Updating aspects of pharmacological tests with class I drugs in Brugada syndrome

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Brugada syndrome (BrS) is a clinical-inherited autosomal dominant familial/hereditary (»37%) or sporadic (»63% of cases) with incomplete penetrance, arrhythmogenic-electrocardiographic channelopathy associated with an increased risk for dizziness, agonal respiration, syncope or resuscitated sudden cardiac death (SCD) / sudden cardiac arrest (SCA) consequence of developing malignant polymorphic ventricular tachyarrhythmia (PVT) / ventricular fibrillation (VF) precipitated by vagotonia often occurring during sleep or at rest especially after a large meal or in the presence of fever as trigger, mainly in children with male predominance in apparently healthy adults, in their third to fourth decade of life, less frequently in children or in the elderly, with minor structural abnormalities in the right ventricular outflow tract (RVOT) (**Gray et al 2018**) and whose obligatory electrocardiographic pattern for the diagnosis is the so-called type 1 ECG Brugada pattern, Brugada sign (**Tomcsanyi, Arabadzisz, & Tomcsanyi, 2018**) or coved-type ST segment elevation characterized by rSr' or rSR' pattern, J-point and ST segment elevation ≥ 2 mm convex to the top or rectilinear oblique descendent followed by negative symmetric T wave in at least one right precordial lead (≥1 right precordial lead) positioned in the second2nd, third3rd, or4th intercostal space (ICS) (**Priori, Wilde, Horie, Cho, Behr, Berul, Blom, Brugada, Chiang, Huikuri, Kannankeril, Krahn, Leenhardt, Moss, Schwartz, Shimizu, Tomaselli, & Tracy, 2013**), spontaneously or unmasked by class Ia sodium channel blockers (i.e. ajmaline and pilsicainide, procainamide, disopyramide, or propafenone have been used for the drug challenge test in BrS). Table 1(**Priori et al., 2015**).
12-lead surface ECG has represented the primary source of information for diagnosis and prognosis, but the specificity and accuracy (Brugada phenocopies) of the abnormal ECG pattern are relatively low (**Antzelevitch et al., 2016**).
Day-by-day fluctuations are frequent in the ECG pattern may occur in the same patient, including a concealed Brugada ECG (normal pattern) (**Richter et al., 2009**).
Serial ECGs can assist with risk stratification based on the fraction of ECGs that display a spontaneous type 1 Brugada ECG pattern (**Castro Hevia et al., 2019**).
The table 1 shows the Sodium channel blockers used for the drug challenge test in Brugada syndrome.

Table 1

Drug	Doses and administration
Ajmaline Class 1a	≤1mg/kg IV over 5 min. False-positive responses is possible with >1mg/kg. (**Sung AY 2019***)
Flecainide Class/Subclass 1c	2mg/kg IV over 10min
Flecainide Class/Subclass 1c	Oral at single dose of 400 mg(**Dubner et al., 2013**)
Pilsicainide Class/Subclass 1c	1mg/IV over 10 min
Procainamide Class /Subclass 1c	10mg/kg IV over 10 min

*(**Sun AY.Drug Provocation Testing in Brugada Syndrome: A Test of Uncertain Significance. JACC Clin Electrophysiol. 2019 Apr;5(4):513-515. doi: 10.1016/j.jacep.2019.03.00**)

The outcome of the sodium-channel blocker challenge was significantly affected by the drug used, with ajmaline more likely to provoke a type 1Brugada electrocardiographic pattern compared with procainamide.
Patients undergoing the sodium-channel blocker challenge may have contrasting results depending on the drug used, with potential clinical, psychosocial, and socioeconomic implications.(**Cheung CC, Mellor G, Deyell MW, Ensam B, Batchvarov V, Papadakis M, Roberts JD, Leather R, Sanatani S, Healey JS, Chauhan VS, Birnie DH, Champagne J9, Angaran P, Klein GJ, Yee R, Simpson CS, Talajic M, Gardner M, Yeung-Lai-Wah JA, Chakrabarti S, Laksman ZW, Sharma S, Behr ER, Krahn AD. Comparison of Ajmaline and Procainamide Provocation Tests in the Diagnosis of Brugada Syndrome. JACC Clin Electrophysiol. 2019 Apr;5(4):504-512. doi: 10.1016/j.jacep.2019.01.026**).

