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Review Article

Brugada Syndrome: Diagnosis and Management

Reza Octavianus, Yoga Yuniadi

Brugada syndrome associated with high incidence of sudden death in young and otherwise healthy adults in many parts of the world. The Brugada syndrome which is characterized by an ST-segment elevation in the right precordial ECG leads, is a familial disease that displays an autosomal dominant mode of transmission with incomplete penetrance. The first and only gene to be linked to Brugada syndrome is *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel gene. More than 80 mutations in *SCN5A* have been linked to the syndrome.
Based on ECG characteristics the syndrome divided into three types. Brugada syndrome is definitively diagnosed when a type 1 ST-segment elevation is observed in >1 right precordial lead (V1 to V3) in the presence or absence of a sodium channel– blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electricalstimulation, syncope, or nocturnal agonal respiration. Currently, an implantable cardioverter defibrillator (ICD) is the only proven effective treatment for the disease.

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Keywords: Brugada syndrome, review

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Tinjauan Pustaka

Sindrom Brugada: Diagnosis dan Tatalaksana

Reza Octavianus, Yoga Yuniadi

Sindrom Brugada menyebabkan insiden kematian mendadak yang tinggi pada orang muda yang normal secara fisik. Sindrom Brugada yang ditandai dengan elevasi segmen ST di sadapan prekordial kanan merupakan suatu penyakit familial dengan transmisi autosomal dominan yang tidak lengkap. The first and only gene to be linked to Brugada syndrome is *SCN5A* merupakan gen yang pertama diketahui dan juga satu-satunya yang berkaitan dengan sindrom Brugada. Gen ini melakukan encoding subunit αdari gen kanal natrium jantung. Terdapat lebih dari 80 mutasi *SCN5A* yang berkaitan dengan sindrom Brugada. Berdasarkan karakteristik EKG, sindrom Brugada dibagi menjadi 3 tipe. Diagnosis pasti sindrom Brugada ditegakkan bila didapatkan gambaran EKG tipe 1 yaitu elevasi segmen ST di V1 sampai V3 baik dalam keadaan dengan atau tanpa obat penghambat kanal kalsium, disertai adanya salah satu berikut ini: VF terdokumentasi, VT polimorfik, riwayat keluarga dengan kematian jantung mendadak pada usia kurang dari 45 tahun, gambarn EKG coved pada anggota keluarga, terinduksi VT pada stimulasi elektrik, sinkop, atau adanya respirasi agonal nokturna. Saat ini ICD merupakan satu-satunya terapi yang terbukti efektif untuk sindrom ini.

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Kata kunci: sindrom Brugada, tinjauan pustaka

Introduction

Since its introduction as a clinical entity in 1992, the Brugada syndrome has attracted great interest because of its high incidence in many parts of the world and its association with high risk for sudden death in young and otherwise healthy adults and, less frequently, in infants and children. In recent years, an exponential rise in the number of reported cases and a striking proliferation of articles defining the clinical, genetic, cellular, ionic, and molecular aspects of the disease have occurred.[1,2]

A number of ambiguities exist concerning the diagnosis of Brugada syndrome. The electrocardiographic signature of the syndrome is dynamic and often concealed,[3] so it is difficult to estimate the true prevalence of the disease in the general

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population.[4] Normalization of the ECG signature of this syndrome by whatever mechanism may lead to an underestimation of the prevalence of the disease, thus placing some patients at risk. It is, therefore, of some importance to identify whether patients with the concealed versus overt syndrome are at similar risks for arrhythmic events and, if so, to identify an approach to unmask those cases that are concealed.[5]

Polymorphic ventricular tachycardia (VT) and ventricular fibrillation (VF) developing in patients with structurally normal hearts accounts for 5% to 12% of the >300 000 sudden deaths of Americans each year. Approximately half of these are attributed to the Brugada syndrome.[6]

Clinical Characteristics and Epidemiology

The Brugada syndrome is characterized by an ST-segment elevation in the right precordial ECG leads and a high incidence of sudden death in patients with structurally normal hearts and unrelated to ischemia, electrolyte imbalance.[3] The syndrome typically manifests during adulthood, with a mean age of sudden death of 41±15 years. The youngest patient clinically diagnosed with the syndrome is 2 days old and the oldest is 84 years old. The syndrome is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts. The prevalence of the disease is estimated to be 5/10 000 inhabitants and, apart from accidents, is the leading cause of death in men < 40 years old, particularly in countries in which the syndrome is endemic.[4] Because the ECG is so dynamic and often concealed, it is difficult to estimate the true incidence of the disease in the general population.

The Brugada syndrome is a familial disease that displays an autosomal dominant mode of transmission with incomplete penetrance, most diagnosed in males (8:1 ratio of males:females) of Asian origin.[7] The syndrome occurs more commonly in Southeast Asians, with the highest incidence occurring in the peoples of Nothern Thailand. The prevalence of the Brugada syndrome among the general population in Europe and the United States is thought to be much lower, although among Southeast Asian immigrants it may be as high as it is in Southeast Asia itself.[8,9]

Genetic Factors Underlying The Brugada Syndrome

Inheritance of Brugada syndrome occurs via an autosomal dominant mode of transmission, so offspring of people with the mutant gene have a 50% chance of inheriting it from their affected parent. The first and only gene to be linked to Brugada syndrome is *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel gene. More than 80 mutations in SCN5A have been linked to the syndrome since 2001.[10]

