The Brugada syndrome:
update 2006.
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Summary
Over the last 14 years - since the Brugada syndrome was first recognized as a distinct clinical/electrocardiographical entity - a considerable number of papers have been published on its various aspects.

It has been defined as the combination of a typical ST-segment elevation in the right precordial leads and a predisposition for malignant ventricular arrhythmias occurring in the absence of structural heart disease. From the outset, controversy arose about the diagnostic criteria to be applied. This issue has been clarified since the announcement of a first (2002) and second (2005) consensus report. Our review will discuss the clinical characteristics and different possible pathophysiological mechanisms underlying the specific ECG-abnormalities and susceptibility for malignant arrhythmias. Nowadays, the main issue of discussion revolves essentially around its prognostic features, especially in asymptomatic patients.

This review will compare the results of different follow-up studies and yields a possible explanation for the differences in event rates and in the identification of useful sudden-death predictors. Finally, the most recent data concerning new diagnostic techniques, gene identification and future therapeutic options will also be discussed.

Résumé
Le syndrome de Brugada : actualisation 2006.

Ces quatorze dernières années, depuis que le syndrome de Brugada a été la première fois reconnu en tant qu’entité clinique/électrocardiographique distincte, un nombre considérable d’articles ont été consacrés à ses multiples aspects.


Cet article compare les résultats des différentes études menées et apporte une explication possible de leurs divergences concernant l’occurrence d’événements cardiaques, ainsi qu’une identification de signes utiles de prédiction de la mort subite. Enfin, les données les plus récentes sur les nouvelles techniques diagnostiques, l’identification génique et les futures options thérapeutiques seront également abordées.

INTRODUCTION

In 1992, Brugada and Brugada [1] first described a new clinical entity consisting of syncopal and sudden death episodes due to malignant arrhythmias (VF or polymorphic VT) in the absence of structural heart disease. All eight patients studied showed a right bundle branch morphology with similar ST-segment elevation in the right precordial leads. This typical ECG pattern, either occurring spontaneously or elicited by antiarrhythmic drugs, has come to be considered a distinguishing
feature of the Brugada syndrome (BS). Because of its recognition as a major cause of sudden cardiac death all over the world and the devastating consequences for these predominantly young patients, this syndrome has gained significant interest over the last 14 years, and its clinical heterogeneity, pathophysiology and genetic background have been extensively explored.

This review will focus on the most recent developments in this field.

EPIDEMIOLOGY

Since the recognition of the BS, numerous prospective cohort studies [2-6] about the prevalence of the Brugada ECG pattern have been reported. Its prevalence varies between 0.05% (Europe, USA) and 1% (Asia) in adult populations. In one large-scale Japanese study [3], where approximately 16,300 schoolchildren were screened, only one ECG compatible with BS was identified (0.0006%), suggesting that manifestation of the ECG pattern primarily occurs during adulthood. In the absence of structural heart disease, BS is responsible for at least 20% of sudden cardiac deaths. In 2002, Atta, et al. provided evidence that the Sudden Unexpected Nocturnal Death Syndrome (SUNDS), which has been endemic in South-East Asia for many decades, is clinically and genetically similar to the BS [7].

CLINICAL CHARACTERISTICS

The mean age at diagnosis is forty years, with a wide range between two months and 77 years. Males predominantly are affected (M/F-ratio 3/1). There is a wide spectrum of clinical manifestations, ranging from asymptomatic carriers to sudden death. The majority of asymptomatic cases are family members of patients diagnosed with the syndrome who were identified during family screening. However, because of increasing awareness, sporadic asymptomatic individuals, in whom an ECG was recorded for various reasons, are also being increasingly recognized. Symptomatic patients present with syncope (due to ventricular tachycardia), seizures, palpitations, nocturnal agonal respiration or (aborted) sudden cardiac death (due to ventricular fibrillation). Up to 20% of the patients have concomitant supraventricular ventricular tachycardias [8], most frequently atrial fibrillation, which can also be the first presenting symptom.

