Mechanoelectrical Feedback as Novel Mechanism of Cardiac Electrical Remodeling

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**Background**—Altered electrical activation of the heart by pacing or disease induces profound ventricular electrical remodeling (VER), manifested electrocardiographically as T-wave memory and ultimately as deleterious mechanical remodeling from heterogeneous strain. Although T-wave memory is associated with altered expression of sarcolemmal ion channels, the biophysical mechanisms responsible for triggering remodeling of cardiac ion channels are unknown.

**Methods and Results**—To test the hypothesis that mechanoelectrical feedback triggered by regional strain is a mechanism for VER, dogs (n=6) underwent 4 weeks of ventricular pacing to induce VER. Multisegment transmural optical action potential imaging of left ventricular wedges revealed profound and selective prolongation of action potential duration in late-activated (288±29 ms) compared with early-activated (250±9 ms) myocardial segments (P<0.05), providing the first experimental evidence that amplification of repolarization gradients between segments of left ventricle is the electrophysiological basis for T-wave memory. In vivo tagged magnetic resonance imaging revealed a 2-fold and preferential increase in circumferential strain in late-activated segments of myocardium, which exactly coincided with segments undergoing VER. VER could not be attributed to structural remodeling because it occurred without any histological evidence of cellular hypertrophy.

**Conclusions**—The mechanism responsible for triggering remodeling of ion channel function in VER was locally enhanced electrical heterogeneities in the heart. (Circulation. 2007;115:000-000.)

**Key Words:** action potentials ■ electrocardiography ■ mechanics ■ pacing ■ remodeling

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**Clinical Perspective**

VER is easily induced in humans and animal models. Altering the normal sequence of ventricular electrical activation induces profound and long-lasting T-wave changes ascribed to “T-wave memory,” a common clinical manifestation of VER. In contrast to atrial remodeling, VER is associated, interestingly, with prolongation rather than shortening of cellular repolarization. Attenuation of the transient outward potassium current (Iₒ) and mRNA to its α-subunit Kv4.3 has been proposed to underlie the repolarization changes in T-wave memory. Altered Kv4.3 in memory may be regulated by calcium and angiotensin II through the cyclic AMP response element binding protein transcriptional pathway. However, the physiological triggers responsible for inducing memory remain unknown.

At present, no accepted biophysical mechanisms exist to explain why the direction through which ventricular myocytes receive their excitatory current (ie, a change in propa-
adequate time period for induction of VER. To monitor for atrioventricular delay in each heart (ranging from 10 to 50 ms) that completely driven by pacing. This was achieved by using an logical) activation while ensuring that ventricular propagation was which resulted in 99% ventricular paced beats at the animal's change in ventricular activation independent of heart rate, we voltage (0.5 mV) resolutions from 256 sites spanning the entire LV.

Methods

Experimental Model of VER
Adult male mongrel dogs were anesthetized with propofol (10 mg/kg), intubated, ventilated, and maintained on inhalational isoflurane. After lateral thoracotomy, a unipolar lead (Medtronic 4965, Medtronic, Minneapolis, Minn) was implanted on the atrium, and an epicardial pacing lead (Myopore sutureless pacing lead, Guidant, Minneapolis, Minn) was implanted on either the anterior basal left ventricle (n = 6) or posterior basal left ventricle (n = 3). The atrial and ventricular leads were connected to a pulse generator (Discovery II, Guidant, Minneapolis, Minn), which was implanted subcutaneously.

In previous studies, VER was induced by pacing the ventricle at a supraphysiological heart rate to ensure that the majority of beats were indeed ventricularly paced. To evaluate VER induced by a change in ventricular activation independent of heart rate, we implemented a model of VER using 4 weeks of VDD mode pacing, which resulted in 99% ventricular paced beats at the animal’s intrinsic sinus rate. VDD pacing mode permitted sinus (ie, physiological) activation while ensuring that ventricular propagation was completely driven by pacing. This was achieved by using an atrioventricular delay in each heart (ranging from 10 to 50 ms) that produced ECG evidence of complete ventricular capture without fusion. Previous studies have found 3 to 4 weeks of pacing to be an adequate time period for induction of VER. To monitor for progression of VER (ie, T–wave memory), the pulse generator was temporarily switched off (5 to 10 minutes), and ECG was recorded in normal sinus rhythm at weekly intervals thereafter.

