Computer Model of Mechanisms Underlying Dynamic Electrocardiographic T-wave Changes

by

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering in the Graduate School of Duke University

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ABSTRACT

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Abstract

Sudden death from arrhythmia is a major cause of mortality in the United States. Unfortunately, no current diagnostic test can accurately predict risk for sudden arrhythmic death. Because ventricular arrhythmias often result from abnormalities of repolarization, assessment of myocardial repolarization using the electrocardiogram (ECG) can aid in prediction of arrhythmia risk. Non-linear, rate-dependent changes in myocardial repolarization can promote the development of arrhythmia, but few studies examine how these dynamic changes in repolarization affect the ECG. This dissertation describes the use of a computer model to investigate the effect of dynamic changes in myocardial repolarization on the ECG T wave.

To simulate action potential conduction from the endocardium to the epicardium of the free wall of the canine left ventricle, 1-dimensional multicellular computer fiber models were created. Each fiber model was composed of endocardial, midmyocardial, and epicardial cells. For each cell type, existing mathematical models were modified to approximate experimental data for four types of dynamic repolarization behavior: (1) dynamic restitution, the response to steady-state pacing; (2) S1-S2 restitution, the response to a premature or postmature stimulus; (3) short-term memory (STM), the response to an abrupt change in pacing rate; and (4) repolarization alternans, beat-to-beat alternation in cellular repolarization time. Repolarization times were obtained from endocardial, midmyocardial, and epicardial regions in the fiber model and compared to parameters measured from a computed transmural ECG.
Spatial differences in repolarization created two voltage gradients that influenced the ECG: an endocardial-midmyocardial (endo-mid) gradient and a midmyocardial-epicardial (mid-epi) gradient. Epicardial dynamic restitution changes altered the mid-epi gradient, influencing the rising phase of the ECG T wave, and endocardial dynamic restitution changes altered the endo-mid gradient, influencing the falling phase of the T wave. Changes in epicardial or endocardial repolarization due to S1-S2 restitution or STM caused transient changes in the rising or falling phase of the T wave, respectively.

During repolarization alternans, an alternating, asymmetric distribution of extracellular potential around the fiber influenced the measurement of T-wave alternans (TWA) in the ECG. Presence of a resistive barrier in the fiber model altered the magnitude of repolarization alternans as well as the TWA amplitude in the ECG with effects dependent on barrier location. The resistive barrier also modified the relationship between cellular repolarization alternans magnitude and TWA amplitude.

The results presented in this dissertation explain basic mechanisms by which dynamic changes in myocardial repolarization affect the ECG T wave. These mechanisms form the foundation for the development of techniques to identify arrhythmogenic, dynamic changes in the myocardium using the ECG. Future studies in higher-dimensional, more complex models will build upon these results by considering the influence of additional voltage gradients, more realistic tissue geometries, and heterogeneities in the volume conductor.
Contents

Abstract.................................................................................................................................................. iv
List of Tables ............................................................................................................................................ x
List of Figures .......................................................................................................................................... xi
List of Abbreviations ............................................................................................................................ xv

1. Introduction........................................................................................................................................ 1
   1.1 Significance of Research in Cardiac Electrophysiology................................................................. 1
   1.2 Dynamic Repolarization of Cardiac Tissue ..................................................................................... 2
      1.2.1 Electrical Restitution: The 1:1 Domain ................................................................................ 2
      1.2.2 Action Potential Duration Alternans: The 2:2 Rhythm ....................................................... 7
   1.3 Dynamic ECG Changes .................................................................................................................. 8
   1.4 Motivation for Using a Computer Model ....................................................................................... 9
      1.4.1 Advantages of Using a Computer Model ............................................................................... 9
      1.4.2 Limitations of Using a Computer Model .............................................................................. 10
   1.5 Research Goals and Specific Aims ............................................................................................... 11

2. Methods.............................................................................................................................................. 13
   2.1 Computer Fiber Model .................................................................................................................. 14
      2.1.1 Overview ............................................................................................................................... 14
      2.1.2 Fiber Model for Restitution Studies .................................................................................... 18
      2.1.3 Fiber Model for Repolarization Alternans Studies ............................................................. 21
   2.2 Models of Cellular Electrical Activity .......................................................................................... 22
      2.2.1 Model for Dynamic Restitution Study .................................................................................. 23
2.2.2 Model for S1-S2 Restitution and Short-Term Memory Study................. 25
2.2.3 Model for Repolarization Alternans Studies........................................ 27
2.3 Numerical Methods and Simulation ......................................................... 29
  2.3.1 Simulation Tools................................................................................. 29
  2.3.2 Numerical Methods............................................................................. 30
  2.3.3 Pacing Protocols............................................................................... 30
2.4 Generation of the Computed ECG ......................................................... 31
2.5 Measurement of Cellular and ECG Parameters ..................................... 33
  2.5.1 Cellular Measures of Activation and Repolarization......................... 33
  2.5.2 ECG Parameters Measured................................................................. 35
3. ECG Manifestations of Dynamic Restitution ......................................... 37
  3.1 Introduction.......................................................................................... 37
  3.2 Results.................................................................................................. 38
    3.2.1 Cellular Activation and Repolarization........................................... 38
    3.2.2 ECG Characteristics...................................................................... 39
    3.2.3 Cellular Repolarization Relation to T-Wave Parameters............... 40
    3.2.4 Intercellular Voltage Gradients Responsible for ECG Waveforms..... 49
  3.3 Discussion............................................................................................ 52
    3.3.1 Effect of Spatial Differences in Dynamic Restitution on the ECG .... 52
    3.3.2 Implications for the Use of ECG Parameters to Assess Myocardial
         Repolarization....................................................................................... 57
  3.4 Limitations............................................................................................ 59
4. ECG Manifestations of S1-S2 Restitution and Short-Term Memory.......... 61
4.1 Introduction.................................................................................................................. 61
4.2 Results.......................................................................................................................... 62
   4.2.1 Cellular Activation and Repolarization ................................................................. 62
   4.2.2 Effects of Cellular Short-Term Memory Changes on the ECG ......................... 63
   4.2.3 Effects of Cellular S1-S2 Responses on the ECG ............................................... 72
4.3 Discussion....................................................................................................................... 75
4.4 Limitations ................................................................................................................... 76

5. Effect of Electrode Placement on T-Wave Alternans Measurement ......................... 78
5.1 Introduction .................................................................................................................. 78
5.2 Results ......................................................................................................................... 79
   5.2.1 Cellular Repolarization Alternans and Tissue Repolarization Gradients .... 79
   5.2.2 T-Wave Alternans Amplitude Relation to Repolarization Alternans .......... 80
   5.2.3 T-Wave Amplitude and T-Wave Alternans Amplitude as a Function of
        Electrode Position ................................................................................................... 82
   5.2.4 Extracellular Potential Distributions Produced by Alternating Repolarization
        Gradients .................................................................................................................. 86
5.3 Discussion ..................................................................................................................... 88
5.4 Limitations ................................................................................................................... 90

6. Effect of a Resistive Barrier on Repolarization Alternans and T-Wave Alternans ... 92
6.1 Introduction .................................................................................................................. 92
6.2 Results ........................................................................................................................ 93
   6.2.1 Cellular Activation and Conduction .................................................................... 93
   6.2.2 Resistive Barrier Effects on Cellular Repolarization ......................................... 93
   6.2.3 Resistive Barrier Effects on Alternans of ECG Time Parameters ............... 97
6.2.4 Resistive Barrier Effects on Repolarization Alternans and T-wave Alternans ......................................................................................................................... 98

6.3 Discussion ................................................................................................................................. 100

6.4 Limitations ................................................................................................................................. 102

7. Conclusions .................................................................................................................................. 104

7.1 Summary of Findings .................................................................................................................... 104

7.2 Limitations and Future Directions ............................................................................................ 105

Appendix A. Modification of Models of Cellular Electrical Activity ........................................ 110

A.1 Model for Dynamic Restitution Study ..................................................................................... 110

A.2 Model for S1-S2 Restitution and Short-Term Memory Study ................................................. 112

A.3 Model for Repolarization Alternans Studies ............................................................................ 113

References ....................................................................................................................................... 115

Biography ......................................................................................................................................... 124
List of Tables

Table 4.1: STM beat constants for cellular repolarization times and ECG parameters for a fiber with control mean conductivity................................................................. 63

Table 4.2: STM beat constants for cellular repolarization times and ECG parameters for a fiber with reduced mean conductivity................................................................. 67

Table 4.3: STM beat constants for cellular repolarization times and ECG parameters for a fiber with enhanced mean conductivity. ........................................................................ 69

Table 4.4: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with control conductivity. ......................... 73

Table 4.5: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with reduced conductivity. ......................... 74

Table 4.6: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with enhanced conductivity........................ 74

Table 5.1: T-wave measurements for representative electrode distances................................. 83

Table 5.2: T-wave measurements for representative lead angles ............................................. 84
List of Figures

Figure 1.1: Illustration of APD response to steady-state pacing (dynamic restitution). Stimuli are applied at a fixed interval (BCL) and produce a fixed APD and fixed DI........ 4

Figure 1.2: Dynamic restitution curves for simulated canine endocardial, midmyocardial, and epicardial cells. Data are shown for the modifications of the MV model described in section 2.2.1 in the fiber described in section 2.1.2 used to investigate dynamic restitution at control conductivity. ................................................................. 4

Figure 1.3: Illustration of APD response to a premature stimulus during steady-state pacing (S1-S2 restitution). A premature stimulus applied to a system previously at steady state produces an APD that is different from steady-state APD.............................. 5

Figure 1.4: STM response of endocardial, midmyocardial, and epicardial cells in response to an abrupt change in BCL from 1000 to 600 ms. Data are shown for the modifications of the FMG model described in section 2.2.2 in the fiber described in section 2.1.2 used to investigate S1-S2 restitution and STM at reduced conductivity................................. 6

Figure 1.5: Two types of repolarization alternans. Red lines indicate a long alternating action potential, and blue lines indicate a short alternating action potential. APD in different regions of the myocardium alternate in phase with each other during concordant alternans and out of phase with each other during discordant alternans...................... 8

Figure 2.1: Schematic of fiber model with distinct cellular regions and ECG electrodes, being paced from the endocardial end. ................................................................. 13

Figure 2.2: Core conductor model for the fiber model ............................................. 15

Figure 2.3: Axial conductivity values along the length of fiber models used in (A) dynamic restitution study and (B) S1-S2 restitution and short-term memory study. ....... 20

Figure 2.4: Conductivity of fiber with resistive barrier (black) and conductivity of fiber of equivalent, homogeneous mean conductivity (blue) ........................................... 22

Figure 2.5: (A) Endocardial, midmyocardial, and epicardial APD as a function of BCL for modified MV model. Experimental values are indicated with X’s. (B) Endocardial, midmyocardial, and epicardial AP tracings at BCL of 4000, 1000, 800, and 500 ms........ 24

Figure 2.6: APD and APD alternans magnitude along the fiber model for repolarization alternans studies at a BCL of 220 ms................................................................. 28
Figure 2.7: Electrodes for study of effect of electrode location on T-wave alternans placed at distance $d$ from fiber center and angle $\theta$ with respect to fiber axis. .......................... 32

Figure 2.8: Parameters measured from ECG. ........................................................................................................... 36

Figure 3.1: Local CV measured at a BCL of 1000 ms for fiber at control, reduced, and enhanced conductivity. ....................................................................................................................... 39

Figure 3.2: Epicardial AP tracings plotted with ECG tracings showing the correspondence between epicardial AP downstroke time and T-wave upstroke time for (A) representative BCL and (B) different levels of tissue conductivity. ............................... 41

Figure 3.3: Epicardial AP tracings plotted with ECG tracings showing the correspondence between epicardial repolarization time and QT$_{\text{peak}}$ intervals for (A) representative BCL and (B) different levels of tissue conductivity. ........................................... 42

Figure 3.4: Endocardial AP tracings plotted with ECG tracings showing the correspondence between endocardial AP downstroke time and T-wave downstroke time for (A) representative BCL and (B) different levels of tissue conductivity. ......................... 43

Figure 3.5: Midmyocardial AP tracings plotted with ECG tracings showing the correspondence between midmyocardial repolarization time and threshold-approximated QT interval for (A) representative BCL and (B) different levels of tissue conductivity. ........................................... 45

Figure 3.6: Midmyocardial AP tracings plotted with ECG tracings showing the correspondence between midmyocardial repolarization time and tangent-approximated QT interval for (A) representative BCL and (B) different levels of tissue conductivity. ........................................... 46

Figure 3.7: TDR and (A) threshold-approximated T$_{\text{peak}}$-T$_{\text{end}}$ interval or (B) tangent-approximated T$_{\text{peak}}$-T$_{\text{end}}$ interval plotted as a function of BCL at control, enhanced and reduced conductivity. TDR is defined at degrees of repolarization that best match each approximation method for T$_{\text{peak}}$-T$_{\text{end}}$ interval at control conductivity and a BCL of 1000 ms. ....................................................................................................................... 48

Figure 3.8: Midmyocardial-epicardial (mid-epi) and endocardial-midmyocardial (endo-mid) voltage gradients shown for (A) representative BCL and (B) different levels of tissue conductivity. The sum of the two gradients closely approximates the transmural ECG. (C) Maximum magnitude of voltage gradient as a function of BCL at different levels of tissue conductivity. (D) Magnitude of gradient of repolarization time between midmyocardial node and epicardial node (mid-epi) and between endocardial node and midmyocardial node (endo-mid) as a function of BCL at different levels of tissue conductivity. ....................................................................................................................... 51
Figure 4.1: Repolarization phase of endocardial (endo), midmyocardial (mid), and epicardial (epi) cellular action potentials, ECG T waves, and tissue voltage gradients for a fiber with homogeneous STM beat constant (black) and (A) reduced endocardial STM beat constant (red) or (B) reduced epicardial STM beat constant (red). Results shown here are for a fiber with control mean conductivity................................................. 65

Figure 4.2: Repolarization phase of endocardial (endo), midmyocardial (mid), and epicardial (epi) cellular action potentials, ECG T waves, and tissue voltage gradients for a fiber with homogeneous STM beat constant (black) and (A) reduced endocardial STM beat constant (red) or (B) reduced epicardial STM beat constant (red). Results shown here are for a fiber with reduced mean conductivity.............................................................. 68

Figure 4.3: Repolarization phase of endocardial (endo), midmyocardial (mid), and epicardial (epi) cellular action potentials, ECG T waves, and tissue voltage gradients for a fiber with homogeneous STM beat constant (black) and (A) reduced endocardial STM beat constant (red) or (B) reduced epicardial STM beat constant (red). Results shown here are for a fiber with enhanced mean conductivity............................................................ 71

Figure 5.1: Repolarization times of endocardial, midmyocardial, and epicardial nodes in fiber model for two alternating beats at various repolarization alternans magnitudes. .... 80

Figure 5.2: Gradient of repolarization times in the fiber model for two alternating beats at various repolarization alternans magnitudes................................................................. 80

Figure 5.3: T-wave amplitude plotted as a function of repolarization gradient. A regression line highlights the linear relationship between T-wave amplitude and repolarization gradient. ........................................................................................................... 82

Figure 5.4: TWA amplitude plotted as a function of repolarization gradient alternans. A regression line highlights the linear relationship between TWA amplitude and repolarization gradient alternans................................................................. 82

Figure 5.5: Potential distribution around fiber model at instant of peak of (A) tall T wave and (B) short T wave. Representative electrode locations are marked with a black “X.” 88

Figure 6.1: Cellular repolarization times, tissue voltage gradients, and T waves for two consecutive beats during alternans for a fiber with homogeneous conductivity of 1.25 mS/cm (red lines) and a fiber with homogeneous conductivity of 1.1364 mS/cm (black lines).................................................................................................................. 94

Figure 6.2: Cellular repolarization times, tissue voltage gradients, and T waves for two consecutive beats for a fiber with a resistive barrier (red lines) or a fiber of equivalent, homogeneous mean conductivity (black lines)............................................................................. 96
Figure 6.3: (A) Maximum cellular alternans magnitude and (B) TWA amplitude for various resistive barrier strengths as a function of barrier location in the fiber. Values given for the fiber with no barrier are for a fiber of homogeneous conductivity equivalent to the mean conductivity of a fiber with a barrier. (C) TWA amplitude as a function of maximum cellular alternans magnitude for representative barrier locations. A regression line illustrates the quasi-linear relationship between TWA and cellular alternans. (D) Gain (slope) of the relationship between TWA amplitude and maximum cellular alternans magnitude as a function of barrier location. Gain for the data plotted in panel C is indicated. .......................................................... 99
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APD</td>
<td>action potential duration (measured in ms)</td>
</tr>
<tr>
<td>BCL</td>
<td>basic cycle length (measured in ms)</td>
</tr>
<tr>
<td>CV</td>
<td>conduction velocity (measured in cm/s)</td>
</tr>
<tr>
<td>DI</td>
<td>diastolic interval (measured in ms)</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>FMG</td>
<td>Fox-McHarg-Gilmour (model)</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>MV</td>
<td>minimal ventricular (model)</td>
</tr>
<tr>
<td>STM</td>
<td>short-term memory</td>
</tr>
<tr>
<td>TDR</td>
<td>transmural dispersion of repolarization (measured in ms)</td>
</tr>
<tr>
<td>TWA</td>
<td>T-wave alternans</td>
</tr>
</tbody>
</table>
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1. Introduction

1.1 Significance of Research in Cardiac Electrophysiology

Sudden death from arrhythmia kills roughly 310,000 Americans per year (46). Unfortunately, no current diagnostic test can accurately predict which individuals are most at risk for sudden arrhythmic death. Since basic research has shown that the development of arrhythmia is tied to abnormalities in repolarization, methods that assess repolarization have the potential to evaluate susceptibility to sudden arrhythmic death. Given the risk and expense involved in invasive electrophysiologic testing, assessment of repolarization using noninvasive signals such as the body surface electrocardiogram (ECG) is ideal.

Several studies have attempted to assess repolarization and spatial heterogeneity of repolarization using ECG techniques, such as QT dispersion (12, 22, 49, 86), T-wave lability (3, 37, 54), and various forms of T-wave morphology analysis (20, 56, 57, 97-99). However, none of these methods assess the rate-dependent, nonlinear changes in repolarization due to electrical restitution. Currently, the effects of dynamic changes in myocardial repolarization on extracellular signals such as the ECG are largely unknown.

The main focus of this study is to determine how spatial and temporal dynamic changes in repolarization within myocardial tissue affect the ECG. This work is significant in that new knowledge has been obtained that can form the foundation to develop novel noninvasive methods of sudden death risk stratification using ECG measurements.
1.2 Dynamic Repolarization of Cardiac Tissue

Abnormalities in repolarization, particularly in temporal and spatial dispersion of repolarization, are associated with increased susceptibility to arrhythmia. A large degree of repolarization dispersion in tissue results in some areas repolarizing and becoming available for subsequent activation before others. A premature stimulus can then result in unidirectional block: activation propagates in the direction in which tissue has repolarized and blocks in the direction in which tissue has not yet repolarized. The activation wave may then propagate around the region of block and activate the previously refractory region, leading to reentry, a self-sustaining, spiral wavefront that can degenerate to arrhythmia. Several studies have demonstrated that intrinsic heterogeneity in action potential duration (APD) (i.e. dispersion of repolarization) exists across the free wall of the left ventricle (LV) in several species, including rabbits (39, 69), dogs (75-77, 96), and man (33). However, the APD within each ventricular layer is not static but is dependent upon stimulation rate through a phenomenon known as electrical restitution. Since each cardiac myocyte can exhibit unique restitution behavior, spatial variation of APD heterogeneity within tissue, and by extension susceptibility to arrhythmia, could change drastically in response to changes in stimulation rate.

1.2.1 Electrical Restitution: The 1:1 Domain

Electrical restitution is often described using the APD restitution curve (RC), which relates the APD to the preceding diastolic interval (DI), the period during which transmembrane voltage remained at rest. However, APD restitution is more complex than this sole nonlinear relationship. In this study, I investigated three different types of
restitution behavior: dynamic restitution, S1-S2 restitution, and short-term memory (STM).

