Properties and ionic mechanisms of action potential adaptation, restitution, and accommodation in canine epicardium

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1Cardiac Bioelectricity and Arrhythmia Center, Department of Biomedical Engineering, Washington University in St. Louis; St. Louis, Missouri; 2Departments of Cardiology and Mathematics, Maastricht University, Maastricht, The Netherlands; 3Department of Pediatrics, University of Chicago, Pritzker School of Medicine; Chicago, Illinois; and 4Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa

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Decker KF, Heijman J, Silva JR, Hund TJ, Rudy Y. Properties and ionic mechanisms of action potential adaptation, restitution, and accommodation in canine epicardium. Am J Physiol Heart Circ Physiol 296: H1017–H1026, 2009. First published January 23, 2009; doi:10.1152/ajpheart.01216.2008.—Computational models of cardiac myocytes are important tools for understanding ionic mechanisms of arrhythmia. This work presents a new model of the canine epicardial myocyte that reproduces a wide range of experimentally observed rate-dependent behaviors in cardiac cell and tissue, including action potential (AP) duration (APD) adaptation, restitution, and accommodation. Model behavior depends on updated formulations for the 4-aminopyridine-sensitive transient outward current (Ito1), the slow component of the delayed rectifier K+ current (IKs), the L-type Ca2+ channel current (ICa,L), and the Na+-K+ pump current (INaK) fit to data from canine ventricular myocytes. We found that Ito1 plays a limited role in potentiating peak ICa,L and sarcoplasmic reticulum Ca2+ release for propagated APs but modulates the time course of APD restitution. IKs plays an important role in AP shortening at short diastolic intervals, despite a limited role in AP repolarization at longer cycle lengths. In addition, we found that ICa,L plays a critical role in APD accommodation and rate dependence of APD restitution. Ca2+ entry via ICa,L at fast rate drives increased Na+-Ca2+ exchange Ca2+ extrusion and Na+ entry, which in turn increases Na+ extrusion via outward INaK. APD accommodation results from this increased outward INaK. Our simulation results provide valuable insight into the mechanistic basis of rate-dependent phenomena important for determining the heart’s response to rapid and irregular pacing rates (e.g., arrhythmia). Accurate simulation of rate-dependent phenomena and increased understanding of their mechanistic basis will lead to more realistic multicellular simulations of arrhythmia and identification of molecular therapeutic targets.

arrhythmia; cardiac electrophysiology; mathematical modeling; ion channels

CARDIAC ARRHYTHMIAS and sudden death involve complex myocardial activation patterns, including unidirectional block, re-entry, and fibrillation. To understand the relations and transitions between these patterns, the ionic determinants of the response of healthy and diseased cardiac myocytes to complex patterns of excitation must be understood. The single-cell response to such excitation patterns depends on the complex interaction between ionic currents, intracellular ion concentrations, and membrane voltage. Computational cell models provide critical tools for exploring these interactions, allowing the development and testing of hypotheses about underlying ionic mechanisms based on careful integration of available experimental data (37). The dog is a common animal model for studying cell electrophysiology in a range of disease states. Our group and others have developed detailed mathematical models of the canine action potential (AP) (11, 20, 58). Although these models have been used to study arrhythmia mechanisms after heart failure (58) and myocardial infarction (5, 17), as well as ionic mechanisms of alternans (11, 26), they are limited in their ability to simulate important rate-dependent phenomena (6), including the dependence of steady-state AP duration (APD) on pacing cycle length (CL; i.e., APD adaptation), the dependence of APD on diastolic interval (DI; i.e., APD restitution), and the time course of the adjustment of APD to changes in rate [short-term memory (12) or APD accommodation (56)]. These limitations extend to ionic models of other species, including the human (6). We hypothesized that canine epicardial APD adaptation, restitution, and accommodation could be simulated and understood on the basis of available descriptions of subcellular ionic processes. We incorporated updated and validated formulations of the 4-aminopyridine-sensitive transient outward current (Ito1), the slow component of the delayed rectifier K+ current (IKs), the L-type Ca2+ channel current (ICa,L), and the Na+-K+ pump current (INaK) into a previously published model of the canine epicardial myocyte (17, 20, 26). Model behavior was examined in single-cell and multicellular (strand) simulations. Our work provides new insight into ionic mechanisms underlying important rate-dependent AP properties, including APD restitution, adaptation, and accommodation. Specifically, our studies highlight the importance of Ito1 and IKs in APD restitution and the role of ICa,L and INaK in APD accommodation and rate-dependent APD restitution.

