VILNIUS UNIVERSITY
MEDICAL FACULTY

The Final thesis

Brugada syndrome

Noah-Jonas Leon Lohmüller, VI year, 3 group

Institute of Clinical Medicine, Clinic of Cardiac and Vascular Diseases

Supervisor Prof. Germanas Marinskis

The Head of Department/Clinic Prof. Sigita Glaveckaitė

2023

Email of the student: noah-jonas.lohmueller@mf.stud.vu.lt

Table of Contents

List of abbreviations

AP	Action potential
BrP	Brugada Phenocopy
BrS	Brugada syndrome
ECG	Electrocardiogram
EPS	Electrophysiological study
ICD	Implantable cardioverter defibrillator
LQT3	Long QT syndrome 3
RFA	Radiofrequency ablation
RV	Right ventricle
RVOT	Right ventricular outflow tract
SDC	Sudden cardiac death
SUNDS	Sudden unexplained nocturnal death syndrome
VAs	Ventricular arrhythmias
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Keywords

Brugada syndrome, SCN5A gene, right ventricular outflow tract, ventricular tachycardia, ST-segment elevation, sudden cardiac death.

Overview

In 1992, the Brugada brothers, Pedro and Josep, made a groundbreaking discovery by describing a previously unknown clinical condition that exhibited distinctive features such as right bundle branch block, persistent ST-segment elevation and sudden cardiac death in eight patients. This condition, later named as "Brugada syndrome," gained international recognition in the subsequent years (1).
Brugada syndrome (BrS) is a rare inherited condition causing ventricular fibrillation (VF) and increasing the risk of sudden cardiac death (SCD), especially in young to middle-aged men and is more commonly diagnosed in individuals of Asian descent (2).

The estimated prevalence is 1–5 in 10.000, men are more commonly affected than women and typically display a more pronounced phenotype (3,4). Patients can present with a range of symptoms such as palpitations or dizziness to recurrent syncope, nocturnal agonal breathing and a (survived) sudden cardiac death as the most severe manifestation (5). However, many patients are asymptomatic at the time of diagnosis and throughout the course of the disease (6). The typical age of onset is between the third and fifth decade of life, although the disease can occur at any age (7).

Ventricular fibrillation in BrS is known to typically occur during nighttime or resting phases, and can be triggered by monomorphic ventricular extrasystoles originating from the right ventricular outflow tract (8). Additionally, supraventricular arrhythmias, particularly atrial fibrillation, are found in a significant number of BrS patients. It is important to note that fever and certain medications are among the known triggers for the occurrence of cardiac arrhythmias in BrS and should be promptly addressed to reduce the risk of sudden cardiac death (8). Proper management and early detection of BrS is crucial to prevent potentially fatal outcomes (9).
The condition is characterized by changes in the electrocardiogram (ECG), including coved ST-segment elevation and a negative T-wave in the right precordial leads. These characteristic changes are commonly referred to as ECG Type 1, while it is important to note that there are also two other types present in Brugada syndrome.

Intermittent alterations in the electrocardiogram (ECG) may arise in response to fever or when exposed to sodium channel blockers during provocation testing.
Although the majority of cases of Brugada syndrome are not attributed to a single causative gene variant, it is widely accepted that the SCN5A gene plays a prominent role as the main responsible gene for this condition (9).
At present, the management of Brugada syndrome involves taking conservative measures in asymptomatic patients, such as avoiding drugs that can trigger arrhythmias and managing fever promptly. In contrast, symptomatic patients usually receive implantable cardioverter defibrillators (ICDs) and those with recurrent arrhythmia may benefit from treatment with quinidine or epicardial ablation (9).
This thesis aims to review the contemporary understanding of BrS and practical approach to diagnosing and managing the condition.

Epidemiology

In Western countries the prevalence is much less, whereas in Southeast Asia, especially in Thailand and the Philippines, BrS is one of the most common causes of death among young and appears to be associated with the sudden unexplained nocturnal death syndrome (SUNDS), which has been common among the population in Asia for years and is referred to differently among the indigenous population (5). In 2002, Vatta et al. demonstrated that SUNDS and BrS share similarities in terms of phenotype, genetics and functionality (10).

Consequently, the prevalence in Asian countries, where the syndrome is considerate as endemic is much higher, at 12–58 in 10.000 inhabitants in a study performed in Japan, than in Europe or the United States of America. In more detail, the prevalence for the ECG type 1 had been 12 in 10.000 inhabitants, while the ECG type 2 and 3 which are not considerate as a diagnostical sign of the BrS had been much more prevalent with 58 in 10.000 inhabitants (2). Especially in endemic areas, BrS is a significant cause of death in young people who die unexpectedly during sleep and it is also associated with car accidents, despite the absence of detected structural cardiac diseases (11).

A 2018 meta-analysis revealed that the worldwide prevalence of BrS is 0.5 per 1,000. In more detail, southeast Asians have the highest prevalence rate (3.7 per 1,000), while North

Africans have the lowest (0 per 1,000). The meta-analysis concluded, that the prevalence of BrS in Asians is nine times higher than in Caucasians and 36 times more common than in Hispanics. As such, BrS remains a significant health concern, particularly in Asia (12).

However, the actual prevalence of BrS in the population is difficult to estimate, as diagnosis is hampered by the often-hidden ECG changes in asymptomatic patients (5). Men are primarily affected and present much more often symptomatic compared to females, in more detail the clinical phenotype is eight to ten times more prevalent in males than in females (13). Individual studies suggest that the gender-specific differences in the prevalence of BrS are related to the level of testosterone in the blood (14).

Patients with BrS usually present asymptomatic, in most patients the disease does not manifest until adulthood. The mean age of symptomatic occurrence is around the third and fourth decade of life, more precisely 41 ± 15 years, but the age of manifestation varies from one to 84 years of life (5).

Patients with BrS are notable for syncope with a tendency to ventricular tachyarrhythmias and are otherwise structurally heart healthy. In 80% of patients, self-terminating polymorphic ventricular tachycardia or self-terminating episodes of ventricular fibrillation led to recurrent syncope, which often precedes sudden cardiac death (15).
The symptomatic expression seems to be just as variable as the ECG changes, ranging from asymptomatic patients to recurrent syncope to (survived) sudden cardiac death. This suggests that various modulating factors influence the symptomatology.

Sudden cardiac death and arrythmias usually occurs at night, during sleep or in the early morning hours (11), most frequently from 12AM to 6AM and less frequently in the evening and at least during daytime (5). This suggests a circadian dependency and can most likely be explained by the increased vagal tonus at this time. Thus, the sympatho-vagal balance seems to play an important role in the nocturnal arrhythmogenesis of the BrS (16).
In addition, it has been shown that spontaneous ST-segment changes are often observed in BrS patients after the ingestion of sufficiently large meals, which are known to increase vagal activity. This type of increase in vagal tone can therefore also act as a trigger for severe arrhythmogenic events (17). Consistent with this, is the observation of Thai Ministry of

Public Health that increased numbers of people after ingesting large portion glutinous rice ("sticky rice") died of SUNDS during the night (18).

In addition to increased vagal tone hypokalemic conditions and increased body temperature can also trigger arrhythmogenic events. For example, potassium deficiency is endemic in some areas of Thailand and had been associated with a higher prevalence of SUNDS (19). Several studies and case reports showed that, Brugada-like ECG changes and symptoms such as syncope or episodes of ventricular tachycardia occurred under elevated body temperature and disappeared again when the temperature returned to normal. This can be explained by a reduced ionic current via the cardiac sodium channel at higher temperatures. A study performed by Adler et al. in 2013, showed that type 1 ECG pattern of the BrS had been 20 times more common in the febrile group compared to the afebrile group (20).

Apparently, the syndrome is associated with increased prevalence of supraventricular arrhythmias: it has been described, that about 20% of patients with BrS develop supraventricular arrhythmias (21). Atrial fibrillation (AFib), atrioventricular (AV) reentry tachycardia and Wolf-Parkinson White syndrome have been reported, as well prolonged sinus node recovery times, prolonged sinoatrial conduction times and atrial arrest are as well associated with BrS (22).

