Cellular Basis for the Normal T Wave and the Electrocardiographic Manifestations of the Long-QT Syndrome

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Background—This study probes the cellular basis for the T wave under baseline and long-QT (LQT) conditions using an arterially perfused canine left ventricular (LV) wedge preparation, which permits direct temporal correlation of cellular transmembrane and ECG events.

Methods and Results—Floating microelectrodes were used to record transmembrane action potentials (APs) simultaneously from epicardial, M-region, and endocardial sites or subendocardial Purkinje fibers. A transmural ECG was recorded concurrently. Under baseline and LQT conditions, repolarization of the epicardial action potential, the earliest to repolarize, coincided with the peak of the T wave; repolarization of the M cells, the last to repolarize, coincided with the end of the T wave. Thus, the action potential duration (APD) of the longest M cells determine the QT interval and the Tpeak–Tend interval serves as an index of transmural dispersion of repolarization. Repolarization of Purkinje fibers outlasted that of the M cell but failed to register on the ECG. The morphology of the T wave appeared to be due to currents flowing down voltage gradients on either side of the M region during phase 2 and phase 3 of the ventricular action potential. The interplay between these opposing forces determined the height of the T wave as well as the degree to which the ascending or descending limb of the T wave was interrupted, giving rise to bifurcated T waves and “apparent T-U complexes” under LQT conditions. Spontaneous and stimulation-induced polymorphic ventricular tachycardia with characteristics of torsade de pointes (TdP) developed in the presence of dl-sotalol.

Conclusions—Our results provide the first direct evidence that opposing voltage gradients between epicardium and the M region and endocardium and the M region contribute prominently to the inscription of the ECG T wave under normal conditions and to the widened or bifurcated T wave and long-QT interval observed under LQT conditions. Our data suggest that the “pathophysiological U” wave observed in acquired or congenital LQTS is more likely to be a second component of an interrupted T wave, and argue for use of the term T2 in place of U to describe this event. (Circulation. 1998;98:1928-1936.)

Key Words: cells ■ electrophysiology ■ waves ■ action potentials ■ electrocardiography ■ long-QT syndrome

It is generally accepted that the QT interval encompasses the time from the earliest activation to the latest repolarization of ventricular myocardium and that the T wave is the result of repolarization gradients within the ventricles of the heart.1,2 Previous studies have described various degrees of heterogeneous repolarization along the endocardial and epicardial surfaces in the heart of several species.3–7 Transmembrane action potentials (APs) recorded from the right ventricle are usually longer than those from the left, and APs from the apical regions are generally longer than those recorded near the base. Such apico-basal repolarization gradients have been proposed to contribute to the electrocardiographic T wave,8 although the magnitude and direction of ventricular gradients within the hearts remain poorly defined. Prominently lacking are data relative to transmural gradients across the ventricular wall. As a consequence, the mechanisms responsible for the T wave under normal as well as pathophysiological conditions are not well understood.

The congenital and acquired long-QT syndromes (LQTS) represent pathophysiological states characterized by the appearance in the ECG of LQT intervals, notched T waves, prominent U waves, and an atypical polymorphic ventricular tachycardia known as torsade de pointes (TdP). Although the ionic bases for the different forms of LQTS are coming into focus,9,10 the cellular basis for the ECG manifestations of the disease remains poorly understood. Recent studies have implicated M cells located in the intramural layers of the ventricular myocardium in the manifestation of these repolarization phenomenon and arrhythmic sequelae.10,11 The present study provides a direct test of the hypothesis that transmural voltage gradients contribute prominently to the T wave and the ECG manifestations of LQTS using the perfused wedge preparation described in the adjoining article.12 A preliminary report appeared in abstract form.13
Methods

Arterially Perfused Wedge of Canine Ventricle

The methods for isolation, perfusion, and recording of transmembrane activity from the arterially perfused canine left ventricular (LV, anterior wall) wedge preparation, as well as the viability and electrical stability of the preparation, are described and discussed in the accompanying article.11

A transmural ECG was recorded using electrodes consisting of AgCl half cells attached to Tyrode’s solution–filled tapered polyethylene electrodes, placed in the Tyrode’s solution bathing the preparation 1.0 to 1.5 cm from the epicardial and endocardial surfaces, along the same vector as the transmural recordings (Epi:“+”pole). The electrical field of the preparation as a whole was measured using this technique. Thus, the ECG registration represents a pseudo-ECG of that part of the LV. To differentiate it from local electrogram activity, we refer to it as an ECG. In one series of experiments, 4 pairs of electrodes were used to simultaneously record ECG signals at 0°, 45°, −45°, and 90° relative to the transmural axis. LV wedges spanning at least 5 cm along the apico-basal axis were also used in this series. The QT interval was defined as the time interval between the initial deflection of the QRS complex and the point at which a tangent drawn to the steepest portion of the terminal part of the T wave crossed the isoelectric line.

