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Role of the Purkinje system and right ventricular outflow tract in malignant ventricular arrhythmias and sudden death

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Abbreviations
AVM: MVA: malignant ventricular arrhythmias
PVC: premature ventricular contractions
RVOT: right ventricular outflow tract
RVOT-PVC: right ventricular outflow tract premature ventricular contractions
RVOT-VT: right ventricular outflow tract ventricular tachycardia
VF: ventricular fibrillation
VT: ventricular tachycardia

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ABSTRACT
The Purkinje system and the right ventricular outflow tract play a pivotal role in relation to malignant ventricular arrhythmias (ventricular tachycardia and fibrillation, torsades de pointes) and sudden cardiac death. Details such as their pathophysiology, origin involvement (triggering extrasystoles) maintenance of such arrhythmias, and ablative possibilities to reduce recurrences and electrical storm events are discussed herein. The differential diagnosis between benign and malignant ventricular tachycardia related to the right ventricular outflow tract, and the relationship between genetic, structural, electroanatomical and functional factors (inflammation, fibrosis) with clinical events and vulnerability to arrhythmias are presented. Some of these diseases need to be reclassified as they are now seen in their organic-functional character (Brugada syndrome, for example), and this implies radical changes in some classical concepts as well as a new perspective on risk stratification and therapeutic management.
Keywords: Purkinje system, Right ventricular outflow tract, Premature ventricular contractions, Malignant ventricular arrhythmias

Papel del sistema Purkinje y del tracto de salida del ventrículo derecho en las arritmias ventriculares malignas y la muerte súbita

RESUMEN
El sistema Purkinje y el tracto de salida del ventrículo derecho tienen un papel trascendente en relación con las arritmias ventriculares malignas (taquicardia y fibrilación ventriculares, torsión de puntas) y con la muerte súbita cardíaca. Se discuten su fisiopatología, participación en el origen (extrasístoles desencadenantes) y mantenimiento de estas arritmias, y las posibilidades ablativas para disminuir las recurrencias y los episodios de tormenta eléctrica. Se expone el diagnóstico diferencial entre variantes benignas y malignas de la taquicardia ventricular relacionada con el tracto de salida del ventrículo derecho y la relación entre factores genéticos, estructurales, electroanatómicos y funcionales (inflamación, fibrosis), con los eventos clínicos y la vulnerabilidad a las arritmias. Se necesita reclasificar algunas de estas enfermedades, vistas ahora en su carácter orgánico-funcional (síndrome de Brugada, por ejemplo), lo cual implica cambios revolucionarios en algunos conceptos clásicos y una nueva visión en cuanto a la estratificación de riesgo y la conducta terapéutica.
Palabras clave: Sistema Purkinje, Tracto de salida del ventrículo derecho, Extrasístoles ventriculares, Arritmias ventriculares malignas

INTRODUCTION

Controversies in arrhythmology, as in any field of knowledge, have always been there and will always be. Some can be traced back in time –a clear sign of unresolved issues– while others are more recent. They all allow for development, provided they are rational. Such is the case of premature ventricular contractions (PVC) when it comes to their innocence or perversity, their risk or appropriate therapeutic management (whether to treat them or not).

The role of premature ventricular contractions (PVC) in starting and maintaining malignant ventricular arrhythmias (MVA) has gone through several stages, but at some point it was claimed and proven that those originating in the Purkinje system and the right ventricular outflow tract (RVOT) could trigger MVA and go so far as to cause sudden death[1,2]. The same is true for PVC and RVOT-related ventricular tachycardia (VT), in terms of their benign and malignant variants, and the clues that may help differentiate them.

Purkinje PVC, RVOT, and RVOT-VT ablative techniques that have proven effective in preventing relapses and electrical storms have certainly opened up a promising field. Another widely discussed issue is that concerning Brugada syndrome: whether it is a pure genetic functional electrical phenomenon; whether there is a structural factor or both coexist; and, therefore, whether the classical concept should be changed and conceived as an organic-functional disorder. That would be the crux of such debates.

