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The Pathophysiological Mechanism Underlying Brugada Syndrome. Depolarization versus Repolarization

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Abstract

This Point/Counterpoint presents a scholarly debate of the mechanisms underlying the electrocardiographic and arrhythmic manifestations of Brugada syndrome (BrS), exploring in detail the available evidence in support of the repolarization vs. depolarization hypothesis.

Introduction

In this Point/Counterpoint we will, after a short introduction, discuss our views on the pathophysiological mechanism behind the electrocardiographic signature of Brugada syndrome. Brugada syndrome is characterized by specific ST segment changes in the right precordial ECG leads known as the type-1 or coved-type Brugada ECG. It shows familial segregation and is associated with malignant arrhythmias which may lead to sudden death [1, 2]. As with other inheritable arrhythmia syndromes, there is large variability in phenotype among patients. Fortunately, most patients with the signature type-1 ECG and several other criteria [2] do not develop arrhythmias throughout life when they refrain from certain drugs and fever is immediately treated [2–6]. Nevertheless, a substantial number of patients with Brugada syndrome may indeed die suddenly or experience multiple arrhythmia episodes. Hence, it is critical to understand the pathophysiological mechanism behind this syndrome, so as to enable better risk stratification for sudden death, timely treatment, and prevention of sudden death.

However, the pathophysiological mechanism of Brugada syndrome (let alone risk stratification) remains a matter of debate [7,8]. Although there seems to be consensus on a right ventricular origin and on the positive association between the type-1 ECG and arrhythmias, the underlying mechanisms are, in our view still, not very clear. We will discuss the two leading hypotheses. The ‘repolarization hypothesis’ on one hand was initiated by studies in canine wedge preparations [9]. This hypothesis relies on transmural dispersion of repolarization

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between the right ventricular (outflow tract) endocardium and epicardium. In contrast, the 'depolarization hypothesis' relies on RV conduction slowing and involvement of (mild) structural abnormalities [8]. Certainly, these hypotheses are not mutually exclusive and ongoing research will give better and/or new insights in the (near) future.

Point Wilde/Postema

Conduction delay

Conduction delay as part of the clinical presentation of Brugada syndrome, i.e. right bundle branch block and prolonged HV-intervals, was already described in the first report on Brugada syndrome [1]. Most evidence in favor of right ventricular conduction delay as part of the pathophysiology mechanism behind Brugada syndrome is derived from clinical studies. In these studies, body surface, epicardial and endocardial mapping, electrophysiological studies as well as cardiac imaging consequently point to conduction delay as a prominent feature of the type-1 ECG and being most evident in the right ventricle [10–19]. Provocation tests with sodium channel blockers (e.g. ajmaline or flecainide), used to uncover the type-1 ECG, also evoke severe conduction slowing in atria and ventricles while the type-1 ECG develops [20–24]. Conduction slowing by reduced sodium current induced by sodium channel blockers and its relation to Brugada syndrome is furthermore mirrored in the association between Brugada syndrome and loss-of-function mutations in *SCN5a* (the gene that encodes for the α -subunit of the cardiac sodium channel) [25,26]. Also, late potentials, which reflect delayed and discontinuous ventricular depolarization, have often been observed. These late potentials have been associated with the development of arrhythmias and can be uncovered or become more pronounced when sodium channel blockers are introduced to unmask a type-1 Brugada ECG [13,16,19,27]. Further, slowed and discontinuous conduction were found in computer models simulating decreased sodium current.[28]

Structural abnormalities

In conjunction with the observed right ventricular conduction delay as part of the manifestation of the type-1 ECG and arrhythmias, there is growing evidence for structural abnormalities as part of the syndrome. This notwithstanding, there is an obligatory absence of gross structural abnormalities [2]. Right from the first reports of Brugada syndrome it was described that there were no apparent signs of ischemia, infarction or scar, right ventricular cardiomyopathy, hypertrophic or dilated cardiomyopathy or other forms of structural heart disease [1]. However, from earlier and later publications the notion appears that there might indeed be structural changes involved, albeit relatively mild changes which may not become evident using conventional cardiac imaging modalities (echocardiography, magnetic resonance imaging). In an explanted heart and in right ventricular biopsies it was found that structural abnormalities (fibrosis, myocarditis, apoptosis) were present [14,29]. These findings are in concordance with the observed late potentials and fragmented electrograms which reflect discontinuous conduction through diseased myocardium [13,15,19,27,30].