METHODS

Model. The Hund-Rudy dynamic model (Fig. 1) of the canine epicardial myocyte (17, 20, 26) serves as the basis for these simulations. Updates to intracellular Ca2+ ([Ca2+]i) handling in a recent study of APD and [Ca2+]i transient (CaT) alternans are included (26). Ion channel formulations, including ICa,L, Ito1, IKs, and INaK, have been updated on the basis of additional data from canine ventricular myocytes. Model parameters were fit to experimental data from the literature (Fig. 2). Experimental data that represented the consensus of a wide range of experimental results or were obtained from the most complete available study were chosen. [See supplemental Figs. S2 (ICa,L) and S4 (Ito1) in the online version of this article for comparison...
of model behavior with a wider range of available data.] A new Markov model of $I_{\text{Ca,L}}$ was formulated to reproduce a wide range of experimental data while maintaining computational tractability to facilitate long-term multicellular simulations. The state structure (see supplemental Fig. S1) of the model reflects the hypothesis that Ca$^{2+}$ binding to calmodulin removes a “brake” and speeds up voltage-dependent inactivation (28, 33). The model reproduces the $I_{\text{Ca,L}}$ current-voltage ($I$-$V$) relationship (36) (Fig. 2E), time constant of voltage-dependent inactivation (1), and recovery from inactivation (51) in canine ventricular myocytes. A model of $I_{\text{tot}}$ was developed and fit to the $I$-$V$ relationship (Fig. 2C), time to peak (Fig. 2D), time constant of inactivation (27), and slow time constant of recovery from inactivation (25) in canine epicardial myocytes. A Markov model of $I_{\text{Ks}}$ (43) previously developed in our laboratory was adopted and fit to data from canine ventricular myocytes. The model accurately reproduces the kinetics of $I_{\text{Ks}}$ based on underlying voltage sensor transitions and has provided insight into the role of $I_{\text{Ks}}$ in APD adaptation in the guinea pig and humans (43). The model fits canine ventricular data on the time course of activation (Fig. 2F) (53) and voltage dependence of current accumulation (Fig. 2F) (47). $I_{\text{Ks}}$ density was scaled to fit data from canine epicardial myocytes (24). A recently developed formulation of $I_{\text{NaK}}$ based on data from canine ventricular myocytes (13) was also incorporated into the model. Model $I_{\text{NaK}}$ density matches epicardial myocyte data (Fig. 2G) and results in intracellular Na$^{+}$ ([Na$^{+}$]$_{i}$) at rest and during pacing (CL = 0.5 s) consistent with experimental results (Fig. 2).

Fig. 2. A and B: model $I_{\text{Ca,L}}$ current-voltage ($I$-$V$) relationship and steady-state inactivation fit to experimental data from canine epicardial myocytes (36, 48). C and D: model $I_{\text{tot}}$ $I$-$V$ curve and time to peak fit to data from canine epicardial myocytes (27). E and F: model $I_{\text{Ks}}$ activation and accumulation fit to data from canine ventricular myocytes (47, 53). G and H: model $I_{\text{NaK}}$ density and steady-state intracellular Na$^{+}$ concentration ([Na$^{+}$]$_{i}$) fit to data from canine ventricular myocytes (13). $V_{\text{test}}$, test potential; CL, cycle length.
2H). [See the online version of this article for complete model equations and more detailed descriptions.]

Single-cell simulations. Steady-state results are shown after 1,800 s of pacing at a given CL with a conservative K+ stimulus (18). This simulation time resulted in a beat-to-beat change in APD and maximum intracellular Na+ ([Na+]i, max) and Ca2+ ([Ca2+]i, max) <0.1%. Restitution results were obtained for an additional beat after pacing to steady state as described. Accommodation simulations involved pacing to steady state at a given CL (CLS1) followed by pacing to steady state at a different CL (CLS2).

Strand simulations. One-dimensional simulations of propagation were performed in a strand of 96 cells following previous work from our laboratory (40). Cell 1 was directly stimulated, and simulation results are shown for a central cell (cell 48). Simulation protocols were similar to those used for single cells (1,800 s of pacing), resulting in beat-to-beat changes in APD and [Na+]i, max and [Ca2+]i, max <0.1%. Gap junction conductance of 2.5 μS gave a maximum upstroke velocity (dV/dt, max) (7) and conduction velocity (45) consistent with experimental results in canine epicardial tissue. [See supplemental information in the online version of this article for additional parameters used in multicellular simulations.]

