

Brugada syndrome: A comprehensive review of pathophysiological mechanisms and risk stratification strategies

Ka Hou Christien Li^{a,b}, Sharen Lee^b, Chengye Yin^c, Tong Liu^d, Tachapong Ngarmukos^e, Giulio Conte^f, Gan-Xin Yan^g, Raymond W. Sy^{h,i}, Konstantinos P. Letsas^j, Gary Tse^{d,k,*}

^a Faculty of Medicine, Newcastle University, Newcastle, United Kingdom

^b Laboratory of Cardiovascular Physiology, Li Ka Shing Institute of Health Sciences, Hong Kong, SAR, PR China

^c School of Biological and Chemical Sciences, Queen Mary University of London, London, United Kingdom

^d Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, PR China

^e Department of Medicine Faculty of Medicine Ramathibodi Hospital Mahidol University, Bangkok, Thailand

^f Division of Cardiology, Cardiocentro Ticino, Lugano, Switzerland

^g Lankenau Institute for Medical Research and Lankenau Medical Center, Wynnewood, PA, USA

^h Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

ⁱ Sydney Medical School, University of Sydney, Camperdown, New South Wales, Australia

^j Second Department of Cardiology, Laboratory of Cardiac Electrophysiology, Evangelismos General Hospital of Athens, Athens, Greece

^k Xiamen Cardiovascular Hospital, Xiamen University, Xiamen, China

ARTICLE INFO

Article history:

Received 22 March 2019

Received in revised form 1 January 2020

Accepted 2 January 2020

Keywords:

Brugada syndrome

Ion channel

Repolarization

Depolarization

Risk stratification

ABSTRACT

Brugada syndrome (BrS) is an inherited ion channel channelopathy predisposing to ventricular arrhythmias and sudden cardiac death. Originally believed to be predominantly associated with mutations in SCN5A encoding for the cardiac sodium channel, mutations of 18 genes other than SCN5A have been implicated in the pathogenesis of BrS to date. Diagnosis is based on the presence of a spontaneous or drug-induced coved-type ST segment elevation. The predominant electrophysiological mechanism underlying BrS remains disputed, commonly revolving around the three main hypotheses based on abnormal repolarization, depolarization or current-load match. Evidence from computational modelling, pre-clinical and clinical studies illustrates that molecular abnormalities found in BrS lead to alterations in excitation wavelength (λ), which ultimately elevates arrhythmic risk. A major challenge for clinicians in managing this condition is the difficulty in predicting the subset of patients who will suffer from life-threatening ventricular arrhythmic events. Several repolarization risk markers have been used thus far, but these neglect the contributions of conduction abnormalities in the form of slowing and dispersion. Indices incorporating both repolarization and conduction based on the concept of λ have recently been proposed. These may have better predictive values than the existing markers. Current treatment options include pharmacological therapy to reduce the occurrence of arrhythmic events or to abort these episodes, and interventions such as implantable cardioverter-defibrillator insertion or radiofrequency ablation of abnormal arrhythmic substrate.

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* Corresponding author.

E-mail address: gary.tse@doctors.org.uk (G. Tse).

<https://doi.org/10.1016/j.ijcha.2020.100468>

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1. Introduction

Brugada syndrome (BrS) is an inherited cardiac disorder first described by Pedro and Josep Brugada in 1992. The term “Brugada syndrome” was coined later in recognition of their identification of this important disease [1]. Four years after Yan and Antzelevitch [2] approached the cellular basis underlying the ECG abnormalities displayed by patients affected by Brugada syndrome ECG, BrS is frequently associated with mutations in the SCN5A gene, which encodes for the pore-forming alpha subunit of the cardiac Na⁺ channels. To date, multiple pathogenic variants of genes have been shown to alter the normal function of Na⁺, K⁺, Ca²⁺ and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which mediate the ionic currents responsible for the cardiac action potentials [3]. Both depolarization and repolarization abnormalities have been described in BrS [4,5]. Patients with this syndrome can present with aborted sudden cardiac death, agonal breathing syncope, or palpitations. Precipitating factors include fever, increased vagal tone and other drugs such as tricyclic antidepressants and alcohol [6,7]. These in turn predispose to malignant ventricular tachycardia and fibrillation (VT/VF) and sudden cardiac death (SCD) [8]. BrS was also found to be associated with sick sinus syndrome (SSS) [9], atrial flutter, atrial fibrillation [10], AV nodal reentrant tachycardia and Wolff-Parkinson-White syndrome [11].