Additionally. a positive ajmaline response was observed in a large proportion of unexplained cardiac arrest (UCA) or sudden unexplained death (SUD). families.
Ajmaline has potential for confounding possibly false-positive responses in this population, particularly at high doses, which could possibly lead to a misdiagnosis.
Clinicians should consider all alternative causes in UCA/SUD and avoid ajmaline doses >1 mg/kg. Ajmaline provocation testing appears to be safe and feasible in the pediatric population when performed in an appropriate setting by an experienced team.
A positive response is more common in patients with a family history of BrS in a first-degree relative, and there may be an age-related penetrance to the test. (**McMillan MR, Day TG, Bartsota M, Mead-Regan S, Bryant R, Mangat J, Abrams D, Lowe M, Kaski JP. Feasibility and outcomes of ajmaline provocation testing for Brugada syndrome in children in a specialist paediatric inherited cardiovascular diseases centre. Open Heart. 2014 Feb 12;1(1):e000023. doi: 10.1136/openhrt-2013-000023**).
Ajmaline challenge to rule out the presence of BrS should be considered prior to propafenone “Pill-in-the-pocket” (PIP) treatment with type IC drugs for cardioversion of recent-onset AF. PIP therapy in AF patients who are identified to have SCN5A R1193Q polymorphism. (**Li L, Ruan Y, Liu N, Zhao Q, Zhang M, Li X, Zuo S, Le J, Wu K, Bai R, Ma C."Pill-in-the-Pocket" Treatment of Propafenone Unmasks ECG Brugada Pattern in an Atrial Fibrillation Patient With a Common SCN5A R1193Q Polymorphism. Front Physiol. 2019 Mar 29;10:353. doi: 10.3389/fphys.2019.00353**)

Class 1 Antiarrhythmic Drugs classification (Lei M, Wu L, Terrar DA, Huang CL. Modernized Classification of Cardiac Antiarrhythmic Drugs. Circulation. 2018 Oct 23;138(17):1879-1896. doi: 10.1161/CIRCULATIONAHA.118.035455.)

I.**Class: Ia; Subclass:**
Nav1.5 open state; intermediate (τ≈1–10 seconds) dissociation kinetics; often concomitant K+ channel block;
Pharmacological Target:
Reduction in peak INa, AP generation, and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant IK block increasing APD and ERP; increase in QT intervals16–23;
Electrophysiological effects:
Reduction in peak INa, AP generation, and (dV/dt) max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; concomitant IK block increasing APD and ERP; increase in QT intervals16–23;
Examples of drug:
Quinidine, Ajmaline and Disopyramide;
Major Clinical Applications:
Supraventricular tachyarrhythmias, particularly recurrent AF; VT, VF (including SQTS and BrS). for the drug challenge test in BrS (Ajmaline) and treatment (Quinidine);

II.**Class:1; Subclass:**1b;
Pharmacological Target:
Nav1.5 open state; rapid dissociation (τ≈0.1–1 second); INa; window current;
Electrophysiological effects:
Reduction in peak INa, AP generation and (dV/dt)max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; shortening of APD and ERP in normal ventricular and Purkinje myocytes; prolongation of ERP and post repolarization refractoriness with reduced window current in ischemic, partially depolarized cells Relatively little electrocardiographic effect; slight QTc shortening (.**Gillis A, Singh B, Smith T, Cain M, Kadish A, Weiberg K, Goldberger J. Pharmacologic therapy. In: Zipes D, Jalife JJ, ed. Cardiac Electrophysiology: From Cell to Bedside. 4th ed. Saunders; 2004:911–965**);
Examples of drug:
Lidocaine, mexiletine;
Major Clinical Applications:
Ventricular tachyarrhythmias (ventricular tachycardia, ventricular fibrillation), particularly after myocardial infarction **National Institue of Health Care Excellence. Arrhythmias. 2014.https://bnf.nice.org.uk/treatment-summary/arrhythmias.html. Accessed September 21, 2018**.) (**Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Hlatky MA, Granger CB, Hammill SC, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [published online October 30, 2017]. Circulation. doi: 10.1161/CIR.0000000000000548 https://www.ahajournals.org/ doi/10.1161/CIR.0000000000000548?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed**)

III.**Class: I; Subclass: Ic;**
Pharmacological Target:
Nav1.5 open state; rapid dissociation (τ≈0.1–1 second); INa; window current;
Electrophysiological effects:
Reduction in peak INa, AP generation and (dV/dt) max with increased excitation threshold; slowing of AP conduction in atria, ventricles, and specialized ventricular conduction pathways; reduced overall excitability; prolongation of APD at high heart rates; increase in QRS duration (**Salvage SC, Chandrasekharan KH, Jeevaratnam K, Dulhunty AF, Thompson AJ, Jackson AP, Huang CL. Multiple targets for flecainide action: implications for cardiac arrhythmogenesis. Br J Pharmacol. 2018;175:1260– 1278. doi: 10.1111/bph.13807**);
Examples of drug:
Propafenone, flecainide andPilsicainide.
Major Clinical Applications:
Supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter, AF, and tachycardias involving accessory pathways) VTs resistant to other treatment in the absence of structural heart disease, premature ventricular contraction (PVC), catecholaminergic polymorphic ventricular tachycardia (CPVT). (**Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA 3rd, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM; Evidence Review Committee Chair‡. 2015 ACC/AHA/HRS guideline for the management of adult patients with supraventricular tachycardia: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society.Circulation. 2016;133:e506–e574. doi: 10.1161/CIR.0000000000000311**).