

Review

Pathophysiological 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 pathophysiological 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 that 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 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.

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1. 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 [1,2]. It is inherited in an autosomal dominant fashion. The only gene with a proven involvement is SCN5A, which encodes the cardiac sodium (Na) channel (I_{Na}) [3]. Brugada syndrome is a leading cause of death among young men in East/South-

east Asia [4,5], and responsible for a sizeable proportion of the devastating effect of sudden death in young adults worldwide [6,7]. With the pathophysiological mechanisms of its signature ECG and arrhythmias being unknown, the only effective prevention of sudden death are implantable cardioverter-defibrillators (ICDs) [8]. Their prohibitive cost imparts direct clinical relevance to the elucidation of the pathophysiological 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 pathophysiological mechanisms of Brugada syndrome.

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2. General clinical properties

2.1. Demography

Since its recognition as a distinct subgroup of idiopathic ventricular fibrillation (VF), Brugada syndrome is described increasingly worldwide. The clinical presentation is heterogeneous, including palpitations, dizziness, syncope, and (aborted) sudden death, although many subjects are asymptomatic [9,10].

Brugada syndrome is endemic in East/Southeast Asia, where it underlies the Sudden Unexpected Death Syndrome [4]. It is particularly prevalent in Japan and Thailand, [5,11] while in China and Korea the reported incidence is lower [12,13]. In Europe, it is extensively described [14,15], except in Scandinavian countries [16]. Although its prevalence is not totally resolved, [10,17,18] it represents a rare syndrome, with an estimated 5–50 cases per 10,000 [7]. In the USA, Brugada syndrome is also rare [19]. Arrhythmic events occur at all ages, from childhood to the elderly [1], with a peak around the fourth decade [20]. It is believed to cause 4–12% of all sudden cardiac deaths and up to 20% among patients without identifiable structural abnormalities [6].

Strikingly, males have a higher disease prevalence, particularly in regions where Brugada syndrome is endemic, despite equal genetic transmission among both genders [5,20]. Sex hormones may underlie this gender disparity [21].

2.2. 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 beat-to-beat variation in amplitude and morphology

[22]. Of note, accentuation of ST elevation immediately preceding VF [23,24] links these phenomena. Two morphologies of ST segment elevation exist (see Fig. 1). The coved-type morphology is required for the diagnosis [25], while the saddle-back type is an intermediate form that requires confirmation using pharmacological challenge (conversion into coved-type) or genetic analysis [26]. Pharmacological challenge utilizes class IA-IC I_{Na} blockers (except quinidine), but not class IB [27–30]. The diagnostic yield and safety of such tests are incompletely elucidated and require further investigation [14,30–33].

The signature ST elevations are usually confined to leads V1–V3, with rare occurrences in inferior or lateral leads [34,35]. 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 inscribe the most severe abnormalities [36,37] (Fig. 1), as demonstrated with body surface mapping (BSM) [38,39]. Therefore, these leads must be scrutinized when Brugada syndrome is suspected [25]. Similarly, 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.

2.3. Other electrocardiographic features

Brugada syndrome is often accompanied by (atypical) right bundle branch block. Signs of conduction defects are found at many levels, particularly in patients with SCN5A mutations [40]: QRS widening [41], electrical axis deviation [1,9,34,42,43], and PQ prolongation, presumably reflecting prolonged HV conduction time [1,7,9,25,34,40,44]. Moreover sinus node dysfunction is reported [43,45]. In contrast, QTc duration is generally within the normal range [7,25] but it may be occasionally prolonged [1].