**Dynamic restitution** describes the relationship between APD and DI during steady-state pacing at a constant basic cycle length (BCL), where the BCL is the period of time between successive stimuli. After pacing at a single BCL for some period of time, the APD and DI at a specific tissue site reach steady state, producing a unique APD for a given DI (Figure 1.1). This relationship is described by the dynamic RC, a plot of steady-state APD value as a function of steady-state DI (Figure 1.2). Each cardiac cell has a single dynamic RC that is largely determined by the cell’s ion channel distribution and intracellular calcium-handling mechanism. Although the mechanisms underlying dynamic restitution are not completely understood, the shortening of APD with decreasing BCL is thought to be due to time-dependent activity of ion channels (13). After an action potential, the state of ion channel gates return to steady state over time. Pacing at a shorter BCL allows less time for ion channel gates to return to steady state, and ion channel current is different than at steady state. Because each ion channel species has different kinetics, pacing at a different BCL alters the contribution of each ion channel current to the action potential, resulting in a different APD at each BCL.
Figure 1.1: Illustration of APD response to steady-state pacing (dynamic restitution). Stimuli are applied at a fixed interval (BCL) and produce a fixed APD and fixed DI.

Figure 1.2: Dynamic restitution curves for simulated canine endocardial, midmyocardial, and epicardial cells. Data are shown for the modifications of the MV model described in section 2.2.1 in the fiber described in section 2.1.2 used to investigate dynamic restitution at control conductivity.

S1-S2 restitution describes the APD response of a system previously at steady state to a perturbation in cycle length. An S1-S2 restitution response is elicited by steady-state pacing at a fixed BCL (S1 stimuli) followed by a single premature or postmature stimulus (known as the S2 stimulus) delivered after a certain duration (the S1-S2
coupling interval) (Figure 1.3). The resulting S1-S2 response is dependent on the BCL and, like dynamic restitution, can vary between cells. As with dynamic restitution, the mechanism behind S1-S2 restitution is not known but is likely due to time-dependent activity of ion channels (13). Pacing at an S1-S2 coupling interval that is shorter than the preceding BCL allows less time for ion channel gates to return to steady state, and ion channel current is different than when paced at a fixed BCL. Pacing at a different S1-S2 coupling interval thus alters the contribution of each ion channel current to the action potential, resulting in a different APD for each S1-S2 coupling interval.

![Diagram](image)

**Figure 1.3:** Illustration of APD response to a premature stimulus during steady-state pacing (S1-S2 restitution). A premature stimulus applied to a system previously at steady state produces an APD that is different from steady-state APD.

**Short-term memory**, also known as “accommodation,” refers to the transient process by which APD monotonically approaches a stable steady-state value in response to an abrupt change in BCL. The plot of APD as a function of time or beat number is a decaying monoexponential (Figure 1.4), and the short-term memory (STM) response can be fit to equations 1.1 or 1.2:

\[
APD(t) = APD_{old} + (\Delta APD)e^{-\frac{t}{\tau}}
\]  

1.1
\[ APD(n) = APD_{old} + (\Delta APD)e^{-\frac{n}{\tau_{\text{beat}}}} \]  \hspace{1cm} (1.2)

STM response is therefore defined by the time constant, \( \tau \), or beat constant, \( \tau_{\text{beat}} \). Time constant and beat constant are related by equation 1.3:

\[ \tau = (BCL_{\text{new}})(\tau_{\text{beat}}) \]  \hspace{1cm} (1.3)

STM time constant is site-dependent in rabbit ventricle (52, 63), but limited data exists on spatial differences in STM in the dog and human. Simulation studies suggest that the mechanism responsible for STM is a slow change in intracellular sodium concentration due to slow dynamics of the sodium-potassium pump current (23).

![Figure 1.4: STM response of endocardial, midmyocardial, and epicardial cells in response to an abrupt change in BCL from 1000 to 600 ms. Data are shown for the modifications of the FMG model described in section 2.2.2 in the fiber described in section 2.1.2 used to investigate S1-S2 restitution and STM at reduced conductivity.](image)

Dynamic restitution, S1-S2 restitution, and STM have profound effects on susceptibility to arrhythmia. Nolasco and Dahlen used a mapping model of dynamic APD restitution and found that APD instability (and thus increased potential for arrhythmia) occurred for BCLs at which the S1-S2 RC slope is greater than one (55). This
dependence of APD instability on increased RC slope has been supported by experimental (42, 43) and modeling (5, 6, 41, 68) studies that demonstrate induction of APD alternans, an unstable and arrhythmogenic APD response, for dynamic and S1-S2 RC slopes greater than one. However, several other studies have demonstrated a stable APD at points where the dynamic RC slope is greater than one (5, 6, 40). Since Nolasco and Dahlen only investigated dynamic and S1-S2 restitution, one possible reason for this discrepancy in results is the effect of STM. Cherry and Fenton demonstrated that APD alternans could be suppressed at steep restitution by adding STM to an ionic model (18). However, STM is not always antiarrhythmic. Fenton and coworkers found that stable reentry in a computer model degenerated to arrhythmia when STM behavior was added to the model (31). Thus, the effects of steady-state restitution, S1-S2 restitution, and short-term memory should all be considered when investigating restitution behavior.

1.2.2 Action Potential Duration Alternans: The 2:2 Rhythm

APD alternans is a beat-to-beat alternation in APD that typically occurs at fast pacing rates. It can be a result of alternation in conduction velocity (CV), alternation in cellular repolarization, or both. Experimental studies have shown that APD alternans may be arrhythmogenic (59). Two types of APD alternans exist: concordant alternans and discordant alternans (Figure 1.5). During concordant alternans, APD from all regions alternate in phase with each other. Concordant alternans can degenerate to discordant alternans (89), in which APD of one region alternates out phase with another region. Because it involves a higher degree of spatiotemporal dispersion of repolarization,
discordant alternans is thought to be more arrhythmogenic than concordant alternans (59).

Figure 1.5: Two types of repolarization alternans. Red lines indicate a long alternating action potential, and blue lines indicate a short alternating action potential. APD in different regions of the myocardium alternate in phase with each other during concordant alternans and out of phase with each other during discordant alternans.

T-wave alternans (TWA) is the ECG manifestation of APD alternans. Beat-to-beat alternation in myocardial repolarization causes beat-to-beat changes in the amplitude and morphology of the ECG T wave (59). TWA is therefore a useful risk stratification tool because of the association between APD alternans and arrhythmia (53). In my studies, I chose to investigate the relationship between concordant repolarization alternans and TWA. Although discordant alternans is more arrhythmogenic, the large temperospatial dispersion of repolarization causes alternation in T-wave polarity in my models, making comparison of T wave parameters difficult.

1.3 Dynamic ECG Changes

No ECG analysis method currently exists that assesses the rate-dependent, nonlinear changes in repolarization due to electrical restitution. Prolongation of the QT interval of the ECG is widely associated with an increased risk for sudden death (70, 73,
Physiologically, the QT interval lengthens at low heart rates and shortens at high heart rates. Thus, the QT interval is a dynamic ECG change: its value changes due to changes in pacing rate. However, in typical clinical use, the QTc (“QT corrected”) interval is calculated to “correct” for this rate-dependence in QT interval, either by dividing QT interval by the square root (7) or the cube root (34) of the RR interval on the ECG (i.e., the heart rate). These correction methods are based on data nearly a century old that were not designed for correction of QT interval for risk stratification purposes. Furthermore, the use of rate-correction methods assumes that there is a fixed relationship between ECG parameters and heart rate. From experimental studies, it has been established that myocardial electrical activity is nonlinear, rate-dependent, and time-dependent due to electrical restitution. Because the ECG is reflective of myocardial electrical activity, ECG parameters should similarly be nonlinear, rate-dependent, and time-dependent. Methods such as QT interval correction ignore or distort these dynamic changes in the ECG. The goal of this study, therefore, is to clarify the link between dynamic changes in cellular repolarization and dynamic changes in the ECG T wave.

1.4 Motivation for Using a Computer Model

1.4.1 Advantages of Using a Computer Model

In investigating the relationship between cellular dynamics and the ECG, a computer model has several advantages over an experimental preparation.

Simplicity

Because this study seeks to uncover basic mechanisms by which cellular repolarization dynamics affect the ECG, a simple model is the best choice to provide
general insights on this relationship. Effects that are predominant in a simple computer model may be lost in an experimental preparation due to the presence of confounding variables such as inter-animal variability and inaccuracies in measurement.

**Manipulation of settings**

A computer model allows manipulation of settings that would be difficult or impossible to achieve in an experimental preparation. For example, in chapter 4, the STM properties of one region of tissue are altered to determine the effect of regional STM changes on the ECG. Settings can also be manipulated to mimic pathologic or physiologic states.

**Access to output parameters**

Because all input settings are defined, a computer model provides output data that may be experimentally inaccessible. These data are useful for postulating mechanisms that can later be tested with more advanced experimental techniques.

**1.4.2 Limitations of Using a Computer Model**

Proper use of a computer model involves acknowledgement of its limitations.

**Processing power**

As model complexity increases, computational time also increases. For my simulations, which consisted of a simple 1-dimensional structural model and ionic models of moderate complexity, two minutes of simulated pacing took two to five hours of real time. Therefore, studies that require long-term pacing are time-consuming. However, this limitation is somewhat mitigated by the use of parallel processing to simultaneously run multiple simulations with different settings. For example, rather than
running one simulation with a pacing protocol involving a decrease in BCL every 20 s, separate simulations can be run that each consist of 20 s of pacing at a particular BCL.

**Model approximation of physiology**

A computer model relies on experimentally-obtained data to use as inputs and simulation settings. Unfortunately, experimental data are often not available for all parameters that are modeled. For example, in chapter 4, STM time constants were not available for all regions of the canine LV free wall. Input data must then be based on approximations from other tissues. Although the results from such simulations are not as accurate as results from an experimental preparation, they can still provide insight on important mechanisms that contribute to the modeled phenomenon.

**1.5 Research Goals and Specific Aims**

The effects of temporal and spatial differences in cellular repolarization dynamics on the ECG are not well known. The goal of my research was to investigate the ECG manifestations of temporal and spatial differences in dynamic restitution, S1-S2 restitution, STM, and repolarization alternans and to explore the mechanisms that modify the relationship between cellular dynamics and ECG dynamics. I hypothesize that spatial differences in repolarization dynamics alter voltage gradients that influence the ECG. My specific aims to investigate this hypothesis were as follows:

**Specific Aim 1:** Determine how spatial heterogeneity of APD and of dynamic restitution, S1-S2 restitution, and STM affect the T wave of the ECG.

**Specific Aim 2:** Determine how changes in electrode position alter the measurement of TWA.
Specific Aim 3: Determine how presence and location of a resistive barrier alter TWA and repolarization alternans.

My approach used 1-dimensional computer fiber models to approximate conduction from the endocardium to the epicardium of the canine LV free wall. The canine LV free wall was selected because of the availability of data on APD dynamics throughout the wall as well as the electrophysiologic similarity of the canine LV to human LV. I modified models of cellular electrical activity to approximate spatial differences in dynamic restitution, S1-S2 restitution, STM, and repolarization alternans. I paced the fiber models to elicit dynamic behavior, and I analyzed the dynamic behavior in the ECG. I also investigated the effects of changes in tissue conductivity, which can alter temporal and spatial differences in repolarization.

Because no current model approximates dynamic restitution, S1-S2 restitution, STM, and repolarization alternans for different regions of the canine LV free wall, these effects were studied separately. The results of specific aim 1 are described in chapter 3 (dynamic restitution) and chapter 4 (S1-S2 restitution and STM). The results of specific aim 2 are described in chapter 5. The results of specific aim 3 are described in chapter 6.
2. Methods

This chapter describes the components and implementation of the computer simulations used to study the relationship between dynamic behavior in the electrocardiogram (ECG) and cellular repolarization dynamics in underlying myocardium. The general setup is similar among all studies performed (Figure 2.1). Modifications made to this general approach for each study are described in detail below and are summarized in each chapter. Briefly, a multicellular, 1-dimensional computer fiber model was created to simulate the free wall of the canine left ventricle (LV). Modifications of existing mathematical models were used to simulate electrical activity of each cell in the fiber model and to approximate experimentally-observed cellular repolarization dynamics. The fiber model was simulated with different pacing protocols to elicit various types of dynamic behavior. A computed ECG was calculated using cellular voltage data from the fiber model. Measurements of cellular repolarization were compared with ECG parameters to determine the relationship between cellular repolarization dynamics and dynamic behavior in the ECG.

![Figure 2.1: Schematic of fiber model with distinct cellular regions and ECG electrodes, being paced from the endocardial end.](image)

13
2.1 Computer Fiber Model

2.1.1 Overview

To simulate action potential (AP) conduction from the endocardium to the epicardium of the free wall of the canine LV, a 1-dimensional, monodomain, multicellular fiber model was created. The model consisted of either 100 or 130 nodes (study-dependent, see below), each representing a 100-µm-long cylindrical cardiac myocyte, placed 0.01 cm (100 µm) apart in a 2-dimensional Cartesian coordinate system from $x = 0$ to $x = 0.99$.

Previous computer modeling studies have used a 1-dimensional model to simulate planar conduction from the endocardium to the epicardium of the LV free wall (35, 87, 88). For our purposes, use of a 1-dimensional fiber model as a surrogate for transmural propagation in the canine LV free wall involves several assumptions:

1. The assumption that conduction occurs primarily in a planar fashion from the endocardial surface to the epicardial surface of the LV free wall. This conduction pattern is supported by data from Durrer and coworkers, who suggested that activation of the Purkinje system rapidly activated the endocardial LV surface, resulting in a broad planar activation wavefront that propagates towards the epicardial surface (29).

2. The assumption that the major gradient of repolarization is in the transmural direction. This assumption has been supported by numerous experimental studies of the canine LV wedge preparation demonstrating a large non-monotonic
gradient of repolarization time from the endocardium to the epicardium (79, 80, 95, 96).

3. The assumption that the gradient of repolarization in the transmural direction is the main source of the ECG T wave. Although the source of the T wave in the whole heart is debated (58), the source of the T wave in an isolated canine LV wedge preparation has been shown to be largely due to this transmural repolarization gradient (95).

An equation for current flow through the fiber model can be derived using the cable equations (64). Figure 2.2 shows the core conductor model, an electrical representation of the fiber model, in which $\Phi_i$ is potential along the intracellular path, $\Phi_e$ is potential along the extracellular path, $r_i$ is the resistance per unit length along the intracellular path, $r_e$ is the resistance per unit length along the intracellular path, $I_i$ is the axial current in the intracellular path, $I_e$ is the axial current in the extracellular path, and $i_m$ is the transmembrane current per unit length.

![Core conductor model](image)

**Figure 2.2:** Core conductor model for the fiber model.
By Ohm’s law, the decrease in potential along the fiber is equivalent to the axial resistance multiplied by the axial current:

\[
\frac{\partial \phi_e}{\partial x} = -I_e r_e \tag{2.1}
\]

\[
\frac{\partial \phi_i}{\partial x} = -I_i r_i \tag{2.2}
\]

Assuming conservation of current, the following equations can be derived for transmembrane current:

\[
\frac{\partial I_e}{\partial x} = i_m \tag{2.3}
\]

\[
\frac{\partial I_i}{\partial x} = -i_m \tag{2.4}
\]

Transmembrane voltage, \( V_m \), is defined as follows:

\[
V_m = \Phi_i - \Phi_e \tag{2.5}
\]

The spatial derivative of \( V_m \) can be found by taking the spatial derivative of equation 2.5 and substituting equations 2.1 and 2.2:

\[
\frac{\partial V_m}{\partial x} = \frac{\partial \Phi_i}{\partial x} - \frac{\partial \Phi_e}{\partial x} = -I_i r_i + I_e r_e \tag{2.6}
\]

Deriving equation 2.6 by \( x \) gives the following:

\[
\frac{\partial^2 V_m}{\partial x^2} = -r_i \frac{\partial I_i}{\partial x} + r_e \frac{\partial I_e}{\partial x} \tag{2.7}
\]

Substituting equations 2.3 and 2.4 gives the following:

\[
\frac{\partial^2 V_m}{\partial x^2} = (r_i + r_e)i_m \tag{2.8}
\]
In all simulations in this dissertation, the fiber model is taken to be in a large, unbounded volume conductor, and \( r_e \) can be assumed to be equal to zero:

\[
\frac{\partial^2 V_m}{\partial x^2} = r_i m \tag{2.9}
\]

Resistance per unit length, \( r_i \), can be expressed in terms of resistivity, \( R_i \), or conductivity, \( \sigma_i \), where \( a \) in the following equation is fiber radius:

\[
r_i = \frac{R_i}{\pi a^2} = \frac{1}{\sigma \pi a^2} \tag{2.10}
\]

Combining equations 2.9 and 2.10 gives the following:

\[
i_m = \sigma_i \pi a^2 \frac{\partial^2 V_m}{\partial x^2} \tag{2.11}
\]

Transmembrane current per unit length, \( i_m \), can be converted to transmembrane current per unit area, \( I_m \), by dividing by the circumference of the fiber cross section:

\[
I_m = \frac{i_m}{2\pi a} \tag{2.12}
\]

Substituting equation 2.12 into equation 2.11 yields the following:

\[
I_m = \frac{\sigma_i a}{2} \frac{\partial^2 V_m}{\partial x^2} \tag{2.13}
\]

Equation 2.14 below shows that \( 2/a \) is the surface area to volume ratio of the fiber, which will be designated with the letter \( \beta \) (\( l \) denotes fiber length in equation 2.14):

\[
\frac{SA}{V} = \frac{2\pi al}{\pi a^2 l} = \frac{2}{a} = \beta \tag{2.14}
\]

Substituting \( \beta \) into equation 2.13 gives the following:

\[
I_m = \frac{\sigma_i}{\beta} \frac{\partial^2 V_m}{\partial x^2} \tag{2.15}
\]
Transmembrane current per unit area is a result of ionic currents ($I_{ion}$) as well as the capacitive current:

$$I_m = I_{ion} + C_m \frac{\partial V_m}{\partial t}$$  \hspace{1cm} (2.16)

Combining equations 2.15 and 2.16 and rearranging gives equation 2.17, the equation solved in all computer simulations in this dissertation,

$$\sigma_i \frac{\partial^2 V_m}{\partial x^2} = \beta \left( C_m \frac{\partial V_m}{\partial t} + I_{ion} \right)$$  \hspace{1cm} (2.17)

where $x$ is distance along the fiber, $t$ is time, $\sigma_i$ is axial conductivity (study-dependent, see below), $\beta$ is surface-area-to-volume ratio (study-dependent, see below), $C_m$ is membrane capacitance (1 $\mu$F/cm$^2$), $V_m$ is the cellular transmembrane voltage in mV, and $I_{ion}$ is the sum of ionic currents in $\mu$A/cm$^2$ defined by the chosen model of cellular electrical activity (study-dependent, see section 2.2). For all simulations, no-flux (“sealed end”) boundary conditions were used. The fiber model was considered to be surrounded by an unbounded, homogeneous volume conductor of conductivity 20 mS/cm, equal to that of 0.9% saline at 37° Celsius (51).

**2.1.2 Fiber Model for Restitution Studies**

Fiber models for the restitution studies (chapters 3 and 4) were based on experimental values for canine LV wall thickness and LV tissue conductivity from the endocardium to the epicardium (96). Each fiber model consisted of 130 nodes, spaced 0.01 cm apart from $x = 0$ to $x = 1.29$. This setup resulted in fiber models of length 1.3 cm, closely approximating the experimental value of mean canine LV wall thickness, 1.29 cm
Each node represented a 100-µm-long cylindrical cardiac myocyte with diameter 20 µm, giving surface-area-to-volume ratio, $\beta$, of 2000 cm$^{-1}$.

