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Pathophysiologic Mechanisms of Brugada Syndrome: Depolarization Disorder, Repolarization Disorder or more?

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Abstract

After its recognition as a distinct clinical entity, Brugada Syndrome is increasingly recognized worldwide as an important cause of sudden cardiac death. Brugada syndrome exhibits autosomal dominant inheritance with *SCN5A*, which encodes the cardiac sodium channel, as the only gene with a proven involvement in 20-30% of patients. Its signature feature is ST segment elevation in right precordial ECG leads and predisposition to malignant ventricular tachyarrhythmias. The pathophysiologic mechanism of ST elevation and ventricular tachyarrhythmia, two phenomena strongly related, is controversial. Here, we review clinical and experimental studies as they provide evidence to support or disprove the two hypotheses on the mechanism of Brugada syndrome which currently receive the widest support: (1) nonuniform abbreviation of right ventricular epicardial action potentials ("repolarization disorder"), (2) conduction delay in the right ventricular outflow tract ("depolarization disorder"). We also propose a schematic representation of the depolarization disorder hypothesis. Moreover, we review recent evidence to suggest that other pathophysiologic derangements may also contribute to the pathophysiology of Brugada syndrome, in particular, right ventricular structural derangements.

In reviewing these studies, we conclude that, similar to most diseases, it is likely that Brugada syndrome is not fully explained by one single mechanism. Rather than adhering to the notion that Brugada syndrome is a monofactorial disease, we should aim for clarification of the contribution of various pathophysiological mechanisms in individual Brugada syndrome patients and tailor therapy considering each of these mechanisms.

Introduction

The Brugada Syndrome is characterized by sudden cardiac death from ventricular tachyarrhythmias, in conjunction with a typical ECG signature of ST segment elevation in the right precordial leads [1-3]. It is inherited in an autosomal dominant fashion. So far, the only gene with a proven involvement is *SCN5A*, which encodes the cardiac sodium (Na) channel (I_{Na}) [4]. While its prevalence is unknown, Brugada syndrome may be a leading cause of death among young men in East and Southeast Asia [5, 6]. It may also be responsible for a sizeable proportion of the devastating effect of sudden death in young adults worldwide [7-9].With the electrophysiologic mechanisms of the signature ECG and arrhythmias of Brugada syndrome being unknown, the only effective prevention of sudden death so far are implantable cardioverter-defibrillators (ICDs) [10, 11]. Among others, the prohibitive cost of ICDs imparts direct clinical relevance to the elucidation of the pathophysiologic basis of Brugada syndrome. Furthermore, these insights may prove invaluable in increasing our understanding of arrhythmia mechanisms in general, including common acquired disease. Accordingly, the aim of this study is to review clinical and experimental studies to clarify the electrophysiologic mechanisms of Brugada syndrome.

General clinical properties

Demography

Since its recognition as a distinct subgroup of idiopathic ventricular fibrillation (VF) in 1992, Brugada syndrome is increasingly described worldwide, although its distribution and prevalence remain unclear [12, 13]. The clinical presentation is heterogeneous and may include palpitations, dizziness, syncope, and (aborted) sudden death, but many subjects are asymptomatic [14, 15].

Brugada syndrome is endemic in East and Southeast Asia, where it underlies the Sudden Unexpected Death Syndrome [5]. It is particularly prevalent in Japan [16] and Thailand, being the leading cause of sudden death among young men [6]. In China and Korea, the reported incidence is lower [17-19]. In Europe, Brugada syndrome is

extensively described [20, 21], except in Scandinavian countries [22]. While its prevalence remains unresolved [14], it is probably rare, with an estimated 5-50 cases per 10.000 [9, 23]. In the USA, Brugada syndrome is also rare [24]. Arrhythmic events in Brugada syndrome occur at all ages, from childhood to the elderly, [1, 7, 18, 25], with a peak around the fourth decade [26]. It is estimated that Brugada syndrome causes 4-12% of all sudden cardiac deaths, and up to 20% among patients without identifiable structural abnormalities [8].

A striking property is the higher disease prevalence in males, particularly in regions where Brugada syndrome is endemic, despite equal genetic transmission among both genders [6, 26]. That sex hormones may underlie this gender disparity was suggested by the demonstration that castration was associated with attenuation of ST elevation [27].

Diagnosis and ST segments

The diagnosis revolves around characteristic ST segment elevations. However, the ST segment in Brugada syndrome is typically highly dynamic, exhibiting profound day-to-day, and even beat-to-beat variations in amplitude and morphology [28, 29]. Of note, accentuation of ST elevation immediately preceding VF [30-32] links these phenomena.

Two morphologies of ST segment elevation exist in Brugada syndrome. The coved-type morphology is required for the diagnosis [33], while a saddle-back shaped ST elevation is an indeterminate form that requires confirmation (conversion into coved-type) using pharmacological challenge or genetic analysis [34]. Pharmacological challenge utilizes I_{Na} blockers of Vaughan-Williams/Singh class IA or IC (except quinidine), but not class IB [35-41]. The diagnostic yield and safety of such tests are incompletely elucidated and require further investigation [20, 39, 40, 42-45].