RESULTS

APD rate dependence in a single cell and a multicellular strand. Figure 3 shows the rate dependence of APD in a cell and a strand during different pacing protocols. The rate dependence of simulated steady-state APs is shown in Fig. 3A (left). Cell and strand simulations exhibit the spike-and-dome morphology characteristic of canine epicardium (Fig. 3A, right) (25). Steady-state APs in the strand show a reduced upstroke amplitude and velocity compared with the single cell due to electronic load during propagation. Maximum upstroke voltage (V, max) and dV/dt, max match experiments in canine ventricular epicardium at CL = 0.8 s (7): experimental V, max = 13.1 ± 4.7 mV, dV/dt, max = 151.8 ± 39.8 V/s; model V, max = 9.24 mV, dV/dt, max = 162.6 V/s. The model reproduces the decreased rate dependence of the depth of the phase 1 notch generally observed in tissue (Fig. 3A) (3, 7, 25). The cause of different AP spike-and-dome morphology in different tissue experiments is unknown, but possibilities include heterogeneity in the density and recovery kinetics of Ibol due to age (31), sex (59), and precise apicobasal or transmural location (25, 49).

We next characterized APD restitution in our single-cell and strand models. After pacing to steady state at a given CL (CLS1), additional stimuli (S2) scanning the DI were applied to generate restitution curves plotting APD vs. S2 coupling interval (CLS2) (Fig. 3B, left). As the basic pacing CL (CLS1) decreases, restitution curves in the single-cell and strand models shift toward shorter APD, consistent with experimental measurements (Fig. 3B, right) (4, 6, 9, 15). The model also reproduces tissue AP restitution kinetics as a function of DI (see below; also see Fig. 6 and supplemental Fig. S5). Figure 3C (left) shows the time course of APD in a model cell and a strand after pacing to steady state at CLS1 = 1 s followed by sustained pacing at CLS2 = 0.5 s starting at time 0. APD at the new CL approaches steady state after several minutes of pacing, a process referred to as accommodation (56), consistent with experiments in canine ventricle (Fig. 3C, right) (39).

Previous simulation studies (6, 34) showed that direct simulation in single cells and electrotonic loading in tissue can
lead to different AP dynamics. Figure 4 compares cell and tissue steady-state APs and ion accumulation in the new model. A
\( V_0 = 80 \, \mu A/\mu F \), 0.5-ms stimulus was used in single-cell simulations (Fig. 4A). In the strand, excitatory axial current in well-coupled tissue (Fig. 4A) consists of 1) an initial transient depolarizing current, 2) a transient repolarizing current as the cell supplies charge to depolarizing downstream cells, and 3) a small sustained repolarizing current (Fig. 4A, inset). The biphasic axial current in the tissue reduces AP upstroke velocity relative to its value in the single cell (Fig. 4B). In addition, steady-state tissue APD is reduced slightly (Fig. 4C) as a result of the sustained repolarizing axial current (Fig. 4A, inset). APD adaptation in cell and strand simulations (Fig. 4C) is consistent with experimental results (25). Cell and strand simulations show an increase in \( \text{Ca}^{2+} \) transient amplitude (\( \text{CaTAMP} \), Fig. 4D) (44) and maximum \( [\text{Na}^+] \) (\( [\text{Na}^+]_{\text{max}} \); Fig. 4E) (13) with pacing rate, consistent with experimental results. Differences in \( \text{CaTAMP} \) and \( [\text{Na}^+]_{\text{max}} \) in cell and strand simulations are minimal. Subsequent results are from strand simulations unless otherwise specified.

