European Heart Journal Supplements (2024) **26** (Supplement 1), i69–i73
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae021

Brugada syndrome: identification of subjects at risk and therapy

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KEYWORDS
Brugada syndrome;
Sudden death;
Quinidine;
ICD (implantable cardioverter defibrillator);
Epicardial transcatheter ablation

Brugada syndrome mainly affects young subjects with structurally normal heart and can cause x syncope or sudden death due to ventricular arrhythmias, even as the first manifestation, in approximately 5–10% of cases. To date, two questions remain open: how to recognize subjects who will experience arrhythmic events and how to treat them. The guidelines suggest treating subjects with a previous history of cardiac arrest or arrhythmogenic syncope, while they are unconclusive about the management of asymptomatic patients, who represent ~90% of Brugada patients. We recently demonstrated that in asymptomatic patients, the presence of spontaneous Brugada type 1 electrocardiogram (ECG) pattern and inducibility of ventricular arrhythmias at electrophysiological study allows us to identify a group of patients at greater risk who deserve treatment. Regarding treatment, there are three options: implantable cardioverter defibrillator, drugs, and epicardial transcatheter ablation. Recent studies have shown that the latter is effective and free from serious side effects, thus opening a new scenario in the treatment of Brugada patients at risk. Subjects who present drug-induced-only type 1 Brugada ECG pattern, in whom a spontaneous type 1 pattern has been ruled out with repeated ECGs and 12-lead 24-h Holter monitoring, represent a very low-risk group, provided they adhere to behavioural recommendations and undergo regular follow-up.

Introduction

Brugada syndrome belongs to the cardiac ion channels diseases (channelopathies), which include in chronological order of description: long QT syndrome (1963), catecholaminergic ventricular tachycardia syndrome (1978), Brugada syndrome (1992), short QT syndrome (2003), and malignant early repolarization syndrome (2010).

All these channelopathies have some common features:

- They affect young subjects without clinical signs of structural heart disease and cardiac imaging examinations such as echocardiogram and cardiac magnetic resonance imaging are normal.
- The diagnosis is mainly based on the electrocardiogram (ECG).
- They can cause sudden death and this often occurs as the first symptom.

While in the other channelopathies, the prevalence in the general population is very low (<0.1‰), the prevalence of Brugada syndrome is markedly higher, varying in the different case series from 0.5 to 7‰; it is more frequent in Asian countries and in males than females. The high prevalence explains why it can be considered responsible for approximately one-third of sudden deaths in young males without clinical signs of structural heart disease.[1]

The diagnosis of type 1 Brugada ECG pattern is made when the ECG shows a J point greater than 2 mm, followed by

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coved-type ST-segment elevation and negative T wave, in the right precordial leads (V1 and V2) (*Figure 1*).

A possible mechanism proposed to explain these electrocardiographic manifestations is the imbalance between the inward sodium (Na^+) and calcium (Ca^{++}) currents and the transient outward potassium (K^+) current (I_{to}). This occurs predominantly in the epicardium of the right ventricular outflow tract (RVOT), where the I_{to} channel is much more represented.[1]

A second mechanism, supported by the results on the RVOT epicardial mapping and by endomyocardial biopsies, links the appearance of the Brugada pattern to a conduction delay, due to the presence of interstitial fibrosis, increased collagen, and reduction of the gap junctions at this level[2,3]; this conduction delay can be increased by the administration of sodium channel blocker drugs.[4]

Regardless of the hypothesis we accept, Brugada syndrome is an RVOT disease. As the anatomical position of the RVOT can vary from one patient to another, the RVOT should be electrocardiographically mapped, by positioning V1 and V2 electrodes not only in the IV intercostal space (standard position) but also in the II and III intercostal space.[5] This should always be done when recording an ECG in a subject with a known or suspected Brugada pattern.