The signature ST elevations in Brugada syndrome are usually confined to leads V1-V3, with rare occurrences in inferior or lateral limb leads [46-48]. More strikingly, leads positioned cranially from V1 and V2 in the third ($V1_{IC3}$ and $V2_{IC3}$) or second ($V1_{IC2}$ and $V2_{IC2}$) intercostal spaces often show the most severe abnormalities, both in the presence and absence of pharmacological challenge [49, 50] (Figure 1), as

demonstrated with body surface mapping (BSM) [51, 52]. Therefore, these leads must be scrutinized when Brugada syndrome is suspected [53]. At the same time, these observations firmly place the right ventricular outflow tract (RVOT) at the heart of the disease process which underlies Brugada syndrome. Overwhelming evidence, discussed below, indicates primary right ventricle (RV) involvement in Brugada syndrome.

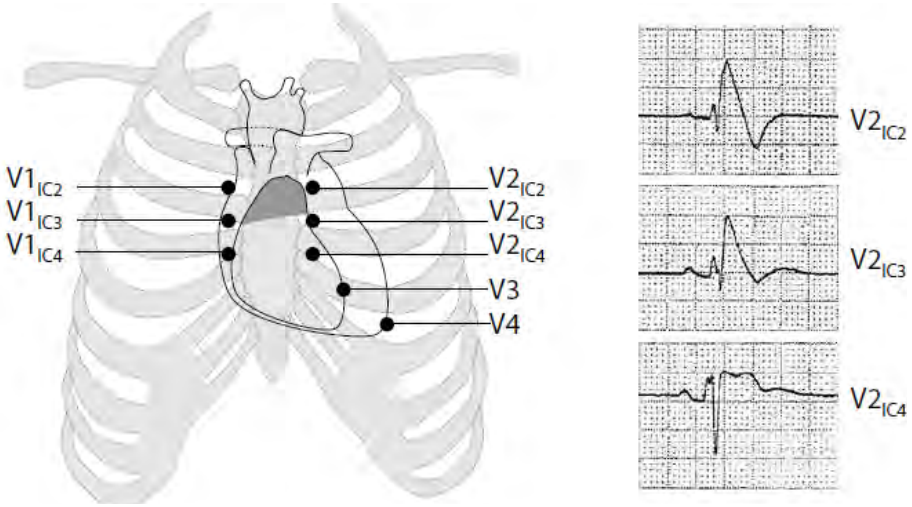

Figure 1: *ECG from a Brugada Syndrome patient showing most severe ST-T abnormalities in leads overlying right ventricular outflow tract (shaded area): coved-type ST segment in the second and third intercostal space ($V2_{IC2}$ and $V2_{IC3}$). Intermediate ST-T abnormalities (saddleback-type) are recorded in the fourth intercostal space ($V2_{IC4}$).*

Other Electrocardiographic Features

Brugada syndrome is often accompanied by right bundle brunch block, thought atypical because of the absence of wide S wave in the left lateral leads. Signs of conduction defects are found at many levels, particularly in patients with a *SCN5A* mutation (see below) [54]: QRS widening [55], electrical axis deviation [1, 15, 48, 56, 57], and PQ prolongation, presumably reflecting prolonged His-ventricular (HV) conduction time [1, 9, 15, 33, 48, 54, 58]. Moreover, sinus node dysfunction [57, 59, 60] and AV node dysfunction [38, 54, 61] were reported. In contrast, QTc duration generally is within the normal range [9, 33, 62] but it may be occasionally prolonged [1].

Types and Mode of Onset of Arrhythmias

Sudden death results from fast polymorphic ventricular tachycardia (VT) that originates in the RVOT [44]. Monomorphic VT rarely occurs [47, 63-65], especially in patients treated with antiarrhythmic drugs [10]. Selfterminating VT may provoke syncope [10, 66-68]. An estimated 80% of subjects with documented VT/VF have a history of syncope [20]. Supraventricular tachycardia is also more prevalent and episodes of atrial flutter/fibrillation are often documented [1, 30, 69-73] with an estimated prevalence of 10-30% [74, 75]. Given the correlation between a history of atrial arrhythmias and VT/VF inducibility during electrophysiologic study (EPS), Brugada syndrome patients with paroxysmal atrial arrhythmias may constitute a population at higher risk with a more advanced disease state [62], but these data are still limited [76].

Ventricular arrhythmias and sudden death in Brugada syndrome typically occur at rest when the vagal tone is augmented [77], and at night [75, 78]. Although premature ventricular complexes (PVCs) are rare [31, 79, 80], their prevalence increases prior to VF [31]. From stored electrograms of ICDs, these PVCs appear to have the same morphology as the first VT beat, and different VT episodes are initiated by similar PVCs in the same subject [79, 81]. Further confirmation of the role of these initiating PVCs derives from the clinical benefit resulting from their elimination via catheter ablation [82].

These PVCs have a left bundle branch block morphology [83] and endocardial mapping localized their origin in the RVOT [82]. The triggering PVCs have a variable coupling interval [1, 8, 31, 79, 80]. No variations in QTc intervals precede spontaneous VF episodes [1, 79]. However, right precordial QTc prolongation was reported upon emergence of flecainide-induced ST elevations [84], possibly reflecting RVOT AP prolongation [85]. Changes in autonomic tone [31, 37, 86], body temperature [87], or the use of antiarrhythmic drugs [38] may modulate VT/VF susceptibility, since they affect ST segment elevation [35, 88-90].

