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Therapy for the Brugada Syndrome

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Abstract

The Brugada syndrome is a congenital syndrome of sudden cardiac death first described as a new clinical entity in 1992. Electrocardiographically characterized by a distinct coved-type ST segment elevation in the right precordial leads, the syndrome is associated with a high risk for sudden cardiac death in young and otherwise healthy adults, and less frequently in infants and children. The ECG manifestations of the Brugada syndrome are often dynamic or concealed and maybe revealed or modulated by sodium channel blockers. The syndrome may also be unmasked or precipitated by a febrile state, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, and hypokalemia, as well as by alcohol and cocaine toxicity. An implantable cardioverter-defibrillator (ICD) is the most widely accepted approach to therapy. Pharmacological therapy aimed at rebalancing the currents active during phase 1 of the right ventricular action potential is used to abort electrical storms, as an adjunct to device therapy, and as an alternative to device therapy when use of an ICD is not possible. Isoproterenol and cilostazol boost calcium channel current, and drugs like quinidine inhibit the transient outward current, acting to diminish the action potential notch and thus suppress the substrate and trigger for ventricular tachycardia/fibrillation (VT/VF).

Keywords

Brugada syndrome; Phase 2 reentry; ST segment elevation; I_{Na} ; I_{to} ; Implantable cardioverter-defibrillator (ICD); VT; *SCN5A* mutations; Sudden death; Bradycardia

1 Clinical Characteristics and Diagnostic Criteria

The Brugada syndrome typically manifests in the third or fourth decade of life (average age of 41 ± 15 years), although patients have been diagnosed with the syndrome at an age as young as 2 days and as old as 84 years. The prevalence of the disease is estimated to be at least 5 per 10,000 inhabitants in Southeast Asia, where the syndrome is endemic (Nademanee et al. 1997). In Japan, a Brugada syndrome ECG (type 1) is observed in 12 per 10,000 inhabitants; type 2 and type 3 ECGs, which are not diagnostic of Brugada syndrome, are much more prevalent, appearing in 58 per 10,000 inhabitants (Miyasaka et al. 2001). The true prevalence of the disease in the general population is difficult to estimate because the ECG pattern is often concealed (Brugada et al. 2003). Sudden unexplained nocturnal death syndrome (SUNDS also known as SUDS) and Brugada syndrome have been shown to be phenotypically, genetically, and functionally the same disorder (Vatta et al. 2002).

Although syncope and sudden death are a consequence of ventricular tachycardia/fibrillation (VT/VF), approximately 20% of Brugada syndrome patients also develop supraventricular arrhythmias (Morita et al. 2002). Atrial fibrillation (AF) is reported in approximately 10%-20% of cases. Atrio-ventricular (AV) nodal reentrant tachycardia (AVNRT) and Wolf-Parkinson-White (WPW) syndrome have been described as well (Eckardt et al. 2001). Prolonged sinus

node recovery time and sino-atrial conduction time (Morita et al. 2004) as well as slowed atrial conduction and atrial standstill have been reported in association with the syndrome (Takehara et al. 2004). A recent study reports that ventricular inducibility is positively correlated with a history of atrial arrhythmias (Bordachar et al. 2004). The incidence of atrial arrhythmias is 27% in Brugada syndrome patients with an indication for ICD vs 13% in patients without an indication for ICD, suggesting a more advanced disease process in patients with spontaneous atrial arrhythmias (Bordachar et al. 2004).

The Brugada syndrome is characterized by an ST segment elevation in the right precordial leads. Three types of ST segment elevation are generally recognized (Wilde et al. 2002a,b). Type 1 is diagnostic of Brugada syndrome and is characterized by a coved ST segment elevation exceeding or at 2 mm (0.2 mV) followed by a negative T wave (Fig. 1). Brugada syndrome is definitively diagnosed when a type 1 ST segment elevation is observed in more than one right-precordial lead (V_1 - V_3), in the presence or absence of sodium channel blocking agent, and in conjunction with one of the following: documented ventricular fibrillation, polymorphic ventricular tachycardia, a family history of sudden cardiac death (SCD) (<45 years old), coved type ECGs in family members, inducibility of VT with programmed electrical stimulation, syncope, or nocturnal agonal respiration. The electrocardiographic manifestations of the Brugada syndrome, when concealed, can be unmasked by sodium channel blockers, but also during febrile state or with vagotonic agents (Brugada et al. 2000b,c; Miyazaki et al. 1996; Antzelevitch and Brugada 2002). Sodium channel blockers, including flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide are used to aid in a differential diagnosis when ST segment elevation is not diagnostic under baseline conditions (Brugada et al. 2000c; Shimizu et al. 2000a; Priori et al. 2000).

Type 2 ST segment elevation has a saddleback appearance with an ST segment elevation of ≥ 2 mm followed by a trough displaying ≥ 1 -mm ST elevation followed by either a positive or biphasic T wave (Fig. 1). Type 3 has either a saddleback or coved appearance with an ST segment elevation of less than 1 mm. Type 2 and type 3 ECG are not diagnostic of the Brugada syndrome. These three patterns may be observed spontaneously in serial ECG tracings from the same patient or following 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 more than one 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 need also be present.

Placement of the right precordial leads in a superior position (two intercostal spaces above normal) can increase the sensitivity of the ECG for detecting the Brugada phenotype in some patients, both in the presence and absence of a drug challenge (Shimizu et al. 2000b; Sangwatanaroj et al. 2001).

While most cases of Brugada syndrome display right precordial ST segment elevation, isolated cases of inferior lead (Kalla et al. 2000) or left precordial lead (Horigome et al. 2003) ST segment elevation have been reported in Brugada-like syndromes, in some cases associated with SCN5A mutations (Potet et al. 2003).

Minor prolongation of the QT interval may accompany ST segment elevation in the Brugada syndrome (Alings and Wilde 1999; Bezzina et al. 1999; Priori et al. 2000). The QT-interval is prolonged more in the right vs left precordial leads, probably due to a preferential prolongation of action potential duration (APD) in right ventricular (RV) epicardium secondary to accentuation of the action potential notch (Pitzalis et al. 2003). Depolarization abnormalities including prolongation of P wave duration, PR and QRS intervals are frequently observed,

particularly in patients linked to *SCN5A* mutations (Smits et al. 2002). PR prolongation likely reflects HV conduction delay (Alings and Wilde 1999a).

2 Genetic Basis

The only gene thus far linked to the Brugada syndrome is *SCN5A*, the gene encoding for the α -subunit of the cardiac sodium channel gene (Chen et al. 1998). *SCN5A* mutations account for 18%-30% of Brugada syndrome cases. Nearly 100 mutations in *SCN5A* have been linked to the syndrome over the past 4 years (see Antzelevitch 2001a; Priori et al. 2002; Balser 2001; Tan et al. 2003 for references; also see . Approximately 30 of these mutations have been studied in expression systems and shown to result in loss of function due to: (1) failure of the sodium channel to express; (2) a shift in the voltage- and time-dependence of sodium channel current (I_{Na}) activation, inactivation or reactivation; (3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly; or (4) accelerated inactivation of the sodium channel. Inheritance of the Brugada syndrome is via an autosomal-dominant mode of transmission. A second locus on chromosome 3, close to but apart from the *SCN5A* locus, has recently been linked to the syndrome (Weiss et al. 2002).

