Risk stratification in Brugada Syndrome – Current Status and Emerging Approaches

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Word count: 2259

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Brugada syndrome (BrS) remains one of the most common inherited channelopathies associated with an increased risk of sudden cardiac death (SCD), with a worldwide prevalence of approximately 0.05% (1-3). It is accepted that appropriate utilization of the ICD in high-risk patients with aborted SCD and haemodynamically compromising arrhythmias is life saving. However, there remains a lack of consensus on the management of patients with BrS and no history of ventricular arrhythmias or aborted SCD especially in the context of a resting Type 1 coved ECG pattern. The current guidelines (4) and consensus statement (5) recommend ICD implantation in patients with BrS with spontaneous type 1 ECG pattern and probable arrhythmic-related syncope, the latter being heavily dependent on the quality of the syncope history. This recommendation is based on several studies having demonstrated a higher risk of arrhythmic events in such patients compared to those without these factors present (2, 3, 6, 7). However, whether other clinical factors are better predictors or facilitate more refined risk stratification before any arrhythmic event is still up for debate. This is especially important, as the first clinical event may be cardiac arrest. Indeed, the recent SABRUS study that specifically evaluated patients presenting with a lethal arrhythmic event found 25% of patients did not reach the current ICD implantation criteria (8).

*i) Brugada ECG pattern or BrS*

Before refining risk stratification strategies, it is important to clarify what establishes a diagnosis of BrS. Guidelines recommend that the presence of a type 1 Brugada ECG pattern whether drug-induced or spontaneous (4, 5). However, others argue that without the presence of symptoms the ECG features only indicate the presence of a Brugada pattern ECG and not the syndrome itself. This argument stems from the

yearly cardiac event only being 0.5% in these patients compared to a yearly cardiac event rate of 1.9% in patients with a history of syncope (3). With the annual risk of death from any cause being around 0.4% in the middle aged male population most commonly affected (9), the additional risk of BrS induced cardiac arrest appears minimal in the asymptomatic population (10). Therefore it can be argued that labeling patient with only a type 1 Brugada ECG pattern and no symptoms with a syndrome and proposing that they are at a significant enhanced risk of SCD might be inappropriate. Offering advise on the aggressive treatment of a fever, avoidance of type 1 ECG pattern provoking drugs and offering review in the presence of symptoms may be sufficient for this cohort of patients. This is supported by the up-to-date guidelines that provide a class I recommendation for observation without therapy in these patients (4). However, there is a spectrum of risk. *Sacher F et al.* (10) showed that 12% of BrS patients that were asymptomatic at ICD implantation had appropriate ICD therapy during a 10-year follow-up period. Further to this, the presence of spontaneous type 1 ECG pattern alone has been shown to be associated with a lower cumulative survival (2), twice the risk of arrhythmic events (3, 11, 12) and shorter time to first arrhythmic event (3) compared to drug-induced type 1 ECG pattern. Therefore, the diagnosis of an isolated Brugada ECG pattern should potentially be restricted to those patients with only drug-induced type 1 ECG pattern and exclude those with a spontaneous type 1 ECG pattern. Furthermore, as the presence of both spontaneous type 1 ECG pattern and syncope has been shown to be associated with a significantly higher risk of cardiac arrest compared to spontaneous type 1 ECG pattern alone, those with the former should potentially be labeled as a high-risk group whilst the latter an intermediate-risk group (3).

*ii) Ajmaline testing*

Another area that requires clarification is the use of Ajmaline testing. Ajmaline is used to provoke the presence of a type 1 Brugada ECG pattern. Along the same lines as already discussed, the presence of a provoked type 1 ECG pattern in the absence of symptoms is not associated with a significant risk of SCD-0.3%/3 years (3). This raises the question of whether performing this investigation is appropriate if it will not result in a change in patient management and might not only lead to enhanced patient anxiety but also unnecessary risk associated with ajmaline testing. This is of particularly importance as studies have reported high rates of concealed type 1 Brugada ECG pattern in asymptomatic patients (13) and should thereby all of these patients be labeled with a syndrome that has life-long implications?

However, if patients are symptomatic, ajmaline testing should be warranted due to the increased risk of SCD seen in these patients with BrS (10). Further to this, in those with a family history of SCD in first-degree relatives, ajmaline testing can help to explain the cause of death in the proband but also if positive allows the identification of family members with potential high-risk features (5).

*iii) Risk Stratification in BrS*

Identifying factors that are associated with an increased risk of ventricular arrhythmias and SCD in BrS is now a significant challenge. With ICDs being associated with a life-long complication risk of up-to 45% (14) it is essential that the decision to implant these devices be not taken lightly. Indeed, although the advent of subcutaneous ICDs could reduce the risk of transvenous lead problems long-term;

there still remains the morbidity of inappropriate device therapies and risks of infection with multiple generator changes over time.

