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Programmed electrical pacing of the heart in Brugada Syndrome. Part II: Variations on the same topic

Estimulación eléctrica programada del corazón en el síndrome de Brugada. Parte II: Variaciones sobre un mismo tema

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ARTICLE INFORMATION

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In this second part, various criteria on programmed electrical pacing of the heart (PEPH) for risk stratification in Brugada syndrome (BrS) are summarized. Conflicting and contradictory results were noticed, thus the readers may form their own opinions. But there is a warning for those who like to arrive at a consensus: *THERE IS NO CONSENSUS!*

Paul *et al*[1] published a meta-analysis of 15 studies, published in *Medline* (1999-2006), to establish the utility of PEPH for risk stratification in BrS. The results were divergent, limited and uncertain; however, some conclusions about its actual usefulness were drawn, especially in asymptomatic cases. The International Brugada Registry may overestimate some figures such as sudden death (SCD) and ventricular fibrillation (VF), perhaps because it includes the first years where the most obvious and riskier cases were identified.

The study by Paul *et al*[1] did not find a significant role for PEPH —inducibility of malignant ventricular arrhythmia (MVA) in a laboratory— with regard to future arrhythmic events in asymptomatic patients with Brugada type electrocardiogram (ECG). Therefore, it was not possible to identify high risk subjects, except in the Brugada series with results that are divergent from the rest (14 studies), which greater inducibility to predict future MVA was explained due to the fact that these were more severe cases and used different protocols (unproven issues). There was a high percentage of asymptomatic patients with positive PEPH and subsequent clinical VF, and it was considered that patients at risk were identified that way. This needs to be reassessed because there was a reduction in the series itself (from 28% to 8%, and to 5% of spontane-

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ous MVA after the study, in asymptomatic patients) in their subsequent publications[1,2]. The inducibility of VF in BrS was higher in survivors of cardiac arrest (CA), intermediate in those patients with syncope and lower in asymptomatic patients. The use of PEPH is not as strict as before, it has specific roles, for example, in the associated supraventricular tachycardias [due to the possibility of radiofrequency ablation (RFA)] and some others, but the way to manage asymptomatic carriers remains very difficult[1].

In considering the divergence between the Brugada series vs. the other 14, it is concluded that PEPH is not useful, or is of little use to stratify risk in BrS[1,3-6]. Furthermore, a nonclinical arrhythmia may be induced in the laboratory, one that will not occur later in the follow up; and vice versa, that is, the arrhythmia which will occur later may not be induced in the laboratory[4,5].

When deciding on the use of an implantable cardioverter-defibrillator (ICD), it is vital to assess very well the risk-benefit ratio, because complications are frequent (inappropriate shocks, infection, T-wave oversensing, proarrhythmia and broken wires). A European study reported 28% of serious problems, with 1% of lives saved per year for asymptomatic BrS patients with MVA inducibility in the laboratory. There are alternatives such as subcutaneous extracardiac ICD with only shock therapy or the use of quinidine (in asymptomatic BrS, it becomes what the beta blocker is for asymptomatic long QT syndrome)[7-16]. Viskin[4] and Sacher *et al*[9] hope that the same will not happen in asymptomatic subjects with J wave or with a sign of short QT, and state that it did not happen with long QT because of the different historical moment, otherwise many devices would have been implemented unnecessarily.

In the European Multicenter Study on ICD, the device was not needed in most children with asymptomatic BrS. This has led to heated debates. Brugada notes that "...defining the role of electrophysiological testing in asymptomatic Brugada syndrome is probably the most heated debate in arrhythmology nowadays"[17].