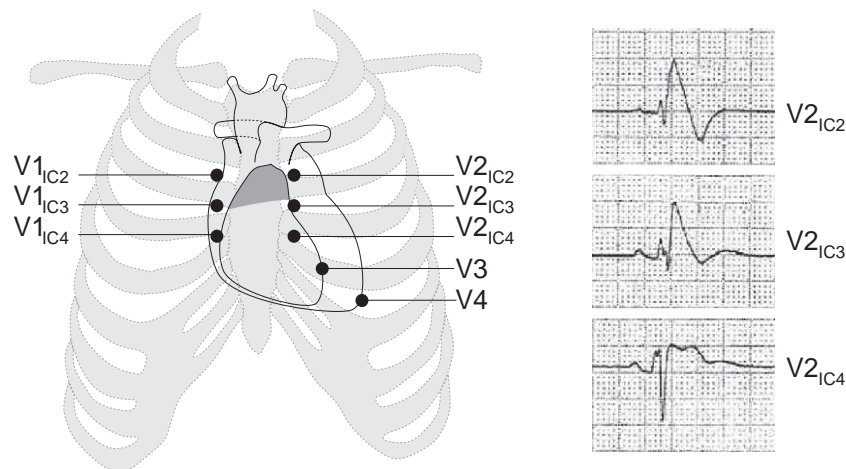


Fig. 1. ECG from a Brugada syndrome patient showing most severe ST–T abnormalities in leads overlying right ventricular outflow tract (shaded area): coved-type ST segment in second and third intercostal space (V2_{IC2} and V2_{IC3}). Intermediate ST–T abnormalities (saddleback-type) are recorded in fourth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

2.4. Types and mode of onset of arrhythmias

Sudden death results from polymorphic ventricular tachycardia (VT) originating in the RVOT [46]. Monomorphic VT rarely occurs [35,47], especially in patients taking antiarrhythmic drugs [8]. An estimated 80% of subjects with documented VT/VF has a history of syncope [14], caused by self-terminating episodes [8]. Supraventricular tachycardias are more prevalent in Brugada syndrome [1,23,48–50] and atrial flutter/fibrillation is described with a prevalence of 10–30% [51,52]. Given the correlation between a history of atrial arrhythmias and VT/VF inducibility during electrophysiological study (EPS), patients with atrial arrhythmias may constitute a population with higher risk and more advanced disease [53], but these data are still limited [54].

Sudden death typically occurs at rest, when the vagal tone is augmented [55], often at night [52]. Although premature ventricular complexes (PVCs) are rare [24,56], their prevalence increases before VF [24]. From stored ICD electrograms, these PVCs show the same morphology as the first VT beat, and different VT episodes are initiated by similar PVCs in the same subject [56,57]. Further confirmation of the role of initiating PVCs derives from the clinical benefit resulting from their elimination via catheter ablation [58].

These triggering PVCs have a left bundle branch block morphology [59], variable coupling intervals [1,6,24,56] and endocardial mapping localizes their origin in the RVOT [58]. No variations in QTc intervals precede VF [1,56]. However, right precordial QTc prolongation was reported upon emergence of flecainide-induced ST elevations [60], possibly reflecting RVOT action potential (AP) prolongation [61]. Changes in autonomic tone [24,28], body temperature [62], or the use of antiarrhythmic drugs [29] may modulate VT/VF susceptibility, since they affect ST segment elevation [27,63,64].

2.5. Evidence of a functional basis

Structural cardiac abnormalities are undetected using routine cardiologic diagnostic tools [1,2,65]. However, fatty replacement and RV fibrosis were reported from myocardial biopsies and autopsies [44]. Indeed, in all hearts studied histologically, some structural derangements were found [44,66–68]. Still, the notion that Brugada syndrome constitutes a functional defect gained almost unanimous acceptance by its linkage, in 1998, to mutations in SCN5A, which encodes the α subunit of the cardiac Na channel [3]. While SCN5A is the only gene with a proven involvement, the subsequent discovery that the proportion of patients with a SCN5A mutation is 30% at most [14,40], indicates a heterogeneous genetic basis of Brugada syndrome. Linkage to a second locus on chromosome 3p22–24 was demonstrated (which overlaps the previously reported ARVD5 locus at 3p23) [69], but other genes still await identification.