3 Cellular and Ionic Basis

The ability of the RV action potential to lose its dome, giving rise to phase 2 reentry and other characteristics of the Brugada syndrome, were identified in the early 1990s and evolved in parallel with the clinical syndrome (Antzelevitch et al. 1991, 2002; Krishnan and Antzelevitch 1991; Krishnan and Antzelevitch 1993).

The ST segment elevation in the Brugada syndrome is thought to be secondary to a rebalancing of the currents active at the end of phase 1, leading to accentuation of the action potential notch in RV epicardium (see Antzelevitch 2001a for references). A transient outward current (I_{to})-mediated spike and dome morphology, or notch, in ventricular epicardium, but not endocardium, generates a voltage gradient responsible for the inscription of the electrocardiographic J wave in larger mammals and in man (Yan and Antzelevitch 1996). ST segment is normally isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Under pathophysiologic conditions, accentuation of the RV notch leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave, causing an apparent ST segment elevation (Antzelevitch 2001a). The repolarization waves take on a saddleback or coved appearance depending on the timing of repolarization of epicardium relative to endocardium. A delay in epicardial activation and repolarization time leads to progressive inversion of the T wave. The down-sloping ST segment elevation, or accentuated J wave, observed in the experimental wedge models often appears as an R', suggesting that the appearance of a right bundle branch block (RBBB) morphology in Brugada patients may be due at least in part to early repolarization of RV epicardium, rather than to marked impulse delay or conduction block in the right bundle. Indeed, RBBB criteria are not fully met in many cases of Brugada syndrome (Gussak et al. 1999).

Accentuation of the RV action potential notch can give rise to the typical Brugada ECG without creating an arrhythmogenic substrate (Fig. 2). The arrhythmogenic substrate arises when a further shift in the balance of currents leads to loss of the action potential dome at some epicardial sites but not others. 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. A closely coupled extrasystole can then capture this vulnerable window and induce a reentrant arrhythmia. Loss of the epicardial action potential dome is usually heterogeneous, leading to the development of epicardial dispersion of repolarization. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2

reentry mechanism, leading to the development of the very closely coupled extrasystole, which triggers a circus movement reentry in the form of VT/VF (Lukas and Antzelevitch 1996; Yan and Antzelevitch 1999). The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in epicardium, the QRS complex is largely composed of a negative Q wave, which serves to accentuate the inverted T wave, giving the ECG a more symmetrical appearance, a morphology commonly observed in the clinic preceding the onset of polymorphic VT. Support for these hypotheses derives from experiments involving the arterially perfused RV wedge preparation (Yan and Antzelevitch 1999). Further evidence in support of these mechanisms derives from the recent studies of Kurita et al. in which monophasic action potential (MAP) electrodes were positioned on the epicardial and endocardial surfaces of the RV outflow tract (RVOT) in patients with the Brugada syndrome (Kurita et al. 2002; Antzelevitch et al. 2002).

Figure 3 shows the ability of terfenadine-induced phase 2 reentry to generate an extrasystole, couplet, and polymorphic VT/VF. Figure 3d illustrates an example of programmed electrical stimulation-induced VT/VF under similar conditions.

Although the genetic mutation is equally distributed between the sexes, the clinical phenotype is 8 to 10 times more prevalent in males than in females. The basis for this sex-related distinction was recently shown to be due to a more prominent I_{to} -mediated action potential notch in the RV epicardium of males vs females (Di Diego et al. 2002). The more prominent I_{to} causes the end of phase 1 of the RV epicardial action potential to repolarize to more negative potentials in tissue and arterially perfused wedge preparations from males, facilitating loss of the action potential dome and the development of phase 2 reentry and polymorphic VT. The gender distinction is not seen in all families; a recent report describes a family without a male predominance of the Brugada phenotype (Hong et al. 2004).

The available information supports the hypothesis that the Brugada syndrome is the result of amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. The amplification is secondary to a rebalancing of currents active during phase 1, including a decrease in I_{Na} or I_{Ca} or augmentation of any one of a number of outward currents including I_{Kr} , I_{Ks} , $I_{Cl(c/a)}$ or I_{to} (Fig. 4). ST segment elevation occurs as a consequence of the accentuation of the action potential notch, eventually leading to loss of the action potential dome in RV epicardium, where I_{to} is most prominent. Loss of the dome gives rise to both a transmural as well as epicardial dispersion of repolarization. The transmural dispersion is responsible for the development of ST segment elevation and the creation of a vulnerable window across the ventricular wall, whereas the epicardial dispersion leads to phase 2 reentry, which provides the extrasystole that captures the vulnerable window, thus precipitating VT/VF. The VT generated is usually polymorphic, resembling a very rapid form of torsade de pointes (TdP) (Fig. 4).

4 Factors That Modulate ECG and Arrhythmic Manifestations of the Brugada Syndrome

ST segment elevation in the Brugada syndrome is often dynamic. The Brugada ECG is often concealed and can be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, α -adrenergic agonists, β -adrenergic blockers, tricyclic or tetracyclic antidepressants, a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and by alcohol and cocaine toxicity (Brugada et al. 2000b c; Miyazaki et al. 1996; Babalarios and Hurst 2002; Goldgran-Toledano et al. 2002; Tada et al. 2001; Pastor et al. 2001; Ortega-Carnicer et al. 2001; Nogami et al. 2003; Araki et al. 2003). These agents may also induce acquired forms of the Brugada syndrome (Table 1). Until a definitive list of drugs to

avoid in the Brugada syndrome is formulated, the list of agents in Table 1 may provide some guidance.

Acute ischemia or myocardial infarction due to vasospasm involving the RVOT mimics ST segment elevation similar to that in Brugada syndrome. This effect is secondary to the depression of I_{Ca} and the activation of I_{K-ATP} during ischemia, and suggests that patients with congenital and possibly acquired forms of Brugada syndrome may be at a higher risk for ischemia-related SCD (Noda et al. 2002).

VF and sudden death in the Brugada syndrome usually occur at rest and at night. Circadian variation of symaptho-vagal balance, hormones, and other metabolic factors likely contribute this circadian pattern. Bradycardia, due to altered symaptho-vagal balance or other factors, may contribute to arrhythmia initiation (Kasanuki et al. 1997; Proclemer et al. 1993; Mizumaki et al. 2004). Abnormal ^{123}I -MIBG uptake in 8 (17%) of the 17 Brugada syndrome patients but none in the control group was demonstrated by Wichter et al. (2002). There was segmental reduction of ^{123}I -MIBG in the inferior and the septal left ventricular wall, indicating presynaptic sympathetic dysfunction. Of note, imaging of the right ventricle, particularly the RVOT, is difficult with this technique, so insufficient information is available concerning sympathetic function in the regions known to harbor the arrhythmogenic substrate. Moreover, it remains unclear what role the reduced uptake function plays in the arrhythmogenesis of the Brugada syndrome. If indeed the RVOT is similarly affected, this defect may alter the symaptho-vagal balance in favor of the development of an arrhythmogenic substrate (Litovsky and Antzelevitch 1990; Yan and Antzelevitch 1999).

More recently, Kies and coworkers (Kies et al. 2004) assessed autonomic nervous system function noninvasively in patients with the Brugada syndrome, quantifying myocardial presynaptic and postsynaptic sympathetic function by means of positron emission tomography with the norepinephrine analog 11C-Hydroxyephedrine (11C-HED) and the nonselective β -blocker 11C-CGP 12177 (11C-CGP). Presynaptic sympathetic norepinephrine recycling, assessed by 11C-HED, was found to be globally increased in patients with Brugada syndrome compared with a group of age-matched healthy control subjects, whereas postsynaptic β -adrenoceptor density, assessed by 11C-CGP, was similar in patients and controls. This study provides further evidence in support of an autonomic dysfunction in Brugada syndrome.