Priori *et al*[6] (PRELUDE study, PRogrammed Electrical stimUlation preDictive valuE) enrolled patients with ECG pattern of Brugada type 1, spontaneous or induced by drugs, with no history of CA or sustained MVA; with a uniform protocol, as aggressive as those used before; with two cycle lengths and three extrastimuli at two sites of the right ventricle, limited by coupling intervals and followed up for 36 months. Fourteen of them (4.5%; 1.5% annually) experienced the primary endpoint (13 with appropriate intervention of the ICD and 1 revived from CA). There were no deaths. The main finding was that arrhythmia-free survival was almost identical in those with and without induced sustained MVA. PEPH was not sensitive in predicting arrhythmic events (sensitivity 35.7%, specificity 58.8%). The former declined to 25% with a slight increase in the latter (74%) when only those subjects with induction related to 1 or 2 extrastimuli were included. The frequency of episodes after four years was slightly higher, without being statistically significant, among non-inducible (4.9%) compared to inducible ones (3.9%). A negative PEPH was not associated with a low risk of arrhythmic episode. The PRELUDE study showed that the immediate reproducibility of a positive PEPH was only 34% and has provided so far the most rigorous evidence of its poor usefulness for stratifying risk in patients with BRS. There is no clear explanation of why some authors report a predictive value of PEPH, contrary to the PRELUDE and other studies. There may be not known differences in patient characteristics, protocols, treatments and follow-up, which are responsible for the discrepancies.

Ventricular fibrillation was inducible in 37% of asymptomatic carriers in the France Italy Netherlands Germany (FINGER[18]) study vs. 57% in the Registry of Japan. Spontaneous arrhythmia was low in both studies, compared with other research, without the influence of inducibility or non-inducibility during PEPH. The long-term prognosis of patients with BrS was investigated, as well as the associated arrhythmic risk (especially in asymptomatic subjects) and risk factors for SCD. This study included data from 11 tertiary centers in 4 European countries, patients with type 1 ECG (spontaneous or with drug), 6% of them resuscitated from SCD, 30% with syncope episodes and 64% were asymptomatic subjects. There were arrhythmic events during follow-up in 5% of subjects (7.7% per year in the SCD group, 1.9% in syncopal subjects and 0.5% in asymptomatic subjects). It was concluded that symptoms and type 1 ECG were independent predictors of arrhythmias; while gender, a family history of SCD, the inducibility of MVA in PEPH and SCN5A mutation were not independent predictors of arrhythmias. The number of episodes in asymptomatic patients was low (0.5% per year, SCD was 0.4%). It was considered that

PEPH does not stratify the arrhythmic risk nor allows a decision on the treatment (ICD). Previously, the Brugada type ECG was seen as an indicator of high risk for SCD; the second consensus raised PEPH as the cornerstone for stratification and therapeutic decision making: if it was positive in asymptomatic patients, an ICD was recommended (something with which other authors do not agree).

PRELUDE[6] was a study with predetermined inclusion and exclusion criteria, and standard protocols. Errors were reduced but not entirely eliminated. It found other indices with significant independent predictive value in terms of arrhythmias, with changes in sensitivity and specificity for PEPH: spontaneous BrS type 1 (92.9% but with a low specificity of 47.5%); greater specificity for QRS fragmentation, 93.5% (fragmentation, spike, asynchronous electrical activation due to non-uniform anisotropic propagation); and a combination of syncope and spontaneous type 1 pattern (90.5% specificity and a relatively low sensitivity of 42.9%). The absence of spontaneous type 1 pattern and ventricular refractory period greater than or equal to 200 ms showed a greater probability of survival free from arrhythmic events than a negative PEPH.

Viskin and Rosso[19] state: "In recent years, numerous asymptomatic individuals worldwide have undergone electrophysiological studies 'only' because they have a pathological ECG indicative of Brugada syndrome". He spoke of the risk of SCD in the asymptomatic BrS, indicating that it was not as high as previously thought nor as low as one would like... and concluded that: "The realization that we have done more harm than good to many asymptomatic individuals has reopened the debate on the optimal management of asymptomatic Brugada syndrome"[4,5]. There are many views and discussions on an issue that is far from closed. In a 3 years follow-up, 3-4% of asymptomatic patients with ICD due to a positive PEPH had spontaneous arrhythmia[5].

