Further insights into inheritable arrhythmia syndromes: Focus on electrocardiograms
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Chapter 08

INTRODUCTION

The Brugada syndrome was described as a distinct clinical entity by the brothers Pedro and Josep Brugada in 1992. In their initial publication, they reported eight patients with a specific ECG pattern (figure 1) and repeated episodes of aborted sudden cardiac death. The contemporary concept of Brugada syndrome is a disorder characterized by sudden cardiac death at relatively young age, with familial segregation, an apparent absence of gross structural abnormalities or ischemic heart disease, and specific electrocardiographic characteristics. Sudden cardiac death is caused by fast polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) that typically occur in situations associated with an increased vagal tone. In some patients with Brugada syndrome, the electrocardiographic characteristics and the life-threatening arrhythmias are provoked by fever or drugs.

Brugada syndrome is characterized on the electrocardiogram (ECG) by ST segment elevations directly followed by a negative T-wave in the right precordial leads and in leads positioned one intercostal space higher (figure 2), also referred to as a coved type Brugada ECG, or type 1 Brugada ECG. This specific ECG hallmark typically fluctuates over time, and in some patients it may only be elicited after provocation with class 1A or class 1C antiarrhythmic drugs.

In retrospect, similar type 1 ECGs have been described as early as 1953 in three otherwise healthy patients who presented with atypical substernal discomfort or for routine medical testing. One year later, ten more patients were described with ST elevation in the right precordial leads, including again clear-cut type 1 ECGs, without apparent heart disease and lack of events during follow-up. Furthermore, only 3 years before the publication of Brugada and Brugada in 1992, the specific Brugada ECG has been described in one out of six cases of ventricular fibrillation without apparent heart disease.

In the late 1970s and 1980s in the United States, unexplained nocturnal death affected many refugees from East and Southeast Asia, mainly men. This pattern of sudden death during sleep was already known for many centuries in Japan by the name Pokkuri (sudden unexpected death at night), and it was often prayed for as to end life without pain and suffering. In the Philippines it is long known as Bangungut (moaning and dying during sleep), in northeast

![Figure 1: Brugada ST morphologies](image)

ST segment morphologies recognized in Brugada syndrome: type 1, type 2, and type 3.
Thailand as Lai-Tai (died during sleep) and in Laos as non-laitai (sleep death).\textsuperscript{14,15} When studied, a considerable amount of these patients displayed a Brugada type ECG.\textsuperscript{14}

Different genes have been associated with Brugada syndrome since its description. First, in the late 1990s, sodium channel mutations were documented in Brugada syndrome patients.\textsuperscript{16,17} Furthermore, it was shown with heterologous expression in Xenopus oocytes that sodium channels with the missense mutation recover more rapidly from inactivation than wild-type controls and that the frameshift mutation causes nonfunctional sodium channels. At present, over 90 SCN5A mutations are correlated with Brugada syndrome.\textsuperscript{18} However, SCN5A mutations are only discovered in about 15%–30% of clinically diagnosed cases.\textsuperscript{19,20} Second, the gene which encodes for the glycerol-3-phosphate dehydrogenase 1-like protein, was correlated with Brugada syndrome in a single large family.\textsuperscript{21,22} In their report, London and co-workers report a reduction of sodium current in human embryonic kidney (HEK) cells expressing the mutated GPD1L gene versus wild-type controls, alike the SCN5A mutations linked with Brugada syndrome.\textsuperscript{23} Third, loss-of-function missense mutations in the genes encoding for the L-type calcium channel (CACNA1C, encoding the \( \alpha_1 \) subunit, and CACNB2 encoding the \( \beta_2b \) subunit) were reported in 9% of Brugada syndrome patients.\textsuperscript{24} Additionally, in a subset of these patients carrying a calcium channel mutation, the heart rate corrected QT interval appeared to be shorter than normal. Finally, loss-of-function mutations in SCN1B and SCN3B and gain-of-function mutations in KCNE3 gene have been associated with Brugada syndrome.\textsuperscript{25–27}

Notwithstanding the identification of yet unknown genetic mutations or pathophysiologic mechanisms, clinical decision making in Brugada syndrome remains a daunting task. Risk stratification in asymptomatic patients specifically, is heavily debated. Implantation of an implantable cardioverter-defibrillator (ICD) is the only generally accepted therapy for the prevention of sudden death in patients affected by Brugada syndrome.\textsuperscript{28,29} Albeit that oral therapy with quinidine may also prove valuable.\textsuperscript{30–34} Irrespective of the notion that sudden death can be the first manifestation of Brugada syndrome, it is still unclear how to correctly identify the large number of patients who will not develop life threatening arrhythmias despite the placement of the ECG leads in Brugada syndrome. For use in practice, V3 and V5 are often relocated from their original positions to V1ic3 and V2ic3 (adapted from ECGpedia.org with permission).
diagnosis of Brugada syndrome. Currently used risk stratification for the selection of the best candidates for ICD implantation is imperfect, not only in Brugada syndrome however.\[^{35}\] Thereby leaving some patients unprotected while they will develop these arrhythmias, and at the same time, many patients who receive an ICD will never need its intervention. The latter group of patients would therefore not require an –expensive– ICD which gives rise to a high risk for serious complications in this specific and young population.\[^{36}\]