\( I_{\text{to1}} \), peak \( I_{\text{Ca,L}} \), and \( \text{CaTAMP} \) in cell and strand. Experimental (38) and computational (14) studies have suggested that \( I_{\text{to1}} \), by controlling phase 1 repolarization, is an important modulator of \( I_{\text{Ca,L}} \) activation and sarcoplasmic reticulum (SR) \( \text{Ca}^{2+} \) release. We examined differences in the effect of \( I_{\text{to1}} \) on \( I_{\text{Ca,L}} \) activation and SR \( \text{Ca}^{2+} \) release in cell and strand simulations. Figure 5A shows that although blockade of \( I_{\text{to1}} \) leads to a significant reduction in \( \text{CaTAMP} \) in cell simulations, reduction of \( \text{CaTAMP} \) after \( I_{\text{to1}} \) blockade in tissue simulations is minimal. The interplay between membrane potential (\( V_m \)), \( I_{\text{to1}} \), \( I_{\text{Ca,L}} \), and SR \( \text{Ca}^{2+} \) release in a cell and a strand is examined in Fig. 5, B–E. We note several important differences between simulated APs in the strand and in the isolated cell. These unique features of the strand AP include 1) reduced peak upstroke voltage (Fig. 5B), 2) reduced \( I_{\text{to1}} \) activation (Fig. 5C), and 3) minimal dependence of peak \( I_{\text{Ca,L}} \) on \( I_{\text{to1}} \) activation (Fig. 5D). Reduced peak upstroke voltage in the strand leads to a reduction in peak \( I_{\text{to1}} \) due to the approximately linear dependence of \( I_{\text{to1}} \) activation on \( V_m \). This reduction in \( I_{\text{to1}} \) activation leads to a reduction in \( \text{phase 0} \) repolarization. Arrows in Fig. 5B denote \( V_m \) at the peak of \( I_{\text{Ca,L}} \) activation in a cell and a strand, respectively. In cell simulations, a large \( I_{\text{to1}} \) repolarizes \( V_m \) (Fig. 5C) toward the peak of the \( I_{\text{Ca,L}} \)-\( I-V \) relationship (Fig. 5B), promoting \( I_{\text{Ca,L}} \) activation (Fig. 5D) and SR \( \text{Ca}^{2+} \) release (Fig. 5E). When \( I_{\text{to1}} \) is blocked in the cell, \( I_{\text{Ca,L}} \) activation occurs at a \( V_m \) that is far from the peak of the \( I-V \) curve (Fig. 5B), decreasing peak \( I_{\text{Ca,L}} \) (Fig. 5D) and SR \( \text{Ca}^{2+} \) release (Fig. 5E). For a propagating action potential, however, increased load decreases peak up-
stroke voltage, so that it is near the peak of the $I_{Ca,L}$ $V$ curve (Fig. 5B, $\sim 10$ mV). Maximal $I_{Ca,L}$ activation occurs shortly after the peak upstroke $V_m$, such that the depth of the phase 1 notch plays little role in determining $V_m$ as $I_{Ca,L}$ is peaking. Consequently, blockade of $I_{lo1}$ in the strand has little effect on peak $I_{Ca,L}$ (Fig. 5D) and SR Ca$^{2+}$ release (Fig. 5E). Furthermore, reduced phase 1 repolarization (Fig. 5B) due to reduced $I_{lo1}$ activation (Fig. 5C) also suggests a diminished importance of $I_{lo1}$ in the strand relative to the cell.

$I_{lo1}$ and APD restitution. Although our results suggest a limited role for $I_{lo1}$ in regulation of peak $I_{Ca,L}$ and SR Ca$^{2+}$ release in multicellular strands, $I_{lo1}$ was found to play an important role in APD restitution. Figure 6A shows that the time course of APD restitution is consistent with experiments in epicardial tissue (42). (See supplemental information and Fig. S5 in the online version of this article for comparison of model restitution kinetics with experiments for a range of CLS1.) In canine epicardium, APD gradually increases as DI increases beyond $0.3$ s. After $100\% I_{lo1}$ block, the increase in APD with increasing DI is more abrupt, as observed in canine epicardium (42) and endocardial (23) tissue experiments. B–D: $V_m$, $I_{lo1}$, and $I_{Kr}$ during APD restitution at S2 coupling intervals (CLS2) of $0.3$ and $2$ s in control and after $I_{lo1}$ block in the strand. Insert in B shows very similar AP after $I_{lo1}$ block at short CLS2 (thick gray trace) and long CLS2 (thin gray trace).

