Ionic mechanism of electrical alternans

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The duration of the cardiac action potential is determined in large part by the preceding diastolic interval. This relationship between action potential duration and diastolic interval, known as the action potential duration restitution relation, is an important determinant of cardiac dynamics (17). In particular, if the slope of the restitution relation is ≥ 1, an alternation of action potential duration, or electrical alternans, commonly develops during high-frequency pacing (2, 8).

It has been suggested that rate-dependent electrical alternans may be a precursor to the development of ventricular arrhythmias, particularly ventricular fibrillation (VF) (6, 10, 19, 22). In support of this idea, several recent experiments (5, 11, 23) have shown that when the slope of the restitution relation is ≥ 1, rapid pacing induces both alternans and fibrillation in isolated ventricles. If the slope of the restitution relation is reduced to < 1, neither electrical alternans nor fibrillation occurs (5, 11, 12, 23). Unfortunately, the interventions used to date to suppress alternans and fibrillation [high-dose calcium channel blockers (23), hyperkalemia (12), and bretylium (5)] have limited clinical utility. More effective means of suppressing alternans need to be identified, a process that would be facilitated by a more complete understanding of the ionic basis for alternans.

One approach to determining the ionic basis for alternans is to use a computer model, several of which have been developed. For example, Luo and Rudy (15, 16), using data obtained primarily from guinea pig myocytes, developed a comprehensive ionic model (LR1) that subsequently was updated (LRd) to include formulations for the rapid and slow components of the delayed rectifier potassium current (I_{Kd}) and for the calcium current (I_{Ca}). Recently, Winslow et al. (26) modified the LRd model using data for ionic currents obtained from canine ventricular myocytes (CVM) and a formulation for calcium dynamics developed originally in guinea pig myocytes (9). An alternative formulation for calcium dynamics has been proposed by Chudin et al. (1) in their modification of the LR1 model.

Each of the models described above has limitations with respect to the study of the ionic basis for electrical alternans. The Winslow and LRd models do not produce sustained alternans at rapid pacing rates, whereas the Chudin model, which does generate electrical alternans, lacks formulations for repolarizing potassium currents likely to contribute importantly to alternans [I_{Ks}, I_{Ko}, and the transient outward potassium current (I_{to})].

Given that a complete ionic model that generates electrical alternans is not currently available, we set out to develop such a model, guided by the results obtained from our experimental studies in the canine ventricle (11, 23). Our initial objectives were to develop an ionic model of the CVM that exhibits stable electrical alternans and to use the model to identify the ionic currents responsible for alternans. Once the relevant ionic currents were identified, we then manipulated these currents to eliminate alternans. Our expectation is that the same ionic manipulations that suppress alternans in the ionic model will suppress fibrillation.

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in vivo, in which case the results of the present study may suggest novel approaches to the prevention of VF.