About two dozen of the these mutations have been studied in expression systems and shown to result in loss of function due either to: (1) a failure of the sodium channel to express, (2) a shift in the voltage- and time-dependence of INa activation, inactivation, or reactivation, (3) an entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly, (4) an accelerated inactivation of the sodium channel *SCN5A* mutations account for approximately 18-30% of Brugada syndrome cases. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases.[11] Of note, negative *SCN5A* results generally do not rule out causal gene mutations, since in general the promoter region, cryptic splicing mutations or presence of gross rearrangements is not part of routine investigation.[12]

Based on findings to date, knowledge of a specific mutation may not provide guidance in formulating a diagnosis or determining a prognosis. Mutations have been reported throughout the *SCN5A* gene, and it is not as yet clear which of these if any are associated with a greater risk of arrhythmic events or sudden death. Genetic testing is recommended for support of the clinical diagnosis, for early detection of relatives at potential risk, and particularly for the purpose of advancing research and consequently our understanding of genotype–phenotype relations.[12]

Types Of Brugada Syndrome

Three ECG repolarization patterns in the right precordial leads are recognized : [3] (1) Type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST-segment elevation ≥ 2 mm (0.2 mV) followed by a negative T wave, (2) Type 2 ST-segment elevation has a saddleback appearance with a high takeoff ST-segment elevation of ≥ 2 mm, a trough displaying ≥1 mm ST elevation, and then either a positive or biphasic T wave,

(3) Type 3 has either a saddleback or coved appearance with an ST-segment elevation of <1 mm (**Figure 1**).

Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. These 3 patterns may be observed

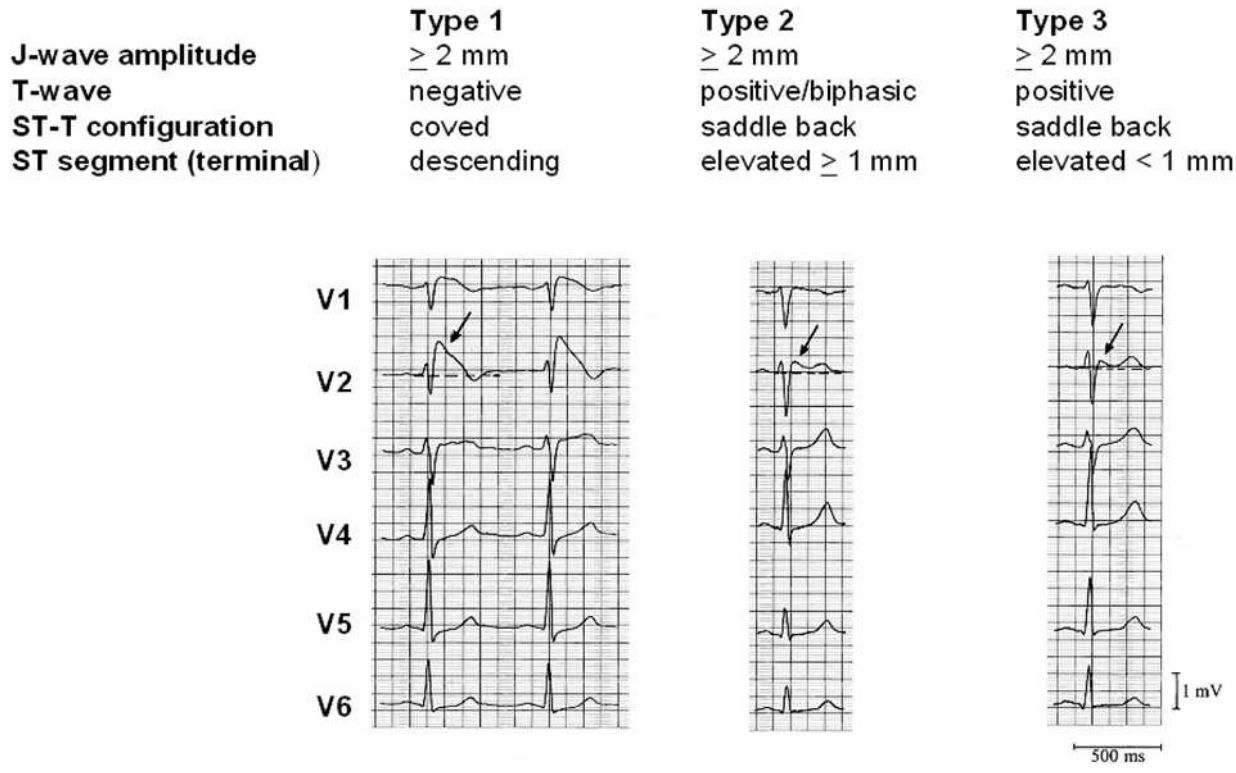

Figure 1. Precordial leads of patient with Brugada syndrome (BS) Three types of SCG feature (type 1, type 2, and type 3) are documentred in patient with BS. Arrow indicate the J-wave. (taken from 13)

spontaneously in serial ECG tracings from the same patient or after the introduction of specific drugs.[3]

Electrocardiography Manisfestation

A slight prolongation of the QT interval is sometimes observed in association with ST-segment elevation in Brugada syndrome. The QT interval is prolonged more in the right precordial leads than it is in the left precordial leads, presumably because of a preferential prolongation of action potential duration in right ventricular epicardium secondary to accentuation of the action potential notch. Depolarization abnormalities including prolongation of P wave duration and PR and QRS intervals, are frequently observed, particularly in patients linked to *SCN5A* mutations. PR prolongation likely reflects HV conduction delay.[4]