APs were simultaneously recorded from the epicardial, M, and endocardial or subendocardial Purkinje sites using 3 separate intracellular floating microelectrodes as described in the accompanying article.12 Impalements were obtained from the cut surface as well as epicardial and endocardial surfaces of the preparation at positions approximating the transmural vector of the ECG recording. In all Figures, graphic correlation of transmembrane and ECG activity was achieved by dropping a dotted line from the point of full repolarization of each AP (APD90—approximated by eye) to the ECG trace.

To ensure that transmembrane activity recorded at the cut surface of the preparation was representative of the activity in the intramural layers, we used unipolar electrodes in some experiments to measure the activation-recovery interval (ARI) in the deeper layers of the wedge. The ARI values were then compared with values for action potential duration (APD) recorded at the surface. Plunge electrodes consisting of silver wire (120 μm diameter), Teflon insulated except at the tip, were introduced to the center of the preparation. Each electrode was referenced to the bath ground (AgCl electrode). Caution was exercised to ensure that the position of the bath ground did not influence the morphology of the unipolar electrogram. Each unipolar recording was differentiated and the ARI approximating the APD at each site was measured as the interval between the time minimum of the first derivative (Vmin) of the QRS deflection and the maximum first derivative (Vmax) of the T wave. ARI was compared with either APD at 90% repolarization (APD90) or the interval between Vmax and Vmin of the differentiated AP trace. Validation of the use of this technique for the approximation of APD at transmural sites within canine ventricular myocardium was recently provided by El-Sherif and coworkers.13

Amplified signals were digitized, stored on magnetic media and WORM-CD, and analyzed using Spike 2 (Cambridge Electronic Design).

Statistics

Statistical analysis of the data was performed using Student’s t test for paired data or 1-Way ANOVA coupled with Scheffé’s test. Data are presented as mean±SD unless otherwise indicated.

Results

Contribution of Epicardium, M Region, Endocardium, and the Purkinje Network to Repolarization Waves in the ECG

Figure 1 illustrates the temporal relationship between transmembrane APs simultaneously recorded from the epicardium, M region, and endocardium or subendocardial Purkinje and the ECG T wave. Repolarization of the M cell (deep subendocardium–mid myocardium) is temporally aligned with the end of the T wave, whereas repolarization of the epicardial cells is coincident with the peak of the T wave. Similar results were obtained in 20 of 20 preparations studied. The APD of endocardial cells was usually intermediate, as in Figure 1A, although in preparations obtained very close to the septum, repolarization of endocardium closely approximated the end of the QT interval. This is most likely due to the fact that in this part of the LV, M cells are located in the deep subendocardium and exert a strong electrotonic influence to prolong neighboring endocardial cells.

Interestingly, the APD of subendocardial Purkinje fibers was always longer than that of the M cell, but the delayed repolarization of the Purkinje system failed to register on the ECG (Figure 1B). In 14 experiments in which APs from M cells and subendocardial Purkinje fibers were simultaneously recorded, APD90 was 260±21 and 299±17 ms in M and Purkinje, respectively, (P<0.01) at BCL=1000 ms.

These temporal relations between cellular electrical activity and the QT complex in the ECG remain constant over a wide range of conditions. In Figure 2, the wedge was perfused with Tyrode’s solution containing different [K+]o. The changes observed are very similar to those observed clinically with hypo- and hyperkalemia. Low [K+]o, (2 mmol/L) prolonged the QT interval and flattened the T wave, whereas high [K+]o, (6 mmol/L) abbreviated the QT interval and gave rise to tall upright T waves. Throughout this protocol, repolarization of epicardium defines the peak of the T wave and repolarization of the M region defines the end of the T wave, so that the interval between the peak and the end of the T wave approximates the transmural dispersion of repolarization (difference in repolarization times between epicardium and the M region).
The temporal association between cellular electrical activity and the QT interval was also observed with variation of stimulation rate as illustrated in Figure 3 (n=15). Rate-dependent changes in the QT peak and QT end intervals are closely approximated by the rate-dependent changes in the APD plus activation time (AT) of epicardium and of the M cells, respectively. Moreover, rate-dependent changes in the interval between the start of the QRS and the peak of the T wave (QT peak) closely approximate the rate-dependent changes in the repolarization time of epicardium. A disproportionate prolongation of the AP in the M region accounts for the prolongation of the QT interval and the widening of the T wave. Significant transmural dispersion of repolarization is evident at BCL =1000 ms and is more accentuated at slower rates.

