Electrocardiographic methods for diagnosis and risk stratification in the Brugada syndrome

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The Brugada syndrome (BrS) is a malignant, genetically-determined, arrhythmic syndrome manifesting as syncope or sudden cardiac death (SCD) in individuals with structurally normal hearts. The diagnosis of the BrS is mainly based on the presence of a spontaneous or Na+ channel blocker induced characteristic, electrocardiographic (ECG) pattern (type 1 or coved Brugada ECG pattern) typically seen in leads V1 and V2 recorded from the 4th to 2nd intercostal (i.c.) spaces. This pattern needs to be distinguished from similar ECG changes due to other causes (Brugada ECG phenocopies). This review focuses mainly on the ECG-based methods for diagnosis and arrhythmia risk assessment in the BrS. Presently, the main unresolved clinical problem is the identification of those patients at high risk of SCD who need implantable cardioverter-defibrillator (ICD), which is the only therapy with proven efficacy. Current guidelines recommend ICD implantation only in patients with spontaneous type 1 ECG pattern, and either history of aborted cardiac arrest or documented sustained VT (class I), or syncope of arrhythmic origin (class IIa) because they are at high risk of recurrent arrhythmic events (up to 10% or more annually for those with aborted cardiac arrest). The majority of BrS patients are asymptomatic when diagnosed and considered to have low risk (around 0.5% annually) and therefore not indicated for ICD. The majority of SCD victims in the BrS, however, had no symptoms prior to the fatal event and therefore were not protected with an ICD. While some ECG markers such as QRS fragmentation, infero-lateral early repolarisation, and abnormal late potentials on signal-averaged ECG are known to be linked to increased arrhythmic risk, they are not sufficiently sensitive or specific. Potential novel ECG-based strategies for risk stratification are discussed based on computerised methods for depolarisation and repolarisation analysis, a composite approach targeting several major components of ventricular arrhythmogenesis, and the collection of large digital ECG databases in genotyped BrS patients and their relatives.

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Introduction

The Brugada syndrome (BrS) is a malignant arrhythmia syndrome manifesting as recurrent syncope or sudden cardiac death (SCD) due to polymorphic ventricular (VT) or ventricular fibrillation (VF) in the absence of overt structural heart disease or myocardial ischemia [1,2]. The prevalence of the syndrome is estimated at around 15 per 10,000 in South East Asia, including Japan and around 2 per 10,000 in the Western countries [3,4]. One study on a southern Turkish population suggested that the prevalence of BrS in the Middle East may be lower than in South East Asia and higher than in the West [5]. The BrS may be responsible for up to 4% of all sudden cardiac deaths (SCD) and at least 20% of SCDs in patients with structurally normal hearts [6]. It is eight to ten times more prevalent in males than in females [7]. In South East Asia, the BrS is the leading cause of non-traumatic death in men younger than 40 years [8]. The purpose of this article is to briefly summarise current knowledge about the electrocardiography (ECG) based methods for diagnosis and assessment of the risk of malignant arrhythmias in patients with the BrS. Before that, the cellular and genetic mechanisms of the BrS are discussed briefly.

Genetics and cellular mechanisms

BrS has been considered a heritable autosomal dominant disease [9] and more than 390 mutations have been identified in the SCN5A gene encoding the α-subunit of the cardiac I Na channel [10]. However, presently SCN5A mutations are found only in 11–37% of the genotyped patients [11,12]. Many patients with the BrS have no family history, presumably due to under-diagnosis in other family members, low penetrance, or sporadic disease [13]. Recent data has suggested that heritability may not be strictly monogenic, but may in fact relate to common genetic variation [14].

