A membrane model of electrically remodelled atrial myocardium derived from in vivo measurements

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Submitted 18 March 2005, and accepted after revision 3 May 2005

Abstract

Aims Contemporary ionic-based membrane models are computationally expensive and are not intended to match the properties of a given experimental preparation. The aim of this work was to use measured restitution properties of electrically remodelled atrial tissue to develop a simplified membrane model based on the Fenton–Karma (FK) equations amenable to large-scale simulation of chronic atrial fibrillation (CAF).

Methods Two membrane models, the FK-CAF and FK-CNTRL parameter sets, were developed to match action potential duration (APD) and conduction velocity (CV) restitution properties of rapid-pacing-induced electrically remodelled sheep atria and healthy atria, respectively. The models were tested by inducing reentry in a two-dimensional anisotropic monodomain and comparing the resulting cycle lengths (CL) with measured CLs.

Results Parameters for the FK models were obtained that reproduced APD and CV restitution properties measured in the CAF and healthy sheep atria. Using the FK-CAF parameters, reentry was sustained in a 2.5 by 2.5 cm sheet with a CL = 91.0 ± 3.0 ms. Reentry (CL = 113.2 ± 5.2 ms) could only be sustained in the FK-CNTRL model after the tissue was first activated at a fast rate (136.5 ms).

KEYWORDS
atrial fibrillation; Fenton–Karma model; action potential duration restitution; conduction velocity restitution

* Financial support for this work was provided by the National Institutes of Health, Heart, Lung, and Blood Institute Grants NIH-HL64238 and NIH-HL76767, the National Science Foundation Grants PHY-9982860 and PHY-0243584, and the National Institutes of Health Grant R01-HL-72831.

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Conclusions The FK-CAF model is shown to approximate the restitution properties of remodelled sheep atria and can be used to simulate reentry with short CLs similar to those measured during AF episodes.

Introduction

Atrial fibrillation (AF) is a debilitating disease characterized by multiple reentrant circuits. In recent years, several sophisticated computer models have been developed to explore the mechanisms of AF using simulation [1-6]. These models provide a means to link local action potential properties to large-scale dynamics of wavefront interactions. Various membrane models have been used in these simulations to define the local action potential kinetics. Current atrial membrane models such as the Courtemanche et al. (CRN) [7] and Nygren et al. [8] models and their variants can involve more than 20 state variables. When used with a large-scale model of three-dimensional atrial anatomy [9] simulations of multiple seconds of activity are extremely time-consuming. In addition, these ionic-based models are not easy to modify to reproduce the action potential properties of a specific region of atrial tissue under study, making it more challenging to interpret the electrical and structural changes resulting from prolonged AF.

One such property of interest to reproduce is restitution, the ability of tissue to respond to changes in rate by altering action potential duration (APD) and conduction velocity (CV). Because AF wavefronts activate the atrial myocardium at varying rates, an atrial membrane model should reproduce APD and CV restitution.

Fenton and Karma developed a simplified membrane model with three state variables that can be used to replicate the dynamics of more complicated ionic-based membrane models and experimental data. The advantage of these models is that they are computationally efficient and thus, enable insight into a given phenomenon before investing in detailed ionic models that will significantly increase simulation time. In this paper, the parameters of the FK membrane model were adjusted to reproduce the restitution properties of both normal sheep atrial tissue and sheep tissue that was remodelled after months of chronic atrial fibrillation (CAF) induced by prolonged rapid pacing. The FK-CAF model is shown to produce cycle lengths (CLs) of reentry that are consistent with those measured in the sheep.

Methods

Data acquisition and analysis

All animal procedures were approved by the Duke University Institutional Animal Care and Use Committee. CAF was induced in five sheep by pacing the atria at 400 beats per minute as previously described by our group [10]. Unipolar electrograms and monophasic action potential (MAP) data were acquired during AF episodes, pacing, and normal sinus rhythm (NSR) from healthy sheep and sheep that had been in AF for at least 15 weeks.

APD measurements

APD was measured in three CAF sheep and eight healthy sheep using the following methods. After animal preparation, an MAP recording electrode catheter (EP Technologies/Boston Scientific, San Jose, California) was introduced through the left external jugular vein and placed in the right atrium. The catheter was then connected to a custom-designed mapping system [11] that amplified the signal by a factor of 500 and applied a low-pass filter at 500 Hz.

Sheep in AF were electrically cardioverted to NSR [10]. Pacing at a CL of 550 ms began within 10 min when possible, and the rate was decreased in 50 ms steps until the atrial tissue was no longer reliably captured. To ensure that steady-state had been reached, the atria were paced for at least 1 min at each CL prior to MAP data acquisition [12].