Voltage Gradients at the Level of the Action Potential Plateau Contribute Prominently to Inscription of the T wave

Although ventricular gradients (generally defined as transmural gradients in the timing of phase 3) have been the focus in the past, our data suggest that much of the T wave is inscribed as a result of voltage gradients present at the level of the plateau (Figures 4 and 5). This parameter has not been quantified previously because of the lack of adequate methodology. To assess the contribution of voltage gradients on either side of the M region to the registration of the T wave, we constructed voltage difference plots (eg, Figure 4). APs simultaneously recorded from endocardial, epicardial, and M-region sites are shown in the top trace. The middle trace in each panel displays the ECG recorded across the wedge and the bottom grouping shows the computed voltage differences between the epicardium and M-region APs ($\Delta V_{M-Epi}$) and between the M region and endocardium responses ($\Delta V_{Endo-M}$). If these traces are representative of the opposing voltage gradients on either side of the M region (responsible for inscription of the T wave), then the weighted sum of the 2

**Figure 2.** Simultaneous recording of APs from epicardium (Epi) and M region (M), together with a transmural ECG. The wedge was perfused with Tyrode’s solution containing 2, 4, or 6 mmol/L $[K^+]_0$, and paced at BCL=1000 ms. The temporal relationship between the cellular events and the ECG remain constant at different $[K^+]_0$.

**Figure 3.** Relationship between the ECG QT interval, QT peak, and APD$_{90}$ plus activation time (AT) recorded from endocardial (Endo), M-region (M) and epicardial (Epi) sites at BCL=500 to 4000 ms. Rate-dependent changes in the QT interval were closely approximated by the rate-dependent changes in the APD$_{90}$ of the M cells. The wedge was stimulated from the endocardial surface. AT represents impulse conduction time from endocardium to recording site. Error bars represent SEM.

**Figure 4.** Interruption of the descending limb of the T wave. Each panel shows APs recorded from epicardial (Epi), M-region (M), and endocardial (Endo) sites (top), a transmural ECG (middle), and the calculated voltage differences between epicardial and M-cell APs (M-Epi) and between the M-cell and endocardial responses (Endo-M) (bottom). The middle trace is the sum of the 2 voltage-difference plots. The traces were simultaneously recorded from an isolated arterially perfused canine LV wedge under control conditions (A) and in the presence of dl-sotalol (100 µM, B). Superimposition of the traces provides evidence of the fact that the start of the T wave is due to divergence of the plateau phase of the M-cell AP from that of epicardium and endocardium. dl-Sotalol produced a preferential prolongation of the M-cell AP leading to the appearance of a notched T wave and a long-QT interval in the ECG.
traces should yield a trace (middle trace in bottom grouping) resembling the ECG, which it does. A weighting coefficient of 0.7 was applied to $V_{\text{Endo-M}}$ in this and other experiments in calculating the sum of $\Delta V_{\text{M-Epi}}$ and $\Delta V_{\text{Endo-M}}$. So that they more accurately reflect opposing currents responsible for the T wave. This coefficient reflects the ratio of average tissue resistance between Endo-M and M-Epi regions.\textsuperscript{12}

Under control conditions, the T wave begins when the plateau of the epicardial AP separates from that of the M cell (Figure 4A). As epicardium repolarizes, the voltage gradient between epicardium and the M region continues to grow, giving rise to the ascending limb of the T wave. The voltage gradient between the M region and epicardium ($\Delta V_{\text{M-Epi}}$) reaches a peak when the epicardium is fully repolarized—this marks the peak of the T wave. On the other end of the ventricular wall, the endocardial plateau deviates from that of the M cell, generating an opposing voltage gradient ($\Delta V_{\text{Endo-M}}$) that limits the amplitude of the T wave and contributes to the initial part of the descending limb of the T wave. The voltage gradient between the endocardium and the M region reaches a peak when the endocardium is fully repolarized, creating a notch in the descending limb. The remainder of the T wave is due to repolarization of the M cells. It is noteworthy that the dl-sotalol–induced increase in dispersion of repolarization across the wall is accompanied by a corresponding increase in the $T_{\text{peak}}-T_{\text{end}}$ interval in the ECG.

