Estimates of Repolarization Dispersion From Electrocardiographic Measurements

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Background—Repolarization dispersion (Rd) is frequently mentioned as a predictor of cardiac abnormalities. We present a new measure of Rd based on the root-mean-square (RMS) curve of an ECG lead set and compare its performance with that of the commonly used QT dispersion (QTd) measure with the use of recovery times measured from directly recorded canine electrograms.

Methods and Results—Using isolated, perfused canine hearts suspended in a torso-shaped electrolytic tank, we simultaneously recorded electrograms from 64 epicardial sites and ECGs from 192 “body surface” sites. RMS curves were derived from 4 lead sets: epicardial, body surface, precordial, and a 6-lead optimal set. Repolarization was altered by changing cycle length, temperature, and activation sequence. Rd, calculated directly from recovery times of the 64 epicardial potentials, was then compared with the width of the T wave of the RMS curve and with QTd for each of these 4 lead sets. The correlation between T-wave width and Rd for each lead set, respectively, was epicardium, 0.91; body surface, 0.84; precordial, 0.72; and optimal leads, 0.81. The correlation between QTd and Rd for each lead set was epicardium, 0.46; body surface, 0.47; precordial, 0.17; and optimal leads, 0.11.

Conclusions—RMS curve analysis provides an accurate method of estimating Rd from the body surface. In contrast, QTd analysis provides a poor estimate of Rd. (Circulation. 2000;102:685-691.)

Key Words: fibrillation • electrocardiography • arrhythmia

In 1940, Wiggers postulated that ventricular fibrillation could be initiated by applying a stimulus during “late systole, at which time certain elements have passed out of their refractory phase.” He recognized the fact that disparity in repolarization times across the ventricles left them vulnerable to arrhythmias. Since that time, there have been a large number of studies that have investigated the disparity of repolarization, how it is reflected in the T wave, and its relation to ventricular arrhythmias.

Unfortunately, until recently, clinical evaluation of repolarization dispersion (Rd) was seldom attempted. Little clinical interest in measures of disparity resulted from the impracticality of applying the 2 primary techniques, body surface mapping and direct epicardial or endocardial recording, on a large scale. Only recently have investigators attempted to use standard ECGs to assess Rd. Some studies have found that QT dispersion (QTd) across standard ECG leads is a statistical predictor for various clinical abnormalities. On the basis of these results, they infer that these measurements reflect Rd. However, relatively little work has been done that directly associates QTd with Rd.

The research presented here had 2 purposes: first, to introduce a new technique to estimate Rd based on the width of the root-mean-square (RMS) T wave generated from a set of ECG leads; and second, to investigate the relation between QTd and Rd. We accomplished both of these objectives through the use of isolated, perfused canine hearts suspended in a torso-shaped electrolytic tank that permitted simultaneous measurement of epicardial electrograms and tank surface ECGs. Two hypotheses were tested to accomplish these goals: First, the width of the RMS T wave is correlated with Rd, and second, QTd is correlated with Rd. It is important to note that we investigated these hypotheses by using data from the following 4 different lead sets: (1) 64 epicardial electrograms from which recovery times were actually measured, (2) 192-lead ECG body surface, (3) 6 standard precordial ECG leads, and (4) an “optimal” 6-lead set (see Figure 1), which Fuller et al have shown to provide good estimates of ST-segment shifts across the entire body surface.

Through the use of these various lead sets, we believe that we have investigated the ability of both techniques to predict Rd both in an idealized setting and in conditions similar to those facing the clinician.

