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Editorial

Programmed electrophysiological stimulation for risk prediction in patients with Brugada syndrome: closing time?

La estimulación eléctrica programada para la predicción del riesgo en pacientes con síndrome de Brugada: ¿tiempo de cierre?

Andrea Mazzanti,[a,b,c,d] Alessandro Trancuccio,[a,b,d] and Silvia G. Priori[a,b,c,d,*]

[a] Department of Molecular Cardiology, IRCCS Istituti Clinici Scientifici Maugeri, Pavia, Italy
[b] Department of Molecular Medicine, University of Pavia, Pavia, Italy
[c] European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN Guard-Heart)
[d] Department of Molecular Cardiology, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

INTRODUCTION

In a recent article published in *Revista Española de Cardiología*, Rodríguez-Mañero et al.[1] report their experience in the validation of 3 different multiparametric scores proposed over the last decade to help predict the risk of sudden cardiac death (SCD)[2–4] in patients with Brugada syndrome (BrS). The population of this multicenter retrospective cohort included 831 patients with BrS who underwent an electrophysiological study (EPS) with programmed electrical stimulation (PES) and was followed up clinically for an average of 10 years.

The key finding of the study was that the 3 scores had only a modest predictive ability, mainly when applied to asymptomatic patients.[1] The results are relevant because implantable cardioverter-defibrillators (ICD) still represent the only option for protecting patients with BrS with a "sufficiently high" risk of SCD. However, the decision to implant an ICD needs to be carefully weighed, as it is not devoid of consequences.

AN UPDATED APPRAISAL OF THE RISK OF SCD IN PATIENTS WITH BrS

Before addressing the problem of risk stratification, it is necessary to critically assess the contemporary risk of SCD in patients with BrS. The perceived lethality of the condition derives from the first reports dating back to the 1990s when BrS was considered a rare condition with an extraordinarily high rate of fatal arrhythmias, estimated to approach 30% at 3 years.[5] As expected, when describing a novel clinical entity, a large proportion of the first cohorts included patients with the most severe clinical phenotype (ie, survivors of a cardiac arrest),[1] thus overestimating the actual risk.

Over the following 2 decades, BrS has morphed into a common condition, with a current estimated prevalence of 1 in 1000,[6] and concurrently, the event rate associated with the disease has declined conspicuously. Nowadays, the largest cohorts report a risk of ventricular arrhythmias well below 1% per year for asymptomatic patients.[3,7–9] In line with this trend, Rodríguez-Mañero et al. observed an annual rate of approximately 0.6% in their variegate population, including cardiac arrest survivors, patients with syncope, and asymptomatic patients.[1] In this latter group, the authors report 21 arrhythmic events in 677 patients after 10 years of follow-up, which estimates the incidence of arrhythmic events in asymptomatic BrS at 0.3% per year. Recently, Probst et al.[10] provided comparable results in 1613 French patients with BrS prospectively enrolled from 1993 to 2016. In this sizable multicenter registry, the annual event rate in asymptomatic patients ranged from 0.3% to 0.6% for drug-induced or spontaneous type 1 electrocardiogram (ECG), respectively.[10]

The results of Rodríguez-Mañero et al. are clinically important since, included among the authors, are expert physicians who had reported significantly higher event rates in the past[5]: therefore, we must assume that the above-described phenomenon is not a statistical anomaly but, on the contrary, implies that, even in highly specialized centers that treat the most severely affected patients, the event rate for BrS is now much lower than initially outlined.

Furthermore, in evaluating survival data, we must acknowledge the imprecision of the estimation of rare events (ie, those occurring at a rate $< 1\%$ per year), as is the incidence of cardiac arrest in BrS patients, unless cohorts of at least 1000 patients are available.[11] While acknowledging that estimates from smaller series should no longer be considered reliable, we congratulate Rodríguez-Mañero et al. for collecting their large group of patients that demonstrates how long-term observations are essential to understand BrS, as 90% of the arrhythmic events occurred more than 4 years after the start of follow-up.[1]

The updated and more realistic vision on the true peril associated with BrS should now be part of frank communication with patients, who, unfortunately, still frequently harbor outdated ideas of the magnitude of risk associated with the condition. Importantly, physicians should consider and discuss other competing causes of death that become increasingly more prevalent and relevant with advancing age. After the fourth decade of life, for instance, coronary heart disease becomes progressively more significant as a cause of SCD, accounting for up to three-quarters of all sudden deaths.[12] In this light, action aimed at correcting modifiable risk factors for coronary heart disease,

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* Corresponding author: Molecular Cardiology – IRCCS ICS Maugeri, Via Maugeri 10, 27100 Pavia, Italy.
E-mail address: silvia.priori@icsmaugeri.it (S.G. Priori).