Diagnosis

In 2005, the second consensus report [9] endorsed by the Heart Rhythm Society and the European Heart Rhythm Association was published with recommendations regarding the diagnosis of BS. Three different ECG patterns, all exhibiting ST-segment elevation in the right precordial leads, have been recognized. Type 1 is the only pattern that is diagnostic for BS. It consists of a coved type ST-segment elevation ≥ 2 mm, followed by a negative T-wave in at least one right precordial lead (V1-V3) (fig. 1). Because of the dynamic nature of these ECG changes, with day-to-day variation in morphology and possible transient normalization, a pharmacological challenge with class I sodium channel blockers is performed to unmask the concealed coved type ECGs [10]. A definite diagnosis is made when the coved type ECG pattern, either spontaneous or drug-induced, is found in association with symptoms or documented ventricular arrhythmias or a family history of SCD. Type 2 is a saddleback ST-pattern (fig. 2) with a high initial augmentation, followed by an ST-elevation of ≥ 2 mm in at least one right precordial lead. The T-wave can be positive or biphasic. Type 3 ST-segment elevations (fig. 3) are < 1 mm, with either coved or saddleback morphology. It should be emphasized that the type 2 and type 3 ECG patterns are not considered diagnostic for BS. In patients showing type 2 or 3 ECG pattern, BS can only be diagnosed if conversion to the coved type I ECG occurs after administration of sodium channel blockers.

In the last years, conflicting data have been published whether upward positioning of the right precordial leads increases diagnostic sensitivity or inappropriately causes over diagnosis of the syndrome. Further large prospective studies are necessary to clarify this issue.

Fig. 1 – Exemple du trace d’ ECG de type I.
Fig. 1 – Example of the type I ECG pattern. 12 lead ECG of a 9 years old girl presenting with syncope and a family history of sudden death and Brugada syndrome. Note the marked coved type I ST elevation in leads V1 and V2 (arrows), diagnostic for BS. Note also the first degree AV block and left posterior hemiblock, frequently observed in the syndrome.

Fig. 2 – Exemple du trace d’ ECG de type II.
Fig. 2 – Example of the type II ECG pattern. 12 lead ECG of a 47 years old asymptomatic male. Spontaneous type I coved ECG pattern was an incidental finding on a routine ECG (not shown). 2 weeks later the 12 lead ECG shown below shows only saddle back type II ST elevation in lead V2 (arrow), which in itself is not diagnostic for Brugada syndrome.
In a very recent publication [11], Ikeda, et al. proposed ‘the full stomach test’ as a novel diagnostic technique identifying patients with a Brugada type ECG and high risk for arrhythmic events in a series of 35 patients. This method is based on the observation that gastric distension induces an enhanced vagal tone with resulting coved type I ST-elevation in BS.

Class I antiarrhythmic drug test

Four class I antiarrhythmic drugs are used for diagnostic purposes in Brugada syndrome: ajmaline (fig. 4), flecainide, procainamide and pilsicainide. Recently, Hong and Brugada [12] investigated the value of the ajmaline test in four large families with SCN5A mutations (147 individuals). They found that the sensitivity and specificity of the ajmaline test in identifying gene carriers was 80% and 94.5% respectively, with an increase of phenotype penetrance from 32% to 78%, thereby reflecting the importance of the test. This study also suggested that family members with normal spontaneous ECG’s should be suspected of being gene carriers whenever a first degree AV block and/or saddleback ST-segment elevation is documented.

In another recent study [13], Wolpert, et al. compared the effect of intravenous ajmaline and flecainide regarding their ability to unmask the coved type I Brugada ECG pattern. Both drugs induced similar changes in PQ and QRS intervals, suggesting equal effects on sodium channel currents. On the other hand, the Ito-current was significantly more affected by flecainide compared to ajmaline, making the latter more effective and reliable. In this study 32% of 22 ajmaline positive patients had a negative flecainide test. Although a similar comparative study for procainamide is not available, there is general agreement that the sensitivity of the test with this drug is even lower. It should be noted that the class I antiarrhythmic drug test is a helpful diagnostic tool, however, its specificity in identifying patients at risk for sudden death is currently unknown.