Hypokalemia has been implicated as a contributing cause for the high prevalence of SUDS in the northeastern region of Thailand, where potassium deficiency is endemic (Nimmannit et al. 1991; Araki et al. 2003). Serum potassium in the northeastern population is significantly lower than that of the population in Bangkok, which lies in the central part of Thailand, where potassium is abundant in the food. A recent case report highlights the ability of hypokalemia to induce VF in a 60-year-old man who had asymptomatic Brugada syndrome, without a family history of sudden cardiac death (Araki et al. 2003). This patient was initially treated for asthma by steroids, which lowered serum potassium from 3.8 mmol/l on admission to 3.4 and 2.9 mmol/l on the seventh day and eighth day of admission, respectively. Both were associated with unconsciousness. VF was documented during the last episode, which reverted spontaneously to sinus rhythm.

Accelerated inactivation of the sodium channel in *SCN5A* mutations associated with the Brugada syndrome has been shown to be accentuated at higher temperatures (Dumaine et al. 1999), suggesting that a febrile state may unmask the Brugada syndrome by causing loss of function secondary to premature inactivation of I_{Na} . Indeed, numerous case reports have emerged since 1999 demonstrating that febrile illness could reveal the Brugada ECG and precipitate VF (Gonzalez Rebollo et al. 2000; Madle et al. 2002; Saura et al. 2002; Porres et al. 2002; Kum et al. 2002; Antzelevitch and Brugada 2002; Ortega-Carnicer et al. 2003;

Dzielinska et al. 2004). Anecdotal reports point to hot baths as a possible precipitating factor. Of note, the northeastern part of Thailand, where the Brugada syndrome is most prevalent, is known for its very hot climate.

5 Approach to Therapy

Table 2 lists the device and pharmacologic therapies evaluated clinically or suggested on the basis of experimental evidence.

5.1 Device Therapy

An implantable cardioverter-defibrillator (ICD) is the only proven effective device treatment for the disease (Brugada et al. 1999,2000a). Recommendations of the Second Brugada Syndrome Consensus Conference (Antzelevitch et al. 2005) for ICD implantation are illustrated in Fig. 5 and summarized as follows:

- Symptomatic patients displaying the type I Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD without additional need for electrophysiologic study (EPS). Similar patients presenting with related symptoms such as syncope, seizure, or nocturnal agonal respiration should also undergo ICD implantation after non-cardiac causes of these symptoms have been carefully ruled out. EPS is recommended in symptomatic patients only for the assessment of supraventricular arrhythmia.

- Asymptomatic patients displaying a type I Brugada ECG (spontaneously or after sodium channel block) should undergo EPS if there is a family history of SCD suspected to be due to Brugada syndrome. EPS may be justified when the family history is negative for SCD if the type I 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. As additional data become available, these recommendations will no doubt require further fine-tuning.

The effectiveness of ICD in reverting VF and preventing sudden cardiac death was 100% in a recent multicenter trial in which 258 patients diagnosed with Brugada syndrome received an ICD (Brugada et al. 2004). 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 4%, 6%, 9%, 17%, and 37% at 1, 2, 3, 4, and 5 years of follow-up, respectively.

A recent report highlights the need for therapy other than with ICD. The case involves a patient with the Brugada syndrome who experienced multiple electrical storms, leading to numerous inappropriate ICD discharges. The patient was eventually given a heart transplant (Ayerza et al. 2002).

5.2 Pharmacologic Approach to Therapy

ICD implantation is not an appropriate solution for infants and young children or for patients residing in regions of the world where an ICD is out of reach because of economic factors. Although arrhythmias and sudden cardiac death generally occur during sleep or at rest and have been associated with slow heart rates, a potential therapeutic role for cardiac pacing remains largely unexplored. A recent interesting report by Haissaguerre and coworkers (Haissaguerre et al. 2003) points to focal radiofrequency ablation as a potentially valuable tool in controlling arrhythmogenesis by focal ablation of the ventricular premature beats that trigger VT/VF in the Brugada syndrome. However, data relative to a cryosurgical approach or the use of ablation therapy are very limited at this point in time.

A pharmacologic approach to therapy, based on a rebalancing of currents active during the early phases of the epicardial action potential in the right ventricle so as to reduce the magnitude of the action potential notch and/or restore the action potential dome, has been a focus of basic and clinical research in recent years. Table 2 lists the various pharmacologic agents thus investigated. Antiarrhythmic far agents such as amiodarone and β -blockers have been shown to be ineffective (Brugada et al. 1998). Class IC drugs antiarrhythmic (such as flecainide and propafenone) and class IA agents, such as procainamide, are contraindicated because of their effects to unmask the Brugada syndrome and induce arrhythmogenesis. Disopyramide is a class IA rhythmic antiarrhythmic that has been demonstrated to normalize ST segment elevation in some Brugada patients but to unmask the syndrome in others (Chinushi et al. 1997).

Because the presence of a prominent transient outward current, is central to the mechanism I_{to} underlying the Brugada syndrome, the most rational approach to therapy, regardless of the ionic or genetic basis for the disease, is to partially inhibit I_{to} . Cardioselective and I_{to} -specific blockers are not currently available. 4-Aminopyridine (4-AP) is an agent that is ion-channel specific at low concentrations, but is not cardioselective in that it inhibits I_{to} present in the nervous system. Although it is effective in suppressing in wedge arrhythmogenesis models of the Brugada syndrome (Yan and Antzelevitch 1999; Fig. 6), it is unlikely to be of clinical benefit because of neural-mediated and other side effects.

The only agent on the market in the United States with significant I_{to} blocking properties is quinidine. It is for this reason that we suggested several years ago that this agent might be of therapeutic value in the Brugada syndrome (Antzelevitch et al. 1999a). Experimental studies have since shown quinidine to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic experimental v_T in models of the Brugada syndrome (Fig. 6; Yan and Antzelevitch 1999). Clinical evidence of the effectiveness of quinidine in normalizing ST segment elevation in patients with the Brugada syndrome has been reported (Figs. 1 and 7; Belhassen et al. 2002; Alings et al. 2001; Belhassen and Viskin 2004).

The effects of quinidine to prevent inducible and spontaneous VF was recently reported by Belhassen and coworkers (Belhassen and Viskin 2004) in a prospective study of 25 Brugada syndrome patients (24 men, 1 woman; 19 to 80 years of age) orally administered $1,483 \pm 240$ mg quinidine bisulfate. There were 15 symptomatic patients (7 cardiac arrest survivors and 7 with unexplained syncope) and 10 asymptomatic patients. All 25 patients had inducible v_T at baseline electrophysiological study. Quinidine prevented induction VF in 22 of the 25 patients (88%). After a follow-up period of 6 months to 22.2 years, all patients were alive. Of 19 patients treated with oral quinidine for 6 to 219 months (56 ± 67 months), none developed arrhythmic events. Administration of quinidine was associated with a 36% incidence of side effects, principally diarrhea, that resolved after drug discontinuation. The authors concluded that quinidine effectively suppresses VF induction as well as spontaneous arrhythmias in patients with Brugada syndrome and may be useful as an adjunct to ICD therapy or as an alternative to ICD in cases in which an ICD is refused, unaffordable, or not feasible for any reason. These results are consistent with those reported the same group in prior years (Belhassen et al. 1999 2002) and more recently by other investigators (Hermida et al. 2004; Mok et al. 2004). The data highlight the need for randomized clinical trials to assess the effectiveness of quinidine, preferably in patients with frequent events who have already received an ICD.