The intra- and inter-daily fluctuations are typical of the Brugada ECG pattern, making a correct diagnosis often difficult. In doubtful cases, this diagnostic type 1 ECG pattern can be highlighted in two ways:

(1) with prolonged ECG recording, using 12-lead 24-h Holter, with V1 and V2 electrodes positioned both in the IV and II and/or III intercostal space, in order to explore the entire extension of the RVOT; and
(2) with a pharmacological test, by infusion of sodium channel blocking drugs (ajmaline 1 mg/kg or flecainide 2 mg/kg in 10 min); ajmaline pharmacological test should be avoided in paediatric age, due to an increased arrhythmic risk.[1]

In the 30 years since the first description of Brugada syndrome, multiple studies have attempted to identify whether, in addition to the presence of spontaneous type 1 pattern, there were other ECG markers of greater arrhythmic risk. Some of these studies and the electrocardiographic parameters considered are shown in *Figure 2*. Most of the ECG markers of increased arrhythmic risk are expression of a conduction delay in the RVOT.[6]

According to current guidelines, the electrocardiographic appearance of Brugada can be defined as 'syndrome' only when a spontaneous type 1 pattern is documented or when the drug-induced type 1 pattern is associated with symptoms, such as syncope or resuscitated cardiac arrest.[7]

Unlike other channelopathies where the risk of sudden death is generally very high, 'only' the ~10% of patients with Brugada syndrome experience major arrhythmic events during their lifetime and this justifies the need for correct risk stratification, to differentiate this 10% of patients from those who will not have arrhythmic events throughout their life.[8]

In 2009, a study conducted by our group in a population of approximately 200 patients with Brugada ECG pattern[9] demonstrated that in the few patients resuscitated from cardiac arrest, the probability of having a new potentially fatal arrhythmic event was 17%/year, 3%/year in patients with previous history of unexplained syncope and 0.5%/year in asymptomatic patients. These data were later confirmed by the FINGER study (France, Italy, Netherlands, and Germany), which included a larger population of over 1000 patients.[10]

Sudden death can occur in all age groups but more frequently between 30 and 50 years and is more frequent in males than in females.[1]

Factors that can precipitate arrhythmic events are as follows:

- vagal activation, as suggested by the fact that most deaths occur after large meals or at night;

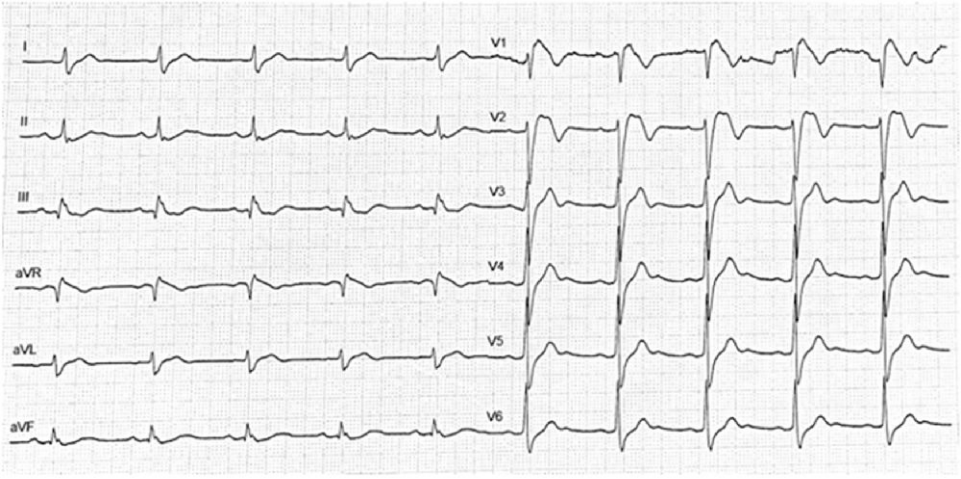

Figure 1 Electrocardiogram with spontaneous type 1 Brugada pattern.

