Brugada syndrome

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Abstract

The Brugada syndrome demonstrates characteristic electrocardiogram features and is a significant cause of sudden death in young adults with overtly normal cardiac structure and function. The genetic basis has not yet been fully elucidated but our understanding of the causative mutations and modifiers of arrhythmic events is advancing rapidly alongside sequencing technologies. We expect that the future will include risk stratification according to genotype and management tailored to the genetic diagnosis.

Introduction

The Brugada syndrome (BrS) was recognized as a distinct clinical entity in 1992 by brothers Pedro and Josep Brugada.¹ It consists of right ventricular conduction delay and ST segment elevation in the right precordial electrocardiogram (ECG) leads in association with syncope and sudden death due to ventricular fibrillation (VF).² BrS is thought to be responsible for 4% of all sudden cardiac death (SCD) and up to 12% of sudden death in patients with structurally normal hearts.^{2,3} There is a particularly high prevalence and rate of sudden death reported in young men of South East Asian origin and BrS assumes a number of alternative names including *Lai Tai* in Thailand, *Pokkuri* in Japan and *Bangungut* in the Philippines.⁴ Men are affected more than women and the clinical phenotype manifests in adulthood with a mean age of 41 years.²

The type 1 Brugada ECG pattern describes classical coved ST segment elevation of ≥ 0.2 mV followed by a negative T wave (Figure 1). A type 1 Brugada ECG pattern is found rarely in the European population, but appears more common in South East Asia, with estimated prevalence of 0.12% in Japan.⁵⁻⁸ Type 2 and 3 Brugada ECG patterns also exist. These are more prevalent but do not support a diagnosis of BrS (Figure 2). Type 1 Brugada ECG patterns are occasionally seen in the inferior ECG leads and these patients tend to be more symptomatic.⁹

Diagnosis

The diagnosis of BrS is made when the type 1 ECG is observed in the right precordial leads (V_1 - V_3) in conjunction with other clinical features (Table 1).^{2,10} Although the second consensus document of 2005 specified that ≥ 2 adjacent leads were required to show the type 1 Brugada pattern, current opinion supports the validity of a single diagnostic lead.^{2,10} The ECG abnormality may be dynamic and can be induced by fever, vagal stimulation and sodium channel blocking agents such as ajmaline and flecainide. An ajmaline challenge can therefore be used to aid diagnosis, although this is not completely sensitive and reproducible (Figure 3). Placing right precordial leads in a higher position (second and third intercostal spaces) has been shown to increase the sensitivity of detection of the type 1 Brugada ECG.^{2,11}

Genetics

BrS is inherited as an autosomal dominant trait with incomplete penetrance. It has been associated with more than 250 mutations in eleven different genes (Table 2). Mutations in the *SCN5A* gene, encoding the α subunit of the $Na_v1.5$ sodium channel, are identified in 21% of index cases (proband).¹² In one series, loss of function mutations in genes *CACNA1C*, *CACNB2* and *CACNA2D1*, encoding the L-type calcium ion channel, accounted for a further 12% of Brugada cases, some of whom also exhibited a short QT interval.¹³ Mutations in genes encoding proteins that interact with *SCN5A* have been identified in a few cases and result in loss of function with impaired inward sodium current, I_{Na} . These include *SCN1B* and *SCN3B* β subunits and channel interacting proteins *GPD1L* and *MOG1*.^{14,15} There is one example of a gain of function mutation in *KCNE3*, the putative β subunit for potassium current I_{K0} and more recently another two of gain of function mutations in *KCNQ3*, the α subunit.¹⁶ A gain of function mutation in *Kir6.1* the α subunit for potassium current I_{KATP} has also been described in one patient.¹⁷

