Introduction

The Brugada syndrome was first described in 1992, and constitutes a new and distinct clinical entity outlined by characteristic electrocardiograms (ECGs) and an associated high risk of sudden cardiac death (SCD). Since the initial description, there have been two consensus conferences to refine understanding about the syndrome, with a published report in 2002 outlining the diagnostic criteria and a subsequent report in 2005 addressing risk stratification guidelines and approaches to therapy. This review provides an overview of the molecular, genetic, epidemiological, and clinical aspects of Brugada syndrome as well as possible approaches to management.

Underlying mechanism

Brugada syndrome as described in 1992 was initially thought of as a channelopathy, an exclusively electrophysiological disorder produced by dysfunction of a cardiac ion channel involved in the generation of the action potential (AP) in a structurally normal heart. This notion has been challenged and is subject to debate, as the first report on Brugada syndrome patients by Corrado et al in 1996 had an underlying structural abnormality. Over time, more studies reported patients with the Brugada ECG patterns showing structural abnormalities of the right ventricle. This supports the theory that the pathophysiological mechanism of Brugada syndrome may be due to slowing of conduction in the RV, accompanied by mild structural abnormalities.

Currently, no single causal factor links all patients and thus, the pathophysiological mechanism remains elusive. Two hypotheses have been proposed—the depolarisation theory and the repolarisation theory. To explain the pathophysiology of the type-1 ECG pattern and susceptibility to ventricular arrhythmias (VAs), two hypotheses have been proposed. Brugada stated that there are a multitude of possible aetiologies that manifest as the phenotype of the Brugada syndrome ECG. To date, none of these proposed hypotheses have been irrefutably demonstrated.

Repolarisation (channelopathy) hypothesis

The repolarisation hypothesis was first proposed in 1999, and followed up by a decade of experimental studies. According to this hypothesis, rebalancing of currents at the end of phase 1 of the AP leads to accentuation of the AP notch in the epicardium of the RV. Such accentuation was believed responsible for the characteristic ST-segment elevation (Fig 1).

Under normal conditions there is a non-homogeneous expression of the transient outward potassium current (\(I_{to}\)) between the epicardium and endocardium, with the epicardium having an increased expression of \(I_{to}\) (Fig 1a). In the presence of pathophysiological conditions, such as a SCN5A mutation (leading to sodium channel loss-of-function), outward currents overwhelm inward currents, and the epicardium may then exhibit all-or-none repolarisation at the point where the phase-1 AP reaches...
布魯格達氏綜合症候群
自從1992年發現布魯格達氏綜合症候群開始，此病便與年青男性高風險的心臟性猝死有關。患者可出現如暈厥、心悸、中止心臟性猝死的症狀，又或者沒有任何症狀。布魯格達氏綜合症候群的三個代表性心電圖模式可以自發性地出現，或受到鈉離子通道阻斷劑的影響。風險分層和治療方法取決於病人症狀、心電圖、家族病史和電誘導性，來辨別唯一有效的治療（自動體外心臟去顫器）是否適當。本文重點討論布魯格達氏綜合症候群以及此病的不同層面，包括建議機制、流行病學、臨床表現、遺傳學、診斷、危險分層和治療方案。

-30 mV。groups The resulting loss of AP dome at some, but not all, epicardial sites could create marked epicardial dispersion of repolarisation (EDR) [Fig 1d]. This gives rise to a transmural dispersion of repolarisation (TDR) between the epicardium and endocardium which manifests as the characteristic ST-segment elevation of the ECG.5,7,12 In addition, the T-wave remains positive when epicardial repolarisation precedes that of myocardial and endocardial regions, resulting in the characteristic type-2 or saddleback ECG [Fig 1b].5 When sites in the epicardial region exhibit prolongation of the AP, reversed direction of repolarisation across the RV wall may ensue, producing the inverted T-wave and resulting in the type-3 coved-type ECG [Fig 1c].5

The repolarisation hypothesis could also explain the mechanism of VA initiation. When EDR and TDR occur via all-or-none repolarisation at some epicardial sites, an arrhythmogenic substrate is formed. This creates a vulnerable window when an AP can propagate from sites with normal repolarisation to sites with early repolarisation (Fig 1e). The conduction of an AP dome leads to local re-excitation via a phase 2 re-entry mechanism at sites of early excitation, and facilitates the development of extrasystolic beats from these sites.5,7,12 These extrasystolic beats have been shown to initiate circus movement re-entry7 and thus give rise to malignant VAs.7

Depolarisation (conduction delay and mild structural defects) hypothesis
This hypothesis for the Brugada ECG and susceptibility to VAs proposes a conduction delay in the right ventricular outflow tract (RVOT).8,9 Accordingly, the AP is not fundamentally altered; rather conduction delay in the RVOT slows AP development in the right ventricle. This pathophysiological mechanism was believed to result in the Brugada ECG pattern and provide an arrhythmogenic substrate via a re-entry circuit.

