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Brugada Syndrome: Cellular Mechanisms and Approaches to Therapy

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Introduction

Nearly 15 years have passed since Pedro and Josep Brugada introduced the syndrome of ST-segment elevation and right bundle branch block (RBBB) associated with a high incidence of ventricular tachycardia/ventricular fibrillation (VT/VF) as a new clinical entity.[1] Over 16 years have transpired since the introduction of the concept of phase 2 reentry (induced by sodium channel block), the mechanism believed to underlie the development of arrhythmogenesis in this clinical syndrome.[2,3] Thus, the entity, which in 1996 came to be known as the Brugada syndrome,[4,5] evolved in the experimental laboratory and in the clinic along parallel but separate tracks until the late 1990s.[6]

The Brugada syndrome has attracted great interest because of its prevalence and its association with a high risk of sudden death, especially in males as they enter their third and fourth decade of life. A consensus report published in 2002 delineated diagnostic criteria for the syndrome.[7,8] A second consensus conference report published in 2005 focused on risk stratification schemes and approaches to therapy.[9,10] This chapter provides an overview of the genetic, molecular, and cellular aspects of the Brugada syndrome and considers the various approaches to therapy.

Brugada Syndrome

Clinical Characteristics

A brief description of clinical characteristics is included to provide a perspective for our discussion of mechanisms and therapy. This subject is more thoroughly dealt with in Chapter 32 (this volume). The Brugada syndrome is characterized by an ST- segment elevation in the right precordial electrocardiogram (ECG) leads and a high incidence of sudden death. The average age at the time of initial diagnosis or sudden death is 40 ± 22, although the range is wide with youngest patient diagnosed at 2 days of age and the oldest at 84 years.

The ECG manifestations of the Brugada syndrome are often concealed, but can be unmasked by sodium channel blockers, a febrile state, or vagotonic agents.[5,11–13] Three types of repolarization patterns in the right precordial leads are recognized (Table 33–1).[7,8] Type 1 ST-segment elevation 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. Type 2 ST-segment elevation has a saddleback appearance with a high take-off ST-segment elevation of ≥2 mm followed by a trough displaying ≥1 mm ST elevation followed by either a positive or biphasic T wave. Type 3 ST-segment elevation has either a saddleback or coved appearance with an ST-segment elevation of <1 mm. These three patterns may be observed sequentially in the same patient or following the introduction of specific drugs. Type 2 and Type 3 ST-segment elevation should not be considered diagnostic of the Brugada syndrome. A Brugada ECG refers to the manifestation of a Type 1 ST-segment elevation. Brugada syndrome is definitively diagnosed when a Type 1 ST-segment elevation (Brugada ECG) is observed in more than one right-precordial lead (V1–V3), in the presence or absence of a sodium channel blocking agent, and in conjunction with one or more of the following: documented VF, polymor-

Table 33–1. Diagnostic criteria for Brugada syndrome.[a]

	ST-segment abnormalities in leads V1–V3		
	Type 1	Type 2	Type3
J point	≥2 mm	≥2 mm	≥2 mm
T wave	Negative	Positive or biphasic	Positive
ST-T configuration	Coved type	Saddleback	Saddleback
ST segment (terminal portion)	Gradually descending	Elevated ≥1 mm	Elevated <1 mm

Source: From Wilde *et al.*,[7] with permission.
[a]From the first consensus document. 1 mm = 0.1 mV. The terminal portion of the ST segment refers to the latter half of the ST segment.

phic 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.[7–10]

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 can be converted to the diagnostic Type 1 pattern that occurs upon exposure to a sodium channel blocker (ST-segment elevation should be ≥2 mm). One or more of the clinical criteria described above should also be present. Drug-induced conversion of Type 3 to Type 2 ST-segment elevation is considered inconclusive for diagnosis of Brugada syndrome.

The ECG manifestations of the syndrome are often concealed, but can be unmasked using sodium channel blockers. Definitive diagnosis is difficult when the degree of basal ST-segment elevation is relatively small and the specificity of sodium channel blockers such as flecainide, ajmaline, procainamide, disopyramide, propafenone, and pilsicainide[12,14,15] to identify patients at risk is uncertain. A comparison of intravenous ajmaline and flecainide in the same cohort of patients revealed that ajmaline is more effective in unmasking the syndrome.[16] Flecainide failed in 7 of 22 cases (32%) unmasked by ajmaline. A greater inhibition of transient outward current (I_{to}) by flecainide renders it less effective than ajmaline. False-positive as well as false-negative responses have been reported with ajmaline, as well.[17,18] Itoh *et al.* demonstrated that a missense mutation in SCN5A, the gene that encodes the α subunit of the sodium channel, although responsible for the disease, prevented ajmaline from unmasking the syndrome, due to loss of the ability of the drug to produce use-dependent inhibition of sodium channel current.[18]

Most cases of Brugada syndrome display right precordial ST-segment elevation, although isolated cases of inferior lead[19,20] or left precordial lead[21] ST-segment elevation have been reported in Brugada-like syndromes, in some cases associated with *SCN5A* mutations. In rare cases, ST-segment elevation is observed in all precordial leads (unpublished observation).

Placement of the right precordial leads in a superior position (up to the second intercostal spaces 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] Studies are underway to ascertain whether the greater sensitivity is at the cost of a lower specificity and whether a Type I ECG in the elevated leads is as predictive of events as a Type I ECG the in the standard leads. A recent report demonstrates that as many as 1.3% of normal Korean males display a Type 2, but not Type 1, ST-segment elevation when the right precordial leads are recorded from a superior position.[24]

A slight prolongation of the QT interval is sometimes associated with the ST-segment elevation.[15,25,26] The QT interval is prolonged more in the right than the left precordial leads, presumably due to a preferential prolongation of action potential duration (APD) in right ventricular (RV) epicardium secondary to accentuation of the action potential notch.[27] A QTc > 460 msec in V2 has been shown to be associated with arrhythmic risk.[28] Depolarization abnormalities including prolongation of P wave duration, PR, and QRS intervals are frequently observed, particularly in patients linked to *SCN5A* mutations.[29] PR prolongation likely reflects HV conduction delay.[25]

In many cases arrhythmia initiation is bradycardia related.[30] This may contribute to the higher incidence of sudden death at night in individuals with the syndrome and may account for the success of pacing in controlling the arrhythmia in isolated cases of the syndrome.[31] Makiyama and co-workers reported that loss-of-function SCN5A

mutations resulting in Brugada syndrome are distinguished by profound bradyarrhythmias.[32] Related to this observation is the recent report by Scornik and co-workers[33] demonstrating expression of the cardiac sodium channel gene, SCN5A, in intracardiac ganglia. This interesting finding suggests that loss of function mutations in SCN5A may not only create the substrate for reentry in ventricular myocardium, but may also increase vagal activity in intracardiac ganglia, thus facilitating the development of arrhythmias in patients with the Brugada syndrome.

A polymorphic VT is most commonly associated with the Brugada syndrome. Monomorphic VT is observed infrequently and is generally more prevalent in children and infants.[34–39]

The majority of congenital Brugada syndrome patients are believed to possess a structurally normal heart, consistent with the notion that this is a primary electrical heart disease.[40] While fibrosis and myocarditis may exacerbate or indeed trigger events in patients with the Brugada syndrome, it seems clear that in the vast majority of cases these structural changes are unrelated to arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

Prognosis and Risk Stratification

Risk stratification of patients with the Brugada syndrome has been an issue of lively debate. It is generally accepted that Brugada syndrome patients presenting with aborted sudden death are at high risk for recurrence and that they should be protected by an implantable cardiac defibrillator (ICD). There is also little argument that patients presenting with syncope, particularly when the clinical history suggests an arrhythmic syncope (as opposed to typical vasovagal syncope) and the ECG shows a Type I abnormality, are at high risk. In contrast, risk stratification of asymptomatic patients has met with considerable debate.[41–45] Several invasive and noninvasive parameters have been proposed for identification of patients at risk of sudden death, including the presence of spontaneous Type 1 ST-segment elevation, the characteristics of the S wave,[46] the presence of late potentials,[47] and inducibility of VT/VF using programmed electrical stimulation (PES).[48]

In 1998, Brugada *et al.*[49] reported that over a 34-month follow-up period, 27% of previously asymptomatic patients experienced a first VF or SCD. This figure corresponds to an occurrence of life-threatening events of approximately 10%/year. In 2002, with a mean follow-up of 27 ± 29 months, Brugada *et al.*[41] reported that 8% of previously asymptomatic patients had become symptomatic, an occurrence of a life-threatening event of 3.5%/year. In 2005, Brugada *et al.*[43] reported that 6% of asymptomatic patients displayed a first event during a mean follow-up of 42 ± 42 months, corresponding to an event rate of 1.7%/year. This progressive decline in first event rate in previously asymptomatic patients most likely reflects a reduced severity of phenotypes referred to the Brugada registry in subsequent years. In contrast, Priori *et al.* in 2002[42] reported that asymptomatic patients have a cumulative probability of 14% for developing a cardiac arrest by age 40 years, corresponding to a natural history incidence of cardiac arrest of 0.35%/year. In 2005, they reported a first event rate of 3% (4/132) over a 31-month follow-up period, corresponding to an event rate of 1%/year.[44]

The reason behind the disparity in the data generated by these two groups is not clearly evident. It was suggested by Brugada *et al.*[43] that the difference my be due to the inclusion by Priori and co-workers of patients with Type 2 and 3 ST-segment elevation, which is not considered diagnostic of the Brugada syndrome.[7–10] Priori and co-workers argue that exclusion of Type 2 and 3 from the diagnosis of the syndrome can lead to missed diagnosis of the disease.[44] While this is clearly the case, it may be a rare occurrence, and the exclusion appears justified on the basis that it avoids a large number of false-positive diagnoses. As a result of the failure to exclude individuals with Type 2 and 3 ST-segment elevation, the European registry may contain many individuals who do not have the syndrome. However, a recent report by Eckardt and co-workers[45] suggests that other factors may be involved. They report that 1 out of 123 asymptomatic individuals with a Type 1 ECG (0.8%) had a first arrhythmic event during a 40 ± 50-month follow-up. This translates into a first event rate of 0.24% per year, considerably less than the other two registries. Thus, as additional data have become available, it has become clear

that the prognosis of asymptomatic patients is associated with much less risk than was initially perceived.

The large registry studies agree that Brugada syndrome patients at higher risk for the development of subsequent events are those presenting with a spontaneous Type 1 ST-segment elevation or Brugada ECG and/or those with a previous VT/VF or SCD.[45] The registries also agree that PES inducibility is greatest among patients with previous VT/VF or syncope. Approximately one-third of asymptomatic patients are inducible. In the studies by Priori *et al.*[44] and Eckardt *et al.*[45] inducibility of VT/VF in asymptomatic patients was not associated with risk. The lack of association between inducibility and spontaneous VF in Brugada patients was also reported by a number of smaller studies, such as that of Kanada *et al.*[50]

In sharp contrast, Brugada *et al.*[51] found that the risk for developing VT/VF is considerably greater in patients who are inducible during PES, whether or not a Type 1 ST-segment elevation is spontaneously present and whether or not they were symptomatic. The reason for the marked disparity in the predictive power of PES inducibility among the different studies is not immediately apparent. The discrepancies may be due to differences in patient characteristics and the use of multiple testing centers with nonstandardized or noncomparable stimulation protocols.[52] Additional studies are clearly needed to further define risk stratification strategies for asymptomatic patients.

It is noteworthy that in experimental models of the Brugada syndrome involving the coronary-perfused wedge preparation, polymorphic VT is readily inducible with a single ventricular extrastimulus, but only when applied on the epicardial surface of the wedge. Inducibility is not possible or much more difficult when extrastimulation is applied to the endocardial surface. The shorter refractory period of epicardium allows extrastimuli direct access to the vulnerable window across the ventricular wall, thus facilitating the induction of reentry. These relationships suggest that PES applied to the epicardium may provide a more accurate assessment of risk than the current clinical approach in which stimuli are applied to the endocardial surface. In support of this hypothesis, Carlsson *et al.* reported that a Brugada syndrome patient with recurrent syncope due to polymorphic ventricular tachycardia could not be induced with right ventricular endocardial stimulation. However, epicardial stimulation from a left ventricular site through the coronary sinus led to the development of polymorphic VT.[53]

Gehi *et al.*[54] recently reported the results of a meta-analysis of 30 prospective studies that included 1545 patients with a Brugada ECG to assess predictors of events. The meta-analysis suggested that a history of syncope or SCD, the presence of a spontaneous Type I Brugada ECG, and male gender predict a more malignant natural history. The findings, however, did not support the use of a family history of SCD, the presence of an SCN5A gene mutation, or electrophysiologic study to guide the management of patients with a Brugada ECG. The results of the meta-analysis should be viewed with some reservation in that the study pooled data from prognostic studies that used very different criteria to identify patients with Brugada syndrome. Moreover the six studies that were used to evaluate the role of electrophysiological study in risk stratification of patients were quite heterogeneous. A prospective study termed PRELUDE (PRogrammed ElectricaL stimUlation preDictivE) currently underway in Italy is designed to provide further insight into the ongoing debate.