More than 50 SCN5A mutations are linked to Brugada syndrome [70–72]. Their common effect is I_{Na} reduction, resulting from changes in the functional properties (gating) of the mutant Na channels, or failure of expression in the sarcolemma (trafficking) [73–76]. Of interest, SCN5A mutations are also implicated in Long QT syndrome type 3 (LQT3) and Lev–Lenègre disease [71,73,77], and some SCN5A mutations may cause combinations of Brugada syndrome and LQT3 or Lev–Lenègre disease within the same family or individual [78,79]. While LQT3 associated SCN5A mutations generally increase I_{Na} during the action potential plateau phase due to noninactivating current, those associated with Lev–Lenègre disease or Brugada syndrome reduce it [73]. One mutation co-segregated with Brugada syndrome in male members in a family, but with Lev–Lenègre disease in female members [79], mirroring the more prevalent clinical expression of Brugada syndrome in males.

2.6. The case for reentry

General mechanisms of arrhythmias include reentry, early afterdepolarizations (EADs), delayed afterdepolarizations (DADs), and abnormal automaticity. Reentry is regarded as the dominant mechanism in Brugada syndrome, based on: 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, which is, however, not present in Brugada syndrome; furthermore, quinidine's efficacy in preventing tachyarrhythmias [80,81], while also causing QT prolongation, argues against a causative role of EADs. DADs are even less likely: DADs typically occur during calcium (Ca) overload, e.g., fast heart rates. Attenuation of ST elevations by catecholamines [82] provides further evidence against DADs, as catecholamines generally increase Ca overload and facilitate DADs [83]. 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.

3. Proposed electrophysiological mechanisms

The cause of ST elevation in Brugada syndrome and its strong linkage to VT/VF remains unresolved [52]. Clearly, pathophysiological mechanisms responsible for ST segment changes must operate during the cardiac repolarization phase. Also, these mechanisms must be based on I_{Na} reduction. The proposed mechanism which presently appears to receive the widest support, both from experimental [84–87] and clinical studies [23,60,88–90], ascribes Brugada syndrome to a primary repolarization disorder, as it revolves around abnormal shortening of epicardial AP duration. However, we propose that Brugada

syndrome may involve a depolarization disorder, revolving around conduction slowing, as put forward in other clinical [24,50,91–95] and experimental [96] 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 they support other mechanisms, in particular, structural derangements or the presence of node-like tissues (see paragraph 8.2).

4. 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 (Fig. 2) [84,97]. This model revolves around unequal expression of the transient outward potassium current (I_{to}) between epicardium and other transmural layers. I_{to} drives early repolarization. Stronger I_{to} expression in epicardium than in endocardium [98,99] renders epicardium more susceptible to the effects of reduced depolarizing force. Thus, in epicardium, when I_{Na} is reduced (e.g., when mutants Na channel produce 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 (Fig. 2B). To

account for the negative T wave in coved-type ST elevation, prolongation of epicardial AP dome is invoked, which causes AP duration to become longer than in endocardium (Fig. 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 the AP dome. This loss is, however, heterogeneous, generating epicardial dispersion of repolarization (Fig. 2D). This dispersion creates a vulnerable window, which allows phase 2 reentry [87] to cause a premature impulse, which triggers VT/VF based on reentry between transmural layers [6,87,100] (Fig. 2E). This hypothesis requires that AP shape in endocardium remain unaltered by I_{Na} reduction; this is explained by less I_{to} expression in endocardium in many species, including humans [86,99,101–104]. Similarly, the presence of the ECG changes in right, but not left, precordial leads is explained by larger I_{to} expression in RV than LV epicardium [85], while the higher disease prevalence in males is paralleled by higher epicardial I_{to} density in males than females [105].