Ionic Mechanism

It is now well established that a transient outward current (*I*to)–mediated phase 1, which gives rise to a notched appearance of the action potential (AP), is more prominent in epicardium than in endocardium of the ventricles of many species. Transmural differences in the contribution of *I*to, first suggested in 1988 on the basis of AP data, have now been demonstrated by use of whole-cell patch-clamp techniques in canine, feline, rabbit, rat, and human ventricular myocytes. Recent studies also indicate the presence of a much larger *I*to-mediated notch in right versus left canine ventricular epicardium.[14,15]

The presence of a prominent AP notch in epicardium but not endocardium causes a transmural voltage gradient during ventricular activation that has been shown to underlie the J-wave and J-point elevation in the ECG. The presence of a prominent *I*to-mediated notch also predisposes canine ventricular epicardium to all-or-none repolarization under a variety of conditions, including ischemia. Loss of the AP dome (plateau) in epicardium but not endocardium produces a

voltage gradient during ventricular repolarization that is thought to underlie elevation of the ST segment, similar to that found in patients with the Brugada syndrome. In isolated sheets of canine right ventricular (RV) epicardium, heterogeneous loss of the AP dome has been shown to induce a marked increase in dispersion of repolarization as well as phase 2 reentry, which is responsible for the closely coupled extrasystole that initiates VT.[16,17] (**Figure 2**)

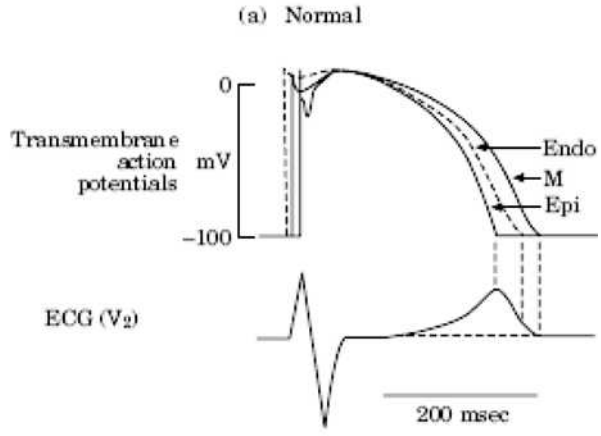

Figure 2. Normal relation between right ventricular epicardial, endocardial, and M cell action potential and its relevance with precordial ECG (taken from 7)

The cellular basis for the Brugada syndrome is thought to be due to an outward shift in the ionic current active during phase 1 of the right ventricular epicardial action potential.[18] A rebalancing of the currents contributing to the early phases of the action potential can accentuate the action potential notch or lead to all-or-none repolarization at the end of phase 1, causing loss of the epicardial action potential dome and marked abbreviation of the action potential at that site. A variety of pathophysiological conditions (e.g. ischaemia, metabolic inhibition, hypothermia, pressure) and some pharmacological interventions are known to effect these changes in canine and feline ventricular cells in which Ito is prominent. Under these pathophysiological conditions or in response to agents that reduce INa or ICa or agents that activate IK-ATP or augment IKr, ICl(Ca) or Ito, canine ventricular epicardial cells exhibit an accentuation of the spike and dome morphology of the action potential, resulting in a delay in the development of the dome, secondary to widening of the action potential notch. A further shift in the balance of current leads to loss of the action potential dome and marked abbreviation of the epicardial response. The dome fails to develop because the outward currents flowing at the end of phase 1 overwhelm the inward currents that normally give rise to the secondary upstroke and action potential plateau.[7] When phase 1 reaches approximately –30 mV, all-or-none repolarization of the action potential ensues leading to loss of the dome as the outward currents overwhelm the inward currents.[12]

Under normal conditions, the J wave is relatively small, in large part reflecting the left ventricular action potential notch, since that of the right ventricular epicardium is usually buried in the QRS. The ST segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau .Accentuation of the right ventricular notch under pathophysiological conditions is attended by exaggeration of transmural voltage gradients and thus exaggeration of the J wave or J point elevation and/or the appearance of a saddleback configuration of the repolarization waves . The development of a prominent J wave can also be construed as ST segment elevation. Under these conditions, the T wave remains positive because epicardial repolarization precedes repolarization of the cells in the M and endocardial regions. Further accentuation of the notch may be accompanied by prolongation of the epicardial action potential such that the direction of repolarization across the right ventricular wall and transmural voltage gradients are reversed, thus leading to the development of a coved-type of ST segment elevation and inversion of the T wave , typically observed in the ECG of Brugada patients. A delay in epicardial activation may also contribute to inversion of the T wave.[7] (**Figure 3**)

It is interesting to note that although the typical Brugada morphology is present in the substrate for reentry is not. A further shift in the balance of current, leads to loss of the action potential dome at some epicardial sites, which would manifest in the ECG as a further ST segment elevation. The loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia. Because loss of the action potential dome in the epicardium is generally not spatially uniform, we see the development of a striking epicardial dispersion of repolarization.[7]

