Dynamics of action potential head-tail interaction during reentry in cardiac tissue: ionic mechanisms

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Hund, Thomas J., Niels F. Otani, and Yoram Rudy. Dynamics of action potential head-tail interaction during reentry in cardiac tissue: ionic mechanisms. Am J Physiol Heart Circ Physiol 279: H1869–H1879, 2000.—In a sufficiently short reentry pathway, the excitation wave front (head) propagates into tissue that is partially refractory (tail) from the previous action potential (AP). We incorporate a detailed mathematical model of the ventricular myocyte into a one-dimensional closed pathway to investigate the effects of head-tail interaction and ion accumulation on the dynamics of reentry. The results were the following: 1) a high degree of head-tail interaction produces oscillations in several AP properties; 2) $[Ca^{2+}]_i$-transient oscillations are in phase with AP duration oscillations and are often of greater magnitude; 3) as the wave front propagates around the pathway, AP properties undergo periodic spatial oscillations that produce complicated temporal oscillations at a single site; 4) depending on the degree of head-tail interaction, intracellular $[Na^+]_i$ accumulation during reentry either stabilizes or destabilizes reentry; and 5) elevated extracellular $[K^+]_e$ destabilizes reentry by prolonging the tail of postrepolarization refractoriness.

Reentry is the underlying mechanism of many common cardiac arrhythmias (11, 32, 36), which are a major cause of death and disability. Effective diagnosis, prevention, and treatment of these life-threatening arrhythmias require an in-depth understanding of the reentrant action potential (AP).

During reentry in a sufficiently short pathway, the excitation wave front (head) propagates into tissue that is still refractory (tail) from the previous excitation. Interaction between the head and tail of an AP is a common phenomenon in the heart. It has been observed in an anatomically defined reentry pathway (18), along the arm of a spiral wave (21), and in the leading circle of functional reentry (2). Head-tail interaction is also known to have a profound effect on the dynamics of the reentrant AP. For example, a significant degree of head-tail interaction produces oscillations in key AP properties such as AP duration (APD), conduction velocity ($\theta$), and cycle length (CL) (8, 18, 21, 34, 42). Such oscillations often precede spontaneous termination of reentry (14, 17, 32) or breakup of the reentry loop into multiple pathways resulting in fibrillation.

Theoretical studies of reentry (8, 21, 33, 42) have used relatively simple models of the cardiac AP (4, 15, 29, 30) that lack realistic elements such as intracellular calcium handling and dynamic intracellular ion concentration changes during excitation. Changes in the intracellular concentrations of ions such as $Ca^{2+}$ ($[Ca^{2+}]_i$) and $Na^+$ [Na+] during rapid pacing, drug application, and ion-channel dysfunction (35). Importantly, intracellular ions accumulate during reentrant tachyarrhythmias due to the rapid repetitive excitation of the cells. These ionic changes affect the AP through various membrane currents and modify the dynamics of reentry. In this study, we examine reentry in a one-dimensional closed pathway using the Luo-Rudy dynamic (LRd) model of a mammalian ventricular myocyte (28, 39, 43, 46). This model accounts for dynamic intracellular concentration changes of $Na^+$, $Ca^{2+}$, and $K^+$ during excitation. It also incorporates the effects of such changes on transmembrane currents that determine the AP, including currents through ion channels, pumps, and exchangers. The aims of this study are to examine: 1) the response of the reentrant AP to varying degrees of head-tail interaction and 2) the effect of ion accumulation on this relationship.

METHODS

The reentry pathway. By connecting individual LRd ventricular cell models (28, 39, 43, 46) with passive resistances to represent gap junctions (38), a ring of cells is created (33) that represents a closed pathway in the heart (a schematic is shown in Fig. 1). Simulations were conducted for gap-junction conductances ($g_j$) of 0.076 and 0.285 mS. The simulated behavior of interest, namely the effect of ion accumulation on reentry dynamics, did not depend on the particular value of $g_j$. Results for $g_j = 0.076$ mS are presented unless otherwise stated. With this choice, we could use a shorter pathway and significantly reduce computing time. Also, $g_j = 0.076$ mS produced slowed conduction, which is a prerequisite for sus-
Spatial Action Potential

Head

Direction of propagation

Tail

L number of LRd cells connected through gap junctions.

I<sub>Na</sub>, I<sub>Na,b</sub>, I<sub>Ca(L)</sub>, I<sub>NaCa</sub>, I<sub>K(Ca)</sub>, I<sub>Ca(T)</sub>, I<sub>Ca,b</sub>, g<sub>j</sub>,

Sarcoplasmic Reticulum

Troponin I<sub>T</sub>, I<sub>rel</sub>, Ca<sup>2+</sup>, JSR; and network SR (NSR).

