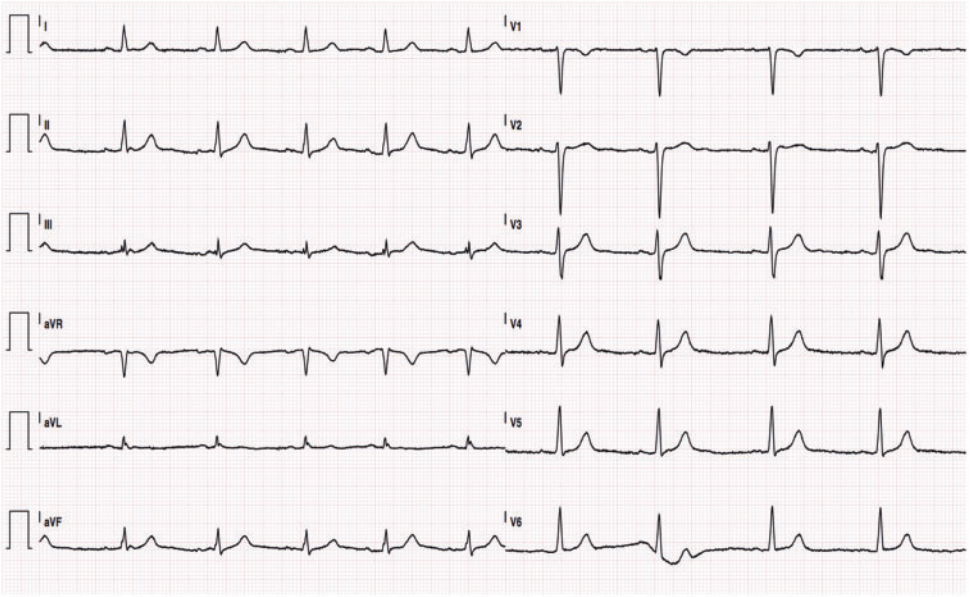

Figure 1 Non-diagnostic ECG at first presentation.

The test is overall considered safe but both ajmaline and flecainide detain well known pro-arrhythmic properties, even in the general population.[6,9] Moreover, the treatment of patients with life-threatening arrhythmias during these challenges is also not well defined.

Case reports and case studies

A few months ago, the authors [presentation of Toniolo M. at Cardiostim EHRA Europace Congress 2016] met the case of a 32-year-old woman who underwent an ajmaline challenge for a suspected BS and non-diagnostic ECG (*Figure 1*); a previous ECG recorded to her 5-year-old daughter had shown a typical coved type ST-segment elevation in the right precordial leads.

The test was conducted according to current best practice[6,10] at the dose of 1 mg/kg at an infusion rate of 10 mg/min with continuous 12-lead ECG and blood pressure monitoring. During the test, just a slight prolongation of the QRS (from 104 to 115 ms) was observed and a Brugada type I pattern progressively emerged (*Figure 2*). At the end of the infusion (50 mg), the patient developed a haemodynamically stable monomorphic ventricular tachycardia (VT) at 130 bpm that was treated with a rapid infusion of 0.2 mg isoproterenol and 150 mEq/L sodium bicarbonate 8.4% (3 ampules) according to previous experiences.[11–16] After this treatment, the QRS became narrower (from 200 to 150 ms), but the VT became more rapid (200 bpm), polymorphic (*Figure 3*), and caused haemodynamic instability and loss of consciousness. An external defibrillation with three direct current (DC) shock at 200 J was then tried but it was ineffective and converted the VT to ventricular fibrillation (VF). Advanced cardiopulmonary resuscitation (CPR) was therefore started according to current guidelines[17] but, after a prolonged resuscitation with 14 DC shocks, VF persisted and evolved in an agonal rhythm with very fine waves. Therefore, the patient was placed on mechanical ventilation; moreover, mechanical chest compression with LUCAS-2™ device (Physio-Control/Jolife AB, Lund, Sweden) was started. The patient was then transferred to our hospital (50 km away) in about 40 min in order to provide advanced haemodynamic support with veno-arterial (VA) extracorporeal membrane oxygenation (ECMO). At the admission to Interventional Catheterization Laboratory, the cardiac rhythm was still a fine wave, agonal, VF. The estimated low flow time was 180 min and haemogasanalysis showed a metabolic acidosis (pH 7.12) with very elevated serum lactates (17 mmol/L). Surgical placement of an ECMO was performed in about 15 min. After 30 min from ECMO placement, a transcutaneous ventricular pacing was effective and in further 35 min the recovery of spontaneous sinus rhythm with narrow QRS was witnessed (all the rhythm's sequence is represented in *Figure 4*). The clinical conditions improved dramatically in a few days: on hospital day 4, ECMO was removed. The patient was extubated on hospital day 5 and presented completely normal cerebral function (CPC 1)[18] after discontinuation of sedatives. To the best of our knowledge, there is only another published report of survival from cardiac arrest without neurological sequels after a comparable time to the return of spontaneous circulation; in that case, the cardiac arrest was secondary to ischaemia during a myocardial infarction.[19]