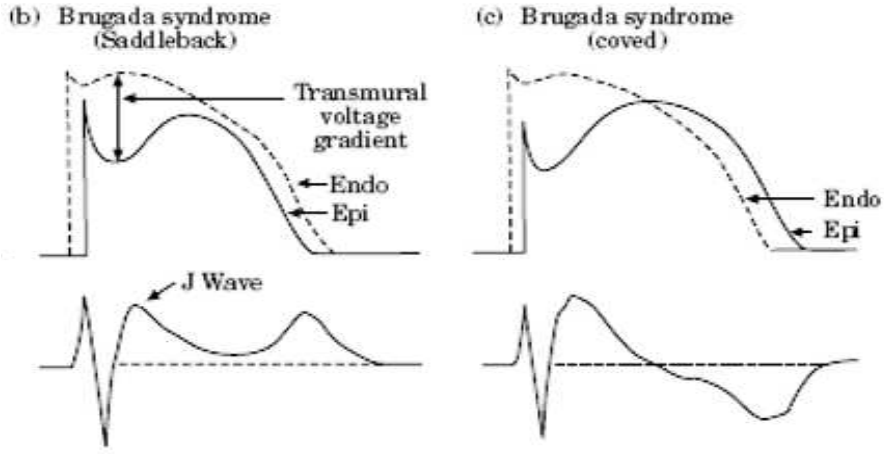

Figure 3. Mechanism of ST-elevation an upright and inverted T in Brugada syndrome (taken from 7)

Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local reexcitation via a phase 2 reentry mechanism, leading to the development of a closely coupled extrasystole, capable of triggering circus movement reentry The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in the epicardium the QRS is largely comprised of a Q wave, which serves to accentuate the negative deflection of the inverted T wave, thus giving the ECG a more symmetrical appearance. This morphology is often observed in the clinic preceding the onset of polymorphic ventricular tachycardia.[18,19]

The influence of the autonomic nervous system on STsegment elevation in patients with Brugada syndrome is well established.[2,3] An increase in vagal activity is known to cause an ST-segment elevation in the right precordial leads (V1 through V3), whereas sympathetic agonists normalize the ST segment. In the wedge, acetylcholine (ACh, 1 to 5 μmol/L) depressed the AP plateau in RV epicardium but not endocardium in 3 of 5 preparations, leading to an ST-segment elevation.[4]

Diagnosis

Brugada syndrome is definitively diagnosed when a type 1 ST-segment elevation is observed in >1 right precordial lead (V1 to V3) in the presence or absence of a sodium channel– blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electrical

stimulation, syncope, or nocturnal agonal respiration. The ECG manifestations of the Brugada syndrome, when concealed, can be unmasked primarily by sodium channel blockers but also during a febrile state or with vagotonic agents. Drug challenge generally is not performed in asymptomatic patients displaying the type 1 ECG under baseline conditions because the additional diagnostic value is considered to be limited, the added prognostic value is not clear, and the test is not without risk for provoking arrhythmic events.[20,21]

Importantly, confounding factor or factors that could account for the ECG abnormality or syncope should be carefully excluded, including atypical right bundle-branch block, left ventricular hypertrophy, early repolarization, acute pericarditis, acute myocardial ischemia or infarction, pulmonary embolism, Prinzmetal angina, dissecting aortic aneurysm, various central and autonomic nervous system abnormalities, Duchenne muscular dystrophy, thiamin deficiency, hyperkalemia hypercalcemia, arrhythmogenic right ventricular dysplasia/cardiomyopathy, pectus excavatum, hypothermia, and mechanical compression of the right ventricular outflow tract (RVOT) as occurs in mediastinal tumor or hemopericardium.[4]

Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. These 3 patterns may be

observed spontaneously in serial ECG tracings from the same patient or after the introduction of specific drugs. The diagnosis of Brugada syndrome is also considered positive when a type 2 (saddleback pattern) or type 3 ST-segment elevation is observed in >1 right precordial lead under baseline conditions and conversion to the diagnostic type 1 pattern occurs after sodium channel blocker administration (ST-segment elevation should be ≥ 2 mm). One or more of the clinical criteria described above also should be present. Drug-induced conversion of type 3 to type 2 ST-segment elevation is considered inconclusive for a diagnosis of Brugada syndrome.[7]

Placement of the right precordial leads in a superior position (up to the second intercostal space above normal) can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients, both in the presence or absence of a drug challenge .[22,23] Although previous reports suggested that none of the control patients displayed type 1 ST elevation when the V1 to V3 leads were displaced upward, a prospective study with a larger number of controls will be required to exclude the possibility of false-positive results via this method.[7] (**Figure 4**)

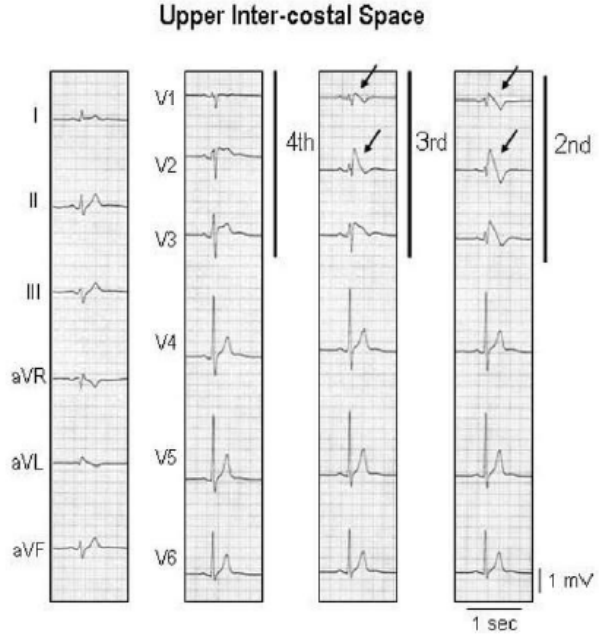

Figure 4. Shift of right precordial leads to 2nd and 3rd intercostal space unmasks a type 1 Brugada ECG (Taken from 12)

