Journal of Clinical and Experimental Cardiology

Delise, J Clin Exp Cardiolog 2019, 10:11

Review Article Open Access

Drug-Induced Brugada Type 1 ECG Pattern: Concealed Brugada Syndrome or By-Stander Electrocardiographic Sign?

Pietro Delise*

Division of Cardiology, Hospital P Pederzoli, Peschiera del Garda, Verona, Italy

***Corresponding author:** Delise P, Division of Cardiology, Hospital P Pederzoli, Peschiera del Garda, Verona, Italy, Tel: +0438 663613; E-mail: pietro.delise@libero.it

Received: November 18, 2019; **Accepted:** December 02, 2019; **Published:** December 09, 2019

Abstract

In the clinical setting, drug testing is currently used to unmask a concealed Brugada Syndrome (BrS) both in patients with unexplained syncope and also in asymptomatic subjects with only suspect ECG signs. Recent studies, however, suggest that the induction of a Brugada type 1 ECG (Br type 1 ECG) by drugs may be an aspecific and/or a by-stander ECG sign. This is no idle hypothesis, as in clinical practice drug-induced Br type 1 ECG and BrS are often used as synonyms, feeding worldwide terror of this disease and resulting in an excess of inappropriate aggressive therapies in otherwise healthy subjects.

Condensed abstract: Drug testing is currently used to unmask a concealed Brugada Syndrome in patients with unexplained syncope and also in asymptomatic subjects with suspect ECG signs. Recent studies, however, suggest that the induction of a Brugada type 1 ECG by drugs may be an aspecific and/or a by-stander ECG sign.

Keywords: Brugada syndrome; Aborted sudden death; Drug-induced Brugada type 1 ECG; Cardiac arrest; Early repolarization; J-wave syndromes

Introduction

In 1992, Pedro and Josep Brugada [1] introduced a new clinical and electrocardiographic syndrome named Brugada syndrome (BrS). This syndrome may cause cardiac arrest in the absence of obvious heart disease. The diagnosis of BrS is mainly based on a characteristic electrocardiographic pattern showing J-point elevation of at least 2 mm and down-sloping ST elevation followed by negative T wave (Br type 1 ECG). The first eight cases of BrS that were described displayed a spontaneous Br type 1 ECG [1].

What's New?

In asymptomatic and symptomatic subjects, a Brugada type 1 ECG (BrS type 1 ECG) during drug testing (ajmaline, pilsicainide etc.) is generally considered indicative of a concealed BrS. However, recent studies, including one by our group, suggest that the induction of a Brugada type 1 ECG by drugs may be an aspecific and/or a by-stander ECG sign. The consequence of the confusion surrounding BrS is worldwide terror of this disease and an unacceptable excess of inappropriate aggressive therapies in otherwise healthy subjects.

Review

The cause of BrS is debated. Defects of genes encoding or regulating Na+ channels (SCN5A etc.) have been identified as possible causes [2,3]. This possibility has been validated by laboratory experiments using drugs, such as pilsicainide, which are able to block Na+channels [4]. In animal studies, the use of Na+channel blockers has proved able to provoke characteristic modifications of the action potential in the subepicardial myocardium of the right ventricular outflow tract (RVOT), reproducing the Br type 1 ECG pattern [4]. These experimental studies have also reproduced malignant arrhythmias arising from the RVOT.

More recently, an alternative interpretation of the electrophysiologic mechanism of BrS has been proposed in humans. Indeed, in patients with symptomatic BrS, some authors [5], have documented delayed depolarization over the anterior aspect of the RVOT epicardium, and have reported that ablation of this abnormal area normalizes the ECG and prevents the inducibility of ventricular fibrillation by ventricular stimulation. Apart from the mechanism of electrophysiologic alterations, the RVOT site of such alterations explains why, in the clinical setting, a Br type 1 ECG pattern is recorded in V1-V3 leads and/or on positioning the same electrodes over the III and II intercostal spaces.

On the basis of the above-mentioned observations, a drug test (using ajmaline, flecainide, pilsicainide etc.) was introduced into clinical practice, in order to discover a concealed BrS in patients with syncope of unexplained origin [6,7]. In recent years, this pharmacological test has been progressively used worldwide, even in asymptomatic subjects with a suspect ECG pattern (type 2 or type 3 Br ECG or other aspecific ECG alterations). Consequently, a great number of subjects have been found to display a Br type 1 ECG after drug administration (drug-induced Br type 1 ECG) even in the absence of clinical manifestations.