**CLINICAL PRESENTATION**

**Epidemiology**

Since its description as a distinct clinical entity associated with sudden cardiac death in 1992, the prevalence of the Brugada ECG is increasingly recognized world wide and the prevalence is estimated at 1 per 2000.\[^{2}\] This is quite similar to Long QT syndrome with an estimated prevalence of 1 per 2000,\[^{37}\] but less than Hypertrophic cardiomyopathy with a prevalence of 1 per 500.\[^{38}\] However, the exact prevalence of Brugada-like ECGs is difficult to estimate partly because the specific ECG pattern typically fluctuates over time and can be intermittently concealed. Furthermore, many patients with a spontaneous or inducible Brugada ECG are and remain asymptomatic, and therefore may well remain without diagnosis. The prevalence of the spontaneous Brugada syndrome ECG seems to vary between different regions in the world (figure 3). Brugada syndrome would be most prevalent in East and Southeast Asia, particularly Japan, Thailand and the Philippines, where it is part of the sudden unexplained (nocturnal) sudden death syndrome (SUDS or SUNDS), which is a leading cause of death among young men.\[^{14,39,40}\] In Europe, Brugada syndrome is quite extensively described.\[^{19,28,41,42}\] In the United States,\[^{43}\] its prevalence seems to be lower. The world wide prevalence of the spontaneous type 1 Brugada ECG from the current prevalence studies (figure 3) is 0.06±0.14% and of the type 2–3 ECG this is 0.17±1.37% (n=333,685).

The patient

Malignant arrhythmic events can occur at all ages, from childhood to the elderly,\[^{1,44,45}\] with a peak around the 4th decade.\[^{2}\] The youngest patient clinically diagnosed with Brugada syndrome was 2 days old,\[^{46}\] and the oldest 85 years old.\[^{47}\] It is estimated that Brugada syndrome underlies 4%-12% of all sudden cardiac death and up to 20% of sudden cardiac death in patients without apparent structural heart disease.\[^{48}\] It may also be a cause of sudden infant death syndrome (SIDS).\[^{44,49}\] The clinical presentation is heterogeneous and may include a full blown form with syncope and (aborted) sudden cardiac death due to ventricular tachycardia or ventricular fibrillation, or milder forms with palpitations or dizziness. However, increasingly the clinical scenario is the detection of a Brugada syndrome ECG in an asymptomatic individual.\[^{41,50,51}\]
In a recent meta-analysis of 1217 Brugada syndrome patients (defined by a spontaneous or inducible Brugada ECG and excluding case reports), the majority of patients was asymptomatic (59%, range 0%–80%).

When sudden death occurs, this is most likely the result of fast polymorphic VT originating from the right ventricle / right ventricular outflow tract, which subsequently degenerates into VF leading to cardiocirculatory arrest. The onset of these life threatening arrhythmias typically occurs in situations with an augmented vagal tone, during sleep, or after large meals. Indeed, the latter gave rise to the suggestion of the use of a ‘full stomach

**Figure 3** Prevalence of the Brugada syndrome ECG

Combined prevalence data of the Brugada syndrome ECG in different parts of the world from 2000 to 2009. Bars represent mean prevalence in percentages. Only reports in English were considered. Prevalence studies in adolescents or children were discarded for this figure. As the type 1 ECG was only recognized after the first consensus report, prevalence in two studies was acknowledged as type 1 only, a coved type ECG was acknowledged as type 1, a saddleback or suspicious ECG as type 2–3. Note that the populations studied and the methods used vary importantly.

USA $43,193-198$ n = 211272, type 1 0.03% (range 0–0.43), type 2–3 0.02% (range 0.01–0.15). Finland $42$ n = 3021, type 1 0%, type 2–3 0.60% (one study). Austria $197$ n = 4491, type 1 0.25%, type 2–3 0.27% (one study, note that this population is highly selected, another cohort revealed one type 1 out of 47606 ECGs: 0.002%). France $31,198$ n = 36309, type 1 0.03% (range 0.03–0.1), type 2–3 0.20% (range 0.04–6). Italy $199$ n = 12012, type 1 0.02%, type 2–3 0.27% (one study, note that this population is highly selected, another cohort revealed one type 1 out of 47606 ECGs: 0.002%). Greece $200$ n = 11488, type 1 0.02%, type 2–3 0.20% (one study). Turkey $201$ n = 1238, type 1 0.08%, type 2–3 0.40% (one study). Israel $202$ n = 592, type 1 0%, type 2–3 0.85% (one study). Iran $203$ n = 3895, type 1 0.36%, type 2–3 2.21% (one study). Pakistan $204$ n = 1100, type 1 0.18%, type 2–3 0.64% (one study). Japan $192,205-208$ n = 44135, type 1 0.20% (range 0.05–0.42), type 2–3 0.45% (range 0.09–0.93). South Korea $209$ n = 225, type 1 0%, type 2–3 1.33% (one study). Philippines $210$ n = 3907, type 1 0.18%, type 2–3 2.23% (one study). Combined prevalence; n = 333,685, type 1 0.06% (range 0–0.43), type 2–3 0.17% (range 0.01–6).
test’ as a diagnostic tool.\textsuperscript{58}