The relationship between *SCN5A* mutations and BrS may be more complex than proposed following the original candidate gene studies. Recent evidence has demonstrated genotype-phenotype discordance. A study of families with putatively pathogenic *SCN5A* mutations found that the type 1 Brugada ECG was not inducible in nearly half the mutation carriers but was inducible in a minority of gene negative family members. This suggests that in some families the *SCN5A* variant represents a genetic modifier rather than a causative mutation.¹⁸

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In patients with BrS comprehensive *SCN5A* targeted genetic testing can be useful, principally for the purposes of family screening. Predictive genetic testing is recommended for family members and appropriate relatives following the identification of the BrS-causative mutation in an index case. Genetic testing is not recommended in a patient with an isolated type 2 or 3 Brugada ECG pattern.¹⁹⁻²¹

Pathophysiology

Functional studies of sodium channel mutations in heterologous expression systems have demonstrated that loss of function mutations due to failure of channel expression (trafficking) or changes in functional properties (gating), result in reduced inwards depolarizing sodium current I_{Na} .¹² This has resulted in two competing hypotheses for the arrhythmogenic mechanism.

The repolarization hypothesis

The repolarization theory suggests that unopposed action of repolarizing potassium current I_{K0} in right ventricular (RV) epicardium leads to loss of the action potential dome (Figure 4). Dispersion of repolarization allows re-entry during phase 2 of the action potential providing the substrate for initiation of ventric-

ular arrhythmia. Evidence for abnormal repolarization in BrS comes from the canine right ventricular wedge preparation.²² In this model, sodium channel blockade, acetylcholine and slow ventricular pacing facilitated reproduction of the type 1 Brugada ECG pattern and initiation of ventricular extrasystoles at sites of earlier repolarization. Quinidine and isoproterenol (through blockade of I_{to} and augmentation of depolarizing calcium current I_{Ca} respectively) restored the balance of depolarization and repolarization and attenuated these ECG changes.²² Other evidence is the presence of mutations in BrS patients directly affecting I_{to} .^{14,15}

The depolarization hypothesis

The depolarization theory suggests that delayed conduction in the right ventricular outflow tract (RVOT) facilitates re-entry and subsequent arrhythmia (Figure 4).²³ This has been accompanied by increasing evidence to suggest that the type 1 Brugada ECG pattern is a marker of subtle structural heart disease as evidenced by histopathological and cardiac imaging studies. Prior to the original description of BrS, a case series of patients with idio-

pathic VF and right precordial ST segment elevation documented RV structural abnormalities.²⁴ Subsequent histopathological studies of autopsies in sudden death cases with prior ECGs suggestive of BrS have demonstrated evidence of fibro-fatty infiltration in the RV. This suggested an overlap of BrS with arrhythmogenic right ventricular cardiomyopathy.²⁵ In endomyocardial biopsies from living patients with BrS, a variety of structural changes have been seen including myocyte hypertrophy, mild fibrosis and fatty infiltration.²⁶ In BrS patients cardiac magnetic resonance (CMR) studies have shown increased RV volumes and RV regional wall motion abnormalities, while sodium channel blockade during tissue Doppler echocardiography has demonstrated delays in RV contraction.^{27,28} In addition 2D strain using speckle tracking echocardiography has shown mild systolic and diastolic abnormalities in RV segments, independent of the type 1 Brugada ECG pattern.²⁹

Electrocardiographic features of delayed conduction have also lent support to this hypothesis. Late potentials on the signal averaged ECG (SAECG) and fragmentation of QRS complexes on the standard ECG are associated with structural heart disease and conduction delay and both of these are found frequently in sympto-

Table 1. Diagnostic criteria for the Brugada syndrome.

Diagnostic ECG criteria	One of the following must also be present
Type 1 BrS pattern in ≥ 1 ECG lead (V_1 - V_3)*	Documented VF Documented polymorphic VT Family history of SCD < 40 years old Type 1 BrS patterns in family members Syncope Nocturnal agonal respiration

* In the presence or absence of a sodium channel blocking agent. ECG, electrocardiogram; VF, ventricular fibrillation; VT, ventricular tachycardia; SCD, sudden cardiac death; BrS, Brugada syndrome.