Genetic Basis

Brugada syndrome shows an autosomal dominant mode of inheritance. The first gene to be linked to the syndrome is SCN5A, the gene that encodes the α subunit of the cardiac sodium channel gene.[55] Figure 33–1 highlights the diversity of SCN5A mutations associated with the Brugada syndrome. Of note, mutations in SCN5A are also responsible for the long QT3 (LQT3) form of the long QT syndrome and cardiac conduction disease. A number of mutations have been reported to cause overlapping syndromes; in some cases all three phenotypes are present.[56] Nearly 100 mutations in SCN5A have been associated with the syndrome in recent years (see Antzelevitch *et al.*[57] for references; also see www.fsm.it/cardmoc).

Only a fraction of these mutations has been studied in expression systems and shown to result in loss of function. A number of mechanisms have

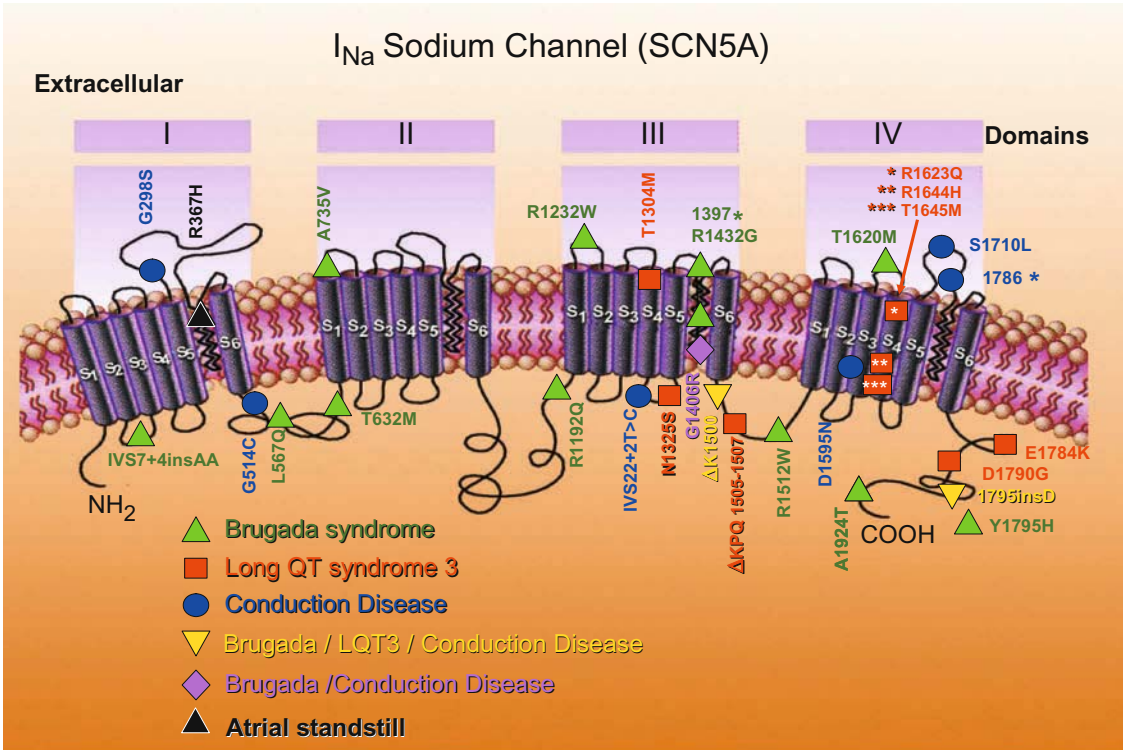


FIGURE 33–1. Schematic of SCN5A, the gene that encodes the α subunit of the sodium channel, illustrating mutations linked to Brugada syndrome, long QT3 syndrome, conduction disease, and atrial standstill. Some mutations are associated with combined phenotypes. (Modified from Antzelevitch C. Brugada syndrome. *PACE* 2006;29(10):1130–1159.)

been delineated for the reduction in sodium channel current (I_{Na}), including[58–62] (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. In *in vitro* expression systems, the premature inactivation of the sodium channel is sometimes observed at physiological temperatures, but not at room temperature.[63] Acceleration of I_{Na} inactivation was still more accentuated at higher than physiological temperatures, suggesting that the syndrome may be unmasked, and that patients with the Brugada syndrome may be at an increased risk during a febrile state.[63] A number of Brugada patients displaying fever-induced polymorphic VT have been identified since the publication of this report.[13,36,64–71]

Mutation in the *SCN5A* gene account for approximately 18–30% of Brugada syndrome cases. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases.[59] It is important to recognize that a negative *SCN5A* result does not rule this gene out as a cause, since the promoter region, cryptic splicing mutations, or the presence of gross rearrangements are generally not part of a routine investigation. A recent report by Hong *et al.*[72] provided the first report of a dysfunctional sodium channel created by an intronic mutation giving rise to cryptic splice site activation in SCN5A in a family with the Brugada syndrome. The deletion of fragments of segments 2 and 3 of domain IV of SCN5A caused complete loss of function.

Evidence in support of the hypothesis that an SCN5A promoter polymorphism common in Asians modulates variability in cardiac conduction, and may contribute to the high prevalence of Brugada syndrome in the Asian population,

was recently advanced by Bezzina and coworkers.[73] Sequencing of the SCN5A promoter identified a haplotype variant consisting of six polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in whites and blacks. These findings demonstrate that sodium channel transcription in the human heart may vary considerably among individuals and races and may be associated with variable conduction velocity and arrhythmia susceptibility.

A second locus on chromosome 3, close to but distinct from SCN5A, has been linked to the syndrome[74] in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. The gene was recently identified as the glycerol-3-phosphate dehydrogenase 1-like gene (GPD1L). In a preliminary report, a mutation in GPD1L was shown to result in a partial reduction of I_{Na}.[75]

It is generally accepted that identification of specific mutations may not be very helpful in formulating a diagnosis or providing a prognosis. Mutations have been reported throughout the SCN5A gene and no hotspots have been identified. It is not clear whether some mutations 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 our understanding of genotype–phenotype relations.

Cellular and Ionic Mechanisms Underlying the Development of the Brugada Phenotype

Transmural Cellular and Ion Channel Distinctions

Ventricular myocardium is known to be comprised of at least three electrophysiologically and functionally distinct cell types: epicardial, M, and endocardial cells.[76,77] These three principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics. Ventricular epicardial and M, but not endocardial, cells generally display a prominent phase 1, due to a large 4-aminopyridine (4-AP)-sensitive transient outward current (I_{to}), giving the action potential a spike and dome or notched configuration. These regional differences in I_{to}, first suggested on the basis of action potential data,[78] have now been directly demonstrated in canine,[79] feline,[80] rabbit,[81] rat,[82] and human[83,84] ventricular myocytes. Differences in the magnitude of the action potential notch and corresponding differences in I_{to} have also been described between right and left ventricular epicardium.[85] Similar interventricular differences in I_{to} have also been described for canine ventricular M cells.[86] This distinction is thought to form the basis for why the Brugada syndrome, a channelopathy-mediated form of sudden death, is a right ventricular disease.

The molecular basis for the transmural distribution of I_{to} has long been a subject of debate. The transmural gradient of I_{to} in dogs has been ascribed to a transmural distribution of (1) the KCND3 gene (Kv4.3), which encodes the α subunit of the I_{to} channel,[87] (2) KChIP2, a β subunit that coassembles with Kv4.3,[88] and (3) IRX5, a transcriptional factor regulating KCND3.[89]

Myocytes isolated from the epicardial region of the left ventricular wall of the rabbit show a higher density of cAMP-activated chloride current when compared to endocardial myocytes.[90] I_{to2}, initially ascribed to a K^+ current, now thought to be primarily due to the calcium-activated chloride current ($I_{Cl(Ca)}$), is also thought to contribute to the action potential notch, but it is not known whether this current differs among the three ventricular myocardial cell types.[91]

Recent studies involving canine ventricular myocytes have shown that calcium current (I_{Ca}) is similar among cells isolated from epicardium, M, and endocardial regions of the left ventricular wall.[92,93] One study, however, reported differences in Ca^{2+} channel properties between epicardial and endocardial canine ventricular cells. In that study, I_{Ca} was found to be larger in endocardial than in epicardial myocytes (3.4 ± 0.2 vs. 2.3 ± 0.1 pA/pF). A low-threshold, rapidly activating and inactivating Ca^{2+} current that resembled the T-type current was also recorded in all endocardial myocytes, but was small or absent in epicardial myocytes. The T-like current was comprised of two components: an Ni^{2+}-sensitive T-type current and a tetrodotoxin-sensitive Ca^{2+} current.[94]

The surface epicardial and endocardial layers are separated by transitional and M cells. M cells

are distinguished by the ability of their action potential to prolong disproportionately relative to the action potential of other ventricular myocardial cells in response to a slowing of rate and/or in response to action potential duration (APD)-prolonging agents.[76,95,96] In the dog, the ionic basis for these features of the M cell includes the presence of a smaller slowly activating delayed rectifier current (I_{Ks}),[97] a larger late sodium current (late I_{Na}),[98] and a larger Na–Ca exchange current ($I_{Na\text{-}Ca}$).[99] In the canine heart, the rapidly activating delayed rectifier (I_{Kr}) and inward rectifier (I_{K1}) currents are similar in the three transmural cell types. Transmural and apicobasal differences in the density of I_{Kr} channels have been described in the ferret heart.[100] I_{Kr} message and channel protein are much larger in the ferret epicardium. I_{Ks} is larger in M cells isolated from the right than from the left ventricles of the dog.[86]

Cellular Basis for the Electrocardiographic J Wave

The presence of a prominent action potential notch in epicardium but not endocardium gives rise to a transmural voltage gradient during ventricular activation that manifests as a late delta wave following the QRS or what more commonly is referred to as a J wave[4] or Osborn wave. A distinct J wave is often observed under baseline conditions in the ECG of some animal species, including dogs and baboons. Humans more commonly display a J point elevation rather than a distinct J wave. A prominent J wave in the human ECG is considered pathognomonic of hypothermia[101–103,103] or hypercalcemia.[104,105]

A transmural gradient in the distribution of I_{to} is responsible for the transmural gradient in the magnitude of phase 1 and action potential notch, which in turn gives rise to a voltage gradient across the ventricular wall responsible for the inscription of the J wave or J point elevation in the ECG.[78,79,106] Direct evidence in support of the hypothesis that the J wave is caused by a transmural gradient in the magnitude of the I_{to}-mediated action potential notch derives from experiments conducted in the arterially perfused right ventricular wedge preparation showing a correlation between the amplitude of the epicardial action potential notch and that of the J wave recorded during interventions that alter the appearance of the electrocardiographic J wave, including hypothermia, premature stimulation (restitution), and block of I_{to} by 4-AP.[4]

Transmural activation within the thin wall of the RV is relatively rapid causing the J wave to be buried inside the QRS. Thus, although the action potential notch is most prominent in RV epicardium, RV myocardium would be expected to contribute relatively little to the manifestation of the J wave under normal conditions. These observations are consistent with the manifestation of the J wave in ECG leads in which the mean vector axis is transmurally oriented across the left ventricle and septum. Accordingly, the J wave in the dog is most prominent in leads II, III, aVR, and aVF, and mid to left precordial leads V3 through V6. A similar picture is seen in the human ECG.[105,107] In addition, vectorcardiography indicates that the J wave forms an extra loop that occurs at the junction of the QRS and T loops.[108] It is directed leftward and anteriorly, which explains its prominence in leads associated with the left ventricle.

The first description of the J wave was in the 1920s in animal experiments involving hypercalcemia.[104] The first extensive description and characterization appeared 30 years later by Osborn in a study involving experimental hypothermia in dogs.[109] The appearance of a prominent J wave in the clinic is typically associated with pathophysiological conditions, including hypothermia[101,107] and hypercalcemia.[104,105] The prominent J wave induced by hypothermia is the result of a marked accentuation of the spike-and-dome morphology of the action potential of M and epicardial cells (i.e., an increase in both width and magnitude of the notch). In addition to inducing a more prominent notch, hypothermia produces a slowing of conduction, which permits the epicardial notch to clear the QRS so as to manifest a distinct J wave. Hypercalcemia-induced accentuation of the J wave[104,105,110] may also be explained on the basis of an accentuation of the epicardial action potential notch, possibly as a result of an augmentation of the calcium-activated chloride current and a decrease in I_{Ca}.[111] Accentuation of the action potential notch also underlies the electrocardiographic and arrhythmogenic manifestations of the Brugada syndrome.