Evidence of a Functional Basis

Typically, structural cardiac abnormalities are not detected using routine cardiologic diagnostic tools [1, 3, 91]. However, some authors have reported, using myocardial biopsy and autopsy findings, that fatty replacement and fibrosis in RV may be present [58]. Indeed, in all hearts of Brugada syndrome patients studied histologically, some structural derangements were found [58, 92-94]. Still, the notion that Brugada syndrome constitutes a functional defect gained almost unanimous acceptance by the discovery, in 1998, that it may be linked to mutations in *SCN5A*, which encodes the pore-forming α subunit of the cardiac Na channel [4]. Such a defect is believed to involve conduction slowing or transmural heterogeneity in AP duration (see below). While *SCN5A* is presently the only gene with a proven involvement, the discovery, in later studies, that the proportion of Brugada syndrome patients who carry a *SCN5A* mutation is 30% at most [20, 54], indicates that the genetic basis of Brugada syndrome is heterogeneous. Linkage to a second locus on chromosome 3p22-24 was demonstrated (which overlaps with the previously reported ARVC5 locus at 3p23) [95], but other genes still await identification.

More than 50 *SCN5A* mutations are linked to Brugada syndrome [96-98]. Their common effect is reduction in I_{Na}, resulting from changes in the functional properties (gating) of the mutant Na channels, or their failure to be expressed in the sarcolemma (trafficking) [99-101]. The latter may result from their impaired binding to ankyrin G [102]. Of interest, *SCN5A* mutations are also implicated in Long QT Syndrome type 3 (LQT3) and Lev-Lenègre disease [97, 99, 103], and some *SCN5A* mutations may cause a combination of Brugada syndrome and LQT3 or Lev-Lenègre disease within the same family or even within the same individual [104, 105]. While LQT3 associated *SCN5A* mutations generally increase I_{Na}, those associated with Lev-Lenègre disease reduce it, similar to those in Brugada syndrome [99]. One mutation co-segregated with Brugada syndrome in male members in a family, but with Lev-Lenègre disease in female members [105], mirroring the more prevalent clinical expression of Brugada syndrome in males.

The Case for Reentry

General electrophysiologic mechanisms of arrhythmias include reentry, early afterdepolarizations (EADs), delayed afterdepolarizations (DADs), and abnormal automaticity. It is commonly believed that reentry is the dominant mechanism in Brugada syndrome. Properties in accordance with this belief include: conduction slowing, easy VT/VF induction during EPS, and the polymorphic nature of the arrhythmias. Although polymorphic tachycardias and tachycardia onset during slow heart rates are also compatible with EADs, EADs typically require QT prolongation. However, QT prolongation is not present in Brugada syndrome; furthermore, quinidine's efficacy in preventing tachyarrhythmias in Brugada syndrome [106, 107] (see below), while also prolonging the QT interval, argues against a causative role of EADs. Evidence to render DADs unlikely appears even less controversial: DADs typically occur during calcium overload, e.g., fast heart rates. Moreover, attenuation of the hallmark ST elevations in Brugada syndrome by catecholamines [86] provides further evidence against DADs. Finally, abnormal automaticity does not usually present as a polymorphic tachycardia and exhibits a warm-up phenomenon, rather than the abrupt tachyarrhythmia onset seen in Brugada syndrome.

Proposed Electrophysiologic Mechanisms

The cause of ST elevation in Brugada syndrome and its strong linkage to VT/VF remain unresolved [75]. The proposed mechanism which presently appears to receive the widest support, both from experimental [108-112] and clinical studies [30, 84, 113-115], ascribes Brugada syndrome to a repolarization disorder, as it revolves around abnormal shortening of epicardial action potential (AP) duration. However, we propose that Brugada syndrome may involve a depolarization disorder, revolving around conduction slowing, as put forward in other clinical [31, 73, 116-120] and experimental [121] studies. Accordingly, we here review clinical and experimental studies to analyze whether they support the "repolarization disorder hypothesis", "depolarization disorder hypothesis", or both. Moreover, we analyze whether these studies support other mechanisms, in particular, structural derangements or the presence of node-like tissues.

The Repolarization Disorder Model

By studying arterially perfused RV wedge preparations of dogs, Yan and Antzelevitch developed a model to explain Brugada syndrome as a repolarization disorder (Figure 2) [109, 122]. This model revolves around inequal expression of the transient outward potassium current (I_{to}) between epicardium and other transmural layers. I_{to} drives early repolarization, i.e., phase 1 of the AP. Strong I_{to} expression in epicardium and weak I_{to} expression in endocardium [123, 124] renders epicardium more susceptible to the effects of reduced depolarizing force. Thus, in epicardium, when I_{Na} is reduced (e.g., when a mutant Na channel produces reduced I_{Na} in the presence or absence of I_{Na} blockers), a "spike-and-dome" AP shape arises, manifesting as saddle-back ST elevation (Figure 2B). To account for the negative T wave in coved-type ST elevation, prolongation of epicardial AP dome is evoked, which causes AP duration to become longer than in the endocardium (Figure 2C). With further I_{Na} reduction, I_{to} repolarizes the membrane beyond the voltage at which L-type Ca channels (I_{Ca-L}) are activated, resulting in loss of AP dome. This loss, however, occurs nonuniformly: epicardial cells where AP dome is maintained ensure that negative T waves remain present (Figure 2D). This dispersion of repolarization also creates a vulnerable window, which allows phase 2 reentry [112] to cause a premature impulse, which triggers VT/VF based on reentry between transmural layers [8, 112, 125-127] (Figure 2E). This hypothesis requires that the AP shape in endocardium remains unaltered by this I_{Na} reduction; this is accounted for by less I_{to} expression in endocardium in many species, including humans [108, 111, 124, 128-131]. Similarly, the presence of the ECG changes in right, but not left, precordial leads in Brugada syndrome is explained by larger I_{to} expression in RV than LV epicardium [110], while the higher disease prevalence in males is paralleled by higher epicardial I_{to} density in males than in females [132].