The usefulness of this test in unselected asymptomatic subjects, however, has been questioned by many authors [8-14]. Indeed, a number of prospective studies have demonstrated that asymptomatic subjects with a drug-induced Br type 1 ECG have an excellent prognosis [8,11,13,15]. In particular, in a multicenter study that included our group [13], subjects with a drug-induced Br type 1 ECG who did not undergo ICD implantation, in the absence of major risk factors, showed a risk of SD during follow-up that was very low, being similar to and slightly lower than that of the general population. Consequently, the doubt that a drug-induced Br type 1 ECG is always a sign of a concealed BrS appears reasonable. On the contrary, the

above-cited data suggest that a drug-induced Br type 1 ECG may be an aspecific ECG sign in the majority of cases.

In contrast with these reassuring data, in the real world too many asymptomatic patients with drug-induced Br type 1 ECG undergo ICD implantation [9] or RVOT ablation [15]. In patients with idiopathic aSD (and non-diagnostic resting ECG), drug testing has also been employed in order to unmask a concealed BrS as a possible cause of the potentially lethal event. In subjects with aSD and a positive drug test, a BrS is currently considered the cause of cardiac arrest. In this case, too, however, many doubts arise.

In a recent paper [16], we analyzed 243 cases of aSD published by various authors and also collected by us (Italian cohort). In these 243 patients, a BrS was considered the cause of cardiac arrest on the basis of a spontaneous or drug-induced Br type 1 ECG. Interestingly, we found that, while in patients enrolled by Brugada et al. before 2002 [17], the prevalence of drug-induced Br type 1 ECG was only 14%, in those enrolled in more recent years by us [16], and by Probst et al. [18] the prevalence rose to 42%-50%.

The high number of drug-induced Br type 1 ECG in patients with aSD in our study [16], certainly depended on the progressive diffusion of drug testing in patients with idiopathic cardiac arrest. However, these data are at least surprising. Indeed, according to all prospective studies [8, 19-24], patients at highest risk of malignant arrhythmias are those with a spontaneous Br type 1 ECG, while those with a drug-induced Br type 1 ECG have a significantly lower risk. Consequently, if a BrS had really been the cause of aSD in this population, we should have expected a much higher number of patients with a spontaneous Br type 1 ECG than a drug-induced Br type 1 ECG. Specifically, in the Italian cohort (26 cases) 42% of patients had a drug-induced Br type 1, while less than 10% displayed a spontaneous Br type 1 ECG during follow-up [16].

This striking discrepancy between prospective and retrospective studies is not easy to explain. However, a recent paper by Nagayama et al. [25], offers an intriguing interpretation. These authors collected 44 cases of aSD which was attributed to BrS. Indeed, 29 patients had a spontaneous Br type 1 ECG, while in the remaining 15 the Br type 1 ECG was induced by pilsicainide. A fragmented QRS was also recorded in right precordial leads in 69% of patients with spontaneous Br type 1, but in no case in those with drug-induced Br type 1 ECG. By contrast, in patients with a drug-induced Br type 1 ECG, on basal ECG early repolarization in inferior leads was present in 87%, as opposed to 10% of those with a spontaneous Br type 1 ECG. In addition, in 26 cases, the ECG was recorded immediately after ventricular fibrillation (VF).

Interestingly, in 75% of patients with a spontaneous Br type 1 ECG just after VF, ST elevation in leads V1-V3 was increased (in comparison with the basal resting ECG). By contrast, in those with a drug-induced Br type 1 ECG after VF, no ST elevation in right precordial leads was observed, while clear early repolarization in inferior leads was visible in 90% of cases. In one of these latter patients, VF recurred during hospital monitoring; just before VF, enhanced early repolarization was visible in concomitance with very premature ventricular beats which triggered VF.

The authors therefore concluded that, in their population, spontaneous Br type 1 ECG and drug-induced Br type 1 ECG were probably two distinct clinical conditions. Indeed, in patients with spontaneous Br type 1 ECG, a BrS was clearly the cause of aSD, and the source of malignant arrhythmias was located in the outflow tract of the right ventricle. By contrast, in patients with drug-induced Br type 1 ECG, the cause of cardiac arrest was presumably an early repolarization syndrome (ERS), in which the source of malignant arrhythmias is generally located in the inferior aspect of the right or left ventricle [26]. In this paper, however, no hypothesis was proposed to explain the role of a drug-induced Br type 1 ECG in association to ERS in the genesis of malignant arrhythmias.

On the basis of these data, an important question arises: in subjects with resuscitated cardiac arrest and drug-induced Br type 1 ECG, is the Brugada ECG pattern a contributory cause (concealed BrS) in conjunction with ERS, or might it be only a by-stander ECG finding?