Genetics

Brugada Syndrome has been linked to changes in 22 different genes so far, the first and as well the most common/relevant gene for which a connection with BrS could be proven is the SCN5A gene (on chromosome 3p21), which codes for α-subunit of the cardiac sodium channel $Na_v1.5$ (voltage-gated channel) (23, 24).
Loss-of-function variants in the SCNA5 gene result subsequently in shortening of the action potential duration via the following assumed ways: first, due to an expression defect of the sodium channel, so that it is present in low numbers or second, by a kinetic dysfunction of the ion channel, due to change in time and voltage dependent activation, inactivation or reactivation of I_{Na} or temporary inactivation state of the channel with prolonged recovery phase or accelerated inactivation of the channel (5). The end result is a decrease in the maximum current carried by the sodium ion [I_{Na}], leading to a slower rise of the initial phase

(phase 0) of the action potential. (15) However, mutations in the SCN5A are only detected in 20-30% of cases and are currently the only one considered as disease causing (25).
According to a survey that investigated arrhythmic events in 678 Brugada syndrome (BrS) patients, the prevalence of the SCN5A mutation was found to be higher among individuals of white ethnicity than among Asians (40.1% vs. 13.2%) as shown in Figure 1 (12).

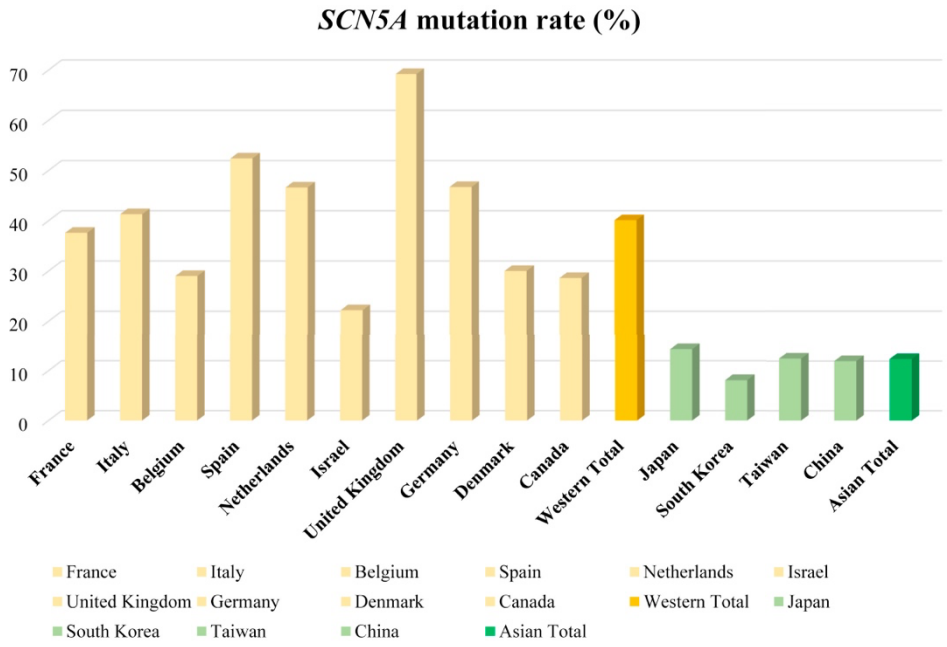

Figure 1. Mean SCN5A mutation rates in Western and Asian countries (SABRUS).
Reproduced from: (12)

Mutations in the SCN5A gene are as well often associated with other arrhythmias e.g. the long QT-syndrome type 3 (LQT3) in which a gain of function mutation leads to the corresponding phenotype. Interestingly, sometimes the same mutations in the SCN5A gene can lead to either a loss-of-function Brugada phenotype or gain-of-function LQT3 phenotype in different individuals (27).
Other genes, that are associated with the Brugada syndrome are typically rare in occurrence and found in individual cases or specific BrS-families. A full comprehensive list of genes associated with BrS can be found in Table 1 (12). These mutations generally lead to either a reduced depolarizing current (I_{Na} or $I_{Ca,L}$) or an increased repolarizing current (I_{to} and "ATP-sensitive potassium current" [$I_{K\text{-}ATP}$]) (12).

Table 1: Genes associated with BrS

Name	Gene	Protein	Prevalence
BrS1	*SCN5A*	α-Subunit Nav1.5 sodium channel	20%-25%
BrS2	*GPD1L*	Glycerol-3-phosphate dehydrogenase 1-like	Rare
BrS3	*CACNA1C*	α-Subunit α1C Cav1.2 calcium channel	1%-2%
BrS4	*CACNB2B*	β-Subunit Cavβ2b calcium channel	1%-2%
BrS5	*SCN1b*	β-Subunit Navβ1 sodium channel	Rare
BrS6	*KCNE3*	β-Subunit MiRP2 potassium channel	Rare
BrS7	*SCN3b*	β-Subunit Navβ3 sodium channel	Rare
BrS8	*HCN4*	Hyperpolarization-activated cyclic nucleotide-gated channel 4	Rare
BrS9	*KCND3*	α-Subunit KV4.3 potassium channel	Rare
BrS10	*KCNJ8*	α-Subunit KIR6.1 potassium channel	Rare
BrS11	*CACNA2D1*	δ-Subunit Cavα2δ1 calcium channel	Rare
BrS12	*KCNE5*	β-Subunit potassium channel	Rare
BrS13	*RANGRF*	RAN guanine nucleotide release factor	Rare
BrS14	*KCND2*	α-Subunit KV4.2 potassium channel	Rare
BrS15	*TRPM4*	Calcium-activated nonselective ion channel	Rare
BrS16	*SCN2B*	β-subunit Navβ2 sodium channel	Rare
BrS17	*PKP2*	Plakophilin 2	Rare
BrS18	*ABCC9*	ATP-sensitive potassium channels	Rare
BrS19	*SLMAP*	Sarcolemma-associated protein	Rare
BrS20	*KCNH2*	α-Subunit of HERG potassium channel	Rare
BrS21	*SCN10A*	α-Subunit Nav1.8 sodium channel	1%-16%
BrS22	*FGF12*	Fibroblast growth factor 12	Rare
BrS23	*SEMA3A*	Semaphorin family protein	Rare

Source: (12)

Despite the existence of a few other susceptibility genes that have been identified, their occurrence is relatively rare and their association with the BrS phenotype is currently limited (12, 15).

A second gene locus, not linked to SCN5A, was found on chromosome 3p22-p24. The corresponding gene, identified as the glycerol-3-phosphate dehydrogenase 1-like (GPD-1L), influences the intracellular transport of the newly synthesized cardiac sodium channel to the cell surface and thus reduces the sodium current by ~ 50% via a reduced channel density and results as well in reduced expression of the SCN5A (28).

In other, although rare cases, mutations in the SCN1B gene, coding for the ß1-subunit of the cardiac sodium channel, could be found. Mutations in the ß3-subunit of the cardiac sodium channel (SCN3B) were found as well in the association with a Brugada ECG phenotype (15).

In 2007, Antzelevitch et al. showed interestingly, that not only mutations leading to loss of function in the sodium channel (either through SCN5A or GPD-1L) but as well loss of function mutations in the genes for the cardiac L-type calcium channel can also lead to the phenotype of Brugada syndrome. In more detail, the CACNA1C and CACNB2 encode the α1 and β2b subunits of the cardiac L-type calcium channel. However, patients with these mutations also showed a shortened QT-time, so Antzelevitch assumed a new clinical entity with combined Brugada and short QT syndrome (18).

Most recently, Burashnikov et al. identified another mutation in the cardiac L-type calcium channel in patients with Brugada syndrome: CACNA2D1 encodes the alpha-2/delta-1 subunit of the calcium channel. Functional impairments in the calcium channel result in reduced calcium inward current into myocardial cell. The comparatively slow calcium inward current after the rapid depolarization by the sodium inward current into the cell is responsible for the maintenance, the so-called plateau phase of the action potential in the myocardium. Due to the plateau phase, the absolute refractory period of the heart muscle cell is continuing until the end of the contraction, thus this means that the heart muscle cannot be tetanized. Therefore, patients with a mutation of the calcium channel may have a shorter myocardial action potential, which also reflected in a shortened QT time (29).
In other rare cases, mutations in the KCNE3 gene, coding for the ß-subunit of the cardiac potassium channel had been identified as well (30).

