

The Brugada Syndrome: Clinical, Electrophysiologic and Genetic Aspects

IHOR GUSSAK, MD, PhD,* CHARLES ANTZELEVITCH, PhD, FACC,†
PREBEN BJERREGAARD, MD, DMSc, FACC,* JEFFREY A. TOWBIN, MD, FACC,‡
BERNARD R. CHAITMAN, MD, FACC*

St. Louis, Missouri; Utica, New York, and Houston, Texas

This review deals with the clinical, basic and genetic aspects of a recently highlighted form of idiopathic ventricular fibrillation known as the Brugada syndrome. Our primary objective in this review is to identify the full scope of the syndrome and attempt to correlate the electrocardiographic manifestations of the Brugada syndrome with cellular and ionic heterogeneity known to exist within the heart under normal and pathophysiologic conditions so as to identify the cellular basis and thus potential diagnostic and therapeutic approaches. The available data suggest that the Brugada syndrome is a primary electrical disease resulting in abnormal electrophysiologic activity in right ventricular epicardium. Recent genetic data linking the Brugada syndrome to an ion channel gene mutation (SCN5A) provides further support for the hypothesis. The electrocardiographic manifestations of the Brugada syndrome show transient normalization in many patients, but can be unmasked using sodium channel blockers such as

flecainide, ajmaline or procainamide, thus identifying patients at risk. The available data suggest that loss of the action potential dome in right ventricular epicardium but not endocardium underlies the ST segment elevation seen in the Brugada syndrome and that electrical heterogeneity within right ventricular epicardium leads to the development of closely coupled premature ventricular contractions via a phase 2 reentrant mechanism that then precipitates ventricular tachycardia/ventricular fibrillation (VT/VF). Currently, implantable cardiac defibrillator implantation is the only proven effective therapy in preventing sudden death in patients with the Brugada syndrome and is indicated in symptomatic patients and should be considered in asymptomatic patients in whom VT/VF is inducible at time of electrophysiologic study.

(J Am Coll Cardiol 1999;33:5-15)

©1998 by the American College of Cardiology

In the United States alone, sudden death due to cardiac arrest occurs with an incidence of more than 300,000 per year (1). Recent interest has focused on unexpected arrhythmogenic death occurring in individuals with minimal or no structural heart disease, estimated to represent 3% to 9% of out-of-hospital cases of ventricular fibrillation unrelated to myocardial infarction (2). In addition to the ventricular preexcitation syndrome and the long QT syndrome, a new electrocardiographic (ECG) marker of sudden death in otherwise healthy individuals has been identified. Referred to as the Brugada syndrome, clinical cases have been reported in countries worldwide (3-53). World Wide Web Home Page for the Brugada syndrome has been introduced on the Internet (54).

The Brugada syndrome is characterized by a) a peculiar ST segment elevation in the right precordial leads often accom-

panied by apparent conduction block in the right ventricle, b) structurally normal heart and c) a propensity for life-threatening ventricular tachyarrhythmias. Originally described by Pedro and Josep Brugada as "right bundle branch block and persistent ST segment elevation in V₁-V₃" in patients with no apparent structural heart disease, this ECG abnormality and its role in malignant arrhythmogenicity has become the subject of increasing attention and controversy. Transient forms of the disease in which the ECG manifestations normalize for a period of time have been described more recently (17,19,40,41,43). The prevalence of ventricular fibrillation (VF) associated with this ECG phenomenon have been estimated in some countries as high as 40% to 60% of all cases of idiopathic VF (55). Certain electrophysiologic similarities have been found between ECG markers of the Brugada syndrome, early repolarization syndrome (56-58) and hypothermia (59-62). A strong link has been identified between the Brugada syndrome and sudden and unexpected death syndrome in Southeast Asian men (17,29,24). Possible overlap with arrhythmogenic right ventricular dysplasia (ARVD) and apoptosis has been suggested (7-9,11,33), although the Brugada syndrome and ARVD appear to be caused by defects in different chromosomal loci. An ion channel defect resulting in heterogeneous loss of the action potential dome in right ventricular epicardium has been proposed as a mechanism underlying

From the *St. Louis University Health Science Center, St. Louis, Missouri; †Masonic Medical Research Laboratory, Utica, New York, and ‡Baylor College of Medicine, Houston, Texas. Supported by grants from the National Institutes of Health (HL47678) and American Heart Association, New York State Affiliate and by the Masons of New York State and Florida.

Manuscript received January 8, 1998; revised manuscript received August 12, 1998, accepted September 15, 1998.

Address for correspondence: Dr. Ihor Gussak, St. Louis University Health Science Center, Internal Medicine, Division of Cardiology, 1034 Brentwood Blvd., Suite 1550, St. Louis, Missouri 63117. E-mail: ibgussak@ecglab.org.

Abbreviations and Acronyms

ARVD	= arrhythmogenic right ventricular dysplasia
ECG	= electrocardiographic
ERS	= early repolarization syndrome
I_{Ca}	= calcium current
ICD	= implantable cardiac defibrillator
I_{K-ATP}	= adenosine triphosphate-sensitive potassium current
I_{Na}	= sodium current
I_{to}	= transient outward current
RBBB	= right bundle branch block
SUDS	= sudden and unexplained death syndrome
TdP	= Torsade de Pointes
VF	= ventricular fibrillation
VT	= ventricular tachycardia

both idiopathic ST segment elevation in the right precordial leads and the dispersion of repolarization that predisposes the heart to the development of malignant reentrant ventricular arrhythmias (59–61). Recent genetic data linking the Brugada syndrome to an ion channel gene mutation provides further support for the hypothesis that the Brugada syndrome is a primary electrical disease (55).

Our primary objective in this review is to identify the full scope of this syndrome and attempt to correlate the electrocardiographic manifestations of the Brugada syndrome with cellular and ionic heterogeneity known to exist within the heart under normal and pathologic conditions so as to identify the cellular basis and thus potential diagnostic and therapeutic approaches.

Electrocardiographic Markers of the Brugada Syndrome

In 1991–1992 Pedro and Josep Brugada described eight otherwise healthy patients with sudden and aborted cardiac death, in whom they found “right bundle branch block and persistent ST segment elevation in leads V_1 – V_3 ” (3,4). Based on those clinical cases they outlined a new “distinct clinical and electrocardiographic syndrome,” which has subsequently been called the Brugada syndrome.

The electrocardiographic pattern of ST segment elevation and inversion of the T wave in the right precordial leads with and without right bundle branch block (RBBB) have been described in apparently healthy individuals since 1953 (63–67). This striking ECG phenomenon had been largely ignored until Martini et al. (7) and Aihara et al. (24) brought attention to a possible link between this ventricular repolarization abnormality and sudden death in their patients.

The QRS complex in the Brugada syndrome ends with a positive deflection (or prominent J wave) followed by an elevated down-sloping ST segment and a negative T wave with a normal (38) or even short (24) QT interval. Leads V_1 to V_3 show the most prominent changes, with the degree of ST segment elevation tapering off in adjacent leads and often associated with varying degrees of conduction block in the

right bundle branch. In lead V_1 , the terminal portion of the QRS complex is elevated as an r' or a J wave followed by a down-sloping ST segment ending in a negative deflection. In adjacent leads the changes may be similar, but often the ST segment elevation is more horizontal and less prominent. It is a characteristic finding that the ST segment elevation in the right precordial leads is not accompanied by reciprocal ST segment depression in opposite leads (Fig. 1A). Repolarization abnormalities are often more prominent in the right chest leads placed on intercostal space higher than usual (42). Clinicians have identified this “bizarre, extremely special form of ST segment elevation” (13) as: a) major (coved type or dome shape), b) minor (saddle-back type) and c) triangular (31). Whereas a) is related to acute episodes of electrical instability, b) is thought to be due to a chronic course of the disease (47).

ST segment elevation in the right chest leads is observed in a variety of clinical and experimental settings (Table 1) and is not unique or highly specific for the Brugada syndrome. A clear distinction cannot be made on the basis of an ECG alone. However, ST segment elevation in the right precordial leads in the absence of ischemia, electrolyte or metabolic disorders, pulmonary or inflammatory diseases or abnormalities of central or peripheral nervous system may identify the Brugada syndrome. In such cases, the term “idiopathic” is appropriate.

