Epicardial Activation of Left Ventricular Wall Prolongs QT Interval and Transmural Dispersion of Repolarization
Implications for Biventricular Pacing

Jeffrey M. Fish, DVM; José M. Di Diego, MD; Vladislav Nesterenko, PhD; Charles Antzelevitch, PhD

Background—Epicardial pacing of the left ventricle (LV) has been shown to prolong the QT interval and predispose to the development of torsade de pointes arrhythmias. The present study examines the cellular basis for QT prolongation and arrhythmogenesis after reversal of the direction of activation of the LV wall.

Methods and Results—A transmural ECG and transmembrane action potentials were simultaneously recorded from epicardial, M, and endocardial cells of arterially perfused canine LV wedge preparations. QT interval increased from 297.6±3.9 to 314.0±5.7 ms (n=12; P<0.001) and transmural dispersion of repolarization (TDR) increased from 35.5±5.2 to 70.3±6.2 ms (n=12; P<0.001) as pacing was shifted from endocardium to epicardium. Conduction time between M and epicardial cells increased from 12.1±1.2 to 24.2±1.5 ms (n=12; P<0.001). Amplification of TDR was further accentuated in the presence of rapidly activating delayed rectifier potassium current blockers (E-4031 and cisapride), increasing from 50.5±7.6 to 86.1±6.2 ms (n=8; P<0.01). Torsade de pointes arrhythmias could be induced during epicardial, but not endocardial, pacing of LV in the presence of rapidly activating delayed rectifier potassium current blockade.

Conclusions—Reversal of the direction of activation of the LV wall, as occurs during biventricular pacing, leads to a prominent increase in QT and TDR as a result of earlier repolarization of epicardium and delayed activation and repolarization of the midmyocardial M cells. The increase in TDR creates the substrate for the development of torsade de pointes under long-QT conditions. (Circulation. 2004;109:2136-2142.)

Key Words: electrocardiography • torsade de pointes • heart failure • pacemakers • electrophysiology

Recent studies have highlighted the benefits of resynchronization therapy involving biventricular pacing for patients with congestive heart failure, demonstrating enhanced cardiac output and New York Heart Association class improvement.1–4 Despite improvements in hemodynamics and patient quality of life, the incidence of sudden death in patients treated with biventricular pacing remains high.5,6 Recent reports document the development of R-on-T ventricular extrasystoles and ventricular tachyarrhythmias after the initiation of biventricular pacing.7,8

Resynchronization therapy most commonly involves the placement of one stimulating catheter in the right ventricular (RV) apex and another in contact with the left ventricular (LV) epicardium via the coronary sinus. Although the mechanical benefits of resynchronization therapy have been studied extensively, little attention has been directed toward the consequences of reversing the electric activation of the LV free wall. Using a rabbit wedge preparation, Medina-Ravell et al9 demonstrated the development of early afterdepolarizations and increased dispersion of epicardial and endocardial repolarization after reversal of the transmural sequence of activation, suggesting that these mechanisms may underlie the development of torsade de pointes in patients undergoing resynchronization therapy.

Our laboratory first described the contribution of M cells to transmural dispersion of repolarization (TDR) in 19919–11 and in more recent years has shown these cells to be the chief culprits in the development of torsade de pointes under a wide variety of conditions.12 The present study tests the hypothesis that delayed activation and repolarization of M cells, coupled with earlier activation and repolarization of epicardial cells, results in QT prolongation, development of transmural heterogeneity, and torsade de pointes after a shift from endocardial to epicardial activation of the LV wall in the absence and presence of rapidly activating delayed rectifier potassium current (I\text{\textsubscript{K\textsubscript{r}}}) blockade. The hypothesis is tested in a 1-dimensional mathematical model of transmural conduction as well as in the coronary-perfused canine LV wedge preparation.