After successful induction of VER, the hearts were harvested, and the left ventricle (LV) was anatomically divided into 3 segments (anterior, lateral, and posterior), as shown in Figure 1. Wedges of myocardium obtained from these segments were arterially cannulated and perfused with normal Tyrode’s solution at 36 ± 0.5°C, as described previously. The wedge preparation was stained with a voltage-sensitive dye, di-4-ANEPPS (15 μmol/L), by direct arterial perfusion for 10 minutes and perfused continuously with cytochalasin-D (2 to 6 μmol/L) to eliminate motion artifact from the optical recordings without significantly altering action potential properties.

Multisection Transmural Optical Mapping
Previously, we designed a system capable of recording action potentials with high spatial (0.7 to 1.2 mm), temporal (0.5 ms), and voltage (0.5 mV) resolutions from 256 sites spanning the entire LV.

Tagged Magnetic Resonance Imaging
In a separate group of dogs (n = 5), tagged magnetic resonance imaging was performed in vivo to measure the effect of pacing direction on mechanical strain in different segments of LV. Dogs were anesthetized with propofol (10 mg/kg), intubated, ventilated, and maintained on inhalational isoflurane. After lateral thoracotomy, pacing leads were implanted on the epicardial surface of the atrium, anterior, and posterior LV wall at sites identical to those used to induce VER in the aforementioned experiments. Magnetic resonance images were acquired with a 1.5-T Siemens Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) with body-array and spine-array coils. ECG-triggered, tagged, short-axis magnetic resonance images were acquired at basal, midventricular, and apical levels with anterior pacing, posterior pacing, and atrial pacing (sinus activa-
Tagging resolution was 4 mm, with a temporal resolution of 14 to 19 frames per cardiac cycle. Magnetic resonance images were analyzed with a cardiovascular magnetic resonance image analysis tool described previously. The tagging mesh was tracked with a Harmonic Phase–based semiautomatic method. Homogeneous strain analysis was performed to calculate 2D Lagrangian strain tensor, which was further diagonalized to yield principal strains $E_1$ (radial shortening) and $E_2$ (circumferential strain).

**Structural and Histological Analysis**

To rule out the possibility that electrical remodeling was secondary to structural remodeling, after the hearts were harvested, the transmural wall thickness of early- and late-activated segments from VER induced by anterior ($n=6$) and posterior pacing ($n=3$) was measured in the relaxed state and compared with controls ($n=5$). For histological analysis, cut sections of myocardium were obtained from early- and late-activated segments (anterior and posterior pacing) and compared with identical segments in unpaced control. The sections were fixed in 10% buffered formalin for 24 hours and embedded in paraffin. Transmural surface was sectioned from 3 layers (epicardial, midmyocardial, or endocardial) $\approx 2$ mm and stained with hematoxylin-eosin. Tissue sections were analyzed for hypertrophy, fibrosis, or necrosis by 1 investigator (J.S.) who was blinded to control and pacing interventions.

**Statistical Analysis**

The Student $t$ test was used to test for difference between transmural dispersion of repolarization (TDR) and segmental dispersion of repolarization (SDR) in control and VER hearts. ANOVA for repeated measures was used to test different groups for differences in ECG vector angle, APD, dispersion of repolarization, and strain measurements. To test for difference between individual means, post hoc analysis with Newman-Keuls test was performed. $P<0.05$ was considered significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**ECG Changes Characterizing T-wave Memory**

Figure 2 (top panel) illustrates the time course of VER after anterior LV pacing on the in vivo ECG. At baseline, the polarity of the T wave was similar to the QRS (concordance). During ventricular pacing, the polarity of the T wave is opposite to the QRS (discordance). After progressive periods of pacing, progressive and persistent change in polarity of the T wave takes place. The bottom panel shows the range of T-wave vector frontal plane angles observed from all experiments at baseline (unpaced) and after VER is induced by anterior or posterior LV pacing.
Action Potential Changes in VER