The cellular basis of the BrS is still not completely clear [15]. According to the repolarisation theory, genetically determined or drug-induced reduction of the inward Na+ current leads to unopposed transient outward (Ito) current in some (but not all) epicardial regions of the right ventricular outflow tract (RVOT), which causes either delayed expression of the action potential (AP) dome and epicardial AP prolongation or loss of the dome and AP shortening. The net effect is magnification of repolarisation dispersion between the RVOT endo- and epicardium, and between different RVOT epicardial regions, which is potentially arrhythmogenic. The repolarisation theory was initially promoted on the basis of experimental studies [16–18]. It was later supported by clinical studies, which demonstrated a ‘spike and dome’ configuration with deep notching of monophasic action potentials (MAP) from the RVOT epicardium but not endocardium [19], paradoxical shortening of the RVOT epicardial activation-recovery intervals (ARI) during augmentation of Brugada-type ST segment elevation.

Abbreviations

| Abbreviation | Description                  |
|--------------|------------------------------|
| AP           | action potential             |
| ARI          | activation-recovery intervals|
| BrS          | Brugada syndrome             |
| ECG          | electrocardiogram            |
| EPS          | electrophysiology study      |
| ICD          | implantable cardioverter-defibrillator |
| IHD          | ischaemic heart disease      |
| LBBB         | left bundle branch block     |
| MAP          | monophasic action potential  |
| MI           | myocardial infarction        |
| PCA          | principal component analysis |
| RVOT         | right ventricular outflow tract |
| SAECG        | signal-averaged electrocardiogram |
| SCD          | sudden cardiac death         |
| SNP          | single-nucleotide polymorphism |
| VF           | ventricular fibrillation      |
| VT           | ventricular tachycardia       |
| WT           | wavelet transform             |
[20], steep AP duration restitution (slope > 1) in the RVOT[21–23] (both clinically and experimentally), and longer ARI in the RVOT epicardium recorded from the conus branch of the right coronary artery than in the endocardium of patients with BrS and type 1 ECG pattern, but not in controls [24].

There is also mounting evidence from experimental [22], histopathological [25], computational [25], clinical electrophysiological [23,26], and imaging [27] studies for the presence of conduction abnormalities in the RVOT and their importance for the genesis of ventricular arrhythmias in BrS [22,23] (depolarisation theory). A mechanism explaining the Brugada ECG type solely by delay of the RVOT activation relative to the rest of the RV has also been proposed [28]. The presence of late potentials and prolonged filtered QRS duration on signal-averaged ECG (SAECG) as well as increased notching and fragmentation of the QRS on the standard ECG are linked to increased arrhythmic risk in BrS [29–32]. A third hypothesis unifying the above two explains the BrS with abnormal expression of the neural crest cells during the embryological development of the RVOT. This defect in the embryogenesis of the RVOT leads to both abnormally augmented electrical gradients during repolarisation as well as to delayed activation of the RVOT [33].

From the electrocardiographic point of view, the characteristic elevation of the J point and ST segment of the diagnostic Brugada type 1 pattern (see below) results from early relative (intracellular) positivity of the unaffected zone (RVOT
endocardium according to the repolarisation theory or normally activated myocardium outside the RVOT according to the depolarisation theory), whereas the negative T wave is an expression of late epicardial relative (intracellular) positivity in the affected RVOT zone, due to either prolongation of the epicardial APs or its delayed activation.

Clinical manifestations

The symptoms associated with the BrS are due to re-entry ventricular arrhythmias typically arising in the affected zone of the RV. If they last briefly (seconds) and terminate spontaneously they can be asymptomatic or cause palpitations, syncope or nocturnal agonal respiration, or can degenerate into VF and lead to cardiac arrest. Since the duration of the arrhythmia is unpredictable and every arrhythmic episode can be fatal, the assessment of the degree of arrhythmic risk and the need for prophylactic treatment is by far the most important aspect of the management of these patients (see below).