Methods

Computer Simulation

We reconstructed the pseudo-ECG as a volume integral of the longitudinal current dipoles13 generated by action potentials propagating along a 2-cm linear cable composed of 200 myocardial cells (LR1 model14) coupled through gap junctions. In the homogeneous cable model, action potential duration was the same in all cells along the cable. In the heterogeneous model, the action potential duration...
(APD<sub>90</sub>) was varied by altering the maximal conductance of the delayed rectifier (g<sub>x</sub>), which was linearly increased from 0.450 pA/pF (endocardial) to 0.650 pA/pF (epicardial). A longer APD<sub>90</sub> was simulated in the M region (cells 60 to 140) by a uniform decrease of g<sub>x</sub>, with the longest APD<sub>90</sub> being in the cell 85 (endocardial side of midmyocardium). Distribution of intercellular coupling was simulated in both the homogeneous and the heterogeneous cable models according to experimental data obtained from the canine ventricular wedge preparation (from Yan et al; Figure 5). In both cable models, stimulation was applied on either the “endocardial” side or the “epicardial” side of a cable. The end of the T wave was determined as the time when the simulated ECG signal falls below 4% of the T wave amplitude.

**Canine Arterially Perfused LV Wedge**

Dogs weighing 20 to 30 kg were anticoagulated with heparin and anesthetized with sodium pentobarbital (30 to 35 mg/kg IV). The chest was opened via a left thoracotomy, and the heart was excised, placed in Tyrode’s solution, and transported to a dissection tray. Transmural LV wedges with dimensions of approximately 12×35×12 mm were dissected from the mid-to-basal anterior region or posterolateral region of the LV wall, and a diagonal branch of the left anterior descending coronary artery or a descending branch of the circumflex branch of the left coronary artery was cannulated to deliver the perfusate (Tyrode’s solution). The composition of the Tyrode’s solution was as follows (in mmol/L): NaCl 129, KCl 4, Na<sub>2</sub>HPO<sub>4</sub> 0.9, NaHCO<sub>3</sub> 20, CaCl<sub>2</sub> 1.8, MgSO<sub>4</sub> 0.5, D-glucose 5.5 (pH = 7.4). Transmembrane action potentials were recorded from epicardial and subendocardial regions (M) with the use of floating microelectrodes. A transmural pseudo-ECG was recorded with the use of 2 AgCl half cells placed approximately 1 cm from the epicardial (++) and endocardial (−) surfaces of the preparation and along the same axis as the transmembrane recordings.

The ventricular wedge preparations were allowed to equilibrate in the chamber for 2 to 3 hours while paced at basic cycle lengths (BCLs) of 2000 ms with the use of silver bipolar electrodes contacting the center of the endocardial surface. During endocardial versus epicardial pacing, the basic stimulus (S<sub>1</sub>) was delivered to either the epicardium or endocardium at a BCL of 2000 ms. After every fifth S<sub>1</sub>, a premature stimulus (S<sub>2</sub>) was delivered to the epicardium at varying S<sub>1</sub>-S<sub>2</sub> intervals. The electrodes were placed across from each other close to the center of the endocardial and epicardial surfaces. The temperature of the perfusate was maintained at 35°C to 35.5°C. Cisapride was dissolved in 100% dimethyl sulfoxide (stock solution = 5 mmol/L) and added to the Tyrode’s solution to a final concentration of 0.2 μmol/L. Dimethyl sulfoxide alone produced no effect on the electric function of the wedge at concentrations of up to 0.1%. E-4031 was dissolved in distilled water to form a stock solution of 5 mmol/L.

Statistical analyses were performed with either paired or unpaired t test, as appropriate. All data are reported as mean±SEM.
Results

Figure 1 shows the results of a computer simulation of transmural conduction. In the absence of electric heterogeneity (Figure 1, top), endocardial stimulation generates a positive QRS and negative T wave; epicardium is the last to be activated and the last to repolarize. TDR is 22 ms, equivalent to the transmural conduction time, and the interval between the peak and end of the T wave (Tp-Te), the ECG index of transmural dispersion, is 32 ms. The QT interval is 330 ms. When the direction of activation is reversed (Figure 1, top right), the QRS and T wave are inverted, but QT interval, Tp-Te, and TDR remain unchanged. Incorporation of transmural heterogeneity through simulation of distinct epicardial, M, and endocardial action potentials results in an upright QRS and T wave during endocardial stimulation (Figure 1, bottom left). Epicardium is the last to activate but the first to repolarize, and the M cells are the last to repolarize, determining the end of the T wave and QT interval (345 ms). TDR and Tp-Te are 58 ms. Reversal of the transmural direction of activation (Figure 1, bottom right) leads to inversion of the QRS but further augmentation of amplitude of the positive T wave. TDR and Tp-Te increase to 81 and 75 ms, respectively, because of the earlier activation and repolarization of epicardium and delayed activation and repolarization of the cells in the M region. The QT interval increases to 358 ms. Thus, reversal of the transmural activation sequence is predicted to prolong the QT interval and, importantly, to amplify TDR and Tp-Te.