Pathophysiological mechanisms underlying the Brugada syndrome

In order to understand the underlying pathophysiology of the syndrome more precisely, it is important to recall the physiological phases of excitation of the working myocardial cell, which finally results in the formation of the action potential (AP).
The process of generating an action potential is divided into five distinct phases, each of which is characterized by the predominance of a specific, directional ionic current.
Time and potential dependent changes in membrane permeability for Na^+, Ca^{2+} and K^+ are responsible for the generation of an action potential.
The first phase, the rapid depolarization occurs through the opening and subsequent inactivation of myocardial sodium channel. This leads to an avalanche-like influx of sodium into the interior of the cell, driven by the high electrochemical potential gradient for sodium.
The phase of rapid depolarization is followed by the plateau phase, in which there is an increase in membrane conductivity for calcium and thus a slow, depolarizing Ca^{2+} influx into the muscle fibers, as well the beginning of an outward K^+ current.
During this phase, the inward electrical driving force for calcium ions is balanced by the outward force for potassium ions, which helps to maintain the plateau phase.
After the plateau phase, there is a rapid repolarization phase, in which the membrane permeability to potassium increases rapidly, leading to a K^+ outflow from the myocardial cell.
This is followed by a final phase of slow repolarization, during which the inward electrical driving force for K^+ ions is smaller than the outward one, which results in a continued K^+ outflow from the cell (31).

Since the discovery of Brugada syndrome, several experimental findings supporting both supposed underlying pathophysiological mechanism, which are referred to the repolarization and depolarization hypotheses and have led to considerable controversy about the exact mechanism underlying the pathophysiology of Brugada syndrome (32).
In 1999, Yan and Antzelevitch first described in their research work “cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-Segment elevation “the concept of transmural repolarization variation as the cause of ST-segment elevation in the right precordial leads (33).
The repolarization hypothesis postulates a disturbed balance between depolarizing inward currents ("sodium current" [I_{Na}] and "L-type calcium current" [$I_{Ca,L}$]) and the prominent

transient outward potassium current [I_{to}] during early repolarization in the epicardial right ventricular outflow tract (RVOT) (8).

For the pathophysiological understanding of the involved mechanism in the development of the transmural variation or dispersion, the potassium channel plays an essential role, due to a fundamental difference in in transient outward current (I_{to}), which is mostly strongly expressed in the right ventricular epicardium, but comparatively very low in endocardial. This creates a transmural voltage gradient, as some cells in the epicardium are still depolarized while other areas are already repolarized. The voltage gradient is manifested in the ECG as ST-segment elevation/J-point elevation in leads V1-V3 (32).

In combination with a reduction in depolarizing current, in conditions such as SCN5A or GPD-1L mutations (leading to loss of the physiological function of the sodium channel), the before mentioned transmural gradient can be further increased. Since the Na^+ channel is an antagonist of the I_{to} channel, in Brugada syndrome the transmural gradient between the endocardium and epicardium and corresponding ECG changes occurs with increasing functional impairment of the Na^+ channel. This finally results in loss of action potential dome in RVOT (32).

If the epicardial repolarization phase is terminated before the endocardial repolarization, the T-wave remains positive and a saddle-shaped ECG result. Additional loss of Na^+ channel function, such as that caused by Na^+ channel blockers, can lead to amplification of this transmural gradient and ultimately to prolongation of the epicardial repolarization phase. (33). The endocardial repolarization then ends before the epicardial repolarization phase and the T wave becomes negative, the ECG then shows the coved shaped Brugada type I ECG (32).

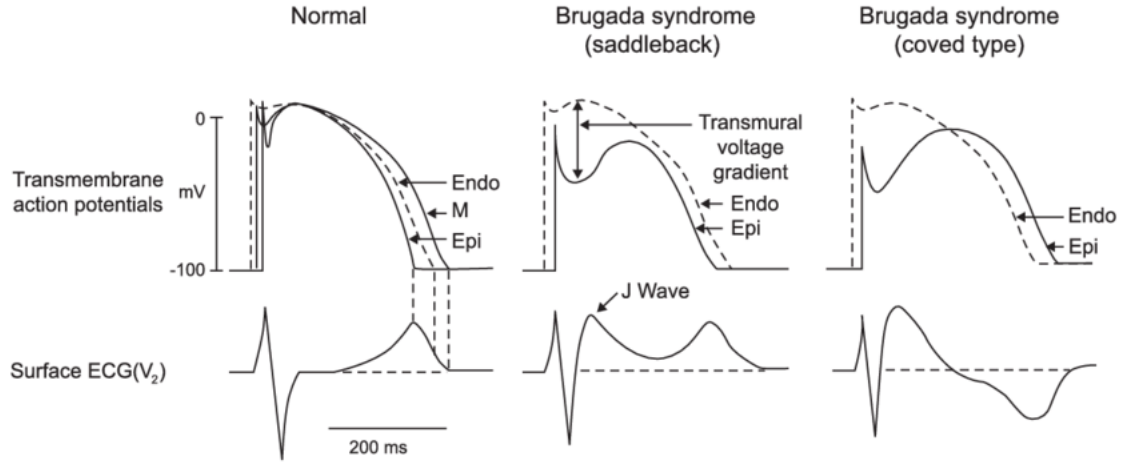

Figure 2. Schematic representation of the changes in the action potential in the right ventricular endocardium. Reproduced from: (56)

The repolarization hypothesis could also be an explanation for the mechanism of ventricular arrhythmia initiation, as the different duration of repolarization in adjacent myocardial cells that follows hereby provides a vulnerable window for reentry tachycardia (32). This finally results to local re-excitation through a phase 2 re-entry mechanism, which in turn promotes the generation of extrasystoles from these sites. Studies have demonstrated that these extrasystolic beats can trigger circus motion re-entry, ultimately leading to the emergence of malignant ventricular arrhythmias (34).

The depolarization hypothesis on the other hand proposes a conduction delay, especially in the right ventricular outflow tract. In more detail, according to this theory the AP is not fundamentally changed but delayed in respect to the AP of the right ventricle, due to to reduced I_{Na} and conduction discontinuity. It has been suggested that this pathological mechanism gives rise to the characteristic ST-segment elevation, due to the before mentioned conduction delay in the RVOT. According to this theory, ventricular arrythmias are a consequence of the abnormal current created by delayed depolarization of the RVOT (32, 35).
Findings from electrophysiological investigations, predominantly with the use of mapping of the endocardium and epicardium but as well treatment options like ablation, which will be discussed later in detail, favor the depolarization theory over the repolarization theory due to the evidence of slow conduction of the electrical impulse at the regions of the RVOT.
A very interesting study performed by Nademanee et al. showed that ablation of abnormal epicardial sites in patients with BrS resulted in significantly reduced occurrence of arrythmias and normalization of the BrS ECG pattern, thus contributes and supports the theory of depolarization (36).

Diagnostics

Diagnosis of the Brugada syndrome involves a combination of clinical evaluation, electrocardiogram interpretation, provocation testing and genetic testing. The ECG is the cornerstone of the diagnosis of Brugada syndrome. The ECG findings in Brugada syndrome are dynamic and may not be present at all times. Therefore, multiple ECGs may be necessary for the diagnosis.

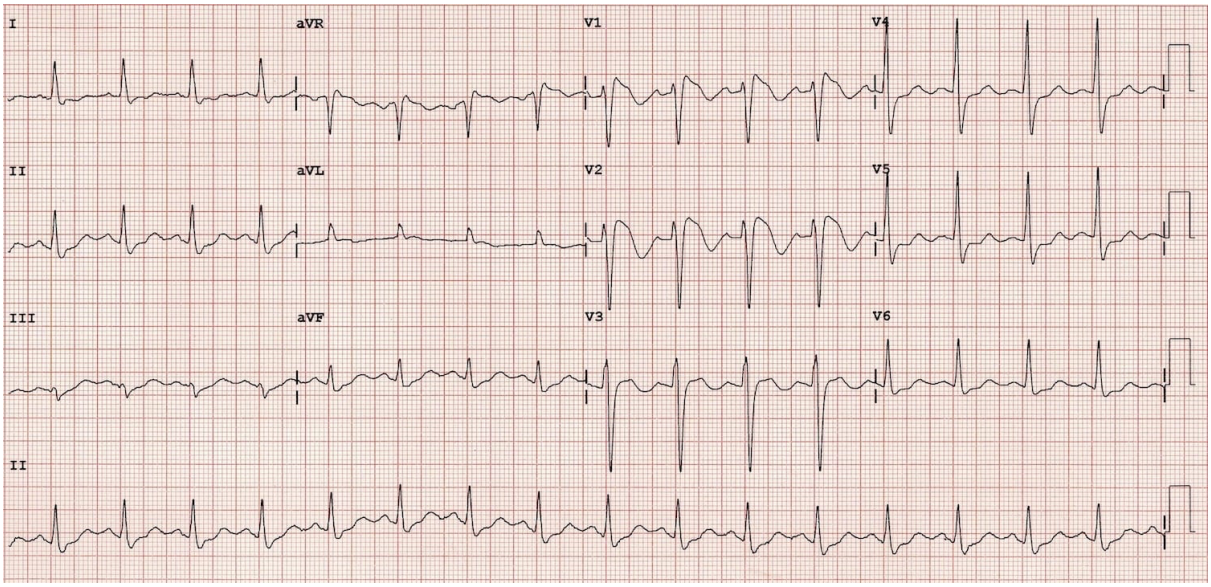

Figure 3. Type 1 Brugada ECG, right bundle branch block morphology in lead V1. ST segment elevations in leads V1-V3. Typically, there is a maximal manifestation with a coved-shaped ST segment (coved type ECG) that resembles a shoulder.