Some studies demonstrate that patients with the concealed form of the disease are at a similar risk for ventricular fibrillation and sudden death as those who manifest ST-segment elevation and RBBB persistently. These findings suggest that the syndrome may be underdiagnosed and that failure to unmask the disease may place patients at considerable risk.[5]

The mechanisms responsible for the electrocardiographic actions of class I antiarrhythmia agents in patients with Brugada syndrome have been the subject of extensive study by Antzelevitch and others. On the basis of these studies, the working hypothesis is that a strong sodium channel block facilitates the loss of the right ventricular epicardial action dome (plateau phase) by altering the balance of current at the end of phase 1 of the action potential from inward to outward. The result is an all or none repolarization of the right ventricular epicardial action potential and marked abbreviation of the epicardial action potential duration. The loss of the dome in right ventricular epicardium but not endocardium creates a transmural voltage gradient that manifests as an STsegment elevation in the right precordial leads of the ECG and a transmural dispersion of refractoriness that can serve as the substrate for the development of functional reentry.[5]

The specificity of sodium channel blockers such as flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide to identify patients at risk is uncertain. The recommended dosages are listed in **Table 1**. Drug challenge should be performed while the patient is continuously monitored (12 lead ECG and blood pressure) and with defibrillator and advanced coronary life support facilities close at hand. Accurate lead position and correct venous access should be ascertained. And should be terminated when the diagnostic type 1 Brugada ECG develops, the ST segment in type 2 ECG increases by ≥ 2 mm, premature ventricular beats or other arrhythmias develop, or QRS widens to ≥130% of baseline.[4,5]

Monitoring is recommended until the ECG has normalized (plasma half-life of flecainide is 20 hours, of procainamide is 3 to 4 hours, and ajmaline inactivated within a few minutes).

Table 1. Drugs Used to Unmask Brugada Syndrome

Drugs	Dosage and Administration
Ajmaline	1 mg/kg over 5 min, iv
Flecainide	2 mg/kg over 10 min, iv (400 mg, PO)
Procainamide	10 mg/kg over 10 min, iv
Pilsicainide	1 mg/kg over 10 min, 1v

Serious ventricular arrhythmias, including ventricular fibrillation (VF), may occur during the test. Immediate discontinuation of the drug is required, and isoproterenol infusion might be needed to treat the arrhythmias (1 to 3 μg/min isoproterenol).[4]

The greater sensitivity to ajmaline may be attributable to differences in the effectiveness of the two drugs in blocking the sodium channel current INa at the doses used. In the case of flecainide and ajmaline, INa inhibition reduces inward current, whereas Ito inhibition counters this action of the drugs by blocking outward current. Ajmaline and flecainide, in addition to reducing the peak amplitude of Ito, significantly accelerated the decay of the current, causing a marked reduction in the total charge contributing to phase 1 of the epicardial action potential and the charge available to oppose the reduction of Ina. Data suggest the lesser effectiveness of flecainide largely results from its more potent inhibition of Ito. Differences in INa inhibition at the doses used are difficult to completely rule out as a contributing factor.[24] (**Figure 5**)

Procainamide is a class IA antiarrhythmic agent that displays a more rapid dissociation from the sodium channel and consequently a lower level of use-dependent sodium channel block.

This characteristic of the drug is believed to underlie its lesser potency compared with class IC agents such as flecainide in unmasking the syndrome. In contrast to ajmaline and flecainide, procainamide produces no block of Ito at clinically relevant drug concentrations.[25]

Anzelevitch et al, have previously proposed a cellular mechanism for the Brugada syndrome in which accentuation of the epicardial action potential notch and eventual loss of the epicardial action potential dome results in ST segment elevation, phase 2 reentry, and polymorphic VT/VF.[10] The proposed mechanism involves a rebalancing of the currents available at the end of phase 1 of the epicardial action potential. Diminution of inward currents (INa and ICa) or enhancement of outward currents (Ito, IK-ATP) can result in a slowing of the second upstroke of the epicardial action potential, eventually leading to loss of the action potential dome as a consequence of all-or-none repolarization at the end of phase 1.

Based on this schema, we hypothesized that combined INa and ICa block would be more effective in unmasking the syndrome.[27]

The ability of combined INa and ICa block to cause

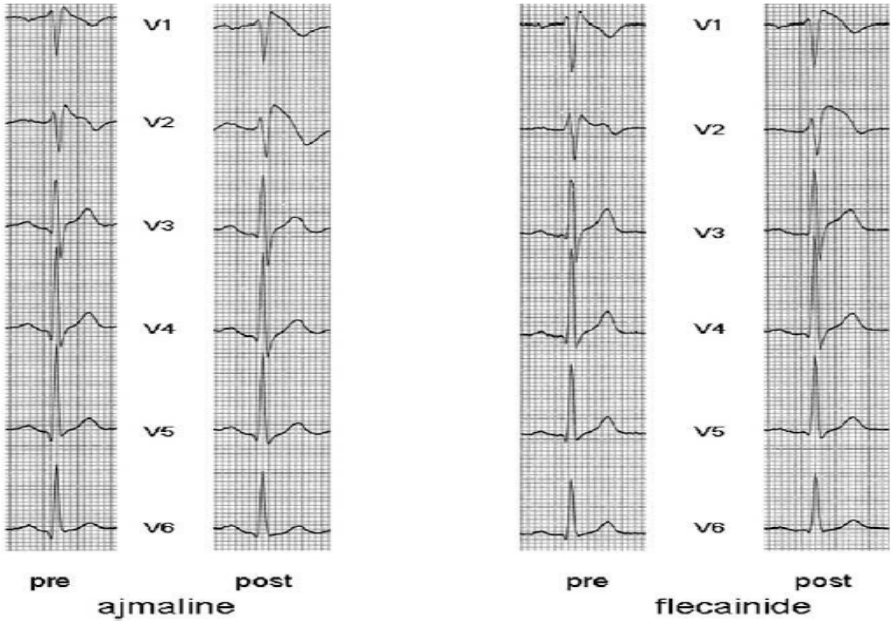

Figure 5. Left: Precordial leads before (pre) and after (post) ajmaline. **Right:** ECG before (pre) and after (post) flecainide. Induction of ECG changes after the two corresponding tests in the same patient is clearly visible
(Taken from 24)