Figure 3 illustrates representative epicardial action potentials recorded from the 3 LV segments in (unpaced) control (n=5) and VER induced by anterior LV pacing (n=6). In controls (ie, without previous alteration of activation sequence), APD and morphology were similar across all LV segments (top panel). Note that the characteristic “spike and dome” morphology depicted by the optically recorded epicardial action potentials in controls corresponds closely to that reported previously with the use of microelectrode techniques.23 By contrast, in VER (Figure 3, middle panel), the anterior (ie, early-activated) segment exhibited modest APD prolongation with clear attenuation of the phase1 notch (reflecting diminished \( I_o \) activity), consistent with previous reports.11 In the lateral segment, APD was slightly shortened, but the phase1 notch was maintained. Interestingly, the most significant APD remodeling occurred in the late-activated posterior segment, which, paradoxically, was farthest from the site of pacing. These myocytes (Figure 3, action potential on right) exhibited marked APD prolongation compared with posterior wall myocytes from unpaced controls (APD prolonged by 63 ms) and compared with anterior wall myocytes from the same heart (APD prolonged by 50 ms). Also note that the phase1 notch amplitude in the highly remodeled posterior segment remained unchanged, suggesting that remodeling of APD was not attributable to \( I_o \).

The Table provides a summary of APD remodeling changes (induced by anterior LV pacing) in epicardial, midmyocardial, and endocardial cells. Compared with unpaced controls, it was apparent again that regardless of cell type, anterior LV pacing consistently induced the greatest VER (ie, \( \Delta \)APD was greatest) in late-activated posterior segment myocytes (\( P<0.01 \)). The anterior segments also exhibited APD prolongation in all 6 experiments compared with unpaced (control) anterior segments; however, the mean APD increase did not quite achieve statistical significance (\( P=0.07 \)). Although VER was most often associated with APD prolongation, this was not always the case, specifically in lateral LV segments that exhibit a trend toward APD shortening (ie, negative \( \Delta \)APD; \( P=NS \)). Finally, multisegment transmural optical mapping revealed that after the induction of T-wave memory, transmural dispersion of APD (eg, compare epicardial with midmyocardial cell APD in the Table) was relatively small compared with dispersion of APD between myocardial segments.

**Electrophysiological Basis for T-wave Memory**

Because the maximum TDR occurs at the interface between epicardial and midmyocardial myocytes,16,17 TDR was defined as the difference in mean APD between epicardial and midmyocardial cells. SDR was defined as the difference in mean APD (including all cell types) between any 2 ventricular segments, ie, anterior to lateral, lateral to posterior, or anterior to posterior, TDR from anterior, lateral, and posterior segments and SDR between anterior-lateral, lateral-posterior, and anterior-posterior segments are compared in Figure 4. In controls (left panel), TDR was not only similar in all 3 LV segments but significantly greater than SDR, suggesting that in normal sinus rhythm TDR makes the greatest contribution to gradients of repolarization that form the ECG T wave. By contrast, after VER induced by anterior LV pacing (right panel), although TDR remained unchanged (compared with control values), SDR increased ~5-fold (relative to control; \( P<0.05 \)) because of the significant and preferential prolongation of APD in the late-activated posterior segments (Figure 3). Therefore, in T-wave memory, SDR, but not TDR, represented the largest source of APD gradients in the LV, which could explain the significant change in T-wave vector

<table>
<thead>
<tr>
<th>APD Remodeling in Epicardial, Midmyocardial, and Endocardial Cells</th>
<th>Anterior Segment</th>
<th>Lateral Segment</th>
<th>Posterior Segment</th>
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<tr>
<td></td>
<td>Control</td>
<td>VER</td>
<td>( \Delta )APD</td>
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<tr>
<td>Epicardial, ms</td>
<td>213±12</td>
<td>237±12</td>
<td>24</td>
</tr>
<tr>
<td>Midmyocardial, ms</td>
<td>241±11</td>
<td>266±13</td>
<td>25</td>
</tr>
<tr>
<td>Endocardial, ms</td>
<td>235±11</td>
<td>256±11</td>
<td>21</td>
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\( *P<0.01. \)
associated with memory. As expected, APD gradients between the posterior and lateral segments (Figure 4, L-P) made the largest contribution to SDR because VER most markedly prolonged APD of posterior wall myocytes while shortening APD of lateral wall myocytes.

