The Brugada syndrome accounts for approximately 20% of cases of sudden cardiac death in patients with structurally normal hearts (1–3). The syndrome is characterized by an ST-segment elevation in right precordial leads (V1 to V3) unrelated to ischemia, electrolyte disturbances or obvious structural heart disease, and is sometimes accompanied by a right bundle branch block (RBBB) morphology of the QRS. This electrocardiographic (ECG) signature was reported as early as 1953, but it was first described as a distinct clinical entity associated with a high risk of sudden cardiac death by Pedro and Josep Brugada in 1992 (4). These characteristics of the Brugada syndrome are similar to those reported by Nademanee et al. (5) for patients with sudden unexplained death syndrome, and recent study has advanced data suggesting the two syndromes are genetically and functionally the same disorder (6).

The ECG sign of the Brugada syndrome is dynamic and often concealed, but it can be readily unmasked by potent sodium channel blockers, such as flecainide, ajmaline, procainamide and psilicainide (7). Although intravenous administration of these agents is most effective in unmasking the syndrome, oral formulations are useful as well. In general, the effectiveness of sodium channel blockers to unmask the syndrome is inversely proportional to the rate at which the drug dissociates from the sodium channel (8). Class IC antiarrhythmics (flecainide) dissociate from the sodium channel more slowly, display the greatest use-dependence and are less effective. Class IA agents (disopyramide, procainamide) dissociate more rapidly than class IC agents, display less use-dependent block of INa and are less effective. Class IA agents with actions to block the transient outward current (Ito) in addition to INa (quinidine) may exert an opposite effect, leading to normalization of the ST-segment. Finally, class IB agents, which display little use-dependence owing to rapid dissociation from the sodium channel, are not at all effective in unmasking the Brugada syndrome.

Both the specificity of these effects of sodium channel blockers to uncover the syndrome and the prognostic significance of these effects are slowly coming into better focus. Recent studies have shown that asymptomatic patients whose Brugada sign is only present after a sodium challenge have a much better prognosis than those whose ECG sign is present spontaneously (9).

The sensitivity to sodium channel block is consistent with linkage of the syndrome to a defect in the sodium channel gene. The only gene thus far linked is that encoding for the alpha subunit of the cardiac sodium channel gene, SCN5A (3,10–14), the same gene implicated in the LQT3 form of the long QT syndrome and in progressive conduction disease. Bezina et al. (14) uncovered a mutation in SCN5A (1795InsD) capable of producing both the Brugada and LQT3 phenotypes, and Kyndt et al. (15) have recently reported an SCN5A gene mutation capable of producing both the Brugada syndrome and progressive conduction disease. The SCN5A mutations linked to the Brugada syndrome cause a reduction in the availability of INa, secondary to either: 1) failure of the sodium channel to express, 2) a shift in the voltage–time-dependence of INa activation, inactivation or reactivation, and/or 3) acceleration of the inactivation of the sodium channel (3,11,12,14). Premature inactivation of the sodium channel can be temperature sensitive (11), providing a possible explanation for the effect of fever to unmask the syndrome in some Brugada patients (16).

Another locus on chromosome 3, close to but distinct from SCN5A, has recently been linked to the syndrome (17). The Brugada syndrome in this single large pedigree was associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. In addition to SCN5A, gene mutations that alter the intensity or kinetics of INa, Ito, I,Ks, I,Kr, I,Kr-ATP, I,Ca or Icl(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 that directly modulate ion current density and/or alter the expression of channels in the membrane (e.g., sympathetic control of INa) (18,19).

Cellular mechanisms responsible for development of the Brugada syndrome are also coming into better focus. Electrocardiographic manifestations of the syndrome have been attributed to one of two basic mechanisms: 1) conduction delay in the right ventricular (RV) epicardial-free wall in the region of the outflow tract, or 2) premature repolarization of the RV epicardial action potential secondary to loss of the action potential dome.

A schematic representation of the cellular changes believed to underlie the Brugada phenotype in hypothesis 2 is shown in Figure 1 (18,20). In larger mammals, the presence of an Ito-mediated spike and dome morphology, or notch, in
ventricular epicardium, but not endocardium, creates a transmural voltage gradient responsible for the inscription of the ECG J-wave (21). Under normal conditions, the J-wave is relatively small, in large part reflecting the left ventricular action potential notch, as that of RV 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 (Fig. 1A). Accentuation of the RV 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 (Fig. 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 RV wall and transmural voltage gradients are reversed, leading to the development of a coved-type ST-segment elevation and inversion of the T-wave (Fig. 1C), typically observed in the ECG of Brugada patients.