Substantial overlap with clear structural cardiac disease such as (familial) arrhythmogenic cardiomyopathy may thus be suspected [10]. Also, there may be support for both a congenital (familial) and an acquired form of Brugada syndrome. The latter is for example supported by the observation of type-1 ECGs provoked by ajmaline in Chagas' disease which involves myocarditis [31]. In contrast, the former is supported by the association between loss-of-function mutations in *SCN5a* with Brugada syndrome and (RV) structural abnormalities in both human and mice [25,32,33]. Structural abnormalities may also lead to conduction slowing itself and *SCN5a* loss-of-function mutations may provoke decreased excitability and hampered conduction through decreased connexin expression [33,34]. Although mutations which lead to dysfunctional or less sodium channels at the cellular membrane are only found in

approximately 10 to 30% of Brugada syndrome patients, it appears that decreased sodium channel expression is just as apparent in Brugada syndrome patients with a sodium channel mutation as in those without a sodium channel mutations [35]. Likewise, it has recently been noted that *SCN5A* mutations may not be directly causal to the occurrence of Brugada syndrome and that genetic background may play a powerful role in its pathophysiology.[36]

As far as arrhythmias are concerned, in general these surface in the third or fourth decade of life. This advocates that there is a time dependent process that either is acquired later in life or that takes many years to eventually trigger the arrhythmias or to constitute a sufficient arrhythmogenic substrate. The development of structural abnormalities could be such a process [33]. When this occurs, the effects of reduction in wave length due to conduction slowing are exacerbated by augmented anisotropy and discontinuous conduction due to decreased sodium current and the interstitial changes. Conduction block, reentry and wave break will be promoted, and may be the elements to cause arrhythmias. In this concept, tissue discontinuities are required, and may already be relevant when relatively mild, because they conspire with functional impairments, e.g., loss-of-function *SCN5A*-mutations, decreased sodium channel function or expression, with or without mutations in modifying genes[37] and/or environmental stressors such as sodium channel blocking drugs,[2,21] vagal stimulation[13] or fever [38].

Repolarization hypothesis

Along with these arguments in favor of the ‘depolarization hypothesis’, there are also arguments against the ‘repolarization hypothesis’. The main argument being that if there would be transmural dispersion of repolarization at the time of a type-1 ECG to an extent as de canine wedge preparations show, this would indeed be extremely arrhythmogenic. This arrhythmogenicity of the transmural dispersion of repolarization is also always found in the canine wedges [7,9]. However, although the type-1 ECG is indeed associated with arrhythmias, most patients do *not* have any arrhythmias throughout their life although they show a constant or intermittent type-1 ECG. Also when a type-1 ECG is evoked by drugs, the occurrence of arrhythmias is rare. Furthermore, such transmural dispersion of repolarization would require complete uncoupling of endocardium and epicardium,[30] which in our view is not physiological possible in the human heart. Hence, conduction slowing and mild structural abnormalities seem to be a more logical substrate for arrhythmias to develop.

Type-1 ECG

While RV conduction slowing seems to be part of the signature ECG of Brugada syndrome, how can it cause that signature ECG? We have earlier advocated that conduction slowing in the RV will result in very late activation of the RV outflow tract (RVOT, figure 1A) [8]. The RVOT action potential (Fig. 1B, top) is thus delayed with respect to other RV action potentials (figure 1B, bottom). During the hatched phase of the cardiac cycle in figure 1D, the membrane potential in the RV is more positive than in RVOT, thus acting as a source, and driving intercellular current to RVOT, which acts as a sink (Fig. 1C, a). To ensure a closed-loop circuit, current passes back from RVOT to RV in the extracellular space (figure 1C, c), and an ECG electrode positioned over the RVOT (V2 in the 3rd intercostal space for example) inscribes a positive signal, as it records the limb of this closed-circuit which travels towards it (figure 1C, b). Thus, this electrode inscribes ST elevation during this phase of the cardiac cycle (figure 1D, bottom, bold line). Reciprocal events are recorded in the left precordial leads, as demonstrated using BSM [18]. Here, current flowing from the extracellular space into RV (figure 1C, d) causes ST depression. In the next phase of the cardiac cycle (following the upstroke (figure 1F, hatched phase) of the delayed action potential in RVOT), the potential gradients between RV and RVOT are reversed, as membrane potentials are now more positive in RVOT than RV. Thus, the RVOT now acts as the source, driving the closed-loop circuit in the opposite direction (figure 1E), with current now passing away from the right precordial

lead (figure 1E, d), thus resulting in the negative T-wave (figure 1F, bottom, bold line). Note that in figure 1D and 1F, the delayed action potential of the RVOT is abbreviated in comparison to other RV action potentials (and in comparison to figure 1B, where action potentials of isolated cells are shown). As there is electrotonic interaction between RV and RVOT (which is present when the RV and RVOT are electrically well-coupled) the severe conduction delay in the RVOT will accelerate repolarization of RVOT action potential [39].