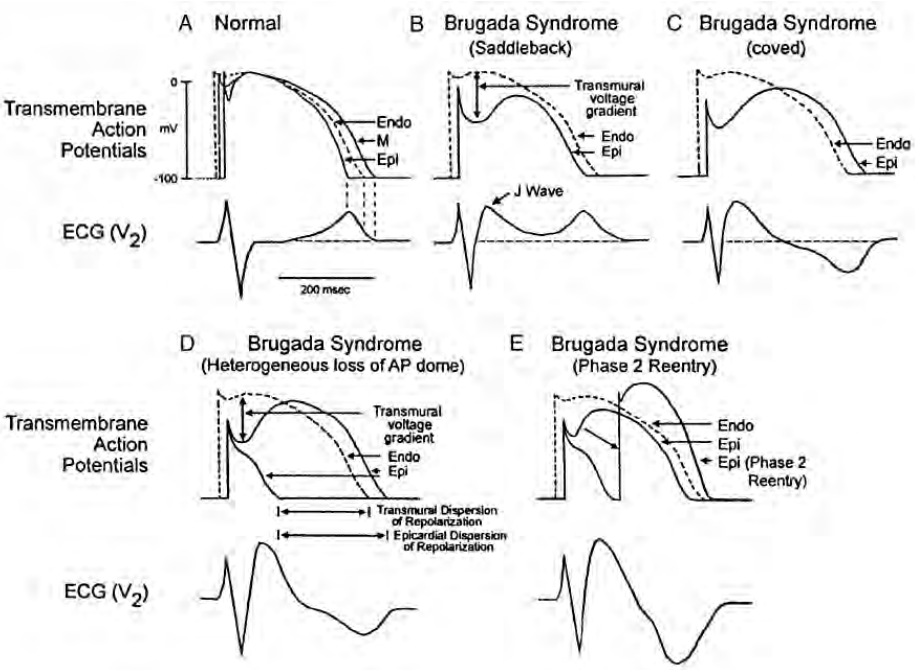

Figure 2: *Representation of the repolarization disorder hypothesis. For explanation see text.*

The Depolarization Disorder Model

100 An alternative explanation for the signature ST elevations and negative T waves in Brugada syndrome, which does not need to invoke fundamentally different AP shapes, is based on conduction delay in RVOT (Figure 3). The RVOT AP (Figure 3B, top) is delayed with respect to the RV AP (Fig 3B, bottom). During the hatched phase of the cardiac cycle in Figure 3D (the phase between the upstroke of the early AP in RV and the upstroke of the delayed AP in RVOT), the membrane potential in the RV is more positive than in the RVOT, thus acting as a source, and driving intercellular current to the RVOT, which acts as a sink (Figure 3C, a). To ensure a closed-loop circuit, current passes back from RVOT to RV in the extracellular space (Figure 3C, c), and an ECG electrode positioned over the RVOT ($V2_{IC3}$) inscribes a positive signal, as it records the limb of this closed-circuit which travels towards it (Figure 3C, b). Thus, this electrode inscribes ST elevation during this phase of the cardiac cycle (Figure 3D, bottom, bold line). Reciprocal events are

recorded in the left precordial leads, as demonstrated using BSM [52]. Here, current flowing from the extracellular space into the RV muscle (Figure 3C, d) causes ST depression. In the next phase of the cardiac cycle (following the upstroke of the delayed AP in RVOT), the potential gradients between RV and RVOT are reversed, as membrane potentials are now more positive in RVOT than in RV. Thus, RVOT now acts as the source, driving the closed-loop circuit in the opposite direction (Figure 3E), with current now passing away from ECG lead $V2_{IC3}$ (Figure 3E, d), thus resulting in the negative T wave (Figure 3F, bottom, bold line). Note that in Figures 3D and 3F, the delayed AP of RVOT is abbreviated in comparison to RV AP (and in comparison to Figure 3B, where APs of isolated cells are shown), as electrotonic interaction between RV and RVOT (which is present when RV and RVOT are electrically well-coupled) accelerates repolarization of RVOT AP (the mass of RV strongly exceeding that of RVOT) [133].