Fauchier *et al*[20] (2013), published a meta-analysis of the prognostic value of PEPH in BrS with global data from 13 series, each with 20 or more patients, released in the years 2002-2005, 2007, 2009, 2010 and 2012; with a total of 2743 patients (the largest meta-analysis of this type ever), 77% of them underwent PEPH. Three subgroups were considered according to their clinical presentation: revived from CA, unexplained syncope, and asymptomatic individuals, enabling more homogeneity. The inducibility of ventricular tachycardia (VT)/VF was associated with higher risk of arrhythmia during follow-up, without statistical significance, but heterogeneity was found in the 13 studies. The risk was greater when there was inducibility in syncope and asymptomatic subjects groups, but not in the CA groups. Current guidelines indicate that PEPH may be considered useful for stratifying risk in asymptomatic subjects with spontaneous ST segment elevation, which contradicts two previous meta-analyses, which did not identified its value according to the initial clinical presentation. Risk stratification is problematic in asymptomatic or mildly symptomatic subjects with positive PEPH, and the proposition of using the device in them continues in full discussion, while in the CA subjects its indication is not debated. The inducibility of sustained MVA is higher in patients with CA (72%) and syncope (59%) than in asymptomatic patients (40%). During the follow-up, the arrhythmic episode (sustained VT, VF, SCD or ICD therapy) was seen in 8% of patients, representing 3.0% of arrhythmic events per year (13.5% in CA, 3.2% in syncope and 1.0% in asymptomatic subjects). The induction of MVA is not absolutely reliable and does not have a clear relationship with the risk of subsequent arrhythmias.

The decision of using an ICD in asymptomatic patients faces the risk of potential future MVA versus the risk of inappropriate shocks and their impact on the future quality of life of patients.

Clinical electrophysiology began in Cuba in December 1984, and the National Registry of SCD in subjects without demonstrable structural heart disease by conventional methods and the National Registry of BrS, in 2000.

In our daily experience, it has been observed a poor reproducibility of MVA in the laboratory in patients with a clinical history of them (false negatives) and vice versa, that is, the induction in the lab of MVA that had not existed in real life nor were present during the follow-up (false positives). Therefore, the use of an ICD based on PEPH could be wrong, both for stratifying the risk of MVA onset and specifying the recurrences and electrical storms in the follow-up of those who had had a previous episode.

Then some questions arise: What is the true value of PEPH for stratifying risk in inherited arrhythmogenic syndromes and how much influence does it have in the therapeutic decision to place an ICD? What is the value of the inducibility of MVA in the laboratory to predict the onset or recurrence in the follow up? What

is its importance in asymptomatic subjects? How important it is in the need to link antiarrhythmic drugs to ICD?

We had the experience with idiopathic VF, an important group among the subjects without structural heart disease resuscitated from episodes of SCD. In general, they are young people with a normal life expectancy, in whom the inducibility of clinical VF is not always achieved in PEPH, and the risk of future recurrences cannot be predicted. The catastrophic event may be the onset, and few can be resuscitated. VF is the most serious arrhythmia and causes most of the arrhythmic SCD[21-24].

When considering electrical SCD in general, the various channelopathies, and idiopathic VF in particular, there was a high frequency of recurrences (including electrical storms) and low inducibility of the MVA responsible for the SCD episode[21,25,26].

Therefore, major conflicts are faced: the low recovery of patients with episodes of SCD (about 5%) and frequent recurrences of MVA in the follow-up. The problem is that there are no blind or randomized studies but records and expert opinions. Asymptomatic patients with Brugada type ECG pose an even greater problem, just as the carriers of J wave and short QT without symptoms[27-31].

In the group of idiopathic VF, there is no doubt about the management. It is imperative to implant a device, but it is important to know which patients are at a higher risk of recurrence in the follow-up, and predict recurrences in those who already have an ICD, to associate antiarrhythmic agents in those patients prone to recurrences. These drugs reduce arrhythmias but have other drawbacks such as increasing the threshold to defibrillation and pacing of the pacemaker joined to the ICD, decreased VF threshold, and morbidity and mortality due to the primary and secondary pro-arrhythmogenic capacity of antiarrhythmic agents [21,22,32,33].

Other conflicts may be that the episode of MVA is not proven, because of the extreme urgency of the situation, and that the asymptomatic subjects have transient electrical signals. In cases of idiopathic VF, in the laboratory there is a substrate that is not searchable, artificial triggers and a non-adaptable modulator.

The inducibility of VF during PEPH is higher in the BrS than in idiopathic VF. Myerburg *et al*[34] point out that it is only 12%. The role of PEPH in general has changed over time and has important limitations (it causes non-clinical arrhythmias or does not reproduce the truly clinical ones)[35-37]. It is said that five years after the CA, there is a chance of recurrence of VF in 30% of cases (aborted or not by the ICD), the rest is free of symptoms during follow up. The challenge is to identify the subjects at high risk of having a first episode (only 5% can recover), anticipating the onset of the MVA or its recurrence, because there are many electrical predictors at present, but they are elusive.