5. The depolarization disorder model

An alternative explanation for the ECG signature in Brugada syndrome, which does not invoke fundamentally

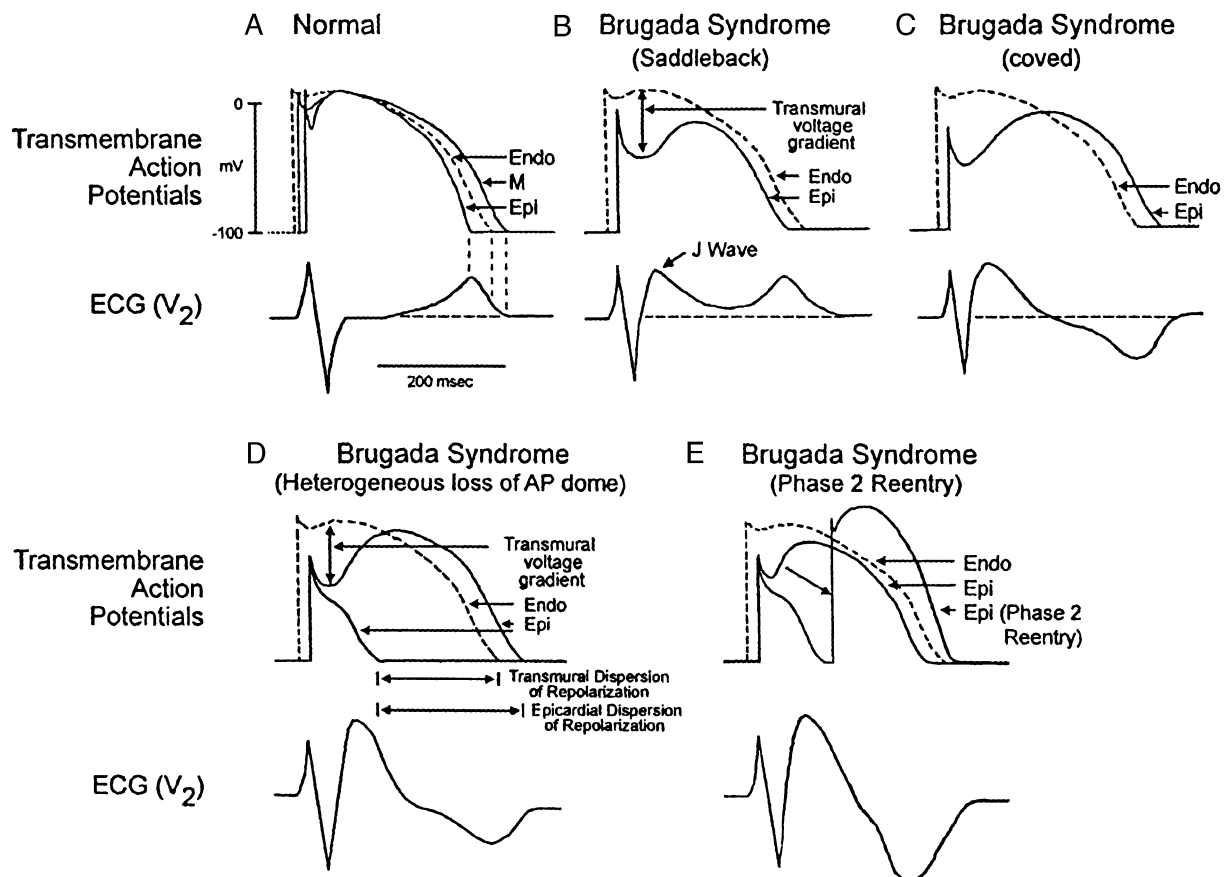


Fig. 2. Representation of the repolarization disorder hypothesis. For explanation see text. (Modified from Ref. [100] with permission).