2. Types of Brugada ECG patterns

Brugada patterns can be divided into two types (Fig. 1) [12]. Type 1 pattern has a characteristic coved-shaped ST segment

elevation (STE) ≥ 2 mm, J-point elevation, a gradually descending ST segment which terminates with a negative T-wave in the right precordial leads (V₁, V₂ and V₃) with or without a class I anti-arrhythmic drug challenge, such as flecainide [13]. Type 2 pattern is characterized by a saddleback morphology with a minimum 2 mm J-point elevation along with ST segment elevation of at least 1 mm. A type 2 pattern can be converted to a type 1 pattern upon pharmacological challenge or other stressors such as fever.

3. Epidemiology

In 1992, the Brugada investigators initially estimated that BrS was responsible for 12% of SCD cases in the general population [14], but recent epidemiological studies suggested the prevalence to be much lower, at least 0.05% with marked regional variability [15,16]. It was also found that Southeast Asians are at an increased risk of BrS as compared to other ethnicities, with only 0.1% showing BrS-type ECG pattern [17]. This variance is supported by comparing epidemiological studies in Denmark against Chinese subjects. In Denmark, a low prevalence of 0.001% was found as compared to the 3.3% found in Chinese subjects (although a Type 1 pattern was only observed in 0.08% of these subjects) [18,19]. In terms of gender distribution, BrS has a strong male correlation, affecting men four times more frequently than women and also affecting younger adults than infants or children [20]. Recent insights from SABRUS a multi-center survey, which reported important ethnic differences [21]. They found that Asians present almost exclusively as male adults, with a higher frequency of aborted SCD and spontaneous type 1 ECG pattern but showed

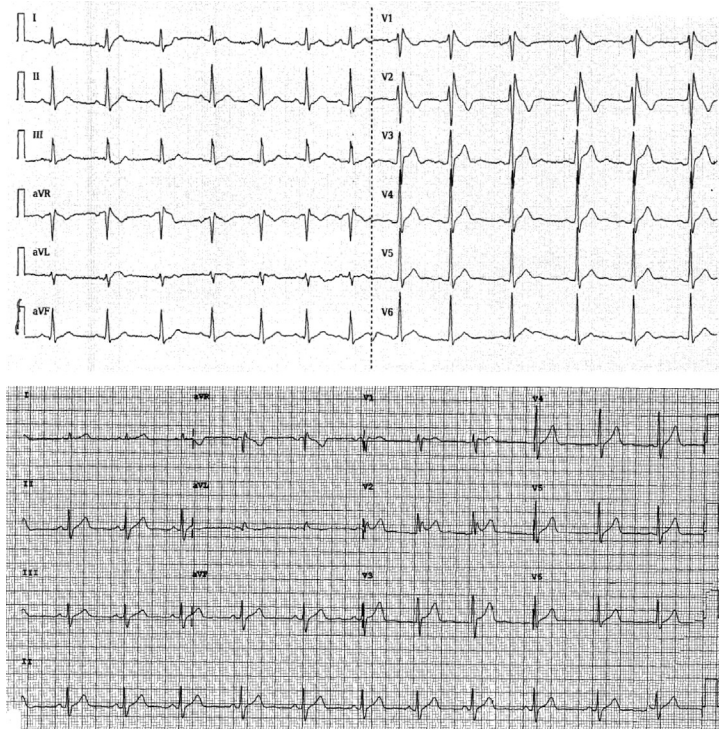


Fig. 1. Type 1 (top) and type 2 (bottom) Brugada ECG patterns.

lower frequency of family history of SCD and SCN5A mutations compared to Caucasians.

4. Genetic basis and heterogeneity underlying BrS

There is significant genetic heterogeneity underlying BrS. The most common mutation is loss-of-function mutations in SCN5A, the gene responsible for the α -subunit of the Na⁺ channel, are frequently associated with a type 1 pattern. Since 2001 there have been more than 80 mutations in SCN5A gene that have been associated with Brugada syndrome [22]. These lead to reduced expression or function of Na⁺ channels, leading to conduction or repolarization abnormalities that produce the characteristic ECG patterns of right bundle branch block and ST segment elevation primarily observed in the right precordial leads [23]. Type 2 pattern has also been associated with mutations in SCN5A, glycerol-3-phosphate dehydrogenase 1-like (GPD1L), which is the domain responsible for a site homologous to SCN5A [24], and CACNA1C, the gene responsible for the α -subunit of cardiac L-type calcium channels (LTCC) [25].