The prevalence of idiopathic ST segment elevation is reported to be 2.1% to 2.65% (14). An elevated ST segment limited to the right precordial leads occurs in less than 1% of all cases of elevated ST segment (68). The combination of ST segment elevation in these leads and RBBB was found in 12 out of 22,027 subjects in Japan (0.05%). All 12 individuals were male with no structural heart disease; four had a history of sudden cardiac death (39). Sixty-three patients (60 male) with RBBB, persistent ST segment elevation and a normal QT interval are currently being followed in 34 medical centers in Japan. So far, 12 have experienced episodes of syncope and 17 suffered ventricular fibrillation (35,47).

In many patients with the Brugada syndrome, the ECG manifestations transiently normalize (40,41,43), leading to underdiagnosis of the syndrome (38). Strong sodium channel blockade using agents such as procainamide, ajmaline and flecainide can unmask the ST segment elevation in V_1 – V_3 and right bundle branch block-like pattern in many patients (61). A number of other agents, including adrenergic and cholinergic neurohormones, are capable of modulating the degree of ST segment elevation in Brugada syndrome patients. Beta-adrenoreceptor stimulation and alpha-adrenoreceptor blockade reduce the magnitude of ST segment elevation, but not necessarily the degree of conduction delay in the right ventricle in patients with the Brugada syndrome, whereas beta-adrenergic blockade, alpha-adrenergic stimulation, sodium channel blockade and muscarinic stimulation augment the ST segment elevations (29,42,50). More prominent ST segment elevation in the right chest leads (but not RBBB) has been observed immediately before (49,70) (Fig. 1B) and after

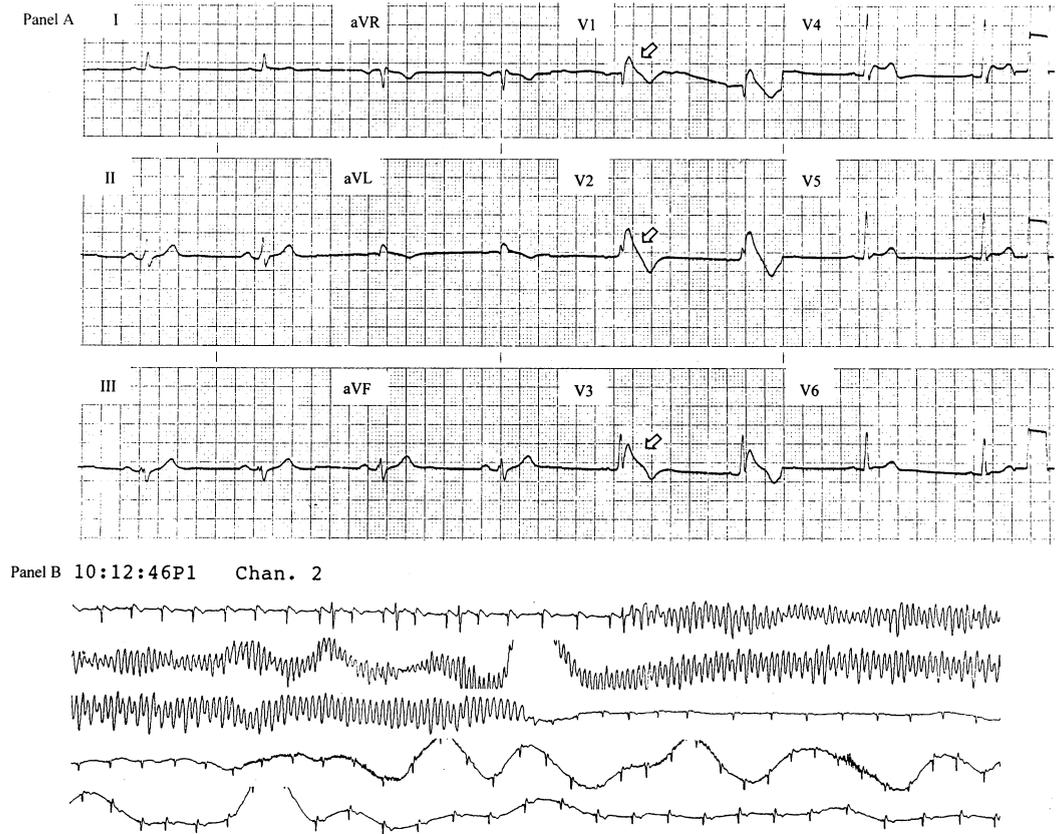


Figure 1. (A) Twelve-lead electrocardiogram of a patient with the Brugada syndrome. The right precordial leads, V₁ to V₃, display a down-sloping ST segment elevation. QRS is normal but QT dispersion between V₂ and V₆ is larger than normal (120 ms). (B) Self-terminating polymorphic ventricular tachycardia (continuous recording) in a patient with the Brugada syndrome. Closely coupled premature ventricular contractions precede the onset of tachyarrhythmia. Note the disappearance of the repolarization abnormalities following the arrhythmia.

episodes of aborted sudden cardiac death in some patients (29,35).

The role of RBBB in the Brugada syndrome has been a matter of some controversy. In surveying 80 published ECGs obtained from patients with the Brugada syndrome, we found that at least one third of those classified as RBBB did not meet the ECG criteria for RBBB. Kasanuki et al., using body-surface mapping, demonstrated a conduction delay in the anterior wall and RV outflow tract in six patients with the Brugada syndrome, only when a secondary R wave was present in lead V₁ (29). Prolongation of the H-V interval has been documented in many clinical cases (4,15,28,50). However, there appears to be no correlation between RBBB and sudden cardiac death (69), whereas a definite link exists between the magnitude of ST segment elevation and incidence of the life-threatening arrhythmic events in patients with the Brugada syndrome. Thus, conduction delay in the right ventricle may be associated with the Brugada syndrome, but does not appear to be an integral part of the syndrome.

Brugada Syndrome and Early Repolarization Syndrome

Early repolarization syndrome (ERS), although characterized by idiopathic ST segment elevation, is different from the

Brugada syndrome in that it is generally not associated with arrhythmias.

Electrocardiographically, both syndromes resemble a pattern of reversed Wolff-Parkinson-White syndrome with distinct slur or notch on the downstroke of the R wave. However, the elevated ST segment in ERS can be differentiated from ST segment elevation in the Brugada syndrome by its localization and pattern. The elevated ST segment in ERS is usually localized in leads V₂ to V₄ (5) and has an upward concavity with positive T wave polarity accompanied by a notched J point (71), whereas ST segment elevation in the Brugada syndrome is limited to the right precordial leads, is slowly down-sloping and is followed by a negative T wave.

Electrophysiologically, ERS and the Brugada syndrome share some common mechanisms of drug- and neuromodula-

Table 1. Abnormalities That Can Lead to ST Segment Elevation in the Right Precordial Leads

In the Clinic:	
Right or left bundle branch block, left ventricular hypertrophy (66,108)	
Acute myocardial infarction (109)	
Left ventricular aneurysm (109)	
Exercise test-induced (110)	
Acute myocarditis (111)	
Right ventricular infarction (112)	
Dissecting aortic aneurysm (113)	
Acute pulmonary thromboemboli (114)	
Various central and autonomic nervous system abnormalities (115,116)	
Heterocyclic antidepressant overdose (117)	
Duchenne muscular dystrophy (118)	
Friedreich ataxia (119)	
Thiamine deficiency (120)	
Hypercalcemia (121)	
Hyperkalemia (108,122)	
Compression of the right ventricular outflow tract by metastatic tumor (123)	
Cocaine intoxication (124)	
In Experimental models:	
Isolated sheets of canine ventricular epicardium exposed to potassium channel openers, sodium and calcium channel blockers, acetylcholine, metabolic inhibition and ischemia (59-61,89-103)	
Injection of potassium salts into blood perfusing the coronary arteries (125) or into subepicardium (126,127)	
Potassium chloride application on the pericardial surface (128)	
Right ventricular infarction (129)	

tion. As with the Brugada syndrome, isoproterenol is known to reduce or even eliminate the ST segment elevation in individuals with ERS, whereas propranolol increases the magnitude of ST segment elevation (56).