A cardiac magnetic resonance (CMR) could not demonstrate any structural cardiac diseases and excluded out-of-range ventricular dimensions,[20] whereas the ECG progressively evolved showing a spontaneous Brugada type I pattern. Genetic testing was carried out

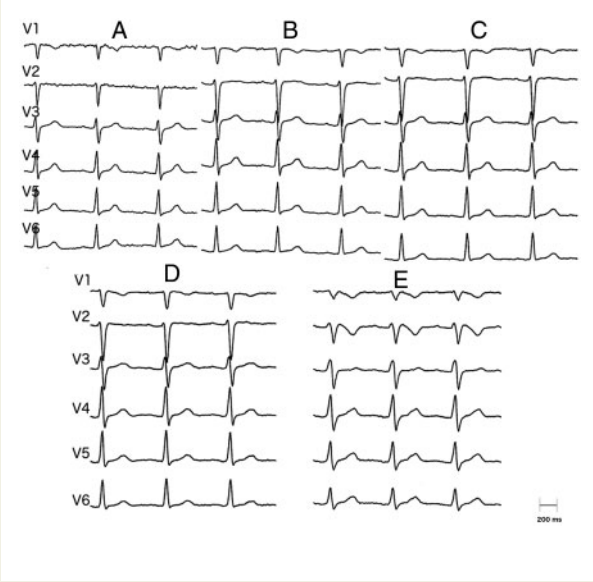

Figure 2 (*A*) ECG at 1 min, after the first bolus of ajmaline. (*B*) ECG at 2 min, after the second bolus of ajmaline. (*C*) ECG at 3 min, after the third bolus of ajmaline. (*D*) ECG at 4 min, after the fourth bolus of ajmaline, showing a slight, though not significative, prolongation of the QRS. (*E*) ECG at 5 min, after the last infusion of ajmaline, showing significative QRS prolongation and emergence of Brugada type 1 pattern.

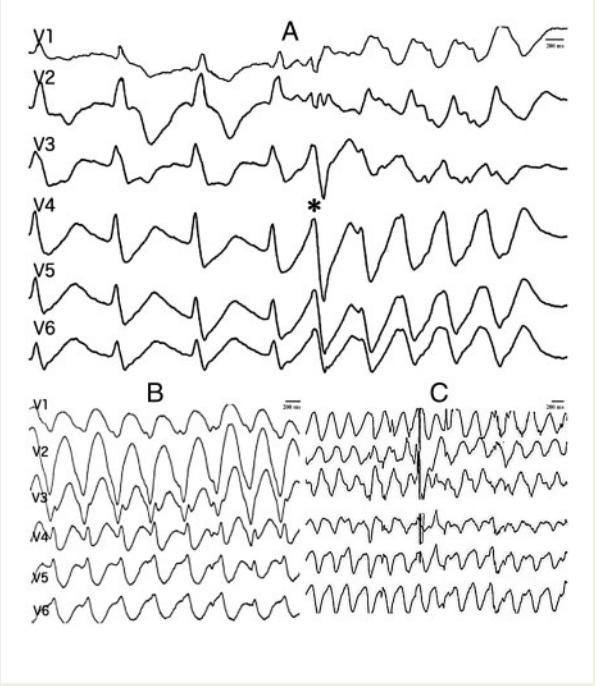

Figure 3 (*A*) ECG showing ventricular tachycardia induction by a premature ventricular contraction (*). (*B*) ECG showing monomorphic ventricular tachycardia (130 bpm) before the infusion of isoproterenol. (*C*) ECG after the infusion of isoproterenol showing a more rapid (200 bpm) ventricular tachycardia with a narrower QRS.