$K_s$ and APD adaptation. The role of $K_s$, in canine APD adaptation is examined in Fig. 7. As shown in 7A, $100\%$ block of $I_{Ks}$ leads to a modest prolongation of APD at steady state. Percent APD prolongation after $I_{Ks}$ blockade decreases as CL decreases (“use-dependent” block), except at short CL, where percent prolongation begins to increase again. The biphasic effect of $I_{Ks}$ block on APD is consistent with the rate dependence of $I_{Ks}$ activation shown in Fig. 7B. $I_{Ks}$ activation in Fig. 7B is smallest at CLS1 = $0.5$ s (Fig. 7B), corresponding to the smallest percent prolongation of APD after $I_{Ks}$ block in Fig. 7A. $I_{Ks}$ activation at CLS1 = $0.25$ and $1$ s is increased relative to CLS1 = $0.5$ s, leading to a relative increase in percent APD prolongation after $I_{Ks}$ block at these rates. Figure 7, C–E, examines the rate dependence of $I_{Ks}$ state occupancy, following previously published analysis in the guinea pig (43). The 17-state $I_{Ks}$ model can be divided into two open states, five zone 1 closed states that can activate rapidly, and 10 “deep” zone 2 closed states, which require slow transitions to zone 1 before activation is possible. At CLS1 = $0.5$ and $1$ s, all channels reside in zone 2 at the start of the AP (Fig. 7C) and activate slowly upon depolarization (Fig. 7B). Slow activation from zone 2 and small peak density in the dog dictate that $I_{Ks}$ plays a limited role in APD repolarization at longer CL. At CLS1 = $0.25$ s, the DI is insufficient for activated channels to return to zone 2. Channels activated during the previous beat remain in zone 1 (Fig. 7D) and the open state (Fig. 7E) as the next stimulus is applied, resulting in more rapid channel activation (Fig. 7B) and an increased role for $I_{Ks}$ in APD shortening at fast rate.

$I_{Ks}$ and APD restitution. We also examined the role of $I_{Ks}$ in APD restitution (Fig. 8). Simulation results show that the percent increase in APD after $100\% I_{Ks}$ block is largest at the shortest CLS2 (Fig. 8B). At CLS2 = $0.26$ and $0.3$ s, a significant

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Fig. 7. A: percent increase in steady-state APD after $100\% I_{Ks}$ block as a function of CLS1, B–E: $I_{Ks}$ current density and state occupancy of zone 2, zone 1, and open state at steady-state for CLS1 = $0.25$, $0.5$, and $1$ s.
fraction of channels activated during the previous AP remain in the open state (Fig. 8D), while an additional fraction occupies zone 1 (Fig. 8F). When a premature stimulus is applied, channels that are already open and those moving rapidly from zone 1 for restitution protocol in A.

To understand the link between \( I_{Ca,L} \), \([Na^+]\) and accommodation, we examined the sarcolemmal \( Ca^{2+} \) and \( Na^+ \) flux (\( \mu M/S \)) via currents, pumps, and exchangers after a change from CL = 1 s to CL = 0.5 s. Fluxes were calculated at steady state at CL = 1 s and for each subsequent beat after a change to CL = 0.5 s. At steady-state CL = 1 s, \( Ca^{2+} \) influx (primarily \( I_{Ca,L} \)) and efflux (primarily \( I_{Na,Ca} \)) are balanced (Fig. 10A). After a change to CL = 0.5 s, the shorter DI does not provide sufficient time for \( I_{Na,Ca} \) to extrude \( Ca^{2+} \) that entered via \( I_{Ca,L} \). Excess \( Ca^{2+} \) influx leads to \( Ca^{2+} \) accumulation after the first beat and with continued pacing at CL = 0.5 s (Fig. 10B). \( Ca^{2+} \) accumulation provides feedback by decreasing [\( Ca^{2+} \)] influx through \( Ca^{2+} \)-dependent inactivation of \( I_{Ca,L} \) and increased [\( Ca^{2+} \)] efflux (through forward-mode \( I_{Na,Ca} \)). This feedback promotes decreased net \( Ca^{2+} \) entry increases, channels move from zone 1 and the open state to zone 2, resulting in less prominent \( I_{Ks} \) activation for more mature stimuli and reduced (\( \sim 2.5\% \)) APD prolongation after \( I_{Ks} \) block.