BrS was believed to be a Mendelian disease with an autosomal dominant inheritance pattern with incomplete penetrance [26]. However recent evidence suggests that this may not be completely true [27]. There is a poor genotype-phenotype correlation. A recent study investigated co-segregation of SCN5A mutations amongst large genotyped families, demonstrating that some affected family members did not carry the familial mutation [28]. This could mean that mutations in other genes are responsible for BrS [29,30]. Another possibility is incomplete penetrance despite the presence of the mutated gene or variable expressivity [31]. This has been observed in a frameshift mutation in SCN5A found in a proband from Spain with recurrent episodes of ventricular fibrillation and presenting bradycardia and paroxysmal atrial fibrillation without a spontaneous or drug-induced Brugada pattern [32]. By contrast, two family members of the proband showed type 1 BrS following flecainide challenge, and another suffered from only permanent atrial fibrillation. Some putatively pathogenic genetic mutations do not produce an abnormal clinical phenotype [33]. Recently, a genome-wide association study successfully identified two common genetic variants in SCN5A-SCN10A and HEY2, a translational repressor [34]. This approach will continue to elucidate the role of proteins that may serve as genetic modifiers to influence the disease phenotype [35].

5. Differential diagnosis: J-wave syndromes and other causes of Brugada pattern

BrS has been classified as part of the J-wave syndromes that include early repolarization (ER) variants. Antzelevitch's group suggested dividing ER syndrome into three types [36]. Type 1 ER pattern in lateral precordial leads is prevalent in healthy male athletes and rarely observed in VF survivors. Type 2 refers to ER pattern in inferior or inferolateral leads and is associated with idiopathic VF and is also prevalent in healthy young males. Type 3 refers to ERS pattern observed globally in the inferior, lateral and right precordial leads. This subtype is thought to be high risk of VT/VF [37]. Another classification scheme divides ERS into benign and malignant forms [38]. A J-wave followed by an ascending ST segment is considered benign, whereas J-wave followed by horizontal or descending ST segment is considered malignant. A recent consensus conference report addresses the similarities and differences between BrS and ERS [39]. ERS continue to be associated with higher risk of SCD [40]. The estimated prevalence of ERS spans between 1 and 13% of the general population and is thought to contribute to 15 to 70% of idiopathic VF cases [41,42].

The cellular basis of J-point elevation has been intensively studied in pre-clinical models using coronary-perfused wedge preparations. Thus, the ventricular epicardium expresses the transient outward current (I_{to}) in high levels, resulting in an AP notch, whereas the ventricular endocardium expresses I_{to} at low levels and therefore does not have this notch [43,44]. These differences therefore create a transmural repolarization gradient that is responsible for J-point elevation seen in ERS. However, it has been pointed out that a wedge is not a heart, and the electrophysiological mechanisms may be different in the intact heart [45].

The term Brugada phenocopy (BrP) has been coined to describe a group of heterogeneous conditions that induce Brugada ECG patterns [46], such as hyperkalaemia [47], hypokalaemia [48], left ventricular aneurysm [49], pericarditis [50], pulmonary embolism [51], and many other causes. These conditions must be distinguished from true BrS as these are potential reversible causes and do not necessitate invasive treatments such as implantable cardioverter-defibrillator (ICD) insertion. The diagnosis of BrP is established with a negative drug challenge [52].

6. Electrophysiological mechanisms underlying arrhythmogenesis in Brugada syndrome

To understand the electrophysiological basis of BrS, the ionic determinants of the normal cardiac action potential (AP) need to be discussed. AP depolarization (phase 0) is mediated by voltage-gated Na⁺ channels (I_{Na}) [53]. This is followed by early repolarization (phase 1) due to activation of the fast and slow transient outward potassium currents, $I_{to,f}$ and $I_{to,s}$. The AP plateau (phase 2) is determined by a balance between inward currents mediated by the voltage-gated L-type Ca²⁺ channel (LTCC, $I_{Ca,L}$) and Na⁺-Ca²⁺ exchanger (I_{NCX}), and outward currents mediated by the voltage-gated delayed rectifier K⁺ channels (I_K : I_{Kr} and I_{Ks}) [54]. During delayed repolarization (phase 3), relatively greater outward K⁺ currents compared to inward currents are due to LTCC inactivation.