Exaggeration of the J Wave as the Basis for ST-Segment Elevation in Brugada Syndrome

Amplification of epicardial and transmural dispersion of repolarization secondary to the presence of genetic defects, pathophysiological factors, and pharmacological influences leads to accentuation of the J wave and eventually to loss of the action potential dome, giving rise to extrasystolic activity in the form of phase 2 reentry. Activation of I_{to} leads to a paradoxical prolongation of APD in canine ventricular tissues,[112] but to abbreviation of ventricular APD in species that normally exhibit brief action potentials (e.g., mouse and rat).[113] Pathophysiological conditions (e.g., ischemia, metabolic inhibition) and some pharmacological interventions (e.g., I_{Na} or I_{Ca} blockers or $I_{K\text{-}ATP}$, I_{to}, I_{Kr}, or I_{Ks} activators) can lead to marked abbreviation of APD in canine and feline[114] ventricular cells where I_{to} is prominent. Under these conditions, canine ventricular epicardium exhibits an all-or-none repolarization as a result of the shift in the balance of currents flowing at the end of phase 1 of the action potential. All-or-none repolarization of the action potential occurs when phase 1 reaches approximately −30 mV. This leads to loss of the action potential dome as the outward currents overwhelm the inward currents. Loss of the dome generally occurs at some epicardial sites but not others, resulting in the development of a marked dispersion of repolarization within the epicardium as well as transmurally, between epicardium and endocardium. Propagation of the action potential dome from the epicardial site at which it is maintained to sites at which it is abolished can cause local reexcitation of the preparation. This mechanism, termed phase 2 reentry, produces extrasystolic beats capable of initiating circus movement reentry[115] (Figure 33–2). Phase 2 reentry has been shown to occur when right ventricular epicardium is exposed to (1) K^+ channel openers such as pinacidil,[116] (2) sodium channel blockers such as flecainide,[3] (3) increased $[Ca^{2+}]_o$,[111] (4) calcium channel blockers such as verapamil, (5) metabolic inhibition,[117] and (6) simulated ischemia.[115]

Exaggerated or otherwise abnormal J waves have long been linked to idiopathic ventricular fibrillation as well as to the Brugada syndrome.[1,19,118–121] The Brugada syndrome is characterized by an exaggerated J wave that manifests as an ST-segment elevation in the right precordial leads.[1] A number of studies have emphasized the similarities between the conditions that predispose to phase 2 reentry and those that attend the appearance of the Brugada syndrome. Loss of the action potential dome in epicardium, but not endocardium, generates a transmural current that manifests on the ECG as an ST-segment elevation, similar to that encountered in patients with the Brugada syndrome.[4,117,122] Evidence in support of a phase 2 reentrant mechanism in humans was recently provided by Thomsen *et al.*[123,124]

Parasympathetic agonists like acetylcholine facilitate loss of the action potential dome[125] by suppressing I_{Ca} and/or augmenting potassium

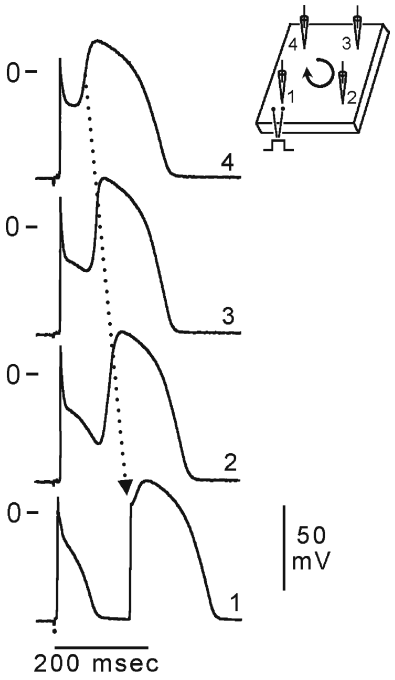


FIGURE 33–2. Phase 2 reentry. Reentrant activity induced by exposure of a canine ventricular epicardial preparation (0.7 cm^2) to simulated ischemia. Microelectrode recordings were obtained from four sites as shown in the schematic (upper right). After 35 min of ischemia, the action potential dome develops normally at site 4, but not at sites 1, 2, or 3. The dome then propagates in a clockwise direction reexciting sites 3, 2, and 1 with progressive delays, thus generating a closely coupled reentrant extrasystole (156 msec) at site 1. In this example of phase 2 reentry, propagation of the dome occurs in a direction opposite to that of phase 0, a mechanism akin to reflection. Basic cycle length (BCL) = 700 msec. (Modified from Lukas and Antzelevitch,[115] with permission.)

current. β-Adrenergic agonists restore the dome by augmenting I_{Ca}. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome via a negative shift in the voltage at which phase 1 begins.[2,3] These findings are consistent with accentuation of ST-segment elevation in patients with the Brugada syndrome following vagal maneuvers or Class I antiarrhythmic agents as well as normalization of the ST-segment elevation following β-adrenergic agents and phosphodiesterase III inhibitors.[4,5,126] Loss of the action potential dome is more readily induced in right than in left canine ventricular epicardium[85,117,122] because of the more prominent I_{to}-mediated phase 1 in action potentials in this region of the heart. As previously noted, this distinction is believed to be the basis for why the Brugada syndrome is an RV disease.

Hence, accentuation of the RV epicardial action potential notch underlies the ST-segment elevation. Eventual loss of the dome of the RV epicardial action potential further exaggerates ST-segment elevation. A vulnerable window is created both within epicardium, as well as transmurally, which serves as the substrate for the development of reentry. Phase 2 reentry provides the extrasystole that serves as the trigger that precipitates episodes of VT and fibrillation in the Brugada syndrome. Evidence in support of this hypothesis was recently provided in an arterially perfused canine RV experimental model of the Brugada syndrome (Figure 33–3).[127] The VT and VF generated in these preparations are usually polymorphic, resembling a rapid form of torsade de pointes (TdP). This activity is likely related to the migrating spiral wave shown to generate a pattern resembling a polymorphic VT.[128,129]

In the past, much of the focus has been on the ability of a reduction in sodium channel current to unmask the Brugada syndrome and create an arrhythmogenic substrate. A recent report shows that a combination of I_{Na} and I_{Ca} block is more effective than I_{Na} inhibition alone in precipitating the Brugada syndrome in the arterially perfused wedge preparation (Figure 33–4).[130] High concentrations of terfenadine (5 μM) produce a potent block of I_{Na} and I_{Ca}, leading to accentuation of the epicardial action potential notch following acceleration of the rate from a basic cycle length (BCL) of 800 msec to 400 msec. Accentuation of the notch is due to the effect of the drug to depress phase 0, augment the magnitude of phase 1, and delay the appearance of the second upstroke. With continued rapid pacing, phase 1 becomes more accentuated, until all-or-none repolarization occurs at the end of phase 1 at some epicardial sites but not others, leading to the development of both epicardial (EDR) and transmural (TDR) dispersion of repolarization (Figure 33–4C). Propagation of the dome from the region where it is maintained to the region at which it is lost results in the development of local phase 2 reentry (Figure 33–4D). Figure 33–5 shows the ability of terfenadine-induced phase 2 reentry to generate an extrasystole, couplet, and polymorphic VT/VF. Figure 33–5D illustrates an example of programmed electrical stimulation to initiate VT/VF under similar conditions.

The ST-segment elevation associated with the Brugada syndrome has been attributed to (1) a conduction delay in the RV epicardial free wall in the region of the outflow tract (RVOT)[131] and/or (2) accentuation of the RV epicardial action potential that may lead to loss of the action potential dome.[132] The cellular mechanism thought to be responsible for the development of the Brugada phenotype via hypothesis 2 is schematically illustrated in Figure 33–6.[133,134]

The ST segment is usually isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau (Figure 33–6A). Accentuation of the RV notch under pathophysiological conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave or to J point elevation. When epicardial repolarization precedes repolarization of the cells in the M and endocardial regions the T wave remains positive. This results in a saddleback configuration of the repolarization waves (Figure 33–6B). Further accentuation of the notch may be accompanied by a prolongation of the epicardial action potential such that the direction of repolarization across the RV wall and transmural voltage gradients are reversed, leading to the development of a coved-type ST-segment elevation and inversion of the T wave (Figure 33–6C), typically observed in the ECG of Brugada patients. A delay in epicardial activation may also contribute to inversion of the T wave. The downsloping ST-segment elevation observed in the experimen-

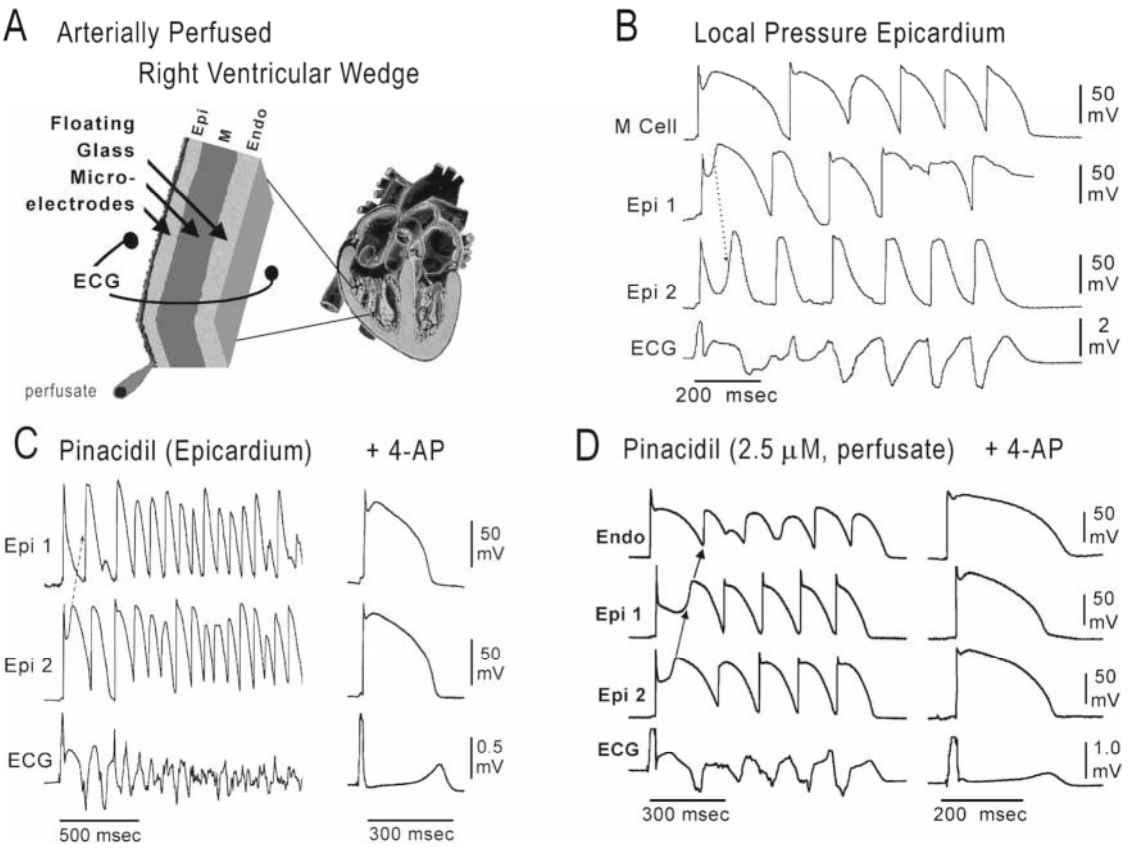


FIGURE 33–3. An ECG and arrhythmias with typical features of the Brugada syndrome recorded from canine coronary-perfused right ventricular wedge preparations. (A) Schematic of arterially perfused right ventricular wedge preparation. (B) Pressure-induced phase 2 reentry and VT. Shown are transmembrane action potentials simultaneously recorded from two epicardial (Epi 1 and Epi 2) and one M region (M) sites, together with a transmural ECG. Local application of pressure near Epi 2 results in loss of the action potential dome at that site but not at the Epi 1 or M sites. The dome at Epi 1 then reexcites Epi 2 giving rise to a phase 2 reentrant extrasystole that triggers a short run of ventricular tachycardia. Note the ST-segment elevation due to loss of the action potential dome in a segment of epicardium. (C) Polymorphic VT/VF induced by local application of the potassium channel opener pinacidil (10 μM) to the epicardial surface of the wedge. Action potentials from two epicardial sites (Epi 1 and Epi 2) and a transmural ECG were simultaneously recorded. Loss of the dome at Epi 1 but not Epi 2 creates a marked dispersion of repolarization, giving rise to a phase 2 reentrant extrasystole. The extrasystolic beat then triggers a long episode of ventricular fibrillation (22 sec). Right panel: Addition of 4-aminopyridine (4-AP, 2 mM), a specific I_{to} blocker, to the perfusate restored the action potential dome at Epi 1, thus reducing dispersion of repolarization and suppressing all arrhythmic activity. BCL = 2000 msec. (D) Phase 2 reentry gives rise to VT following addition of pinacidil (2.5 μM) to the coronary perfusate. Transmembrane action potentials forming two epicardial sites (Epi 1 and Epi 2) and one endocardial site (Endo) as well as a transmural ECG were simultaneously recorded. Right panel: 4-AP (1 mM) markedly reduces the magnitude of the action potential notch in epicardium, thus restoring the action potential dome throughout the preparation and abolishing all arrhythmic activity. (Panel D is from Yan and Antzelevitch,[127] with permission.)

tal wedge models often appears as an R′, suggesting that the appearance of an RBBB morphology in Brugada patients may be due at least in part to early repolarization of RV epicardium, rather than a major impulse conduction block in the right bundle.

