The Editors commissioned this MiniReview to celebrate the 10th anniversary of the description of the Brugada syndrome and to highlight the First Virtual Symposium About the Brugada Syndrome (http://www.brugada-symposium.org/).

—Eduardo Marbán, for the Editors

Brugada Syndrome
A Decade of Progress


Abstract—The Brugada syndrome has gained wide recognition throughout the world and today is believed to be responsible for 4% to 12% of all sudden deaths and ≈20% of deaths in patients with structurally normal hearts. The incidence of the disease is on the order of 5 per 10,000 inhabitants and, apart from accidents, is the leading cause of death of men under the age of 50 in regions of the world where the inherited syndrome is endemic. This minireview briefly summarizes the progress made over the past decade in our understanding of the clinical, genetic, cellular, ionic, and molecular aspects of this disease. (Circ Res. 2002;91:1114-1118.)

Key Words ventricular tachycardia • ventricular fibrillation • arrhythmia • sudden death

This year marks the 10th anniversary of the initial description by Pedro and Josep Brugada of an intriguing new clinical entity characterized by an ST-segment elevation in the right precordial ECG leads and a high incidence of sudden death in individuals with structurally normal hearts.1 The purpose of this minireview is to briefly summarize the progress made over the past decade in our understanding of the clinical, genetic, cellular, ionic, and molecular aspects of this disease.

In 1986, a 3-year-old Polish boy was referred to the Brugada brothers after multiple episodes of syncope. His ECG showed an ST-segment elevation in leads V1 to V3. His sister displayed a similar clinical and electrocardiographic profile and died at 2 years of age. In the succeeding years, six additional cases came to their attention, and in 1992 they reported these eight cases as the basis for a new and distinct clinical entity.1

In 1996, Yan and Antzelevitch2 highlighted the importance of the ST-segment elevation and apparent right bundle-branch block (RBBB) described by Brugada and Brugada as the basis for a substrate capable of giving rise to malignant arrhythmias, naming it the Brugada syndrome. Kobayashi et al3 and Miyazaki et al4 followed suit that same year.

The electrocardiographic pattern of ST-segment elevation and inversion of the T wave in the right precordial leads, with and without RBBB, was described as early as 1953.5 This ECG phenomenon was largely ignored until Martini et al6 and Aihara et al7 brought attention to a possible link between this ventricular repolarization abnormality and sudden death. Martini et al6 maintained that structural or morphological defects contribute importantly to arrhythmogenesis in patients with the Brugada syndrome, whereas Brugada et al8 excluded this from the diagnosis, stressing the functional basis for the syndrome. Corrado et al9 subsequently described a subpopulation of arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) patients displaying features of the Brugada syndrome, including ST-segment elevation in V1 to V3 and polymorphic ventricular tachycardia (VT), suggesting that a subgroup of patients with ARVC can display a Brugada-like phenotype during the relatively early stages of the disease.

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It is noteworthy that arrhythmogenic RV dysplasia/ARVC and Brugada syndromes are quite distinct from the genetic standpoint; the Brugada syndrome has thus far been linked only to mutations in SCN5A, the gene encoding for the α subunit of the sodium channel, whereas arrhythmogenic RV dysplasia/ARVC has been linked to seven different chromosomal sites and three putative genes.9 A recent report by Remme et al10 indicates that the vast majority of Brugada syndrome patients traced in their study showed no evidence of structural disease.
The most typical electrocardiographic features of the Brugada syndrome are illustrated in Figure 1. They include the following: (1) an accentuated J wave appearing principally in the right precordial leads (V1 to V3) and taking the form of an ST-segment elevation, often followed by a negative T wave, very closely coupled extrasystoles, and a rapid polymorphic VT. Modified with permission from Vanzini P, Brugada J. Spontaneous recurrent ventricular fibrillation in a patient with a structurally normal heart. *Pacing Clin Electrophysiol.* 2000;23:266–267,© by permission of Blackwell Publishing, Futura Division ©2000.