I<sub>K</sub>, I<sub>KCa</sub>, I<sub>K1</sub>, I<sub>NaK</sub>, I<sub>L1</sub>, I<sub>Ca(L)</sub>, Na<sup>+</sup>/Ca<sup>2+</sup>

Calmodulin

Calsequestrin

Fig. 1. Dynamic Luo-Rudy (LRd) cell models are connected by intercellular resistive pathways (gap junctions) with conductance (g<sub>j</sub>) to form a closed pathway of reentry. Head and tail of reentrant action potentials (AP) are indicated. Below the reentry pathway a schematic of the LRd cell model is shown with various ion channels, pumps, and exchangers represented in the model: Na<sup>+</sup> channel current (I<sub>Na</sub>); L-type Ca<sup>2+</sup> current (I<sub>Ca(L)</sub>); Na<sup>+</sup>-Ca<sup>2+</sup> exchange current (I<sub>NaCa</sub>); Na<sup>+</sup>-K<sup>+</sup> pump current (I<sub>NaK</sub>); slow delayed-rectifier K<sup>+</sup> current (I<sub>K</sub>); junctional sarcoplasmic reticulum (JSR); and network SR (NSR). LRd model details are provided in the literature (28, 39, 43, 46). This model code can be downloaded from the research section of Web site http://www.cwru.edu/med/CBRTC. See this Web site for additional definitions of the current abbreviations.

tained reentry and is observed in the border zone of a healing infarct (10) and during ischemia (38). Computations converged for the entire range of parameter values used with the chosen spatial and temporal discretization steps [Δx = 100 μm; Δt varies from 0.005 to 1.0 ms (38)].

Once reentry has been initiated in the closed pathway, the path length (L) is reduced by removing 10 cells in the plateau phase of their respective APs, similar to the protocol used by Vinet and Roberge (42). Propagation is allowed to reach a steady state, after which 10 additional cells are removed. This process is repeated until the pathway is sufficiently small such that oscillations in APD are persistent (last more than 10 revolutions). After the onset of oscillations in AP properties, cells are removed two at a time to achieve greater spatial resolution. Close to the point of termination, cells are removed one at a time. In the case of transient oscillations, the system is considered to be in steady state once APD changes by less than 1%. In the case of persistent oscillations, two different protocols are used to determine steady state. In the first protocol, propagation is defined to be in steady state when APD oscillations maintain the same pattern for at least 10 revolutions (“short steady state”). In the second protocol, steady state is declared when an oscillatory pattern repeats itself for at least 100 revolutions (“long steady state”).

The APD is the time between the AP upstroke and 90% repolarization. The peak Ca<sup>2+</sup> transient concentration ([Ca<sup>2+</sup>]<sub>L,peak</sub>) is defined as the maximum value of the Ca<sup>2+</sup> transient following the AP upstroke. Diastolic interval (DI) is measured as the time between 90% repolarization and the next upstroke. In the presence of APD oscillations, DI and APD are recorded around the pathway for several revolutions to create the APD restitution curve (APD as a function of the previous DI). In the absence of oscillations, the restitution curve is created by applying a premature stimulus on the tail of the reentrant AP, which induces transient oscillations in APD and DI (18). These data are then used to create the APD restitution curve. CL is measured as the time between two successive upstrokes at a particular cell. During oscillations, intermediate APD (APD<sub>med</sub>), DI (DI<sub>med</sub>), and [Ca<sup>2+</sup>]<sub>L,peak</sub> ([Ca<sup>2+</sup>]<sub>L,peak,med</sub>) for a single cell are the midpoints between the maximum and minimum values.

In certain simulations, we use a [Na<sup>+</sup>]<sub>Cl</sub> protocol in which [Na<sup>+</sup>]<sub>i</sub> is held at a fixed value and prevented from accumulating as reentry continues. In another simulation, we uncouple cells (set g<sub>j</sub> = 0) away from the AP upstroke. The region of coupled cells and the AP wave front propagate together in the reentry pathway during this simulation. This allows us to minimize the effects of electrical loading on the dynamics during sustained reentry.

RESULTS

The regime of stable AP behavior. Figure 2 shows APD (A), [Ca<sup>2+</sup>]<sub>L,peak</sub> (B), and CL (C) as functions of L for L < 150 cells. The data shown are the steady-state values recorded at each L during the short steady-state protocol. Below a certain L (the bifurcation point, L<sub>crit</sub>, marked with an arrow in Fig. 2A), significant head-tail interaction occurs, and the nonlinear properties of the system become apparent as all AP properties (APD, [Ca<sup>2+</sup>]<sub>L,peak</sub>, CL, DI, and θ) display complex oscillatory behavior (DI and θ are not shown). The shaded region in Fig. 2 indicates the region of oscillatory behavior. For L > L<sub>crit</sub>, reentry is stable (oscillations in AP properties are transient and subside within 10 revolutions). We begin by discussing the dependence of AP properties on L in the stable regime.