Reproduced from: (57)

ECG

Type I (“coved type”) is the most specific and the only diagnostic pattern for the Brugada syndrome, nevertheless initially 3 ECG types had been described (5, 7).
Type I is characterized by a coved-shaped ST-segment elevation of at least 2 mm followed by a negative T-wave in one or more of the right precordial leads (V1 to V3) on the ECG (8). The coved-shaped ST-segment elevation starts at the J-point (the junction between the end of the QRS complex and the beginning of the ST segment) and slopes down gradually to the baseline. The ST segment elevation is typically followed by a negative T-wave, which creates a characteristic "coved" appearance (37).

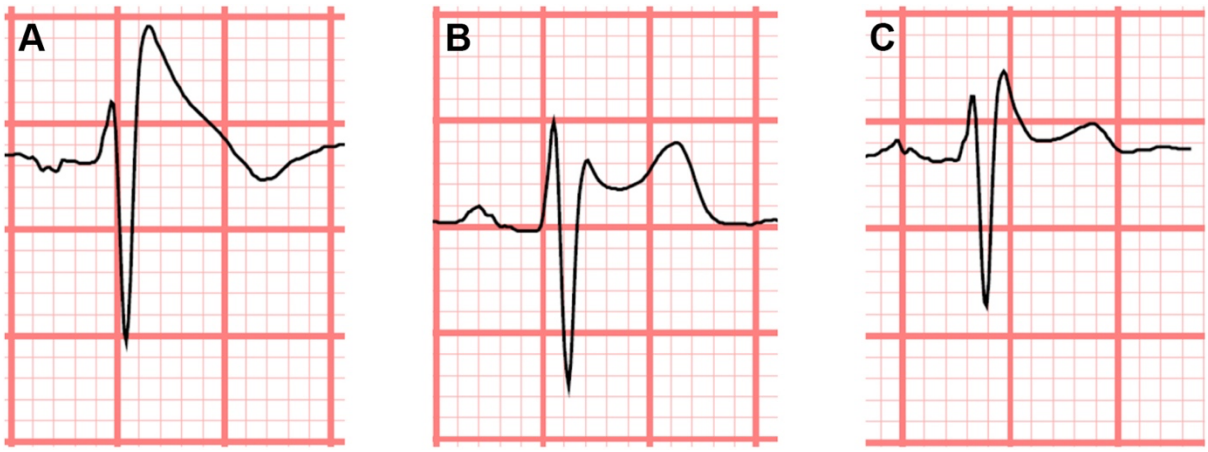

Figure 4. Representative type 1 **(A)**, type 2 **(B)**, and type 3 **(C)**. Brugada pattern electrocardiogram traces originally proposed by Wilde et al. (38)

Type 2 Brugada pattern is another type of ECG pattern seen in Brugada syndrome. It is characterized by a saddleback-shaped ST-segment elevation in one or more of the right precordial leads (V1 to V3): the exit point of the ST segment is clearly elevated at > 0,5 mm (generally > 0.2 mm in V2)(> 0.2mV), but the ST segment falls continuously in the course, always remaining at least 1mm above the zero line – and then ends in a positive or biphasic T wave. The ST-segment elevation in type 2 Brugada pattern is initially steep, then forms a "saddleback" shape with a second positive deflection before returning to baseline. This is followed by a positive or biphasic T-wave, which creates a characteristic "saddleback" appearance (7).
Type 2 and type 3 ECGs are referred to as "indicative" or “suspicious” ECGs and combined into a single type 2 ECG (“saddleback”)(39). It is important to mention, that they are not diagnostically conclusive. This would only be the case after conversion to a type 1 ECG under provocation with sodium channel blockers (9).

To distinguish type 2 ECGs, which strongly suggest BrS, from other Brugada-like patterns observed in athletes, individuals with pectus excavatum and those with arrhythmogenic cardiomyopathy, various additional ECG criteria have been proposed (37). One of these criteria is the beta (ß)-angle, which is the angle between the ascending and descending portions of the r′ wave in leads V1 and V2. The ß-angle serves as a prognostic indicator that aids in distinguishing highly suggestive type 2 ECG patterns of Brugada syndrome from other Brugada-like patterns. A threshold of 58 degrees has been proposed as the optimal predictive value for identifying the conversion to a type 1 Brugada syndrome (BrS) pattern.

At this cut-off value, the positive predictive value is 73%, indicating the likelihood of a true positive result, while the negative predictive value is 87%, indicating the likelihood of a true negative result (37, 40).

An additional criterion to differentiate type 2 ECGs suggestive of BrS from other Brugada-like patterns is the measurement of the base triangle of the r′-wave, taken 5 mm below the peak of the rise point. A threshold of 4 mm has been demonstrated to exhibit high specificity (96%) and sensitivity (85%) in distinguishing the BrS ECG pattern in BrS patients from the ECG pattern of healthy individuals (37, 41).

Placing the right precordial leads in higher positions, such as the 3rd or 2nd intercostal spaces, can improve sensitivity in certain patients with Brugada syndrome. This is related to the variability in the anatomical relationship between the RVOT and leads V1 to V2 in the standard position (37).

Provocation testing

Some patients with BrS may have normal baseline ECG or nonspecific ST-segment changes, which makes the diagnosis challenging. Therefore, pharmacological tests with sodium-channel blockers are indicated in patients with ECG type 2 and 3 and as well for those with a high clinical suspicion or family history for BrS (42).
In patients with an already existing type 1ECG, the test does not provide any additional diagnostic information (7).
Intravenous administration of sodium channel blockers can alter the repolarisation pattern: ST-segment elevation becomes more prominent. In particular, ajmaline (1 mg/kg fractionated in 10 mg steps at intervals of 2 min), flecainide (2 mg/kg over 10 min) and procainamide (10 mg/kg over 10 min) have been used successfully in this context.
Intravenous ajmaline and flecainide are the commonly employed pharmacological agents for diagnosing BrS, as they are widely used. However, in certain countries, procainamide is the sole available Class I intravenous antiarrhythmic drug for BrS diagnosis (42).
Continuous ECG monitoring is imperative during the pharmacological test and vigilant observation is necessary to detect any potential adverse effects. These may encompass QRS widening exceeding 130% of the baseline value, as well as the presence of frequent ventricular premature beats or more intricate ventricular arrhythmias.

If these signs occur or induction of ECG type 1, the administration of the drug should be immediately stopped to avoid ventricular arrhythmias (37).

It should be noted, that approximately 25% of drug-induced tests for Brugada syndrome may result in false-negative results, which can be a concern for patients who have experienced aborted sudden cardiac death but show a negative flecainide test. Therefore, it is recommended to consider a repeat drug test whenever possible to improve the accuracy of diagnosis (43).