with a custom NGS panel (Ion Torrent – Thermofisher) followed by Sanger double strand sequencing for confirmation. A single nucleotide transition leading to a mis-sense mutation in the SCN5A gene (n.3080G > A—p.R1027Q) was identified. This variant was previously reported and showed to impair the sodium current inactivation process.[21] An additional intronic single nucleotide (n.483-18 C > G) with possible but not certain effect on the splicing of SCN5A based on bioinformatics analysis (http://www.fruitfly.org/seq_tools/splice.html) was identified; this latter variant mutation was present also in the daughter, who has a BS phenotype, thus supporting its pathophysiologic role. For these reasons, our index case could harbor a compound heterozygote SCN5A mutation.

Scarce and contrasting data are available in current literature on the incidence of major arrhythmias during pharmacologic challenge with sodium channel blockers: a review of existing reports on ajmaline and flecainide challenges are presented in *Table 1*; one of the largest registries available is that of Conte *et al.*[27] which counts 1043 patients from 1992 to 2013: just 9 out of 503 patients with positive ajmaline challenge (1.8%) presented sustained ventricular arrhythmias (6 VF, 3 haemodynamically instable VT) but they tended to be partially refractory to defibrillation/cardioversion (mean 2.3 DC shocks per patient). Only 1 patient experienced an ECMO placement for refractory cardiac arrest. Data from another large registry[7] reported an even lower prevalence (0.3%) of major arrhythmias; however, in this registry, very strict safety measures were adopted, with 2.4% of tests stopped for QRS widening or premature ventricular complexes (PVCs) and the protocol was slightly less aggressive (1 mg/kg in 5–10 min instead of in 5 min). Similarly, in the registry of Postema *et al.*[24] there were no reported cases of tachyarrhythmias while there was only one case of sinus arrest out of 269 patients tested; the protocol adopted was cautious (10 mg/min up to 1 mg/kg stopping if Brugada type I developed, if there was a QRS widening to ≥140% of basal duration or if arrhythmias occurred); lastly, also the report of Zorzi *et al.*[26] did not document arrhythmic events. Conversely, other groups[22,32,33] had previously reported a higher incidence (from 6.2 to 18%) of major arrhythmias during sodium channel blockers challenge, but this was probably due to the presence of baseline spontaneous Brugada pattern type I ECG in most of the patients enrolled. In 2[32,33] out of 3 of these studies, the drug used was pilsicainide.

In literature, there is also another published case of flecainide challenge in a 16-year-old woman complicated by refractory cardiac arrest (RCA) which needed ECMO placement, but in that case, cardiac CMR and genetic tests revealed the presence of an underlying arrhythmogenic right ventricular cardiomyopathy.[34] The three reported cases of ECMO placement for RCA after sodium channel blockers administration are reported in *Table 2*. Moreover, in literature there are now at least four published case reports demonstrating the successful use of ECMO as salvage therapy following severe flecainide intoxication.[35–38]