Methods

Experimental Paradigm

The experimental preparation used for these studies was an isolated, canine heart placed inside an instrumented, torso-shaped, electrolytic...
This preparation, approved by the University of Utah Institutional Animal Care and Use Committee, has been described elsewhere.10,11 Briefly, circulatory support of the isolated heart was provided in a modified Langendorff manner by a second dog (Figure 2). Both dogs were anesthetized with pentobarbital (30 mg/kg), and the heart of the smaller animal (body weight typically 12 to 15 kg) was removed and perfused by an aortic cannula from the carotid artery of the support dog. The isolated heart beat, under no mechanical load, either at its own intrinsic rate or stimulated by bipolar pacing electrodes inserted into the right atrium or imbedded within the sock. All tubing linking the animals was warmed by heat exchangers. Frequent monitoring of pressures and temperatures ensured adequate perfusion. A mechanical gantry mounted above the electrolytic tank permitted adjustable positioning of the heart inside the tank.

The electrolytic tank used for these studies was a fiberglass shell molded from an adolescent’s thorax, which was filled with an electrolyte of saline and sucrose balanced to offer 500 \( \text{V} \)-cm resistivity, a typical mean value for the human thorax. The electrolyte was circulated through a heat exchanger for temperature control, normally maintained at 37°C. The tank surface contained 192 silver electrodes arranged in a uniformly spaced 16 \( \times \) 12 grid. An epicardial electrode array was fabricated by knotting 64 insulated 0.005-inch-diameter silver wires into a heart-shaped nylon fabric, removing insulation at the knots, and plating with silver chloride to reduce polarization potentials. The array was pulled over the isolated heart and tied to the support structure.

Data Acquisition

Data were recorded simultaneously from the 192 tank and 64 epicardial surface sites. Recordings were taken while stimulating from the atrium or 32 different ventricular sites with the use of twice-threshold, bipolar pacing. To alter repolarization, cycle lengths were varied from 300 to 600 ms, and the temperature of the electrolyte solution was varied from 32° to 40°C. The data were acquired with a 256-channel multiplexer capable of 12-bit resolution and 1000 samples/s. The bandwidth of the recording system was 0.03 to 500 Hz. Three separate preparations were used to obtain data for this study, resulting in 52 separate recordings, details for which are provided in Table 1.

Data Analysis

**QT Interval**

Traditionally, deviation from baseline or intercept of maximum slope with the baseline have been used to determine fiducial points such as the end of the T wave.12 We discarded these approaches because of their sensitivity to noise and their inability to select the start and end points in the presence of wandering baselines. Instead, maximum curvature was used to determine all onset and offset points (see Figure 3). Curvature is a unitless quantity that is calculated as follows:

\[
\text{curvature} = \left| \frac{d^2v}{dt^2} \right| \left/ \left( 1 + \left( \frac{dv}{dt} \right)^2 \right)^{3/2} \right|
\]

Figure 1. Location of 6 optimal leads on torso. The 12\( \times \)16 grid represents location of 192 body surface electrodes on torso-shaped tank. Uppermost and lowest rows of electrodes correspond to levels just below sternal notch and just above umbilicus, respectively. Far right and far left columns of electrodes correspond to vertical regions just left and right of spine, respectively. Stylized sternum shows anterior thoracic midline.

Figure 2. Schematic of torso tank experimental paradigm.

Table 1. Experimental Paradigms Used to Alter Repolarization

<table>
<thead>
<tr>
<th>Animal</th>
<th>No. of Activation Sequences</th>
<th>No. of Cycle Lengths</th>
<th>No. of Electrolyte Temperatures</th>
<th>No. of Recordings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>5</td>
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<td>2</td>
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<td>3</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>25</td>
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</table>

Figure 3. Determination of QT interval (QTI) of ECG recording by maximum curvature.
It is important to remember that curvature is a function of scale and that all waveforms must be normalized to achieve consistent results. Peaks in the curvature function were only considered valid if they were 3 times higher than the RMS noise in the curvature signal during the T-P interval. This meant that there were recordings in almost all runs that were considered to have no T wave.