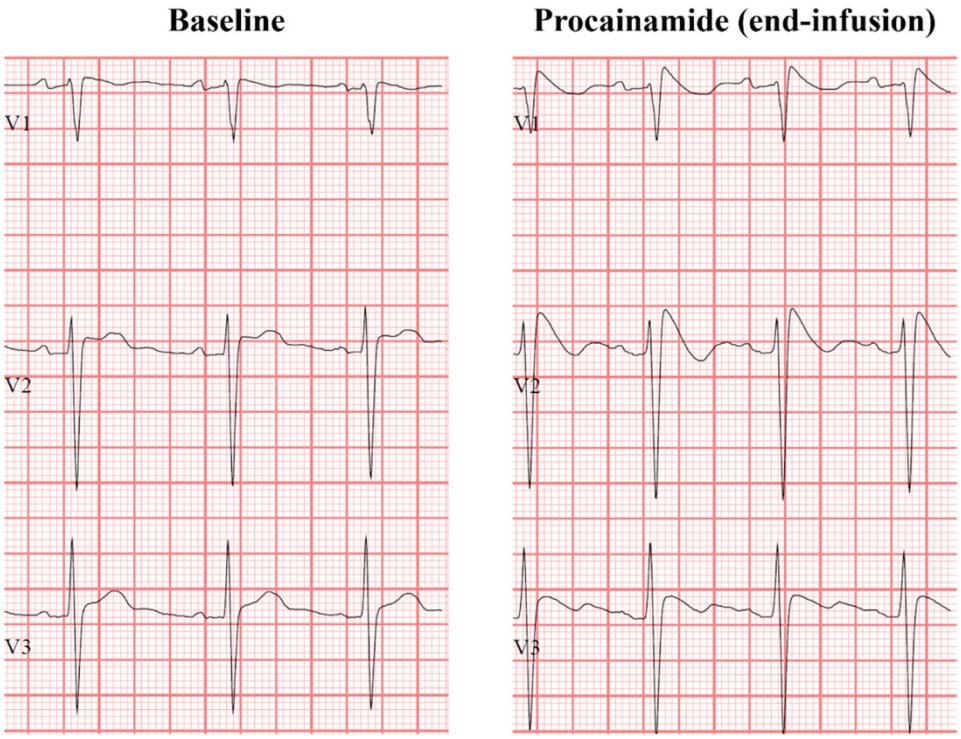

Figure 5. Electrocardiographic pattern of Brugada syndrome induced by procainamide. Reproduced from: (38)

Genetic testing

Individuals showing a type 1 Brugada ECG pattern, whether spontaneous or induced are advised to undergo genetic testing for familial screening purposes (44).
Merely having a pathogenic variant in a Brugada syndrome susceptibility gene is inadequate for a definitive diagnosis of Brugada syndrome. Furthermore, the penetrance of genetic variants associated with the syndrome is approximately 50% and even individuals lacking the variant may still display clinical characteristics of the syndrome. As a result, genetic testing alone cannot be solely relied upon for familial screening, which should primarily be based on clinical screening. The present recommendations indicate to test solely for variants in the SCN5A gene, as the pathogenicity of other potential genes remains uncertain (38).

Diagnostic criteria

It is important to note that the diagnostic criteria for Brugada syndrome have evolved over time. In the past, the classic diagnostic criteria for Brugada syndrome included the presence of a coved-type (shoulder type 1) ST-segment elevation in at least two right precordial leads (V1-3) on a resting ECG, along with one of the following: documented arrhythmia such as polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF), arrhythmia-related symptoms such as syncope, seizure or nocturnal agonal breathing or a positive family history of sudden cardiac death before the age of 45 or Brugada syndrome with a type 1 ECG pattern in first-degree relatives. (7, 8).
However, it is now recognized that the diagnosis of Brugada syndrome may not always be straightforward and that the classic ECG pattern may not always be present on a resting ECG. In addition, the clinical presentation of Brugada syndrome can be variable, with some patients being asymptomatic and others experiencing life-threatening arrhythmias.

The 2013 expert consensus on hereditary arrhythmogenic diseases has updated the diagnostic criteria for Brugada syndrome to increase sensitivity. The clinical criterion has been removed, and now only one lead with ECG changes is required for diagnosis (9).
According to the expert consensus statement: “BrS is diagnosed when a type 1 ST elevation is observed either spontaneously or after intravenous administration of a sodium channel blocker in at least one right precordial lead (V1 and V2), placed in a standard or superior position (up to the 2nd intercostal space)” (9).

In some cases, individuals with a type 1 ECG may not display any symptoms of Brugada syndrome. However, certain findings can support a diagnosis of the condition in asymptomatic patients. These include according to the expert Consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes the following:

1. "The attenuation of ST-segment elevation during peak exercise stress test followed by its appearance during the recovery phase. It should be noted that in certain Brugada syndrome patients, particularly those with SCN5A mutations, ST-segment elevation may become more pronounced during exercise.
2. The presence of first-degree atrioventricular block and left-axis deviation of the QRS.
3. The presence of atrial fibrillation.
4. Signal-averaged ECG with late potentials.
5. Fragmented QRS.
6. ST-T alternans, spontaneous left bundle branch block, and ventricular premature beats during prolonged ECG recording.
7. A ventricular effective refractory period of less than 200 ms recorded during electrophysiological study, as well as an HV interval of more than > 60 ms.
8. The absence of structural heart disease, including myocardial ischemia." (9)

Shanghai Score

The recently developed Shanghai score, as outlined in Table 2, acknowledges the limitations of using induced type 1 ECG changes alone for making a definitive diagnosis.
A score of ≥ 3.5 was assigned to cases diagnosed with probable and/or definite BrS, while possible BrS received a score of 2 to 3 and a score of less than 2 points was given to cases with a nondiagnostic score.
The Shanghai Score System takes into account various factors, including clinical history, family history, ECG findings and genetic testing results, to assign a score to patients suspected of having Brugada syndrome (38).
A study performed by Kawada et al. aimed to validate the Shanghai Score System for the diagnosis of Brugada syndrome and reclassify patients based on their scores.

Patients with a higher score in the Shanghai Score System were found to be at an increasingly higher risk for life-threatening arrhythmias, as evidenced by a larger percentage of these patients experiencing such arrhythmias. The study also observed that many patients with a high score exhibited severe symptoms, had a family history of sudden death and tested positive for genetic abnormalities associated with Brugada syndrome.
Based on these findings, the researchers concluded that the Shanghai Score System is a reliable tool for diagnosing Brugada syndrome and stratifying patients based on their risk of developing malignant arrhythmias (45).

Table 2: Proposed Shanghai Score system for diagnosis of BrS

I. ECG* (12-lead/ambulatory)	Points
A. Spontaneous type 1 Brugada ECG pattern at nominal or high leads	3.5
B. Fever-induced type 1 Brugada ECG pattern at nominal or high leads	3
C. Type 2 or 3 Brugada ECG pattern that converts with provocative drug challenge	2
II. Clinical history	
A. Unexplained cardiac arrest or documented VF/polymorphic VT	3
B. Nocturnal agonal respirations	2
C. Suspected arrhythmic syncope	2
D. Syncope of unclear mechanism/unclear etiology	1
E. Atrial flutter/fibrillation in patients <30 yrs without alternative etiology	0.5
III. Family history	
A. First- or second-degree relative with definite BrS	2
B. Suspicious SCD (fever, nocturnal, Brugada aggravating drugs) in a first- or second-degree relative	1
C. Unexplained SCD <45 yrs in first- or second-degree relative with negative autopsy	0.5
IV. Genetic test result	
A. Probable pathogenic mutation in BrS susceptibility gene	0.5

Only award points once for highest score within this category. Score (requires at least 1 electrocardiographic (ECG) finding): >3.5 points: probable and/or definite Brugada syndrome (BrS); 2 to 3 points: possible BrS: <2 points: nondiagnostic. Source: (38)

Differential diagnosis

Prior to diagnosing BrS, it is necessary to eliminate other potential causes of ST-segment elevation on the ECG. Some instances of ST-segment elevation may be the result of various medical conditions, while others may be attributed to an underlying genetic predisposition. Therefore, a comprehensive evaluation of the ECG pattern, clinical history and other factors is essential to exclude other potential causes before establishing a diagnosis of BrS.
There are various diseases and medical conditions, as listed in Table 3 that can lead to an ECG pattern similar to BrS. These include for example hypothermia, atypical right bundle branch block, electrolyte imbalances (eg. hypokalemia), myocardial ischemia or infarction, acute pericarditis and autonomic nervous system abnormalities. A full comprehensive list can be found in Table 3 (46).

Table 3. ECG abnormalities and diseases that can lead to or exacerbate ST-segment elevation in the right precordial leads.