Similar relationships were observed in varying degrees in 9 of 10 preparations exposed to either 100 $\mu$mol/L dl-sotalol or 5 mmol/L 4-aminopyridine in the presence of normal [K].\textsuperscript{1}\textsuperscript{m}

In the preparation of hypokalemia, $I_{\text{Ks}}$ block causes a more pronounced bifurcation of the T wave, as illustrated in Figure 5. dl-sotalol (100 $\mu$mol/L) and hypokalemia produce a remarkable prolongation of the QT interval and a deeply notched T wave, a configuration that some authors refer to as T-U complex. The rate of repolarization of phase 3 of the AP is slowed, giving rise to small opposing voltage gradients that crossover producing a low amplitude bifid T wave. Initially the voltage gradient between the epicardium and M regions (M-Epi) is greater than that between endocardium and M region (Endo-M). When endocardium pulls away from the M cell, the opposing gradient (Endo-M) increases, interrupting the ascending limb of the T wave. Predominance of the M-Epi gradient is restored when the final segment of the epicardial response undergoes an accelerated repolarization, thus resuming the ascending limb of the T wave. Full repolarization of epicardium marks the peak of the T wave. Repolarization of both endocardium and the M region contributes importantly to the descending limb.

Are we justified in calling this a U wave? Our data would suggest that we may not be. The apparent T-U complex is in fact a T wave whose ascending limb is interrupted. The forces that give rise to this second component or “pathophysiologic U wave” appear no different than those responsible for the T wave.
Figure 6 shows another example of a preparation exposed to \( \text{dl}-\text{sotalol} \) and severe hypokalemia. Recordings from epicardium, M, and endocardial regions are superimposed. It is noteworthy that the T-U complex attending the premature beat (but not that of the basic beat) conforms with the classic definition of a U wave, because the T wave returns to the isoelectric line before the U wave is inscribed, yet clearly it is a second component of the T wave.

Figure 7 graphically illustrates the result of 20 experiments in which the effects of \( \text{dl}-\text{sotalol} \) (100 \( \mu \text{mol/L} \)), 4-aminopyridine (5 mmol/L; blocks \( I_o \) and \( I_k \)), and \( \text{dl}-\text{sotalol} \) (100 \( \mu \text{mol/L} \)) + hypokalemia (1.5 mmol/L) were studied. Drug-induced prolongation of the AP of the M cell is greater than that of the endocardium or epicardium, although this difference is reduced under severe hypokalemic conditions (because electrotonic interactions between these 2 neighboring tissues are enhanced). In contrast, the effects of both 4-aminopyridine and sotalol to prolong the AP in epicardium were much smaller than in the M cell region. The figure also shows that the QT interval is most closely approximated by the APD\(_{90}\) of cells in the M region, that both agents act to increase the transmural dispersion of refractoriness in the presence of normal \( [\text{K}^+]_o \), and that the drug-induced increase of transmural dispersion is smaller under severe hypokalemic conditions.

Transmural Versus Apico-Basal or Anterior-Posterior Repolarization Gradients

Apico-basal and anterior-posterior repolarization gradients are thought to play a prominent role in the registration of the T wave.\(^{8,15}\) Little is known about the relative importance of repolarization gradients perpendicular (transmural) versus parallel to the surface of the heart.

To assess the contribution of repolarization gradients along these different vectors, we simultaneously recorded ECG traces at 0°, 45°, \(-45°\), and 90° relative to the transmural axis. In the representative example illustrated in Figure 8, a prominent T wave recorded along the transmural axis progresses to a flat T wave when the ECG is recorded at a 90° angle to the transmural axis. In wedge preparations that spanned at least 5 cm of the apico-basal length of the LV, T wave amplitude averaged 0.72±0.09 mV along the transmural vector versus 0.06±0.01 mV along apico-basal vector (\( n=4; P<0.01 \)). These findings suggest that inscription of the T wave is largely the result of voltage gradients along the transmural axis in this part of the ventricular wall (anterior, mid apico-basal). Similar experiments will have to be re-
peated using wedge preparations obtained from different parts of the heart and with different stimulation protocols before any definitive conclusions can be made.