As described by Meregalli et al,8 during the initial phase of the cardiac cycle, the RV membrane potential is more positive than in the RVOT, driving
the intercellular current to the RVOT. The current then passes back from the RVOT to the RV possibly via the extracellular space. During this time, an ECG electrode situated over the RVOT inscribes a positive signal and thus yields the ST-elevation of the Brugada ECG. The membrane potentials are thus more positive in the RVOT than the RV and the potential gradient is reversed. The RVOT then drives the current in the opposite direction, away from the RVOT electrode, resulting in a negative T-wave. Further studies point towards a conduction delay as characteristic of the type-1 ECG. The re-entry circuit which leads to conduction slowing in the RV. Whether structural alterations in Brugada syndrome are primary or secondary is still unknown.

Most recently, a third unifying theory combining aspects of the depolarisation and repolarisation hypotheses has been proposed by Hoogendijk et al. However, Brugada suggested that it may be premature to search for a unifying pathophysiological mechanism for this syndrome.

Clinical presentation of Brugada syndrome
The clinical manifestations of Brugada syndrome are highly variable; some patients with the syndrome remain asymptomatic while for others endure sudden death. Nevertheless, when symptoms manifest, consistently they do so around the fourth decade of life. A time-dependent process of arrhythmogenic substrate generation has been suggested. This may entail development of the structural abnormalities.

Recently it was proposed that the embryological development of the RV can explain the electrophysiological heterogeneity in the ventricular myocardium including the RV outflow tract, which could provide the substrate necessary for arrhythmias. In support of the depolarisation hypothesis, Boukens et al found that heterogeneity in expression of connexins and voltage-gated ion channels as well as tissue architecture may contribute to conduction slowing in the RV. Whether structural alterations in Brugada syndrome are primary or secondary is still unknown.

Epidemiology
As the diagnosis of Brugada syndrome relies upon identifying a characteristic ECG pattern, there are inherent difficulties in determining its prevalence. Current prevalence estimates of 5/10 000 may underestimate the true prevalence, as many patients present with silent or concealed forms of the disease, without an available characteristic ECG. Brugada syndrome has been estimated to account for 20% of SCDs in the absence of structural heart disease and may be responsible for between 4% and 12% of all patients with SCD.

The prevalence of Brugada syndrome also varies greatly according to location, being higher in East and South-East Asian populations. A Japanese study reported the prevalence of a type-1 ECG pattern to be 12/10 000. Sudden unexplained nocturnal death syndrome, long identified as endemic to South-East Asian countries, has also been attributed to the Brugada syndrome. Recently, a study of a hospital-based population in Singapore indicated that in those presenting with pre-syncope, syncope and/or palpitations, the prevalence of Brugada syndrome was about 3.1%. In North America and western Europe, the prevalence of the syndrome is relatively lower; one estimate in the US gave a figure of 12/100 000.
also be a significant seasonal peak (spring to early summer).

Gender differences
The Brugada syndrome phenotype is more prevalent in men than in women,12,21,22,26 with the estimated ratio being up to 8-10:1.2 Increased manifestations in men has been explained by the presence of significantly higher density of $I_{Na}$ currents in males versus females (in canines at least).31 According to the repolarisation theory, this increases susceptibility to VAs as a more prominent $I_{Na}$ in RV epicardium facilitates a loss of the AP dome. A second hypothesis proposes a hormonal effect, with clinical studies suggesting that testosterone may be responsible for gender differences,42 while experimental studies suggest a hormonal influence on ion currents.43

Children
There is little information on Brugada syndrome in the paediatric population,29 despite the fact that three of the eight affected patients in the initial description of this syndrome were children.3 Isolated case descriptions exist,44,45 but large-scale studies are lacking. Benito et al28 surmise that Brugada syndrome may ensue/manifest in the paediatric age-group as follows:
(1) febrile episodes that frequently trigger for arrhythmias;
(2) symptoms, especially those with a spontaneous type I ECG that have a high risk of VAs; and
(3) having an implantable cardioverter defibrillator (ICD) implantation, benefits having been shown in those with a poor prognosis, though quinidine treatment may be an alternative.