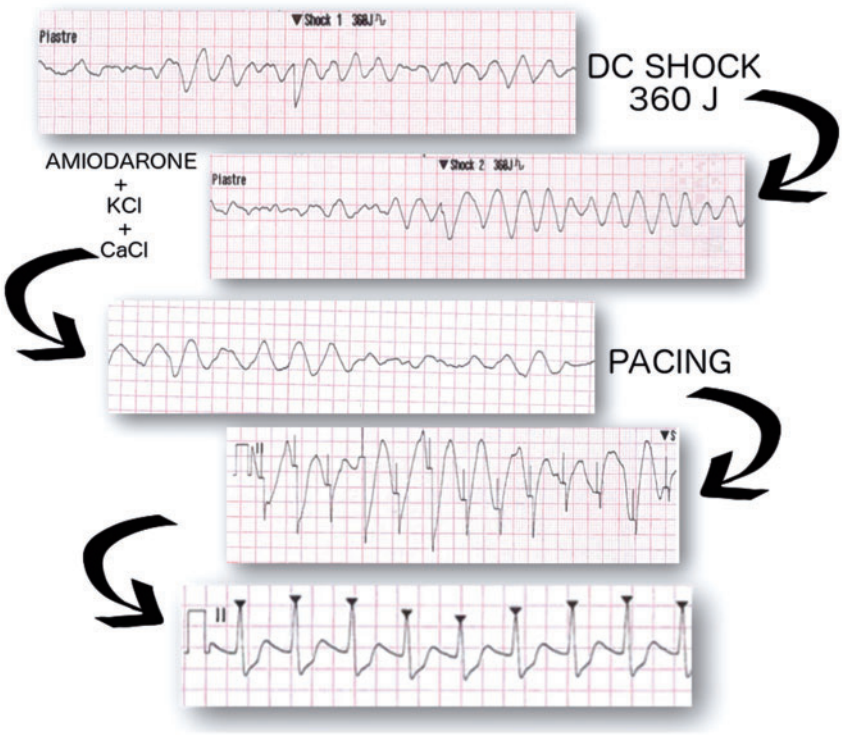

Figure 4 ECG evolution during advanced cardiopulmonary life support after the placement of ECMO. The rhythm evolved from a fine wave fibrillation to a coarse wave fibrillation after 2 DC 360 J shocks. After infusion of amiodarone, potassium chloride and calcium chloride, it became more organized allowing an external pacing to be effective. At last, a spontaneous rhythm occurred.

Risk factors for ventricular arrhythmias

The 2005 consensus conference[39] suggested to adopt cautious protocols interrupting the sodium channel blocker test as soon as Brugada pattern type I emerges, QRS broadens to ≥130% of baseline or frequent PVCs appear. However, this strategy could determine a certain percentage of false negative results, so it was proposed to interrupt the test when the QRS broadens to ≥150% in patients without baseline intraventricular conduction anomalies and when the QRS broadens to ≥125% in patients with baseline intraventricular conduction prolongation.[23] Furthermore, wider than normal basal QRS was associated to major arrhythmias during ajmaline challenge, especially if associated with a positive test (emergence of Brugada type I pattern).[27]

The 2013 expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes[1] and the 2015 guidelines for the management of patients with ventricular arrhythmias[40] explicitly suggest to monitor the patient with right precordial leads positioned also in the upper intercostal spaces (third and second), as it is normal practice for baseline-ECG identification of Brugada Type I. In fact, it was confirmed[25,41,42] that high-positioned right precordial leads are more sensitive in identifying Brugada Type-I during the pharmacologic challenge, with a trend towards a minor dose of ajmaline administrated in case of presence of Brugada Type-I in the high-positioned right precordial leads.[25] However, this practice could result in an overdiagnosis of BS, particularly in patients displaying a Brugada Type-I only after a drug challenge.[43,44] Data suggest the latter population is at very low risk and that the presumed false-positive rate of pharmacologic challenge is not trivial.[45] In addition, Miyamoto *et al.*[46] could not demonstrate the occurrence of cardiac events in the follow-up of patients with a positive class I drugs challenge with both normal and high-positioned right precordial leads. However, it is the authors' opinion that the systematic use of high-positioned right precordial leads should be registered for safety reasons during every sodium channel blockers challenge; in fact, in the case index, it is not possible to rule out that the test would have been interrupted earlier, avoiding the subsequent cardiac complications, if high-positioned right precordial leads had been registered.

Other possible risk factors for ventricular arrhythmias are an history of sinus node dysfunction or atrioventricular conduction disturbances.[14,27] The latter have been reported in association with specific mutations of sodium channels, with increased sensitivity to sodium channels blockers and higher risk of ventricular arrhythmias during ajmaline test.[14] As known, patients harboring SCN5A mutations can be particularly prone to the slowing of intraventricular and atrioventricular conduction[47]; therefore it is advisable to take into account the genetic findings whenever available and to adapt the

Table 1 Published series of ajmaline and flecainide testing for suspected Brugada syndrome