Interestingly, ERS-like isoproterenol-sensitive ST segment elevation often appears on ECGs of patients with high (cervical) spinal cord injury (C₅ to C₆). In contrast to patients with lower spinal cord injury, injury to the cervical cord may completely disrupt cardiac sympathetic influence from higher centers, whereas parasympathetic control remains intact, suggesting that inadequate sympathetic tone in the presence of parasympathetic control of the heart may play a role in generation of the ST segment elevation (72). This observation was confirmed in experiments with spinal cord compression in cats (73) and monkeys (74).

Brugada Syndrome and Sudden and Unexpected Death Syndrome

Sudden and unexpected death of young adults during sleep is endemic to Japan and Southeast Asia. The incidence of sudden and unexpected death syndrome (SUDS) among Asians living in the USA varies among different ethnic groups from 1:2,500 to 1:1,087 (19,75,76). SUDS characteristics include the following: 1) victims are relatively young healthy men leading normal lives; 2) death often occurs during sleep late at night, and 3) autopsy findings are usually negative (77).

Aihara et al. were the first to focus attention on elevation of

the ST segment in the right chest leads in patients with life-threatening ventricular tachyarrhythmias occurring at night or during early morning hours (24). Nademanee et al. identified this ECG phenomenon in the majority of SUDS patients from Thailand; 17 out of 27 victims of either aborted sudden death or syncope (or seizure) had a dynamic pattern of ST segment elevation in precordial leads V₁ to V₃, often accompanied by apparent conduction block in the right ventricle. All were young men with a strong family history of unexpected and unexplained death. In all, electrophysiologic workup revealed a positive signal averaged ECG and inducible polymorphic ventricular tachycardia (VT)/VF, although in most echocardiography, coronary angiography, ventriculography and magnetic resonance imaging revealed no evidence of structural disease. Moreover, exercise normalized the ECG, suggesting that the sympathetic nervous system plays an important role in modulation of this ECG phenomenon (17,19).

Brugada Syndrome and Arrhythmogenic Right Ventricular Dysplasia

The nature of the primary defect in the Brugada syndrome, whether cardiac or extracardiac, structural or functional, has also been a topic of debate. It has been suggested that the Brugada syndrome may represent either: a) a functional abnormality of the electrical activity of the heart or a primary electrical disease (34,37,38,59,60); or b) an early subclinical manifestation of right ventricular dysplasia/cardiomyopathy (2,7-9,33).

Some investigators report remarkable myocardial atrophy with adipose tissue or fibrofatty infiltration in the dilated right ventricle (often involving the conducting tissue), consistent with ARVD, in all of their patients with the Brugada syndrome, whereas others report no structural defects whatsoever in any patient with the same syndrome. In this regard, it is important to emphasize that at the present time we do not have a gold standard for clinical or histologic diagnosis of ARVD. There is no controlled study that examines either the sensitivity or specificity of postmortem findings, quantitative evaluation of the fatty infiltration or the degree of fibrotic tissue involvement (37).

The Brugada syndrome, like ARVD, is also consistent with autosomal dominant inheritance with variable expression (22). However, it is not related to any gene abnormality so far described for ARVD (78,79). It seems premature to draw any definitive conclusions as to whether the Brugada syndrome is or is not an atypical or early manifestation of the ARVD.

It is intriguing to speculate that the Brugada syndrome may start out as a primary electrical disease, but chronically progress to develop structural abnormalities. This hypothesis is suggested by the observation that electrical remodeling in atrial fibrillation and ventricular hibernation precedes structural remodeling (80).

Diagnostic Workup

Programmed electrical stimulation reproducibility induces VT or VF in almost all Brugada syndrome patients with a history of aborted sudden death or syncope. Positive late potentials on signal-averaged ECG are a common finding as well, particularly in patients in whom an elevated ST segment is accompanied by apparent RBBB. Because the ECG manifestations of the syndrome are often transient, the use of sodium channel blocking agents including ajmaline, procainamide and flecainide to unmask the syndrome is recommended in those in whom the syndrome is suspected (81). Imaging techniques, endocardial biopsy and cardiac catheterization are useful in ruling out structural cardiac abnormalities. Finally, extension of the testing to family members is also important (38) because of high incidence of familial occurrence (82).

Clinical Course and Current Concepts of the Treatment Strategy

The mean age of affected individuals is in the mid to late thirties, ranging from 4 to 70 years. All clinical manifestations of the Brugada syndrome are attributed exclusively to the life-threatening ventricular tachyarrhythmias and their complications. Tragically, in some patients sudden death is the first and only clinical event. Diagnosis and prevention of life-threatening ventricular tachyarrhythmias and their complications are the main objective of therapy.

In the majority of cases, malignant tachyarrhythmias occur at rest and in many cases at nighttime, especially in Japan and Southeastern Asia. A sudden rise in vagal activity has been reported to occur just before VF episodes in some patients (29), whereas abnormally high sympathetic tone has been documented in other patients 1 week after episodes of VF (51). In some patients mental stress (18) and alcohol consumption (15) are thought to be provocative factors.

The incidence of arrhythmic events is similar in patients receiving either an implantable cardiac defibrillator (ICD), amiodarone or beta-adrenergic blocking agents. However, only patients with an ICD are protected from sudden death (29,82). The first randomized clinical trial of defibrillator versus treatment with beta-blockers was initiated in 1997 (17). A cardioselective blocker of transient outward current (I_{to}), although not available in today's pharmacologic armamentarium, is expected to be highly effective in protecting patients with the Brugada syndrome against VT/VF (61,81,83). Antiarrhythmic agents with I_{to} blocking properties, such as quinidine, may also prove effective (2,81).

Thus, at present there are no specific pharmacologic treatments for preventing sudden death in patients with the Brugada syndrome. Implantation of an ICD is the only effective intervention for preventing sudden death. Of special interest are individuals displaying the ECG features of the Brugada syndrome, but without arrhythmogenic complications. Their potential risk of sudden death should be evaluated during

electrophysiologic study; inducibility of VT/VF should be considered as an indication for an ICD (82).

Possible Cellular and Ionic Mechanisms

ST segment elevation and phase 2 reentry. A down-sloping ST segment elevation similar to that observed in the Brugada syndrome is a normal characteristic of the ECG of some rodents (84). This manifestation of the ECG is due to a much earlier repolarization of the epicardial action potential due to a more intense I_{to} (85). Accordingly, block of I_{to} with 4-aminopyridine normalizes the Action Potential Duration (APD) of rat/mouse epicardium and endocardium, yielding an isoelectric ST segment (86–88).

An isoelectric ST segment is a normal feature of the ECG in higher mammals. This is due to the fact that the voltage of the early part of phase 2 of the action potential is relatively similar throughout the myocardium, due to the development of a prominent calcium current (I_{Ca})-mediated action potential plateau. The development of a normal plateau phase is dependent on the balance of currents active at the end of phase 1; usually this balance is predominantly inward due to a strong I_{Ca} and relatively weak outward currents such as I_{to} . Under pathophysiologic conditions, the balance of current active at the end of phase 1 can shift outward, causing a loss of the action potential dome. This occurs when the contribution of inward currents at the end of phase 1 is relatively weak and that of the outward currents is relatively strong. Pathophysiologic conditions (e.g., ischemia, metabolic inhibition) and some pharmacologic interventions (e.g., sodium current [I_{Na}] or I_{Ca} blocking agents or adenosine triphosphate-sensitive potassium current [I_{K-ATP}] activators) are capable of causing a marked abbreviation of the action potential in canine and feline ventricular epicardial cells, where I_{to} is prominent, but not endocardial cells. Under these conditions, the ECG displays an ST segment elevation similar to that observed in patients with the Brugada syndrome.