(i) Sodium channels and BrS

The voltage-gated Na⁺ channels are made of α subunits associated with other proteins, such as β subunits (SCN1B, SCN2B and SCN3B). The SCN5A gene encodes for the α subunit of the cardiac sodium channel. Loss-of-function mutations in SCN5A have been associated with BrS [55,56], SSS [57], progressive cardiac conduction defect (PCCD, or Lenegre disease) [58] and overlap disorders between these conditions [59]. Loss-of-function mutations are observed in approximately 25% of BrS cases [60]. These lead to reduced sodium current availability during the phases 0 (upstroke) of the cardiac action potential, which is associated with impaired expression of non-functional proteins and reduced ionic exchange across the cell membrane. Even though most mutations involved in the development of BrS are found in the SCN5A gene, mutations in the associated β subunit proteins have also been observed [61–64]. Interestingly, a study by Hu et al. also discussed the involvement of the SCN10A gene, mainly involved in expressing the sodium channel specific to neurons, in causing a large proportion of BrS cases. However, there is increasing conjecture about the genotype-phenotype correlation between Brugada syndrome and previously reported “pathogenic variants” in genes other than SCN5A [65]. The reduction in sodium current availability is not limited to genes encoding for the sodium channels. Genes expressing the glycerol-3-phosphate dehydrogenase 1-like (GPD1-L) protein [24], cardiac sodium channel regulator MOG1 [66], sarcolemmal membrane-associated protein (SLMAP) [67], desmosomal component plakophilin-2 [68], fibroblast growth factor homologous factor-1 (FGF-2) [69] and the transcriptional factor HEY2 [34] have been suggested to give rise to BrS.

(ii) Calcium channels and BrS

The calcium current is mediated by L-type calcium channels (LTCC). Each LTCC consists of 4 protein subunits $\alpha 1$ (CACNA1C), $\beta 2$ (CACNB2), $\alpha 2$ (CACNA2D), and δ (CACNA2D). Similar to SCN5A mutations, Antzelevitch et al. suggested that loss-of-function mutations in these genes precipitate abnormal trafficking, reduced expression or function of LTCC, leading to reduced calcium influx current during phase 2 [25,70]. As a result, BrS secondary to the reduced functionality of LTCCs are associated with shorter QT intervals compared to classical SCN5A mutation BrS where QT interval remains unaltered.

(iii) Potassium channels and BrS

Gain-of-function mutations in genes encoding for potassium channels have also been implicated in BrS. Genes influencing I_{to} include KCNE3, KCND3 and SEMA3A (semaphoring, an endogenous K^+ channel inhibitor) [71–76] while KCNJ8 and ABCC9 (encoding for SUR2A, the ATP-binding cassette transporter for the K_{ATP} channel) mutations affected the $I_{K,ATP}$ [77,78]. KCNH2, which encodes for I_{Kr} was also proposed by Wang et al. to be involved in BrS development [79]. Most recently, dysfunction in the KCNAB2, which encodes the voltage-gated K^+ channel $\beta 2$ -subunit, was associated with increased I_{to} activity and identified as a putative gene involved in BrS [80].

(iv) Other proteins

The potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4 is a protein mainly found in the pacemaker region of mammalian hearts, encoded by the HCN4 gene, controlling the heart rate [81]. Mutation in the HCN4 gene was

associated with bradycardia and idiopathic VT [82]. Lastly, the transient receptor potential melastatin protein 4 gene (TRPM4), which encode for a calcium-activated nonselective ion channel that mediates transport of monovalent cations across the plasmolemma, was also found to be associated with BrS [83].

7. Brugada phenotypes

There are three leading theories on the electrophysiological mechanisms underlying BrS, which based on abnormal depolarization, abnormal repolarization and current-load-mismatch [4] (Fig. 2).