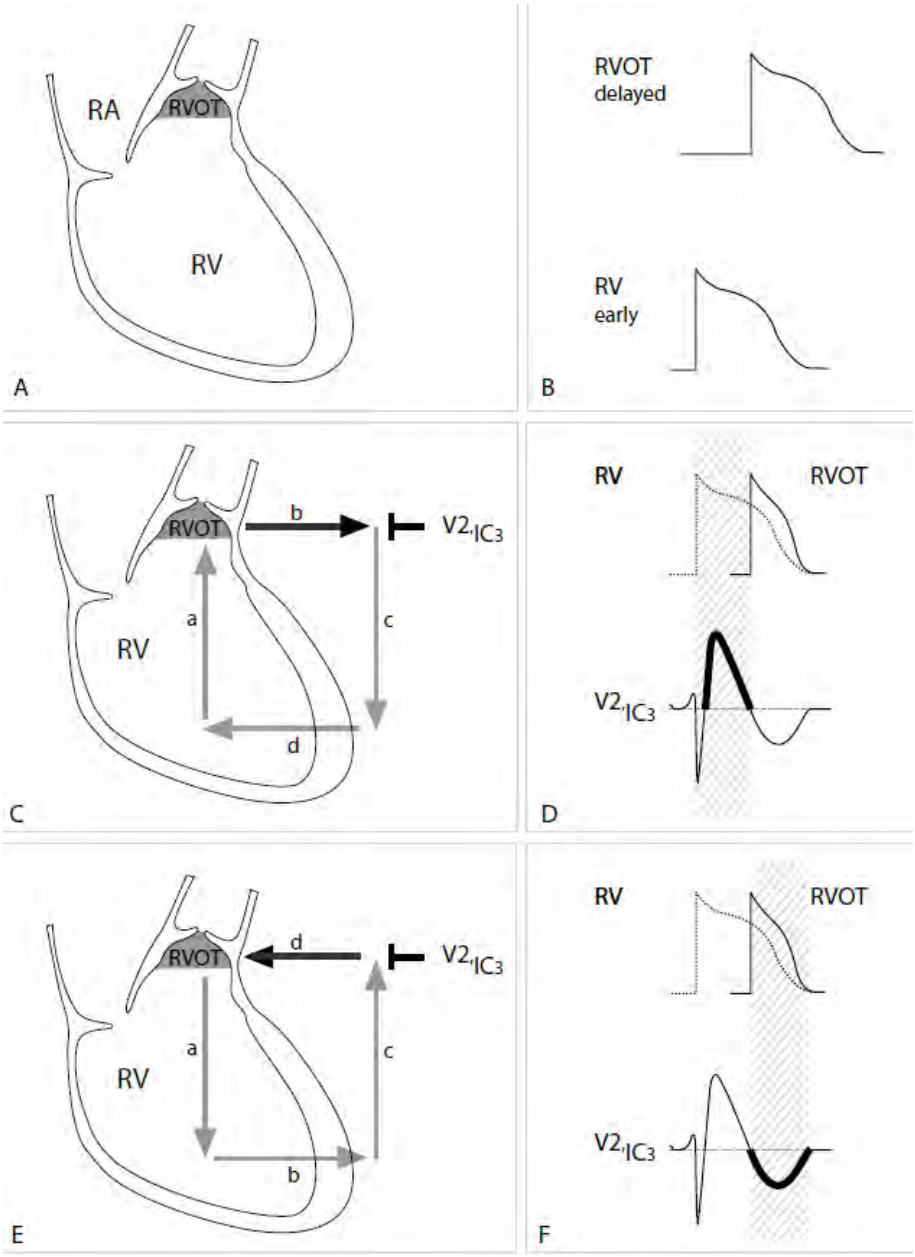

Figure 3: *Qualitative model of the depolarization disorder hypothesis.*

This qualitative model of ST elevation in Brugada syndrome derives from the mechanism that is believed to cause ST elevation in regional transmural ischemia, where large differences in membrane potential exist between adjacent ischemic and nonischemic zones [134]. Similar to regional ischemia, where premature beats which trigger reentrant tachyarrhythmias originate in the border zone between areas with disparate membrane potentials, the first beat of the ventricular tachyarrhythmia in Brugada syndrome may originate in the border zone between early and delayed depolarizations [135].

Evidence for the Repolarization Disorder Hypothesis

Heterogeneity in Repolarization

It is clear that proof of the repolarization disorder hypothesis requires documentation of disparate AP duration between transmural layers. This hypothesis relies heavily on findings in the perfused canine RV wedge preparation which allows simultaneous recordings of transmembrane APs from various transmural layers, in conjunction with ECG-like electrograms [109, 136]. Other *in vitro* studies provide additional support by showing that I_{Na} blockers [112, 137] and ATP-sensitive potassium channel ($I_{K\text{-}ATP}$) openers [138] worsen transmural dispersion of action potentials, and that I_{to} blockers ameliorate them [110, 126, 131]. However, in another isolated canine RV preparation, these findings were only partially confirmed [139]. While I_{Na} blockers and $I_{K\text{-}ATP}$ openers were also required for ST elevations and reentrant arrhythmias, and the first beat of arrhythmia occurred in areas with short recovery times (consistent with phase 2 reentry), arrhythmias did not always involve epicardium. A closed-chest *in vivo* study [85], where signature ST elevations (recorded by conventional 12-lead ECG) were created by cooling a small epicardial RVOT area, was equally ambivalent: cooling did cause a "spike-and-dome" monophasic action potential (MAP) shape in epicardium, but not endocardium, along with ST elevations, and exacerbation of ST elevation and spontaneous VF upon vagal stimulation (see below). However, no loss of AP dome was reported. Of interest, the area needed to cool was small and confined to RVOT, mirroring the small area on the thorax where signature ECG changes are often found in Brugada syndrome patients (Figure 1).