We tested the predictions of the mathematical model using the LV wedge preparation. Figure 2 illustrates floating microelectrode action potential recordings obtained from epicardial, M, and endocardial sites along the transmural surface of the wedge at a BCL of 2000 ms. With endocardial stimulation, both the QRS complex and T wave were positive, and the M cell displayed the longest APD at 262 ms. TDR and Tp-Te were 28 and 29 ms, respectively, and the QT interval was 280 ms. Figure 2B shows recordings obtained 2 seconds later after a shift to epicardial pacing. The same impediments were maintained for all 3 cell types. Although the APD values of the individual cell types were only slightly affected, QT interval increased to 296 ms, and TDR and Tp-Te increased to 68 and 56 ms, respectively. Also noteworthy is the very significant increase in conduction time between M and epicardial sites (14 to 27 ms), leading to a widening of the QRS (36 to 42 ms).

Composite data from 12 wedge preparations are shown in Figures 3 and 4. TDR increased from 35.5 ± 5.2 to 70.3 ± 6.2 ms and Tp-Te from 33.4 ± 2.4 to 61.0 ± 2.8 ms when pacing was shifted from epicardium to endocardium (BCL = 2000 ms; P < 0.001); APD90 of midmyocardial (M) and epicardial
cells did not change significantly (Figure 3). QT interval increased from 297.6±3.9 to 314.0±5.7 ms and JT interval increased from 257.9±2.8 to 266.6±4.6 ms (Figure 4, left), whereas conduction time between M and epicardial impalement sites increased from 12.1±1.2 to 24.2±1.6 ms, leading to an increase in QRS duration (34.0±1.9 to 39.4±2.3 ms; Figure 4, right).

Although the increase in TDR was quite substantial under baseline conditions, it was not sufficient to permit the development of torsades de pointes arrhythmias. Previous studies involving the canine LV wedge preparation have shown that torsades de pointes could be induced with programmed electrical stimulation only when TDR exceeds 80 to 90 ms.16–18 In another series of experiments, we examined the effects of a reversal in the direction of activation of the LV wall in the presence of 2 I_{Kr} blockers, E-4031 and cisapride. Figure 5 illustrates an example of the effect of E-4031. E-4031 (5 μmol/L) prolonged QT from 294 to 373 ms and TDR from 46 to 81 ms. A shift from endocardial to epicardial stimulation caused a further prolongation of QT to 401 ms and of TDR to 105 ms. In 8 similar experiments involving I_{Kr} blockade with the use of E-4031 (n=4) or cisapride (n=4), reversal of the transmural activation sequence increased TDR from 50.5±7.6 to 86.1±6.2 ms (BCL=2000 ms; P<0.01) and Tp-Te from 347.6±6.4 to 363.1±7.7 ms as pacing shifted from endocardium to epicardium (BCL=2000 ms; P<0.001); QT interval increased from 347.6±6.4 to 363.1±7.7 ms and JT interval from 304±10.0 to 314.5±14.3 ms, whereas conduction time between M and epicardial impalement sites increased from 11.5±1.1 to 26.4±1.4 ms, leading to an increase in QRS duration (37.6±1.6 to 43.5±2.6 ms).

APD_{90} of midmyocardial (M) and epicardial cells did not change significantly (Table).