Atypical right bundle branch block
Left ventricular hypertrophy
Myocarditis
Acute pericarditis
Acute myocardial ischemia or infarction
Prinzmetal's angina
Pulmonary embolism
Dissecting aortic aneurysm
Arrhythmogenic right ventricular cardiomyopathy
Mechanical compression of the right ventricular outflow tract
Various central and autonomic nervous system abnormalities
Duchenne muscular dystrophy
Hypokalemia
Hyperkalemia
Hypercalcemia
Hypothermia

Source: (46)

When an ECG demonstrates a pattern similar to type 1 BrS due to external factors, it is referred to as a Brugada ECG phenocopy (BrP). These clinical entities known as Brugada phenocopies that mimic the ECG patterns of Brugada syndrome, are elicited by various other clinical circumstances, making them difficult to differentiate from true congenital Brugada syndrome (47).
To define BrP, several criteria have been established, including the presence of a Brugada type 1 or type 2 ECG pattern, an identifiable underlying condition, resolution of the ECG pattern after resolution of the underlying condition, a low clinical pretest probability of true Brugada syndrome, negative provocative testing with sodium channel blockers and negative genetic testing results (although genetic testing is not mandatory) (46).

A more recent classification system has been proposed, categorizing conditions that may trigger Brugada Phenocopy into six broad etiological categories, based on the underlying mechanisms involved. These categories include metabolic conditions, mechanical compression, myocardial ischemia and pulmonary embolism, myocardial and pericardial disease, ECG modulations and drugs.
Differentiating between BrP and true congenital Brugada syndrome is important for appropriate clinical management, as treatment options may vary depending on the underlying condition. With ongoing research and improved diagnostic techniques, the ability to differentiate between BrP and Brugada syndrome may improve in the future, ultimately leading to better clinical outcomes for patients (46, 48).

Electrocardiogram (ECG) patterns that resemble Brugada syndrome can sometimes display ST-segment abnormalities that may be mistakenly identified as type 1 or type 2 Brugada syndrome ECG patterns. However, these patterns typically exhibit additional alterations in other leads that can aid in the differential diagnosis. Moreover, ST-segment elevation in V1 to V2 is not identical to that of BrS. Type 1 Brugada-like ECGs are often associated with ST-segment elevation due to acute ischemia or occlusion of the left anterior descending artery. While Type 2 Brugada-like ECG patterns are frequently observed and can be caused by several conditions, such as right bundle branch block, left ventricular hypertrophy, pectus excavatum. Similar to Brugada phenocopies, a negative result in the sodium-channel blocker challenge test is often found (49).

Several factors can trigger or worsen the Brugada syndrome ECG pattern, possibly by affecting transmembrane ionic currents. These factors include bradycardia and vagal tone,

which can reduce calcium currents, leading to ST-segment elevation and increased risk of arrhythmias (33). Several drugs have been reported and discussed earlier to induce the type 1 BrS ECG pattern. This type of BrS pattern induction is known as an "acquired form of BrS," and it is unclear whether it results from individual susceptibility due to latent ion channel dysfunction (9).

Treatment

Treatment strategies for BrS aim to reduce the risk of SCD by preventing the occurrence of ventricular arrhythmias or terminating them quickly if they occur. The therapeutic approach to BrS is complex and involves a combination of pharmacologic and non-pharmacologic interventions, as well as careful risk stratification of affected individuals to identify those who would benefit most from aggressive management strategies. In this context, it is essential to understand the current recommendations for the management of BrS, including the use of implantable cardioverter-defibrillators (ICDs), pharmacologic agents such as quinidine and the role of lifestyle modifications in reducing the risk of arrhythmia recurrence.

Lifestyle changes are suggested for all patients (Class I recommendation) diagnosed with BrS. These include avoiding drugs that can induce or exacerbate ST-segment elevation in right precordial leads, excessive alcohol intake and treating fever with antipyretic drugs immediately.

There are several drugs that have been shown to induce or exacerbate BrS by increasing the risk of arrhythmias, particularly in patients with a genetic predisposition to the condition. Some of the most common drugs that can exacerbate BrS include certain antiarrhythmic drugs, such as flecainide and propafenone. These drugs work by blocking sodium channels (Class IC antiarrhythmic drugs) in the heart, leading to a reduction in the inward flow of sodium ions, which is responsible for generating the electrical impulses that regulate the heart rhythm (9).

In BrS patients, in addition to class IC antiarrhythmic drugs, beta-blockers, various psychotropic drugs, anesthetics, antihistamines, cocaine and excessive alcohol consumption can also have a proarrhythmic effect and should therefore be avoided.

Other drugs that have been implicated in the exacerbation of BrS include some antibiotics, such as ciprofloxacin and azithromycin. It is important to note that not all patients with BrS will be affected by these drugs and the severity of the condition can vary depending on individual factors, such as age, sex and overall health (9, 50).

Given the potential risks associated with these drugs, it is important for patients with BrS to be aware of the medications that can exacerbate their condition and to avoid taking them wherever possible. Additionally, healthcare providers should carefully consider the potential risks and benefits of prescribing these drugs to patients with BrS and should monitor them closely for signs of arrhythmia or other adverse effects (9).

A present roster for the latest compilation of medications that are contraindicated, as well as comprehensive information on how to handle situations involving fever, anesthesia and arrhythmologic emergencies can be found at www.brugadadrugs.org (8, 50).

Implantable cardioverter defibrillator

ICD placement is recommended for patients with BrS who have survived a cardiac arrest or have documented spontaneous sustained ventricular tachycardia (VT) with or without syncope (Class I recommendation). Additionally, ICD placement can be useful in patients with a spontaneous diagnostic type 1 electrocardiogram (ECG) who have a history of syncope judged to be likely caused by ventricular arrhythmias (Class IIa recommendation). Patients with BrS who develop ventricular fibrillation (VF) during programmed electrical stimulation (inducible patients) may be considered for ICD placement (Class IIb recommendation). ICD placement is not indicated in asymptomatic BrS patients with a drug-induced type 1 ECG and based on a family history of SCD alone (Class III recommendation) (9).

Until now, the sole confirmed therapeutic approach for preventing SCD in patients with Brugada syndrome (BrS) is the implantable cardioverter-defibrillator (ICD). It should be noted that ICDs come with several drawbacks, particularly for active young patients, who may need multiple device replacements over their lifetime. Several studies have revealed a low incidence of appropriate shocks and a high frequency of complications, predominantly stemming from inappropriate shocks (9, 51).

Pharmacological therapy

Pharmacological therapy can be used to rebalance the epicardial action potential and normalize the action potential dome in the right ventricle, thus preventing arrhythmogenesis in BrS.
On the other hand, while device therapy is aimed to decrease SCD chance in BrS, it does not proactively prevent the occurrence of arrhythmias or symptoms (e.g. syncope or palpitations). Conversely, drug therapy for BrS serves mainly three proposes. Firstly, it can be employed in the acute management of arrhythmic storms. Secondly, it can be used as a preventive measure against arrhythmic events in patients with implantable cardioverter-defibrillator (ICD) who may require multiple shocks. Last but not least, it can be considered as an alternative to ICD implantation (infants and young children) in cases where it is contraindicated, due to several reasons (e.g. refused by the patient) (37).

Quinidine is a class IA antiarrhythmic drug, the primary mechanism behind its effectiveness in preventing arrhythmic events in BrS is its significant I_{to} current blocking property. Research studies have shown that quinidine has the potential to restore the normal action potential dome and ST segment, thereby preventing phase-two re-entry and polymorphic ventricular tachycardia in experimental models of BrS (52, 53).
The argument of supporters of pharmacological therapy is the curative treatment approach, in contrast to ICD implantation. The goal is to restore the balance of ion currents in the early phases of the epicardial action potential, so that the AP plateau can develop normally.
In some cases, quinidine treatment has been found to decrease ST-segment elevation and in certain instances, normalize the ECG. Additionally, approximately 85% of patients have reported suppression of VF following treatment with quinidine (9, 53).

Quinidine can be useful in patients with BrS and a history of arrhythmic storms defined as more than two episodes of VT/VF in 24 hours (Class I recommendation).
Quinidine may also be considered in asymptomatic patients with a diagnosis of BrS and a spontaneous type I ECG (Class IIb recommendation). In patients who qualify for an ICD but have contraindications to the device or refuse it, quinidine may be considered as an alternative therapy. Furthermore, quinidine can be useful in patients with a history of documented supraventricular arrhythmias that require treatment (Class IIa recommendation) (9).