Electrotonic interaction

This scheme directly shows overlap between the repolarization model and the depolarization model: the existence of shortened action potentials in the RVOT either being due to severe conduction delay or due to principal repolarization differences between RVOT endocardium and RVOT epicardium. There is even a third way that may result in ST elevation associated with Brugada syndrome: excitation failure resulting from small structural barriers [40]. Interestingly, in a simulation study (incorporating transmural differences in the density of the transient outward current) shorter action potentials arise in those areas directly surrounding the structural barriers, also believed to be due to electrotonic interaction between excited and unexcited areas [40,41]. Hence, the principal difference between the repolarization and depolarization hypothesis regarding shortening of action potentials, is whether it's a primary or secondary process. We believe it's the latter, a secondary process, simply *the result of* conduction abnormalities possibly augmented by structural discontinuities, just as the Type-1 ECG.

Counterpoint Antzelevitch/Di Diego/Viskin/Morita/Fish

We will attempt to address the major points raised by Wilde and Postema in this Counterpoint. It is correct that conduction delay was part of the clinical presentation of Brugada syndrome; indeed, RBBB was an integral part of the name ascribed to this new clinical entity [1]. However, a rigorous application of simple electrocardiographic criteria, long-used to define RBBB, [42] reveals that a large majority of RBBB-like morphologies encountered in cases of Brugada syndrome do not fit the criteria for RBBB [42]. Moreover, attempts by Miyazaki and coworkers to record delayed activation of the RV in Brugada patients met with failure [43]. The absence of any semblance of an S wave in the left precordial leads in many BrS patients exhibiting a typical Type 1 ST-segment elevation strongly suggests that the r', J wave or ST segment elevation is due to the presence of a prominent notch in epicardium but not endocardium in the region of the RVOT, rather than to a delay of conduction (see [7] for review) (Figure 2). The only clinical study that endeavored to record monophasic action potentials (MAP) from both epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) of patients with the Brugada syndrome provides further direct support for this hypothesis, demonstrating deeply notched action potentials in the RV epicardium of BrS patients, but not in endocardium; on the other hand, no major conduction delays were observed in the RVOT. [44,45]

The repolarization hypothesis was developed based on experimental data generated by models that closely recapitulate the clinical electrocardiographic and arrhythmic manifestation of BrS, [7,9,46–50] as in the example illustrated in Figure 2. It is noteworthy that there is no such experimental model for the BrS depolarization hypothesis, only theoretical armchair and mathematical models for the ECG manifestations of BrS that make assumptions that are open to question (discussed below) and there are no experimental models that we are aware of for the very rapid polymorphic VT (PVT) characteristic of BrS based on the depolarization hypothesis. Indeed, because of the exquisite rate-dependence of conduction, PVT is unlikely to develop when major conduction delays are present at baseline.

Wilde and Postema raise as a chief argument against the repolarization hypothesis the fact that “if there would be transmural dispersion of repolarization at the time of a type-1 ECG to an

extent as the canine wedge preparations show, this would indeed be extremely arrhythmogenic.” They correctly point out that most patients do *not* have any arrhythmias throughout their life although they show a constant or intermittent type-1 ECG. Interestingly, we view this point as a strong argument in favor of the repolarization hypothesis, but against the depolarization hypothesis. As we have repeatedly stressed, with the repolarization hypothesis a typical BrS ECG may be generated without an arrhythmogenic substrate, as illustrated in Fig. 2. Fig. 2B shows the development of a coved type ST segment following exposure of the canine coronary-perfused right ventricular wedge preparation to combined sodium and calcium channel block. Despite the classical BrS ECG, no transmural dispersion of repolarization or any other arrhythmogenic substrate is present. The arrhythmogenic substrate develops when a further shift in the balance of current in the early phases of the action potentials leads to loss of the action potential dome at some epicardial sites but not others (Fig. 2C) resulting in the development of an epicardial dispersion of repolarization, which gives rise to a closely coupled phase 2 reentrant extrasystole. Loss of the dome also results in a marked transmural dispersion of repolarization and refractoriness, creating a vulnerable window during which the closely coupled extrasystole can induce a reentrant arrhythmia. (Fig. 2F). Note that despite the potent block of both sodium and calcium channel currents (the most prevalent genetic defects associated with BrS), conduction is little affected relative to the marked changes in repolarization characteristics. Also noteworthy is the fact that the repolarization hypothesis provides an explanation for both substrate (dispersion of repolarization) and trigger (Phase 2 reentry) underlying the development of PVT. The depolarization hypothesis cannot account readily for the very closely coupled extrasystoles that often precipitate PVT.