In the paediatric population, Probst et al46 failed to identify a male predominance, perhaps due to low levels of testosterone in children of both sexes.

Genetics
Brugada syndrome is inherited via autosomal dominant transmission.2 In 1998, Chen et al26 identified the first associated mutations in the SCN5A gene (locus 3p21), which encodes for the $\alpha$-subunit of the cardiac sodium channel. In recent years, hundreds of mutations in the SCN5A gene have been linked to the syndrome (http://www.fsm.it/cardmoc/). The overall electrophysiological effect31,43,46 is a reduction of transmembrane sodium current by various mechanisms, including a reduction in current density and gating changes.39 Mutations in the SCN5A gene are currently only found in approximately 18 to 30% of Brugada cases,2 with a high frequency of mutations in familial rather than sporadic cases,31 which suggests genetic heterogeneity.31

A second locus on chromosome 3, distinct from SCN5A, has been linked to Brugada syndrome, and identified as the GPD1-L (glycerol-3-phosphate dehydrogenase 1-like) gene. A mutation in the GPD1-L gene results in a reduced inward sodium current.52 More recently, loss-of-function mutations in genes that encode the cardiac L-type calcium channel have been associated with the Brugada syndrome phenotype.53 It has also been suggested that the gain-of-function caused by a mutation in the KCNE3 gene (involved with the $\beta$-subunit of the transient outward potassium current) predisposes affected individuals to develop the Brugada syndrome phenotype.54 Molecular and functional evidence reported in 2011 suggests that a KCND3 gain-of-function mutation leads to enhanced transient outward current, particularly in the RV (where KCND3 expression is highest).55 This latest report provides a basis for the associated pathogenic substrate and phenotypic expression of Brugada syndrome.

Electrocardiographic and clinical diagnostic criteria
The current consensus on the diagnosis of Brugada syndrome relies on both clinical findings and characteristic ECG patterns that occur spontaneously or are induced by the use of a sodium-channel blocking agent. To date, there are three known ECG subtypes (type-1, type-2, and type-3) that can be detected in more than one of the right precordial leads (V1-V3), and have varying diagnostic value (Fig 2).

The type-1 ECG pattern is diagnostic of Brugada syndrome and is characterised by a coved-shape ST-segment elevation greater than 2 mm (0.2 mV) followed by an inverted T wave in one or more of the right precordial leads (V1-V3), and having a saddleback, with an ST-segment elevation of at least 1 mm (0.1 mV) and then either a positive or negative ST-segment elevation greater than 2 mm (0.2 mV), a trough of the ST-segment elevation of at least 1 mm (0.1 mV) and then either a positive or negative T wave (Fig 2b).

In the type-2 pattern, the ST-segment resembles a saddleback, with an ST-segment elevation of at least 2 mm (0.2 mV), a trough of the ST-segment elevation of at least 1 mm (0.1 mV) and then either a positive or biphasic T wave (Fig 2b).

The type-3 pattern consists of either a coved (type-1 like) or saddleback (type-2 like) ST-segment elevation between 1 and 2 mm (0.1-0.2 mV) [Fig 2c]. Both type-2 and type-3 ECG findings occur spontaneously, without the use of a sodium-channel blocking agent, but by themselves they are not considered diagnostic. If, however, either the type-2
or type-3 ECG pattern converts to a type-1 ECG pattern after provocation by a sodium channel-blocking agents, and at least one of the aforementioned characteristic clinical findings is present, a diagnosis of Brugada syndrome can be considered.

A high degree of suspicion is warranted if only clinical findings are present. Given the expected variability in ECG recordings in patients with Brugada syndrome, serial recordings are recommended. An individual patient can show either type-1, type-2, or type-3 ECG patterns or even no pathological ECGs.37

**Diagnostic (electrocardiogram unmasking) agents**

The diagnostic type-1 ECG pattern can occur spontaneously or through administration of sodium channel-blocking or Class I anti-arrhythmic agents (Table39). Other pharmacological agents which may induce Brugada-like ECG patterns include calcium channel blockers, beta-blockers, anti-anginal drugs, psychotropic drugs (tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors, and phenothiazine) as well as dimenhydrinate, cocaine, bupivacaine, and alcohol.2,58

**Risk stratification**

Risk stratification of Brugada syndrome is aimed at identifying individuals most liable to SCD, so that they can receive appropriate management (Fig 32,29). Individuals with a diagnosis of Brugada syndrome based on a spontaneous or induced type-1 ECG pattern may present with or without symptoms. Symptomatic presentations include aborted SCD, syncope, seizure, and nocturnal agonal respiration. Asymptomatic individuals should be assessed for relevant family history, especially instances of unexplained SCD.