Glossary

\( \alpha_h \) Voltage-dependent \( h \) gate parameter
\( \alpha_j \) Voltage-dependent \( j \) gate parameter
\( \alpha_{m} \) Voltage-dependent \( m \) gate parameter
\( \alpha_{X_{to}} \) Voltage-dependent \( X_{to} \) gate parameter
\( \beta_h \) Voltage-dependent \( h \) gate parameter
\( \beta_j \) Voltage-dependent \( j \) gate parameter
\( \beta_m \) Voltage-dependent \( m \) gate parameter
\( \beta_{SR} \) Sarcoplasmic reticulum buffering factor
\( \beta_{X_{to}} \) Voltage-dependent \( X_{to} \) gate parameter
\( \gamma \) Sarcoplasmic reticulum \( Ca^{2+}\)-dependent \( J_{rel} \) factor
\( \eta \) Controls voltage dependence of \( I_{NaCa} \)
\( \sigma \) Extracellular \( Na^+ \) \( I_{NaCa} \) factor
\( \tau_d \) \( I_{Ca} \) activation time constant
\( \tau_f \) \( I_{Ca} \) inactivation time constant
\( \tau_{Ca} \) \( Ca^{2+}\)-dependent \( I_{Ca} \) inactivation time constant
\( \tau_{Kr} \) \( Kr \) activation time constant
\( \tau_{Ks} \) \( Ks \) activation time constant
\( A_{cap} \) Capacitive membrane area
\( APD \) Action potential duration
\( BCL \) Basic cycle length
\( C_{nc} \) Specific membrane capacity
\( \Delta Ca_{max} \) Maximum change in \( Ca^{2+}\)
\( \Delta Ca_{min} \) Minimum change in \( Ca^{2+}\)
\( [Ca^{2+}]_i \) Intracellular \( Ca^{2+}\) concentration
\( [Ca^{2+}]_o \) Extracellular \( Ca^{2+}\) concentration
\( [Ca^{2+}]_{SR} \) Sarcoplasmic reticulum \( Ca^{2+}\) concentration
\( [CMDN]_{tot} \) Total calmodulin concentration
\( [CSQN]_{tot} \) Total casequestrin concentration
\( CVM \) Canine ventricular myocyte
\( d \) \( I_{Ca} \) activation gate
\( d^\infty \) Steady-state \( I_{Ca} \) activation
\( DI \) Diastolic interval
\( E_{Ca} \) \( Ca^{2+}\) equilibrium potential
\( E_K \) \( K^+\) equilibrium potential
\( E_{Ks} \) \( Ks \) equilibrium potential
\( E_{Na} \) \( Na^+\) equilibrium potential
\( f \) \( I_{Ca} \) inactivation gate
\( f^\infty \) Steady-state \( I_{Ca} \) inactivation
\( f_{Ca} \) Steady-state \( Ca^{2+}\)-dependent \( I_{Ca} \) inactivation
\( f_{Ca} \) \( Ca^{2+}\)-dependent \( I_{Ca} \) inactivation gate
\( f_{NaK} \) Voltage-dependent \( I_{NaK} \) factor
\( F \) Faraday constant
\( G_{Cab} \) Peak \( I_{Cab} \) conductance
\( G_{KI} \) Peak \( I_{KI} \) conductance
\( G_{KP} \) Peak \( I_{KP} \) conductance
\( G_{Kr} \) Peak \( I_{Kr} \) conductance
\( G_{Ks} \) Peak \( I_{Ks} \) conductance
\( G_{Na} \) Peak \( I_{Na} \) conductance
\( G_{to} \) Peak \( I_{to} \) conductance
\( h \) Fast \( I_{Na} \) inactivation gate
\( I_{Ca} \) \( L\)-type \( Ca^{2+}\) channel current
\( \tilde{I}_{Ca} \) Maximal \( I_{Ca} \)
\( I_{Ca} \) \( Ca^{2+}\) background current
\( I_{Ca}^{half} \) \( I_{Ca} \) level that reduces \( P_{CaK} \) by one-half
\( I_{CaK} \) \( K^+\) current through the \( L\)-type \( Ca^{2+}\) channel
\( I_{K1} \) Inward rectifier \( K^+\) current
\( I_{Kp} \) Plateau \( K^+\) current
\( I_{Kr} \) Rapid component of the delayed rectifier \( K^+\) current
\( I_{Ks} \) Slow component of the delayed rectifier \( K^+\) current
\( I_{Na} \) \( Na^+\) current
\( I_{NaB} \) \( Na^+\) background current
\( I_{NaCa} \) \( Na^+\)/\( Ca^{2+}\) exchange current
\( I_{NaK} \) \( Na^+\)\(+K^+\) pump current
\( I_{NaK} \) Maximal \( I_{NaK} \)
\( I_{pCa} \) Sarcoplasmal \( Ca^{2+}\) pump current
\( I_{pCa} \) Maximal \( I_{pCa} \)
\( I_{stim} \) Stimulus current
\( j \) Leakage \( Ca^{2+}\) flux from the sarcoplasmic reticulum
\( J_{rel} \) Release \( Ca^{2+}\) flux from the sarcoplasmic reticulum
\( J_{up} \) Uptake \( Ca^{2+}\) flux to the sarcoplasmic reticulum
\( JSR \) Junctional sarcoplasmic reticulum
\( k_{NaCa} \) Scaling factor for \( I_{NaCa} \)
\( k_{nat} \) \( I_{NaCa} \) saturation factor for \( I_{NaCa} \)
\( K_1 \) Steady-state \( I_{K1} \) activation
\( K_{Kp} \) \( Kp \) activation
\( K_{m}^{CMDN} \) \( Ca^{2+}\) half-saturation constant for calmodulin
\( K_{m}^{CSQN} \) \( Ca^{2+}\) half-saturation constant for casequestrin
\( K_{mCa} \) \( Ca^{2+}\) half-saturation constant for \( I_{NaCa} \)
\( K_{mCa} \) \( Ca^{2+}\) half-saturation constant for \( I_{NaCa} \)
\( K_{mCa} \) \( Ca^{2+}\) half-saturation constant for \( f_{Ca} \)
\( K_{mK1} \) \( K^+\) half-saturation constant for \( I_{K1} \)
\( K_{mKo} \) \( K^+\) half-saturation constant for \( I_{Ko} \)
\( K_{mNa} \) \( Na^+\) half-saturation constant for \( I_{NaCa} \)
\( K_{mNa} \) \( Na^+\) half-saturation constant for \( I_{NaCa} \)
\( K_{mNa} \) \( Na^+\) half-saturation constant for \( I_{NaCa} \)
\( K_{mCa} \) \( Ca^{2+}\) half-saturation constant for \( J_{up} \)
\( K_{mCa} \) \( Ca^{2+}\) half-saturation constant for \( J_{up} \)
\( [K^{+}]_{i} \) Intracellular \( K^+\) concentration
\( [K^{+}]_{o} \) Extracellular \( K^+\) concentration
\( LR1 \) Luo and Rudy model
\( LRd \) Updated Luo and Rudy model
\( m \) \( Na^+\) activation gate
\( [Na^{+}]_{i} \) Intracellular \( Na^+\) concentration
\( [Na^{+}]_{o} \) Extracellular \( Na^+\) concentration
\( NSR \) Nonjunctional sarcoplasmic reticulum
\( P_{Ca} \) \( L\)-type \( Ca^{2+}\) channel permeability to \( Ca^{2+}\)
\( \tilde{P}_{CaK} \) \( L\)-type \( Ca^{2+}\) channel permeability to \( K^+\)
\( P_{leak} \) \( Ca^{2+}\) leakage permeability between the sarcoplasmic reticulum and the myoplasm
\( \tilde{P}_{rel} \) \( Ca^{2+}\) maximal release permeability from the sarcoplasmic reticulum
\( R \) Ideal gas constant
Winslow model (26) except that the discontinuities in the 