Several risk factors have been proposed over the years. The FINGER registry, the largest international cohort to date assessed the role of 6 proposed risk factors: syncope, spontaneous type 1 ECG, gender, family history of SCD, inducibility of ventricular tachyarrhythmias during electrophysiological study and presence of an SCN5A mutation in predicting ventricular arrhythmic events. Syncope and spontaneous type 1 ECG pattern were the only significant predictors (3). These factors are the only ones that continue to remain consistent in their predictive role as shown in other studies (3, 6, 15, 16). Other markers however, either yield conflicting data or have only been assessed in a small proportion of studies making it difficult to evaluate their true role in the risk stratification of Brugada patients (Table 1).

*a) Factors with conflicting evidence*

A positive programmed electrical stimulation test is a good example of one of these factors in this pool of conflicting evidence whereby it has been shown to be a strong predictor of ventricular arrhythmias in BrS in some studies (15, 16) whilst many have shown that it plays no role in BrS risk stratification (3, 6, 17, 18). Recent data from the FINGER Registry suggests a positive study with up to 2 extrastimuli could have prognostic significance, and a negative study has a high negative predictive value (15). The presence of an SCN5A mutation (3, 6, 15, 17) and family history of SCD (3, 15, 17) are further factors which role in risk stratification of Brugada patients remains conflicting. Based on these findings utilizing programmed electrical stimulation and genetic mutation testing in the risk stratification of these patients would not be

strongly recommended on a population level unless there is a particularly malignant family history or specific highly arrhythmogenic mutations.

*b) ECG markers with promising predictive value*

The presence of type 1 Brugada pattern in peripheral leads (18), early repolarization (ER) (19-22), avR sign (23) and S wave in lead 1 (17), fragmented QRS (24) (Figure 1) have shown to be associated with an increased risk of ventricular arrhythmia occurrence during follow-up. However, as these factors have not been consistently assessed in a range of studies it is unclear whether their predictive value applies across a general BrS population. The presence of ER has already been associated with a higher risk of ventricular arrhythmic events in patients with idiopathic ventricular fibrillation (25, 26) and it is thereby possible that its presence indicates an arrhythmogenic predisposition. It is plausible that the presence of type 1 Brugada pattern in peripheral leads is indicative of a higher "Brugada substrate burden" and as a result associated with a greater risk of ventricular arrhythmia occurrence. Evaluating all these factors together in a large BrS population is required to effectively establish their importance.

*c) Risk scoring model in Brugada syndrome*

A number of studies have combined risk factors to predict risk of sudden death (11, 16, 27). The initial study by *Delise et al.* (11) showed that no single risk factors was able to identify Brugada patients at high risk of arrhythmic events and that a multi-parametric approach was a more robust strategy. They showed that subjects at highest risk were those with a spontaneous type 1 ECG pattern and at least 2 further risk factors (including syncope, family history of SCD and positive programmed electrical

stimulation). The recent study by *Sieira J et al.* (16) evaluated several factors and proposed a score that included the presence of 1) spontaneous type 1 ECG pattern, 2) early familial SCD (<35 years old), 3) positive programmed electrical stimulation, 4) presentation as syncope or as aborted SCD and 5) sinus node dysfunction and demonstrated a predictive performance of 0.82 for this score. They showed that a score greater than 2 conferred a 5-year event probability of 9.2%. However, it is important to consider several points prior to implementing the use of this score. The factors utilized in this risk score were derived only from univariate analysis. Since no multivariate analysis was conducted, it is unclear whether all these factors have an independent predictive role for ventricular events. Furthermore, the validation of the risk score that established its predictive performance was undertaken in a cohort from the same centre. Since this risk score has not yet been evaluated externally and the baseline characteristics of the cohort used in this study showing several differences to other larger studies it is unclear whether this predictive performance is applicable to a general BrS population. Therefore, even though this approach of integrating risk factors is promising, further validation in several BrS is warranted prior to its use in clinical practise. There is clearly a role for combined risk factor scoring in BrS.

*iv) The Future in BrS*

Several studies have demonstrated prolonged RVOT activation with marked regional conduction delay and fractionated late potentials in patients with BrS (17, 24, 28). As well as utilizing clinical derived clinical risk factors in risk stratification, there may be a role for more refined evaluation of the arrhythmogenic substrate. ECG imaging (ECG-I) has demonstrated marked conduction delays in the right ventricular outflow tract (RVOT) and this area of delay is expanded in the presence of ajamline (29). The

degree and/or area of delay may be another useful biomarker to predict risk-indeed an ECG-I approach to risk has been proposed in a preliminary study utilizing exercise stress (30). Although genetic factors are important, their role to date has been limited to individual mutations-the burden of specific variants may also be utilized in the future to refine risk scoring.