Inducible VT with programmed electrical stimulation was part of the consensus document but is not used currently or routinely for diagnosis.

Figure 1. Electrocardiogram (ECG) from a patient with Brugada syndrome. This demonstrates the characteristic type 1 Brugada ECG pattern in leads V1 and V2 and a type 2 Brugada ECG pattern in lead V3.

Figure 2. Brugada type electrocardiogram (ECG) patterns. Panel A demonstrates the type 1 Brugada ECG pattern with coved ST segment elevation ≥ 0.2 mV followed by a negative T wave. Panel B shows a type 2 Brugada ECG pattern with saddleback ST segment elevation ≥ 0.2 mV with a trough of ≥ 0.1 mV followed by a positive or biphasic T wave. Panel C demonstrates the type 3 Brugada ECG pattern with either coved or saddleback ST segment elevation of ≤ 0.1 mV.

matic BrS patients.³⁰⁻³² Electrophysiological studies of the RV utilizing endocardial mapping systems have also demonstrated conduction abnormalities, with increased electrogram fractionation and activation delay in the RVOT in BrS patients compared with controls.^{33,34} This has been further examined in epicardial mapping studies of the RVOT in very symptomatic BrS patients where very late fractionated potentials were evident.³⁵

Structural changes are however subtle at most and not demonstrated in all BrS. It appears possible that a combination of repolarization and depolarization abnormalities conspire to result in BrS. Or indeed the underlying mechanism may differ between patients.²³

Ventricular arrhythmia in Brugada syndrome

Ventricular arrhythmias usually occur at rest, particularly at night or after large meals, and may be induced by febrile illness and sodium channel blocking agents.² Prior to the onset of arrhythmia, the type 1 Brugada ECG pattern appears to become more prominent and is frequently accompanied by short-coupled ventricular extrasystoles.^{36,37} It seems that the underlying substrate for the type 1 Brugada ECG pattern, whether ultimately due to dispersion of depolarization and/or repolarization is also responsible for the initiation of VF.³⁸

Risk stratification and management

Risk stratification for sudden death in BrS is controversial and the only reliable treatment to prevent SCD is the implantable cardioverter defibrillator (ICD).³⁹ There is general agreement that patients with a prior aborted SCD or

Figure 3. Ajmaline provocation testing in Brugada syndrome. Panel A demonstrates the baseline 12 lead electrocardiogram (ECG). Ajmaline is administered intravenously at a dose of 1 mg/kg over 5 min. Panel B demonstrates ECG changes at peak effect with a type 1 Brugada ECG pattern observed in standard leads V1/V2 and high leads V3/A1/A2/A3.*

*For the purposes of ajmaline provocation testing A1/A2 represent V1/V2 in the third intercostal space and A3/V3 represent V1/V2 in the second intercostal space respectively.

Table 2. Genetic mutations associated with the Brugada syndrome.

BrS Subtype	Gene	Protein	Ion channel	Effect of mutation	Frequency
BrS1	SCN5A	Na _v 1.5	α subunit I_{Na}	Loss of function	21% ¹¹
BrS2	GPD1L	G3PD1L	Interacts with α subunit I_{Na}	Loss of function	-
BrS3	CACNA1C	Ca _v 1.2	α subunit I_{Ca}	Loss of function	5.5% ¹²
BrS4	CACNB2	Ca _v β2	β subunit I_{Ca}	Loss of function	4.9% ¹²
BrS5	SCN1B	Na _v β	β subunit I_{Na}	Loss of function	-
BrS6	KCNE3	MiRP2	β subunit I_{Ks}/I_{to}	Gain of function	-
BrS7	SCN3B	Na _v β3	β subunit I_{Na}	Loss of function	-
BrS8	CACNA2D1	Ca _v α2δ1	α2δ subunit I_{Ca}	Loss of function	1.8% ¹²
BrS9*	MOG1	MOG1	Interacts with I_{Na}	Loss of function	-
BrS10*	KCND3	Kv4.3	α subunit I_{to}	Gain of function	-
BrS11*	KCNJ8	Kir6.1	α subunit I_{KATP}	Gain of function	-