Axial conductivity, $\sigma_i$, varied as a function of length along the fiber to model physiologic heterogeneity in tissue conductivity from the endocardial surface to the epicardial surface. Each fiber model consisted of 10 regions with conductivity based on experimental values of tissue resistivity across the canine LV wall. Experimental resistivity values ranged from 0.149 to 0.411 kΩ·cm, giving conductivity values that ranged from 2.433 to 6.711 mS/cm (96). When used in the fiber model, these values produced mean conduction velocity (CV) that was much higher than physiologic CV. Therefore, the conductivity values used in the model were decreased from the experimental values until the mean conduction velocity (CV) along the fiber was comparable to LV transmural CV recorded in vitro (29, 65, 66, 96). The study of dynamic restitution (chapter 3) and the study of S1-S2 restitution and short-term memory (STM) (chapter 4) used different models of cellular electrical activity, which had different AP conduction properties. Therefore, the actual conductivity values used for the fiber model for each study were different (Figure 2.3). To study the effects of reduction or enhancement in tissue conductivity, tissue conductivity values throughout each fiber were either halved (conductivity reduction) or doubled (conductivity enhancement). By modifying conductivity values throughout the fiber, overall fiber conductivity was reduced or enhanced while maintaining heterogeneity in conductivity.
Figure 2.3: Axial conductivity values along the length of fiber models used in (A) dynamic restitution study and (B) S1-S2 restitution and short-term memory study.

To model transmural heterogeneity in repolarization, the fiber models used in restitution studies consisted of three regions. Each fiber region consisted of nodes with ionic currents determined by a regional modification of the model for cellular electrical activity. The first 13 nodes (0.13 cm) of the fiber consisted of endocardial-type nodes, the middle 78 nodes (0.78 cm) of the fiber consisted of midmyocardial-type nodes, and the final 39 nodes (0.39 cm) consisted of epicardial-type nodes. Sections 2.2.1 and 2.2.2 describe in detail the modifications and properties of these models of cellular electrical activity.
2.1.3 Fiber Model for Repolarization Alternans Studies

Fiber models for the repolarization alternans studies (chapters 5 and 6) consisted of 100 nodes, spaced 0.01 cm apart. Each node represented a 100-µm-long cylindrical cardiac myocyte. For the study of electrode placement and T-wave alternans (chapter 5), each myocyte had diameter 22 µm, giving surface-area-to-volume ratio, $\beta$, of 1818 cm$^{-1}$. For the study of a resistive barrier and T-wave alternans (chapter 6), each myocyte had diameter 20 µm, giving $\beta$ of 2000 cm$^{-1}$.

For the study of electrode placement and T-wave alternans (chapter 5), axial conductivity, $\sigma_i$, was constant at 1.5 mS/cm throughout the length along the fiber. A homogeneous conductivity was chosen to ensure that the effects observed were due to intrinsic spatial differences in cellular repolarization alternans rather than spatial alternans differences modulated by conductivity heterogeneity.

The effects of spatial alternans differences modulated by conductivity heterogeneity were examined in the study of a resistive barrier and T-wave alternans (chapter 6). For the fiber model used in this study, axial conductivity was constant at 1.25 mS/cm throughout most of the fiber. A resistive barrier was placed in one of ten successive 1-mm blocks between the endocardial end and the epicardial end. The barrier consisted of a 10-50% decrease in local conductivity from the control value of 1.25 mS/cm (Figure 2.4). For comparison, fiber models were created with homogeneous conductivity equal to the mean conductivity of each barrier fiber. For example, the mean conductivity of a fiber with a barrier of a 50% decrease in local conductivity is 1.1364.
mS/cm. Therefore, a corresponding fiber model was created with homogeneous conductivity of 1.1364 mS/cm.

![Figure 2.4: Conductivity of fiber with resistive barrier (black) and conductivity of fiber of equivalent, homogeneous mean conductivity (blue)](image)

Fiber models for both repolarization alternans studies consisted of three fiber regions. The first 33 nodes (0.33 cm) of the fiber consisted of endocardial-type nodes, the middle 34 nodes (0.34 cm) of the fiber consisted of midmyocardial-type nodes, and the final 33 nodes (0.33 cm) consisted of epicardial-type nodes. Section 2.2.3 describes in detail the modifications and properties of these models of cellular electrical activity.

### 2.2 Models of Cellular Electrical Activity

No models of cellular electrical activity exist that approximate cellular repolarization dynamics of the endocardium, midmyocardium, and epicardium of the canine LV. Therefore, to model these phenomena, existing models were modified to approximate experimental values of action potential duration (APD), STM beat constant, and APD alternans magnitude for each region of the canine LV.
2.2.1 Model for Dynamic Restitution Study

For the study on dynamic restitution, the minimal ventricular (MV) model was modified. The MV model was designed to reproduce AP characteristics of human endocardial, midmyocardial, and epicardial cells (15). Rather than considering separate ionic currents, each with its own gating variables, the MV model lumps the flow of charge across the membrane into three currents and four gating variables. In addition to speeding simulation time, using only four gating variables allows easy modification of the model to fit AP characteristics of other cell types.

A custom constrained nonlinear optimization routine was used to adjust MV model constants to match experimental values of APD over several basic cycle lengths (BCL). Briefly, an action potential template was created consisting of five action potentials with experimental APD values at BCLs of 4000, 2000, 1000, 800, and 500 ms. Each action potential was preceded by a diastolic interval (DI) appropriate for the action potential at that BCL. For example, at a BCL of 4000 ms, an action potential of APD 290 ms would be preceded by a DI of 3710 ms. The optimization routine varied each model constant over a given range and determined the discrepancy between the resulting simulated action potentials and the action potential template. The set of parameters that gave the minimum discrepancy between simulated action potentials and the template was used as the final model modification.

Three model types were created: an endocardial type, midmyocardial type, and epicardial type. Appendix A details the parameter values used to model each cell type. These model types were used in the corresponding location in the fiber model discussed.
in section 2.1.2 (e.g., the endocardial type model was used for the first 13 nodes of the fiber model). For simplicity, all cell types were designed to have similar AP morphology.

The value for maximum $dV_m/dt$ of the model AP upstroke for all cell types ranged from 189 to 224 V/s, within the range of experimental values from 152 V/s for epicardium (25) to 284 V/s for midmyocardium (4). Figure 2.5 shows steady-state APD values of each cell type in the fiber model and experimental values (96) at several BCL. Model APD values differ from experimental values by between 2 and 25 ms (96).

Figure 2.5: (A) Endocardial, midmyocardial, and epicardial APD as a function of BCL for modified MV model. Experimental values are indicated with X’s. (B) Endocardial, midmyocardial, and epicardial AP tracings at BCL of 4000, 1000, 800, and 500 ms.
The MV model and my modifications of the MV model have several limitations. First of all, the model is unable to reproduce STM behavior. Secondly, the model is unable to reproduce sustained alternans in APD or repolarization time. Therefore, my use of the MV model was limited to dynamic (steady-state) restitution. My modification of the MV model also introduced some limitations. By giving all cell types similar AP morphology, I neglected the effect of spatial AP morphology differences on the construction of ECG waveforms. However, this modification was done to ensure that the observed differences in the ECG were a result of differences in cellular repolarization, not a result of differences in AP morphology. The moderate difference between model and experimental values was not ideal but was sufficient to approximate the canine LV.

2.2.2 Model for S1-S2 Restitution and Short-Term Memory Study

For the study on S1-S2 restitution and STM, the Fox-McHarg-Gilmour (FMG) model was modified. The FMG model was designed to model APD alternans at fast rates in the canine ventricle (32). It is an ionic model, with 13 currents and 12 gating variables. Because of the large number of variables, computational time is increased for the FMG model relative to the MV model. However, the introduction of more ionic currents allows the FMG model to simulate time-dependent phenomena that the MV is unable to do, such as STM of APD and APD alternans.

For this study, the FMG model was modified to produce APD and STM beat constants similar to those observed experimentally for endocardial, midmyocardial, and epicardial cells in the canine LV free wall. Steady-state APD was adjusted to approximate experimentally-observed values at BCL ranging from 1000 ms to 600 ms by
altering maximum conductivity of potassium currents and L-type calcium channel permeability (see Appendix A for details). STM beat constant was adjusted to approximate experimentally-observed values due to a change in BCL from 1000 ms to 600 ms by altering the relative volume of the sarcoplasmic reticulum (SR) in the model.

The value for maximum $dV_m/dt$ of the model AP upstroke for all cell types ranged from 377 to 539 V/s, somewhat greater than the experimental values of 152 V/s for epicardium (25) and 284 V/s for midmyocardium (4). Model APD values differ from experimental values by between 3.9 and 38 ms (96). STM beat constant for all cell types due to a change in BCL from 1000 ms to 600 ms ranged from 24.3 to 24.6 beats, comparable to the experimental value of 25.9 beats observed in strips of canine endocardial and epicardial LV myocardium (90). For comparison, a short-STM endocardial cell type and short-STM epicardial cell type were designed, each with an abnormally short STM beat constant relative to the experimental value. Each of these short-STM cell types were used in the fiber model in place of the normal-STM cell type to give a fiber with abnormally short endocardial STM beat constant and a fiber with abnormally short epicardial STM beat constant.

A limitation of my modifications to the FMG model was that all three cell types had similar AP morphology. As in the study on dynamic restitution, this modification was done to ensure that observed effects were due to differences in S1-S2 restitution or STM, not due to differences in AP morphology. Furthermore, steady-state APD values were not as accurate as for the modified MV model. However, accurate STM beat constant was more important than steady-state APD for the purposes of the S1-S2
restitution and STM study. Another limitation of my modifications involved using a model designed to simulate APD alternans to study STM behavior because no models currently exist that are designed specifically to model STM. STM beat constant was adjusted by altering the relative volume of the SR in the model. Physiologically, differences in the SR volume are not known to be a determinant of STM beat constant. Rather, recent work suggests that STM may be modulated by the kinetics of the L-type calcium channel, sodium-calcium exchanger, and sodium-potassium pump (23). However, modification of the maximum value of these currents in the FMG model was unable to substantially alter STM beat constant. Although modification of relative SR volume is not a physiologic mechanism for altering STM beat constant, it was sufficient to alter STM beat constant in the FMG model without substantially altering AP morphology or APD.

2.2.3 Model for Repolarization Alternans Studies

For the studies on repolarization alternans, the FMG model was modified. As mentioned in section 2.2.2, the FMG model is designed to simulate APD alternans at fast rates in the canine ventricle. Therefore, my modifications were designed to adjust APD and APD alternans magnitude in different regions of the fiber model. As with the models for the restitution studies, endocardial, midmyocardial, and epicardial cell types were designed.

For both studies, APD values were adjusted by altering the maximum conductance of the inward rectifier potassium current, and APD alternans magnitude was adjusted by altering the calcium-dependent inactivation time-constant of the L-type
calcium current (see Appendix A for details). Modification of these parameters to adjust APD and APD alternans magnitude is discussed in the original publication of the FMG model (32).

Figure 2.6 shows APD of steady-state alternating beats and APD alternans magnitude as a function of length along the cable at a BCL of 220 ms. Model APD values were roughly 20 ms lower than experimental APD values at a BCL of 300 ms for endocardium and midmyocardium and 50 ms lower than experimental epicardial values at a BCL of 300 ms (96). APD alternans magnitude matched experimental values of APD alternans for each cell type at a BCL of 250 ms (19).

Figure 2.6: APD and APD alternans magnitude along the fiber model for repolarization alternans studies at a BCL of 220 ms.
Although the FMG model was designed to simulate APD alternans in the canine ventricle, the model and my modifications of it have limitations. First of all, the model only produces stable alternans (i.e. alternans that does not diminish over time) at relatively short BCL, between 150 and 210 ms. By modifying model properties, I was able to induce stable alternans at a BCL of 220 ms, but this rate is still much higher than physiologic rates during normal cardiac conduction. Because experimental data on APD and APD alternans magnitude are not available at this BCL, I extrapolated model values of APD from a BCL of 300 ms and APD alternans magnitude from a BCL of 250 ms. Furthermore, epicardial APD was modeled to be significantly lower than expected from experimental values in order to produce a positive T wave. I designed the model to produce positive T waves to facilitate comparison of results between repolarization alternans studies and electrical restitution studies. Another limitation is that the FMG model produces APD alternans solely via repolarization alternans. However, several studies have noted the importance of CV alternans to arrhythmia inducibility (17, 28, 89). Finally, when modifying the model to produce endocardial, midmyocardial, and epicardial cell types, I altered parameters that did not produce differences in AP morphology. As with the restitution studies, AP morphology was similar among all cell types in order to isolate the effects of spatial differences in repolarization alternans.

2.3 Numerical Methods and Simulation

2.3.1 Simulation Tools

Simulations for all studies were created using the CardioWave software package (67). CardioWave is a modular simulation system that allows the user to create custom
executables from a variety of simulation modules. Different modules exist for numerical methods, pacing protocols, models of cellular electrical activity, output formats, and other simulation options. The user can therefore use the same settings on several models without the need to rewrite code for each simulation.

Simulations were run on the Duke Shared Cluster Resource, a cluster of Linux machines running the Sun Grid Engine queuing system. Using the cluster, multiple simulations could be run on separate machines at the same time. The cluster was therefore a useful tool for screening the effect of model parameter changes on APD and STM beat constant for the FMG model modification used in chapter 4. Simulations were run with varying values for every model parameter, and the resulting APD and STM beat constant were analyzed. Based on these results, certain parameters were identified as modulators of APD and STM beat constant, and these parameters were further adjusted until a satisfactory approximation of experimental data was achieved.

2.3.2 Numerical Methods

Equation 2.17 was solved using a semi-implicit Crank-Nicolson scheme (21) with a conjugate gradient solver (38) using a dx of 0.01 cm. For simulations using the modified MV model, dt was 0.005 ms. For simulations using modified versions of the FMG model, dt was 0.004 ms. The values for time steps were the largest possible values that did not allow the solution to diverge.

2.3.3 Pacing Protocols

For all simulations, the fiber model was paced from the most endocardial node using a suprathreshold, intracellular stimulus of duration 0.5 ms or less. For the dynamic
restitution study, the fiber model was paced using a downsweep pacing protocol from a BCL of 4000 ms to 500 ms, with steps of 500 ms between BCL 4000 ms and 1500 ms and steps of 100 ms from BCL 1500 ms to 500 ms. Five stimuli were delivered at each BCL such that all nodes in the fiber reached steady-state APD. For the S1-S2 restitution and STM study, the fiber model was paced at a BCL of 1000 ms for 125 s to allow the fiber to reach steady state. The model was then either paced at a BCL of 600 for 125 s to elicit STM behavior or given a premature S2 stimulus at an S1-S2 coupling interval of 900, 800, 700, or 600 ms. For the repolarization alternans studies, the models were paced at a constant BCL of 220 ms for 60 s.

2.4 Generation of the Computed ECG

For each simulation, an ECG was calculated by calculating the difference in potential between two points in the volume conductor (virtual electrodes). Generally, these points were located roughly one fiber length away from each fiber end. For example, for the restitution studies (chapters 3 and 4), these electrodes were 1.5 cm from each fiber end, along the fiber axis. For the study of the effect of a resistive barrier on T-wave alternans (chapter 6), the electrodes were 1 cm from each fiber end, along the fiber axis. For the study of the effect of electrode location on T-wave alternans (chapter 5), multiple electrodes in the volume conductor were considered. Electrodes were located at distance \(d\) between 1.5 and 10.5 cm from the fiber center at an angle \(\theta\) ranging from 0 to 80 degrees with respect to the fiber axis (Figure 2.7). All ECGs were computed by subtracting the electrode potential on the endocardial side of the fiber (negative electrode) from the electrode potential on the epicardial side of the fiber (positive electrode).
Figure 2.7: Electrodes for study of effect of electrode location on T-wave alternans placed at distance $d$ from fiber center and angle $\theta$ with respect to fiber axis.

Potential at each virtual electrode in the volume conductor was calculated from the spatial gradient of $V_m$ using a monopole current source approximation as described by equation 2.18,

$$
\phi_e(x',y',z') = \frac{I_m}{4\pi \sigma_e r} \int dV
$$

(2.18)

where $\phi_e(x',y',z')$ is the potential in mV of an electrode at coordinates $(x',y',z')$, $I_m$ is the transmembrane current per unit volume of tissue in $\mu$A/cm$^3$, $\sigma_e$ is the conductivity of the volume conductor in mS/cm, and $r$ is the distance in cm between the current source and the electrode. For a 1-dimensional fiber, equation 2.18 simplifies to equation 2.19,

$$
\phi_e(x',y',z') = \frac{a^2}{4\sigma_e} \int \frac{\sigma_i}{r} \frac{\partial^2 V_m}{\partial x^2} dx
$$

(2.19)

where $a$ is the fiber radius in cm, and $\sigma_i$ is the axial tissue conductivity in mS/cm.
2.5 Measurement of Cellular and ECG Parameters

2.5.1 Cellular Measures of Activation and Repolarization

For the restitution studies, cellular measurements were obtained for every fifth node of the fiber model. For the repolarization alternans studies, measurements were obtained for every node of the fiber model. Cellular activation time was defined as the time at which \( V_m \) increased to 10% of the peak AP voltage (-70 mV for the MV model and -81 mV for the FMG model). Local CV was calculated as the distance between two measured nodes divided by the difference in their activation times. Mean CV for a fiber was calculated as the distance from the most endocardial node to the most epicardial node divided by the difference in their activation times.

For the dynamic restitution study (chapter 3), repolarization times were defined as the time after stimulus that \( V_m \) decreased a certain percentage from peak \( V_m \) to rest \( V_m \) (e.g. 90% repolarization, 92% repolarization, etc.). AP downstroke time was defined as the time after stimulus of maximum decrease in membrane voltage (time of minimum \( dV_m/dt \)). For the S1-S2 restitution and STM study (chapter 4), repolarization times were measured at ~99% repolarization (-93 mV) in order to best compare cellular repolarization to ECG parameters. For both repolarization alternans studies (chapters 5 and 6), repolarization times were measured at ~90% repolarization (-81 mV). The cellular alternans magnitude is the parameter of interest in alternans studies, so the selection of 90% repolarization time as opposed to, say, 95% repolarization time is unimportant. For all studies, epicardial repolarization time was defined as the repolarization time at the most epicardial node of the fiber, and endocardial repolarization time was defined as the
repolarization time at the most endocardial node of the fiber. Midmyocardial repolarization time was defined at the node in the midmyocardial region with the latest repolarization time in the fiber.

Gradient of repolarization time, or repolarization gradient, was defined in the fiber model by equation 2.20,

\[
\nabla_{repol} = \frac{t_{repol}(endo) - t_{repol}(mid)}{x_{repol}(mid) - x_{repol}(endo)} + \frac{t_{repol}(mid) - t_{repol}(epi)}{x_{repol}(epi) - x_{repol}(mid)} \tag{2.20}
\]

where \(t_{repol}\) is the repolarization time of the node indicated, and \(x_{repol}\) is the location of the node. A positive repolarization gradient signifies that the endocardial end of the fiber has later repolarization time than the epicardial end of the fiber.

Voltage gradients were also calculated from the fiber model. Transmural ECG waveforms were influenced by two opposing main voltage gradients: the midmyocardial-epicardial (mid-epi) voltage gradient and the endocardial-midmyocardial (endo-mid) voltage gradient. The mid-epi gradient was computed as the voltage difference between the midmyocardial node and epicardial node, divided by the fiber distance between the cells. The endo-mid gradient was computed in a similar fashion but between the endocardial node and midmyocardial node. These voltage gradients approximate the first spatial derivative of \(V_m\) in the fiber and are closely related to extracellular potential. Equation 2.19 shows the monopole current source approximation for extracellular potential, which is calculated using the second spatial derivative of \(V_m\). An alternative method for calculating extracellular potential involves the dipole source approximation method shown by equation 2.21,
\[ \phi_e(x', y', z') = \frac{a^2}{4\sigma_e} \int \sigma_i \left[ -\frac{\partial V_m}{\partial x} \tilde{a}_x \right] \left[ \nabla \left( \frac{1}{r} \right) \right] dx \]  

(2.21)

where \( \tilde{a}_x \) is a unit vector in the axial direction from the endocardial fiber end to the epicardial fiber end. Because the dipole source approximation uses the first spatial derivative of \( V_m \), the link between voltage gradient and extracellular potential is clear.

We used the monopole source approximation (equation 2.19) in our simulations because it is the method used in the CardioWave software package, but voltage gradients can still be compared to extracellular potential because of the relationship implied by equation 2.21.