Investigator	Number of patients	Age (years)	Males	Brugada ECG Type 1	Brugada ECG Type 2	Ajmaline	Flecainide	Number of symptomatic patients	Syncope/ pre-syncope	Aborted sudden death	Familial SCD	Positive test	Complications
Rolf *et al.* 2003[6]	158	42 (11–89)	NA	0	5	158 (100%)	0 (0%)	119	95	21	56	37 (23%)	2 sustained ventricular Tachycardia (1 53 year old female; 1 40 year old male)
Gasparini *et al.* 2003[22]	22	34 (15–63)	19 (86%)	19	NA	0 (0%)	21 (95%)	10	8	2	8	21 (95%)	2 sustained ve ntricular Tachycardia (gender and age not specified)
Hong *et al.* 2004[3]	71	NA	NA	24	NA	71 (100%)	0 (0%)	NA	NA	NA	NA	30 (42%)	None reported
Wolpert *et al.* 2005[8]	22	NA	NA	15	NA	22 (100%)	22 (100%)	11	11	NA	NA	22 (100%)	1 Urticaria 3 isolated premature ventricular beats (gender and age not specified)
Batchvarov *et al.* 2009[23]	148	36 ± 15	92 (62%)	0	NA	148 (100%)	0 (0%)	NA	24	19	46	30 (20%)	3 short runs of ventricular Tachycardia (1 50 year old male, 1 57 year old male, 1 40 year old female)
Veltmann *et al.* 2009[7]	677	42.5 ± 16 (6–83)	393 (58%)	0	110	677 (100%)	0 (0%)	246	196	12	25	262 (39%)	8 isolated premature ventricular beats (gender and age not specified) 1 atrial fibrillation (female) 1 short non-sustained ventricular Tachycardia (gender and age not specified) 1 rapid polymorphic non-sustained Ventricular Tachycardia (35 year old male) 1 ventricular fibrillation with recovery after single DC shock (61 year old male)
Postema *et al.* 2010[24]	269	42 ± 14	149 (55%)	0	NA	269 (100%)	0 (0%)	60	47	13	135	91 (34%)	1 sinus arrest (gender and age not specified)
Govindan et al 2010[25]	183	36 ± 14	112 (61%)	0	NA	183 (100%)	0 (0%)	NA	26	18	83	31 (16%)	None reported
Zorzi *et al.* 2012[26]	153	42 ± 14	128 (83%)	0	91	79 (52%)	74 (48%)	41	36	5	36	76 (50%)	None
Conte *et al.* 2013[27]	1043	40.7[a]	292 (28%)[a]	0[a]	66[a]	1043 (100%)	0 (0%)	232[a]	130[a]	18[a]	240[a]	503 (48%)	6 ventricular fibrillation (one with recovery after more than 10 shocks and ECMO implantation)-5 females; mean age 26 and 1 29 year old male 3 sustained ventricular Tachycardia (with necessity of DC shock)—3 males; mean age 27

Continued

Table 1 *Continued*

Investigator	Number of patients	Age (years)	Males	Brugada ECG Type 1	Brugada ECG Type 2	Ajmaline	Flecainide	Number of symptomatic patients	Syncope/ pre-syncope	Aborted sudden death	Familial SCD	Positive test	Complications
McMillan *et al.* 2014[28]	95	12.5 ± 3.3 (5–18)	54 (56%)	0	0	95 (100%)	0 (0%)	9	5	0	39	19 (20%)	None
Gandjbakhch *et al.* 2014[14]	3	50.3 ± 14.6 (34–62)	2 (66%)	0	1	3 (100%)	0 (0%)	1	1	0	0	1 (33%)	3 syncopal polymorphic ventricular Tachycardia after widening of QRS (2 males; 1 female)
Conte *et al.* 2014[29]	169	<12	24 (60%)[a]	0[a]	3[a]	169 (100%)	0 (0%)	10[a]	8[a]	2[a]	24[a]	40 (24%)	3 ventricular fibrillation with recovery after DC shock (gender and age not specified) 1 polymorphic ventricular Tachycardia terminated by a high dose of isoproterenol infusion (7 year old male)
Wong *et al.* 2014[30]	2	10.5	1 (50%)	0	NA	2 (100%)	0 (0%)	NA	NA	NA	2	2 (100%)	None reported
Andorin *et al.* 2016[31]	70	13.7	NA	0	NA	42 (60%)	27 (39%)	7	NA	NA	NA	70 (100%)	2 non-sustained ventricular Tachycardia (16 and 17 year old, gender not available)

SCD, sudden cardiac death.
[a]Data are available only for the population with positive provocative test.