The second argument leveled against the repolarization hypothesis is that “such transmural dispersion of repolarization would require complete uncoupling of endocardium and epicardium,[30] which in our view is not physiological possible in the human heart.” We are at a loss to understand this argument since all models of BrS developed, including the one cited, have demonstrated the development of major dispersion of repolarization with relatively little or no slowing of conduction, suggesting that such repolarization heterogeneity can occur without any loss of cellular coupling between epicardium and endocardium.

The issue of structural changes associated with BrS is an important one, but one also mired in debate. Because of space constraints, we will not pursue this here in that it is amply discussed in a variety of reviews (e.g., [7,51]). The most recent study on the subject concluded that only a small subset of BrS patients display significant histopathological abnormalities in biopsy samples of the RVOT that could be linked to the ECG phenotype [52]. Suffice it to say that some cases BrS may be associated with a mild fibrosis or other structural changes.

We disagree with the premise that late potentials or wall motion abnormalities in BrS patients necessarily denote the presence of structural changes and conduction delays. Signal averaged ECG (SAECG) recordings have demonstrated late potentials in patients with the Brugada syndrome, especially in the anterior wall of the right ventricular outflow tract (RVOT) [16, 27,53–57]. Although traditionally ascribed to conduction delays, in cases of BrS these late potentials could arise from the delayed second upstroke of the epicardial action potential in the RVOT or to a concealed phase 2 reentry [7,53]. Wall motion abnormalities have also been detected in BrS patients [58]. Although such contractile abnormalities are commonly considered pathognomonic of structural disease, in case of BrS syndrome they could well be the result of loss of the action potential dome in the right ventricular epicardium [53,59]. Loss of the dome would lead to contractile dysfunction because calcium entry into the cells would be greatly diminished and sarcoplasmic reticulum calcium stores would be depleted.

We have previously suggested that the rate-dependence of the ST segment elevation in BrS may be helpful in discriminating between the repolarization and depolarization hypotheses

[7]. If the ST segment elevation is due predominantly to delayed conduction in the RVOT, acceleration of the rate would be expected to further aggravate conduction and thus accentuate the ST segment elevation and the RBBB morphology of the ECG. If, on the other hand, ST segment elevation or BrS sign is secondary to accentuation of the epicardial action potential notch, acceleration of the rate would be expected to normalize the ECG, by reducing the action potential notch and restoring the action potential dome in RV epicardium. This occurs because the transient outward current, which is at the heart of this mechanism, is slow to recover from inactivation and is less available at faster rates. Although there are relatively few reports of the effects of pacing, most investigators in the field agree that there is a tendency for the Brugada ECG to normalize during an increase in heart rate consistent with the repolarization hypothesis. [60–62] There are however also reports of ST segment elevation or J point elevation with exercise. Amin et al. recently reported J point elevation in BrS patients (both SCN5A+ and SCN5A-) during exercise.[63] The principal difference between studies showing a decrease vs. increase of the J point in response to exercise appears to be the presence of a prominent ST segment elevation at baseline in the former.

Fig. 3 shows the effect of exercise on a 12 lead ECG of a 33 years old asymptomatic BrS male with a family history of SCD and a loss of function SCN5A missense mutation (R878C). At baseline all three right precordial leads displayed a marked ST segment elevation and V3 displayed a notched QRS suggesting major conduction delay in the RVOT. Interestingly, the conduction defect was exaggerated during exercise as evidenced by the further fragmentation of the QRS in V3, but despite this the ST segment elevation in all right precordial leads was reduced. These findings suggest that the ST segment elevation is due to a repolarization defect and not to the clearly apparent depolarization defect.

Additional support for the repolarization hypothesis derives from the demonstration that quinidine normalizes ST segment elevation and suppresses late potentials recorded in patients with Brugada syndrome [64–67]. These effects of the drug are presumably due to inhibition of I_{to} leading to diminution of the epicardial action potential notch and normalization of the repolarization heterogeneities. If the ST segment elevation or the late potentials were due to delayed conduction, quinidine-induced I_{Na} inhibition would be expected to accentuate their appearance.