Pathophysiology

Based on arterially perfused wedge preparations in dogs, Antzelevitch, et al. [14] described a ‘repolarisation disorder’ as a possible explanation for the ST-abnormalities in BS. There is a striking difference in action potential morphology in the epicardial, endocardial and M-cells, especially during phase two and three (fig. 5). Whereas the epicardial AP shows a prominent notch and dome immediately following phase one depolarization, the endocardium AP is more gradually shaped during early repolarization. The transmural gradient originating from this shape difference represents the ST-segment on the surface ECG. Alterations of spike and dome morphology (phase two), especially in the epicardium, are predominantly mediated by the transient outward current (Ito). In BS, the loss of RVOT-epicardial (not endocardial) AP dome and plateau amplitude, due to an increase in Ito and simultaneous decrease in (inward) INa, underlies the prominent J-wave and ST-segment elevation (mimicking RBBB morphology). The conduction of the action potential dome from sites at which it is maintained to sites at which it is lost allows local reexcitation via a phase two reentry mechanism when a closely coupled extrasystole occurs in the vulnerable window. These premature beats might eventually trigger the malignant arrhythmia. Since the balance of currents at the onset of phase two determines the maintenance of the AP dome, acquired forms of the BS can originate from an increase in outward currents (Ito, IK-ATP, IKs).
and $I_K$) or a decrease in inward currents ($I_{Ca-L}$, $I_{Na}$). Case reports over the last 13 years described ST-changes as in BS caused by drugs, RVOT-ischaemia, electrolyte disturbances, hyper- and hypothermia, elevated insulin levels and mechanical compression of the RVOT (table I).

However, it is well known, that especially in patients with a SCN5A mutation, clinical signs of conduction slowing in the forms of PR, HV and QRS prolongation can be observed. Accordingly, recently, Meregalli, et al. [15] presented an alternative ‘depolarization disorder’ theory, rendering another possible explanation for the Brugada ECG abnormalities. This model is based on a conduction delay in the RVOT. Due to AP-differences between the RVOT and the rest of the right ventricle a closed-loop current originates between these two regions, creating an initial ST-elevation followed by a negative T-wave at the level of the right precordial leads (fig. 6). It is also possible that both of the above mentioned mechanisms operate in the pathophysiology of the Brugada ECG pattern and the ventricular arrhythmias.

Genetic background

The BS is transmitted in an autosomal dominant fashion with variable expression. The first mutation linked to BS, identified in 1998 by Chen, et al. [26], was located in the SCN5A gene (chromosome 3p21), encoding for the pore forming β-subunit of the sodium channel. The SCN5A-gene mutations were previously described in Romano-Ward long QT-syndrome (LQT3) and in Lenegre syndrome. Currently, over 70 SCN5A mutations have been identified accounting for approximately 25% of all BS-patients, suggesting that

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Acute ischaemia in the RVOT [20]

Electrolyte disturbances [21]

Hyperkalemia

Hypercalcaemia

Hyperthermia and hypothermia [22-24]

Elevated insulin level [25]

Mechanical compression of the RVOT
other gene mutations may be operative. All SCN5A mutations modify the sodium channel function by either creating a truncated protein or by increasing the channel inactivation, resulting in a shortened AP due to rapid phase one depolarization or by creating trafficking problems of the channel. In contrast, SCN5A mutations causing LQT3 augment the function of sodium channels, resulting in a (dangerous) prolongation of AP. In 2002, Weiss, et al. [27] located a second locus linked to BS on chromosome 3 and recently the same group identified the causative mutation in the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L).

**Differential Diagnosis**

**Overlapping phenotypes**

Several families have been reported in which the same SCN5A mutation manifests in one family member as long QT-3 syndrome, in another family member as BS and in a third one as a combination of the two [28-30]. Similar overlapping phenotypes with cardiac conduction defects have also been reported. These cases prove that beside the likely causative SCN5A mutations other genetic (polymorphism) and environmental factors also influence the phenotype.