(i) Depolarization hypothesis

Conduction velocity (CV) of the propagating cardiac action potentials involves both sodium channel activation leading to cellular depolarization, followed by gap junction conduction across successive cardiomyocytes. Any form of disruption to the normal AP generation or propagation can lead to conduction defects and arrhythmogenesis [84]. Approximately a quarter of BrS cases have been attributed to loss-of-function mutations in the SCN5A gene, leading to a decreased inward current during phase 0 [85]. The resulting slower upstroke during phase 0 and the consequent delay in AP generation has been shown to play an important role in mediating ventricular arrhythmogenesis in BrS. Martini and colleagues in 1989 observed fibrotic changes in the right ventricles, which may produce the RBBB and ST segment elevation on the ECG [86]. This theory has been supported by multiple studies investigating the disruption of SCN5A in mice models, which found targeted disruption of *Scn5a* (*Scn5a*^{+/-}), *Scn5a*^{1798insD/+} and *Scn5a*^{G1408R} mice to be associated with reduced CV in interstitial

Arrhythmogenic Mechanisms in Brugada syndrome

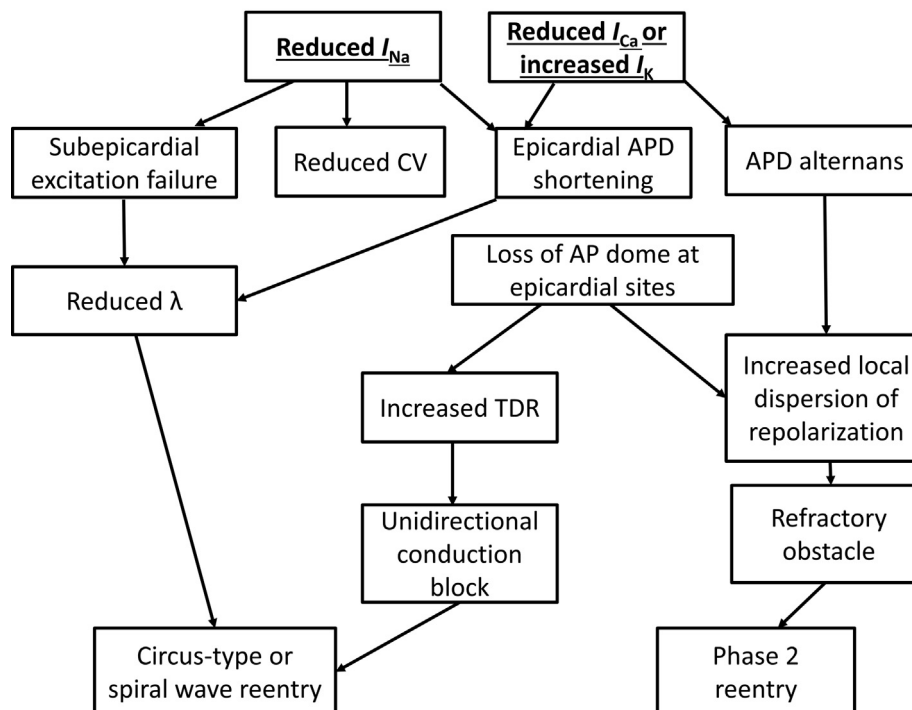


Fig. 2. Summary of arrhythmogenic mechanisms underlying Brugada syndrome. Adapted from [189] with permission.

fibrosis [87–89]. *Scn5a*^{+/-} mice also show progressive conduction defects that are suggestive of Lenègre disease [90]. In an explanted heart and in right ventricular biopsies it was found that structural changes such as fibrosis, apoptosis and myocarditis were present [91,92]. These findings are in concordance with the observed late potentials and fragmented electrograms, which reflect discontinuous conduction through a diseased myocardium [93,94].

Under physiological conditions, the specific subcellular distribution of gap junctions together with the tight packaging of the rod-shaped cardiomyocytes underlies anisotropic conduction, which is continuous at the macroscopic scale. Due to its nature, it was initially assumed that gap junctions were predominantly found at the ends of the cardiomyocytes to facilitate AP conduction, away from sodium channel sites. However, it was shown by Cohen et al. in 1996 that both sodium channels and gap junctions co-exist at the intercalated disks [95]. This phenomenon was later confirmed by numerous studies by the macrostructure known as the connexome. The concept of the connexome revolves around the notion that the cardiac intercalated disc is the host of a protein interacting network including desmosomes, gap junctions and sodium channel complexes [96]. Autopsy findings support the idea that components of the connexome are not independent of each other, by demonstrating increased myocardial fibrosis from collagen deposition and reduced gap junction expression in the RVOT of hearts from BrS patients [97].