Although there is no experimental model of BrS based on the depolarization hypothesis, we have developed a model of ischemia-induced changes, which corresponds to what has been proposed as the depolarization hypothesis.[67,68] Fig. 4 illustrates the development of a very significant transmural delay as a consequence of exposure of ventricular wedge preparation to global ischemia. Progressive delay leads to a gradual prolongation of the R wave and inversion of the T wave. The ECG at first glance resembles a BrS phenotype, but with closer inspection it is clear that the depolarization hypothesis does not lead to an ST segment elevation, but rather to an R wave prolongation. Fig 4B shows that the marked conduction delay is due to a discontinuity in conduction in the deep subepicardium. Conduction under these conditions is exquisitely sensitive to rate, with acceleration leading to block and inexcitability. Fig. 4B shows that with continued ischemia the R wave prolongs and 2:1 conduction block develops. This causes disappearance of the T wave in alternate beats, which is generally not observed in BrS, but is a common characteristic of ischemia-induced tombstone morphology of the ECG, induced by coronary spasm, as illustrated in Fig. 4C.[69] A similar phenomenon is observed in right ventricular wedge preparations following exposure to hyperkalemic conditions [70]. Our data suggest that reduced I_{Na} availability in ventricular epicardium contributes to its greater sensitivity to electrical depression under a variety of clinical conditions including acute myocardial ischemia and severe hyperkalemia, predisposing to reduced excitability, slowed transmural conduction, which is responsible for dramatic prolongation of the R wave.

Thus, the available data, both basic and clinical, point to the repolarization hypothesis, i.e., transmural voltage gradients that develop secondary to accentuation of the epicardial notch, at times leading to loss of the action potential dome, as the predominant mechanism underlying the Brugada syndrome ECG signature and arrhythmogenesis. There is no doubt in our minds that in some cases, particularly those associated with sodium channel loss of function, conduction slowing may contribute to the development of arrhythmias. It is our view, however, that conduction slowing or structural defects are by no means obligatory.

Rebuttal Wilde & Postema

In this rebuttal we aim to address the concerns raised by Antzelevitch et al. about the depolarization hypothesis and to react to the points raised in favor of the repolarization hypothesis.

RBBB and terminal right ventricular delay

We agree that RBBB is not the hallmark of the syndrome as our colleagues argued [42]. The wide S-wave in infero-lateral leads does not represent a typical RBBB morphology but represents conduction delay in the RVOT [8]. This is supported by vigorous electrocardiographic studies on the location of the conduction delay in BrS which occurs in the final *not the first* part of the QRS complex [19]. There are indeed studies which do show conduction delay, [10–19] whereas others do not. [43,45] We have to realize from the well known ‘inverse problem’, that multiple conduction and repolarization patterns may result into identical ECGs.

Role of animal models

There is a clear-cut difference in opinion between us and our opponents about the value and significance of an animal model. We do not see how the absence of an animal model in case of the depolarization model can be used as either an argument in favor of the repolarization hypothesis or against the depolarization hypothesis. The wedge preparation has been demonstrated by others [71] to have certain important shortcomings. Data from whole (experimental) heart but in particular human data have our preference.

Role of repolarization

As to the role of transmural (endo-epi) or epicardial dispersion of repolarization, we do not agree with the statement that “Fig 2B shows [...] despite the classical BrS ECG, no transmural dispersion of repolarization or any other arrhythmogenic substrate ...”. The reason for the negative T-wave in this part of the model is actuated by transmural dispersion of repolarization between the shorter endocardial action potential and the longer epicardial action potential, whereas the ST-segment elevation would result from epi-epi dispersion. Hence we doubt the supposed stable and not-arrhythmogenic state of this part of the repolarization model.