Electrocardiographic diagnosis of the Brugada syndrome

The diagnostic hallmark of the BrS is a characteristic ECG pattern consisting of J point elevation with slowly descending or concave ST segment elevation merging into a negative or reaching the isoelectric line symmetric T wave, described as ‘coved’ or type 1 Brugada ECG pattern [7,34] (Fig. 1). Most frequently, it is observed in leads V1 and V2 (less frequently in V3 [35]) especially when recorded from the 3rd or 2nd intercostal (i.c.) space [36] (Fig. 2) but sometimes it can be observed in the inferior [37–40] or lateral [41,42] leads (atypical BrS). One study found that bipolar precordial leads between the V2 electrode (positive pole) and V4 or V5 electrodes (negative pole) computed from the standard unipolar leads V2, V4 and V5 are more sensitive and equally specific compared to lead V2 for detecting of Brugada type 1 pattern (Fig. 3) [43].

Another ECG pattern of J point and ST segment elevation with a positive T wave in the right precordial leads, the so-called saddle-back pattern,
is considered suspicious but not diagnostic of BrS. The saddle back patterns are further divided into type 2 and type 3 Brugada ECG pattern, depending on the level of J point and ST segment elevation (Fig. 4). A recently published expert consensus report on the ECG characteristics of the BrS [34] proposed type 2 and type 3 patterns to be unified into one saddle-back Brugada pattern because, according to the authors’ opinion, the small morphological differences between the

Figure 6. Examples of typical type 1 Brugada ECG pattern with (left panel) and without QRS notching/fragmentation. Lead V1 from the 4th, 3rd and 2nd i.c. space is shown. (A) Fractionated QRS complex in a 25-year-old asymptomatic male patient with BrS (ajmaline-induced type 1 Brugada ECG pattern); (B) Spontaneous type 1 Brugada ECG pattern in a 53-year-old man with aborted cardiac arrest, implanted ICD, and subsequently multiple appropriate shocks of the device. No considerable fractionation of the QRS complex can be seen. See the text for details. The examples above suggest that although the presence of QRS notching/fragmentation is linked to increased risk of sudden cardiac death in the BrS, its sensitivity and specificity may not be very high. See the text for details.

Figure 7. (A) A signal-averaged ECG (SAECG) with abnormal late potentials in a 60-year-old man with no previous history of arrhythmic symptoms and spontaneous type 1 Brugada ECG pattern. The total filtered QRS duration, the duration of the high frequency low amplitude (HFLA) <40 μV and the root-mean-square voltage (RMS) in the terminal 40 ms of the QRS are 137 ms, 55 ms and 15 μV, respectively (all three parameters are abnormal). The noise level is 0.25 μV, the number of averaged complexes is 214 and the filter settings are 40–240 Hz. (B) Resting ECG of the same patient. Only lead V1–V3 from 4th to 2nd i.c. space are shown. Note the presence of typical type 1 Brugada ECG pattern in many leads, with QRS fractionation in leads V1 (4th and 3rd i.c. space) and V2 (3rd and 2nd i.c. space). Note also that the type 1 Brugada pattern generally becomes more pronounced when moving the recording electrodes cranially from 4th to 2nd i.c. space (it is present even in lead V3 when recorded 2 i.c. spaces higher (lead V32), which is a relatively rare finding).
two patterns had no diagnostic or prognostic significance. In the latest HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes published in December 2013 [7], however, type 2 and type 3 Brugada ECG patterns are mentioned separately. Up to 40% of patients with the BrS present with normal or non-diagnostic, resting ECG [44]. In these patients, the diagnostic ‘coved’ ECG pattern can be elicited by IV administration of sodium channel blocker (ajmaline, procainamide, flecainide) [45,46] (Fig. 5). It is important to distinguish between type 2 Brugada ECG pattern and the r′-pattern (incomplete right bundle branch block (IRBBB) pattern) in leads V1 and V2 (especially when recorded from the 3rd or 2nd i.c. space), which can be observed in healthy subjects, and frequently in athletes [47]. It has been reported that a broader angle between the ascending and descending limb of the r′-wave [48] or a broader base of the triangle formed by the two limbs of the r′-wave measured at 5 mm from the highest point [49,50] can reliably distinguish type 2 Brugada ECG pattern from IRBBB pattern.

