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Hypothetical "Anatomy" Of Brugada Phenomenon: "Long Qt Sine Long Qt" Syndrome Implicating Morphologically Undefined Specific "Brugada's Myocells"

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Abstract

The Brugada syndrome (BrS) is associated with increased risk of ventricular arrhythmias and sudden cardiac death. It generates genetically mediated arrhythmias posing a true pathophysiological challenge. In search of the similarities between BrS and long QT syndrome some novel insights are suggested. In patients with BrS the duration of QT interval is usually normal. Some investigators have found prolonged QT interval in the syndrome's natural course or the duration of QT segment have been extended by provocative tests unmasking BrS. Thus, BrS might be characterized as "long QT sine long QT" syndrome. The existence of two functional types of myocytes is suspected. Regarding structure and function the majority of ventricular myocardium is probably mostly healthy. The rest of myocardium (preferably the subepicardium of right ventricular outflow tract) due to its genotypic peculiarities demonstrates no negative influence on ventricular performance until early adulthood is reached and/or other unstable preconditions are fulfilled (nocturnal time, fever, specific drugs, etc.). Based on published findings of positive outcomes, following the epicardial ablation of the right ventricular outflow tract region, a new hypothetical concept suggesting the presence of specific, genetically affected "Brugada's myocells" is proposed. These cells as a suitable arrhythmogenic substrate reside intramurally within the subepicardial region of the outflow tract of right ventricle. In the daytime these cells likely are dormant but at rest their nocturnal proarrhythmic behavior is activated occasionally. Presumptions regarding the pathophysiology of BrS might be the focus of further discussion.

Introduction

The Brugada syndrome (BrS) was first described in 1992[1] as a unique set of electrocardiographic signs associated with sudden death in otherwise healthy adults without structural heart disease. It is an inherited arrhythmogenic disorder characterized by a typical Brugada-type ECG pattern of ST-segment and is associated with malignant ventricular arrhythmias.[1], [2] Increased ventricular vulnerability typically occurs at rest and during night time.[2], [3] Up to 20% of patients with BrS may suffer from supraventricular arrhythmias.[3]-[5]

A heated debate is ongoing about the underlying mechanisms of the genesis of VF.[6] Some authors[7] state, that BrS is always associated with a considerable prolongation of right ventricular repolarization. The electrical disorder is primary, that is, without concomitant underlying heart disease.[8] In early 2009 it was declared that BrS is a disease mainly of the right ventricle.[8] There is a consensus related to the right ventricular outflow tract (RVOT) which is the most likely substrate site regardless of the underlying mechanism.[6], [9]-[12] The purpose of this review is to develop refined understanding based on the findings of some similarities associated with BrS and long QT syndrome (LQTS). The abnormalities of repolarization and depolarization may be tracked in both syndromes. The existence of some specific/defected but morphologically still undefined "Brugada's myocells" is suspected; such a substrate most likely is responsible for VF/VT attacks.

Key Words

Brugada syndrome, arrhythmogenic substrate, ventricular arrhythmias, Brugada's myocells, "long QT sine long QT" syndrome.

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Various aspects of BrS as a baseline for new assumptions

BrS is attributed to the genetically determined entity i.e., a channelopathy that causes dysfunction of a cardiac channel participating in the action potential[8]; an electrical dysfunction favors the development of arrhythmias. The cardiac sodium channel gene, SCN_5A, is involved in two of such arrhythmogenic diseases, the BrS and one form of the long QT syndrome (LQT_3).[13] The mutation in the SCN_5A cardiac-voltage-gated sodium channel gene actually leads to a reduction in the fast sodium channel current and a premature termination of the ventricular epicardial action potential .[14], [15] Some reports have shown that different causes may mimic BrS. [16], [17] The Brugada signs are also known to be produced by drugs such as class IA and IC anti-arrhythmic agents, cocaine, tricyclic antidepressants.[14]