 MATERIALS AND METHODS

To study the ionic mechanism of electrical alternans in canine myocytes, we constructed a CVM model using appropriate formulations of ionic currents from the LRd, Winslow, and Chudin models, altered as necessary to fit experimental voltage-clamp data from CVM. It has been well established that cellular electrical properties in the canine ventricle vary, both between right and left ventricles and within a given ventricle, according to whether a cell resides in the epicardium, endocardium, or midmyocardium (13, 14). Because the Winslow model is the only existing ionic model based on the electrical properties of the canine ventricle, we elected to use that model as the basis for the CVM model. Consequently, the CVM model, like its predecessor, recreates the midmyocardial or M cell action potential. Further alterations of various currents, including \( I_{Ks}, I_{to} \) and \( I_{Na,Ca} \), would be required to model the electrical activity of canine endocardial and epicardial myocytes (13, 29).

The CVM model contains the following ionic current formulations:

\[
\frac{dV}{dt} = -I_{stim} + I_{Na} + I_{Kr} + I_{Ks} + I_{to} + I_{Kp} + I_{NaK} + I_{Na,Ca} + I_{Ca} + I_{Ca,Ca} + I_{Ca,CaK}
\]

**Stimulus current.** \( I_{stim} \) used to drive the model was a square wave pulse consisting of \(-80 \mu A/\mu F\) of current for 1 ms.

**Sodium current.** \( I_{Na} \) was the same as that used in the Winslow model (26) except that the discontinuities in the \( h \) and \( j \) gate formulations were removed.

\[
I_{Na} = \frac{G_{Na,m} \alpha_m h_j (V - E_{Na})}{1 - e^{-0.1(V + 47.13)}}
\]

\[
\frac{d\alpha_m}{dt} = \alpha_m (1 - \alpha_m) - \beta_m \alpha_m
\]

\[
\frac{d\beta_m}{dt} = \alpha_m (1 - \alpha_m) - \beta_m \beta_m
\]

\[
\frac{d\alpha_h}{dt} = \alpha_h (1 - \alpha_h) - \beta_h \alpha_h
\]

\[
\frac{d\beta_h}{dt} = \alpha_h (1 - \alpha_h) - \beta_h \beta_h
\]

**Inward rectifier K\(^+\) current.** \( I_{K1} \) was formulated to agree with data from Freeman et al. (4). These data indicate a smaller outward current at depolarized potentials than is seen in the Winslow model:

\[
I_{K1} = \frac{G_{K1} [K^+]_o}{[K^+]_o + K_{mK1}} (V - E_K)
\]

\[
K_{mK1} = \frac{1}{2 + e^{0.122(V - E_K)}}
\]

\[
E_K = \frac{RT}{F} \ln \left( \frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_o + 0.01833[Na^+]_o} \right)
\]

**Rapid component of the delayed rectifier K\(^+\) current.** \( I_{Kr} \) was fit to the data from Gintant (7). In particular, we reproduced the voltage-clamp experiment used to generate Fig. 2 in his paper. The Winslow formulation of the current was altered to increase rectification, slow kinetics at depolarized potentials, and increase maximum conductance:

\[
I_{Kr} = \frac{G_{Kr} R(V) X_{Kr}}{4} (V - E_K)
\]

\[
\frac{dX_{Kr}}{dt} = \frac{X_{Kr}^e - X_{Kr}}{\tau_{Kr}}
\]