The Purkinje System: Several questions regarding this system (some answered, some unanswered)

Why is it that some patients with Purkinje PVC do not develop ventricular fibrillation (VF)? What causes such a difference in sensitivity? How many non-fibrillating individuals have undetected Purkinje PVCs? Why would a patient with PVC experience VF or not at different times? Are there autonomic, electrolytic, metabolic, ionic factors that actually determine all of this?

Some features of Purkinje PVCs

They are typically characterized by a narrow QRS complex and can be triggers of MVA –as they are involved in its starting and maintenance– and also of automatic, reentrant and triggering phenomena, in scenarios such as idiopathic VF, Brugada and early repolarization syndromes, torsades de pointes and polymorphic catecholaminergic VT. These premature ventricular contractions have short coupling intervals; could be responsible for MVA and also be linked to reentrant phenomena and triggered activity, with more frequent late post-depolarizations[1-3]. In addition, MEPPC (multifocal ectopic Purkinje premature contractions) has been described with a mutation in the SCN5A gene, which is the same gene involved in Brugada and long QT type 3 syndromes, sinoauricular dysfunction, idiopathic VF associated with early repolarization, atrial fibrillation and conduction system disease. This entity, which usually responds to treatment with quinidine[4], is related to gain in Na channel function, Purkinje system hyperexcitability, unsustained VT and sudden death events.

A "ping-pong" model has been defined at the level of the Purkinje system, a reciprocating bigeminy involving repetitive beat-to-beat axis alternation from right to left ventricle. It is applicable to bidirectional and polymorphic VT, and to other electrical disturbances as well. Several options are available for this model: right bundle branch block with alternating axis, alternating right bundle branch block and left bundle branch block, and alternating QRS axis with narrow QRS. Some of the possible combinations are shown in the **box**[5,6].

Purkinje's cells: A little bit of history[1-3,7-10]

- 1839: Purkinje described a jelly-like subendocardial fiber network. Tawara later specified its function.
- 1970: Transitional Purkinje-myocardial cells with histological differences, rapid repolarization at

Box. Possible combinations of the "ping-pong" model at the level of the Purkinje system[5,6].

Possibility 1		Possibility 2
Left bundle branch block	+	Right bundle branch block
Right bundle branch block with left axis deviation	+	Right bundle branch block with right axis deviation
Left bundle branch block	+	Right bundle branch block with right axis deviation
Left bundle branch block	+	Right bundle branch block with left axis deviation
Left axis deviation	+	Right axis deviation with normal QRS

phase 1 of the action potential, contributing to unidirectional Purkinje-muscle block, were targeted.
- 1974-78: Reentry into the His-Purkinje system with shorter duration of action potential and refractory period, notch in its ascending portion, prominent Ito, potential automatism (controlled by sinus rhythm); with different location, cellular ultrastructure, electrophysiology and excitation-contraction phenomenon was considered.
- 1998: Reentry involving the Purkinje-muscle junction was specified.
- 2002: Haissaguerre succeeded in mapping and performing ablation of dominant triggering PVC in an idiopathic VF patient. He addressed the distal Purkinje system achieving a decrease in recurrences and electrical storm events.
- 2002-2009: A multicenter study of VF ablation in 38 cases with idiopathic VF (no structural disease), with relapses and new arrhythmia foci was published. The study was based on 20 reports and comprised 200 patients with and without an implantable cardioverter-defibrillator (note that ICD prevents death, not the arrhythmic event). Premature ventricular contractions originated in the right and left Purkinje system and in the myocardium (including diseases such as Brugada and long QT syndromes, monomorphic or polymorphic VT, and ischemic heart disease)[1-3,7-10].

Purkinje cells are large, thin, with rapid uniform conduction, resistant to hypoxia, with high glycogen content and low myofibrils. At the level of the Purkinje system, there may be muscle-Purkinje (antidromic) or Purkinje-muscle (ortho-dromic) re-entry[1-3].

What is the Purkinje system?