The development of a more cardioselective and I_{to} -specific blocker would be a most welcome addition to the limited therapeutic armamentarium currently available to combat this disease. Another agent being considered for this purpose is the drug tedisamil, currently being evaluated for the treatment of atrial fibrillation. Tedisamil may be more potent than quinidine because it lacks the inward current blocking actions of quinidine, while potentially blocking I_{to} . The

effectiveness of tedisamil to suppress phase 2 reentry and VT in a wedge model of the Brugada syndrome is illustrated in Fig. 8 (Fish et al. 2004b).

Quinidine and tedisamil can suppress the substrate and trigger for the Brugada syndrome due to inhibition of I_{to} . Both, however, have the potential to induce an acquired form of the long QT syndrome, secondary to inhibition of the rapidly activating delayed rectifier current, I_{Kr} . Thus, the drugs may substitute one form polymorphic VT for another, particularly under conditions that promote TdP, such as bradycardia and hypokalemia. This effect of quinidine is minimized at high plasma levels because, at these concentrations, quinidine block of I_{Na} counters the effect of I_{Kr} block to increase transmural dispersion of repolarization, the substrate for the development of TdP arrhythmias (Antzelevitch et al. 1999b; Antzelevitch and Shimizu 2002; Belardinelli et al. 2003). Relatively high doses of quinidine (1,000-1,500 mg/day) are recommended in order to effect I_{to} block, but prevent TdP.

Another potential candidate is an agent recently reported to be a relatively selective I_{to} and I_{Kur} blocker, AVE0118 (Fish et al. 2004a). Figure 9 shows the effect of AVE0118 to normalize the ECG and suppress phase 2 reentry in a wedge model of the Brugada syndrome. This drug has the advantage that it does not block I_{Kr} , and therefore does not prolong the QT-interval or have the potential to induce TdP. The disadvantage of this particular drug is that it undergoes first-pass hepatic metabolism and is therefore not effective with oral administration.

Appropriate clinical trials are needed to establish the effectiveness of all of the above pharmacologic agents as well as the possible role of pacemakers.

Agents that boost the calcium current, such as β -adrenergic agents like isoproterenol, are useful as well (Antzelevitch 2001a; Yan and Antzelevitch 1999; Tsuchiya et al. 2002). Isoproterenol, sometimes in combination with quinidine, has been shown to be effective in normalizing ST segment elevation in patients with the Brugada syndrome and in controlling electrical storms, particularly in children (Alings et al. 2001; Shimizu et al. 2000b; Suzuki et al. 2000; Tanaka et al. 2001; Belhassen et al. 2002; Mok et al. 2004).

A recent addition to the pharmacological armamentarium is the phosphodiesterase III inhibitor, cilostazol (Tsuchiya et al. 2002), which normalizes the ST segment, most likely by augmenting calcium current (I_{Ca}) as well as by reducing I_{to} secondary to an increase in heart rate.

Finally, another potential pharmacologic approach to therapy is to augment I_{Na} active during phase 1 of the epicardial action potential. This theoretical approach will oppose I_{to} and should prevent the development of both the substrate (transmural dispersion of repolarization) and trigger (phase 2 reentry) for the Brugada syndrome.

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References

- Alings M, Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. *Circulation* 1999;99:666–673. [PubMed: 9950665]
- Alings M, Dekker L, Sadee A, Wilde A. Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. *Pacing Clin Electrophysiol* 2001;24:1420–1422. [PubMed: 11584468]
- Antzelevitch C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *f Cardiovasc Electrophysiol* 2001a;12:268–272.

- Antzelevitch C. The Brugada syndrome. Diagnostic criteria and cellular mechanisms. *Eur Heart J* 2001b; 22:356–363. [PubMed: 11207076]
- Antzelevitch C, Brugada R. Fever and the Brugada syndrome. *Pacing Clin Electrophysiol* 2002;25:1537–1539. [PubMed: 12494608]
- Antzelevitch C, Shimizu W. Cellular mechanisms underlying the long QT syndrome. *Curr Opin Cardiol* 2002;17:43–51. [PubMed: 11790933]
- Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, Gintant GA, Liu DW. Heterogeneity within the ventricular wall: electrophysiology and pharmacology of epicardial, endocardial and M cells. *Circ Res* 1991;69:1427–1449. [PubMed: 1659499]
- Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R.; Nademanee, K.; Towbin, JA. The Brugada syndrome. In: Camm, AJ., editor. *Clinical approaches to tachyarrhythmias*. Futura Publishing Company; Armonk: 1999a. p. 1-99.
- Antzelevitch C, Shimizu W, Yan GX, Sicouri S, Weissenburger J, Nesterenko V, Burashnikov A, Di Diego JM, Saffitz JE, Thomas GP. The M cell: Its contribution to the ECG and to normal and abnormal electrical function of the heart. *J Cardiovasc Electrophysiol* 1999b;10:1124–1152. [PubMed: 10466495]
- Antzelevitch C, Brugada P, Brugada J, Brugada R, Shitmizu W, Gussak I, Perez Riera AR. Brugada syndrome: a decade of progress. *Circ Res* 2002;91:1114–1118. [PubMed: 12480811]
- Antzelevitch C, Brugada P, Borggreffe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Riera ARP, Tan H, Shimizu W, Schulze-Bahr E, Wilde A. Brugada syndrome. Report of the Second Consensus Conference. *Circulation* 2005;111:659–670. [PubMed: 15655131]
- Araki T, Konno T, Itoh H, Ino H, Shimizu M. Brugada syndrome with ventricular tachycardia and fibrillation related to hypokalemia. *Circ J* 2003;67:93–95. [PubMed: 12520160]
- Ayerza MR, de Zutter M, Goethals M, Wellens F, Geelen P, Brugada P. Heart transplantation as last resort against Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13:943–944. [PubMed: 12380937]
- Babaliaros VC, Hurst JW. Tricyclic antidepressants and the Brugada syndrome: an example of Brugada waves appearing after the administration of desipramine. *Clin Cardiol* 2002;25:395–398. [PubMed: 12173907]
- Balser JR. The cardiac sodium channel: gating function and molecular pharmacology. *J Mol Cell Cardiol* 2001;33:599–613. [PubMed: 11273715]
- Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. *Trends Pharmacol Sci* 2003;24:619–625. [PubMed: 14654302]
- Belhassen B.; Viskin, S. Pharmacologic approach to therapy of Brugada syndrome: quinidine as an alternative to ICD therapy. In: Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R., editors. *The Brugada syndrome: from bench to bedside*. Blackwell Futura; Oxford: 2004. p. 202-211.
- Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome [see comments]. *J Cardiovasc Electrophysiol* 1999;10:1301–1312. [PubMed: 10515552]
- Belhassen B, Viskin S, Antzelevitch C. The Brugada syndrome: is ICD the only therapeutic option. *Pacing Clin Electrophysiol* 2002;25:1634–1640. [PubMed: 12494624]
- Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, Van Langen IM, Tan-Sindhunata G, Bink-Boelkens MT, Der Hout AH, Mannens MM, Wilde AA. A single Na(+) channel mutation causing both long-QT and Brugada syndromes. *Circ Res* 1999;85:1206–1213. [PubMed: 10590249]
- Bolognesi R, Tsialtas D, Vasini P, Conti M, Manca C. Abnormal ventricular repolarization mimicking myocardial infarction after heterocyclic antidepressant overdose. *Am J Cardiol* 1997;79:242–245. [PubMed: 9193039]
- Bordachar P, Reuter S, Garrigue S, Cai X, Hocini M, Jais P, Haissaguerre M, Clementy J. Incidence, clinical implications and prognosis of atrial arrhythmias in Brugada syndrome. *Eur Heart J* 2004;25:879–884. [PubMed: 15140537]

- Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3. A marker for sudden death in patients without demonstrable structural heart disease. *Circulation* 1998;97:457–460. [PubMed: 9490240]
- Brugada J, Brugada R, Brugada P. Pharmacological and device approach to therapy of inherited cardiac diseases associated with cardiac arrhythmias and sudden death. *J Electrocardiol* 2000a;33(Suppl): 41–47. [PubMed: 11265735]
- Brugada P, Brugada R, Brugada J, Geelen P. Use of the prophylactic implantable cardioverter defibrillator for patients with normal hearts. *Am J Cardiol* 1999;83:98D–100D. [PubMed: 10073791]
- Brugada P, Brugada J, Brugada R. Arrhythmia induction by antiarrhythmic drugs. *Pacing Clin Electrophysiol* 2000b;23:291–292. [PubMed: 10750126]
- Brugada, P.; Brugada, R.; Antzelevitch, C.; Nademanee, K.; Towbin, f; Brugada, J. The Brugada syndrome. In: Gussak, I.; Antzelevitch, C., editors. *Cardiac repolarization. bridging basic and clinical sciences*. Humana Press; Totowa: 2003. p. 427–446.
- Brugada, P.; Bartholomay, E.; Mont, L.; Brugada, R.; Brugada, J. Treatment of Brugada syndrome with an implantable cardioverter defibrillator. In: Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R., editors. *The Brugada syndrome: from bench to bedside*. Blackwell Futura; Oxford: 2004. p. 194–201.
- Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000c;101:510–515. [PubMed: 10662748]
- Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggreffe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schultze-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanisms for idiopathic ventricular fibrillation. *Nature* 1998;392:293–296. [PubMed: 9521325]
- Chinushi M, Aizawa Y, Ogawa Y, Shiba M, Takahashi K. Discrepant drug action of disopyramide on ECG abnormalities and induction of ventricular arrhythmias in a patient with Brugada syndrome. *J Electrocardiol* 1997;30:133–136. [PubMed: 9141608]
- Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez Gj, Scornik FS, Antzelevitch C. Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. *Circulation* 2002;106:2004–2011. [PubMed: 12370227]
- Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko V, Nesterenko DV, Brugada J, Brugada R, Antzelevitch C. Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. *Circ Res* 1999;85:803–809. [PubMed: 10532948]
- Dzielinska Z, Bilinska ZT, Szumowski L, Grzybowski J, Michalak E, Przybylski A, Lubiszewska B, Walczak P, Ruzyllo W. [Recurrent ventricular fibrillation during a febrile illness as the first manifestation of Brugada syndrome—a case report]. *Kardiologia Polska* 2004;61:269–273. [PubMed: 15531939]
- Eckardt L, Kirchhof P, Johna R, Haverkamp W, Breithardt G, Borggreffe M. Wolff-Parkinson-White syndrome associated with Brugada syndrome. *Pacing Clin Electrophysiol* 2001;24:1423–1424. [PubMed: 11584469]
- Fish JM, Antzelevitch C. Role of sodium and calcium channel block in unmasking the Brugada syndrome. *Heart Rhythm* 2004;1:210–217. [PubMed: 15851155]
- Fish JM, Extramiana F, Antzelevitch C. AVE0118, an Ito and IKur blocker, suppresses VT/VF in an experimental model of the Brugada syndrome. *Circulation* 2004a;110:III–193.
- Fish JM, Extramiana F, Antzelevitch C. Tedisamil abolishes the arrhythmogenic substrate responsible for VT/VF in an experimental model of the Brugada syndrome. *Heart Rhythm* 2004b;1:S158.(abstr)
- Fujiki A, Usui M, Nagasawa H, Mizumaki K, Hayashi H, Inoue H. ST segment elevation in the right precordial leads induced with class IC antiarrhythmic drugs: insight into the mechanism of Brugada syndrome [see comments]. *J Cardiovasc Electrophysiol* 1999;10:214–218. [PubMed: 10090224]
- Gasparini M, Priori SG, Mantica M, Napolitano C, Galimberti P, Ceriotti C, Simonini S. Flecainide test in Brugada syndrome: a reproducible but risky tool. *Pacing Clin Electrophysiol* 2003;26:338–341. [PubMed: 12687841]
- Goldgran-Toledano D, Sideris G, Kevorkian JP. Overdose of cyclic antidepressants and the Brugada syndrome. *N Engl J Med* 2002;346:1591–1592. [PubMed: 12015405]

