Cellular Basis for the Brugada Syndrome and Other Mechanisms of Arrhythmogenesis Associated With ST-Segment Elevation

Gan-Xin Yan, MD, PhD; Charles Antzelevitch, PhD

Background—The Brugada syndrome is characterized by marked ST-segment elevation in the right precordial ECG leads and is associated with a high incidence of sudden and unexpected arrhythmic death. Our study examines the cellular basis for this syndrome.

Methods and Results—Using arterially perfused wedges of canine right ventricle (RV), we simultaneously recorded transmembrane action potentials from 2 epicardial and 1 endocardial sites, together with unipolar electrograms and a transmural ECG. Loss of the action potential dome in epicardium but not endocardium after exposure to pinacidil (2 to 5 μmol/L), a K\(^+\) channel opener, or the combination of a Na\(^+\) channel blocker (flecainide, 7 μmol/L) and acetylcholine (ACh, 2 to 3 μmol/L) resulted in an abbreviation of epicardial response and a transmural dispersion of repolarization, which caused an ST-segment elevation in the ECG. ACh facilitated loss of the action potential dome, thus reducing or eliminating the ST-segment elevation. Heterogeneous loss of the dome caused a marked dispersion of repolarization within the epicardium and transmurally, thus giving rise to phase 2 reentrant extrasystole, which precipitated ventricular tachycardia (VT) and ventricular fibrillation (VF). Transient outward current (\(I_{to}\)) block with 4-aminopyridine (1 to 2 mmol/L) or quinidine (5 μmol/L) restored the dome, normalized the ST segment, and prevented VT/VF.

Conclusions—Depression or loss of the action potential dome in RV epicardium creates a transmural voltage gradient that may be responsible for the ST-segment elevation observed in the Brugada syndrome and other syndromes exhibiting similar ECG manifestations. Our results also demonstrate that extrasystolic activity due to phase 2 reentry can arise in the intact wall of the canine RV and serve as the trigger for VT/VF. Our data point to \(I_{to}\) block (4-aminopyridine, quinidine) as an effective pharmacological treatment.

Key Words: electrophysiology ▪ ventricles ▪ electrocardiography ▪ J wave ▪ fibrillation ▪ tachycardia

The Brugada syndrome is characterized by marked ST-segment elevation in the right precordial ECG leads (unrelated to ischemia, electrolyte abnormalities, or structural heart disease) and is associated with a high risk for sudden death\(^1\)–\(^6\) (for review see References 7 through 9). Although this syndrome is observed worldwide, it is more common in Asian countries, including Thailand, Japan, Laos, Cambodia, Vietnam, the Philippines, and China. It is a leading cause of death among young men in the northeastern region of Thailand (1:2500), second only to automobile accidents.\(^4\) However, the mechanisms responsible for the ST-segment elevation and the genesis of ventricular tachycardia/ventricular fibrillation (VT/VF) in this syndrome remain unknown.

It is now well established that a transient outward current (\(I_{to}\))–mediated phase 1, which gives rise to a notched appearance of the action potential (AP), is more prominent in epicardium than in endocardium of the ventricles of many species. Transmural differences in the contribution of \(I_{to}\) first suggested in 1988 on the basis of AP data,\(^11\) have now been demonstrated by use of whole-cell patch-clamp techniques in canine, feline, rabbit, rat, and human ventricular myocytes. Recent studies also indicate the presence of a much larger \(I_{to}\)-mediated notch in right versus left canine ventricular epicardium.\(^1\) For a review, see Reference 9.