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such as hypertension, diabetes mellitus and smoking, may prove to be more lifesaving than focusing on BrS. Well aware of this problem, Rodríguez-Mañero et al. rightly included competing causes of death in their analysis on survival in patients with BrS.[1]

RISK ASSESSMENT IN BrS: TO EACH THEIR OWN

The correct evaluation of the various tools at our disposal for risk stratification of patients with BrS requires some introductory reflections, as not all patients are alike.

Survivors of a cardiac arrest represent a small subset of patients who possibly pose the least challenge to risk stratification. With a risk of recurrent ventricular fibrillation exceeding 10% per year in most published series,[7,13] these patients represent natural candidates for ICD implantation.[6] This concept is supported by the results of the study by Rodríguez-Mañero et al., as these authors included only 3% of cardiac arrest survivors in their cohort, who nonetheless experienced more than 20% of all events at follow-up. Of note, the choice to include high-risk patients in their study might have resulted in bias introduction and modification of the performance of the risk scores. Corroborating the aforementioned are the sensitivity analyses performed in asymptomatic patients, which showed a decrease in the predictive power of the models. On the other hand, the inclusion of cardiac arrest survivors offers essential conceptual insights into the limits of PES for risk assessment in BrS. Of note, the finding that a history of cardiac arrest did not correlate with a significantly increased propensity to inducibility represents a humbling reminder of the biological complexity of the arrhythmic substrate in BrS, which PES cannot faithfully reproduce.

For patients in primary prevention of SCD, we and others have shown that a history of syncopal spells is consistently linked to a worse outcome, primarily when patients also manifest a spontaneous type 1 ECG pattern.[7,14] The coexistence of these factors increases the risk of life-threatening arrhythmias substantially, and the guidelines indicate that ICD implantation should be considered without further risk assessment.[6] The results of Rodríguez-Mañero et al. support this widely shared view as a history of syncope also represents a decisive predictive factor in their validation cohort.[1]

Finally, most patients with BrS start receiving medical attention after an incidental finding of a type 1 ECG pattern and without having experienced symptoms. In this context, evidence supports that the isolated presence of a drug-induced type 1 ECG pattern generally requires no further intervention, beyond periodic clinical monitoring, due to the low expected prevalence of SCD. Accordingly, only 2/184 (1%) individuals from this group (ie, those with a Delise score = 0) in the cohort of Rodríguez-Mañero et al. experienced an arrhythmic event over 10 years of follow-up. It is challenging to foresee additional factors that might routinely justify an ICD implant in such patients. Here, the clinical usefulness of EPS might also be questioned, since, with an inducibility rate as high as 33%, it leads to an excess of ICD implantation, with the known risk of complications and a low expected usefulness.

Improved risk assessment is instead a pressing need for asymptomatic patients with the documentation of a spontaneous type 1 ECG pattern. While raising the arrhythmic risk compared with its drug-induced analog, this single ECG parameter is not sufficient, *per se*, to identify patients with such a burden of risk to always require an ICD implant. Here, other noninvasive and invasive parameters may be useful to improve risk stratification, including the inducibility of polymorphic ventricular tachycardia or ventricular fibrillation at PES.

ARE MULTIPARAMETRIC SCORES THE RIGHT TOOL FOR RISK ASSESSMENT IN PATIENTS WITH BrS?

Most prognostic indices recommended for patients with BrS, either alone or combined in risk scores, derive from single-center experiences and have not been validated in large independent cohorts. The work by Rodríguez-Mañero et al. has profound clinical implications because it engages in the difficult task of evaluating the performance of the 3 scores proposed over the last decade to stratify arrhythmic risk in patients with BrS, a key step in the pathway to their general clinical use.

The first score was proposed by Delise et al.[2] in 2011, attempting to offer an easy-to-use tool for risk stratification. Besides the inducibility of ventricular fibrillation during PES, the parameters considered were a spontaneous type 1 ECG pattern, a history of syncope, and a family history of SCD. While constructing the prognostic score, the authors attributed equal importance to each parameter without considering the relative risk associated with each of them, as calculated by a multivariable analysis. Therefore, it comes as no surprise that the score showed poor calibration in the validation cohort. Additionally, a sensitivity analysis in asymptomatic patients of the validation cohort showed that this score was not predictive due to the power loss secondary to the removal of missing data. Overall, the validation results suggest against using the Delise score as a standard clinical tool to guide ICD implantation.

The Shanghai multiparametric score was proposed in 2015, as a consensus of 17 experts, to improve the diagnosis of patients with suspected BrS.[4] Rodríguez-Mañero et al. attempted to validate it also for predictive purposes. This point system, which does not include PES among the factors included, classifies as "intermediate risk" all patients with a spontaneous type 1 ECG who asymptomatic and without a family history of SCD (ie, the largest proportion of patients with BrS). Therefore, the score does not contribute to risk assessment beyond what has already been known for decades, and Rodríguez-Mañero et al. confirmed its modest predictive value. Of note, two-thirds of the events in their cohort occurred in individuals classified as "low" or "intermediate" risk by the Shanghai score, and therefore without an indication for ICD implantation. Similarly disappointing results on the performance of the Shanghai score were recently published by Probst et al.,[10] whose data confirmed that the score could not "stratify patients at intermediate risk". In light of the above, it is clear that this diagnostic tool should not be used for risk stratification, especially not in asymptomatic patients with a spontaneous type 1 pattern.