There is a close relationship between BrS phenotype on the ECG and RVOT abnormalities. An abnormal delayed potential was recorded from the epicardium of the RVOT in patients with BrS through the electrode inserted into the conus branch of the right coronary artery (RCA) [98]. Also, individuals with a normal ECG at baseline occasionally display BrS-type ECG patterns during an AMI of the RVOT [99]. Most recently, a panoramic ventricular mapping study in humans showed electrogram prolongation and fractionation, reflecting reduced CV and increased CV dispersion [100]. Defective depolarization may contribute to the pathology to different extents depending on the subtype. For example, in cases of BrS where abnormal function in calcium or potassium is observed, repolarization abnormalities may play a dominant role since the currents mediated by these channels contribute to the plateau rather than the depolarizing phase of the cardiac action potential.

(ii) Repolarization hypothesis

The repolarization theory states that differential action potential duration (APD) shortening across the myocardial wall is primarily responsible for the BrS phenotype. Loss-of-function *SCN5A* mutations can have opposing effects on the fast and slow inactivation of Na⁺ channels with distinct effects on repolarization [101]. Disruptions in fast inactivation leads to a sustained Na⁺ current, which prolongs repolarization at slow heart rates. However, the intermediate kinetic component of slow inactivation is augmented, delaying Na⁺ channel recovery, reducing the Na⁺ current and shorten APD at fast heart rates. This biphasic behaviour of APD of prolongation followed by shortening has subsequently been observed in a panoramic mapping study in BrS patients [100].

Experiments conducted on transmural ventricular wedges of canines have provided important information on the mechanism underlying the heterogeneities in repolarization and re-entry due to reduced inward currents [8,102,103]. Comparing APD values obtained from the epicardium (specifically the RVOT epicardium) with those obtained from the endocardium, shortening of the APD was seen at greater degree in the epicardium due to a relatively greater transient outward current (*I_{to}*). This is reflected in the more prominent loss of dome-shaped AP morphology seen in the epicardium. This is thought to underlie reentry by a phase 2

reentrant mechanism, initially hypothesized by Yan and Antzelevitch in 1999. Phase 2 reentry requires electrotonic interactions and propagation of epicardial sites with an AP dome to sites where this dome is abolished [104]. It could well underlie the R-on-T phenomenon leading to an extrasystolic action potential that can initiating ventricular arrhythmias in the presence of favourable reentrant substrates [8]. Steep and reversal of repolarization gradients lead to the ST segment elevation and T-wave inversion, respectively, in the ECG. Increased *T_{peak} - T_{end}*, an ECG marker of repolarization, is observed in BrS patients and associated with higher incidence of arrhythmic events or sudden cardiac death [105]. Indeed, studies of electrogram recordings have found a combination of steep repolarization gradient and delayed repolarization at the right ventricular outflow tract (RVOT) [100]. In patients with BrS due to defective calcium or potassium currents, a defective repolarization is the likely cause of VT/VF. Indeed, a reentrant mechanism as a result of loss-of-function Ca²⁺ channel mutation has been proposed [25].

Lastly, the restitution hypothesis states that a slope of the APD restitution curve >1 has been associated with the generation of repolarization alternans [106]. APD alternans can produce steep gradients in repolarization and refractoriness, unidirectional conduction block, wavebreak, and reentry. Both abnormal restitution and T-wave alternans have been observed in BrS [107–110].

(iii) Current-load-mismatch, depolarization-repolarization balance and excitation wavelength (λ)

In 2010, Hoogendijk and colleagues introduced the current-to-load mismatch phenomenon in the subepicardium to underlie ventricular arrhythmias in patients with BrS signs. This was performed using computer simulations of right ventricular structural discontinuities. Reduction in sodium current due to channel dysfunction or size of the pores was found to cause subepicardial excitation failure or delayed activation by current-to-load mismatch. Computational modeling work also showed that disruption to the inward-outward current equilibrium could affect excitation and therefore causing ST segment elevation subsequently [111,112]. It was confirmed in an explanted human heart model that only the failure of local excitation correlated with ST-elevation, not delayed activation or early repolarization [113]. Therefore, by altering the *I_{to}* or *I_{Ca}* accordingly to compensate for reduced sodium current, the extent of ST-elevation will decrease [111]. In order to simulate similar conditions of ST-elevation in pseudo-ECG recordings, conduction block and excitatory failure via sodium channel blocking was induced using ajmaline [112]. At sites of local ST-segment elevation, the subepicardium was interspersed with adipose tissue and contained more fibrous tissue than either the left ventricle or control hearts [114].