The APD at 70% repolarization (APD70) was measured from the MAP data for four consecutive paced beats at each CL and plotted against the preceding diastolic interval (DI). Baseline voltage was calculated as the average of 10 ms of data (obtained at 2 kHz) prior to either the pacing spike (during pacing) or the activation upstroke (during AF). In two CAF sheep, MAP data were also acquired during AF episodes. Data were unavailable from the third CAF sheep.

CV measurements

In four sheep with CAF and one control sheep, the chest was opened via median sternotomy or left
Thoracotomy and the heart was suspended in a pericardial cradle. A left atrial multi-electrode recording array with 192 Ag–AgCl electrodes was attached to the epicardium. Unipolar electrograms were recorded during both pacing and multiple episodes of AF, when applicable. The data were amplified by a factor of 100 and bandpass filtered with cutoffs at 0.05 Hz and 500 Hz. NSR was recorded in three CAF sheep immediately following electrical cardioversion so that intracellular conductivity of the model, \( \sigma \), could later be adjusted, ensuring that during normal propagation, CV in the model matched the experimental CV.

CLs were calculated as the difference between consecutive activation times at each electrode over at least 8 s of recorded activity. Activation time, which occurs at the maximum negative derivative of an extracellular unipolar recording [13], was automatically chosen at the instant when the negative derivative of the recorded extracellular potential fell below \(-0.2\) mV/ms. Activation times were then manually edited to remove markers placed at sites of far-field ventricular activity or noise.

CV was measured at each interior electrode for six consecutive beats using the following procedure. Given a set of nine electrodes arranged in a square, the CV at the middle electrode, \( e \), was calculated from the inverse of the magnitude of the gradient of activation times (\( t_a \)) as shown below [14].

\[
F = \begin{bmatrix} t_{e1} & t_{e2} & t_{e3} \\ t_{e4} & t_{e} & t_{e5} \\ t_{e6} & t_{e7} & t_{e8} \end{bmatrix}
\]

\[
CV = \frac{1}{\sqrt{\left(\frac{x}{Z}\right)^2 + \left(\frac{y}{Z}\right)^2}}
\]

CV in goat atria can measure up to 145 cm/s [15]. As such, velocities greater than 150 cm/s were assumed to be artificial and were therefore excluded. The average of the remaining values was calculated and recorded as the average CV over all interior electrodes.

**Matching restitution properties**

The FK membrane model is described in detail in [16]. Two sets of FK parameters were sought: the first was to reproduce the APD and CV restitution curves obtained in healthy sheep, while the other was to reproduce the restitution properties measured in sheep with CAF. APD restitution curves define the relationship between APD and preceding DI, while CV restitution curves define the relationship between CV and CL. These parameter sets will be referred to as the FK-CNTRL and FK-CAF models, respectively.

Using the procedure described by Oliver [14], the various FK parameters were adjusted to match APD and CV restitution of the remodelled and healthy sheep atrial tissues. An initial parameter set based on Oliver’s FK parameters [14] for the CRN model [7] was chosen, and the corresponding APD and CV restitution curves were generated. These curves were compared with the desired restitution curves, and the appropriate parameters that would affect specific portions of the curve were manually adjusted, iteratively, in a model of propagation under a specific pacing protocol. The goal was to achieve differences between the measured and computed curves such that the error was less than 15% for the majority of the corresponding points.

A continuous monodomain formulation of propagation was used, where current flow is described by the following equation:

\[
P \times D \frac{\partial V}{\partial t} = \beta \left( \frac{\partial V}{\partial t} - I_{\text{ion}} \right) - I_s
\]

(3)

\( C_m \) is the membrane capacitance (1.0 \( \mu \)F/cm\(^2\)), \( I_{\text{ion}} \) is the sum of ionic currents (\( \mu \)A/cm\(^2\)), \( V_m \) is the transmembrane voltage (mV), \( \beta \) is the surface to volume ratio (cm\(^{-1}\)), \( D \) is the conductivity tensor (mS/cm) for each point in space, and \( I_s \) is the stimulus current (mA/cm\(^3\)). The ‘sealed end’ boundary conditions were used in all simulations. The FK membrane model equations, described in detail in [16], were used to determine the value of \( I_{\text{ion}} \) at each time step.

Simulations to match APD and CV restitution curves were performed in a one dimensional form of Eq. (3). The fibre had a length 1.5 cm, with \( dx = 100 \) \( \mu \)m, \( D = 10.0 \) mS/cm, \( \beta = 2000 \) cm\(^{-1}\). Point stimuli were applied at one end of the cable and membrane potential was measured 1.0 and 1.25 cm from the stimulus site so that electrotonic effects were not seen at the recording sites. Stimulus duration was 0.5 ms and strength was twice the measured threshold (300 \( \mu \)A).