Gussak and co-workers pointed out that a majority of RBBB-like morphologies encountered in cases of Brugada syndrome do not fit the criteria for RBBB.[135] Moreover, attempts by Miyazaki and co-workers to record delayed activation of the RV in Brugada patients met with failure.[5]

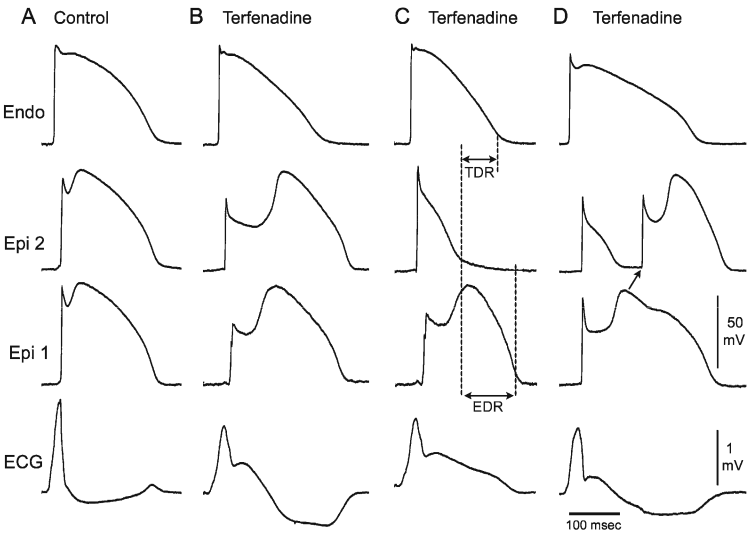


FIGURE 33–4. Terfenadine-induced ST-segment elevation, T wave inversion, transmural and endocardial dispersion of repolarization, and phase 2 reentry. Each panel shows transmembrane action potentials from one endocardial (top) and two epicardial sites together with a transmural ECG recorded from a canine arterially perfused right ventricular wedge preparation. (A) Control (BCL = 400 msec). (B) Terfenadine (5 μM) 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. The first beat was recorded after changing from BCL 800 msec to BCL 400 msec. (C) Continued pacing at BCL = 400 msec 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. (Modified from Fish and Antzelevitch,[130] with permission.)

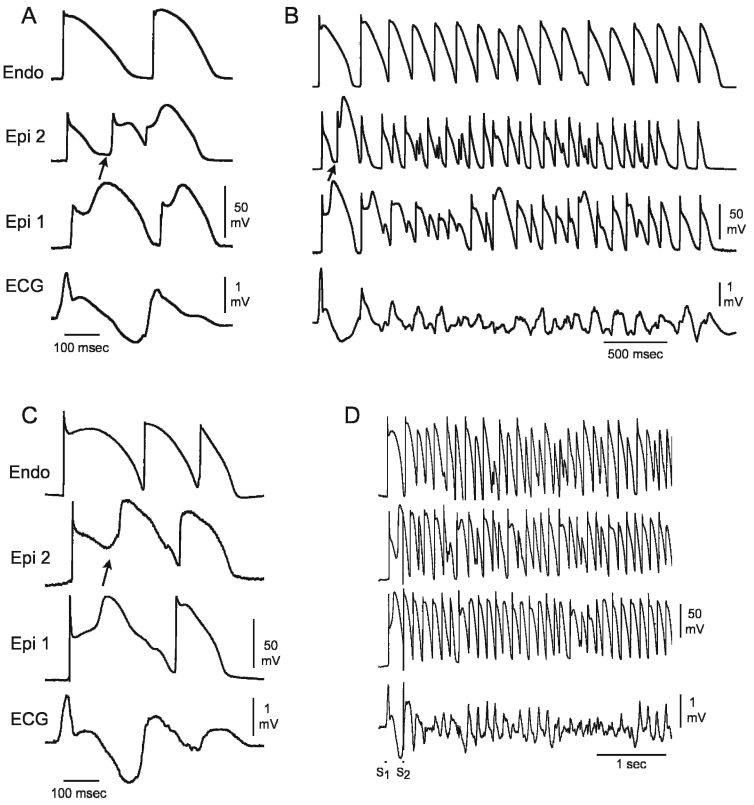


FIGURE 33–5. Spontaneous and programmed electrical stimulation-induced polymorphic VT in RV wedge preparations pretreated with terfenadine (5–10 μM). (A) Phase 2 reentry in epicardium gives rise to a closely coupled extrasystole. (B) Phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. (C) Phase 2 reentry followed by a single circus movement reentry in epicardium gives rise to a couplet. (D) Extrastimulus (S1 − S2 = 250 msec) applied to epicardium triggers a polymorphic VT. (Modified from Fish and Antzelevitch,[130] with permission.)

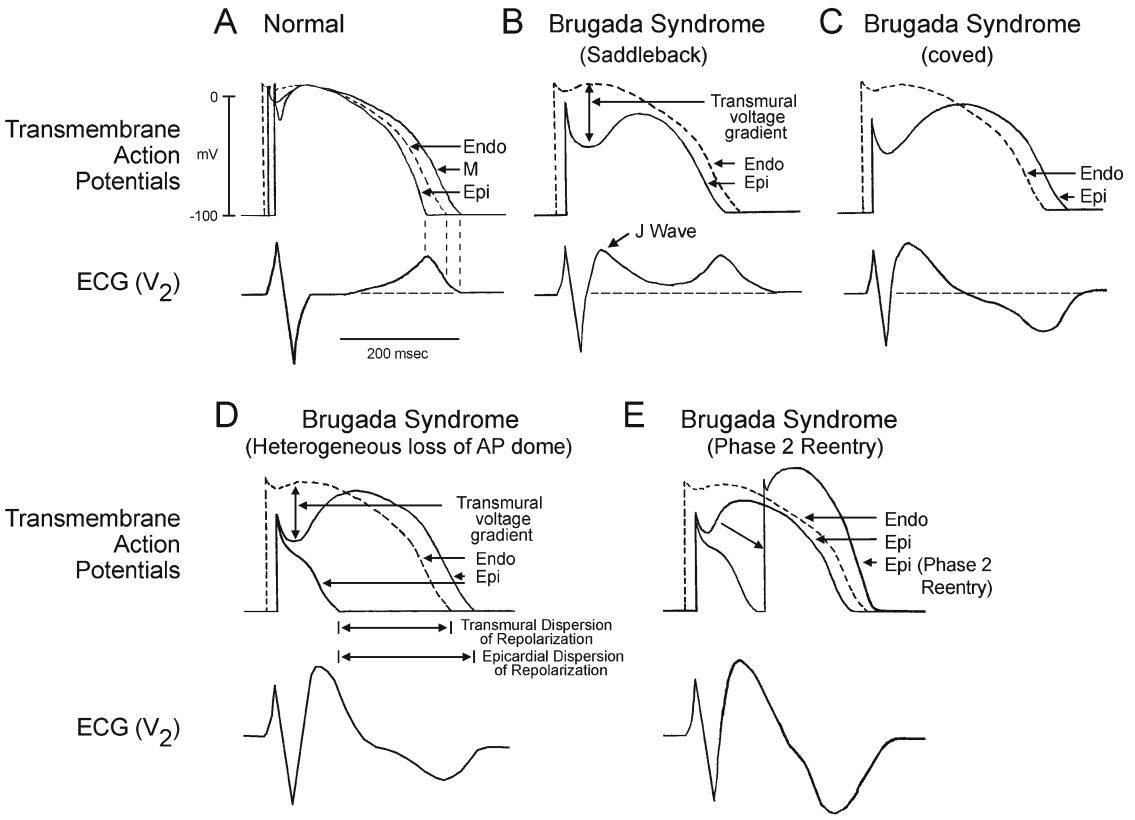


FIGURE 33–6. Schematic representation of right ventricular epicardial action potential changes (A–E) proposed to underlie the electrocardiographic manifestation of the Brugada syndrome. (Modified from Antzelevitch,[133] with permission.)

It is important to point out that although the typical Brugada morphology is present in Figure 33–6B and C, an arrhythmogenic substrate is absent. The arrhythmogenic substrate is thought to develop when a further shift in the balance of current leads to loss of the action potential dome at some epicardial sites but not others (Figure 33–6D). 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. 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 very closely coupled extrasystole, which captures the vulnerable window across the wall, thus triggering a circus movement reentry in the form of VT/VF (Figure 33–6E).[115,127] The phase 2 reentrant beat fuses with the T wave of the basic response, thus accentuating the negative T wave. This morphology is often observed in the clinic preceding the onset of polymorphic VT.

Studies involving the arterially perfused right ventricular wedge preparation provide evidence in support of these hypotheses.[127] Aiba *et al.*[136] used a high- resolution optical mapping system that allows simultaneous recording of transmembrane action potentials from 256 sites along the transmural surface of the arterially perfused canine RV wedge preparation to demonstrate that a steep repolarization gradient between the region at which the dome is lost and the region at which it is maintained is essential for the development of a closely coupled phase 2 reentrant extrasystole. This study also showed that reentry initially rotates in the epicardium and gradually shifts to

a transmural orientation, responsible for nonsustained polymorphic VT or VF.

Kurita *et al.* placed monophasic action potential (MAP) electrodes on the epicardial and endocardial surfaces of the RVOT in patients with the Brugada syndrome and demonstrated an accentuated notch in the epicardial response, thus providing support for this mechanism in humans.[137,138]

The marked accentuation of the epicardial action potential dome and the development of concealed phase 2 reentry suggest that activation forces may extend beyond the QRS in Brugada patients. Indeed, signal averaged ECG (SAECG) recordings have demonstrated late potentials in patients with the Brugada syndrome, especially in the anterior wall of the RVOT.[139–144] The basis for these late potentials, commonly ascribed to delayed conduction within the ventricle, is largely unknown. Endocardial recordings have been unrevealing. Nagase and co-workers[142] introduced a guide wire into the conus branch of the right coronary artery to record signals from the epicardial surface of the anterior wall of the RVOT in patients with the Brugada syndrome. The unipolar recordings displayed delayed potentials, which coincided with late potentials recorded in the SAECG, particularly after administration of Class IC antiarrhythmic agents. It was concluded that recordings from the conus branch of the right coronary artery can identify an "epicardial abnormality" in the RVOT that is accentuated in the presence of IC agents, thus uncovering part of the arrhythmogenic substrate responsible for VT/VF in Brugada syndrome, which may be related to the second upstroke or a concealed phase 2 reentrant beat. Late potentials are often regarded as being representative of delayed activation of the myocardium, but in the case of the Brugada syndrome other possibilities exist as discussed above. The second upstroke of the epicardial action potential, thought to be greatly accentuated in Brugada syndrome,[133] might be capable of generating late potentials when RVOT activation is otherwise normal. Moreover, the occurrence of phase 2 reentry, especially when concealed (i.e., when it fails to trigger transmural reentry), may contribute to the generation of delayed unipolar and late SAECG potentials.

The rate dependence of the ST-segment elevation may be useful in discriminating between these two hypotheses. If the Brugada ECG sign is due to delayed conduction in the RVOT, acceleration of the rate would be expected to further aggravate conduction and thus accentuate the ST-segment elevation and the RBBB morphology of the ECG. If, on the other hand, the Brugada ECG sign is secondary to accentuation of the epicardial action potential notch, at some point leading to loss of the action potential dome, acceleration of the rate would be expected to normalize the ECG, by restoring the action potential dome and reducing the notch. This occurs because the transient outward current, which is at the heart of this mechanism, is slow to recover from inactivation and is less available at faster rates. It should be noted that the presence of sodium channel blockers with strong use-dependent properties may confound the results, since in their presence accentuation of the action potential notch will occur as the stimulation rate is increased.