Cardiac structural abnormalities are observed in BrS patients, specifically in the right ventricle (RV) and RVOT, predisposes to current-load-mismatch and excitation failure. This was confirmed recently by Ten Sande and colleagues using cardiac activation mapping, illustrating that structural abnormalities in the subepicardial sites in the RV and RVOT are the likely cause of conduction changes and ST segment elevation [114]. This structural-electro physiological relationship is in keeping with ventricular arrhythmias found in BrS patients in their 30 s, when cardiac interstitial fibrosis is more evident [91]. Another study suggested that current-to-load mismatches at discontinuities were capable of causing a degree of conduction block, which explains the RBBB morphology found in BrS patients. It should also be recognized that discontinuities are usually associated with depolarization abnormalities when producing arrhythmia in BrS [115]. It also interacts with action potential repolarization and recovery to determine the

Table 1
Electrocardiographic indices for risk stratification in Brugada syndrome.

Depolarization	Repolarization	Depolarization-repolarization
Prolonged QRS Increased QRS dispersion fQRS Epsilon-like waves Concomitant RBBB	QT and QTc intervals QT and QTc dispersion $T_{\text{peak}}-T_{\text{end}}$, $T_{\text{peak}}-T_{\text{end}}/QT$ ratio, $T_{\text{peak}}-T_{\text{end}}$ dispersion JT_{peak} , JT_{peak} dispersion Early repolarization pattern (in ≥ 2 contiguous inferior/lateral leads)	iCEB (QRS/QT), iCEBc
First degree AV block RVOT delay signs: positive R-wave in aVR, S-wave in lead I, SII > SIII Positive Tzou criteria: V1 R-wave > 0.15 mV V6 S-wave > 0.15 mV V6 S-wave: R-wave ratio > 0.2		

excitation (λ) given by $CV \times ERP$. Decreased λ has been associated with increased likelihood of reentrant arrhythmias not only in pre-clinical animal models, but also in BrS patients [116,117].

8. Therapy and arrhythmic risk stratification

Since the underlying cause of BrS is reduced magnitude of inward currents, pharmacological agents that act to increase the inward currents or decrease the outward currents can restore the balance. Currently available drugs which are effective in preventing arrhythmic episodes in BrS are quinidine (a Class Ia Na^+ channel and I_{to} inhibitor), bepridil (I_{to} inhibitor and I_{Na} enhancer) and cilostazol (phosphodiesterase III inhibitor) [118–121]. Beta agonists and phosphodiesterase III inhibitors can be used to treat VF storms [122,123]. Future therapy can aim to restore the inward-outward balance, by enhancing Ca^{2+} currents (e.g. with cilostazol or milrinone [124]) or suppressing I_{to} (e.g. 4-aminopyridine [125]) to reduce the AP notch, TDR and the likelihood of phase 2 reentry. Interventional options include ICD insertion and radiofrequency ablation [126,127]. ICD insertion appears to be safe in the long term and reduces cardiovascular mortality in BrS patients [128,129]. However, its use is not without significant morbidity, as complications such as lead failure and infections can occur [130]. Moreover, the quality of life is affected from inappropriate shocks, most often due to the presence of supraventricular arrhythmias [127]. In some cases, radiofrequency ablation can be used to successfully prevent VT/VF occurrence [131]. The electrophysiological substrates have frequently been localized to the RVOT in BrS. Once the location of the substrates are confirmed by epicardial and endocardial mapping, they can be eliminated using radiofrequency ablation [132]. A multicenter randomized study, Ablation in Brugada Syndrome for the Prevention of VF Episodes (BRAVE study), will provide exciting findings on the utility of ablation without the need of ICD insertion [132].

There are many risk factors that have been associated with higher likelihood of developing VT/VF [133–135]. These include male gender [136,137], occurrence of syncope [138], genetic mutations in SCN5A [139,140], the presence of a spontaneous type 1 Brugada pattern [141,142], early repolarization pattern in inferolateral leads [143], S-wave in lead I [144], T-wave alternans [145], fragmented QRS morphology [94], burden of Brugada ECG pattern on Holter monitoring [146], augmented ST elevation during exercise recovery [147], an abbreviated ventricular refractory period of <200 ms [148], activation-recovery interval prolongations [149], and inducible arrhythmias observed during programmed electrical stimulation [150]. Several ECG repolarization markers have been proposed to stratify arrhythmic risk in the BrS population (Table 1) [151]. First, $T_{\text{peak}} - T_{\text{end}}$, the interval between the peak and the end of the T wave, have been associated

