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The Brugada syndrome: A new malignant cardiac channelopathy

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The Brugada syndrome was first described in 1986, although there is an earlier, less-cited, description. The syndrome is a congenital disorder of sodium cardiac channel function characterized by typical ECG changes (Figure 1) and a high incidence of sudden cardiac death that is often preceded by multiple episodes of loss of consciousness. It is now appreciated that the clinical picture of Brugada syndrome fits the description of a variety of sudden-death syndromes in south-eastern Asian communities. These syndromes are characterized by sudden arrhythmic death, often occurring at times of concomitant autonomic arousal and often during sleep. By definition, these deaths occur in the setting of a normal QT interval with no other abnormalities of cardiac function, other than the occasional fluctuating ECG stigmata of Brugada syndrome. These syndromes have a variety of names such as Lai Tai (death during sleep) in Thailand, Bangungut (scream followed by sudden death) in the Philippines, and Pokkuri (unexpected death at night) in Japan. Although once thought to be exotic and obscure, it now seems these rare epidemiological foci of higher frequency sodium channel mutations are, in fact, a window to a congenital defect that appears to be worldwide. There is a resemblance to the more widely understood, congenital, long QT syndrome family of disorders; however, the main difference in the Brugada syndrome is that the link from genotype to phenotype is more conjectural, as are questions of natural history, optimal investigation, and medical management.

Definition

The Brugada syndrome is a primary, functional, electrical disorder of sodium cardiac-channel function, characterized by malignant, ventricular arrhythmias (usually polymorphic ventricular tachycardia [VT] or syncope) and a variety of fairly common ECG abnormalities. The most specific ECG characteristics of Brugada syndrome are illustrated in Figures 1 and 2 and include:

- A complete or incomplete right bundle branch block (RBBB) with ST-segment elevation (0.2 mV or more at the J wave) in V1 to V3, in association with a prolonged PR interval;
- A widened S wave (or Wilson wave) in lead 1 and lateral ECG leads, typical for RBBB, is rare in patients with Brugada syndrome;
- Two ST-segment morphologies in leads V1 to V3: convex curved or coved and saddle-shaped ST elevation.

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Figure 1: A typical Brugada ECG phenotype is illustrated. Note the dramatic ST segment elevation confined to the right-sided precordial leads, in a pattern of an atypical incomplete RBBB without a concomitant deep S wave in lead I. Note that the ST segment elevation is characterized by a slowly descending ST segment in continuation with a negative T wave. The QT and QTc intervals are normal.

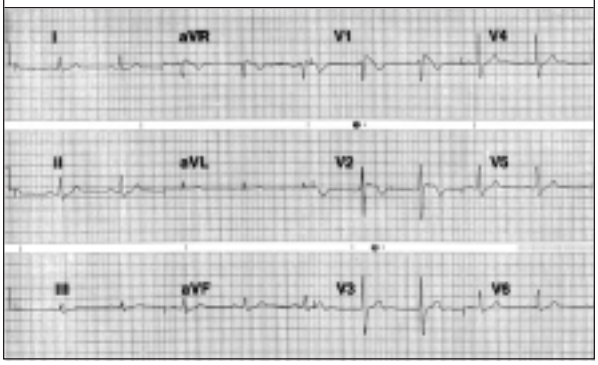
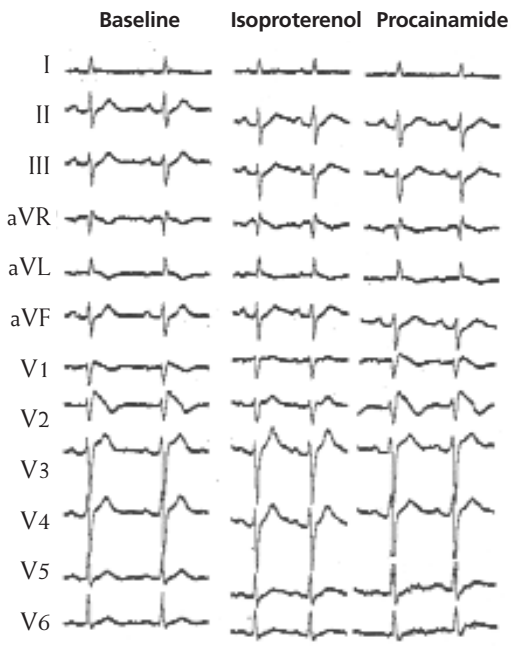


Figure 2: A recent case seen by the arrhythmia service of a 79-yr-old Caucasian male who presented with syncope. All non-invasive and invasive cardiac functional and structural studies were normal. At presentation, the Brugada type ECG phenotype was recognized (left-hand column). This was largely abolished with infusion of isoproterenol 4 mcg/min (middle column). The abnormal ECG pattern was then restored and increased after the infusion of 300 mg intravenous procainamide over 20 min. At invasive studies, a polymorphic ventricular tachycardia was induced with double ventricular extra stimuli. The patient was implanted with a dual chamber ICD.



