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# Cellular and Ionic Mechanisms Underlying the Brugada Syndrome

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This year marks the tenth 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 past decade has witnessed an exponential rise in the number of reported cases and a dramatic proliferation of papers serving to define the clinical, genetic, cellular, ionic and molecular aspects of this disease. The purpose of this brief review is to summarize the cellular and ionic mechanisms thought to underlie the Brugada syndrome.

Sudden cardiac death occurring in individuals with structurally normal hearts accounts for an estimated 3 to 9% of out-of-hospital cases of ventricular fibrillation (VF).[2] Many of these cases are thought to be due to a primary electrical disease. Prominent among these is the Brugada syndrome, a syndrome characterized by an ST segment elevation in right precordial leads ($V_1$ to $V_3$) unrelated to ischemia, electrolyte disturbances or obvious structural heart disease, displaying a RBBB QRS morphology. This electrocardiographic signature was reported as early 1953, but first described as a distinct clinical entity associated with a high risk of sudden cardiac death by Pedro and Josep Brugada in 1992.[1] (see[3-6] for review). These characteristics of the Brugada Syndrome are similar, in many cases nearly identical, to those reported by Nademanee and co-workers[7] for patients with Sudden Unexpected Death Syndrome (SUDS). Tragically, sudden death from Brugada syndrome is often the first symptom of the disease.

The Brugada phenotype is much more prevalent in males (8:1 ratio of males:females) of Southeast Asian origin. The remarkable gender difference appears to be due to a more prominent $I_{to}$ in males vs. females.(Di Diego et al, Circulation, in press) The syndrome is familial, displaying an autosomal dominant mode of transmission with incomplete penetrance. Arrhythmic events are observed at an average age of approximately 40, but have been reported in infants over a very wide range of ages, from infants to those in their late 70's (1 to 77 years). Although structural heart disease must be ruled out by echocardiography and/or magnetic resonance imaging in order to make the diagnosis of Brugada syndrome, postmortem examination has revealed some fatty infiltration into the deep subepicardium in isolated cases. It is noteworthy that a typical ECG pattern and a high risk of sudden arrhythmic death have been reported for a segment of the patient population with structural heart disease in the setting of arrhythmogenic right ventricular cardiomyopathy (ARVC) endemic to the Veneto region of Italy [8]. However, the clinical presentation in the vast majority of ARVC patients bears little resemblance to that of the Brugada syndrome. Moreover, ARVC does not appear to be linked to the same chromosomal loci as the Brugada syndrome.

The electrocardiographic signature of the Brugada syndrome is dynamic and often concealed, but can be unmasked by potent sodium channel blockers such as flecainide, ajmaline, procainamide and psilicainide.[9] Although intravenous administration of these agents is most effective in unmasking the syndrome, oral formulations of flecainide have been reported to be effective as well. The specificity of these effects of sodium channel blockers to uncover the syndrome and the prognostic significance of this finding remain to be fully elucidated.

The cellular basis for the Brugada syndrome is thought to be due to an outward shift in the ionic current active during phase 1 of the right ventricular epicardial action potential.[3;10] A rebalancing of the currents contributing to the early phases of the action potential can accentuate the action potential notch or lead to all-or-none repolarization at the end of phase 1, causing loss of the epicardial action potential dome and marked abbreviation of the action potential at that site. A variety of pathophysiologic conditions (e.g., ischemia, metabolic inhibition, hypothermia, pressure) and some pharmacologic interventions are known to effect these changes in cells in which $I_{to}$ is prominent. Under these pathophysiologic conditions or in response to agents that reduce $I_{Na}$ or $I_{Ca}$ or agents that activate $I_{K\text{-}ATP}$ or augment $I_{Kr}$, $I_{Cl(Ca)}$ or $I_{to}$, canine ventricular epicardial cells exhibit an accentuation of the spike and dome morphology of the action potential, resulting in a delay in the development of the dome, secondary to widening of the action potential notch. A further shift in the balance of current leads to loss of the action potential dome and marked abbreviation of the epicardial response. The dome fails to develop because the outward currents flowing at the end of phase 1 overwhelm the inward currents that normally give rise to the secondary upstroke and action potential plateau.