- Gonzalez Rebollo G, Madrid H, Carcia A, Garcia de Casto A, Moro AM. Recurrent ventricular fibrillation during a febrile illness in a patient with the Brugada syndrome. *Rev Esp Cardiol* 2000;53:755–757. [PubMed: 10816181]
- Gussak I, Antzelevitch C, Bjerregaard P, Towbin JA, Chaitman BR. The Brugada syndrome: clinical, electrophysiological and genetic aspects. *J Am Coll Cardiol* 1999;33:5–15. [PubMed: 9935001]
- Haissaguerre M, Extramiana F, Hocini M, Cauchemez B, Jais P, Cabrera JA, Farre G, Leenhardt A, Sanders P, Scavee C, Hsu LF, Weerasooriya R, Shah DC, Frank R, Maury P, Delay M, Garrigue S, Clementy J. Mapping and ablation of ventricular fibrillation associated with long-QT and Brugada syndromes. *Circulation* 2003;108:925–928. [PubMed: 12925452]
- Hermida JS, Denjoy I, Clerc J, Extramiana F, Jarry G, Milliez P, Guicheney P, Di Fusco S, Rey JL, Cauchemez B, Leenhardt A. Hydroquinidine therapy in Brugada syndrome. *J Am Coll Cardiol* 2004;43:1853–1860. [PubMed: 15145111]
- Hong K, Berruezo-Sanchez A, Pongvarin N, Oliva A, Vatta M, Brugada J, Brugada P, Towbin JA, Dumaine R, Pinero-Galvez C, Antzelevitch C, Brugada R. Phenotypic characterization of a large European family with Brugada syndrome displaying a sudden unexpected death syndrome mutation in SCN5A. *J Cardiovasc Electrophysiol* 2004;15:64–69. [PubMed: 15028074]
- Horigome H, Shigeta O, Kuga K, Isobe T, Sakakibara Y, Yamaguchi I, Matsui A. Ventricular fibrillation during anesthesia in association with J waves in the left precordial leads in a child with coarctation of the aorta. *J Electrocardiol* 2003;36:339–343. [PubMed: 14661171]
- Kalla H, Yan GX, Marinchak R. Ventricular fibrillation in a patient with prominent J (Osborn) waves and ST segment elevation in the inferior electrocardiographic leads: a Brugada syndrome variant. *J Cardiovasc Electrophysiol* 2000;11:95–98. [PubMed: 10695469]
- Kasanuki H, Ohnishi S, Ohtuka M, Matsuda N, Nirei T, Isogai R, Shoda M, Toyoshima Y, Hosoda S. Idiopathic ventricular fibrillation induced with vagal activity in patients with out obvious heart disease. *Circulation* 1997;95:2277–2285. [PubMed: 9142005]
- Kies P, Wichter T, Schafers M, Paul M, Schafers KP, Eckardt L, Stegger L, Schulze-Bahr E, Rimoldi O, Breithardt G, Schober O, Camici PG. Abnormal myocardial presynaptic norepinephrine recycling in patients with Brugada syndrome. *Circulation* 2004;110:3017–3022. [PubMed: 15520312]
- Krishnan SC, Antzelevitch C. Sodium channel blockade produces opposite electrophysiologic effects in canine ventricular epicardium and endocardium. *Circ Res* 1991;69:277–291. [PubMed: 1650294]
- Krishnan SC, Antzelevitch C. Flecainide-induced arrhythmia in canine ventricular epicardium: phase 2 reentry. *Circulation* 1993;87:562–572. [PubMed: 8425300]
- Krishnan SC, Josephson ME. ST segment elevation induced by class IC antiarrhythmic agents: underlying electrophysiologic mechanisms and insights into drug-induced proarrhythmia. *J Cardiovasc Electrophysiol* 1998;9:1167–1172. [PubMed: 9835260]
- Kum L, Fung JWH, Chan WWL, Chan GK, Chan YS, Sanderson JE. Brugada syndrome unmasked by febrile illness. *Pacing Clin Electrophysiol* 2002;25:1660–1661. [PubMed: 12494630]
- Kurita T, Shimizu W, Inagaki M, Suyama K, Taguchi A, Satomi K, Aihara N, Kamakura S, Kobayashi J, Kosakai Y. The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. *J Am Coll Cardiol* 2002;40:330–334.
- Litovsky SH, Antzelevitch C. Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circ Res* 1990;67:615–627. [PubMed: 2397572]
- Littmann L, Monroe MH, Svenson RH. Brugada-type electrocardiographic pattern induced by cocaine. *Mayo Clin Proc* 2000;75:845–849. [PubMed: 10943241]
- Lukas A, Antzelevitch C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. The antiarrhythmic effects of 4-aminopyridine. *Cardiovasc Res* 1996;32:593–603. [PubMed: 8881520]
- Madle A, Kratochvil Z, Polivkova A. [The Brugada syndrome]. *Vnitr Lek* 2002;48:255–258. [PubMed: 11968588]
- Matana A, Goldner V, Stanic K, Mavric Z, Zaputovic L, Matana Z. Unmasking effect of propafenone on the concealed form of the Brugada phenomenon. *Pacing Clin Electrophysiol* 2000;23:416–418. [PubMed: 10750149]

- Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N, Kamakura S. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:508–512. [PubMed: 9607459]
- Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, Matsumoto N, Iwasaka T. Prevalence and mortality of the Brugada-type electrocardiogram in one city in Japan. *J Am Coll Cardiol* 2001;38:771–774. [PubMed: 11527631]
- Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061–1070. [PubMed: 8609322]
- Mizumaki K, Fujiki A, Tsuneda T, Sakabe M, Nishida K, Sugao M, Inoue H. Vagal activity modulates spontaneous augmentation of ST elevation in daily life of patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2004;15:667–673. [PubMed: 15175062]
- Mok NS, Chan NY, Chi-Suen CA. Successful use of quinidine in treatment of electrical storm in Brugada syndrome. *Pacing Clin Electrophysiol* 2004;27:821–823. [PubMed: 15189543]
- Morita H, Kusano-Fukushima K, Nagase S, Fujimoto Y, Hisamatsu K, Fujio H, Haraoka K, Kobayashi M, Morita ST, Nakamura K, Emori T, Matsubara H, Hina K, Kita T, Fukatani M, Ohe T. Atrial fibrillation and atrial vulnerability in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;40:1437. [PubMed: 12392834]
- Morita H, Fukushima-Kusano K, Nagase S, Miyaji K, Hiramatsu S, Banba K, Nishii N, Watanabe A, Kakishita M, Takenaka-Morita S, Nakamura K, Saito H, Emori T, Ohe T. Sinus node function in patients with Brugada-type ECG. *Circ J* 2004;68:473–476. [PubMed: 15118291]
- Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S, Tatsanavivat P. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595–2600. [PubMed: 9355899]
- Nimmannit S, Malasit P, Chaovakul V, Susaengrat W, Vasuvattakul S, Nilwarangkur S. Pathogenesis of sudden unexplained nocturnal death (lai tai) and endemic distal renal tubular acidosis. *Lancet* 1991;338:930–932. [PubMed: 1681278]
- Noda T, Shimizu W, Taguchi A, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S. ST-segment elevation and ventricular fibrillation without coronary spasm by intracoronary injection of acetylcholine and/or ergonovine maleate in patients with Brugada syndrome. *J Am Coll Cardiol* 2002;40:1841–1847. [PubMed: 12446069]
- Nogami A, Nakao M, Kubota S, Sugiyasu A, Doi H, Yokoyama K, Yumoto K, Tamaki T, Kato K, Hosokawa N, Sagai H, Nakamura H, Nitta J, Yamauchi Y, Aonuma K. Enhancement of J-ST-segment elevation by the glucose and insulin test in Brugada syndrome. *Pacing Clin Electrophysiol* 2003;26:332–337. [PubMed: 12687840]
- Ortega-Carnicer J, Bertos-Polo J, Gutierrez-Tirado C. Aborted sudden death, transient Brugada pattern, and wide QRS dysrhythmias after massive cocaine ingestion. *J Electrocardiol* 2001;34:345–349. [PubMed: 11590577]
- Ortega-Carnicer J, Benezet J, Ceres F. Fever-induced ST-segment elevation and T-wave alternans in a patient with Brugada syndrome. *Resuscitation* 2003;57:315–317. [PubMed: 12804811]
- Pastor A, Nunez A, Cantale C, Cosio FG. Asymptomatic Brugada syndrome case unmasked during dimenhydrinate infusion. *J Cardiovasc Electrophysiol* 2001;12:1192–1194. [PubMed: 11699532]
- Pitzalis MV, Anaclerio M, Iacoviello M, Forleo C, Guida P, Troccoli R, Massari F, Mastropasqua F, Sorrentino S, Manghisi A, Rizzon P. QT-interval prolongation in right precordial leads: an additional electrocardiographic hallmark of Brugada syndrome. *J Am Coll Cardiol* 2003;42:1632–1637.
- Porres JM, Brugada J, Urbistondo V, Garcia F, Reviejo K, Marco P. Fever unmasking the Brugada syndrome. *Pacing Clin Electrophysiol* 2002;25:1646–1648. [PubMed: 12494626]
- Potet F, Mabo P, Le Coq G, Probst V, Schott Jf, Airaud F, Guihard G, Daubert JC, Escande D, Le Marec H. Novel Brugada SCNSA mutation leading to ST segment elevation in the inferior or the right precordial leads. *J Cardiovasc Electrophysiol* 2003;14:200–203. [PubMed: 12693506]
- Priori SG, Napolitano C, Gasparini M, Pappone C, Della BP, Brignole M, Giordano U, Giovannini T, Menozzi C, Bloise R, Crotti L, Terreni L, Schwartz PJ. Clinical and genetic heterogeneity of right

bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. *Circulation* 2000;102:2509–2515.