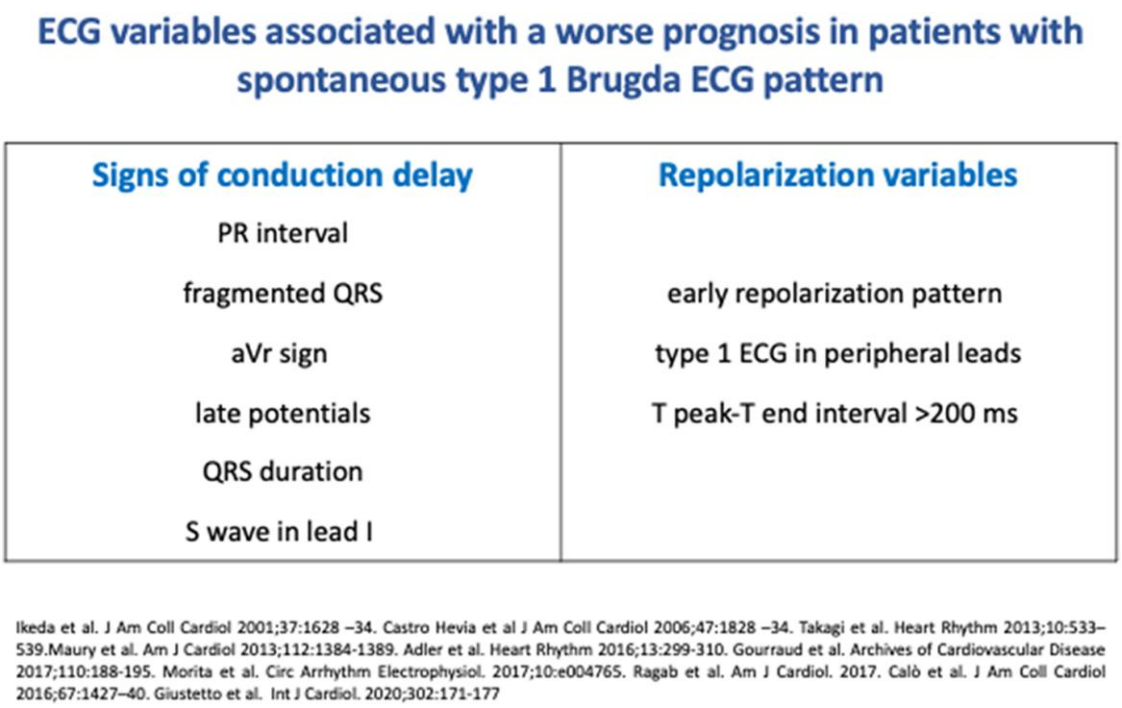

Figure 2 Electrocardiographic criteria associated with increased arrhythmic risk in patients with spontaneous type 1 Brugada pattern. ECG, electrocardiogram.

- some drugs, such as most antiarrhythmics and antidepressants (see www.brugadadrugs.org)[11]; and
- fever that, by altering the function of the Na^+ channel, can unmask or increase the type 1 pattern.

Which patients with the Brugada pattern need to be treated?

There is common agreement that patients who have already had an arrhythmic event, such as resuscitated cardiac arrest or arrhythmic syncope, should be considered at greater risk. This group of patients represents approximately 10% of all patients with the Brugada ECG pattern. Therefore, the clinically open problem is how to identify among the asymptomatic patients, who are approximately 90% of patients with Brugada ECG pattern, those who may experience a major arrhythmic event and who, therefore, must be treated.

To answer this question that has troubled the cardiologists for the last 30 years, multiple studies have been published. The most recent, with the largest series and longest follow-up, is the one published in 2023 by our group, which presents data from 1149 asymptomatic patients with Brugada ECG pattern, prospectively followed for over 6 years.[12]

The main findings of this study were as follows:

(1) Asymptomatic patients with a spontaneous type 1 pattern have a 14 times higher risk of major arrhythmic events compared with patients with a drug-induced-only Brugada ECG pattern; in the population of 539 asymptomatic patients with spontaneous type 1 pattern, there were 16 patients (3%) who, over an average follow-up of 6 years, had an arrhythmic event [10 cardiac arrests, of which only 3 resuscitated and 6 appropriate implantable cardioverter defibrillator (ICD) interventions] (*Figure 3*).