different AP shapes, is based on conduction delay in RVOT (Fig. 3). The RVOT AP (Fig. 3B, top) is delayed with respect to the RV AP (Fig. 3B, bottom). During the hatched phase of the cardiac cycle in Fig. 3D, the membrane potential in RV is more positive than in RVOT, thus acting as a source, and driving intercellular current to RVOT, which acts as a sink (Fig. 3C, a). To ensure a closed-loop circuit, current passes back from RVOT to RV in the extracellular space (Fig. 3C, c), and an ECG electrode positioned over the RVOT (V_{2IC3}) inscribes a positive signal, as it records the limb of this closed-circuit which travels towards it (Fig. 3C, b). Thus, this electrode inscribes ST elevation during this phase of the cardiac cycle (Fig. 3D, bottom, bold line). Reciprocal events are recorded in the left precordial leads, as demonstrated using BSM [39]. Here, current flowing from the extracellular space into RV (Fig. 3C, d) causes ST depression. In the next phase of the cardiac cycle (following the upstroke (Fig. 3F, hatched phase) 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 RV. Thus, RVOT now acts as the source, driving the closed-loop circuit in the opposite

direction (Fig. 3E), with current now passing away from lead V_{2IC3} (Fig. 3E, d), thus resulting in the negative T wave (Fig. 3F, bottom, bold line). Note that in Fig. 3D and F, the delayed AP of RVOT is abbreviated in comparison to RV AP (and in comparison to Fig. 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) [106].

This qualitative model of ST elevation in Brugada syndrome derives from the mechanism believed to cause ST elevation in regional transmural ischemia, where large differences in membrane potential exist between ischemic and nonischemic zones [107]. 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 [107].

6. Evidence for the repolarization disorder hypothesis

6.1. Heterogeneity in repolarization

Clearly, 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, along with ECG-like electrograms [84,108]. Other in vitro studies provide additional support by showing that I_{Na} blockers [87,109] and ATP-sensitive potassium channel (I_{K-ATP}) openers [110] worsen transmural dispersion of APs, and that I_{to} blockers ameliorate them [85,104]. However, in another isolated canine RV preparation, these findings were only partially confirmed [111]. While I_{Na} blockers and I_{K-ATP} openers were also required for ST elevations and reentrant arrhythmias, and the first arrhythmia beat occurred in areas with short recovery times (consistent with phase 2 reentry), arrhythmias did not always involve epicardium. A closed-chest in vivo study [61], where signature ST elevations 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. However, no loss of AP dome was reported. Of interest, the area needed to cool was small and confined to RVOT, mirroring the small thorax area where signature ECG changes are often found in Brugada syndrome patients (Fig. 1).

Validation of this hypothesis in patients is more challenging, because it requires simultaneous electrogram