The presence of a prominent AP notch in epicardium but not endocardium causes a transmural voltage gradient during ventricular activation that has been shown to underlie the J-wave and J-point elevation in the ECG.\(^12\) The presence of a prominent \(I_{to}\)-mediated notch also predisposes canine ventricular epicardium to all-or-none repolarization under a variety of conditions, including ischemia.\(^13\)–\(^16\) Loss of the AP dome (plateau) in epicardium but not endocardium produces a voltage gradient during ventricular repolarization that is thought to underlie elevation of the ST segment, similar to that found in patients with the Brugada syndrome. In isolated sheets of canine right ventricular (RV) epicardium, heterogeneous loss of the AP dome has been shown to induce a marked increase in dispersion of repolarization as well as
phase 2 reentry, which is responsible for the closely coupled extrasystole that initiates VT.16

A demonstration of these mechanisms in the intact wall of the heart and their direct relationship to the Brugada syndrome has been lacking. The present study uses an arterially perfused wedge preparation to provide a direct test of the hypotheses that depression or loss of the AP dome can occur in ventricular epicardium, that the resultant transmural voltage gradients cause an ST-segment elevation, and that heterogeneous loss of the epicardial AP dome predisposes the ventricle to the development of phase 2 reentrant extrasystoles, which precipitate VT/VF.

**Methods**

**Arterially Perfused Wedge of Canine RV**

The methods used for isolation, perfusion, and recording of transmembrane activity from the arterially perfused canine RV (anterior wall) wedge preparation, as well as the viability and electrical stability of the preparation, are detailed in previous studies (see References 17 and 18). Time controls have demonstrated the electrical stability of the wedge preparations for a period of >4 hours.

Briefly, a transmural wedge of the canine RV free wall was isolated and perfused through a coronary artery. A transmural pseudo-ECG was recorded along the same vector as the transmembrane recordings (Epi: “+” pole). Transmembrane APs were recorded simultaneously from 2 epicardial and 1 endocardial sites by use of 3 separate intracavitary floating microelectrodes.

Except where noted, all drugs used in this study were dissolved in Tyrode’s solution and infused into the wedge preparation via its native coronary artery. Amplified signals were digitized, stored on magnetic media and CD, and analyzed with Spike 2 (Cambridge Electronic Design).

**Statistics**

Statistical analysis of the data was performed with a Student’s t test for paired data or 1-way ANOVA coupled with Scheffe’s test. Each wedge preparation served as its own control. All results are expressed as mean±SD unless otherwise indicated.

**Results**

**Mechanism Responsible for the ST Elevation**

The most prominent ECG feature of the Brugada syndrome is paroxysmal ST-segment elevation in the right precordial leads (V1 through V3).1,2 suggesting the presence of a transmural voltage gradient during repolarization of the RV.

A direct test of this hypothesis is illustrated in Figure 1, recorded from an arterially perfused RV wedge preparation. Action potentials from 1 endocardial and 2 epicardial sites (Epi, and Epi2) were recorded simultaneously, together with a transmural ECG. Under control conditions, a prominent notch in epicardium but not endocardium gives rise to a prominent J wave in the ECG (Figure 1A). We used the potassium channel opener pinacidil (3 μmol/L) to produce an outward current, slightly reducing the degree of ST-segment elevation (Figure 1B, second beat). In the continued presence of pinacidil, acceleration of the stimulation rate from a basic cycle length (BCL) of 2000 to 1000 ms for 2 minutes restored the epicardial AP dome and normalized the ST segment. As will be discussed later, these effects of prematurity and rate are secondary to a diminished availability of Ito (Figure 1C).

Any agent or agency capable of reducing the magnitude of the epicardial AP notch, either by direct inhibition of Ito or by other modification of the balance of currents active during phases 1 and 2, would be expected to restore the AP dome and lead to normalization or reduction of the ST-segment elevation. Figures 2 and 3 illustrate 2 examples. In Figure 2,
the addition of pinacidil (2.5 μmol/L) leads to a gradual loss of epicardial AP dome (middle panel), resulting in a progressive depression of the plateau and abbreviation of epicardial APD. Corresponding changes are observed in the ST segment, with progressive elevation as the transmural voltage gradient increases. Pinacidil (1 to 5 μmol/L) induced a complete loss of AP dome in RV epicardium in ~70% (18 of 26) of the preparations. The addition of 4-aminopyridine (4-AP), an I_{Na} blocker, to the perfusate restored the epicardial AP dome and normalized the ST segment (Figure 2, right). Qualitatively similar results were obtained with quinidine (5 μmol/L, Figure 3, n=6) and disopyramide (10 μmol/L, not shown, n=4), both of which have been shown to inhibit I_{Na}. The effect of 4-AP, quinidine, and disopyramide on the magnitude of phase 1 (AP peak to end of phase 1) of the RV epicardial AP is summarized in the Table. 4-AP was most potent and disopyramide least potent. Washout of the drug readily reversed the effects of pinacidil in all cases.