Quinidine, like other antiarrhythmic drugs, have potential side effects in patients with Brugada syndrome. Some of the common side effects of quinidine include gastrointestinal disturbances such as nausea, vomiting, diarrhea and abdominal pain. In addition, quinidine can cause a decrease in blood pressure and heart rate, leading to dizziness and fainting. More serious side effects of quinidine include drug-induced lupus, thrombocytopenia and heart rhythm disturbances. Therefore, the use of quinidine in BrS patients should be closely monitored and administered (53).

Other medication with some benefit in preventing arrhythmic events include beta-sympathomimetics such as isoproterenol. These agents augment L-type calcium channels, making them effective in controlling VF storms either alone or in combination with quinidine. The effectiveness of isoproterenol in controlling VF storms has also been observed in children and pregnant women with BrS. Current guidelines recommend the administration of isoproterenol for BrS patients experiencing VF storms (class IIA) (9).

Ablation therapy

Catheter ablation may be considered in patients with a history of arrhythmic storms or repeated appropriate ICD shocks (Class IIb recommendation) (9).
The principle of catheter ablation is based on the destruction of the arrhythmogenic myocardial substrate through intracardiac energy delivery via a catheter. The current method for ablation involves the use of radiofrequency energy.

Haïssaguerre et al. first described in 2003 an alternative adjuvant therapy for BrS with recurrent VF (54). Eight years later, there was a significant shift in the treatment approach for BrS when Nademanee and colleagues reported the remarkable effectiveness of epicardial ablation in reducing the burden of VF.
In more detail, Nademanee et al. prevented further VT/VF episodes in 9 highly symptomatic Brugada syndrome patients (>4 ICD discharges per month) by performing targeted catheter ablation in the right ventricular outflow tract, achieving normalization of Brugada-typical ECG changes in 89% of cases (5, 11).

A study conducted by Pappone et al. provided significant insights into the pathophysiology, mechanisms and management of BrS in consecutive patients.
The study aimed to investigate the efficacy and safety of epicardial substrate elimination using radiofrequency ablation (RFA) in patients with BrS. The researchers enrolled 135 consecutive patients with symptomatic or asymptomatic BrS and inducible ventricular arrhythmias (VAs) during electrophysiological study (EPS). All patients underwent extensive mapping of the RVOT and right ventricular (RV) free wall with a 3D mapping system during EPS, followed by epicardial RFA of abnormal electrograms.
The findings from the research indicate that symptomatic patients with BrS exhibit a distinct anatomical and electrophysiological substrate, characterized by abnormal ventricular electrograms that are solely located in the anterior RVOT and RV anterior free wall.
The study uncovered that ajmaline administration could accurately identify the extension and distribution of the substrate, making it a viable target for successful ablation in BrS.
Additionally, the research established a clear relationship between the degree of type 1 ECG pattern and the extent of the substrate. Specifically, a broader abnormal area correlated with increased ST-segment elevation and a coved-type appearance on the ECG.
The research findings have important clinical implications, demonstrating the efficacy of epicardial ablation as a therapeutic intervention for preventing VF in a significant number of high-risk BrS patients with recurrent VT or VF. During a median follow-up period of 10 months, only two out of 135 symptomatic BrS patients experienced a single episode of VT/VF after the procedure, with one case attributed to an electrolyte imbalance as the triggering factor. This underscores the favorable outcomes of epicardial ablation in this patient population.
These findings have important clinical implications, as radiofrequency ablation may provide a definitive treatment for patients with BrS who are at risk of sudden cardiac death, potentially avoiding the need for ICD therapy. However, further studies with longer follow-up are needed to confirm the long-term efficacy and safety of this approach (55).

In conclusion, the management of BrS involves a multifaceted approach that includes lifestyle modifications, pharmacological therapy, and in some cases, ICD placement or catheter ablation. Treatment decisions should be individualized based on a patient's risk profile, comorbidities and preferences. It is important for clinicians to stay up-to-date with current guidelines and recommendations to provide optimal care for patients with BrS.

Conclusion and Future perspective

In conclusion, Brugada syndrome is a complex and potentially life-threatening cardiac condition that requires vigilant recognition, diagnosis and management. This rare genetic disorder is characterized by distinctive ECG patterns and an increased risk of ventricular arrhythmias, which can result in sudden cardiac death.

The pathophysiology of Brugada syndrome is still not fully understood, as multiple factors contribute to a heterogeneous phenotype characterized by a impaired right ventricular outflow tract. Although abnormalities in the NaV1.5 ion channel are frequently reported, further research is needed to better understand the specific contributions of I_{to} and I_{CaL} in the context of Brugada syndrome.

Furthermore, the genetic basis of BrS is complex and confounding, with changes in the interpretation of genetic testing leading to a reduction in the number of cases attributed to a specific genetic variant in recent times. Further research is needed to unravel the intricate mechanisms underlying BrS and to better understand the relative roles of various ion channels and genetic factors in its pathogenesis.

It is crucial for clinicians to have a high index of suspicion for Brugada syndrome in patients with a family history of sudden cardiac death or unexplained syncope and to conduct thorough evaluations in order to confirm the diagnosis.

Management of Brugada syndrome involves a multifaceted approach, including risk stratification, lifestyle modifications and medical therapy with medications such as quinidine. Implantation of an implantable cardioverter-defibrillator may also be indicated in high-risk patients. Additionally, patient education and counseling about avoiding triggers such as certain medications, fever and electrolyte imbalances, are crucial to reduce the risk of arrhythmia episodes.

Researchers are exploring new technologies for the diagnosis and monitoring of BrS. Currently, the diagnosis of BrS is based on the presence of certain ECG patterns, which can be difficult to detect in some patients. Researchers are investigating the use of wearable devices, such as smartwatches and patches, to monitor the heart's electrical activity and detect arrhythmias in real-time. These devices may provide a more accurate and convenient way to diagnose and monitor BrS in the future.

Ablation therapy has emerged as a promising approach for the management of Brugada syndrome (BrS), offering potential benefits for select patients. While the current guidelines for BrS do not specifically recommend ablation as a routine treatment, there are ongoing research efforts exploring the utility of ablation in certain subsets of BrS patients and future perspectives in this area are intriguing.

In conclusion, early recognition, accurate diagnosis and appropriate management of Brugada syndrome are vital in preventing sudden cardiac death and improving patient outcomes. As healthcare professionals, it is our responsibility to remain vigilant, educate our patient and work collaboratively to ensure the best possible care for individuals affected by Brugada syndrome.

Bibliography

1. *Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. J Am Coll Cardiol. 1992 Nov 15;20(6):1391-6.*

2. *Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, et al. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. J Am Coll Cardiol. 2001 Sep;38(3):771-4.*

3. *Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, et al. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol. 2008 Nov 4;52(19):1567-73.*

4. *Ackerman MJ, Priori SG, Willems S, et al.* HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the HRS and the EHRA. Heart Rhythm. 2011 Aug;8(8):1308-39.

5. *Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005 Feb 8 and 111(5):659-70.*

6. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL et al. Long-term prognosis of patients diagnosed with Brugada syndrome: Results from the FINGER Brugada Syndrome Registry. Circulation. 2010 Feb 9;121(5):635-43.

7. Wilde AA, Antzelevitch C, Borggrefe M et al. ; Study Group on the Molecular Basis of Arrhythmias of the European Society of Cardiology. Proposed diagnostic criteria for the Brugada syndrome: consensus report. Circulation. 2002 Nov 5;106(19):2514-9.

8. Steinfurt J, Biermann J, Bode C, Odening KE. The Diagnosis, Risk Stratification, and Treatment of Brugada Syndrome. Dtsch Arztebl Int. 2015 Jun 5 and 112(23):394-401.

9. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS. in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013 Dec; 10(12):1932-63.

10. Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, et al. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet. 2002 Feb 1 and 11(3):337-45.

11. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation. 1997 Oct 21;96(8):2595-600.

12. Nakano Y, Shimizu W. Brugada Syndrome as a Major Cause of Sudden Cardiac Death in Asians. JACC Asia. 2022 Jul 19;2(4):412-421.

13. Wataru Shimizu, Clinical features of Brugada syndrome, Journal of Arrhythmia, 2013, Volume 29, Issue 2, Pages 65-70.

14. Shimizu W, Matsuo K, Kokubo et al. H. Sex hormone and gender difference--role of testosterone on male predominance in Brugada syndrome. J Cardiovasc Electrophysiol. 2007 Apr;18(4):415-21.