### 2.5.2 ECG Parameters Measured

From each ECG tracing, the following parameters were measured: T-wave amplitude, T-wave upstroke time, \( QT_{\text{peak}} \) interval, T-wave downstroke time, QT interval, and \( T_{\text{peak}} - T_{\text{end}} \) interval (Figure 2.8). T-wave amplitude was measured as the voltage difference between the T-wave peak and the isoelectric line. T-wave upstroke time was measured as the time difference between initial Q-wave deflection and the time of maximal increase in T-wave voltage (maximum dV/dt). \( QT_{\text{peak}} \) interval was measured as the time difference between initial Q-wave deflection and the time of the T-wave peak. T-wave downstroke time was measured as the time difference between initial Q-wave deflection and the time of maximal decrease in T-wave voltage (minimum dV/dt). QT interval was measured as the time difference between initial Q-wave deflection and the T-wave end, measured using both the tangent and threshold method. By the tangent method, the T-wave end was defined as the point at which a line drawn tangent to the T
wave at T-wave downstroke time intersects the isoelectric line. By the threshold method, the T-wave end was defined as the point at which ECG voltage decreased to 0.2 µV. This voltage was chosen because T-wave voltage approaches but does not reach the isoelectric line before the next stimulus in simulated ECGs, due to high voltage resolution. $T_{\text{peak}} - T_{\text{end}}$ time was measured as the time difference between the time of T-wave peak and both tangent-approximated and threshold-approximated T-wave end. The amount of alternation in each of these parameters during T-wave alternans (TWA) is denoted as “alternans of parameter,” where parameter describes any of the temporal parameters described above. Alternation in the amplitude of the T wave during alternans is denoted as TWA amplitude.

**Figure 2.8:** Parameters measured from ECG.
3. ECG Manifestations of Dynamic Restitution

3.1 Introduction

Multiple electrocardiographic (ECG) measures of repolarization have been proposed as clinically important parameters that represent repolarization in the tissue. Attempts have been made to correlate ECG waveforms with the timing of cellular events in the underlying myocardium. For example, some studies have shown that the QT interval approximates the repolarization time of the midmyocardium and that the QT\textsubscript{peak} interval approximates the repolarization time of the epicardium in the free wall of the canine left ventricle (LV) (35, 75-77, 95). These same studies have suggested that the T\textsubscript{peak}-T\textsubscript{end} interval correlates with the transmural dispersion of repolarization (TDR), which has been linked to arrhythmia susceptibility. While these studies have shown a relationship between measurements in the ECG and events in the myocardium, these correlations have been largely qualitative, comparing ECG measurements with visually-approximated repolarization from action potential tracings. In addition, these studies have been performed during static, steady-state rates. Little is known of the effect of dynamic tissue repolarization changes on ECG parameters such as the QT interval, QT\textsubscript{peak} interval, and T\textsubscript{peak}-T\textsubscript{end} interval.

Repolarization changes in tissue have also been linked to defects in tissue conductivity (16, 61, 66). Several factors have been shown to alter tissue conductivity by modulating gap junctions, such as pharmacologic agents (24), aging (1, 36, 62, 82), heart failure (66), ischemia (8), and infarction (61). The effect of changes in tissue conductivity
on the correlation between tissue repolarization and ECG parameters has not been thoroughly investigated.

The goal of this chapter was to quantify how ECG markers of repolarization correspond to cellular repolarization. For this study, I used the 1.3-cm-long fiber model with heterogeneous tissue conductivity discussed in section 2.1.2 and the modified minimal ventricular (MV) model discussed in section 2.2.1. I investigated the effects of dynamic repolarization changes by pacing the fiber over basic cycle lengths (BCL) ranging from 4000 to 500 ms. Tissue repolarization times and TDR were compared with the following ECG parameters: T-wave upstroke time, QT_{peak} interval, T-wave downstroke time, and QT interval. In addition, I investigated the effects of gap junction conductance by pacing the fiber model at control conductivity, reduced mean conductivity, and enhanced mean conductivity.

3.2 Results

3.2.1 Cellular Activation and Repolarization

The mean conduction velocity (CV) for the fiber at control conductivity was between 40.8 and 42.6 cm/s for all BCL, which approximated left ventricular transmural conduction velocity recorded \textit{in vitro} (29, 65, 66, 96). Due to heterogeneity in tissue conductivity, local CV ranged from 27.8 cm/s at the epicardial end to 50 cm/s in the middle of the tissue (Figure 3.1). Reduction or enhancement in tissue conductivity resulted in a decrease or increase from CV at control conductivity, respectively. At reduced mean conductivity, the fiber had mean CV of 30.1 – 31.5 cm/s with local CV
ranging from 20.8 to 35.7 cm/s. At enhanced mean conductivity, the fiber had mean CV of 56.3 – 58.4 cm/s with local CV ranging from 36.4 to 71.4 cm/s.

Figure 3.1: Local CV measured at a BCL of 1000 ms for fiber at control, reduced, and enhanced conductivity.

The epicardial region of the fiber was the first to repolarize, followed by the endocardial region and the midmyocardial region. At control conductivity and long BCL, the location where final repolarization occurred in the fiber was 0.6 cm away from the endocardial fiber end. At short BCL, the location of final repolarization was 0.7 cm from the endocardial fiber end.

3.2.2 ECG Characteristics

Nearly all ECG tracings exhibited positive T waves. T-wave inversion occurred at reduced mean conductivity and short BCL (500-600 ms) because epicardial
repolarization occurred later than endocardial repolarization. The decreased CV caused by reduced mean conductivity delayed activation and subsequent repolarization of the epicardial cell relative to the endocardial cell. These T waves were not included in analysis because ECG parameters used in the study were designed for positive T waves.

T-wave amplitude was dependent on BCL and fiber conductivity. For all fiber conductivities, T-wave amplitude slightly decreased as BCL decreased. T-wave amplitude was largest at enhanced mean conductivity and smallest at reduced mean conductivity.

3.2.3 Cellular Repolarization Relation to T-Wave Parameters

Epicardial AP downstroke time relation to T-wave upstroke time

Epicardial action potential (AP) downstroke time (time of minimum dV_m/dt) corresponded to T-wave upstroke time, but this relationship was altered by both pacing rate and conductivity. Figure 3.2 shows epicardial AP tracings and ECG tracings with epicardial AP downstroke times and T-wave upstroke times indicated. At enhanced conductivity and long BCL, epicardial AP downstroke time was within 5 ms of T-wave upstroke time. However, as conductivity and BCL decreased, this correspondence decreased substantially.
Figure 3.2: Epicardial AP tracings plotted with ECG tracings showing the correspondence between epicardial AP downstroke time and T-wave upstroke time for (A) representative BCL and (B) different levels of tissue conductivity.

Epicardial repolarization time relation to QT\textsubscript{peak} interval

Figure 3.3 shows epicardial AP tracings plotted with the corresponding ECG tracings with epicardial repolarization times and QT\textsubscript{peak} intervals indicated. At control conductivity, QT\textsubscript{peak} interval ranged from 248.2 ms at a BCL of 4000 ms to 212.6 ms at a BCL of 500 ms, comparable to experimental values recorded from a wedge of LV free wall that range from approximately 260 ms at a BCL of 4000 ms to approximately 218 ms at a BCL of 500 ms (estimated by eye from figure in reference 95). At reduced conductivity, QT\textsubscript{peak} interval ranged from 256.9 to 225.5 ms, and at enhanced conductivity, QT\textsubscript{peak} interval ranged from 242.4 to 206.8 ms. No experimental data exists on QT\textsubscript{peak} interval at altered conductivity.
At control conductivity and a BCL of 1000 ms, the $QT_{\text{peak}}$ interval coincided closely with 91% epicardial repolarization. However, this temporal association was modulated by both tissue conductivity and BCL. As BCL shortened, the $QT_{\text{peak}}$ interval decreased more than the epicardial repolarization time. Consequently, at short BCL, the T-wave peak occurred prior to the 91% repolarization level in the epicardium. As mean tissue conductivity decreased, the epicardial repolarization time increased more than the $QT_{\text{peak}}$ interval. Therefore, with reduced conductivity, the T-wave peak occurred prior to the 91% repolarization point in the epicardium.

Figure 3.3: Epicardial AP tracings plotted with ECG tracings showing the correspondence between epicardial repolarization time and $QT_{\text{peak}}$ intervals for (A) representative BCL and (B) different levels of tissue conductivity.
Endocardial AP downstroke time relation to T-wave downstroke time

Just as epicardial AP downstroke time coincided with T-wave upstroke time, endocardial AP downstroke time coincided with T-wave downstroke time. However, the correspondence between endocardial AP downstroke time and T-wave downstroke time was closest under conditions of reduced conductivity and short BCL (Figure 3.4). This relationship is in contrast to the correspondence between epicardial AP downstroke time and T-wave upstroke time, which had best agreement under conditions of enhanced conductivity and long BCL.

Figure 3.4: Endocardial AP tracings plotted with ECG tracings showing the correspondence between endocardial AP downstroke time and T-wave downstroke time for (A) representative BCL and (B) different levels of tissue conductivity.
Midmyocardial repolarization time relation to QT interval

QT interval was measured using both the tangent method and the threshold method in order to investigate whether one method is more predictive of dynamic repolarization changes. At control conductivity, threshold-approximated QT interval ranged from 309.8 to 243.2 ms at BCL ranging from 4000 to 500 ms. Tangent-approximated QT interval was slightly smaller, ranging from 301.5 to 231 ms for the same BCL. Both measures were comparable to experimental values recorded from a wedge of LV free wall from approximately 318 ms at a BCL of 4000 ms to approximately 230 ms at a BCL of 500 ms (estimated by eye from figure in reference 95). At reduced conductivity, threshold-approximated and tangent-approximated QT interval ranged from 310.1 to 250.8 ms and from 302.3 to 240.9 ms, respectively. At enhanced conductivity, threshold-approximated and tangent-approximated QT interval ranged from 317.1 to 257.1 ms and from 302.4 to 231.3 ms, respectively. No experimental data exists on QT interval at altered conductivity.

Figure 3.5 shows midmyocardial AP tracings plotted with the corresponding ECG tracings with midmyocardial repolarization times and threshold-approximated QT interval indicated. At a BCL of 1000 ms and control conductivity, the threshold-approximated QT interval closely approximated 93% midmyocardial repolarization. As BCL lengthened, the midmyocardial repolarization time increased more than the threshold-approximated QT interval. Consequently, threshold-approximated QT interval was not an accurate predictor of midmyocardial repolarization time at slow rates. As mean tissue conductivity decreased, the threshold-approximated QT interval decreased
whereas the midmyocardial repolarization time increased. At enhanced mean conductivity, the threshold-approximated QT interval was longer than 93% midmyocardial repolarization time, and at reduced mean conductivity, the threshold-approximated QT interval was shorter than 93% repolarization time.

Figure 3.5: Midmyocardial AP tracings plotted with ECG tracings showing the correspondence between midmyocardial repolarization time and threshold-approximated QT interval for (A) representative BCL and (B) different levels of tissue conductivity.

Figure 3.6 shows midmyocardial AP tracings plotted with the corresponding ECG tracings for representative BCL and levels of tissue conductivity. At a BCL of 1000 ms and control conductivity, the tangent-approximated QT interval closely approximated 80% midmyocardial repolarization. As BCL lengthened, the midmyocardial repolarization time increased more than the tangent-approximated QT interval such that 80% repolarization time was longer than the QT interval. As mean tissue conductivity
decreased, the midmyocardial repolarization time increased whereas the tangent-approximated QT interval remained relatively constant. Consequently, at enhanced mean conductivity, the tangent-approximated QT interval was longer than 80% midmyocardial repolarization time, and at reduced mean conductivity, the tangent-approximated QT interval was shorter than 80% repolarization time.

Figure 3.6: Midmyocardial AP tracings plotted with ECG tracings showing the correspondence between midmyocardial repolarization time and tangent-approximated QT interval for (A) representative BCL and (B) different levels of tissue conductivity.

**TDR relation to \( T_{\text{peak}} - T_{\text{end}} \) interval**

The model showed that the relationship between the \( T_{\text{peak}} - T_{\text{end}} \) interval and TDR was sensitive to dynamic repolarization changes. At control conductivity and a BCL of 1000 ms, the threshold-approximated \( T_{\text{peak}} - T_{\text{end}} \) interval best approximated TDR defined as the difference between 93% midmyocardial repolarization and 91% epicardial
repolarization, degrees of repolarization that best corresponded to the threshold-approximated T-wave end and T-wave peak at a BCL of 1000 ms. Using this definition of TDR, the threshold-approximated T\textsubscript{peak}-T\textsubscript{end} interval was shorter than TDR at a BCL of 4000 ms and longer than TDR at a BCL of 500 ms (Figure 3.7A). At reduced mean conductivity, the threshold-approximated T\textsubscript{peak}-T\textsubscript{end} interval was shorter than TDR, with greater discrepancies occurring at longer BCL. At enhanced mean conductivity, the T\textsubscript{peak}-T\textsubscript{end} interval was longer than TDR at short BCL and was shorter than TDR at long BCL.

In summary, the threshold-approximated T\textsubscript{peak}-T\textsubscript{end} interval approximated TDR to within 5 ms when the fiber was paced at medium and short BCL for control conductivity, at short BCL for reduced conductivity, and at long BCL for enhanced conductivity.

At control conductivity and a BCL of 1000 ms, the tangent-approximated T\textsubscript{peak}-T\textsubscript{end} interval best approximated TDR when defined as the difference between 80% midmyocardial repolarization and 91% epicardial repolarization, degrees of repolarization that corresponded best to the tangent-approximated T-wave end and T-wave peak at a BCL of 1000 ms. Using this definition of TDR, tangent-approximated T\textsubscript{peak}-T\textsubscript{end} interval was shorter than TDR at long BCL but longer than TDR at short BCL under conditions of control and enhanced conductivity (Figure 3.7B). At reduced conductivity, tangent-approximated T\textsubscript{peak}-T\textsubscript{end} interval was shorter than TDR for all BCL, with greater discrepancies occurring at long BCL. At enhanced mean conductivity, the T\textsubscript{peak}-T\textsubscript{end} interval was longer than TDR at short BCL and was shorter than TDR at long BCL. Tangent-approximated T\textsubscript{peak}-T\textsubscript{end} interval approximated TDR to within 5 ms at medium BCL for control and enhanced conductivity and at short BCL for reduced
conductivity. The discrepancies between TDR and T\textsubscript{peak}\textendash T\textsubscript{end} interval occur because the T-wave peak and T-wave end correspond to different degrees of cellular repolarization at different BCL and tissue conductivities.

Figure 3.7: TDR and (A) threshold-approximated T\textsubscript{peak}\textendash T\textsubscript{end} interval or (B) tangent-approximated T\textsubscript{peak}\textendash T\textsubscript{end} interval plotted as a function of BCL at control, enhanced and reduced conductivity. TDR is defined at degrees of repolarization that best match each approximation method for T\textsubscript{peak}\textendash T\textsubscript{end} interval at control conductivity and a BCL of 1000 ms.
3.2.4 Intercellular Voltage Gradients Responsible for ECG Waveforms

To determine the mechanism for the discrepancies in ECG and cellular measures, I analyzed tissue voltage gradients. Transmural ECG waveforms were influenced by two opposing main voltage gradients: the midmyocardial-epicardial (mid-epi) voltage gradient and the endocardial-midmyocardial (endo-mid) voltage gradient. The mid-epi gradient was computed as the voltage difference between the midmyocardial node and epicardial node, divided by the fiber distance between the cells. The endo-mid gradient was computed in a similar fashion but between the endocardial node and midmyocardial node. Figures 3.8A and 3.8B show these voltage gradients over time for representative BCL and mean tissue conductivities. The sum of these two gradients closely approximated the transmural ECG waveform.

The relative contribution of each gradient to the ECG was dependent on both BCL and tissue conductivity. Figure 3.8C shows the effects of BCL and conductivity changes on the maximum magnitude of each voltage gradient. As BCL shortened, the relative reduction in the maximum mid-epi gradient was greater than the relative reduction in the endo-mid gradient. Decreased mean tissue conductivity augmented the mid-epi gradient at long BCL but not short BCL. In contrast, decreased mean conductivity augmented the endo-mid gradient at all BCL. Thus, as BCL shortened, the endo-mid gradient played a larger role in inscribing the ECG than at longer BCL, resulting in changes in the degree of cellular repolarization that corresponded to the QT_peak interval or QT interval. This effect was particularly pronounced at reduced conductivity.
Changes in maximum voltage gradient due to BCL and conductivity closely approximated changes in spatial differences in repolarization. Figure 3.8D shows the time difference between 90% midmyocardial repolarization and 90% epicardial repolarization or 90% endocardial repolarization divided by the distance between the measured nodes. (90% repolarization was arbitrarily chosen, but the results are similar for other degrees of repolarization.) The similarity between figure 3.8C and 3.8D implicates the role of spatial differences in repolarization in determining the strength of voltage gradients that influence the ECG. Because of intrinsic differences in cellular restitution, these spatial repolarization differences change as a function of BCL and conductivity, modifying the voltage gradients that influence the ECG and altering the correlation of ECG parameters to cellular repolarization.
Figure 3.8: Midmyocardial-epicardial (mid-epi) and endocardial-midmyocardial (endo-mid) voltage gradients shown for (A) representative BCL and (B) different levels of tissue conductivity. The sum of the two gradients closely approximates the transmural ECG. (C) Maximum magnitude of voltage gradient as a function of BCL at different levels of tissue conductivity. (D) Magnitude of gradient of repolarization time between midmyocardial node and epicardial node (mid-epi) and between endocardial node and midmyocardial node (endo-mid) as a function of BCL at different levels of tissue conductivity.
3.3 Discussion

Several investigators have studied the relationship between tissue repolarization events in the transmural wedge model and the resultant waveforms in the transmural ECG, either with an experimental preparation (30, 75, 76, 78, 95) or a computer model (35, 44). However, this study is the first to investigate the effects of dynamic, rate-dependent changes in cellular repolarization on the ECG. I have shown that the correlation between cellular repolarization and T-wave parameters change with BCL and tissue conductivity. These changes are due to spatial differences in cellular repolarization dynamics, which alter the relative contribution of voltage gradients to the ECG.

3.3.1 Effect of Spatial Differences in Dynamic Restitution on the ECG

The peak of the ECG T wave occurs when the net voltage gradient between ECG leads is at its maximum. The T-wave end occurs when the net voltage gradient diminishes. If the mid-epi gradient were the only gradient in the fiber model, full (100%) epicardial repolarization would maximize the magnitude of the gradient, inscribing the T-wave peak, and full (100%) midmyocardial repolarization would eliminate the gradient, resulting in the T-wave end. However, I have shown that these ECG parameters correspond to cellular repolarization at times earlier than 100% repolarization. This effect is due to the contribution of the endo-mid gradient to the formation of the ECG. The relative contributions of the mid-epi and endo-mid gradient to the ECG change based on pacing rate and mean tissue conductivity. Several of the findings in this chapter can be explained by considering the increased contribution of the endo-mid gradient to the ECG at short BCL and reduced conductivity. These effects are detailed below.
Epicardial AP downstroke time relation to T-wave upstroke time

Epicardial AP downstroke time (time of minimum $dV_m/dt$) corresponded best to T-wave upstroke time at long BCL and at enhanced conductivity (Figure 3.2). Under these conditions, the mid-epi gradient is the dominant gradient in the tissue, and the rising phase of the T wave is inscribed as the epicardial end of the fiber begins to repolarize. Thus, it logically follows that epicardial AP downstroke time, the maximum change in repolarization voltage in the cell, results in a maximum change in the mid-epi gradient, which inscribes the maximum positive change in T-wave voltage, the T-wave upstroke time. However, as BCL shortens and conductivity decreases, the magnitude of the endo-mid gradient increases relative to the mid-epi gradient. The increased influence of the endo-mid gradient causes the T-wave upstroke time to occur earlier than epicardial AP downstroke time. Consequently, the correlation between epicardial AP downstroke time and T-wave upstroke time is less robust.