Hyperthermia, for example fever, may also provoke the ECG or arrhythmias in a subset of affected patients.\textsuperscript{34,59-62} Furthermore, a large number of drugs have been reported to induce Brugada syndrome, or Brugada syndrome like, ECG characteristics, under which antiarrhythmic drugs, antianginal drugs, psychotropic drugs and also substances like cocaine and alcohol.\textsuperscript{2,3}

Some Brugada syndrome patients experience agonal respiration at night, when arrhythmias are most prevalent.\textsuperscript{14,55} This may be explained by self-terminating VT which can provoke (recurrent) syncope.\textsuperscript{63-66} Clinical presentation with sustained monomorphic ventricular tachyarrhythmia, although quite uncommon, has also been described.\textsuperscript{67-71}

In most patients premature ventricular complexes are scarce during 24 hour holter monitoring, but they may occur very frequently, up to 500 per day,\textsuperscript{63} and may increase before the spontaneous onset of VF.\textsuperscript{72} Repetitive episodes of ventricular fibrillation were initiated by premature ventricular contractions of similar morphology.\textsuperscript{72} Most premature ventricular contractions have a left bundle branch block morphology, indicating an origin in the right ventricle. There seems to be a predilection site of origin in the right ventricular outflow tract, but also extra systoles from the right ventricular free wall, septum and apex contribute and are capable of initiating VF.\textsuperscript{53} Further confirmation of the relationship between these right ventricular extra systoles and VF was derived from a study in three Brugada syndrome patients using endocardial catheter ablation of focal triggers of ventricular fibrillation at different sites in the right ventricle.\textsuperscript{73} This therapy resulted in the absence of further episodes of tachyarrhythmias during short-term follow-up. Large studies using this strategy with long-term follow-up are lacking however.

Although the most impressive ECG characteristics in Brugada syndrome are the changes in the right precordial leads, there are more remarkable observations to be made from the ECG. Supraventricular arrhythmias for example, mainly atrial fibrillation, are very common with a prevalence between 10\% and 39\%.\textsuperscript{74-77} Supraventricular arrhythmias were found to be more prevalent in patients who had an indication for ICD for either symptoms or inducible VT/VF during electrophysiological study.\textsuperscript{78,79} Although this could be inherent to a more severe form of the disease, data is still limited. Importantly, atrial arrhythmias may often lead to inappropriate ICD shocks.\textsuperscript{36,78,80}

For a syndrome that inherits an autosomal dominant trait with equal transmission to both genders, there is a striking male to female ratio of 4 to 1.\textsuperscript{52,81} Testosterone is probably a contributor to this gender disparity; surgical castration of two Brugada syndrome patients for prostate cancer normalized their ECGs,\textsuperscript{82} and testosterone levels in Brugada syndrome patients are higher when compared to controls.\textsuperscript{83} Sex hormones appear to modulate potassium and calcium currents during the repolarization phase of the action potential.\textsuperscript{84} Where testosterone may shorten the action potential duration,\textsuperscript{85} estrogen may lengthen action potential duration.\textsuperscript{86}
Furthermore, a different distribution of certain ion channels, particularly $I_{to}$, in males versus females may contribute.85

**ELECTROCARDIOGRAPHY AND DIAGNOSIS**

**The Brugada ECG**

Since its description in 1992, the signature sign of Brugada syndrome is its characteristic ECG.1,28 Patients with a spontaneous Brugada ECG and symptoms are at a high risk for sudden death secondary to VT/VF.28,29,41,81 The electrocardiographic manifestation of Brugada syndrome is typically dynamic and may often be concealed. The latter has important consequences for risk stratification and follow-up of these patients as particularly patients with dynamic ECGs might be at risk for future arrhythmic events.56,87,88 Furthermore, the ECG may be influenced or elicited by hyperthermia and drugs.

The diagnosis of Brugada syndrome requires the demonstration of a ‘type 1’ ECG pattern (figure 1).2,3 This type 1 Brugada ECG consists of 2 mm J elevation in at least two of the three right precordial leads (V1 to V3), gradually descending into a negative T wave (also known as a ‘coved type’ morphology of the ST-T segment).3 The presence of a type 1 morphology in the third intercostal space above V1 and V2 (V1ic3 and V2ic3) accompanied by a type 1 morphology in V1 or V2,5,6,89 is by almost all authors also considered as diagnostic for a Brugada ECG. Furthermore, in some patients, Brugada syndrome is exclusively diagnosed on a type 1 ECG in the leads positioned in the third intercostal space.5,6,90 Importantly, with the placement of leads in the third intercostal space above V1 and V2 (figure 2), sensitivity increases and there do not seem to be false positive test results. Also the prognosis of patients with a spontaneous type 1 morphology exclusively in the leads positioned in the 3rd intercostal seems to be similar to patients with a spontaneous type 1 morphology in V1 and V2.91 However, large prospective studies in the use of V1ic3 and V2ic3 are lacking. The type 1 ECG may be spontaneously present or provoked by drugs or hyperthermia. Furthermore, the definite diagnosis of Brugada syndrome requires additional to the type 1 ECG either: documented VT/VF, a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, syncope, inducibility of VT/VF with programmed electrical stimulation or nocturnal agonal respiration.3,89