The current American College of Cardiology, American Heart Association, and Heart Rhythm Society Guideline for Management of Ventricular Arrhythmias recommend catheter ablation or quinidine for: a) patients experiencing recurring shocks for ventricular arrhythmias, and b) for patients with spontaneous type 1 pattern and symptomatic ventricular arrhythmias who either are not candidates for an ICD or decline an ICD (class of recommendation: I; Level of evidence "B – non-randomized for both") (31). Two studies have shown that with epicardial catheter ablation performed in the RVOT, with a view of eliminating this arrhythmogenic electrophysiological substrate resulted in the normalization of the Brugada ECG in majority of patients even after ajmaline (32, 33). In the study with the larger cohort of patients (32) the current follow-up is less than a year therefore a longer follow-up period is required to ensure that the ablation effect is permanent. Indeed a clinical trial is now in progress to evaluate the role of prophylactic ablation in BrS (Clinical trial registration- NCT02641431)– however, given the fact that the condition may be a progressive disease issues relating to risk stratification even after ablation will remain with us for the foreseeable future.

*Disclosures*

Prof. Lambiase PD receives educational and research grants from Boston Scientific.

*Table 1- The studies that have evaluated factors in their role in predicting ventricular arrhythmia occurrence and/or SCD during follow-up in patients with Brugada syndrome.*

| Studies | Factors assessed | Predictive risk factors HR (95% CI)[**] | Follow-up Median (range) Mean ± SD |
|---|---|---|---|
| **Probst V et al. 2010 (3)** | Syncope | Yes 3.4 (1.6-7.4), p=0.002 | 31.9 months (14-54.4) |
| | Spontaneous type 1 ECG | Yes 1.8 (1.03-3.33), p=0.04 | |
| | Male gender | No | |
| | SCN5A mutation +ve | No | |
| | Family history of SCD[*] | No | |
| | PES[^] +ve | No | |
| **Priori SG et al. 2012 (6)** | Spontaneous type 1 ECG +Syncope | Yes 4.20 (1.38-12.79), p=0.012 | 36 ± 8 months |
| | QRS fragmentation | Yes 4.94 (1.54-15.8), p=0.007 | |
| | VRP$^T$<200ms | Yes 3.91 (1.03-12.79), p=0.045 | |
| | PES +ve | No | |
| **Sroubek J et al. 2016 (15)** | PES +ve | Yes 2.66 (1.44-4.92), p<0.001 | 38 months (20.9-60.3) |
| **Sieira J et al. 2017 (16)** | Syncope | Yes 3.7 (1.6–8.6), p<0.01 | 80.7 ± 57.2 months |
| | Spontaneous type 1 | Yes 2.7 (1.3–5.4), p<0.01 | |
| | Male gender | Yes 2.7 (1.2–6.2), p=0.02 | |
| | Sinus node dysfunction | Yes 5.0 (1.5–16.3), p<0.01 | |
| | PES +ve | Yes 4.7 (2.2–10.2), p<0.01 | |
| | Proband status | Yes 2.1 (1.0–4.200, p=0.04 | |
| | QRS duration >120ms | Yes 1.03 (1.01–1.04), p<0.01 | |
| | Family history of SCD | No 0.6 (0.3–1.3), p=0.20 | |
| **Calo L et al. 2016 (17)** | S wave pattern in lead 1 | Yes 39.1 (5.34-287.10), p<0.0001 | 48 ± 38.6 months |
| | Presence of AF | Yes 3.70 (1.59-8.73), p=0.0024 | |

| | | | |
|---|---|---|---|
| | Male gender | No | |
| | Family history of SCD | No | |
| | First degree heart block | No | 11 |
| | QTc prolongation | No | |
| | Early repolarization | No | |
| | Epsilon wave present | No | |
| | QRS fragmentation | No | |
| | QRS duration >120ms | No | |
| | SCN5A mutation +ve | No | |
| | PES +ve | No | |
| **Kamakura S et al. 2009 (19)** | Family history of SCD | Yes<br>3.28 (1.42-7.60), p=0.005 | 48.7 ± 14.9 months |
| | Early repolarization | Yes<br>2.66 (1.06-6.71), p=0.03 | |
| | Spontaneous type 1 ECG | No | |
| | PES +ve | No | |
| **Tokioka K et al. 2014 (22)** | Syncope | Yes<br>28.57 (6.14-142.86), <0.001 | 45.1 ± 44.3 months |
| | QRS fragmentation | Yes<br>5.21 (1.69-16.13), p=0.004 | |
| | Early repolarization | Yes<br>2.87 (1.16-7.14), p=0.023 | |

* *Multivariate analysis except *Sieira J et al.* (16)

which is univariate analysis

*SCD- sudden cardiac death

^PES- programmed electrical stimulation

ᵀVRP- ventricular refractory period

FIGURE LEGEND

*Figure 1A-D-* Demonstrates proposed ECG markers that have shown to have role in predicting ventricular arrhythmias in Brugada syndrome A) Type 1 Brugada pattern in peripheral leads B) avR sign (dominant R wave in avR) C) Early repolarization (ST elevation in the inferolareral leads) D) S wave in lead I.

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