Genetic mutations that affect these same currents are capable of producing the Brugada syndrome. The only gene thus far linked to the syndrome is the α subunit of the cardiac sodium channel gene, SCN5A,[11-16] the same gene implicated in the LQT3 form of the long QT syndrome. In fact, Bezzina and co-workers[16] recently reported a mutation in SCN5A (1795InsD) capable of producing both the Brugada and LQT3 phenotypes. Three types of mutations in SCN5A have been uncovered thus far, and shown to result in: 1) failure of the sodium channel to express; 2) reduced current due to a shift in the voltage- and time-dependence of $I_{Na}$ activation, inactivation or reactivation; and 3) reduced contribution of $I_{Na}$ during the early phases of the action potential due to accelerated inactivation of the sodium channel. Insertion of two nucleotides (AA) at the 5' end, deletion of a single nucleotide (A) at codon 1397 leading to an in-frame stop codon [11] and some missense mutations (R1432G) [14] result in disruption of protein formation and failure of channel expression. Other insertion mutations (1795InsD) cause a positive shift of activation and negative shift of inactivation curves resulting in a reduction of $I_{Na}$.[16] In the case of the T1620M missense mutation, inactivation of $I_{Na}$ is accelerated such that $I_{to}$ is left unopposed during phase 1 of the action potential, resulting in a strong predominance of the outward repolarizing current at the end of phase 1, thus providing the substrate for the Brugada syndrome. [13] This change in the function of the sodium channel is observed at physiological temperatures, but not at room temperature, typically used in studies of function involving heterologous expression systems. It is interesting that this characteristic of the mutant channel is exaggerated at temperatures above the physiological range, suggesting the possibility that patients with the Brugada syndrome may be at more risk during a febrile state. [13] A number of Brugada patients displaying fever-induced polymorphic VT have been identified since the publication of this report. (see [17] for references). Accelerated inactivation of the channel has also been demonstrated for the L567Q mutation in SCN5A linked to the Brugada syndrome [18]

When combined with the R1232W missense mutation in SCN5A, T1620M was found to cause failure of the channel to express secondary to a trafficking problem. [19;20] In another series of studies, T1620M and a number of other mutations in SCN5A linked to the Brugada syndrome, were found to cause the channel to enter a mid-inactivation state form which it recovers more slowly. (see [21] for references). As a consequence, $I_{Na}$ is less avaialbel at accelerated rates. It is not clear how this finding fits into our understanding of the Brugada syndrome, since arrhythmogenesis in the the Brguada syndrome is usually bradycardia- and not tachycardia-dependent.

In addition to SCN5A, gene mutations that alter the intensity or kinetics of either $I_{to}$, $I_{Kr}$, $I_{Ks}$, $I_{K\text{-}ATP}$, $I_{Ca}$ or $I_{Cl(Ca)}$ so as to increase the activity of the outward currents and/or diminish that of the inward currents are candidates for the Brugada syndrome. Other candidate genes include those encoding for autonomic receptors which directly modulate ion current density and/or alter the expression of channels in the membrane (e.g., sympathetic control of $I_{to}$).

Earlier this year, another locus on chromosome 3, close to but distinct from SCN5A, was linked to the syndrome.[22] The Brugada syndrome in this single large pedigree was associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis.

The cellular mechanisms responsible for the development of the Brugada syndrome are also coming into better focus. The electrocardiographic manifestations of the syndrome have been attributed to one of two basic mechanisms: 1) premature repolarization of the right ventricular epicardial action potential secondary to loss of the action potential dome and 2) some degree of conduction delay in the right ventricular epicardial free wall in the region of the outflow tract (RVOT).

A schematic representation of the cellular changes believed to underlie the Brugada phenotype in hypothesis 2 is shown in Figure 1 [5;6]. In larger mammals, the presence of an $I_{to}$-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 [23]. Under normal conditions, the J wave is relatively small, in large part reflecting the left ventricular action potential notch, since that of right ventricular epicardium is usually buried in the QRS complex. The ST segment is isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau (Figure 1A). Accentuation of the right ventricular notch under pathophysiologic conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave or to J point elevation. This would be expected to give rise to a saddleback configuration of the repolarization waves (Figure 1B). The development of a prominent J wave under these conditions is indistinguishable from an ST segment elevation. Under these conditions, the T wave remains positive because epicardial repolarization precedes repolarization of the cells in the M and endocardial regions. Further accentuation of the notch may be accompanied by a prolongation of the epicardial action potential such that the direction of repolarization across the right ventricular 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 1C), typically observed in the

