Journal of Clinical and Experimental Cardiology

Delise et al., J Clin Exp Cardiolog 2019, 10:1
DOI: 10.4172/2155-9880.1000624

Short Communication Open Access

Brugada Syndrome 26 Years Later: More Questions than Answers

Pietro Delise[1*], Giuseppe Allocca[2] and Nadir Sitta[2]

[1]*Division of Cardiology, Clinica Pederzoli, Peschiera, Verona, Italy*

[2]*Division of Cardiology, Hospital of Conegliano, Treviso, Italy*

[*]**Corresponding author:** Pietro Delise, Division of Cardiology, Clinica Pederzoli, Peschiera, Verona, Italy, Tel: +041975205; E-mail: pietro.delise@libero.it

Received date: December 06, 2018; **Accepted date:** January 17, 2019; **Published date:** January 24, 2019

Abstract

Brugada Syndrome and Brugada type 1 ECG pattern (BrS type 1 ECG) are currently used as synonyms. However, in the vast majority of cases, BrS type 1 ECG is a benign finding, and only few patients with this pattern have a Brugada Syndrome; that is to say, they present with, or are prone to, malignant arrhythmias.

Brugada Syndrome, when defined only on the basis of the BrS type 1 ECG, has several characteristics which conflict with those of other channellopathies such as Long-QT syndrome (LQTS). For example, there is no correlation between the magnitude of ECG anomalies and prognosis, and a genetic defect is rarely recognized. In addition, patients with malignant arrhythmias in prospective and retrospective studies have different characteristics. Indeed, prospective studies have identified a number of risk factors which are useful (singly or in combination) in identifying patients who will present with malignant arrhythmias: spontaneous BrS type 1 ECG, syncope of presumed cardiac origin, familial juvenile SD (Sudden Death), positive Electrophysiology Studies (EPS) etc. By contrast, in retrospective studies, subjects with aborted SD in whom a BrS type 1 ECG has been identified after the potentially catastrophic event generally have no major risk factors, and 40% of them have a drug-induced BrS type 1. In other words, they are theoretically not at risk. In these latter cases, a spontaneous question arises: was a Brugada syndrome really the cause of cardiac arrest, or might the BrS type1 ECG have been a by-stander sign?

In conclusion, in Brugada syndrome, too many questions remain unanswered. In our opinion, Brugada Syndrome is an entity which needs to be re-defined on the basis of more scientific information, which is, as yet, partially lacking. In any case, the diagnosis of Brugada Syndrome should not be made only on the basis of a BrS type 1 ECG pattern.

Keywords: Brugada syndrome; ECG pattern

Introduction

In 1992, the Brugada brothers observed that some patients with idiopathic cardiac arrest (i.e., without obvious heart disease) had a particular ECG pattern. This pattern was characterized by elevation of the J point and down-sloping ST elevation followed by a negative T wave in right precordial leads (BrS type 1 ECG). On the basis of this observation, they introduced a new syndrome, named Brugada Syndrome [1].

This observation created panic among cardiologists and (presumed) patients worldwide. Indeed, as this ECG pattern is not so rare, the first obvious question was: are all subjects with a BrS type 1 ECG at risk of sudden death (SD), or only some of them?

Similar questions have frequently arisen in the history of medicine when an instrumental sign has been associated to a dangerous disease at risk of SD. For instance, more than seventy years ago, negative T waves were defined as subepicardial ischemia and were correlated with coronary heart disease [2]. Only after several decades was it established that negative T waves were not pathognomonic of ischemia, but may be determined by many causes, including physiologic variants.

Another example is mitral valve prolapse (MVP) which was also associated with the risk of SD. In this case, too, only after many years were it established that MPV is very frequent in the general population and is almost always benign. Indeed, only recently, autopsy studies have demonstrated that the few patients who suddenly die have fibrosis of the papillary muscles and myxomatosis of the mitral leaflets, thus indicating that mitral valve prolapse is a consequence of this disease and not the cause of SD [3].