Correspondence Between the Electrical Activity of Surface and Intramural Layers

APs recorded from the cut surface of the wedge can be influenced by poor coupling of the surface layers to deeper layers or the juxtaposition of healthy cells to injured cells. When present (during the healing over process), these influences are obvious based on AP, conduction, and/or ECG characteristics (eg, poor correspondence between transmural activation times and the phase of the QRS). These indications notwithstanding, it is important to assess whether the electrical heterogeneity recorded at the surface is representative of the rest of the perfused wedge preparation. This is particularly significant when attempting to correlate transmembrane and ECG data. To address this issue, we monitored the ARI using unipolar plunge electrodes inserted into regions subtending the area mapped with the transmembrane electrodes. Figure 9 compares the ARI measurements made in the intramural layers with APD measurements of the transmembrane AP recorded at the surface, under control conditions, and following exposure to 100 μmol/L dl-sotalol to exaggerate the dispersion of repolarization. The data show good correspondence between the transmembrane activity recorded at the cut surface and activation recovery intervals recorded in subtending intramural sites (Figure 10). Comparable results were obtained in 2 other experiments. In control, APD/ARI averaged 227±7/230±8 and 282±6/280±6 ms in Epi and M cells, respectively, whereas after dl-sotalol (100 μmol/L), the APD/ARI values averaged 270±6/272±10 and 363±17/359±15 ms in Epi and M cells, respectively (n=3). A slightly longer ARI than APD in epicardium and a slightly shorter ARI than APD in the M cells was a consistent finding; we attribute this to the “wider field of view” of the unipolar electrode.

Torsade de Pointes

The development of a large dispersion of transmural repolarization as seen in response to \( I_{K} \) block would be expected to provide the substrate for intramural reentry. In previous studies, we have demonstrated both spontaneous and programmed stimulation-induced (PES) TdP arrhythmias in the wedge following exposure to dl-sotalol and ATX-II. Figure 10 illustrates examples of spontaneous and PES-induced TdP in wedge preparations in response to dl-sotalol (100 μmol/L). In Figure 10A, dl-sotalol increased transmural dispersion of repolarization to 74 ms and the QT interval to 398 ms. No early afterdepolarization (EAD), EAD-induced triggered activity, or premature beats induced by any mechanisms were observed. An extrastimulus introduced to the epicardial surface at an S1-S2 of 250 ms induces a long episode of polymorphic ventricular tachycardia in which the QRS is seen to twist about the isoelectric line, typical of TdP. The episode self-terminates after 231 s. Programmed stimulation

Figure 9. Correspondence between APD recorded at the cut surface of the wedge and ARI recorded using unipolar electrodes placed in the intramural layers subtending the surface recording sites (center of wedge). APs and electrograms were recorded from epicardium and M region before and after exposure to 100 μmol/L dl-sotalol to exaggerate the dispersion of repolarization. Below each AP and unipolar electrogram is the first derivative of each trace. ARI is measured as the interval between \( V_{\text{min}} \) of QRS and \( V_{\text{max}} \) of the T wave of the unipolar electrogram. APD is measured as the interval between \( V_{\text{max}} \) of the upstroke and \( V_{\text{min}} \) of phase 3 of the AP. Numbers represent ARI or APD values for each trace.

Figure 10. Spontaneous and stimulation-induced polymorphic ventricular tachycardia with features of TdP. A, Stimulation-induced TdP in a LV wedge preparation pretreated with dl-sotalol (100 μmol/L). S1-S1=2000 ms; S1-S2=250 ms. S2 was applied to epicardium. B, Spontaneous TdP in a preparation pretreated with dl-sotalol (100 μmol/L). BCL=2000 ms. A spontaneous premature beat with a coupling interval of 348 ms, likely originating from subendocardial Purkinje system, initiates an episode of TdP.
applied during the predrug control period failed to induce TdP. TdP was induced with PES in 5 of 8 perfused wedge preparations pretreated with dl-sotalol. TdP was much more difficult to induce with S2 applied to endocardium. In Figure 10B, dl-sotalol increased transmural dispersion of repolarization to 83 ms. A spontaneous premature beat with a coupling interval of 348 ms initiates an episode of TdP that self-terminates after 6.2 s. The tall, upright and narrow configuration of the QRS of the premature beat suggests that it originates in the subendocardial Purkinje system.