The determination of QT interval is often difficult when there are multiple deflections during repolarization (T and U waves). In this study, the termination was always chosen at the end of the final deflection. The motivation for this was based on the observation that almost every recording that had multiple deflections on the body surface map, as well as the cardiac surface map, was a “transition waveform” between two other leads, one having an early T wave and the second a later T wave. Because these waveforms were a transition between two others, the selection of their end point had no practical effect on the analysis, since other leads had both earlier and later end T times.

To ensure that this new technique gave results similar to traditional methods of QT interval determination, we compared it with the maximum slope method.12 A comparison of QT intervals over 700 ECG leads taken from all 3 animal experiments showed that the 2 methods produced highly correlated intervals \( r = 0.95 \), with large discrepancies only present when there was baseline wander in the signal, causing the maximum slope method to fail.

**Recovery Times**

As previously stated, the measurements from which Rd was determined was the recovery times of the 64 epicardial leads. Both RMS T-wave width and QT dispersion were compared with this standard. The determination of recovery times for the epicardial leads is described below.

Time zero was arbitrarily defined as QRS onset of the epicardial RMS curve generated from each recording. Then, for each individual epicardial electrogram, the time of maximum slope near the peak of the T wave was defined as the recovery time (Figure 4). This measurement has been documented to reflect time of action potential downstroke as measured from floating microelectrodes located within 1 mm of the unipolar electrodes.13,14 Electrograms that were equivocal, either because of noise or because of possible multiple inflections, were discarded. We considered the peak derivative associated with repolarization to be valid only if it was 3 times bigger than the RMS noise of the derivative signal in the T-P segment.

**Determination of Recovery Time and QT Interval Dispersion**

For both QTd and Rd, we used range (maximum value minus minimum value) as measures of repolarization dispersion. Although standard deviation may be statistically more robust, range is used in most clinical studies. Furthermore, in our experience, both in these and other experiments, range of Rd is consistently \( \approx 4 \) times its standard deviation. QTd was calculated for the 64 epicardial lead set, the 192-lead body surface map, and the 2 6-lead subsets of the body surface map: precordial and “optimal” (see Figure 1).

**Generation of RMS Curves**

From each of the 52 recordings, 4 RMS curves were generated. 1 from each of the 4 different lead sets: epicardium, torso surface, precordial leads, and optimal 6 leads. For the torso data, the RMS curve was generated from the 192 individual leads according to the following formula

\[
\text{RMS}(t) = \sqrt{\frac{\sum_{i=1}^{192} v_i(t)^2}{192}}
\]

where \( v_i \) is the voltage on lead \( i \). Both the precordial and optimal lead set RMS curves were computed in a similar manner from the 6 potentials in their respective lead sets. Finally, an epicardial RMS curve was computed on the basis of the 64 epicardial electrograms.

**Analysis**

We tested the following 2 hypotheses: (1) The width of the T wave of the RMS waveform is correlated with Rd. For each of the 52 experimental paradigms shown in Table 1, recovery times from all 64 epicardial leads were computed (also see Figure 6). Rd, defined as the range (maximum minus minimum) of all recovery times, was then determined. This value of Rd, determined from the 64 epicardial leads, was the standard to which both the width of RMS T waves and QTd were compared. Four RMS T-wave widths, 1 from each of the 4 lead sets, were then determined for each experimental run. (2) QTd is correlated with Rd. With the use of the same calculation of Rd as in hypothesis 1, Rd was compared with QTd. As with Rd, QTd was defined as the range of all QT times over a particular lead set. The result was a comparison of Rd of the 64 epicardial leads with 4 different QTds, 1 for each of the 4 lead sets. Scatterplots and correlation coefficients were used for comparison of Rd and QTd.
Results

Basic Waveform Analysis

On the basis of the exclusion criteria described above, 8 RMS curves in which the start point of the T wave could not be determined were excluded from further analysis. All of these were from animal 3, in which we stimulated from 32 different ventricular sites as well as during supraventricular pacing. Only 24 of the 32 ventricular sites produced RMS curves from which we could determine a start point of the RMS T wave. The eliminated curves were linear from the J-point to the peak of the T wave, and hence there was no visible start of the T wave. The discrepancy between the number of paradigms in our methods description and those in Table 1 are a result of the elimination of these experiments.