**Slow component of the delayed rectifier K\(^+\) current.** \( I_{Ks} \) was fit to data from Varro et al. (25), specifically the results shown in Fig. 2 of their paper. The Winslow model was altered to increase the magnitude of the current and shift activation to less positive voltages:

\[
I_{Ks} = \frac{G_{Ks} X_{Ks}^e (V - E_K)}{4}
\]

\[
E_{Ks} = \frac{RT}{F} \ln \left( \frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_o + 0.01833[Na^+]_o} \right)
\]

\[
\frac{dX_{Ks}}{dt} = \frac{X_{Ks}^e - X_{Ks}}{\tau_{Ks}}
\]

\[
X_{Ks}^e = \frac{1}{1 + e^{0.1809(V - 10)}}
\]

**Transient outward K\(^+\) current.** \( I_{to} \) in the model was the same as that in the Winslow model:

\[
I_{to} = \frac{G_{to} X_{to} (V - E_K)}{1 - e^{0.00541(V + 33.5)/5}}
\]

\[
\frac{dX_{to}}{dt} = \alpha_{to} (1 - X_{to}) - \beta_{to} X_{to}
\]

\[
\frac{dY_{to}}{dt} = \alpha_{to} (1 - Y_{to}) - \beta_{to} Y_{to}
\]
Plateau $K^+$ current. $I_{Kp}$ was the same as that in the Winslow model

$$I_{Kp} = \tilde{G}_{Kp}K_{p}(V-E_{K})$$

$$K_{p} = \frac{1}{1 + e^{0.485V-98.69}}$$

Na$^+$/Ca$^2+$ pump current. $I_{NaK}$ was the same as that in the LRd model

$$I_{NaK} = I_{NaKf_{NaK}} \frac{[K^+]_o}{1 + \left( \frac{K_{mNa}}{[Na^+]_o} \right)^{\tau}}$$

$$f_{NaK} = \frac{1}{1 + 0.1245e^{-0.395RT} + 0.0365re^{-0.65RT}}$$

$$\sigma = \frac{1}{2\sqrt{2}} \left( e^{[Na^+]_o/97.3} - 1 \right)$$

Na$^+$/Ca$^2+$ exchange current, sarcotemmmal pump current, and Ca$^{2+}$- and Na$^+$ background currents. $I_{NaCa}$, $I_{Ca}$, $I_{Ca}$, and $I_{Na}$ were the same as those in the Winslow model

$$I_{NaCa} = \tilde{G}_{NaCa}(V-E_{Na})$$

$$I_{Ca} = \tilde{G}_{Ca}(V-E_{Ca})$$

$$E_{Ca} = \frac{RT}{2F} \ln \left( \frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \right)$$

$L$-type Ca$^{2+}$ channel current. $I_{Ca}$ in the model was a modified version of that found in the LRd model. A time-dependent, enhanced Ca$^{2+}$-induced inactivation was used, as well as a decrease in the current magnitude. These changes produced a smaller, more rapidly inactivating Ca$^{2+}$ current, in agreement with experimental observations by A. C. Zygmunt (personal communication)

$$I_{Ca} = I_{Ca}f_{Ca}$$

$$f_{Ca} = \frac{1}{1 + e^{0.712V+12.505}}$$

$$I_{Ca} = \frac{P_{Ca}4VF^2}{C_{act}RT} \left[ \frac{[Ca^{2+}]_o e^{0.67FRT}}{1 + 0.341[Ca^{2+}]_o e^{0.67FRT}} \right]$$

$$\tau_{f} = 30 + \frac{200}{1 + e^{0.1V+20.053}}$$

$$\frac{df}{dt} = f - f$$

$$\frac{dt}{\tau_{f}} = \frac{\tau_{f}}{\tau_{f}}$$

$$d^{+} = \frac{\tau_{d}}{\tau_{d}}$$

$$\frac{dd}{dt} = \frac{d^{+} - d^{+}}{\tau_{d}}$$

$$\frac{df_{Ca}}{dt} = \frac{f_{Ca} - f_{Ca}}{\tau_{f_{Ca}}}$$

$$\tau_{f_{Ca}} = 30$$

$K^+$ current through the $L$-type Ca$^{2+}$ channel. $I_{CaK}$ was also a modified version of the LRd formulation

$$I_{CaK} = P_{CaK}\frac{f_{Ca}}{C_{act}} \frac{1000VF^2 \left[ K^+ \right]^{1+\gamma} [Ca^{2+}]^{\gamma} [Ca^{2+}]_{SR}}{RT \left[ K^+ \right]^{1+\gamma} [Ca^{2+}]^{\gamma} [Ca^{2+}]_{SR} - 1}$$