It is well known that Brugada patients usually display a normalization of their ECG or no change when the heart rate is increased, thus favoring the second hypothesis as the predominant mechanism. Further evidence in support of this hypothesis derives from the recent of observations of Shimizu and co-workers.[145] Using a unipolar catheter introduced into the great cardiac vein, they recorded unipolar activation recovery intervals (ARIs), a measure of local APD, from the epicardial surface of the RVOT in a 53-year-old Brugada patient. The ARIs in the RVOT were observed to abbreviate[146] dramatically whenever the ST segment was elevated in V2 following a pause or the administration of a sodium channel blocker. Additional support for the hypothesis derives from the demonstration by Watanabe and co-workers[147] that quinidine *suppresses* late potentials recorded in a patient with Brugada syndrome. This effect of the drug is presumably due to inhibition of I_{to} leading to diminution of the epicardial action potential notch and normalization of the repolarization heterogeneities. If the late potentials were due to delayed conduction, quinidine-induced I_{Na} inhibition would be expected to accentuate the appearance of the late potentials. Finally, magnetocardiograms recorded from patients with complete RBBB have been shown to generate currents from RVOT to the upper left chest that are opposite from those recorded in patients with Brugada syndrome.[146] Thus, the available data, both basic and clinical, point to

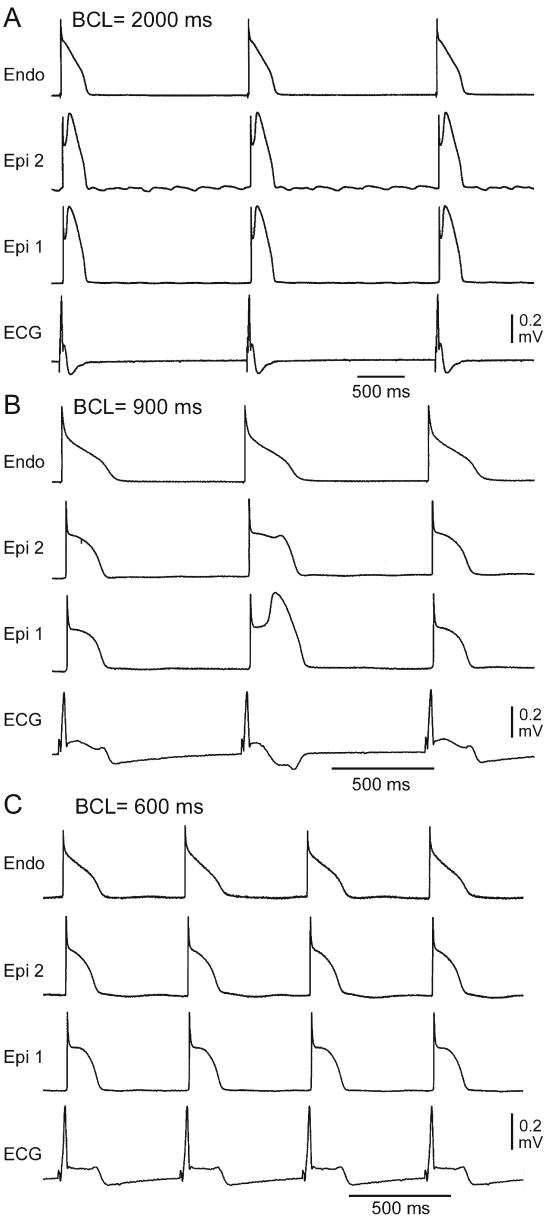


FIGURE 33–7. Verapamil (1 μM)-induced loss of the epicardial action potential dome in alternate beats causes T wave alternans in a canine arterially perfused right ventricular wedge preparation. (A) At a BCL of 2000 msec, endocardial and epicardial action potentials repolarize almost simultaneously, generating little or no T wave on the ECG. (B) Decreasing the cycle length to 900 msec induces heterogeneous loss of the epicardial action potential dome in alternate beats while the endocardial response remains constant, resulting in profound T wave alternans. (C) Decreasing the cycle length to 600 msec leads to homogeneous loss of the action potential dome on all beats, leading to ST-segment elevation but no T wave alternans in the ECG. (Fish and Antzelevitch, unpublished.)

transmural voltage gradients that develop secondary to accentuation of the epicardial notch and loss of the action potential dome as being in large part responsible for the Brugada ECG signature.

These facts notwithstanding, there are likely to be cases in which a conduction defect may predominate. The presence of a prominent S wave displaying rate-dependent boarding was observed in intracavitary unipolar leads.[148]

T Wave Alternans

T wave alternans (TWA) is characterized by beat-to-beat alteration in the amplitude, polarity, and/or morphology of the electrocardiographic T wave. TWA has been reported in patients with the Brugada syndrome and is thought to be associated with an increased risk for development of VT/VF.[149–156] Experimental studies suggest that T wave alternans is due to at least two cellular mechanisms, including (1) loss of the epicardial action potential dome on alternate beats (Figure 33–7) and (2) concealed phase 2 reentry on alternating beats (Figure 33–8).[130,157]

Acquired Forms of Brugada Syndrome and Modulating Factors

The electrocardiographic and arrhythmic manifestations of the Brugada syndrome can be induced and modulated by a large number of agents and factors. The Brugada ECG can be unmasked or modulated by sodium channel blockers, a febrile state, vagotonic agents, α-adrenergic agonists, β-adrenergic blockers, tricyclic or tetracyclic antidepressants, first generation antihistaminics (dimenhydrinate), a combination of glucose and insulin, hyperkalemia, hypokalemia, hypercalcemia, and by alcohol and cocaine toxicity (Figure 33–9)[5,11,12,158–165] These agents may also induce acquired forms of the Brugada syndrome (Table 33–2). Although a definitive list of drugs to avoid in the Brugada syndrome is not yet formulated, the list of agents in Table 33–2 may provide some guidance. One of the more recent additions to this group is lithium. This widely used drug is a blocker of cardiac sodium channels and can unmask patients with the Brugada syndrome.[166]

Myocardial infarction or acute ischemia due to vasospasm involving the RVOT mimics

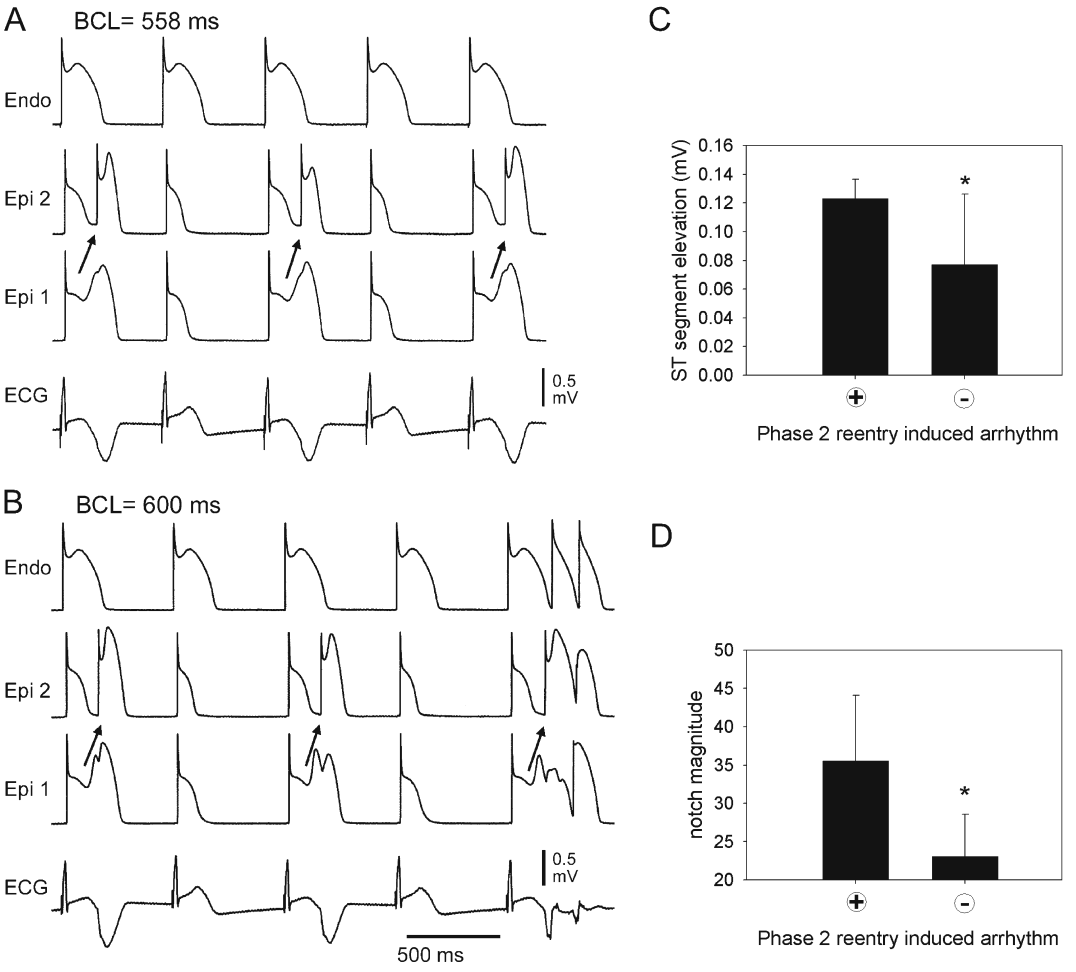


FIGURE 33–8. Verapamil (1 μM)-induced concealed phase 2 reentry in alternate beats leading to T wave alternans in the coronary-perfused right ventricular wedge preparation. (A) T wave alternans occurs as a result of concealed phase 2 reentry. The dome propagates from Epi 1 to Epi 2 on alternating beats while the endocardial response remains constant. The concealed phase 2 reentry results in a negative T wave. BCL = 558 msec. (B) Increasing the cycle length to 600 msec exaggerates the T wave alternans. The phase relationship between Epi 1, Epi 2, and Endo shifts slightly, allowing the previously concealed phase 2 reentry to propagate transmurally, leading to two extrasystoles. (C) The ST-segment elevation, measured 50 msec after the end of the QRS, is greater during alternans secondary to concealed phase 2 reentry compared to alternans due to alternating loss of the epicardial action potential dome [$n = 10$ phase 2 reentry plus (+) and 12 phase 2 reentry minus (–) episodes, $^*p = 0.027$]. (D) The size of the epicardial action potential notch magnitude (ph2 amp − ph1 amp/ph2 amp) at BCL = 2000 msec during control was significantly smaller in preparations not displaying phase 2 reentry-induced arrhythmias than in those that did ($n = 5$ for each category, $^*p = 0.025$). (Fish and Antzelevitch, unpublished.)

ST-segment elevation similar to that seen in Brugada syndrome. This effect is secondary to the depression of I_{Ca}, inactivation of I_{Na}, and the activation of $I_{K\text{-}ATP}$ during ischemia, and suggests that patients with congenital and possibly acquired forms of Brugada syndrome may be at a higher risk for ischemia-related sudden cardiac death.[167]

Although the coexistence of Brugada syndrome and vasospastic angina in the same patient is not rare, Chinushi *et al.* have failed to observe an enhanced susceptibility to VF or a proarrhythmic effect of Ca antagonist in this setting.[168]

Hypokalemia has been suggested to be a contributing factor in the high prevalence of sudden

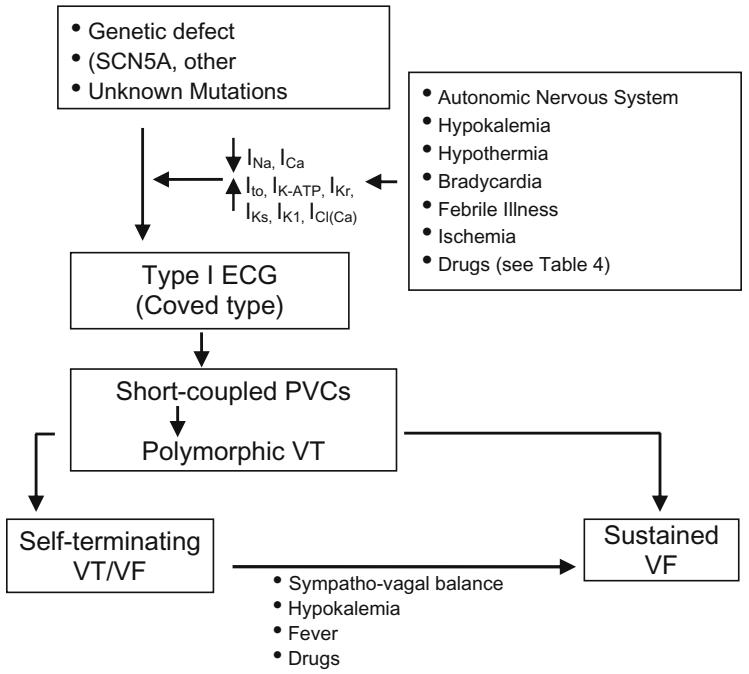


FIGURE 33–9. Factors predisposing to the electrocardiographic and arrhythmic manifestations of the Brugada syndrome. (Modified from Nademanee *et al.*,[206] with permission.)

TABLE 33–2. Drug-induced Brugada-like ECG patterns.

I. Antiarrhythmic drugs
  1. Na^+ channel blockers
     Class IC drugs (flecainide,[12,14,140,207,208] pilsicainide,[145,209] propafenone[210])
     Class IA drugs (ajmaline,[12,211] procainamide,[5,12] disopyramide,[5,8] cibenzoline[150,212])
  2. Ca^{2+} channel blockers
     Verapamil
  3. β Blockers
     Propranolol intoxication[213]

II. Antianginal drugs
  1. Ca^{2+} channel blockers
     Nifedipine, diltiazem
  2. Nitrate
     Isosorbide dinitrate, nitroglycerine[214]
  3. K^+ channel openers
     Nicorandil

III. Psychotropic drugs
  1. Tricyclic antidepressants[215]
     Amitriptyline,[216,217] nortriptyline,[166] desipramine,[158] clomipramine[159]
  2. Tetracyclic antidepressants
     Maprotiline[216]
  3. Phenothiazine
     Perphenazine,[216] cyamemazine
  4. Selective serotonin reuptake inhibitors
     Fluoxetine[217]
  5. Lithium[166]

IV. Other drugs
  1. Histaminic H1 receptor antagonists
     Dimenhydrinate[161]
     Diphenhydramine[218]
  2. Cocaine intoxication[162,219]
  3. Alcohol intoxication

Source: Modified from Antzelevitch *et al.*[62] and Shimizu,[220] with permission.

unexpected nocturnal death syndrome (SUNDS) in the northeastern region of Thailand where potassium deficiency is endemic.[164,169] 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.[164] This patient was initially treated for asthma by steroids, which lowered serum potassium from 3.8 mmol/liter on admission to 3.4 and 2.9 mmol/liter on day 7 and 8 of admission, respectively. Both were associated with unconsciousness. Ventricular fibrillation was documented during the last episode, which reverted spontaneously to sinus rhythm. Hypokalemia may exert these effects by increasing the chemical gradient for K^+ and thus the intensity of I_{to}.