There are two other ECG patterns recognized in Brugada syndrome, a type 2 and a type 3 ECG, although they are not specific and, importantly, not diagnostic (figure 1). A type 2 Brugada ECG displays a ‘saddleback’ appearance; it consists of 2 mm J elevation followed by a descending ST segment that does not reach the baseline and then gives rise to a positive or biphasic T wave.3 A type 3 Brugada ECG has the morphology of a type 1 or type 2 ECG with 2 mm J elevation but is characterized by a smaller magnitude of the ST elevation (1 mm).3 Due to its typical dynamic nature, the type 1 ECG can change from and to a type 2, type 3
or normal ECG spontaneously or under influence of hyperthermia or drugs. Interestingly, the magnitude of ST elevation does not differ between Brugada syndrome patients with or without SCN5A mutation.\textsuperscript{20}

As discussed earlier in this chapter, many drugs and substances are capable of inducing a type 1 ECG in patients with Brugada syndrome. For clinical purposes this knowledge is used as a diagnostic tool to evoke a type 1 ECG in patients suspected of Brugada syndrome who do not display a spontaneous type 1 ECG, for example in case of symptoms (syncope, aborted sudden cardiac death) or as part of familial screening for Brugada syndrome. For this purpose the sodium channel blockers ajmaline, flecainide, pilsicainide or procainamide are mostly used (table 1).\textsuperscript{2,3} The diagnostic accuracy of drug challenge in patients suspected of Brugada syndrome is higher with the use of ajmaline over flecainide, while equally safe.\textsuperscript{92,92} Safety of drug challenges for Brugada syndrome is ensured when the test is performed while the patient is continuously monitored with 12-lead ECG, with cardioverter defibrillators and advanced cardiac life support close at hand and discontinuation of the test when a type 1 ECG is reached, when ventricular extra systoles or VT develops or when the QRS duration increases more than 30%.\textsuperscript{3}

As a type 1 ECG is associated with ventricular arrhythmias, drugs or substances associated with a type 1 ECG need to be avoided in patients diagnosed with Brugada syndrome (table 2). Particular attention should also be given to general anesthesia in Brugada syndrome patients.\textsuperscript{93-96} The administration of isoprotenerol, a ß-receptor agonist, and/or quinidine may effectively be used to treat repetitive ventricular arrhythmias or electrical storms.\textsuperscript{31,97-100}

As mentioned earlier, hyperthermia may also evoke a type 1 ECG or ventricular arrhythmias in a subset of Brugada syndrome patients. Several reports revealed the presence of a type 1 ECG or –sometimes fatal– episodes of arrhythmias during febrile illness, often in children.\textsuperscript{34,59,62,70,101,102} Elevation of the core body temperature during hot baths for example may have a similar effect.\textsuperscript{103} Treating fever with antipyretic agents such as paracetamol (US: Acetaminophen) and/or antibiotics may prove valuable in these cases. If hyperthermia persists and arrhythmias cannot be counteracted, cooling the patient by all means may be the ultimate rescue (personal communication dr. Pedro Brugada, ESC congress 2006).

There is a wide differential diagnosis of clinical conditions accompanied by coved-like or elevated ST segments in the right precordial ECG leads, and these should be ruled out before a

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Drug} & \textbf{Dosage and administration} \\
\hline
Ajmaline & Max. 1 mg/kg i.v. \\
Flecainide & Max. 2 mg/kg i.v. \\
Pilsicainide & Max. 1 mg/kg i.v. \\
Procainamide & Max. 10 mg/kg i.v. \\
\hline
\end{tabular}
\caption{Provocation of the Brugada ECG}
\end{table}

\textsuperscript{I.v. denotes intravenously. Ajmaline administration particularly differs between studies (e.g., bolus every minute versus continuous administration, 5 minutes versus 10 minutes). Adapted from Antzelevitch et al.}
A conclusive diagnosis of Brugada syndrome can be made (Table 3). Relatively common causes include: early repolarization, myocardial infarction or ventricular aneurisms, vasospastic angina, electrolyte disturbances such as hyperkalemia or hypercalcemia, pericarditis or myocarditis, left or right bundle branch block and left ventricular hypertrophy.