A delay in epicardial activation may also contribute to inversion of the T-wave. The downsloping ST-segment elevation, or accentuated J-wave, observed in the experimental wedge models often appears as an R’, suggesting that the appearance of an RBBB morphology in Brugada patients may be due at least in part to early repolarization of RV epicardium, rather 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 (22). Moreover, attempts by Miyazaki et al. (23) to record delayed activation of the right ventricle in Brugada patients met with failure. Although the typical Brugada morphology is present in Figures 1B and 1C, the substrate for re-entry 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 (Fig. 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 develop-

---

**Figure 1.** Schematic representation of right ventricular epicardial action potential changes proposed to underlie the electrocardiographic (ECG) manifestation of the Brugada syndrome. Modified from Antzelevitch (20), with permission.
opment of a vulnerable window during which a premature impulse or extrasystole can induce a re-entrant arrhythmia. Loss of the action potential dome in epicardium is usually heterogeneous, leading to the development of epicardial dispersion of repolarization (Fig. 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 re-entry mechanism, leading to the development of a very closely coupled extrasystole, which captures the vulnerable window across the wall, thus triggering a circus movement re-entry in the form of ventricular tachycardia (VT)/ventricular fibrillation (VF) (Fig. 1E) (24,25). The phase 2 re-entrant 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 RV wedge preparation (25).

These characteristics of ventricular epicardium suggest that activation forces, generated by the second upstroke of the RV epicardial action potential and/or phase 2 re-entry, may extend beyond the QRS complex in Brugada patients. Indeed, signal-averaged ECG (SAECG) recordings have demonstrated late potentials in patients with the Brugada syndrome, especially in the anterior wall of the RV outflow tract (RVOT) (26,27). The basis for these late potentials, commonly ascribed to delayed conduction within the ventricle, are largely unknown. Endocardial recordings have been unrevealing. A study by Nagase et al. (28), reported in this issue of the Journal, sheds some light on this subject. The investigators introduced a guide wire into the conus branch of the right coronary artery to record signals from the epicardial surface of the anterior wall of the RVOT in patients with the Brugada syndrome. This novel approach yielded unipolar recordings displaying delayed potentials, which coincide with late potentials recorded in the SAECG. The study demonstrates extension of the delayed unipolar potentials and ECG late potentials further into diastole following the administration of class IC antiarrhythmic agents. The investigators conclude that recordings from the conus branch of the right coronary artery to record signals from the epicardial action potential notch, at some point leading to loss of the action potential dome, acceleration of the rate would be expected to normalize their ECG or no change when heart rate is increased, thus favoring the second hypothesis (Fig. 1). Further evidence in support of this hypothesis derives from the recent observations of Shimizu et al. (30). Using a unipolar catheter introduced into the great cardiac vein, they recorded unipolar activation recovery intervals (ARIs), a measure of local action potential duration, from the epicardial surface of the RVOT in a 53-year-old Brugada patient. The ARIs in the RVOT were observed to abbreviate dramatically whenever the ST-segment elevation and the RBBB morphology of the ECG. Conversely, if the Brugada sign is secondary to accentuation of the epicardial action potential notch, at some point leading to loss of the action potential dome, acceleration of the rate would be expected to normalize the ECG, by restoring the action potential dome and reducing the notch. This occurs because the transient outward current, which is at the heart of this mechanism, is slow to recover from inactivation and is less available at faster rates. The fact of the matter is that Brugada patients usually display a normalization of their ECG or no change when heart rate is increased, thus favoring the second hypothesis (Fig. 1).

How then can we discriminate between the two? One approach is to examine the rate-dependence of the ECG sign. If the Brugada ECG sign is due to delayed conduction in the RVOT, acceleration of the rate would be expected to further aggravate conduction and thus accentuate the ST-segment elevation and the RBBB morphology of the ECG. Conversely, if the Brugada sign is secondary to accentuation of the epicardial action potential notch, at some point leading to loss of the action potential dome, acceleration of the rate would be expected to normalize the ECG, by restoring the action potential dome and reducing the notch. This occurs because the transient outward current, which is at the heart of this mechanism, is slow to recover from inactivation and is less available at faster rates. The fact of the matter is that Brugada patients usually display a normalization of their ECG or no change when heart rate is increased, thus favoring the second hypothesis (Fig. 1).

Further evidence in support of this hypothesis derives from the recent observations of Shimizu et al. (30). Using a unipolar catheter introduced into the great cardiac vein, they recorded unipolar activation recovery intervals (ARIs), a measure of local action potential duration, from the epicardial surface of the RVOT in a 53-year-old Brugada patient. The ARIs in the RVOT were observed to abbreviate dramatically whenever the ST-segment was elevated in lead V2 following a pause or the administration of a sodium channel blocker. Thus, the available data, both experimental and clinical, point to transmural voltage gradients that develop secondary to accentuation of the epicardial notch and loss of the action potential dome as being in large part responsible for the Brugada ECG signature.

Reprint requests and correspondence: Dr. Charles Antzelevitch, Masonic Medical Research Laboratory, 2150 Bleecker Street, Utica, New York 13501-1787. E-mail: ca@mmrl.edu.
REFERENCES