- Priori SG, Napolitano C, Gasparini M, Pappone C, Della BP, Giordano U, Bloise R, Giustetto C, De Nardis R, Grillo M, Ronchetti E, Faggiano G, Nastoli J. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 2002;105:1342–1347. [PubMed: 11901046]
- Proclemer A, Facchin D, Feruglio GA, Nucifora R. Recurrent ventricular fibrillation, right bundle-branch block and persistent ST segment elevation in V1-V3: a new arrhythmia syndrome? A clinical case report [see comments]. *G Ital Cardiol* 1993;23:1211–1218. [PubMed: 8174872]
- Rolf S, Bruns HJ, Wichter T, Kirchhof P, Ribbing M, Wasmer K, Paul M, Breithardt G, Haverkamp W, Eckardt L. The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003;24:1104–1112. [PubMed: 12804924]
- Rouleau F, Asfar P, Boulet S, Dube L, Dupuis JM, Alquier P, Victor J. Transient ST segment elevation in right precordial leads induced by psychotropic drugs: relationship to the Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:61–65. [PubMed: 11204086]
- Sangwatanaroj S, Prechawat S, Sunsaneewitayakul B, Sitthisook S, Tosukhowong P, Tungsanga K. New electrocardiographic leads and the procainamide test for the detection of the Brugada sign in sudden unexplained death syndrome survivors and their relatives. *Eur Heart J* 2001;22:2290–2296. [PubMed: 11728150]
- Saura D, Garcia-Alberola A, Carrillo P, Pascual D, Martinez-Sanchez J, Valdes M. Brugada-like electrocardiographic pattern induced by fever. *Pacing Clin Electrophysiol* 2002;25:856–859. [PubMed: 12049381]
- Shimizu W. Acquired forms of Brugada syndrome. In: Antzelevitch, C.; Brugada, P.; Brugada, J.; Brugada, R., editors. *The Brugada syndrome: from bench to bedside*. Black-well Futura; Oxford: 2004. p. 166-177.
- Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N, Takaki H, Sunagawa K, Kamakura S. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *J Cardiovasc Electrophysiol* 2000a;11:1320–1329. [PubMed: 11196553]
- Shimizu W, Matsuo K, Takagi M, Tanabe Y, Aiba T, Taguchi A, Suyama K, Kurita T, Aihara N, Kamakura S. Body surface distribution and response to drugs of ST segment elevation in Brugada syndrome: clinical implication of eighty-seven-lead body surface potential mapping and its application to twelve-lead electrocardiograms. *J Cardiovasc Electrophysiol* 2000b;11:396–404. [PubMed: 10809492]
- Shimizu W, Aiba T, Kurita T, Kamakura S. Paradoxical abbreviation of repolarization in epicardium of the right ventricular outflow tract during augmentation of Brugada-type ST segment elevation. *J Cardiovasc Electrophysiol* 2001;12:1418–1421. [PubMed: 11798001]
- Smits JP, Eckardt L, Probst V, Bezzina CR, Schott JJ, Remme CA, Haverkamp W, Breithardt G, Escande D, Schulze-Bahr E, LeMarec H, Wilde AA. Genotype-phenotype relationship in Brugada syndrome: electrocardiographic features differentiate SCN5A-related patients from non-SCN5A-related patients. *J Am Coll Cardiol* 2002;40:350–356. [PubMed: 12106943]
- Suzuki H, Torigoe K, Numata O, Yazaki S. Infant case with a malignant form of Brugada syndrome. *J Cardiovasc Electrophysiol* 2000;11:1277–1280. [PubMed: 11083249]
- Tada H, Nogami A, Shimizu W, Naito S, Nakatsugawa M, Oshima S, Taniguchi K. ST segment and T wave alternans in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2000;23:413–415. [PubMed: 10750148]
- Tada H, Sticherling C, Oral H, Morady F. Brugada syndrome mimicked by tricyclic antidepressant overdose. *J Cardiovasc Electrophysiol* 2001;12:275. [PubMed: 11232630]
- Takehara N, Makita N, Kawabe J, Sato N, Kawamura Y, Kitabatake A, Kikuchi K. A cardiac sodium channel mutation identified in Brugada syndrome associated with atrial standstill. *J Intern Med* 2004;255:137–142. [PubMed: 14687250]
- Takenaka S, Emori T, Koyama S, Morita H, Fukushima K, Ohe T. Asymptomatic form of Brugada syndrome. *Pacing Clin Electrophysiol* 1999;22:1261–1263. [PubMed: 10461307]
- Tan HL, Bezzina CR, Smits JP, Verkerk AO, Wilde AA. Genetic control of sodium channel function. *Cardiovasc Res* 2003;57:961–973. [PubMed: 12650874]

- Tanaka H, Kinoshita O, Uchikawa S, Kasai H, Nakamura M, Izawa A, Yokoseki O, Kitabayashi H, Takahashi W, Yazaki Y, Watanabe N, Imamura H, Kubo K. Successful prevention of recurrent ventricular fibrillation by intravenous isoproterenol in a patient with Brugada syndrome. *Pacing Clin Electrophysiol* 2001;24:1293–1294. [PubMed: 11523620]
- Tsuchiya T, Ashikaga K, Honda T, Arita M. Prevention of ventricular fibrillation by cilostazol, an oral phosphodiesterase inhibitor, in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 2002;13:698–701. [PubMed: 12139296]
- van Den Berg MP, Wilde AA, Viersma TJW, Brouwer J, Haaksma J, van der Hout AH, Stolte-Dijkstra I, Bezzina TCR, Van Langen IM, Beaufort-Krol GC, Cornel JH, Crijns HJ. Possible bradycardic mode of death and successful pacemaker treatment in a large family with features of long QT syndrome type 3 and Brugada syndrome. *J Cardiovasc Electrophysiol* 2001;12:630–636. [PubMed: 11405394]
- Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C, Towbin JA. Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. *Hum Mol Genet* 2002;11:337–345. [PubMed: 11823453]
- Weiss R, Barmada MM, Nguyen T, Seibel JS, Cavlovich D, Kornblit CA, Angelilli A, Villanueva F, McNamara DM, London B. Clinical and molecular heterogeneity in the Brugada syndrome. A novel gene locus on chromosome 3. *Circulation* 2002;105:707–713. [PubMed: 11839626]
- Wichter T, Matheja P, Eckardt L, Kies P, Schafers K, Schulze-Bahr E, Haverkamp W, Borggrefe M, Schober O, Breithardt G, Schafers M. Cardiac autonomic dysfunction in Brugada syndrome. *Circulation* 2002;105:702–706. [PubMed: 11839625]
- Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation* 2002a;106:2514–2519. [PubMed: 12417552]
- Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Eur Heart J* 2002b;23:1648–1654. [PubMed: 12448445]
- Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic Jwave. *Circulation* 1996;93:372–379. [PubMed: 8548912]
- Yan GX, Antzelevitch C. Cellular basis for the Brugada Syndrome and other mechanisms of arrhythmogenesis associated with ST segment elevation. *Circulation* 1999;100:1660–1666. [PubMed: 10517739]

Fig. 1.

Twelve-lead electrocardiogram (ECG) tracings in an asymptomatic 26-year-old man with the Brugada syndrome. *Left:* Baseline: type 2 ECG (not diagnostic) displaying a “saddleback-type” ST segment elevation is observed in V_2 . *Center:* After intravenous administration of 750 mg procainamide, the type 2 ECG is converted to the diagnostic type 1 ECG consisting of a “coved-type” ST segment elevation. *Right:* A few days after oral administration of quinidine bisulfate (1,500 mg/day, serum quinidine level 2.6 mg/l), ST segment elevation is attenuated, displaying a nonspecific abnormal pattern in the right precordial leads. VF could be induced during control and procainamide infusion, but not after quinidine. (Modified from Beihassen et al. 2002, with permission)

Fig. 2a-d.