### Other electrocardiographic characteristics

Other remarkable ECG characteristics associated with Brugada syndrome include conduction defects in the atria, conduction system and ventricles. Frequently present are broad P waves, long PQ intervals, prolonged corrected sinus node recovery times, prolonged His-ventricle (HV) intervals which may or may not be accompanied by prolonged atrio-His (AH) intervals, sinus and AV node dysfunction, QRS axis deviation, and broad QRS complexes. Conduction interval prolongation is frequently associated with the presence of SCN5A mutations. Furthermore, SCN5A mutations in Brugada syndrome patients may, similar to Lev-Lenègres disease, worsen the phenotypic expression of the disease with aging and may lead to the necessity of pacemaker implantation.

Although there is some variability of the heart rate corrected QT interval (QTc), it does not seem to prolong importantly when a type 1 Brugada ECG or ventricular fibrillation develops. This clearly demonstrates distinction from Long QT syndrome where excessive QTc prolongation is the hallmark of the disease. Overlap syndromes between Brugada syndrome and Long QT syndrome (type 3) exist, based on a multidysfunctional sodium channel caused by specific SCN5A mutations. Interestingly, the phenotype of one of these
mutations (SCN5A 1795insD) seems to be similar in a mouse model carrying the murine equivalent mutation (SCN5A 1798insD) with bradycardia, right ventricular conduction slowing, an increased vulnerability for arrhythmias and QTc prolongation. Conversely, shortened QTc intervals were noted in a subset of Brugada syndrome patients with calcium channel mutations. However, data regarding the calcium channel mutation and/or shortened QTc intervals is presently limited.

Wide S waves in the inferior leads are frequently observed before and after a type 1 ECG develops during drug challenge, which may reflect simultaneous slowing of right ventricular activation. Furthermore, S waves ³80 ms in V1 appeared to be a good predictor for a history of ventricular fibrillation.

Signal averaged ECGs show more variation in filtered QRS duration and late potentials in symptomatic patients. Late potentials are generally regarded as delayed and disorganized ventricular activation and are related to ventricular tachyarrhythmias. In Brugada syndrome however, other mechanisms have also been proposed: late potentials might for example represent a delayed second upstroke of the epicardial action potential, a local phase 2 reentry or an interventricular conduction delay. These latter proposals have however not yet been validated as primary or cooperative pathophysiologic mechanisms of late potentials in Brugada syndrome.

In some case reports of patients who presented with ventricular fibrillation, ST elevation in the inferior and/or lateral leads has been described in the absence of electrolyte disturbances, hypothermia or myocardial ischemia. In a French family, different SCN5A mutation carrying family members displayed either inferior or right precordial coved type ST
segment elevation.\textsuperscript{136} At present it is uncertain if these patients represent the same population as has been described by solely right precordial coved type ST segments.

**PATHOPHYSIOLOGY AND GENETICS**

**Arrhythmia mechanisms**

Ventricular arrhythmias in Brugada syndrome often originate from ventricular extra systoles in the right ventricle, which subsequently initiate polymorphic ventricular tachycardia or ventricular fibrillation. The exact pathophysiology behind Brugada syndrome is, however, not clear and there might be different electrophysiological mechanisms involved. It seems clear that an increased vulnerability of the ventricles is present before the onset of ventricular fibrillation. The coupling interval (i.e. the timing) of the premature ventricular complex, for example, may be important. In several electrophysiological studies, short coupled extra systoles (<200 ms) were necessary to induce ventricular fibrillation while the coupling interval of the first premature ventricular complex of spontaneous ventricular fibrillation is often (far) more than 300 ms.\textsuperscript{54,72} There might furthermore be a relation between the vulnerability of the ventricle and the preceding RR interval following for example an extra systole, which may augment ST elevation and eventually degenerate into ventricular fibrillation.\textsuperscript{137}

Notwithstanding the associated risk for sudden cardiac death of a type 1 ECG, it is not necessary for arrhythmias in Brugada syndrome. This was shown in holter and ICD recordings documenting the onset of ventricular fibrillation,\textsuperscript{54,72} suggesting that there might be distinct –albeit possibly related– electrophysiological mechanisms involved. Moreover, numerous patients with spontaneous type 1 ECGs will never have any symptoms.\textsuperscript{9,10,138}

**The coved type morphology**

Ever since the first descriptions of Brugada syndrome, authors have been addressing possible mechanisms for this characteristic ECG feature to occur.\textsuperscript{1,8,10,139-141,141,142} Currently, there are two leading theories addressing the coved type morphology of the right precordial ST segments in Brugada syndrome; the depolarization model and the repolarization model.\textsuperscript{143}

The repolarization model has been developed by Yan and Antzelevitch in canine right ventricular wedge preparations.\textsuperscript{144} In this model, simultaneously measured epicardial and endocardial electrograms showed loss of action potential dome in the epicardium only when the wedge preparation was exposed to a potassium channel opener (pinacidil) or a combination of a sodium channel blocker (flecainide) and acetylcholine. This resulted in a transmural dispersion of repolarization with different lengths of action potentials across different cardiac layers, ST segment elevation on the ECG and it created a vulnerable window for (“phase 2”) re-entry to occur between these layers and degenerate into ventricular tachyarrhythmias. Isoprotenerol, 4-aminopyridine and quinidine were able to restore this loss
of action potential dome, normalize the ST segments and prevent the ventricular arrhythmias.