These characteristics are dynamic and may change or disappear on follow-up (Figure 2). Serial changes of ST segment elevation over time, up to transient normalization, have been noted in 80% of cases with Brugada-type ECG signs and are modulated by autonomic balance. Right precordial ST elevation indicates that this pattern is limited to the right ventricle (RV) parietal, rather than septal block. A structural His-Purkinje system disease may underlie the electrophysiological finding of a prolonged HV interval (and the correlate of a prolonged surface PR interval) seen in many patients.

Epidemiology

It is very difficult to estimate the incidence of Brugada syndrome because it has been described only recently and there is a lack of recognition. However, idiopathic ventricular fibrillation (VF) accounts for 3%-5% of all sudden cardiac death, and estimates suggest that up to 20% of these patients actually suffer from Brugada syndrome. Arrhythmias in Brugada syndrome usually appear after the third decade of life, with no warning or preceding acceleration of heart rate as in catecholamine-dependent VT.

The Brugada syndrome has been recognized worldwide, but its incidence is higher in south-eastern Asia, varying from 0.6% to 0.0006%. In north-eastern Thailand, sudden unexplained death is the leading cause of death in young men; 40% of these patients have a family history of sudden death with an estimated incidence of 1 sudden death per 1000 persons per year. Recent data suggest that this syndrome is not rare in western countries and in North America. The prevalence of the full syndrome is hard to estimate with accuracy, although the Brugada ECG phenotype has been estimated to be up to 1.4% in Japan. With the exception of family history, other demographic variables are not helpful in establishing the diagnosis. Ultimately, it is hoped that genetic evaluation will aid in diagnosing asymptomatic patients (ie, those with an abnormal ECG only) or family members of affected patients and identifying the presence of an abnormal sodium channel gene. As in many areas of research into gene mutation carriage, new point mutations will occur and new family kindreds will undoubtedly arise, and as a result, early hopes of a simple blood test to establish a genotype that would reliably predict clinical events in any arrhythmia now seem facile. In one study, clinical data from 163 patients with Brugada syndrome demonstrated VF or sudden death in 22% and showed the following demographic variables: a 12:1 male: female ratio; 58% of Asian origin; mean-age at first arrhythmic event 22 to 65

years, with a peak around the fourth decade; and a family history of syncope.

Prognosis

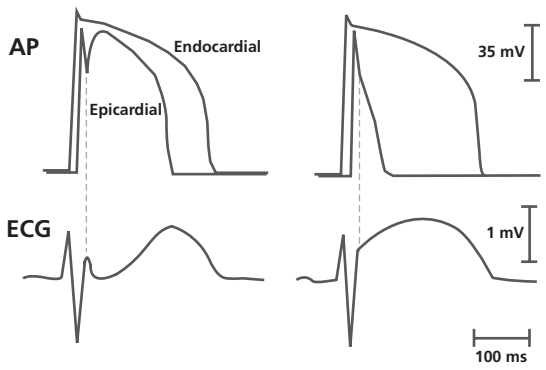
The natural history of the disease was reported initially by Brugada et al through a prospective evaluation of 63 patients followed for a mean of 34 months. The study showed that the syndrome is associated with a 27% incidence of sudden death or syncope, even in asymptomatic patients or occult forms of the disease. The prognosis is poor if untreated, with 10% mortality after a few years of follow-up. Other studies, however, suggest a much lower risk of premature death, even in symptomatic patients, though the differences may relate to case selection or follow-up duration. It has been suggested that the relatively high prevalence of the ECG phenotype implies a relatively benign course for the majority of individuals, but there are clear gaps in understanding the optimal method of risk stratification among asymptomatic individuals.