Most of the characterization of this phenomenon and its arrhythmic sequelae is the result of work conducted in the canine heart (59–61,89–103). The presence of a prominent I_{to} -mediated notch predisposes canine ventricular epicardium to all-or-none repolarization and phase 2 reentry. Under ischemic conditions and in response to a variety of drugs, including sodium and calcium channel blocking agents, canine ventricular epicardium exhibits an all-or-none repolarization as a result of the rebalancing of currents flowing at the end of phase 1 of the action potential. Failure of the dome to develop occurs when the outward currents (principally I_{to}) overwhelm the inward currents (chiefly I_{Ca}), resulting in a marked (40% to 70%) abbreviation of the action potential (59–61,89–103). Under these conditions the action potential plateau (dome) is usually abolished at some epicardial sites but not others, causing a marked dispersion of repolarization. Propagation of the action potential dome from sites 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,

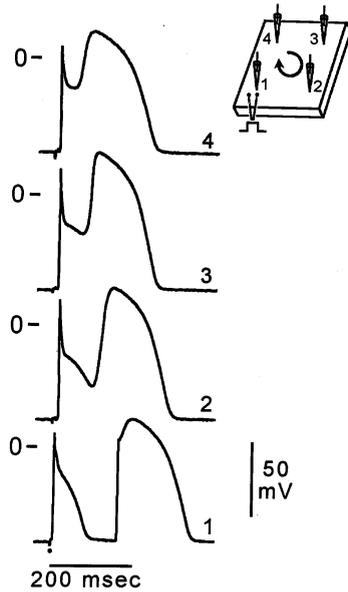


Figure 2. Phase 2 reentry. Reentrant activity was induced by exposure of a canine ventricular epicardial preparation to simulated ischemia. Microelectrode recordings were obtained from four sites as shown in the schematic (upper right). After 35 min of ischemia, the action potential dome develops normally 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 reentrant extrasystole with a coupling interval of 156 ms at site 1. basic cycle length = 700 ms. A similar phenomenon is observed upon exposure of right ventricular epicardium to acetylcholine, potassium channel openers and inhibitors of sodium and calcium inward currents. Adapted with permission from Lukas and Antzelevitch (92).

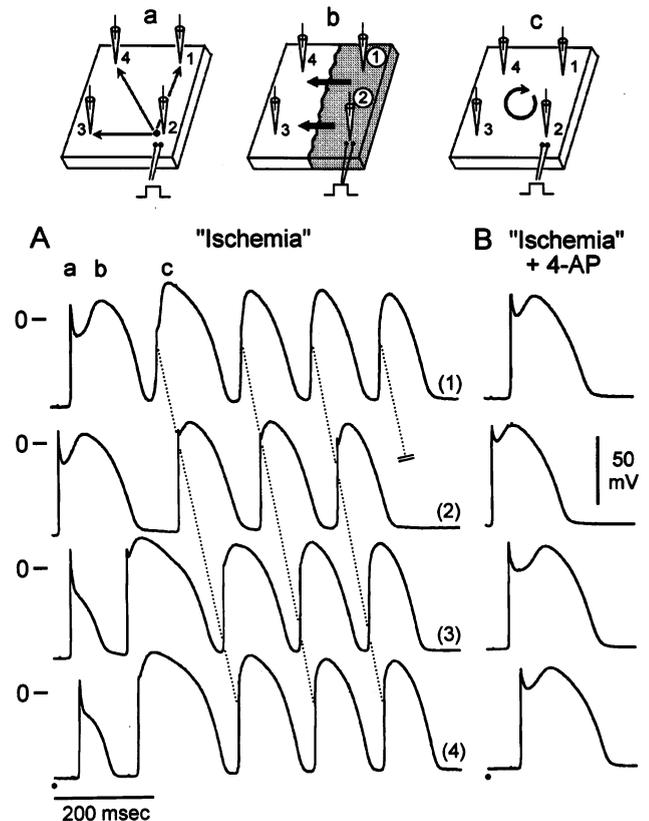
produces closely coupled extrasystolic beats, which can then initiate one or more cycles of circus movement reentry (92) (Figs. 2 and 3). Under ischemic conditions (Figs. 2 and 3) the contribution of I_{Ca} is reduced, thus shifting the balance of current at the end of phase 1 to net outward in canine epicardium (92). Similar electrical heterogeneity leading to phase 2 reentry occurs in canine epicardium exposed to: a) K^+ channel openers such as pinacidil (96); b) sodium channel blockers such as flecainide (97); c) increased $[Ca^{2+}]_o$ (95), and d) metabolic inhibition (100). Because the level of I_{to} is pivotal, I_{to} block restores electrical homogeneity and abolishes reentrant activity in all cases (Fig. 3).

Phase 2 reentry as a trigger for idiopathic ventricular fibrillation. As already discussed, loss of the action potential dome (plateau) in epicardium but not endocardium would be expected to cause elevation of the ST segment, similar to that found in patients with the Brugada syndrome (98,100). Because loss of the dome is caused by an outward shift in the balance of currents active at the end of phase 1 of the action potential (principally I_{to} and I_{Ca}), autonomic neurotransmitters like acetylcholine facilitate loss of the action potential dome (101) by suppressing calcium current and augmenting potassium current, whereas beta-adrenergic agonists such as isoproterenol and dobutamine restore the dome by augmenting I_{Ca} . Sodium channel blockers also facilitate loss of the

canine right ventricular action potential dome as a result of a negative shift in the voltage at which phase 1 begins (97,102).

Accentuation of the ST segment elevation in patients with the Brugada syndrome following vagal maneuvers or sodium channel blockers, as well as normalization of the ST elevation following beta-adrenergic agents are concordant with the findings in isolated tissue preparations (50,60). The appearance of the ST segment elevation only in right precordial leads in patients with the Brugada syndrome is also consistent with the observation that loss of the action potential dome is much more easily induced in right than left canine ventricular epicardium (98,100) because of the higher density of I_{to} in

Figure 3. Phase 2 reentry-initiated circus movement tachycardia abolished with transient outward current inhibition. (A) Exposure of canine right ventricular epicardial sheet to simulated ischemia results in loss of the dome at sites 3 and 4 but not at sites 1 and 2 (basic cycle length = 1100 ms). Conduction of the basic beat proceeds normally from the stimulation site (site 2; see schematic a). Propagation of the action potential dome from the right half of the preparation causes reexcitation of the left half via a phase 2 reentry mechanism (see schematic b). The extrasystolic beat generated by phase 2 reentry then initiates a run of tachycardia that is sustained for four additional cycles via a typical (phase 0) circus movement reentry mechanism. The proposed reentrant path is shown in Schematic c. Note that phase 2 reentry provides an activation front roughly perpendicular to that of the basic beat. (B) Recorded 5 min after addition of 1 mmol/L 4-aminopyridine (4-AP), an inhibitor of the transient outward current. In the continued presence of ischemia, 4-AP restores the dome at all epicardial recording sites within 3 min. Thus electrical homogeneity is restored and all reentrant activity abolished. Adapted with permission from Lukas and Antzelevitch (92).



right than left ventricular epicardium (103,104). These similarities in electrophysiology, pharmacology and ECG have prompted us to speculate that a depressed right ventricular epicardial action potential dome underlies the ST segment elevation and that phase 2 reentry may provide the trigger for episodes of ventricular fibrillation in patients with the Brugada syndrome (81).

A test of these hypotheses has recently been performed in arterially perfused canine right ventricular wedge preparations. Preliminary results using the perfused wedge preparation support the hypothesis that ST segment elevation in patients with the Brugada syndrome may be the result of loss of the action potential dome in right ventricular epicardium, where I_{to} is most prominent, but not in endocardium, where I_{to} is weak. Initiation of VT/VF under these conditions is via phase 2 reentry secondary to heterogeneous loss of the epicardial action potential dome (59). The VT generated in these preparations was sometimes polymorphic, resembling a rapid form of Torsade de Pointes (TdP). This activity may be mechanically related to the migrating spiral wave shown by Pertsov et al. (105) to generate a pattern resembling TdP associated with a normal QT interval. Both in the perfused wedge and in isolated tissues, agents that inhibit I_{to} , including 4-aminopyridine, quinidine and disopyramide, proved effective in restoring the action potential dome, thus restoring electrical homogeneity and aborting all arrhythmic activity. Thus class I antiarrhythmic agents that block I_{Na} much more potently than I_{to} (procainamide, ajmaline and flecainide) appear to unmask or exacerbate the ECG pattern of the Brugada syndrome, whereas those with actions to block both I_{Na} and I_{to} (quinidine and disopyramide) exert an ameliorative effect.