Programmed electrical stimulation in the form of a single extrastimuli applied to epicardium successfully precipitated torsades de pointes in 2 of 8 wedge preparations pretreated with the I_{Kr} blockers. Figure 6 illustrates an example. In this example, cisapride (0.2 μmol/L) increased QT and TDR to 322 and 40 ms, respectively, during endocardial stimulation. Programmed electrical stimulation failed to induce torsades de pointes under these conditions. When basic stimulation was shifted to epicardium, QT and TDR increased to 332 and 90 ms, and an extrastimulus applied to epicardium at an S1-S2 interval of 204 ms succeeded in precipitating torsades de pointes. Torsades de pointes could not be induced at any coupling interval tested during endocardial pacing.

Figure 7 shows a plot of Tp-Te as a function of TDR for 23 preparations recorded under control conditions, after I_{Kr} blockade (E-4031 (5 μmol/L) or cisapride (0.1 to 5 μmol/L)) and under a variety of other conditions, including endocardial stimulation, epicardial stimulation, BCL=2000 ms, BCL=500 ms, [K]_{o}=3, or [K]_{o}=4 mmol/L. A linear regression of this relationship has an R value of 0.75 (P<0.001).

Discussion
Our mathematical simulation and experimental data complement each other and provide evidence in support of the
Composite Data for Endocardial Stimulation vs Epicardial Stimulation During Control and During \( I_K \) Blockade (0.2 \( \mu \)mol/L Cisapride or 5 \( \mu \)mol/L E-4031) (n=5–8)

<table>
<thead>
<tr>
<th>Endo Stim</th>
<th>Epi Stim</th>
<th>Endo Stim</th>
<th>Epi Stim</th>
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<th>Endo Stim</th>
<th>Epi Stim</th>
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<tbody>
<tr>
<td>EPAPD(_{90})</td>
<td>( 228.0 \pm 8.2 )</td>
<td>( 230.3 \pm 7.5 )</td>
<td>( 279.0 \pm 3.3 )</td>
<td>( 279.5 \pm 3.0 )</td>
<td>( 299.0 \pm 5.5 )</td>
<td>( 314.8 \pm 7.9^* )</td>
<td>( 37.2 \pm 2.4 )</td>
</tr>
<tr>
<td>( I_K ) block</td>
<td>( 262.9 \pm 5.8^\dagger )</td>
<td>( 262.0 \pm 7.3^\dagger )</td>
<td>( 324.9 \pm 9.3^\dagger )</td>
<td>( 321.8 \pm 8.6^\dagger )</td>
<td>( 347.6 \pm 6.4^\dagger )</td>
<td>( 363.1 \pm 7.7^\dagger )</td>
<td>( 50.5 \pm 4.1^\dagger )</td>
</tr>
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Endo Stim indicates endocardial stimulation; Epi Stim, epicardial stimulation. All numbers are in milliseconds.

*\( P<0.05 \) vs Endo Stim.

\( \dagger \) \( P<0.02 \) vs control.

The hypothesis that intrinsic heterogeneity exists within the ventricular myocardium and that this electrical heterogeneity is amplified when the normal direction of activation of the ventricular wall is reversed. Epicardial activation augments TDR because the epicardial action potential activates and repolarizes earlier and the M cells with the longest APD located in the deep subendocardium activate and repolarize later compared with endocardial activation of the ventricular wall. The additional conduction delay encountered between epicardial and M regions during epicardial stimulation contributes to the amplification of TDR. The extra delay in conduction between epicardium and the M region is likely due to the increased tissue resistivity in the deep subepicardium of the canine heart previously described by our group.\(^{15}\) Conduction time is briefer in the endocardial to epicardial direction, most likely because the region of high resistivity is approached by a broader wave front when endocardium is activated. This distinction is not observed in the computer model because of the unidimensional nature of the simulation.

Our results demonstrate the pivotal role of the M cell in QT prolongation, amplification of TDR, and induction of torsade de pointes that develop after a shift from endocardial to epicardial activation of the LV myocardium. The delayed activation and repolarization of the M cells, when coupled with earlier activation of repolarization of epicardial cells, creates the substrate for the development of reentry. Under baseline conditions, the increase in TDR caused by epicardial activation is not arrhythmogenic because the threshold for induction of torsade de pointes, 80 to 90 ms in the canine heart, is not achieved. However, when TDR is initially augmented by other means, such as exposure an \( I_K \) blocker, the threshold for induction of torsade de pointes can be readily achieved as a consequence of reversing the activation sequence across the ventricular wall (Figure 5).