Currently, the diagnosis of BrS is definite when type 1 pattern is observed in at least one of leads V1 and V2 recorded from the 4th, 3rd or 2nd i.c. space, either spontaneously or following administration of Na+ channel [7]. The presence of gene mutations is not considered essential for the diagnosis [2,7].

The classical diagnostic type 1 Brugada ECG pattern needs to be distinguished from similar Brugada-like patterns caused by atypical right bundle branch block, septal hypertrophy, arrhythmogenic right ventricular cardiomyopathy (ARVC), pectus excavatum and other conditions, and also from the transient appearance of the typical Brugada pattern in the cause of various acute processes such as acute ischaemia, Prinzmetal angina, pulmonary embolism, pericarditis, metabolic disorders, various medications and others (the so-called Brugada phenocopies) [51].

The use of inappropriate high-pass filters during ECG acquisition (e.g. non-linear phase, high-pass filter of 0.5 Hz instead of the recommended 0.05 Hz) [52] can cause considerable ST segment distortion which can mimic type 1 or 2 Brugada pattern [34,53,54].

The ECG in BrS shows considerable dynamic variability; it can be completely normal at one time and demonstrate diagnostic type 1 pattern at another [55]. Vagal influences (slow heart rate, postprandial state, night-time) tend to augment the J point and ST segment elevation and the type 1 pattern [56], whereas exercise and catecholamine infusion have the opposite effect (in selected BrS patients the ST segment elevation might become more prominent during exercise) [57]. Autonomic influences also play important roles in the genesis of malignant arrhythmias because most arrhythmic events in BrS occur at night [2], and long RR intervals often precede episodes of VT/VF [58], whereas catecholamine infusion is used as a first line treatment of such episodes [59]. Patients with BrS have increased incidence (10–53%) of atrial fibrillation (AF) [60,61].

In asymptomatic patients with spontaneous or induced by Na-channel blockers type 1 pattern, the diagnosis of BrS is supported by the presence of atrial fibrillation, atrio-ventricular or intraventricular conduction abnormalities (first degree A-V block, left axis deviation of the QRS complex, fragmented QRS (Fig. 6), late potentials on the signal-averaged ECG (SAECG) (Fig. 7), HV interval >60 ms), ventricular ectopic beats with left bundle branch block (LBBB) morphology, and short (<200 ms) ventricular effective refractory period during electrophysiology study (EPS) [7].

Risk stratification – the most important clinical problem in the Brugada syndrome

Currently, this is by far the most important and yet unresolved clinical problem in the BrS. It is similar to one of the main (and also unresolved) problems of modern cardiology – the identification of patients with ischaemic heart disease (IHD) at high risk of dying suddenly who need a prophylactic implantable cardioverter-defibrillator (ICD).

In BrS patients with a previous history of arrhythmic syncope or aborted cardiac arrest, the annual event rate of sustained VT or VF is relatively high – between 1.9% [62] and 8.8% [63], and between 7.7% [62] and 13.8% [63], respectively. They are indicated for ICD, which is the single therapy with proven efficacy (class I indication for those with aborted cardiac arrest or spontaneous sustained VT and class IIa for those with syncope) [7]. However, the majority of BrS patients (64% in the largest reported series of 1029 BrS patients, the FINGER study [62]) have no symptoms at the time of establishment of diagnosis. The annual rate of SCD or sustained VT in these patients is low – between 0% [64,65] and 0.8 [66] (0.5% in the FINGER study [62], 0.4–1% in three Japanese studies [67–69]) and cannot justify ICD implantation in all of them. On the other
hand, the majority of these patients have structurally normal hearts and are young or middle aged when diagnosed (median age 45 years in the FINGER study), and therefore the low annual risk translates into considerable cumulative arrhythmic risk for the next several decades of their life expectancy. In fact, the majority of victims of SCD in BrS come from this ‘low risk’ (according to current standards) population. Among patients with the BrS who have died suddenly, 68% had no previous history of arrhythmia-related symptoms and therefore had not been protected by ICD [13]. Currently, there are no reliable methods for identification of these patients (see below). Similarly, the largest absolute number of patients with IHD who die suddenly also comes from a patient population considered to have low risk (i.e. with relatively preserved ejection fraction) [70].