Epicardial repolarization time relation to $QT_{peak}$ interval

At long BCL and enhanced conductivity, $QT_{peak}$ interval corresponded to later degrees of epicardial repolarization (Figure 3.3). Again, the influence of the mid-epi gradient is greater than that of the endo-mid gradient under these conditions. At shortened BCL and reduced conductivity, the increased influence of the endo-mid gradient causes the T-wave peak to occur at earlier degrees of epicardial repolarization.

Endocardial AP downstroke time relation to T-wave downstroke time

Endocardial AP downstroke time corresponded well with T-wave downstroke time, particularly at short BCL and reduced conductivity (Figure 3.4). This finding
contrasts with the relation between epicardial AP downstroke time and T-wave upstroke time, which are closely associated at long BCL and enhanced conductivity. At short BCL and reduced conductivity, the endo-mid gradient has a large relative contribution to the ECG, and the time of maximum magnitude of the endo-mid gradient is temporally associated with the T-wave downstroke time (Figure 3.8). This association is intuitive because the maximum magnitude of the endo-mid gradient occurs after the T-wave peak and opposes the mid-epi gradient, resulting in a sharp decrease in T-wave voltage, the T-wave downstroke. However, at long BCL and enhanced conductivity, the increased influence of the mid-epi gradient causes T-wave downstroke time to occur earlier than endocardial AP downstroke time. As a result, the correspondence between endocardial AP downstroke time and T-wave downstroke time decreased.

**Midmyocardial repolarization time relation to QT interval**

The changes in correlation of endocardial or epicardial AP downstroke time and their respective T-wave parameters due to changes in BCL or conductivity can be explained by changes in the contribution of the mid-epi and endo-mid gradients to the ECG. Scenarios with large contribution from the mid-epi gradient (long BCL and enhanced conductivity) result in good correlation between epicardial AP downstroke time and T-wave upstroke time and between late epicardial repolarization time and $QT_{peak}$ interval. Scenarios with increased contribution from the endo-mid gradient (short BCL and reduced conductivity) result in good correlation between endocardial AP downstroke time and T-wave downstroke time. The effect of changes in BCL and conductivity on the relationship between midmyocardial repolarization time and QT interval is not as clear.
because both the mid-epi and endo-mid gradient are affected by changes in midmyocardial repolarization time.

If the mid-epi gradient were the major gradient in the fiber model, full (100%) midmyocardial repolarization would eliminate the gradient, resulting in the T-wave end. Thus, it is somewhat counterintuitive that both tangent-approximated and threshold-approximated QT interval coincided with earlier midmyocardial repolarization times at long BCL, when the mid-epi gradient is predominant, and with later repolarization time at medium to short BCL, when the endo-mid gradient has a larger influence (Figures 3.6 and 3.7). The effect may be partially explained by the timing of the maximum magnitude of the endo-mid gradient. Figure 3.8A shows that at short BCL, the maximum magnitude of the endo-mid gradient occurs soon after the T-wave peak. However, as BCL increases, the maximum magnitude of the endo-mid gradient occurs closer to the T-wave end. Thus, at long BCL, the endo-mid gradient may have a greater effect on the timing of the T-wave end, even though its total contribution to the ECG is less than at short BCL.

Both tangent-approximated and threshold-approximated QT interval coincided with earlier repolarization times as conductivity decreased. Figure 3.8B shows that changes in the timing of the maximum magnitude of the endo-mid gradient are less pronounced for changes in conductivity than for changes in BCL and are therefore less likely to be responsible for this effect than when BCL is decreased. The effect of tissue conductivity on ECG voltage may largely influence the timing of the QT interval. From equation 2.19, we see that increased tissue conductivity, $\sigma_i$, increases extracellular potential, which increases ECG voltage. Thus, the same voltage gradients will generate a
larger or smaller ECG voltage due to tissue conductivity. For example, in figure 3.8B, the sum of the voltage gradients all peak at roughly 50 mV/cm. This same voltage gradient creates a T wave of amplitude 18 µV for enhanced conductivity, 10 µV for control conductivity, and 3 µV for reduced conductivity. Accordingly, the threshold voltage of 0.2 µV corresponds to a different sum of repolarization gradients, depending on tissue conductivity. The voltage threshold represents a smaller sum of voltage gradients for the enhanced conductivity case than for the control conductivity case. Because this smaller sum occurs later in time, threshold-approximated QT interval is prolonged. Similarly, the same threshold voltage represents a larger sum of voltage gradients for the reduced conductivity case. This sum of voltage gradients appears earlier in time, and the threshold-approximated QT interval is shortened.

Because increased tissue conductivity increases ECG voltage, T-wave amplitude is also increased. Larger T-wave amplitude likely explains why tangent-approximated QT interval is coincident with later degrees of repolarization under conditions of enhanced tissue conductivity. As T-wave amplitude increases, the line drawn tangent to T-wave downstroke shifts upward, and the intercept of this line with the isoelectric line occurs later. Thus, increased T-wave amplitude from increased tissue conductivity results in prolonged tangent-approximated QT interval, which coincides with a later degree of midmyocardial repolarization.
3.3.2 Implications for the Use of ECG Parameters to Assess Myocardial Repolarization

Although my study was limited to a model of the LV free wall, the results have implications for the use of ECG parameters as indicators of repolarization within the whole heart. Based on experimental studies correlating the $T_{peak}-T_{end}$ interval in the transmural ECG to TDR (75, 76, 78, 95), investigators have begun using the $T_{peak}-T_{end}$ interval of the 12-lead ECG as a surrogate for global dispersion of repolarization in vivo (10, 83, 84, 91-94).

As I have shown, ECG parameters correspond to different degrees of cellular repolarization due to the influence of voltage gradients that change with pacing rate and tissue conductivity. The 3-D geometry of the whole heart introduces many more voltage gradients than what I have investigated in my 1-D model. Additionally, the orientation of the particular lead used to compute the ECG alters the relative contribution of each lead to the ECG. Left precordial leads would reflect gradients within the left ventricular free wall, right precordial leads would illustrate right ventricular gradients, and limb leads would consolidate baso-apical and interventricular gradients (2). Without detailed knowledge of the regional variation of cellular repolarization dynamics in the heart, it is difficult to predict where the major repolarization gradients exist, how they may manifest in different leads, and how they may change with heart rate. Thus, when using the $T_{peak}-T_{end}$ interval as a surrogate for global dispersion of repolarization, it is difficult to determine the particular degree of repolarization being measured (e.g. 83% repolarization
vs. 95% repolarization) and how predictive this degree of repolarization is for arrhythmia risk.

Many of the studies using the $T_{peak} - T_{end}$ interval as a surrogate for global dispersion of repolarization have been done either at a single BCL (92-94) or with some form of heart rate correction (10, 83, 84, 91). As I have demonstrated, changes in BCL alter the relationship between the $T_{peak} - T_{end}$ interval and TDR, and it is possible to erroneously conclude that the $T_{peak} - T_{end}$ interval approximates repolarization dispersion if only a single BCL is investigated. RR interval correction methods (7, 34) attempt to adjust for $T_{peak} - T_{end}$ shortening at short BCL but are empiric and unable to account for spatial differences in cellular voltage dynamics that affect the ECG.

In conclusion, I have shown that ECG markers of repolarization correspond to different degrees of cellular repolarization at different pacing rates and under different tissue conductivities. These changes are due to spatial differences in cellular repolarization dynamics throughout the tissue that manifest as dynamic voltage gradients and alter the composition of the ECG. In addition, physiologic and pathologic alterations in tissue conductivity can modulate the activation and subsequent repolarization pattern of tissue as well as the electrotonic effect between cells, further altering the relationship between repolarization and ECG parameters. Because repolarization dynamics, gap junction distribution, and tissue geometry are more complex in the whole heart than in my model, I propose that the relationship between ECG markers of repolarization and cellular repolarization is more complicated in vivo.
3.4 Limitations

As with any modeling study, my results are limited by the model’s approximations of physiology. These approximations were made not only for simulation tractability but also because of limited data on regional APD in the canine LV free wall over multiple BCL. My principal approximation involved the structure and cellular composition of the canine LV free wall. By modeling the wedge as a 1-dimensional fiber, I neglected the effects of conduction and repolarization heterogeneity in the baso-apical and anterior-posterior axes. Although repolarization heterogeneity in the baso-apical direction had previously been thought to significantly influence the T wave of the transmural ECG, Yan and Antzelevitch have shown that is contribution is minimal (95). Thus, my use of a 1-dimensional fiber is a reasonable approximation of the canine LV free wall for ECG studies. I also approximated the cellular distribution of the LV wedge by using only three cell types. Physiologically, the LV free wall is likely composed of a vast number of electrophysiologically distinct cells, each with its own unique composition of transmembrane channels, transporters, and Ca-handling mechanisms, with no clear criteria for classification into cell types. However, by using only three cell types, I was still able to adequately approximate the transmural distribution of APD over many BCL. Finally, I gave each cell type a similar action potential morphology, which may influence my results because the degree of cellular repolarization is highly dependent on the morphology of the action potential foot. Thus, my estimates of the degree of cellular repolarization are likely to change when investigated using different membrane models with different action potential morphologies. However, the
mechanisms described in this study that alter the relationship between ECG markers of repolarization and cellular repolarization are due to spatial differences in dynamic cellular repolarization and are prominent even in the absence of action potential morphology differences.
4. ECG Manifestations of S1-S2 Restitution and Short-Term Memory

4.1 Introduction

The response of myocardium to a sudden change in pacing rate is manifest as S1-S2 restitution (response to one stimulus) and short-term memory (STM) (response to a long train of stimuli at constant basic cycle length (BCL)). These time-dependent changes in cellular repolarization have been shown to modulate the development of arrhythmia in both computer models (31, 90) and experimental preparations (52). S1-S2 restitution and STM are present in the electrocardiogram (ECG) (9), but the relationship between S1-S2 restitution and STM in the ECG to S1-S2 restitution and STM of underlying myocardium is poorly understood.

In this chapter, I used the fiber model described in section 2.1.2 and the modification of the Fox-McHarg-Gilmour (FMG) model described in section 2.2.2 to investigate the relationship between S1-S2 restitution and STM in the ECG and in underlying myocardium. I paced the fiber at a BCL of 1000 ms for 125 s to reach steady state. I then delivered a premature stimulus at an S1-S2 coupling interval of 900, 800, 700, or 600 ms to elicit an S1-S2 response. To study the STM response, the premature stimulus at a BCL of 600 ms was followed by a train of stimuli at a BCL of 600 ms for 125 s. I compared repolarization times from the endocardium, midmyocardium, and epicardium to ECG parameters. I also compared STM beat constants of cellular repolarization times to STM beat constants of ECG parameters. I chose to compare beat constants rather than time constants because my models are based on experimental data.
presented in beat constants (90). Three STM conditions were considered: One in which the STM beat constant was similar for all cells in the fiber, one in which the STM beat constant was abnormally short at the endocardial fiber end, and one in which the STM beat constant was abnormally short at the epicardial fiber end. I also investigated the effect of changes in tissue conductivity by investigating these phenomena at control conductivity, reduced mean fiber conductivity, and enhanced mean fiber conductivity (see section 2.1.2 for details).

4.2 Results

4.2.1 Cellular Activation and Repolarization

The mean conduction velocity (CV) for the fiber at control conductivity was 45.7 cm/s, which approximated left ventricular transmural conduction velocity recorded in vitro (29, 65, 66, 96). Due to heterogeneity in tissue conductivity, local CV ranged from 27.8 cm/s at the epicardial end to 55.6 cm/s in the middle of the tissue. At reduced mean conductivity, the fiber had mean CV of 30.9 cm/s with local CV ranging from 18.5 to 38.5 cm/s. At enhanced mean conductivity, the fiber had mean CV of 66.5 cm/s with local CV ranging from 41.7 to 83.3 cm/s. Neither mean nor local CV changed due to the premature S2 stimulus or due to pacing at the new BCL of 600 ms. CV also remained constant when STM properties at either end of the fiber were altered.

For all simulations, the epicardial region of the fiber was the first to repolarize, followed by the endocardial region and the midmyocardial region. Final repolarization in the fiber occurred 0.35 to 0.4 cm away from the endocardial fiber for control mean
conductivity, 0.5 to 0.55 cm away for reduced mean conductivity, and 0.25 cm away for enhanced mean conductivity.

4.2.2 Effects of Cellular Short-Term Memory Changes on the ECG

Fiber with control mean conductivity

As a basis for comparison, a fiber was created with all nodes having a similar STM beat constant (fiber with spatially homogeneous STM beat constant). In response to an abrupt change in BCL from 1000 ms to 600 ms, repolarization times for all nodes exhibited monoexponential decay with a beat constant on the order of 24 beats, similar to the experimental value of 25.9 beats observed in strips of canine endocardial and epicardial LV myocardium (90). ECG parameters also exhibited monoexponential decay with a similar beat constant (Table 4.1, first data column).

Table 4.1: STM beat constants for cellular repolarization times and ECG parameters for a fiber with control mean conductivity.

<table>
<thead>
<tr>
<th>STM beat constant (beats)</th>
<th>Fiber with homogeneous STM</th>
<th>Fiber with reduced endocardial STM</th>
<th>Fiber with reduced epicardial STM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial repolarization</td>
<td>24.02</td>
<td>21.52</td>
<td>22.10</td>
</tr>
<tr>
<td>Midmyocardial repolarization</td>
<td>23.90</td>
<td>21.88</td>
<td>21.51</td>
</tr>
<tr>
<td>Epicardial repolarization</td>
<td>24.18</td>
<td>23.74</td>
<td>13.78</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>24.38</td>
<td>23.77</td>
<td>14.08</td>
</tr>
<tr>
<td>QT&lt;sub&gt;peak&lt;/sub&gt; interval</td>
<td>24.13</td>
<td>23.32</td>
<td>16.80</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>23.60</td>
<td>21.26</td>
<td>21.72</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>23.95</td>
<td>21.39</td>
<td>22.37</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>23.85</td>
<td>21.38</td>
<td>22.13</td>
</tr>
</tbody>
</table>

To evaluate the effect of spatial differences in STM, STM beat constant for endocardial nodes (the first 13 nodes of the fiber) was reduced (see Appendix A for details). Due to electrotonic effects, STM beat constant reduction of endocardial nodes created a gradient of short to long STM beat constant from endocardium to epicardium.
(Table 4.1, second data column). STM beat constant for T-wave upstroke time and QT<sub>peak</sub> interval were similar to epicardial cellular STM beat constant. STM beat constant for T-wave downstroke time and both threshold-approximated and tangent-approximated QT interval were similar to that of the endocardial cell. Figure 4.1A shows the repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced endocardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. At beat 1, red and black lines overlap, indicating very little difference in cellular repolarization, T-wave voltage, or tissue voltage gradient due to STM differences. However, at beats 10 and 25, endocardial repolarization occurs earlier in the fiber with decreased endocardial STM beat constant, altering tissue voltage gradients and causing an earlier downstroke phase of the T wave. By beat 100, there is again little difference in cellular repolarization or T-wave voltage as both the fiber with homogeneous STM beat constant and the fiber with reduced endocardial STM beat constant have approached steady state.
To investigate further the effect of spatial differences in STM, STM beat constant for epicardial nodes (the last 39 nodes of the fiber) was reduced (see Appendix A for details). As with endocardial STM beat constant reduction, electrotonic effects created a gradient of STM beat constant, this time from short beat constant in the epicardium to long beat constant in the endocardium (Table 4.1, third data column). Again, STM beat constants for T-wave upstroke time and $QT_{peak}$ interval were similar to epicardial cellular
STM beat constant, and STM beat constants for T-wave downstroke time and both approximates of QT interval were similar to endocardial cellular STM beat constant. Figure 4.1B shows the repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced epicardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. As with the fiber with reduced endocardial STM beat constant, the reduced epicardial beat constant caused transient changes in both cellular repolarization and the T wave when compared to the fiber with homogeneous STM beat constant in the fiber. The reduction in epicardial STM beat constant resulted in earlier epicardial repolarization times at beats 10 and 25. The earlier repolarization time altered the midmyocardial-epicardial (mid-epi) voltage gradient, resulting in earlier upstroke of the ECG T wave. By beat 100, repolarization times were similar for the fiber with reduced epicardial beat constant and the fiber with homogeneous beat constant. Consequently, tissue voltage gradients and T waves were similar for both fibers at beat 100.

**Fiber with reduced mean conductivity**

At reduced mean fiber conductivity, results for the fiber with homogeneous STM beat constant were similar to those at control conductivity. STM beat constants for all nodes were on the order of 24 beats, and STM beat constants for ECG parameters were also on the order of 24 beats (Table 4.2, first data column).
Table 4.2: STM beat constants for cellular repolarization times and ECG parameters for a fiber with reduced mean conductivity.

<table>
<thead>
<tr>
<th>STM beat constant (beats)</th>
<th>Fiber with homogeneous STM</th>
<th>Fiber with reduced endocardial STM</th>
<th>Fiber with reduced epicardial STM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial repolarization</td>
<td>23.86</td>
<td>20.35</td>
<td>23.44</td>
</tr>
<tr>
<td>Midmyocardial repolarization</td>
<td>23.87</td>
<td>21.96</td>
<td>21.93</td>
</tr>
<tr>
<td>Epicardial repolarization</td>
<td>24.11</td>
<td>24.23</td>
<td>9.64</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>24.22</td>
<td>23.97</td>
<td>11.08</td>
</tr>
<tr>
<td>QT\textsuperscript{peak} interval</td>
<td>23.84</td>
<td>22.96</td>
<td>14.35</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>23.18</td>
<td>21.02</td>
<td>19.36</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>23.89</td>
<td>20.31</td>
<td>23.70</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>23.00</td>
<td>20.81</td>
<td>20.03</td>
</tr>
</tbody>
</table>

The reduction in endocardial STM beat constant resulted in a smaller endocardial STM beat constant for the reduced conductivity fiber than for the control conductivity fiber. Because reduced fiber conductivity decreases electrotonic effects, the spatial difference in STM beat constant from endocardium to epicardium was greater for the reduced conductivity fiber than for the control conductivity fiber (Table 4.2, second data column). Consistent with results in the fiber with control conductivity, STM beat constants for T-wave upstroke time and QT\textsuperscript{peak} interval were similar to epicardial cellular STM beat constant. STM beat constants for T-wave downstroke time and QT interval were similar to endocardial cellular STM beat constant. Figure 4.2A shows the repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced endocardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. Cellular repolarization and T-wave changes are similar to those in figure 4.1A but are more prominent due to the shorter endocardial STM beat constant for the reduced conductivity fiber than for the control conductivity fiber.
Figure 4.2: Repolarization phase of endocardial (endo), midmyocardial (mid), and epicardial (epi) cellular action potentials, ECG T waves, and tissue voltage gradients for a fiber with homogeneous STM beat constant (black) and (A) reduced endocardial STM beat constant (red) or (B) reduced epicardial STM beat constant (red). Results shown here are for a fiber with reduced mean conductivity.

When epicardial STM beat constant was reduced, the decreased electrotonic effect from reduced tissue conductivity resulted in an increased spatial difference in STM beat constant when compared to the fiber with control conductivity (Table 4.2, third data column). STM beat constants for T-wave upstroke time and QT\textsubscript{peak} interval were similar to epicardial STM beat constant, and STM beat constants for T-wave downstroke time and QT interval were similar to endocardial STM beat constant. Figure 4.2B shows the
repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced epicardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. As with the case of reduced endocardial STM beat constant, cellular repolarization and T-wave changes are similar to those in figure 4.1B but are more prominent due to the shorter epicardial STM beat constant for the reduced conductivity fiber than for the control conductivity fiber.

**Fiber with enhanced mean conductivity**

At enhanced mean fiber conductivity, results for the fiber with homogeneous STM beat constant were similar to those at control and reduced conductivity. STM beat constants for all nodes were on the order of 24 beats, and STM beat constants for ECG parameters were also on the order of 24 beats (Table 4.3, first data column).