**Arrhythmologenic right ventricular dysplasia**

Over the last decades, several reports have been published on the similarities between BS and arrhythmologenic right ventricular dysplasia. However, it should be emphasized that in spite of many efforts to prove otherwise, in BS, in contrast to ARVC there is no macroscopic structural heart disease present. On the other hand, recent evidence suggests that microscopic structural alterations might be present in patients with BS (with or without SCN5A mutation). In a recent small study [31], Frustaci, et al. performed histological analysis of biventricular biopsies in 18 consecutive probands who where clinically diagnosed with BS. Angiography documented morphological abnormalities in seven patients and all non SCN5A mutation carriers showed histological changes (myocarditis, fibrofatty infiltrations). They concluded that environmental factors such as viral infections and inflammation can cause myocardial damage underlying the ECG changes in BS. The most correct conclusion from this study should have been that myocarditis can simulate BS.

In another recent case report [32], Coronel, et al. describes genetic, morphological and electrophysiological characteristics of an explanted heart of a young patient who previously was diagnosed with BS and who underwent heart transplantation because of incessant, therapy refractory VF. This post-mortem analysis identified discrete interstitial changes (mainly fibrosis) in the RV causing RV-conduction delay. No transmural AP-gradient was identified. In this particular case, the underlying mechanism supports the previously mentioned depolarization theory rather than the repolarization theory.

**Prognosis and therapy**

Risk stratification in BS is currently an active area of research, since the ideal approach is still controversial. Several study groups are trying to identify risk factors predicting which patients will die suddenly due to ventricular arrhythmias and which will remain asymptomatic for all their life. Aborted sudden death, syncope of unknown origin, EP study, the presence of spontaneous ECG abnormalities, SAECG, QT-interval in lead V1 have all been investigated and proposed as risk predictors. To further complicate the picture the only proven effective treatment in the prevention of sudden death is an ICD, which is costly and is not without risks. General agreement exists that the most important predictors of future arrhythmic events are the presenting symptoms. Survivors of cardiac arrest and patients with a history of syncope of unknown origin have a high risk of life threatening arrhythmic events (17 to 62% in the following 4-7 years and 6 to 19% in the following 2-3 years, respectively) and therefore should receive an ICD [33-35].

On the other hand, controversy exists concerning asymptomatic carriers (either identified during family screening or fortuitous cases) [36]. Our international registry follow-up data of 547 patients with a type 1 Brugada ECG with or without syncope but without previous cardiac arrest identified in 2003 in multivariate analysis two statistically significant predictors for malignant events: a history of syncope (p < 0.01) and inducibility of sustained ventricular arrhythmia (p < 0.0001) [34] Spontaneously abnormal ECG and male sex were significant predictors in univariate but not longer in multivariate analysis.

Priori, et al. reported in 2002 the follow-up of 200 patients (130 probands, 70 family members) diagnosed with Brugada syndrome from a multicenter Italian registry [33]. A much lower event rate was reported compared with our results (partially explained by inclusion of saddleback type ECG’s) and inducible ventricular arrhythmias during EPS were considered not predictive. In multivariate analysis the combined presence of a spontaneous ST elevation and a history of syncope was predictive of future cardiac events. Accordingly, the proposed clinical risk stratification scheme consists of a three-layer pyramid. The high risk group represents the patients with syncope and spontaneous ECG pattern (saddle or coved), in these patients they recommend ICD implantation. The intermediate group consists of patients who have spontaneous ECG abnormality without syncope; unfortunately in this group no treatment is determined. The lower risk group consists of patients who has normal ECG with or without syncope, which represents 49% of the studied population, should be reassured.

Eckardt, et al [35] recently reported the results of the second largest multi-centre registry data. Two hundred and twelve patients with a coved type I ECG were included, 165 of whom were probands. In total, only nine arrhythmic events occurred in 17% of patients with prior cardiac arrest. 6% of the syncope group and only 1% of asymptomatic patients (one out of 123, being a 45-year old fortuitous case). A previous history of abor-
ted sudden death or syncope and the presence of spontaneous type I ST elevation were predictive of future arrhythmic events in univariate analysis in the presence of low statistical power (p = 0.0039 and p = 0.046, respectively). As for programmed electrical stimulation, a low positive predictive value and a high negative predictive value were noted. All asymptomatic non-inducible patients remained asymptomatic. Evidently, it is difficult - if not impossible - to conclude about the predictive value of any parameter with such a low event rates.