To determine APD and CV restitution, the following pacing protocol was applied. At a CL of 300 ms, a train of 30 stimuli was delivered to one end of the cable. The CL was decreased to 250 ms, and 30 additional stimuli were delivered. This procedure was repeated as CL was decreased in the following sequence: 200, 175, 150, 140, 130, 120, 110, 100, and 90 ms. APD\(_{70}\), CV, and preceding
DI were determined for the final activation at each CL using the steady-state pacing protocol.

To determine if the CLs predicted from the model were consistent with those observed during an AF episode in the sheep, reentry was simulated in a two-dimensional anisotropic monodomain (Eq. (3)). The tissue was 2.5 cm on each side with 100 \( \mu \)m internodal spacing and Neumann boundary conditions applied at all edges. The CV ratio was set at 4:1 (longitudinal CV = 84.8 cm/s and transverse CV = 21.0 cm/s) to mimic anisotropic regions within and near the pulmonary veins. Reentry was induced using a simple cross-stimulation protocol [17].

All simulations were performed on a Linux workstation (1.7 GHz AMD Athlon MP) using the CardioWave simulation package, developed at Duke University [18]. Eq. (3) was solved using the Forward Euler method with a 5 \( \mu \)s time step.

**Results**

In order to match the restitution curves generated by the FK model to restitution curves measured in the sheep, average restitution curves were developed for the CAF and healthy sheep. The curves consisted of (DI, APD\(_{70}\)) data points referred to as Target Values. The x-axis of the restitution curve, which represents DI, was divided into bins, and an APD target value was assigned for each DI bin. Additionally, target values were assigned for the minimum DI, minimum APD, and CV restitution data points. Target values for the CAF sheep will be referred to in the text as A-1, A-2, ..., A-13. Target values for the healthy sheep will be referred to as B-1, B-2, ..., B-21.

**Action potential duration**

**CAF sheep**

Examples of MAPs recorded during CAF and during pacing are shown in Fig. 1. APD\(_{70}\) was measured from MAPs in three sheep during pacing. FK-CAF restitution curves were matched to target values derived from experimental measurements. Average APD values across the three CAF sheep during pacing were 80.6 ms (DI range: 156–186 ms) and 86.6 ms (DI range: 200.5–220.5 ms). Based on these data, Target Value A-1 (DI = 210 ms) and Target Value A-2 (DI = 170 ms) were assigned APD\(_{70}\) values of 86.6 ms and 80.6 ms, respectively.

Forty-seven (DI, APD\(_{70}\)) data points gathered during an AF episode in one CAF sheep and 55 data points from another CAF sheep determined the target values for the low-end of the FK-CAF APD restitution curve. These data are shown in Fig. 2. DIs in each data set were rounded to the nearest tens digit according to the following rule: all APDs with DIs between 75.01 and 85.0 were placed in the bin at DI = 80 ms, and similar boundaries were set for all other (DI, APD\(_{70}\)) pairs. Target Values A-3 through A-8 for DIs of 80, 70, 60, 50, 40, and 30 ms were set equal to average binned APD values and are listed in Table 1.

![Figure 1](http://example.com/figure1.png)

**Figure 1** MAP recordings taken during (a) pacing at 400 ms and (b) an AF episode was used to determine APD\(_{70}\). In panel (A), the pacing spike extends in the negative direction. The baseline value of these action potentials occurs at approximately \(-24 \text{ mV}\). The upstroke of the action potential extends above \(-17 \text{ mV}\). The maximum voltage used to calculate the height of the action potential is approximately \(-19.5 \text{ mV}\). In panel (B), no pacing spike is present. The variation in activations is due to the random nature of AF.
APD\textsubscript{70} values calculated from the first AF episode had a range of 58.5–119.5 ms and DIs had a range of 16.5–115.5 ms. APD\textsubscript{70} values calculated from the second AF episode had a range of 30.5–92.0 ms and DIs had a range of 24.0–82.5 ms. Target Value A-9 (minimum APD\textsubscript{70}) and Target Value A-10 (minimum DI) were assigned to 57.5 ms and 35.5 ms, respectively, the average of the points below which 10% of the experimental APD and DI values calculated during the CAF episodes lie.