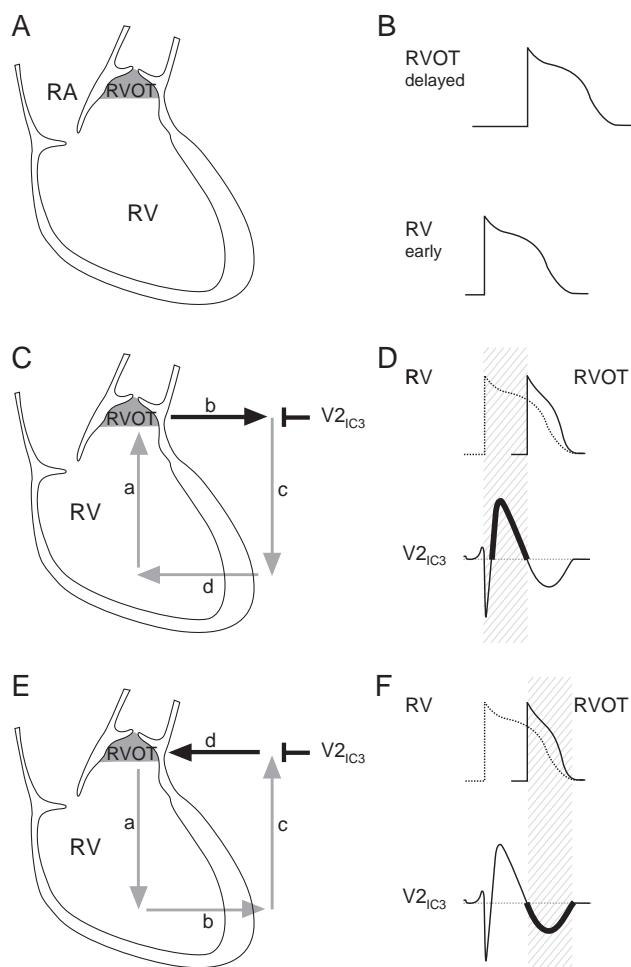


Fig. 3. Qualitative model of the depolarization disorder hypothesis. For explanation see text.

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 [88]. In this patient, 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 [90]. 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 (Fig. 2), and clinically observed ST segments (Fig. 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 (Fig. 2B) must be present in the fourth intercostal space, because “saddle-back ST elevations” are observed there (Fig. 1, V_{2IC4}). Concurrently, AP lengthening with “spike-and-dome” morphology in epicardium (Fig. 2C) accounts for “coved-type ST elevation” in the third intercostal space (Fig. 1, V_{2IC3}), and nonuniform loss of AP dome (Fig. 2D) underlies more accentuated “coved-type ST elevations” in the second intercostal space (Fig. 1, V_{2IC2}). This large spatial dispersion in epicardial AP morphology would not be expected when electrical coupling is normal. Still, some authors suggest that ST segment and T wave alternans after class I antiarrhythmic drugs [42,112] support the repolarization disorder hypothesis; however, whether this observation truly reflects a repolarization or depolarization disorder is unresolved.

6.2. Effects of autonomic modulation

Autonomic modulation strongly affects ST elevations in Brugada syndrome [24,28,89,113]. Parasympathetic stimulation increases ST elevation, presumably by reducing I_{Ca-L} during the AP plateau [114], rather than inducing coronary spasm [28,89], while heart rate variability analysis revealed an increased vagal tone preceding VF episodes [24]. Accordingly, opposing effects of sympathetic stimulation were reported, as isoproterenol reduced ST elevation and prevented VT/VF inducibility [28,82]. Interestingly, abnormal norepinephrine recycling was identified in Brugada syndrome [115] indicating that abnormal autonomic innervation may cause ST elevation.

6.3. Effects of I_{to} blockade

The repolarization disorder hypothesis predicts that removal of the transmural gradient in I_{to} counteracts the pathophysiological mechanisms of Brugada syndrome, 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 [84,100], consistent with the clinical efficacy of quinidine, an antiarrhythmic drug with I_{to} blocking properties, in normalizing the ECG pattern [28,116] and preventing spontaneous or induced arrhythmias [80,117]. However, these effects may be due to quinidine’s anticholinergic action [118,119], while prolongation of AP duration by blockade of the delayed rectifier potassium channel [120,121] may also act to suppress reentrant arrhythmias.

6.4. Effects of heart rate

The observations that long RR intervals [23,50] augment ST elevations and that VT/VF occurs at night were used as support for the repolarization disorder hypothesis. These observations were ascribed to slow gating kinetics of I_{to}, which increase this current at slow heart rates [99]. Accordingly, pacing provided an effective therapy against bradycardia-related VT/VF onset in a Brugada syndrome patient [122]. Yet, ST elevations may also increase at fast heart rates [42,112,123,124]. While particular circumstances may be responsible (enhanced intermediate inactivation of the mutant Na channel [123] or the use of class IC antiarrhythmic drugs with use-dependence [42,112]), this phenomenon was also described in the absence of such confounders [42,112].