CL is the time it takes for the reentrant wave front to propagate once around the pathway. As L becomes shorter (for L > L<sub>crit</sub>), the wave front takes less time to travel around the reentry pathway and CL decreases (Fig. 2C). A smaller CL implies that every cell in the reentry pathway is being stimulated at a more rapid rate, which results in reduced APD (Fig. 2A) and in-
creased \([\text{Ca}^{2+}]_{\text{i,peak}}\) (Fig. 2B). These rate-dependent AP changes are manifestations of rate-adaptation cellular processes that are well understood (43, 46).

**Time dependence of the critical \(L\) for bifurcation.** For \(L < L_{\text{crit}}\), APD, DI, \([\text{Ca}^{2+}]_{\text{i,peak}}\), CL, and \(\theta\) begin to oscillate. In Fig. 2, corresponding to the short steady-state protocol, \(L_{\text{crit}} = 80\) cells. However, if reentry in an 80-cell pathway continues for another 400 revolutions, the stable beat-to-beat APD alternans (2:2 stimulus-response ratio) observed after 50 revolutions disappears. In Fig. 3 (shown on a scale of only 70 cells to expand the region of oscillatory behavior), the long steady-state protocol is implemented. In this figure, \(L_{\text{crit}} = 64\) cells compared with 80 cells in Fig. 2. Note in Fig. 3 the division of the oscillatory region into subregions with distinct oscillatory patterns. (These patterns are discussed in Figs. 7 and 8.) With models that do not account for dynamic changes in intracellular ion concentrations (e.g., Beeler-Reuter; see Ref. 4), AP properties begin oscillating at a well-defined (fixed) \(L_{\text{crit}}\) that does not decrease with time (8, 21, 34, 42). The LRd model used in this study accounts for dynamic intracellular ion concentration changes that occur when cells are stimulated rapidly during reentry. With these physiological processes, \(L_{\text{crit}}\) shows strong time dependence (compare Figs. 2 and 3).

**Time dependence of oscillations for a relatively large \(L\) (weak head-tail interaction) and ionic mechanism.** Insight into the time-dependent processes responsible for damping of oscillations and reduction of \(L_{\text{crit}}\) is provided in Figs. 4 and 5. Figure 4, left, shows APD restitution curves during reentry in a pathway with \(L = 80\) cells. Figure 4, right, shows corresponding APD values recorded at every cell in the pathway during one revolution of reentry. Oscillations in APD persist after 150 revolutions (Fig. 4A, right). The corresponding APD restitution curve (Fig. 4A, left) has a slope \((m)\).
whose maximum value \( (m_{\text{max}}) \) is >1, which agrees with theoretical and experimental observations that \( m_{\text{max}} \approx 1 \) for oscillations in APD to occur (8, 18, 21, 24). After 950 revolutions (Fig. 4B), the oscillations in APD cease (right), and \( m_{\text{max}} < 1 \) (left). In addition, \([Na^+]_i\) (not shown) accumulates from 18 to 21 mM, in agreement with experimental findings that \([Na^+]_i\) increases by about 30% during rapid pacing (7). Furthermore, APD_{med} decreases from 75.6 to 71.8 ms, and DI_{med} increases from 26.4 to 30.4 ms over the course of 800 revolutions.

\([Na^+]_i\) accumulation dampens oscillations after 950 revolutions through the following mechanism. The point about which APD and DI oscillate (the operating point, discussed further in Fig. 10) is determined by the intersection of the line \( \text{APD} = \text{DI} + \text{CL} \) and the APD restitution curve (31). \([Na^+]_i\) accumulation decreases APD (shifts the restitution curve downward, Fig. 4B) relative to control (Fig. 4A). Assuming CL remains constant (a good assumption because CL changes are very small relative to changes in APD and DI), a downward displacement of the restitution curve (decrease in APD_{med}) shifts the operating point to a larger DI where \( m_{\text{max}} < 1 \), and oscillations disappear.

Evidence for this is given in Fig. 4C, where \([Na^+]_i\) during reentry after 950 revolutions is reset to its value after 150 revolutions. When \([Na^+]_i\) is decreased in such a manner, APD_{med} increases from 71.8 to 76.2 ms, and DI_{med} decreases from 26.4 to 30.4 ms. Consequently, \( m_{\text{max}} > 1 \) (left), and oscillations in APD resume (right).

