Published in final edited form as:
Isr Med Assoc J. 2008 June ; 10(6): 462–464.

Risk Strataification of Brugada Syndrome Revisited

Eyal Nof, MD and **Charles Antzelevitch, PhD FACC FAHA FHRS**
Masonic Medical Research Laboratory, Utica, NY, USA

Keywords

Brugada syndrome; sudden cardiac death; ventricular tachycardia; ventricular fibrillation; implantable cardioverter device; electrophysiological studies

Brugada syndrome is a widely recognized syndrome associated with a high risk of sudden death, particularly in males as they approach their third and fourth decades of life. It is characterized by an ST-segment elevation in the right precordial electrocardiogram leads, which is often concealed but can be unmasked with potent sodium channel blockers or by recordings obtained with the right precordial leads raised two intercostal spaces [1,2]. A consensus report published in 2002 delineated diagnostic criteria for the syndrome [3,4]. A second consensus conference report published in 2005 focused on risk stratification schemes and approaches to therapy [5,6].

Despite a flurry of publications reporting numerous studies as well as two meta-analyses [7, 8], major controversies remain, particularly regarding risk stratification. It is generally accepted that patients who have suffered a life-threatening arrhythmia, such as aborted sudden cardiac death or who experience nocturnal agonal respiration, are at high risk for recurrences [5]. There is no argument that these patients need the protection of an implantable cardioverter device without the need for further risk assessment. There is also little argument that patients with the clinical picture of arrhythmia-mediated syncope and a type 1 ST-segment elevation should receive an ICD[1] [5].

The most debated issue has to do with risk stratification of asymptomatic patients. Brugada et al. [9,10] reported that the risk for developing ventricular tachycardia/ventricular fibrillation is much greater in patients who are inducible during electrophysiological studies, whether or not a type 1 ST-segment elevation is spontaneously present and whether or not they are symptomatic. In asymptomatic spontaneous type 1 electrocardiogram patients, multivariate analysis showed that the only predictor of arrhythmic events is inducibility during EPS[2].

In sharp contrast, other studies [7,8,11-13] failed to find an association between inducibility and cardiac arrhythmic events. The incidence of VT/VF[3] events during follow-up was too low (annual event rate of 0.8-1% [11,12] to demonstrate value for risk stratification based on EPS

Correspondence: Dr. C. Antzelevitch, Executive Director/Director of Research, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, NY 13501-1787, USA., Phone: (1-315) 735-2217 ext. 117; Fax: (1-315) 735-5648 email: ca@mmrl.edu.

1

ICD
implantable cardioverter device

2

EPS
electrophysiological studies

inducibility. Of note, the last consensus conference published in 2005 [5] recommended that asymptomatic patients displaying a type 1 ST segment elevation (either spontaneously or after sodium channel blockade) undergo EPS if a family history of sudden cardiac death is suspected to be the result of Brugada syndrome. EPS was also considered justified with a negative family history but a spontaneous type 1 ST-segment elevation. If inducible for ventricular arrhythmia, implantation of an ICD was recommended either as a class IIa or IIb indication, meaning that conflicting evidence exists concerning usefulness and that the weight of evidence is either in favor of usefulness (class IIa) or usefulness is not well established (class IIb). The report also recommended that asymptomatic patients with no family history who develop a type 1 ST segment elevation only after sodium channel blockade should be closely followed. Since the appearance of the last consensuses statement, the large number of studies that have failed to demonstrate an association between inducibility and risk call into question the value or need for EPS in asymptomatic Brugada patients. The reason for the large disparity between the results of the Brugada brothers and those from other centers is not clearly evident.

It is noteworthy that in experimental models of the Brugada syndrome involving the coronary-perfused wedge preparation, polymorphic VT is readily inducible with a single ventricular extra-stimulus, but only when applied on the epicardial surface. Inducibility is not possible or much more difficult when extra-stimulation is applied to the endocardial surface. The shorter refractory period of epicardium allows extra-stimuli direct access to the vulnerable window across the ventricular wall, thus facilitating the induction of reentry. These relationships suggest that programmed electrical stimulation applied to the epicardium may provide a more accurate assessment of risk than the current clinical approach in which stimuli are applied to the endocardial surface. In support of this hypothesis, Carlsson et al. [14] reported that a Brugada patient with recurrent syncope due to polymorphic ventricular tachycardia could not be induced with right ventricular endocardial stimulation. However, epicardial stimulation from a left ventricular site through the coronary sinus led to the development of polymorphic VT. This approach may also be useful in inducing Brugada patients and might prove helpful in predicting future arrhythmic events.