This model resolves around a heterogeneous expression of the transient outward potassium current $I_{to}$. This current seems to be stronger expressed in the canine epicardium over endocardium, stronger in the right ventricle than in the left ventricle, and stronger in males than in females, resulting in a higher susceptibility for $I_{to}$ augmentation over other currents and a consequential higher risk for ventricular tachyarrhythmias. Augmentation of $I_{to}$ would be enhanced by sodium current ($I_{Na}$) reduction, either by a sodium channel mutation or sodium channel blockade. Furthermore, reduction of the calcium current ($I_{Ca}$) and augmentation of the ATP driven potassium current ($I_{K-ATP}$) would give similar effects.

Another model explaining the coved type morphology resolves around a depolarization disorder. In this model conduction slowing or conduction delay in the right ventricular outflow tract (RVOT) causes the type 1 morphology in the right precordial leads. Most evidence for this model is derived from clinical studies. Furthermore, conduction slowing may create the vulnerability for re-entry of the right ventricle and give rise to ventricular extra systoles. The marked conduction slowing in atria and ventricles which is seen during drug challenges with sodium channel blockers and in SCN5A mutation carriers particularly, further supports this model.

However, neither the depolarization model nor the repolarization model fully explains the coved type morphology, the vulnerability for ventricular arrhythmias and the observed clinical and experimental data in Brugada syndrome. Alike many diseases, it is likely that Brugada syndrome is not explained by one single mechanism. The final common pathway of a spontaneous or inducible coved type ECG and the vulnerability for ventricular arrhythmias may be started by distinct but cooperative mechanisms and may require tailored risk stratifications and treatment. Moreover, there might be other cooperative pathophysiological mechanisms involved like structural myocardial abnormalities and gene-gene interactions.

**Structural changes**

The most recent consensus criteria for Brugada syndrome recommend the exclusion of structural myocardial derangements in conjunction with the documentation of a type 1 ECG and the presence of at least one of the obligatory additional elements (see section Electrocardiography and diagnosis) before a conclusive diagnosis of Brugada syndrome can be made. This reflects the hypothesis that Brugada syndrome is a pure electrical disease involving only myocardial channel abnormalities and thus the absence of structural changes. This issue has however been debated in the last years. A similarity between Brugada syndrome and arrhythmogenic right ventricular dysplasia/cardiomyopathy has been advocated. Biventricular endomyocardial biopsies in 18 Brugada syndrome patients showed myocarditis, cardiomyopathy-like changes or fatty infiltration in the right ventricle of all patients (without
Brugada syndrome

Furthermore, in eight out of these 18 patients (45%) there were similar findings in the left ventricle. Both magnetic resonance imaging (MRI) and echocardiography were negative for structural heart disease in all patients. Interestingly, the patients displaying fatty infiltration and cardiomyopathy-like changes all had a SCN5A mutation.

In another case, right ventricular fibrosis and epicardial fatty infiltration was documented in the explanted heart of a SCN5A mutation carrying Brugada syndrome patient who experienced intolerable numbers of ICD discharges (up to 129 appropriate shocks in 5 months). This patient also had no clinically detected cardiac structural abnormalities. However, MRI was performed 10 years before transplantation. In a study using endocardial mapping it was noted that Brugada syndrome patients showed increased electrogram fractionation and abnormal conduction velocity restitution, both also related to structural derangements.

These reports suggest that there might be cooperative functional and structural derangements in Brugada syndrome which may be enhanced by mutations in the cardiac sodium channel. In support of this hypothesis, mice and human data illustrate that SCN5A mutations may lead to impressive fibrosis accompanied by conduction disturbances, mainly in the right ventricle, which worsens with aging. Fibrosis is probably missed in clinical practice as the clinical modalities to assess structural changes are incapable of detecting mild or diffuse abnormalities. Interestingly, a meta-analysis into risk stratification for ventricular tachyarrhythmias did not find an increased risk for patients carrying a SCN5A mutation.

 Genetic aspects

Mutations in cardiac ion channels have been identified in only 15-30% of patients. Although recent efforts in screening 16 putatively associated genes did document the association between Brugada syndrome and the calcium channel besides the sodium channel, still this only resulted in a mutation diagnosis in 24% of patients.