The Purkinje system is a small fraction of myocardial mass; specialized fibers isolated from the underlying ventricular myocardium until growing arborized in the muscle. Some areas of the system are more susceptible to maintaining VF than others[1-3]. Examples of Purkinje premature ventricular contractions are presented in **Figures 1** and **2**.

Right ventricular diseases, especially of its outflow tract

Why is the RVOT arrhythmogenic? Some facts have been raised: relatively high M cell ratio (related to late post-depolarization), thinner surrounding myocardium −which decreases the electrotonic effects inhibiting arrhythmia propagation−, unique three-dimensional structure and singular ion channel architecture. They play a role in idiopathic VF, Brugada syndrome, polymorphic catecholaminergic VT and torsades de pointes[11,12].

Other RVOT-related issues (some answered and some to be answered)

Why is the RVOT more arrhythmogenic if disturbances are found over the whole ventricular wall? What does this fact bring about? Would MVA triggers ablation resolve electrical storm events?

There are specific RVOT depolarization and repolarization areas and premature ventricular contractions in this area may originate both benign arrhythmias and malignant events in subjects without structural cardiopathy [11,12].

The RVOT is the preferred site for the origin of arrhythmias even in relation to their embryology. The heart's development overlaps with −outflow tract, Brugada syndrome, and to a lesser extent right ventricular arrhythmogenic cardiomyopathy− tachycardias. The right ventricular outflow tract is formed with a slow conduction phenotype and does not express the genetic program of the working myocardium. Therefore, its phenotypes are different from those of the right and left ventricular free wall. In adults, RVOT ventricular arrhythmias develop with postnatal evolution and age plays to some extent a role in the progression of the disease. Slow conduction and spontaneous activity promote arrhythmias

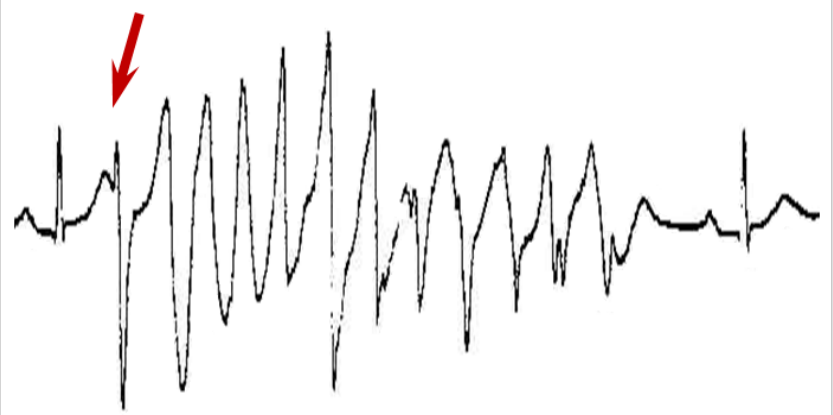

Figure 1. Patient with no structural heart disease. Purkinje premature ventricular contractions (arrow) leading to torsades de pointes and later ventricular fibrillation. An implantable cardioverter-defibrillator was implanted.