(2) All 539 asymptomatic patients with spontaneous type 1 pattern were advised to undergo an electrophysiological study (EPS) for better risk stratification, which was accepted by 63%. The EPS was positive for induction of ventricular fibrillation in 30% of cases. In these patients, the risk of experiencing a major arrhythmic event at follow-up was 0.7%/year, while in subjects with negative EPS, this risk, although not zero, was only 0.2%/year. These data therefore confirm the usefulness of the EPS in identifying a population at greater risk among patients with spontaneous type 1 pattern.

(3) Asymptomatic patients with drug-induced-only Brugada ECG pattern have an extremely low risk of death (1/610, 0.03%/year) (*Figure 3*). This low mortality, the lowest reported so far in the literature in patients with the Brugada pattern, was not completely in the absence of therapy, since all the patients received the recommendations that we define as the 'first therapeutic step' and that consist in informing the patients of the situations and medications to avoid. Furthermore, all patients with drug-induced-only Brugada pattern should undergo repeated (at least one per year) 12-lead 24-h Holter monitoring (with V1 and V2 electrodes positioned both in the IV and in the II or III intercostal space). This strategy made it possible to identify the spontaneous type 1 pattern in approximately 20% of patients incorrectly considered at low risk and move

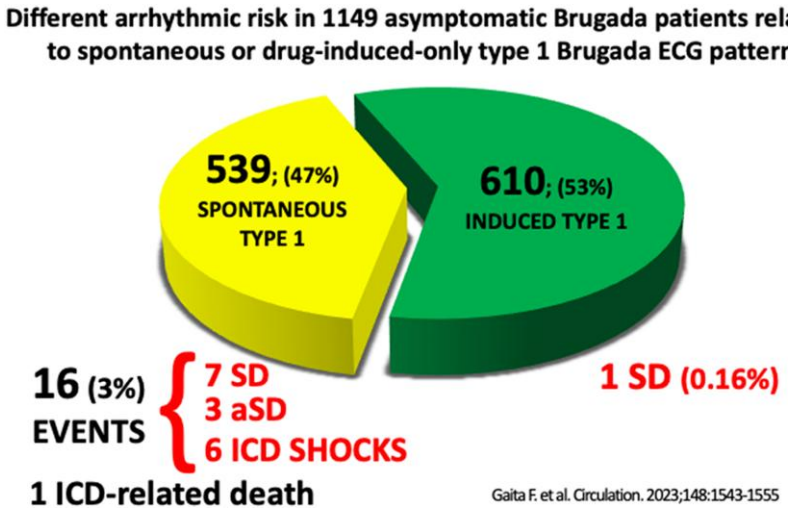

Figure 3 Data from Gaita *et al*.[12] Of 1149 asymptomatic patients, 539 (47%) showed a spontaneous type 1 pattern at the baseline electrocardiogram or at 12-lead 24-h Holter monitoring, while 610 (53%) had a drug-induced-only type 1 pattern; in the latter group, the absence of spontaneous type 1 pattern was confirmed by repeated electrocardiograms and multiple 12-lead Holter (with V1 and V2 leads recorded simultaneously on the IV, III, and II intercostal space), which were always negative. In the group of 539 patients with spontaneous type 1 pattern, 16 patients (3%) experienced an arrhythmic event during the follow-up (7 sudden deaths, 3 aborted sudden deaths, and 6 appropriate implantable cardioverter defibrillator interventions); in the group of 610 patients with drug-induced-only type 1 pattern, only 1 (0.16%) had an event (sudden death). ECG, electrocardiogram; ICD, implantable cardioverter defibrillator.