Terfenadine-induced ST segment elevation, T wave inversion, transmural and epicardial dispersion of repolarization, and phase 2 reentry. Each panel shows transmembrane action potentials from one endocardial (top) and two epicardial sites together with a transmural ECG recorded from a canine arterially perfused right ventricular wedge preparation. **a** Control (BCL 400 ms). **b** Terfenadine (5 μ M) accentuated the epicardial action potential notch creating a transmural voltage gradient that manifests as an ST segment elevation or exaggerated J wave in the ECG. First beat recorded after changing from BCL 800 ms to BCL 400 ms. **c** Continued pacing at BCL 400 ms results in all-or-none repolarization at the end of phase 1 at some epicardial sites but not others, creating a local epicardial dispersion of repolarization (*EDR*) as well as a transmural dispersion of repolarization (*TDR*). **d** Phase 2 reentry occurs when the epicardial action potential dome propagates from a site where it is maintained to regions where it has been lost. (Note: d was recorded from a different preparation.) (From Fish and Antzelevitch 2004, with permission)

Fig. 3a-d.

Spontaneous and programmed electrical stimulation-induced polymorphic VT in RV wedge preparations pretreated with terfenadine (5-10 μ M). a Phase 2 reentry in epicardium gives rise to a closely coupled extrasystole. b Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. c Phase 2 reentrant extrasystole triggers reentry d Same impalements and pacing conditions as c, however an extra stimulus = 250 ms) applied to epicardium (S1-S2 = 250 ms) applied to epicardium triggers a polymorphic VT. (From Fish and Antzelevitch 2004, with permission)

Fig. 4.

Proposed mechanism for the Brugada syndrome. A shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within epicardium as well as across the wall. Epicardial dispersion leads to the development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/VF via a circus movement reentry mechanism. (Modified from Antzelevitch 2001b, with permission)

Fig. 5.
Indications for ICD implantation in patients with the Brugada syndrome

Fig. 6a,b.

Effects of I_{to} blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in the arterially perfused RV wedge preparation. In both examples, 2.5 mmol/l pinacidil produced heterogeneous loss of A_P dome in epicardium, resulting in ST segment elevation, phase 2 reentry, and VT (*left*); 4-AP (a) and quinidine (b) restored epicardial AP dome, reduced both transmural and epicardial dispersion of repolarization, normalized the ST segment, and prevented phase 2 reentry and VT in continued presence of pinacidil. (From Yan and Antzelevitch 1999, with permission)

Fig. 7.
Precordial leads recorded from a Brugada syndrome patient before and after quinidine (1,500 mg/day). (Modified from Alings et al. 2001, with permission)

Fig. 8a-c.

Effects of I_{to} block with tedisamil to suppress phase 2 reentry induced by terfenadine in an arterially perfused canine RV wedge preparation. a Control, BCL 800 ms. b Terfenadine ($5\mu\text{M}$) induces ST segment elevation as a result of heterogeneous loss of the epicardial action potential dome, leading to phase 2 reentry, which triggers an episode of poly VT (BCL 800 ms). c Addition of tedisamil ($2\mu\text{M}$) normalizes the ST segment and prevents loss of the epicardial action potential dome and suppresses phase 2 reentry induced polymorphic VT (BCL 800 ms)

Fig. 9a-c.

Effects of I_{to} blockade with AVE0118 to suppress phase 2 reentry induced by terfenadine in an arterially perfused canine RV wedge preparation. a Control, BCL 800 ms. b Terfenadine (5 μ M) induces ST segment elevation as a result of heterogeneous loss of the epicardial action potential dome, leading to phase 2 reentry³ which triggers a closely coupled extrasystole (BCL = 800 ms). c Addition of AVEO 118 (7 μ M) prevents loss of the epicardial action potential dome and phase 2 reentry-induced arrhythmias (BCL = 800 ms)

Table 1**Drug-induced Brugada-like ECG patterns**

I. Antiarrhythmic drugs	
1. Na ⁺ channel blockers	Class IC drugs [Elevainide (Krishnan and Josephson 1998; Fujiki et al. 1999; Shimizu et al. 2000a; Brugada et al. 2000c; Gasparini et al. 2003), Pilsicainide (Takenaka et al. 1999; Shimizu et al. 2001), Propafenone (Matana et al. 2000)] Class IA drugs [Ajmaline (Brugada et al. 2000c; Rolf et al. 2003), Procainamide (Miyazaki et al. 1996; Brugada et al. 2000c), Disopyramide (Miyazaki et al. 1996; Wilde et al. 2002a), Cibenzoline (Tada et al. 2000)]
2. Ca ²⁺ channel blockers	Verapamil
II. Antianginal drugs	
1. Ca ²⁺ channel blockers	Nifedipine, diltiazem
2. Nitrate	Isosorbide dinitrate, nitroglycerine (Matsuo et al. 1998)
3. K ⁺ channel openers	Nicorandil
III. Psychotropic drugs	
1. Tricyclic antidepressants	Amitriptyline (Bolognesi et al. 1997; Rouleau et al. 2001), Nortriptyline (Tadaet al. 2001), desipramine (Babaliaros and Hurst 2002), clomipramine (Glodgran-Toledano et al. 2002)
2. Tetracyclic antidepressants	Maprotiline (Bolognesi et al. 1997)
3. Phenothiazine	Perphenazine (Bolognesi et al. 1997), cyamemazine
4. Selective serotonin reuptake inhibitors	Fluoxetine (Rouleau et al. 2001)
IV. Other drugs	
1. Histaminic H1 receptor antagonists	Dimenhydrinate (Pastor et al. 2001)
2. Cocaine intoxication	(Ortega-Carnicer et al. 2001; Littmann et al. 2000)

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Table 2

Device nad pharmacologic apaproach to therapy of the Brugada syndrome

Devices and Ablation
ICD (Brugada et al. 2000a)
?Ablation or Cryosurgery (Haissaguerre et l. 2003)
?Pacemaker (vn den Berg et al. 2001)
Pharmcaologic Approach to Therapy
<i>Ineffective</i>
Amiodarone (Brugada et al. 1998)
β -Blockers (Brugadaa et al. 1998)
Class iC antiarrhythmics
Flecainide (Shimizu et al. 2000a)
Propafenone (Matana et al. 2000)
?Disopyramide (Chinushi et al. 1997)
Class IA aaantiarrhythmics
Procainaamide (Brugada et al. 2000c)
<i>Effective for treatment of electrical storms</i>
β -Adrenergic agonists—isooproterenol (Miyazaki et al. 1996; Shihmizu et al. 2000b)
Phosphodiesterase III inhibitors—cilostazol (Tsuchiya et al. 2002)
<i>Effective general therapy</i>
Class IA antiarrythmics
Quinidine (Belhassen and Viskin 2004; Alings et al. 2001; Belhassen et al. 1999, 2002; Yan and Antzelevitch 1999; Hermida et al. 2004; Mok et al. 2004)
<i>Experimental therapy</i>
I_{to} blockers—cardioselective and ion channel specific
Quinidine (Yan and Antzelevitch 1999)
4-Aaminopyridine (Yan and Antzelevitch 1999)
Tedisamil (Fish et al. 2004b)
AVE0118 (Fish et al. 2004a)