Table 2 Characteristics of patients who experienced ECMO implantation for untreatable ventricular arrhythmias after sodium channel blockers challenge: all patients were young females

Author	Age	Sex	Drug (mg)	Previous symptoms	Life-threatening arrhythmia	Numbers of DC shock before ECMO implantation	Death or neurological damages	SCN5A mutation	Diagnosis
Conte *et al.* 2013[27]	24	Female	Ajmaline (no reported dose)	Syncope	Ventricular fibrillation	>10	No	No	Brugada syndrome
Corrado *et al.* 2016[34]	16	Female	Flecainide (50 mg)	NA	Atrioventricular block and ventricular fibrillation	NA	No	No	ARVC with Brugada ECG pattern
Poli *et al.*	32	Female	Ajmaline (50 mg)	None	Ventricular tachicardia and ventricular fibrillation	20	No	Yes	Brugada syndrome

ARVC, arrhythmogenic right ventricular cardiomyopathy.

administration protocols with a slower injection rate. The R1027Q variant, present in our index case, was identified several years ago by comparison of the available cardiac sodium channels human clones derived from heart tissue (and used for functional assessment of mutants) with the human sequence derived from the genome project. It was then found to be a very rare variant in the population (frequency 0.005% in the population according to the ExAc genome aggregator database—http://exac.broadinstitute.org/gene/ENSG00000183873). The presence of a glutamine (Q) in position 1027 is associated with a negative shift of steady state inactivation and a significantly slower channel recovery[21], leading to a loss of function phenotype as compared with the most widely expressed (wild type) sodium channel variant. It is still presently not known if this variant is associated with a greater risk of arrhythmia compared with other variants.

The patient described in the index case, presented a normal QRS at baseline and just slight QRS widening at the end of the test, with the simultaneous appearance of Brugada type I pattern. In addition, she had no history of abnormalities of sinus node or atrioventricular junction. These aspects confirm the intrinsic presence of a not negligible risk connected with sodium channel blockers, even adopting a safe and cautious protocol in patients without known risk factors.

In BS, male sex has been found to confer a higher arrhythmic risk.[48] In spite of it, we find it interesting to note that ECMO, in all the reported cases, was exclusively used in females.

Benito *et al.*[49] found that women showed more conduction disturbances and longer QTc interval in response to sodium channel blockers than men. For these electrocardiographic characteristics, even if men display a greater risk profile at baseline, women could have a higher arrhythmic risk in response to sodium-blockers. In line with this hypothesis, Sieira *et al.*[50] described a high proportion (1.9%) of sustained ventricular arrhythmias in a cohort of 210 women submitted to the drug challenge test but they did not give the same datum for males. Moreover, 3 out of 4 reported cases of ECMO use in flecainide intoxication,[35,37,38] were females. However, it is the authors' opinion that with only a few reported cases in the literature, this hypothesis must be taken with caution. In fact, neither Batcharov *et al.*[23] in a cohort of 148 patients, nor Conte *et al.*[27] in a cohort of 1043 patients, could find significant differences between men and women in the incidence of all ventricular arrhythmias during pharmacologic challenge in their case series.