7. Evidence for the depolarization disorder hypothesis

7.1. General conduction slowing

Most evidence to favor the depolarization disorder hypothesis derives from clinical studies [24,50,91–95], with a modeling study providing further confirmation [96]. Given the numerous ECG signs of conduction slowing in Brugada syndrome, the first studies into its pathophysiological mechanisms were based on the hypothesis that it 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 [94], has received particular attention. Late potentials are not only highly prevalent in Brugada syndrome [24,50,92,94,112,125], but also independent predictors of VT/VF inducibility (as opposed to QTc dispersion and T wave alternans) [94,95]. Noteworthy, late potentials coincide with spontaneous ST elevation and late r’ in V₁–V₃ [24], while Holter analysis of multiple spontaneous VF episodes shows that ST elevation—late r’ in V₁ correlates with VF onset [24]. Moreover, flecainide elicits late potentials along with ST elevations [50]. Of further support for the role of conduction slowing, VT/VF inducibility during EPS is associated with longer HV intervals [126].

7.2. 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 to the RVOT. Accordingly, epicardial electrograms were recorded from the conus branch of the right coronary artery, which runs over the RVOT surface [92]. Activation delay was found here, but not endocardially. Of note, this delay increased with class IC drug challenge. In another study [127], BSM localized areas of conduction delay to 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 BSMs [125], late potentials coincided with ST elevation and were mapped to the RVOT. RV conduction delay was also demonstrated using tissue Doppler echocardiography, as the amplitude of ST elevation in Brugada syndrome patients correlated with delay in RV contraction [91]. Still, some studies failed to document delayed potentials of RV [28].

8. Evidence for other pathophysiological mechanisms

8.1. 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 undetectable by standard diagnostic tools [44,67,128]. Similarities between Brugada syndrome and ARVC were further substantiated by the discovery of SCN5A mutations in an ARVC family [129]. While linkage to SCN5A has drawn attention to functional derangements [3], recent evidence now rekindles support for an abnormal structural RVOT component in Brugada syndrome.

Electron beam CT scan studies revealed RV enlargement, abundant adipose tissue [130] and RV wall motion abnormalities whose localization correlated with the origin

of spontaneous PVCs following an arrhythmic event [131]. Of note, spontaneous PVCs may originate in areas where VT/VF is most readily inducible during EPS, usually the RVOT free wall [132]. The link between structural and functional derangements was further tightened by an other electron beam CT scan study, in which wall motion abnormalities were exacerbated/provoked with a pharmacological challenge [133]. Using cardiac magnetic resonance imaging, a sensitive tool for detection of RV structural abnormalities [134], significant RVOT enlargement was found in Brugada syndrome patients [135]. 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 the RVOT, while LV was normal [68]. 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 [68]. Finally, the efficacy of catheter ablation in preventing VT/VF suggests a structural basis of Brugada syndrome [58].

While these studies demonstrate a link between structural and functional derangements in Brugada syndrome, strengthening the tie between Brugada syndrome and ARVC [136], recent studies have raised the intriguing possibility that the functional derangements, i.e., I_{Na} reduction, may cause these structural derangements. A boy with compound heterozygosity for two SCN5A mutations exhibited severe degenerative changes in the specialized conduction system [137], while transgenic mice with SCN5A haploinsufficiency developed cardiac fibrosis as they aged [138].

8.2. The role of slow conducting tissues

Another explanation for RVOT conduction slowing may involve the presence of slow conducting tissues in the RVOT, i.e., node-like tissues whose AP upstroke is I_{Ca-L} dependent. Cardiac development may hold the key for this premise, and explain the intriguing RVOT involvement in Brugada syndrome. RV has a different embryological origin