APD\textsubscript{70} was measured in three sheep with rapid-pacing-induced CAF. These sheep exhibited bi-phasic APD restitution, in which APD decreased with increasing DI for all DIs greater than 200 ms. Biphasic APD restitution can be reproduced by adding an extra current and variable to the FK model [19]. Repolarization in this four-current model, however, is non-physiological and exhibits step-function-like behaviour. Because APD restitution during AF has been shown to increase monotonically with an increase in DI [15,20], the three-variable FK model was used to reproduce only the restitution properties at DIs less than 200 ms.

**Control sheep**

APD\textsubscript{70} values were rounded to the nearest tens digit according to the same rule used for the CAF sheep. Various curve fits were attempted and the coefficient of determination, \( r^2 \), was maximized for the exponential curve fit shown below:

\[
\text{APD}_{70} = X + Y \ln(DI)
\]

The average APD\textsubscript{70} at each DI bin was calculated for each sheep. APD\textsubscript{70} was then calculated for all

**Table 1**  FK-CAF model target values

<table>
<thead>
<tr>
<th>Description</th>
<th>Target</th>
<th>FK-CAF value</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>APD\textsubscript{70} (DI = 210 ms)</td>
<td>86.6 ms</td>
<td>82.3 ms</td>
</tr>
<tr>
<td>A-2</td>
<td>APD\textsubscript{70} (DI = 170 ms)</td>
<td>80.6 ms</td>
<td>81.4 ms</td>
</tr>
<tr>
<td>A-3</td>
<td>APD\textsubscript{70} (DI = 80 ms)</td>
<td>88.9 ms</td>
<td>77.0 ms</td>
</tr>
<tr>
<td>A-4</td>
<td>APD\textsubscript{70} (DI = 70 ms)</td>
<td>68.4 ms</td>
<td>76.0 ms</td>
</tr>
<tr>
<td>A-5</td>
<td>APD\textsubscript{70} (DI = 60 ms)</td>
<td>68.4 ms</td>
<td>74.8 ms</td>
</tr>
<tr>
<td>A-6</td>
<td>APD\textsubscript{70} (DI = 50 ms)</td>
<td>70.6 ms</td>
<td>73.2 ms</td>
</tr>
<tr>
<td>A-7</td>
<td>APD\textsubscript{70} (DI = 40 ms)</td>
<td>72.1 ms</td>
<td>71.3 ms</td>
</tr>
<tr>
<td>A-8</td>
<td>APD\textsubscript{70} (DI = 30 ms)</td>
<td>78.2 ms</td>
<td>68.8 ms</td>
</tr>
<tr>
<td>A-9</td>
<td>APD\textsubscript{70} minimum</td>
<td>57.5 ms</td>
<td>68.0 ms</td>
</tr>
<tr>
<td>A-10</td>
<td>DI minimum</td>
<td>35.5 ms</td>
<td>28.0 ms</td>
</tr>
<tr>
<td>A-11</td>
<td>CV (CL = 200 ms)</td>
<td>78.8 cm/s</td>
<td>76.0 cm/s</td>
</tr>
<tr>
<td>A-12</td>
<td>CV (CL = 120 ms)</td>
<td>45.1 cm/s</td>
<td>56.8 cm/s</td>
</tr>
<tr>
<td>A-13</td>
<td>CV minimum</td>
<td>30.5 cm/s</td>
<td>27.9 cm/s</td>
</tr>
</tbody>
</table>
unfilled bins using the appropriate exponential fit. The average APD\textsubscript{70} at each binned DI was calculated and used as the target value for the FK-CNTRL model. Values are listed in Table 2. Minimum APD\textsubscript{70} (Target Value B-17) was set to 68.3 ms, the shortest APD measured during pacing in all of the healthy sheep. Target Values B-1 through B-16, which correspond to DIs every 10 ms between 200 ms and 50 ms, inclusive, are listed in Table 3. Minimum DI (Target Value B-18) was taken from the FK-CAF model target value and is equal to 35.5 ms.