For these concepts to be considered as applicable to humans, it is important to demonstrate the presence of a large I_{to} in human epicardium but not endocardium. Two separate studies have shown these distinctions in myocytes isolated from the respective regions of the human heart (106,107). An important difference between man and dog is that I_{to} reactivation is much faster in human epicardium than in the dog epicardium, suggesting that electrical heterogeneity and phase 2 reentry might occur over a much wider range of heart rates and be less influenced by heart rate in the human ventricle.

Candidate genes for the Brugada syndrome. One of the easiest means to induce ST segment elevation and phase 2 reentry in isolated epicardial tissue preparations is through block of the sodium channel. Sodium channel blockers facilitate loss of the canine right ventricular action potential dome as a result of a negative shift in the voltage at which phase 1 begins (97,102). Gene mutations that diminish the density or conductance of the sodium channel are therefore prime candidates. Such mutations would also be consistent with the conduction disturbances that sometimes accompany the Brugada syndrome. Based on the results discussed above, other candidates include gene mutations that alter the intensity or kinetics of either I_{to} or I_{Ca} so as to augment the activity of the former and diminish that of the latter during the early phases

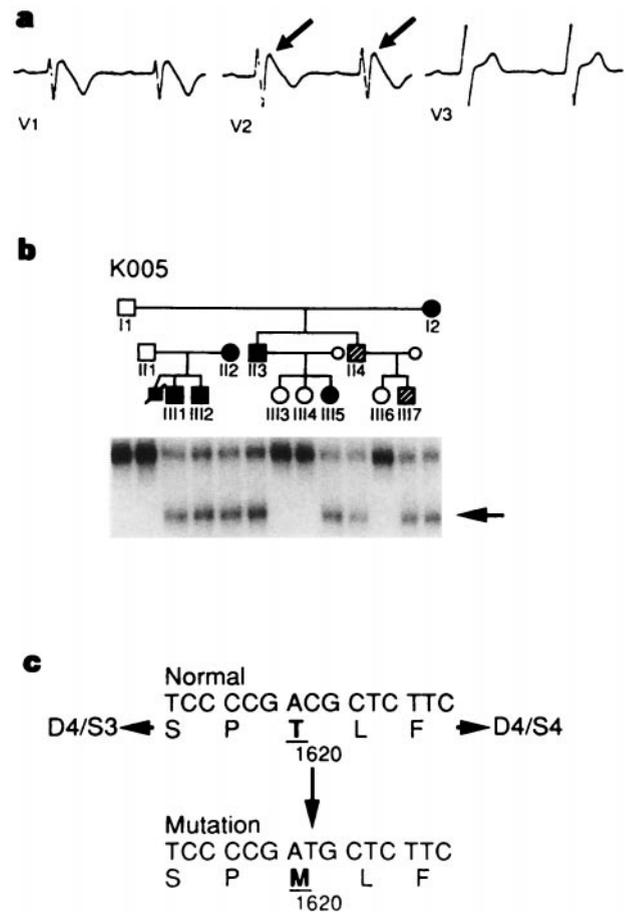


Figure 4. Cardiac sodium channel gene *SCN5A* missense mutation cosegregating with the Brugada syndrome. (A) Electrocardiogram of an affected individual. Note the elevated ST segment in leads V₁ to V₃. (B) Pedigree structure and mutation analysis using single strand conformation polymorphism analysis with primers amplifying exon 28 of the cardiac sodium channel gene, *SCN5A*. Affected individuals are filled circles (female) and filled squares (male). Unaffected individuals are empty symbols, and individuals without clinical data are shown as hatched. The individual who suffered sudden cardiac death is slashed. (C) Deoxyribonucleic acid and amino-acid sequences of the *SCN5A* missense mutation associated with the Brugada syndrome. Deoxyribonucleic acid sequence analysis revealed a C to T substitution, which causes the substitution of a highly conserved threonine by a methionine at codon 1,620 (T1620M mutation) in the extracellular loop between DIVS3 and DIVS4. Adapted with permission from Chen et al. (55).

of the action potential. Genes of autonomic receptors that modulate the activity or expression of these channels as well as those that regulate I_{K-ATP} are candidates as well.

The first gene to be linked to the Brugada syndrome was reported in early 1998. Chen and colleagues in the laboratory of Drs. Wang and Towbin studied six small families and two sporadic cases of the Brugada syndrome using molecular genetic methods. Based on the presumed pathophysiology leading to the electrocardiographic findings, a candidate gene approach was taken. A variety of ion channels were screened for mutations and, in three families, mutations in the cardiac sodium channel gene, *SCN5A*, the same gene responsible for

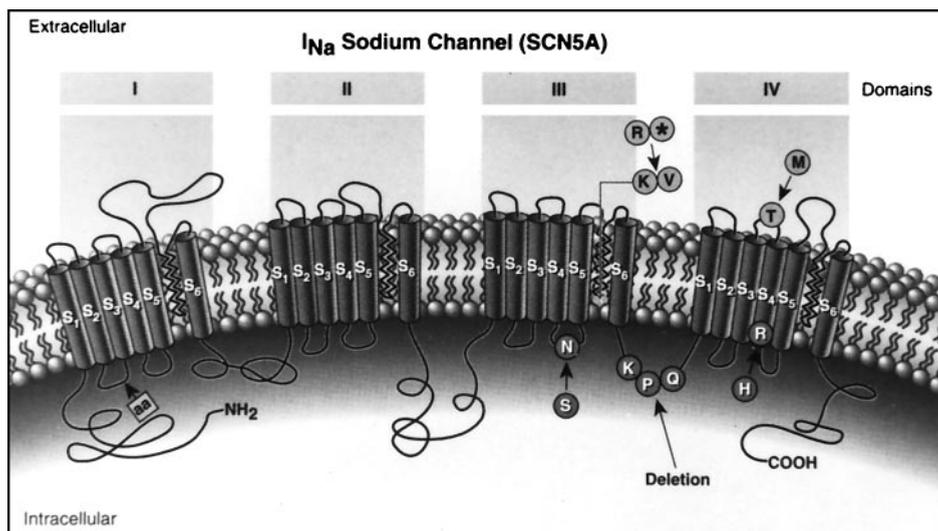


Figure 5. The predicted secondary structure of the cardiac sodium channel and locations of mutations causing the Brugada syndrome and chromosome 3-linked long QT syndrome. The channel consists of four putative transmembrane domains (DI-DIV), with each domain containing six transmembrane segments (S1-S6). The Brugada syndrome mutations are shown in **circles with dark lettering** and long QT syndrome-associated mutations are in **circles with white lettering**. Adapted with permission from Chen et al. (55).

LQT3, were identified (Fig. 4) (55). It should be emphasized that the mutations were at sites other than those known to contribute to the LQT3 form of the long QT syndrome, and the QT interval was not prolonged in these patients (Fig. 5). The mutations encountered in the Brugada syndrome patients caused either an acceleration of the recovery of the sodium channel (missense mutation) or nonfunctional sodium channels (insertion and deletion mutations). Electrophysiologically these mutations are thought to cause VF due to heterogeneity of the refractory period caused by the presence of both normal and mutated sodium channels in the same tissue (i.e., in the case of the missense mutation) or by the reduction in the number of functional sodium channels (as seen in the deletion and insertion mutants), which as previously discussed would be expected to promote the development of reentrant arrhythmias.

SCN5A was excluded as the gene causing the Brugada syndrome in at least one family, leading to the speculation that genetic heterogeneity exists in the Brugada syndrome. These findings provide further support for a primary electrical disease as the basis for the Brugada syndrome form of idiopathic VT/VF.

Summary and Future Directions

The available data suggest that the Brugada syndrome is a familial primary electrical disease caused by a defect in an ion channel gene, resulting in premature repolarization of some

right ventricular epicardial sites. The resulting transmural repolarization gradient underlies the phenotypic ST segment elevation, and the intraepicardial dispersion of repolarization gives rise to closely coupled phase 2 reentrant extrasystoles that can precipitate VT/VF. Patients at risk often show periodic normalization of the ST segment, leading to underestimation of the syndrome. Sodium channel blockers can be used to unmask the syndrome and should be avoided by Brugada patients unless they also significantly block I_{to} . Implantable cardiac defibrillator implantation is the only unequivocally effective treatment and should be considered in symptomatic and asymptomatic individuals with positive electrophysiologic testing. These observations notwithstanding, our knowledge of this and other idiopathic VF syndromes remains scant. Future studies will be aimed at further genetic linkage analysis of large families affected by the Brugada syndrome to examine the full scope of the genetic basis for the disease as well as to assess pharmacologic therapy using I_{to} blockers and other agents.