On the other hand, the decision to offer an ICD even to a BrS patient with a syncope is often difficult because unlike IHD patients, most of them are relatively young, apparently healthy, and without any previous awareness of cardiac problems. In addition, it is often very difficult to exclude non-arrhythmic cause of the syncope. Finally, the rate of ICD-related complications (20–30% annually including inappropriate shocks) is higher than the rate of appropriate activation of the device (2.6–8% annually) [71–73]. This suggests that novel, better methods of risk-stratification are needed even in the group of patients with currently accepted indications for ICD therapy (those with aborted cardiac arrest or syncope).

Problems with current methods of risk stratification in the BrS

While two studies [74,75] reported increased occurrence of arrhythmic events in BrS patients with SCN5A mutations, these findings have not been confirmed by other studies [76,77]. Some specific mutations or common single-nucleotide polymorphism (SNP) might have prognostic significance [7]. The genetic analysis is expensive, time-consuming, and available only in specialised centres. Male gender [11] and presence of AF [60,61] are linked to increased risk of malignant ventricular arrhythmias. The role of programmed ventricular stimulation (PVS) during EPS for induction of VT and/or assessment of the ventricular effective refractory period for the purpose of risk stratification have been an object of controversy and debate since the first descriptions of the BrS. While some studies support its value for risk stratification mainly due to its high negative predictive value [78,79], most recent studies have failed to confirm its independent predictive value [80,81,71]. Likewise, in the FINGER study [62], inducibility during EPS did not predict arrhythmic events in multivariate analysis, whereas in the multicentre PRELUDE study which tested uniform protocol of PVS during EPS in all 308 patients, the rate of arrhythmic events during an average follow-up of three years showed no difference between the 126 inducible (3.9%) and the 182 non-inducible patients (4.9%) [82]. Currently, its role of EPS for risk stratification is accepted only as a Class IIb (‘may be considered’) indication [7,83]. The method is inherently limited by its invasive character and probably also by the labile nature of the underlying electrophysiologic substrate [84].

ECG-based methods for risk stratification

Apart from the spontaneous (as opposed to drug-induced) appearance of the diagnostic type 1 pattern, currently no other ECG feature has consistently shown an indication for increased arrhythmic risk.

In contrast with acute myocardial infarction (MI), the number of leads displaying type 1 pattern and the degree of J point or ST-segment elevation do not seem to correlate with the arrhythmic risk [35,36]. The high (3rd or 2nd i.c. space) positions of leads V1 and V2 are diagnostically more sensitive than their standard positions in the 4th i.c. space [85–87], but, prognostically, their value is the same [88]. Similar to other diseases with intraventricular conduction abnormalities such as IHD and cardiomyopathies, the presence of notched or fragmented QRS [82,32], (Fig. 6) and abnormal late potentials on the signal-averaged ECG (SAECG) [31] (Fig. 7) seems to indicate increased arrhythmic risk in the BrS. However, currently, the presence of notching/fractionation is assessed only visually with arbitrary descriptive terms (e.g. number of QRS peaks). The role of the standard time-domain SAECG in BrS is limited by (a) inability to detect conduction abnormalities within the QRS complex, (b) uncertain value in patients with bundle branch block, and (c) the use of a single-lead ECG complex, which is derived from the XYZ orthogonal leads and does not contain any regional information. Limited data suggest that a number of ECG parameters may indicate BrS patients at higher risk of malignant arrhythmias: changes in repolarisation dynamics (QT/RR and \( T_{peak} - T_{end}/RR \) intervals relations); [89] deep negative T wave in lead V1; [90] QTc interval more than 460 ms in
lead V2 and prolonged $T_{peak} - T_{end}$ interval; [91] dynamic alterations in the amplitude of the ST elevation; [92] presence of infero-lateral early repolarisation; [93,94] the presence of horizontal (as opposed to rapidly ascending) ST segment after the J point; [68] prolonged PR-interval; [90] the presence of atrial arrhythmias; [95] and augmentation of the ST segment elevation during the early recovery phase of exercise test [96].