The influence of the autonomic nervous system on ST-segment elevation in patients with Brugada syndrome is well established. An increase in vagal activity is known to cause an ST-segment elevation in the right precordial leads (V1 through V3), whereas sympathetic agonists normalize the ST segment. In the wedge, acetylcholine (ACh, 1 to 5 μmol/L) depressed the AP plateau in RV epicardium but not endocardium in 3 of 5 preparations, leading to an ST-segment elevation (Figure 4) that was readily reversed with atropine (1 μmol/L, not shown). ACh alone did not lead to loss of the AP dome in RV epicardium, but it facilitated loss of the dome in the presence of pinacidil or flecainide (Figure 5). Similar results were obtained in 4 other experiments. The sympathetic agonist isoproterenol (0.1 to 1 μmol/L) normalized the ST segment by restoring the epicardial AP dome in 5 of 5 experiments (eg, see Figure 5D).

Mechanism Underlying Ventricular Arrhythmias in the Brugada Syndrome: Role of Phase 2 Reentry

In isolated tissues, loss of the dome occurs at some RV epicardial sites but not others, resulting in a marked dispersion of repolarization that underlies the development of local reexcitation via a mechanism called phase 2 reentry.

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**Table**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Magnitude of Phase 1 of the Epicardial Action Potential, mV</th>
<th>n</th>
<th>P</th>
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<tr>
<td>Control</td>
<td>38.3±8.8</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>4-AP 2 mmol/L</td>
<td>8.8±4.3</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>38.3±7.1</td>
<td>6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Quinidine 5 μmol/L</td>
<td>14.7±4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>33.4±2.1</td>
<td>4</td>
<td>0.09</td>
</tr>
<tr>
<td>Disopyramide 10 μmol/L</td>
<td>25.7±4.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Effect of quinidine on pinacidil-induced ST-segment elevation. Each panel shows transmembrane APs simultaneously recorded from 1 Endo and 2 Epi sites, together with a transmural ECG. Left, Control. Middle, Pinacidil (2.5 μmol/L)–induced ST-segment elevation. Right, Quinidine (5 μmol/L) restores epicardial AP dome, thus normalizing ST segment. BCL=2000 ms. Abbreviations as in Figure 1.

**Figure 4.** ACh-induced ST-segment elevation. Transmembrane APs from Epi and Endo and an ECG were recorded simultaneously. Superimposed traces were recorded under control conditions and after addition of 3 μmol/L ACh. ACh depresses AP plateau in Epi but not Endo, resulting in an ST-segment elevation. BCL=2000 ms. Abbreviations as in Figure 1.

**Figure 5.** Synergistic effect of a combination of I_{Na} block and ACh to cause ST-segment elevation and of isoproterenol (iso) to reverse it. Each panel shows transmembrane APs recorded simultaneously from 1 Endo and 2 Epi sites, together with a transmural ECG. A, Control. B, Flecainide (7 μmol/L). C, Flecainide plus ACh (2 μmol/L) caused loss of epicardial AP dome, thus giving rise to an ST-segment elevation in ECG. D, Iso (0.5 μmol/L) in presence of flecainide and ACh (2 μmol/L) restored epicardial AP dome and normalized ST segment. BCL=1000 ms. Abbreviations as in Figure 1.
Similar electrical heterogeneity is observed in the wedge (Figure 6). Figure 6A shows the effect of pinacidil (2.5 μmol/L) to cause loss of the AP dome at some sites (Epi 1) but not others (Epi 2), resulting in marked dispersion of repolarization on the epicardial surface. Dispersion was more pronounced during the plateau phase of the AP, as reflected by a greater epicardial dispersion of repolarization time at APD_{50} versus APD_{90}. 4-AP (2 mmol/L, Figure 6A, right) restored the dome and greatly diminished dispersion of repolarization. Summary data are shown in Figure 6B.