**Table 4.3: STM beat constants for cellular repolarization times and ECG parameters for a fiber with enhanced mean conductivity.**

<table>
<thead>
<tr>
<th>STM beat constant (beats)</th>
<th>Fiber with homogeneous STM</th>
<th>Fiber with reduced endocardial STM</th>
<th>Fiber with reduced epicardial STM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocardial repolarization</td>
<td>24.11</td>
<td>22.30</td>
<td>20.22</td>
</tr>
<tr>
<td>Midmyocardial repolarization</td>
<td>24.06</td>
<td>22.36</td>
<td>20.27</td>
</tr>
<tr>
<td>Epicardial repolarization</td>
<td>24.06</td>
<td>23.25</td>
<td>17.02</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>24.08</td>
<td>23.26</td>
<td>16.86</td>
</tr>
<tr>
<td>$\text{QT}_{\text{peak}}$ interval</td>
<td>24.17</td>
<td>22.99</td>
<td>17.91</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>24.13</td>
<td>22.39</td>
<td>20.22</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>24.13</td>
<td>22.25</td>
<td>20.59</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>24.09</td>
<td>22.42</td>
<td>20.14</td>
</tr>
</tbody>
</table>

Reduction in endocardial STM beat constant did not yield as great a reduction in STM beat constant as a similar reduction in fibers with reduced or control conductivity. Due to enhanced isoelectric interactions as a result of enhanced conductivity, the spatial
The difference in STM beat constant was not as great as for fibers with reduced or control conductivity (Table 4.3, second data column). However, STM beat constants for ECG parameters still matched cellular STM beat constants. STM beat constant for T-wave upstroke time and QT_{peak} interval were similar to epicardial STM beat constant, and STM beat constant for T-wave downstroke time and QT interval were similar to endocardial STM beat constant. Figure 4.3A shows the repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced endocardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. Results are similar to those described for figure 4.1A and figure 4.2A but less prominent due to the small difference in STM beat constants between the fiber with reduced endocardial beat constant and the fiber with homogeneous STM beat constant.
Figure 4.3: Repolarization phase of endocardial (endo), midmyocardial (mid), and epicardial (epi) cellular action potentials, ECG T waves, and tissue voltage gradients for a fiber with homogeneous STM beat constant (black) and (A) reduced endocardial STM beat constant (red) or (B) reduced epicardial STM beat constant (red). Results shown here are for a fiber with enhanced mean conductivity.

Reduction in epicardial STM beat constant did not yield as large a reduction in beat constant as in the fibers with control and reduced conductivity. Also, due to increased electrotonic effects, the spatial difference in cellular STM beat constants was not as great as in the fibers with control or reduced conductivity (Table 4.3, third data column). As with all other STM simulations, STM beat constant for T-wave upstroke time and QT<sub>peak</sub> interval were similar to epicardial STM beat constant, and STM beat
constant for T-wave downstroke time and QT interval were similar to endocardial STM beat constant. Figure 4.3B shows the repolarization phase of cellular action potentials, the ECG T wave, and tissue voltage gradients for the fiber with homogeneous STM beat constant (black lines) and the fiber with reduced epicardial STM beat constant (red lines) for multiple beats following the transition to a BCL of 600 ms. Results are similar to those described for figure 4.1B and figure 4.2B but less prominent due to the small difference in STM beat constants between the fiber with reduced epicardial beat constant and the fiber with homogeneous STM beat constant.

4.2.3 Effects of Cellular S1-S2 Responses on the ECG

Fiber with control mean conductivity

For S1-S2 studies, fiber models with spatially homogeneous STM beat constant were paced at an S1 BCL of 1000 ms for 125 s. A premature S2 stimulus was then delivered at an S1-S2 coupling interval of 900, 800, 700, or 600 ms. Table 4.4 shows repolarization times and ECG parameters for a fiber with control mean conductivity. Values are given for the S1 (steady-state) response and the S2 response for each coupling interval. Change in repolarization time or ECG parameter was greater as S1-S2 coupling interval decreased. Change in cellular repolarization time was greatest at the endocardial end of the fiber and smallest at the epicardial end of the fiber. The change in epicardial repolarization time due to a premature stimulus was similar to the change in T-wave upstroke time and QT_{peak} interval. The change in endocardial repolarization time due to a premature stimulus was similar to the change in T-wave downstroke time or either
approximation of QT interval. These results are similar to the results from the STM simulations.

Table 4.4: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with control conductivity.

<table>
<thead>
<tr>
<th></th>
<th>Steady-state value</th>
<th>Change from steady-state value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1 1000 ms</td>
<td>$S2$ 900 ms</td>
</tr>
<tr>
<td>Endocardial repolarization time</td>
<td>287 ms</td>
<td>-0.6 ms</td>
</tr>
<tr>
<td>Midmyocardial repolarization time</td>
<td>291.2 ms</td>
<td>-0.5 ms</td>
</tr>
<tr>
<td>Epicardial repolarization time</td>
<td>237.5 ms</td>
<td>-0.6 ms</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>220.8 ms</td>
<td>-0.5 ms</td>
</tr>
<tr>
<td>QT&lt;sub&gt;peak&lt;/sub&gt; interval</td>
<td>234 ms</td>
<td>-0.6 ms</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>255.9 ms</td>
<td>-0.7 ms</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>280.9 ms</td>
<td>-0.7 ms</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>271.8 ms</td>
<td>-0.7 ms</td>
</tr>
</tbody>
</table>

Fiber with reduced mean conductivity

When conductivity of the fiber was reduced, the change in repolarization time due to a premature stimulus increased slightly for the endocardial end of the fiber and decreased slightly for the epicardial end of the fiber (Table 4.5). The change in epicardial repolarization time due to a premature stimulus was similar to the change in T-wave upstroke time. The change in QT<sub>peak</sub> interval, however, was closer to the change in midmyocardial repolarization time than the change in epicardial repolarization time. The change in endocardial repolarization time due to a premature stimulus was similar to the change in T-wave downstroke time or either approximation of QT interval.
Table 4.5: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with reduced conductivity.

<table>
<thead>
<tr>
<th></th>
<th>Steady-state value</th>
<th>Change from steady-state value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1 1000 ms</td>
<td>S2 900 ms S2 800 ms S2 700 ms S2 600 ms</td>
</tr>
<tr>
<td>Endocardial repolarization time</td>
<td>285 ms</td>
<td>-0.7 ms -1.7 ms -2.9 ms -4.5 ms</td>
</tr>
<tr>
<td>Midmyocardial repolarization time</td>
<td>300.2 ms</td>
<td>-0.5 ms -1.2 ms -2.2 ms -3.5 ms</td>
</tr>
<tr>
<td>Epicardial repolarization time</td>
<td>246.3 ms</td>
<td>-0.5 ms -1.1 ms -1.9 ms -3 ms</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>230.2 ms</td>
<td>-0.5 ms -1.2 ms -2 ms -3.1 ms</td>
</tr>
<tr>
<td>QT peak interval</td>
<td>240.7 ms</td>
<td>-0.6 ms -1.3 ms -2.2 ms -3.4 ms</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>254 ms</td>
<td>-0.7 ms -1.5 ms -2.6 ms -4.1 ms</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>269.6 ms</td>
<td>-0.8 ms -1.7 ms -3 ms -4.7 ms</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>268.7 ms</td>
<td>-0.7 ms -1.6 ms -2.7 ms -4.3 ms</td>
</tr>
</tbody>
</table>

Fiber with enhanced mean conductivity

When conductivity of the fiber was enhanced, the change in repolarization time due to a premature stimulus was similar throughout the fiber, differing by only 0.4 ms (Table 4.6). Thus, the change in ECG parameters due to the premature stimulus could not be precisely compared with changes in cellular repolarization.

Table 4.6: Repolarization times and ECG parameters for S1 (steady-state) pacing and S2 (premature) stimuli. Results are for a fiber with enhanced conductivity.

<table>
<thead>
<tr>
<th></th>
<th>Steady-state value</th>
<th>Change from steady-state value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S1 1000 ms</td>
<td>S2 900 ms S2 800 ms S2 700 ms S2 600 ms</td>
</tr>
<tr>
<td>Endocardial repolarization time</td>
<td>282.6 ms</td>
<td>-0.6 ms -1.4 ms -2.4 ms -3.8 ms</td>
</tr>
<tr>
<td>Midmyocardial repolarization time</td>
<td>284.2 ms</td>
<td>-0.6 ms -1.3 ms -2.3 ms -3.6 ms</td>
</tr>
<tr>
<td>Epicardial repolarization time</td>
<td>236.3 ms</td>
<td>-0.5 ms -1.2 ms -2.2 ms -3.4 ms</td>
</tr>
<tr>
<td>T-wave upstroke time</td>
<td>217.5 ms</td>
<td>-0.5 ms -1.3 ms -2.2 ms -3.4 ms</td>
</tr>
<tr>
<td>QT peak interval</td>
<td>230.9 ms</td>
<td>-0.5 ms -1.3 ms -2.2 ms -3.4 ms</td>
</tr>
<tr>
<td>T-wave downstroke time</td>
<td>253.9 ms</td>
<td>-0.6 ms -1.3 ms -2.3 ms -3.7 ms</td>
</tr>
<tr>
<td>Threshold QT interval</td>
<td>291.6 ms</td>
<td>-0.6 ms -1.4 ms -2.4 ms -3.8 ms</td>
</tr>
<tr>
<td>Tangent QT interval</td>
<td>267.6 ms</td>
<td>-0.6 ms -1.3 ms -2.3 ms -3.7 ms</td>
</tr>
</tbody>
</table>
4.3 Discussion

I have demonstrated that S1-S2 and STM changes in cellular repolarization cause transient changes in the ECG. Specifically, changes in epicardial STM or S1-S2 response resulted in concomitant changes in T-wave upstroke time and QT_{peak} interval. Changes in endocardial STM or S1-S2 response resulted in associated changes in T-wave downstroke time and QT interval. Changes in cellular S1-S2 response or STM influence the ECG through modification of tissue voltage gradients. Manifestations of cellular S1-S2 restitution and STM in the ECG are therefore largely dependent on the contribution of each voltage gradient to the ECG waveform. For example, as seen in figure 4.1B, the mid-epi voltage gradient has the greatest magnitude during the rising phase of the T wave. Thus, changes to the mid-epi gradient, such as changes in epicardial repolarization, are manifest in the ECG as changes to the rising phase of the T wave. Similarly, changes to the endo-mid gradient, such as changes in endocardial repolarization, result in changes to the falling phase of the T wave. In this model, then, S1-S2 and STM behavior of underlying tissue is evident in the upstroke time and downstroke time of the T wave.

Although spatial differences in STM time constant have not been investigated in the canine LV, Mironov and coworkers found spatial variation in STM time constant in a whole heart rabbit model (52). Furthermore, when paced to repolarization alternans, myocardial regions with lower STM time constant were found to exhibit alternans with unstable nodal lines, indicative of high propensity to arrhythmia. In contrast, regions with higher STM time constant had a more stable form of alternans. Thus, the identification of
regions of tissue with abnormal S1-S2 and STM behavior may aid in predicting arrhythmia.

Because I have shown that S1-S2 restitution and STM in the myocardium are evident in the ECG, my results have implications for the use of the ECG to assess arrhythmia risk. T waves from different ECG leads can be monitored for changes in morphology over time due to a change in paced heart rate. A transient change in T-wave morphology may indicate spatial differences in STM of underlying myocardium. For example, transient widening of the T wave, such as that shown in figure 4.1B, could indicate a smaller STM time constant for the earliest tissue to repolarize in the lead examined. Unfortunately, the whole heart has many more voltage gradients than my model, so further work is necessary to determine how S1-S2 and STM changes in the whole heart would manifest in different ECG leads.

4.4 Limitations

This study was limited by a lack of experimental data on spatial differences in STM beat constant in the canine left ventricle (LV). My models were based on data from Watanabe and coworkers (90), who found no significant difference in STM beat constant between endocardial and epicardial canine LV preparations. However, spatial heterogeneity in STM time constant has been demonstrated in rabbit ventricle (63) and has been found to differentially influence proarrhythmic conditions (52). Therefore, to study heterogeneity in STM beat constant, I artificially reduced endocardial or epicardial STM beat constant. STM beat constant for the endocardial and epicardial models was reduced to 8 beats when tested in a patch (single cell) model. However, when placed in
the fiber model, reduction in STM beat constant was limited due to electrotonic interactions, which reduced STM beat constant throughout the fiber, not just in the region of interest.

Experimental data on spatial differences in S1-S2 restitution in the canine LV were also not available. I therefore used the same model for S1-S2 studies as I did for STM studies because the two phenomena are related (i.e. an S2 response is the first STM response). However, the FMG model does not exhibit a large change in repolarization time for a single premature stimulus. Consequently, spatial differences in cellular S1-S2 responses were on the order of a few ms, making comparison between cellular responses and ECG S1-S2 responses difficult, particularly when increased electrotonic interactions reduced spatial heterogeneity in S1-S2 responses.
5. Effect of Electrode Placement on T-Wave Alternans Measurement

5.1 Introduction

In this chapter, I explore the relationship between cellular repolarization alternans in the fiber model and T-wave alternans (TWA) in the electrocardiogram (ECG). I also investigate the effect of electrode position on T-wave amplitude and TWA amplitude. While it is known from previous animal studies that alternans of cellular repolarization within the myocardium is manifest as TWA in the ECG (59), the relationship between the magnitude of cellular alternans within the tissue, the amplitude of TWA in the ECG, and the position of the ECG lead is unclear.

The effect of electrode lead placement on the measured TWA amplitude may be affected by the amplitude of the ECG T wave. Intracardiac effects, such as the degree of cellular alternans and electrophysiologic heterogeneity of the tissue, and extracardiac effects, such as heterogeneity of the volume conductor, all likely affect measured T-wave and TWA amplitudes. By idealizing the tissue geometry as a fiber, considering it in a large, homogeneous volume conductor, and controlling the degree of cellular repolarization alternans, we limit these effects and are able to make general inferences about the relationship between the magnitude of cellular alternans within the tissue, the amplitude of TWA in the ECG, and the position of the ECG lead.

For this study, I used the 1-dimensional fiber model with homogeneous tissue conductivity discussed in section 2.1.3 and the modified Fox-McHarg-Gilmour (FMG) model discussed in section 2.2.3. I paced the model at a basic cycle length (BCL) of 220
ms to initiate stable repolarization alternans. By using different modifications of the FMG model, I investigated the effect of various repolarization alternans magnitudes and several electrode positions within the volume conductor on measured T-wave amplitude and TWA amplitude. I studied the relationship between TWA amplitude and T-wave amplitude by using the “TWA index” (47, 48). The results of this study have been published (27).

5.2 Results

5.2.1 Cellular Repolarization Alternans and Tissue Repolarization Gradients

Figure 5.1 shows endocardial, midmyocardial, and epicardial repolarization times in the fiber for two consecutive alternating beats at various repolarization alternans magnitudes. Epicardial repolarization preceded endocardial repolarization, which preceded midmyocardial repolarization. For all simulations, endocardial alternans magnitude was greatest and epicardial alternans magnitude was least. Figure 5.2 shows the repolarization gradient, calculated using equation 2.20, for alternating beats at each level of repolarization alternans.
Figure 5.1: Repolarization times of endocardial, midmyocardial, and epicardial nodes in fiber model for two alternating beats at various repolarization alternans magnitudes.

Figure 5.2: Gradient of repolarization times in the fiber model for two alternating beats at various repolarization alternans magnitudes.

5.2.2 T-Wave Alternans Amplitude Relation to Repolarization Alternans

For simulations with no repolarization alternans in the fiber, TWA was not present in any of the ECG leads examined. For simulations with any repolarization alternans in the fiber, TWA was present in all leads examined. Larger repolarization alternans magnitudes in the fiber resulted in larger TWA amplitudes. Temporal matching
of ECG T-waves with simultaneous repolarization gradients during TWA revealed that the shorter alternating T-wave is coincident with a smaller (shallow) repolarization gradient and that the taller alternating T-wave is coincident with a larger (steep) repolarization gradient. Least-squares linear regression showed good correlation between T-wave amplitude from all simulations and corresponding repolarization gradient, with an \( r^2 \) value of 0.93 (Figure 5.3). Therefore, in this model, an increase in repolarization gradient produces an increase in T-wave amplitude. In addition, TWA amplitude from all simulations correlated well with the beat-wise difference in the repolarization gradient in the fiber, with an \( r^2 \) value of 0.88 (Figure 5.4). A larger beat-wise difference in repolarization gradient results in a larger TWA amplitude. For these correlations, T-wave amplitudes and TWA amplitudes were measured from electrodes 1.5 cm from the fiber center, along the fiber axis. The strength of the correlation between T-wave amplitude or TWA amplitude and corresponding repolarization gradients was independent of ECG lead configuration.
5.2.3 T-Wave Amplitude and T-Wave Alternans Amplitude as a Function of Electrode Position

To evaluate the effect of electrode position on T-wave amplitude and TWA amplitude, four scenarios were considered. In each case, the positive electrode was
modeled to the right (epicardial) end of the fiber and the negative electrode was to the left (endocardial) end of the fiber (Figure 2.7, page 32). Scenarios 1, 2, and 3 involved varying electrode distance from the fiber center for electrodes along the fiber axis. Scenario 4 involved changing the lead angle (the angle of the line between the two electrodes with respect to the fiber axis) for electrodes at an equal, fixed distance from the fiber center. T-wave amplitudes of consecutive beats and TWA amplitude were obtained for each electrode configuration. In addition, a “TWA index” was calculated by dividing the TWA amplitude by the T-wave amplitude of the short alternating T-wave. Results are presented for only one level of cellular alternans, but the trends described are similar for all levels of cellular alternans investigated. Results for this section are summarized in Tables 5.1 and 5.2.

Table 5.1: T-wave measurements for representative electrode distances

<table>
<thead>
<tr>
<th>Electrode distance from fiber center (cm)</th>
<th>1.5</th>
<th>3.5</th>
<th>6.5</th>
<th>10.5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scenario 1: Move both electrodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>35.6</td>
<td>6.24</td>
<td>1.80</td>
<td>0.689</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>227</td>
<td>39.8</td>
<td>11.5</td>
<td>4.39</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>191</td>
<td>33.6</td>
<td>9.67</td>
<td>3.70</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.170</td>
<td>0.170</td>
<td>0.170</td>
<td>0.170</td>
</tr>
<tr>
<td><strong>Scenario 2: Move positive electrode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>15.5</td>
<td>3.24</td>
<td>1.21</td>
<td>0.689</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>161</td>
<td>25.3</td>
<td>8.32</td>
<td>4.39</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>146</td>
<td>22.1</td>
<td>7.11</td>
<td>3.70</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.101</td>
<td>0.137</td>
<td>0.157</td>
<td>0.170</td>
</tr>
<tr>
<td><strong>Scenario 3: Move negative electrode</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>22.2</td>
<td>3.73</td>
<td>1.27</td>
<td>0.689</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>71.6</td>
<td>19.0</td>
<td>7.54</td>
<td>4.39</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>49.4</td>
<td>15.2</td>
<td>6.27</td>
<td>3.70</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.366</td>
<td>0.218</td>
<td>0.184</td>
<td>0.170</td>
</tr>
</tbody>
</table>
Table 5.2: T-wave measurements for representative lead angles

<table>
<thead>
<tr>
<th>Lead angle with respect to fiber axis (°)</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Each electrode 1.5 cm from fiber center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>35.6</td>
<td>29.6</td>
<td>16.2</td>
<td>5.50</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>227</td>
<td>189</td>
<td>103</td>
<td>35.0</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>191</td>
<td>160</td>
<td>86.9</td>
<td>29.5</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.170</td>
<td>0.169</td>
<td>0.171</td>
<td>0.171</td>
</tr>
<tr>
<td><strong>Each electrode 3 cm from fiber center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>8.51</td>
<td>7.33</td>
<td>4.16</td>
<td>1.43</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>54.4</td>
<td>46.7</td>
<td>26.6</td>
<td>9.16</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>45.9</td>
<td>39.4</td>
<td>22.4</td>
<td>7.73</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.170</td>
<td>0.170</td>
<td>0.170</td>
<td>0.169</td>
</tr>
<tr>
<td><strong>Each electrode 6 cm from fiber center</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TWA amplitude (µV)</td>
<td>2.11</td>
<td>1.83</td>
<td>1.05</td>
<td>0.360</td>
</tr>
<tr>
<td>Tall T-wave amplitude (µV)</td>
<td>13.5</td>
<td>11.6</td>
<td>6.69</td>
<td>2.32</td>
</tr>
<tr>
<td>Short T-wave amplitude (µV)</td>
<td>11.4</td>
<td>9.81</td>
<td>5.65</td>
<td>1.96</td>
</tr>
<tr>
<td>TWA index</td>
<td>0.170</td>
<td>0.170</td>
<td>0.170</td>
<td>0.170</td>
</tr>
</tbody>
</table>

**Scenario 1- Symmetric movement of recording electrodes:** In this case, both electrodes are placed 1.5 cm from the fiber center and are moved symmetrically away from the fiber center along the fiber axis until each is 10.5 cm away. As distance between the electrodes increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the distance from either electrode to the fiber center. Because both TWA amplitude and T-wave amplitude decrease by the same proportion, the TWA index remained relatively constant for all electrode distances examined.

