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Special Article

Programmed electrical pacing of the heart in Brugada Syndrome. Part I: A current view

Estimulación eléctrica programada del corazón en el síndrome de Brugada. Parte I: Una visión actual

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A NECESSARY INTRODUCTION

After 48 years of being established as a clinical procedure, several of the uses and concepts of programmed electrical stimulation of the heart (PESH) have changed, and some of its limitations have been identified (although it remains an essential tool in arrhythmology). Its foundations were experimental electrophysiology, clinical electrophysiology and electrocardiography. Then there were drastic changes; there was a move from classic arrhythmology to interventional arrhythmology, the diagnostic approach gave way to therapy. Moreover, PESH, arrhythmia surgery and direct current fulguration were the foundation for the development of a new therapeutic procedure: radiofrequency ablation (RFA). All this was also experienced in Cuba, and the role of the clinical electrophysiology laboratory changed from diagnosis and experimentation to therapy. However, there is an absolute connection between both aspects: the understanding of the arrhythmic substrates and their ablation; because there can be no divorce between clinical electrophysiology and electrotechnology, as both support each other[1-3].

In 2007, Callans said: "Many of us began practicing electrophysiology before its interventional era, when this field was intensely intellectual but less successful at protecting patients from future harm." It was the same in our Department[3,4].

This emerging subspecialty underwent rapid changes that led it to become a major subspecialty, which faced, and still faces today, major challenges.

Programmed electrical stimulation of the heart, used routinely in humans, began in 1967, in Paris (Coumel) and Amsterdam (Durrer) simultaneously. Gradually, diagnostic electrophysiology gave way to therapeutic electrophysiology with RFA in 1987; until its

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goals changed, establishing its real usefulness to stratify risk, indicate prognosis (including channelopathies), predict sudden cardiac death (SCD) and approach the risk of malignant ventricular arrhythmias (MVA)[1-3].

With regard to PESH, at the beginning, Brugada said that the interest grew like the snowball effect and changed the role of the clinical electrophysiology laboratory. Like any new procedure, its usefulness, as well as its limitations, began to be noticed. At first its value was regarded as paramount, then it was realized that it was not absolute and that it was necessary to know what could or could not be expected from it. Brugada said at the beginning: "Problems, not in technology but in the way we use it and in the sometimes unfounded expectations of it. Expectations must always exist. I still have many... My greatest hope is, however, see the doctors who use this technique to realize the reality of its value and limitations. This can only be achieved by looking at its possibilities and limitations in a very realistic manner"[5]. This statement with regard to PESH, said in another historic moment, may be applied today to the new problems concerning its true role in risk stratification in inherited arrhythmogenic syndromes.

No other cardiovascular subspecialty has undergone as radical changes as the study and treatment of arrhythmias.

The usefulness of PESH grew in three fundamental directions, a) diagnosis: tachycardia with wide QRS, non-documented arrhythmias, syncope of unknown cause, episodes of SCD, assessment of the reserve of the His-Purkinje system, precision of the beginning and maintenance of arrhythmias, specific cases of sinoatrial dysfunction, assessment of the effectiveness of certain antiarrhythmic drugs (AAD) and proarrhythmia; b) the prognosis; and c) therapeutic use.

Among the many and elusive warning signs of SCD, all are important but none is paramount, including PESH (a non-clinical arrhythmia may be induced in the laboratory, or the clinical arrhythmia may not be reproduced). Risk stratification and calculation of prognosis is very difficult and sometimes impossible. At present, there is an effort to establish the true importance of PESH, which uses artificial triggers, that may not correspond to the clinical ones, and does not control modulating elements (autonomic nervous system)[6-12].

The triangle of all arrhythmias is being studied in depth —it includes the arrhythmic substrate, the triggers and the modulators— and there is an effort to integrally insert it in the arrhythmogenic process, taking into account the possible variability from one electrophysiology study to another one. New functions have been assigned to the clinical laboratory, and to PESH as a marker for risk stratification in various situations such as: asymptomatic carriers of accessory pathways, prediction of recurrence or the presentation of MVA in structural heart disease; and later its usefulness was seen in patients with inherited arrhythmogenic syndromes, depending on the inducibility of MVA in the electrophysiology laboratory and its relationship with its presentation at the clinical follow-up[13-18].