Using isolated epicardial sheets, we previously demonstrated that loss of the epicardial AP dome at some sites but not others generates large voltage gradients between the epicardial sites at which the dome is maintained and those at which it is lost and that these electrotonic forces can produce an extrasystole via local reexcitation (phase 2 reentry), which in turn can initiate circus movement reentry.16 In the present study, we induced ventricular arrhythmias via phase 2 reentry in 19 of 28 arterially perfused RV wedge preparations by exposure of the preparations to pinacidil, cold, local pressure on the epicardial surface, a Ca^{2+} channel blocker (CdCl), or a combination of ACh and pinacidil (Figures 7 and 8). We did not study the effects of cold and pressure on phase 2 reentry systemically. In our experiments, the RV wedge is cannulated in cold Tyrode’s solution and then transported to a warm bath. During the warming period, phase 2 reentry–induced ventricular arrhythmias were observed in 5 preparations. The arrhythmias disappeared at higher temperatures (>33°C). The process was reversible, ie, reducing temperature resulted in reappearance of phase 2 reentry–induced VT/VF. In 2 preparations, local pressure caused loss of the AP dome at the contact site on the epicardial surface, leading to phase 2 reentry. Release of pressure abolished the arrhythmias. Local pressure on endocardium or the M region failed to induce phase 2 reentry (n=2). Phase 2 reentry–induced VT/VF was observed in 2 of 5 preparations exposed to Ca^{2+} channel block and 12 of 18 preparations exposed to pinacidil. The arrhythmias generally appeared within 30 minutes after each intervention. The loss of the AP dome and development of phase 2 reentry were largely dependent on the initial magnitude of the \( I_{K} \)–mediated AP notch in epicardium. The phase 1 magnitude was 39.9±7.7 mV (n=19) in the group that developed phase 2 reentry versus 29.1±4.6 mV (P<0.05) in the group that failed to develop phase 2 reentry.

Figure 7 illustrates an example of phase 2 reentry–induced VF developing after exposure of RV epicardium to pinacidil (10 μmol/L). Loss of the AP dome at some epicardial sites caused an ST-segment elevation similar to that observed in patients with the Brugada syndrome. Propagation of the dome from sites at which it is maintained to those at which it is lost
gives rise to an extrasystole via phase 2 reentry (first grouping). In the second grouping, phase 2 reentry generates an extrasystole with a slightly longer coupling interval, which succeeds in precipitating VF. Thus, heterogeneous loss of the AP dome leads to phase 2 reentry, thus providing a closely coupled extrasystole, which in turn triggers VF. 4-AP (2 mmol/L, Figure 8A), quinidine (5 μmol/L, Figure 8B), and disopyramide (10 μmol/L, data not shown) restored homogeneity by restoring the epicardial AP dome at sites at which it was abolished, thus terminating all arrhythmic activity.

Discussion

ST-Segment Elevation and Phase 2 Reentry

In the ECG, particularly in the precordial leads, an ST-segment deviation is usually the result of a transmural voltage gradient caused by differences in the level of the AP plateau among cells spanning the ventricular wall. Our findings indicate that loss of the AP dome in RV epicardium but not endocardium gives rise to a transmural voltage gradient that underlies ST-segment elevation, similar to that observed in the ECG of Brugada syndrome patients. Loss of the dome is critically dependent on the presence of a prominent Ito-mediated phase 1 or spike and dome (notch) morphology of the epicardial AP. Under normal conditions, the presence of an AP notch in epicardium but not endocardium gives rise to a transmural current that is responsible for the inscription of the J wave of the ECG.12 Under pathophysiological conditions, the J wave may become progressively larger (due to accentuation of the AP notch) during the transition to ST-segment elevation (due to loss of the dome) (Figure 5).