Validation of this hypothesis in patients is more challenging, because it requires simultaneous electrogram recordings from epicardium and endocardium. Accordingly, RVOT activation recovery intervals (ARIs) were recorded using an epicardial catheter in the great cardiac vein, at a reasonably small distance from a corresponding endocardial catheter [113]. In this single patient study, during augmented ST elevation, epicardial, but not endocardial, ARIs shortened. In another study, MAPs were recorded from RVOT epicardium during open-chest surgery, along with MAPs from endocardial catheters [115]. Here, RVOT epicardial "spike-and-dome" AP shapes were found; these phenomena were neither found endocardially, nor in control subjects. However, there was no loss of epicardial AP dome. More fundamentally, comparison between the ST segment morphology, which would be predicted by this model (Figure 2), and clinically observed ST segments (Figure 1) reveals that the proposed changes in epicardial AP shape/duration must take place in a very limited space. Thus, abbreviated "spike-and-dome" APs in epicardium (Figure 2B) must be present in the fourth intercostal space, because "saddle-back ST elevations" are observed there (Figure 1, $V2_{IC4}$). Concurrently, AP lengthening with "spike-and-dome" morphology in epicardium (Figure 2C) accounts for "coved-type ST elevation" in the third intercostal space (Figure 1, $V2_{IC3}$), and nonuniform loss of AP dome (Figure 2D) underlies more accentuated "coved-type ST elevations" in the second intercostal space (Figure 1, $V2_{IC2}$). This large spatial dispersion in epicardial AP morphology would not be expected in the presence of normal electrical coupling (see below). Still, some authors have suggested that ST segment and T wave alternans after class I antiarrhythmic drugs [56, 140, 141] may support the repolarization disorder hypothesis; however, whether this observation truly reflects a repolarization or depolarization disorder is unresolved.

Effects of Autonomic Modulation

Autonomic modulation strongly affects the amplitude of ST elevation in Brugada syndrome [31, 37, 114, 142]. Parasympathetic stimulation increases ST elevation, presumably because it reduces $I_{Ca\text{-}L}$ during the AP plateau [143], rather than through induction of coronary spasm [37, 114], while heart rate variability analysis revealed

a rise in vagal tone preceding VF episodes [31]. Accordingly, other studies showed opposing effects of sympathetic stimulation, as isoproterenol reduced ST elevation and prevented VT/VF inducibility [37, 86, 144, 145]. Interestingly, autonomic dysfunction due to abnormal norepinephrine recycling was identified in Brugada syndrome [146] indicating that abnormal autonomic innervation may cause ST elevation.

Effects of I_{to} Blockade

The repolarization disorder hypothesis predicts that removal of the transmural gradient in I_{to} counteracts the pathophysiologic mechanisms of Brugada syndrome, thereby attenuating ST elevation and VT/VF occurrence. Accordingly, 4-aminopyridine, which blocks I_{to}, restored the AP dome and electrical homogeneity in the canine wedge preparation [109, 127]. This is consistent with the clinical efficacy in Brugada syndrome patients of quinidine, a class IA antiarrhythmic drug with I_{to} blocking properties, in normalizing the ECG pattern [37, 147] and preventing spontaneous or induced arrhythmias [106, 148-150]. However, it is possible that this effect is due to quinidine's anticholinergic actions [151, 152], while quinidine's effect to prolong AP duration by blockade of the delayed rectifier potassium channel [153-156] may also act to suppress reentrant arrhythmias.

Effects of Heart Rate

The observation that long RR intervals [30, 73] augment ST elevations in Brugada syndrome is used as support for the repolarization disorder hypothesis. This observation is consistent with the nocturnal occurrence of VT/VF and was ascribed to slow gating kinetics of I_{to}, which increase this current at slow heart rates [124]. Accordingly, pacing provided an effective therapy against bradycardia-related VT/VF onset in a Brugada syndrome patient [157]. In contrast, ST elevations may also increase at fast heart rates [56, 141, 158, 159]. While particular circumstances may sometimes be responsible (enhanced intermediate inactivation of the mutant Na^+ channel [158], or the use of class IC antiarrhythmic drugs with use-dependence [56, 141], this phenomenon was also described in the absence of such confounders [56, 141].

Evidence for the Depolarization Disorder Hypothesis

General Conduction Slowing

Most evidence to favor the depolarization disorder hypothesis is derived from clinical studies [31, 73, 116-120], with a modeling study providing further confirmation [121]. Given the numerous ECG signs of conduction slowing in Brugada syndrome, the first studies into the pathophysiologic mechanisms of Brugada syndrome were based on the hypothesis that Brugada syndrome revolves around conduction slowing and found strong supportive evidence. Analysis of ventricular late potentials, which reflect delayed and fragmented ventricular conduction, and are strong predictors of ventricular arrhythmias [119], has received particular attention. Late potentials are not only highly prevalent in Brugada syndrome [31, 73, 117, 119, 141, 160, 161], but also independent predictors of VT/VF inducibility (as opposed to QTc dispersion and T wave alternans) [119, 120]. Of note, late potentials coincide with spontaneous ST elevation and late r' in V1-V3 [31], while Holter analysis of multiple spontaneous VF episodes shows that ST elevation-late r' in V1 correlates with VF onset [31]. Also, flecainide elicits late potentials along with ST elevations [73]. Of further support for the role of conduction slowing, Brugada syndrome patients in whom VT/VF is inducible during EPS have longer HV intervals than non-inducible patients [162].