In the UCARE (Unexplained Cardiac Arrest Registry of Europe), stimulation obtained 50% of inducibility, with low negative and positive predictive value. According to Champagne *et al*[22], it failed to predict subsequent episodes (sensitivity and specificity of 43 and 64%, respectively) and its predictive values were not clinically useful. Others find a low positive value and a high negative value[7,22].

In the electrophysiology laboratory, where a complex and invasive study is done, there are no definitive markers to stratify risk and, in general, it is not useful, or is of little use, in inherited arrhythmogenic syndromes. In our series of idiopathic VF[21], the MVA was only induced in 15% of subjects, a figure that is contradictory in the literature[3]. The induction of clinical arrhythmia in the lab does not ensure future recurrences. Thus it loses its value in establishing a prognosis of recurrence, which is one of the major objectives of performing it. Recurrences were very common, patients who would have died if they had not had the device. False negatives (non-inducibility) are noteworthy, with the presence of MVA after PEPH. One of our patients had ventricular flutter and VF when the passing of the catheters (external electric shock was needed); however, arrhythmia could not be induced with the immediate stimulation and a subsequent intervention of the ICD has not been necessary. This gives an idea of how random laboratory reproducibility could be and the enormous potential variability of results.

The cases of idiopathic VF are more frequently recognized after resuscitation from CA, and this is very low. It would be necessary to find specific markers that help identify predisposed individuals, in order to anticipate the disastrous episode in those suspected to be at risk because of their family history or due to some premonitory electrical signal (T wave abnormalities, early repolarization and others). That is difficult, and, in general, impossible.

In the BrS, we must distinguish between the true

BrS and patients with Brugada type ECG (without MVA, syncope, or episodes of SCD). There is no doubt about the therapeutic decision (ICD) in the subpopulation recovered from SCD. There may be some doubts in syncope patients (sometimes the origin is unclear, and there may be coexistence of BrS and epilepsy, cases that are interpreted as vasovagal episodes or epilepsy when they are true BrS and vice versa)[38]. In asymptomatic subjects, who are the majority when making the diagnosis, there is urgency for stratifying risk and major conflicts arise. The questions have no single answer and literature has been very inconsistent over the years. It is an unsolved problem and many questions remain without convincing answers nowadays[39-47].

In some Japanese studies, the annual incidence of SCD in asymptomatic subjects with type 1 ECG is 0.4-0.5%. Italian data show a very low number of arrhythmic events (0.48%). The FINGER study found 0.5% per year. In a subgroup with a 66 months follow-up (the longest so far), 4.5% had arrhythmic events with an incidence of 0.8% per year; and in the PRELUDE study, arrhythmia was present in 4.5% of subjects (1.5% incidence) in a 36 months follow-up[6,18,48-50].

PEPH alone cannot decide whether a device is implanted or not. It is true that the greater inducibility is found in those resuscitated from CA, is greater in symptomatic than in asymptomatic subjects, and greater in these compared to normal subjects (which would correspond to false positives). It has been used to determine if a sustained VT can be induced, it "may be considered for risk stratification in asymptomatic Brugada syndromes patients with spontaneous…" The debate persists as well as the lack of uniform and significant evidence, but it continues being used to stratify risk in symptomatic and asymptomatic patients, with and without spontaneous ST segment elevation[51].

Gasparini *et al*[52] have suggested that asymptomatic subjects have the arrhythmic substrate but do not have the trigger of VF, that PEPH serves to expose the substrate rather than to predict arrhythmia, and that its inducibility is unrelated to future episodes.

Gehi *et al*[53] published a meta-analysis of 30 prospective clinical studies (1 545 patients) and concluded that PEPH does not predict the risk of MVA; it was present from 0.8 to 4% of cases at follow-up. The meta-analyzes of Gehi *et al*[53], Paul *et al*[1], and PRELUDE[6] agreed that it does not predict arrhythmic events in BrS; in addition, Eckardt *et al*[54] found fewer incidents in the follow-up, unlike the Brugada series.