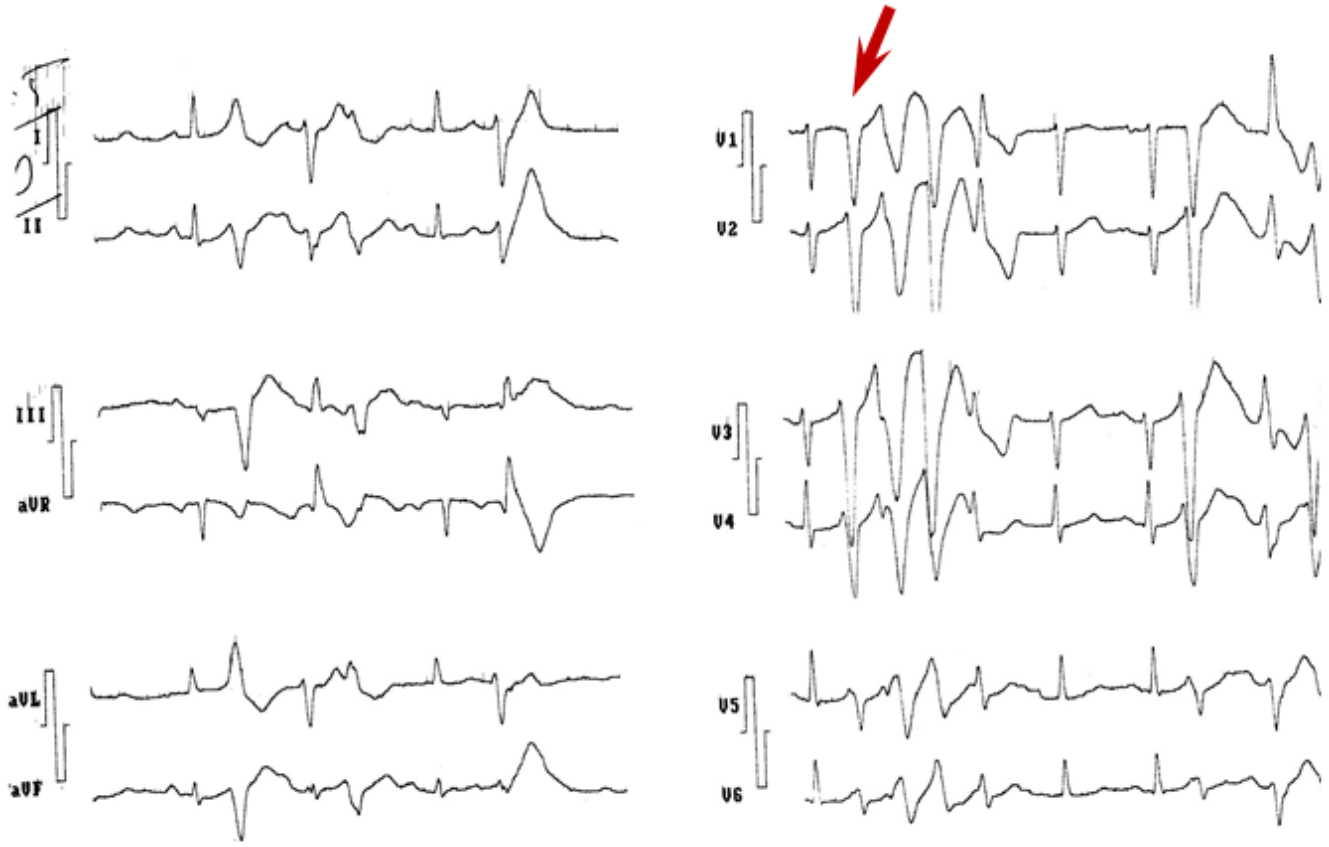

Figure 2. Purkinje premature ventricular contractions (arrow) showing ultra-short coupling interval of various morphologies. Repetitive ventricular responses.

that become unmasked and even increase after birth. The age of the heart will reveal the arrhythmic nature of a region with a remnant of the embryonic phenotype in the adult myocardium. The heart grows, starts remodeling and maturing; and then eventually plays a role in arrhythmogenesis, with a relationship between the RVOT development and arrhythmias. In the adult heart, the RVOT myocardium −having a working myocardial phenotype−, has lower expression than that in the right and left ventricles, which favors slow conduction and low excitability[13].

Other issues may be added to these RVOT-related facts, such as fibrosis, patient age, wall stress, arrhythmic substrate and a possible modulating mutation. All of which leads to arrhythmogenia.

The most common type of VT in subjects without structural heart disease originates in the RVOT. This tachycardia exhibits a left bundle branch block (rS in V_1 lead) and prominent R wave in lower leads (D_{II}, D_{III} and aVF) pattern, and from a clinical point of view, does not present hemodynamic decompensation.