Right Ventricular Conduction Slowing

While these findings confirm the strong correlation between conduction slowing and VT/VF in Brugada syndrome, validation of the depolarization disorder hypothesis requires that conduction delay is mapped in the RVOT. Accordingly [117], epicardial electrograms were recorded from the conus branch of the right coronary artery, which runs over the RVOT surface. Activation delay was found here, but not endocardially. Of note, this delay increased with class IC drug challenge. In another study [163], BSM localized areas of conduction delay to the anterior thorax overlying the RVOT. Conduction delay here increased with I_{Na} blockers and decreased after isoproterenol. Of interest, changes in ARIs paralleled these changes, arguing against premature repolarization. In a study where

signal averaged ECGs were calculated from various BSM leads [161], late potentials coincided with ST elevation and were mapped to the RVOT. The role of RV conduction delay was also confirmed using tissue Doppler echocardiography, as the amplitude of ST elevation in Brugada syndrome patients correlated with delay in RV contraction [116]. Still, some studies failed to document delayed potentials of the right ventricle [37].

Evidence for Other Pathophysiologic Mechanisms

Structural Disorders

Given its predominant RV involvement, some initially considered Brugada syndrome a RV cardiomyopathy, akin to arrhythmogenic right ventricular cardiomyopathy (ARVC), with subtle structural abnormalities not detectable by standard diagnostic tools [58, 93, 164]. Similarities between Brugada syndrome and ARVC were further substantiated by the discovery of *SCN5A* mutations in an ARVC family [165]. While the discovery of linkage to *SCN5A* has since drawn attention to functional derangements in Brugada syndrome [4], recent evidence now rekindles support for an abnormal structural RVOT component in Brugada syndrome.

Electron beam CT scan studies revealed RV enlargement, along with abundant adipose tissue in some patients [166], and RV wall motion abnormalities whose localization correlated with the origin of spontaneous PVCs following an arrhythmic event [167]. Of note, spontaneous PVCs may originate in the area where VT/VF is most readily inducible during EPS, usually the RVOT free wall [168]. The link between structural and functional derangements was further tightened by an electron beam CT scan study, in which wall motion abnormalities were exacerbated/provoked [169]. Using cardiac magnetic resonance imaging, a sensitive tool for detection of RV structural abnormalities [170], significant RVOT enlargement was found in Brugada syndrome patients versus controls [171]. Also, the explanted heart of a Brugada syndrome patient with a *SCN5A* mutation and electrical storms revealed substantial structural derangements (fatty replacement and intense fibrosis) in RVOT, while the LV was normal. This study found no spike-

and-dome configuration in RV epicardium, but prominent conduction slowing, and VT/VF origin in endocardium, not epicardium. These findings argue against the repolarization disorder hypothesis and in favor of the depolarization disorder hypothesis [94].

Finally, the efficacy of catheter ablation in preventing VT/VF suggests a structural basis of Brugada syndrome [82].

While these studies demonstrate a link between structural and functional derangements in Brugada syndrome, thereby strengthening the tie between Brugada syndrome and ARVC [172], recent studies have raised the intriguing possibility that the functional derangements, i.e., I_{Na} reduction, may *cause* these structural derangements. A girl with compound heterozygosity for two *SCN5A* mutations exhibited severe degenerative changes in the specialized conduction system [173], while transgenic mice made haploinsufficient by splicing one *SCN5A* allele developed cardiac fibrosis as they aged [174] .

The Role of Slow Conducting Tissues

Another explanation for RVOT conduction slowing may involve the presence of slow conducting tissues in the RVOT. Cardiac development may hold the key for this premise, as it may also explain the intriguing prominence of RVOT involvement in Brugada syndrome. The right ventricle has a different embryological origin than the left ventricle [175], and the outflow tract derives from the same group of cells that compose the atrioventricular region, thus possessing slow conduction properties [176, 177]. While these node-like cells are essential for peristaltic blood movement in the embryonic heart which has yet to develop cardiac valves [178], remnants of these cells may constitute the substrate for arrhythmias originating in the RVOT [179]. We here propose that these cells may be incorporated in the depolarization disorder hypothesis in Brugada syndrome (Figure 4, right panel).