The first mutation in Brugada syndrome patients was presented in a collaborative effort of clinics in Europe and the United States in 1998. A loss of function mutation in the SCN5A gene, encoding the pore-forming a-subunit of the human cardiac sodium channel protein (Na\text{v}1.5), was present in three out of six families with Brugada syndrome. Mutations leading to loss of sodium channel function can lead to a variety of disorders: Brugada syndrome (OMIM 601144), (progressive) cardiac conduction defects also known as Lev-Lenègres disease (OMIM 113900), sick sinus syndrome (OMIM 608567), Sudden infant death syndrome (OMIM 272120) and dilated cardiomyopathy associated with conduction defects and arrhythmias (OMIM 601154). In combination with other (atrial specific modifier) genes, a loss of function defect may cause atrial standstill. Mutations leading to a gain of function of the channel may cause Long QT syndrome type 3 (OMIM 603830) and also Sudden infant death syndrome (OMIM 272120). As mentioned earlier, certain
mutations in the sodium channel gene may lead to combined phenotypes of loss of function and gain of function mutations, also referred to as an overlap syndrome.\textsuperscript{119,121,122} SCN5A promoter polymorphisms in a haplotype variant may lead to variability in phenotypic expression as was shown recently in a study demonstrating slower cardiac conduction with a gene-dose effect in patients from Asian origin.\textsuperscript{173} The same holds for common SCN5A polymorphisms or the combination of different SCN5A mutations which may modulate the expression of the mutant gene(s) and disease.\textsuperscript{174-177} Loss of function cardiac calcium channel mutations have recently been demonstrated in Brugada syndrome patients.\textsuperscript{24} These mutations involved the L-type calcium channel encoded by CACNA1c for the pore-forming Ca\textsubscript{v}1.2 \( \alpha \textsubscript{1} \) subunit, and CACNB2 for the Ca\textsubscript{v}\( \beta \textsubscript{2b} \) subunit involved in channel activation modulation of the \( \alpha \textsubscript{1} \) subunit. Mutations in the GPD1L gene have also been linked to Brugada syndrome in a single family.\textsuperscript{21,22} The function of this gene is poorly understood at present but it may be involved in sodium channel trafficking and probably does not contribute more than 1% in Brugada syndrome.\textsuperscript{178,179} Exon mutations or duplications in the SCN5A gene and a large number of other candidate genes (Caveolin-3, Irx-3, Irx-4, Irx-5, Irx-6, Plakoglobin, Plakophilin-2, SCN1B, SCN2B, SCN3B, SCN4B, KCNH2, KCNQ1, KCNJ2, KCNE1, KCNE2, KCNE3, KCND3, KCNIP2, KCNJ11 and CACNA2D1) have recently been investigated in SCN5A mutation negative Brugada syndrome patients with little success.\textsuperscript{24,179} Nevertheless, recently also mutations in several of these genes (SCN1B, SCN3B and KCNE3) have been associated with Brugada syndrome.\textsuperscript{25-27} SCN1B and SCN3B encode for subunits of the cardiac sodium channel and these mutations cause a loss-of-function resulting in a Brugada Syndrome phenotype. KCNE3 encodes for a subunit of MiRP2 which is involved in the transient outward current and a gain-of-function mutation resulted in the Brugada syndrome phenotype. Interestingly, a recent study revealed common gene expression levels in Brugada syndrome patients irrespective of the culprit gene.\textsuperscript{180} This expression pattern involved not only cardiac sodium channel and its subunits, but also potassium channels and calcium channels.

Typically for Brugada syndrome, and other mendelian disorders, is an incomplete penetrance and variable expression of the disease.\textsuperscript{181} Hence, not all mutation carriers are affected by the same degree and will thus not require the same treatment. Even so, the importance of diagnosing mutation carriers with little or no phenotypic expression of the disease is important because they still have a 50% chance of transmitting the genetic defect to their offspring, who in turn may be seriously symptomatic at young age. It is however not clear whether pre-symptomatic genetic testing in children of Brugada syndrome patients is to be advised.\textsuperscript{182} As symptomatic Brugada syndrome is rare in children particularly, risk stratification is imperfect and treatment may do more harm than good (see also the section on Clinical decision making), the consequences of a positive test result of presymptomatic genetic testing should be carefully considered.
Risk stratification

After diagnosing Brugada syndrome, risk stratification for future ventricular arrhythmias is mandatory. The prognosis and risk stratification of Brugada syndrome patients is, however, debated. Risk for future ventricular arrhythmias is generally accepted to be high in patients who are known to have already experienced life threatening ventricular arrhythmias, that is, patients with a history of aborted sudden cardiac death. Syncope and also dizziness or nocturnal agonal respiration, can also be caused by ventricular arrhythmias and are thus often regarded as high risk. However, this assumption can be erroneous so other causes of these symptoms should also be sought.

A recent meta-analysis combined a history of sudden cardiac death and/or syncope as representative for a history of ventricular arrhythmias and found a relative risk (RR) of 3.34 (95% confidence interval (CI) 2.13-4.93) for the combined event of sudden cardiac death, syncope or ICD shock during follow up. Also male gender, RR 3.47 (95% CI 1.58-7.63), and a spontaneous type 1 ECG versus a drug induced type 1 ECG, RR 4.65 (95% CI 2.25-9.58), were positively associated with the occurrence of the combined events during follow up. A family history of sudden cardiac death, a SCN5A mutation or inducible ventricular arrhythmias during electrophysiological study were not associated with events during follow up. Importantly, these risk factors are probably not independent.