Although the most effective therapy for Brugada syndrome is the implantation of an ICD, the rate of serious complications is high. In two recent reported series [15,16], 28-36% of the patients had serious complications. The main long-term complication was inappropriate shocks. It is not clear why these patients have a high incidence of inappropriate shocks. It is important to highlight the fact that when compared with other ICD implanted populations, Brugada patients are much younger and more physically active. Given that many are engaged in regular sport activities, inappropriate shocks may be due to episodes of sinus tachycardia [15]. In retrospective analysis of some of the inappropriate shock cases [15], those with lead-related problems were also younger and more active than those without lead-related complications. Brugada patients are also known to have more supraventricular arrhythmias [17,18] and inappropriate shocks may be due to failure of the ICD to discriminate between atrial and ventricular arrhythmias.

Another treatment option is the use of I_{to} blockers such as quinidine [19,20]. Among the disadvantages of oral quinidine are gastrointestinal side effects, particularly at the high doses needed to achieve I_{to} block. The effect of quinidine in blocking the rapidly and slowly activating delayed rectifier currents, I_{Kr} and I_{Ks}, can predispose to the development of acquired long QT syndrome. This effect of quinidine is minimized at high plasma levels, because at these concentrations quinidine also blocks the inward sodium channel current, I_{Na}, which serves to

3

VT/VF

ventricular tachycardia/ventricular fibrillation

counter the effect of I_{Kr} and I_{Ks} block to increase spatial dispersion of repolarization and triggered activity, the substrate and trigger for the development of torsade de pointes arrhythmias [21,22].

In this issue of *IMAJ*, Rosso and colleagues [23] present the results of a multicenter trial conducted in Israel that examined outcomes of an ICD implantation study in patients with Brugada syndrome (ISRABRU). The study was conducted at 12 Israeli centers. Based on the results, the authors conclude that: a) appropriate ICD therapy among participants was limited only to sudden death survivors; b) syncope, spontaneous type 1 ECG or EPS was not predictive of future cardiac arrhythmic events; and c) ICD implantation in these patients was associated with a high rate of serious complications (32%), as in previous reports of similar populations. The principal reason for ICD complications in this as well as previous studies was inappropriate shocks.

While the inability of EPS to predict future arrhythmic events is consistent with most previous studies, it is important to note that the different centers enrolled in the study used different EPS protocols. The protocol used in 21 of 59 patients included extrastimuli at the shortest coupling intervals that allowed ventricular capture. The full significance of using such an aggressive protocol in this patient population is not known. The consensus report recommended a minimal coupling interval of 200 ms [5]. Using a more aggressive protocol may lead to a false positive EPS, as acknowledged by the authors.

There are several disparities between the results of this study and those of others. Previously published data from several registries [7,8,11-13] have shown that not only aborted sudden cardiac death, but also syncope or spontaneous type 1 ECG are reliable predictors of cardiac arrhythmic events [5]. Moreover, these registries also demonstrated that EP inducibility was greatest among patients with prior VT/VF or syncope. In the present study by Rosso et al. [23], inducibility rates between symptomatic and asymptomatic patients were not significantly different and even a bit higher in the asymptomatic group (89.2% vs. 93.3%; not significant). The latter might be explained by the use of a more aggressive protocol in a large number of patients included in this study. Another confounding factor was the inclusion of patients with type 2 ST-segment elevation who did not undergo a sodium challenge test. Although all six patients with type 2 ECG included were symptomatic (n=5) or with a family history of sudden cardiac death (n=1), it is not clear whether these patients have a clear diagnosis of Brugada syndrome. While this issue is still debated in the literature [11], both consensus reports require a type 1 ECG to establish a diagnosis of Brugada syndrome [4,5]. The inclusion of these patients contributes to differences in prognosis between studies.

The lack of predictability of EPS and the high rate of ICD complications in this report and others highlight the need for additional risk assessment factors as well as alternative treatment modalities for Brugada syndrome. In the present study as in previous studies [19,24], quinidine was effective in preventing inducibility of VF in a high percent of patients and at present remains the only alternative to ICD therapy. The largest prospective study of the effect of oral quinidine (1483 ± 240 mg) was reported by Belhassen and co-workers [19] who showed that quinidine prevents VF induction in 88% of patients. Of 19 patients treated with oral quinidine for an average of 56 ± 67 months, none developed arrhythmic events. Administration of quinidine was associated with a 36% incidence of side effects, principally diarrhea which resolved after drug discontinuation. The authors concluded that quinidine effectively suppresses VF induction as well as spontaneous arrhythmias in patients with the syndrome and may be useful as an adjunct to ICD therapy. They also suggested that EPS-guided quinidine therapy may be used *as an alternative* to ICD in cases in which an ICD is refused or unaffordable. These results are consistent with those reported by the same group in prior years [25,26] and more recently by other investigators [23,27-29]. These data notwithstanding, there

is a clear need for a large randomized controlled clinical trial to assess the effectiveness of quinidine, preferably in patients with frequent events who have already received an ICD.

In summary, this study raises further questions regarding risk markers in patients with Brugada syndrome and provides additional evidence in support of the failure of a positive EPS to forecast arrhythmic events as well as further evidence of the value of quinidine therapy in this syndrome.