The International Registry of Brugada syndrome reported that 25% (178/724) of this population experienced SCD or VF during their lifetime, at a mean age of 42 (standard deviation, 15) years.29 Recently, in a larger series of patients, the aborted SCD frequency was estimated to be 7.7%; 1.9% in patients with syncope only, and 0.5% in entirely asymptomatic patients.39 Other factors denoting increased risk of an adverse cardiac event include aborted SCD, syncope, spontaneous or unmasked type-1 ECG patterns, family history of SCD, and inducibility of VT or VF during an electrophysiological study (EPS).

Among patients presenting with aborted SCD, the risk of its recurrence or VF was 62% (44/71) with a mean follow-up time of 54 months.24 This cohort is at highest risk for future cardiac events, regardless of other risk factors. These patients have the most compelling indication for treatment with an ICD, the only treatment option demonstrated to be effective to date.24

Even if there is no history of cardiac arrest, Brugada syndrome is reported to carry an 8.2% (45/547) risk of SCD or VF over 24 months.25 These individuals experience a type-1 ECG pattern spontaneously or after provocation by a sodium channel-blocking agent. Subjects with spontaneous type-1 ECGs may present with a 7.7-fold greater risk of developing an arrhythmic event during their lifetime compared with those with non-spontaneously occurring type-1 ECGs.2

In patients with Brugada syndrome, inducibility of VAs by electrophysiological means is a predictor of poorer prognostic outcome. Patients with EPS-inducible VAs reportedly have a hazard ratio of 8.3 (95% confidence interval [CI], 2.8-25.0) for aborted SCD when compared to patients with no inducible VAs.40 In asymptomatic patients, 63% (11/167) developed aborted sudden death, the strongest predictor of VF being inducible arrhythmia following programmed ventricular stimulation (P<0.008).40 Therefore EPS seems to be a useful prognostic tool to complement the risk stratification in patients with no history of aborted SCD. Inducible VT or VF by EPS warrants ICD treatment even for asymptomatic
patients if they show a spontaneous type-1 ECG or have a family history of sudden death. All other patients warrant close follow-up. However, some have questioned whether inducibility on EPS is associated with increased risk of adverse cardiac events. A meta-analysis that included 1500 patients concluded that an inducible EPS carried a relative risk of only 1.88 (95% CI, 0.62-5.73, P=0.27). Priori et al also failed to find a relationship between recurrences of VAs and EPS inducibility or non-inducibility.

In one of the largest series of Brugada syndrome patients to date (n=1029), it was shown that predictors of arrhythmic events were spontaneous type-1 ECGs and symptoms. Apparently a familial history of SCD, male gender, presence of an SCN5A mutation, and inducibility of VAs during EPS were not predictive. Other studies, however, have found that male gender per se carries a poorer prognosis for adverse cardiac events (hazard ratio=5.3; 95% CI, 1.6-16.6). In asymptomatic patients with a spontaneous type-1 ECG pattern and EPS inducibility, there is currently no evidence.

In contrast to the recommendations of the Second Consensus on Brugada syndrome the ACC/AHA/HRS 2008 Practice Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities, the following differences in the levels of evidence for ICD implantation in patients with Brugada syndrome are shown:

- For cardiac syncope, the level is Class IIa;
- For documented VT not resulting in cardiac arrest, the level is Class Ila;
- In asymptomatic patients with a spontaneous type-1 ECG pattern and EPS inducibility, there is currently no evidence.

**FIG 3. Risk stratification and treatment of the Brugada system**

SCD denotes sudden cardiac death, ECG electrocardiogram, Na sodium, EPS electrophysiological study, VT/VF ventricular tachycardia/fibrillation, and ICD implantable cardioverter defibrillator

* EPS study is still controversial

**Treatment**

To date treatment options for Brugada syndrome have been limited to device-related and pharmacological therapies. However, education and prevention of arrhythmias via lifestyle awareness should also be considered in line with broader recommendations for other cardiac conditions about which more is known.