with increased arrhythmic risk [152]. Experiments conducted in arterially-perfused canine wedge preparations showed that the end of epicardial repolarization coincided with the T_{peak} and at the M-cell coincided with T_{end} suggesting that $T_{\text{peak}} - T_{\text{end}}$ reflected increased TDR [153]. Subsequent experiments in swines later reported that $T_{\text{peak}} - T_{\text{end}}$ was a marker of global rather than transmural dispersion of repolarization [152,154,155]. $T_{\text{peak}} - T_{\text{end}}$ changes with heart rate and demonstrate significant inter-individual variability [156]. Dividing it by the QT interval produces relatively constant values of 0.17 to 0.23 and has been proposed to be a better indicator for arrhythmia prediction [156]. Increases in $T_{\text{peak}} - T_{\text{end}}$ and $(T_{\text{peak}} - T_{\text{end}}) / QT$ have been associated with arrhythmia inducibility. Thus, Letsas and colleagues reported that patients with spontaneous or drug-induced Type 1 Brugada pattern with inducible VT/VF displayed an increased $T_{\text{peak}} - T_{\text{end}}$ interval in leads V_2 (88.82 vs. 78.33 ms) and V_6 (76.33 vs. 66.66) and a greater $(T_{\text{peak}} - T_{\text{end}})/QT$ ratio in lead V_6 (0.214 vs. 0.180) compared with those without arrhythmias [157]. Recent meta-analyses conducted by our group confirmed the value of both indices for risk stratification in BrS [158,159]. Moreover, markers based on conduction have also demonstrated utility for risk stratification. Fragmented QRS complex, represents an increased dispersion of conduction [160–162], can create unidirectional block, whereas wide QRS reflecting reduced conduction velocity, will shorten the excitation wavelength [163]. Both will predispose to reentrant arrhythmias.

Given the insights from pre-clinical studies, it was recognized that conduction abnormalities need to be incorporated into the risk markers to increase their accuracy of risk prediction [164–169]. For example, the index of Cardiac Electrophysiological Balance (iCEB), given by QT / QRS , is a surrogate marker of λ and its use has led to improved risk stratification [170,171]. Furthermore, abnormal action potential restitution appears to contribute to the arrhythmic substrate [172,173], and given recent work has developed restitution indices in clinical cohorts [174–176], whether they will incremental value in risk stratification in patients with Brugada syndrome remains to be elucidated. Finally, given the dynamicity in both the Brugada pattern [177–179] and arrhythmic risk [180], it would follow that temporal variability in ECG indices could offer additional value for risk stratification. Indeed, a high temporal burden of type 1 ST-segment elevation assessed using 24-hour Holter monitoring has been associated with an increased arrhythmic risk in BrS [146,178].

Other techniques such as electroanatomical mapping are also crucial for aiding risk stratification. For example, endocardial unipolar voltage mapping of the RVOT can detect low voltage areas that possibly reflect epicardial structural lesions in BrS [181]. We have recently shown that BrS patients with broad endocardial unipolar voltage abnormalities are more vulnerable

to VF induction during programmed ventricular stimulation. On the contrary, subjects with normal electroanatomical maps were non-inducible [182]. Detection of magnetic signals has traditionally been used to characterize structural properties [183–185], but recent work shown that magnetocardiography can provide incremental value for arrhythmic risk prediction [186–188].

9. Conclusion

The Brugada syndrome is an inherited primary arrhythmia syndrome originally thought to involve structurally normal hearts. Recent evidence implicates structural alterations of fibrotic change in the right ventricle. Risk stratification is based on a combination of genetic studies, symptoms, the presence of spontaneous or induced Brugada pattern on the ECG, ECG conduction and repolarization parameters as well as programmed electrical stimulation procedures to test for VT inducibility. High risk patients require ICD implantation. New developments such as subcutaneous ICDs might reduce the complication rates of transvenous ICDs, but its use is limited by the considerable rate of sensing screening failure. If electrophysiological substrates arising from the RVOT are confirmed by mapping, they can be eliminated using catheter ablation.

Acknowledgements

GT thanks the Croucher Foundation of Hong Kong for the support of his Clinical Assistant Professorship.

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