ECG of Brugada patients. 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 Brugada patients may be due to at least in part to early repolarization of right ventricular (RV) epicardium, rather to impulse 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 [24]. Moreover, attempts by Miyazaki and coworkers to record delayed activation of the RV in Brugada patients met with failure [25]. Although the typical Brugada morphology is present in Figures 1B and C, the substrate for reentry is not. We believe that the arrhythmogenic substrate arises 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 1D). 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. Loss of the action potential dome in epicardium is usually heterogeneous, leading to the development of epicardial dispersion of repolarization (Figure 1D). Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2 reentry mechanism, leading to the development of 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 (Figures 1E)[10;26]. The phase 2 reentrant beat fuses with the negative T wave of the basic response. Because the extrasystole originates in epicardium, the QRS complex is largely comprised of 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 preceding the onset of polymorphic VT. Support for these hypotheses derives from experiments involving the arterially perfused right ventricular wedge preparation[10] and from a recent study by Kurita and coworkers in which MAP electrodes where positioned on the epicardial and endocardial surfaces of the RVOT in a patient with the Brugada syndrome.[27].

Phase 2 reentry is observed in canine epicardium exposed to: 1) $K^+$ channel openers; 2) sodium channel blockers; 3) increased $[Ca^{2+}]_o$; 4) metabolic inhibition; 5) simulated ischemia and 6) local pressure applied to RV epicardium (see [28] for references). Phase 2 reentry has been shown to trigger circus movement reentry in isolated sheets of right ventricular epicardium[26] as well as in the intact wall of the canine right ventricle. [23;29] The arrhythmia commonly takes the form of a polymorphic VT, resembling a rapid Torsade de Pointes, often indistinguishable from VF. In other cases, the experimental model displays monomorphic VT. Both are observed in patients with the Brugada syndrome, although the polymorphic form is much more common.

Local pressure alone applied to a discrete RV site can also produce loss of the action potential, ST segment elevation, phase 2 reentry and VT/VF in the arterially-perfused RV wedge preparation.[10] This mechanism may be responsible for the Brugada-like syndrome caused by a mediastinal tumour compressing the right ventricular outflow tract.[30]

The mechanism proposed to underlie the Brugada syndrome is one that provides the substrate for the development of circus movement reentry in the form of epicardial and transmural dispersion of repolarization, as well as the trigger for VT/VF in the form of a phase 2 reentrant extrasystole.

The experimental findings suggest a depressed right ventricular epicardial action potential dome as the basis for the accentuated J wave or ST segment elevation and to phase 2 reentry as a trigger for episodes of circus movement reentry responsible for VT and VF in Brugada patients. There are a number of similarities between the conditions that give rise to ST segment elevation and phase 2 reentry in the experimental models and those that attend the appearance of the Brugada syndrome. Accentuation of the action potential notch or loss of the action potential dome in epicardium but not endocardium leads to elevation of the ST segment with either a saddleback or coved appearance, similar to those recorded in patients with the Brugada syndrome.[23-25]. In Brugada patients , as in the wedge preparation, VT/VF is inducible in the majority of cases. In the wedge preparation, VT/VF is most easily induced by the application of an extrastimulus to the site of briefest refractoriness, always located on the epicardial side. In the clinic, programmed stimulation is most commonly applied to RV endocardium. An epicardial approach is possible via the coronary sinus and it is of interest that in a recent case report VT/VF was shown to be non-inducible with endocardial extrastimualtion, but readily inducible using an electrode placed deep within the coronary sinus.[31]

In isolated epicardial tissues as well as in wedge preparations, loss of the action potential dome and phase 2 reentry are readily induced in right ventricular preparations, but are more difficult to induce in the left ventricle. These findings are due to the presence of a much more prominent $I_{to}$ in right vs. left ventricular epicardium and are consistent with the appearance of the ST segment elevation only in right precordial leads in patients with the Brugada syndrome. Normalization of the ST segment in response to an increase in rate is observed in the wedge

model as well as in some Brugada patients[25], and is consistent with a decreased availability of $I_{to}$ (due to relatively slow recovery from inactivation) which diminishes the notched configuration of the epicardial action potential. Not all Brugada patients display rate-dependent changes in ST. With some mutations, such as those involving a slowing of reactivation of the sodium channel, or in the presence of sodium channel blockers with strong use-dependence, acceleration may be attended by an ST segment elevation.