Both VT/VF and sudden death in the Brugada syndrome usually occur at rest and at night. Circadian variation of sympathovagal balance, hormones, and other metabolic factors is likely to contribute to this circadian pattern. Bradycardia, due to altered sympathovagal balance or other factors, may contribute to initiation of arrhythmia.[30,170,171] Abnormal [^{123}I]metaiodobenzylguanidine (MIBG) uptake in 8 (17%) of the 17 Brugada syndrome patients but none in the control group was demonstrated by Wichter *et al.*[172] Segmental reduction of [^{123}I]MIBG in the inferior and the septal left ventricular wall was observed indicating presynaptic sympathetic dysfunction. Of note, imaging of the RV, particularly the RVOT, is difficult with this technique, so that 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 the RVOT is similarly affected, this defect may indeed alter the sympathovagal balance in favor of the development of an arrhythmogenic substrate.[125,127]

The Thai Ministry of Public Health Report (1990) found an association between a large meal on the night of death in SUNDS patients.[169] Consistent with this observation, a recent study by Nogami *et al.* found that glucose and insulin could unmask the Brugada ECG.[163] Another possibility is that sudden death in these patients is due to the increased vagal tone produced by the stomach distention. A recent study by Ikeda *et al.*[173] has shown that a full stomach after a large meal can unmask a Type I ECG, particularly in Brugada syndrome patients at high risk for arrhythmic events, thus suggesting that this technique may be of diagnostic and prognostic value.

Accelerated inactivation of the sodium channel caused by *SCN5A* mutations associated with the Brugada syndrome has been shown to be accentuated at higher temperatures[63] suggesting that a febrile state may unmask the Brugada syndrome. Indeed, several case reports have emerged recently demonstrating that febrile illness could reveal the Brugada ECG and precipitate VF.[13,64,65,174–176] A recent report from Keller *et al.*[177] has identified a missense mutation, F1344S, in SCN5A in a patient with Brugada syndrome and fever-induced VT/VF. Expression of F1344S showed a shift in the voltage dependence of activation, which was further accentuated at high temperatures mimicking fever. Thus fever may also cause a loss of function in I_{Na} by accelerating inactivation as well as producing a shift in the voltage dependence of activation.

Anecdotal data 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. A study is underway to assess whether this extreme climate influences the prognosis of the disease.

Sex-Related Differences in the Manifestation of the Brugada Syndrome

Although the mutation responsible for the Brugada syndrome 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 has been shown to be due to a more prominent I_{to}-mediated action potential notch in the RV epicardium of males than in females[178] (Figures 33–10 and 33–11). The more prominent I_{to} causes the end of

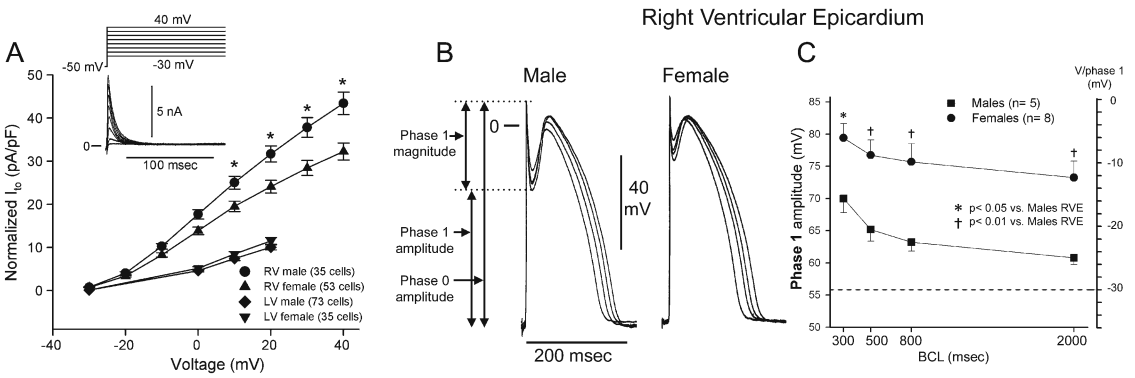


FIGURE 33–10. Sex-based and interventricular differences in I_{to}. (A) Mean I–V relationship for I_{to} recorded from RV epicardial cells isolated from hearts of male and female dogs. Inset: Representative I_{to} current traces and voltage protocol. I_{to} density was significantly greater in male than in female RV epicardial cells. No sex differences were observed in LV. (B) Transmembrane action potentials recorded from isolated canine RV epicardial male and female tissue slices. BCLs = 300, 500, 800, and 2000 msec. (C) Rate dependence of phase 1 amplitude and voltage at the end of phase 1 (V/phase 1, mV) in males (solid squares) versus females (solid circles). (Modified from Di Diego *et al.*,[178] with permission.)

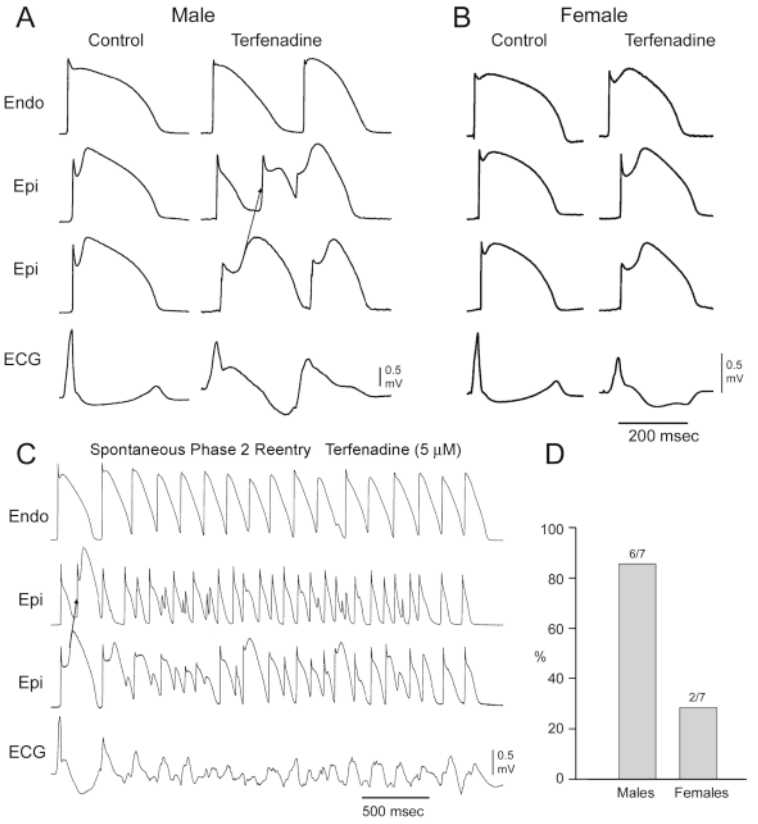


FIGURE 33–11. Terfenadine induces the Brugada phenotype more readily in male than female RV wedge preparations. Each panel shows action potentials recorded from two epicardial sites and one endocardial site, together with a transmural ECG. Control recordings were obtained at a BCL of 2000 msec, whereas terfenadine data were recorded at a BCL of 800 msec after a brief period of pacing at a BCL of 400 msec. (A) Terfenadine (5 μM)-induced, heterogeneous loss of action potential dome, ST-segment elevation, and phase 2 reentry (arrow) in a male RV wedge preparation. (B) Terfenadine fails to induce Brugada phenotype in a female RV wedge preparation. (C) Polymorphic VT triggered by spontaneous phase 2 reentry in a male preparation. (D) Incidence of phase 2 reentry in male (six of seven) versus female (two of seven) RV wedge preparations when perfused with 5 μM terfenadine for up to 2 h. (Modified from Di Diego *et al.*,[178] with permission.)

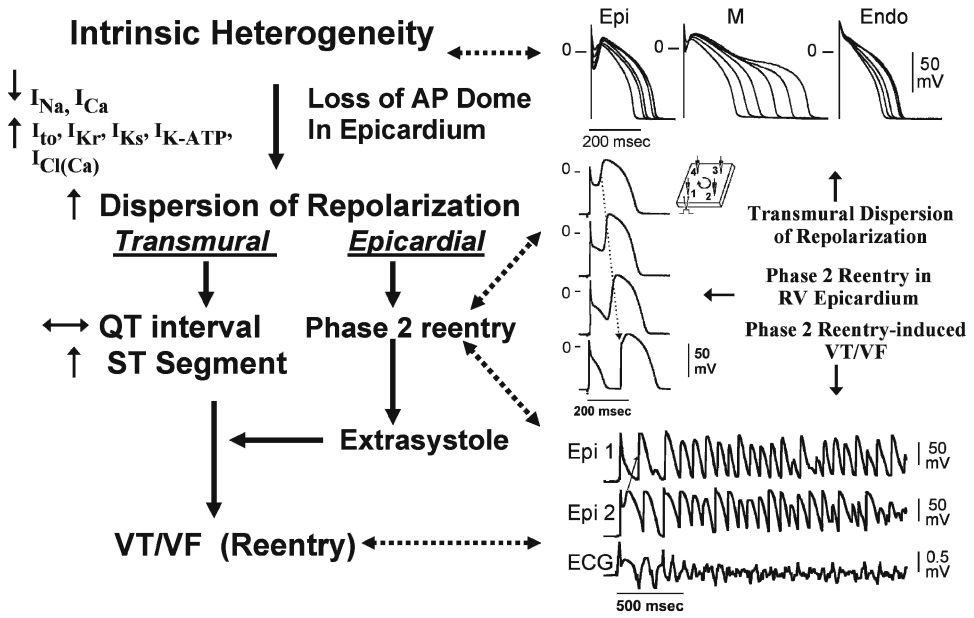


FIGURE 33–12. Proposed mechanism for the Brugada syndrome. A shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within the 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,[134] with permission.)

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 proposed cellular mechanism for the Brugada syndrome is summarized in Figure 33–12. Available data support the hypothesis that the Brugada syndrome results from amplification of heterogeneities intrinsic to the early phases of the action potential among the different transmural cell types. This 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. ST-segment elevation similar to that observed in patients with the Brugada syndrome 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 is responsible for 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).

Approach to Therapy

Device Therapy

The only proven effective therapy for the Brugada syndrome is an ICD (Table 33–3).[179,180] Recommendations for ICD implantation from the Second Consensus Conference [9,10] are presented in Table 33–4 and are summarized as follows.

TABLE 33–3. Device and pharmacological approach to therapy.

- Devices and ablation
  - ICD[179]
  - ? Ablation or cryosurgery[181]
  - ? Pacemaker[221]
- Pharmacological approach to therapy
  - Ineffective
    - Amiodarone[49]
    - β Blockers[49]
    - Class IC antiarrhythmics
      - Flecainide[14]
      - Propafenone[210]
    - ? Disopyramide[186]
    - Class IA antiarrhythmics
      - Procainamide[12]
  - Effective for treatment of electrical storms
    - β Adrenergic agonists—isoproterenol[5,22]
    - Phosphodiesterase III Inhibitors—cilostazol[126]
    - Quinidine[204]
  - Effective general therapy
    - Quinidine[38,127,184,189,190,192–194,204]
  - Experimental therapy
    - I_{to} Blockers—cardioselective and ion channel specific
      - Quinidine[127]
      - 4-Aminopyridine[127]
      - Tedisamil[197]
      - AVE0118[201]

Symptomatic patients with a Type 1 ST-segment elevation or Brugada ECG (either spontaneously or after sodium channel blockade) who present with aborted sudden death should receive an ICD as a Class I indication without additional need for electrophysiological study (EPS). Similar patients presenting with related symptoms such as syncope, seizure, or nocturnal agonal respiration should also undergo ICD implantation as a Class I indication after vasovagal syncope has been excluded on clinical grounds and noncardiac causes of these symptoms have been carefully ruled out. The Task Force recommended that symptomatic patients undergo EPS only for the assessment of supraventricular arrhythmia.

Asymptomatic patients with a 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. An EPS may be justified when the family history is negative for sudden cardiac death if the Type 1 ST-segment elevation occurs spontaneously. If inducible for ventricular arrhythmia, the patient should receive an ICD. This was recommended as a Class IIa indication for patients presenting with a spontaneous Type I ST-segment elevation and as a Class IIb for patients who display a Type I ST-segment elevation only after sodium block challenge. More recent data have called these recommendations into question and suggest that it might be more appropriate to consider both as Class IIb indications.