### Table 2  FK-CNTRL model target values

<table>
<thead>
<tr>
<th>Description</th>
<th>Target</th>
<th>FK-CNTRL value</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-1 APD\textsubscript{70} (DI = 200 ms)</td>
<td>174.8 ms</td>
<td>183.7 ms</td>
<td>5.1</td>
</tr>
<tr>
<td>B-2 APD\textsubscript{70} (DI = 190 ms)</td>
<td>170.8 ms</td>
<td>179.0 ms</td>
<td>4.8</td>
</tr>
<tr>
<td>B-3 APD\textsubscript{70} (DI = 180 ms)</td>
<td>173.0 ms</td>
<td>174.0 ms</td>
<td>0.6</td>
</tr>
<tr>
<td>B-4 APD\textsubscript{70} (DI = 170 ms)</td>
<td>169.2 ms</td>
<td>168.8 ms</td>
<td>0.2</td>
</tr>
<tr>
<td>B-5 APD\textsubscript{70} (DI = 160 ms)</td>
<td>162.9 ms</td>
<td>163.0 ms</td>
<td>0.1</td>
</tr>
<tr>
<td>B-6 APD\textsubscript{70} (DI = 150 ms)</td>
<td>154.8 ms</td>
<td>157.0 ms</td>
<td>1.4</td>
</tr>
<tr>
<td>B-7 APD\textsubscript{70} (DI = 140 ms)</td>
<td>153.6 ms</td>
<td>150.8 ms</td>
<td>1.8</td>
</tr>
<tr>
<td>B-8 APD\textsubscript{70} (DI = 130 ms)</td>
<td>150.4 ms</td>
<td>144.1 ms</td>
<td>4.2</td>
</tr>
<tr>
<td>B-9 APD\textsubscript{70} (DI = 120 ms)</td>
<td>144.3 ms</td>
<td>137.2 ms</td>
<td>4.9</td>
</tr>
<tr>
<td>B-10 APD\textsubscript{70} (DI = 110 ms)</td>
<td>139.8 ms</td>
<td>130.7 ms</td>
<td>6.5</td>
</tr>
<tr>
<td>B-11 APD\textsubscript{70} (DI = 100 ms)</td>
<td>136.1 ms</td>
<td>123.9 ms</td>
<td>9.0</td>
</tr>
<tr>
<td>B-12 APD\textsubscript{70} (DI = 90 ms)</td>
<td>126.3 ms</td>
<td>117.0 ms</td>
<td>7.4</td>
</tr>
<tr>
<td>B-13 APD\textsubscript{70} (DI = 80 ms)</td>
<td>116.8 ms</td>
<td>110.1 ms</td>
<td>5.8</td>
</tr>
<tr>
<td>B-14 APD\textsubscript{70} (DI = 70 ms)</td>
<td>107.9 ms</td>
<td>103.1 ms</td>
<td>4.5</td>
</tr>
<tr>
<td>B-15 APD\textsubscript{70} (DI = 60 ms)</td>
<td>97.3 ms</td>
<td>95.3 ms</td>
<td>2.1</td>
</tr>
<tr>
<td>B-16 APD\textsubscript{70} (DI = 50 ms)</td>
<td>84.4 ms</td>
<td>87.2 ms</td>
<td>3.3</td>
</tr>
<tr>
<td>B-17 APD\textsubscript{70} minimum</td>
<td>68.3 ms</td>
<td>67.8 ms</td>
<td>0.7</td>
</tr>
<tr>
<td>B-18 DI minimum</td>
<td>35.5 ms</td>
<td>26.9 ms</td>
<td>24.2</td>
</tr>
<tr>
<td>B-19 CV (CL = 250 ms)</td>
<td>112.6 cm/s</td>
<td>104.6 cm/s</td>
<td>7.1</td>
</tr>
<tr>
<td>B-20 CV (CL = 200 ms)</td>
<td>102.5 cm/s</td>
<td>94.7 cm/s</td>
<td>7.6</td>
</tr>
<tr>
<td>B-21 CV minimum</td>
<td>34.7 cm/s</td>
<td>42.8 cm/s</td>
<td>23.4</td>
</tr>
</tbody>
</table>

### Conduction velocity

#### CAF sheep

The four sheep mapped during CAF episodes had an average CV of 45.1 ± 29.9 cm/s and an average AF cycle length of 121.7 ± 17.5 ms. Average CV from three of these four sheep during pacing at a CL of 200 ms was 78.8 ± 26.6 cm/s. Pacing data were not available for the fourth sheep. Target Value A-11 (CL = 200 ms) was therefore chosen to have a CV of 78.8 cm/s and Target Value A-12 (CL = 120 ms) was chosen to have a CV of 45.1 cm/s. Target Value A-13 (minimum CV) was assigned to 30.5 cm/s, the value below which 10% of the mean centred CVs fall. Because average CV during NSR was 85.9 ± 28.5 cm/s, intracellular conductivity (\(\sigma\)) of the FK-CAF model was chosen so that CV during NSR was 85.9 cm/s.