I_{Na} depolarizing inward sodium current (fast); I_{Ca} depolarizing inward L-type calcium current (slow); I_{Ks} repolarizing outward slow rectifying potassium current; I_{to} transient outward potassium current; *putative subtypes.

unexplained syncope are at high risk and should receive an ICD.^{2,40} However the majority of sudden death victims have no recorded premorbid symptoms and in asymptomatic BrS patients the event rate appears to be lower than initially expected at 0.5% *per annum*.⁴¹⁻⁴⁴ Asymptomatic patients with spontaneous type 1 Brugada ECG pattern appear to be at higher risk although this has not been a consistent finding.^{2,45} Although electrophysiological testing (EPS) to induce sustained polymorphic VT or VF has been used to aid risk stratification, meta-analyses have failed to find an association between inducibility and risk.^{46,47} Programmed electrical stimulation in asymptomatic patients may however have useful negative predictive value although low event rates have made this hard to assess.^{41,46} A combined approach incorporating clinical features and EPS in patients with spontaneous and drug induced type 1 Brugada ECGs found major arrhythmic events occurred in 14% of subjects with positive EPS, no subjects with negative EPS and 5.3% of subjects without EPS.⁴⁸ Other markers for higher risk such as male gender and South East Asian ethnicity may assist in patient management.^{2,47} ECG markers for conduction delay such as late potentials on SAECG and QRS fragmentation are more frequently seen in symptomatic individuals but are not considered independent risk factors as yet.^{30,49}

While patients with multiple *SCN5A* mutations present at a younger age than those with a single mutation, positive genotype alone is not an independent risk factor for SCD.¹² One recent study has suggested earlier and more frequent recurrence of VF in symptomatic BrS patients with *SCN5A* mutations compared to those without.⁵⁰ The severity of the biophysical consequence in I_{Na} resulting from an *SCN5A* mutation does appear to influence phenotype and possibly risk, with an increased frequency of syncope and longer PR and QRS durations in patients with mutations leading to protein truncation compared to missense mutations.⁵¹ Common genetic variation may also play a role and alter ECG characteristics and clinical phenotype. A potentially protective polymorphism H558R that prevents the trafficking defect associated with BrS *SCN5A* mutations has been identified.⁵² The functional impact of mutations

and the presence of common variants acting as genetic modifiers may therefore support novel risk stratification strategies in the future.

A more accurate risk stratification of asymptomatic BrS patients is therefore vital, particularly as ICD implantation is not without complication. Currently, given the low event rate in BrS, the frequency of device related complications exceeds rates of appropriate shock therapy.⁵³ Inappropriate shock therapy for sinus tachycardia and atrial arrhythmia is common because patients tend to be young and physically active and *SCN5A* mutation carriers are prone to atrial arrhythmias. Long term endovascular lead placement in young patients is also associated with lead failure resulting in inappropriate shock therapy and requiring lead extraction. This may, however, be reduced in future by new leadless ICD technologies.⁵⁴

General management of BrS beyond ICD therapy involves the avoidance of drugs known to exacerbate the condition, principally by blocking inward sodium and/or calcium currents (see www.brugadadrugs.org), as well as use of paracetamol or ibuprofen to reduce fever. Isoproterenol is effective at suppressing VF in BrS patients who present with electrical storm.⁵⁵ Quinidine, a class Ia antiarrhythmic agent with Ito blocking effects, appears to suppress ventricular arrhythmias in patients with an ICD and recurrent appropriate shocks.⁵⁶ As yet there are insufficient prospective studies to consider quinidine a first-line treatment and a registry has been set up to address this.⁵⁷ Ablation of focal ventricular ectopy that acts as a trigger for VF has been used successfully to treat patients with recurrent arrhythmia.⁵⁸ Epicardial ablation of the RVOT has recently been shown to normalize the type 1 ECG pattern and prevent VT/VF recurrence in BrS.⁵⁵ An endocardial approach with regional substrate ablation of the RVOT also appears promising.⁵⁹ Catheter ablation may therefore prove to be an alternative strategy in patients with recurrent symptoms.