A possible explanation for the higher event rates in our registry as compared to the other two registries, as also proposed by Eckardt, et al, is a selection bias due to the inclusion of more severe patients and families from the 1990’s when the syndrome was first described. At this time only patients and families with the most severe presentations were diagnosed. To evaluate this explanation, recently we conducted a study from our international registry in patients who were asymptomatic and who has had no family history of sudden death or Brugada syndrome (fortuitous individuals). 168 individuals were identified. The ECG was spontaneously abnormal in 92% of them. During a mean follow up of 28 months five sudden deaths and seven VF events (6%) occurred. All five SD occurred in individuals who did not undergo an EP study and had no ICD (55), emphasizing once more the predictive role of the EP study. It is difficult to explain the differences in the three registries in the predictive value of the EP study. The different stimulation protocols and different inclusion criteria might play a role. Furthermore, it should be noted that in the presence of very low event rates and relatively short follow up in a disease with lifelong risk of arrhythmias, it is not possible to draw any definitive conclusions over the predictive value of an examination.

Based on the above mentioned data from the international registries, our current treatment approach incorporates the currently known three best predictors of future arrhythmic events: the presence of aborted sudden death, syncope and spontaneous ECG abnormality (fig. 7). Taking into consideration the controversies around the predictive value of the EP study and the current absence of any other better method for risk stratification, we reserve the EP study for asymptomatic patients with spontaneous covered type I ECG. This stratification model is based on the assumption that due to a lack of long-term follow-up data and insufficient comprehension of etiological mechanisms (since only 20% of gene mutations are currently recognized); we simply don’t wish to risk losing healthy young patients.

In all patients with suspected BS structural heart disease should be excluded using non-invasive (NMR, echocardiography exercise testing) and if necessary invasive (angiography, myocardial biopsy) methods. All patients diagnosed with the syndrome should avoid class I antiarrhythmic drugs (with the exception of quinidine). If they have fever it should be aggressively treated. The patients should be advised to seek medical attention in case of syncope of unknown origin during follow-up. Furthermore, in all patients diagnosed with the syndrome the first degree relatives should be screened.

**Pharmacological treatment**

Given the side effects, costs and risks of the ICD therapy, efforts to find an effective drug are continuing and should be encouraged. Recently, dimethyl lithospermate B, an extract of Danshen, a traditional Chinese herbal remedy has been tested with promising results in an animal model of Brugada syndrome [37].

Two other studies recently examined the role of quinidine therapy in the treatment of Brugada syndrome. Hermida, et al. [38] performed a preliminary study evaluating the efficacy of long-term hydroquinidine administration in reducing arrhythmogenic tendency. Unfortunately, 31 out of the 34 patients studied were asymptomatic patients, who were inducible during EPS. In 76% of the asymptomatic patients, VT/VF inducibility was prevented. In another study, including 15 symptomatic and 10 asymptomatic patients quinidine prevented EP inducibility in 88% of the patients [39]. Although none of the patients died during follow-up, administration of quinidine was associated with a 36% incidence of side effects that resolved after drug discontinuation. Currently, in our clinical practice we use quinidine in cases where ICD implantation is contraindicated, in cases of recurrent shocks or for the treatment of supraventricular arrhythmias. However, the success rate of quinidine has been very low.

**CONCLUSION**

In the last years, many questions have been answered regarding the etiology, pathophysiology and natural history of the Brugada syndrome. However, at least as many new questions were raised and many of them remained unanswered. Just to mention a few examples; it is largely unknown why the disease only manifest in adulthood in the majority of cases, what factors determine the conversion from asymptomatic to symptomatic status in a given individual and which other genes are responsible for the disease.
Références