#### Control sheep

CV was measured in one healthy sheep during NSR, pacing at 250 ms, and pacing at 200 ms. Average CVs measured over six consecutive beats were 113.6 ± 26.5 cm/s for NSR, 112.6 ± 24.9 cm/s for pacing at 250 ms, and 102.3 ± 29.0 cm/s for pacing at 200 ms. Target values were assigned based on these data to be 112.6 cm/s at a CL of 250 ms (Target Value B-19) and 102.3 cm/s at a CL of 200 ms (Target Value B-20). Because of the lack of AF mapping data from healthy sheep, minimum CV

### Table 3  Fenton–Karma model parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>FK-CAF</th>
<th>FK-CNTRL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\tau_d)</td>
<td>0.125 ms</td>
<td>0.125 ms</td>
</tr>
<tr>
<td>(k)</td>
<td>10.0</td>
<td>10.0</td>
</tr>
<tr>
<td>(v_f)</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>(\tau_T)</td>
<td>70.0 ms</td>
<td>65.0 ms</td>
</tr>
<tr>
<td>(\tau_{si})</td>
<td>114.0 ms</td>
<td>47.0 ms</td>
</tr>
<tr>
<td>(\tau_o)</td>
<td>32.5 ms</td>
<td>32.5 ms</td>
</tr>
<tr>
<td>(\tau_{v_1})</td>
<td>5.75 ms</td>
<td>5.75 ms</td>
</tr>
<tr>
<td>(\tau_{v_2})</td>
<td>82.5 ms</td>
<td>160.0 ms</td>
</tr>
<tr>
<td>(\tau_{w_2})</td>
<td>60.0 ms</td>
<td>40.0 ms</td>
</tr>
<tr>
<td>(\tau_{w_1})</td>
<td>300.0 ms</td>
<td>300.0 ms</td>
</tr>
<tr>
<td>(u_c)</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>(u_v)</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>(u_{si})</td>
<td>0.85</td>
<td>0.85</td>
</tr>
</tbody>
</table>
(Target Value B-21) was based on an optical mapping study of healthy sheep performed by Gray et al., where CVs as low as 34.7 cm/s were measured [21]. Intracellular conductivity ($\sigma$) of the FK-CNTRL model was chosen so that CV at a CL of 700 ms was 113.6 cm/s.

Matching restitution curves

FK-CAF model

The FK parameters $t_w$, $\tau_r$, $t_{v1}$, and $t_{v2}$ were chosen for adjustment because of their effect on APD restitution, minimum APD, CV restitution curve shape, and minimum DI, respectively [14,16]. Fig. 3 shows that as $t_w$ increases, APD decreases, and as $\tau_r$ decreases, APD also decreases. These data are consistent with Oliver’s findings [14]. Through organized trials, a combination of $\tau_r = 70.0$ ms, $t_w = 400.0$ ms, $t_{v1} = 82.5$ ms, and $t_{v2} = 60.0$ ms was found to produce an acceptable APD restitution curve.

Intracellular conductivity was adjusted to $\sigma = 6.85$ mS/cm so that CV at a CL of 700 ms equaled the target value of 85.9 cm/s. The final FK-CAF parameters are listed in Table 3. The APD and CV restitution curves were regenerated using an intracellular conductivity of $\sigma = 6.85$ mS/cm. Fig. 4 shows these curves and target values. An overview of measured data, associated target values, and values obtained using the FK-CAF model is listed in Table 1. Minimum APD$_{70}$ is 68.0 ms, which is less than 11 ms from the target value of 57.0 ms. Minimum DI was 28.0, which is 7 ms from the target value of 35.0 ms. APD$_{70}$ values at DIs between 30 ms and 80 ms are also less than 15% from their respective targets. APD$_{70}$ at DIs between 156.0 and 220.5 ms falls within 5% of the specified targets.

CV values also closely approximate target values. The model produced a minimum CV of 27.9 cm/s, which is less than 3 cm/s slower than the target value of 30.5 cm/s. At a CL of 120 ms, CV was 56.8 cm/s, which is less than 12 cm/s faster than the target value of 45.1 cm/s. At a CL of 200 ms, CV was 76.0 cm/s, which is less than 4% slower than the target value of 78.8 cm/s.

FK-CNTRL model

The first parameter adjusted for the FK-CNTRL model was $\tau_r$, due to its effect on minimum APD. The value was decreased, thereby decreasing the minimum APD. $\tau_{sl}$ was subsequently decreased to raise the maximum APD. This cycle was repeated until the APD restitution curve values matched the target values listed in Table 2, resulting in values of $\tau_r = 65$ ms and $\tau_{sl} = 47$ ms. The APD restitution curve was close to all target values, but required the addition of slight curvature in the DI range.

![Figure 3](image-url)  
Figure 3  Altering FK parameters shifted the resulting restitution curves. The changes in APD restitution properties are shown for the variables (A) $t_w$ and (B) $\tau_r$. As $t_w$ is increased, the APD restitution curve shifts downward. As $\tau_r$ is increased, the APD restitution curve shifts upward.
of 90–140 ms which was achieved by decreasing $t_w/C255$ from its nominal value of 100 to 90 ms. These three adjusted values produced an APD restitution curve that closely matched target values.