Pathophysiology

Brugada syndrome is a hereditary disease and inheritance appears to be autosomal dominant with variable penetrance, however, sporadic cases have also been reported. More than three different mutations in the cardiac sodium channel gene SCN5A on chromosome 3 have been described so far. These mutations are a single residue substitution, leading to an amino acid change, and resulting in the loss of the inward sodium current. Understanding the cellular implications of the loss of inward sodium current requires an understanding of action potential morphological heterogeneity and its implications for the heart. Starting in the late 1980s, Antzelevitch and colleagues identified a large mass of mid-myocardial ventricular muscle cells with Purkinje-like, long-action potential durations. These so-called M-cells have a role in the genesis of the surface ECG U wave and are important in the pathophysiology of torsades de pointes polymorphic ventricular tachycardia. Antzelevitch and others went on to explore the transmural heterogeneity of action potential morphology (and hence repolarization heterogeneity) throughout the ventricular wall. The epicardial action potential of both ventricles has a distinct spike and dome morphology. The initial early repolarization, after the action potential upstroke is due to the presence in these cells of a transient outward current (ie, repolarizing or moving the cell potential from a positive to a more negative potential) carried by potassium called I_{to}. This outward current is counterbalanced by a sodium inward current. It is now believed that it is this sodium current that is attenuated in the SCN5A mutations of Brugada syndrome. This loss of the inward sodium current, at the plateau of the cardiac action potential, leaves I_{to} unopposed across the wall of the right ventricle. This shortens the epicardial AP duration and causes loss of the action potential dome, increasing both transmural heterogeneity of refractory periods and ST elevation in V1 to V3 (Figure 3). The relative contribution of an abnormality of an epicardial action potential to the surface ECG is felt to be more prominent in the right ventricle because of the thinness of its wall and the more pronounced I_{to} current in the RV epicardium. There is experimental evidence suggesting that the heterogeneous distribution of action potential durations across the RV wall may be the basis for the preferential right precordial ST elevation in Brugada syndrome, with resultant initiation of phase 2 re-entry arrhythmia from RV origin (ie, cells with a shorter action potential duration can be pre-excited by adjacent cells with a normal duration).

There is some evidence to suggest an overlap between one long QT syndrome genetic variant (also on the

Figure 3: A schematic of two action potentials, one from the epicardium and one from the endocardium. The left panel shows the normal pattern with a prominent 'spike and dome' appearance to the epicardial action potential due to the transient inward current (I_{to}) activation just after the upstroke, which is counterbalanced by a sodium inward current. It is thought that this phenomena explains the electrocardiographic J wave, seen in the simultaneously recorded surface ECG. On the right side is a schematic of the same two cells from a patient with Brugada syndrome; there is attenuation of the sodium inward current such that the epicardial I_{to} is less opposed with a resultant shorter action potential, with resultant ST-segment elevation. There is experimental evidence to demonstrate that this phenomenon enhances repolarization heterogeneity and leads to re-entrant arrhythmias.



Alings M, Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. *Circulation* 1999;5:666-73.

SCN5A gene, see below) that prolongs the QT interval via increased sodium inward current during the action potential plateau and the Brugada syndrome. As well, RV dysplasia that is associated with ventricular arrhythmia has, in some cases, been preceded by a Brugada ECG phenotype. Further research is needed to define the relationship between these three electrical disorders more clearly. Such research may allow more specific diagnostic tests and better links than the current one between a malignant arrhythmia and a relatively non-specific surface ECG phenotype.

Investigation

A high index of suspicion is needed to diagnose Brugada syndrome because it is diagnosed by the exclusion of structural heart disease (normal Holter monitoring, echocardiogram, coronary anatomy, QT interval and cardiac MRI) to exclude arrhythmogenic RV dysplasia in patients with unexplained syncope or ventricular arrhythmia. An associated typical Brugada phenotypic ECG is required to make the diagnosis, supported by a family history of sudden cardiac death. Challenge tests of uncertain sensitivity and specificity are often used to help confirm the diagnosis

Provocative challenge tests

It has been suggested that pharmacological challenge tests should be performed before dismissing the diagnosis in patients with a possible or suggestive Brugada phenotype. These all involve acute administration of intravenous sodium channel blockers such as procainamide (10 mg/kg in 10 min), or in Europe, flecainide or ajmaline. The test is considered positive if an additional 1 mm elevation appears in V1-V3, along with the RBBB patterns.