It is well-known that long QT interval is associated with an increased

propensity to ventricular arrhythmias.[18] The conditions comprising long QT syndrome and the BrS account for a substantial proportion of sudden cardiac deaths when no anatomic abnormalities are found.[19] However the precise mechanism of ventricular fibrillation/tachycardia (VF/VT) and ECG pattern in patients with BrS remains unresolved.[20] There are theories based on repolarization and depolarization abnormalities.[20]-[22] Excellent insights of Wilde and colleagues[21] have shown have shown support for the repolarization hypothesis as the predominant mechanism underlying BrS. This hypothesis relies on transmural dispersion of repolarization between the right ventricular (outflow tract) endocardium and epicardium.[21] In some prediction models[23] both repolarization and depolarization-related parameters seems to contribute to VF risk. A third hypothesis based on electrotonic current posits that current-to-load mismatch in the right ventricle and RVOT subepicardium is responsible for ST segment elevation.[24] Intermittent functional shift, interference or partial superimposition of repolarization/depolarization processes covering different myocardial regions may be assumed. Transmural inhomogeneity in repolarization is also indicated.[25] Hoogendijk and collegues[11] hypothesize that electrophysiological mechanism of the BrS could cause structural derangements. A comprehensive overview of BrS by Tse et al.[26] provides more insights into elctrophysiological mechanisms of arrhythmogenesis.

BrS seems to occur in individuals with structurally and functionally normal hearts.[8], [27] However, mild structural abnormalities are suspected.[28] Study by Nademanee et al.[29] suggests that microscopic fibrosis plays a role in the pathophysiology of BrS. Regardless of whether it is a late-stage by-product, or the original primary cause of BrS, this can lead to conduction impairment.[22] Whether structural alterations in BrS are primary or secondary is still unknown.[30]

A growing body of evidence suggests that a structural arrhythmogenic substrate underlying BrS may be located in RVOT.[20] Some clinical cases have demonstrated that a component of BrS substrate is functional rather than fixed structural replacement with fibrosis.[20] This viewpoint is favorably supported by the fact that BrS-type ECG pattern or VT/VF episodes may be provoked by fever.[12], [31], [32] Prompt and aggressive control of fever by antipyretics is helpful.[12], [31] There are reports related to the fever-induced QT interval prolongation and VF episodes while sleeping in healthy individuals.[34]

Three types of repolarization abnormalities have been described but only the coved-type ST-segment elevation (type-1 ECG pattern) renders the diagnostic value.[8], [31] Interestingly, the ECG typically fluctuates over time in Brugada patients, and then can change from type-1 to type-2 or type-3, or even be transiently normal.[8] Fragmented or prolonged QRS complexes in the same leads are also observed.[35], [36]

Brief characteristics of QT interval duration

Cyclic electrical processes in the ventricles consist of two alternating phases – depolarization and repolarization. The QT interval extends from the beginning of the QRS complex up to the end of the T wave. This interval represents the algebraic sum of the individual action potential of the ventricular myocytes, including both depolarization (the QRS complex or QJ interval) and repolarization (the T wave or JT interval).[37] Conventional ECG reflects the repolarization of all ventricular myocells.[37]

Commonly the QT intervals in BrS patients fall in the normal range.[38] Pitzalis and colleagues[7] however have stressed that typical ECG pattern of BrS is characterized by a considerable prolongation of QTc interval in right precordial leads. On the other hand, there is a wide range of QT interval duration that is considered abnormal, without a significant increase in risk.[39]

The sleep is accompanied by increased parasympathetic tone or by withdrawal of the sympathetic one[40], [41] and prolongs the QT interval independently of the slowing heart rate.[42], [43] This information is fundamental in understanding the potential mechanism(s) or VF/VT at rest or in night time in BrS patients. It is also well-known that marked lengthening of the QT interval is almost inevitably associated with the risk of sudden death and with increased temporal dispersion of repolarization which in turn, increases the duration of vulnerable period as well as decreases the threshold for VF.[19], [37] Temporal dispersal of the repolarization process may occur as a result of premature repolarization of some myocardial cells or as abnormally delayed repolarization of other cells.[37] An appeal to "other cells" by Kenny and Sutton[37] might be interpreted as a hint on the potentially existence of conglomerate of specific myocells. The putative accumulation of cells within the circumscribed region of right ventricle might be named as "Brugada's myocells". Likely the mass of "Brugada's myocells" is measurable and powerful enough to induce the dispersion/abnormality of repolarization reflecting on precordial ECGs. Reportedly, the abnormally delayed dispersion of premature ventricular repolarization poses a risk for VF/VT.[39], [44], [45]