To further explore the role of TDR versus SDR as the electrophysiological basis for T-wave memory, the T-wave polarity measured in vivo was compared with T-wave polarity measured or calculated from wedge preparations, as shown in Figure 5. The in vivo ECG measured from an unpaced control (Figure 5, left panel) revealed the typical upright (upward arrow) T-wave polarity. Transmural ECG measured from a wedge preparation isolated from the same heart revealed T-wave polarity similar to that in the in vivo ECG, suggesting that spatial gradients of action potentials across the transmural wall accounted for the in vivo T wave. This is further supported by the transmural ECG calculated by subtracting action potentials recorded from epicardial and midmyocardial cells measured from the same wedge preparation, again revealing an upright T wave. In contrast, the “segmental ECG” calculated from the difference in APD between midmyocardial cells recorded from 2 different LV segments by incorporating previously published activation time between segments failed to recapitulate the upright polarity of the T wave, suggesting that SDR cannot account for the T-wave polarity in control hearts.

In T-wave memory (Figure 5, right panel), the in vivo ECG was characterized by inversion of T-wave polarity (downward arrow). Interestingly, in this case, both the measured and calculated transmural ECG failed to recapitulate T-wave

**Figure 4.** SDR and not TDR underlies T-wave memory. TDR from all LV segments and SDR between anterior-lateral (A-L), lateral-posterior (L-P), and posterior-anterior (P-A) segments in control and VER induced by anterior LV pacing are shown. In control (left), TDR is significantly greater than SDR and gives rise to the normal T wave. In VER induced by anterior LV pacing (right), TDR is unchanged compared with control; however, a 5-fold increase in SDR is observed. This is secondary to selective prolongation of APD in late-activated posterior segment, and hence a large gradient was seen between L-P segments.

**Figure 5.** Electrophysiological basis for T-wave memory. In control (left), the polarity of the T wave on the in vivo ECG is similar to QRS (upward arrow indicates concordance of QRS and T-wave polarity). Transmural ECG recorded from wedge preparation reveals T wave of polarity similar to that of the in vivo ECG. A transmural ECG is calculated by subtracting action potentials from epicardial (EPI) and midmyocardial (M) cells. The calculated transmural ECG reveals T-wave polarity identical to the in vivo ECG, suggesting that repolarization heterogeneities that exist between the transmural cell types underlie the normal T wave. To examine the contribution of repolarization differences between LV segments, segmental ECG is calculated from M cells recorded from 2 different segments with the use of known activation time between segments. The segmental ECG in controls reveals a flat T wave, suggesting that repolarization differences between LV segments do not contribute to the T wave in controls. In T-wave memory, the in vivo ECG is characterized by profound change in T-wave polarity with respect to the QRS (downward arrow indicates discordance of QRS and T-wave polarity). Interestingly, transmural ECG measured or calculated from a wedge preparation after VER (right) has a T wave with polarity opposite that of the in vivo ECG, suggesting that transmural dispersion could not explain the significant change in T-wave polarity in VER. A segmental ECG calculated in VER reveals a T wave with polarity similar to that of the in vivo ECG, demonstrating that repolarization differences between LV segments underlie the electrophysiological basis for T-wave memory. POST indicates posterior; LAT, lateral.
inversions measured in vivo, indicating that transmural gradients of repolarization did not account for T-wave changes associated with memory. However, the segmental ECG revealed a T-wave with polarity similar to that of the in vivo ECG. Therefore, SDR and not TDR underlies the electrophysiological basis for T-wave memory.

Regional Strain as Mechanism for Triggering VER

**VER Is Dependent on Direction of Propagation**

The aforementioned results demonstrate that altered activation sequence induces preferential and marked VER of posterior LV myocytes that were latest to depolarize during anterior LV pacing. To determine whether VER was dependent solely on activation sequence or was related to intrinsic properties of posterior LV myocytes, additional experiments were performed in which propagation direction was reversed by pacing the posterior LV wall (n=3) for 4 weeks. In contrast to the T-wave vector change induced by anterior LV pacing, the shift in the T-wave vector induced by posterior LV pacing was localized to a significantly (P<0.05) different region (Figure 2), suggesting that VER affected myocytes in localized ventricular regions and that the regions affected were determined by activation sequence. These findings are further reaffirmed by comparing action potential remodeling induced by anterior versus posterior LV pacing (Figure 3).