Physiological or pharmacological beta-adrenergic stimulation (eg, isoproterenol) can normalize the ECG (decrease ST elevation as in Figure 2, middle panel). Conversely, enhanced ST elevation has also been noted after either beta-blockade or vagal stimulation. This elevation may occur transiently during sleep and explains the increased incidence of sudden death at night.

The role of programmed electrical stimulation

Programmed electrical stimulation is of limited value in identifying patients at risk of sudden cardiac death with known Brugada syndrome (positive predictive value 51% in 116 patients, rising to only 70% in those with a documented malignant arrhythmia). Efforts to improve this value with infusions of edrophonium or an alpha adrenergic receptor antagonist are promising, but unproven, as are optimal stimulation techniques developed to investigate scar-related reentrant arrhythmias. The role of a negative electrophysiological (EP) study in a known Brugada syndrome patient (ie, with a clinical event, in addition to an abnormal ECG) is also unclear. A relatively high negative predictive value of 94% is suggested; however, the nature of the disorder requires a very long follow-up before this number can be firmly established. There are similar concerns about the importance of positive and negative predictive values from EP studies in data collected from asymptomatic Brugada ECG patients. However, there was the suggestion that a non-inducible EP test may be of value in a cohort of younger-aged patients with typical presentation, although the follow-up times were fairly short.

Management

Secondary prevention of recurrent syncope or resuscitated arrest

Given the current rarity of this syndrome and the short time since its description, there are no controlled evaluations of any therapy. No single antiarrhythmic agent is considered adequate and, as a result, the general view is that implantable cardioverter defibrillator (ICD) therapy is the first choice in any patient with symptoms (eg, syncope or resuscitated VT/VF), the typical ECG, and a positive family history of unexplained sudden death. Transient normalization of ECG does not decrease the need for ICD. The therapeutic decision should not be based only on EP induction ability in symptomatic patients. This is largely because of the intermittent nature of the electrical instability, the lack of clarity for an optimal stimulation protocol, and the true positive and negative predictive value of the information obtained.

Primary prevention of malignant arrhythmias/syncope in asymptomatic patients

The management of asymptomatic patients with a spontaneous or provoked ECG with Brugada-type abnormalities, with or without family history, is

controversial. The aggressive clinical management of asymptomatic patients with a typical spontaneous or provoked ECG is based on a single case series. Invasive EP studies have been advocated as a guide to therapy in asymptomatic patients (ie, those with only with the ECG phenotype), in family members (with or without an abnormal ECG), and in those with a compelling family history. In these groups, some clinicians have advocated that an ICD be considered in patients with a spontaneous or provocable typical ECG and inducible VT or VF. Others feel that an invasive study is too unclear to be of use, other than as one of a variety of risk-stratifying variables.

The most recent compilation of the Brugada case series includes 136 asymptomatic patients with a spontaneous or provocable Brugada phenotype ECG, of whom, 45 had inducible VT/VF and received an ICD. After an average of 25± 27 months of follow-up, 6 patients had recurrent arrhythmic events, while such events occurred in only 1 of 91 asymptomatic Brugada ECG patients who were non-inducible. Importantly, the first arrhythmic event occurred an average of 17 months after the invasive study. An alternative is to consider an automatic recording implantable loop recorder (ILR) for asymptomatic patients or family members with a malignant family history. This would allow the documentation of arrhythmia before considering primary prevention ICD therapy, albeit with the unknown risk that the first presentation may be fatal. Recent Japanese investigations using an ECG database approach, linked to both clinical records and vital statistics from a large, defined area, support this approach. They report a relatively benign clinical course in patients with asymptomatic Brugada-type ECG abnormalities who have no suggestive family history.

Ultimately, primary prevention risk stratification to decide on prophylactic ICD implantation will include a host of differently weighted variables including: the results of invasive studies, family history, gender, patient age, severity of ECG abnormality, and ultimately, the characteristics of the genetic defect.

Conclusion

Brugada syndrome is a relatively new channelopathy of the sodium cardiac channel with a well-understood pathophysiology, but variable incidence and clinical presentation. The diagnosis is based on Brugada-type ECG and a history of syncope or ventricular arrhythmias, especially in patients with a positive family history of sudden cardiac death. The treatment of choice at this time is secondary, and in some cases, primary prevention ICD therapy. More data are needed on specificity and sensitivity of pharmacological challenge tests, as well as programmed electrical stimulation and its utility to predict future arrhythmic events. Further research is also needed before final recommendations are made in asymptomatic patients and in family members with a strong malignant family history.