**APD accommodation.** We sought to gain insight into the ionic mechanism of APD accommodation by examining underlying ionic currents and concentrations. The transition from steady state at CL = 1 s to steady state at CL = 0.5 s is examined in Fig. 9. APD accommodation exhibits several properties consistent with experimental observations. Equilibration of APD after a change in CL occurs after several minutes of pacing, consistent with experiments in canine ventricular tissue (39). Consistent with the effect of nisoldipine on rabbit ventricular myocytes (50), 100% block of \( I_{Ca,L} \) in the model diminishes APD accommodation. In addition, accommodation persists after 100% block of SR \( Ca^{2+} \) uptake (uptake current) and release (release current), consistent with effects of ryanodine and thapsigargin on rabbit myocytes (50). Figure 9B shows changes in \([Na^+]\) during APD accommodation. In control and when SR release and uptake are blocked, accumulation of \([Na^+]\) occurs with a time course similar to that of APD shortening. When \( I_{Ca,L} \) is blocked, APD shortening and \([Na^+]\) accumulation are diminished. When \([Na^+]\) is clamped to its steady-state value at CL = 0.5 s, APD accommodation is eliminated. Figure 9C demonstrates that, in control, \([Na^+]\) accumulation leads to a large increase in outward \( I_{Na,K} \) from the first beat to the steady-state beat after a change in CL. After \( I_{Ca,L} \) block, there is a smaller difference in \( I_{Na,K} \) from the first beat to the steady-state beat. Collectively, these simulations suggest that \( I_{Ca,L} \) is responsible for the increases in \([Na^+]\) and outward \( I_{Na,K} \) that underlie APD accommodation.
per cycle, so that [Ca^{2+}]_{i1} approaches equilibrium within the 1st minute of pacing at the new CL.

Na^+ influx exceeds efflux after change from CL_{S1} = 1 s to CL_{S2} = 0.5 s (Fig. 10C). As with Ca^{2+}, the shortened DI provides insufficient time for complete extrusion of Na^+ that entered during the AP, primarily via forward-mode \( I_{\text{NaCa}} \) and the fast Na^+ current \( (I_{\text{Na}}) \). Increased forward-mode \( I_{\text{NaCa}} \) as [Ca^{2+}]_{i1} accumulates further increases Na^+ influx. The imbalance of Na^+ influx and efflux drives [Na^+]_{i} accumulation (Fig. 9B) until Na^+ efflux via \( I_{\text{NaK}} \) increases to match influx after minutes of pacing (Fig. 10C). The time course for equilibration of Na^+ influx and efflux in our simulations (on the order of minutes) agrees with the slow time course of Na^+ accumulation seen experimentally (13, 34). The increasingly outward \( I_{\text{NaK}} \) as Na^+ influx and efflux approach equilibrium is the primary cause of APD shortening during accommodation. This ionic mechanism by which \( I_{\text{CaL}} \) drives [Na^+]_{i} accumulation and \( I_{\text{NaK}} \) increase via \( I_{\text{NaCa}} \) is consistent with effects of nisoldipine and ryanodine/thapsigargin on rabbit ventricular myocytes (50). Block of \( I_{\text{CaL}} \) (nisoldipine) eliminates a critical driving force for [Na^+]_{i} accumulation (greater forward-mode \( I_{\text{NaCa}} \), which promotes Ca^{2+} extrusion and Na^+ entry). After \( I_{\text{CaL}} \) blockade, Ca^{2+} (Fig. 10A) and Na^+ (Fig. 9C) influx barely exceeds Ca^{2+} and Na^+ efflux after a change to CL = 0.5 s. [Ca^{2+}]_{i1} (Fig. 10B) and [Na^+]_{i1} (Fig. 9B) accumulation after \( I_{\text{CaL}} \) block are diminished, resulting in diminished APD accommodation. Block of SR Ca^{2+} release (ryanodine) and SR Ca^{2+} uptake (thapsigargin) eliminates SR Ca^{2+} cycling, but the mechanism of \( I_{\text{CaL}} \)-driven increase in [Na^+]_{i} remains intact. Although block of SR function eliminates Ca^{2+} transients, intact \( I_{\text{CaL}} \) leads to an increase in cell [Ca^{2+}], Forward-mode \( I_{\text{NaCa}} \) must increase to extrude Ca^{2+}, and [Na^+]_{i} accumulation and APD accommodation persist.