In almost all the remaining runs, some QT and/or recovery time measurements were discarded because of failure to meet the measurement criteria. Typically, QT measurements were discarded because of the lack of a significant T wave, which resulted in no valid curvature maximum at the end of the waveform. Recovery time measurements were discarded if the T-wave derivative maximum did not meet requirements described in the Methods section. Statistics for excluded measurements, both from the body surface and epicardial measurements, are presented in Table 2.

Estimates of Rd

With the use of the 52 data sets from the qualifying runs, Rd was compared with both RMS T wave width and QTd. Rd from the 64 epicardial leads was plotted against QTd and RMS T-wave width for all 4 lead sets. These scatterplots are presented in Figure 7, along with the least-squares regression line for each lead set. Correlation coefficients for Rd versus both RMS T-wave width and QTd are presented in Table 3.

Discussion

The main purpose of this study was to investigate whether repolarization dispersion could be accurately estimated from body surface ECG measurements. We have demonstrated that

| Table 2. Mean±SD of Number of QT Intervals and Recovery Times That Had to Be Eliminated From Each Recording |
|-------------------------------------------------|-----------------|----------------|
| Body Surface QT                                 | 5.3±11.0        |
| Epicardial QT                                   | 0.7±1.7         |
| Recovery Times                                  | 3.5±4.0         |
the T-wave width of the RMS curve calculated from body surface potentials provides a reasonable estimate of dispersion. In direct contrast, QTd is poorly correlated with dispersion, and its use as an estimate of Rd must be questioned. This confirms previous studies in our laboratory that showed that QTd changes reflected lengthening of recovery times only and failed to show any change with local shortening of repolarization.15 Although the correlation between precordial T-wave width and Rd is significant, the “optimal” lead T-wave width is obviously a better choice.

How an optimal lead set is determined deserves a brief explanation. The technique used5 attempts to optimize the estimation of potentials over the entire torso. Each lead is selected because it provides as much independent information as possible about potential distribution across the body surface. The iterative process picks the first lead by examining its correlation with all other leads on a 192-lead torso map. The lead with the highest mean correlation with all other leads is selected. After removing information predicted by the first lead, a second lead is chosen in a similar manner. This process is usually repeated until the RMS error of the predicted potentials is reduced to some predetermined value. An important point to note is that this optimization was done across a series of 42 subjects and need not be repeated on a patient-to-patient basis. The resulting lead sets “optimization” is then minimization of RMS error when predicting potentials across the entire torso.

Other Methods of Estimating Repolarization Irregularities

The technique presented here provides a method of estimating Rd on a beat-to-beat basis. However, it does not provide a total picture of repolarization. Another method that was originally suggested by Wilson et al16 is the QRST integral map. Wilson et al postulated that if all action potentials throughout the ventricles had the same duration, the integrals (areas) of QRS and ST-T waveforms in any ECG lead should be equal in magnitude and opposite in polarity, thus canceling on their algebraic combination. The obvious corollary to this hypothesis is that when the QRS and ST-T areas of any ECG lead do not add to zero, the result is an indication of the disparity of action potential duration as seen by that lead. An important theoretical17,18 and experimentally observed19 property of the QRST integral is that it is nearly independent of activation sequence. Thus, the QRST integral of an ECG lead during supraventricular activation of the ventricles is almost the same as that obtained during ectopic ventricular activation. This feature is attractive from the standpoint that it suggests that the QRST integral could be used to assess repolarization disparity during ventricularly paced beats or in the presence of ventricular conduction defects. However, as pointed out by Geselowitz,18 the QRST integral is actually a function of differences (3D gradients) of action potential integrals, thus making the index sensitive to differences of action potential durations as well as amplitude and resting potential differences. This has tempered enthusiasm for use of the index. Despite this, its use in assessing increased repolarization disparity in relation to increased arrhythmia susceptibility has been demonstrated.20,21