The recording of MVA in the follow-up of asymptomatic subjects may be poor, in the absence of the ICD as an exceptional witness. The use of antiarrhythmic drugs associated with the device or in asymptomatic patients may alter the natural history of arrhythmias and distort their true rate in the follow-up. All of which makes it difficult to interpret the results of the electrophysiological study.

There are cases with more than one such study and variability between them, that is, inducibility in one and its absence in another, which demonstrates the randomness of the results because an arrhythmia requires the presence of the three elements: the substrate (that in this disease is molecular, constant, not searchable, and with different electrophysiological properties), the trigger and the modulator.

Despite the questionable value of PEPH, even with its uncertainties and limitations, it is not discounted altogether and there are things to be done in terms of monitoring, protocols, records, sites of stimulation, and genetic and genomic studies[55-61].

Patients with type 1 BrS in right precordial leads, episodes of VF or polymorphic VT, syncopal events or those resuscitated from SCD should receive an ICD. But risk stratification in those with poorly documented or asymptomatic MVA is very complex, and it would be important, for example, to decide the use of an antiarrhythmic agent in addition to the ICD.

Brugada and Antzelevitch raised the utility PEPH to stratify risk and decide the placement of an ICD, although the number of episodes of MVA in the monitoring of these patients was much lower in other authors' studies[1,2,17,36,62,63].

Sometimes the registries report more frequently the symptomatic, most serious and complex cases, and the asymptomatic cases may escape medical diagnosis. In a recently known disease, morbidity and mortality are often overestimated. Eventually, asymptomatic cases are better identified and a more realistic perception of the problem is achieved[4,19,64]. In subsequent reports of BrS in asymptomatic subjects with VF during follow-up, the number has decreased in the Brugada series itself (although the first patients were included in subsequent publications)[1,2,60-63].

Brugada, Antzelevitch and others think that the inducibility of MVA in PEPH predicts future episodes, stratifies the risk and should be taken into account when deciding the placement of an ICD in asympto-

matic subjects[17,60-62,65,66]; other authors disagree[1,3,6,18,22,34,48,50,52-54,64] and state that the inducibility does not always predict the onset or future recurrence of MVA, nor allows a decision on the use of an ICD in asymptomatic subjects (low positive and negative predictive value).

Similar problems were discussed before about the value of PEPH in other clinical situations: ischemia, cardiomyopathy, accessory pathways, to define its true role, to stratify the prognosis of malignant episodes.

Antzelevitch *et al*[41] considered that BrS is responsible for 4% of all SCD and for more than 20% in individuals without structural heart disease. Takagi[50] reviewed data published on the use of PEPH to identify high-risk patients in the BrS and proposed four key issues for discussion: 1) evidence supporting the view that PEPH predicts cardiac events in BrS; 2) evidence that deny their predictive value; 3) meta-analyzes; and 4) possible reasons for such divergent results regarding the predictive value for future cardiac events. This author concludes that most of the previous studies and meta-analyzes found poor utility of PEPH to stratify risk in BrS (without unequivocal explanation for the divergent results), and that a combined clinical and electrophysiological approach or a protocol with 500 ms basic cycle length and two extrastimuli may be useful in establishing the risk profile in the BrS, especially in asymptomatic patients.

Symptomatic subjects are not the problem in terms of making a treatment decision, the real conflict is about those subjects with Brugada type ECG in whom we should determine the risk, and whether the treatment should be aggressive or not. Asymptomatic subjects with a Brugada pattern and inducible VF can receive an unnecessary aggressive treatment because of a positive PEPH that allegedly identified patients at risk of death (as said before, other authors do not confirm this), and it may be a time bomb if it is presented like this to the patient and his/her family[4,11].

The association between the vulnerability to spontaneous MVA and its inducibility gives PEPH a diagnostic value. However, this does not mean necessarily that its prognostic value allows a decision on the therapeutic option; and, in general, its negative predictive value is accepted but not the positive predictive value.

About asymptomatic individuals, it has been said: "Our present therapeutic approach to asymptomatic Brugada syndrome is probable causing more harm than good" (Viskin, Shimizu, Antzelevitch, Wilde and Belhassen, from the US, Holland, Israel and Japan)[11].