**Scenario 2: Asymmetric movement of positive electrode:** In this case, the negative electrode is fixed at 10.5 cm from the fiber center while the positive electrode is moved from 1.5 cm to 10.5 cm away from the fiber center. As distance from the positive electrode to the fiber center increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the distance from the
positive electrode to the fiber center. However, in contrast to scenario 1, as distance increases, T-wave amplitude of the short T-wave decreases out of proportion to TWA amplitude, resulting in an increase in the TWA index.

**Scenario 3: Asymmetric movement of negative electrode:** In this case, the positive electrode is fixed at 10.5 cm from the fiber center while the negative electrode is moved from 1.5 cm to 10.5 cm away from the fiber center. The results of this scenario were essentially the reverse of scenario 2, but the magnitude of the effect was larger. As with scenarios 1 and 2, as distance from the negative electrode to the fiber center increased, both TWA amplitude and T-wave amplitude decrease roughly as a function of the square of the inverse of the electrode-fiber distance. In addition, as distance increases, TWA amplitude decreases out of proportion to T-wave amplitude, resulting in a large decrease in TWA index. The decrease in TWA index when the negative electrode is moved is larger than the increase in TWA index when the positive electrode is moved.

**Scenario 4: Rotation of electrode axis relative to fiber:** To evaluate the effect of lead angle on T-wave amplitude and TWA amplitude, the positive and negative electrodes were kept at an equal, fixed distance away from the fiber center, but the angle $\theta$ between the fiber axis and the electrodes was varied. As the angle increased from 0 to 80°, TWA amplitude and T-wave amplitude decreased monotonically in roughly the same proportion, giving a TWA index that is independent of lead angle. Slight fluctuations in TWA index were present for electrode configurations closer to the fiber but diminished at larger distances from the fiber.
5.2.4 Extracellular Potential Distributions Produced by Alternating Repolarization Gradients

To explore further the effect of repolarization alternans on potential fields that are detected by ECG electrodes, I used equation 2.19 to create plots of extracellular potential around the fiber at the instant of the peak of each T-wave (Figure 5.5). Figure 5.5A illustrates extracellular potential during the peak of the taller alternating T-wave, and figure 5.5B illustrates extracellular potential during the peak of the shorter alternating T-wave. In both panels, reference electrode locations are indicated with a black “X.” The potential distribution of both panels resembled the potential distribution produced by two dipoles of different magnitudes. At the instant of the T-wave peak, two voltage gradients existed in the fiber: an endocardial-midmyocardial (endo-mid) gradient and a midmyocardial-epicardial (mid-epi) gradient. Because the mid-epi gradient was larger in magnitude, its effects on the potential distribution were apparent distant from the fiber. This finding is evidenced by the isopotential lines distant from the fiber converging at a site in the fiber between the midmyocardium and the epicardium. The smaller endo-mid gradient had mostly proximal effects, as evidenced by the isopotential lines located around the endocardial end of the fiber that converge at a site between the endocardial region and midmyocardial region. However, the influence of the endo-mid gradient can be seen in the shift of the zero-potential line towards the epicardial end. If no endo-mid gradient were present, the potential distribution around the fiber would be that of a dipole, and the zero-potential line would be roughly orthogonal to the fiber axis. Because the voltage gradients are of unequal magnitude and at different locations in the fiber, the
potential distribution surrounding the fiber is asymmetric in both magnitude and geometry. The isopotential lines distant from the fiber are closer together on the epicardial end than on the endocardial end, indicating a greater change in potential for movement of a positive electrode over a certain distance than for movement of a negative electrode over that same distance. As a result, the change in T-wave amplitude and TWA amplitude due to movement of the positive electrode differs in magnitude and direction from the change due to movement of the negative electrode.

In summary, cellular repolarization alternans in the fiber causes alternation in the cellular repolarization gradient. The magnitude of alternation in the cellular repolarization gradient is directly proportional to the TWA amplitude in the ECG. Alternation in the cellular repolarization gradient produces an alternating, asymmetric potential distribution around the fiber, which can alter ECG T-wave measurements depending on electrode placement.
5.3 Discussion

The results presented here demonstrate that changes in the repolarization gradient within tissue result in changes in the T-wave that can be recorded distant from the tissue. As the tissue repolarization gradient increases (becomes more steep), T-wave amplitude...
increases. Similarly, a decrease in tissue repolarization gradient results in a decrease in T-wave amplitude. During cellular alternans, alternation in the tissue repolarization gradient leads to alternation of the T-wave amplitude. The extracellular potential distributions created by alternating repolarization gradients are asymmetric and differ both in magnitude and in geometry on a beat-wise basis. Consequently, if an electrode is moved a certain distance away from the fiber, T-wave amplitude and TWA amplitude may decrease out of proportion to each other due to asymmetry and beat-wise differences in extracellular potential distribution.

Current clinical TWA testing uses a set threshold of TWA amplitude in the microvolt range as an indicator of pathology (11). However, as I have shown, an increased difference in intracardiac repolarization gradients results in increased TWA amplitude. Therefore, TWA amplitude may be indicative of the severity of the pathology. I have also shown that TWA amplitude is sensitive to changes in distance and angle, making comparison of serial TWA amplitude measurements in the same patient difficult. Furthermore, two individuals with the same magnitude of cellular alternans may exhibit different TWA amplitude measurements due to differences in extracardiac factors, such as torso size and shape. For these reasons, I investigated the effect of electrode position on the TWA index, which has been suggested as a correction factor for extracardiac effects (47, 48). However, I have shown that even in an unbounded, homogeneous volume conductor with a simple model of alternans, TWA index is dependent on electrode position, particularly when recording electrodes are at unequal distances from the tissue. Curiously, TWA index remained relatively constant with respect to changes in
lead angle. This effect may be due to the geometry of the potential distribution surrounding the fiber: As the lead angle was increased, the measuring electrodes moved across few isopotential lines, resulting in small and relatively symmetric changes in T-wave amplitude.

5.4 Limitations

The model used in this chapter has several limitations, particularly with respect to the simplicity of the structural model and of the volume conductor. In modeling the left ventricle (LV) as a 1-dimensional fiber, I neglect baso-apical and left-right repolarization gradients that could alter the potential field around the LV. As I have demonstrated, asymmetries in intracardiac voltage gradients create asymmetric potential distributions such that changes in electrode placement can drastically alter T-wave amplitude and TWA amplitude. Consequently, the contribution of additional voltage gradients is likely to further substantiate my findings. For example, addition of a baso-apical gradient may influence T-wave amplitude and TWA amplitude when the lead angle is changed by introducing a dipole orthogonal to the ones investigated in this study.

Extracardiac factors can also alter the effect of electrode location on T-wave amplitude and TWA amplitude. In this study, I found electrode-dependent T-wave changes in a homogeneous, unbounded volume conductor. These changes are likely to be modulated further by a bounded volume conductor with conductivity heterogeneity. For example, a high-conductivity inhomogeneity in the volume conductor, such as intraventricular blood, would amplify extracellular potentials when placed along the fiber axis but would diminish potentials if placed tangential to the axis (14). Similarly, a low-
conductivity inhomogeneity, such as a lung, would diminish potentials when placed along the fiber axis but would amplify potentials when placed tangential to the axis. Despite these limitations, the results presented in this chapter describe the mechanism by which repolarization changes during alternans result in nonlinear changes in T-wave amplitude and TWA amplitude. Further work in higher-dimensional models can elucidate the effect of the additional intracardiac and extracardiac factors not investigated in this chapter.
6. Effect of a Resistive Barrier on Repolarization Alternans and T-Wave Alternans

6.1 Introduction

In this chapter, I investigate the effect of a resistive structural barrier on the relationship between cellular repolarization alternans and T-wave alternans (TWA) in the electrocardiogram (ECG). Experimental and computer simulation studies have shown that an insulating structural barrier in tissue promotes cellular repolarization alternans (45, 60). Cellular repolarization alternans appeared at a lower heart rate and with increased cellular alternans magnitude in preparations with a structural barrier than in those without one.

Similarly, several investigators have found that individuals with structural heart disease, such as coronary heart disease, hypertensive heart disease, and dilated and hypertrophic cardiomyopathy, are more likely to exhibit TWA than those without heart disease (50, 71, 85). Paralleling the results from experimental preparations, individuals with structural heart disease exhibit TWA at a lower heart rate (85) and have greater TWA amplitude (71) than those without heart disease.

Structural inhomogeneities in tissue appear to be associated with increased cellular repolarization alternans in tissue and increased TWA in the ECG. However, the mechanism by which structural inhomogeneities alter cellular repolarization alternans and TWA in the ECG has not been thoroughly explored.

In this chapter, I used the 1-dimensional fiber model discussed in section 2.1.3 and the modification of the Fox-McHarg-Gilmour (FMG) model discussed in section
2.2.3. I paced the model at a basic cycle length (BCL) of 220 ms to initiate stable repolarization alternans and measured the resulting manifestations of alternans in the ECG. I compared fibers with a local decrease in tissue conductivity (a resistive barrier) to fibers of equivalent, homogeneous mean conductivity, and I investigated the effects of the location and strength of the barrier on cellular repolarization alternans and TWA. The results of this chapter have been accepted for publication (26).

6.2 Results

6.2.1 Cellular Activation and Conduction

Mean conduction velocity (CV) was measured from the middle 0.8 cm of each fiber to minimize end effects. Mean CV was 38.9, 38.6, 38.3, 37.9, and 37.5 cm/s for a fiber with 10%, 20%, 30%, 40%, and 50% decrease in conductivity (resistive barrier) in the distal midmyocardium. Fibers with resistive barriers in other locations matched these mean CV values to within 5%. Fibers with equivalent, homogeneous mean conductivity to the fibers with resistive barriers matched these CV values to within 2%. For the fibers with resistive barriers, local CV (measured between each node in the fiber) decreased by 5 – 41% of the mean CV in the region containing the resistive barrier, with greater CV decreases concomitant with greater conductivity decreases. No appreciable CV alternans was observed in any fiber.

6.2.2 Resistive Barrier Effects on Cellular Repolarization

Regardless of presence, strength, or location of resistive barrier, earliest repolarization always occurred at the epicardial end of the fiber, and latest repolarization occurred in the middle of the fiber. Figure 6.1 shows cellular repolarization times for
each node in the fiber and the corresponding voltage gradients and T waves for two consecutive beats during alternans in two fibers with homogeneous conductivity. A decrease in homogeneous conductivity increased cellular alternans and altered repolarization throughout the fiber. These repolarization changes altered tissue voltage gradients, which influenced the ECG. Consequently, a decrease in conductivity increased TWA amplitude.

**Figure 6.1**: Cellular repolarization times, tissue voltage gradients, and T waves for two consecutive beats during alternans for a fiber with homogeneous conductivity of 1.25 mS/cm (red lines) and a fiber with homogeneous conductivity of 1.1364 mS/cm (black lines).

Addition of a resistive barrier to a fiber with homogeneous conductivity necessarily decreases mean conductivity of the fiber. As shown in figure 6.1, decreased fiber conductivity increases cellular repolarization alternans throughout the fiber and increases TWA amplitude in the ECG. Therefore, to separate the effects of decreased conductivity throughout the fiber from the effects of decreased local conductivity (i.e. a

* The midmyocardial-epicardial (mid-epi) voltage gradient was computed as the voltage difference between the midmyocardial node and epicardial node, divided by the fiber distance between the cells. The endocardial-midmyocardial (endo-mid) gradient was computed in a similar fashion but between the endocardial node and midmyocardial node.
resistive barrier), I compared fibers with a resistive barrier to fibers with an equivalent, homogeneous mean conductivity. For example, a fiber with a 50% resistive barrier (reduction in local conductivity of 50% from control value of 1.25 mS/cm) would be compared to a fiber with homogeneous conductivity of 1.1364 mS/cm*. Both fibers therefore have the same mean conductivity but different distributions of conductivity in the fiber. Figure 6.2 shows cellular repolarization times and the corresponding voltage gradients and T waves for two consecutive beats in selected fibers with a resistive barrier and for a fiber with equivalent, homogeneous mean conductivity. Spatial heterogeneity in repolarization time was greater across a resistive barrier than across the corresponding region in a fiber of homogeneous conductivity. In addition, the presence of a resistive barrier altered repolarization times throughout the fiber. For example, as seen in figure 6.2C, an epicardial barrier had a significant effect on repolarization in the endocardium. The degree and location of changes in repolarization times was dependent on barrier location. The presence of a resistive barrier also increased or decreased cellular alternans throughout the fiber, with the effect dependent on the location of the barrier.

* The value of 1.1364 mS/cm is a weighted harmonic mean. The fiber with the resistive barrier has conductivity of 1.25 mS/cm over 90% of the fiber and conductivity of 0.625 mS/cm over 10% of the fiber (i.e. the resistive barrier). Therefore, the mean conductivity of the fiber is \(1/[(0.9)/(1.25 \text{ mS/cm}) + (0.1)/(0.625 \text{ mS/cm})] = 1.1364 \text{ mS/cm.}\)
Figure 6.2: Cellular repolarization times, tissue voltage gradients, and T waves for two consecutive beats for a fiber with a resistive barrier (red lines) or a fiber of equivalent, homogeneous mean conductivity (black lines).
6.2.3 Resistive Barrier Effects on Alternans of ECG Time Parameters

The location of the resistive barrier also altered tissue voltage gradients that influence the ECG. As shown in figure 6.2, the presence of a resistive barrier altered the timing and magnitude of the endo-mid voltage gradient more than the epi-mid voltage gradient. These voltage gradient changes altered T-wave morphology, with effects dependent on location of the barrier. These effects can be seen in the T waves in figure 6.2 and are manifest as difference in alternans of ECG time parameters. Alternans of \( QT_{\text{peak}} \) interval was less than 3 ms for all fibers, except for fibers with a resistive barrier in the distal subepicardium, where \( QT_{\text{peak}} \) interval alternans was as high as 19.2 ms. As seen in figure 6.2B, this effect was due to a delay in the timing of the peak of one of the alternating T waves. Interestingly, in this case the voltage gradients for the fiber with the resistive barrier and the fiber with no barrier are similar yet produce drastically different T waves. Thus, the effects in figure 6.2B are likely influenced not by a change in voltage gradients but by the direct effect of the change in local conductivity on the ECG. (As seen in equation 2.19, tissue conductivity alters potential at an electrode.) For all fibers, magnitude of T-wave upstroke time alternans matched the magnitude of epicardial cellular repolarization alternans to within 0.21 ms. Magnitude of T-wave downstroke time alternans matched the magnitude of endocardial cellular repolarization alternans to within 1 ms for all fibers except for those with a resistive barrier in the distal midmyocardium or proximal subepicardium, which matched to within 3.5 ms. As illustrated in figure 6.2A, this effect was caused by tissue voltage gradients that resulted in premature downstroke of the shorter alternating T wave.
6.2.4 Resistive Barrier Effects on Repolarization Alternans and T-wave Alternans

The presence of a resistive barrier substantially altered cellular alternans magnitude and repolarization times throughout the fiber. Maximum cellular alternans magnitude always occurred at the endocardial end of the fiber. Figure 6.3A shows that an increase in barrier strength (larger local decrease in conductivity) altered endocardial alternans magnitude, with effects dependent on the location of the barrier. The presence and strength of a resistive barrier also altered TWA amplitude, again dependent on barrier location (Figure 6.3B).

The model predicted that TWA amplitude was proportional to the maximum cellular alternans magnitude within the fiber. As demonstrated in figure 6.3C, I used least squares linear regression to fit TWA amplitude data to cellular alternans magnitude data using equation 6.1,

\[ TWA \text{ amplitude} = slope \times (\text{max cellular alternans}) \quad (6.1) \]

The intercept was fixed at zero because I expect no TWA when there is no cellular alternans in the fiber. A separate fit was performed for each barrier location as well as a fit for fibers with homogeneous conductivity. Each data point used in the fit represented the maximum cellular alternans magnitude and TWA amplitude for a fiber with a particular barrier strength. For fibers with homogeneous conductivity, each data point represented the maximum cellular alternans magnitude and TWA amplitude for a fiber of a particular mean conductivity. As shown in figure 6.3D, the location of the resistive barrier changed the gain (slope) of the relationship between maximum cellular alternans
and TWA. For example, a 10 ms increase in maximum cellular alternans magnitude resulted in a larger increase in TWA amplitude for a subepicardial barrier than for a subendocardial barrier. Thus, the location of a resistive barrier alters not only cellular repolarization alternans and TWA but also changes the relationship between them.

Figure 6.3: (A) Maximum cellular alternans magnitude and (B) TWA amplitude for various resistive barrier strengths as a function of barrier location in the fiber. Values given for the fiber with no barrier are for a fiber of homogeneous conductivity equivalent to the mean conductivity of a fiber with a barrier. (C) TWA amplitude as a function of maximum cellular alternans magnitude for representative barrier locations. A regression line illustrates the quasi-linear relationship between TWA and cellular alternans. (D) Gain (slope) of the relationship between TWA amplitude and maximum cellular alternans magnitude as a function of barrier location. Gain for the data plotted in panel C is indicated.
6.3 Discussion

The presence of a barrier to conduction is an important element that links dynamic repolarization instability and the induction of reentry and arrhythmias (60). In this chapter, I demonstrated that a conduction barrier can have significant effects on cellular repolarization alternans and TWA. My results demonstrate that a resistive barrier within the myocardium non-uniformly alters the magnitude of cellular repolarization alternans and the amplitude of TWA in the ECG. The presence of a resistive barrier in one region of the myocardium can have significant effects on cellular alternans in areas remote from that location. In addition, the barrier’s location appears to modulate the relationship between alternans magnitude within the myocardium and the degree to which it is manifest in the ECG T-wave by altering tissue voltage gradients.

Several groups have demonstrated that a resistive barrier alters cellular repolarization by enhancing intrinsic repolarization heterogeneity due to decreased electrotonic interactions (72, 88). This mechanism appears to be responsible for my results and is manifest in the large spatial change in repolarization time between nodes across the resistive barrier (Figure 6.2). A resistive barrier located in a fiber region with large intrinsic repolarization heterogeneity, such as the midmyocardial-epicardial transition region, provides the largest increases in both repolarization alternans and TWA. Due to electrotonic effects, the resistive barrier changes the repolarization time of not only those cells within the barrier but also nearly all cells in the fiber. Consequently, tissue repolarization gradients that influence the T wave are altered, thus changing T-
wave morphology and the relationship between TWA and cellular repolarization alternans in a location-dependent manner.

In this study, I have modeled the left ventricle (LV) free wall as having homogeneous conductivity in the transmural direction, and I introduced regions of decreased conductivity. However, the actual canine LV free wall exhibits physiologic heterogeneity in conductivity (65, 96), with some similarity to my fibers with resistive barriers in the proximal and distal epicardium. Interestingly, an epicardial barrier resulted in a decrease in epicardial cellular alternans magnitude, consistent with studies that show a small epicardial alternans magnitude compared to endocardial and midmyocardial alternans in the canine LV free wall (19, 75). These spatial differences in cellular alternans magnitude may be partially due to intrinsic cellular differences. However, decreased tissue conductivity may aid in decreasing epicardial alternans magnitude in situ by decreasing the electrotonic effect between epicardial cells and neighboring midmyocardial cells.