Calcium handling. A modified form of the intracellular calcium dynamics from Chudin et al. (1) was used. We included buffering from calcimodulin in the cytoplasm and calsequestrin in the SR, omitted spontaneous release of calcium from the SR, and combined the concentrations of calcium in the JSR and NSR into a single variable

$$\frac{d[Ca^{2+}]_o}{dt} = \beta_{i} \left( J_{rel} + J_{cax} - J_{Ca} - A_{Ca} \frac{C_{act}}{2FV_{NSR}} \right)$$

$$\beta_{i} = \left( 1 + \frac{[CMDN]\gamma}{K_m^{CMDN} + [Ca^{2+}]^2} \right)^{-1}$$

$$J_{rel} = P_{rel}f_{Ca}$$

$$J_{cax} = \frac{V_{up}}{1 + \left( \frac{K_{Ca}^{up}}{[Ca^{2+}]_o} \right)^2}$$

$$J_{Ca} = \frac{[Ca^{2+}]_SR - [Ca^{2+}]_o}{V_{SR}}$$

$$J_{Ca} = \beta_{SR}(J_{up} - J_{lock} - J_{rel}) \frac{V_{max}}{V_{SR}}$$

Numerical methods. The equations listed above were solved using parameter values and initial conditions found in Table 1. The simulations were run on Macintosh G3 and G4 computers using a program written in C. The numerical integration scheme was similar to that used in Luo and Rudy (15, 16) and in Rush and Larsen (24). Briefly, the time steps of integration were made small enough so that the changes in voltage and in calcium concentrations remained below maximum values, $\Delta V_{max}$ and $\Delta Ca_{max}$. If the changes in voltage and calcium concentration were below a minimum value $(\Delta V_{min}$ and $\Delta Ca_{min}$), the time step was increased. By keeping the changes in voltage small, we could solve the linear gate variable equations exactly during each time step. We used the following values: $\Delta V_{max} = 0.8 mV$, $\Delta V_{min} = 0.2 mV$, $\Delta Ca_{max} = 1.067 \times 10^{-2} \mu M$, and $\Delta Ca_{min} = 2.67 \times 10^{-3} \mu M$. (See Refs. 15, 16, and 24 for more details.) The other time-dependent variables in the model were solved using the adaptive fourth-order Runge-Kutta method (21). The errors were normalized as described in Jafri et al. (9). We used a maximum error of $1 \times 10^{-6}$, a minimum time step of 0.005 ms, and a maximum time step of 0.5 ms. During the stimulus, the step size was fixed at 0.005 ms.

To further increase computational speed, lookup tables were used to avoid repeatedly calculating exponentials and other computationally expensive functions. The lookup tables were calculated once before each simulation for 15,000 values.
of voltages ranging from $-100$ to $+100$ mV. Values of voltages lying between the indexes of the lookup table were calculated using linear interpolation. To check that these numerical techniques did not affect the accuracy of the simulation, simulations also were run using no lookup tables, with a maximum time step of 0.1 ms. The action potential durations throughout a pacedown from a pacing cycle length of 400 ms to a cycle length of 90 ms differed by $<1\%$ between the two simulations.

Restitution relations were generated using the procedure described in Koller et al. (11), where action potential duration was expressed as a function of the preceding diastolic interval. The magnitude of action potential duration alternans was defined as the difference in action potential duration between two consecutive action potentials. Action potential duration was measured to 95\% of repolarization.

**RESULTS**

**Action potential and ionic currents.** Figure 1 illustrates the action potentials, ionic currents, and $Ca^{2+}$ transients generated by the CVM model at a pacing cycle length of 400 ms. The action potential (Fig. 1A) was characterized by the familiar spike-and-dome morphology of canine midmyocardial cells. $I_{Ca}$ (Fig. 1B) was of smaller magnitude and inactivated more rapidly than $I_{Ca}$ in previous models, in agreement with the recent experimental observations of A. C. Zygmunt (private communication). The time course and magnitude of $[Ca^{2+}]_{i}$ (Fig. 1D) was similar to experimental results reported previously (1, 26), indicating that the simplified calcium handling in the CVM model generated realistic $Ca^{2+}$ transients.

As shown in Fig. 1F, $I_{Kr}$ increased significantly toward the end of plateau, in good agreement with the data from Gintant (7). In contrast, $I_{Kr}$ was too small to contribute significantly to repolarization at this cycle length (Fig. 1G, note the current scale compared with Fig. 1F), primarily because of its very slow recovery from deactivation (25).

**Electrical alternans.** The CVM model generated electrical alternans at physiologically relevant pacing cycle lengths. Figure 2 shows the action potential and selected plateau currents at a cycle length of 180 ms, where the CVM model produced stable alternans of large magnitude. Note that $I_{Ca}$, $f_{Ca}$, and the $Ca^{2+}$ transient were significantly different between the long and short action potentials, whereas peak $I_{Kr}$ and peak inward $I_{NaCa}$ were not. $I_{Kr}$ varied in magnitude between the long and short action potentials, but the peak current magnitude remained small.