We are indebted to Drs. Pedro Brugada, Josep Brugada and Ramon Brugada for their helpful comments. Our special appreciation for Dr. Yasuhiro Yokoyama for helping with translation from Japanese.

References

1. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function and time-dependence of risk. *Circulation* 1992;85 Suppl I:2-10.
2. Viskin S, Lesh MD, Eldar M, et al. Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. *J Cardiovasc Electro-physiol* 1997;8:1115-20.
3. Brugada P, Brugada J. A distinct clinical and electrocardiographic syndrome: right bundle-branch block, persistent ST segment elevation with normal QT interval and sudden cardiac death (abstr). *PACE Pacing Clin Electrophysiol* 1991;14:746.
4. Brugada P, Brugada J. Right bundle-branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391-6.
5. Ferracci A, Fromer M, Schläpfer J, Pruvot E, Kappenberger L. Fibrillation ventriculaire primitive et récidive précoce; a propos d'un cas associant bloc

- de branche droit et sus-décalage persistant du segment ST. Arch Mal Coeur Vaisseaux 1994;87:1359-62.
6. D'Onofrio, A, Cuomo S, Musto B, Bocalatte A. Right bundle branch block, persistent ST-segment elevation in V1-V3 and sudden cardiac death: always a distinct syndrome? G Ital Cardiol 1995;25:1171-5.
 7. Martini B, Nava A, Thiene G, et al. Ventricular fibrillation without apparent heart disease. Description of six cases. Am Heart J 1989;118:1203-9.
 8. Martini B, Nava A, Cancinani B, Thiene G. Right bundle branch block, persistent ST segment elevation and sudden cardiac death (letter). J Am Coll Cardiol 1993;22:633.
 9. Naccarella F. Malignant ventricular arrhythmias in patients with a right bundle-branch block and persistent ST segment elevation in V1-V3: a probable arrhythmogenic cardiomyopathy of the right ventricle (editorial comment). G Ital Cardiol 1993;23:1219-22.
 10. Brugada P, Brugada J. Let us do not get confused, please! . . . G Ital Cardiol 1994;26:797-9.
 11. Fontaine G. Familial cardiomyopathy associated with right bundle branch block, ST segment elevation and sudden death (letter). J Am Coll Cardiol 1996;28:540.
 12. Miyanuma H, Sakurai M, Odaka H, et al. Two cases of idiopathic ventricular fibrillation with interesting electrocardiographic findings. Kokyo Junkan (Respir Circ) 1993;41:287-91.
 13. Brugada P, Geelen P, Brugada J. Further observations on the syndrome of right bundle branch block with ST segment elevation and sudden cardiac death. N Trends Arrhythmias 1993;9:333-4.
 14. Sumita S, Yoshida K, Ishikawa T, et al. ST level in healthy subjects with right bundle branch block in relation to Brugada syndrome (abstr). Eur J Cardiac Pacing Electrophysiol 1996;6:270:#1076.
 15. Shimada M, Miyazaki T, Miyoshi S, et al. Sustained monomorphic ventricular tachycardia in patient with Brugada syndrome. Jpn Circ J 1996;60:364-70.
 16. Viskin S, Belhassen B. Clinical problem-solving: when you live twice. N Engl J Med 1995;332:1221-5.
 17. Nademane K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation 1997;96:2595-600.
 18. Sumiyoshi M, Nakata Y, Hisaoka T, et al. A case of idiopathic ventricular fibrillation with incomplete right bundle branch block and persistent ST segment elevation. Jpn Heart J 1993;34:661-6.
 19. Nademane K. Sudden unexplained death syndrome in Southeast Asia. Am J Cardiol 1997;79:10-1.
 20. Brugada J, Brugada P. Further characterization of the syndrome of right bundle branch block, ST segment elevation, and sudden death. J Cardiovasc Electrophysiol 1997;8:325-31.
 21. Proclemer A, Faccin D, Feruglio GA, Nucifora R. Recurrent ventricular fibrillation, right bundle branch block, persistent ST segment elevation in V1-V3: a new arrhythmogenic syndrome? A case report. G Ital Cardiol 1993;23:1211-8.
 22. Corrado D, Nava A, Buja G, et al. Familial cardiomyopathy underlies syndrome of right bundle branch block, ST segment elevation and sudden death. J Am Coll Cardiol 1996;27:443-8.
 23. Aihara N, Ohe T, Shimomura K. Time-domain and frequency-domain analyses of the signal-averaged ECG in patients with sustained ventricular tachyarrhythmia and nonischemic heart diseases. J Electrocardiol 1994;27 Suppl:194-201.
 24. Aihara N, Ohe T, Kamakura S, et al. Clinical and electrophysiologic characteristics of idiopathic ventricular fibrillation. Shinzo 1990;22 Suppl 2:80-6.
 25. Scheinman MM. Is Brugada syndrome a distinct clinical entity? J Cardiovasc Electrophysiol 1997;8:332-6.
 26. Douard H, Saqardiluz J, Chevalier L, Labbe L, Broustet JP. Incidental discovery of Brugada syndrome in an asymptomatic seventy-year-old sportsman. Ann Cardiol Angeiol (Paris) 1996;45:577-80.
 27. Ohe T. Idiopathic ventricular fibrillation of the Brugada type—an atypical form of arrhythmogenic right ventricular cardiomyopathy (editorial). Intern Med 1996;35:595.
 28. Kobayashi T, Shintani U, Yamamoto T, et al. Familial occurrence of electrocardiographic abnormalities of the Brugada-type. Intern Med 1996;35:637-40.
 29. Kasanuki H, Ohnishi S, Ohtuka M, et al. Idiopathic ventricular fibrillation induced with vagal activity in patients without obvious heart disease. Circulation 1997;95:2277-85.
 30. Villacorta H, Faig Torres RA, Ribeiro Sim es de Castro I, Lambert H, de Araujo Conzales Alonso R. Sudden death in patient with right bundle branch block and persistent ST segment elevation. Arq Bras Cardiol 1996;66:229-31.
 31. Fontaine G, Piot O, Sohal P, et al. Right precordial leads and sudden death. Relation with arrhythmogenic right ventricular dysplasia. Arch Mal Coeur Vaiss 1996;89:1323-9.
 32. Brembilla-Perrot B, Beurrier D, Jacquemin L, et al. Incomplete bundle-branch block and ST-segment elevation: syndrome associated with sustained monomorphic ventricular tachycardia in patients with apparently normal heart. Clin Cardiol 1997;20:407-10.
 33. Morgera T, Sinagra GF, Viel E, Ricci C, Bussani R, Camerini F. The syndrome of right bundle branch block, persistent ST segment elevation and sudden cardiac death. Which is the histological substrate? Eur Heart J 1997;18:1190-1.
 34. Lorga Filho A, Primo J, Brugada J, Brugada P. Right bundle-branch block, the ST elevation of the ST segment in V1 to V3 and sudden death: the diagnostic and therapeutic approach. Rev Port Cardiol 1997;16:443-7.
 35. Nomura M, Mori H, Saitoh K, Ito S. Brugada syndrome. Ryoikibetsu Shokogun Shirizu 1996;12:181-3.
 36. Chinushi M, Aizawa Y, Ogawa Y, Shiba M, Takahashi K. Discrepant drug action of disopyramide on the ECG abnormalities and induction of ventricular arrhythmias in a patient with Brugada syndrome. J Electrocardiol 1997;30:133-6.
 37. Brugada P, Brugada J, Brugada R. Brugada syndrome: a structural cardiomyopathy or a functional electrical disease? In: Ravieli A, editor. Cardiac Arrhythmias 1997. Berlin: Springer-Verlag, 1997:323-32.
 38. Bjerregaard P, Gussak I, Antzelevitch C. The enigmatic ECG manifestation of Brugada syndrome. J Cardiovasc Electrophysiol 1998;9:109-11.
 39. Tohyou Y, Nakazawa K, Ozawa A, et al. A survey in the incidence of right bundle branch block with ST elevation among normal population. Jpn J Electrocardiol 1995;15:223-6.
 40. Nakazawa K, Matsumoto N, Takenobu H, Akagi T, Miyake H, Murayama M. Characteristics of idiopathic ventricular fibrillation: with reference to electrocardiographic morphology of RBBB and ST elevation. Heart (Jpn) 1994;26:26-31.
 41. Nakazawa K, Murayama M. The significance of autonomic nervous tone with idiopathic ventricular fibrillation in patients with right bundle branch block with ST elevation on ECG. Heart (Jpn) 1995;27:364-73.
 42. Veerakul G, Nademane K. Dynamic changes in the RBBB and ST-elevation in the right precordial leads observed in patients with idiopathic ventricular fibrillation: evidence of phase 2 repolarization abnormality (abstr). Circulation 1996;98 Suppl:I-626:#3669.
 43. Brugada J, Brugada P. Right bundle branch block, ST segment elevation and sudden cardiac death. Symptomatic, asymptomatic and intermittent forms (abstr). J Am Coll Cardiol 1995;93A:#719-6.
 44. Brugada J, Brugada P, Brugada R. Ajmaline unmasks right bundle branch block-like and ST segment elevation in V1-V3 in patients with idiopathic ventricular fibrillation (abstr). PACE Pacing Clin Electrophysiol 1996;19 (Part II):599:#134.
 45. Viskin S, Lesh MD, Eldar M, et al. Mode of onset of malignant ventricular arrhythmias in idiopathic ventricular fibrillation. J Cardiovasc Electrophysiol 1997;8:1115-20.
 46. Namiki T, Ogura T, Kuwabara Y, et al. Five-year mortality and clinical characteristics of adult subjects with right bundle branch block and ST elevation. Circulation 1995;92 Suppl:1-334.
 47. Atarashi H, Ogawa S, Harumi K, et al. Characteristics of patients with right bundle branch block and ST-segment elevation in right precordial leads. Am J Cardiol 1996;78:581-3.
 48. Brugada J, Brugada P. What to do in patients with no structural heart disease and sudden arrhythmic death? Am J Cardiol 1996;78 Suppl 5A:69-75.
 49. Bjerregaard P, Gussak I, Kotar SL, et al. Recurrent syncope in a patient with prominent T-wave. Am Heart J 1994;127:1426-30.
 50. 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;27:1061-70.
 51. Nakazawa K, Matsumoto N, Akagi T, et al. Analysis of the role of the autonomic nervous system in near sudden death cases due to idiopathic ventricular fibrillation. Ther Res 1994;15:52-6.