To provide insight into the ionic mechanism by which APD decreases with time and oscillations cease, we compare APs (Fig. 5A) and ionic currents (Fig. 5, B–E) observed at a single cell after 150 revolutions (solid line) to those observed after 950 revolutions (dashed line). Accumulation of \([Na^+]_i\) after 950 revolutions increases the reverse-mode activity (\(Na^+\) extru-
sion with 3Na\(^+\)-1Ca\(^{2+}\) stoichiometry of the Na\(^+\)-Ca\(^{2+}\) exchanger \(I_{\text{NaCa}}\) (Fig. 5B). This results in an increase of an outward repolarizing current. Similarly, elevated [Na\(^+\)]\(_i\) increases the repolarizing Na\(^+\)-K\(^+\) pump current \(I_{\text{NaK}}\), which has a 3Na\(^+\)-2K\(^+\) stoichiometry (Fig. 5C). As a consequence of this increase in the total repolarizing current secondary to [Na\(^+\)]\(_i\) accumulation, APD\(_{\text{med}}\) decreases (downward shift of the APD restitution curve).

The slow component of the repolarizing delayed rectifier K\(^+\) current \(I_{\text{Ks}}\) (Fig. 5D) is reduced after 950 revolutions and therefore does not contribute to APD shortening with time. The reduction of \(I_{\text{Ks}}\) is the result of an increase in DI secondary to shortening of APD, which allows \(I_{\text{Ks}}\) more time to deactivate after its activation. The depolarizing L-type Ca\(^{2+}\) current \(I_{\text{Ca,L}}\) (Fig. 5E) does not contribute to the downward shift of the restitution curve either. This is apparent in Fig. 5E, which shows after 950 revolutions a larger \(I_{\text{Ca,L}}\) (arrow) during the plateau of a shorter AP (Fig. 5A).

It is important to note that in addition to [Na\(^+\)]\(_i\) accumulation, there is also [Ca\(^{2+}\)]\(_i\) accumulation ([Ca\(^{2+}\)]\(_i\),peak,med increases from 2.24 to 2.62 \(\mu\)M after 800 revolutions, not shown). When [Na\(^+\)]\(_i\) accumulation is prevented, [Ca\(^{2+}\)]\(_i\) does not accumulate either, making it difficult to state whether [Na\(^+\)]\(_i\) accumulation leads to [Ca\(^{2+}\)]\(_i\) accumulation or vice versa. However, Ca\(^{2+}\)-sensitive currents in the model \(I_{\text{Ca,L}}, I_{\text{Ca,R}}\), and forward-mode \(I_{\text{NaCa}}\) do not contribute to the downward shift of the restitution curve. Furthermore, resetting [Na\(^+\)]\(_i\) is sufficient to reverse the time-dependent change in dynamics. These results suggest that [Na\(^+\)]\(_i\) accumulation is primarily responsible for the downward shift of the restitution curve with time.

**Temporal oscillations in AP properties at a single site.** Once bifurcation occurs \((L < L_{\text{crit}})\), oscillations in AP properties measured at a single cell (the temporal domain) may assume a number of complicated patterns. Figure 6, *left*, shows temporal oscillations in APD (Fig. 6A), DI (Fig. 6B), and CL (Fig. 6C). The theoretical oscillatory patterns agree with experimental measurements (Fig. 6, *right*) conducted by Frame and Simson (18) in the canine tricuspid orifice ring as well as with theoretical studies performed in other ring models (8, 21, 42). Importantly, the maximal percent changes in APD and DI (33% and 153%, respectively) during oscillations are much greater than the maximal percent change in CL (6%). Furthermore, APD and DI oscillations are 90° out of phase relative to the CL oscillations (i.e., APD and DI oscillations are maximal where CL oscillations are minimal, as indicated by arrows in Fig. 6).

Examples of temporal oscillations in APD from the short steady-state (Fig. 2) and the long steady-state (Fig. 3) protocols are shown in Fig. 7 and may be classified as either periodic or quasi-periodic. Only APD \((left)\) and [Ca\(^{2+}\)]\(_i\),peak \((right)\) are shown, but other AP properties (DI, \(\theta\), and CL) display a similar behavior. A periodic 2:2 behavior (stable beat-to-beat alternans) appears in Fig. 7A, and a 5:5 periodicity (pattern repeats itself every five beats) is shown in Fig. 7B. These oscillatory patterns agree with patterns observed experimentally (Fig. 7, A and B). A periodic window \((L < L_{\text{crit}})\) is interrupted by a small window of periodicity at \(L = 61\) cells (Fig. 3). As \(L\) is reduced, the oscillatory behavior passes through a quasi-periodic regime that is interrupted by a small window of periodicity at \(L = 61\) cells (Fig. 3). We discuss the factors that contribute to the formation of these different patterns in the next section.