Role of late potentials

Regarding late potentials, our colleagues argue that “late potentials could arise from the delayed second upstroke of the epicardial action potential in the RVOT or to a concealed phase 2 reentry” so as in figure 2B, 2C or 2D. Let us first state that the concept of phase 2 reentry is in fact not justified. We are dealing with a triggered beat and not with the continuation of a preceding activation front. Apart from this there are several arguments against this assumption. The association between late potentials and concealed phase 2 reentry seems unlikely as late potentials are much more often recognized in Brugada syndrome patients than arrhythmias. [13,19,27,30] Late potentials correlate closely to fragmented QRS complexes as reported by one of our antagonists (Dr. Morita) [30] and are associated with depolarization abnormalities

in the RVOT.[16,17,19] Alternatively, that would only leave the association between a delayed second upstroke of the epicardial action potential in the RVOT as in figure 2B/2C and late potentials. But then, why would late potentials be associated with a delayed second upstroke of the epicardial action potentials in the RVOT only? Late potentials in Brugada syndrome patients are already observed when they *do not* have a type-1 ECG. They exacerbate when the type-1 ECG develops, especially in the RVOT region.[13,19] With a discontinuously traveling electrical impulse through structurally abnormal cardiac tissue this is easily explained. In addition, superimposed sodium channel blockade may increase conduction delay further. In Brugada syndrome patients this augments late potentials and augmented late potentials are related to higher incidence of arrhythmias [30,72,73]. How can we understand the presence of late potentials on the basis of the repolarization hypothesis? It is highly improbable that a delayed and relatively slow upstroke in phase 2 and 3 of the epicardial action potential in the RVOT could affect the global recording of high frequency late potentials with more or less simultaneous repolarization of the bulk of the cardiac mass.

Effects of exercise

As to the effect of tachycardia during exercise on ST elevation in Brugada syndrome, our experience,[63] is very different than that of our discussants. In Figure 3 the exercise example with lower ST elevation than at baseline, shows a heart rate of 75 beats/min (Post Ex [0 min]), which may present standing, but not exercise. In a relatively large group of Brugada syndrome patients versus controls we have shown that there is J elevation during exercise (and thereafter). [63] Figure 5 gives an example of a Brugada syndrome patient with a tachycardia during exercise. Not only there is more (not less) ST-elevation with tachycardia, but interestingly the ST-elevation is alternating indicative for 2:1 late activation of myocardial tissue (probably the RVOT). But indeed, there are some examples of a decrease during exercise, albeit followed by post-exercise augmentation of J elevation.[61] Either way, the only series in this matter, [63] supports the depolarization hypothesis.

Ischemia model

In Brugada syndrome ischemia plays no role. For this reason and also because of space limitation, we consider the issues raised in relation with Figure 4 as less relevant. However, our discussants argue that the “disappearance of the T wave in alternate beats [...] is never observed in BrS, but is a common characteristic of ischemia-induced tombstone morphology of the ECG, induced by coronary spasm, as illustrated in Fig. 4C”. We would like to add to this issue that there are in fact several published Brugada cases in whom the T-wave does ‘disappear’ in alternate beats (e.g. Figure 6).[74–76] As agreed by our colleagues, this is in favor of the depolarization hypothesis.

About triggers and substrates...

It is true that the repolarization hypothesis explains both the substrate of the Brugada’s syndrome type-1 ECG and the triggering event within the context of that hypothesis. Our colleagues argue that this is an advantage. It is true that the depolarization hypothesis only explains the substrate of the Brugada’s syndrome type-1 ECG. The triggering event can come from anywhere, albeit that structural abnormalities added to conduction abnormalities create a substrate for ‘true’ reentry. In our opinion the identical location of both triggering event and electrophysiological substrate in the scenario of the repolarization hypothesis would render such an arrhythmogenic risk that it is not easy to understand how such patients could stay alive over substantial time spans. At least we may point to the fact that extra beats that provoke VTs in Brugada syndrome patients may arise both from the right and the left ventricle as has been reported by Morita et al.[77]

CONCLUSION - Wilde/Postema

In summary, in our view principal depolarization abnormalities form the basis of the Brugada syndrome and the observed repolarization abnormalities on the ECG (the coved-type ST-segment) are the result of depolarization abnormalities probably in combination with (mild) structural abnormalities.

Rebuttal Antzelevitch/Di Diego/Viskin/Morita/Fish

Lack of Experimental Model Consistent with Depolarization Hypothesis

With all due respect to our esteemed colleagues, the inability to generate an experimental animal or *in vitro* model of BrS supporting the depolarization hypothesis is not a trivial matter. It is not merely that it does not exist, but that attempts to create such a model by mimicking the genetic defects responsible for BrS result in experimental models exhibiting characteristics consistent with the repolarization hypothesis. Loss of function mutations in I_{Na} and I_{Ca} and gain of function mutations in I_{to} recreated using pharmacological agents that inhibit I_{Na} and I_{Ca} [9,24,46–49] or that augment I_{to} [78] recapitulate all the electrocardiographic and arrhythmic manifestations of BrS via a repolarization hypothesis mechanism in the coronary perfused right ventricular wedge preparation. Even when sodium channel inhibition is reduced by a full 50%, thus mimicking a total loss of function mutation heterozygously expressed, depolarization factors contribute little to the manifestation of BrS phenotype (Fig. 2). The only means by which we are able to mimic the depolarization hypothesis is with ischemia (Fig. 4) and the ECG and functional characteristics are clearly different from those of BrS [67,68].