Because accentuation of the notch and/or loss of the dome are caused by an outward shift in the balance of currents active at the end of phase 1 (principally $I_{to}$ and $I_{Ca}$), autonomic neurotransmitters like acetylcholine facilitate these changes in the action potential [32] by suppressing $I_{Ca}$ and/or augmenting potassium current, whereas β adrenergic agonists restore the dome by augmenting $I_{Ca}$. As a consequence, in the arterially perfused wedge, vagal and sympathetic influences exaggerate and reduce ST segment elevation, respectively. [23] Accentuation of the ST segment elevation in patients with the Brugada syndrome following vagal maneuvers and normalization of the ST segment following β adrenergic agents are consistent with these findings[25].

The effect of sodium channel blockers to facilitate loss of the RV epicardial action potential dome in the wedge and in isolated tissues [33] is consistent with their ability to [23]unmask the Brugada syndrome in the clinic.[9] Moreover, the linkage of the Brugada syndrome to mutations in SCN5A is consistent with the conduction disturbances that sometimes accompany the Brugada syndrome. [34]

One of the emost intriguing aspects of the Brugada syndrome is the much greater prevalence of the Brugada phenotype in males (10:1 ratio of males/females). The basis for this sex-related distinction was the subject of a recent study invovling epicardial tissue slices, arterially-perfused wedge preparations and dissociated epicardial myocytes isolated from male and female canine hearts. RV epicardium action potential (AP) phase 1 amplitude was 64.8 ± 2.0% of phase 2 in males compared to 73.8 ± 4.4% in females ($p<0.05$) at a cycle length of 2000 msec. $I_{to}$ density was 26% smaller and time constant for inactivation 17% smaller at +40 mV in female vs. male RV epicardial cells ($p<0.05$). The other functional characteristics of $I_{to}$, including the voltage dependence of inactivation and time-course of reactivation, were no different between the sexes. Pinacidil caused loss of AP dome in male, but not female, RV epicardial tissue slices. Terfenadine (5 uM) induced phase 2 reentry in 6/7 male but only 2/7 female arterially perfused wedge preparations. 2/6 male and 1/2 female preparations developed polymorphic VT/VF. These results of our suggest suggest that the predominance of the Brugada phenotype in males is due to the presence of a more prominent $I_{to}$ in males vs. females. (Di Diego et al, Circulation, in press)

While augmentation of $I_{to}$ may precipitate phase 2 reentry and the Brugada syndrome, it is not a prerequisite. However, the presence of a prominent $I_{to}$ is essential. Because of the pivotal role of $I_{to}$, agents that inhibit $I_{to}$, including 4-aminopyridine and quinidine, restore the action potential dome and electrical homogeneity, thus suppressing all arrhythmic activity.[10;29]. Agents that potently block $I_{Na}$, but not $I_{to}$ (flecainide, ajmaline and procainamide), exacerbate or unmask the Brugada syndrome, whereas those with actions to block both $I_{Na}$ and $I_{to}$ (e.g., quinidine and disopyramide) may exert an ameliorative effect.[10] The anticholinergic effects of quinidine and disopyramide may also contribute to their effectiveness.

Although great progress has been made in the identification and characterization of the Brugada syndrome over the past decade, relatively ; little progress has been made in the approach to therapy. ICD implantation is the only established effective treatment for the disease.[35;36] This however is not the optimal solution for infants and young children or for adults residing in regions of the world where an ICD is not an option because of economic constraints.

The pharmacologic approach to therapy has been geared to a rebalancing of currents active during the early phases of the right ventricular epicardial action potential so as to reduce the magnitude of the action potential notch and/or restore the action potential dome. Experimental studies have suggested use of agents that block $I_{to}$, such as quinidine or tedisamil, or agents that boost the calcium current, such as isoproterenol, may be useful.[10;37] 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. [38-41], but other than the study by Belhassen and coworkers involving quinidine, none have shown long term efficacy in the prevention of sudden death. [42;43]. The most recent addition to the pharmacologic armamentarium is the phospodiesterase III inhibitor,

cilostazol, [44] which probably normalizes the ST segment by reducing $I_{to}$ secondary to an increase in heart rate as well as by augmenting $I_{Ca}$.