Dependence of APD restitution on pacing rate. Several experimental studies have shown that the APD restitution curve shifts to shorter APD as basic pacing CL decreases (shorter CL_{S1}) (4, 6, 9, 15). Consistent with these experimental observations, our model reproduces the dependence of restitution on the rate of S1 pacing (Fig. 11). These simulations also provide insight into the underlying ionic mechanism. Fast pacing (short CL_{S1}; Fig. 11A) is accompanied by [Na^+]_{i} accumulation (Fig. 11B), as described above in the case of accommodation (Fig. 9). [Na^+]_{i} accumulation, in turn, promotes an increase in repolarizing \( I_{\text{NaK}} \) (Fig. 11C), which decreases APD, thereby shifting the APD restitution curve to shorter APDs.

DISCUSSION

The rate-dependent phenomena examined in this study are thought to play an important role in the dynamics of arrhythmia (2, 22, 29). The model presented here reproduces experimentally observed APD adaptation, restitution, and accommodation in cell and tissue. Although the rate dependence of model APD, CaT, and [Na^+]_{i} accumulation is similar in cell and strand, our simulation results show that the effects of \( I_{\text{to1}} \) block on ion accumulation differ. Other simulation results (34) have suggested that APD restitution kinetics and the transition to APD alternans and more complex excitation patterns in cell and tissue also differ. Taken together, these results suggest that experimental findings in isolated myocytes should be extrapolated to the multicellular tissue with caution.

Recent studies have emphasized limitations in our mechanistic understanding of the rate dependence of APD (6). The detailed, physiologically based mathematical descriptions of critical ionic currents, pumps, and exchangers incorporated into the model lead to novel insight into underlying ionic mechanisms. Specific mechanistic insights generated by our study include the following. 1) \( I_{\text{to1}} \) potentiates \( I_{\text{CaL}} \) and SR Ca^{2+} release during early AP repolarization in isolated cells, but not in multicellular tissue. 2) \( I_{\text{to1}} \) plays an important role in APD restitution because of its slow recovery kinetics. As DI increases, \( I_{\text{to1}} \) recovery and phase 1 notch depth increase, suppressing \( I_{\text{Ks}} \) activation and lengthening APD. 3) \( I_{\text{Ks}} \) plays a limited role in repolarization of paced APs but plays an important role in APD shortening for premature stimuli. 4) \( I_{\text{CaL}} \) plays a critical role in APD accommodation and memory. As a response to Ca^{2+} entry via \( I_{\text{CaL}} \) at fast rates, forward-mode \( I_{\text{NaCa}} \) increases, leading to increased Ca^{2+} efflux and Na^+ influx. Na^+ accumulates and repolarizing...
I\textsubscript{NaK} increases, leading to APD shortening during accommodation. 5) I\textsubscript{Ca,L}-dependent increase in [Na\textsuperscript{+}], and I\textsubscript{NaK} at fast rates is responsible for the shift in APD restitution curves toward shorter APD.

Previous experiments and simulation studies have suggested that I\textsubscript{to1}, by increasing phase 1 repolarization, increases peak I\textsubscript{Ca,L} (the trigger for SR release) and, consequently, SR Ca\textsuperscript{2+} release (14, 38). These studies showed enhanced I\textsubscript{Ca,L} and SR Ca\textsuperscript{2+} release when phase 1 repolarization increases the I\textsubscript{Ca,L} driving force. Although this scenario is relevant to an isolated, directly stimulated myocyte, model simulations indicate that it does not apply to the situation in vivo, where electrotonic loading from neighboring cells weakens the AP upstroke. Our simulations suggest that, for propagating APs, I\textsubscript{to1}-dependent phase 1 repolarization has little effect on peak I\textsubscript{Ca,L} and SR Ca\textsuperscript{2+} release. In addition, simulations show that the weakened AP upstroke in the tissue decreases I\textsubscript{to1} activation and phase 1 repolarization. I\textsubscript{to1} has been accorded a role in conduction (16, 55) and in electrophysiological remodeling in various diseased states (21, 27, 60). Our results suggest that predictions of the effect of I\textsubscript{to1} and I\textsubscript{to1} block based on single-cell simulations and experiments may not apply to the in vivo situation. In contrast, model simulations predict that I\textsubscript{to1} plays a significant role in APD restitution. The interplay between IK\textsubscript{s} activation and the slow recovery kinetics of I\textsubscript{to1} leads to a gradual increase in APD during restitution, whereas I\textsubscript{to1} block results in a more abrupt APD increase. This result provides a mechanistic explanation for the correlation between notch depth and APD observed in canine ventricular tissue (23). The time course of APD restitution is thought to play an important role in the stability of ventricular arrhythmias (22). Our results suggest that experimentally observed heterogeneity in I\textsubscript{to1} density and recovery kinetics (30, 32) may play a role in the stability of arrhythmias in different species, regions of tissue, or pathophysiological states. Canine experiments have shown transmural heterogeneity in I\textsubscript{NaK} (61), I\textsubscript{to1} (25), IK\textsubscript{s} (24), and I\textsubscript{NaCa} (62). The epicardial model accurately reproduces endocardial restitution kinetics after blocking only I\textsubscript{to1}, suggesting that I\textsubscript{to1} is the dominant determinant of heterogeneity in restitution between the two cell types.