However, none of the above ECG-based parameters has consistently shown sufficiently high risk predictive value. As a result, currently the only class I indications for ICD implantation (‘ICD is recommended’) in patients diagnosed with the BrS endorsed by the 2013 HRS/EHRA/APHRS Expert Consensus Statement [7] is history of aborted cardiac arrest or documented spontaneous sustained VT (with or without syncope). The Consensus Statement-endorsed history of syncope is judged to be likely caused by ventricular arrhythmias only as a Class IIa indication (‘ICD can be useful’) which reflects the difficulty of excluding a non-cardiac origin of syncope. The guidelines of the Japanese Cardiac Society of 2011 accept practically the same Class I indications, whereas for Class IIa indications they require the presence of at least two of the following risk factors: history of syncope, family history of sudden cardiac death, and inducible VF during EPS [97].

In summary, the current indications for ICD implantation in the BrS are based solely on the presence of arrhythmia-related symptoms, spontaneous appearance of type 1 (‘coved’) Brugada ECG pattern and, in some institutions, inducibility of sustained VT/VF during EPS [98].

ECG-based methods for risk stratification in the BrS – some suggestions for future directions

Obvious obstacles to the development of novel methods for risk stratification in the BrS are the low rate of arrhythmic events (i.e. endpoint events in prospective follow-up), the small number of patients in the individual centres (since the prevalence of the disease outside South East Asia is generally low), difficult organisation of big multi-centre prospective studies and, possibly, inherent

Figure 8. Principal component analysis (PCA) of the ST-T wave (from the J point to the end of the T wave) in the right precordial leads of ECGs recorded during diagnostic ajmaline test. (A) Positive ajmaline test in a 15-year-old girl with the BrS and a past history of syncope of presumable arrhythmic origin. (B) Negative ajmaline test in a 67-year-old asymptomatic man with a family history of BrS and sudden cardiac death. Each bar represents the PCA value (ratio of the 2nd/1st eigenvalue) from analysis of one 10-s ECG recording. Two to five 10-s ECGs were recorded during the test. On the X-axis, time is shown in minutes from the beginning of the test. ECGs were recorded at baseline (b) as well as up to 15 min after the start of the drug administration. PCA has been applied to the V1–V3 leads (blue diamonds) and to leads V1–V3 recorded from the 3rd i.c. space (red diamonds). Data are presented as mean ± standard deviation (SD) of all complexes within one 10-s ECG. Generally, higher values reflect more heterogeneous (and, hence, more abnormal and potentially more arrhythmogenic) ventricular repolarisation. The figures show that the appearance of diagnostic type 1 Brugada ECG pattern during the positive test (A) is accompanied by a striking increase in the PCA ratio, whereas during a negative test, there is practically no change in PCA (the SD deviation bars are hidden within the diamond bars). Adapted from [100].
differences between various patient populations (e.g. Western vs. Japanese [66]).

In our view, another, less appreciated obstacle is the fact that currently ECG research studies (as well as everyday clinical practice) generally still use 12-lead paper ECGs (or digital ECG images), which are amenable only to visual assessment and simple manual measurement. Over the last decades, computerised mathematical methods for quantitative assessment of QRS and ST-T wave abnormalities have been developed and successfully tested in various cardiac diseases [98,99], but they require the availability of digital ECGs (digital files containing the raw ECG signal and not just digital image files). Small pilot studies have already shown the potential usefulness of some methods for arrhythmia risk stratification in patients with positive ajmaline test. In the latter group, PCA of the QRS is similar to those with negative ajmaline tests. See the text for details. Adapted from [101].