Our data also provide support for Tp-Te as a noninvasive index of TDR.\(^{10,26}\) Reversal of the transmural activation sequence increased Tp-Te and TDR by 83% and 98%, to 61.0±2.8 and 70.3±6.2 ms, respectively, under baseline conditions (Figure 3) and to 81.5±3.4 and 86.1±6.2 ms, respectively, in the presence of an \( I_K \) blocker. The value of Tp-Te as an index of TDR is illustrated in Figure 7. Our results support the hypothesis that TDR is a principal substrate for the development of torsade de pointes\(^ {12} \) and that Tp-Te is a valuable index to predict torsade de pointes in patients with long-QT syndrome, consistent with the results of a study recently reported by Yamaguchi and coworkers.\(^ {21}\)

Concordant with our findings, a prominent increase in Tp-Te as a consequence of reversal of the direction of activation of the LV wall was recently reported in a patient who developed torsade de pointes after the initiation of biventricular pacing for resynchronization therapy. Tp-Te increased from 92 to 133 ms as pacing shifted from RV endocardium to LV epicardium, whereas the QT increased from 485 to 580 ms.\(^ {8}\)

Taken together, these findings provide support for the presence of intrinsic electrical heterogeneity in the intact human heart, similar to that found in the canine heart. As our simulation study illustrates, a lack of transmural heterogeneity, as recently proposed by Taggart et al,\(^ {22}\) should yield a
negative T wave and a short Tp-Te equivalent to the conduction time across the LV wall. Moreover, reversal of the activation sequence across the LV wall should produce no change in QT interval, TDR, or Tp-Te (Figure 1, top). The presence of a positive T wave and sizable Tp-Te argue for the presence of intrinsic heterogeneity in the human heart, consistent with the findings of Drouin et al.23,24 and Li and coworkers.25 In addition, the appearance of a prominent increase in QT and Tp-Te intervals after a shift from endocardial to epicardial stimulation of the LV is best explained by amplification of electrical heterogeneities intrinsic to the ventricular myocardium of the human heart (Figures 1 (bottom), 2, and 3).

Clinical Implications

Although the clinical benefits of resynchronization therapy are well documented, the rate of sudden cardiac death remains high. This observation is at odds with the expectation that an improvement in ejection fraction and overall mechanical function of the heart should reduce arrhythmogenesis. Our findings, as those of Medina-Ravell and coworkers,8 suggest that a subpopulation of patients with prolonged QT intervals, secondary to heart failure and or exposure to agents with class III actions, may be predisposed to malignant arrhythmias such as torsade de pointes, largely because of epicardial to endocardial activation of the LV wall. Because the clinical benefits of resynchronization therapy can be realized with biventricular pacing with the use of RV and LV endocardial electrodes via a transseptal approach for the placement of LV leads,26 this approach may be preferable in individuals in whom epicardial stimulation is likely to be problematic because TDR is unlikely to be accentuated. Although this technique is not widely utilized, further investigation into its benefit in the long-QT subpopulation at risk for sudden cardiac death may be advisable.

Limitations of the Study

Previous studies have shown that changes in transmural activation sequence can lead to enduring changes in cardiac repolarization (ie, “remodeling”).27,28 These observations serve to highlight an important limitation of this study: Our observations indicate what might be expected in the short term but not necessarily over the long term. Thus, our findings apply to changes to be expected during the first hour of epicardial pacing but may be either mitigated or further exacerbated hours or days later. Further studies are needed to resolve this issue.

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Figure 7. Tp-Te in ECG provides an index of TDR. Tp-Te is plotted as a function of TDR recorded in 23 preparations under a variety of conditions in control and after I_{kr} blockade with cisapride (0.1 to 5 μmol/L) or E-4031 (5 μmol/L). TDR was modulated by altering stimulation rate (BCL=2000 or 500 ms), stimulation site (endocardium vs epicardium), and [K^+], from 4 to 3 mmol/L.. R^2=0.57, R=0.72, P<0.001.
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References
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