Then, in a patient without heart disease who suffers from palpitations and presents RVOT premature ventricular contractions (RVOT-PVC), a possible sustained VT well tolerated and related to such structure may well be considered. However, it is also the site of origin of VF (in Brugada syndrome and idiopathic VF).

There are polymorphic arrhythmias accompanied by syncope or cardiac arrest, short-coupled premature ventricular contractions (at the peak of the T wave), and also monomorphic VT, which is more common; presenting palpitations and frequent long-coupled premature ventricular contractions. A distinction has to be made between benign monomorphic VT related to RVOT and polymorphic malignant VT or VF triggered by RVOT-PVC. It is an idiopathic RVOT-VT or an idiopathic malignant VT. Viskin and Antzelevitch[14] rightly speak of "the worst nightmare" when a subject with "benign" ventricular

arrhythmias suffers from sudden cardiac death or when there is a risk of stratifying a young person with benign arrhythmia who would later suffer from sudden cardiac death. Neither the number of PVCs, nor their coupling interval will allow for an absolute differentiation between polymorphic and monomorphic RVOT-VT; however, there certainly are some clues[14-16]:

- The coupling interval of premature ventricular contractions (T wave descending lead or earlier), prone to malignancy, is "intermediate" between the shorter idiopathic VF interval and the longer benign monomorphic RVOT-VT interval.
- A shorter interval points to polymorphic arrhythmia and malignancy, although their absence would not entirely affect the possibility of polymorphic RVOT-VT.
- Polymorphic RVOT-VT is usually faster than monomorphic and started by short PVC interval, which can be called "short coupled RVOT-VT type".
- Other clues may be PVC QRS duration (wider than in idiopathic VF and benign forms), and shorter RR interval[14-16].

The right ventricular outflow tract-PVC intermediate coupling is among the shortest in idiopathic VF (ultra-short) and the longest in idiopathic monomorphic, polymorphic and benign VT[14-16]. There is a malignant variant due to RVOT-PVC (idiopathic VF-polymorphic VT) but benign idiopathic VT due to RVOT-PVC also occurs in patients without structural heart disease, which may lead to polymorphic VF/VT and occasionally to sudden death. Radiofrequency ablation can be applied in both cases[14-16].

Haissaguerre *et al*[10] performed ablation on patients with idiopathic VF triggered by distal Purkinje system or RVOT stimuli. By doing so, these are eliminated and action is taken on the VF and polymorphic VT substrate (at its origin and surroundings), in addition to the implantation of an implantable cardioverter-defibrillator if necessary[7-10].

Premature ventricular contractions and RVOT-VT provide a left bundle branch block image (QRS predominantly negative in V_1), with a lower axis (ventricular complex positivity in D_{II}, D_{III} and aVF) and short coupling interval (not as much as in idiopathic VF and torsades de pointes). There is a functional blockage and conduction delay due to a rapid triggered "switch on" or micro-release (single or multiple close focus). It may also be associated with chaotic fibrillatory conduction and the presence of polymorphic VF or VT with no delayed organic conduction zone and changes in the QRS shape[14-16]. **Figure 3** shows an example of RVOT-PVC.

Comprehensive approach for PVC assessment

"The frequency and complexity of ventricular ectopy is related to risk, yet it is not an accurate predictor of risk ventricular arrhythmias for individual patients". No doubt such a statement by Lindsay[9] is a truth to be recalled. Several factors should be taken into account when assessing PVCs: the sufferer, age, presence or not of structural heart disease, hemodynamic repercussion, left ventricular ejection fraction, transient causes (electrolyte or metabolic disorders), other devices and systems disease, heart rate, MVA site of origin, density in 24 hours, coupling interval, uniform or non-uniform morphology, width, triggering events (repetitive ventricular or other MVA responses), RR interval, sustained or non-sustained VT, ventricular ectopic QRS interval, QT interval, T wave amplitude, disease progression, channelopathy (if any) and use of antiarrhythmic drugs[17,18].

How do you tell the difference between harmless and harmful PVCs?

Stratifying the risk of PVC proves difficult, as it happens when evaluating cases with J-wave, electrical memory, QRS notches and other electrical signs; none of them absolute but none of them negligible.