Further evidence in support of the repolarization hypothesis as the predominant mechanism derives from the observation that the ECG and arrhythmic characteristics of BrS are similar whether depolarizing (SCN5A mutations causing loss of function in I_{Na}) or repolarizing (KCNE3 mutations causing a gain of function in I_{to}) currents are affected [79]. This is difficult indeed to explain if the major substrate in the former, but not in the latter, is due to markedly delayed conduction.

Effects of exercise

Our challengers have acknowledged the fact that a substrate that causes a major conduction delay should be sensitive to an acceleration of rate and they point to their recent study [63], the only one thus far published, demonstrating that in most of their BrS patients the ST segment is further elevated during exercise. It is noteworthy that another study has recently been completed evaluating the effect of exercise. In a recent preliminary report by Makimoto et al. [80] evaluating 93 BrS patients, a J point elevation was observed during peak exercise in only 9% of cases, but even in these few, ST segment elevation was reduced. Thus in 0 out of 93 BrS patients and 0 of 22 controls was ST segment elevated during peak exercise. One interpretation of this is that in these cases J point elevation reflects conduction delay in the RVOT, but the reduction in ST segment elevation reflects a decrease in the amplitude of the epicardial action potential notch and a reduction of the BrS substrate. Interestingly, in 34% of the BrS patients in the Makimoto and co-worker's [80] series, ST segment was elevated during the early period of recovery from exercise, consistent with a period of enhanced vagal tone, which is known to accentuate the epicardial action potential notch. These results provide compelling evidence in support of the repolarization hypothesis.

Alternating appearance of T waves

Our colleagues point to the alternating appearance of T waves as evidence in support of the depolarization hypothesis. Indeed this is the case when accompanied by a tombstone

morphology of the R wave as we illustrated in Figure 2, but in its absence this phenomenon may be more consistent with a repolarization hypothesis as illustrated in Figure 7 [81].

Role of Late Potentials

As previously noted, we are of the opinion that that late potentials observed in BrS patients [16,27,53–57] do not necessarily denote the presence of structural defects and conduction delays as perfunctorily presumed in many studies because in BrS late potentials could arise from the delayed second upstroke of the epicardial action potential in the RVOT or to a concealed phase 2 reentry [7,53]. Our colleagues indicate that “it is highly improbable that a delayed and relatively slow upstroke in phase 2 and 3 of the epicardial action potential in the RVOT could affect the global recording of high frequency late potentials with more or less simultaneous repolarization of the bulk of the cardiac mass.” The feasibility of this manifestation is illustrated in Figure 8. It is noteworthy that exposure inhibition of I_{to} with 4-aminopyridine or quinidine abolished the repolarization heterogeneities leading to disappearance of the late potentials, consistent with the ability of quinidine to abolish SAECG late potentials in patients with BrS. If late potentials observed in BrS patients were due to delayed conduction, quinidine’s effect to inhibit I_{Na} would be expected to exacerbate their appearance.

CONCLUSION - Antzelevitch/Di Diego/Viskin/Morita/Fish

We conclude that the available data provide compelling evidence in support of the repolarization hypothesis as the predominant mechanism underlying BrS. Slowed conduction and mild structural defects in some BrS cases, particularly in those involving I_{Na} loss of function, is undeniable and is likely to contribute to the Brugada phenotype, but in our view is not obligatory. The marked accentuation of the epicardial action potential notch can not only account for the ST segment elevation associated with BrS, but can facilitate loss of the action potential dome leading to a marked dispersion of repolarization that when invaded by a premature beat can encounter marked conduction delay, thus setting the stage for the development of reentrant arrhythmias.

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Figure 1. Qualitative model of the depolarization hypothesis for the Type-1 Brugada syndrome ECG. For explanation, see text. Modified from Ref. [8] with permission.

Figure 2.