Interestingly, for a relatively low degree of head-tail interaction (Fig. 7A) the maximal percent change in [Ca\(^{2+}\)]\(_i\),peak \((94\%, right)\) during oscillations is much greater than the maximal percent change in APD \((17\%, left)\). This difference disappears as the degree of head-tail interaction increases (Fig. 7, B and C). Furthermore, [Ca\(^{2+}\)]\(_i\),peak oscillations appear only in the presence of APD oscillations, and in general the two are in phase with the larger Ca\(^{2+}\) transient corresponding to the longer AP. An exception to this in-phase relationship is observed during the 5:5 periodic pattern shown in Fig. 7B. The AP labeled A \((left)\) is slightly longer than the AP labeled B \((77.0\) ms com-
oscillatory regions in Fig. 3. In Fig. 8B, \( \Lambda/L = 5/3 \) such that 5 revolutions accommodate an integer multiple of \( \Lambda (5L = 3 \Lambda) \), which produces the 5:5 periodic pattern at a single site (Fig. 7B). For a shorter \( L \) (Fig. 8C), the magnitude of CL oscillation increases, and \( \Lambda L \) decreases to slightly less than 5/3. Now five revolutions fit slightly more than 3\( \Lambda \), producing a shift in the spatial oscillation pattern every revolution, which generates the quasi-periodic pattern at a single site (Fig. 7C).

Two factors are responsible for the formation of different temporal oscillatory patterns. First, increased head-tail interaction increases CL oscillations and the complexity of the spatial oscillation pattern (which accounts for the difference between Fig. 7, B and C). Second, \( \Lambda \) changes with time (the difference between Fig. 7, A and B), a phenomenon that is discussed in the next section.

Time dependence of oscillations for relatively small \( L \) (strong head-tail interaction). The \( \Lambda \) of the spatial oscillation pattern from a 70-cell pathway (relatively small \( L \)) increases from 0.29\( L \) (Fig. 9A, shown previously in Fig. 8A) after 150 revolutions to 0.39\( L \) after another 760 revolutions (Fig. 9B). Simultaneously, \([Na^+] \) increases from 19.7 to 21.8 mM (not shown), and the APD restitution curve shifts downward (Fig. 9B). In contrast to the decrease of \( m_{max} \) observed in Fig. 4, \( m_{max} \) increases from 1.31 to 1.51 in response to this downward shift. Consequently, the difference (APD) between the maximum value of APD (APD_{max}) and the minimum value of APD (APD_{min}) increases from 12.4 to 16.3 ms, reflecting an increase in the magnitude of oscillations. Note that the data in Fig. 4 come from a relatively long pathway (\( L = 80 \) cells) in the presence of weak head-tail interaction. In contrast, Fig. 9 corre-

Fig. 7. Different temporal oscillatory behavior observed at a single site during reentry. APD (left) and \([Ca^{2+}]_{i,peak} \) (right) oscillations were recorded from pathways with three different \( L \) values: A: beat-to-beat AP alternans in a 70-cell reentry pathway; B: 5:5 periodic behavior (pattern repeats every five beats) in a 61-cell pathway \([APD_{max} = 77 \text{ ms and } [Ca^{2+}]_{i,peak} = 3.4 \text{\,mM}]; \text{ and } APD_{min} = 67.8 \text{ ms and } [Ca^{2+}]_{i,peak} = 3.6 \text{\,mM}]); and C: quasi-periodic behavior in a 60-cell pathway. Short steady-state protocol is used in A; long steady-state protocol is used in B and C. Experimental CL oscillations are shown for comparison in A (18) and B (14). In these simulations \( \varepsilon_i = 0.076 \text{ mS} \) was used.

Spatial oscillations of AP properties. To understand the different temporal oscillation patterns presented in Fig. 7, it is helpful to consider how AP properties change in space along the entire pathway (spatial domain) during reentry. Figure 8 shows CL as a function of location for consecutive revolutions of the reentrant wave front under the same circumstances as in Fig. 7. Importantly, Fig. 8 reveals that spatial oscillations in CL are sinusoidal during reentry. Spatial oscillations in APD, DI, \( \theta \), and \([Ca^{2+}]_{i,peak} \) are also sinusoidal (not shown). The wavelength of spatial sinusoidal variation of AP properties is referred to as the oscillation wavelength (\( \Lambda \)). The 2:2 temporal behavior in Fig. 7A is the result of a spatial oscillation pattern with \( \Lambda/L = 2/7 \) (Fig. 8A). In this case, two revolutions accommodate an integer multiple of \( \Lambda (2L = 7 \Lambda) \), which gives rise to beat-to-beat alternans observed temporally at a single site (in Fig. 8, values recorded at a single site for consecutive revolutions are marked with an \( x \)).

Figure 8 also shows spatial oscillatory patterns from the 5:5 periodic (Fig. 8B) and quasi-periodic (Fig. 8C)
responds to a relatively short pathway (L = 70 cells) where there is strong head-tail interaction.