After posterior LV pacing (Figure 3, bottom panel), the epicardial action potential from the posterior segment (ie, early-activated segment) exhibited clear attenuation of the phase1 notch, whereas the most profound remodeling (ie, APD prolongation) occurred in the late-activated anterior segment. These findings essentially mirrored the pattern of cellular remodeling induced by anterior pacing.

Figure 6 illustrates spatial gradients of APD formed between and within anterior, lateral, and posterior segments of LV from representative examples. It is evident in unpaced controls in which an intersegmental gradient is absent (Figure 4, left panel, and Figure 6, left panel). In contrast, anterior LV pacing (Figure 6, middle panel) induced a relatively modest spatial gradient of APD (dashed line) in proximity to the pacing site, which was attributable to slight APD prolongation near the site of pacing and APD shortening within several centimeters of the site of pacing. However, the APD failed to shorten but exhibited the greatest degree of prolongation in the late-activated posterior segment that was on the opposite side of the ventricle (Figure 5, middle panel). Hence, VER was characterized on the one hand by subtle APD shortening along the propagation path close to the pacing site and on the other hand by marked APD prolongation occurring in ventricular segments opposite the site of pacing. Importantly, this pattern of remodeling was completely reversed by pacing the posterior LV wall (Figure 6, compare middle and right panels), reaffirming that APD remodeling was driven exclusively by propagation direction and was not an inherent property of myocytes residing in any particular ventricular region.

**Circumferential Strain as Mechanism Triggering VER**

A key question is why myocytes most remote from the site of pacing underwent the greatest VER. Therefore, we tested the hypothesis that activation-dependent alterations in regional myocardial strain trigger VER. Figure 7 illustrates the relationship between regional action potential remodeling and myocardial strain. Representative action potentials from anterior (red) and posterior (blue) LV epicardial segments (top panels) are compared with the time and amplitude of peak circumferential strain measured from identical segments (middle panel). The results from all experiments (n=5) are summarized in the lower panels. During sinus activation (control), action potential waveforms recorded from both anterior and posterior LV segments were essentially identical. Similarly, the timing and amplitude of peak strain were almost identical in both segments, consistent with temporally synchronized LV contraction. The absence of segmental

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**Figure 6.** VER is dependent on direction of propagation. Representative example of midmyocardial cell APD across the 3 LV segments in control and VER induced by anterior (ANT) and posterior (POST) LV pacing is illustrated. In control (left), APDs in all LV segments are similar. In VER induced by anterior LV pacing (middle), slight prolongation of APD is noted in the early-activated segment, with shortening of APD toward the lateral (LAT) segment. This is presumably due to electrotonic flow-mediated shortening of APD downstream from site of pacing. The dashed line shows the plausible effect of electrotonic-mediated shortening of APD downstream from site of pacing. However, marked APD prolongation is observed in late-activated posterior segment, inconsistent with an electrotonic effect. This is reversed in the right panel when VER is induced by pacing the posterior LV.
differences in strain (Δstrain) and APD (ΔAPD) was observed consistently across all experiments (Figure 7A, lower panel). In contrast to sinus activation, after anterior LV pacing (Figure 7B), marked APD prolongation was observed of posterior (blue) compared with anterior (red) LV myocytes. This was paralleled by a substantial increase in circumferential strain in the late (blue point) relative to the early activated (red point) myocardial segments. After reversing the direction of propagation by pacing the posterior LV wall (Figure 7C), essentially the identical but inverted pattern of circumferential strain and VER was produced. Taken together, under each of the 3 circumstances tested, localized VER was closely paralleled by regional circumferential strain. Furthermore, we measured and examined the role of radial strain in triggering VER. In control, significantly larger radial strain was observed in posterior segment (0.26±0.04) compared with anterior (0.16±0.08; P<0.05). This pattern was unchanged during anterior LV pacing. Moreover, during posterior LV pacing, homogenous strain was observed in both anterior (0.20±0.11) and posterior (0.23±0.07; P=NS) LV segments. Therefore, no relationship existed between radial strain and VER.