With regard to Brugada Syndrome, a similar scenario appears probable. Indeed, the BrS type 1 ECG is relatively frequent and, in most cases, is discovered by chance [4]. In an increasing number of cases, it is discovered after the administration of drugs such as 1 C antiarrhythmic drug to treat atrial fibrillation or administered as a diagnostic test to discover this ECG pattern.

The vast majority of patients with a BrS type 1 ECG have a benign prognosis, particularly those with a drug-induced BrS type 1 ECG [5-6]. We recently published cumulative data from a multicenter prospective study which collected over 1500 patients with a BrS type 1 ECG without ICD, the majority of whom were clinically judged to be at low risk [7]. In these patients, the incidence of SD during follow-up was very low. Specifically, those with a spontaneous BrS type 1 ECG had an incidence of SD which was only slightly higher than that of the general population, while those with a drug-induced type 1 BrS type 1 ECG had an incidence of SD death similar (slightly lower) to that of the general population. It is therefore evident that BrS type 1 ECG and Brugada syndrome are not synonyms, in contrast with the suggestions of current European Guidelines [8].

Genetic Basis of Brugada Syndrome

It is currently accepted that Brugada Syndrome is determined by defects of SCN5A gene which encodes the alpha subunit of the main sodium channel Nav1.5. [9], leading to a loss of its function.

However, a defect of this gene is found in no more than 30% of patients with a Brugada syndrome.

In addition, in families with SCN5A mutations, the BrS type 1 ECG is present in only 47% of mutation carriers, while among genotype negative subjects 5% have a BrS type 1 ECG [10].

Furthermore, similar genetic defects may be found in other diseases such as in Lenegre disease, sick sinus syndrome, conduction defects, early repolarization syndrome etc. (J wave syndromes) [11].

Finally, in families with SCN5A mutations some patients present with a BrS type 1 ECG, some present with conduction disturbances and other both ECG anomalies [12].

Although it is difficult to reach a conclusion, all these data suggest that SCN5A mutations are not directly causal to the occurrence of a BrS type 1 ECG and that other factors (genetic and non-genetic) may play a role on the occurrence of the BrS type 1 ECG. Among these factors a subepicardial fibrosis of the right ventricular outflow tract has been suggested [13].

Risk Stratification in Individuals with Brugada Type 1 ECG

Several prospective studies [14-26] have identified a number of risk factors which may be useful in identifying patients with Brugada syndrome (at risk of malignant arrhythmias) among the great number of subjects with a BrS type 1 ECG: familial juvenile SD, syncope of presumed cardiac origin, spontaneous BrS type 1 ECG, first degree AV block, fragmented QRS, positive EPS etc. Unfortunately these factors singly considered, generally have a low positive predictive value and, as a consequence, they present with a little clinical usefulness to decide a therapy or not [24].

Recently, an increasing number of prospective studies have suggested that patients at highest risk are those with multiple risk factors [27-30]. Of note all these studies included patients with and without ICD in whom malignant events were considered ventricular arrhythmias recorded by ICD and cardiac arrest in those without ICD.

Interestingly, also in our cumulative prospective study of patients without ICD [7], the few patients who suffered SD/aSD had multiple risk factors in addition to a BrS type 1 ECG (i.e. they should have undergone ICD implantation).

Discrepancies between Brugada Syndrome and Other Channellopaties

If every patient with a BrS type 1 ECG is regarded as having a Brugada syndrome, a number of discrepancies arise on comparing these patients with those affected by other channellopathies, such as LQTS [31, 32]:

In patients with a Brugada type 1 ECG, there is no correlation between the magnitude of ECG anomalies and prognosis. By contrast, in LQTS, the longer the QT the worse the prognosis. Paradoxically, patients with Brugada syndrome and cardiac arrest frequently have only mild anomalies, while subjects with a benign prognosis may display marked ECG changes [Figures 1-3] [33].