We provide the following hypothesis for the mechanism by which [Na\(^+\)]\(_i\) accumulation increases oscillations and \(\Lambda\) in a relatively short pathway. As discussed previously, [Na\(^+\)]\(_i\) accumulation decreases APD at every DI (downward shift of the restitution curve; Fig. 9), shifting the operating point to a larger DI. At very short DIs (high degree of head-tail interaction), the APD restitution curve begins to flatten (decreased \(m\)) as DI decreases. Consequently, a slight shift of the operating point to a larger DI increases \(m\) and the magnitude of oscillations. The result is an increase in \(\Delta\text{APD}\) of the spatial APD oscillation pattern, which increases spatial gradients of the membrane potential and the limit on flattening of the APD restitution curve for short DIs. The increase in oscillations with [Na\(^+\)]\(_i\) accumulation for a high degree of head-tail interaction is dependent on flattening of the APD restitution curve for short DIs. Experimental studies have shown a similar flattening of the APD restitution curve for short DIs and have attributed it to increased latency between the stimulus and the AP upstroke (6, 24). In our study, the restitution curve flattens because for very short DIs the Ca\(^{2+}\) transient begins to decrease significantly, which is in agreement with experimental observations (26). A smaller peak Ca\(^{2+}\) transient results in reduced Ca\(^{2+}\)-dependent inactivation of \(I_{\text{Ca(L)}}\) (not shown) and therefore an increase in depolarizing current during the plateau of the AP, which acts to oppose APD shortening.

**Elevated [K\(^+\)]\(_o\) Experiments have shown that K\(^+\) accumulates in extracellular clefts during rapid pacing (23). To investigate the effect of extracellular K\(^+\) concentration ([K\(^+\)]\(_o\)) accumulation on the dynamics of reentry, we increase [K\(^+\)]\(_o\) from 4.5 mM (control) to 7 and 12 mM in a 78-cell pathway. In the control ([K\(^+\)]\(_o\) = 4.5 mM), oscillations during reentry disappear within 600 revolutions. When [K\(^+\)]\(_o\) is increased to 7 mM, the resting \(V_m\) depolarizes from \(-83\) to \(-76\) mV, and oscillations persist for over 1,000 revolutions despite a decrease of APD\(_{\text{med}}\) from 72 to 63 ms (not shown). If [K\(^+\)]\(_o\) is elevated instead to 12 mM, the resting \(V_m\) depolarizes to \(-65\) mV, and reentry terminates within one revolution. Thus elevated [K\(^+\)]\(_o\) acts to enhance oscillations and destabilize reentry.

**DISCUSSION**

**Summary of findings.** Important findings of this study are: 1) a high degree of head-tail interaction produces oscillations in AP properties and in the Ca\(^{2+}\) transient; 2) the Ca\(^{2+}\) oscillations are generally in phase with APD oscillations; 3) the magnitude of Ca\(^{2+}\) oscillations is greater than the magnitude of APD oscillations for moderate degrees of head-tail interaction; 4) [Na\(^+\)]\(_i\) accumulation shifts the APD restitution curve downward to smaller APD values which, depending on the degree of head-tail interaction, may either stabilize or destabilize reentry; 5) for a relatively low degree of head-tail interaction, accumulation of [Na\(^+\)]\(_i\) tends to stabilize the dynamics of the reentrant AP; 6) for a higher degree of head-tail interaction, [Na\(^+\)]\(_i\) accumulation is accompanied by increased wavelength of spatial oscillations, which augments CL oscillations; and 7) elevated [K\(^+\)]\(_o\) increases oscillations and destabilizes reentry.

**Changes in [Na\(^+\)]\(_i\) alter the dynamics of reentry.** We find that the behavior of reentry evolves in time due to accumulation of [Na\(^+\)]\(_i\). Previous experimental and theoretical studies have shown that the APD restitution curve shifts downward (to smaller APD values) in response to an increase in pacing rate (5, 46). It has been proposed that the mechanism for this downward
shift is either \([Ca^{2+}]_i\) accumulation (5, 46) or \([K^+]_o\) accumulation (5). In this study we observe that while \([Ca^{2+}]_i\) accumulates along with \([Na^+]_i\), \([Na^+]_i\) is the primary cause of APD shortening and the downward shift of the restitution curve. This downward shift may shift the point about which APD oscillates (the operating point) to less steep (Fig. 4) or more steep (Fig. 9) portion of the restitution curve, depending on the degree of head-tail interaction. Therefore, this shift may either suppress or augment AP oscillations.

A schematic is used in Fig. 10 to summarize the effects of \([Na^+]_i\) accumulation on the APD restitution curve and the dynamics of reentry for low and high degrees of head-tail interaction. The APD restitution curve in the presence of \([Na^+]_i\) elevation (dashed line) is shifted downward relative to the control curve (solid line). The operating point about which APD and DI oscillate is determined by the intersection of the line \(APD = -DI + CL\) (dashed-dotted line) with the restitution curve. For a low degree of head-tail interaction (\(CL_A\)), the operating point occurs where \(m = 1\) in the control case but where \(m < 1\) in the presence of elevated \([Na^+]_i\), which dampens oscillations. For a high degree of head-tail interaction (\(CL_B < CL_A\)), the operating point in the presence of elevated \([Na^+]_i\) occurs where the slope is steeper than in the control case, which increases the amplitude of oscillations. The schematic in Fig. 10 illustrates the differential effect \([Na^+]_i\) accumulation has on the dynamics of reentry depending on the degree of head-tail interaction in the pathway.