There are a large number of conflicting studies2,6,8,22–25 that examine the relation between QTd and various cardiac diseases. The underlying assumption in these studies is that QTd is a measure of repolarization dispersion. The fundamental question of the relation between the two, however, has received relatively little attention. Zabel et al26 compared endocardial monophasic action potential duration dispersion with 12-lead QTd and found a correlation of 0.67. Because the study recorded from an average of only 8±3 endocardial sites, overall significance of the findings may be weakened.

### TABLE 3. Correlation Coefficients of Repolarization Range Versus Both T-Wave Width and QT Range

<table>
<thead>
<tr>
<th></th>
<th>T-Wave Width</th>
<th>QTd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicardial</td>
<td>0.91</td>
<td>0.46</td>
</tr>
<tr>
<td>Body surface</td>
<td>0.84</td>
<td>0.47</td>
</tr>
<tr>
<td>Precordial</td>
<td>0.72</td>
<td>0.17</td>
</tr>
<tr>
<td>Optimal</td>
<td>0.81</td>
<td>0.11</td>
</tr>
</tbody>
</table>
In a study of isolated rabbit ventricles, the correlation between QTd and action potential duration was 0.58. Interestingly, the same study found that the correlation between T-wave area and action potential duration was 0.82. The authors also found that the correlation between time from peak to end of T waves and action potential duration was 0.81, results that compare well with our study.

Other studies that seem to further weaken the relation between QTd and repolarization dispersion were done by Kautzner et al and Punske et al. Kautzner et al found that the “parameters that characterize dispersion in the 12-lead ECG are not reproducible, both between subsequent recordings (relative error 25% to 35%) and between observers (relative error 28% to 33%).” Punske et al demonstrated that the main factor influencing the time of the end of the T wave was its proximity to the zero potential line, which is highly dependent on activation sequence and hence repolarization sequence.

**Study Limitations**

A major limitation of our study is that our sample of recovery times came from the epicardium only. We do not have a good estimate of how our results would change if we, instead, sampled data throughout the myocardium. We plan further research with intramural needles with equally spaced electrodes instead of a sock to obtain a better sample of recovery times.

Another limitation of this study was the inability to test the sensitivity of the various lead sets to repolarization changes in localized areas. Since the perturbations done were not regional, it was impossible to test sensitivity of each lead set to changes in repolarization as a function of regional changes. Local heating and cooling of the epicardium in future experiments will help to answer these questions.

Finally, we were unable to see if there was a significant difference in the behavior of QTd or RMS T-wave width during atrial stimulation versus ventricular stimulation. One might expect different results during these different activation sequences. Unfortunately, we had insufficient data to allow such an analysis. Although the current data show consistent results during both types of stimulation, in the future it would be beneficial to concentrate on atrial stimulation because of its similarity to clinical conditions.

**Future Work**

We believe that further information, such as activation dispersion, may also be available from the width of the RMS curve. By examining the QRS portion of the RMS curve and the histogram of activation times in Figure 5, one can see that the dispersion of activation times is probably reflected in the QRS width, just as T-wave width reflects Rd. Similarly, mean activation and recovery times should be available by computing the mean time of the QRS and T waves of the RMS curves. We have preliminary data that support these hypotheses, but the distribution of data from the experiments in this study are not varied enough to confirm them.

**Significance**

It is clear that the disparity of repolarization plays an important role in arrhythmogenesis. However, the use of QTd as a clinical measure of repolarization dispersion must be called into question, not only from the results presented here but also from the conflicting results in clinical studies. Therefore, a reliable noninvasive measure of repolarization dispersion is needed to assess patient risk. The RMS curve may not only provide information about Rd but also other activation and repolarization parameters.

**Acknowledgments**

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