As also asymptomatic patients may experience ventricular arrhythmias in the future there is a dire need for reliable risk stratification in these patients. The role of the inducibility of ventricular arrhythmias during electrophysiological study in this matter has been debated in the recent years. A meta-analysis to assess its prognostic role was not able to identify a significant role with regard to arrhythmic events during follow-up. In a combined effort of 14 centers in France and Japan, it was shown that 45% of the 220 studied Brugada syndrome patients received an ICD following inducibility of ventricular arrhythmias during electrophysiological study whilst being asymptomatic. In this study there was an 8%rate of appropriate shocks for ventricular arrhythmias during >3 years follow up. A relatively low (2 to 5 times lower) rate of appropriate shocks in asymptomatic patients compared to the patients with syncope or aborted sudden cardiac death was documented, however. There were no other factors (like a spontaneous type 1 ECG) apart from a clinical history of syncope or aborted sudden cardiac death predicting appropriate shocks. Of importance, circa 20% of patients in each group suffered from inappropriate shocks during follow-up.

Noninvasive risk stratification has been attempted in relatively small cohorts of patients and yielded the strongest predictive value in spontaneous changes in the right precordial ST segments. A standard cardiology work-up including echocardiogram, 24 hour Holter and an exercise test may be valuable to exclude differential diagnoses and to
assess baseline conditions. Thorough cardiac imaging using MRI or CT does not seem to add significant clinical value at present, unless arrhythmogenic right ventricular cardiomyopathy needs to be excluded.

A summary of the current literature on risk stratification suggests that symptoms likely to be related to ventricular arrhythmias identify the patients at highest risk for future life-threatening arrhythmic events. Conversely, as asymptomatic patients have a very low risk of experiencing these arrhythmias, and the currently available treatment options may do more harm than good, they should be identified as low risk. A spontaneous type 1 ECG, whether or not accompanied by inducible arrhythmias during electrophysiological study, is by some identified as an increased risk (see also section on Treatment). Naturally, risk stratification should be re-evaluated in all patients during long term follow-up with up-to-date consensus criteria.

**TREATMENT**

The most effective therapy to treat ventricular arrhythmias in Brugada syndrome is implantation of an ICD. Patients may, however, experience intolerable numbers of ICD shocks, up to 150 a day, as an ICD does not lower the vulnerability of the heart for ventricular arrhythmias. In some patients heart transplantation has been considered the only remaining option. Cardiologists should carefully weigh benefits versus possible harm, quality of life and costs of ICDs as event rates are generally low and complications (in particular inappropriate shocks) are high in this population. ICD implantation in the young specifically denotes several battery replacements, re-implantations over many decades and increased morbidity. However, some Brugada syndrome patients may benefit from an ICD when they lost a family member due to sudden cardiac death and intolerable anxiety diminishes their quality of life and impairs their daily activities.

Acute lowering of the vulnerability of the heart for ventricular arrhythmias may be accomplished by treating hyperthermia (e.g. cooling, antipyretics, antibiotics), correcting electrolyte disturbances and the administration of quinidine and/or isoproterenol. Further chronic oral treatment with quinidine or several other agents may prove valuable. Excluding differential diagnoses in case of acute events is mandatory as ventricular tachycardias not due to Brugada syndrome may display a devastating response on isoproterenol.

All patients with Brugada syndrome should receive a list of avoidable drugs and substances, including a number of antiarrhythmic drugs (class Ia, Ic and β-blockers), tricyclic antidepressants (with a relative contraindication for non-tricyclic antidepressants), local anesthetics, opioid analgesics, propofol, potassium channel antagonists, lithium, cocaine and excessive use of alcohol (see www.brugadadrugs.org). Furthermore, patients should be instructed to obtain an ECG in case of fever at least once to assess whether their form of Brugada syndrome is hyperthermia sensitive. Long term follow-up is mandatory in all
Brugada syndrome patients. Symptomatic patients will have more frequent visits, but also asymptomatic patients should be seen with regular intervals for re-assessment of the risk for arrhythmic events and genetic counseling in case of children for example. Genetic counseling should be advised for all adult patients.

**Future research**

As Brugada syndrome is a rather new entity, the knowledge and awareness of Brugada syndrome will continue to evolve in the following years. In the first years after the description in 1992, many heavily symptomatic patients were recognized, which led to the notion that Brugada syndrome is a malignant disease that is hard to manage.\(^1\)\(^,\)\(^2\)\(^8\) More recently, many asymptomatic patients have been diagnosed and one of the great challenges for the future years is to develop a reliable risk stratification for arrhythmic events in these patients.\(^8\)\(^8\) Risk stratification and treatment in the pediatric population affected with Brugada syndrome, although limited in numbers, should also receive greater attention. The pathophysiology of the ventricular arrhythmias and the coved type ECG in the right precordial leads has been and will continue as a major area of research. Although many animal and computer models became available recently, detailed descriptions of human data will continue to be important and will guide therapeutic interventions. Finally, further characterization of the genetic origin of Brugada syndrome will help to identify those silent carriers, and their offspring, who might be at risk and may clarify the complicated genotype-phenotype relationship in Brugada syndrome patients.

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