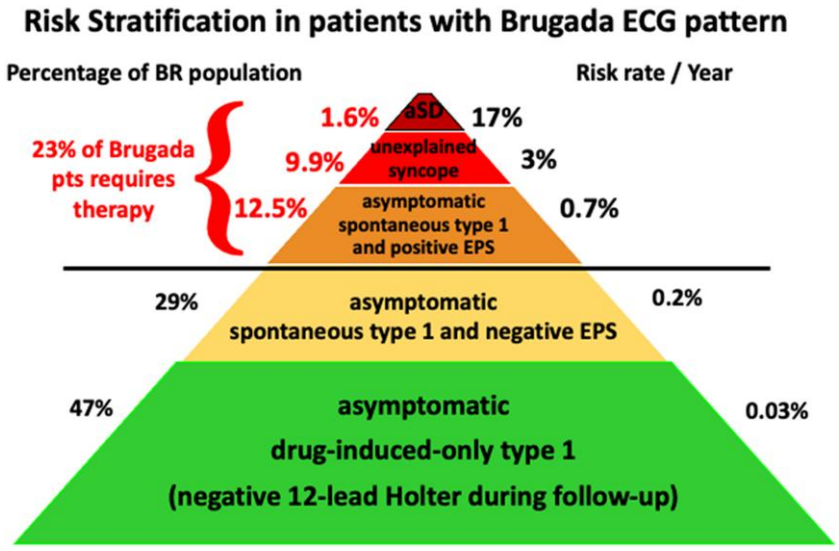

Figure 4. On the left, the percentages of patients according to clinical presentation, the presence of spontaneous type 1 electrocardiogram pattern and result of the electrophysiological study (47% asymptomatic patients with drug-induced-only type 1 electrocardiogram pattern; 29% asymptomatic patients with spontaneous type 1 pattern and negative electrophysiological study; 12.5% asymptomatic patients with positive electrophysiological study; 9.9% patients with unexplained syncope; and 1.6% patients with resuscitated cardiac arrest). On the right, the annual risk of arrhythmic events at follow-up for each subgroup. Based on this distribution, approximately one in four patients deserves treatment. ECG, electrocardiogram; EPS, electrophysiological study.

them into the group of patients at greater risk with spontaneous type 1 pattern, to whom EPS should be recommended.[7] Unlike all previous case series, the Brugada patients included in our study as drug-induced-only during the 6 years of mean follow-up underwent multiple ECGs and 12-lead 24-h Holter monitoring, reducing the possibility of losing the appearance of spontaneous type 1 pattern.

At present, we can state that a series of clinical and electrocardiographic parameters and the result of the EPS allow us to identify, among the asymptomatic patients with Brugada ECG pattern, those at greater risk, deserving therapy (*Figure 4*).

Therapy

Three therapeutic approaches are currently available:

- the ICD (transvenous or subcutaneous);
- drug therapy (hydroquinidine or cilostazol); and
- transcatheter ablation of the epicardial substrate.

The guidelines consider the ICD as the only therapy for patients with cardiac arrest (Class I C) and arrhythmic syncope (Class IIa).[7]

However, the most recent data in the literature show possible therapeutic alternatives to the ICD, considering the high risk of complications, approximately 30%, including, in addition to psychological discomfort, inappropriate shocks, lead fractures, infections, and even risk of death in case of lead extraction.[13]

Concerning pharmacological therapy, the available literature agrees on the effectiveness of quinidine in preventing sudden death in patients with Brugada syndrome, but, unfortunately, approximately 30% of patients have to discontinue the therapy due to side effects.[14,15]

Over the last decade, the possibility of treating Brugada patients by modifying the substrate with epicardial transcatheter ablation of the RVOT has been documented.[3,4] This procedure, performed in centres with great experience, has demonstrated a very high success rate, with mild side effects in the acute phase (mainly pericarditis).[16–18]

In conclusion, today, we have sufficient data on how to identify the patients at greater risk among the asymptomatic with Brugada ECG pattern. Concerning treatment, we believe that it is time to update the guidelines, adding epicardial transcatheter ablation of the arrhythmic substrate among the therapeutic strategies.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

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