loss of the epicardial action potential dome and phase 2 reentry in the canine right ventricular wedge preparation. High concentrations of terfenadine, in this case 5 μ M, produced an accentuation of the epicardial action potential notch following acceleration of the rate from a BCL of 800 msec to 400 msec. The dramatic accentuation of the notch was due to the effect of the drug to depress the phase 0, augment the magnitude of phase 1, and delay the appearance of the second upstroke. The electrocardiographic manifestations of these changes in action potential characteristics include an elevation of J point, augmentation of the J wave, and inversion of the T wave.[27]

Action potential duration at 90 percent repolarization (APD90) was significantly ($p<0.05$) shorter in epicardium than the endocardium in control. In the presence of 5 μ M terfenadine, APD90 of Epi 2 was significantly shorter than that of both Epi 1 and endocardium ($P < 0,001$).[27]

In another series of experiments, we evaluated the effects of three sodium channel blockers (ajmaline, $\leq$20 μ M, flecainide, $\leq$7.5 μ M, and procainamide, $\leq$300 μ M) traditionally used to unmask the Brugada syndrome in the clinic. Phase 2 reentry was observed in 1/17 preparations (5.9%) exposed to ajmaline, flecainide, or procainamide compared with 15/20 (75%) exposed to terfenadine or the combination of sodium channel block with procainamide or ajmaline and calcium channel block with verapamil. Polymorphic VT/VF was not observed with ajmaline, flecainide, or procainamide alone (0/17), but was induced in 7/20 preparations (35%) exposed to terfenadine or sodium channel blockade (procainamide or ajmaline) and verapamil.

Sodium channel blockade (procainamide or ajmaline) and verapamil induced phase 2 reentry

in 3 out of 4 preparations while verapamil alone ($\leq$20 μ M) induced phase 2 and verapamil induced phase 2 reentry in 3 out of 4 preparations while verapamil alone ($\leq$20 μ M) induced phase 2 in only 1 out of 4 preparations.[27]

Electrophysiological studies (EPSs) may be helpful in risk stratification and in some cases in establishing the diagnosis. A complete EPS is recommended in all symptomatic patients.

In VF survivors, EPS may be of little or no diagnostic value, but may be helpful in providing further insight into the predictive value of available diagnostic tools. In the absence of data on sensitivity or specificity of any EPS protocol, we suggest a protocol using 2 stimulation sites (right ventricular apex [RVA] and right ventricular outflow tract), at least 3 cycle lengths (600, 430, and 330 ms), 1, 2, and 3 extrastimuli, and a minimal coupling interval of 200 ms.[4]

Risk Stratification

Identification of patients at risk for sudden death is an important goal of investigators worldwide. Brugada et al found that patients initially presenting with aborted sudden death are at the highest risk for a recurrence (69%), whereas those presenting with syncope and a spontaneously appearing Brugada ECG sign have a recurrence rate of 19%.[28,29]

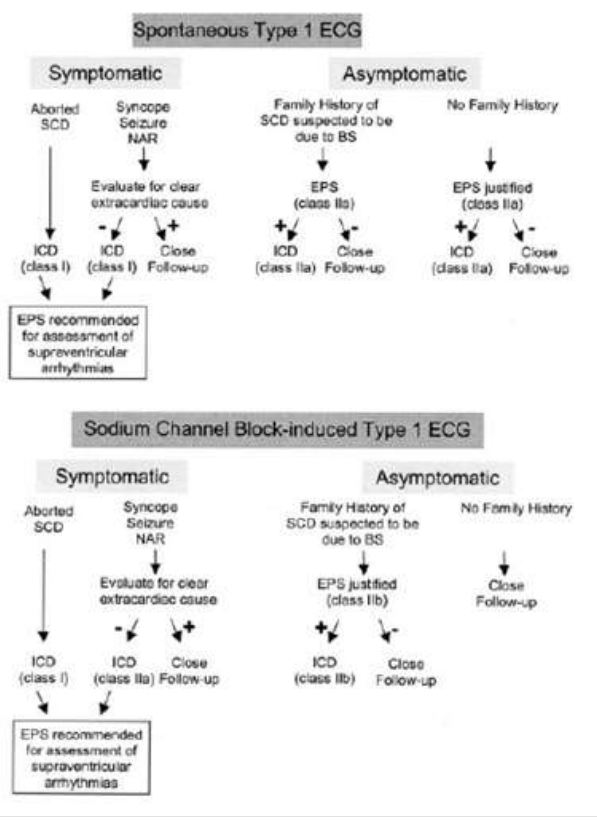

Figure 6. Indications for ICD implantation in patients with Brugada syndrome. Class I designation indicates clear evidence that the procedure or treatment is useful or effective; Class II, conflicting evidence about usefulness or efficacy; Class IIa, weight of evidence is in favor of usefulness or efficacy; and Class IIb, usefulness or efficacy is less well established. BS indicates Brugada syndrome; NAR, nocturnal agonal respiration; and SCD, sudden cardiac death (Taken from 12)