Finally, in 2017 Sieira et al.[3] developed a score that combines clinical, genetic/familial, and PES data based on a study of 400 patients with BrS and also performed an external validation on an additional 150 patients. This score, which is more robustly conceived than the previous 2, nonetheless showed incomplete discriminatory ability when tested in the cohort of Rodríguez-Mañero et al.,[1] and especially in asymptomatic patients (with a c-index of 0.69). As above, the clinical implication of the poor predictive power of the score resulted in 48% of the arrhythmic events occurring in patients classified as "low" risk (ie, ≤ 2). Interestingly, the evaluation of the Sieira score based on the number of extra stimuli (1 or 2 vs 3) used to perform the PES during the electrophysiologic study did not substantially improve event prediction. Along the same line, Probst et al.[10] and Chow et al.[15] recently reported similar results on the dubious clinical usefulness of the Sieira score, with a c-index of 0.59 and 0.58, respectively. In perfect symmetry with the data of Rodríguez-Mañero et al., the French study reported that 48% of arrhythmic events occurred in patients classified by the score as low or intermediate risk.[10]

IS THERE A ROLE FOR PES IN THE RISK STRATIFICATION OF BrS?

The data of Rodríguez-Mañero et al. question the usefulness of the prognostic scores in patients at intermediate risk. The question remains whether EPS is an appropriate tool that aids physicians in identifying patients who could benefit from an ICD.

In line with our data showing that less aggressive PES protocols may be more helpful in predicting arrhythmia in intermediate-risk individuals,[16] Rodríguez-Mañero et al. stratified the usefulness of PES according to the number of extrastimuli used (up to 2 vs up to 3 extrastimuli). The authors showed that induction with fewer extrastimuli was associated with higher arrhythmic risk, but the number of extrastimuli used did not substantially improve the event prediction of the scores. This finding may be explained by the multicenter nature of the validation study, with different centers adopting different stimulation protocols, both in terms of the number of extrastimuli administered, the indications for the examination, and the stimulation site. These factors may influence not only the percentage of inducible patients and the number of implanted devices but also the clinical usefulness of PES in terms of sensitivity and specificity.

Regardless of the lack of positive results, the work by Rodríguez-Mañero et al. is relevant because it highlights the limitations of PES that have persisted over the past 2 decades.

Today, according to the most extensive case series available, the sensitivity of PES is likely to be around 60% when conducted with an aggressive protocol (up to 3 extrastimuli) and drops to 30% when a less aggressive protocol is used.[7,8,16,17] This suggests that 40% to 70% of patients with a cardiac arrest had had a negative PES. These data are confirmed by Rodríguez-Mañero et al., who report a sensitivity of PES that ranges between 57% (3 extrastimuli) and 32% (2 extra stimuli).[1]

On the other hand, the specificity of PES ranges between 60% and 80% (up to 3 and up to 2 extrastimuli, respectively), so at least 20% of patients will have an ICD implant but will not sustain arrhythmic events at follow-up.[7,8,16,17] In line with these previous data, Rodríguez-Mañero et al. report a specificity between 69% and 88% (up to 3 and 2 extrastimuli, respectively).[1]

Finally, a novel concept that further complicates the predictive value of PES introduced by Rodríguez-Mañero is the time dependency of its result. According to their results, the predictive ability of PES seems to be time-dependent, so that it may be necessary to re-execute it periodically.[1]

CONCLUSIONS

The main conclusion drawn from the work by Rodríguez-Mañero et al.[1] is the identification of the forthcoming pathway for risk stratification in BrS, as current risk stratification strategies are inefficacious in patients with the greatest clinical need.

The next leap forward will come from a study focusing only on asymptomatic patients with a spontaneous type 1 pattern, in whom uncertainties abound, and contextually, the clinical need is greatest. Considering the low event rate in this subset of patients, such a study will need to enroll more than 1000 patients and follow them up for a long period to have sufficient power to identify prognostic factors. Should such a study aim to test the usefulness of PES, it will have to be devised in such a way that uniform PES protocols and uniform study endpoints are used to allow for relevant conclusions to be drawn.

Until then, risk stratification will have to be based on the traditional model, particularly in asymptomatic patients with a spontaneous type 1 pattern. Clinicians will rely on their own experience to recognize potential warning signs using the patient's personal medical history, family history, clinical data, and genetics.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest regarding the topics discussed in the present manuscript.

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