Management of acute malignant arrhythmias or electrical storms includes early defibrillation and resuscitation of the patient, followed by admission to a specialised cardiac care facility. Any provocative circumstances such as fever should be treated with antipyretics and/or cooling. Any
intake of arrhythmogenic drugs/substances should be discontinued. Pharmacological treatment with isoprenaline (1-2 µg bolus intravenously followed by continuous infusion of 0.15-2.0 µg/min) and/or quinidine (300-1500 mg/day) has been used for electrical storms. In children, dosing is often tailored to bodyweight. The suggested quinidine dosage for children is 30 to 60 mg/kg/day given in four divided doses.\(^4\)\(^6\)\(^{15}\)\(^{44}\)

**Device treatment**

For Brugada syndrome, the most recent Consensus Report\(^2\) regards ICDs as the only established form of effective treatment. Best practice entails ICD implantation according to the aforementioned risk stratification outline. In summary, an ICD should be offered to all symptomatic patients presenting with Brugada syndrome. All asymptomatic patients should undergo further risk stratification to assess their indication for an ICD.

In symptomatic patients treated with an ICD, the average annual shock rate was reported to be 2.6\% and for asymptomatic patients it was 1.5\%.\(^6\)^\(^5\) Thus far, data on cryosurgical ablation in Brugada syndrome have been limited.\(^6\)

**Complications of implantable cardioverter defibrillator**

Although ICDs are very effective in treating VF and the implantation procedure is usually very safe, there may be surgical complications. These include bleeding, pneumothorax, perforation of vascular structures, cardiac tamponade, and infections. Post-implantation issues include displacement or fracture of leads, false shocks (eg inappropriately shocking a patient with fast AF or exercise-related sinus tachycardia), and the need to replace the device because of battery depletion.

**Role of drugs as long-term treatment**

Relatively small case series describe the use of drugs as potentially beneficial in Brugada syndrome patients, though none of these agents are proven to completely prevent arrhythmias. Moreover, some of these drugs have not been tested to an appreciable extent in Brugada syndrome patients; others may have unacceptable side-effects. In the absence of provoking drugs, only severely symptomatic or high-risk patients may be candidates for long-term pharmacological treatment, preferably in a medical centre with suitable expertise and experience. Currently, quinidine seems to be the treatment of choice for such therapy.\(^6\)\(^6\)

Pharmacological therapies are directed at rebalancing the ion channel currents. These are active for the duration of phase 1 of the epicardial AP in the RV, and thereby minimise the magnitude of the notch, and restore the normal dome of the AP or both.\(^2\)\(^9\)

Irrespective of the ion channel involved, a prominent \(I_{\text{to}}\) (transient outward potassium current) seems to play a predominant role in arrhythmogenesis. Consequently, blocking the \(I_{\text{to}}\) channel is a logical approach and this can be done with quinidine.\(^6\) Quinidine, a class Ia anti-arrhythmic, is the most studied pharmacological treatment in Brugada syndrome. Its mechanism of action relies on its \(I_{\text{to}}\) blocking properties.\(^2\) More specifically, Benito et al\(^6\)\(^6\) state that quinidine is effective in the suppression of phase-2 re-entry in experimental models, and has demonstrable clinical efficacy (decreasing inducible VF and spontaneous VF during follow-up). It is also used as adjunctive therapy with ICD implants to control electrical storms and as a viable treatment option in children.\(^6\) Clinical evidence also demonstrates that it can normalise ST-segment elevation in patients with Brugada syndrome.\(^6\)^\(^9\)

Belhassen et al\(^6\)\(^6\) claimed to have used quinidine effectively as the sole therapy (without ICD back-up) for patients with symptomatic Brugada syndrome, including those with prior spontaneous VF. In a recent study, none of the 50 patients with symptomatic or asymptomatic Brugada syndrome developed symptomatic VAs while on quinidine therapy during follow-up periods ranging from 3 months to more than 10 years.\(^6\)^\(^6\) However, quinidine often causes side-effects (diarrhoea, thrombocytopenia, hepatitis) that resolve after drug discontinuation. The main concern relates to the potential pro-arrhythmic activity of quinidine, there being an estimated 2 to 8\% risk for torsades de pointes in treated patients. Most instances of quinidine-induced torsades de pointes occur soon after initiation of therapy, which therefore warrants close monitoring during the first few days of therapy. Torsades de pointes ensuing long after the onset of therapy is often caused by drug interactions or hypokalaemia,\(^6\)^\(^9\) for which meticulous avoidance of risk factors may reduce the likelihood.

In view of the limited evidence base for the use of pharmacotherapies such as quinidine, the mainstay of treatment continues to be ICD implantation. Quinidine therapy may be an alternative in those who are ineligible or persons refusing such an intervention.

**Miscellaneous**

It is recommended that patients diagnosed with Brugada syndrome are counselled, such that they and their relatives are informed. Patient education should include advice on avoidance of provoking agents, as well as cardiopulmonary resuscitation training for family members.
References