Discussion
Although ECG recordings have been used as important diagnostic tools for more than a century, correspondence between cellular events, especially of intramural structures, and the various components of the surface ECG has not been well established. The cellular bases for the ECG, repolarization waves in particular, have been less than completely understood because earlier studies have not been able to provide simultaneous and direct recordings of transmembrane APs from intramural sites throughout the ventricular wall together with a transmural ECG. Our recently developed arterially perfused canine ventricular wedge preparation provides this capability, permitting a direct temporal correlation of cellular transmembrane and ECG events.

The chief findings of the present study are that the morphology of the electrocardiographic T wave measured across the LV wall appears to be due in large part to currents flowing down voltage gradients present on either side of the M region, during both phase 2 and phase 3 of the ventricular AP. Our data indicate that the interplay between these opposing currents determines the height of the T wave as well as the degree to which either the ascending or descending limb of the T wave is interrupted, leading to a bifurcated or notched appearance. The voltage gradients are the results of a more positive AP plateau (phase 2) in the M region versus epicardium or endocardium and differences in the timing of phase 3 of the AP of the 3 predominant ventricular cell types. Under baseline and LQT conditions, the epicardial response is always the earliest to repolarize and the M-cell AP is the last. Full repolarization of the epicardial AP was always coincident with peak of the T wave and repolarization of the M cells coincided with the end of the T wave. The duration of the M-cell AP was found to determine the duration of the QT interval under a wide variety of conditions in which the QT interval was altered, including changes in pacing rate, prematurity, alterations in \([K^+])\), and exposure to APD-prolonging drugs. Finally, the T\(_{\text{peak}}\)-T\(_{\text{end}}\) interval is shown to provide an index of transmural dispersion of repolarization.

Our demonstration of a correspondence between cellular events and components of the ECG is based on the assumption that the activity recorded from surface cells is representative of cells within the respective layers of the wall throughout the wedge. Such validation is provided in this study (Figure 9; see also reference 10). ARI values recorded from intramural electrograms correspond well to APD values recorded at the surface, even when heterogeneity is amplified with sotalol or ATX-II, indicating that the electrical heterogeneity recorded at the surface of the perfused wedge is representative of the rest of the preparation.

Correspondence of Cellular Transmembrane and ECG Activity
Under baseline conditions, the first structure to repolarize is the last to depolarize. The early repolarization of epicardium provides for a T wave displaying the same polarity as that of the QRS. The start of the T wave, often so gradual as to be indeterminate, is caused by the more rapid rate of decline of the plateau or phase 2 of the epicardial AP, creating a voltage gradient and electrotonic current flow across the wall (Figures 4 and 5). The gradient gradually increases as the epicardial AP continues to repolarize, reaching a maximum with full repolarization of epicardium; this juncture marks the peak of the T wave. Divergence of the plateau of the endocardial AP from that of the M cell occurs soon after that of epicardium, causing a voltage gradient between endocardium and the M region and thus a current opposite to that generated by the voltage gradient that develops between epicardium and the M region. Under normal conditions, current flow between the M region and epicardium is greater than that between the M region and endocardium, resulting in the inscription of the ascending limb of the upright T wave. Once epicardium is fully repolarized, continued repolarization of endocardium leads to a progressively larger voltage gradient between endocardium and the M region, giving rise to the initial descending limb of the upright T wave. The last cells to repolarize are the M cells, contributing to the final segment of the T wave. Full repolarization of the M region marks the end of the T wave. The time interval between the peak and the end of the T wave therefore represents the maximum difference in final repolarization time or the dispersion of repolarization across the ventricular wall.

In the presence of \(I_{\text{Kb}}\) blockers, M cells in the deep layers of the wedge display the greatest prolongation of APD. The APD prolongation of the M region is less than that observed in isolated tissues and cells, and the prolongation of APD observed in epicardium and endocardium is greater than in isolated tissues and cells (see companion article\(^{12}\)).\(^{16–18}\) These differences are expected and are accounted for by the greater electrotonic interaction among the 3 cell types when in the intact wedge. Electrotonic influences are also responsible for the slower repolarization of the AP, particularly in epicardium and endocardium. In isolated tissues and cells, phase 3 is invariably steeper than in the functional syncytium represented by the wedge. Phase 3 is still more gradual in preparations exposed to hypokalemia (Figures 5 and 6). This may be due to (1) a smaller \(I_{\text{Ks}}\) and \(I_{\text{K1}}\) at the lower \([K^+]_o\); (2) more potent drug-induced inhibition of \(I_{\text{Kc}}\) at the lower \([K^+]_o\);\(^{19}\) and (3) the longer space constant expected at the lower \([K^+]_o\). Our data suggest that the electrotonic influence of the M cells may be greater on endocardium than it is on epicardium because of: (1) the closer proximity of the longest M cells to endocardium;\(^ {12}\) and (2) the greater tissue resistivity between the midmyocardium and the epicardium.\(^ {12}\) The considerable electrotonic interaction between endocardium and the M region becomes apparent when the endocardium is
excised from the wedge; this procedure gives rise to a much longer M-cell AP.20