The possibility that a drug-induced Br type 1 ECG might be a contributory cause is supported by the observation that both BrS and ERS may be provoked by dysfunctions of Na+ channels (J-wave syndromes) [3]. However, it is difficult to explain why, both in our paper and in that of Nagayama, only 20% of patients with aSD and drug-induced Br type 1 ECG had SCN5A gene mutations. The hypothesis that a drug-induced Br type 1 ECG is a by-stander finding in patients with idiopathic aSD and non-diagnostic basal ECG therefore emerges as a possible explanation.

To test this hypothesis, the prevalence of a drug-induced Br type 1 ECG should be compared in a large population of patients with idiopathic aSD and in an asymptomatic general population with normal basal ECG. If the prevalence of a drug-induced Br type 1 ECG were higher in patients with idiopathic aSD than in the general population, a causative/contributory role of BrS would be suggested. By contrast, if the prevalence of a drug-induced Br type 1 ECG were similar in patients with idiopathic aSD and in the general population, a by-stander role of drug-induced Br type 1 ECG should be hypothesized. Unfortunately, no such study has ever been conducted. Thus, in patients with idiopathic aSD and a drug-induced Br type 1 ECG, the contributory role of a concealed BrS cannot be supported; likewise, the possibility that a drug-induced Br type 1 ECG is a by-stander finding cannot be ruled out.

Whether a drug-induced Br type 1 ECG may be a by-stander finding and not always proof of a concealed BrS is not an idle question in clinical practice, particularly in asymptomatic subjects or in those with syncope of uncertain origin. Indeed, in clinical practice, the terms drug-induced Br type 1 ECG and BrS are often used as synonyms, and current guidelines identify the Brugada Syndrome with the Br type 1 ECG, whether spontaneous or drug-induced [27]. Our opinion, and that of other authors [12], is that this is not correct, as all available data suggest that only a minority of patients with a drug-induced Br type 1 ECG really do have a BrS, while the vast majority of them have no risk of SD.

In the history of medicine, similar mistakes have been made many times in the past when an ECG sign has been equated to a disease. For example, more than 60 years ago, negative T waves were defined by the Mexican School [28] as "ischemia" and this ECG anomaly was identified with coronary artery disease. This error was corrected only after many decades, when it was demonstrated that negative T waves were not always a manifestation of myocardial ischemia; rather, they may be an aspecific finding or may be due to various heart diseases (hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, pulmonary embolism, etc.). The consequence of the confusion surrounding BrS is worldwide terror of this disease and an unacceptable excess of inappropriate aggressive therapies in otherwise healthy subjects [29-31].

Conclusion

In patients with aSD, too, the hypothesis that a drug-induced Br type 1 ECG is a by-stander finding is not idle. Indeed, if the real cause of cardiac arrest in these cases is ERS and not Brugada Syndrome, then the electrophysiologic substrate of VF is not located in the RVOT but at other sites (i.e., inferior aspects of ventricles), and ablation of the RVOT is useless. Brugada syndrome and Br type 1 ECG pattern is not always the same thing.