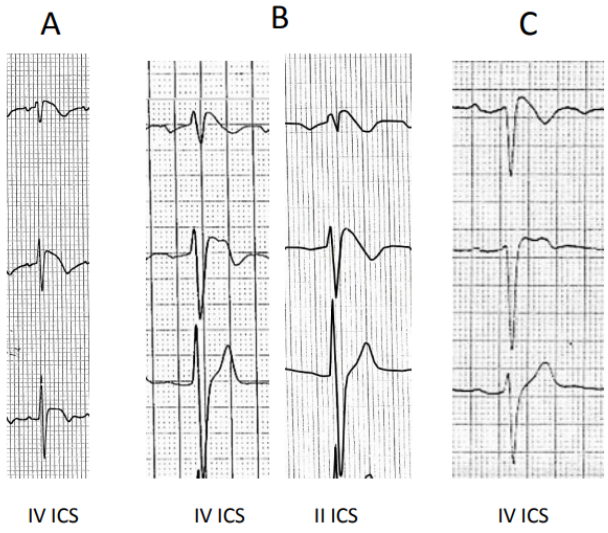

Figure 1: Three patients with aborted sudden death (A and B) or sudden death (C). A=male of 42 years; B=male of 17 years; C=male of 26 years. In A and B the ECG were recorded after the cardiac arrest, in C the ECG was recorded one year before. ICS=intercostal space.

Only in a few cases (less than 30%) is a genetic defect found in Brugada Syndrome. By contrast, in LQTS, a genetic defect is present in over 70% of cases.

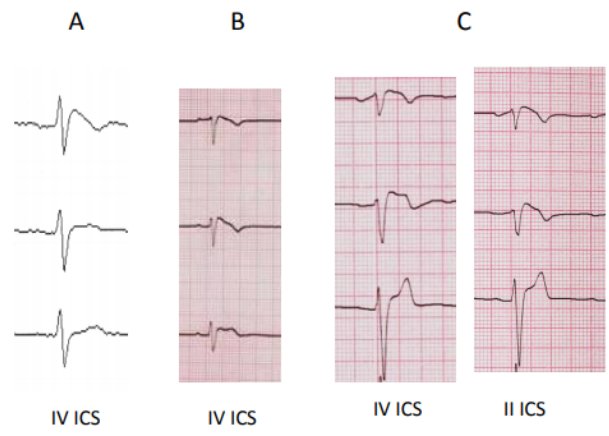

Figure 2: Three patients with BrS type 1 ECG who reived an ICD in primary prevention. All of them during follow up received an appropriate shock. A=male of 42 years; B=male of 58 years; C= male of 37 years. ICS=intercostal space.

In patients with the BrS type 1 ECG, prospective and retrospective studies do not show overlapping characteristics. Accordingly, we recently published a study [34] including over 200 published cases and 23 personal cases of patients resuscitated from cardiac arrest in which

a Brugada Syndrome was retrospectively diagnosed on the basis of a BrS type 1 ECG recorded after the event. Interestingly, in the personal cases and in those published in the last 10 years, a spontaneous BrS type 1 ECG was recorded after the event in only 60% of patients, while in the remaining 40% it was observed after administration of a class 1 C drug. In addition, few patients had a family history of Brugada syndrome and/or of SD, previous syncope or other commonly recognized risk factors. In other words, most of these patients could not be classified before the event as being at risk on the basis of risk factors identified by prospective studies.