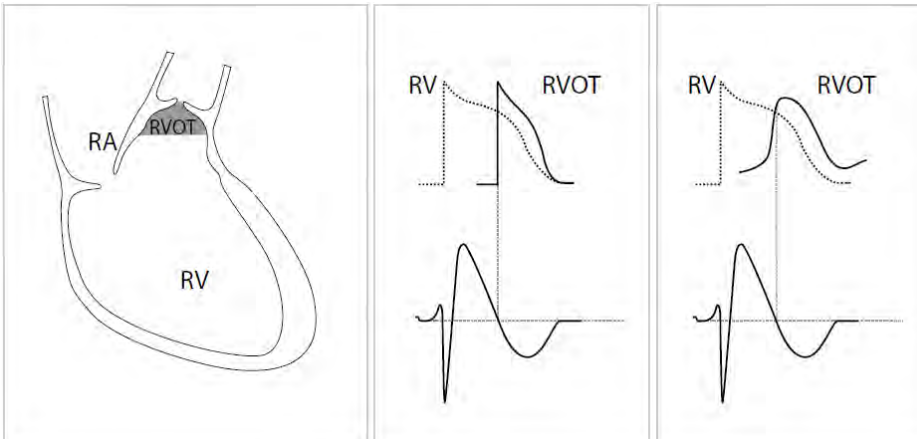

Figure 4: *Model of depolarization disorder hypothesis with incorporation of node-like cells in right ventricular outflow tract (right panel, RVOT). Similar to Figure 3, delayed activation of node-like cells causes potential gradients, resulting in coved-type ST elevation (right panel).*

This would not only comfortably account for RVOT conduction slowing, but also for the observation that the most severe ST elevations are present in leads overlying the RVOT (Figure 1, $V2_{IC2}$ and $V2_{IC3}$), as these cells are localized close to the pulmonary valve [179]. Furthermore, it would also explain suppression of ST elevation and arrhythmias by isoproterenol, as isoproterenol-induced enhancement of $I_{Ca\text{-}L}$ increases conduction velocity in these cells, whose AP upstroke is driven by $I_{Ca\text{-}L}$. Conversely, smaller $I_{Ca\text{-}L}$ expression in males than in females [180] may explain higher disease prevalence in males.

Synthesis

It is clear that no single clinical or experimental study reviewed here provides irrefutable proof of one hypothesis regarding the pathophysiologic basis of Brugada syndrome while rejecting all other hypotheses. For instance, if Brugada syndrome were only a depolarization disorder or repolarization disorder, it is not understood why subjects who take flecainide do not all have Brugada syndrome ECGs, as I_{Na} reduction sets off both hypotheses. Other derangements (possibly secondary to the primary derangement) therefore seem necessary. For instance,

fibrosis may be secondary to I_{Na} reduction, and lead to electrical uncoupling. Clearly, uncoupling would not only facilitate slow conduction, thereby supporting the depolarization disorder hypothesis, but may also be required for the repolarization disorder hypothesis, because, while this hypothesis revolves around strong electrophysiological heterogeneity within the ventricular wall [111, 131, 181], *in vivo* studies have raised doubts on the presence of large heterogeneity when electrical coupling is normal [133, 182-184].

In conclusion, clinical and experimental studies provide ample evidence to support the depolarization disorder hypothesis in Brugada syndrome, as well as the repolarization disorder hypothesis (see Table). Similar to most diseases, it is likely that Brugada syndrome is not fully explained by one single mechanism. While most studies reviewed here may provide evidence to support either hypothesis over the other, no study provides irrefutable proof against either hypothesis. Moreover, recent studies highlight the role of other pathophysiologic derangements, e.g., fibrosis. The insight now emerges that we must move away from the notion that Brugada syndrome is a monofactorial disease, because adhering to this notion may hinder the development of rational and effective therapies. Rather, we should perhaps aim for clarification of the contribution of each mechanism in individual Brugada syndrome patients, so as to render rational and effective therapy, tailored to each of these mechanisms, a realistic aim in the near future.

Clinical and Experimental Evidence to Suggest the Electrophysiologic Mechanism of Brugada Syndrome

Support for Repolarization Disorder Hypothesis:
Sodium channel blockers exacerbate/provoke ST elevations [35]
Linkage with *SCN5A* mutations exhibiting reduced sodium current [4]
Quinidine normalizes ECG and prevents arrhythmias [106, 107, 147]
More prevalent phenotype in males [6, 26, 132]
ST elevations are usually facilitated by slow heart rates [30, 73]
ST elevations are accompanied by epicardial action potential abbreviation [113]
"Spike-and-dome" configuration of epicardial monophasic AP during heart surgery [115]
ST elevation is associated with reduced ejection time of right ventricle but not of left ventricle [116]
Support for Depolarization Disorder Hypothesis:
Sodium channel blockers exacerbate/provoke ST elevations [35]
Linkage with *SCN5A* mutations exhibiting reduced sodium current [4]
ECG signs of general conduction slowing: axis deviation, PQ/QRS prolongation, sinus/AV node dysfunction [1, 15, 48, 54, 56-59]
High prevalence of late potentials [73, 117, 119, 141, 161]
Late potentials indicate increased risk of arrhythmic events [119, 161]
Flecainide induces greater QRS widening in Brugada Syndrome patients than in controls [38]
Conduction delay in right ventricular outflow tract (body surface mapping) [31, 163]
Longer HV interval predicts VT/VF inducibility [162]
ST elevation correlates with delay in right ventricle contraction [116]
Arrhythmogenic area is confined to small RVOT region (initiating PVCs, VT/VF inducibility, efficacy of catheter ablation) [82, 168]
Structural derangements, including fibrosis, in histological studies in Brugada Syndrome patients [58, 93, 164, 172]
Progression of ECG abnormality localized in the area overlying the RVOT [49-52]

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