The CV restitution curve obtained using the new parameters $\tau_r = 65$, $\tau_{sl} = 47$, and $t_w/C255 = 90$ was near the target value at NSR. However, CVs at short CLs were not slow enough to match the minimum CV target value. The CV restitution curve was decreased at short CLs by significantly increasing the value of $t_{v1}$ from 82.5 ms to 160 ms. At this new value, the APD restitution curve was unchanged and the CV restitution curve more closely matched desired values at short CLs.

Intracellular conductivity was adjusted to $\sigma = 12.13 \text{ mS/cm}$ so that CV at a CL of 700 ms equalled the target value of 113.6 cm/s. Fig. 5 shows the APD and CV restitution curves generated with the new conductivity value. Table 2 lists all target values and associated FK-CNTRL values. APD$_{70}$ calculated for the FK-CNTRL model differed from target APD$_{70}$ values by less than 10% for all values, with 12 of the 17 values differing by no more than 5%. Calculated CV values differed from

![Figure 4](image-url) **Figure 4** (A) APD$_{70}$ and (B) CV restitution generated using the FK-CAF parameters. APD restitution is plotted as a function of DI, while CV restitution is plotted as a function of CL. Stars (*) represent APD and CV target values based on data from rapidly paced sheep. Filled circles (●) represent the data points generated by the model. Both restitution curves approximate the target values.

![Figure 5](image-url) **Figure 5** (A) APD$_{70}$ and (B) CV restitution generated using the FK-CNTRL parameters. APD restitution is plotted as a function of DI, while CV restitution is plotted as a function of CL. Stars (+) represent APD and CV target values and are based on data obtained from healthy sheep. Filled circles (●) represent the data points generated by the model. Both restitution curves approximate the target values.
their target values by no more than 10%. Two values, minimum DI and minimum CV, differed from target values by less than 25%. Although the error is high, minimum CV was within 10 cm/s of the target value and minimum DI was within 10 ms of the target value.

The final FK-CAF and FK-CNTRL parameter sets listed in Table 3 were chosen because their APD and CV restitution properties approximated the acquired animal data. In addition, the action potentials obtained by pacing the models at a range of CLs have a reasonable shape, as shown in Fig. 6.

Simulations of reentry

Using both the FK-CAF and FK-CNTRL models, reentry was simulated in a uniform anisotropic monodomain. Resulting CLs from the simulations were compared with CLs measured during AF episodes in sheep.

The FK-CAF parameters produced a rotor with a CL of 90.7 ± 2.9 ms, and the FK-CNTRL parameters produced a rotor with a CL of 113.2 ± 5.2 ms. All CLs sustained by the FK-CAF model were less than 100 ms, with 87.1% being less than 95 ms, and 41.9% being less than 90 ms. All CLs sustained by the FK-CNTRL model, however, were less than 130 ms, with 89.9% being less than 120 ms and only 4.7% being less than 105 ms. Unlike the FK-CAF model, the FK-CNTRL model was not able to produce the short CLs (<100 ms) measured during AF episodes in sheep with rapid-pacing-induced CAF. Additionally, the FK-CNTRL model was only able to sustain average CLs near 113 ms after it was first paced at a CL of 136.5 ms, which prepared the tissue for fast activation.

Discussion

Two sets of FK parameters were identified: one having APD and CV restitution properties similar to those measured in sheep with CAF, and one having such properties similar to those measured in healthy sheep. It is important to note that other parameter sets based on different initial parameters might have produced acceptable restitution properties and could have also been chosen to represent the atrial tissue [14].

In two sheep studied at the time of pacemaker implant and after AF, the steady-state CAF APD restitution curves generated using a down-sweep pacing protocol had shorter APDs at longer DI than those measured at shorter DI. This phenomenon was also shown by Allessie et al. in chronically instrumented goats, where effective refractory period, which is proportional to APD [22], was shorter at longer CLs [15]. In addition, right atrial MAPs measured at long CLs have been shown to be shorter than those measured at short CLs [23].

Biphasic restitution cannot be replicated by the FK equations without the addition of a fourth ionic current [19]. This current both increases computation time and adversely affects repolarization. Thus, a limitation of the FK-CAF model is that it is only valid for CLs less than 200 ms, i.e. outside the biphasic restitution range. It should be noted, however, that 99.0% of the more than 13,000 CLs measured during AF episodes in the sheep studied were less than 200 ms.