The therapeutic decision must consider clinical, genetic and common sense elements. Inducibility not always predicts future episodes; and it is possible to induce non-clinical arrhythmias, or fail to induce the clinical ones. All elements are important but none is absolute to stratify risk. Standard protocols, longer studies, longer follow-ups are required. Then the risk-benefit ratio would be better assessed (remember the 28% of complications with ICD). An isolated PEPH is not enough to make a decision. It is necessary to compare the real risk of MVA with ICD complications and the quality of life of the patient.

Moreover, it is important to remember the possible use of quinidine associated with ICD in some cases to prevent recurrences and electrical storms or supraventricular arrhythmias that could cause inappropriate shocks from the device. It is the oldest antiarrhythmic drug, the most effective or the only one in some diseases (BrS, short QT syndrome, early repolarization, idiopathic VF, electrical storm). It normalizes short ventricular refractory period and blocks Ito currents. There was an attempt to eliminate it from the market for purely commercial reasons. Viskin has described it as an "endangered species", "The fall and rise of Quinidine" and "Quinidine, a life-saving medication for Brugada syndrome, is inaccessible in many countries"[16,41-43].

To stratify the prognosis in patients with BrS, it is necessary to take into account sex, mutations, low heart rate, increased PQ interval, ST horizontal or downward morphology after J wave, genetics, sinoatrial dysfunction and early repolarization (especially if it is persistent, frequent and in several leads)[59] —some important data to take into account appear in the **Figure**—; and then, with all these elements, it is possible to come closer to the risk stratification in a given patient.

There are electrical signals that range from normal to arrhythmogenic such as electrical memory, the notches of the R wave, T wave abnormalities, high and narrow QRS complex, the signals of long QT and short QT. As for the J wave, there are debates from 1936 to date, "the tale of 2 js", innocent or guilty. Its configuration, extension, width, location, and course are studied; and it may be a sign, a syndrome, a malignancy marker, a different form of SCD or coexist with other clinical situations[28-30].