**VER Is Not Secondary to Structural Remodeling**

In hearts subjected to VER by anterior LV pacing, LV wall thickness did not differ between anterior (1.5±0.05 cm) and posterior (1.6±0.2 cm; P=NS) LV segments, nor was it different from that in control LV segments (anterior 1.5±0.04 cm and posterior 1.5±0.07 cm; P=NS). Representative hematoxylin-eosin stains (Figure 8) of epicardium from anterior and posterior segments in control and VER revealed no evidence of myocyte hypertrophy, fibrosis, or necrosis, suggesting that VER observed in these experiments was not attributable to structural remodeling.

**Discussion**

Although the term T-wave memory was coined by Rosenbaum in 1981,9 the electrophysiological basis for T-wave memory and the mechanisms responsible for triggering ventricular and atrial electrical remodeling have remained elusive. Identifying these mechanisms has important implica-
tions for the pathophysiology of common heart diseases involving cardiac remodeling, as well as mechanisms for establishment of electrophysiological heterogeneities during cardiac development. In this report, high-resolution, multi-segment, transmural optical mapping was used as a strategy for assessing, in detail, the relative contributions of VER between myocytes spanning the transmural wall compared with VER between myocardial segments that span the LV. This proved to be of critical importance not only to deriving insights into the electrophysiological basis for T-wave memory but also to identifying mechanisms for triggering the VER.

Genesis of the T Wave in Normal (Unremodeled) Hearts

Yan and Antzelevitch proposed that the T wave originates from spatial gradients of repolarization between cells that span the transmural LV wall. This hypothesis is based on measurements of relatively sparsely placed floating microelectrodes along the transmural LV surface. Previously, we demonstrated that the spatial topology of midmyocardial cells, which are largely responsible for TDR, is inherently complex, necessitating high-resolution methods to fully evaluate their contribution to the action potential gradient that forms the ECG. Moreover, limited data exist comparing the relative contribution of TDR to SDR on the genesis of the T wave. In vivo monophasic action potential recordings in humans and swine have demonstrated minimal action potential heterogeneity between segments of the LV but were limited to the epicardial and endocardial surface and failed to account for transmural electrophysiological heterogeneity of myocytes.

The present study is the first to provide detailed action potential measurements from all cell types spanning the transmural wall, in addition to multiple segments of the LV, to determine the source of action potential gradients that underlie the T wave and T-wave memory. In the normal heart (left panels of Figures 4 and 5), TDR accounted for the largest spatial gradient of repolarization in the LV and fully recapitulated the upright T-wave polarity measured in vivo (Figure 5). These findings provided experimental validation that the origin of the T wave arises from heterogeneities of cellular repolarization between transmural muscle layers. Our analysis was limited to segments of myocardium in which viable wedge preparations could be extracted; hence, it is possible that other unmeasured segments could have made greater contributions to the T wave.

Electrophysiological Basis for T-wave Memory

In the present study, the time course and magnitude of T-wave changes induced by a change in activation sequence (Figure 2) were comparable to those reported previously. In contrast to previous studies, we used VDD pacing mode to induce memory to alter the activation sequence without imposing supraphysiological heart rates. Our findings therefore indicate that the change in ventricular activation pattern rather than rate triggers the induction of memory.

The present study provides several lines of evidence that SDR is the electrophysiological basis for T-wave memory. Specifically, the induction of VER as evidenced by profound reversal of in vivo T-wave polarity (1) was associated with disproportionate and localized APD prolongation of late-activated myocardial segments (Figure 3); (2) was not associated with changes in TDR (Figure 4); and (3) could not be recapitulated on the transmural ECG (Figure 5). Moreover, the relatively narrow range of T-wave vector angles induced in memory (Figure 2) was consistent with previous reports and is explained in our study by the segmental nature of APD remodeling underlying T-wave memory. The focal nature of VER can explain why T-wave memory is often only apparent in selected ECG leads.