Cellular basis for electrocardiographic and arrhythmic manifestation of BrS. Each panel shows transmembrane action potentials from one endocardial (**top**) and two epicardial sites together with a transmural ECG recorded from a canine coronary-perfused right ventricular wedge preparation. **A:** Control (Basic cycle length (BCL) 400 msec). **B:** Combined sodium and calcium channel block with terfenadine (5 μ M) accentuates the epicardial action potential notch creating a transmural voltage gradient that manifests as a ST segment elevation or exaggerated J wave in the ECG. Despite the appearance of a typical BrS ECG, an arrhythmogenic substrate is absent. **C:** Continued exposure to sodium and calcium blockade results in all-or-none repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial dispersion of repolarization (EDR) as well as a transmural dispersion of repolarization (TDR). **D:** Phase 2 reentry occurs when the epicardial action potential dome propagates from a site where it is maintained to regions where it has been lost giving rise to a closely coupled extrasystole. **E:** Extrastimulus (S1–S2 = 250 msec) applied to epicardium triggers a polymorphic VT. **F:** Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. (Modified from [48] with permission)

Figure 3.

Opposite effects of exercise on QRS fragmentation and ST segment elevation in right precordial leads of a 33 year old asymptomatic male with Brugada syndrome secondary to a loss of function SCN5A missense mutation (R878C).

Figure 4.

Electrophysiologic effect of ischemia in the ventricular wedge model. A: Each panel shows (from top to bottom) simultaneous recordings of transmembrane action potentials from endocardium (Endo) and epicardium (Epi) and the ECG recorded across the bath along the same axis. Recordings were obtained from a RV wedge displaying a relatively small phase 1 in the epicardial action potential under control conditions, following 10 and 25 min of no-flow ischemia, and 1 and 40 min of reperfusion. Progressive ischemia-induced delay of transmural conduction leads to a gradual prolongation of the R wave (apparent ST-segment elevation) and inversion of the T wave. B: Recordings obtained at 25–30 min of no-flow ischemia (BCL=800 msec). From top to bottom: Five unipolar electrograms (EGs) recorded between endocardium and epicardium (Endo, M3, M2, M1 and Epi), Endo action potential, Epi action potential and a transmural electrocardiogram (ECG). A 90 msec-step delay (discontinuous conduction) in transmural conduction occurs between EG-M2 and EG-M1 giving rise to a prolonged R wave (tombstone morphology) and negative T wave in the ECG of alternate beats. 2:1 intramural conduction block occurs at site EG-M2 leading to a disappearance of the ECG-T wave, which is concurrent with the absence of the Epi AP response. Arrows denote the activation time at each of the unipolar electrograms. C: Shown side-by-side are recordings from an arterially-perfused right ventricular wedge preparation following 25–30 min of ischemia (BCL=800 msec) (Left) and an example of the tombstone effect and T wave alternans appearing in the right precordial leads following vasospastic ischemia as well as normalization of the ECG following spontaneous reperfusion. (Panels A, B and the left part of panel C are modified from [67] and right part of panel C is from Childers [69], with permission).

Figure 5.

Exercise in a Brugada syndrome patient. It is clear that the tachycardia induced by exercise is accompanied by a sharp rise in ST-elevation and a coved-type morphology in V1, and, interestingly, alternating in this particular case. Courtesy of A.S. Amin, MD, and H.L. Tan, MD, PhD.

Figure 6. Alternating T-waves in a Brugada syndrome patient. Courtesy of H.L. Tan, MD, PhD.

Figure 7.

Appearance of T wave in alternate beats in an experimental model of BrS generated by exposing a canine right ventricular wedge preparation to verapamil (1 μ M). T wave alternans occurs as a result of concealed phase 2 reentry. The dome propagates from Epi 1 to Epi 2 on alternating beats while the endocardial response remains constant. The concealed phase 2 reentry results in a negative T wave in alternate beats only. BCL=558 ms. Modified form [81], with permission.

Figure 8.

Late potentials due to the delayed second upstroke of the epicardial response or to concealed phase 2 reentry generated in a canine right ventricular wedge model of Brugada syndrome.

A: Control. **B:** BrS phenotype develops following exposure to the I_{Na} and I_{Ca} inhibitor terfenadine (5 μ M); a late potential is registered in the epicardial electrogram following an 80 ms delay coincident with the upstroke of phase 2 of the action potential (arrow). **C:** Further exposure to terfenadine leads to loss of the action potential dome at some epicardial sites (Epi 1) but not others leading to the development of a concealed phase 2 reentry which registers in the epicardial electrogram as a late potential with a 148 ms delay (arrow). Modified from [82], with permission.