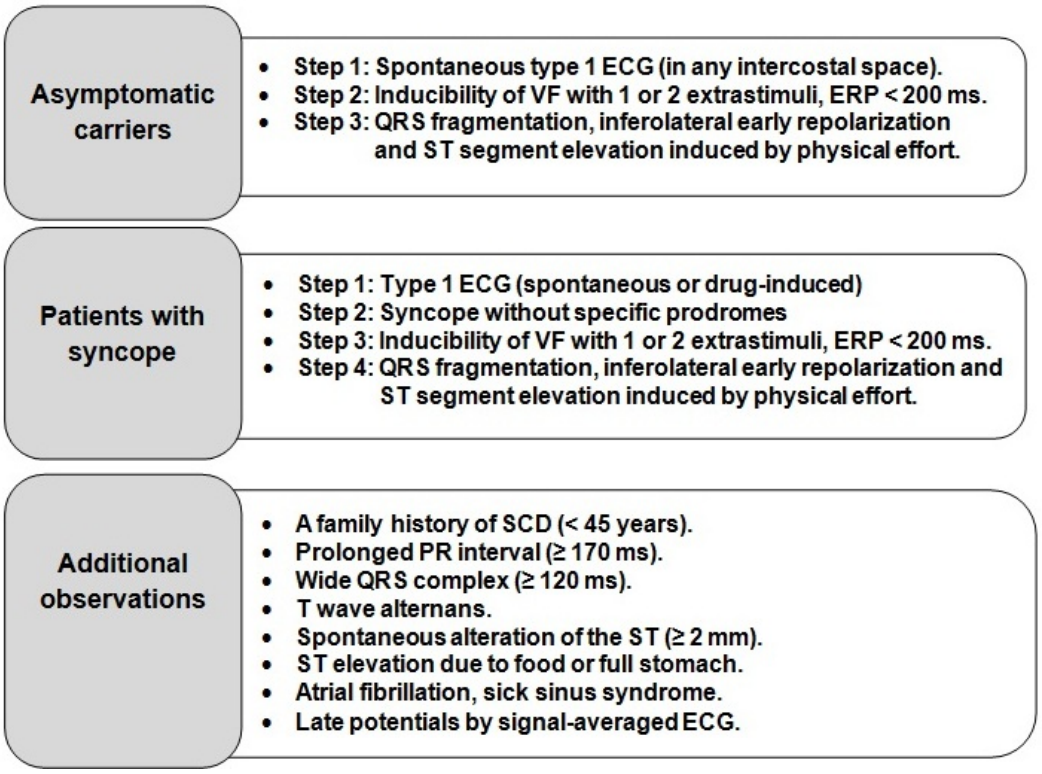

Figure. Proposition for stratifying risk in BrS. Modified from Wada T, Morita H. J Arrhythmia 2013;29:100-9[59]. VF: ventricular fibrillation, SCD: sudden cardiac death, ms: milliseconds, ERP: effective refractory period.

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APPENDIX

Summary of some studies on inducibility of MVA in PEPH and the prediction of subsequent events in patients with BrS [1,2,6,17,18,49,50,53,54,60,62,65].

1. It predicts arrhythmic events

- Brugada and colleagues: They were the first to propose that the inducibility of sustained MVA in PEPH was useful to identify high risk for SCD. At the follow-up of patients with spontaneous type 1 BrS, they found a significantly higher frequency of arrhythmic events in patients with inducible MVA (17%) than in those who did not had it (2%), and in cases without previous CA it was 13% vs. 1.1%.
- Benito: Prospective study. In patients with inducibility, the incidence of events was significantly higher (74.1%) than in those who did not have it (27.6%).
- Delise: Combined clinical and electrophysiological study for risk stratification. In type 1, without previous CA, serious arrhythmic events (VF or SCD) were seen in 14% of patients with inducibility of MVA, in 0% in those without inducibility and in 5.3% of those in which PEPH was not performed. There was no single clinical risk factor able to identify patients at a higher risk, including positive PEPH; poor prognosis patients had spontaneous type 1 and at least two of the following factors: a family history of SCD, syncope and positive PEPH. The prognostic value of PEPH alone or in combination with other risk factors was established.

2. Its predictive value is refuted

- Priori: It was raised that a high inducibility could lead to unnecessary overtreatment with ICD. PEPH was performed in patients with BrS and sustained VF or polymorphic VT was induced in 66% (sensitivity and specificity of 66 and 34%, respectively). Survival analysis after CA did not show an association between inducibility and spontaneous occurrence.
- Other long multicenter studies: The value of the inducibility of MVA to identify high-risk patients was not confirmed.
- Eckardt: PEPH was performed in 188 patients with type 1 ECG; 9 had some type of arrhythmic episode in the follow-up, MVA had been induced in 5 of them during PEPH (56%). The positive and negative predictive values were low.

- FINGER: Multicenter European study, PEPH was performed in 638 of 1 029 subjects. Sustained MVA was induced in 41% of them. Inducibility was higher in symptomatic (46%) than in asymptomatic subjects (37%), and only 3% of inducible ones developed spontaneous VF in the following 5 years. The low positive predictive value of PEPH excludes its use for clinical decision making. There was no significant difference between subgroups of CA, syncope and asymptomatic subjects (44%, 47% and 37%, respectively).
- Recent Japanese studies: Multicenter, prospective, large-scale studies.
  - Kamakura: 330 patients, with PEPH in 232. It achieved a higher inducibility. In 172 patients with type 1 ECG, MVA was induced in 66% of patients with VF, in 78% of those with syncope and in 57% of asymptomatic subjects, with no significant differences. In the follow-up of patients with Brugada type ECG, inducibility was not an independent predictor of arrhythmic events.
  - Takagi: 188 patients with PEPH in 146 (31 with VF, 52 with syncope and 63 asymptomatic), VF or polymorphic VT was induced in 74%, 79% and 79%, respectively, without significant differences between the groups.
  - Another study by the same authors: 460 patients, with PEPH in 334 (62 with VF, 91 syncope subjects and 181 asymptomatic subjects). VF or polymorphic VT was induced in 60%, 73% and 67%, respectively. Inducibility was not useful in predicting events during follow-up in all patients, nor in those without documented VF. Some studies have some diagnostic value because the frequency of inducibility of MVA is higher in symptomatic than in asymptomatic subjects, but all refute the prognostic value of PEPH for predicting arrhythmic events.