15. Mizusawa Y, Wilde AA. Brugada syndrome. Circ Arrhythm Electrophysiol. 2012 Jun 1;5(3):606-16.

16. Mizumaki K, Fujiki A, Tsuneda T, et al. Vagal activity modulates spontaneous augmentation of ST elevation in the daily life of patients with Brugada syndrome. J Cardiovasc Electrophysiol. 2004 Jun;15(6):667-73.

17. Ikeda T, Abe A, Yusu S, et al. The full stomach test as a novel diagnostic technique for identifying patients at risk of Brugada syndrome. J Cardiovasc Electrophysiol. 2006 Jun;17(6):602-7.

18. Antzelevitch C. Brugada syndrome. Pacing Clin Electrophysiol. 2006 Oct;29(10):1130-59.

19. Araki T, Konno T, Itoh H, et al. Brugada syndrome with ventricular tachycardia and fibrillation related to hypokalemia. Circ J. 2003 Jan;67(1):93-5.

20. Adler A, Topaz G, Heller K, et al. Fever-induced Brugada pattern: how common is it and what does it mean? Heart Rhythm. 2013 Sep;10(9):1375-82.

21. Morita H, Kusano-Fukushima K, Nagase S, et al. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. J Am Coll Cardiol. 2002 Oct 16;40(8):1437-44.

22. Antzelevitch C, Patocskai B. . Brugada Syndrome: Clinical, Genetic, Molecular, Cellular, and Ionic Aspects. Curr Probl Cardiol. 2016 Jan and 41(1):7-57.

23. Campuzano O, Allegue C, Brugada R. Genética de la muerte súbita inexplicada [Genetics of sudden unexplained death]. Med Clin (Barc). 2014 Mar 20;142(6):265-9. Spanish.

24. Chen Q, Kirsch GE, Zhang D et al. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature. 1998 Mar 19;392(6673):293-6.

25. Kapplinger JD, Tester DJ, Alders M, et al. An international compendium of mutations in the SCN5A-encoded cardiac sodium channel in patients referred for Brugada syndrome genetic testing. Heart Rhythm. 2010 Jan;7(1):33-46.

26. Milman A, Andorin A, Postema PG, et al. Ethnic differences in patients with Brugada syndrome and arrhythmic events: New insights from Survey on Arrhythmic Events in Brugada Syndrome. Heart Rhythm. 2019 Oct;16(10):1468-1474.

27. Remme CA, Wilde AA, Bezzina CR. Cardiac sodium channel overlap syndromes: different faces of SCN5A mutations. Trends Cardiovasc Med. 2008 Apr;18(3):78-87.

28. London B, Michalec M, Mehdi H, et al. Mutation in glycerol-3-phosphate dehydrogenase 1 like gene (GPD1-L) decreases cardiac Na+ current and causes inherited arrhythmias. Circulation. 2007 Nov 13;116(20):2260-8.

29. Burashnikov E, Pfeiffer R, Barajas-Martinez H et al. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. Heart Rhythm. 2010 Dec;7(12):1872-82.

30. Delpón E, Cordeiro JM, Núñez L, et al. Functional effects of KCNE3 mutation and its role in the development of Brugada syndrome. Circ Arrhythm Electrophysiol. 2008 Aug;1(3):209-18.

31. Amboss. Cardiac physiology. Amboss. [Online] 9 December 2022. [Cited: 16 October 2022.] https://next.amboss.com/us/article/zo0reS?q=cardiac+action+potential#Za5ddc0be2731d2676b2cbf59440350c1.

32. Wilde AA, Postema PG, Di Diego JM, Viskin S, Morita H, Fish JM, et al. The pathophysiological mechanism underlying Brugada syndrome: depolarization versus repolarization. J Mol Cell Cardiol. 2010 Oct;49(4):543-53.

33. Yan GX, Antzelevitch C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation. 1999 Oct 12;100(15):1660-6.

34. Jellins J, Milanovic M, Taitz DJ, Wan SH, Yam PW. Brugada syndrome. Hong Kong Med J. 2013 Apr;19(2):159-67.

35. Meregalli PG, Wilde AA, Tan HL. Pathophysiological mechanisms of Brugada syndrome: depolarization disorder, repolarization disorder, or more? Cardiovasc Res. 2005 Aug 15;67(3):367-78.

36. Nademanee K, Veerakul G, Chandanamattha P, et al. Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior right ventricular outflow tract epicardium. Circulation. 2011 Mar 29;123(12):1270-9.

37. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Aug 28;72(9):1046-1059.

38. Krahn A, Behr E, Hamilton R, et al. Brugada Syndrome. J Am Coll Cardiol EP. 2022 Mar, 8 (3) 386–405.

39. Bayés de Luna A, Brugada J, Baranchuk A, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012 Sep;45(5):433-42.

40. Chevallier S, Forclaz A, Tenkorang J, et al. New electrocardiographic criteria for discriminating between Brugada types 2 and 3 patterns and incomplete right bundle branch block. J Am Coll Cardiol. 2011 Nov 22;58(22):2290-8.

41. Serra G, Baranchuk A, Bayés-De-Luna A, et al. New electrocardiographic criteria to differentiate the Type-2 Brugada pattern from electrocardiogram of healthy athletes with r'-wave in leads V1/V2. Europace. 2014 Nov;16(11):1639-45.

42. Antzelevitch C, Yan GX, Ackerman MJ, et al. J-Wave syndromes expert consensus conference report: Emerging concepts and gaps in knowledge. Europace. 2017 Apr 1;19(4):665-694.

43. Chauveau S, Le Vavasseur O, Chevalier P. Delayed diagnosis of Brugada syndrome in a patient with aborted sudden cardiac death and initial negative flecainide challenge. Clin Case Rep. 2017 Oct 31;5(12):2022-2024.

44. Gollob MH, Blier L, Brugada R, et al. Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death:. Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. Can J Cardiol. 2011 Mar-Apr;27(2):232-45. [Online]

45. Kawada S, Morita H, Antzelevitch C, et al. Shanghai Score System for Diagnosis of Brugada Syndrome: Validation of the Score System and System and Reclassification of the Patients. JACC Clin Electrophysiol. 2018 Jun;4(6):724-730. .

46. Dendramis G. Brugada syndrome and Brugada phenocopy. The importance of a differential diagnosis. Int J Cardiol. 2016 May 1;210:25-7.

47. Baranchuk A, Nguyen T, Ryu MH, et al. Brugada phenocopy: new terminology and proposed classification. Ann Noninvasive Electrocardiol. 2012 Oct;17(4):299-314.

48. Gottschalk BH, Anselm DD, Baranchuk A. Brugada phenocopies are the leading differential diagnosis of Brugada syndrome. Clin Med (Lond). 2015 Jun;15(3):308-9.

49. Moncayo-Arlandi J, Brugada R. Unmasking the molecular link between arrhythmogenic cardiomyopathy and Brugada syndrome. Nat Rev Cardiol. 2017 Dec;14(12):744-756.

50. Postema PG, Wolpert C, Amin AS, et al. Drugs and Brugada syndrome patients: review of the literature, recommendations, and an up-to-date website (www.brugadadrugs.org). Heart Rhythm. 2009 Sep;6(9):1335-41.

51. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multicenter study. Circulation. 2006 Nov 28;114(22):2317-24. .

52. Brodie OT, Michowitz Y, Belhassen B. Pharmacological Therapy in Brugada Syndrome. Arrhythm Electrophysiol Rev. 2018 Jun;7(2):135-142.

53. Márquez MF, Bonny A, Hernández-Castillo E, et al. Long-term efficacy of low doses of quinidine on malignant arrhythmias in Brugada syndrome with an implantable cardioverter-defibrillator: a case series and literature review. Heart Rhythm. 2012 Dec;9(12):1.

54. Haïssaguerre M, Extramiana F, Hocini M, et al. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. Circulation. 2003 Aug 26;108(8):925-8.

55. Pappone C, Brugada J, Vicedomini G, et al. Electrical Substrate Elimination in 135 Consecutive Patients With Brugada Syndrome. Circ Arrhythm Electrophysiol. 2017 May;10(5):e005053.

56. Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol. 2001 Feb;12(2):268-72.

57. Larkin J. and Mike Cadogan. Brugada Syndrome. Life in the Fastlane. [Online] September 21, 2022. [Cited: 18 December 2022] https://litfl.com/brugada-syndrome-ecg-library/