Accumulation of \([Na^+]_i\) is known to promote spontaneous activity, which may trigger an arrhythmia (12, 35). Our results illustrate how \([Na^+]_i\) accumulation may affect the time course of an arrhythmia once initiated. This effect can be stabilizing or destabilizing, depending on the degree of head-tail interaction of the circulating AP. For relatively slow tachycardias (weak head-tail interaction), the effect may be stabilization of reentry due to a shift of the operating point to a less steep portion of the restitution curve. In contrast, \([Na^+]_i\) accumulation may act to destabilize reentry during rapid tachycardias (strong head-tail interaction) leading to either its termination or transition to fibrillation.

**Longer \(\Lambda\) leads to greater CL oscillations.** We observe that \([Na^+]_i\) accumulation with time produces spatial oscillation patterns with different \(\Lambda\). The existence of different \(\Lambda\) has been predicted by Courtemanche, Glass, and Keener (8), who proposed a delay-difference equation to describe the evolution of AP properties as the reentry wave front propagates. They solved for all \(\Lambda\) values (eigenmodes, Eq. 1), which yield solutions to the delay-difference equation once bifurcation occurs

\[
\Lambda_k = \frac{2L}{2k + 1} - \frac{4L^2\alpha}{(2k + 1)^2\pi^2}, \quad k = 0, 1, 2, \ldots \tag{1}
\]

where \(\alpha\) is proportional to the slope of the dispersion relation (\(\theta\) as a function of DI) and \(k\) is the mode number. Because \(k\) can assume any positive integer value, an infinite number of oscillatory modes can occur in the delay-difference model. The spatial oscillation patterns with different \(\Lambda\) shown in Fig. 8 correspond to different eigenmodes in this equation. The implication of the possible existence of many oscillatory modes is discussed in the following text.

In our simulations, we observe that a longer \(\Lambda/L\) promotes CL oscillations (Fig. 9 and corresponding text). Fig. 11 presents two hypothetical spatial oscillation patterns in \(1/\theta\) (the reciprocal of conduction velocity) to explain this behavior. The pattern in Fig. 9A has a relatively long \(\Lambda\) relative to \(L\), whereas that in Fig. 9B has a short \(\Lambda\). It is assumed that the magnitude of

![Fig. 11. Mechanism by which a spatial oscillation pattern with a longer \(\Lambda\) yields greater CL oscillations. Reciprocal of conduction velocity, \(1/\theta\), is plotted around the reentry pathway for one revolution. Spatial oscillation patterns with long \(\Lambda\) (A) and short \(\Lambda\) (B) are presented. CL in each panel is area beneath the curve, and shaded area represents the amount by which CL is greater than the intermediate CL value.](image-url)
the oscillations in $\theta$ in Fig. 9A and B, is the same and that the only difference is in $\Lambda$. CL for one revolution is given by

$$\text{CL} = \int_{x-L}^{x} \frac{1}{\theta} \cdot ds$$

where $x$ is the current position of the wave front. The CL calculated in Fig. 9A and B, is therefore greater than the intermediate CL (corresponding to no oscillations with a fixed $\theta = \theta_{\text{mea}}$) by an amount equal to the area of the shaded region. The larger shaded area in Fig. 9A implies that a spatial oscillation pattern with a longer $\Lambda$ augments CL oscillations.

Experiments have shown that the existence of CL oscillations favors spontaneous termination of reentry (14, 17, 18, 32). In our study, we find that $[\text{Na}^{+}]_{i}$ accumulation with time increases $\Lambda$ of a spatial oscillation pattern, which in turn augments CL oscillations (Fig. 9). This result suggests that lengthening of $\Lambda$ with time (transition from one eigenmode to another) could be one mechanism by which reentry spontaneously terminates. Furthermore, it has been shown that AP oscillations in a one-dimensional ring occur for the same rotation periods as does spiral-wave breakup in two-dimensional models, a phenomenon that produces a disordered fibrillatory state (21, 44). This suggests that lengthening of $\Lambda$ with time and the consequent increase in oscillations may promote spiral-wave breakup and could be one mechanism for the transition from ventricular tachycardia to fibrillation.

Effect of elevated $[K^{+}]_{o}$ on the dynamics of reentry. A previous study from our laboratory (39) showed that elevated $[K^{+}]_{o}$ by depolarizing the resting membrane potential, caused prolonged post-polarization refractoriness as a result of prolonged recovery from inactivation of $I_{\text{Na}}$ following an AP. During reentry, this phenomenon acts to prolong the tail of refractoriness and reduced excitability that follow the AP; thus the degree of head-tail interaction increases despite APD shortening. In this study, we observe that a moderate elevation of $[K^{+}]_{o}$ promotes AP oscillations, although a more severe elevation leads to termination of reentry. The simulated values of elevated $[K^{+}]_{o}$ (7 and 12 mM) are representative of hyperkalemia during acute ischemia (39). The results suggest that hyperkalemia may have a destabilizing effect on reentry and may contribute to its termination or its disintegration into multiple reentrant circuits and a fibrillatory state.