From relative obscurity, the Brugada syndrome has rapidly gained acceptance as a major cause of sudden cardiac death. In the span of ten years, the syndrome has gained wide recognition throughout the world and today is believed to be responsible for 4-12% of all sudden deaths and approximately 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 40 in regions of the world where the syndrome is endemic. The syndrome continues to occupy a prominent portion of time devoted to cardiac arrhythmias at national meetings (AHA, ACC and NASPE) and publications on the subject continue to rise at an brisk rate. Although a great deal of progress has been realized over the past decade, there is little doubt that we remain relatively ignorant as to many of the clinical, genetic, molecular and cellular aspects of this fascinating syndrome.

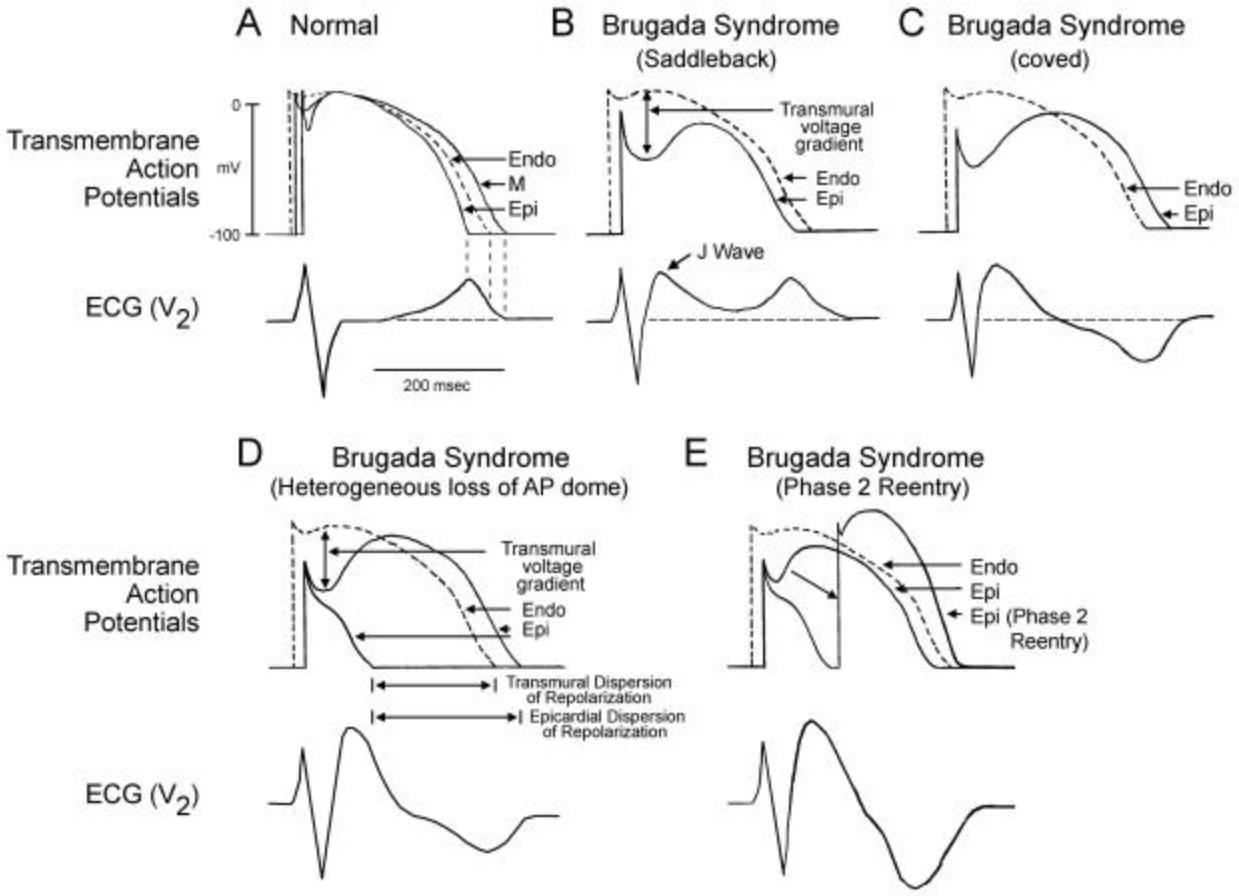


**Figure 1.** Schematic representation of right ventricular epicardial action potential changes proposed to underlie the electrocardiographic manifestation of the Brugada syndrome. Modified from [6] with permission.

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