Figure 9. PCA of the QRS complex of leads V1–V3 from the 3rd i.c. space recorded during positive ajmaline test in patients with previous history of arrhythmia-related symptoms (n = 6, brown bars), during positive ajmaline test in asymptomatic patients (n = 17, yellow bars) and in patients with negative ajmaline tests (n = 73, blue bars). Data are presented as mean ± standard error (SE) of all ECG complexes recorded during one minute of the tests as well as at baseline. Note the distinctly different pattern of PCA of the QRS in symptomatic and asymptomatic BrS patients with positive ajmaline test. In the latter group, PCA of the QRS is similar to those with negative ajmaline tests. See the text for details. Adapted from [101].

Principal component analysis (PCA) is a known method for quantitative assessment of depolarisation and repolarisation heterogeneity with established diagnostic and prognostic value in patients with different cardiac diseases [98]. PCA of the ST-T wave can detect increased repolarisation heterogeneity and help establish the diagnosis in patients with suspected BrS and non-diagnostic resting ECGs (Fig. 8) [100], whereas PCA of the QRS complex has been shown to have prognostic value (Fig. 9) [101].

A small pilot study on genotyped BrS patients demonstrated that wavelet transform (WT) of the QRS complex and ST-T wave of leads V1 and V2 leads from the 2nd and 3rd i.c. space can distinguish patients with mutations (n = 12) from those without mutations (n = 14) [102]. WT is particularly suitable for analysis of time-varying, quickly changing signals such as the QRS complex and the interval around the J point where the main events in BrS take place.

Therefore, the development of novel ECG-based risk stratification approaches in the BrS requires the collection of a large high-quality databases of digital ECGs acquired in genotyped symptomatic and asymptomatic patients with the BrS and their relatives both at rest as well as continuously during dynamic conditions (exercise stress test, ambulatory conditions, pharmacologic testing with Na+ channel blockers). Preferably, leads V1 and V2 should be recorded simultaneously in both the standard as well as higher positions (4th, 3rd and 2nd i.c. spaces) since the anatomic relation between the RV and the electrode positions is individually specific, and any of the three intercostal spaces could be closest to the RVOT [103].

Finally, the development of sustained VT/VF in the BrS is likely a complex event resulting from interaction between the arrhythmic substrate (repolarisation and depolarisation abnormalities) and various triggering and modifying factors (e.g. ventricular ectopic beats, atrial arrhythmias, autonomic modulations such as vagal surge, fever, etc.) [22,15,104]. A successful ECG-based risk stratification in BrS approach, therefore, should likely involve the combined quantitative assessment of several of the most important elements of arrhythmogenesis. For example, one possible composite approach could involve:

(a) Assessment of QRS heterogeneity (PCA, WT, possibly other methods) and repolarisation heterogeneity (PCA) in the right precordial leads;
(b) Assessment of the spontaneous (continuous rest ECG, Holter recordings) or induced (by graded exercise, autonomic or pharmacologic provocations) variability of depolarisation and repolarisation (variability of the parameters identified in presence of microvolt T wave alternans, etc.);
(c) Assessment of cardiac autonomic control (heart rate variability, heart rate turbulence, etc.) from ambulatory Holter recordings or short-term continuous recordings.

Conclusions
While the diagnosis of the BrS is relatively straightforward with the available, mainly
ECG-based methods, the identification of all patients at high risk of dying suddenly who need ICD implantation is still a largely unresolved problem. With the current methods for risk stratification, the majority of potential victims of SCD remain unidentified and hence unprotected by ICD before the fatal event. While some ECG markers of depolarisation and repolarisation abnormalities are known to be linked to increased arrhythmic risk, their sensitivity or specificity seems low, and they have not been tested in large prospective studies. The development of novel ECG-based methods for risk stratification would likely require the availability of large digital ECG databases in patients with BrS and their relatives, application of new computerised methods for quantitative assessment of depolarisation and repolarisation abnormalities, and the design of composite risk-stratification approaches targeting all major elements of ventricular arrhythmogenesis in the BrS.

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