Acknowledgment

Supported by grant HL 47678 from the National Institutes of Health and the Masons of New York State and Florida.

References

1. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. J Am Coll Cardiol 1992;20:1391–6. [PubMed: 1309182]
2. Antzelevitch C. Brugada syndrome. PACE 2006;29:1130–59. [PubMed: 17038146]
3. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: Consensus Report. Eur Heart J 2002;23:1648–54. [PubMed: 12448445]
4. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation 2002;106:2514–19. [PubMed: 12417552]
5. Antzelevitch C, Brugada P, Borggrefe M, 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. [PubMed: 15655131]
6. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference. Heart Rhythm 2005;2:429–40. [PubMed: 15898165]
7. Gehi AK, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the brugada electrocardiogram: a metaanalysis. J Cardiovasc Electrophysiol 2006;17:577–83. [PubMed: 16836701]
8. Paul M, Gerss J, Schulze-Bahr E, et al. Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. Eur Heart J 2007;28:2126–33. [PubMed: 17483540]
9. Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V_1 through V_3. A marker for sudden death in patients without demonstrable structural heart disease. Circulation 1998;97:457–60. [PubMed: 9490240]
10. Brugada P, Brugada R, Brugada J. Patients with an asymptomatic Brugada electrocardiogram should undergo pharmacological and electrophysiological testing. Circulation 2005;112:279–85. [PubMed: 16009809]
11. Priori SG, Napolitano C. Management of Patients with Brugada syndrome should not be based on programmed electrical stimulation. Circulation 2005;112:285–91.
12. Eckardt L, Probst V, Smits JP, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation 2005;111:257–63. [PubMed: 15642768]
13. Ohkubo K, Watanabe I, Takagi Y, et al. Electrocardiographic and electrophysiologic characteristics in patients with brugada type electrocardiogram and inducible ventricular fibrillation. Circ J 2007;71:1437–41. [PubMed: 17721024]
14. Carlsson J, Erdogan A, Schulte B, Neuzner J, Pitschner HF. Possible role of epicardial left ventricular programmed stimulation in Brugada syndrome. PACE 2001;24:247–9. [PubMed: 11270709]
15. Sarkozy A, Boussy T, Kourgiannides G, et al. Long-term follow-up of primary prophylactic implantable cardioverter-defibrillator therapy in Brugada syndrome. Eur Heart J 2007;28:334–44. [PubMed: 17251258]
16. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation 2006;114:2317–24. [PubMed: 17116772]

17. Bordachar P, Reuter S, Garrigue S, et al. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. Eur Heart J 2004;25:879–84. [PubMed: 15140537]

18. Francis J, Antzelevitch C. Atrial fibrillation and brugada syndrome. J Am Coll Cardiol 2008;51:1149–53. [PubMed: 18355651]

19. Belhassen, B.; Viskin, S. Pharmacologic approach to therapy of Brugada syndrome: quinidine as an alternative to ICD therapy?. In: Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R., editors. The Brugada Syndrome: From Bench to Bedside. Blackwell Futura; Oxford, UK: 2004. p. 202-11.

20. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004;110:1731–7. [PubMed: 15381640]

21. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. Trends Pharmacol Sci 2003;24:619–25. [PubMed: 14654302]

22. Antzelevitch C. Ionic, molecular, and cellular bases of QT-interval prolongation and torsade de pointes. Europace 2007;9:iv4–15. [PubMed: 17766323]

23. Hermida JS, Denjoy I, Clerc J, et al. Hydroquinidine therapy in Brugada syndrome. J Am Coll Cardiol 2004;43:1853–60. [PubMed: 15145111]

24. Rosso R, Glocl A, Glikson M, et al. the Israeli Working Group on Cardiac Pacing and Electrophysiology. Outcome after implantation of implantable cardioverter defribrillator in patients with Brugada syndrome: a multicenter Israeli study (ISRABRU). IMAJ 2008;10:00–00.

25. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:1301–12. [PubMed: 10515552]

26. Belhassen B, Viskin S, Antzelevitch C. The Brugada syndrome: is an implantable cardioverter d \Defibrillator the only therapeutic option? PACE 2002;25:1634–40. [PubMed: 12494624]

27. Mok NS, Chan NY, Chi-Suen CA. Successful use of quinidine in treatment of electrical storm in Brugada syndrome. PACE 2004;27:821–3. [PubMed: 15189543]

28. Marquez MF, Rivera J, Hermosillo AG, et al. Arrhythmic storm responsive to quinidine in a patient with Brugada syndrome and vasovagal syncope. PACE 2005;28:870–3. [PubMed: 16105018]

29. Mizusawa Y, Sakurada H, Nishizaki M, Hiraoka M. Effects of low-dose quinidine on ventricular tachyarrhythmias in patients with Brugada syndrome: low-dose quinidine therapy as an adjunctive treatment. J Cardiovasc Pharmacol 2006;47:359–64. [PubMed: 16633076]