Overlap syndromes

BrS has been described in association with other arrhythmogenic phenotypes including

short QT syndrome, premature cardiac conduction disease (Lev-Lenegre's disease), long QT syndrome (LQTS) and sinus node disease (Table 3).⁶⁰⁻⁶³ While BrS with a short QT interval has been associated with calcium channel mutations as described above, *SCN5A* mutations appear to be responsible for the other spectrum of disease. Specific biophysical properties of the mutations appear to underlie these overlap syndromes, with diminished initial sodium channel opening and current density accounting for slowed conduction, sinus node dysfunction and the Brugada phenotype, and late channel re-activation with a late sodium current responsible for prolonged repolarization and the long QT syndrome phenotype. Identification of mutations capable of phenotypic overlap is clinically important. For example, sodium channel blockers have been identified as a potential management strategy in the LQT3 subtype of LQTS associated with *SCN5A* mutations. Class 1C drugs such as flecainide have been shown to reduce the QT interval experimentally in some LQTS3 patients but also frequently induce the BrS type ECG pattern in patients with overlap syndromes and in these individuals would therefore not be an appropriate therapeutic choice.⁶²

Overlap has also been suggested between BrS and early repolarization syndrome (ERS). Mutations in *CACNA1C*, *CACNB2* and *CACNA2D1* have been demonstrated in 16% of ERS and 12% of BrS probands respectively and an identical *KCNJ8* mutation was found in two patients, one with BrS and one with ERS.^{13,17} There are similarities between early repolarization and BrS, including male predominance, peak incidence of death in the fourth decade

Figure 4. Proposed mechanisms of the Brugada type 1 ECG pattern. Loss of the action potential dome at the right ventricular subepicardium but not the subendocardium causes ST segment elevation and relative action potential prolongation at adjacent sites causes the negative T wave (repolarization hypothesis). Late activation of the right ventricle epicardium causes ST segment elevation and delayed repolarization of the same myocardium causes the negative T wave (depolarization hypothesis). Modified from Hoogendijk et al.²³ with permission.

Table 3. Clinical syndromes associated with *SCN5A* mutations.

Inherited cardiac sodium channel disease

Brugada syndrome
Long QT syndrome
Premature cardiac conduction disease (Lev-Lenegre's disease)
Sinus node disease
Atrio-ventricular block
Familial atrial fibrillation
Sudden infant death syndrome
Dilated cardiomyopathy

and response to isoproterenol and quinidine. This has led to the suggestion that both form part of the same spectrum of disease, the *J wave syndromes*.⁶⁴ However important differences exist. Early repolarization changes are not provoked by sodium channel blocker administration and in ERS the SAEKG rarely demonstrates abnormal late potentials.⁶⁵ In addition BrS can be exacerbated by pyrexia while ERS has been reported to be exacerbated by hypothermia.⁶⁶

Conclusions

Our understanding of the Brugada syndrome has greatly improved over the last 20 years. Future directions will likely include development of *gene-specific* therapy to directly counteract functional consequences of mutations and improve management of affected individuals. Future research is likely to focus on the pathophysiology and genetics of the condition fueled by novel genomic, functional and sequencing technologies, as well as novel non-invasive and invasive tools for risk stratification. The goal will be to develop patient and gene specific therapies and to stratify risk in a way that will guide drug, ICD implantation and ablation strategies.

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