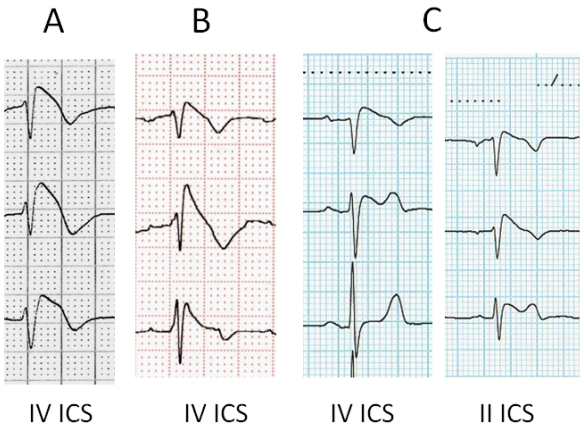

Figure 3: Three patients with a BrS type 1 ECG at low risk who had no therapy. A=male of 35 years, no clinical risk factor, negative EPS, follow up 12 years; B=male of 60 years, no clinical risk factor, negative EPS, no arrhythmias after 5 years (loop recorded implanted); C=female of 60 years, no clinical risk factor, negative EPS. ICS=intercostal space.

The high number of drug-induced BrS type 1 ECG found in our study [34], certainly depended on the progressive diffusion of drug testing in patients with idiopathic cardiac arrest. Consequently, the question arises as to whether the cause of cardiac arrest in these cases was a Brugada syndrome, or whether the BrS type 1 ECG might have been a by-stander sign. Indeed, even if we accept that a "Brugada defect" is the cause of the ECG anomaly, and a possibly a co-factor, it is possible that other, unrecognized, causes might contribute to SD/aSD in these patients.

Unfortunately, there is no answer to these questions, mainly because no study has ever compared the prevalence of the BrS Type 1 ECG (retrospectively diagnosed) in subjects with idiopathic aSD with that of the general population. Therefore, it is not possible to demonstrate a by-stander role of BrS type 1 ECG in these subjects. Nor is it possible, however, to demonstrate the contrary.

Conclusion

26 years after the description of Brugada syndrome, too many questions remain and too few answers are available. In our opinion, Brugada Syndrome is an entity which needs to be re-defined on the basis of more scientific information, much of which is, as yet, lacking. In any case, we believe that the diagnosis of Brugada Syndrome should not be made only on the basis of a BrS type 1 ECG pattern. Rather, risk stratification in subjects with a BrS type 1 ECG should be performed on the basis of data available from prospective studies, which have clearly identified several risk factors and have clearly demonstrated that subjects at highest risk are those with multiple risk factors. Consequently, aggressive treatment (ICD, ablation) in subjects with only a BrS type 1 ECG pattern, and without other risk factors, is not ethically justified.

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. Cabrera E, Sodi Pallares D (1943) El gradient ventricular y la componente anormal en el diagnostico de los infartos del miocardio. Arch Inst Cardiol Mex 7: 356.
3. Basso C, Perazzolo MM, Rizzo S, De Lazzari M , Giorgi B, et al. (2015) Arrhythmic mitral valve prolapse and sudden death. Circulation 132: 556-566.
4. Anselm DA, Evans JM, Baranchuk A (2014) Brugada phenocopy: a new electrocardiogram phenomenon. World J Cardiol 26: 81-86.
5. Misuzawa Y, Wilde AM (2012) Brugada syndrome. Circ Arrhythm electrophysiol 5: 606-616.
6. 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.
7. 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.
8. Priori SG, Blomstrong-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, et al. (2015) 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac arrest. Eur Heart J 36: 2793-2867.
9. Li Wu, Yin L, Shen C, Hu K, Ge J, et al. (2018) SCN5A variants: association with cardiac disorders. Front Physiol 9: 1372.
10. Probst V, Wilde A, Barc J, Sacher F, Babuty D, et al. (2009) SCN5A mutations and the role of genetic back ground in the pathopysiology of Brugada syndrome. Circ Cardiovasc Genet 2: 552-557.
11. Antzelevitch C, Yan G, Ackerman M, Borggrefe M, Corrado D, et al. (2016) J-Wave syndromes expert consensus conference report: emerging concepts and gaps in knowledge. J Arrhythm 32: 315-339.
12. Probst V, Allouis M, Sacher F, Pattier S, Babuty D, et al. (2006) Progressive conduction defect is the prevailing phenotype in carriers of a Brugada syndrome SCN5A mutation. J Cardiovasc Electrophysiol 17: 270-275.
13. Nademanee K, Veerakul G, Cahannadanamattha P, Chaothawee L, Ariyachaipanich A, et al. (2011) Prevention of ventricular fibrillation episodes in Brugada Syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation 123: 1270-1279.
14. 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.
15. Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M, et al. (2007) Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with Brugada Syndrome. J Cardiovasc Electrophysiol 18: 1244-1251.
16. Brugada P, Brugada R, Mont L, Rivero M, Geelen P, et al. (2003) Natural history of Brugada Syndrome: the prognostic value of programmed electrical stimulation of the heart. J Cardiovasc Electrophysiol 14: 455-457.
17. Morita H, Kusano KF, Miura D, Nagase S, Nakamura K, et al. (2008) Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada Syndrome. Circulation 118: 1697-1704.