In the wedge as in the clinic, \( I_{Kr} \) blockers lead to the development of long-QT intervals and either smooth broad T waves, notched T waves, or pathophysiological T-U complexes. Our results indicate that a notch on the descending limb of the T wave results when the current generated as a result of the voltage gradient between endocardium and the M region changes abruptly during the descending limb of the T wave; this occurs as endocardium approaches full repolarization (Figure 4).

A notch on the ascending limb of the T wave occurs when a gradient develops between endocardium and the M region capable of generating current sufficient to change the direction of net current flow across the wall (Figures 5 and 6). This usually occurs under the condition of hypokalemia where the slope of phase 3 of the AP is greatly reduced. The ascending limb of the T wave is interrupted until the voltage gradient between the epicardium and the M region becomes large enough to overcome the current flowing between endocardium and the M region, at which point the ascending limb proceeds upward once more. The notch often gives rise to a bifurcated T wave, the second component of which is often referred to as a U wave in the literature. Our observations suggest that the second component is not a U wave but rather the resumption of an interrupted T wave (Figures 5 through 7). The data clearly demonstrate that the sources responsible for the second component of the T wave are no different from those generating the first component.

These results and interpretations are consistent with those of Lehmann et al.,21 who demonstrated the presence of two components of the T wave (T1, T2) together with a U wave in patients with the long-QT syndrome and used these observations to argue against the labeling of T2 as a U wave. Our results indicate that a notch on the descending limb of the T wave with or without a notch on the ascending limb when \([K^-]\) is normal (Figure 4). Mild hypokalemia can exaggerate dispersion of repolarization across the ventricular wall, whereas severe hypokalemia has the opposite effect. Severe hypokalemia reduces the slope of phase 3 of the AP and increases the space constant, thus decreasing transmural voltage gradients and currents. As a consequence, the amplitude of the T wave is low and more likely to be bifurcated. Although a smaller dispersion of transmural repolarization may reduce arrhythmic risk, an increased propensity for development of EADs under these conditions would have the opposite effect.

The appearance of bifurcated or notched T waves of large amplitude clearly denotes the presence of a large transmural dispersion of repolarization and refractoriness. Such ECG manifestation in the acquired or congenital LQTS has been shown to be associated with increased risk21,36 for the development of TdP. In our experimental model, as in the clinical syndromes, marked transmural dispersion of repolarization signified by these ECG changes is associated with the development of TdP. The characteristics of the arrhythmia induced by dl-sotalol are similar to those described for d-sotalol. Although it is beyond the scope of this article to deal with the mechanism underlying TdP, our data in the wedge point to a reentrant mechanism as the basis for maintenance of the arrhythmia and triggered activity as the initiating mechanism.10,11

**Limitations of the Study**

We would like to stress that the T wave measured in the intact organism is generated by more than transmural ventricular gradients. Apico-basal gradients are thought to influence the morphology of the T wave in the dog, and may do so in the human as well. The present study indicates that such gradients are not nearly as accentuated as transmural voltage gradients, but the data presented do not permit a full assessment of the extent to which apico-basal or antero-posterior versus transmural gradients contribute to the ECG. Further studies are clearly needed to address these points.

**Acknowledgments**

This work was supported by grant HL-47678 from the National Institutes of Health and grants from the SADS Foundation and the Sixth and Seventh Manhattan Masonic Districts. It was also supported by the Masons of New York and Florida. We gratefully acknowledge the expert technical assistance of Judy Hefferton, Di Hou, Tengxian Liu, and Robert Goodrow. We are grateful to Dr Wataru Shimizu for conducting the experiments involving recording of multiple ECG signals from the perfused wedge preparation.

**References**

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doi: 10.1161/01.CIR.98.18.1928

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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