In some species, including dogs, Ito is relatively slow to recover from inactivation. As a consequence, changes in rate of prematurity of the impulse can alter the availability of Ito and thus the ability to abolish the AP dome (Figure 1). Although reactivation of Ito is faster in humans than in dogs, rate-dependent changes in the manifestation of the ST segment have been reported in some Brugada patients.7,21 Because Ito and the AP notch are much smaller in left ventricular epicardium,11,22 loss of the AP dome and phase 2 reentry are much more difficult to induce. These observations are consistent with the appearance of ST-segment elevation only in the right precordial leads in patients with the Brugada syndrome.

Loss of the AP dome is critically dependent on the balance of currents active during phase 1 of the AP (principally Ito, INa, and ICa). Any agent capable of causing an outward shift in the current active at the end of phase 1 of RV epicardium (eg, increase in IK,ATP and/or IK,AC, and decrease in ICa and INa) can contribute to loss of the AP dome. These include K+ channel openers such as pinacidil, Ca2+ channel blockers such as CdCl, sodium channel blockers such as flecainide, and parasympathetic agonists such as ACh. All of these agents are shown to facilitate loss of the dome in RV epicardium in the wedge preparation.

Although we demonstrated this phenomenon using 6 very different methods to alter the balance of current at the end of phase 1, we chose to focus on the ability of pinacidil to mimic the Brugada syndrome because the data obtained most likely apply to other syndromes involving ST-segment elevation, particularly acute ischemia. It is important to recognize that the fundamental mechanism underlying arrhythmogenesis under these conditions is similar regardless of the specific current altered.
Sodium and calcium channel block facilitates all-or-none repolarization by leaving the strong \( I_{\text{Na}} \) in RV epicardium less opposed, resulting in termination of phase 1 at more negative potentials, at which the availability of \( I_{\text{Ca}} \) may be reduced. The class IC antiarrhythmic agents, including flecainide, are especially effective in causing loss of the AP dome because of their slow dissociation from the sodium channel. This feature of the drug gives rise to strong use-dependent block of the channel, thus causing profound \( I_{\text{Na}} \) inhibition at relatively slow rates at which \( I_{\text{Na}} \) has had sufficient time to reactivate. Once again, the availability of \( I_{\text{Na}} \) is pivotal. It is noteworthy that our data fail to demonstrate an important effect of flecainide to inhibit \( I_{\text{Ks}} \) at the concentration used. The combination of sodium channel block and ACh (Figure 5) is synergistic in that loss of the AP dome occurs via a reduction in both \( I_{\text{Na}} \) and \( I_{\text{Ca}} \), as well as augmentation of \( I_{\text{KCa}} \). These findings parallel 2 additional very important features of the Brugada syndrome: (1) vagally induced ST-segment elevation and (2) sodium channel block unmasking of the syndrome.5,6,8,23,24

The first demonstration of phase 2 reentry accompanying loss of the AP dome involved the use of high concentrations of flecainide to block the sodium channels.14 The sodium channel thus became a primary gene candidate for the Brugada syndrome. Either a decrease in the density or an acceleration of inactivation of the sodium channel would leave \( I_{\text{Na}} \) unopposed during the early phases of the AP. In addition to the sodium channel gene \( SCN5A \), other candidates include gene mutations that alter the intensity or kinetics of either \( I_{\text{Na}} \) or \( I_{\text{Ca}} \), \( I_{\text{KCa}} \), \( I_{\text{KATP}} \), or autonomic receptors.