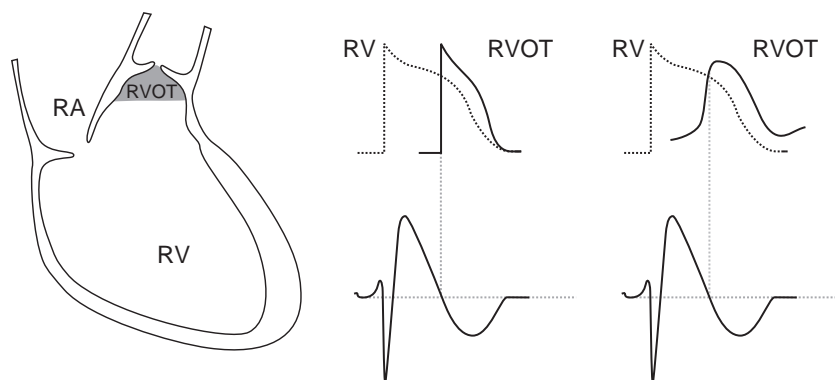


Fig. 4. Model of depolarization disorder hypothesis with incorporation of node-like cells in right ventricular outflow tract (right panel, RVOT). Similar to Fig. 3, delayed activation of node-like cells causes potential gradients, resulting in coved-type ST elevation.

Table 1

Clinical and experimental evidence to suggest the electrophysiological mechanism of Brugada syndrome

Support for repolarization disorder hypothesis

Sodium channel blockers exacerbate/provoke ST elevations [27]
 Linkage with SCN5A mutations exhibiting reduced sodium current [3]
 Quinidine normalizes ECG and prevents arrhythmias [80,81,116]
 More prevalent phenotype in males [5,20,105]
 ST elevations are usually facilitated by slow heart rates [23,50]
 ST elevations are accompanied by epicardial action potential abbreviation [88]
 “Spike-and-dome” configuration of epicardial monophasic AP during heart surgery [90]
 ST elevation is associated with reduced ejection time of RV but not of LV [91]

Support for depolarization disorder hypothesis

Sodium channel blockers exacerbate/provoke ST elevations [27]
 Linkage with SCN5A mutations exhibiting reduced sodium current [3]
 ECG signs of general conduction slowing: axis deviation, PQ/QRS prolongation, sinus/AV node dysfunction [1,9,34,40,42–45]
 High prevalence of late potentials [50,92,94,112,125]
 Late potentials indicate increased risk of arrhythmic events [94,125]
 Flecainide induces greater QRS widening in Brugada s. patients than controls [29]
 Conduction delay in right ventricular outflow tract (body surface mapping) [24,127]
 Longer HV interval predicts VT/VF inducibility [126]
 ST elevation correlates with delay in right ventricle contraction [91]
 Arrhythmogenic area is confined to small RVOT region (initiating PVCs, VT/VF inducibility, efficacy of catheter ablation) [58,132]
 Structural derangements, including fibrosis, in histological studies in Brugada Syndrome patients [44,67,128,136]
 Progression of ECG abnormality localized in the area overlying the RVOT [36–39]

than LV [139], and the outflow tract derives from the same group of cells that compose the atrioventricular region, thus possessing slow conduction properties [140,141]. While these node-like cells are essential for peristaltic blood movement in the embryonic heart which has yet to develop cardiac valves [142], remnants of these cells may constitute the substrate for arrhythmias originating in the RVOT [143]. We here propose that these cells may be incorporated into the depolarization disorder hypothesis in Brugada syndrome (Fig. 4, right panel). This would not only explain RVOT conduction slowing, but also the observation that the most severe ST elevations are present in RVOT leads (Fig. 1, V_{2IC2} and V_{2IC3}), as these cells are localized close to the pulmonary valve [143]. Furthermore, it would explain suppression of ST elevation and arrhythmias by isoproterenol, as isoproterenol-induced enhancement of I_{Ca-L} increases conduction velocity in these cells. Conversely, smaller I_{Ca-L} expression in males than females [144] may explain higher disease prevalence in males.

9. Synthesis

Clearly, no single clinical or experimental study reviewed here provides irrefutable proof of one hypothesis regarding

the pathophysiology 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) 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 [86,104,145], in vivo studies have raised doubts on the presence of large heterogeneity when electrical coupling is normal [106,146,147].

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 (Table 1). Similar to most diseases, it is likely that Brugada syndrome is not fully explained by one single mechanism. While most studies reviewed here 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 pathophysiological 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.

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