52. Gussak I. The significance of the electrocardiographic J wave: from hypothermia to Brugada syndrome. *Med World* 1997;2:237-9.
53. Manios E, Fenelon G, Malacky T, Fo AL, Brugada P. Life threatening ventricular arrhythmias in patients with minimal or no structural heart disease: experience with implantable cardioverter defibrillator. [Internet] <http://www.heartweb.org/heartweb/0197/icd0003.htm> [1997;2:U 24-U 30].
54. Brugada P, Brugada R, Brugada J. Brugada syndrome. [Internet] <http://www.netvision.be/brugada> [1997, Nov 23].
55. Chen Q, Kirsch GE, Zhang D, et al. Genetic basis and molecular mechanisms for idiopathic ventricular fibrillation. *Nature* 1998;392:293-45.
56. Morace G, Padeletti L, Porciani MC, Fantini F. Effect of isoproterenol on the early repolarization syndrome. *Am Heart J* 1979;97:343-7.
57. Harumi K, Burgess MJ, Abdelskov JA. A theoretical model of the T-wave. *Circulation* 1966;34:657-68.
58. Spach MS, Barr RC. Origin of epicardial ST-T wave potentials in the intact dog. *Circ Res* 1976;39:475-87.
59. Yan GX, Antzelevitch C. Cellular basis for idiopathic VT/VF syndrome (abstr). *Circulation* 1996;94:I-625.
60. Yan G-X, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372-9.
61. Antzelevitch C, Nesterenko VV, Yan GX. Ionic processes underlying the action potential. In: Liebman J, editor. *Electrocardiology '96: From the Cell to the Body Surface*. Singapore: World Scientific Publishing Co. Pte. Ltd., 1996:219-29.
62. Gussak I, Bjerregaard P, Greenwalt T, Chaitman BR. Electrophysiological peculiarities of the ECG J wave: from hypothermia to Brugada syndrome. In: Liebman J, editor. *Electrocardiology '96: From the Cell to the Body Surface*. Singapore: World Scientific Publishing Co. Pte. Ltd., 1996:261-54.
63. Osher HL, Wolff L. Electrocardiographic pattern simulating acute myocardial injury. *Am J Med Sci* 1953;226:541-5.
64. Edeiken J. Elevation of RS-T segment, apparent or real in right precordial leads as probably normal variant. *Am Heart J* 1954;48:331-9.
65. Roesler H. An electrocardiographic study of high take-off of the R(R')-T segment in right precordial leads. Altered repolarization. *Am J Cardiol* 1960;6:920-8.
66. Marriott HJL. *Practical Electrocardiography*. 7th ed. Baltimore: Williams & Williams, 1988.
67. Calo AA. The triad secondary R wave, RS-T segment elevation and T waves inversion in right precordial leads: a normal electrocardiographic variant. *G Ital Cardiol* 1975;5:955-60.
68. Parisi AF, Beckmann CH, Lancaster MC. The spectrum of ST elevation in the electrocardiograms of healthy adult men. *J Electrocardiol* 1971;4:137-44.
69. Tate RB, Manfreda J, Cuddy TE. Electrocardiographic abnormalities and the risk of sudden death: the Manitoba follow-up study, 1948-1993 (abstr). *Circulation* 1997;96 Suppl:#2272.
70. Matsuo K, Shimizu W, Kurita T, et al. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:508-12.
71. Wasserburger RH, Alt WJ, Lloyd CJ. The normal RS-T segment elevation variant. *Am J Cardiol* 1961;8:184-92.
72. Lehman KG, Shandling AH, Yusi AU, Froulicher VF. Altered ventricular repolarization in central sympathetic dysfunction associated with spinal cord injury. *Am J Cardiol* 1989;63:1498-504.
73. Eidelberg EE. Cardiovascular response to experimental spinal cord compression. *J Neurosurg* 1973;38:326-31.
74. Evans DE, Kobrine AI, Rizzoli HV. Cardiac arrhythmias accompanying acute compression of the spinal cord. *J Neurosurg* 1980;52:52-9.
75. Munger RG. *Sudden Death in Sleep Among Asian Adults*. PhD dissertation, University of Washington. Ann Arbor: University Microfilms International, 1987.
76. Baron RC, Thacker SB, Corelkin L, Vernon AA, Taylor WR, Choi K. Sudden death among Southeast Asian refugees. *JAMA* 1983;250:2947-51.
77. Gotoh K. A histopathological study on the conduction system of the so-called Pokkuri disease (sudden unexpected cardiac death of unknown origin in Japan). *Jpn Circ J* 1976;40:753-68.
78. Severini GM, Krajcinovic M, Pinamonti B, et al. A new locus for arrhythmogenic right ventricular dysplasia on long arm chromosome 14. *Genomics* 1996;31:193-200.
79. Rampazzo A, Nava A, Miorin M, et al. ARVD4, a new locus for arrhythmogenic right ventricular cardiomyopathy, maps to chromosome 2 long arm. *Genomics* 1997;15:45:259-63.
80. Ausma J, Wijffels M, Vaney G, et al. Dedifferentiation of atrial cardiomyocytes as a result of chronic atrial fibrillation. *Am J Pathol* 1997;151:985-97.
81. Antzelevitch C. The Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:513-6.
82. 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;97:457-60.
83. Gussak I. I_{to} blockade by 4-aminopyridine: a new approach to stabilize the electrical activity of the heart. In: Anand R, Smith P, Warne P, editors. *Emerging Therapeutic Targets*. London: Ashley Publications Ltd, 1997:133-5.
84. Suzuki J, Tsubone H, Sugano S. Characteristics of ventricular activation and recovery patterns in the rat. *J Vet Med Sci* 1992;54:711-6.
85. Barry DM, Nerbonne JM. Myocardial channels: electrophysiological and molecular diversity. *Annu Rev Physiol* 1996;58:363-94.
86. Langer GA, Brady AJ, Tan ST, Serena SD. Correlation of the glucoside response, the force staircase, and the action potential configuration in the neonatal rat heart. *Circ Res* 1975;36:744-52.
87. Couch JR, West TC, Hoff HE. Development of the action potential of the prenatal rat heart. *Circ Res* 1969;24:19-31.
88. Bernard C, Gargouil YM. Acquisitions successives, chez l'embryon de rat, des perméabilités de la membrane myocardique. *CR Acad Sci (Paris)* 1970;270:1495-8.
89. Litovsky SH, Antzelevitch C. Transient outward current prominent in canine ventricular epicardium but not endocardium. *Circ Res* 1988;62:116-26.
90. Antzelevitch C, Sicouri S, Litovsky SH, et al. Heterogeneity within the ventricular wall. *Circ Res* 1991;69:1427-49.
91. Antzelevitch C, Litovsky SH, Lukas A. Epicardium versus endocardium: electrophysiology and pharmacology. In: Zipes D, Jalife J, editors. *Cardiac Electrophysiology, From Cell to Bedside*. New York: WB Saunders, 1990:386-95.
92. 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.
93. Lukas A, Antzelevitch C. The contribution of K⁺ currents to electrical heterogeneity across the canine ventricular wall under normal and ischemic conditions. In: Dhalla NS, Pierce GN, Panagia V, editors. *Pathophysiology of Heart Failure*. Boston: Academic Publishers, 1996:440-56.
94. Sun ZQ, Antzelevitch C. Ionic basis for the electrocardiographic J wave (abstr). *Circulation* 1996;94:I-669.
95. Di Diego JM, Antzelevitch C. High [Ca²⁺]-induced electrical heterogeneity and extrasystolic activity in isolated canine ventricular epicardium: phase 2 reentry. *Circulation* 1994;89:1839-50.
96. Di Diego JM, Antzelevitch C. Pinacidil-induced electrical heterogeneity and extrasystolic activity in canine ventricular tissues: does activation of ATP-regulated potassium current promote phase 2 reentry? *Circulation* 1993;88:1177-89.
97. Krishnan SC, Antzelevitch C. Flecainide-induced arrhythmia in canine ventricular epicardium: phase 2 Reentry? *Circulation* 1993;87:562-72.
98. Lukas A, Antzelevitch C. Differences in the electrophysiological response of canine ventricular epicardium and endocardium to ischemia: role of the transient outward current. *Circulation* 1993;88:2903-15.
99. Litovsky SH, Antzelevitch C. Rate dependence of action potential duration and refractoriness in canine ventricular endocardium differs from that of epicardium: the role of the transient outward current. *J Am Coll Cardiol* 1989;14:1053-66.
100. Antzelevitch C, Sicouri S, Lukas A, et al. Clinical implications of electrical heterogeneity in the heart: the electrophysiology and pharmacology of epicardial, M and endocardial cells. In: Podrid PJ, Kowey PR, editors. *Cardiac Arrhythmia: Mechanism, Diagnosis and Management*. Baltimore, MD: William & Wilkins, 1995:88-107.
101. 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;67:615-27.
102. Krishnan SC, Antzelevitch C. Sodium channel blockade produces opposite

