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How much do we need to provoke? Challenges and opportunities in refining the pharmacological tests to unmask Brugada syndrome

Sudden cardiac death(SCD) is a particularly traumatic event especially when it strikes healthy young individuals. SCD is a common outcome in many structural heart diseases and ischemic heart diseases. 5–15% of SCD victims fail to demonstrate any structural heart problems in autopsy [1–3]. The term idiopathic ventricular fibrillation(IVF) had been first used in 1997 in an attempt to standardize the clinical evaluation and management of survivors of out of hospital cardiac arrest with structurally normal heart [4]. The past 2 decades have witnessed an increasing understanding of genetic channelopathies among this cohort of IVF. However, incomplete penetrance and variable levels of expressions of the genetic mutations made the distinctive electrocardiologic patterns of these disorders concealed many a times [5].

Brugada Syndrome(BrS) is an arrhythmogenic channelopathy characterized by a loss of function mutations affecting the sodium(Na) Channels or rarely a gain of function affecting the I_{to} type of Potassium channels [6–8]. However, genetic testing could identify disease causing mutations only in 30% of the cases of phenotypical BrS [9]. Typical "Type 1" BrS is characterized by ST segment elevation which has a 'Coved up' morphology along with a partial right bundle branch block(RBBB) in the right precordial leads (V1to V3). This ECG pattern however could be intermittent and may be unmasked by pharmacological challenge with Na Channel blockers like Flecainide, Ajmaline, Procainamide or Pilcicainide.

The only effective therapy in high risk individuals is implantation of ICD as no effective drug therapy has been definitely proven to reduce the burden of SCD. Risk assessment is crucial in deciding management of suspected BrS patients.

Pharmacologic challenge tests: Utility in the real world.

The utility of sodium channel blockers to unmask the ECG pattern of type 1 Brugada syndrome was first demonstrated by Miyazaki et al., in 1996 where they injected procainamide in 3 patients with nondiagnostic ECG and all the 3 developed type 1 Brugada pattern in few seconds [10].

Later Brugada et al. demonstrated 100% sensitivity of ajmalin challenge in 34 cardiac arrest survivors with intermittent Brugada pattern in ECG [11]. The excellent sensitivity of sodium channel blockade in unmasking Brugada pattern has lead to widespread acceptance of this test in "diagnosing" Brugada syndrome.

Multiple studies have demonstrated false positive results to sodium channel blockers, anywhere between 4% and 12% depending on the agent used and also the location of the chest leads placement for ECG recording [12].

Observational data from large patient series have demonstrated that the disease is less aggressive than initially thought, and the annual incidence of cardiac arrest between 1% and 2%. Presence of spontaneous type1 ECG, together with history of syncope identified high risk subgroup requiring ICD therapy [13,14].

The long term risk of patients with BrS diagnosed by drug challenge tests is significantly lower than those with spontaneous type1 BrS and hence J wave syndromes expert consensus conference report suggests the development of type1 St segment elevation in response to sodium channel block challenge should be considered as "probabilistic, rather than binary" [15].

In this issue of IPEJ, Rai et al. [16] presents an interesting observation based on changes in limb lead II in patients undergoing Flecainide challenge. Features suggesting a shortened phase 2 and 3 of repolarization in lead II evidenced as shortened ST segment, shortened ST/QT ratio and lack of an isoelectric segment along with a slurred QRS complex predicted a positivity of flecainide challenge quite accurately, in their retrospective analysis which was tested prospectively and they were successful in duplicating the results with 100% sensitivity and a 100% negative predictive value. This would make this observation an ideal screening tool for suspected BrS when a drug challenge is contemplated. However, more than three fourths (78%) of the tested cohort were asymptomatic and it raises a question if a drug challenge is indicated in this patients and how to confirm if the positive results are true positives. With very few patients with symptoms, this hypothesis needs further testing in a prospective fashion in indicated population. The reason why the authors selected lead II also remains less clear along with the question of similar changes were present in other inferior leads viz. leads III and aVF.

The biggest challenge in managing BrS is about asymptomatic individuals. Sodium channel blockade can provide a more definitive diagnosis especially in those with type 2 and 3 ECG patterns, but no therapeutic intervention is recommended in this subset since the long term risk in this subgroup is significantly lower than those with spontaneous type 1 pattern. The emotional consequences of a patient who is undergoing a test which could yield a positive test and not followed by a definitive therapy also needs to be addressed and ultimately it should be an informed decision from the patient himself. If the added information from lead II changes help to screen cases more efficiently, it would avoid unnecessary testing and associated economic and emotional consequences.

References

[1] Bowker TJ, Wood DA, Davies MJ, Shepard MN, Cary NRB, Hobson HL, et al. A national survey of sudden unexpected cardiac or unexplained death in adults (SADS). Heart 1996;75:80.
[2] Corrado D, Basso C, Thiene G. Sudden cardiac death in young people with apparently normal heart. Cardiovasc Res 2001;50:399–408.

Peer review under responsibility of Indian Heart Rhythm Society.

[3] Puranik R, Chow CK, Duflou JA, Kilborn MJ, McGuire MA. Sudden death in the young. Heart Rhythm 2005;2:1277—82.

[4] Survivors of out-of-hospital cardiac arrest with apparently normal heart: need for definition and standardized clinical evaluation: consensus statement of the Joint Steering Committees of the Unexplained Cardiac Arrest Registry of Europe and of the Idiopathic Ventricular Fibrillation Registry of the United States. Circulation 1997;95:265—72.

[5] Fuster V, Walsh RA, Harrington RAPriori SG, Napolitano C. Genetics of channelopathies and clinical implications. In: Fuster V, Walsh RA, Harrington RA, editors. Hurst's The Heart. thirteenth ed. New York, NY: McGraw Hill; 2011. p. 897—991.

[6] Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the second consensus conference: endorsed by the heart Rhythm Society and the European heart Rhythm Association. Circulation 2005;111:659—70.

[7] Watanabe H, Darbar D, Kaiser DW, Jiramongkolchai K, Chopra S, Donahue BS, et al. Mutations in sodium channel beta1 and beta2 subunits associated with atrial fibrillation. Circ Arrhythm Electrophysiol 2009;2:268—75.

[8] London B, Michalec M, Mehdi H, Zhu X, Kerchner L, Sanyal S, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation 2007 Nov 13;116(20):2260—8.

[9] Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace 2011;13:1077—109.

[10] Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with brugada syndrome. J Am Coll Cardiol 1996;27(5):1061—70. http://dx.doi.org/10.1016/0735-1097(95)00613-3.

[11] Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 2000 Feb 8;101(5):510—5.

[12] Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AAM. Everybody has brugada syndrome until proven otherwise? Heart Rhythm 2015;12(7):1595—8. http://dx.doi.org/10.1016/j.hrthm.2015.04.017.

[13] Priori S, Gasparini M, Napolitano C, Della Bella P, Ghidini Ottonelli A, Sassone B, et al. Risk stratification in Brugada Syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) Registry. J Am Coll Cardiol 2012;59:37—45.

[14] Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada Syndrome Registry. Circulation 2010;121:635—43.

[15] Antzelevitch C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, Guo J, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Heart Rhythm 2016 Oct;13(10):e295—324.

[16] Rai MK, Prabhu MA, Shenthar J, Kumaraswami N, Venkariya R, Kamath P, et al. Evaluation of baseline ECG in patients undergoing Oral Flecainide Challenge test for suspected Brugada Syndrome: An analysis of lead II. Indian Pacing Electrophysiol J May 2017;17(4):102—17.

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