Haissaguerre, entirely devoted to malignancies, described the Purkinje System and RVOT´s PVC as triggering MVA (primarily in idiopathic VF) with sudden death events. Their mapping and ablation prevent recurrences and electrical storm events. He also outlined that J-wave may possibly be a predictor of MVA and sudden death[10].

Pathophysiology of Brugada syndrome: the role of RVOT and radiofrequency ablation

The RVOT is a thin structure, complex from the embryonic stage, with fusion of diverse structures, combining structural and physiological properties differing from those of other regions[19]. Some experimental studies found that radiofrequency applied to both epicardium and RVOT suppressed PVC in Brugada syndrome. Brugada and Pappone[20] reported a structural abnormality (spikes indicating early ventricular activation in either the right Purkinje system or the RVOT) and abnormal local, less extensive, fractionated electrograms. Radiofrequency results in fewer

recurrences, ST-segment normalization and absence of MVA. An electroanatomical substrate and arrhythmogenic vulnerability are considered in the syndrome; which includes electroanatomical and histological RVOT abnormalities together with the clinical and genetic aspects, in both symptomatic and asymptomatic patients[19-22].

The right ventricular outflow tract role in Brugada syndrome

There are several theories regarding the physiopathology of the syndrome [19,21,22]:

1. Both electrical signs and arrhythmogeny are explained by a repolarization disorder and the RVOT/right ventricular transmural dispersion.
2. By this, we mean a depolarization disorder involving delayed subepicardial right ventricle-RVOT and infraHis bundle block activation (seen in the signal-averaged electrocardiogram) with late potentials and fractions.
3. Presence of electrotonic currents. There is a mixture of structural and functional disorders including right ventricle/RVOT epicardial excitation failure (current-to-load mismatch).
4. Abnormal expression of the neural crest during DVST development (the neural crest plays a key role in the RVOT morphogenesis through embryogenesis).