Figure 1. Typical electrocardiographic characteristics of Brugada syndrome include an accentuated J wave appearing principally in the right precordial leads (V1 to V3) and taking the form of an ST-segment elevation, often followed by a negative T wave, very closely coupled extrasystoles, and a rapid polymorphic VT. Modified with permission from Vanzini P, Brugada J. Spontaneous recurrent ventricular fibrillation in a patient with a structurally normal heart. *Pacing Clin Electrophysiol.* 2000;23:266–267,© by permission of Blackwell Publishing, Futura Division ©2000.

In addition to sodium channel blockers and febrile state, vagotonic agents, α-adrenergic agonists, β-adrenergic blockers, tricyclic antidepressants, first-generation antihistaminics (dihydramine), and cocaine toxicity have been shown to unmask the Brugada syndrome or to accentuate ST-segment elevation in patients with the syndrome.\(^4,11,12,18–23\) Like the long-QT syndrome, the Brugada syndrome has both congenital and acquired forms; the latter is just beginning to be appreciated.

Identification of patients at risk for sudden death has been a primary goal of research teams worldwide.\(^{24,25}\) Patients initially presenting with aborted sudden death are at highest risk for a recurrence (69%), whereas those presenting with syncope and a spontaneously appearing Brugada ECG sign have a recurrence rate of 19%. A study by Brugada et al\(^{24}\) found an 8% occurrence of cardiac events in initially asymptomatic patients. Asymptomatic patients at highest risk were those who displayed the Brugada sign spontaneously; those in whom ST-segment elevation appeared only after provocation with sodium channel blockers appeared to be at minimal or no risk for arrhythmic events. The Brugada et al\(^{24}\) study also suggested that among asymptomatic patients, inducibility of VT during electrophysiological study may be prognostic of risk. Studies by Priori et al,\(^{25}\) Kanda et al,\(^{26}\) and Eckardt et al\(^{27}\) failed to find an association between inducibility and recurrence of VT/VF among patients with Brugada syndrome (both asymptomatic and symptomatic).

**Genetic Aspects**

The hereditary nature of the syndrome, characterized by an autosomal dominant mode of transmission, is well established. Chen et al\(^{28}\) were the first to link the syndrome to the α subunit of the cardiac sodium channel gene, SCN5A, in 1998. Several dozen SCN5A mutations have been linked to the syndrome over the past 4 years (for references see Priori et al,\(^{25}\) Antzelevitch,\(^{29}\) and Balser\(^{30}\)) and shown to result in either (1) failure of the sodium channel to express; (2) reduced current due to a shift in the voltage and time dependence of sodium channel current (I\(_{Na}\)) activation, inactivation, or reactivation; or (3) reduced contribution of I\(_{Na}\) during the early phases of the action potential resulting from accelerated inactivation of the sodium channel. The premature inactivation of the channel was observed at physiological temperatures, but not at room temperature.\(^{13}\) Moreover, because this characteristic of the mutant channel was exaggerated at temperatures above the physiological range, we suggested that the syndrome may be unmasked, and that patients with the Brugada syndrome may be at an increased risk, during a febrile state.\(^{31}\) A number of Brugada syndrome patients displaying fever-induced polymorphic VT have been identified since this report (see Antzelevitch and Brugada\(^{32}\) for references). Another locus on chromosome 3, close to but distinct from SCN5A, was recently linked to the syndrome.\(^{33}\) Only 20% of Brugada syndrome cases have been linked to SCN5A mutations. A long list of candidate genes encoding for a variety of ion channels and other proteins have been proposed.\(^{20,34}\)

**Cellular and Ionic Mechanisms**

The cellular mechanisms believed to underlie the Brugada syndrome evolved on a parallel but separate track from that of the clinical syndrome. The concepts of all-or-none repolar-
ization of the ventricular epicardial action potential and of phase 2 reentry secondary to sodium channel block or ischemia were developed in the early 1990s.\textsuperscript{35–37} ST-segment elevation in the Brugada syndrome is thought to be due to a rebalancing of the currents active at the end of phase 1, leading to an accentuation of the action potential notch in RV epicardium (for published reports, see Reference 29).