A limitation to the comparison between TDR and SDR is that TDR is measured over a smaller spatial scale than SDR. Therefore, the comparison between TDR and SDR may overestimate the spatial gradients of APD between myocardial segments. On the other hand, our definition of TDR...
Mechanical Strain as Mechanism Triggering VER

Previously, the mechanisms responsible for triggering VER in response to a change in activation sequence were poorly understood. Understanding these mechanisms requires resolution of a fundamental unresolved question: Why would time- and voltage-dependent sarcolemmal ion channels be sensitive to the direction through which the myocyte receives excitatory current? Such “directional dependence” is not well explained by current understanding of the biophysical properties of excitable cells. Previously, Costard-Jackle et al. proposed that APD is prolonged in proximity to the site of pacing because fully depolarized downstream cells electrotonically maintain and extend the action potential plateau of upstream cells. Indeed, we found that VER was associated with a small but consistent prolongation of APD in early-activated segments with progressive shortening of APD in cells within several centimeters from the site of pacing (Figure 3). However, if electrotonic forces were the only operative mechanism, one would predict progressive shortening of APD even farther from the pacing site. Instead, we found the most significant APD remodeling distal, not proximal, to the site of pacing, and APDs at distal sites were markedly prolonged rather than shortened (Figure 6). Such findings cannot be explained by electrotonic interactions between myocytes. Therefore, as discussed below, we hypothesized that VER in late-activated segments is triggered by mechanoelectrical feedback induced by the change in cardiac activation sequence.

During normal (ie, His-Purkinje) activation (controls), circumferential strain was uniform across all myocardial segments (Figure 7). This was closely paralleled by uniform distribution of APD between these identical segments (Figure 3). In contrast, altering activation sequence by pacing preferentially amplified circumferential strain in late-activated myocardial segments. Similarly altered activation sequence induced marked and parallel prolongation of APD in the same late-activated segments. Moreover, the effects were completely reversible (Figures 6 and 7) because switching the direction of propagation induced essentially identical correspondence between regional circumferential strain and cellular VER. These findings suggest that myocardial strain strongly influences repolarization properties of myocytes. Although transmural optical mapping in the canine wedge preparation provided a unique advantage for assaying membrane potential of all transmural cell types from several distinct segments of myocardium, these preparations were mechanically unloaded when the electrophysiological measurements were obtained. However, it is unlikely that the relatively short period of unloading had a major effect on the long-term action potential changes associated with VER. Pacing-induced VER causes repolarization changes that persist days to weeks after the cessation of pacing. By contrast, electrical recordings in our experiments were made within 120 minutes after myocardial wedges were harvested from intact and paced hearts.

Our findings suggest a mechanoelectrical feedback mechanism for triggering VER. VER no doubt involves a complex cascade of events that may be initiated by stretch but also probably involves a stretch sensor, signaling pathways responding to the stretch stimulus, transcriptional regulatory pathways regulating expression of ion channel genes, and, finally, remodeling of cellular repolarization. The intermediary mechanisms linking stretch to electrical remodeling are not well understood. Recognition is increasing of mechanosensitive ion channels, cytoskeletal proteins involved in mechanotransduction, and stretch-activated signal transduction pathways. In contrast to this report, previous studies have focused on the effect of acute rather than chronic mechanical stretch on electrophysiological properties of the heart. The effect of acute stretch is dependent on the type and duration of applied stretch. Passive stretch during systole in isolated myocytes causes membrane depolarization and prolongs the APD. In chronic volume- or pressure-overload models (eg, atrioventricular block dog) downregulation of repolarizing potassium currents causes prolongation of the APD. Although acute stretch induces transient and reversible action potential changes, our study is the first to demonstrate a potential role of stretch on long-term remodeling of ionic processes of cardiac myocytes in the absence of mechanical remodeling (eg, hypertrophy, heart failure). Although we observed a close relationship between VER and circumferential strain, radial strain was not correlated with VER. This result suggests that the orientation of stretch with respect to the cellular cytoskeleton or intercalated disks may be an important determinant of VER induced by mechanoelectrical mechanisms. The major signaling pathways activated by cytoskeletal deformation that have been implicated in structural remodeling include angiotensin and mitogen-activated protein kinases. The present study should motivate further investigations of mechanisms linking strain-induced cell deformation to remodeling of ion channels in disease and modeling of ion channels during development.