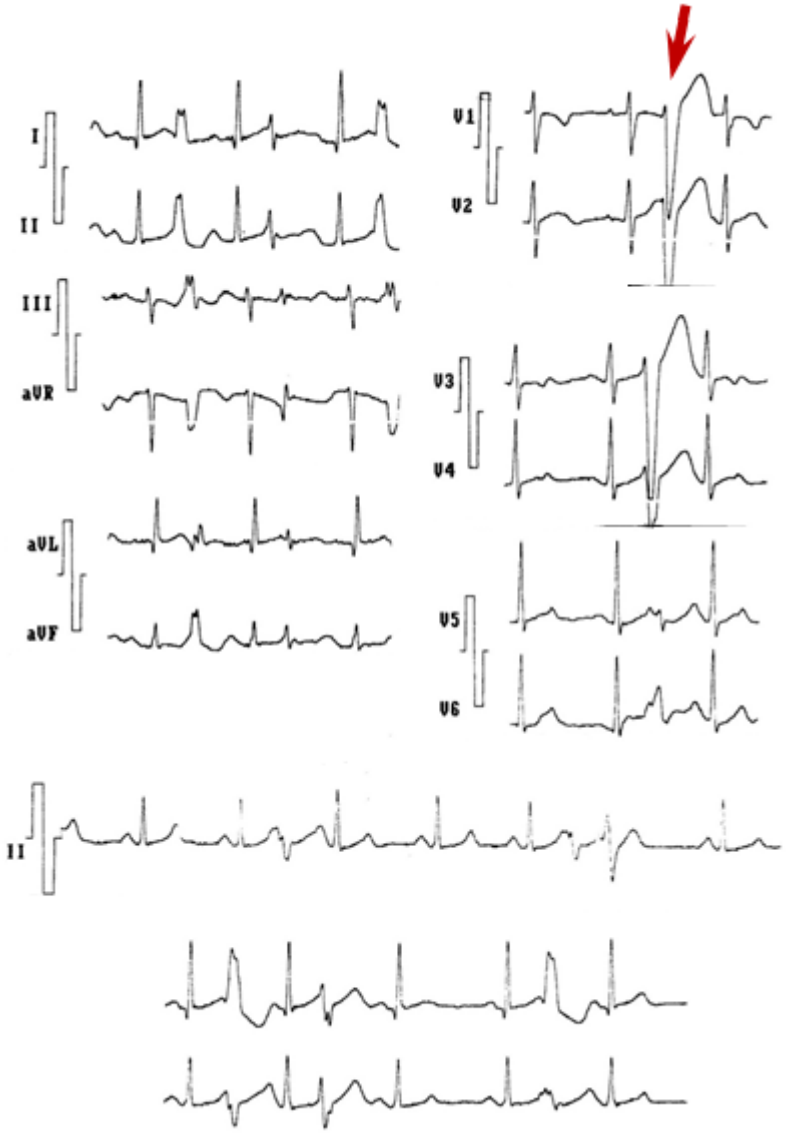

Figure 3. Right ventricular outflow tract premature ventricular contractions showing left bundle branch block morphology (rS in V_1, arrow) and high R wave in D_{II}, D_{III} and aVF. Another tracing showing runs of repetitive ventricular ectopic beats.

A reclassification of Brugada syndrome has been proposed in terms of a combination of structural and electroanatomical defects (**Figure 4**) involving an arrhythmic substrate. This would require further changes in its stratification and treatment (RVOT anti-inflammatory drugs would reduce arrhythmias) with a gradient of the pathological substrate from epicardium to endocardium (myocardial inflammation: abnormal electrocardiogram and MVA). It would be more of an organic-functional problem with a late phenotype (development of the arrhythmic substrate) where both fibrosis and adiposis would be involved[19-22]. Of particular note is that one of the papers addressing these changes concerning the concept of the syndrome belongs, among others, to Ramon Brugada[19].

More and more questions about Brugada syndrome and RVOT physiopathology

Is there a link between inflammation and Brugada syndrome? Is the first to blame? What is the relationship between genetic testing, electroanatomical alterations and the anatomopathological substrate?

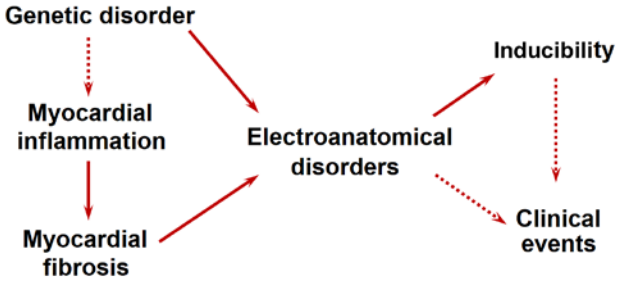

Figure 4. Pathophysiology of Brugada syndrome.

What causes the diagnostic test to be negative? Would there be another component such as fat instead? Is it a purely electrical process, solely structural, or do both coexist? Would it be possible that RVOT inflammation simply adds to a genetic predisposition leading to arrhythmic events and sudden death? Why is the pattern often variable with non-event genetics and normal electrocardiogram? Why is RVOT affected by low-voltage areas?

Epilogue (Purkinje system and RVOT)

- Both play a major role in arrhythmogenesis (MVA and sudden cardiac death).
- Both are complex and unique in terms of embryology, histology, anatomy, physiology and pathophysiology.
- They are involved in the genesis (triggers) and maintenance of a number of MVAs (VF, VT, polymorphic VT, malignant RVOT tachycardias and so on).
- Genetics, arrhythmic substrate, structural, electroanatomical and functional factors (inflammation, fibrosis) are related to clinical events and vulnerability to arrhythmias.
- These concepts are critical for risk stratification and therapeutic measures; especially ablative measures (Purkinje PVC, and RVOT areas), which achieve healing of some of them by destroying the triggers and some specific regions.
- It is compulsory to redefine some diseases currently known as organic-functional diseases. This would imply revolutionary changes of classical concepts.

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