3. Meta-analyses (2006 and 2007). The role of PEPH as a predictor of these episodes

- Gehi: Data from 30 prospective studies, 1 545 patients. The relative risk and the difference of episodes in the BrS (syncope, SCD or ICD shock) were assessed for a variety of factors. PEPH was performed in 785 patients and the follow-up of inducibility was not an independent predictor of arrhythmic episodes.
- Paul: 15 studies, 1 217 patients with BrS and 1 036 with PEPH. Inducibility was higher in symptomatic than in asymptomatic subjects (66% in VF, 55% in syncope and 25% in asymptomatic subjects). Inducibility did not show independent predictive value for subsequent occurrence of MVA (which was raised in the series of Brugada, with a difference between his findings and those of other studies).

4. Takagi: Possible explanations for these differences

a) Methodological differences in PEPH protocols: Number of extrastimuli, minimum coupling interval (greater than 200 ms or refractoriness), site of stimulation (right ventricular apex or outflow track, or both) and amplitude of the electrical impulse during stimulation. Brugada stimulated the apex, with 3 extrastimuli and minimum coupling interval of 200 ms; The FINGER study and two recent Japanese prospective studies stimulated from the apex and the outflow tract, with 3 extrastimuli. The FINGER used a minimum coupling interval of 200 ms, while the Japanese used ventricular refractoriness. The conclusion is that the stimulation protocol influences the inducibility of the MVA.

The minimum coupling interval of the extrastimuli (determining the rate of inducibility of FV) is greater than 200 ms in the FINGER study and shorter in the Japanese study (less than the ventricular refractory period). As a result, the percentage of inducibility of VF is higher in the Japanese study than in the FINGER study (57% vs. 37%). The percentage of patients with spontaneous VF in the follow-up of both studies is lower than in the Brugada series and is not influenced by the results of the PEPH.

- A study in a single center and a multicenter study: Uniform protocol of PEPH, 108 patients with type 1 ECG (26 with VF, 40 syncopal and 42 asymptomatic subjects), maximum of 3 extrastimuli from the apex and outflow tract to ventricular refractoriness or to 180 ms of coupling interval. Inducibility was not associated with increased risk of VF. Those who were inducible with 1 or 2 extrastimuli had a worse prognosis than those who required 3 (in all, including those with undocumented VF). The MVA that was inducible with 2 extrastimuli had a better positive or negative predictive value than that of the MVA inducible with 3 extrastimuli. It was concluded that one or two extra stimuli were

adequate as a prognostic marker and that the site of stimulation and the coupling interval were not adequate in BrS.

- PRELUDE: Prospective registry to investigate the predictive reliability of MVA induction by PEPH, 10 centers, 308 patients with type 1 ECG, without a history of CA, with a uniform protocol, two cycles of 600 and 400 ms, and 3 extrastimuli the apex and outflow tract, with a minimum extrastimuli interval of 200 ms (S2, S3) and ventricular refractoriness for S4. At the follow-up, the inducibility of VF or polymorphic VT was not associated with the occurrence of arrhythmic events (VF or appropriate intervention of the ICD), 3.9% in those who were induced vs. 4.9% in those who were not. The protocol was more aggressive but its negative predictive value was lower. It was concluded that the inducibility of VF or polymorphic VT has no predictive value for the occurrence of arrhythmic events, which agrees with the results of two meta-analyzes, the FINGER and the Japanese multicenter prospective studies, and differs from others. Inducibility is identical in the PRELUDE and the Brugada series, but the frequency of cardiac events during follow-up was significantly lower in the former. There was a similar inducibility with 3 extrastimuli, but the predictive value of PEPH was different, perhaps due to some bias in the Brugada series.

b) The time of the day affects the results of the PEPH. The magnitude of the increase of the ST segment in the right precordial leads in BrS is an arrhythmogenic substrate which varies with the days and during the day. It is generally greater at night, and PEPH is often performed by day.
c) It is discussed whether asymptomatic subjects must undergo PEPH, as Brugada says. There is a relatively low frequency of spontaneous events (except in his data), due to differences in monitoring, patient characteristics and techniques of induction; making it difficult to establish the predictive value of PEPH in the emergence of future cardiac events.