- electrophysiologic effects in canine ventricular epicardium and endocardium. *Circ Res* 1991;69:277–91.
103. Di Diego JM, Sun ZQ, Antzelevitch C. I_{to} and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 1996;27:H548–61.
 104. Kilborn MJ, Fedida D. A study of the developmental changes in outward currents of the rat ventricular myocytes. *J Physiol* 1990;430:37–60.
 105. Pertsov AM, Davidenko JM, Salomonsz R, Baxter WT, Jalife J. Spiral waves of excitation underlie reentrant activity in isolated cardiac muscle. *Circ Res* 1993;72:631–50.
 106. Wettwer E, Amos GJ, Posival H, Ravens U. Transient outward current in human ventricular myocytes of subepicardial and subendocardial origin. *Circ Res* 1994;75:473–82.
 107. Nabauer M, Beuckelmann DJ, Uberfuhr P, Steinbeck G. Regional differences in current density and rate-dependent properties of the transient outward current in subepicardial and subendocardial myocytes of human left ventricle. *Circulation* 1996;93:168–77.
 108. Rowlands DJ. *Clinical Electrocardiography*. Philadelphia: J.B. Lippincott Company, 1991.
 109. Goldberger AL. *Myocardial Infarction: Electrocardiographic Differential Diagnosis*. 4th ed. St. Louis, MO: Mosby-Year Book Inc., 1991.
 110. Kobayashi H, Tsuchihashi K, Hashimoto A, et al. Exercise-induced STV1 elevation: a sign of right ventricular dysfunction in recent inferior myocardial infarction. *Can J Cardiol* 1994;10:355–62.
 111. Spodick DH, Greene TO, Saperia G. Acute myocarditis masquerading as acute myocardial infarction. *Circulation* 1995;91:1886–7.
 112. Andersen HR, Falk E, Nielsen D. Right ventricular infarction. The evolution of ST-segment elevation and Q wave in right chest leads. *J Electrocardiol* 1989;22:181–6.
 113. Myers GB. Other QRS-T pattern that may be mistaken for myocardial infarction. IV. Alterations in blood potassium: myocardial ischemia; subepicardial myocarditis; distortion associated with arrhythmias. *Circulation* 1950;2:75–93.
 114. Sreeram N, Cheriex EC, Smeets JL, Gorgels AP, Wellens HJ. Value of the 12-lead electrocardiogram at hospital admission in the diagnosis of pulmonary embolism. *Am J Cardiol* 1994;73:298–303.
 115. Abbott JA, Cheitlin MD. The nonspecific camel-hump sign. *JAMA* 1976; 235:413–4.
 116. Hersch C. Electrocardiographic changes in head injuries. *Circulation* 1961;23:853–60.
 117. Bolognesi R, Tsialtas D, Vasini P, Contu M, Manca C. Abnormal ventricular repolarization mimicking myocardial infarction after heterocyclic antidepressant overdose. *Am J Cardiol* 1997;79:242–5.
 118. Perloff JK, Henze E, Schelbert HR. Alterations in regional myocardial metabolism, perfusion, and wall motion in Duchenne muscular dystrophy studied by radionuclide imaging. *Circulation* 1984;69:33–42.
 119. Grauer K. Bizarre ECG in a young adult. *Intern Med* 1997;19:56.
 120. Hundley JM, Ashburn LL, Sebrell WH. The electrocardiogram in chronic thiamine deficiency in rats. *Am J Physiol* 1945;144:404–14.
 121. Douglas PS, Carmichael KA, Palevsky PM. Extreme hypercalcemia and electrocardiographic changes. *Am J Cardiol* 1984;54:674–5.
 122. Levine HD, Wanzer SH, Merrill JP. Dialyzable currents of injury in potassium intoxication resembling acute myocardial infarction or pericarditis. *Circulation* 1956;13:29–36.
 123. Farre J, Tarmn N, Moro C. What do you think of this ECG? [Internet] 8th Madrid Arrhythmia Meeting. <http://www.mam.arrakis.es> [1997, Nov 2nd].
 124. Lipski J, Stimmel B, Donoso E. The effect of heroin and multiple drugs abuse on the electrocardiogram. *Am Heart J* 1973;86:663–8.
 125. Lanari A, Chait LO, Capurro C. Electrocardiographic effects of potassium. I. Perfusion through the coronary bed. *Am Heart J* 1964;67:357–63.
 126. Wolferth CC, Bellet S, Livezey MM, Murphy FD. Negative displacement of RS-T segment in the electrocardiogram and its relationship to positive displacement: an experimental study. *Am Heart J* 1945;29:220–45.
 127. Hellerstein HK, Katz LN. The electrical effects of injury at various myocardial locations. *Am Heart J* 1948;36:184–220.
 128. Wiggers CJ. Monophasic and deformed ventricular complexes resulting from surface application of potassium salts. *Am Heart J* 1929;5:346–50.
 129. Geft IL, Shah PK, Rodrigues L, et al. ST elevations in leads V_1 to V_3 may be caused by right artery occlusion and acute right ventricular infarction. *Am J Cardiol* 1984;53:991–6.