References

1. Brugada P, Brugada J (1992) Right bundle branch block, persistent ST-segment elevation and sudden cardiac death: A distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 20: 1391-1396.
2. Antzelevich C (2012) Genetic, molecular and cellular mechanisms underlying the J wave syndrome. Circ J 76: 1054-1065.
3. Antzelevich C, Yan GX, Ackerman MJ, Borggrefe M, Corrado D, et al. (2016) J wave syndrome expert consensus conference: Emerging concepts and gaps in knowledge. Journal of Arrhythmias 32: 315-339.
4. Morita H, Zipes DP, Wu JB (2009) Brugada syndrome: Insight of ST elevation, arrhythmogenicity, and risk stratification from experimental observations. Heart Rhythm 6: 53-64.
5. Nademanee K, Veerakul G, Chandanamattha P, Chaothwee L, Ariyachaipanich A, et al. (2011) Prevention of ventricular fibrillation episodes in Brugada Syndrome by catheter ablation over the anterior right verntricular outflow tract epicardium. Circulation 123: 1270-1279.
6. Rolf S, Brun HJ, Wichter T, Kirchof P, Ribbling M, et al. (2003) Ajmaline challenge in Brugada Syndrome: Diagnostic, impact, safety and recommended protocol. Eur Heart J 24: 1104-1112.
7. Roos M, Sarkozy A, Brodbeck J, Hemkens S, Chierchia GB, et al. (2012) The importance of class-I antyarrhythmic drug test in the evaluation of patients with syncope: Unmasking Brugada Syndrome. J Cardiovasc Electrophysiol 23: 290-295.
8. Misuzawa Y, Wilde AM (2012) Brugada syndrome. Circ Arrhythm Electrophysiol 5: 606-616.
9. Sacher F, Probst V, Maury P, Babuty D, Mansourati J, et al. (2013) Outcome after implantation of cardioverter-defibrillator in patients with Brugada Syndrome: A multicenter study-part 2. Circulation 128: 1739-1747.
10. Viskin S, Rosso R, Friedensohn L, Havakuk O, Wilde AA (2015) Everybody has Brugada Syndrome until proven otherwise? Heart Rhythm 12: 1595-1598.
11. Sieira J, Ciconte G, Conte G, de Asmundis C, Chierchia GB, et al. (2017) Long-term prognosis of drug-induced Brugada syndrome. Heart Rhythm 14: 1427-1433.
12. Viskin S, Rosso R (2017) Read my lips: A positive ajmaline test does not always mean you have Brugada Syndrome. J Am Coll Cardiol EP 12: 1409-1411.
13. Delise P, Probst V, Allocca G, Sitta N, Sciarra L, et al. (2018) Clinical outcome of patients with the Brugada type 1 ECG without prophylactic ICD in primary prevention: A cumulative analysis of seven large prospective studies. Europace 20: f77-f85.
14. Havakuk O, Viskin S (2016) A tale of two diseases: The history of Long-QT syndrome and Brugada Syndrome. J Am Coll Cardiol 67: 100-108.
15. Brugada J, Pappone C, Berruezo A, Vicedomini G, Manguso F, et al. (2015) Brugada Syndrome phenotype elimination by epicardial substrate ablation. Circ Arrhythm Electrophysiol 8: 1373-1381.
16. Delise P, Allocca G, Sitta N, Migliore F, Dagradi F, et al. (2018) Cardiac arrest and Brugada Syndrome: Is drug-induced type 1 Ecg pattern always a marker of low risk? Int J Cardiol 254: 142-145.
17. Brugada J, Brugada R, Antzelevich C, Towbib J, Nademanee K, et al. (2002) Long-term follow up of individuals with the elecrocardiographic pattern of right bundle – branch block and ST-segment elevation in precordial leads V1 to V3. Circulation 105: 73-78.
18. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, et al. (2010) Long-term prognosis of patients diagnosed with Brugada Syndrome. Results from the FINGER Brugada Syndrome Registry. Circulation 121: 635-643.
19. Eckardt L, Probst V, Smits JPP, Bahr ES, Wolpert C, et al. (2005) Long-term prognosis of individuals with right precordial ST-segment elevation Brugada Syndrome. Circulation 111: 257-263.
20. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, et al. (2009) Long–term prognosis of probands with Brugada-pattern ST elevation in leads V1-V3. Circ Arrhythmia Electrophysiol 2: 495-503.
21. Delise P, Allocca G, Marras E, Giustetto C, Gaita F, et al. (2011) Risk stratification in individuals with the Brugada type 1 ECG pattern without previous cardiac arrest: Usefulness of a combined clinical and electrophysiologic approach. Eur Heart J 32: 169-176.
22. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ghidini Ottonelli G, et al. (2012) Risk stratification in Brugada Syndrome. Results of the PRELUDE Registry. J Am Coll Cardiol 59: 37-45.
23. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, et al. (2017) A score model to predict risk of events in patients with Brugada Syndrome. Eur Heart J 38: 1756-1763.
24. Kawada S, Morita H, Antzelevitch C, Morimoto Y, Nakagawa K, et al. (2018) Shanghai Score System for diagnosis of Brugada Syndrome. Validation of the score system and reclassification of the patients. JACC Clin Electrphysiol 4: 724-730.
25. Nagayama T, Nagase S, Kamakura T, Wada M, Ishibashi K, et al. (2019) Clinical and electrocardiographic differences in Brugada syndrome with spontaneous or drug-induced type 1 electrocardiogram. Circ J 83: 532-539.
26. Cabrera E, Sodi Pallares D (1943) Gradient ventriculr y la componente anormal en el diagnostico de los infartos del miocardio. Arch Inst Cardiol Mex 7: 356.
27. Haissaguerre M, Nademanee K, Hocini M, Cheniti G, Duchateau, et al. (2019) Depolarization versus repolarization abnormality underlying J-wave syndromes: new concepts in sudden cardiac death with apparently normal hearts. Heart Rhythm 16: 781-790.
28. Priori SG, Wilde AA, Horie M, Cho Y, Behr E, et al. (2013) HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm 10: 1932-1963.
29. Viskin S (2018) Radiofrequency ablation of asymptomatic Brugada Syndrome. Don't go burning my heart. Circulation 137: 1883-1884.
30. Delise P, Allocca G, Sitta N (2017) Brugada type 1 electrocardiogram: should we treat the electrocardiogram or the patient?. World J Cardiol 9: 737-741.
31. Delise P, Allocca G, Sitta N (2019) Brugada syndrome 26 years later: More questions than answers. J Clin Exp Cardiol 10: 625-629.