There is an effort to clarify its real usefulness in some channelopathies, the possibility of first episodes of MVA (especially in asymptomatic subjects), and recurrence or electrical storm in symptomatic patients.

The fact that this topic has been discussed for so many years, the amount of published studies and the many conflicting opinions among prominent researchers indicate that the problem is still unresolved.

For example, in idiopathic ventricular fibrillation (IVF) the contradiction is that in some subjects who have been resuscitated from episodes of SCD the clinical MVA will not be reproduced in the lab, and the study would serve to predict future recurrences and determining the need to associate AAD, or not, to the implantable cardioverter-defibrillator (ICD)[13,19]. Its usefulness in other channelopathies has been more difficult to establish, given the small number of these patients (e.g., short QT syndrome). In Brugada syndrome (BrS) there is a greater number of subjects but there may be diversity of clinical symptoms (patients who were resuscitated from SCD, those with syncopal events or asymptomatic subjects).

Wilde[20] has used PESH for risk stratification and prediction of future events in patients with various cardiac diseases: ischemic heart disease, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy and primary electrical diseases. In ischemic heart disease, the inducibility of MVA in the laboratory seems to identify patients at high risk (but it does not have sufficient negative predictive value), however, in other diseases, its promising potential is not sustained.

It was suggested that the inducibility of MVA during PESH allowed classifying the patients with inherited arrhythmogenic syndromes into high and low risk of presenting them clinically (for the first time or as a re-

currence), and it was proposed as a risk stratifier[21]. However, others have questioned this concept[22,23].

Some series and meta-analyzes have reported that the inducibility in BrS was significantly higher in patients with cardiac arrest (CA) than in asymptomatic patients; which gave some prognostic value to the finding. The question then arose: is the value of PESH high enough to make a clinical decision? According to some people the answer is no. There are several potential reasons for the divergence of views which influence the final result and include variables in PESH such as the number of extrastimuli, minimum coupling interval or refractoriness, site of stimulation (apex and/or outflow tract of the right ventricle) and wavelength of the electrical impulse used[21,24-28].

The role of PESH for risk stratification in patients with inherited arrhythmogenic syndromes is under debate. Idiopathic ventricular fibrillation is more common than previously recognized, it occurs in 1% of the survivors of CA and more than 8% of CSD. The big problem is that MVA is the beginning of the disease in apparently healthy young patient, and just 5% of them recover from it. It is very important to find a protocol to stratify risk and identify high risk; unfortunately, even today there is no predictor of a disastrous end. It is considered that five years after the CA, IVF patients have 30% risk of recurrence of the episode; the rest is free of symptoms in the follow up[12].

In the patients of the Unexplained Cardiac Arrest Registry of Europe (UCARE), only 50% of MVA were inducible by PESH: sustained polymorphic ventricular tachycardia or ventricular fibrillation (VF), with low predictive positive and negative values[12]. What about Brs?

Stephenson[18] published a compendium of the usefulness of PESH in various inherited arrhythmogenic syndromes, and he thinks it has a poor predictive value in BrS, with some cases of successful ablation in ventricular tachycardia (VT) and in triggers of VF.

There is great phenotypic variability in BrS, from asymptomatic patients to those with SCD[29]. Therefore, it is necessary to stratify the real risk, something that has been a very controversial issue until now. Especially in asymptomatic cases, preclinical diagnosis and risk stratification are vital to prevent fatal arrhythmias[30].

Some authors consider that PESH is not useful or is not necessary to predict the risk of SCD in BrS (Priori and Eckardt registries)[22,23]; and that it is not useful or

has little use in inherited arrhythmogenic syndromes in general. Priori[22], Stephenson[18] and Ajiro[14], reported very low incidence of serious arrhythmic events, especially in asymptomatic patients, with low positive predictive value of PESH and high negative predictive value; the study would be pertinent if there were supraventricular arrhythmias, but the decision to implant an ICD is independent of the outcome of PESH.

Schimpf[31] established a link between PESH and genetics in cardiac channelopathies; intracardiac records and atrial and ventricular stimulation have contributed to the understanding of cardiac electrophysiology; catheters allow the linking of endocardial signals to anatomical structures, and the understanding of the conduction through healthy and diseased myocardial tissue, as well as arrhythmogenic mechanisms and electrical treatments. If at first it had a major role to stratify risk and was granted the highest reliability in making therapeutic decisions, then all this changed. Its contribution is not refuted, but is not absolute, nor always has the last word. In all novel processes, Brugada said[5], at first there is fantasy, euphoria, excitement and hope; then disillusionment, disappointment and uncertainty as their limitations are discovered. Then you come to a balance, as to what may be expected or not, finally achieving an approximation to reality.