Treatment of life-threatenig ventricular arrhythmias

The optimal treatment of life-threatening ventricular arrhythmias refractory to multiples DC shock is not clearly established. It seems logical that the first approach should be pharmacologic. The use of oral quinidine or intravenous isoproterenol in patients with BS to treat electrical storms is supported by literature.[11–13,51] Quinidine, a class IA antiarrhythmic exerts its beneficial effects in BS by inhibiting the Ito outward current, thereby restoring electrical homogeneity; in addition, it prolongs ventricular refractoriness.[52,53] Conversely isoproterenol, stimulating beta-adrenoceptors, and augmenting Ica, reduces ST segment elevation in patients with BS.[54] Isoproterenol was effective in suppressing VF in a 36-year-old male with BS[12] and subsequently determined the disappearance of the short-coupled PVCs, which are the triggers of VF. The efficacy of isoproterenol was also confirmed in a case series of Watanabe *et al.*,[13] in which ventricular arrhythmias were successfully abolished after the infusion of isoproterenol in 6 patients with BS. However, the role of both quinidine and isoproterenol to treat iatrogenic VT in suspected BS is not clear and has not been previously described. Moreover, quinidine is often not available in Emergency Departments and Intensive Care Units due to supply shortages in the market.[55] Sodium bicarbonate is an appropriate treatment of sodium channel blockers-induced cardiotoxicity[56] and its indications are cardiac arrest, widening of QRS complex and hypotension refractory to intravenous fluid therapy.[57] After administration of sodium bicarbonate as an antidote, the QRS duration narrows with possible normalization of the ECG. The efficacy of sodium bicarbonate is supported by animal studies and human cases both in adults and in children.[14–16,56,58] The effect is likely mediated by systemic alkalaemia and provision of sodium ions to myocardial fast-acting sodium channels. Magnesium is usually the drug of choice to treat torsade de pointes[40] but not to treat VT induced by sodium channel blockers. A case report describing its use in flecainide-toxicity has been published[59], but available data do not support this indication. Anyway, survival and complete recovery of patients with cardiac arrest and very prolonged time to return of spontaneous circulation seem to be rare. On the other hand, recent advances in resuscitative medicine have provided interesting tools to promote survival in the appropriate setting. ECMO is an option of treatment for refractory cardiogenic shock or cardiac arrest in patients with reversible underlying pathology.[60] Acute poisoning represents an indication for ECMO because restoring circulation allows for intrinsic drug metabolism and elimination.[61] This strategy is limited to a restricted number of centres with capabilities to implant ECMO and manage patients on this support. As an additional therapy to traditional advanced CPR management, ECMO has improved outcomes in terms of survival to hospital discharge and outcomes at 1 year.[62] The authors' opinion is that sodium channel blockers challenge should be performed under close supervision in an appropriate environment with all advanced CPR facilities available, ideally including the possibility of performing a VA ECMO in case of untreatable ventricular arrhythmias.

Safety of sodium channel-blockers challenge in children

Concerning the role of ajmaline challenge in children, data on safety are quite conflicting: Mc Millan *et al.*[28] could not demonstrate the occurrence of ventricular arrhythmias in 98 children with a positive test in 20% of the individuals. On the other hand, Conte *et al.*[29] reported their experience of 40 positive ajmaline challenges in children younger than 12 years, where 10% of tests were complicated by arrhythmias. In their survey, ajmaline-induced sustained ventricular arrhythmias were observed more frequently in children compared with older patients (10% vs. 1.3%). However, BS seems to have a benign behaviour in children and it is likely characterized by an age-dependent penetrance too. The use of pharmacologic challenges at a young age appears to be questionable, because of the low risk of life-threatening arrhythmias in patients without a spontaneous type I

ECG pattern.[30] It must also be considered that the management of young patients is further made difficult by a different benefit-risk ratio of implantable device: in this subgroup, positioning an Implantable Cardioverter Defibrillator (ICD) has a higher risk of inappropriate shocks and infections, not considering the higher probability of catheter dislocation related to body growth.[63]

On this topic, Andorin *et al.*[31] have recently published a proposal of evidence based management of children with a suspected BS, in which genetic tests play a crucial role in the decision for or against the implantation of an ICD, regardless of pharmacologic challenges.

Conclusions

This review supports the evidence that sodium channel blockers challenge in suspected BS can have major, though rare, complications and should always be carried out in a safe and monitored environment, strictly adhering to protocols. Moreover, the possible occurrence of a cardiac arrest refractory to ordinary CPR maneuvers should be kept in mind, especially when dealing with young patients; however, in these circumstances the clinical outcome after a prolonged cardiac arrest seems to be excellent. Therefore, the availability of advanced CPR techniques should always be checked. The creation of an international registry of untreatable ventricular arrhythmias during sodium channel blockers challenge would be desirable in order to describe their actual epidemiology and to improve their management.

Conflict of interest: none declared.

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