Figure 3 shows the relationship between action potential duration and the pacing cycle length over the range of cycle lengths that produced electrical alternans ($400–90$ ms; Fig. 3A) and over a wider range of cycle lengths ($8,000–90$ ms; Fig. 3C). Action potentials generated at several different pacing cycle lengths are shown in Fig. 3D. The model generated electrical alternans over a wide range of pacing cycle lengths, in association with a region of the restitution relation having a slope equal to 1 (Fig. 3B). At cycle lengths $<150$ ms, alternans was absent. The initial increase in alternans magnitude as the pacing cycle length was shortened, followed by a subsequent decrease in alternans magnitude with a further shortening of the cycle length, is in good agreement with experimental data (11).

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<td>$[Ca^{2+}]_{s}$, μmol</td>
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<td>$Y_{io}$</td>
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See Glossary for abbreviations.
Fig. 1. Action potentials, ionic currents, and Ca^{2+} transients generated by the CVM model after 50 beats at a cycle length of 400 ms. A: action potentials; B: $I_{Ca}$; C: $f_{Ca}$; D: [Ca^{2+}]; E: $I_{NaCa}$; F: $I_{Kr}$; G: $I_{Ks}$. See Glossary for abbreviations.
Fig. 2. Action potentials, ionic currents, and Ca\(^{2+}\) transients generated by the CVM model after 50 beats at a cycle length of 180 ms. A: action potentials; B: \(I_{Ca}\); C: \(f_{Ca}\); D: \([Ca^{2+}]_i\); E: \(I_{NaCa}\); F: \(I_{Ks}\); G: \(I_{Kr}\).
Role of plateau Na\(^+\) and Ca\(^{2+}\) currents in alternans.

The large difference in \(I_{Ca}\) between the long and short action potentials shown in Fig. 2 suggests that \(I_{Ca}\) contributes significantly to the development of alternans. Experiments using calcium channel blockers also have indicated that \(I_{Ca}\) may mediate alternans (23). To simulate the effects of a generic calcium channel blocker in the model, we decreased the magnitude of \(I_{Ca}\) by 20%. Figure 4 shows the action potential and plateau currents in the decreased \(I_{Ca}\) model at a pacing cycle length of 180 ms. No alternans of \(I_{Ca}\) or action potential duration occurred at this or any other pacing cycle length. As expected, the restitution relation lacked a region of slope equal to 1 (Fig. 5A).

The elimination of alternans in the reduced \(I_{Ca}\) model was mediated primarily by alterations of calcium-induced inactivation of \(I_{Ca}\) and the resultant changes in action potential duration (Fig. 6A). After a long diastolic interval, calcium-induced inactivation recovered to a nearly maximal value, which resulted in a large \(I_{Ca}\) during the next action potential and a correspondingly long action potential duration. Because of the long action potential duration, the next diastolic interval was shortened. Consequently, the calcium-induced inactivation gate did not recover fully by the time the next stimulus was applied. The subsequent \(I_{Ca}\) was smaller, causing a shorter action potential duration. A long diastolic interval followed the short action potential duration, and the cycle repeated.

When \(I_{Ca}\) was diminished, the action potential duration was shortened, resulting in a prolongation of diastolic interval (Fig. 6B). The longer diastolic interval allowed for complete recovery of \(I_{Ca}\). Consequently, \(I_{Ca}\) was constant for each action potential, although reduced in magnitude.

According to the scenario described above, not only should a reduction of \(I_{Ca}\) decrease alternans magnitude, but an increase in \(I_{Ca}\) should increase alternans...
Fig. 4. Action potentials, ionic currents, and Ca²⁺ transients generated by the reduced $I_{Ca}$ CVM model at a pacing cycle length of 180 ms. A: action potentials; B: $I_{Ca}$; C: $f_{Ca}$; D: $[Ca^{2+}]_i$; E: $I_{NaCa}$; F: $I_{Kc}$; G: $I_{Kr}$. 

H524 IONIC MECHANISM OF ELECTRICAL ALTERNANS

AJP-Heart Circ Physiol • VOL 282 • FEBRUARY 2002 • www.ajpheart.org
To test this hypothesis, the magnitude of \( I_{\text{Ca}} \) was varied, and the resultant magnitude of action potential duration alternans was measured. As shown in Fig. 7, alternans magnitude was proportional to the magnitude of \( I_{\text{Ca}} \). In addition, alternans magnitude could be altered predictably by varying the time constant for calcium-induced inactivation (\( \tau_{\text{ICa}} \)), where decreasing \( \tau_{\text{ICa}} \) eliminated alternans of \( I_{\text{Ca}} \) and action potential duration, secondary to a reduction in the magnitude of \( I_{\text{Ca}} \), and increasing \( \tau_{\text{ICa}} \) had the opposite effects.

The magnitude of action potential duration alternans also could be altered by changing the magnitude of \( I_{\text{Na}} \) and \( I_{\text{NaCa}} \) (Fig. 7). As \( I_{\text{Na}} \) was increased (by increasing \( G_{\text{Na}} \)), alternans magnitude decreased. Conversely, alternans magnitude was increased after a reduction of \( I_{\text{Na}} \). Both increases and decreases of \( I_{\text{NaCa}} \), secondary to alterations of \( k_{\text{NaCa}} \), reduced the magnitude of action potential duration alternans.