Fig. 2 illustrates the relationship between APD and DI during two CAF episodes. Because the scatter in the relationship has previously been shown in restitution data from ventricular fibrillation...
episodes [24], scatter during AF is not unexpected. The cause of the scatter, while unknown, may be due to the difficulty associated with measuring APDs during fibrillation.

For all of the experiments performed, the model data were acquired using only a down-sweep protocol in a cable, while the animal data were acquired both with a down-sweep protocol and during an AF episode in a whole heart. In the CAF animals studied, pacing at short CLs often caused a loss of 1:1 capture and the induction of AF. In a cable model, however, pacing at short CLs cannot induce fibrillation. Therefore, it was necessary to use CAF data to approximate restitution properties at short DIs.

Because APD has been shown to increase following electrical cardioversion [25], electrophysiological properties of paced atrial tissue may differ from those measured during the CAF episodes. In Fig. 4, it is shown that the resulting FK-CAF APD restitution curve falls within the range specified by the CAF target values. At DIs greater than 150 ms, the curve is also within the range specified by the target values. However, its values fall towards the lower end of this range of target values, compensating for APD lengthening that may have occurred following cardioversion.

APD restitution characteristics in goats with induced AF were similar to those seen in the CAF sheep in this study. APD80 values decreased with increasing CL [23], lending further support to the phenomenon of biphasic restitution. APD80 measured in the right atrium of goats with AF was 91 ms and 67 ms for pacing at CLs of 180 ms and 400 ms, respectively [23]. APD70 in the right atrium of the sheep with CAF was between 80.8 and 81.8 ms for pacing at a CL of 200 ms. The sheep data are in agreement with the reported goat APDs, which are expected to be minimally greater due to the fact that they were measured at 80%, rather than 70% repolarization.

The FK-CNTRL APD restitution curve is greater than those measured in healthy goats [23] and dogs [26]. However, APD90 values measured in humans are slightly higher than the APD70 values measured in the healthy sheep [20,27]. While these two statistics cannot be directly compared, APD90 will be greater than APD70, such that the control human APD restitution data falls within the same range of values as does the control sheep APD restitution data.

The CV values are similar to those measured in both animals and humans. Gaspo et al. measured the CV in the right atrial free wall of dogs with rapid-pacing-induced CAF and measured CVs between 80 and 120 cm/s when pacing at CLs between 150 ms and 400 ms. In one dog, a CV of 80 cm/s was measured at a CL of 150 ms [28], which is the same value seen in the CAF sheep. In a different study, Konings et al. measured CV in the right atrium of patients with induced AF and reported values ranging from 38 to 61 cm/s [29]. Finally, Spach and Dolber found the atrial CV in older patients to be 58–78 cm/s [30]. CVs measured in humans without AF ranged from 68 cm/s to 103 cm/s [31], values similar to those found in the healthy sheep.

Rotors in an anisotropic sheet

Simulations in a sheet of anisotropic tissue showed that both the FK-CAF and FK-CNTRL models are capable of sustaining a reentrant rotor in a 2.5 cm square geometry. However, only the FK-CAF model is capable of producing CLs less than 100 ms. Reentrant CLs stabilized after two to three beats, and thus, it is unlikely that the FK-CNTRL model CLs would decrease to below 100 ms with additional simulation time. An increase in CV may allow the FK-CNTRL model to produce faster CLs, but such an alteration in the geometry would render the simulation non-physiological.

In the sheep studied, 21.3% of the AF CLs were less than 100 ms. Therefore, an important feature in a model used to simulate AF is the ability to sustain short CLs. Because the FK-CNTRL model cannot sustain CLs less than 100 ms, it is not an acceptable model to use when studying fibrillation. The FK-CAF model, however, is able to sustain these short CLs, and is useful for simulating CAF.

Conclusion

We identified two sets of FK parameters: one that is valid for electrically remodelled sheep atrial myocardium and one that is valid for healthy sheep atrial myocardium for DIs less than or equal to 200 ms. The computationally efficient FK-CAF and FK-CNTRL models have APD70 and CV restitution properties that are reasonable approximations of restitution in the sheep atria. The ability of the FK-CAF model to sustain reentrant rotors with short CLs makes it useful for the study of fibrillatory conduction and AF maintenance.

Acknowledgements

The authors would like to thank Ned Danieley, Ellen Dixon-Tulloch, and Rajesh Kurpad for their assistance and expertise. Financial support for this
work was provided by the National Institutes of Health, Heart, Lung, and Blood Institute Grants NIH-HL64238 and NIH-HL76767, the National Science Foundation Grants PHY-9982860 and PHY-0243584, and the National Institutes of Health Grant R01-HL-72831.

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