The only gene thus far linked to the Brugada syndrome is \( SCN5A \).25 Chen et al25 found several mutations different from those known to contribute to the LQT3 form of the long-QT syndrome. The gene defects caused either an acceleration of the recovery of the sodium channel from inactivation (missense mutation) or nonfunctional sodium channels (frameshift mutation). Other Brugada patients were found not to be linked to \( SCN5A \), suggesting genetic heterogeneity of the disease.

These genetic findings provide support for the hypothesis that the Brugada syndrome is a primary electrical disease and further validate our perfused-wedge model as a surrogate of the clinical syndrome. The \( SCN5A \) defect also provides us with an understanding of the basis for conduction disturbances that sometimes accompany the Brugada syndrome26 and why sodium channel blockers, particularly ajmaline and flecainide, are so effective in unmasking the syndrome in the clinic.5,6,8,23,24,27,28

Isoproterenol, through its actions to increase \( I_{\text{Ca}} \), is especially effective in restoring the AP dome in the wedge. This finding parallels the clinical observation that ST-segment elevation in patients with the Brugada syndrome is reduced or totally normalized after \( \beta \)-adrenergic agonists.2,29

Because \( I_{\text{Na}} \) plays a pivotal role in this mechanism, it is not surprising that agents that block this current are also capable of restoring the AP dome, normalizing the ST segment, and preventing arrhythmogenesis. 4-AP and quinidine, and to a lesser extent disopyramide, restored the AP dome, normalized the ST segment, and prevented arrhythmias in the wedge. All 3 agents inhibit \( I_{\text{Na}} \). The vagolytic effects of the class I antiarrhythmic agents may also contribute to the actions of the drug. Actions of these agents to block \( I_{\text{Ks}} \) and \( I_{\text{KATP}} \) have contributed to their ability to restore the AP dome, although block of \( I_{\text{Na}} \) is clearly the predominant effect. However, selective \( I_{\text{Ks}} \) or \( I_{\text{KATP}} \) blockers are not able to restore the epicardial AP dome under similar conditions. Our results, demonstrating a therapeutic effect of quinidine, may explain the success of Belhassan and coworkers31 in treating patients with idiopathic VF.

**VT and Fibrillation**

Loss of the dome at some epicardial sites but not others creates a marked dispersion of repolarization within epicardium (Figure 6), leading to local reexcitation via phase 2 reentry. Transmural dispersion of repolarization, also present under these conditions, may facilitate the induction of phase 2 reentry and provides further substrate for the development of VT/VF. It has long been appreciated that a circus movement reentry underlies most cases of VT and VF and that an extrasystole is often required to trigger the arrhythmia. The mechanism we describe in this report not only provides the substrate for reentry in the form of epicardial and transmural dispersion of repolarization but also provides its own extrasystole to trigger the arrhythmia. Extrasystolic beats generated via phase 2 reentry are generally closely coupled, falling on the T wave (Figures 7 and 8). This malignant R-on-T phenomenon is always observed in patients with idiopathic VF.4,32

The heterogeneous loss of the AP dome in RV epicardium appears to be largely a result of a heterogeneous distribution of \( I_{\text{Na}} \) along the RV epicardial surface.11,16,22,33 Our data argue against a contribution of heterogeneous distribution of \( I_{\text{KATP}} \) channels, because pinacidil exerts similar effects in the 3 cell types in the presence of \( I_{\text{Na}} \) blocking concentrations of 4-AP.

**Additional Clinical Correlates**

The similarity between the ECG manifestation of the Brugada syndrome and that of acute myocardial infarction suggests that the mechanism responsible for arrhythmogenesis in patients with the Brugada syndrome is similar to that responsible for early ventricular arrhythmias in patients with acute myocardial infarction. The Brugada model may therefore represent a stable (ischemia-free) model of the early phases of ischemia. A test of this hypothesis has been conducted in isolated epicardial tissues16,22 and is currently under way in the perfused wedge. This experimental model may also apply to other mechanisms of arrhythmogenesis associated with ST-segment elevation.8

**Acknowledgments**

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