An 8% occurrence of cardiac events was observed in initially asymptomatic patients. Among asymptomatic patients, those at highest risk displayed the Brugada sign spontaneously; those in whom ST segment elevation appeared only after provocation with sodium channel blockers appear to be at minimal or no risk for arrhythmic events. Brugada patients at highest risk are males with inducible VT/VF and a spontaneously elevated ST segment.[12]

Brugada et al[30] recently reported on 547 individuals diagnosed with Brugada syndrome and no previous cardiac arrest. In 124 patients the abnormal electrocardiogram was identified after one or multiple episodes of syncope and in 423 individuals during routine electrocardiographic screening or during study because they were family members of patients with the syndrome. Structural disease was ruled out in all patients.

This study, evaluating the clinical outcome of the largest population of Brugada patients thus far reported, concluded that:

1. A spontaneously abnormal Type I ECG carried a 7.7-fold higher risk of developing an arrhythmic event during a lifetime as compared to individuals in whom the electrocardiogram diagnostic of Brugada syndrome was evident only after sodium channel blocker challenge
2. Male gender is another risk factor for sudden death, because males had a 5.5 higher risk of sudden death as compared to females
3. Programmed electrical stimulation resulting in inducibility of a sustained ventricular arrhythmia is the strongest marker of risk, associated with a 8-fold higher risk of (aborted) sudden death than noninducible patients
4. Familial forms of the disease are not associated with a worse prognosis than sporadic cases, because a positive family history of Brugada syndrome did not predict outcome. They found a 27.2% probability of an event by logistic regression analysis in a patient with a spontaneously abnormal ECG, a previous history of syncope, and inducible sustained ventricular arrhythmias

Thus, inducibility of ventricular arrhythmias and a previous history of syncope are suggested to be markers of a poor prognosis in Brugada syndrome. Symptomatic patients require protective treatment even when they are not inducible. Asymptomatic patients can be reassured if they are noninducible.[30]

Therapy

Currently, an implantable cardioverter defibrillator (ICD) is the only proven effective treatment for the disease. In a multicenter trial of 690 patients with Brugada syndrome, in which 258 individuals received an ICD, efficacy of the device in reverting VF and preventing sudden cardiac death was 100%; appropriate shocks were delivered in 14, 20, 29, 38, and 52% of cases at 1, 2, 3, 4, and 5 years of follow-up, respectively. In the case of initially asymptomatic patients, appropriate ICD discharge was delivered in 4, 6, 9, 17, and 37% at 1, 2, 3, 4, and 5 years of follow-up, respectively.[31,32]

Current recommendations for ICD implantation are summarized as follows:

1. Symptomatic patients displaying the Type 1 Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD without additional need for EPS. Similar patients presenting with related symptoms such as syncope, seizure, or noctural agonal respiration should also undergo ICD implantation after noncardiac causes of these symptoms have been carefully ruled out. EPS is recommended in symptomatic patients only for the assessment of supraventricular arrhythmia.
2. Asymptomatic patients displaying a Type 1 Brugada ECG (spontaneously or after sodium channel block) should undergo EPS if there is a family history of sudden cardiac death suspected to be due to Brugada syndrome. EPS may be justified when the family history is negative for sudden cardiac death if the Type 1 ECG occurs spontaneously. If inducible for ventricular arrhythmia, the patient should receive an ICD. Asymptomatic patients who have no family history and who develop a Type I ECG only after sodium channel blockade should be closely followed up.

Although there is no room for discussion regarding the excellent and uniform efficacy of ICDs for terminating VF, the effect is confined to the termination of VF, and ICDs cannot contribute to the prevention of VF. Therefore, there are some concerns regarding ICD therapy. The first is electrical storm associated with VF or polymorphic ventricular tachycardia, which is defined as frequent appropriate ICD shock deliveries for ventricular tachyarrhythmias of >3 times over 24 hours. Chalvidan et al.[33],

reported a patient who suffered from incessant VF episodes (electrical storm) and became near-fatal, but subsequently fully recovered.

The second is ICD related complications including lead dislodgment, inappropriate shock delivery, infection requiring ICD removal and so on.[34,35]

The third is the indication of ICDs for infant cases of Brugada syndrome, in which the size of the ICD is too large for implantation.[34,35]

A new therapy other than ICD implantation to overcome these concerns seems to be urgent.

The pharmacological approach to therapy, based on experimental data, has been tailored to a rebalancing of currents that are active during the early phases of the epicardial action potential in the right ventricle to reduce the magnitude of the action potential notch, restore the action potential dome, or both Antiarrhythmic agents such as amiodarone and β-blockers have been shown to be ineffective.[36] Class IC antiarrhythmic drugs (eg, flecainide and propafenone) and class IA agents (eg, procainamide) are contraindicated for reasons enumerated previously. Specific class IA agents such as quinidine and tedisamil, however, may exert a therapeutic action because of their *I*to-blocking properties. Because the presence of a prominent transient outward current, *I*to, in the right ventricle is at the heart of the mechanism underlying Brugada syndrome, any agent that inhibits this current may be protective. Cardioselective and *I*to-specific blockers are not available. The only agent on the US market with significant *I*to-blocking properties is quinidine. It is for this reason that it was suggested that this agent may be of therapeutic value in Brugada syndrome.[37] Studies have shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and