Role of repolarizing \( K^+ \) currents in alternans. The effects of altering \( I_{\text{to}}, I_{\text{Kp}}, I_{\text{K1}}, I_{\text{Kr}}, \) and \( I_{\text{Ks}} \) on alternans also were determined (Fig. 7). The magnitude of each of the currents was increased individually until alternans no longer occurred during pacing at any cycle length.

Elimination of alternans occurred after increasing \( I_{\text{to}} \) by \( \geq 10\% \), \( I_{\text{K1}} \) by \( \geq 7\% \), or \( I_{\text{Kr}} \) by \( \geq 62\% \). A substantially greater increase in the magnitude of \( I_{\text{Ks}} \) or \( I_{\text{Kp}} \) was required to eliminate alternans. Decreasing the magnitude each of the \( K^+ \) currents increased the magnitude of action potential duration alternans with the exception of \( I_{\text{to}} \), where decreasing the magnitude of the current decreased the alternans magnitude.

Increasing \( I_{\text{K1}}, I_{\text{Kr}}, \) or \( I_{\text{Ks}} \) reduced action potential duration from a control value of 220 ms to 211, 211, and 197 ms, respectively, at a pacing cycle length of 1,000 ms. Despite the reduction in action potential duration, the magnitudes of \( I_{\text{Ca}} \) and the \( \text{Ca}^{2+} \) transient were minimally affected, both at short pacing cycle lengths (compare Figs. 2 and 8) and at a cycle length of 1,000 ms: peak \( I_{\text{Ca}} \) magnitudes for control and elevated \( I_{\text{K1}}, I_{\text{Kr}}, \) and \( I_{\text{Ks}} \) were \(-1.57, -1.57, -1.57, \) and \(-1.58 \text{ pA/\mu F}, \) respectively, and peak \([\text{Ca}^{2+}]_i\) magnitudes were \(2.15, 2.10, 2.12, \) and \(2.04 \text{ \mu M}, \) respectively.

**DISCUSSION**

We developed an ionic model of the canine ventricular muscle cell that generates physiologically realistic
action potential duration alternans characterized by a large magnitude and a wide range of pacing cycle lengths over which they appear. Action potential duration alternans was caused primarily by an alternans of \( I_{Ca} \), where the latter resulted from the time-dependent behavior of the calcium-induced inactivation gate, \( f_{Ca} \). Alternans was suppressed by reducing the magnitude of \( I_{Ca} \) as well as by increasing the magnitude of selected repolarizing \( K^+ \) currents. Although the CVM model has some limitations, as discussed below, it is the first ionic model of the CVM that reproduces physiological alternans at rapid pacing rates. As such, it provides a useful simulation tool for studying the complicated interactions of cardiac membrane currents.

Fig. 6. Relationship among the kinetics of the calcium-induced inactivation gate (\( f_{Ca} \)), APD, DI, and the time course of \( I_{Ca} \) in the normal CVM model (A) and in the reduced \( I_{Ca} \) model (B) at a pacing cycle length of 180 ms. See text for discussion and Glossary for abbreviations.
Role of I_{Ca} in alternans. The development of action potential duration alternans required that 1) the duration of the action potential have a sensitive dependence on I_{Ca} and 2) the recovery of I_{Ca} have a sensitive dependence on diastolic interval. The first condition applied so long as there was a relative balance of repolarizing K^+ current and I_{Ca} during the action potential plateau. The second condition was manifest during pacing at short cycle lengths, where partial recovery of I_{Ca} after short diastolic intervals resulted in short action potential durations, followed by long diastolic intervals. Nearly complete recovery of I_{Ca} after long diastolic intervals produced action potentials with long durations, followed by short diastolic intervals. By this mechanism, a self-perpetuating sequence of long-short action potential durations was established. A similar mechanism likely contributed to action potential duration alternans in previously published ionic models (1, 22), although alternans of I_{Ca} was not specifically reported in those studies.

After the magnitude of I_{Ca} was reduced by decreasing P_{Ca} or increasing calcium-induced inactivation, the balance of I_{Ca} and repolarizing K^+ currents was shifted in favor of the repolarizing currents, resulting in shorter action potential durations. The resultant longer diastolic intervals allowed for complete recovery of I_{Ca}, albeit to a lesser magnitude, during pacing at cycle lengths that induced alternans in the control model. At even shorter pacing cycle lengths, diastolic intervals were too short to allow full recovery of I_{Ca}. However, because of the reduced magnitude of I_{Ca} and rate-dependent accumulation of incompletely deactivated K^+ current, the dependence of action potential duration on I_{Ca} was minimized and action potential durations remained consistently short. A similar mechanism accounts for the attenuation of alternans in the control model at very short pacing cycle lengths (Fig. 3).