Electrical and mechanical oscillations. The LRd model computes both the AP and the $[\text{Ca}^{2+}]_{i}$ transient. This enables us to study oscillations in APD and $[\text{Ca}^{2+}]_{i}$ for different degrees of head-tail interaction. Studies suggest that T wave alternans in the electrocardiogram reflects APD oscillations and indicates an increased risk for cardiac arrhythmia and sudden death (20, 37, 40). Similar to APD alternans, beat-to-beat alternation in the force generated by cardiac muscle (mechanical alternans) has also been observed at rapid rates (25), and intracellular $[\text{Ca}^{2+}]_{i}$ cycling causing $[\text{Ca}^{2+}]_{i}$ oscillations has been suggested as a mechanism (22, 25). Some studies have hypothesized that mechanical alternans generates electrical alternans (20, 25, 41), and others have proposed the converse to be true (27). The hypothesis that mechanical alternans causes electrical alternans is supported by observations of mechanical alternans in the absence of electrical alternans (41). In our study oscillations in APD and $[\text{Ca}^{2+}]_{i}$, always appear together. However, over a certain range of head-tail interaction, percent changes in $[\text{Ca}^{2+}]_{i}$, during oscillations are much larger than percent changes in APD, which may explain why mechanical alternans has been observed without detection of electrical alternans. In general, APD and the $[\text{Ca}^{2+}]_{i}$ transient oscillate in phase (a large $[\text{Ca}^{2+}]_{i}$ transient corresponds to a long APD). However, occasionally an out-of-phase relationship (a large $[\text{Ca}^{2+}]_{i}$ transient with a short APD) may occur (Fig. 7B).

Study limitations. The limitations of this study were the following. The ring model in this study is used to investigate an important property of reentrant excitation, namely the interaction between the head and tail of the reentrant AP. The center (core) of the reentry pathway in this model of “anatomical reentry” (16) is inexitable and represents an anatomical obstacle. In functional forms of reentry, such as leading-circle or anisotropic reentry (2, 10) or during spiral-wave activity (13), the core is excitable. In the leading-circle concept, the core is created by the collision of centripetal wavelets generated by the reentrant wave front propagating along the smallest possible pathway (the “leading circle”) (2). Although the nature of the core is different, important properties of leading-circle reentry are represented in the ring model. For example, there is no excitable gap in leading-circle reentry because of a high degree of head-tail interaction (2), as is the case for reentry in a small pathway in our simulations.

Another limitation of our model is the absence of heterogeneities in cell properties [e.g., midmyocardial M cells (43)] or tissue architecture [e.g., anisotropy due to fiber orientation (10)]. Although such inhomogeneities will affect the oscillatory patterns observed during reentry, the principles established here regarding the dynamics of head-tail interaction and its time dependence can provide insight into these phenomena in the inhomogeneous myocardium.

In the spiral-wave concept, a high degree of curvature at the tip of the reentrant wave front creates a source-sink mismatch that leaves a central core of unexcited but excitable tissue (13). The absence of an unexcited but excitable core in our model is significant because such a core influences the reentrant AP via electrotonic interaction (3). Nevertheless, the phenomenon of head-tail interaction explored here occurs along the arm of a spiral wave (21). Furthermore, in many instances, a drifting spiral wave anchors to an anatomical obstacle, such as a small artery (9). In such situations, the distinction between anatomical and spiral-wave reentry becomes less obvious.
The use of a one-dimensional model of reentry allowed us to use a detailed model of the cardiac cell that accounts for dynamic changes of ionic concentrations (e.g., [Na⁺], accumulation) over many reentrant cycles. With this approach, we could characterize the temporal evolution of the AP and the dynamics of reentry. The focus of this study is on head-tail interaction, AP oscillations (alternans), and stability of reentrant activity. Other properties of reentrant excitation, such as the ionic activity in the core of a spiral wave or the effects of anisotropy, must be studied using higher-dimensional models. The insights obtained from the present study can guide such simulations where the use of a detailed cell model during many reentry cycles still constitutes a major computational challenge. Moreover, the time scale investigated in this study is still relatively short. It allows for ion accumulation to occur but does not take into account changes due to electrical remodeling (1, 19, 45) that occur over a much longer time frame. Remodeling involves changes in ion channels, gap junctions, and tissue structure. Many of these changes can be incorporated within the framework of the detailed cell model used here and will be an important subject of future modeling studies.

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