A transient outward current (I\textsubscript{to})--mediated spike and dome morphology, or notch, in ventricular epicardium, but not endocardium, creates a transmural voltage gradient responsible for the inscription of the electrocardiographic J wave in larger mammals and in humans.\textsuperscript{2} Under normal conditions, the ST segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the RV notch under pathophysiological conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave, causing an apparent ST-segment elevation (see Figure I of Antzelevitch\textsuperscript{29}). The repolarization waves take on a saddleback or coved appearance depending on the timing of repolarization of epicardium relative to endocardium. A delay in epicardial activation may also contribute to inversion of the T wave. The down-sloping ST-segment elevation, or accentuated J wave, observed in the experimental wedge models often appears as an R', suggesting that the appearance of a RBBB morphology in patients with Brugada syndrome may be due at least in part to early repolarization of RV epicardium rather than to marked impulse delay or conduction block in the right bundle. Indeed, a rigorous application of RBBB criteria reveals that a large majority of RBBB-like morphologies encountered in cases of Brugada syndrome do not fit the criteria for RBBB.\textsuperscript{38} The arrhythmogenic substrate is believed to arise when a further shift in the balance of current leads to loss of the action potential dome at some epicardial sites but not at others. Loss of the action potential dome in epicardium but not in 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. Loss of the action potential dome in epicardium is usually heterogeneous, leading to the development of epicardial dispersion of repolarization. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local 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.\textsuperscript{39,40} The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in epicardium, the QRS complex largely comprises a Q wave, which serves to accentuate the negative deflection of the inverted T wave, giving the ECG a more symmetrical appearance. This morphology is often observed in the clinic before the onset of polymorphic VT. Support for these hypotheses derives from experiments involving the arterially perfused RV wedge preparation\textsuperscript{49} and from recent studies by Kurita et al\textsuperscript{41} in which monophasic action potential electrodes were positioned on the epicardial and endocardial surfaces of the RV outflow tract in patients with the Brugada syndrome (Figure 2).

**Therapy**

Despite substantial progress in the identification and characterization of the Brugada syndrome over the past decade, relatively little progress has been made in the approach to therapy. Implantation of a cardioverter-defibrillator is the only established effective treatment for the disease.\textsuperscript{42,43} This, however, is not an adequate solution for infants and young children or for adults residing in regions of the world where an implantable cardioverter-defibrillator is not an option because of economic constraints.

The pharmacological approach to therapy is focused on a rebalancing of currents active in the early phases of the RV epicardial action potential so as to reduce the magnitude of the action potential notch and/or restore the action potential dome. Experimental studies suggest that agents that block the transient outward current (I\textsubscript{to}), such as quinidine or tedisamil, or agents that boost the calcium current, such as isoproterenol, may be useful.\textsuperscript{29,40} Both have been shown to be effective in normalizing ST-segment elevation in patients with the Brugada syndrome and in controlling electrical storms, particularly in children.\textsuperscript{44–46} but other than the study by Belhassen and colleagues\textsuperscript{47,48} involving quinidine, none have demonstrated long-term efficacy in the prevention of sudden death. A recent addition to the pharmacological armamentarium is the phosphodiesterase III inhibitor cilostazol,\textsuperscript{49} which normalizes the ST segment most likely by reducing I\textsubscript{to}, secondary to an increase in heart rate as well as by augmenting calcium channel current (I\textsubscript{Ca}).

**Epilogue**

In the span of 10 years, the Brugada syndrome has gained wide recognition worldwide. The syndrome occupies a prominent portion of time devoted to cardiac arrhythmias at national and international meetings, and publications on the subject continue to appear at a brisk rate. A virtual symposium on the subject,
held exclusively over the Internet, took place November 1–30, 2002 (http://www.brugada-symposium.org/).

Acknowledgments
This work was supported by grants from the NIH (HL 47678 and HL 66169); the American Heart Association, New York State Affiliate and National Center; Mapfre Foundation; Ramon Brugada Sr. Foundation; Doris Duke Foundation; and Masons of New York State and Florida.

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Circ Res. 2002;91:1114-1118
doi: 10.1161/01.RES.0000046046.53721.90
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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