Role of repolarizing K^+ currents in alternans. Beat-to-beat alterations of I_{K1}, I_{Kr}, and I_{Ks} appeared to play...
a minor role in mediating alternans. As expected, $I_{K1}$, which has no time dependence, displayed no beat-to-beat variations in magnitude, whereas the beat-to-beat changes in $I_{Kr}$ were too small to affect action potential duration appreciably at short pacing cycle lengths. Total $I_{Kr}$ also alternated during alternans; however, peak $I_{Kr}$ did not, suggesting that alternation of $I_{Kr}$ resulted from alternans of action potential duration rather than vice versa.

Although the beat-to-beat variations of $I_{K1}$, $I_{Kr}$, and $I_{ks}$ did not contribute appreciably to alternans, increasing any one of these currents sufficiently suppressed alternans. The mechanism for this effect was analogous to that described in Role of $I_{Ca}$ in alternans for the suppressant effects of reducing $I_{Ca}$ on alternans. With elevation of $I_{K1}$, $I_{Kr}$, or $I_{ks}$, the balance of repolarizing $K^+$ currents and $I_{Ca}$ during the action potential plateau was skewed, resulting in consistently short action potential durations. Consequently, the pattern of action potential duration and diastolic interval was similar to that shown in Fig. 6B except that $I_{Ca}$ not only recovered fully but also achieved a larger magnitude.

Fig. 8. $[Ca^{2+}]_i$ (left) and $I_{Ca}$ (right) in the CVM model after increasing $I_{K1}$ (A and B), $I_{Kr}$ (C and D), or $I_{ks}$ (E and F). See Glossary for abbreviations.
Ionic Mechanism of Electrical Alternans

Implications. Decreasing the magnitude of I_{Ca}, either experimentally (23) or in an ionic model (22), has been shown to eliminate alternans and to convert VF into a periodic rhythm. However, this approach clearly is not useful clinically because decreasing I_{Ca} decreases the Ca^{2+} transient, thereby reducing contractile force. With the use of the CVM model to explore other methods for eliminating alternans, we found that alternans was suppressed by increasing the magnitude of three repolarizing K⁺ currents: I_{K1}, I_{Kr}, and I_{Ks}.

Given that increasing I_{K1}, I_{Kr}, and I_{Ks} decreased action potential duration, we determined whether such shortening truncated I_{Ca}, in which case increasing K⁺ conductance might have the same clinical limitation as decreasing Ca^{2+} conductance. However, I_{Ca} was minimally affected both at short and at long pacing cycle lengths, as was the Ca^{2+} transient. Consequently, it is possible, at least in the CVM model, to increase K⁺ conductance to the point of suppressing alternans without reducing contractility.

These simulation results suggest a novel strategy for treating ventricular tachyarrhythmias. Previous attempts at treatment of such arrhythmias with pharmacological agents have been largely unsuccessful. In particular, class III antiarrhythmic drugs, which are designed to block K⁺ currents, have been shown to be proarrhythmic (20). The CVM simulations suggest that a new class of drugs designed to increase the magnitude of selected outward currents may be useful in preventing alternans and, therefore, in preventing the development of arrhythmias such as VF. It should be emphasized, however, that only those K⁺ channel agonists that reduce the slope of the action potential duration restitution relation are expected to suppress VF. Drugs such as ATP-sensitive K⁺ channel current agonists, which markedly increase outward K⁺ current and shorten action potential duration, increase the slope of the restitution relation and, presumably by that mechanism, facilitate the induction of VF (27).

Limitations. While the CVM model successfully reproduces alternans, it has several limitations. First, the formulation of I_{Ca} is based solely on the qualitative characteristics of I_{Ca}. To improve the model, I_{Ca} should conform to the results of quantitative voltage-clamp experiments, where the latter ideally have been conducted under circumstances that preserve the native behavior of I_{Ca} during pacing at short cycle lengths (e.g., no buffering of [Ca^{2+}]), or washout of the intracellular space). Second, although the simplified calcium handling in the model reproduces physiological Ca^{2+} transients, it ignores several of the details of calcium release from the SR. Further work needs to be done to incorporate detailed calcium handling mechanisms such as those in the Winslow model (26). Third, the model does not include the late Na⁺ current, which may contribute significantly to plateau duration (28). A formulation of this current that agrees with voltage-clamp experiments also needs to be included to complete the model. Finally, it has been shown that transmural heterogeneity of the heart is caused by differences in I_{to}, I_{Ks}, I_{NaCa}, and the late Na⁺ current in endocardial, midmyocardial, and epicardial canine heart cells (13, 14, 27, 29). We hope in the future to develop specific models for canine endocardium, midmyocardium, and epicardium cells that will take these differences into account.

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