VER could not be attributed to macroscopic or histological evidence of mechanical remodeling such as hypertrophy, fibrosis, or necrosis. In other words, T-wave memory was produced by “primary VER.” This is important because structural remodeling from hypertrophy, as described above, has been associated with APD prolongation. It is often assumed that VER is secondary to structural remodeling. Our data suggest the intriguing possibility that the reverse may be true. For example, had we extended the period of pacing beyond 4 weeks, segmental hypertrophy would develop in late-activated segments, as demonstrated by Prinzen et al. Therefore, the time course of VER antecedes the development of hypertrophy. Such findings may have important implications for pacing therapies aimed at preventing or reversing structural remodeling.
Ionic Basis for VER

Previously, attenuation of the I_{Na} in epicardial myocytes with subsequent reversal of transmural APD gradient was proposed as the electrophysiological basis for memory. However, the present study demonstrated that TDR was unchanged in VER (Figure 4). Our use of transmural optical action potential mapping permitted direct action potential recording from multiple LV segments, whereas prior studies were limited to microelectrode recordings only from early-activated ventricular segments. The fact that the most significant APD remodeling occurred in myocardial segments where the phase 1 notch was preserved (Figure 3) suggests, but does not prove, that I_{Na} may not play a major role in establishing SDR, which accounted for T-wave memory. It is important to emphasize that the ionic mechanisms underlying APD remodeling cannot be ascertained from our data and are beyond the scope of the present study. Our findings suggest that further studies focusing on intersegmental ionic changes are required to better understand the mechanisms of T-wave memory.

Implications

In addition to explaining the electrophysiological basis for T wave memory, our findings have important implications for development of heterogeneities of repolarization that predispose to arrhythmias in heart disease. The progression of ischemic heart disease, for example, is often associated with alterations of the conduction system causing dys-synchronous contraction, associated with enhancement of local strain and susceptibility to arrhythmias. For example, prolongation of the QRS interval (a measure of LV dyssynchrony) is an independent marker of susceptibility to sudden cardiac death. A mechanoelectrical feedback mechanism for localized VER is expected to amplify heterogeneity of repolarization and susceptibility to arrhythmias under such circumstances. This may have direct implications for the mechanism of both deleterious and beneficial remodeling recently recognized with single versus biventricular pacing, respectively. Interestingly, T-wave changes are well recognized in conditions associated with right ventricular pressure overload, often referred to as “right ventricular strain pattern,” implying that mechanoelectrical feedback mechanisms are operative. Our data provide a scientific basis for these clinical observations. Our findings may also have implications for cardiac development. It is well recognized that ion channel expression changes considerably during embryological development and particularly during the early neonatal period. For example, the T wave is normally inverted in neonates and normalizes later in childhood. It is interesting to speculate that changes in mechanical strain resulting from the LV rather than the right ventricle becoming the systemic pumping chamber at birth are responsible for physiological remodeling of the T wave in children. It is also conceivable that heretofore well-recognized heterogeneities in ion channel expression between myocytes that span the transmural wall could be explained by heterogeneities in strain that are known to exist between endocardial and epicardial layers. Because our results indicated that regional strain may be a potent stimulus for remodeling action potentials, further studies are required to determine whether these mechanisms are operative in the many disease and normal conditions associated with alterations of myocardial strain.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

Altered electrical activation of the ventricle due to pacing or intraventricular conduction delay causes electrical remodeling and manifests on the ECG as T-wave memory. The pathophysiological consequences include structural remodeling, increased susceptibility to arrhythmias, worsening heart failure, and increased mortality. In contrast, biventricular pacing improves survival as a result of favorable mechanical remodeling. Therefore, identifying these mechanisms has important implications for the pathophysiology of common heart diseases involving cardiac remodeling, as well as mechanisms for establishment of electrophysiological heterogeneities during cardiac development. Furthermore, the electrophysiological basis for T-wave memory has remained elusive. Using high-resolution multisection transmural optical imaging, we found that increased dispersion of repolarization between left ventricular segments was increased 5-fold in ventricular electrical remodeling and therefore underlies the significant change in T-wave polarity characteristic of T-wave memory. The most significant remodeling was localized to the ventricular segment that was most distal to the site of pacing. This was caused by enhanced mechanical strain in the late-activated segment. The increased dispersion of repolarization underlies the enhanced susceptibility to arrhythmia and increased mortality observed after univentricular pacing. Furthermore, focal increase in mechanical strain triggers asymmetrical structural remodeling, which could increase cardiac morbidity. These data suggest a novel mechanoelectrical feedback mechanism for inducing physiological and potentially deleterious electrical heterogeneities in the heart.
Mechanoelectrical Feedback as Novel Mechanism of Cardiac Electrical Remodeling
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