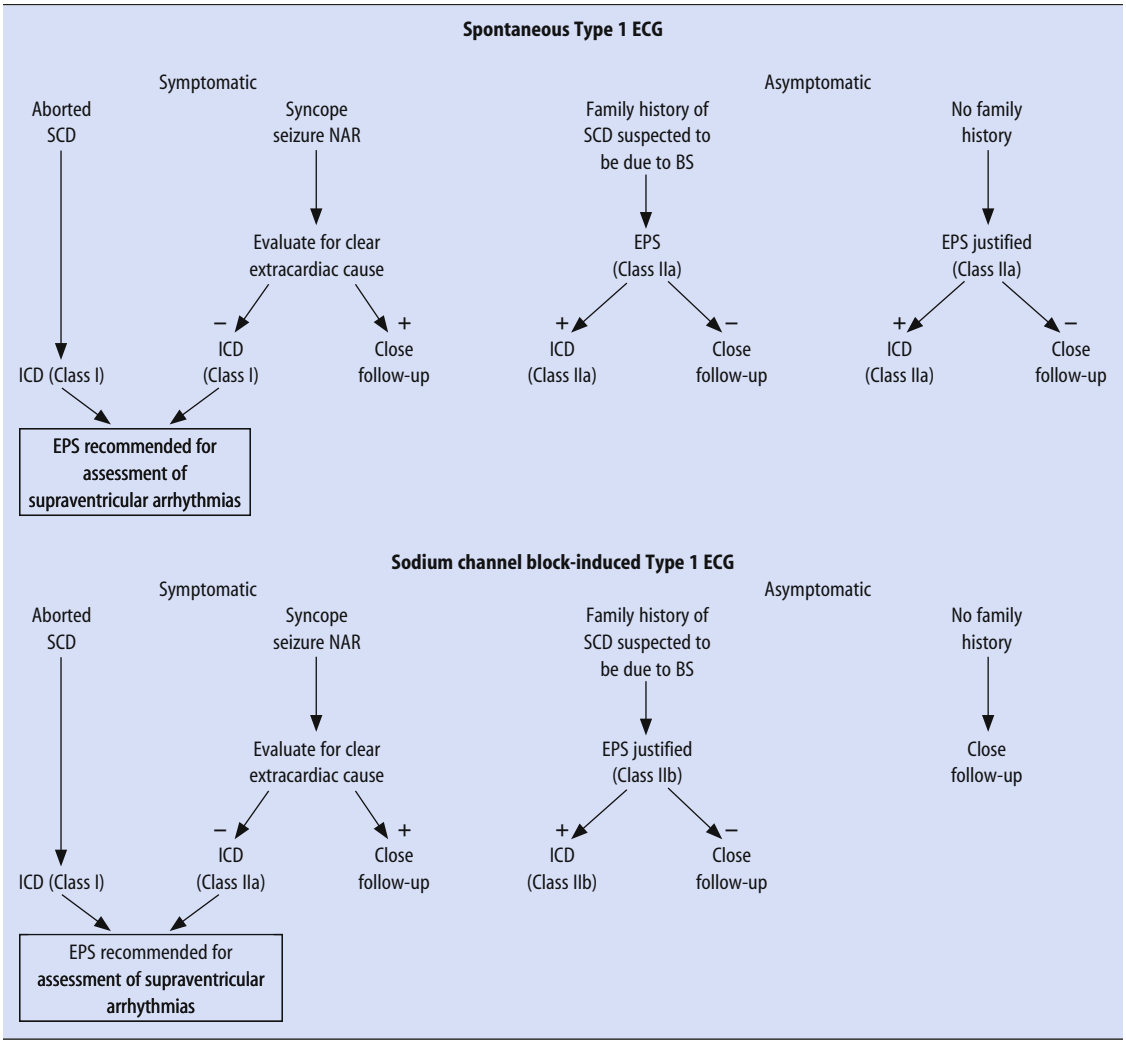
Asymptomatic patients who have no family history and who develop a Type 1 ST-segment elevation only after sodium channel blockade should be closely followed-up. As additional data become available, these recommendations will no doubt require further finetuning.

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. Haissaguerre and co-workers[181] reported that focal radiofrequency ablation aimed at eliminating the ventricular premature beats that trigger VT/VF in the Brugada syndrome may be useful in controlling arrhythmogenesis. However, data relative to a cryosurgical approach or the use of ablation therapy are very limited at this point in time.

Pharmacological Approach to Therapy

Although ICD implantation is the mainstay of therapy for the Brugada syndrome, implantation can be challenging in infants and is not an adequate solution for patients residing in regions of the world where an ICD is unaffordable. Also, ICD implantation in "asymptomatic high-risk patients" is not trivial, in particular because the level of risk is still being debated (see the section on Prognosis and Risk Stratification above). In the Antiarrhythmics versus Implantable Defibrillators (AVID) trial, a multicenter study of ICD implantation for patients with heart disease and malignant arrhythmias, the risk for ICD-related complications serious enough to warrant reintervention was 12%.[182] The rate of serious complications from ICD implantation for patients with Brugada syndrome is likely to be higher than the 12% reported for the patients in AVID, who were relatively old (65 ± 11 years) and had a 3-year mortality rate of

TABLE 33–4. Indications for ICD implantation in patients with the Brugada syndrome.[a]



Source: From Antzelevitch *et al.*[9,10] with permission.

[a]Class I: Clear evidence that the procedure or treatment is useful or effective. Class II: Conflicting evidence concerning usefulness or efficacy. Class IIa: Weight of evidence in favor of usefulness or efficacy. Class IIb: Usefulness or efficacy less well established. BS, Brugada syndrome; EPS, electrophysiological study; NAR, nocturnal agonal respiration; SCD, sudden cardiac death.

25%.[183] Patients with Brugada syndrome are younger, have a very low risk for nonarrhythmic cardiac death, and will remain at risk for ICD-related complications for many more years. In particular, the risk for potentially serious complications such as infection or lead-insulation break leading to inappropriate ICD shocks will increase over the years and after repeated ICD replacements. Therefore, although the ICD represents the most effective way for preventing arrhythmic death in Brugada syndrome, pharmacological solutions may be desirable as an alternative to device therapy for selected cases[184] as well as for minimizing the firing of the ICD in patients with frequent events.[9,57,184,185]

The search for a pharmacological treatment has been focused on rebalancing of the ion channel current active during the early phases of the epicardial action potential in the RV so as to reduce the magnitude of the action potential notch and/

or restore the action potential dome. Table 33–3 lists the various pharmacological agents thus far investigated. Antiarrhythmic agents such as amiodarone and β blockers have been shown to be ineffective.[49] Class IC antiarrhythmic drugs, such as flecainide and propafenone, and Class IA agents, such as procainamide, are contraindicated because they unmask the Brugada syndrome and induce arrhythmogenesis. Disopyramide is a Class IA antiarrhythmic that has been demonstrated to normalize ST-segment elevation in some Brugada patients but to unmask the syndrome in others.[186]

The presence of a prominent I_{to} is fundamental to the mechanism underlying the Brugada syndrome. Consequently, the most prudent general 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 is an agent that is ion-channel specific at low concentrations, but is not cardioselective in that it inhibits I_{to} in the nervous system. Although it is effective in suppressing arrhythmogenesis in wedge models of the Brugada syndrome[127] (Figure 33–13), it is unlikely to be of clinical benefit because of neurally mediated adverse effects.

Quinidine is an agent currently on the market in the United States and other regions of the world with significant I_{to} blocking properties. Accordingly, we suggested several years ago that this agent may be of therapeutic value in the Brugada syndrome.[187] Quinidine has been shown to be effective in restoring the epicardial action potential dome, thus normalizing the ST segment and preventing phase 2 reentry and polymorphic VT in experimental models of the Brugada syndrome (Figure 33–13).[127,188] Clinical evidence of the effectiveness of quinidine in normalizing ST-segment elevation in patients with the Brugada syndrome has been reported as well (Figure 33–14).[184,189–191] Quinidine has also been reported to be effective in suppressing arrhythmogenesis in an infant too young to receive an ICD.[38]

In a prospective study of 25 Brugada syndrome patients orally administered quinidine bisulfate (1483 ± 240 mg), Belhassen and co-workers[190] evaluated the effectiveness of quinidine in preventing inducible and spontaneous VF. There were 15 symptomatic patients (7 cardiac arrest survivors and 7 with unexplained syncope) and 10 asymptomatic patients. All 25 patients had inducible VF at baseline electrophysiological study. Quinidine prevented VF induction 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 (without ICD back-up) 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, which resolved after drug discontinuation. It was concluded that quinidine effectively suppresses VF induction as well as spontaneous arrhythmias in patients with Brugada syndrome and may be

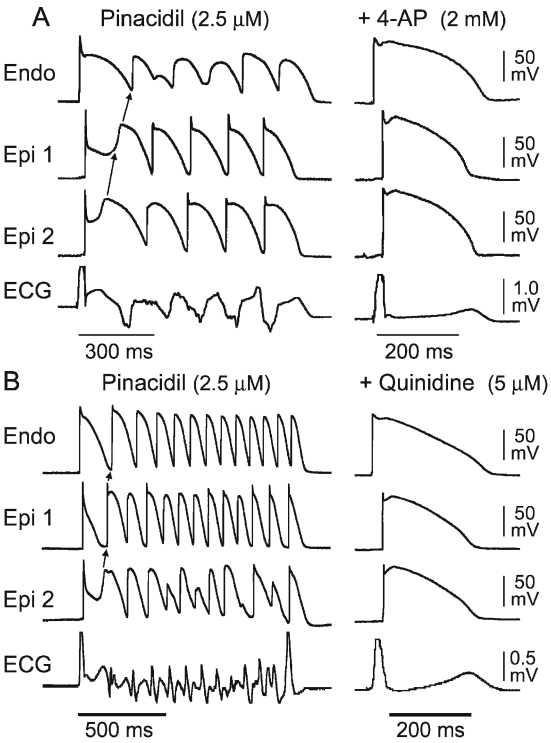


Figure 33–13. Effects of I_{to} blockers 4-AP and quinidine on pinacidil-induced phase 2 reentry and VT in the arterially perfused RV wedge preparation. In both examples, 2.5 mM pinacidil produced heterogeneous loss of AP dome in epicardium, resulting in ST-segment elevation, phase 2 reentry, and VT (left); 4-AP (A) and quinidine (B) restored the epicardial AP dome, reduced both transmural and epicardial dispersion of repolarization, normalized the ST segment, and prevented phase 2 reentry and VT in the continued presence of pinacidil. (From Yan and Antzelevitch,[127] with permission.)

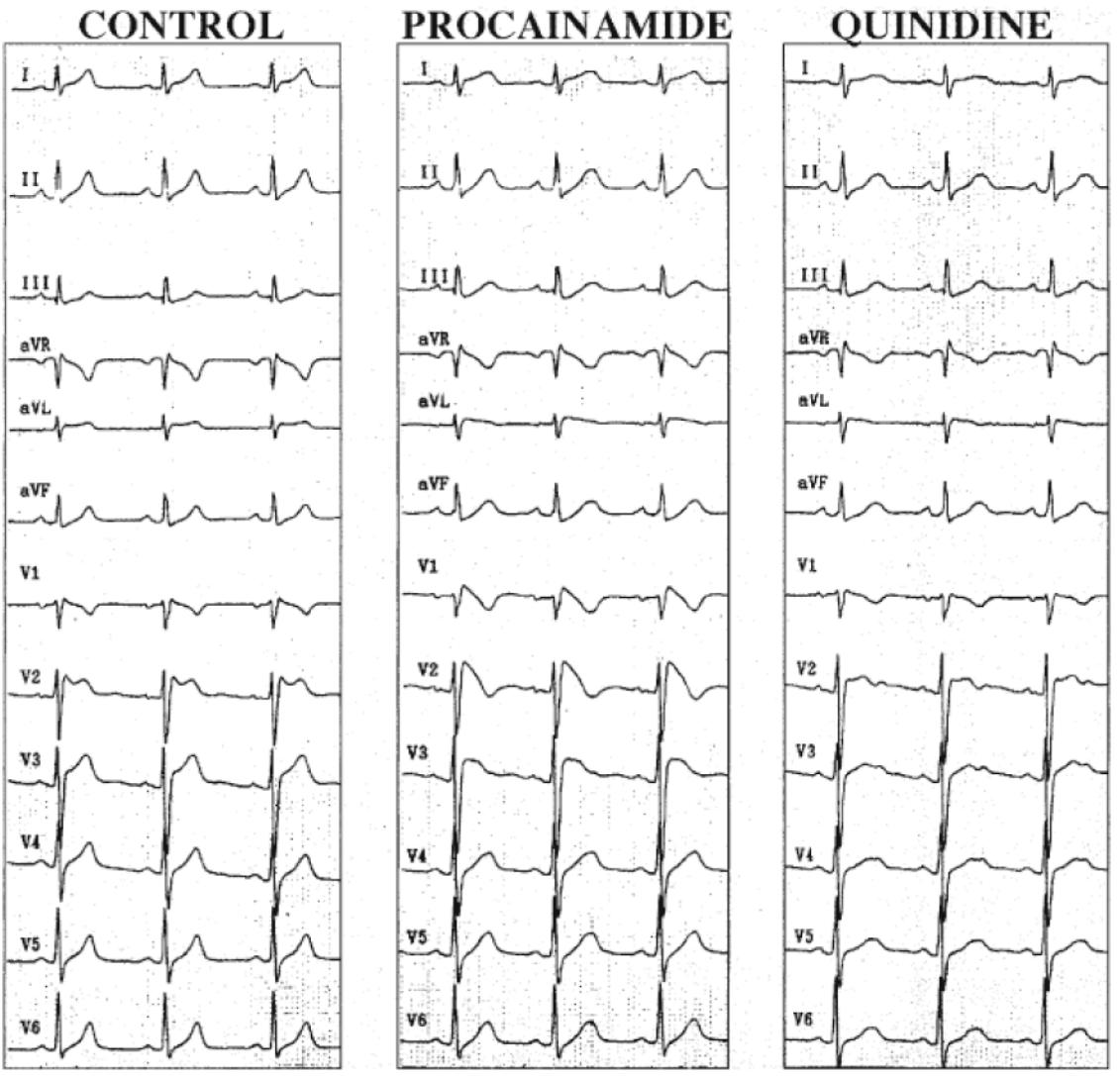


FIGURE 33–14. Twelve-lead electrocardiogram (ECG) tracings in an asymptomatic 26-year-old man with the Brugada syndrome. Left: Baseline: Type 2 ECG (not diagnostic) displaying a "saddle-back-type" ST-segment elevation is observed in V2. Center: After intravenous administration of 750 mg procainamide, 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 (1500 mg/day, serum quinidine level 2.6 mg/liter), ST-segment elevation is attenuated in the right precordial leads. VF could be induced during control and procainamide infusion, but not after quinidine. (From Belhassen *et al.*,[184] with permission.)