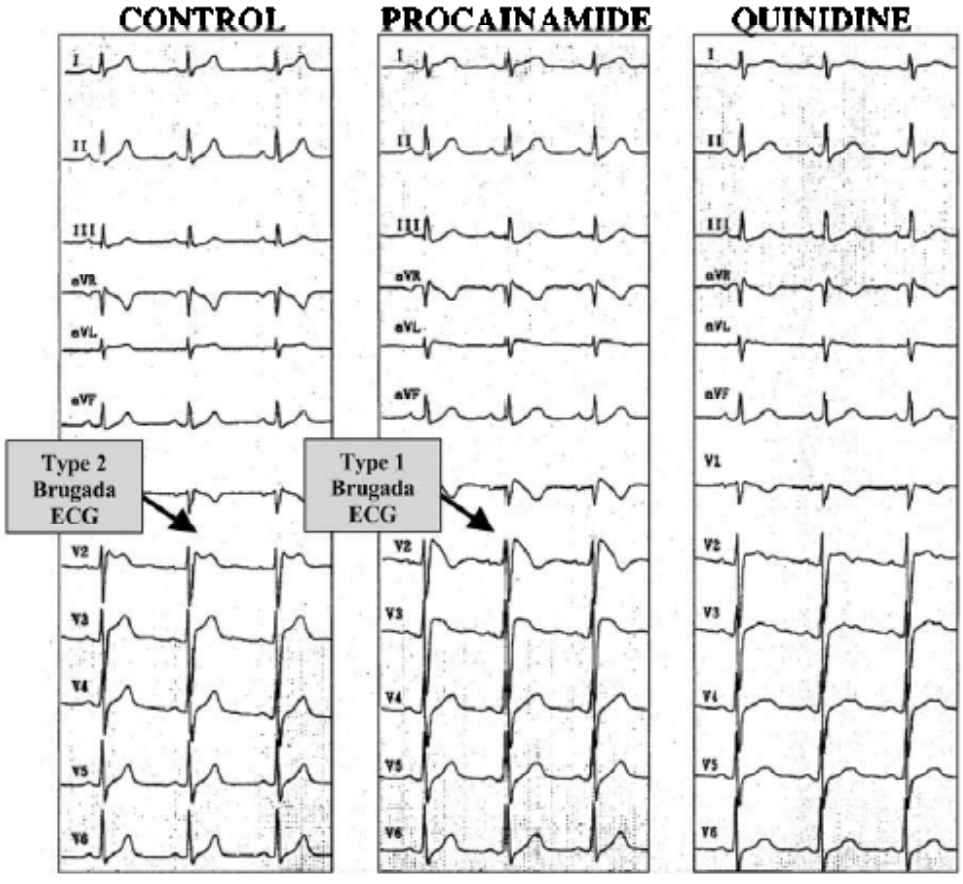

Figure 7. A few days after oral administration of quinidine bisulfate (1500 mg/day, serum quinidine level 2.6 mg/L), ST-segment elevation is attenuated displaying a nonspecific (neither Type 1-3 Brugada ECG) abnormal pattern in the right precordial leads

polymorphic VT in experimental models of Brugada syndrome. Clinical evidence of the effectiveness of quinidine in normalizing ST-segment elevation in patients with Brugada syndrome has been reported (see Figure 1) although clinical trials designed to assess the efficacy of this agent are limited.[38] Relatively high doses of quinidine are recommended (1200 to 1500 mg/d). Agents that boost the L-type calcium current, such as isoproterenol,[10] may be useful as well. Both types of agents (*I*to blocker and agents that augment *I*Ca) have been shown to be effective in normalizing ST-segment elevation in patients with Brugada syndrome and in controlling "electrical storms," particularly in children. (**Figure** 7)

The most recent addition to the pharmacological armamentarium is a phosphodiesterase III inhibitor, cilostazol, [39] which normalizes the ST segment most likely by augmenting the calcium current (*I*Ca), as well as by reducing *I*to secondary to an increase in heart rate. Finally, an experimental antiarrhythmic agent, tedisamil, with potent action to block *I*to among other outward currents has been suggested as a therapeutic candidate.[10] Tedisamil may be more potent than quinidine because it lacks the relatively strong inward current–blocking actions of quinidine. The development of a cardioselective and *I*to-specific blocker would be a most welcome addition to the limited therapeutic armamentarium available to combat this disease. Appropriate clinical trials are needed to establish the effectiveness of all of the above pharmacological agents as well as the possible role of pacemakers in some forms of the disease.

Summary

1. The syndrome is estimated to be responsible for at least 4% of all sudden deaths and at least 20% of sudden deaths in patients with structurally normal hearts.
2. The electrocardiographic signature of the syndrome is dynamic and often concealed. Normalization of the ECG signature of this syndrome by whatever mechanism may lead to an underestimation of the prevalence of the disease, thus placing some patients at risk.
3. Diagnose of Brugada syndrome is the presence of type 1 ST-segment elevation observed in >1 right precordial lead (V1 to V3) in the used or absence of a sodium channel– blocking agent, and in conjunction with one of the following: documented ventricular fibrillation (VF), polymorphic ventricular tachycardia (VT), a family history of sudden cardiac death at <45 years old, coved-type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration.
4. The ECG manifestations of the Brugada syndrome, when concealed, can be unmasked primarily by sodium channel blockers and calcium channel blocker but also during a febrile state or with vagotonic agents.
5. Implantable cardioverter defibrillator (ICD) is the only proven effective treatment for the disease. Because of its limitation, a new therapy other than ICD implantation to overcome these concerns seems to be urgent (pharmacotherapy, pacing therapy)

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