The debate on PESH (its sensitivity, specificity and the protocols used) in the BrS is a contemporary version of the earliest discussions regarding its use after myocardial infarction. In the first one, it attempts to identify an arrhythmogenic substrate in the absence of structural or hemodynamic abnormalities, define the specific arrhythmic risk and even serve as a guide to appropriate therapy. It is to be used to establish the risk of death in these patients who have survived a CA, but it is known that arrhythmias are influenced by different factors (substrate, trigger and modulator), and that PESH deals with the first one, with an artificial trigger and a limited use of the modulator. The BrS is a molecular disorder (which is not analogous to an anatomical disorder), and this influences its inducibility and risk prediction, more limited than in other clinical situations. The substrate is constant but the electrocardiogram and electrophysiology are variable, spontaneously, perhaps due to the effect of modulators and triggers[32].

In some BrS, VF has a unique regional substrate on the epicardial layer of the anterior outflow tract of the right ventricle. Low voltage and fractionated electro-

grams appear to contribute to the physiological hete-rogeneity (would be a potential target for ablation and sites that can be identified by noninvasive mapping techniques). This is a region that is sensitive to non-uniform activation, which can modulate the properties of repolarization and result in reentry mechanisms. BrS is associated with abnormalities of repolarization, depolarization, and its propagation; ventricular arrhythmias may originate in the outflow tract, with a higher risk if there is a spontaneous electrocardio-graphic pattern or a history of syncope[12,15,22].

Is it a modifying effect on a primarily genetic dis-order that is regionally expressed, similar to what hap-pens in hypertrophic cardiomyopathy? Is it an ac-quired abnormality? Is it a genetic modifier that inter-acts with the primary molecular defect? That is, there is an interaction between the molecular and anatomi-cal aspects, which could explain the inconsistency of the predictive value of PESH, especially if the ana-tomical component was acquired.

The outcome of some patients with BrS may be unpredictable, it would be important to know the real value of PESH and other markers that may predict risk. In the case of patients with syncope or those resus-citated from CSD episodes, actions are clear, and PESH is not necessary to decide the implantation of an ICD (a measure to be taken even if the study conducted was negative). But what must be done with asymp-tomatic subjects? Perform a PESH and implant an ICD depending on the result? This decision is debatable.

Priori[22] developed a risk stratification scheme to quantify the chances of SCD and decide the use of ICD, with emphasis on the natural course of the disease, and found no association between the inducibility of MVA in the laboratory and its subsequent spontane-ous occurrence.

Gussak[30], Eckardt[33] and Ajiro[14] gave importance to late potentials as noninvasive markers to stratify risk in the BrS, and associated them with the inducibility of MVA during PESH, and with the area of ST-segment elevation (inhomogeneous repolarization). Predictors are not always optimal; family history, genetic and pharmacological tests, and inducibility of arrhythmias in PESH have been taken into account[30].

In 2005, there was a controversy on this issue. Brugada[21] on one side said: "Patients with an asymp-tomatic Brugada electrocardiogram should undergo pharmacological and electrophysiological testing" On the other, Priori asked: "Should patients with an asymptomatic Brugada electrocardiogram undergo pharmacological and electrophysiological testing?" And then concluded: "Management of patients with Brugada syndrome should not be based on pro-grammed electrical stimulation."

The studies of Brugada give a high positive predic-tive value to PESH (inducibility of MVA as a prognostic marker) in terms of future clinical events. Priori, how-ever, says it has low predictive value and finds fewer events in the monitoring of asymptomatic individuals. It has been said that to make decisions in a channelo-pathy, it is necessary to have some clinical knowledge, some knowledge of genetics and a lot of common sense[21].

Some researchers[16,24,26,34] think that PESH can pre-dict risk in asymptomatic subjects in which VT is in-duced (a sustained arrhythmia is considered a strong risk marker), while other researchers have found no association between inducibility and recurrence of VT or VF in symptomatic and asymptomatic subjects[22,23].

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