18. Giustetto C, Drago S, Demarchi PG, Dalmasso P, Bianchi F, et al. (2009) Risk stratification of patients with Brugada type electrocardiogram: a community-based prospective study. Europace 11: 507-513.
19. Makimoto H, Nakagawa E, Takaki H, Yamada Y, Okamura H, et al. (2010) Augmented ST-Segment Elevation During Recovery From Exercise Predicts Cardiac Events in Patients with Brugada Syndrome. J Am Cardiol 56: 1586-1594.
20. 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.
21. Sarkozy A, Sorgente A, Boussy T, Casado R, Paparella G, et al. (2011) The value of a family history of sudden death in patients with diagnostic type 1 Brugada ECG pattern. Eur Heart J 32: 2153-2160.
22. Priori SG, Gasparini M, Napolitano C, Della Bella P, Ottonelli AG, et al. (2012) Risk stratification in Brugada Syndrome. Results of the PRELUDE Registry. J Am Coll Cardiol 59: 37-45.
23. Maury P, Rollin A, Sacher F, Gourraud JB, Raczka F, et al. (2013) Prevalence and prognostic role of various conduction disturbances in patients with the Brugada syndrome. Am J Cardiol 112: 1384-1389.
24. Delise P, Allocca G, Sitta N, Di Stefano P (2014) Event rates and risk factors in patients with Brugada syndrome and no prior cardiac arrest: a cumulative analysis of the largest available studies distinguishing ICD-recorded fast ventricular arrhythmias and sudden death. Heart Rhythm 11: 252-258.
25. Sroubeck J, Probst V, Mazzanti A, Delise P, Hevia JC, et al. (2016) Programmed ventricular stimulation for risk stratification in the Brugada Syndrome. A pooled analysis. Circulation 133: 622-630.
26. Migliore F, Testolina M, Zorzi A, Bertaglia E, Silvano M, et al. (2018) First-degree atrioventricular block on basal electrocardiogrm predicts future arrhythmic events in patients with Brugada syndrome: a long-term follow-up studyfrom the Veneto region of Northest Italy. Europace p.144.
27. 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.
28. Okamura H, Kamakura T, Morita H, Tokioka K, Nakajima I, et al. (2015) Risk stratification in patients with Brugada Syndrome without previous cardiac arrest. Prognostic value of combined risk factors. Circulation Journal 79: 310-317.
29. 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.
30. 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.
31. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti B, et al. (2003)Risk stratification in the long-QT syndrome. N Engl J Med 348: 1866-1874.
32. Schwartz PJ, Crotti L, Insolia R (2011) Long-QT syndrome 1993-2011 criteria. Circulation 15: 2181-2183.
33. 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.
34. Nagase S, Kamakura T, Kataoka N, Wada M, Yamagata K, et al. (2018) Low-voltage type 1 ECG is associated with fatal ventricular tachyarrhythmia in Brugada syndrome. J Am Heart Assoc 7e009713.