One of the physiologic manifestations of a resistive barrier is a change in gap junction expression, distribution, or function. Because gap junction remodeling has been demonstrated in a number of pathologies, such as heart failure (66), ischemia (8), and infarction (61), the resulting changes in tissue conductivity may alter TWA and underlying cellular repolarization alternans. Furthermore, because the gain of TWA amplitude is dependent on barrier location, the location of such a structural defect may increase or decrease TWA amplitude for a given amount of cellular alternans. A local decrease in subepicardial conductivity due to ischemia, for example, may produce greater
TWA than a similar decrease in the subendocardium, because of both increased cellular alternans magnitude and increased gain in TWA amplitude for the subepicardial defect compared to the subendocardial defect. Future work needs to be done to establish whether the location-dependent effect of increasing cellular alternans magnitude is proarrhythmic. In addition, future work must clarify whether the presence of a structural barrier in certain myocardial regions facilitates or hinders TWA detection.

In summary, my modeling results demonstrate the effect of a resistive barrier on cellular repolarization alternans within a myocardial fiber in TWA in the ECG. These results suggest that the location and strength of a resistive barrier in myocardial tissue may significantly alter repolarization properties both near and distant from the barrier and may variably influence cellular repolarization alternans in the myocardium and TWA in the ECG.

6.4 Limitations

First, because the fiber model consisted of only 100 nodes and was 1-dimensional, electrotonic interactions played a large role in determining cellular repolarization times. Thus, inclusion of a resistive barrier, which decreased electrotonic interactions, had a large influence on repolarization times in the fiber model. It remains unknown whether a resistive barrier will produce less of an effect on repolarization times in a higher-dimensional model with electrotonic contributions from cells in other dimensions. Secondly, my model studied the effects of a resistive barrier for a fiber in which all cells exhibited repolarization alternans. The effects of a resistive barrier on a small region of alternating myocardium remain unknown. Finally, my model did not exhibit CV
alternans, which has been studied as a modulator of arrhythmia inducibility. Further work in more complex models is needed to explore the effects of these limitations on cellular repolarization alternans and TWA.
7. Conclusions

7.1 Summary of Findings

The electrocardiographic (ECG) manifestations of cellular repolarization dynamics have remained largely unexplored. In this dissertation, I have investigated the effect of spatial differences in dynamic restitution, S1-S2 restitution, short-term memory (STM), and repolarization alternans on the ECG. Although my model was limited in scope, it provides a foundation for future work in higher dimensional, more complex, and more realistic models.

ECG manifestations of dynamic restitution

In chapter 3, I showed that the correlation between cellular repolarization and T-wave parameters change with basic cycle length (BCL) and tissue conductivity. These changes are due to spatial differences in cellular repolarization dynamics, which alter the relative contribution of voltage gradients to the ECG. In this model of the free wall of the canine left ventricle (LV), two major voltage gradients influenced the ECG: the endocardial-midmyocardial (endo-mid) gradient and the midmyocardial-epicardial (mid-epi) gradient. Epicardial cellular repolarization changes altered the mid-epi gradient, altering the timing of the rising phase of the T wave. Endocardial cellular repolarization changes altered the endo-mid gradient, altering the timing of the falling phase of the T wave. The relative contribution of these voltage gradients to the ECG is dependent on BCL because of spatial differences in dynamic restitution.
ECG manifestations of S1-S2 restitution and STM

In chapter 4, I demonstrated that spatial differences in S1-S2 restitution and STM in the fiber model resulted in transient changes in ECG parameters. A change in epicardial S1-S2 response or STM altered the mid-epi voltage gradient, influencing the timing of the rising phase of the T wave. A change in endocardial S1-S2 response or STM altered the endo-mid voltage gradient, influencing the timing of the falling phase of the T wave.

Effect of electrode placement on T-wave alternans measurement

In chapter 5, I compared cellular repolarization alternans to T-wave alternans (TWA) and found that TWA amplitude is proportional to the alternation in cellular repolarization gradient. I also found that alternation in the repolarization gradient produces alternating, asymmetric potential distributions around the fiber that influence the measurement of TWA in the ECG.

Effect of a resistive barrier on repolarization alternans and T-wave alternans

In chapter 6, I established that a resistive barrier alters cellular repolarization alternans in the fiber and TWA in the ECG. I also showed that the effects of the resistive barrier are location-dependent and can alter the relationship between cellular repolarization alternans and TWA.

7.2 Limitations and Future Directions

Because this study focused on the basic mechanisms by which cellular repolarization dynamics influenced the ECG, I chose to use a simple, 1-dimensional fiber model that approximated the canine LV free wall. In doing so, my model consisted of
two major voltage gradients that influenced the ECG. Changes in cellular repolarization had a large influence on the ECG via modification of these voltage gradients. Future work should involve expanding the model into multiple dimensions to examine the effect of other voltage gradients. For example, a model of a 3-dimensional wedge of LV would include baso-apical and left-right voltage gradients. The addition of multiple voltage gradients also allows for study of the effect of electrode and lead placement on the measurement of ECG parameters. With multiple gradients influencing the ECG, dynamic repolarization changes within the tissue may be more apparent in some ECG leads than others. These findings can therefore motivate the development of novel lead sets for assessment of cellular repolarization dynamics using the ECG.

Expansion of the model to multiple dimensions would also decrease the electrotonic effect. In my model, local changes such as the addition of a resistive barrier or the reduction in epicardial STM beat constant altered properties throughout the model. These effects may be diminished in a multidimensional model simply due to the increased number of nodes. The effects of isolated local changes in cellular repolarization dynamics or tissue conductivity on the ECG could then be studied.

Finally, reentry and arrhythmia can be simulated in a multidimensional model but not in a fiber model. Studies can be performed on how spatial differences in repolarization dynamics facilitate the development of arrhythmia. These resulting dynamic changes in the ECG may therefore be predictive of arrhythmia. This step is crucial in the development of the model as detection of dynamic behavior in the ECG is only useful if it can be shown to predict reentry and arrhythmia.
Modeling studies can be refined and results can be corroborated using experimental data. Several studies have used the canine LV wedge preparation pioneered by Antzelevitch and coworkers (19, 30, 65, 66, 75-78, 81, 95, 96). Although the LV wedge has been used to investigate the link between repolarization in the LV and ECG parameters, no study has thoroughly investigated the effects of dynamic changes in repolarization on the ECG. The modeling studies in this dissertation have identified mechanisms by which dynamic repolarization changes in myocardium affect the ECG T wave. To test the validity of these results, these modeling studies can be replicated in an experimental canine LV wedge preparation. Specifically, microelectrodes, optical camera, or optical fiber techniques could be used to monitor transmembrane action potentials throughout the LV wall, and a transmural ECG could be obtained using two electrodes in a solution that bathes the preparation (30, 75-78, 81, 95). The preparation would be paced from the endocardial surface using a dynamic pacing protocol, an S1-S2 protocol, and a STM protocol to investigate dynamic restitution, S1-S2 restitution, and STM. Dynamic changes in repolarization time in different LV regions would be compared to dynamic changes in the ECG parameters investigated in this dissertation. The preparation could also be paced at a short enough BCL to elicit repolarization alternans, and the ECG electrodes could be moved in the bath to investigate the validity of the results from chapter 5.

Although the results of this study form the foundation for the development of new ECG risk stratification techniques, much work is necessary before such technology is ready for clinical testing. Nevertheless, clinical studies of dynamic T-wave changes can
motivate the development of these novel risk stratification techniques by demonstrating that dynamic T-wave changes are present in the 12-lead ECG. A variety of techniques could be used to elicit rate-dependent T-wave changes. Among the most invasive approaches would be a clinical electrophysiologic study: A patient under general anesthesia or conscious sedation would be paced using an endovascular catheter at different cycle lengths and with different pacing protocols, and the resulting ECG changes could be recorded from the patient’s body surface. Another option that is slightly less invasive than an electrophysiologic study is transesophageal pacing: A pacing electrode can be placed via the mouth or nose into the esophagus, which is located posterior to the left atrium. The left atrium can then be paced at different cycle lengths and with different pacing protocols, and the resulting ECG changes could be recorded from the patient’s body surface. Even less invasive is an exercise test, during which a patient’s heart rate is increased physiologically. Although this method is the most comfortable for patients, it also has limitations in that pacing rate is not steady state but changes physiologically. Thus, T waves at higher heart rates could be identified as distinct from T waves at lower heart rates, but these could not be considered “steady-state” T waves as the patient’s heart rate changes constantly during exercise. In other words, the responses seen in exercise testing would be due to an indeterminate combination of dynamic restitution, S1-S2 restitution, and STM. However, because it involves less risk than an electrophysiologic study or transesophageal pacing, an exercise test is more promising for development into a clinical risk stratification test. Therefore, understanding the dynamic T-wave responses due to exercise-induced heart-rate changes
is important for the development of risk stratification techniques designed to evaluate dynamic repolarization changes in myocardium.

For all of these clinical studies, T waves would be obtained during steady-state pacing and during transitions in pacing rate. Steady-state and transient changes in T-wave parameters such as $QT_{peak}$ interval and QT interval could then be compared form different ECG leads to determine which leads reveal the greatest dynamic T-wave changes. Based on the orientation of these leads with respect to the heart, one could hypothesize which myocardial voltage gradients are responsible for T-wave changes in those leads. This hypothesis can then be tested in a computer model by simulating these voltage gradients and examining the resulting simulated ECG.
Appendix A. Modification of Models of Cellular Electrical Activity

A.1 Model for Dynamic Restitution Study

The minimal ventricular (MV) model consists of four variables, $u$, $v$, $w$, and $s$, with differential equations for the variables given by equations A.1 to A.4, where $H(x)$ is the Heaviside step function:

\[ \frac{\partial u}{\partial t} = \nabla(D\nabla u) - (J_{fi} + J_{so} + J_{si}) \]  
(A.1)

\[ \frac{\partial v}{\partial t} = (1 - H(u - \theta_v))(v_\infty - v)/\tau_v^- - H(u - \theta_v)v/\tau_v^+ \]  
(A.2)

\[ \frac{\partial w}{\partial t} = (1 - H(u - \theta_w))(w_\infty - w)/\tau_w^- - H(u - \theta_w)w/\tau_w^+ \]  
(A.3)

\[ \frac{\partial s}{\partial t} = (1 + \tanh(k_w(u - u_w)))/2 - s)/\tau_s \]  
(A.4)

The variable $u$ is a dimensionless voltage variable rescaled to mV using equation A.5:

\[ V_{mv} = 100u - 80 \]  
(A.5)

The currents $J_{fi}$, $J_{so}$, and $J_{si}$ are given by equations A.6 to A.8:

\[ J_{fi} = -vH(u - \theta_v)(u - \theta_v)(u_u - u)/\tau_{fi} \]  
(A.6)

\[ J_{so} = (u - u_o)(1 - H(u - \theta_w)))/\tau_o + H(u - \theta_w)/\tau_{so} \]  
(A.7)

\[ J_{si} = -H(u - \theta_w)ws/\tau_{si} \]  
(A.8)

Many of the time constants are functions of $u$ and are given by equations A.9 to A.13:

\[ \tau_v^- = (1 - H(u - \theta_v^-))\tau_{v1}^- + H(u - \theta_v^-)\tau_{v2}^- \]  
(A.9)

\[ \tau_w^- = \tau_{w1}^- + (\tau_{w2}^- - \tau_{w1}^-)(1 + \tanh(k_w(u - u_w)))/2 \]  
(A.10)
\[ \tau_{so} = \tau_{so1} + (\tau_{so2} - \tau_{so1})(1 + \tanh(k_{so}(u - u_{so}))) / 2 \] \hspace{1cm} (A.11)

\[ \tau_{s} = (1 - H(u - \theta_{w}))\tau_{s1} + H(u - \theta_{w})\tau_{s2} \] \hspace{1cm} (A.12)

\[ \tau_{o} = (1 - H(u - \theta_{o}))\tau_{o1} + H(u - \theta_{o})\tau_{o2} \] \hspace{1cm} (A.13)

The infinity values are defined by equations A.14 and A.15:

\[ v_{\infty} = \begin{cases} 1, & u < \theta_{v}^- \\ 0, & u \geq \theta_{v}^- \end{cases} \] \hspace{1cm} (A.14)

\[ w_{\infty} = (1 - H(u - \theta_{o})(1 - u / \tau_{w\infty}) + H(u - \theta_{o})w_{\infty}^* \hspace{1cm} (A.15)\]

Table A.1 shows the parameter values for the MV model used to model dynamic restitution for endocardial, midmyocardial, and epicardial cell types. All parameters are unitless.
Table A.1: Parameter values for each cell type for the dynamic restitution study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Endocardial cell</th>
<th>Midmyocardial cell</th>
<th>Epicardial cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>$u_o$</td>
<td>0</td>
<td>0.905</td>
<td>0.998</td>
</tr>
<tr>
<td>$u_u$</td>
<td>0.860</td>
<td>0.905</td>
<td>0.998</td>
</tr>
<tr>
<td>$\theta_v$</td>
<td>0.0853</td>
<td>0.0173</td>
<td>0.0137</td>
</tr>
<tr>
<td>$\theta_w$</td>
<td>0.187</td>
<td>0.0581</td>
<td>0.198</td>
</tr>
<tr>
<td>$\theta_i$</td>
<td>0.0341</td>
<td>0.0341</td>
<td>0.155</td>
</tr>
<tr>
<td>$u_w$</td>
<td>0.00439</td>
<td>0.00541</td>
<td>0.00462</td>
</tr>
<tr>
<td>$\tau_{v1}$</td>
<td>9.35</td>
<td>55.8</td>
<td>84.0</td>
</tr>
<tr>
<td>$\tau_{v2}$</td>
<td>1010</td>
<td>1010</td>
<td>1010</td>
</tr>
<tr>
<td>$\tau_{v+}$</td>
<td>29.0</td>
<td>28.3</td>
<td>19.4</td>
</tr>
<tr>
<td>$\tau_{w1}$</td>
<td>300</td>
<td>262</td>
<td>250</td>
</tr>
<tr>
<td>$\tau_{w2}$</td>
<td>38.6</td>
<td>78.3</td>
<td>28.6</td>
</tr>
<tr>
<td>$k_w$</td>
<td>235</td>
<td>225</td>
<td>285</td>
</tr>
<tr>
<td>$u_{w*}$</td>
<td>0.341</td>
<td>0.500</td>
<td>0.174</td>
</tr>
<tr>
<td>$\tau_{w+}$</td>
<td>157</td>
<td>158</td>
<td>156</td>
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<tr>
<td>$\tau_{f1}$</td>
<td>0.106</td>
<td>0.100</td>
<td>0.100</td>
</tr>
<tr>
<td>$\tau_{o1}$</td>
<td>548</td>
<td>564</td>
<td>500</td>
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<tr>
<td>$\tau_{o2}$</td>
<td>9.07</td>
<td>8.82</td>
<td>8.34</td>
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<tr>
<td>$\tau_{so1}$</td>
<td>63.9</td>
<td>59.2</td>
<td>55.1</td>
</tr>
<tr>
<td>$\tau_{so2}$</td>
<td>2.68</td>
<td>2.32</td>
<td>3.40</td>
</tr>
<tr>
<td>$k_{so}$</td>
<td>3.61</td>
<td>3.39</td>
<td>3.42</td>
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<tr>
<td>$u_{so}$</td>
<td>0.689</td>
<td>0.673</td>
<td>0.704</td>
</tr>
<tr>
<td>$t_s1$</td>
<td>9.64</td>
<td>2.76</td>
<td>4.23</td>
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<tr>
<td>$t_s2$</td>
<td>14.9</td>
<td>13.6</td>
<td>17.8</td>
</tr>
<tr>
<td>$k_s$</td>
<td>2.28</td>
<td>4.87</td>
<td>3.16</td>
</tr>
<tr>
<td>$u_s$</td>
<td>0.553</td>
<td>0.460</td>
<td>0.665</td>
</tr>
<tr>
<td>$\tau_{si}$</td>
<td>8.29</td>
<td>8.73</td>
<td>8.24</td>
</tr>
<tr>
<td>$\tau_{wv}$</td>
<td>0.00605</td>
<td>0.0104</td>
<td>0.00508</td>
</tr>
<tr>
<td>$w_{w*}$</td>
<td>0.936</td>
<td>0.936</td>
<td>0.936</td>
</tr>
</tbody>
</table>

A.2 Model for S1-S2 Restitution and Short-Term Memory Study

The Fox-McHarg-Gilmour (FMG) model consists of 13 ionic currents, the sum of which form $I_{ion}$:

$$I_{ion} = I_{Na} + I_{K1} + I_{Kr} + I_{Kr} + I_{Ks} + I_{Kp} + I_{NaK} + I_{NaCa} + I_{NaCa} + I_{Cab} + I_{Ca} + I_{CaK}$$  \(\text{(A.16)}\)

$I_{ion}$ is then integrated into equation 2.17. Full model details are described in the original article (32).

Table A.2 shows the parameter values for the FMG model used to model S1-S2 restitution and short-term memory for endocardial, midmyocardial, and epicardial cell
types. Parameters not listed in Table A.2 were the same values as in the original publication of the model.

**Table A. 2: Parameter values for each cell type for the S1-S2 restitution and STM study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Endocardial</th>
<th>Midmyocardial</th>
<th>Epicardial</th>
<th>Endocardial (reduced STM)</th>
<th>Epicardial (reduced STM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max I$<em>{K1}$ conductance, G$</em>{K1}$ (mS/µF)</td>
<td>2.25</td>
<td>2.15</td>
<td>3.20</td>
<td>2.25</td>
<td>3.20</td>
</tr>
<tr>
<td>Max I$<em>{Kr}$ conductance, G$</em>{Kr}$ (mS/µF)</td>
<td>0.0136</td>
<td>0.0005</td>
<td>0.0136</td>
<td>0.0136</td>
<td>0.0136</td>
</tr>
<tr>
<td>Max I$<em>{Kp}$ conductance, G$</em>{Kp}$ (mS/µF)</td>
<td>0.002216</td>
<td>0.0002</td>
<td>0.002216</td>
<td>0.002216</td>
<td>0.002216</td>
</tr>
<tr>
<td>Max I$<em>{Ks}$ conductance, G$</em>{Ks}$ (mS/µF)</td>
<td>0.0245</td>
<td>0.0100</td>
<td>0.0245</td>
<td>0.0245</td>
<td>0.0245</td>
</tr>
<tr>
<td>Ca permeability of I$<em>{Ca}$, P$</em>{Ca}$ (cm/ms)</td>
<td>1.44E-5</td>
<td>1.44E-5</td>
<td>2.26E-5</td>
<td>1.44E-5</td>
<td>2.26E-5</td>
</tr>
<tr>
<td>Volume of sarcoplasmic reticulum, V$_{SR}$ (µL)</td>
<td>1.90E-6</td>
<td>1.78E-6</td>
<td>2.26E-6</td>
<td>3.50E-7</td>
<td>3.50E-7</td>
</tr>
</tbody>
</table>

**A.3 Model for Repolarization Alternans Studies**

For simulations in chapter 5, transmural dispersion of APD and APD alternans magnitude within the fiber were controlled by adjusting the maximum conductance of I$_{K1}$ (G$_{K1}$) and the Ca-dependent I$_{Ca}$ inactivation time constant ($\tau_{fCa}$) of the FMG model. Values of G$_{K1}$ for endocardial, midmyocardial, and epicardial nodes were set at 3.3, 1.8, and 5.0 mS/µF, respectively. To induce action potential duration (APD) alternans within the fiber, $\tau_{fCa}$ of endocardial and epicardial nodes was set at 32 ms, and $\tau_{fCa}$ of midmyocardial nodes was set at a value between 76 and 96 ms, with a larger value of $\tau_{fCa}$ producing an increased degree of APD alternans in the fiber.

For simulations in chapter 6, repolarization time of each cell type was adjusted by changing the G$_{K1}$ parameter of the FMG model to the following values: endocardial 3.3 mS/µF, midmyocardial 2.1 mS/µF, epicardial 5.0 mS/µF. The amount of repolarization
alternans for each cell type was adjusted by changing the $\tau_{\text{fCa}}$ parameter of the FMG model to the following values: endocardial 40.2 ms, midmyocardial 55.2 ms, epicardial 20.0 ms.
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PUBLICATIONS


ABSTRACTS