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Abstracts of Interest

Long term follow up of patients with Brugada Syndrome compared to patients with idiopathic ventricular fibrillation

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The recurrence of cardiac events (CE) in patients (pts) with Idiopathic Ventricular Fibrillation (IVF) compared to pts with Brugada Syndrome (BS) is unknown because BS is a new entity that was classfied as IVF in previous series.

Methods and results: CE were reviewed in 39 survivors of VF treated with an ICD: 16 pts (81% male) with a diagnosis of BS (49±16 years - range 23 to 73) and 23 pts (65%) with IVF (47±15 y - range 25 to 71). All IVF pts received intravenously a sodium channel blocker to exclude a concealed form of BS. All pts had a structurally normal heart as assessed by non-invasive and invasive investigations.

The cumulative occurrence of CE (VF with appropriate shock or non-sustained polymorphic ventricular tachycardia [NSPVT]) after a follow-up (FU) of 24 months was 55% in BS compared to 65% in IVF (Kaplan-Meier) (P=ns). The median time to a first CE was 8±8 months (range 1 to 19) in BS compared to 12±12 months (0.1 to 47) in IVF. In BS pts, 7/16 (44%) had an appropriate shock (AS) for VF (39 episodes of shocks) and 1 other pt had NSPVT detected by ICD without shock. In IVF pts, 9/23 (39%) had a recurrence of VF with AS (33 episodes of shocks) and 7 other pts had NSPVT. Mean FU for pts without any CE are 35 months for IVF and 37 months for BS. Mortality in both groups was 0%. In IVF pts, sustained VT/VF were induced in 10 (43%) and 4 (17%) had NSPVT at electrophysiologic studies. In BS pts, all 16 pts (100%) were inducible. Inducibility failed to predict subsequent CE.

Conclusion: IVF and BS pts experience a similar high recurrence rate of VF or NSPVT after an episode of aborted sudden death and an ICD prevents sudden death during follow-up.

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Asymptomatic patients with Brugada Syndrome: Risk assessment by programmed ventricular stimulation and clinical outcome. A multicentre study.

D Corrado, F Zoppo, G Buja, et al; Italy.

Although symptomatic patients with Brugada syndrome must be protected by implantable cardioverter defibrillator (ICD) due to the high risk of sudden death, risk stratification and therapeutic strategies in asymptomatic patients remain to be established. The aim of the present study was to compare symptomatic and asymptomatic patients with Brugada syndrome with regard to inducibility at programmed ventricular stimulation (PVS) and clinical outcome. We studied 71 consecutive patients (64 males and 7 females, aged 34±19 years) with the distinctive ECG patterns – spontaneous or induced by sodium channel blockers – characterized by high take-off ST-segment elevation (2 mm or more) in right precordial leads, of either "coved" or "saddle-back" type, in the absence of structural heart disease. Nineteen patients experienced relevant symptoms such as syncope in 12 and cardiac arrest in 7; the other 52 patients were asymptomatic. We evaluated inducibility of sustained polymorphic ventricular tachycardia (VT) or ventricular fibrillation (VF) at PVS with 3 extrastimuli from both right ventricular apex and outflow tract in 34 patients (13 symptomatic and 21 asymptomatic). Moreover, we analyzed major arrhythmic events such as cardiac arrest, syncope or appropriate shock discharge by ICD at follow-up in all patients. Fifteen (44%) were inducible at PVS (polymorphic VT in 4 and VF in 11)., Of the 15 inducible patients, 6 were asymptomatic (positive predictive value = 60%), while 4 of the 19 noninducible were symptomatic (negative predictive value = 79%). Eight patients (all symptomatic) received an ICD, and another 9 were treated by antiarrhythmic drugs (beta-blockers in 5, sotalol in 3, amiodarone in 1). During a mean follow-up of 34±14 months, 6 of 71 patients (8.5%) had arrhythmic events, consisting of sudden death in one, VF in 4, and syncopal VT in one. All events occurred in previously symptomatic patients, 6 of whom treated by ICD. None of the asymptomatic patients developed symptoms. In conclusion, asymptomatic patients with Brugada syndrome were noninducible at PVS and had a benign clinical outcome. These data suggest a less aggressive management strategy in this subgroup of Brugada patients.

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