useful as an adjunct to ICD therapy. It was also suggested that EPS-guided quinidine therapy may be used *as an alternative* to ICD in cases in which an ICD is refused or unaffordable as well as when patients who are well informed about the risks and benefits of ICD and EP-guided quinidine therapy prefer medical therapy to device implantation.[191] The results are consistent with those reported by the same group in prior years[184,192] and more recently by other investigators.[193–195] A relatively small recent study by Mizusawa *et al.*[196] also showed that low-dose quinidine (300–600 mg) can prevent electrophysiological induction of VF and has a potential as an adjunctive therapy

for Brugada syndrome in patients with frequent implantable cardioverter defibrillator discharges. There is a clear need for a large randomized controlled clinical trial to assess the effectiveness of quinidine, preferably in patients with frequent events who have already received an ICD.

The quest for additional cardioselective and I_{to}-specific blockers is ongoing. 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 potently blocking I_{to}. The effect of tedisamil to suppress phase 2 reentry and VT in a wedge model of the Brugada syndrome is illustrated in Figure 33–15.[197]

Tedisamil and quinidine are both capable of suppressing the substrate and trigger for the Brugada syndrome via their inhibition of I_{to}. Both, however, also block I_{Kr} and thus have the potential to induce an acquired form of the long QT syndrome. Thus these agents may substitute one form of polymorphic VT for another, particularly under conditions that promote TdP, such as bradycardia and hypokalemia. However, the majority of patients with Brugada syndrome are otherwise healthy males, for whom the risk of drug-induced TdP is small.[198] 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.[77,199,200] High doses of quinidine (1000–1500 mg/day) are recommended in order to effect I_{to} block without inducing TdP.

Another potential therapeutic candidate is an agent reported to be a relatively selective I_{to} and I_{Kur} blocker, AVE0118.[201] Figure 33–16 shows the ability 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 pharmacological agents as well as the potential role of pacemakers in some forms of the disease.

Drugs that increase the calcium current, such as β-adrenergic agents like isoproterenol, are useful as well.[126,127,133] Isoproterenol, sometimes in combination with quinidine, has been shown to be effective in normalizing ST-segment elevation

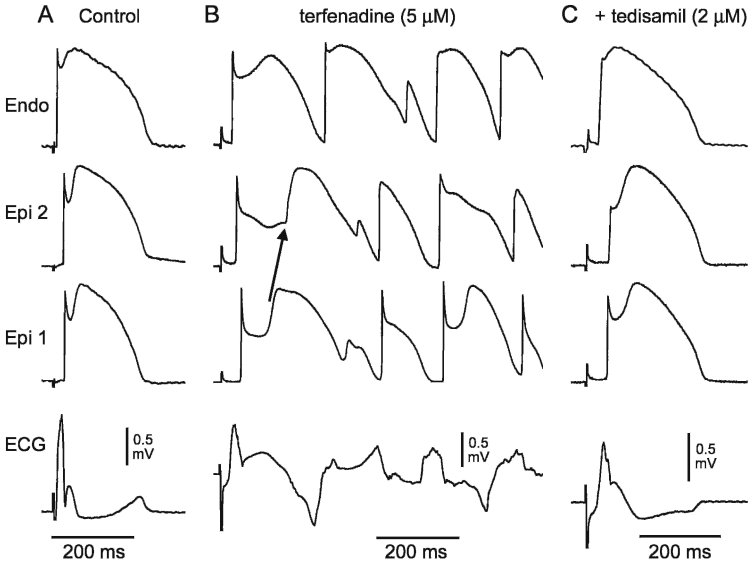


FIGURE 33–15. Effects of I_{to} block with tedisamil to suppress phase 2 reentry induced by terfenadine in an arterially perfused canine RV wedge preparation. (A) Control, BCL = 800 msec. (B) Terfenadine (5 μM) induces ST-segment elevation as a result of heterogeneous loss of the epicardial action potential dome, leading to phase 2 reentry, which triggers an episode of poly VT (BCL = 800 msec). (C) Addition of tedisamil (2 μM) normalizes the ST segment and prevents loss of the epicardial action potential dome and suppresses phase 2 reentry-induced and polymorphic VT (BCL = 800 ms). (From Antzelevitch and Fish,[185] with permission.)

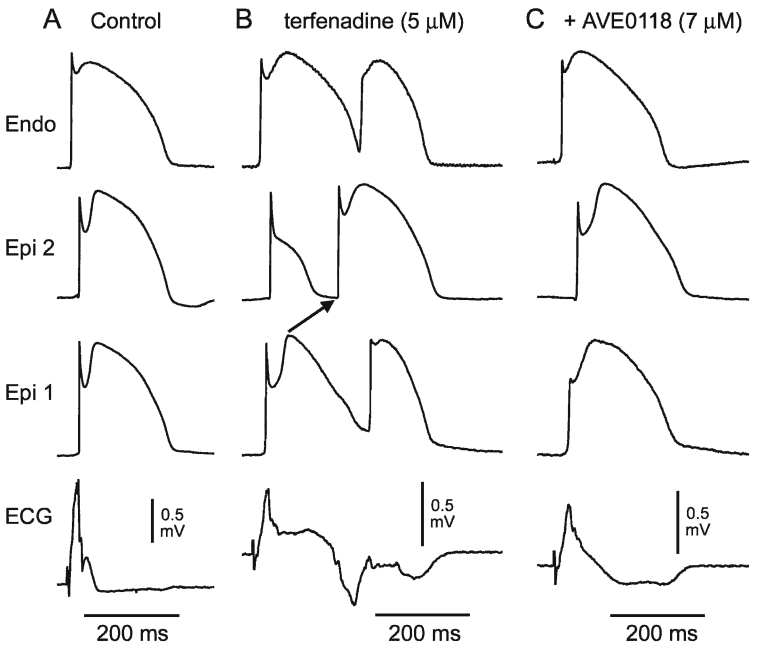


FIGURE 33–16. Effects of I_{to} blockade with AVE0118 to suppress phase 2 reentry induced by terfenadine in an arterially perfused canine RV wedge preparation. (A) Control, BCL = 800 msec. (B) Terfenadine (5 μM) induces ST-segment elevation as a result of heterogeneous loss of the epicardial action potential dome, leading to phase 2 reentry, which triggers a closely coupled extrasystole (BCL = 800 msec). (C) Addition of AVE0118 (7 μM) prevents loss of the epicardial action potential dome and phase 2 reentry-induced arrhythmias (BCL = 800 msec). (From Antzelevitch and Fish,[185] with permission.)

in patients with the Brugada syndrome and in controlling electrical storms, particularly in children.[22,184,189,194,202–204] A new addition to the pharmacological armamentarium is the phosphodiesterase III inhibitor cilostazol,[126] 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.

Another pharmacological approach is to augment a component of I_{Na} that is active during phase 1 of the epicardial action potential. Dimethyl lithospermate B (dmLSB) is an extract of Danshen, a traditional Chinese herbal remedy, which slows inactivation of I_{Na}, but only during a window of time corresponding to the action potential notch. This leads to increased inward current during the early phases of the action potential. Figure 33–17 shows the effectiveness of dmLSB in eliminating the arrhythmogenic substrate responsible for the Brugada syndrome in three different experimental models of the syndrome.[205] The Brugada syndrome phenotype was created in canine arterially perfused RV wedge preparations using either terfenadine or verapamil to inhibit I_{Na} and I_{Ca}, or pinacidil to activate $I_{K\text{-}ATP}$. Terfenadine, verapamil, and pinacidil each induced all-or-none repolarization at some epicardial sites but not others, leading to ST-segment elevation as well as an increase in both epicardial and transmural dispersions of repolarization from 12.9 ± 9.6 msec to 107.0 ± 54.8 msec and 22.4 ± 8.1 msec to 82.2 ± 37.4 msec, respectively ($p < 0.05$, $n = 9$). Under these conditions, phase 2 reentry developed as the epicardial action potential dome propagated from sites where it was maintained to sites at which it was lost, generating closely coupled extrasystoles and VT/VF. Addition of dmLSB (10 μM) to the coronary perfusate restored the epicardial action potential dome, reduced both epicardial and transmural dispersion of repolarization, and abolished phase 2 reentry-induced extrasystoles and VT/VF in nine of nine preparations. Our data suggest that dmLSB may be a candidate for pharmacological treatment of Brugada syndrome in cases in which an ICD is not feasible or affordable or as an adjunct to ICD use.

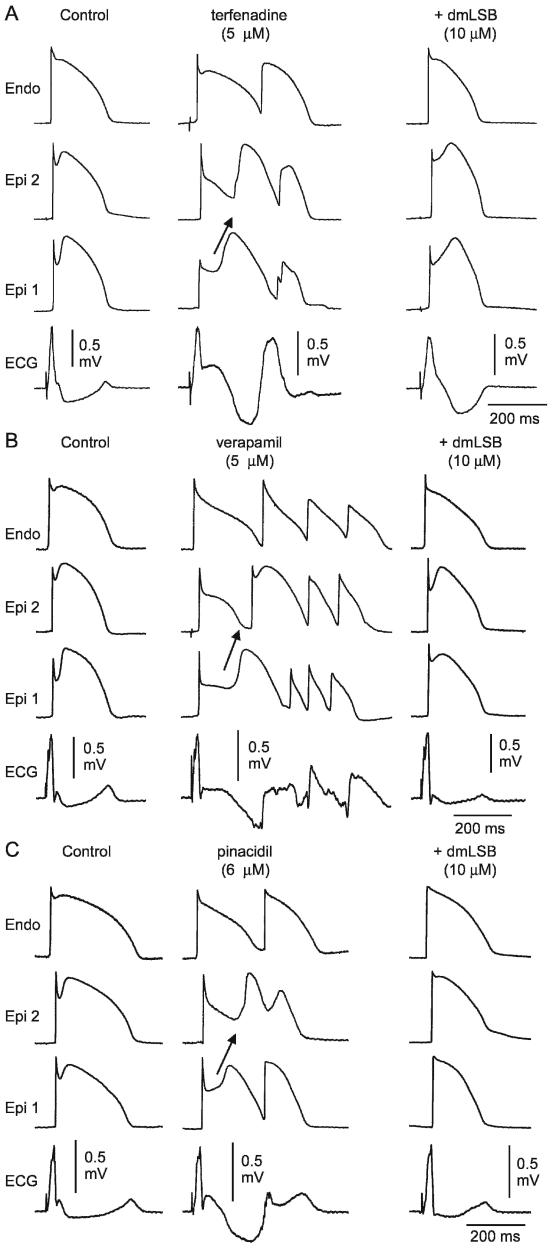


FIGURE 33–17. Effect of dmLSB suppression of the arrhythmogenic substrate of the Brugada syndrome in three experimental models. Phase 2 reentry was induced in three separate models of the Brugada syndrome. Terfenadine (5 μM, A), verapamil (5 μM, B), and pinacidil (6 μM, C) induce heterogeneous loss of the epicardial action potential dome and ST-segment elevation. Phase 2 reentry occurs as the dome is propagated from Epi 1 to Epi 2, triggering either a closely coupled extrasystole or polymorphic ventricular tachycardia. In all three models, addition of dmLSB (10 μM) normalizes the ST segment and abolishes phase 2 reentry and resultant arrhythmias. (From Fish *et al.*,[205] with permission.)

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