Experimental measurements of the effect of IK\textsubscript{s} block on APD in canine ventricle have ranged from near 0 (47) to as much as 30% (41). Varro et al. (52) report a modest prolongation (3–7%) and biphasic CL dependence after chromanol block, consistent with our simulation results. Although the role of IK\textsubscript{s} in repolarization remains controversial, LQT mutations linked to genes for IK\textsubscript{s} α- and β-subunits (46) argue for an important role in repolarization. Our simulations demonstrate that slow activation and relatively low density limit the role of IK\textsubscript{s} in APD restitution at physiological heart rates in the absence of β-adrenergic stimulation, consistent with our previous modeling studies (20). Simulations with a detailed Markov model of IK\textsubscript{s} predict an important role for IK\textsubscript{s} in APD restitution. During deactivation, channels accumulate in closed states (zone 1), where rapid activation in response to a premature stimulus is possible, leading to an important role for IK\textsubscript{s} in APD restitution at short DI. A role for IK\textsubscript{s} in APD shortening at fast CL\textsubscript{51} via accumulation in closed states has been shown in the guinea pig and humans (43). Despite major differences between IK\textsubscript{s} density and kinetics in the guinea pig and dog, the mechanism for enhanced participation of IK\textsubscript{s} at fast CL\textsubscript{51} during adaptation and at short DI during restitution are similar in the two species. Importantly, although large density in the guinea pig ensures an important role for IK\textsubscript{s} at all rates, we find that IK\textsubscript{s} plays a major role in canine restitution at short DI, despite a limited role at longer physiological CL. Although the effect of IK\textsubscript{s} block on paced APs has been studied experimentally, no studies on the role of IK\textsubscript{s} in restitution have been reported. IK\textsubscript{s} is also likely to play an important role in repolarization in the presence of β-adrenergic stimulation (53) or for abnormally prolonged APD (52).

Recent simulations have addressed the role of APD accommodation and short-term memory in the dynamics of arrhythmia (2, 29). Simulations (2) and experiments (50) have emphasized uncertainty about the ionic mechanisms underlying this phenomenon. The results presented here predict a major role for I\textsubscript{Ca,L}-driven [Na\textsuperscript{+}] accumulation in this phenomenon. A role for [Na\textsuperscript{+}] and I\textsubscript{NaK} in gradual APD changes during long-term pacing has been proposed (4, 10, 19). Similarities between the effect of block of I\textsubscript{Ca,L} and SR function in simulations and experiments (50) support for this hypothesis. Although a similar time course of APD accommodation after a CL change has been observed in a range of preparations, APD accommodation in other species and preparations is often more rapid (12, 50, 57). This suggests that other mechanisms may play a role or, alternatively, that additional experiments are required to improve our understanding of equilibration of [Na\textsuperscript{+}] and [Ca\textsuperscript{2+}] during long-term pacing. A role for I\textsubscript{Ca,L} in the dynamics of arrhythmia has been proposed by many investigators, usually through effects on APD restitution (4, 35). Our simulations suggest that the effect of I\textsubscript{Ca,L} on [Na\textsuperscript{+}] and APD accommodation should also be considered. The importance of [Na\textsuperscript{+}] in determining the rate dependence of APD also points to an important limitation of simplified computational models, where intracellular ion concentrations are often held constant.

The predictive value of multicellular simulations of arrhythmia depends on the ability of cell models to reproduce experimental observation. Despite variability across species, cell type, and preparation, APD adaptation, restitution, and accommodation are qualitatively similar in many species. Our model examines the ionic basis of these rate-dependent phenomena in the dog but may provide insight into ionic mechanisms in other species, including humans. In addition, our model will provide a valuable tool for linking initiation and maintenance of arrhythmia to underlying cellular processes and ionic currents through multicellular simulations.

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