Disclosure of arrhythmogenic region by modern treatment and epiloque

Recent studies have demonstrated beneficial clinical effects achieved by subepicardial substrate ablation over the RVOT.[20], [46] Normalization of the ECG and decreased recurrence of VT/VF episodes after ablation suggest that the anterior aspect of the RVOT epicardium is the primary site for the arrhythmogenic substrate in patients with BrS[20]; electroanatomic substrate is identified by endocardial and epicardial mapping system. According to Veerakul and Nademanee[6] we should have more confidence in treating BrS patient subset with catheter ablation alone without implantable cardioverter-defibrillator. Recently, Patocskai, Yoon and Antzelevitch[16] have declared that epicardial radiofrequency ablation exerts its beneficial effects by destroying the cells with the most prominent action potential notch, thus eliminating sites of abnormal repolarization and the substrate VT/VF. That is why the genetically altered myocardium eponymously might be entitled as "Brugada's myocells" which potentially represent fundamental arrhythmogenic substrate in genotype-positive patients. In the broad sense the Brugada's myocells might be characterized as containing robust morphological structure, diseased function and unpredictable behavior. The role of specific Brugada's myocells presumably increases due to decreased sympathetic cardiac tone occurring in the night time. Paradoxically – during a night's sleep the "Brugada's myocells" - as VF/VT triggers - demonstrate their activity (fortunately only occasionally) and vice versa - proarrhythmic cells are dormant in the daytime, while patients are awake.

Likely the volumetric parameters of healthy myocardium outweigh en mass the genetically involved one. The latter, i.e the minor part of myocytes potentially is responsible for the inadequacies or dynamic shift/overlap of depolarization/repolarization processes resulting in life-threatening VF/VT. According to some reports[14], [15] the

ECG changes may be transient over time. Subsequently, a vicious interrelationship of repolarization and depolarization processes is dynamic, unstable and unpredictable.

For many years or even throughout the patient's life time the intact myocells as the largest postion of myocardium with considerable heft considerable functional heft contribute to the maintenance of stable heart rhythm. Let's say the duration of QT interval is normal or close to it. Ventricular myocardium is compromised occasionally due to provoked/triggered activity of Brugada's myocells representing quite a small part of ventricular mass. Nocturnal incidental VF/VT episodes could be explained by occasional prolongation of QT interval which reflects the repolarization and depolarization abnormality. Prolongation of QT interval is probably provoked by the state of rest or sleep (due to vagal imbalance), especially in young or in middle aged patients. Such a consideration allows to construe new characteristics of BrS – "long QT sine long QT" syndrome. In general, any shift in duration of QT interval potentially is proarrhythmic.

Temporary or intermittent hyperpolarization facilitating the release of arrhythmia might not be ruled out.

Conclusions

The presence of specific, genetically implicated, and morphologically undefined ventricular myocells residing subepicardially are yet to be proven. Nocturnal cardiac events in patients with Brugada syndrome most likely manifest due to the triggered activity of putative "Brugada's myocells". These processes are highly influenced by circadian activity of parasympathetic tone. The changes of QT interval are provocative in regards to life-threatening ventricular tachyarrhythmias. Alterations of QT interval, however are not causal per se; they simply reflect mutual interrelationship between the healthy myocardium and relatively small portion of myocells. Taking into account the repolarization and depolarization abnormality in terms of QT duration fluctuation and electrocardiographic dynamicity the Brugada syndrome might be depicted as "long QT sine long QT" syndrome. Meanwhile such a speculative approach to a new explanation of Brugada syndrome remains a topic of discussion.

Conflict Of Interests

None.

Disclosures

None.

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